Intravascular imaging and physiology guided interventions in complex chronic diseases as kidney failure and diabetes mellitus

By

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Abstract

Coronary artery disease (CAD) is the leading cause of death globally. There are a variety of risk factors for the development of CAD including diabetes mellitus (DM), hypertension, hyperlipidemia, smoking, sedentary lifestyle, genetic factors, and others. Together, they exert a significant role in the development of CAD, especially when these risk factors are combined. The burden of cardiovascular diseases (CVDs), secondary to chronic conditions like DM, obesity, hypertension and associated renal disease, is rapidly increasing worldwide, not only in developed countries, but also in low-and medium- income developing countries.

Coronary angiography (CA) is considered the gold standard test for the diagnosis of CAD. An accurate interpretation of CA is of paramount importance in decision-making by the Clinicians to treat patients with CAD. CA has the inherent limitation of being a two-dimensional X-Ray lumeno-gram of a complex three-dimensional vascular structure. Visual assessment of angiogram can lead to both inter- and intra-observer variability in the assessment of the severity and extent of the disease which can lead to differences in management strategies.

Catheterization cardiology has been revolutionized recently and today; modern catheterization laboratories globally are fully equipped with adjunctive technologies. These include Quantitative Coronary Angiography (QCA), Fractional Flow Reserve (FFR), Intra-Vascular Ultra-Sonography (IVUS) and Optical Coherence Tomography (OCT) to help the Clinicians to make a well-informed decision based on detailed anatomical and physiological assessments of a coronary artery rather than judgment based solely on visual assessment.

Despite the introduction of coronary physiology and intravascular imaging in very early cases of coronary intervention, practical use of these techniques in the catheterization laboratory did not begin until the late 1990s. A variety of reasons have been understood as hurdles during the initial adoption of these clinical tools in cardiac catheter laboratories. The technological and theoretical aspects were not well understood initially, and currently used well-matured pressure wires which were not readily available. Nevertheless, coronary physiology and intravascular imaging have established a vital role in decision making process during cardiac catheterization laboratory.

This doctoral thesis, via several previous high impact journal publications, emphasized and supported the role of intracoronary imaging and physiology, mineralocorticoids antagonism and infarct size reduction in various clinical settings. The thesis has highlighted that decision-making with the help of intracoronary imaging and physiology is safe, effective and the clinicians can safely defer the decisions of coronary interventions based on negative value or non-ischemic values (Fractional Flow Reserve, FFR>0.80) based on the physiology. It has also been established that these techniques are cost-effective as well. The presented thesis also highlights the utility and evidence behind these adjunctive techniques, supported by clinical cases and highlights the importance of these techniques to make a well-informed treatment decision.

The thesis for PhD by Publication has clearly demonstrated, and more so, emphasized the clinical utility of intra-coronary imaging and physiology in complex disease processes like diabetes mellitus and chronic kidney disease (CKD).

STUDENT DECLARATION FORM

Concurrent registration for two or more academic awards

I declare that while registered as a candidate for the research degree, I have not been a registered candidate or enrolled as a student for another award of the University or other academic or professional institution.

Signature of Candidate

Type of Award:

PhD by Publications

School of Natural Sciences, UCLAN

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Dedication

This thesis is dedicated to my parents and my wife. As such, I must express my very profound gratitude to my parents and my wife for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. You are the pillars of my life and I stand nowhere without you. This accomplishment would not have been possible without you. Thank you. Special mention to my kids, Zain and Zunairah and Zayyan, you mean everything to me, and I dedicate this thesis to you.

ABBREVIATIONS

ACC-American College of Cardiology

AHA- American Heart Association

AMI-Acute Myocardial Infarction

ACH- Acute Heart Attack

ACS-Acute Coronary Syndrome

BMJ-British Medical Journal

CA-Coronary Angiography

CAD -Coronary artery disease

CHD-Congenital- Heart -Disease

CIN-Contrast-Induced Nephropathy

CFD- Computational Fluid-Dynamic

CKD -Chronic kidney diseases

CSA-Cross Sectional Area

CVD -Cardiovascular- Disease

cFFR- Contrast FFR

cFR-Coronary Flow Reserve

cFFR-Contrast Fractional Flow Ratio

DCM-Diabetic Cardiomyopathy

DN-Diabetic Neuropathy

3D -3-dimensional

DFR- Diastolic Hyperemia-Free Ratio-Diastolic hyperemia-free ratio

DM- Diabètes Mellites

DES-Drug Elution Stents

DHR- Diastolic Hyperemia-Free Ratio

dPR- Diastolic Pressure Ratio

ESC-European Society of Cardiology

EEL-External Elastic Lamina

ESKD-End-stage Renal- Disease

FAME-Fractional Flow Reserve vs Angiograph for Multivessel Evaluation

FFR- Fractional Flow Reserve

FFRCT- Computed Tomography–Derived FFR

GTN- Glyceryl-trinitrate

HF-Heart Failure

HFPEF-Heart Failure with Preserved Ejection Fraction

HTN-Hypertension

iFR- Instantaneous Wave-Free Ratio

IRS-In-stent Restenosis

IVUS- Intravascular Ultrasound

KD-Kidney Failure

LD-Lumen Diameter

LADA – Left Anterior Descending Artery

LMCA-Left Main Coronary Artery

LMS-Left Main Stem

LVH-Left Ventricular Hypertrophy

LMICs-Low- and Middle- Income Countries

LCSD-Left Ventricular Systolic Dysfunction

MACE-Major Adverse Cardiovascular Risks

MLA-Minimum Lumen Area

MI-Myocardial Infarction

MRA-Mineralocorticoid Receptor Antagonist

NHPR- Non- Hyperemic Pressure-Ratio

OA-Orbital Atherectomy

OCT -Optical Coherence Tomography

OCTFFR- Optical Coherence Tomography Derived Fractional Flow Reserve

Pa- Means Aortic Pressure.

PAH-Pulmonary Arterial Hypertension

PCI-Percutaneous Coronary Intervention

Pd- Means of Distal Coronary Pressure.

PhD- Doctor of Philosophy

RBC-Red Blood Corpuscles

PROSPECT-Providing Regional Observation to study Predictors of Events in

Coronary Tree PW-Pressure Wire

QCA-Quantitative Coronary Angiograph

QFR- Quantitative Flow Ratio

RCS-Reactive Carbonyl Species

RFR- Resting Full-Cycle Ratio.

RISK-Reperfusion Injury to Salvage Kinase

ROC-Receiver Operating Characteristic

ROS-Reactive Oxygen Species

SCD-Sudden Cardiac Death

sPR-Systolic Blood Pressure Ratio

SVG-Saphenous Vein Bypass Graft

TCFA-Thin-Cap Fibroatheroma

UCLAN-University of Central Lancashire

VDH-Valvular Heart Disease

vFFR- Vessel FFR

VHD-Vascular Heart Disease

VH-Virtual Histology

USA-United States of America

USAD-United States of America Dollars

VIVA-VH- IVUS Vulnerable Atherosclerosis

VANRWISH-Veteran Affairs N-Q-Wave Interaction Strategies in Hospitals

PROFESSIONAL PROFILE

PROFESSIONAL PROFILE OF CANDIDATE

My name is Yasir Parviz, and I am a fully trained interventional Consultant Cardiologist. I have dual board certification in cardiology and general internal medicine from the United Kingdom (UK). I have received interventional fellowships from highly programs in UK, Canada, and the United States of America (USA). My academic and clinical credentials from Sheffield University UK, Western University Canada, and Columbia University New York, are well suited for the PhD by Publications and fully aligned with my future career aspirations. Moreover, I am unique in the sense that I have the relevant experience in working in Asia, Europe, Canada, and USA. I am not only a qualified interventional Cardiologist, but I also have strong leadership and managerial experience and skills in research and clinical medicine trying to push the boundary of scientific and clinical research further.

I have demonstrated strong leadership and managerial skills, during various clinical and nonclinical settings. I am certified in leadership skills from the Institute of Innovation, London UK. My leadership and managerial skills helped various health care institutions to build the cardiac care program to other sites in the UAE and in the Gulf region. I have certifications in the field of advancing healthcare practice from the Open University in the UK as well as Postgraduate Certificate of Attainment at Improvement Practitioner level from NHS Institute for Innovation and Improvement, London UK. I was selected as an agent to present Chesterfield Royal Hospital for collaborative change via a quality conference at Kings Fund London.

I have attended specified management and leadership courses organized by Health Education Yorkshire (H.E.Y) and Humberside. I was selected as a Chief Fellow at London Health Sciences Center in Canada during my fellowship training, and I was also the SpR representative at Sheffield Teaching Hospital NHS Trust DMT. I was actively involved in the induction and placement of medical students from Sheffield University to the hospital. I have been involved in the design and implantation of the local clinical practice and designing and implementing the new guidelines for the management of various clinical conditions. I was an organizer for PACES examinations for

Royal College of Physicians, UK, and medical rotation manager at Heart of England NHS Trust. I have not only been certified in intervention, but also, I am certified in cardiology, internal medicine and have a particular interest in patients who develop renal diseases.

It is particularly noteworthy that I have an excellent academic background and am actively involved in research and clinical governance. I have previous experience of collaborative research work with world-renowned experts, leading to peer-reviewed publications. I have presented research papers at national and international scientific meetings, and I am fully aware of the current dynamics and conferences being held worldwide and I have presented at world stage forums. I was awarded the best presenter award at the Gulf PCR among delegates from 84 countries globally.

I strongly believe that this PhD thesis via published papers fulfills the criteria set by UCLAN and due to my academic record, credentials, my enthusiasm, and passion about academia. These will be an added feather in my academic credentials and will help in career progression. My previous experience and collaboration with world renowned institutions such as Columbia University New York, Western University Canada, and Sheffield Hallam UK, will be further enhanced by this academic work. My leadership, public speaking, negotiation skills as well as my collaborative skills have allowed me to lead the various teams and I have the vision to develop a strategy to guide and support the directions of various hospitals where I have worked over the years.

I have experience of working in the field of coronary physiology and imaging with world leaders at Columbia Medical Center and Cardiovascular Research Foundation (CRF). These places are leading centers in the field of cardiovascular research. With my experience, I can bring collaboration to various institutions, due to my previous collaboration and networking with these institutes. I have developed a keen interest in imaging and clinical physiology as evidenced by the current thesis and moreover, I can develop a physiology laboratory in the UK to extend the work that I have done at Columbia University.

I have learned the skills of imaging and physiology guided coronary interventions with minimal use of contrast and leading to zero contrast PCI program. I have developed a program for cardiovascular assessment of prerenal transplant patients and extended that to liver and lung transplant and can develop a database to further enhance the knowledge in the utility of intracoronary imaging and physiology in the complex diseases like diabetes and kidney disease. As demonstrated by above-mentioned experience and skills, it is possible to appreciate that I have extensive experience in various healthcare settings, giving me varied skills and the ability to work in widely diversified populations. I firmly believe that I am a suitable, strong and a well-qualified candidate for the awarded of the PhD by publication based on my clinical and research experience. Moreover, I am very enthusiastic in whatever I am doing irrespective of personal sacrifices. I am a conscientious and a hardworking person paying attention to details. I am also flexible, alert, and quick to pick up new skills and eager to learn from others. I am innovative, forward-thinking, and have enthusiasm and various ideas to help in developing cardiovascular care for patients.

Yours sincerely

Dr Yasir Parviz

LIST OF PAPERS TO FORM PhD BY PUBLICATION CLASSIFIED INTO THREE CATAGORIES

A) Intracoronary Imaging and Physiology

1. **Parviz, Y.,** Fall, K., Stone, G., Maehara, A., Ben-Yehuda, O., Mintz, G., and Ali, Z. (2017). Imaging and Physiology to Guide Venous Graft Interventions Without Contrast Administration in Advanced Renal Failure. The Journal of Invasive Cardiology, 29 (11): E163-E165, **(Impact Factor 1.07 and 6 citations).**

2. **Parviz, Y.** and Hanif, S. (**2017).** Intra coronary imaging to detect mal apposition: Are We Seeing Too Much. Heart. (A BMJ Journal), 103 (9): Article 2017; 0- heartjnl-2015-307888v1) (**Impact Factor 5.42 and no citation).**

3. **Parviz, Y.,** Shiofmitz, E., Fall, K.N., Konigstein, M., Maehara, A., M., Jerimias, A., Shlofmitz, R.A., A.S., Mintz, G.S., and Ali, Z.A. (2018). Utility of intracoronary imaging in the cardiac catheterization laboratory: comprehensive evaluation with intravascular ultrasound and optical coherence tomography. British Medical Bulletin, 125(1):79-90. (doi: 10.1093/bmb/ldx049. **(Impact Factor: 3.045 and 18 citations).**

4. **Parviz, Y., P.,** Fall, K.N., , and Ali, ZA. (2016). Using sound advice—intravascular ultrasound as a diagnostic tool. Journal of Thoracic Diseases. 8(10): E1395-E1397. (doi: 10.21037/jtd.2016.10.64. 10.21037/jtd.2016.10.64, **(Impact Factor: 2.365 and 3 citations).**

5. Chin, C., Matsumura, M., Maehara, A., Zhang, W., Lee, C., Yamamoto, M., Song, L., **Parviz, Y.,** Jhalani, N., Mohan, S., Ratner, L., Cohen, D., Ben-Yehuda, O., Stone, G., Shlofmitz,

R., Kakuta, T., Mintz, G., and Ali, Z.A. (2017). Coronary Plaque Characteristics in Haemodialysis-Dependent Patients as Assessed by Optical Coherence Tomography. The American Journal of Cardiology,119(9): 1313-1319. (doi: 10.1016/j.amjcard.2017.01.022. Epub, 2017 Feb 9. **(Impact factor: 2.26 and no citation)**

6. **Parviz, Y.,** Awan, K., Vijayan, S., Sultan, A., and Iqbal, J. (2017). Role Of Intra Coronary Imaging and Physiology in Diagnosis And Management Of Coronary Artery Disease. Journal of Ayub Medical College, Abbottabad: JAMC. 29(3): 516-522. **(Impact Factor 0.481 and 515 citations).**

7. Yamamoto, M.H., Maehara, A., Karimi, G.K, Mintz, G.S., **Parviz. Y**., Kim, S.S., Koyama, K., Amemiya, K., Kim, S.Y., Ishida, M., Losquadro, M., Kirtane, A.J., Haag. E., Sosa, F.A., Stone, G.W., Moses, J.W., Ochiai, M., Shlofmitz, R.A., and Ali Z.A. (2017). Mechanisms of Orbital Versus Rotational Atherectomy Plaque Modification in Severely Calcified Lesions Assessed by Optical Coherence Tomography. JACC Cardiovascular Intervention, 10(24): 2584-2586. (doi: 10.1016/j.jcin.2017.09.031. PMID: 29268891), (**Impact Factor: 11.2 and no citation).**

8. Ali, Z., **Parviz, Y.,** Brinkman, M., Matsumura, M., Redfors, B., Brogno, D., Corral, M., Fall, K., Mintz, G., Stone, G., Maehara, A., Jeremias, A., and Kirtane, A. (2018). Pressure Wire Compared to Microcatheter Sensing for Coronary Fractional Flow Reserve: The PERFORM Study. Euro-Intervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 14(4): e459-e466. doi: 10.4244/EIJ-D-18-00064. **(Impact Factor 6.534 and 5 citations).**

9. Shlofmitz, E., Jeremias, A., **Parviz, Y.,** Karimi, G.K., Redfors, B., Petrossian, G., Edens, M., Matsumura, M., Maehara, A., Mintz, G.S, Stone, G. W., Shlofmitz, R. A., and Ali, Z. (2021). External elastic lamina vs. luminal diameter measurement for determining stent diameter by optical coherence tomography: an ILUMIEN III sub-study. European Heart Journal -

Cardiovascular Imaging. 22(7):753-759. doi: 10.1093/ehjci/jeaa276 **(Impact Factor: 6.875 and no citation).**

10. Israeli, Z., Bagur, R., Murariu, B-D., Wall, S., Alemayehu, M., **Parviz, Y**., Diamantouros, P., and Lavi, S. (2017). Nitro-glycerine-Derived Pd/Pa for the Assessment of Intermediate Coronary Lesions. The Journal of Invasive Cardiology. 29(12): E177-E183. **Impact Factor:1.07 and 1 citation).**

B) Mineralocorticoid (MR) Antagonism and cardiovascular diseases

11. Iqbal, J., Parviz, Y., Pitt B, Newell-Price, J., Al-Mohammad, A., and Zannad, F. (2014). Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure. European Journal of Heart Failure, 16(2):143-150. (doi: 10.1111/ejhf.31. PMID: 24464876), **(Impact Factor of 15.534 and 52 citations).**

12. Iqbal, J., Fay, R., Adlam, D., Squire, I., **Parviz, Y.,** Gunn, J., Pitt, B., and Zannad, F. (2014). Effect of eplerenone in percutaneous coronary intervention-treated post-myocardial infarction patients with left ventricular systolic dysfunction: A sub-analysis of the EPHESUS trial. European Journal of Heart Failure, 16: 685–691, (16.10.1002/ejhf.88**. (Impact Factor 15.534 and 24 citations).**

13. Parviz, Y., Iqbal, J., Pitt, B., Adlam, D., Al-Mohammad, A., and Zannad, F. (2015). Emerging cardiovascular indications of mineralocorticoid receptor antagonists. Trends in Endocrinology and Metabolism, 26 (4):201-211 (doi.26.10.1016/j.tem.2015.01.007), **(Impact Factor: 12.015 and 31 citations).**

C) Infarct Size and Endothelial Function

14. Parviz, Y., Vijayan, S., and Lavi, S. (2017). A review of strategies for infarct size reduction during acute myocardial infarction. Cardiovascular Revascularization Medicine, 18(5): 374-383.

(doi: 10.1016/j.carrev.2017.02.004. (18. 10.1016/j.carrev.2017.02.004), (**Impact Factor: 1.168 and 15 citations).**

15. Parviz, Y., Waleed, M., Vijayan, S., Adlam, D., Lavi, S., Nooryani, A.A.., Iqbal, J., and Stone, G. W. (2019). Cellular and Molecular Approaches to Enhance Myocardial Recovery After Myocardial Infarction. Cardiovascular Revascularization Medicine, 20(4):351-364. (doi: 10.1016/j.carrev.2018.05.021. Epub, (**Impact Factor: 1.168 and 32 citation).**

16. Parviz, Y., Hsia, C., Alemayehu, M., Wall, S., Bagur, R., Abu-Romeh, N., Chin-Yee, I., and Lavi, S. (2016). The effect of fresh versus standard blood transfusion on microvascular endothelial function. American Heart Journal, 181:156-161. (10.1016/j.ahj.2016.05.021. **(Impact Factor 4.749 and 1,315 citations).**

PAGES OF CONTENTS

CHAPTER 1 - LIST OF FIGURES

CHAPTER 1

GENERAL INTRODUCTION

1.1 Cardiovascular Diseases (CVDs)

(A). A historical perspective

Cardiovascular diseases (CADs) are the most common causes of morbidity and mortality in developed countries and it is now getting more prevalent in middle and low income countries globally [1a]. Death from cardiovascular and circulatory diseases (CCDs) have risen by one third between 1990 and 2010. In 2015 one in three deaths worldwide was due to CVDs.[1] Numerous epidemiological studies have helped to elucidate the factors that predispose to CVDs highlighting opportunities for cost-effective prevention. In 2013, the Framingham Heart Study celebrated 65 years since the examination of its first participant in 1948, contributing to understanding of CVDs and their risk factors including stress, diets with high levels of low-density lipoprotein, smoking, sedentary lifestyles, obesity, diabetes, and many others [1a/b].

Data from the 1940s revealed that CVDs had become the number one killer from sudden cardiac death (SCD) and heart failure among American Citizens. This in turn accounted in 1 in 2 deaths. In those days, it was difficult to understand the real causes, prevention, and treatment interventions since these were compounded with the current second world war. As such, the medical profession thought that death from CVDs was unavoidable. It was the President of the United States of America (USA), Franklin Delano Roosevelt who experienced a heart attack due to coronary heart disease (CAD) in the 1940s and decided that Physicians should try to understand the underlying causes, prevention, and treatment interventions. As a result, the Framingham Study was initiated in the USA [1b].

It is now a well-established fact that globally, CVDs are the leading causes of morbidity and mortality and major burden on health economics. CAD is a major clinical condition where the major vessels that supply the heart (coronary arteries) are not able to transport enough blood, oxygen, and nutrients to the heart muscle due to the deposition of fats leading to blockage or a process called atherosclerosis [1a, b].

(B) Risk Factors for CAD

There are a variety of risk factors for the development of CAD. They include diabetes mellitus (DM), obesity, hypertension, hyperlipidemia, smoking, sedentary lifestyle, genetic factors, and others. Either alone or together, they play a significant role in the development of atherosclerosis and subsequently CAD [1a,b]. During the disease process, cholesterol deposits (plaques) in the heart arteries leading to oxidative stress, inflammation and subsequently, to the development of atherosclerotic plaque. As a result, the patient is presented with chest pain or discomfort (angina pectoris) and other associated symptoms like weakness, light-headedness, nausea (feeling sick to his or her stomach), or a cold sweat. Pain or discomfort can be present in either the arms or shoulder [2-4]. Figure 1.1 shows a time course of events leading to the development of CAD and sudden cardiac death (SCD) starting from the risk factors, development of diabetes and hyperglycemia, generation of free radicals, inflammation, deposition of fats in the coronary arteries, plaque formations and subsequently CAD, followed by angina and possible sudden cardiac death.

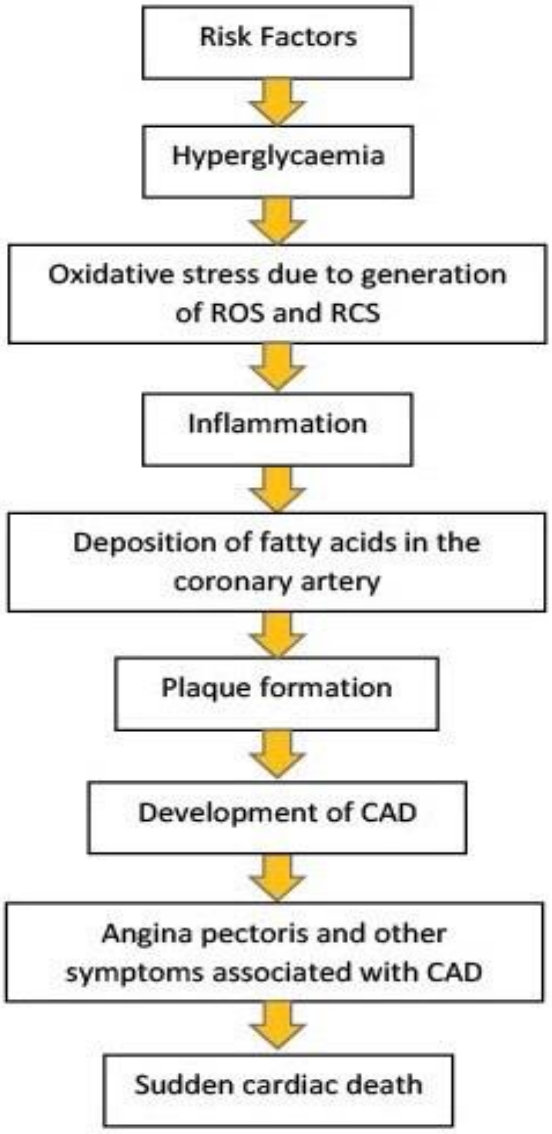


Figure 1.1: Flow diagram showing the development of CAD, angina and subsequently, sudden cardiac death over time (CAD= coronary artery diseases; ROS=reactive oxygen species; RCS reactive carbonyl species. (Diagram drawn by hand).

1.2 Coronary angiography (CA)

Coronary angiography(CA) is considered the gold standard test for the diagnosis of CAD [2]. Angiography can be one of the tests to be considered when a patient experiences the symptoms of CAD, including left arm and severe chest pain (or angina pectoris). Coronary angiography is an important diagnostic clinical tool in a variety of conditions like angina, assessment of valvular heart diseases (VHD) and for conditions of congenital heart disease (CHD). Therefore, an accurate interpretation of coronary angiography is of paramount importance in decision-making by the clinicians to treat patients with CAD [3]. Coronary angiography has the inherent limitation of being a two-dimensional X-Ray lumeno-gram of a complex three-dimensional vascular structure [2]. Original angiography gives good information about the epicardial arteries and possible blockade but on its own, angiography gives limited information about microvascular function [see Figure 1.2 with inset (B).

(A) (B)

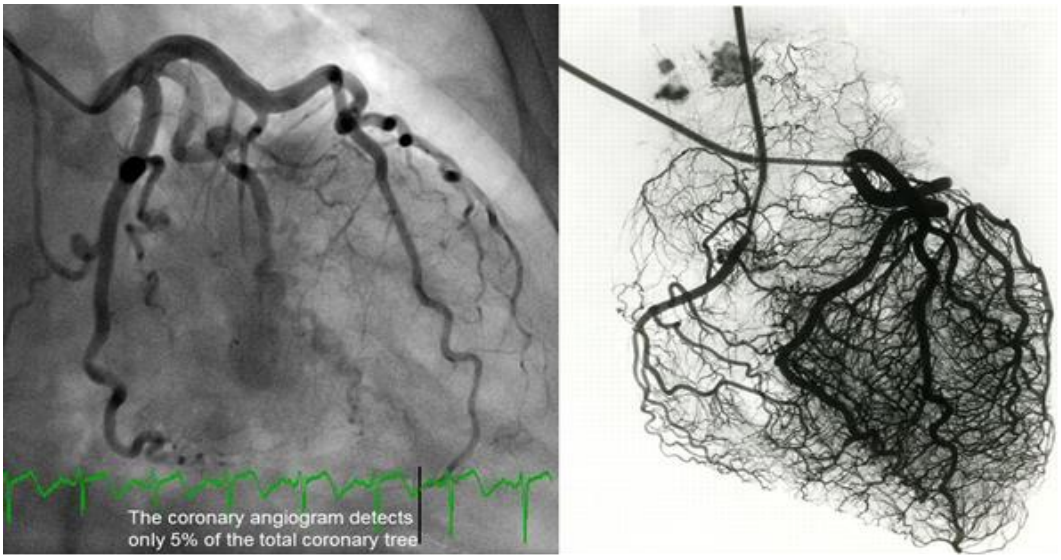


Figure 1.2. (A) Epicardial coronary arteries and (B) microvascular circulation (Taken from reference [8].

Visual assessment of angiogram can lead to both inter- and intra-observer variability in the assessment of the severity and extent of the cardiac disease leading to differences in management strategies [4, 5]. This issue becomes even more relevant when assessing left main stem (LMS), bifurcations, diffuse coronary artery disease or situations involving complex coronary morphology [5]. Interventional cardiology has been revolutionized by recent advances in techniques, and innovative technologies in the catheterization laboratory. Today, a modern catheterization laboratory is equipped with adjunctive technologies, such as Quantitative Coronary Angiography (QCA), Fractional Flow Reserve (FFR), Intra-Vascular Ultra-Sonography (IVUS), and Optical Coherence Tomography (OCT) to help clinicians to make a well-informed decision based on detailed anatomical and physiological assessment of a coronary artery rather than judgment based solely on visual assessment [3, 6].

This doctoral thesis emphasized the role of intracoronary imaging and physiology in various clinical settings, including MR antagonism and infarct size reduction. It has highlighted that decision making based on intracoronary imaging and physiology is safe and effective. It has been established that it is cost-effective as well. It is also possible to highlight the utility and evidence behind these adjunctive techniques in Cath-lab like intracoronary imaging techniques such as OCT and IVUS or physiology techniques like FFR and instantaneous wave-free ratio (iFR). The study also provided examples of clinical cases highlighted in FFR and the importance of these techniques to make a well-informed treatment decision.

1.3 Physiology-based assessment of CAD.

Fractional flow reserve (FFR) is the ratio between the maximum achievable blood flow in a diseased coronary artery and the theoretical maximum flow in a normal coronary artery. An FFR of 1.0 is widely accepted as normal. An FFR lower than 0.75-0.80 is generally considered to be associated with myocardial ischemia. This technique requires the induction of hyperemia. A variety of agents have been used for induction of hyperemia [7].

Intra-coronary imaging modalities like IVUS and OCT provide a detailed anatomical assessment of coronary lesions, but they give limited information about the functional severity of these lesions

[8]. FFR measurement goes one step further in determining the lesion severity as it calculates the ratio between the maximum achievable blood flow in the stenosed segment of the artery and the theoretical maximum flow in a normal segment of the same artery [9].

FFR can be measured by using either a coronary guidewire or a microcatheter (MC) equipped with a pressure sensor that first measures the pressure distal to the stenotic segment of the artery and then measures the aortic pressure under conditions of maximum myocardial hyperemia [10]. In general, if this FFR ratio is lower than 0.80, and then it is generally considered to be associated with myocardial ischemia. The concept of measuring the blood flow across a stenotic lesion is as old as coronary angioplasty itself. FFR technique has further been validated and evaluated to reduce mortality and morbidity associated with the treatment of intermediate coronary lesions [9].

The FAME and FAME II studies have examined the role of FFR in the assessment of multi-vessel CAD. Moreover, there is strong evidence now that a revascularization strategy using FFR yields much better clinical outcomes in patients with stable angina and multi-vessel CAD compared to optimal medical treatment alone [11].

FFR is a diagnostic tool which is used to assess the severity of narrowing or blockages in the coronary arteries that supply blood to the heart muscle. The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study and its follow-up, FAME II, have shown that using FFR-guided revascularization in patients with stable angina and multi-vessel CAD can lead to better clinical outcomes compared to optimal medical treatment alone [12].

In the FAME study, patients with multi-vessel CAD were randomly assigned to either undergo revascularization guided by FFR or angiography-guided revascularization. The study found that patients who underwent FFR-guided revascularization had a lower rate of major adverse cardiovascular events (MACE), including death, myocardial infarction (heart attack), and repeat revascularization, compared to those who underwent angiography-guided revascularization [13, 14].

In the FAME II study, patients with multi-vessel CAD who had ischemia (reduced blood flow to the heart muscle) on non-invasive testing were randomly assigned to either undergo FFR-guided revascularization plus optimal medical therapy or optimal medical therapy alone. The study found that patients who underwent FFR-guided revascularization plus optimal medical therapy had a significantly lower rate of MACE compared to those who received only optimal medical therapy [14-17].

Overall, the evidence from these studies suggests that FFR-guided revascularization may provide better outcomes for patients with stable angina and multi-vessel CAD than optimal medical therapy alone. However, it is important to note that individual patient factors, such as age, comorbidities and the extent of CAD should be taken into account when making treatment decisions [18]. The current guidelines from the American Heart Association (AHA) and European Society of Cardiology (ESC) recommend the use of FFR to assess angiographic intermediate coronary lesions (50%-70% diameter stenosis) and to guide revascularization decisions in patients with stable ischemic heart disease [19, 20].

The 2018 American Heart Association (and the American College of Cardiology (AHA/ACC) guidelines for the management of stable ischemic heart disease state that FFR should be considered to guide revascularization decisions in patients with intermediate coronary lesions, defined as lesions with a diameter stenosis of 40%-70% by visual estimation on angiography. The guidelines also state that FFR-guided revascularization may be reasonable in patients with multivessel CAD. Likewise, the 2019 European Society of Cardiology (ESC) guidelines for the diagnosis and management of chronic coronary syndromes recommend that FFR should be considered for the functional assessment of intermediate coronary lesions, and that FFR-guided revascularization may be beneficial in patients with multivessel disease and stable angina. The aim of developing new techniques to measure pressure across a coronary artery lesion is to make it simpler, quicker, more cost-effective, and with fewer side effects compared to the traditional method of measuring fractional flow reserve (FFR) using hyperemia. One approach is to use non-hyperemic pressure ratios, which are based on the ratio of the distal coronary pressure to the aortic pressure during

rest. These techniques do not require inducing hyperemia and are therefore simpler, quicker, and potentially safer [21].

Non-hyperemic pressure ratios can be further categorized into phase-specific and whole-cycle indices based on the phase of the cardiac cycle during when the pressure measurements are taken [22]. Phase-specific indices are based on pressure measurements during a specific phase of the cardiac cycle, such as diastole (resting phase) or systole (contracting phase) [23]. Examples of phase-specific indices include diastolic pressure ratio (dPR) and systolic pressure ratio (sPR). Moreover, whole-cycle indices, on the other hand, use pressure measurements taken over the entire cardiac cycle. Examples of whole-cycle indices include the instantaneous wave-free ratio (iFR) and the resting full-cycle ratio (RFR). Overall, the development of non-hyperemic pressure ratios may offer a simpler, quicker, and potentially safer alternative to FFR for assessing the hemodynamic significance of coronary artery lesions. However, further studies are needed to confirm the accuracy and clinical utility of these new techniques [24].

1.4 Definition of important physiological terms

Instantaneous wave-free ratio (iFR) is measured as the ratio between the coronary pressure distal to the stenosis (mean distal coronary pressure) [25], and the aortic pressure (mean aortic pressure [26], and this is assessed in the wave-free period and identified at wave intensity analysis [24].

The diastolic pressure ratio (dPR) is defined as the diastolic Pd/Pa ratio under resting conditions. The diastolic period for calculation of dPR is defined based on dP/dt curve of the aortic pressure.

The diastolic hyperemia-free ratio (DFR) is calculated as the Pd/Pa ratio in the diastolic period of the cardiac cycle.

Baseline Pd/Pa, fractional flow reserve (FFR) and resting full-cycle ratio (RFR) are calculated over the entire cardiac cycle.

1.5 Phase-Specific Indices

The instantaneous wave-free ratio (iFR) is a wire-based NHPR evaluating Pd/Pa during a specific phase of diastole, and this is referred to as the wave-free period.

1.6 Comparison of FFR and other pressure indices.

The iFR index is the only non-hyperemic pressure ratio that has been tested in randomized controlled trials as an alternative to FFR. The DEFINE-FLAIR study and the iFR-SWEDEHEART trial both showed that iFR-guided management was not inferior to FFR-guided management in patients with stable angina or non-culprit arteries in acute coronary syndromes [24, 27, 28].

However, about 20% of lesions may present discordant values between iFR and FFR and it is unclear as to what the clinical outcomes are when different treatment decisions are made based on one or the other metric. There is ongoing debate regarding how to manage lesions for which treatment strategies differ between iFR and FFR [29]. American guidelines currently emphasize the larger available evidence behind FFR, while European guidelines suggest that iFR and FFR have an equivalent value [28, 30].

1.7 Pros and Cons.

The advantage of iFR is its elimination of hyperemic medications, with the potential for reduction in time, side effects, and cost.

The drawbacks to iFR include smaller gradients than FFR, thereby making it more sensitive to noise, hydrostatic effects, and wire drift during pullback. Finally, iFR could be more sensitive to variation of hemodynamic conditions (systemic blood pressure and heart rate) that affect baseline coronary flow.

Diastolic Pressure Ratio: The diastolic pressure ratio (dPR) equals the resting ratio of mean diastolic pressure distal to the stenosis to the mean diastolic aortic pressure. Several algorithms

exist for calculating dPR with no significant advantage to any technique. When using iFR as the reference standard, dPR has been shown to have numerical equivalence.

1.8 Pros and Cons of dPR sharing the same trade-offs provided by iFR

Diastolic Hyperemia-Free Ratio-Diastolic hyperemia-free ratio (DFR) is a new resting physiology index (Boston Scientific, Marlborough, MA). DFR provides a resting index derived from the average aortic and distal coronary pressure (Pd/Pa) during the period that occurs when the Pa is less than the mean Pa, and there is a down-sloping Pa.

Resting Pd/Pa Ratio: The resting Pd/Pa ratio is calculated over the entire cardiac cycle and equals the ratio of the mean (non-instantaneous) Pd and Pa over the entire cardiac cycle. Several studies have shown equivalent diagnostic performance for Pd/Pa versus iFR when using various standards. A cutoff of 0.92 for resting Pd/Pa has most often been identified in clinical studies. In addition, Pros and Cons-Pd/Pa offers all the same trade-offs as other NHPRs. Compared with other pressure wire-based indices, it has a wider applicability since it can be measured with any pressure wire monitoring system.

Contrast FFR: Contrast FFR (cFFR) is the lowest mean (non-instantaneous) Pd/Pa value obtained after intracoronary injection of a standard dose of radiographic contrast medium. Rapid Injection of Contrast Medium vs Nitroprusside or Adenosine in Intermediate Coronary Stenoses (RINASCI), The Multi-Center Evaluation of the Accuracy of the Contrast Medium Induced Pd/Pa Ratio in Predicting FFR (MEMENTO-FFR) and Can Contrast Injection Better Approximate FFR Compared to Pure Resting Physiology (CONTRAST) studies clearly reported the ability of cFFR in predicting FFR values in intermediate coronary stenosis.

Pros and Cons of cFFR: cFFR offers the benefit of wide application irrespective of the pressure wire monitoring system and post-processing analysis software. It is thus universally available and virtually free of any side effects, except for those related to the use of contrast media. However, since the hyperemia induced by contrast dye is relatively short-acting and not steady, cFFR is not suitable for pullback analysis.

The RFR index was derived and validated for the first time in the retrospective VALIDATE-RFR study20 with an optimal RFR cutoff of 0.89 to predict a positive FFR. RFR was highly correlated to iFR (R2=0.99, P<0.001), with a diagnostic accuracy of 97.4%, sensitivity of 98.2%, specificity of 96.9%, positive predictive value of 94.5%, negative predictive value of 99.0%. Notably, the RFR was detected outside the diastole in 12.2% of all cardiac cycles and in 32.4% of cardiac cycles in the right coronary artery [20]. In terms of advantages and disadvantages, RFR offers the same trade-offs as all other NHPRs.

1.9 Angiography-Based

Angiography-based simulations have resurfaced to avoid the need to instrument the coronary artery, as required by NHPR, cFFR, and FFR [31]. Quantitative flow ratio (QFR) is an angiography-based index that has a substantial amount of evidence supporting its use [29]. Like FFR, QFR uses the same thresholds for diagnosis. The index is obtained using software packages such as Angio XA 3D or Angio-Plus and involves applying flow equations to 3D reconstructions of the coronary tree, derived from combining at least two angiographic projections at least 25 degrees apart. QFR indirectly derives coronary flow by measuring the thrombolysis in myocardial infarction frame count, although in a revised version, this is no longer required. QFR can be performed either offline or online.

After 3D reconstruction, an estimated contrast flow velocity is derived by identifying the time at which the contrast enters and leaves the vessel under investigation [32]. This flow velocity can be measured either at rest or under hyperemia induced by adenosine infusion. Recent evidence suggests that using resting estimated contrast flow velocity or hyperemic estimated contrast flow velocity produces similar results in predicting FFR [29, 33].

Several studies, including the FAVOR Pilot Study, FAVOR II Europe-Japan, and FAVOR II China, have shown that QFR is superior to 3D quantitative coronary angiography in predicting FFR values [33]. One advantage of QFR is that it can be performed online by trained operators much faster than FFR measurement, with a median time of 5.0 minutes compared to 7.0 minutes for FFR (p<0.001). Recent meta-analysis has confirmed the potential clinical impact of QFR,

reporting a promising diagnostic performance with 84% sensitivity, 88% specificity, 80% positive predictive value, and 95% negative predictive value [32-34].

QFR has some advantages over FFR, such as avoiding the cost, time and risk associated with inserting a pressure wire into a coronary artery [35]. However, QFR has lower accuracy compared to invasive FFR. To use QFR, the operator must have knowledge of selecting the best angiographic views (in case of offline analysis) and correctly identifying the vessel lumen profile. It is important to note that QFR has limitations, and it may not be measurable in cases of aortic-ostial lesions, severe tortuosity, or overlapping vessels on angiogram. Additionally, QFR has not been validated for assessing bifurcations where there is stenosis in both the side branch and the proximal main vessel [32].

Vessel FFR: Vessel FFR (v-FFR) uses 3D quantitative coronary angiography for functional assessment of coronary stenosis. V-FFR is calculated by software CAAS (Pie Medical Imaging, Maastricht, the Netherlands) using 2 angiographic views with at least 30° difference in rotation/angulation to generate the 3D reconstruction of the coronary artery.

The CAAS software calculates the pressure drop across a stenosis by considering physical laws, such as viscous resistance and separation loss effects that occur in coronary flow. To perform this calculation, the actual aortic pressure must be measured and recorded during the coronary angiography procedure. Additionally, maximum hyperemic blood flow is determined by assuming that the proximal coronary velocity is preserved along the vessel of interest. The accuracy of v-FFR has been validated in the FAST study, which demonstrated a strong linear correlation with pressure wire-based FFR (0.89; $P<0.001$) and high diagnostic accuracy (area under the curve, 0.93 [95% CI, 0.88–0.97]) in detecting FFR$\leq$0.80. Furthermore, v-FFR exhibited low interobserver variability [37].

Pros and Cons of v-FFR: v-FFR potentially shares the same benefits and disadvantages with coronary angiography–based methods. However, compared with QFR, the amount of supporting evidence is still limited and based on observational, single-center experience.

FFR-Angio is a resting, adenosine-free angiography-based index that has been developed by Cath-Works, Ltd (K-far-Saba, Israel). The technique involves creating a functional angiogram from a 3D reconstruction of the coronary tree obtained from at least two angiographic projections. The 3D model is then subjected to a hemodynamic evaluation, resulting in an FFR-Angio map by applying a proprietary computational fluid-dynamic model to derive resistance [38]. FFR-Angio shares the same advantages and disadvantages as other angiography-based methods. However, unlike other indices that assess a specific coronary segment, FFR-Angio allows for the simultaneous evaluation of the entire coronary tree, making it an attractive option.

1.10. Intravascular-Imaging Based Methods vs Intravascular Ultrasound–Derived FFR

IVUS-derived FFR is an invasive method that combines grayscale IVUS images and angiography to derive functional assessment of the target vessel. Three out of four proposed methods rely on computer fluid dynamics, which require intense computer time for the calculations of FFR, thereby limiting their potential application for online use. As a result, most reports only include a small sample size. However, IVUS-derived FFR offers the advantage of not requiring a pressure wire, making it a less invasive alternative [39].

1.11 Advantages and disadvantages of IVUS-derived FFR

The advantages of IVUS-derived FFR are several uses in this method, since there is no need for maximal hyperemia, anatomic and functional assessments without wire exchange, whole vessel wall assessment, no aluminography and grayscale IVUS qualitative and quantitative variables in addition to flow [36] . Moreover, this technique is not affected by vessel tortuosity, and it can be assessed in ostial lesions. Currently, IVUS-FFR is a research tool, but clinical prime time could be a realistic option when more clinical data becomes available [37].

1.12 Optical Coherence Tomography–Derived FFR (OCT-FFR)

The OCT-based FFR (OCT-FFR) can be calculated using various methods that apply computational fluid dynamics. One such method is the Optical Flow Ratio (OFR) which has been validated against pressure wire FFR. OFR automatically delineates the lumen contour from the

OCT image pullback and as a result, performs a 3D reconstruction of the coronary lumen, estimating the volumetric flow rate using the reference lumen size and a virtual hyperemic flow velocity of 0.35 m/s [38].

It has been demonstrated that OCT-derived FFR method has good agreement with pressure wire-based FFR (bias=0.01±0.06) and a high correlation with FFR (r=0.89), with a computational time of 10 minutes per pullback [39].

1.13 Advantages and disadvantages of the process

The invasive nature and cost associated with the method are limiting factors for broader adoption. There are potential pitfalls for segmenting the side branches through single main vessel pullback. Side branch ostium disease and side branch angulation can impact on quantification of the side branch size and, consequently, on the vessel-tapering model [38].

1.14 NON-INVASIVE INDICES

(A) Computed Tomography–Derived FFR ((FFRCT)

Computed tomography derived FFR (FFRCT) is a non-invasive technique that uses computational flow dynamics to analyze 3D coronary geometries extracted from coronary computed tomography angiography images [40]. FFRCT calculates the mean coronary pressure distal to a lesion divided by the mean blood pressure in the aorta under simulated maximal hyperemia conditions, making it a potentially useful physiological tool for detecting ischemia in patients with coronary artery disease (CAD) [41]. FFRCT-based clinical decision-making has the potential for cost savings and it also avoids the need for unnecessary invasive coronary angiographies. Previous studies have shown that deferring revascularization based on an FFRCT >0.80 can result in good midterm prognosis in terms of major adverse cardiovascular event rate. FFRCT also provides a rapid and simultaneous three-vessel functional evaluation, which can facilitate management and decision-making in patients with multivessel disease. It is worth noting that the SYNTAX III Revolution trial demonstrated that coronary computed tomography angiography with FFRCT can aid in selecting the best revascularization modality (cardiac surgery vs PCI), with treatment

recommendations being changed in 7% of cases and the revascularization plan being modified in 12% of patients.

1.15 The advantages and disadvantages of FFRCT

It is noteworthy that FFRCT avoids invasive angiography and vessel instrumentations completely, albeit at the cost of reduced diagnostic performance. In this case, many of the same caveats apply as detailed above for QFR: inability to obtain a diagnostic study (present in 10%–15% of cases) and discordance with invasive FFR. Perhaps, the upstream ability to plan revascularization procedures will offset these drawbacks. A novel FFRCT-based tool, Heart Flow Planner (Redwood City, California), uses interactive luminal remodeling of the area to be stented and recalculates FFR after the virtual removal of coronary stenosis, mimicking invasive post-stenting FFR [42].

Physiological assessments have introduced the paradigm shift in the way the treatment decisions are made for CAD. The best modality involves a test that can avoid hyperemia, wire, and invasive catheterization but at the same time, the modality should be so sensitive to make an accurate diagnosis. In the short and midterm, FFR remains the gold standard for detection of myocardial ischemia in guiding revascularization in patients with CAD.

A lot of other techniques like non-hyperemic pressure-ratios (NHPR) and all the current NHPRs have less validation than FFR. Moreover, they all been tested in non-inferiority studies enrolling relatively low-risk cohorts of patients. More importantly, at the present, NHPRs are not supported by the same robust long-term data as for FFR [42] .

The growing amount of current evidence may bring a future in which the first line of functional assessment will be entirely non-invasive, with invasive confirmation using pressure wire free indices (QFR, v FFR, FFR-Angio) as first-line approach. This is mainly done because of their quicker and cheaper nature, with pressure wire-based indices to be adopted for borderline scenarios (bifurcations, left main stem). In this context, it is possible also to speculate about the role of intravascular-imaging–derived FFR that would find application in those cases where the use of

either IVUS or OCT is already anticipated as an integral procedural step for PCI planning (selection of techniques for lesion preparation and selection of stent size and length).

There is ample evidence in the literature and noted from daily practice that when a particular lesion is viewed by different clinical operators, they can assign various degrees of the stenosis to that specific lesion if based solely on visual estimation [3]. On occasion, it is necessary to either reduce or eliminate this inter-observer variability in assessing the degree of stenosis. During the last few decades, Cardiac Clinicians have noted a variety of new cutting-edge techniques and technologies to help in rescuing this inter and intra observer variability in reporting [43].

Several adjunctive techniques have emerged over the years to improve the diagnostic accuracy and help in guiding the decision-making process by the Clinicians in the cardiac catheterization laboratory. Currently, in the era of modern interventional cardiology, interventional cardiologists are performing increasingly complex and challenging cases. A modern catheterization laboratory is now equipped with adjunctive modalities including quantitative coronary angiography (QCA), fractional flow reserve (FFR), intravascular ultrasound (IVUS), and optical coherence tomography (OCT). The use of these adjunctive technologies is of great help and importance when assessing borderline lesions (i.e., diameter stenosis of 40–70%) during the cases of complex left main stem and bifurcation disease [44-46].

The published work in this thesis has provided evidence regarding various modalities and adjunctive technologies that can guide and help to improve the decision- making process. Generally, Cardiologists have demonstrated how the decision-making process has evolved from simple ‘eye-baling’ of coronary angiogram to one that employs intra-coronary imaging techniques and coronary physiology assessment. These modalities, which were predominantly research tools in the past, are now used daily to help in making decisions in critical clinical scenarios.

1.16 Visual assessment based on Coronary Angiography (CA)

X-Ray angiography is widely available and can be learnt with training and supervision in a short period of time. It provides good spatial and temporal resolution and is considered the standard

method for diagnosing CAD. However, the severity of CAD is traditionally assessed through visual estimates based on multiple views of a coronary artery obtained during an angiogram. Numerous studies have shown that there can be significant differences in these visual estimates when reported by different physicians or at different time intervals, which could have harmful implications [19].

Despite these potential drawbacks, visual estimation remains the most used method for evaluating lesions and it is still widely practiced by cardiologists. While it can provide diagnostic information in most cases, it is not very effective at assessing the physiological significance of intermediate lesions. Additionally, X-Ray angiography only provides limited information about microvascular status. There are several factors that can contribute to decreased blood flow across a stenosis area, such as diastolic pressure time, microvascular resistance, and effective luminal area. Visual assessment of the coronary artery does not provide this critical information, which is necessary for making decisions about patient care [47]. The interventional clinical cardiac community is aware of these limitations and has developed many adjunctive modalities to overcome these shortcomings of angiography.

Another limitation of angiography is its inability to accurately assess vascular remodeling. This can lead to errors in determining the true size of vessels and their reference diameters. Due to its focus on the lumen, segments that are considered normal and used as reference vessels can have some degree of flow-limiting disease. This can result in incorrect reference measurements that, when used as a standard, can negatively impact the sizing of devices, leading to the common problem of an undersized stent [48]. Moreover, compensatory remodeling is one good example of how a cardiac disease can increase and change vessel size, while the lumen size remains the same. This phenomenon is visible on a slide and highlights the limitations of angiography in accurately determining vessel size and disease severity [49].

1.17 Quantitative Coronary Angiography (QCA)

The clinical significance of CAD depends on various factors such as the degree of narrowing, shape, length, eccentricity, number of side branches involved, and the presence of subsequent

stenosis in each artery [1, 46]. Simple visual estimation of coronary luminal effective area can be prone to errors, and attempts have been made to improve this assessment [3,4]. Quantitative coronary angiography (QCA) is one of the earliest techniques developed angiographically to quantify the degree of stenosis [5]. Brown and his colleagues [5], manually traced the arterial tree and used computer programming to construct a 3D representation of the arterial segment to calculate not only the degree of stenosis but also obtain physiological data. QCA measurements have demonstrated a good correlation with visual estimates from cinefilm and with hemodynamic significance as depicted by various tests for assessing ischemia [6,7].

Although QCA is a well-validated clinical physiological tool for accurately and reproducibly defining coronary lesion severity, it also has limitations. It requires additional time and effort, and it may not accurately report the variable and diffuse nature of the atherosclerotic lesion due to indirect definition of the anatomy of the vascular wall through inference about the lumen [8]. QCA also has methodological limitations in assessing bifurcation lesions [9]. Several studies have shown that endovascular techniques such as intravascular ultrasound (IVUS), optical coherence tomography (OCT) and angioscopy are better at delineating vascular features that accompany unstable ischemic syndromes alongside plaque morphology [10-12]. Despite its limitations, QCA remains a simple and low-cost tool with easy learning and should be used routinely, especially in healthcare settings where other imaging and physiology-based assessments are difficult to access and implement [13].

1.18 Intra-Vascular Ultrasound (IVUS)

Intravascular ultrasound (IVUS) was first introduced in the 1960s by a Japanese group to study intracardiac structures. IVUS is an intravascular imaging modality that provides detailed information about the coronary anatomy from the inside of a coronary artery due to its high penetration power [50]. IVUS yields real-time 360° images that provide unique point-of-view pictures that are superior to simple angiography or QCA. IVUS is beneficial in complex coronary interventions and its utility is more evident in interventions performed on the left main stem (LMS)

[51]. Moreover, IVUS can provide detailed assessment of lumen, vessel size, dimensions, and plaque morphology. Likewise, spectral analysis of ultrasound has enabled the development of virtual histology IVUS (VH-IVUS) that provides further tissue characterization of plaques.

Furthermore, IVUS is particularly useful in the assessment of intermediate lesions, guiding stent implantation, and understanding the mechanisms of stent failure [52]. It has also been useful in the assessment of cardiac transplant patients, and some institutions have used it to develop a "Zero contrast PCI program" to treat patients at high risk of developing contrast-induced nephropathy. IVUS can be useful in the diagnosis of spontaneous or iatrogenic dissections and in the setting of acute emergencies to diagnose acute aortic and coronary dissections. IVUS is an excellent modality to optimize the results of various stent-based techniques and has been shown to improve outcomes compared with angiography-based treatment [53].

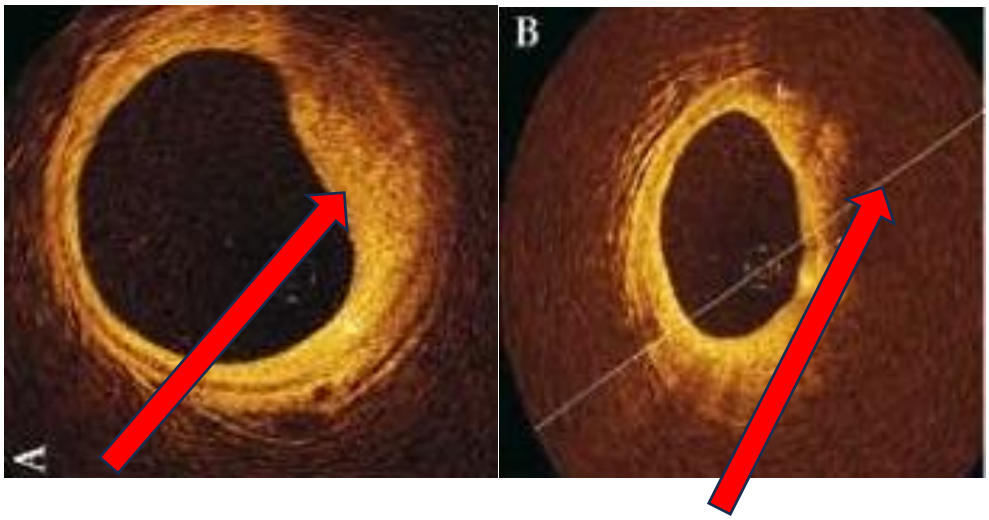
It has been observed that maximum stent area achieved after the procedure dictates the long- term outcomes [54]. In addition, IVUS is one of the modalities that can help to achieve the maximum post implantation in minimum stent area (MSA). The usefulness and efficacy of IVUS have been validated in several studies [46,55]. The potential utility of IVUS has been recognized by various Cardiac Professional Societies, and it is recommended in the decision-making process in the cardiac catheterization laboratory. The cost concerns related to this modality has been addressed, and it has been demonstrated that although it is associated with higher initial cost, IVUS-guided procedures are more cost-effective compared to angiography-based decisions [46, 55].

1.19 Optical Coherence Tomography (OCT)

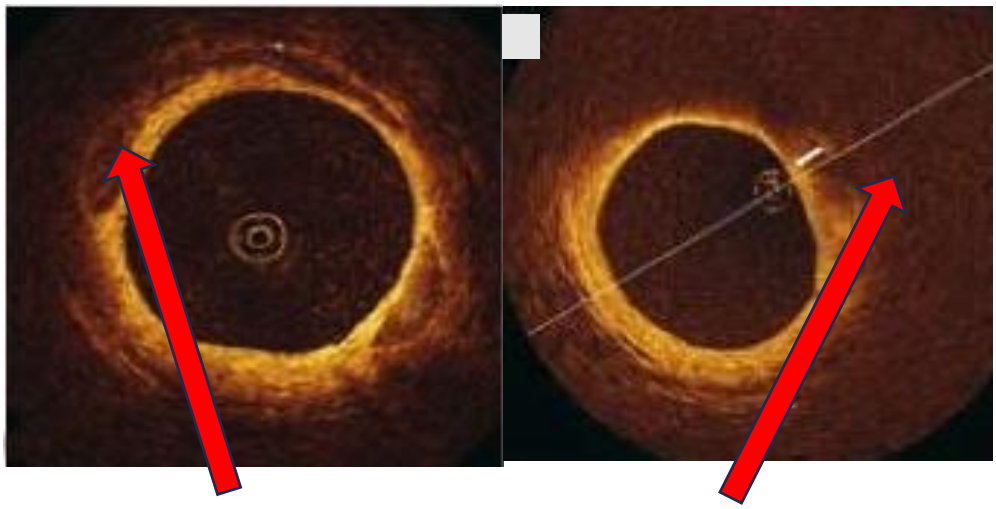
Optical coherence tomography (OCT) is a high-resolution intravascular imaging technique that has become increasingly popular in the field of cardiology [26]. OCT was first developed in the 1990s by Tanno and Fujimoto [1,30] and uses light to produce images with a resolution of 10-15 μ m, which is much higher than the 150-200 μm resolution of intravascular ultrasound (IVUS). OCT can identify and differentiate the three layers of the arterial wall, providing detailed information about tissue characteristics and plaque morphology [56]. Moreover, OCT is particularly useful for post-procedural assessment of stent implantation [57]. The high-resolution

images allow for accurate measurement of stent apposition, detection of intraluminal thrombi (red and white), identification of dissection, and tissue prolapse. OCT can also identify vulnerable plaques, potentially allowing for early treatment before an event occurs [1, 2].

In addition. OCT can precisely measure vessel diameter and lesion length during percutaneous coronary intervention (PCI), providing useful information for optimizing the size of balloons and stents. OCT can also identify the angle and location of dissection flaps, tissue prolapse, stent edge dissection, and stent mal apposition, with greater accuracy than IVUS [58]. Likewise, for post-procedural assessment, OCT can be useful clinical for understanding the potential mechanisms of stent failure [3]. However, the routine clinical use of OCT still requires further clinical trials to validate the technology, establish standard protocols, and test its safety and efficacy in improving clinical outcomes. Cost also remains an important factor in the worldwide uptake of this technology [59]. Current treatment decisions can be guided by the visualization of plaque morphology and Figure 1.3 shows typical examples of various plaque morphologies as observed by OCT, including fibrosis, fibrosis fatty calcified and lipemic tissues.



(a) Fibrous (b) Fibrous fatty



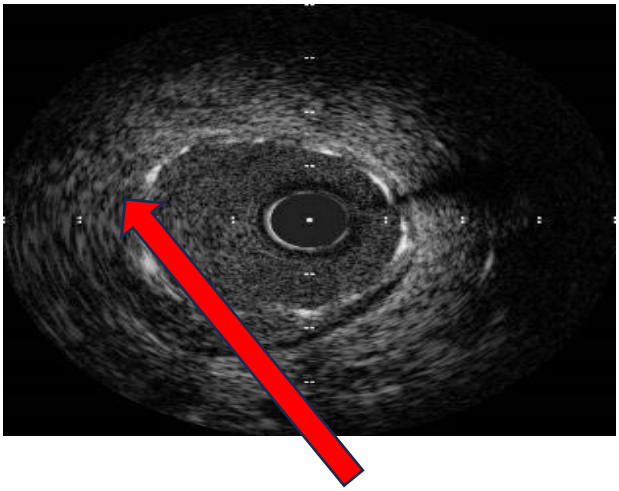
(c) Calcific (d) Lipemic

Figure 1.3: Typical examples various plaque morphologies as observed by OCT in (a) fibrosis, (b) fibrosis fatty, (c) calcified and (d) lipemic tissues [Taken from clinical practice].

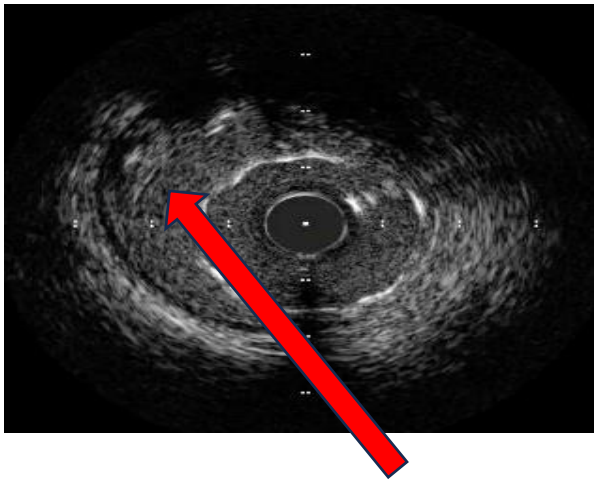
In conclusion, OCT is an extremely useful clinical tool in cases where the mechanism of acute coronary syndrome presentation is unclear. Moreover, it can help to quantify plaque morphology and tissue characterization. It is also useful in cases of stent failure, allowing for a better understanding of the mechanism of restenosis and stent thrombosis [2, 3].

1.20 Treatment of plaques

Once the clinician has diagnosed and examined the type(s) and composition of plaque(s), then it is possible to decide on how to best treat these lesions. Angiography has limitations to define the details and hence, the risk of inadequate treatment. However, with angiography – this delineation is not always clear. A soft fibrous or fibro-fatty plaque responds nicely to balloon angioplasty and stenting and may not require vigorous pre-dilation (see figure 1.3a and b). A calcified plaque may caution the clinician regarding stent apposition especially of concentric nature of the plaque and as such, the clinician may consider rot ablation or high-pressure pre-dilation (see figure 1.3c). On the contrary, the clinician may want to avoid such things when dealing with a necrotic core to prevent risk of embolization (see figure 1.3d).



Mal -Apposition (Top image)



Tissue Protrusion (Bottom image)

Figure 1.4: IVUS images showing Mal apposition (Top image) and tissue protrusion (Bottom image) (Taken from clinical practice).

Figure 1.4 shows IVUS images of tissue protrusion (bottom image) and Mal apposition (top image) involving various post procedural complications which can be seen and assessed by IVUS. It is possible to comprehend that from imaging, not every dissection needs treatment and only flow limiting dissections and with extension to media should be treated. Mal-appositions, in an acute setting, may have no clinical consequences and only if there is a long-term situation then they can have some impact on stent failures like stent thrombosis. Moreover, Both IVUS and OCT are

currently used in clinical cardiac practice globally. It is important to understand the basic differences between the modalities as highlighted in Table 1.1.

Table 1.1: Parameter data measured showing the comparison of IVUS and OCT applications in the diagnosis of CAD (Adapted from references [1,2]).

Parameters measured	**IVUS**	**OCT**
Axial Resolution	100 – 200 µm	15 – 20 µm
Beam Width	200 – 300 mm	20 – 40 mm
Frame Rate	30 frames/s	100 frames/s
Pullback Speed	0.5 - 1 mm/s	20 mm/s
Max. Scan Dia.	15 mm	10 mm
Tissue Penetration	10 mm	1.0 - 2.0 mm
Lines per Frame	256	500
Lateral Sampling (3 mm Artery)	225 µm	19 µm
Blood Clearing	Not Required	Required

It is particularly noteworthy, that both IVUS and OCT have advantages and clinical utilities in different clinical scenarios and settings and as a clinical operator it is important to have familiarity with both modalities to obtain the best outcomes for an individual patient. Table 1.2 shows a comparison of the advantages and disadvantages of IVUS and OCT modality applications.

Table 1.2: Advantages and disadvantages of IVUS and OCT modality applications (Adapted from reference [58]).

Modalities	**Advantages**	**Disadvantages**
IVUS	High tissue penetration Good imaging of fiber, calcium Plaque burden LMCA No flush required. Large installed base Outcomes data Operator Experience	Cost Slow Inferior resolution Difficult to resolve lipid thrombus, stents, dissections. Apposition Dissection Calcium shadowing Virtual histology reliability
OCT	High resolution < 3 second pullback Non-occlusive Follow-up for apposition, dissection High Sens/spec for lesion identification (lipid, calcium, fiber, thrombus) Low crossing profile Bioabsorbable stents	Cost Lack of outcome data Poor tissue penetration Unfamiliar, new technology Adds contrast load. Very tight lesions Very large vessels LMCA

Coronary angiography is a commonly performed test for the assessment of CAD, but it has limitations in providing accurate diagnostic information due to its 2-dimensional nature. This approach relies on operator estimation, which can lead to differences in interpretation of stenosis severity compared to other imaging methods. Additionally, angiography cannot provide anatomical intravascular data or insights into the physiologic correlation of the disease process. To address these limitations, intravascular imaging (IVI) has emerged as a valuable adjunct to angiography in clinical practice. IVI can provide detailed information about vessel anatomy, extent and severity of the disease process, plaque morphology, and precise vessel sizing for stent selection. This information can help to guide decision making and more so, facilitates revascularization with percutaneous coronary interventions (PCI). Modern advances in IVI technology have made it user-friendly and available for routine use in the cardiac catheterization laboratory [46, 48, 55].

Despite the well-established role of IVI and innovations in technology, its everyday use remains low worldwide. However, IVI is of particular importance in treating complex higher risk among indicated patients, including for treatment decisions involving the left main stem and bifurcation disease. Moreover, this process can help to understand the mechanisms underlying stent failures [60, 61].

Cardiologists often need more information about a particular disease process, such as vessel anatomy and plaque characteristics to plan the interventional strategy in a particular case. Visual estimation of stenosis severity can also vary between operators, highlighting the need to reduce inter-observer variability. Therefore, adjunctive techniques like IVI have revolutionized the field of invasive cardiology by improving diagnostic accuracy and guiding the decision-making process to improve clinical outcomes.

1.21 Role of intracoronary imaging and physiology in chronic complex disease process like diabetes mellitus (DM) and chronic kidney failure (CKD)

Cardiovascular diseases (CVDs) due to DM and CKD are becoming more prevalent worldwide, leading to increased morbidity and mortality [62]. Currently, over 535 million people have DM, 250 million are undiagnosed and another 2.5 billion people have prediabetes globally. The prevalence of this metabolic disorder varies from one country to another ranging from 5-40% with an average of 1-14% worldwide. The disorder is more prevalent in the Middle East, China, India and in South America and as DM rises globally, it poses a significant challenge to healthcare systems in terms of treatment cost, primarily due to its link to CVDs and related complications [63]. The morbidity and mortality associated with the diabetic heart and kidney disease is very high as reflected in UK cohort [25].

Diabetic patients are two to four times more likely to develop macrovascular complications such as CAD, hypertension, heart failure or diabetic-induced cardiomyopathy, peripheral vascular disease, and strokes than non-diabetic individuals. [64]. CVDs and renal failure are the major causes (almost 90%) of morbidity and mortality in diabetic patients, with compromised heart function frequently observed [65-67].

Diabetic nephropathy (DN) is more common in patients with type 2 diabetes than type 1 diabetes and it is associated with an increased risk of cardiovascular morbidity and mortality[68]. While hypertensive drugs like angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers can delay DN progression, they cannot prevent damage. Therefore, a thorough understanding of the mechanisms underlying hyperglycemia-induced renal injury is crucial [69].

1.22 Chronic- kidney disease (CKD)

Chronic Kidney disease (CKD) is a well-established major public health problem globally [66]. CKD has been associated with increased morbidity, mortality and rate of hospitalization [65]. CKD is associated with increased risk of CVDs and associated mortality [70]. Patients with CKD have multiple comorbidities and they have well-established risks that increase the risk of CVDs [71].

1.23 DM and CKD

There is a well-established strong association between DM and CKD [72]. One major long-term disease, due to DM, is kidney failure or nephropathy. This results from elevated blood glucose or hyperglycemia due to DM or insulin deficiency or insensitivity exerting excess workload on the kidneys to regulate blood glucose level [70-73]. There is also a well-established strong relationship between DM and the occurrence of CAD, hypertension (HTN) and heart failure (HF) due to the development of cardiomyopathy and well-written literature evidence is available in this regards [64, 69,72] Moreover, there is a higher incidence of HF among patients with DM [64]. Indeed, cardiovascular complications are the most common causes of morbidity and mortality in both T1DM and T2DM patients and more than 80 % of diabetic patients will eventually die from heart diseases and 10% from kidney failure [68]. Patients with DM should be monitored and treated with a close observation by cardiologists [69]. Electrocardiography is an inportant diagnostic tool of ventricular hypertrophy in patients with chronic renal disease and patients who die from kidney failure usually have left ventricular hypertrophy (LVH) (80%) [73]. The incidence can even be higher in patients with hemodialysis [72].

1.24 Management of patients

There is a significant advancement in the various treatment strategies for chronic health conditions like DM and CKD. It is well observed in clinical practice now that with the advent of new drugs, diet modifications, and regular physical activities, diabetic patients seem to enjoy an extra 15-20 years of a better quality of life compared to 25 years ago. Unfortunately, still many diabetic patients do not adhere or comply with the recommendations given by physicians and hence, as a result, they develop diabetes-induced long-term complications including, diabetic cardiomyopathy (DCM), and kidney failure (KF)r, (nephropathy) alongside other systemic complications as well as blindness or retinopathy and nerve damage or neuropathy [25]. Comparing these different long-term complications, most diabetic patients (80%) usually die from CVDs, followed by renal failure (10%) [25]. There is evidence that diabetic patients are at increased risk of arrhythmias and even

SCD and it has been estimated that about 20% of asymptomatic diabetic patients have an abnormal cardiovascular autonomic function [71].

1.25 Steps to Accurate FFR Measurements

The technical procedure in physiologcal assesment is of paramount importance for accutate data collection and interpretaion. The team working in the laboratory needs to be adequatley familiar with the concept of physiological measurements and adequte teaching and training should be given to cathetrisation laboratory staff in performance of the clinical tests and accurate interpretation. All the equipment must be prepared with wires adequatley flushed and kept sterile on the table. All the manifolds need to be normlaised and equalised. The wire and aaortic pressure need to be detetcted on the visual monitor.It is of paramount importance to insert wire into guide and equalize the wire/guide pressures in aorta at tip of the guide. Figures 1.5 (a-d) to 1.8 demonstrate the measurement of Fractional Flow Reserve (FFR) in the right coronary artery. The wire should be handeled very carefully and after crossing the lesion ensure that tip of wire is atleast 2-3cm distal with pressure transducer. The guide cathter should be flushed with saline to confirm adequate aortic wave form. Ideally the operator should take atleast 3 measurements and take an avaerage. When an FFR is done, it is important to infuse the hyperemic agents such as adenosine (150 μg/kg/min) or nicorandil (2 mg) to ensure that the patient is given adequate explanation of the procedure, especially as to what is expected during the hyperemia as in release of a blockade or heat stress, exercise and others. It is equally important to asses carefully the ventricularisation during the hyperemia and also to measure the readings. Moreover, after the completion of clinical test, it is of paramount importane to investigate for the absence of drift using pressure pull back [74].

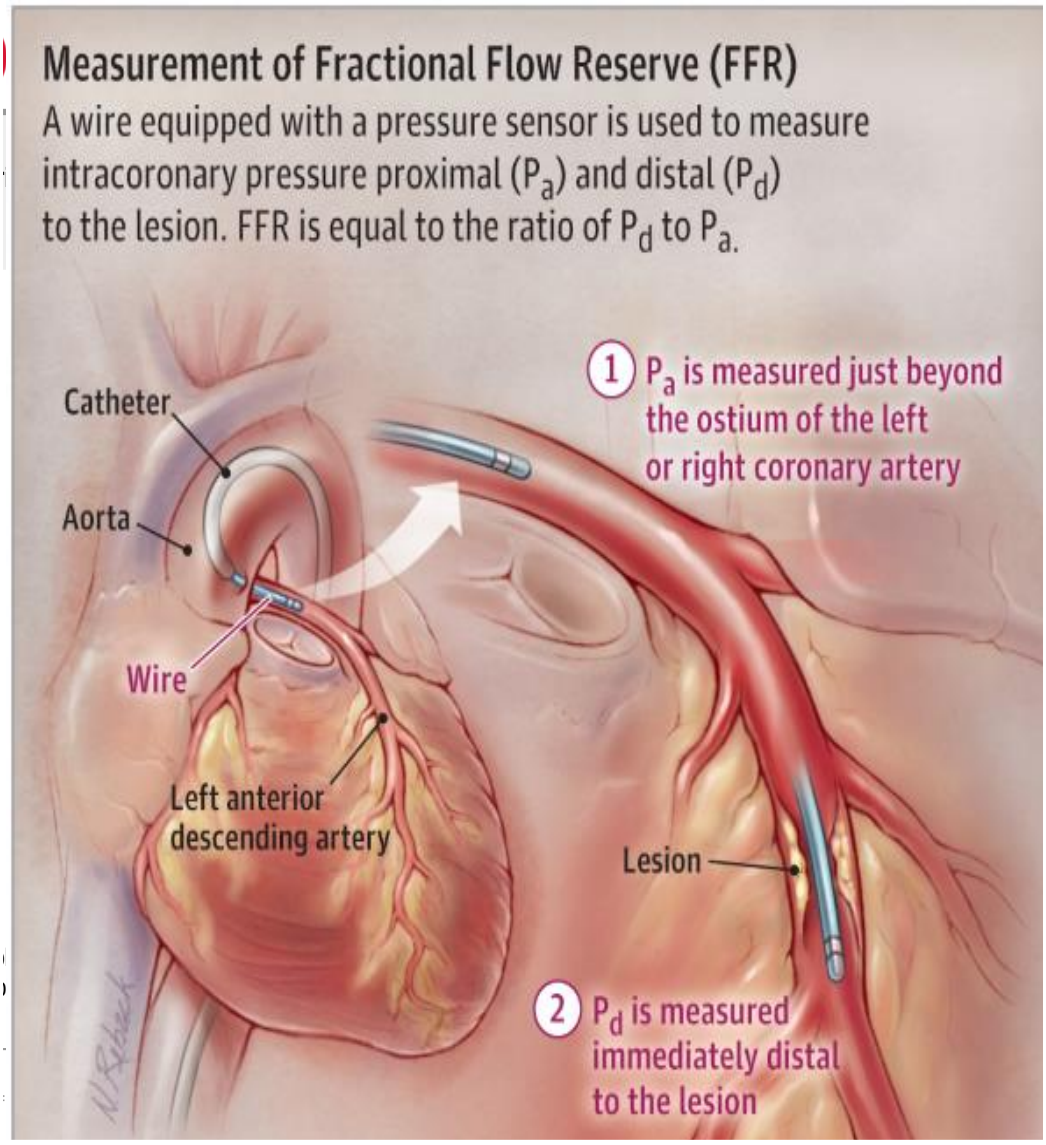
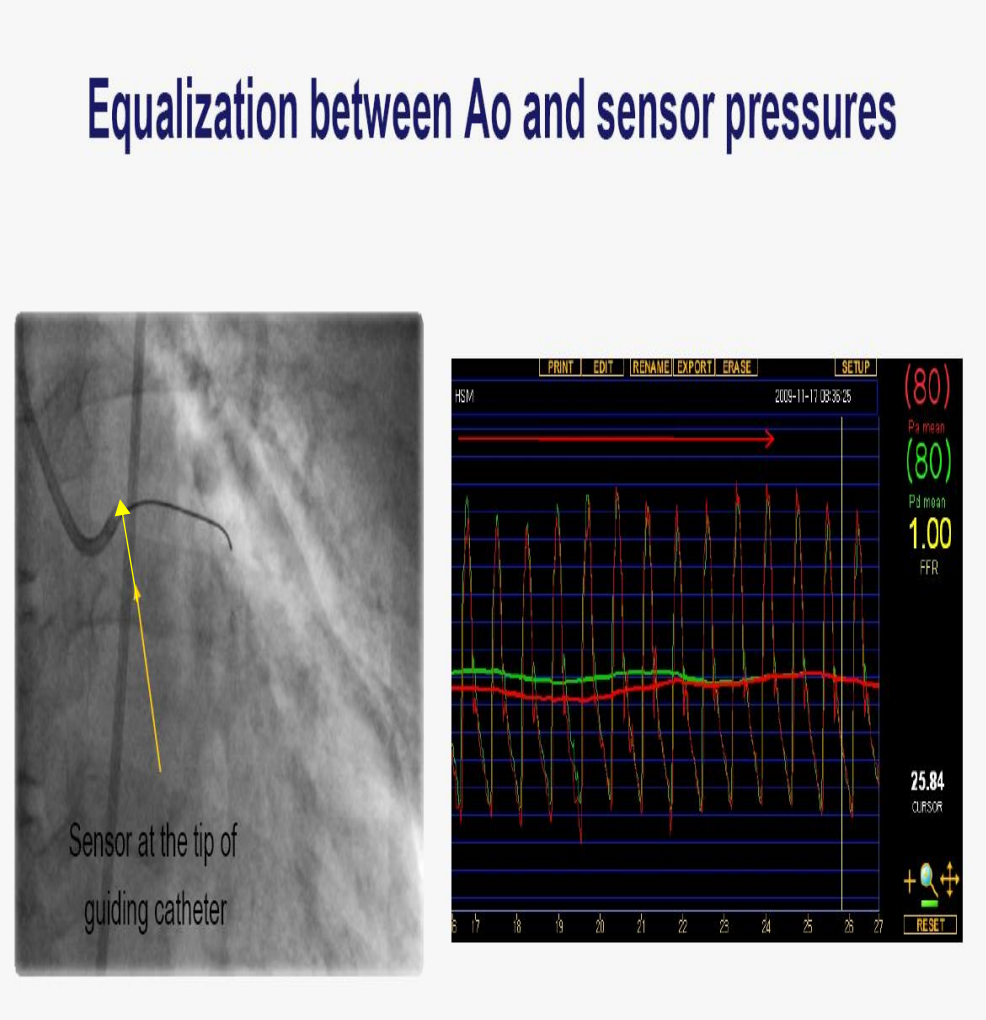


Figure 1.5. Measurement of Fractional Flow Reserve (FFR). (1) Pa is measured just beyond the ostium of the left or right coronary artery and (2) Pd is measured immediately distal to the lesion (Taken from reference [75].



(A) (B)

Figure 1.6: (A) The sensor at the tip of the guiding catheter and (B) the pressure in the Ao-state. It is particularly noteworthy that one of the important steps is to equalize the pressure between aorta and sensor pressures (Taken from clinical practice).

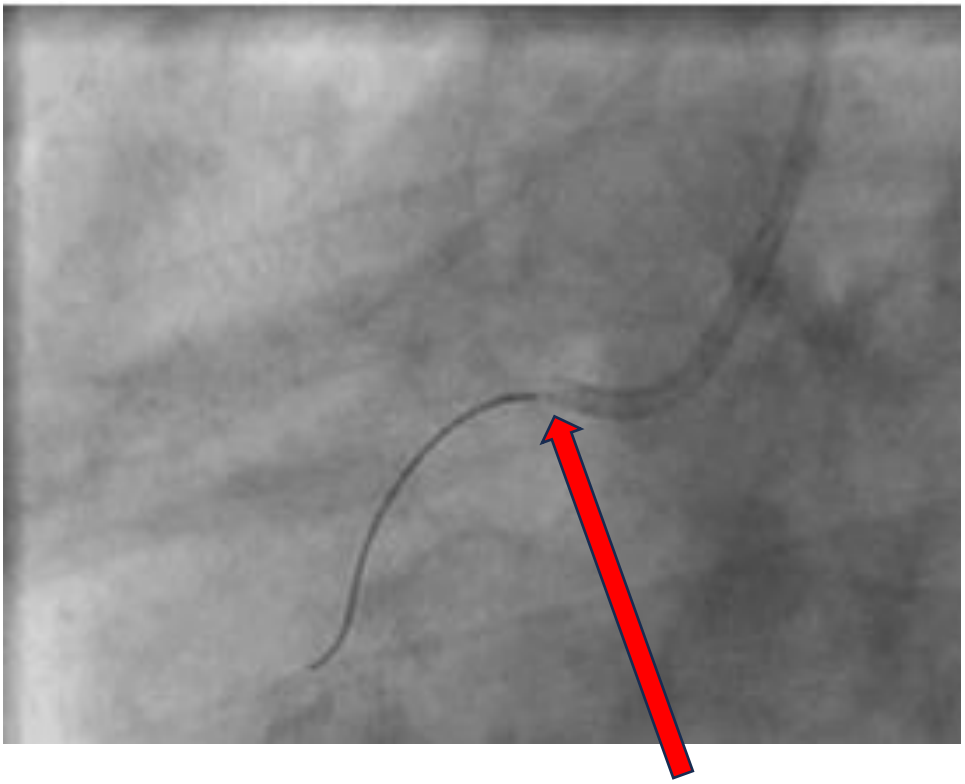


Figure 1.7: Image showing the pressure sensor is just outside the guiding cathter and pressure is equalised. Pressure transducer set-up correctly and zeroed at proper height. Guided catheter pressure should represent AO pressure. Wire introducer removed from Y-Connector (taken from clinical practice).

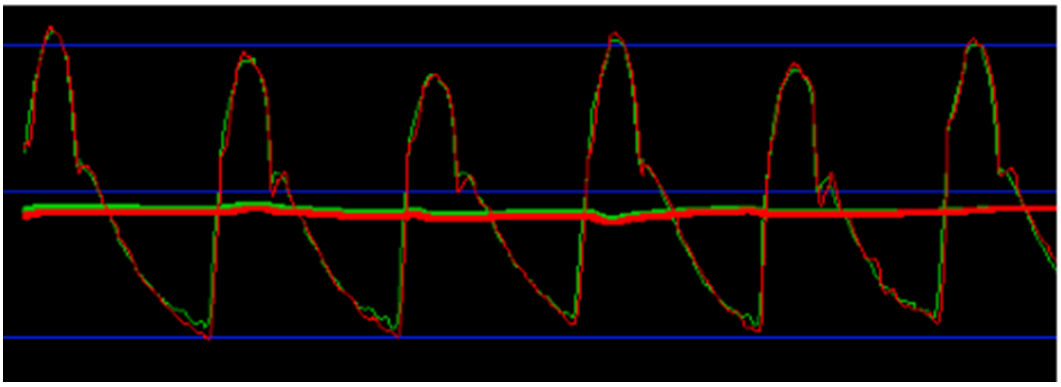


Figure 1.8: Diagram showing equal pressures in Ao and Pressure Wire (Taken from clinical practice)**.**

1.26 Some major points from the introduction

This introduction emphasizes the importance of Coronary Angiography (CA) as a gold standard test for the diagnosis of CAD. An accurate interpretation of CA is of paramount importance in decision-making to treat patients with CAD. CA has the inherent limitation of being a two-dimensional X-Ray lumeno-gram of a complex three-dimensional vascular structure. Visual assessment of angiogram can lead to both inter- and intra-observer variability in the assessment of the severity and extent of the disease which can lead to differences in management strategies. Interventional cardiology has been revolutionized and modern catheterization laboratories globally are fully equipped with adjunctive technologies, such as Quantitative Coronary Angiography (QCA), Fractional Flow Reserve (FFR), Intra-Vascular Ultra-Sonography (IVUS) and Optical Coherence Tomography (OCT) to help cardiac clinicians to make a well-informed decision based on detailed anatomical and physiological assessment of a coronary artery rather than judgment based solely on visual assessment. Figure 1.9 shows a flow diagram of the non-invasive methods in screening for CAD prior to surgical intervention by the clinicians.

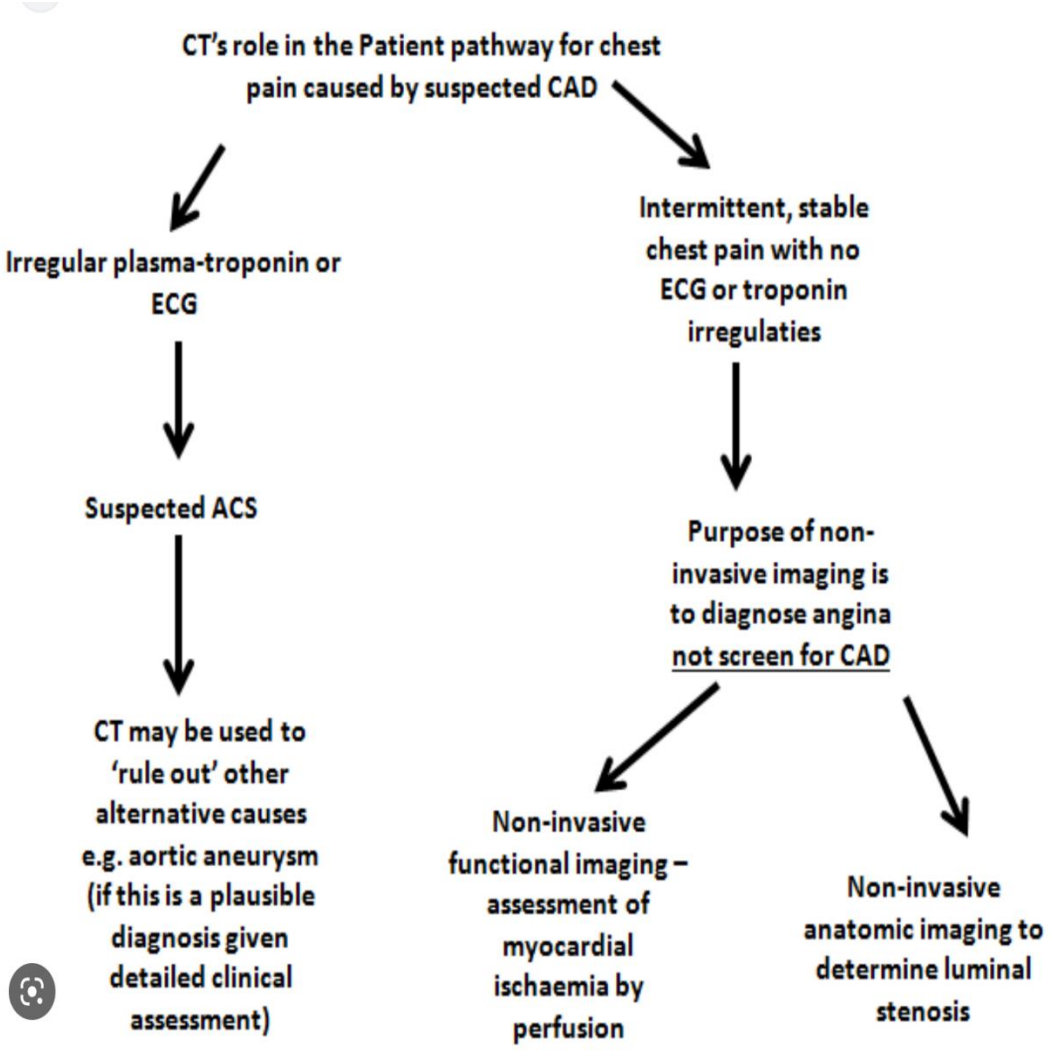


Figure 1.9: Flow diagram showing the various methods in diagnosis for CAD (Taken from Google image).

1.27 Conclusion from the literature review relating to agreement, controversy, growing points and developing new research.

Intracoronary imaging and physiology-guided interventions are important diagnostic tools for guiding decision making in the cardiac catheterization laboratory. The literature review will now support this statement.

Areas of agreement: Coronary angiography has been considered the gold standard test to appropriately diagnose and manage patients with coronary artery disease (CAD), but it has the inherent limitation of being a 2-dimensional x-ray lumeno-gram of a complex 3-dimensional vascular structure.

Areas of controversy: There is well established inter- and intra-observer variability in reporting coronary angiograms leading to potential variability in various management strategies. Intracoronary imaging improves the diagnostic accuracy while optimizing the results of an intervention. Utilization of intracoronary imaging modalities in routine practice however remains low worldwide. Increased costs, resources, time, and expertise have been cited as explanations for low incorporation of these techniques.

Growing points: Intracoronary imaging supplements and enhances an operator's decision-making ability based on detailed and objective lesion assessment rather than a subjective visual estimation. The benefits of intravascular imaging guided by physiological interventions are becoming more profound as the complexity of cases suitable for revascularization increases.

Areas timely for developing research: While the clinical benefits of intravascular ultrasound have been well validated, optical coherence tomography in comparison is a newer technology, with robust clinical trials assessing its clinical benefit are underway.

1.28 How the doctoral standard will be met?

The applicant is well established Consultant Cardiologist with good experience in research resulting in 35 research publications. He also holds the MSc by research (MRes) degree from UCLAN. He also has a very good background in research applications, governance and training which are relevant for a PhD award. Moreover, the candidate possesses knowledge and experience about the research processes including asking research statement and questions, hypotheses, objectives, literature reviews, experimental designs, data collection and statistical analysis using appropriate statistical programs, ethics, health and safety, writing research grants and manuscripts including reviews , presentations to national meetings, power point presentation, member of

professional societies, annual progression and thesis writing. He also has experience in oral examination technique via his MRes award. He is familiar with and has hands on experience with the research processes which are the e basis for doctoral research, thus meeting the requirements of doctoral standards. In addition, the candidate has a strong inclination towards research, and he strongly believes that it keeps him up to date in his field of expertise and learning the latest cutting -edge developments and techniques. Additionally, working in academic cardiovascular units has given me the opportunity to understand the basics of research methodology.

In supporting of his PhD by publication, the candidate is a British-Trained Consultant Cardiologist. He also holds postgraduate training qualifications to become a Cardiologist and the MSc by Res from UCLAN. He has been a clinician for over 18 years, and he would like to continue to enhance his ambitions and dreams in pursuing an academic career and as such, the PhD will help him in this respect. Secondly, the doctoral standard has now been met via the current PhD thesis by publication, like others submitted to UCLAN for the same award.

The candidate is receiving substantial guidance from Professor Jaipaul Singh at UCLAN and Professor Ernest Adeghate in Dubai regarding the preparation of the thesis. Both have supervised many PhD students including PhD by publication. Moreover, both the Professors have the DSc degree which is equivalent to PhD by publication but with more research papers.

1.29 Scope of Study

Chapter 1 of this thesis illustrates a thorough review of the literature in the subject area supported by several figures and tables. Chapter 2 contains a comprehensive explanation and discussion as to how each research paper in each of the three areas has contributed and enhanced knowledge and understanding in the subject area of CAD. Chapter 3 outlines the percentage participation by the candidate to each publication. Chapter 4 is a general, critical, and comprehensive discussion of the major findings in each paper to support the PhD thesis by publication. This chapter is followed by a conclusion, limitations, and recommendations and scope for future studies. Appendix 1 contains the full CV of the candidate and Appendix 2 contains the scanned/PDF copies of the full 16 original research publications which have been used to support the thesis by publication.

1.30 Working hypothesis:

Intracoronary imaging and physiology-guided interventions are crucial in decision making in cardiac catheterisation laboratory in treating complex coronary artery disease (CAD) in patients with chronic kidney disease (CKD) and diabetes mellitus (DM).

1.31 Main aim:

This is a PhD by publication study which is designed to incorporate several relevant publications to support the working hypothesis on the utility of intracoronary imaging and physiology-guided interventions in patients with diabetes mellitus (DM) and chronic kidney disease (CKD) to help in improving the clinical outcomes of the patients. The utility of these techniques is very low in routine daily practice, and it is relevant to encourage the clinicians and general population to understand the importance of these modalities to give the best clinical care to the patients.

1.32 Specific Aims or Objectives:

1. To undertake a thorough literature search around the subject area relating to the coronary artery disease (CAD) and role of intracoronary imaging and physiology in cardiac catheterisation laboratory (Chapter 1).

2. To explain the major findings in each publication in terms of contributing and enhancing knowledge and understanding in the subject area of early diagnosis and sudden cardiac death (Chapter 2).

3. To provide evidence of contribution and support by the candidate (expressed as percentage) for each research publication presented in the PhD thesis by publication (Chapter 3).

4. To discuss critically and compare the results of each paper presented in the thesis by publication with those in the current literature and supported by relevant references and how it is possible to improve early diagnosis and treatment of CAD to prevent sudden cardiac death of the patients (Chapter 4).

5. To provide the CV and sixteen original publications for inspection by the examiners (Appendices 1 and 2)

6. To defend the competence of the candidate and the PhD by publication at an oral examination

CHAPTER 2

ORIGINAL CONTRIBUTION TO THE ADVANCEMENT OF SCIENTIFIC KNOWLEDGE AND UNDERSTANDING BASED ON RESEARCH PUBLICATIONS

2.1 Introduction:

Globally, heart and circulatory diseases, including coronary artery disease (CAD), killed an estimated 9.8 million men and 9.2 million women in their working years in 2019, representing over 1 in 4 (27 per cent) of all global deaths [1a/b, 75]. The global number of deaths from heart and circulatory diseases is projected to rise further, not only in high-income countries but also in low- and middle- income countries. A common cause of CAD is atherosclerosis where a plaque develops, due to the accumulation of fats, especially cholesterol, in the medium and large arteries of the heart. If left untreated, it hardens and narrows (clogged up) the arteries over a period of years, thus reducing the flow of oxygen-rich blood to organs and other parts of body, and leading to serious problems, such as myocardial/cerebral infarction, or even death of the patient.[76, 77].

The initial choice of medical technologies for the diagnosis of CAD depends on the patient's state and history. In general, invasive coronary angiography (ICA) is prescribed to specify the nature and extent of the coronary lesions[78]. However, it is an invasive procedure thus posing certain risks to the patient and moreover, in the case of multiple medium-severity stenoses, the decision on which of the lesions is the main cause of ischemia cannot be deciphered from the angiography data alone [78]. Coronary CT angiography (CCTA) is a noninvasive alternative to the ICA and better than stress test[79]. This provides a 3D representation of the heart and coronary arteries. One of the main advantages of CCTA is that it can identify the characteristics and global extent of CAD together with providing data for the reconstruction of the entire arterial tree lumen. Since CCTA produces 3D datasets, techniques such as curved multiplanar reformation (c-MPR) and 3D volume as well as non-invasive computed fractional flow reserve from computed tomography (CT) can now be used for diagnosing coronary artery disease [80]. However, clinical diagnosis by means of coronary CT imaging is a time-consuming task, due to the large amount of data produced in the scanning process (on average, 300 slices/patient). Interpretation of a CTA study is a labor-intensive and subjective task. CT angiography, can be used in the diagnosing and managing the Chronic Coronary Syndromes (CCS) [81]**.**

The current thesis for PhD by publication is based on sixteen publications and they are related mainly to diagnosis and treatment of CAD to save the lives of patients and provide them with an element of longevity and improving their quality of life. The sixteen papers are categorized into three main areas of research including Intra-coronary imaging and physiology (10 papers), mineralocorticoid receptor antagonists (MRA) (3 papers) and infarct size reduction and endothelial dysfunction (3 papers).

The aim of this chapter is to show how each selected publication in each category of research has contributed to the advancement of knowledge and understanding in each subject area combined with key factors such as impact factor and citation as to how the work in the selected publications has impacted on advancement of science into clinical work by Cardiologists.

2.2 (A) Intra-coronary Imaging and Physiology

1. Parviz, Y., Fall, K., Stone, G., Maehara, A., Ben-Yehuda, O., Mintz, G., and Ali, Z. (2017). Imaging and Physiology to Guide Venous Graft Interventions Without Contrast Administration in Advanced Renal Failure. The Journal of Invasive Cardiology, 29: E163-E165, **(Impact Factor 1.07 and 6 citations).**

2. Parviz, Y. (2017). Intra coronary imaging to detect mal apposition: Are We Seeing Too Much. Heart. (A BMJ Journal), 103 (9): Article 2017; 0- heartjnl-2015-307888v1) (**Impact Factor 5.42 and no citation).**

3. Parviz, Y., Evan, S., Khady N.F., Maayan K., Akiko, M., Allen, J., Richard, A.S., Gary, S.M., and Ziad A.A. (2017). Utility of intracoronary imaging in the cardiac catheterization laboratory: comprehensive evaluation with intravascular ultrasound and optical coherence tomography. British Medical Bulletin, 125(1):79-90. (doi: 10.1093/bmb/ldx049. **(Impact Factor: 3.045 and 18 citations).**

4. Parviz, Y., P., Khady N.F., and Ziad A.A (2016). Using sound advice—intravascular ultrasound as a diagnostic tool. Journal of Thoracic Diseases. 8(10): E1395-E1397. (doi: 10.21037/jtd.2016.10.64. 10.21037/jtd.2016.10.64, **(Impact Factor: 2.365 and 3 citations).**

5.Chin, C., Matsumura, M., Maehara, A., Zhang, W., Lee, C., Yamamoto, M., Song, L., **Parviz, Y.,** Jhalani, N., Mohan, S., Ratner, L., Cohen, D., Ben-Yehuda, O., Stone, G., Shlofmitz, R., Kakuta, T., Mintz, G., and Ali, Z. (2017). Coronary Plaque Characteristics in Haemodialysis-Dependent Patients as Assessed by Optical Coherence Tomography. The American Journal of Cardiology,119(9): 1313-1319. (doi: 10.1016/j.amjcard.2017.01.022. Epub 2017 Feb 9. **(Impact factor: 2.26 and no citation)**

6. **Parviz, Y.,** Awan, K., Vijayan, S., Sultan, A., and Iqbal, J. (2017). Role Of Intra Coronary Imaging and Physiology In Diagnosis And Management Of Coronary Artery Disease. Journal of Ayub Medical College, Abbottabad: JAMC. 29: 516-522. **(Impact Factor 0.481 and 515 citations).**

7. Mamamoto, M.H., Maehara, A., Karimi, G.K, Mintz, G.S., **Parviz. Y**., Kim, S.S., Koyama, K., Amemiya, K., Kim, S.Y., Ishida, M., Losquadro, M., Kirtane, A.J., Haag. E., Sosa, F.A., Stone, G.W., Moses, J.W., Ochiai, M., Shlofmitz, R.A., and Ali Z.A. (2017). Mechanisms of Orbital Versus Rotational Atherectomy Plaque Modification in Severely Calcified Lesions Assessed by Optical Coherence Tomography. JACC Cardiovascular Intervention, 10(24): 2584-2586. (doi: 10.1016/j.jcin.2017.09.031. PMID: 29268891), (**Impact Factor: 11.2 and no citation).**

8.Ali, Z., **Parviz, Y.,** Brinkman, M., Matsumura, M., Redfors, B., Brogno, D., Corral, M., Fall, K., Mintz, G., Stone, G., Maehara, A., Jeremias, A., and Kirtane, A. (2018). Pressure Wire Compared to Microcatheter Sensing for Coronary Fractional Flow Reserve: The PERFORM Study. Euro-

Intervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 14(4): e459-e466. doi: 10.4244/EIJ-D-18-00064. **(Impact Factor 6.534 and 5 citations).**

9.Shlofmitz, E., Jeremias, A., **Parviz, Y.,** Karimi, G.K., Redfors, B., Petrossian, G., Edens, M., Matsumura, M., Maehara, A., Mintz, G., Stone, G., Shlofmitz, R., and Ali, Z. (2020). External elastic lamina vs. luminal diameter measurement for determining stent diameter by optical coherence tomography: an ILUMIEN III sub-study. European Heart Journal of Cardiovascular Imaging, 22(7):753-759. doi: 10.1093/ehjci/jeaa276 **(Impact Factor: 6.875 and no citation).**

10.Israeli, Z., Bagur, R., Murariu, D., Wall, S., Alemayehu, M., **Parviz, Y**., Diamantouros, P., and Lavi, Shahar. (2017). Nitro-glycerine-Derived Pd/Pa for the Assessment of Intermediate Coronary Lesions. The Journal of Invasive Cardiology. 29(12): E177-E183. **Impact Factor:1.07 and 1 citation).**

2.3 Advancement and understanding of the science to enhance knowledge on intra-coronary imaging and physiology in each of the 10 publications.

Manuscript 1. Parviz, Y., Fall, K., Stone, G., Maehara, A., Ben-Yehuda, O., Mintz, G., and Ali, Z. (2017). Imaging and Physiology to Guide Venous Graft Interventions Without Contrast Administration in Advanced Renal Failure. The Journal of Invasive Cardiology, 29: E163-E165, **(Impact Factor 1.07 and citation of 6).**

In this exciting paper, the candidate was the leading author and demonstrated the utility of intracoronary imaging and physiology in managing complex disease process of graft interventions with no contrast use. Patients with previous coronary artery bypass grafting and advanced chronic kidney disease (CKD) are considered at a high risk for revascularization. In comparison to native coronary artery angiography, additional contrast is required to visualize the bypass conduits, increasing the risk of contrast-induced nephropathy (CIN) and need for renal replacement therapy.

As a result, despite the need for revascularization, these patients were frequently under-treated. There is evidence in the literature that intravascular ultrasound (IVUS)-guided interventions can reduce the amount of contrast and its associated risk of CIN.

In addition, this paper described a novel step-by-step "zero-contrast" saphenous vein bypass graft (SVG) intervention using a modified technique. This was the brainchild of the candidate and he worked with his supervisor at Columbia University New York and wrote the manuscript for publication.

The paper concluded that this novel technique could help to guide the Clinicians in treating these complex sets of coronary bypass patients and improve the clinical outcomes by minimizing the contrast use. Similar work is now ongoing widely to treat cardiac patients**.**

Manuscript 2. Parviz, Y. (2017**).** Intra coronary imaging to detect mal apposition: Are we seeing too much intracoronary imaging? Heart: A BMJ Journal) 103 (9): Article 2017 (0- heartjnl-2015-307888v1) (**Impact Factor 5.42 and no citation).**

This was an important editorial letter written by the candidate alone to the Editor of the journal entitled **Heart** as an expert to comment on intracoronary imaging. He made 100% contribution for this clinical informative paper. This was his idea, and he did all the searches and tabulated the results for analysis. In this letter, the candidate outlined a detailed assessment of intracoronary imaging of coronary vessels including diagnosis and treatment. The rationale for this invited editorial article was to enlighten Cardiologists, especially those in training, more on the subject area in terms of making and executing a clinical decision or intracoronary imaging. The candidate highlighted and discussed the various mal-appositions and long -term consequences on diagnosis and treatment.

The novelty and importance of this invited editorial article was to reassure the cardiac clinicians that not all the mal apposition was of clinical significance. As such, they should try to have stent optimally expanded as much as possible. Acute mal apposition can sometime be an issue during the acute procedure as it can lead from time to time a wire behind the stent struts and hence, leading

to potentially avoidable complications during the procedure. Late mal apposition can sometimes be associated with delayed stent thrombosis. The paper is widely cited in related publications, and it has educated the cardiac community about intra-coronary imaging to detect mal apposition.

Manuscript 3. Parviz, Y., Evan, S., Khady N.F., Maayan K., Akiko, M., Allen, J., Richard, A.S., Gary, S.M., and Ziad A.A. (2017). Utility of intracoronary imaging in the cardiac catheterization laboratory: comprehensive evaluation with intravascular ultrasound and optical coherence tomography. British Medical Bulletin, 125(1):79-90. (doi: 10.1093/bmb/ldx049. **(Impact Factor: 3.045 and 18 citations).**

This was a highly landmark paper in which the candidate was the main author. He wrote a comprehensive review based on the available literature on the utility of intracoronary imaging and physiology in cardiac catheterization laboratory. The paper highlighted the various techniques that could be used in the cardiac catheterization laboratory. He was also the main contributor and personally involved in undertaking a comprehensive literature search in the subject area. Moreover, he compiled and analysis of data and subsequently wrote the review. As such, he a major contribution and was the first author in this state -of the art paper. As an expert like his co-authors in intracoronary imaging and physiology, his contribution was more than 70%.

The novelty and clinical importance of this interesting review, which was lacking at the time, helped the Cardiac Clinicians to appreciate the utility and evidence behind adjunctive techniques of intracoronary imaging, optical coherence tomography (OCT) and intravascular ultrasound (IVUS) or physiology techniques like fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR). Moreover, the article provided a few examples of clinical cases to highlight their uses in aiding the Physicians to make a well-informed treatment decision. It is particularly noteworthy that up-to- date knowledge and understanding of intra-coronary imaging and physiology supplements can enhance a clinical operator in decision-making ability based on detailed and objective lesion assessment rather than a subjective visual estimation. The benefits of intravascular imaging and physiology are becoming more profound. especially as the complexity of cases is suitable for revascularization increases.

From the results, the study concluded that modern X-ray angiography is a valuable clinical tool in the cardiac catheterization laboratory to obtain images of coronary arteries. There are inherent limitations of this 2-dimensional technique and adjunctive intravascular techniques (IVUS and OCT) provide precise and detailed data of the 3-dimensional coronary artery tree. Hurdles of procedure-related cost and time are overcome by the benefits gained with intravascular imaging (IVI). Several randomized trials were in progress to evaluate the impact of intracoronary imaging on long-term clinical outcomes. The take home message from the study is that a combination of an algorithmic approach to IVI with sound clinical judgment can improve the decision-making process of the Clinician in helping to improve the clinical outcomes of the patients.

Manuscript 4. Parviz, Y., P., Khady N.F., and Ziad A.A (2016). Using sound advice—intravascular ultrasound as a diagnostic tool. Journal of Thoracic Diseases. 8(10): E1395-E1397. (doi: 10.21037/jtd.2016.10.64. 10.21037/jtd.2016.10.64, **(Impact Factor: 2.365 and 3 citations).**

This was a very interesting commentary paper on the utility of intracoronary imaging during complex clinical scenarios. The Candidate was the first author and lead in the study, first author and he demonstrated the utility of intravascular ultrasound (IVUS) in various clinical settings. The role novelty of the article is that it explained and highlighted the diagnostic use of IVUS in various emergency clinical settings and how IVUS can guide the treatment decisions by the Clinicians in various scenarios of either aortic or coronary artery dissections. Moreover, IVUS can be a modality to differentiate between a true and false lumen. The utility of intracoronary imaging has helped Cardiac Clinicians in terms of knowledge and detailed understanding of various dissections and strategies for the best management of these conditions. IVUS has a very high penetration power and can be used for the differentiation of various dissections. One of the advantages of using IVUS is that the Clinicians can avoid using the contrast material which may be helpful in preventing the propagation and extension of dissection.

This interesting paper also highlighted and more so, emphasised on the fact that due to the higher penetration power of IVUS, the extent of the dissection process may be studied better. However,

due to the low resolution of IVUS systems, IVUS can help to differentiate and distinguish between the false and true lumen and thereby helping to localize the intimal tear. In clinical settings, whenever there is suspicion of dissection on angiography, IVUS can be used to locate the false lumen and it can help facilitate directing the wire into the true lumen. IVUS is superior in many cases of dissection including left main stem (LMS) dissection. In these cases, IVUS does not require the use of contrast and it avoids the hydraulic extension of dissection to other arterial trees. In the cases involving the LMS dissection, IVUS can help to locate the external elastic lamina (EEL) due to high penetration in comparison to other imaging modalities including OCT. This study has provided new knowledge and enhanced understanding of the clinical use of IVUS in diagnosis and subsequent treatment of the patients with CAD or related diseases.

This study concluded that IVUS is highly recommended in cases of left main coronary dissection to determine both the etiology and the extent of dissection and treatment plan. The routine use of IVUS is encouraged in clinical medicine to provide intervention Cardiologists with more confidence using this modality, including the emergency setting.

Manuscript 5. Chin, C., Matsumura, M., Maehara, A., Zhang, W., Lee, C., Yamamoto, M., Song, L., **Parviz, Y.,** Jhalani, N., Mohan, S., Ratner, L., Cohen, D., Ben-Yehuda, O., Stone, G., Shlofmitz, R., Kakuta, T., Mintz, G., and Ali, Z. (2017). Coronary Plaque Characteristics in Haemodialysis-Dependent Patients as Assessed by Optical Coherence Tomography. The American Journal of Cardiology,119(9): 1313-1319. (doi: 10.1016/j.amjcard.2017.01.022. Epub 2017 Feb 9. **(Impact factor: 2.26 and no citation)**

This was a novel, original and collaborative study involving eighteen authors. This study was done when the Candidate was working as a Research Fellowship at Columbia University New York. He had a keen interest in the management of patients with chronic kidney disease (CKD) and in this study, the authors investigated the various plaque morphologies in CKD patients using optical coherence tomography (OCT). The Candidate actively contributed to this paper and this research was based on his original idea. He was involved in the experimental design, collection, compilation, and analysis of data. He was also involved in writing the manuscript. This was a

landmark paper on the complex disease process of CKD and coronary disease plaque characterization as defined using OCT.

In this study, 19 paired distal vessel lesions were employed in the study. Lesion length, minimum lumen area, and area stenosis were measured to ascertain any similarity between groups. The HD-dependent group had greater mean calcium arcs in culprit (54.3 vs 26.4; $p< 0.004$) and non-culprit lesions (34.3 vs 24.5; $p < 0.02$) and greater maximum calcium arc in distal vessel segments (101.6 vs 0; $p<0.03$). There were no differences in lipid arcs between groups. There was a higher prevalence of thin intimal calcium, defined as an arc of calcium >30 within intima <0.5 mm thick, in patients in the HD-dependent group (41.9% vs 4.8%; $p <0.001$). There was a higher prevalence of calcified nodules in the HD-dependent group (24.2% vs 9.7%; $p<0.049$) but no differences in medial calcification or thin-cap fibroatheroma.

The incidence of CKD is rising due to an increase in hypertension, diabetes mellitus (DM) and with increasing age of the population. Currently, patients with CKD are living longer, but it is still possible to see long-term complications like cardio-renal problems more often in a clinical setting. The rising trend in CKD is alarming and Physicians must be aware of the epidemic of disease, and it is of paramount importance that new advances in the field are well understood. The information regarding plaque morphology in these CKD patients is of paramount importance as it can help to guide the decision- making process of the Clinicians. If the patients have significant calcification in their coronary arteries, then the Clinicians need to decide upfront about the plaque modification techniques and try to avoid unnecessary balloon dilatations to prevent or reduce such complications as coronary perforations stent under expansions associated with higher morbidity and mortality. Knowing plaque morphology beforehand can be very cost-effective as it can avoid the use of unnecessary equipment and moreover, minimize contrast use and hence prevent the long-term complications associated with dialysis.

This study concluded that using OCT in HD-dependent patients, compared with matched patients without CKD, had more extensively distributed coronary calcium and uniquely, a higher prevalence of non-atherosclerotic thin intimal calcium. This thin intimal calcium may cause an

overestimation of calcium burden by intravascular ultrasound and may contribute to the lack of correlation between increased coronary artery calcification scores with long-term outcomes in patients with CKD.

Manuscript 6. Parviz, Y., Awan, K., Vijayan, S., Sultan, A., and Iqbal, J. (2017). Role Of Intra Coronary Imaging and Physiology in Diagnosis and Management Of Coronary Artery Disease. Journal of Ayub Medical College, Abbottabad: JAMC. 29: 516-522. **(Impact Factor 0.481 and 515 citations).**

This was a novel paper on the utility of intracoronary imaging and physiology in the coronary artery disease (CAD). The candidate was the first author and one of the main contributors who was solely involved in the collection, compilation, and analysis of data. He also wrote most of the paper supporting his first authorship. This paper was based on his personal idea and as such, he designed all the proforma, manuscript and wrote up the work for publication.

The interesting paper highlights as to why angiography is not adequate to make precise decisions regarding clinical care of cardiac patients with CAD. As such, this information for Cardiologists, as well as the public, is of great significance since coronary angiography has the inherent limitation of being a two-dimensional X-Ray lumeno-gram of a complex three-dimensional vascular structure. Visual assessment of angiogram can lead to both inter- and intra-observer variability in the assessment of the severity and extent of the disease leading to differences in management strategies. This issue becomes even more relevant in complex clinical settings, when assessing left main stem (LMS), bifurcations, diffuse coronary artery disease or situations involving complex coronary morphology. The novelty of this paper is to promote the precise roles of both intra coronary imaging and physiology in the diagnosis and management of patients with CAD and as such, the Cardiac Physicians must not rely on angiography alone.

Manuscript 7. Mamamoto, M.H., Maehara, A., Karimi, G.K, Mintz, G.S., **Parviz. Y**., Kim, S.S., Koyama, K., Amemiya, K., Kim, S.Y., Ishida, M., Losquadro, M., Kirtane, A.J., Haag. E., Sosa, F.A., Stone, G.W., Moses, J.W., Ochiai, M., Shlofmitz, R.A., and Ali Z.A. (2017). Mechanisms of Orbital Versus Rotational Atherectomy Plaque Modification in Severely Calcified Lesions Assessed by Optical Coherence Tomography. JACC Cardiovascular Intervention, 10(24): 2584-2586. (doi: 10.1016/j.jcin.2017.09.031. PMID: 29268891), (**Impact Factor: 11.2 and no citation).**

This novel study involved eighteen clinical collaborators to investigate the comparison of two different techniques for modifying the calcified plaques during the development of CAD. These techniques have different mechanism(s) of actions to ablate the calcified plaques. In large sized vessels, there is differentially more plaque modification. OA is doing more modification of calcified and non-calcified plaque modification. In small vessels, the ablative impact is similar of the devices. This was an international collaborative research study that involved various clinical institutions in USA, UK, and Japan. This was a retrospective study to compare 30 OA cases with 30 RA in severely calcified lesions. The publication received a high impact factor, probably due to its uniqueness and novelty. Unfortunately, there was not citation for this paper.

These procedures were OCT- guided and imaging was performed pre-procedurally, when possible and post-atherectomy and post stenting. These patients were not randomized. Calcium at the site of lesion was studied before and after the atherectomy. To identify calcium with either round, smooth or concave surface, calcium fracture was defined as discontinuity in luminal surface in calcified plaques. Post-device usage involved stent expansion and asymmetry and eccentricity were similar in both groups.

This was a unique trial comparing the 2 modalities of atherectomy for plaque modification. This information is useful to help in deciding which modality was best to use in which setting with calcification. It is important for Clinicians to make informed decisions in this regard as appropriate device selection can avoid potential complications and more so can give the best possible outcome for patients. With advances in interventional cardiology, more elderly, diabetic, and renal failure

patients are being treated and hence more calcification is seen in clinical practice. Familiarity with these device usages is of paramount importance and this can guide in making the best possible decisions for patients and avoiding the complications in these complex scenarios.

Manuscript 8. Ali, Z., **Parviz, Y.,** Brinkman, M., Matsumura, M., Redford, B., Brogno, D., Corral, M., Fall, K., Mintz, G., Stone, G., Maehara, A., Jeremias, A., and Kirtane, A. (2018). Pressure Wire Compared to Microcatheter Sensing for Coronary Fractional Flow Reserve: The PERFORM Study. Euro-Intervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 14(4): e459-e466. doi: 10.4244/EIJ-D-18-00064. **(Impact Factor 6.534 and 5 citations).**

This study was an interesting large- scale head- to- head comparison of pressure wire vs micro catheter for coronary fractional flow reserve. This European collaborative study involved thirteen Clinical Cardiologists and the candidate was one of them. This high impact factor publication and with 5 citations demonstrated that the introduction of micro-catheter could reduce the device success and hyperemic and resting Pd/pa and could reclassify the fractional flow reserve (FFR) into ischemic zone in 1/5 cases. This work was done at Columbia University New York in collaboration with world leaders in the field of intracoronary physiology.

This PERFORM collaborative study was a single-center prospective investigation designed specifically to determine the precision and accuracy of the percutaneous coronary intervention (PCI) compared with the pressure wire (PW) for measurement of FFR. Eligible patients had native coronary artery target lesions with visually estimated diameter stenosis of 40-90%. The independently adjudicated primary endpoint was the difference in hyperemic PW-determined minimal FFR with and without the PC distal to the stenosis. Seventy-four patients (95 lesions) were prospectively analyzed between December 2015 and December 2016. Median hyperemic FFR was 0.84 [IQR 0.78, 0.89] with the PW and 0.79 [IQR 0.73, 0.85] with the PC distal to the stenosis ($p<0.001$). Such differences led to clinical discordance, whereby the PC decreased the hyperemic PW-determined FFR from >0.80 to ≤0.80 in 17 of 95 measurements (19%). Median resting Pd/Pa was lower following introduction of the PC compared with the PW alone (0.93 [IQR

0.90, 0.97] versus 0.90 [IQR 0.86, 0.95], p<0.001). Median pressure drift was not different between the PW and the PC (0.01 [IQR -0.01, 0.05] versus 0.01 [IQR 0.00, 0.02], p=0.38).

The novel and collaborative piece of study concluded that knowledge, awareness and understanding about the micro catheter- based physiology is of great assistance to Cardiac Clinicians especially when they are measuring the physiology at the end of the procedure. This technique can be an added advantage during the cases where repeated assessment of intracoronary physiology is required.

Manuscript 9. Shlofmitz, E., Jeremias, A., **Parviz, Y.,** Karimi, G.K., Redford, B., Petrossian, G., Edens, M., Matsumura, M., Maehara, A., Mintz, G., Stone, G., Shlofmitz, R., and Ali, Z. (2020). External elastic lamina vs. luminal diameter measurement for determining stent diameter by optical coherence tomography: an ILUMIEN III sub-study. European Heart Journal of Cardiovascular Imaging. 22(7):753-759. doi: 10.1093/ehjci/jeaa276 **(Impact Factor: 6.875 and no citation).**

This was a novel, landmark, interesting and collaborative investigation which had a high impact factor but unfortunately with no citation. The study involved thirteen Cardiac Investigators, including the Candidate, and they investigated the various measurement techniques for sizing the stent for coronary intervention. Optical coherence tomography (OCT)-guided external elastic lamina (EEL)-based stent sizing is safe and as effective as intravascular ultrasound in achieving post procedural lumen dimensions. However, when compared with automated lumen diameter (LD) measurements, this approach was time-consuming.

In this study, the Investigators, including the Candidate, demonstrated that EEL-based stent downsizing led to selection of larger stent diameters vs. LD upsizing. While applying a correction factor to automated LD measurements resulted in similar mean diameters to EEL-based measurements. This research was done at Columbia University New York in collaboration with world leaders in the field of intracoronary imaging. The candidate was involved in the data collection and wrote part of the manuscript. He contributed 30 % in the paper. The other authors

assisted in data collection and analysis, correcting the manuscript and they also did some of the literature search for the manuscript. During this study, the authors retrospectively compared EEL-based measurements vs. automated LD in reference segments in 154 OCT acquisitions and derived a correction factor for stent sizing using the ratio of EEL to LD measurements. They then prospectively applied the correction factor in 119 OCT acquisitions. EEL could be adequately identified in 100 acquisitions (84%) at the distal reference to allow vessel diameter measurement. Vessel diameters were larger with EEL-based vs. LD measurements at both proximal (4.12 ± 0.74 vs. 3.14 ± 0.67 mm; p< 0.0001) and distal reference segments (3.34 ± 0.75 vs. 2.64 ± 0.65 mm; p< 0.0001). EEL-based downsizing led to selection of larger stents vs. an LD-based upsizing approach (3.33 ± 0.47 vs. 2.70 ± 0.44; p< 0.0001). Application of correction factors to LD [proximal 1.32 (IQR 1.23-1.37) and distal 1.25 (IQR 1.19-1.36)] resulted in discordance in stent sizing by >0.25 mm in 63% and potentially hazardous stent oversizing in 41% of cases.

The paper concluded that EEL-based stenting is appropriate and Cardiac Clinicians should be aware of this and more so, help in guiding the optimal stenting for these patients with CAD. The new and novel results obtained from this collaborative study are now guiding and leading Cardiac Clinicians to design further large- scale trials of OCT- guided stenting to treat CAD.

Manuscript 10. Israeli, Z., Bagur, R., Murariu, D., Wall, S., Alemayehu, M., **Parviz, Y**., Diamantouros, P., and Lavi, Shahar. (2017). Nitro-glycerine-Derived Pd/Pa for the Assessment of Intermediate Coronary Lesions. The Journal of Invasive Cardiology. 29(12): E177-E183. **Impact Factor:1.07 and 1 citation).**

The candidate contributed actively as the first operator in performance of the procedure of coronary physiology. As a lead team of cardiology interventional fellows, they worked together for performance of procedure, collection, compilation, and analysis of data. This was a landmark paper on intracoronary physiology. This study compared the utility of Nitro-glycerin-Derived Pd/Pa for the Assessment of Intermediate Coronary Lesions. The rationale was to assess the predictive value of Pd/Pa after nitroglycerin administration (Pd/Pa[N]) as compared with standard fractional flow

reserve (FFR). The Candidate was involved in this exciting study during his clinical fellowship at Western University Canada. He was involved in the design, compilation, collection, tabulation, and analysis of the data as graphical representations.

In this original study, 134 patients (27% females; mean age, 65 years) were recruited for the intervention. The diagnostic performance of Pd/Pa(N) and identification of cut-off value for Pd/Pa (N) compared with FFR threshold of 0.8, using receiver-operating characteristic (ROC) area under the curve analysis, was between 0.98 (95% confidence interval, 0.95-1.00; $p<.05$) for 48 µg and 0.86 (95% confidence interval, 0.79-0.94; $p<.05$) for 240 µg adenosine. Pd/Pa(N); $p\leq0.8$ had 100% positive predictive value. Pd/ Pa(N); $p\geq0.94$ provided 100% negative predictive value with a high sensitivity ($p>92\%$). Optimal diagnostic accuracy of Pd/Pa(N) was achieved for values ≤0.84. The Pearson's correlation between Pd/Pa(N) and FFR varied between 0.89 for 24 µg adenosine and 0.77 for 240 µg ($p<.01$).

This study was unique in comparing nitroglycerin and adenosine for measuring coronary physiology. There were many patients, then and even today, who did not normally tolerate the adenosine due to some side effects. Moreover, this study demonstrated that even intracoronary glyceryl trinitrate (GTN) can help in guiding the decision- making process in cardiac catheterization laboratory. This is very cost-effective and easy to administer in the laboratory, without any specific preparations. This technique can be used more frequently and hence, it can help the cardiac clinicians for more frequent use of coronary physiology.

In summary, the results from this study have demonstrated that Pd/Pa(N) correlates well with FFR results. When Pd/Pa(N) is ≤0.8, there is no need for adenosine injection. When Pd/Pa(N) is ≥0.94, there is a high probability of an FFR-negative lesion. Pd/Pa(N)-based strategy may be integrated into the hemodynamic assessment of borderline lesion. Although the paper had a satisfactory impact- factor, the intervention process is used widely by clinical cardiologists for the treatment of patients with CAD or related diseases.

2.4 (B). MR Antagonism and cardiovascular diseases

11. Iqbal, J., Parviz, Y., Pitt B, Newell-Price, J., Al-Mohammad, A., and Zannad, F. (2014). Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure. European Journal of Heart Failure, 16(2):143-150. (doi: 10.1111/ejhf.31. PMID: 24464876), **(Impact Factor of 15.534 and 52 citations).**

12. Iqbal, J., Fay, R., Adlam, D., Squire, I., **Parviz, Y.,** Gunn, J., Pitt, B., and Zannad, F. (2014). Effect of eplerenone in percutaneous coronary intervention-treated post-myocardial infarction patients with left ventricular systolic dysfunction: A sub-analysis of the EPHESUS trial. European Journal of Heart Failure, 16: 685–691, (16.10.1002/ejhf.88**. (Impact Factor 15.534 and 24 citations).**

13. **Parviz, Y.,** Iqbal, J., Pitt, B., Adlam, D., Al-Mohammad, A.,and Zannad, F.. (2015). Emerging cardiovascular indications of mineralocorticoid receptor antagonists. Trends in Endocrinology and Metabolism, April 2015, Vol. 26 (4):201-211 (26.10.1016/j.tem.2015.01.007), **(Impact Factor: 12.015 and 31 citations).**

2.5 Advancement and understanding to science in enhancing knowledge in each of these three areas of mineralocorticoids antagonism and cardiovascular diseases.

Manuscript 11. Iqbal, J., Parviz, Y., Pitt B, Newell-Price, J., Al-Mohammad, A., and Zannad, F. (2014). Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure. European Journal of Heart Failure, 16(2):143-150. (doi: 10.1111/ejhf.31. PMID: 24464876), **(Impact Factor of 15.534 and 52 citations).**

This high impact scientific publication with 52 citations has highlighted the role of mineralocorticoid receptor (MR) antagonists (MRAs) in the treatment of hypertension and heart failure. This was an original paper on a particular MR antagonism. The study highlighted the

established treatment modality for patients with hypertension, heart failure, and left ventricular systolic dysfunction (LVSD) during post-myocardial infarction (MI). The study highlighted emerging data with reference to the potential benefits of MR antagonists in other cardiovascular conditions. Several previous studies have shown an association between MR activation and the development of myocardial fibrosis, coronary artery disease (CAD), metabolic syndrome, and cerebrovascular diseases. This review examined the preclinical and clinical data of MR antagonists for novel indications including heart failure with preserved ejection fraction (HFPEF), pulmonary arterial hypertension (PAH), arrhythmia, sudden cardiac death (SCD), valvular heart disease (VHD), metabolic syndrome, renal disease, and stroke. MR antagonists are not licensed at least in the United Kingdom for these conditions yet, but emerging data suggest that the clinical needs for MR antagonists are likely to broaden and as such further studies are warranted.

When this study was undertaken, there was little or no data of any direct comparative data for beneficial clinical use of spironolactone or eplerenone. It may not be appropriate to compare trials usings either spironolactone or eplerenone in heart failure directly due to vast differences in patient population and trial design. The choice of a specific agent could be based on clinical indications (such as the nature of heart failure), individual patient factors (such as gender, co-morbidities, occurrence of side effects), geographical licensing restriction, and community-level cost–benefit analysis. Based on the data available, the study suggested a simple approach in selecting a particular MRA for various cardiovascular indications.

It is concluded that the information obtained in this paper and literature review can help in guiding the patients in choosing the appropriate therapy for these long- term complex disease processes. The data have compared spironolactone or eplerenone and the results have supported recommendations about best choice of medication to be considered cost-effectively for the patients. Further comparative studies and cost–benefit analyses are also warranted.

Manuscript 12. Iqbal, J., Fay, R., Adlam, D., Squire, I., **Parviz, Y.,** Gunn, J., Pitt, B., and Zannad, F. (2014). Effect of eplerenone in percutaneous coronary intervention-treated post-myocardial infarction patients with left ventricular systolic dysfunction: A sub-analysis of the EPHESUS trial.

European Journal of Heart Failure, 16: 685–691, (16.10.1002/ejhf.88**. (Impact Factor 15.534 and 24 citations).**

This was a collaborative clinical research study involving eight world leaders in the field of mineralocorticoid receptor antagonists (MRA), including the Candidate. This paper carried a very high impact factor of 15.534 and 24 citations. EPHESUS was a multi-center, double-blind clinical trial in which 6,632 patients with acute myocardial infarction (AMI) complicated by left ventricular systolic dysfunction (LVSD) were randomized to receive eplerenone (n = 3,319) or placebo (n = 3,313). This EPHESUS sub-study examined the effects of eplerenone upon cardiovascular outcomes in percutaneous coronary intervention (PCI)-treated patients. The beneficial effects of eplerenone in the EPHESUS trial exist for both PCI- and non-PCI-treated AMI patients with LVSD. The results show that eplerenone has minimal effect upon reducing PCI-related adverse events in the PCI-treated cohort. This work is a joint idea between the Candidate and his international collaborators.

Eplerenone, as an MRA medication, can be used for patients with myocardial infarction and it can also help in reducing the infarct size reduction which is an added benefit to the heart of the patient. The information regarding the use of eplerenone in post AMI patients is very informative and it helps to guide the Cardiologists to make better decisions for the benefit and outcome of patients. Moreover, the drug has been shown to save lives in large scale trials. Eplerenone, in comparison to other MR antagonists, is expensive but the benefits of the medication are exclusive and long-term and as a result, its clinical use is very cost- effective in the long run.

From the results, this important international cardiac study concluded that the beneficial effects of eplerenone on heart failure events and frequent hospitalization seen in the EPHESUS trial are similar for both PCI-treated and non-PCI-treated AMI patients with LVSD. The data also revealed that there is no evidence that MRA, eplerenone reduces the risk of recurrent ischemia-related events including recurrence of angina or the need for repeat revascularization. As such, the recommendation is that eplerenone is extremely useful in AMI patients with LVSD. Nevertheless,

the study also had some limitations. It is a post-hoc analysis with inherent shortcomings of any such study. Patients in the EPHESUSPCI cohort did not have routine angiographic follow-up to documentary effect of eplerenone on angiographic restenosis. However, the assessment of clinical events in this study was perhaps more relevant than angiographic outcomes.

Manuscript 13. Parviz, Y., Iqbal, J., Pitt, B., Adlam, D., Al-Mohammad, A, and Zannad, F.. (2015). Emerging cardiovascular indications of and mineralocorticoid receptor antagonists. Trends in Endocrinology and Metabolism, (4):201-211 (26.10.1016/j.tem.2015.01.007), **(Impact Factor: 12.015 and 31 citations).**

This was both a novel and landmark paper on the mineralocorticoid receptor (MR) antagonism. The paper received a very high impact factor 12.015 and it highlighted the established treatment modality for patients with hypertension, heart failure, and left ventricular systolic dysfunction (LVSD) with post-myocardial infarction (MI). It also emphasized the emerging data which revealed potential benefits of MR antagonists in other cardiovascular conditions. Studies have shown an association between MR activation and the development of myocardial fibrosis, coronary artery disease (CAD), metabolic syndrome, and cerebrovascular diseases. This review examined the preclinical and clinical data of MR antagonists for novel indications including heart failure with preserved ejection fraction (HFPEF), pulmonary arterial hypertension (PAH), arrhythmia, sudden cardiac death, valvular heart disease, metabolic syndrome, renal disease, and stroke. MR antagonists are not licensed for these conditions yet; however, emerging data suggest that indication for MR antagonists are likely to broaden; further studies are warranted. All the authors in this article are well established leaders in the subject of MR antagonism.

It is particularly noteworthy that the beneficial effects of MR antagonism have been robustly demonstrated previously for patients with hypertension and heart failure due to LVSD. Moreover, newer MR antagonist was shown to reduce the hospitalization rate in patients with HF-PEF. However, the emerging data in the literature suggested that MR antagonists might also have a role in the treatment of other cardiac and vascular conditions including atrial fibrillation, pulmonary hypertension, renal failure, and stroke. The beneficial effects of MR antagonists in these conditions

have been shown in pre-clinical or small-scale clinical studies; adequately powered randomized trials are warranted to confirm these findings. This paper has given insight into the utility of these agents in rare conditions that can be treated by these agents.

2.6 (C). Infarct Size and endothelial function

14.Parviz, Y., Vijayan, S., and Lavi, S. (2017). A Review of Strategies for infarct size reduction during acute myocardial infarction. Cardiovascular Revascularization Medicine, vol and Cardiovascular Revascularization Medicine, 18(5): 374-383. (doi: 10.1016/j.carrev.2017.02.004. (18. 10.1016/j.carrev.2017.02.004), (**Impact Factor: 1.168 and 15 citations).**

15.Parviz, Y., Waleed, M., Vijayan, S., Adlam, D., Lavi, S., Nooryani, A., Iqbal, J., and Stone, Gregg. (2018). Cellular and Molecular Approaches to Enhance Myocardial Recovery After Myocardial Infarction. Cardiovascular Revascularization Medicine, 20: Cardiovascular Revascularization Medicine. 20(4):351-364. (doi: 10.1016/j.carrev.2018.05.021. Epub , (**Impact Factor: 1.168 and 32 citation).**

16.Parviz, Y., Hsia, C., Alemayehu, M., Wall, S., Bagur, R., Abu-Romesh, N., Chin-Yee, I., and Lavi, S. (2016). The effect of fresh versus standard blood transfusion on microvascular endothelial function. American Heart Journa,181:156-161. (10.1016/j.ahj.2016.05.021. **(Impact Factor 4.749 and 1,315 citations).**

2.7 Advancement and understanding of the science to enhance knowledge in each of these three areas of infarct size reduction and endothelia function.

Manuscript 14. Parviz, Y., Vijayan, S., and Lavi, S. (2017). A Review of Strategies for infarct size reduction during acute myocardial infarction. Cardiovascular Revascularization Medicine, vol and Cardiovascular Revascularization Medicine, 18(5): 374-383. (doi: 10.1016/j.carrev.2017.02.004. (18. 10.1016/j.carrev.2017.02.004), (**Impact Factor: 1.168 and 15 citations).**

This reviewed article with an impact factor of 1.168 and citation of 15 was the brainchild of the Candidate based on original ideas, including ischemic cascade, microvascular obstruction, assessing infarct size and therapies for infarct size reduction in the field of infarct size reduction in the treatment of CAD. It was the Candidate's conception which he thought about, employing various strategies as to how it was possible to reduce the damage of heart muscle after an anginal heart attack. This work was done in Western University Canada in collaboration with world leaders in the field of infarct size reduction.

Post-infarct complications such as heart failure continue to be a major contributor to cardiovascular morbidity and mortality. Inadequate micro vascular reperfusion leads to worse clinical outcomes and potential strategies to reduce infarct size during periods of ischemia–reperfusion can improve outcomes. The advice from the paper is that Clinicians need to be aware of these findings and carefully follow and observe the various strategies as outlined in the article. In summary, numerous cardio-protective strategies have been tried to help in reducing the infarct size during CAD. Although various agents have shown benefit in small proof of concept studies, identifying a single therapy specifically designed for infarct size reduction in large clinical studies has been unsuccessful so far. Keeping in view the available evidence in this field, Cardiac Clinicians can now use their clinical acumen with evidence and can potentially employ a combination of various therapies tailored to the individual patient.

Manuscript 15. Parviz, Y., Waleed, M., Vijayan, S., Adlam, D., Lavi, S., Nooryani, A., Iqbal, J., and Stone, Gregg. (2018). Cellular and Molecular Approaches to Enhance Myocardial Recovery After Myocardial Infarction. Cardiovascular Revascularization Medicine. 20(4):351-364. (doi: 10.1016/j.carrev.2018.05.021. Epub, (**Impact Factor: 1.168 and 31 citation).**

This manuscript was based on the original and novel idea by the Candidate in the field of cardiac infarct size reduction. This was the second article published in the field (see MS 14 for comparison) in collaboration with seven world leaders who also work on infarct size reduction. The study was based on the idea and conception thought out by the candidate about various strategies and future

research knowledge, understanding and scope for the best way forward in reducing the damage of heart muscle after an anginal heart attack. This work was done at Columbia University in New York and was co-authored with Professor Gregg Stone who is an authority in the field of cardiovascular medicine. This article has an impact factor of 1.168 and with 31 citations in the field of infarct size reduction.

This study was designed to examine the preclinical and clinical evidence for the reduction of infarct size with such clinical strategies and interventions as anti-inflammatory agents, intracellular ion channel modulators, agents affecting the reperfusion injury to salvage kinase (RISK) and nitric oxide signaling pathways, modulators of mitochondrial function, anti-apoptotic agents and stem cell and gene therapy to repair the infarct area. The study reviewed the potential reasons of failures to date and the potential for new strategies to further promote myocardial recovery and improve prognosis.

Based on this study, numerous agents have been demonstrated to reduce infarct size in preclinical models. However, there is limited clinical evidence of benefit to date. As such, emerging strategies affecting valid molecular and cellular targets require further study, especially in humans. Rather than a "one size fits all" approach, individualized tailored therapies may be required for patients with either selected clinical, myocardial, or genetic/cellular characteristics. Nevertheless, these findings have potential and great significance as they can help in making decision when choosing various treatment agents after a myocardial infarction to reduce the damage to myocardium and improve the clinical outcomes in the patients. It is also worth noting that many of the agents outlined in the study are very cost-effective and readily available in clinical practice.

Manuscript 16. Parviz, Y., Hsia, C., Alemayehu, M., Wall, S., Bagur, R., Abu-Romeh, N., Chin-Yee, I., and Lavi, S. (2016). The effect of fresh versus standard blood transfusion on microvascular endothelial function. American Heart Journal,181:156-161. (10.1016/j.ahj.2016.05.021. **(Impact Factor 4.749 and 1,315 citations).**

This was an original research paper that had an impact factor of 4.749 but with a very large citation of 1,315 in the field of blood transfusion and endothelial dysfunction. The high citation is a testimony of its importance in the field of research. This research work was conducted at Western University, London, Ontario. The Candidate designed the study, carried out the experiments and he also collected, compiled, and analyzed data. This was a major work in the field of blood transfusion, with significant clinical impact. The duration of red blood cell (RBC) storage may have a negative impact on endothelial nitric oxide bioavailability. The research tested the hypothesis that transfused fresh blood would have a more favorable effect on micro-vascular endothelial function as compared to older standard issue blood. The results demonstrated that transfusions of standard issue blood are associated with less favorable effect on micro-vascular endothelial function as compared to fresh blood. The Candidate was the main contributor and first author of the study. He reviewed the literature and wrote the manuscript. His contribution was 75 % to this paper. The other authors also participated in the review of the literature and in writing some parts of the manuscript. This article is widely and well cited in the field of blood transfusion.

The duration of red blood corpuscle (RBC) storage may have a negative impact on endothelial nitric oxide bioavailability. As such, it was relevant to test the hypothesis that transfused fresh blood would have a more favorable effect on micro-vascular endothelial function as compared to older standard issue blood.

Twenty-one patients (71 ± 16 years, 52% females) were enrolled. The mean age of fresh blood was 5.5 days (±1.0), and that of standard blood was 24.5 days (±7.9 days). The pretransfusion hemoglobin was 83.1 ± 2.5 g/L; and post transfusion, 98.9 ± 2.6 g/L. An average of 2 U of packed RBCs were transfused. Microvascular endothelial function decreased more frequently after transfusion of standard blood compared to fresh blood. Standard issue blood transfusion was associated with decrease in reactive hyperemia peripheral arterial tonometry index (−0.25 ± 0.63) compared to fresh blood (+0.03 ± 0.49); P = .026. This is a novel study in the field of blood-transfusion and it is now helping clinicians in making strong and more confident decisions about the type of blood to transfuse in different clinical settings. Availability of fresh blood is always not possible, and hence, awareness about the implications of stored RBCs transfusions is of significant

clinical importance. The Government, via the Ministry of Health, should make public awareness about the blood donation campaigns and have as much fresh blood available as possible for transfusion and treatment of the patients.

The study had some limitations including a small number of participants and therefore, the results might be impacted by inter-variability and intra-variability of the Endo-PAT test. Nevertheless, it was of paramount importance to investigate the benefits of fresh blood infusion to patients with fatal hematology and cardiovascular disorders. The long-term impact of repeat blood transfusions was not yet undertaken when this study was done. However, the measurements obtained by the Endo-PAT reflect the microcirculation, and therefore, the results of this study did not reflect the effect of blood transfusion on conduit vessel endothelial function. The study concluded that transfusion of standard issue blood product had a negative acute impact on microvascular endothelial function.

2.8 Discussion and Conclusion

Coronary heart disease (CAD) is a type of heart disease where the coronary arteries of the heart cannot deliver enough oxygen-rich blood to the myocardium due to the deposit of fatty materials leading to blockage. This process is referred to as atherosclerosis, where a plaque becomes clogged up in the medium and large arteries of the heart. If left untreated, it hardens and narrows the arteries over a period of years, thus reducing the flow of oxygen-rich blood to organs and other parts of body, and leading to serious problems, such as myocardial/cerebral infarction, or even sudden cardiac deaths globally in both developed and developing countries [1]. The initial choice of medical technologies for the diagnosis of CAD depends on the patient's state and history. In general, invasive coronary angiography (ICA) is prescribed to specify the nature and extent of the coronary lesions. This study, which comprised of sixteen research papers, is related to CAD in terms of intracoronary imaging and physiology or blood flow, mineralocorticoids antagonism in treating cardiovascular diseases and infarct size reduction and endothelial function. The data presented in the sixteen research papers have played major roles in current understanding of clinical medicine for the diagnosis and treatment of CAD and thus, impacted tremendously on the

advancement of science and in understanding the problem incurred with the diagnosis of CAD and its treatment to obtain a good clinical outcome.

In conclusion, the sixteen research papers presented in this study for a PhD by Publication were published in high impact journals with 4 papers had impact factor between 11-15: 4 papers between 4-6 and 8 papers between 0.4-3. Except for 3 papers, the rest had good citations with one of them obtaining 1,315 citations. The eight papers which received high scores were original studies with an international flavor. In general, international studies usually score high in terms of impact factor and they sometimes receive high citations as well. The other eight papers were both original and reviews and they were published in journals with moderate impact factor. Nevertheless, they were well cited for their originality and comprehensive nature in the field. The sixteen published papers focused mainly on diagnosis and novel surgical, fresh blood and drug treatments of coronary artery diseases (CAD). Some of the studies also employed new and novel surgical treatments for diagnosis including intravascular ultrasound, intracoronary imaging, venous graft interventions, intra coronary imaging and physiology, optical coherence tomography, pressure wire compared to microcatheter sensing, external elastic lamina vs. luminal diameter measurement technique and others. In summary, the sixteen published papers have enhanced knowledge and understanding about plaque formation in coronary arteries, the diagnosis and how the disease can be treated safely with drugs, and various revascularisation techniques to give the patients a longer and better quality of life.

CHAPTER 3

PERSONAL CONTRIBUTION TO EACH PUBLICATION

3.1 Introduction

The Candidate had the privilege and honor to work with world leaders in the field of CAD focusing specifically on intracoronary imaging and physiology, mineralocorticoids antagonism in treating cardiovascular diseases and infarct size and endothelial function. He developed an early interest in the field during his career progression. Over the years, he has been actively involved in clinical research in this exciting field of intracoronary imaging and physiology and other areas relating to diagnosis and treatment of CAD to help in improving the successful outcomes in patients who developed atherosclerosis. Most of his research experience and outputs in clinical research was done at Sheffield University Hospital UK, Western University Canada and Columbia University New York, USA where he gained his expertise in the field of cardiology.

Moreover, he has been the leader, driving force and brainchild of a significant number of publications employed in the thesis and submitted to UCLAN for PhD by Publication. In addition, he has been collaborating with colleagues in the United Kingdom, United States, Canada, and other parts of world in publishing several joint papers on intracoronary imaging and physiology presented in this thesis.

His main collaborators were Cardiovascular Research Foundation, Columbia University of New York, and Western University Canada. Professor Jaipaul Singh encouraged me to submit this work for PhD by publications and that he would be happy to act as my Director of Study. He also supervised me for the MSc by research at UCLAN.

Overall, contributions of the chief investigator or the candidate to the publications include original formulation of the research ideas and topics, literature review, study designs and methodologies, laboratory work, data collection and analysis, preparation, and writing, as well as reviewing all the manuscripts.

Professor Jaipaul Singh, who supervised 77 research students including PhD by publication at UCLAN is part of the supervisory team. He also holds the prestigious degree of DSc via his numerous publications as your mentor and part of the supervisory team. The local supervisor in

Dubai is Professor Ernest Adeghate who is medically qualified and holds both the PhD and DSc and works in the areas of diabetes and cardiovascular biology.

The main objective of this chapter is to summarize the personal percentage input and contribution made by the candidate to each selected for PhD by publications compared to his co-authors.

3.2 (A). Intra-coronary Imaging and Physiology

Manuscript 1. Parviz, Y., Fall, K., Stone, G., Maehara, A., Ben-Yehuda, O., Mintz, G., and Ali, Z. (2017). Imaging and Physiology to Guide Venous Graft Interventions Without Contrast Administration in Advanced Renal Failure. The Journal of Invasive Cardiology, 29: E163-E165, **(Impact Factor 1.07 and 6 citations).**

This was an important commentary paper based on the utility of intracoronary imaging during complex clinical scenarios. The Candidate demonstrated the utility of Intravascular ultrasound (IVUS) in various clinical settings. This was his original idea, and he wrote the manuscript for publication. He also contributed more than 80% in the article. This article has 6 citations. The other authors helped with the reviewing process of the manuscript.

Manuscript 2. Parviz, Y. (2017). Intra coronary imaging to detect mal apposition: Are We Seeing Too Much. Heart. (A BMJ Journal), 103 (9): Article 2017; 0- heartjnl-2015-307888v1) (**Impact Factor 5.42 and no citation).**

This was an invited editorial letter written personally by the Candidate to the Editor of BMJ as an expert commentary about intracoronary imaging. This was his original idea, and he did all the literature search and tabulated the results for analysis. In this letter, he discussed the detailed assessment of intracoronary imaging of coronary vessels and at times when Clinicians were seeing too much detailed information as to how to act in making a clinical decision. The Candidate discussed the various mal appositions and long-term consequences. He made a 100% contribution for this paper. Although the abstract article had a high impact factor, it received no citation.

Manuscript 3. Parviz, Y., Evan, S., Khady N.F., Maayan K., Akiko, M., Allen, J., Richard, A.S., Gary, S.M., and Ziad A.A. (2017). Utility of intracoronary imaging in the cardiac catheterization laboratory: comprehensive evaluation with intravascular ultrasound and optical coherence tomography. British Medical Bulletin, 125(1):79-90. (doi: 10.1093/bmb/ldx049. **(Impact Factor: 3.045 and 18 citations).**

This was a landmark paper in which the Candidate was the main author. He wrote a comprehensive review of the utility of intracoronary imaging and physiology in coronary disease. This article was standard review article in the field of intracoronary imaging and physiology and the authors demonstrated various techniques that could be used in the cardiac catheterization laboratory. Moreover, the candidate was also the main contributor, and involved in collection, compilation, and analysis of data. He made a major contribution and was the first author in this state- of the art paper. His contribution to the publication of this novel paper was more than 70% on the subject. His co-authors in this of paper were all experts in the field of intracoronary imaging and physiology and together, they contributed 30%. The paper had 18 citations.

Manuscript 4. Parviz, Y., P., Khady N.F., and Ziad A.A (2016). Using sound advice—intravascular ultrasound as a diagnostic tool. Journal of Thoracic Diseases. 8(10): E1395-E1397. (doi: 10.21037/jtd.2016.10.64. 10.21037/jtd.2016.10.64, **(Impact Factor: 2.365 and 3 citations).**

In this exciting paper, the Candidate was the leading author and demonstrated the utility of intracoronary imaging and physiology in managing complex disease processes of Graft interventions with no contrast use. The paper was the brainchild of the Candidate and he worked with his supervisor at Columbia University New York and wrote the manuscript for publication. His contribution was more than 80% on the subject. This article has been cited in three references in the field of imaging and physiology. The two other authors made 20% contributions to the paper.

Manuscript 5. Chin, C., Matsumura, M., Maehara, A., Zhang, W., Lee, C., Yamamoto, M., Song, L., **Parviz, Y.,** Jhalani, N., Mohan, S., Ratner, L., Cohen, D., Ben-Yehuda, O., Stone, G., Shlofmitz, R., Kakuta, T., Mintz, G., and Ali, Z. (2017). Coronary plaque characteristics in haemodialysis-dependent patients as assessed by optical coherence tomography. American Journal of Cardiology,119(9): 1313-1319. (doi: 10.1016/j.amjcard.2017.01.022. Epub 2017 Feb 9. **(Impact factor: 2.26 and no citation).**

This was a landmark paper by the Candidate during his fellowship at Columbia University New York. He had a keen interest in the management of patients with chronic kidney disease (CKD) and in this paper the authors investigated the various plaque morphologies in CKD patients using optical coherence tomography (OCT). The Candidate actively contributed to this paper and this research was based on his idea. He was involved in experimental design, data collection, compilation, and analysis of data. He was also involved in writing the manuscript. His contribution was about 45%. The other authors contributed 55% to the successful outcome of the manuscript. Unfortunately, the paper had no citation.

Manuscript 6. Parviz, Y., Awan, K., Vijayan, S., Sultan, A., and Iqbal, J. (2017). Role Of Intra Coronary Imaging and Physiology in Diagnosis and Management of Coronary Artery Disease. Journal of Ayub Medical College, Abbottabad: JAMC. 29: 516-522. **(Impact Factor 0.481 and no citation).**

This was an important paper on the utility of intracoronary imaging and physiology in the coronary artery disease. The Candidate was one of the main contributors and he was also involved in collection, compilation, and analysis of data. Moreover, the paper was based on his original idea and understanding of the subject area. He designed all the proforma and manuscript and wrote up the work for publication. He made a major contribution in the paper in excess 70 %. The other authors assisted in the literature review and review of the manuscript and their contribution was 30%. The paper had a low impact factor and no citation.

Manuscript 7. Mamamoto, M.H., Maehara, A., Karimi, G.K, Mintz, G.S., **Parviz. Y**., Kim, S.S., Koyama, K., Amemiya, K., Kim, S.Y., Ishida, M., Losquadro, M., Kirtane, A.J., Haag. E., Sosa, F.A., Stone, G.W., Moses, J.W., Ochiai, M., Shlofmitz, R.A., and Ali Z.A. (2017). Mechanisms of Orbital Versus Rotational Atherectomy Plaque Modification in Severely Calcified Lesions Assessed by Optical Coherence Tomography. JACC Cardiovascular Intervention, 10(24): 2584-2586. (doi: 10.1016/j.jcin.2017.09.031. PMID: 29268891), (**Impact Factor: 11.2 and no citation found).**

During this investigation, the authors studied the comparison of two different techniques for modifying the calcified plaques in the coronary arteries in the heart. These techniques have different mechanisms of actions to ablate the calcified plaques. This was a collaborative research work that was done by the authors from various institutions in USA, UK, and Japan. The Candidate was involved in the formulation, conception, design, and analysis of data. He contributed 30% to the work. The other authors assisted in the literature review, the data collection and reviewing of the manuscript prior to publication. Together, they made 70% to the successful outcome of the paper. No citation was found for this paper although it obtained a high impact factor.

Manuscript 8. Ali, Z., **Parviz, Y.,** Brinkman, M., Matsumura, M., Redfors, B., Brogno, D., Corral, M., Fall, K., Mintz, G., Stone, G., Maehara, A., Jeremias, A., and Kirtane, A. (2018). Pressure Wire Compared to Microcatheter Sensing for Coronary Fractional Flow Reserve: The PERFORM Study. Euro-Intervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 14(4): e459-e466. doi: 10.4244/EIJ-D-18-00064. **(Impact Factor 6.534 and 5 citations).**

This was a largescale head- to- head comparison of pressure wire vs micro catheter for coronary fractional flow reserve. The authors demonstrated that introduction of micro catheter could reduce the device success and hyperemic and resting Pd/pa and can reclassify the FFR into ischemic zone in 1/5 cases. This work was done at Columbia University New York in collaboration with world leaders in the field of intracoronary physiology. The candidate was the main author who was

involved in designing the study, collection of data, and writing up the manuscript. He contributed 60 % to this paper. The other authors assisted in the data collection and analysis, review of the manuscript and some of the literature review. Their contribution was 30%. The paper had a high impact factor but with only 5 citations.

Manuscript 9. Shlofmitz, E., Jeremias, A., **Parviz, Y.,** Karimi, G.K., Redfors, B., Petrossian, G., Edens, M., Matsumura, M., Maehara, A., Mintz, G., Stone, G., Shlofmitz, R., and Ali, Z. (2020). External elastic lamina vs. luminal diameter measurement for determining stent diameter by optical coherence tomography: an ILUMIEN III sub-study. European Heart Journal of Cardiovascular Imaging. 22(7):753-759. doi: 10.1093/ehjci/jeaa276 **(Impact Factor: 6.875 and no citation).**

This was a landmark study where the authors studied the various measurement techniques for sizing the stent for coronary intervention. In this study the authors demonstrated that EEL-based-stent downsizing led to selection of larger stent diameters vs. LD upsizing. This research was done at Columbia University in New York in collaboration with world leaders in the field of intracoronary imaging. The Candidate was involved in the data collection, and he also wrote part of the manuscript. His contribution 30 % to the paper. The other authors assisted in data collection and analysis, review of the manuscript and some of the literature review. Together, their contribution was 30%. r contribution was 30%. The paper had a high impact factor but with no 5 citations.

Manuscript 10. Israeli, Z., Bagur, R., Murariu, D., Wall, S., Alemayehu, M., **Parviz, Y**., Diamantouros, P., and Lavi, Shahar. (2017). Nitro-glycerine-Derived Pd/Pa for the Assessment of Intermediate Coronary Lesions. The Journal of Invasive Cardiology. 29(12): E177-E183. **Impact Factor:1.07 and 1 citation).**

The Candidate was involved in this exciting study during his clinical fellowship at Western University Canada. He was involved in the design, collection, compilation, and analysis of data. Moreover, he was contributing actively as the first operator in performance of the procedure of coronary physiology. As a team of Cardiology Interventional Fellows, the authors worked together for performance of procedure, collection, compilation, and analysis of data. This was a landmark paper on intracoronary physiology. The contribution of the candidate was 40%. The contribution by the other authors was 60%. This paper had both low impact factor and citation.

3.3 (B). MR Antagonism and cardiovascular diseases

Manuscript 11. Iqbal, J., Parviz, Y., Pitt B, Newell-Price, J., Al-Mohammad, A., and Zannad, F. (2014). Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure. European Journal of Heart Failure, 16(2):143-150. (doi: 10.1111/ejhf.31. PMID: 24464876), **(Impact Factor of 15.534 and 52 citations).**

This was a landmark and high impact paper with 52 citations on the mineralocorticoid receptor (MR) antagonism. This review examined the preclinical and clinical data of MR antagonists for novel indications including heart failure (HF) with preserved ejection fraction (HFPEF), pulmonary arterial hypertension (PAH), arrhythmia, sudden cardiac death (SCD), valvular heart disease *VHD), metabolic syndrome, renal disease, and stroke. The candidate reviewed the methodology and wrote the manuscript. His contribution to this paper was 45%. The other authors assisted in the data collection, review of the manuscript and literature review. Together, they made 55% contribution to the successful outcome of the manuscript.

Manuscript 12. Iqbal, J., Fay, R., Adlam, D., Squire, I., **Parviz, Y.,** Gunn, J., Pitt, B., and Zannad, F. (2014). Effect of eplerenone in percutaneous coronary intervention-treated post-myocardial infarction patients with left ventricular systolic dysfunction: A sub-analysis of the EPHESUS trial. European Journal of Heart Failure, 16: 685–691, (16.10.1002/ejhf.88**. (Impact Factor 15.534 and 24 citations).**

This was a collaborative research study involving world leaders in the field of MR antagonists. This work is a joint idea between the Candidate and his colleagues. He reviewed the methodology including the questionnaire, analyzed the data and wrote part of the manuscript. He contributed about 40% to this high impact paper. The other authors assisted in the data collection, review of the manuscript and literature review. Together, they made 60% contribution to the paper. This article had a very high factor accompanied by 24 citations.

Manuscript 13. Parviz, Y., Iqbal, J., Pitt, B., Adlam, D., Al-Mohammad, A.,and Zannad, F.. (2015). Emerging cardiovascular indications of mineralocorticoid receptor antagonists. Trends in Endocrinology and Metabolism, April 2015, Vol. 26 (4):201-211 (26.10.1016/j.tem.2015.01.007), **(Impact Factor: 12.015 and 31 citations).**

This was a landmark high impact paper of 12.015 with 31 citations on the Mineralocorticoid receptor (MR) antagonism and somewhat related to manuscript 11 above. Like manuscript 11, the authors highlighted the established treatment modality for patients with hypertension, heart failure and left ventricular systolic dysfunction (LVSD) and post-myocardial infarction (MI). The Candidate did a thorough review of the subject area regarding the emerging data and the potential benefits of MR antagonists in other cardiovascular conditions. This work was the original idea of the Candidate, and he formulated the questionnaire, analyzed the data, and wrote the manuscript. He contributed 65 % to this paper. The other authors assisted in the data collection, review of the manuscript and literature review. They contributed 35% to the paper. It is particularly noteworthy that the Co- authors in this article are well established leaders in the subject of MR antagonism.

3.4 (C). Infarct Size and endothelial function

Manuscript 14. Parviz, Y., Vijayan, S., and Lavi, S. (2017). A Review of Strategies for infarct size reduction during acute myocardial infarction. Cardiovascular Revascularization Medicine, vol and Cardiovascular Revascularization Medicine, 18(5): 374-383. (doi:

10.1016/j.carrev.2017.02.004. (18. 10.1016/j.carrev.2017.02.004), (**Impact Factor: 1.168 and 15 citations).**

This manuscript was the idea and brainchild of the Candidate in the field of infarct size reduction. It was his conception, and he thought about various strategies in helping to reduce the damage of heart muscle after a heart attack. He was the main contributor of the paper, and he reviewed the literature and wrote the manuscript. This work was done at Western University Canada in collaboration with world leaders in the field of infarct-size reduction. The Candidate was mainly involved in designing study, with data collection and writing up the manuscript. He contributed 60 % to the paper. The other authors assisted in the literature review, data collection and analysis and in reviewing of the manuscript. Together they contributed 40% to the successful outcome of the manuscript. The paper, although with a reasonable impact fact, had a citation of 15.

Manuscript 15. Parviz, Y., Waleed, M., Vijayan, S., Adlam, D., Lavi, S., Nooryani, A., Iqbal, J., and Stone, Gregg. (2018). Cellular and Molecular Approaches to Enhance Myocardial Recovery After Myocardial Infarction. Cardiovascular Revascularization Medicine. 20(4):351-364. (doi: 10.1016/j.carrev.2018.05.021. Epub , (**Impact Factor: 1.168 and 32 citation).**

10.1016/j.carrev.2018.05.021. Epub, (**Impact Factor: 1.168).**

This manuscript is the original idea of the Candidate in the field of infarct size reduction. This was the second article published in the field in collaboration with world leaders who also worked on infarct size reduction. The idea in designing, undertaking a thorough literature review and the study was the original conception of the Candidate. He thought about various strategies, scope for future research ideas and how to help in reducing the damage of heart muscle after a heart attack. This work was done at Columbia University New York, and was co-authored with Professor Gregg Stone, an authority in the field of cardiovascular medicine. The Candidate was a main contributor, and he was involved in designing the study, collecting the data, formulating, and writing the

manuscript. He contributed 60 % to the paper. The other authors assisted in the data collection and analysis, and review of the manuscript. Together, they made 40% contribution to the successful outcome of the paper. The article is well cited in the field of infarct size reduction. The paper had a good impact factor but with a good citation of 32.

Manuscript 16. Parviz, Y., Hsia, C., Alemayehu, M., Wall, S., Bagur, R., Abu-Romesh, N., Chin-Yee, I., and Lavi, S. (2016). The effect of fresh versus standard blood transfusion on microvascular endothelial function. American Heart Journal,181:156-161. (10.1016/j.ahj.2016.05.021. **(Impact Factor 4.749 and 1,315 citations).**

This was an original research paper with a high impact factor which was accompanied with a very high citation of 1,315 in the field of blood transfusion and endothelial dysfunction. This work was conducted at Western University, London, Ontario. The Candidate designed the proforma and was involved in collection, compilation, and analysis of data. This was a major work in the field of blood transfusion, with significant clinical impact. The duration of red blood cell (RBC) storage may have a negative impact on endothelial nitric oxide bioavailability. The authors tested the hypothesis that transfused fresh blood would have a more favorable beneficial effect on microvascular endothelial function as compared to older standard issue blood. Transfusions of standard issue blood are associated with less favorable effect on microvascular endothelial function as compared to fresh blood.

The Candidate was the main contributor and first author of the study. He reviewed the literature and wrote the manuscript. He contributed 75 % to this paper. The other authors also participated in the review of the literature and the writing of the manuscript. Together they made 25 % contribution to the manuscript. This landmark article is well cited in the field of blood transfusion.

3.5 Conclusion

The sixteen research papers presented in chapter 3 of this thesis for PhD by Publication have clearly demonstrated the important roles played by the candidate in collaboration with his co-authors in the conception of the study, undertaking thorough literature in the different subject area, undertaking the experiments and clinical studies, collecting, and analyzing the data, writing up the papers for publications, submitting the papers and revising and correcting the galley proof before publication. In most of the publications he played a leading role, more than 50%, to achieve a successful outcome for each paper. These academic tasks are an integral part of the training for each PhD student. In addition, he has demonstrated that he possesses excellent communication skills, curiosity as a scientist and clinician, love for learning, conscientious in his work, attention to scientific and clinical details, good project organization and time-management skills, ability to work alone and willingness to collaborate with others and being persistence and resilience at time. Moreover, he possesses vast experience in literature search, experimental design, and clinical experimentations, as well as writing manuscripts successfully for publication in high impact scientific or medical journals. These undertakings strongly support his candidacy for the PhD by Publication. Most of the papers presented in this study on CAD have high impact factor and citations and they helped to explain the problems facing the clinicians when they are treating a patient with atherosclerotic plaque, especially with difficulty involving diagnosis and treatment.

CHAPTER 4

GENERAL DISCUSSION

4.1. Introduction

Cardiovascular diseases (CVDs) are a leading cause of morbidity and mortality globally. When CVDs are combined with either ischemic or coronary heart disease and all forms of stroke, they become the attributed causes of deaths for an estimated 13 million people worldwide in 2010, 17 million in 2013 and 19.9 million in 2019 representing 32% of all global deaths. Of these deaths, 85% were due to heart attacks and strokes [1a/b,2]. Heart disease is the leading cause of death for men, women, and people of most racial and ethnic groups in the Western World including, the United States of America (USA), United Kingdom (UK), the European Union (EU) and other developed countries globally. About 697,000 people die from heart diseases in the USA every year representing 1 in every 5 deaths. Coronary heart disease (CHD) is the most common type of heart disease, killing approximately 382,820 people annually in the USA in 2020 [1,2]. Every year, about 805,000 Americans have a heart attack and about 20.1 million adults aged 20 years and older have CAD (about 7.2%). These figures represent about 2 in 10 deaths from CAD among adults less than 65 years old [1a/b,9]. Moreover, heart diseases cost the USA Government about $229 billion each year from 2017 to 2018. This includes the costs of health care services (diagnosis and treatment including medicines) hospital and home caring and productivity loss due to the illness and death of the patients [1a/b,2]. What is worrying now is that people from low- and middle-income countries (LMIC) die from CVDs representing more than 80% of these cases. Although the risk factors for the development of CVDs are similar throughout the world, the evolving change in lifestyle and health behaviors in LMICs including tobacco use, excess alcohol intake, stress, decreased physical activity, unhealthy diets, obesity, genetic predisposition, and others are contributing to the escalating presence of CVDs and mortality [1a/b].

Since CAD is a major cause of sudden cardiac deaths globally over the years in high, middle- and low- income countries and with high economic cost, it was pertinent to address early diagnosis and treatment by the clinicians. The sixteen papers presented in this study cover three major areas of diagnosis and treatment of CAD including intracoronary imaging and physiology, infarct size reduction and hormones and hearts. The discussion will now focus in these areas of CAD, but first, it is of paramount importance to appreciate and understand a historic perspective of coronary

physiology and second to discuss critically the findings and clinical benefits of the results outlined in the sixteen research papers for PhD by Publication.

This discussion will now focus on the results obtained in the sixteen publications presented in the thesis for the award of the PhD by publications focusing on the three themes namely, intracoronary imaging and physiology (10 publications), antagonism and cardiovascular diseases (3 publications) and infarct size reduction and endothelial function (3 publications).

4.2. Intracoronary imaging and physiology

Firstly, it is relevant to understand what intracoronary imaging is and how it is related to the physiology of the lesions and plaque.

4.2 (A) A historical perspective of coronary physiology

Physiological assessment of lesions is of paramount importance to avoid unnecessary stenting. Likewise, angiography-derived physiological assessment must be involved to enable the s the operating physician to reconstruct the 3D coronary anatomy from two angiographic projections ≥30° apart. A physics-based, mathematical solution is then applied to calculate the translational pressure drop and the 'virtual' FFR (vFFR). The concept of coronary physiology was first introduced in the first percutaneous coronary intervention (PCI) performed by Andreas Grüntzig on September 16, 1977. He used a fluid-filled guiding catheter to measure the trans-stenotic pressure before and after PCI. Hence, the concept of measuring the pressure gradient post procedure is crucial as well [82]. Despite this early introduction of coronary physiology in interventional cardiology, practical use in the catheterization laboratory did not begin until the late 1990s. Several challenges, including technological and theoretical aspects, as well as the unavailability of mature pressure wires, hindered the adoption of coronary physiology [24, 27].

4.2 (B). Intracoronary imaging

Intracoronary imaging provides a more precise assessment of lesions and moreover, it is a critical step when deciding whether the lesion needs to be prepared with atherectomy devices. Heavily calcified coronary artery lesions hinder the delivery of devices and limit stent expansion. As such, this results in low procedural success and poor clinical outcomes driven by an increase in restenosis and stent thrombosis. Intracoronary imaging provides a more precise assessment of lesions and is a critical step when deciding whether the lesion needs to be prepared with atherectomy devices. Physiological assessment of lesion significance is an important consideration to avoid unnecessary stenting.

The modern concept of intracoronary physiology was presented by Dr. Nico Pijls and Bernard De-Bruyne through the introduction of fractional flow reserve (FFR). The relationship between coronary pressure and coronary flow was actively investigated after the notion of hyperemia was introduced. The popularity of FFR grew after advances in technology and theory facilitated its use. Currently, coronary physiology plays a vital role in the decision-making process during cardiac catheterization, with large-scale randomized data from multicenter international studies showing that FFR-guided decision-making is safe, effective, and rational [30].

Intracoronary imaging with intravascular ultrasound (IVUS) was invented by Dr. Paul Yock. Initial IVUS was grayscale, but rapid advances in intracoronary imaging technologies led to the introduction of new versions of imaging catheters. Currently, advanced HD imaging catheters, IVUS radiofrequency tissue characterization, virtual histology (VH)-IVUS, integrated backscatter IVUS, and i-Map are available. Optical coherence tomography (OCT) which was invented by Tunino, could be considered as the light analogue of IVUS with the advantage of higher resolution. This clinical tool can be useful in assessing and treating complex disease processes, and its utility in decision-making during and after procedures has been assessed in large-scale trials [83]. Intracoronary imaging and physiology clinical tools were initially used in research and their utility was not adequately understood in routine daily practice. However, with advances in the practice of cardiology and modern clinical cariology techniques, it has become more evident that these

medical tools have paramount clinical significance and can be routinely used for decision-making in the cardiac catheter laboratory [84].

During cardiac clinical practice, the clinicians routinely encounter scenarios that demand them to make rational and quick decisions about the significance of a disease in a coronary artery. While coronary angiography is the gold standard in interpreting CAD, there is a wide range of inter and intra-observer variability in reporting stenosis. Large-scale randomized trials, such as DEFER, FAME-I, and FAME-II, have established FFR as the gold standard for assessing the significance of a non-left main coronary artery (LMCA) lesion. The DEFER trial demonstrated that it was safe to defer percutaneous coronary intervention of lesions with an FFR >0.75. The FAME-I trial found that treating lesions with an FFR >0.80 using mostly first-generation drug-eluting stents (DES) was harmful, whereas not treating such lesions was cost-saving. The FAME-II trial found that treating lesions with an FFR less than 0.75 with medical therapy was harmful [85].

Coronary flow reserve (CFR**)** measures the relative increase in coronary flow velocity during maximal hyperemia, reflecting both epicardial stenoses and the microcirculation. Moreover, it is influenced by many diseased factors affecting the microcirculation, such as diabetes, ventricular hypertrophy, and prior myocardial infarction.

On the other hand, FFR can measure the actual volume of blood flow through a stenotic coronary artery as a percentage of normal hyperemic flow, because at maximum hyperemia, flow into a myocardial territory is proportional to pressure since the resistance is minimal and constant. FFR is independent of pressure, heart rate, contractility and status of the microcirculation and considers both antegrade and retrograde collateral blood flow, as well as the amount of viable myocardium. There has been a recent renewal of interest in resting indices, such as i-FR (instantaneous wave free ratio) or a hybrid approach combining i-FR and FFR. IFR has been validated in

4.3. Clinical Trials

There are several large-scale trials comparing invasive imaging criteria that are equivalent to FFR or non- invasive testing. It is noteworthy that the IVUS minimum lumen area (MLA) in non-

LMCA lesions is the parameter that best correlates with physiology since the reported IVUS MLA cutoff thresholds range from 2.1 to 4.4 ^{mm2}. These measurements have variations based on basal metabolic index (BMI) of patients and hence, are smaller in Asian patients than in studies of Western populations where the "most common" cutoff is approximately 3.0 ^{mm2}. Most IVUS studies show a relatively high negative predictive value but a low positive predictive value, indicating that using IVUS to justify the need for percutaneous intervention is wrong approximately one-half of the time [86, 87].

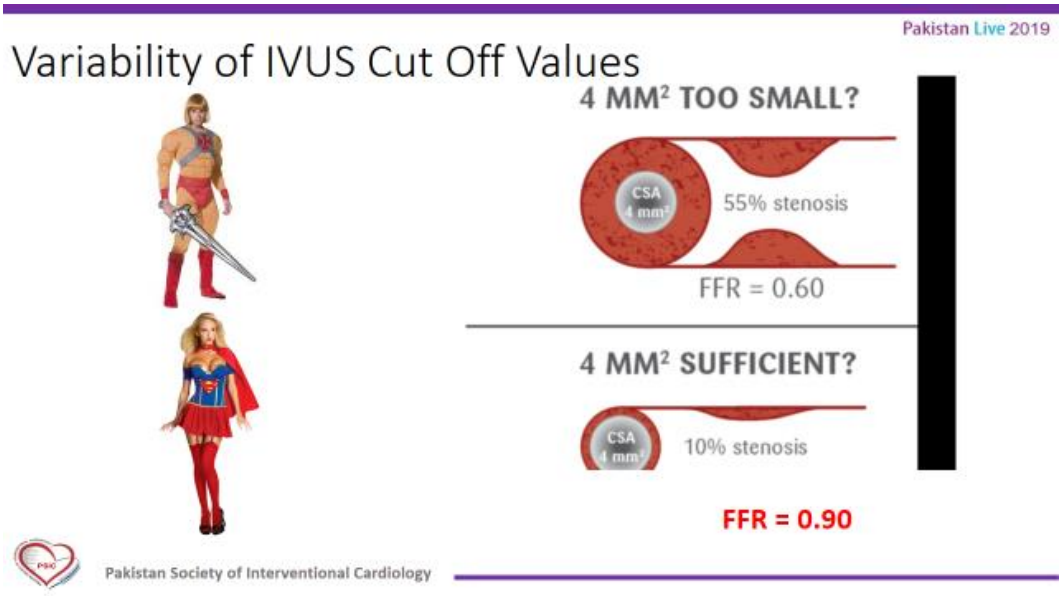
A study by de-la Torre Hernandez et al, [26], suggests that clinical outcomes are similar whether either IVUS or FFR is used to decide which lesions to stent or which to leave alone. There is observation that greater number of lesions and possibly patients are stented with IVUS compared with FFR (72% vs. 51.2%; $p < 0.0001$). There is no strong evidence to demonstrate the role of OCT detection of severity of stenosis. OCT-derived MLA cutoffs are smaller than with IVUS. Some studies have "corrected" for vessel size, but none has factored in subtended viable myocardium.

In PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) Study, non- fibroatheromas were associated with very few events at 3 years of follow-up. This suggests that tissue characterization and plaque composition may be an alternate method to predict lesion stability and defer intervention. The most crucial part of coronary artery tree is the left main coronary artery (LMCA) and the decision making in this region of artery needs to be meticulous to avoid any misinterpretations and hence, mistakes in treatment of individual patients. There are controversies in reporting the left main stem lesions and it has been demonstrated that angiographic studies (2 historic [31,32] and 2 contemporaries [33,34]) indicated that agreement among experts regarding the significance of an LMCA lesion is widely different and can be as low as 30% (see figure. 4.1A).

There have been 2 equivalent FFR and IVUS registry studies in patients with intermediate LMCA lesions in which an FFR >0.80 or an IVUS MLA >6.0 ^{mm2} was used to defer revascularization, with similar long-term results compared with patients with an FFR with an FFR with an FFR <0.80

or an MLA <6.0 mm^2 treated with revascularization [33,35]. A study by Jasti et al. [36] in Western patients indicated that an IVUS MLA <6 mm^2 in the LMCA is best correlated with an FFR <0.80. Likewise, a study in Korean patients suggested that 4.8 mm^2 was the preferred IVUS MLA cutoff [37], which is again consistent with the smaller MLA cutoffs found in Asian patients compared with Western patients. Both IVUS and FFR have limitations in assessing LMCA disease. Ideally, as demonstrated in figure 4.1A-E, when clinically indicated, IVUS should be performed from both the left anterior descending and left circumflex coronary arteries to define the MLA within the LMCA and to accurately assess disease at the left anterior descending and left circumflex ostia [38,39]. Patients with LMCA disease have not typically been included in the many FFR validation studies, and FFR may have limitations in the setting of a significant concomitant LAD stenosis.

(A)

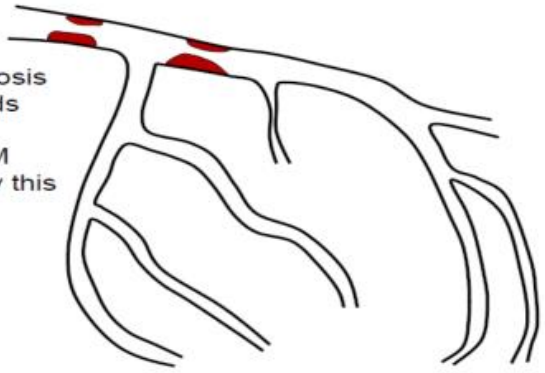


(B)

Left Main Stem Stenoses are Rarely Isolated

The influence of a distal stenosis on the FFR of the LM depends on the extent to which hyperemic flow across the LM stenosis will be decreased by this distal lesion

- Severity
- Myocardial mass



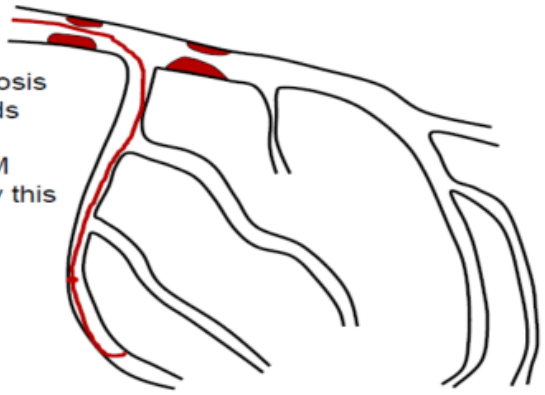
Courtesy Bernard De Bruyne, MD, PhD

(C)

Left Main Stem Stenoses are Rarely Isolated

The influence of a distal stenosis on the FFR of the LM depends on the extent to which hyperemic flow across the LM stenosis will be decreased by this distal lesion

- Severity
- Myocardial mass



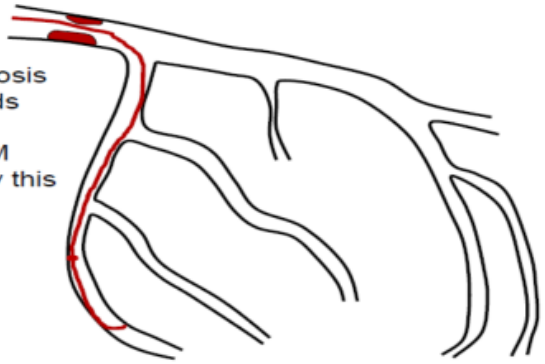
Courtesy Bernard De Bruyne, MD, PhD

(D)

Left Main Stem Stenoses are Rarely Isolated

The influence of a distal stenosis on the FFR of the LM depends on the extent to which hyperemic flow across the LM stenosis will be decreased by this distal lesion

- Severity
- Myocardial mass

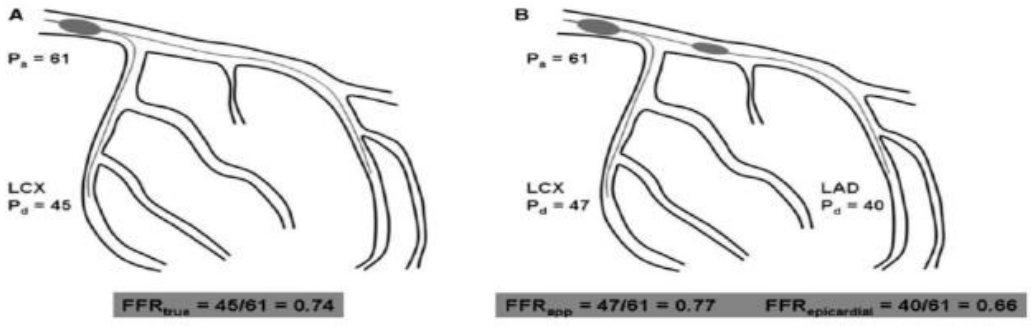


Courtesy Bernard De Bruyne, MD, PhD

(E)

Effect of Epicardial Lesions on FFR Assessment of Intermediate LM Disease

Animal Model



FFR_{true} = 45/61 = 0.74

FFR_{app} = 47/61 = 0.77 $FFR_{epicardial}$ = 40/61 = 0.66

Yong, et al. Circ Cardiovasc Interv 2013;6:161-5.

Figure 4.1: Diagrams showing (A) Variability of IVUS cut off values, (B-C) Left main stem stenosis distally in different locations in the main coronary artery of the heart, (D) left main stem stenoses rarely isolated and (E) the effect of epicardial lesions on FFR using an animal model (Taken from references [37]).

4.4. Where are the culprit lesions?

A heart attack is a severe condition occurring when patients are presented with new onset of cardiac sounding chest pain. The medical terminology of acute coronary syndrome (ACS) is used for the presentation of a heart attack. This can be a life threating situation and it should be evaluated and treated promptly to save the life of the individual patient.

The literature evidence has demonstrated that **i**n ACS, the plaque rupture occurs in 60% to 65% of cases, plaque erosion in 30% to 35%, and a calcified nodule in 5%. All these changes can lead to the formation of thrombus or severe blood clot. One of the crucial steps in treatment decisions of acute heart attack (AHA) is the identification of the type of the culprit lesion and this should be done as soon as possible. The VANQWISH (Veterans Affairs Non-Q-Wave Infarction Strategies in-Hospital) trial demonstrated that nearly 50% of these patients either have no identifiable culprit lesion or have multiple potential culprits [88, 89].

There can be positive remodeling as well as negative remodeling of lesion during presentations with chest pain. Positive remodeling is more common in culprit lesions of patients presenting with ACS and this is seen in association with plaque rupture, yellow plaque color, and thrombus formation. Conversely, negative remodeling is more common in target lesions of patients presenting with stable symptoms. IVUS detects plaque ruptures in approximately one half of ST-segment elevation MI culprit lesions. However, the superior resolution and the obligatory flushing with OCT sharply outline the plaque rupture cavity and residual fibrous cap fragment to optimize ruptured plaque identification. Likewise, other unusual culprit lesion morphologies that can be detected by using both IVUS and OCT include calcific nodules and spontaneous coronary artery dissections [90].

4.5. Role of imaging to assess the vulnerability of plaque.

The predictions of which types of plaque are going to rupture and cause a heart attack is important in the decision making by the Clinician in treating the patients [91]. Intracoronary imaging techniques including IVUS/OCT can investigate the composition of plaque and can help in deciding the vulnerability to rupture. The precursor of the ruptured, thrombotic plaque is the thin cap fibroatheroma (TCFA), the most common type of vulnerable plaque [92, 93].

The Gray scale IVUS study suggested that a large eccentric plaque containing a shallow echo-lucent zone is at increased risk for instability. To date, only VH-IVUS has been shown to predict future non-culprit events. In the PROSPECT study, predictors of non-culprit events at 3 years were associated with the presence of thin cap fibro-atheroma, VH-TCFA and IVUS MLA (almost 70%). These findings, especially the importance of a large plaque burden, were supported by the VIVA (VH-IVUS in Vulnerable Atherosclerosis) and ATHEROREMO-IVUS (European Collaborative Project on Inflammation and Vascular Wall Remodeling) studies. OCT has a imaging technique with superior resolution and more so the ability to identify TCFA, including fibrous cap thickness of 0.4 mm within 7 months. Plaques usually have an increased frequency of intimal laceration in micro-vessels, and these can be a source of blood extravasation and intraplaque hemorrhage with lipid pools, thin cap fibroatheroma (TCFAs), macrophages and intraluminal thrombi. The IVUS sub-studies of the PROSPECT investigation have highlighted the paradox between plaque ruptures and calcified nodules that cause ACS events versus the benign nature of secondary, non-culprit plaque ruptures or calcified nodules that are detected incidentally [66]. Although positive remodeling was not an independent predictor of events in either the PROSPECT, VIVA, or ATHEREMO-IVUS studies, a sub-study from the PROSPECT study found that it is not just positive remodeling, but also the extremes of positive and negative remodeling that predicted events [66]. The appropriateness of using routine invasive imaging to screen for vulnerable plaques as part of either primary or secondary prevention is the subject of debate. Moreover, this also depends on the prevalence of vulnerable plaques, as well as how often and how rapidly they develop spontaneously or either remain unstable or subsequently stabilized with time.

The best outcome in diagnosis and treatment is for the patients and the clinicians to achieve the best possible result after a coronary intervention. The failure of stent, as a result of either stent thrombosis or in-stent restenosis (ISR), is mainly due to under-expanded stent [52, 94], and inflow/outflow track disease (for example during dissections, significant plaque burden or edge stenosis [95-97]. It has been noted that acute mal-apposition is not a cause usually [98]. To get the best possible outcomes for patients, the stent needs to be adequately expanded to avoid stent failure due to stent thrombosis or restenosis (blockade or severe narrowing of the vessel). It is of paramount importance to understand that under-expansion refers to the size of the stent, whereas mal apposition refers to the contact of the stent with the vessel wall. The 2 terms and concepts are not interchangeable, and the term "under-deployment" is imprecise and unclear (see Figure 4.1B-E).

Currently, there is good evidence from four meta-analyses of the randomized IVUS versus angiographic-guided bare-metal stent implantation trials showing that IVUS guidance reduced restenosis, repeat revascularization and major adverse cardiac events [99]. Similarly, the new generation of Drug Eluting Stent trials have demonstrated the benefit of imaging. Four meta-analyses of IVUS versus angiographic-guided DES studies, including the 3 randomized trials and 14 observational studies with 26,503 patients, found that IVUS guidance reduced stent thrombosis [100]. It is also noteworthy that myocardial infarction (MI) can repeat revascularization and mortality in patients and as such, IVUS guidance was associated with a larger post-procedure angiographic minimum lumen diameter with no evidence of increased periprocedural MI.

The ADAPT-DES (Assessment of Dual Antiplatelet Therapy-With Drug Eluting Stents) study suggested that IVUS guidance has a significant impact in improving the outcomes in MI patients. A large-scale data compilation from Spanish registries showed that IVUS guidance reduced cardiac death, MI, and repeat revascularization in patients undergoing DES implantation for unprotected LMCA disease. Moreover, the HORIZONS –MI trial had an IVUS sub-study that has helped the Clinicians in understanding the mechanism(s) of stent thrombosis [101].

It is particularly noteworthy that OCT has better resolution in comparison to IVUs and it can help in detecting a lot of procedural complications in patients and moreover, it can be used to improve the procedural outcomes. A study comparing OCT versus angiographic-guided DES implantation, with relative benefits, found similar results to those obtained in the IVUS meta-analyses. The findings suggest that it might not be the individual imaging technique *per se* that is beneficial, but the increased information provided by either IVUS or OCT in comparison to angiography. OCT has advantages of having superior resolution, enhanced imaging during flushing, ease of image interpretation and the detection of dissections, tissue protrusion, and mal apposition not seen on IVUS [83, 90, 102].

4.6. Role of intracoronary imaging in stent failures

It is well known that intracoronary imaging plays a crucial role in detecting the causes of stent failures, like stent thrombosis and restenosis [103]. OCT can be considered as an imaging technology of choice in cases of stent failure. OCT studies have shown that neo-atherosclerosis occurs earlier after drug-eluting stents (DES) than bare-metal stents. In addition, neo-atherosclerosis also occurs with greater frequency with many types of DES versus bare-metal stents presenting as either the gradual re-narrowing of the stented coronary artery lesion due to arterial damage with subsequent neointimal tissue proliferation or in-stent restenosis (ISR). In some cases, neo-atherosclerosis can occur in very late stent thrombosis [81,82].

The role of physiology in determining the outcome of stent procedure is not well validated. The clinical outcomes in various large scale trials have been related to severity of disease and vulnerability of plaques [104]. The intracoronary imaging is a modality to optimize the outcomes of stent procedure. One of the best utilities of physiology is to assess the flow in the side branch of the artery after a bifurcation technique. This procedure helps in determining whether a jailed-side branch is compromised or otherwise, after a bifurcation stenting. Angiography has limitations in detecting the severity of side branch compromise after the stenting, and FFR is >0.80 because the lumen can be compromised due to carina shift that is eccentric, focal, and not due to plaque shift.

4.7. Role of intracoronary imaging and physiology in complex diseases such as DM, and CKD

Diabetes mellitus (DM) and chronic kidney disease (CKD) are complex conditions that have a high risk of associated cardiovascular complications, leading to significant impacts on the quality of life of the patients and enormous healthcare costs for individuals and Health Care providers worldwide [105, 106]. Patients with CKD and end-stage renal disease (ESRD) are at high risk of early death due to the cardiovascular disease process [70]. Unfortunately, many of these patients are denied treatment due to the complexity of the disease process [107]. When they are given treatments, the procedural outcomes are less favorable [108]. However, there is growing evidence that intracoronary imaging and physiology techniques can guide and optimize treatment, improving outcomes for these patients [86,87].

Patients with CKD/ESRD have a higher morbidity and mortality rate compared to non-CKD patients due to the complexity of the disease, systemic involvement, and multi-organ failures. Diagnosing these patients promptly and accurately is challenging and as such, treatment decisions are equally difficult [109]. There is ample evidence in the literature that cardiovascular morbidity and mortality are very high in patients with CKD, and the disease process differs in ESRD compared to non-ESRD patients. CAD progresses rapidly in ESRD patients due to various inflammatory processes and associated endothelial dysfunction, making them more susceptible to heart attacks. Managing these complex arterial diseases in patients is very complex and challenging for the Clinicians as these plaques are more calcified and prone to complications [109]. Moreover, Physicians treating these complex patients must be aware of these plaque morphologies and have the necessary skills to manage them [110]. Whenever Physicians treat these patients, they should plan the procedure carefully, pay meticulous attention to the clinical status of the patients and conduct a detailed angiographic assessment to improve success rates and reduce morbidity and mortality [111, 112].

Advances in medical technologies have now allowed Physicians to treat these complex patients better. The success rate of procedures is increasing, and morbidity and mortality rates associated with these conditions are decreasing. Physicians in dedicated centers, in collaboration with

expertise in managing patients with CKD/ESRD, can use intracoronary imaging and physiology to improve outcomes. Intracoronary imaging and physiology techniques guide treatment decisions, and physicians can determine the significance of the disease process and whether a lesion needs treatment. Moreover, IVUS and OCT imaging techniques allow physicians to assess the plaque pre-intervention and determine the appropriate treatment modality [113]. If the plaque is fibrous, a clinical operator can use balloon angioplasty leading to stenting. If the lesions are calcified, various plaque modification techniques can ensure the best possible outcomes for the patients. By utilizing these techniques, Physicians can treat complex cases effectively and improve outcomes for patients with CKD/ESRD [110].

4.8. Role of imaging and physiology in complex calcified lesions in DM and CKD

CKD is associated with complex atherosclerotic disease processes with heavily calcified coronary artery plaques. The detailed morphological assessment of plaques is crucial for the treatment of disease process effectively. Furthermore, intracoronary imaging with IVUS is an excellent clinical tool in the detection of calcified lesions. This imaging technique is based on ultrasound waves (i.e., acoustic waves) produced by the oscillatory movement of a transducer. A calcified plaque appears as a hyperdense and hyperechoic and it can be easily detected due to the density. The calcified plaque looks brighter than the reference adventitia and this can be easily differentiated by the clinician. Calcified lesions have another feature and as such, they can generate reverberations, particularly in cases where plaque modification techniques have been used. This is caused by multiple reflections from the oscillation of ultrasound between the transducer and calcium to create concentric arcs at duplicated distances. Dense fibrous tissue is also echo-dense and sometimes even creates shadowing, but it does not create reverberations. IVUS is one of the most reliable diagnostic clinical- tool to detect calcium, but the leading edge of the abluminal calcium is often hidden by the calcium shadow which means that calcium thickness cannot be assessed [88,89].

Optical coherence tomography (OCT) imaging is a near-infrared light-based imaging technique. The OCT appearance of calcium is a signal-poor region with a very sharply delineated edge and low attenuation [110]. The calcified lesion can be differentiated by clear demarcations and as such,

the clinician can even draw a line around the calcium. OCT-detected calcium is often confused with lipid, although the signal-poor regions of lipid rich tissue or a necrotic core show diffuse borders and there is substantial attenuation of the light [110]. Sometimes, it is difficult to differentiate between calcium and thin cap fibroatheroma (TCFA) or macrophage. This often happens due to light attenuation behind TCFA or macrophage when calcified plaque is located at the lumen surface. Unlike IVUS, OCT can measure calcium thickness, area, and volume [89].

It is well established that angiography, on its own, is not sufficient to detect the calcified lesions. Mintz et al, [56] reported that in a study involving 1,155 lesions, angiography detected calcium in 38% of stable lesions (n=440), while IVUS detected 73% (n=841) [3]. The sensitivity and specificity of IVUS for the detection of calcium, excluding microcalcifications, compared with histology (which is the gold standard for the validation) as a reference, has been reported as 89–90% and 97–100%, respectively. CKD is associated with significantly increased calcification in comparison to the non-CKD population. The procedural outcomes are dictated by the adequate expansion of stent in these patients [108]. Hence, it is crucial that Physician treating these lesions should not implant the stent until and unless the lesion is adequately prepared [114].

Intracoronary imaging is vital in these CKD patients with complex calcified lesions than other plaque types, as poor lesion preparation in these cases will lead to stent under-expansion with significant worse late clinical outcomes [115]. Pre-stenting intracoronary imaging delineates plaque constituents and provides accurate measurements of the minimal lumen area, lesion length and reference vessel diameters, as well as calcium arc, length, and thickness, which can be used to plan procedures including adequate lesion preparation and stent sizing [49].

Plaque modification with various adjunctive devices is crucial in these CKD patients. Although there is no specific guideline for plaque modification with atheroma-ablation, there is upcoming evidence that provides practical guidance in the management of these patients. Fujino et al [93], reported an OCT-based scoring system for patients with calcified lesion treated without atherectomy device or scoring device to predict stent under-expansion. In their study, it was observed that a calcium angle >180°, a maximum calcium thickness >0.5 mm, and a calcium length

>5 mm were independent predictors for stent under-expansion. In the validation cohort patients undergoing OCT-guided PCI, lesions with a calcium score of 4 (lesions with calcium deposit with maximum angle >180°, maximum thickness >0.5 mm and length >5 mm) emerged as a relevant predictor for stent under-expansion [93].

Intracoronary imaging can also help in detecting the calcium fracture that can be used as a surrogate marker for better stent expansion. An OCT- guided imaging study demonstrated that patients with a heavily calcified lesion, that have calcium fractures caused by balloon dilatation, were associated with smaller residual percentage diameter stenosis (19 ± 27% versus 38 ± 38%, p=0.030) and subsequent lower risk of ischemic-driven target lesion re-vascularization (7% versus 28%, p=0.046). The information obtained from these studies have demonstrated that OCT-derived calcium parameters can guide optimal strategies for the preparation of the lesion [116, 117] .

Intracoronary imaging can help the Cardiac Physician to guide the decision- making process in treating the eccentric or concentric complex calcified lesions. In general, eccentric calcified plaques (<180°) can be expanded only by means of stretching the non-calcified part of the plaques and/or creating dissection at the edge of calcified plaque, while modifications on calcified plaque may not be observed. Consequently, eccentric calcium allows for adequate stent area, although asymmetric expansion may be expected. This information obtained from intracoronary imaging should be considered to avoid the over stretching of vessel wall and hence perforations.

It is particularly noteworthy that, in concentric calcified lesions, high-pressure ballooning with non-compliant or scoring balloons can achieve lumen gain by creating fracture at the thinnest part of the calcium or creating dissections at the edges or in gaps in the calcium. In the presence of thick calcium deposits (>500 μm) or if no adequate balloon expansion is achieved, an atherectomy device should be considered to ablate the calcium and make it thinner, allowing the fracture of calcified plaque and further lumen gain (see Figure 4.2 for the utility of intracoronary imaging in guiding the treatment of calcified lesions [116-118]).

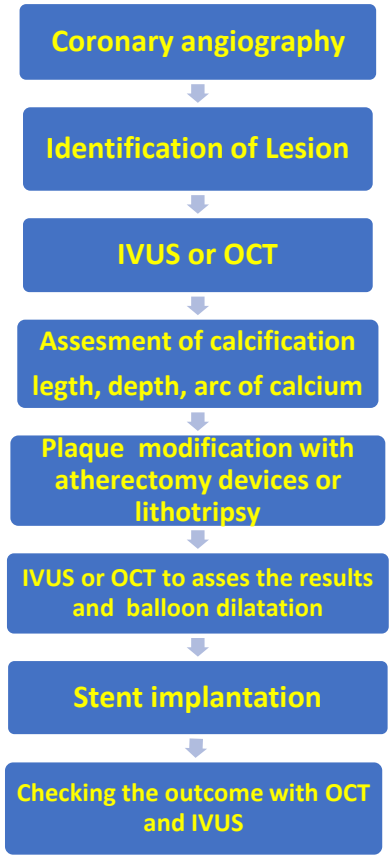


Figure 4.2: A flow diagram (drawn by hand) showing the utility of intracoronary imaging in guiding the treatment of calcified lesions (IVUS=Intravascular Ultrasound; OCT=Optical Coherence Tomography).

Furthermore, the intracoronary imaging has shown that risks of stent under-expansion such as calcium arc (>180°), thickness (>500 µm) and length (>5 mm) are increased and the Physicians need to modify the plaque adequately by various techniques such as non-compliant balloon, high pressure balloons like OPN balloon, and scoring devices. Once the lesion has been treated with either balloon or atherectomy devices, imaging should be performed to look for the presence of fracture and dissection and assess stent size and the success of lesion preparation [113]. It is also important to note that intracoronary imaging is an invasive procedure that carries some risks, such as bleeding, infection, and damage to the artery. However, the benefits of using intracoronary

imaging to guide PCI in patients with calcified lesions generally outweigh the risks, particularly in high-risk patients who are more likely to experience complications without this guidance. In addition, the use of intracoronary imaging during PCI is not always necessary or appropriate for every patient. The decision to use intracoronary imaging should be based on individual patient factors, including the extent and severity of the calcified lesion, the patient's overall health status, and the experience and expertise of the interventional cardiologist performing the procedure. Ultimately, the goal of using intracoronary imaging during PCI is to improve patient outcomes and reduce the risk of complications by providing more accurate and precise information to guide treatment decisions [115].

It is true that the impact of coronary calcification on the physiological significance and fractional flow reserve (FFR) is not well understood, and further research is needed to clarify the relationship between calcification and blood flow in the coronary arteries. As mentioned earlier, some observational studies have suggested that there may be a correlation between the degree of calcification and a decreased correlation between angiographic severity and FFR value in patients with intermediate coronary lesions. This may be related to decreased elasticity of the coronary artery with increasing calcification, which could impact blood flow [113]. Moreover, it is important to note that observational studies cannot establish causality and further research is needed to understand the underlying mechanisms and potential clinical implications. Larger, well-designed studies that consider various factors such as age, gender, comorbidities, and medication use are needed to better understand the relationship between calcification and physiological significance in coronary artery disease. Additionally, other non-invasive tests such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) may also provide additional insights into the impact of calcification on coronary artery disease.

4.9: A critical discussion of the major findings in the sixteen papers to enhance knowledge and understanding in the area

The sixteen research publications presented in this thesis are related mainly to several areas of CAD. They focused mainly on diagnosis using intracoronary imaging and physiology, novel

surgical intervention to detect various plaque morphologies, calcium deposition and various strategies to treat these disease processes. Some of the studies also employed new and novel treatments for diagnosis including intravascular ultrasound to treat complex diseases like venous graft interventions without using contrast. The pioneering studies comparing the pressure wire and microcatheter to measure the pressure gradient is presented in the thesis. The novel ideas for coronary artery stenting using the external elastic lamina vs. luminal diameter measurement as well as other techniques to help improve the outcomes of patients are presented in the thesis.

The sixteen research publications presented in this thesis are related mainly to three areas of assessment management of patients with CAD. The focus is mainly on intracoronary imaging and physiology, mineralocorticoid receptor antagonists and various strategies in infarct size reduction and endothelial function. The discussion now focusses on the three areas.

4.10 (A) Advancement and understanding of the science to enhance knowledge on intra-coronary imaging and physiology in each of the 10 publications.

The initial ten research publications presented in this thesis by publication demonstrated the utility of intracoronary imaging and physiology in managing complex disease processes of venous graft interventions with no contrast use. Patients with previous coronary artery bypass grafting and advanced chronic kidney disease (CKD) are considered at a high risk for revascularization. In comparison to native coronary artery angiography, additional contrast is required to visualize the bypass conduits, increasing the risk of contrast-induced nephropathy (CIN) and need for renal replacement therapy. As a result, despite the need for revascularization, these patients were frequently under-treated. The current study helped in the advancement in knowledge and understanding in the field that intravascular ultrasound (IVUS)-guided interventions can reduce the amount of contrast and its associated risk of CIN. The study described a step-by-step "zero-contrast" saphenous vein bypass graft (SVG) intervention using a modified technique.

As an expert in the field of intracoronary imaging and physiology, the candidate has highlighted and addressed the various misconceptions about various mal-appositions and long -term consequences on diagnosis and treatment of these conditions after stent implantations. The novelty

and importance of this work highlighted that Cardiac Clinicians must consider that not all the mal appositions are of clinical significance during treatment. As such, they should try to have stent optimally expanded as much as possible and not to be concerned in every mal apposition.

The expertise of the candidate in the field has allowed him to write original review articles on the utility of intracoronary imaging and physiology in cardiac catheterization laboratory focussing on various techniques that could be used in the cardiac catheterization laboratory. The novelty and clinical importance of these review articles. which were lacking at the time, helped the Cardiac Clinicians to appreciate the utility and evidence behind adjunctive techniques of intracoronary imaging, optical coherence tomography (OCT) and intravascular ultrasound (IVUS) and physiological techniques like fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR). The present study has demonstrated the reason as to why angiography is not adequate to make precise decisions regarding clinical care of cardiac patients with CAD. As such, this information for Cardiologists, as well as the public, is of great significance since coronary angiography has the inherent limitation of being a two-dimensional X-Ray lumeno-gram of a complex three-dimensional vascular structure. Visual assessment of angiogram can lead to both inter- and intra-observer variability in the assessment of the severity and extent of the disease leading to differences in management strategies.

The papers presented in this study have helped in understanding the utility of intracoronary imaging in the difficult clinical scenarios. They have demonstrated and highlighted the role of IVUS in various emergency clinical settings and how IVUS can guide the treatment decisions by the Clinicians in various scenarios of either aortic or coronary artery dissections. Moreover, IVUS can be a modality to differentiate between a true and false lumen. In clinical settings, whenever there is suspicion of dissection on angiography, IVUS can be used to locate the false lumen and it can help to facilitate directing the wire into the true lumen. IVUS is superior in many cases of dissection including left main stem (LMS) dissection. In these cases, IVUS does not require the use of contrast and it avoids the hydraulic extension of dissection to other arterial trees.

The candidate has been collaborating with other Clinical Cardiologists internationally for several years on the novelty and originality in assessing the various plaque morphologies in CKD patients using optical coherence tomography (OCT). The information regarding plaque morphology in these CKD patients is of paramount importance as it can help to guide the decision- making process of the Clinicians. If the patients have significant calcification in their coronary arteries, then the Clinicians need to decide upfront about the plaque modification techniques and try to avoid unnecessary balloon dilatations to either prevent or reduce such complications as coronary perforations stent under expansions can be associated with higher morbidity and mortality. Knowing plaque morphology beforehand can be very cost-effective as it can avoid the use of unnecessary equipment and moreover, minimize contrast use and hence, prevent long-term surgery and associated complications.

In papers presented in this study, the candidate demonstrated two different techniques for modifying calcified plaques during the development of CAD. These techniques have different mechanism(s) of actions to ablate the calcified plaques. In large sized vessels, there is differentially more plaque modification by Orbital atherectomy. In small vessels, the ablative impact is like devices. With advances in interventional cardiology, more elderly, diabetic, and renal failure patients are being treated and hence, more calcification is seen in clinical practice. Familiarity with these device usages is of paramount importance and this can guide in making the best possible decisions for patients and avoiding the complications in these complex scenarios.

In addition, this study undertook the novel the head- to- head comparison of pressure wire vs micro catheter for coronary fractional flow reserve. The clinical work of PERFORM study was a single-center prospective investigation designed specifically to determine the precision and accuracy of the percutaneous coronary intervention (PCI) compared with the pressure wire (PW) for measurement of FFR. The knowledge, awareness and understanding about micro catheter-based physiology is of great assistance to Cardiac Clinicians especially when they are measuring the physiology at the end of the procedure. This technique can be an added advantage during the cases where repeated assessment of intracoronary physiology is required.

This study has also investigated, via the various publications, the various measurement techniques for sizing the stent for coronary intervention and demonstrated that Optical coherence tomography (OCT)-guided external elastic lamina (EEL)-based stent sizing is safe and as effective as intravascular ultrasound in achieving post procedural lumen dimensions. Furthermore, EEL-based stenting is appropriate and Cardiac Clinicians should be aware of this and more so, help in guiding the optimal stenting for these patients with CAD. The new and novel results obtained from this collaborative study are now guiding and leading Cardiac Clinicians to design further large- scale trials of OCT- guided stenting to treat CAD.

In one published paper (MS 10), the candidate compared the utility of Nitro-glycerin-Derived Pd/Pa for the Assessment of Intermediate Coronary Lesions. The rationale was to assess the predictive value of Pd/Pa after nitroglycerin administration (Pd/Pa[N]) as compared with standard fractional flow reserve (FFR) comparing nitroglycerin and adenosine, two vasodilators for measuring coronary blood flow physiology. There were many patients, then and even today, who did not normally tolerate the adenosine due to some side effects. As such, the results from this interesting paper demonstrated that even intracoronary glyceryl trinitrate (GTN) can help in guiding the decision- making process in cardiac catheterization laboratory. This is very cost-effective and easy to administer in the laboratory, without any specific preparations. This technique can be used more frequently and hence, it can help cardiac clinicians for more frequent use in coronary blood flow physiology.

4.11 (B) Advancement and understanding to science in enhancing knowledge in the field of mineralocorticoids (MR) antagonism and cardiovascular diseases.

The three research papers presented in this study in the field of mineralocorticoid receptors have highlighted the role of mineralocorticoid receptor (MR) antagonists (MRAs) in the treatment of patients with hypertension and heart failure. The results highlighted and established treatment modalities for patients with hypertension, heart failure, and left ventricular systolic dysfunction (LVSD) during post-myocardial infarction (MI). The study highlighted emerging data with

reference to the potential benefits of MR antagonists in other cardiovascular conditions. The study also reviewed and examined the preclinical and clinical data of MR antagonists for novel indications including heart failure with preserved ejection fraction (HFPEF), pulmonary arterial hypertension (PAH), arrhythmia, sudden cardiac death (SCD), valvular heart disease (VHD), metabolic syndrome, renal disease, and stroke. MR antagonists are not licensed at least in the United Kingdom for these conditions yet, but emerging data suggest that the clinical needs for MR antagonists are likely to broaden and as such further studies are warranted.

The evidence presented in the three publications has helped the Cardiac Clinician to guide the patients in choosing the appropriate therapy for these long-term complex disease processes. The data have compared spironolactone with eplerenone, and the results have supported recommendations about best choice of medication to be considered cost-effectively for the patients.

Moreover, the present study has reviewed the beneficial effects of eplerenone in the EPHESUS trial which exists for both PCI- and non-PCI-treated AMI patients with LVSD. The results show that eplerenone has minimal effect in reducing PCI-related adverse events in the PCI-treated cohort. Furthermore, patients in the EPHESUSPCI cohort did not have routine angiographic follow-up to documentary effect of eplerenone on angiographic restenosis. However, the assessment of clinical events in this study was perhaps more relevant than angiographic outcomes.

4.12 (C) Advancement and understanding to science in enhancing knowledge in the field of infarct size reduction and endothelial function.

The three papers on infarct size reduction and endothelial function are related to the various mechanisms leading to damage to myocardium like ischemic cascade, microvascular obstruction and no reflow. Post-infarct complications, including heart failure, ischemia, and others continue to be a major contributor to cardiovascular morbidity and mortality for patients. Inadequate micro -vascular reperfusion leads to worse clinical outcomes and potential strategies to reduce infarct

size during periods of ischemia–reperfusion can improve outcomes. In this study, the Candidate advised physicians that they need to be aware of these findings and carefully follow and observe the various strategies to help in reducing the infarct size in patients. He also highlighted various strategies and stressed the importance of future research in the field to enhance knowledge, understanding and scope for the best way forward in reducing the damage of heart muscle after an heart attack. Based on the current work in this thesis, numerous agents have been demonstrated to reduce infarct size in preclinical as well as clinical models. Rather than a "one size fits all" approach, individualized tailored therapies may be required for patients with either selected clinical, myocardial, or genetic/cellular characteristics. Nevertheless, these findings have potential and great significance as they can help in making decision when choosing various treatment agents after a myocardial infarction to reduce the damage to myocardium and improving the clinical outcomes in the patients.

It is particularly noteworthy that the candidate did novel research studies in the field of blood transfusion. The results show that the duration of red blood corpuscle (RBC) storage may have a negative impact on endothelial nitric oxide bioavailability in the coronary arteries of the myocardium. The research further tested the hypothesis that transfused fresh blood would have a more favorable effect and outcome on micro-vascular endothelial function as compared to older standard issue blood. The paper (MS 16) had a high impact factor and has received 1,315 citations to date.

4.13 Conclusion

This study for PhD by Publication is related to sixteen research papers about coronary artery disease. Some are written review papers based on the findings in the literature while others are based on original studies done in the hospital following the treatment of CAD patients using several clinical cutting-edge techniques. The papers fall under such areas as intracoronary imaging and physiology, hormones, fresh blood transfusions and various strategies for infarct size reduction. Figure 4.3 is a summary flow diagram explaining the etiology of coronary artery

diseases (CAD) starting from the risk factors, plaque formation, signs and symptoms of CAD, diagnosis, and treatments.

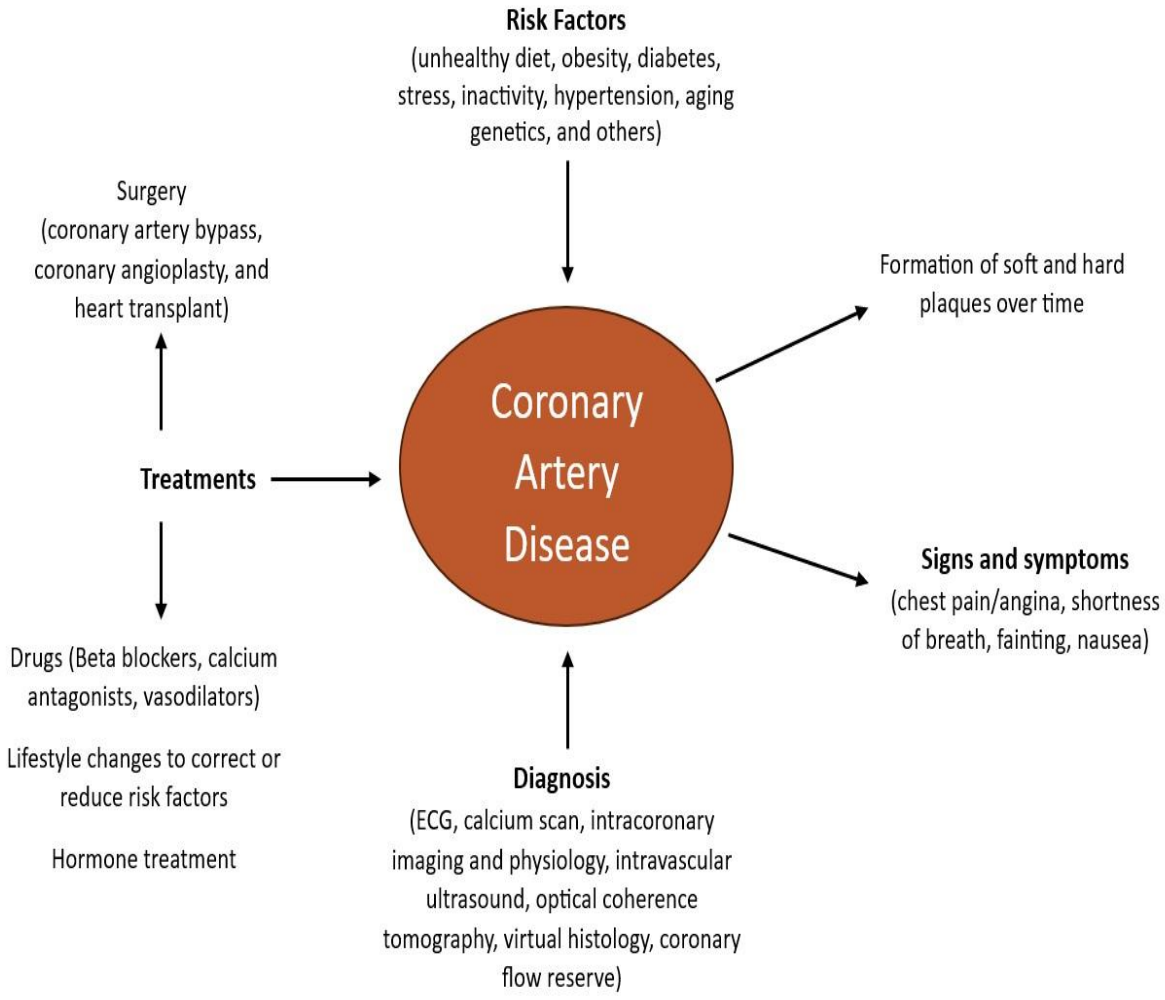


Figure 4.3: Flow diagram summarizing the etiology of coronary heart disease including the risk factors, formation of plaques, signs and symptoms, diagnosis, and surgical, drug and non-pharmacological treatments (Drawn by hand).

4.14 Limitations

The research articles presented in the thesis are the original work and research reviews undertaken by the Candidate during his academic placements at Western University in Canada and Columbia University New York. He fully understands the limitations of the presented work:

The thesis has made a major contribution to the advancement of spread of knowledge about intracoronary imaging and physiology in the literature. The Candidate is aware that it is challenging to demonstrate originality in terms of ideas, methodologies, new and novel findings. An area of limitation in this study is that angiography is still unable to accurately assess cardiac vascular remodelling leading to errors in determining the true size of coronary arteries and their reference diameters.

The published papers presented in the thesis are his own work and have demonstrated his contribution to various articles but still there are limitations regarding copyright or intellectual property of various studies presented in this thesis.

The candidate and his Co-authors had limited access to primary data that were presented during various studies, and this is a limitation to the depth and breadth of the presented research papers.

The replication of this thesis will be challenging, as it involves factors like access to specific datasets, specialized equipment, or proprietary software.

The Candidate is a full-time clinician and doing academic work due to his enthusiasm and commitment to the field of intracoronary imaging and physiology. He wants to continue an academic pathway and his research desire is to design new clinical experiments, collect data, and critically analyse the findings to continuously build on to his research skills and gaining a deeper understanding of the subject area of CAD.

Another limitation in this study is that angiography is still unable to accurately assess cardiac vascular remodelling leading to errors in determining the true size of coronary arteries and their reference diameters.

4.15 Recommendations and Scope for Future Studies

1. It is true that the impact of coronary calcification on the physiological significance and fractional flow reserve (FFR) is not well understood, and further research studies are required to clarify the relationship between calcification and blood flow in the coronary arteries.

2. Further research studies are needed to understand the underlying mechanisms and potential clinical implications relating to a decrease in elasticity of the coronary artery with increasing calcification, which could impact blood flow.

3. In addition, larger, well-designed studies that consider various factors such as age, gender, comorbidities, and medication use are needed to better understand the relationship between calcification and physiological significance in coronary artery disease. Additionally, other non-invasive tests such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) may also provide additional insights into the impact of calcification on coronary artery disease. More studies are needed in these two areas.

4. It is important to undertake a population genetics study on those ethnic groups who are more susceptible to developing CAD.

5. Prevention is better than cure and this is an important area for Governments, globally to tackle the problem of CAD and other diseases associated with the cardiovascular systems in conjunction with the Physicians.

6. Moreover, it is important to note that observational studies cannot establish causality and further research is needed to understand the underlying mechanisms and potential clinical implications. Larger, well-designed studies that consider various factors such as age, gender, comorbidities, and medication use are needed to better understand the relationship between calcification and physiological significance in coronary artery disease. Additionally, other non-invasive tests such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) may also provide additional insights into the impact of calcification on coronary artery disease and as such more research needs to be done in this area.

7. Further studies are required in understanding the molecular, cellular, and subcellular mechanisms underlying the hyperglycemia-induced renal disease/failure.

REFERENCES

1a. Brown, J.C., T.E. Gerhardt, and E. Kwon, *Risk Factors For Coronary Artery Disease*, in *StatPearls*. 2022: Treasure Island (FL; USA).

1b. Mahmood, S.S, Levy, D., Vasan, R.S., and Wang, T.J. The Framingham heart Studt and the epedimiology of cardiovascular diseases. : A historical perspective. Lancet, 2023; 383(9921): 99-108.

2. Fleck, E., W. Maier-Rudolf, and H. Oswald, *Coronary angiography and interventional cardiology.* Curr Opin Radiol, 1991. **3**(4): . 550-560.

3. Fleming, R.M., D.M. Fleming, and R. Gaede, *Training physicians and health care providers to accurately read coronary arteriograms. A training program.* Angiology, 1996. **47**(4): . 349-359.

4. Girasis, C., et al., *Validity and variability in visual assessment of stenosis severity in phantom bifurcation lesions: a survey in experts during the fifth meeting of the European Bifurcation Club.* Catheter Cardiovasc Interv, 2012. **79**(3): . 361-368.

5. Grundeken, M.J., et al., *Visual estimation versus different quantitative coronary angiography methods to assess lesion severity in bifurcation lesions.* Catheter Cardiovasc Interv, 2018. **91**(7): 1263-1270.

6. Fleming, R.M., et al., *Patterns in visual interpretation of coronary arteriograms as detected by quantitative coronary arteriography.* J Am Coll Cardiol, 1991. **18**(4): 945-951.

7. Arumugham, P., et al., *Comparison of intravenous adenosine and intravenous regadenoson for the measurement of pressure-derived coronary fractional flow reserve.* EuroIntervention, 2013. **8**(10): 1166-1171.

8. Tobis, J., *Which do you prefer, OCT or IVUS?* Catheter Cardiovasc Interv, 2015. **86**(2): 236 (An abstract).

9. Barbato, E., et al., *A Prospective Natural History Study of Coronary Atherosclerosis Using Fractional Flow Reserve.* J Am Coll Cardiol, 2016. **68**(21): 2247-2255.

10. Ali, Z.A., et al., *Pressure wire compared to microcatheter sensing for coronary fractional flow reserve: the PERFORM study.* EuroIntervention, 2018. **14**(4): e459-e466.

11. van de Hoef, T.P., M. Meuwissen, and J.J. Piek, *Fractional flow reserve-guided percutaneous coronary intervention: where to after FAME 2?* Vasc Health Risk Manag, 2015. **11**:. 613-622.

12. Kim, H.S., et al., *The impact of sex differences on fractional flow reserve-guided percutaneous coronary intervention: a FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) substudy.* JACC Cardiovasc Interv, 2012. **5**(10): 1037-1042.

13. Dale, A., et al., *Outcomes reporting of the FAME trial.* Lancet, 2016. **387**(10035): 2292 (An abstract).

14. Kirtane, A.J. and J.J. Marshall, *The benefit of ischemia-based revascularization for stable ischemic heart disease: the impact of FAME 2.* Catheter Cardiovasc Interv, 2013. **81**(1): . 1-3.

15. de Man, F.H. and C. von Birgelen, *Fractional flow reserve measurements to identify justified targets for PCI in patients with stable angina: FAME 2 and beyond.* Cardiovasc Diagn Ther, 2012. **2**(4): 261-263.

16. Elguindy, A.M. and R.O. Bonow, *FAME 2 - The best initial strategy for patients with stable coronary artery disease: Do we have an answer at last?* Glob Cardiol Sci Pract, 2012. **2012**(2): 15-17.

17. ElGuindy, A.M., *FAME 2: Reshaping the approach to patients with stable coronary artery disease.* Glob Cardiol Sci Pract, 2015. **2015**(3): 32 (An abstract).

18. Fox, K.A., *COURAGE or FAME...? Who should have percutaneous coronary intervention in stable coronary artery disease?* Heart, 2013. **99**(7): p. 442-454.

19. Levine, G.N., et al., *2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery.* Circulation, 2016. **134**(10): . e123-e155.

20. Bashore, T.M., et al., *2012 American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions expert consensus document on cardiac catheterization laboratory standards update: American College of Cardiology Foundation Task Force on expert consensus documents Society of Thoracic Surgeons Society for Vascular Medicine.* Catheter Cardiovasc Interv, 2012. **80**(3): E37-E49.

21. Berntorp, K., et al., *Instantaneous wave-free ratio compared with fractional flow reserve in PCI: A cost-minimization analysis.* Int J Cardiol, 2021. **344**: . 54-59.

22. Fawaz, S. and C.M. Cook, *Understanding the Basis for Hyperemic and Nonhyperemic Coronary Pressure Assessment.* Interv Cardiol Clin, 2023. **12**(1): . 1-12.

23. Cameron, J.D., *Non-hyperemic pressure-derived indices for guiding coronary intervention: Assessing comparative use and application.* Int J Cardiol, 2023. **372**: 46-47.

24. Davies, J.E., et al., *Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI.* N Engl J Med, 2017. **376**(19): 1824-1834.

25. Adler, A.I., et al., *Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64).* Kidney Int, 2003. **63**(1): 225-232.

26. Bezerra, H.G., et al., *Intracoronary optical coherence tomography: a comprehensive review clinical and research applications.* JACC Cardiovasc Interv, 2009. **2**(11): 1035-1046.

27. Gotberg, M., et al., *Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI.* N Engl J Med, 2017. **376**(19): 1813-1823.

28. Gotberg, M., et al., *5-Year Outcomes of PCI Guided by Measurement of Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve.* J Am Coll Cardiol, 2022. **79**(10): 965-974.

29. Dowling, C., et al., *Diagnostic performance of quantitative flow ratio, non-hyperaemic pressure indices and fractional flow reserve for the assessment of coronary lesions in severe aortic stenosis.* Cardiovasc Diagn Ther, 2022. **12**(3): 314-324.

30. Fearon, W.F., et al., *Clinical Outcomes and Cost-Effectiveness of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease: Three-Year Follow-Up of the FAME 2 Trial*

(Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). Circulation, 2018. **137**(5): 480-487.

31. Berry, C. and D.T.Y. Ang, *Picture perfect? Performance of quantitative coronary angiography-based vessel FFR versus pressure wire-based FFR.* EuroIntervention, 2022. **17**(18): 1463-1465.

32. Xu, B., et al., *Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis.* J Am Coll Cardiol, 2017. **70**(25): 3077-3087.

33. Tu, S., et al., *Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study.* JACC Cardiovasc Interv, 2016. **9**(19): 2024-2035.

34. Westra, J., et al., *Evaluation of Coronary Artery Stenosis by Quantitative Flow Ratio During Invasive Coronary Angiography: The WIFI II Study (Wire-Free Functional Imaging II).* Circ Cardiovasc Imaging, 2018. **11**(3): Article e007107.

35. Scoccia, A., et al., *Correlation of 3D Quantitative Coronary-Angiography Based Vessel FFR With Diastolic Pressure Ratio: A Single-Center Pooled Analysis of the FAST EXTEND and FAST II Studies.* J Invasive Cardiol, 2022. **34**(9): E686-E688.

36. Bezerra, C.G., et al., *Coronary fractional flow reserve derived from intravascular ultrasound imaging: Validation of a new computational method of fusion between anatomy and physiology.* Catheter Cardiovasc Interv, 2019. **93**(2): 266-274.

37. Yong, D., et al., *Diagnostic performance of IVUS-FFR analysis based on generative adversarial network and bifurcation fractal law for assessing myocardial ischemia.* Front Cardiovasc Med, 2023. **10**: Article 1155969.

38. Yu, W., et al., *Diagnostic accuracy of intracoronary optical coherence tomography-derived fractional flow reserve for assessment of coronary stenosis severity.* EuroIntervention, 2019. **15**(2): 189-197.

39. Seike, F., et al., *Intracoronary Optical Coherence Tomography-Derived Virtual Fractional Flow Reserve for the Assessment of Coronary Artery Disease.* Am J Cardiol, 2017. **120**(10): 1772-1779.

40. Li, Q., et al., *Diagnostic performance of CT-derived resting distal to aortic pressure ratio (resting Pd/Pa) vs. CT-derived fractional flow reserve (CT-FFR) in coronary lesion severity assessment.* Ann Transl Med, 2021. **9**(17): Article 1390.

41. Schuijf, J.D., E.E. van der Wall, and J.J. Bax, *Quantification of multi-slice computed tomography coronary angiography: current status and future directions.* Acute Card Care, 2006. **8**(2): 105-106.

42. Aetesam-Ur-Rahman, M., et al., *Coronary Flow Variations Following Percutaneous Coronary Intervention Affect Diastolic Nonhyperemic Pressure Ratios More Than the Whole Cycle Ratios.* J Am Heart Assoc, 2022. **11**(9): Article e023554.

43. Parviz, Y., et al., *Utility of intracoronary imaging in the cardiac catheterization laboratory: comprehensive evaluation with intravascular ultrasound and optical coherence tomography.* Br Med Bull, 2018. **125**(1): 79-90.

44. Parviz, Y., et al., *Role Of Intra Coronary Imaging And Physiology In Diagnosis And Management Of Coronary Artery Disease.* J Ayub Med Coll Abbottabad, 2017. **29**(3): 516-522.

45. Shlofmitz, E., et al., *Intravascular Imaging-Guided Percutaneous Coronary Intervention: A Universal Approach for Optimization of Stent Implantation.* Circ Cardiovasc Interv, 2020. **13**(12): Article e008686.

46. Mintz, G.S. and N.J. Weissman, *Intravascular ultrasound in the drug-eluting stent era.* J Am Coll Cardiol, 2006. **48**(3): 421-429.

47. Mintz, G.S., et al., *Clinical Utility of Intravascular Imaging: Past, Present, and Future.* JACC Cardiovasc Imaging, 2022. **15**(10): 1799-1820.

48. Abizaid, A.S., et al., *One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms.* J Am Coll Cardiol, 1999. **34**(3): 707-715.

49. Stone, G.W., et al., *A prospective natural-history study of coronary atherosclerosis.* N Engl J Med, 2011. **364**(3): 226-235.

50. Parviz, Y., K.N. Fall, and Z.A. Ali, *Using sound advice-intravascular ultrasound as a diagnostic tool.* J Thorac Dis, 2016. **8**(10): E1395-E1397.

51. Case, B.C., et al., *Intravascular ultrasound guidance in the evaluation and treatment of left main coronary artery disease.* Int J Cardiol, 2021. **325**: 168-175.

52. Mintz, G.S., et al., *Intravascular ultrasound in the evaluation and treatment of left main coronary artery disease: a consensus statement from the European Bifurcation Club.* EuroIntervention, 2018. **14**(4): e467-e474.

53. Abizaid, A., et al., *Acute and long-term results of an intravascular ultrasound-guided percutaneous transluminal coronary angioplasty/provisional stent implantation strategy.* Am J Cardiol, 1999. **84**(11): 1298-303.

54. Parviz, Y., et al., *Imaging and Physiology to Guide Venous Graft Interventions Without Contrast Administration in Advanced Renal Failure.* J Invasive Cardiol, 2017. **29**(11): E163-E165.

55. Frobert, O., et al., *Effect of stent inflation pressure and post-dilatation on the outcome of coronary artery intervention. A report of more than 90,000 stent implantations.* PLoS One, 2013. **8**(2): Article e56348.

56. Mintz, G.S., et al., *American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents.* J Am Coll Cardiol, 2001. **37**(5): 1478-1492.

57. Ali, Z., et al., *Optical coherence tomography-guided coronary stent implantation compared to angiography: a multicentre randomised trial in PCI - design and rationale of ILUMIEN IV: OPTIMAL PCI.* EuroIntervention, 2021. **16**(13): 1092-1099.

58. Ali, Z.A., et al., *Outcomes of optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation: one-year results from the ILUMIEN III: OPTIMIZE PCI trial.* EuroIntervention, 2021. **16**(13): 1085-1091.

59. Ali, Z.A., et al., *Imaging-guided pre-dilatation, stenting, post-dilatation: a protocolized approach highlighting the importance of intravascular imaging for implantation of bioresorbable scaffolds.* Expert Rev Cardiovasc Ther, 2018. **16**(6): 431-440.

60. Parrish, R.K., 2nd, et al., *Characterization of Intraocular Pressure Increases and Management Strategies Following Treatment With Fluocinolone Acetonide Intravitreal Implants in the FAME Trials.* Ophthalmic Surg Lasers Imaging Retina, 2016. **47**(5): 426-435.

61. Mintz, G.S., *Intravascular ultrasound and outcomes after drug-eluting stent implantation.* Coron Artery Dis, 2017. **28**(4): 346-352.

62. Mintz, G.S., et al., *Intravascular ultrasound insights into mechanisms of stenosis formation and restenosis.* Cardiol Clin, 1997. **15**(1): 62(4) 306-314.17-29.

63. Nelson, A.J., E.D. Peterson, and N.J. Pagidipati, *Atherosclerotic cardiovascular disease and heart failure: Determinants of risk and outcomes in patients with diabetes.* Prog Cardiovasc Dis, 2019.62 (4): 306-314.

64. Lin, X., et al., *Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025.* Sci Rep, 2020. **10**(1): Article 14790.

65. Ohkuma, T., et al., *Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals.* Diabetologia, 2019. **62**(9): 1550-1560.

66. Alani, H., A. Tamimi, and N. Tamimi, *Cardiovascular co-morbidity in chronic kidney disease: Current knowledge and future research needs.* World J Nephrol, 2014. **3**(4): 156-168.

67. Ardhanari, S., M.A. Alpert, and K. Aggarwal, *Cardiovascular disease in chronic kidney disease: risk factors, pathogenesis, and prevention.* Adv Perit Dial, 2014. 30: 40-53.

68. Valmadrid, C.T., et al., *The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus.* Arch Intern Med, 2000. **160**(8): 1093-1100.

69. Nichols, G.A., et al., *The association between estimated glomerular filtration rate, albuminuria, and risk of cardiovascular hospitalizations and all-cause mortality among patients with type 2 diabetes.* J Diabetes Complications, 2018. **32**(3): 291-297.

70. O'Keefe, J.H., et al., *The elephant in the room: Why cardiologists should stop ignoring type 2 diabetes.* Prog Cardiovasc Dis, 2019, 62(4):364-369 . (Article DOI:10.1016/jpcad.2019.08.001)

71. Boudoulas, K.D., et al., *The Cardio-Renal Interrelationship.* Prog Cardiovasc Dis, 2017. **59**(6): 636-648.

72. Shlipak, M.G., et al., *Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors.* JAMA, 2005. **293**(14): . 1737-145.

73. Al-Maskari, F., M. El-Sadig, and N. Nagelkerke, *Assessment of the direct medical costs of diabetes mellitus and its complications in the United Arab Emirates.* BMC Public Health, 2010. **10**: . 679-685.

74. Ogah, O.S., et al., *Electrocardiographic left ventricular hypertrophy with strain pattern: prevalence, mechanisms and prognostic implications.* Cardiovasc J Afr, 2008. **19**(1): 39-45.

75. Pijls, N.H. and B.D. Bruyne, *Fractional Flow Reserve, Coronary Pressure Wires, and Drift.* Circ J, 2016. **80**(8): 1704-1706.

76. Boerhout, C.K.M. and J.J. Piek, *Pressure gradient post-percutaneous coronary intervention: beyond angiography.* Neth Heart J, 2022. **30**(7-8): 341-342.

77. Ali, Z.A., et al., *Intracoronary optical coherence tomography: state of the art and future directions.* EuroIntervention, 2021. **17**(2): e105-e123.

78. Ali, Z.A., et al., *Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial.* Lancet, 2016. **388**(10060): 2618-2628.

79. Achim, A. and G. Leibundgut, *FAME 3 fails to defame coronary artery bypass grafting: what went wrong in the percutaneous coronary intervention arm?* Eur J Cardiothorac Surg, 2022. **62**(1).Article ezac036 (doi/10.1093/ejcts/ezac036).

80. Kang, S.J., et al., *Usefulness of minimal luminal coronary area determined by intravascular ultrasound to predict functional significance in stable and unstable angina pectoris.* Am J Cardiol, 2012. **109**(7): . 947-53.

81. Waksman, R., et al., *FIRST: Fractional Flow Reserve and Intravascular Ultrasound Relationship Study.* J Am Coll Cardiol, 2013. **61**(9): p. 917-23.

82. Stratmann, H.G., et al., *Comparison based on age of baseline electrocardiographic abnormalities in non-Q-wave myocardial infarction. VANQWISH Trial Research Investigators. Veterans Affairs Non-Q-Wave Infarction Strategies In-Hospital.* J Am Geriatr Soc, 1999. **47**(7): . 870-872.

83. Wexler, L.F., et al., *Non-Q-wave myocardial infarction following thrombolytic therapy: a comparison of outcomes in patients randomized to invasive or conservative post-infarct assessment strategies in the Veterans Affairs non-Q-wave Infarction Strategies In-Hospital (VANQWISH) Trial.* J Am Coll Cardiol, 2001. **37**(1): 19-25.

84. Ali, Z.A., et al., *Intracoronary Optical Coherence Tomography 2018: Current Status and Future Directions.* JACC Cardiovasc Interv, 2017. **10**(24): 2473-2487.

85. Choi, S.Y. and G.S. Mintz, *What have we learned about plaque rupture in acute coronary syndromes?* Curr Cardiol Rep, 2010. **12**(4): 338-433.

86. Ali, Z.A., et al., *Increased thin-cap neoatheroma and periprocedural myocardial infarction in drug-eluting stent restenosis: multimodality intravascular imaging of drug-eluting and bare-metal stents.* Circ Cardiovasc Interv, 2013. **6**(5): 507-517.

87. Al-Lamee, R. and G.S. Mintz, *What are the PROSPECTs and clinical implications of vulnerable plaque?* Eur Heart J, 2021. **42**(45): . 4680-4682.

88. Jacobson, J., A. Maehara, and G.S. Mintz, *Clinical applications of intravascular ultrasound in the implantation of drug-eluting stents.* Expert Rev Cardiovasc Ther, 2012. **10**(5): . 543-547.

89. Jensen, L.O., et al., *Serial intravascular ultrasound analysis of peri-stent remodeling and proximal and distal edge effects after sirolimus-eluting or paclitaxel-eluting stent implantation in patients with diabetes mellitus.* Am J Cardiol, 2009. **103**(8): 1083-1088.

90. Inaba, S., et al., *Acute closure due to extramedial hematoma 3 hours after stenting.* JACC Cardiovasc Interv, 2014. **7**(3): e19-e21.

91. Castagna, M.T., et al., *The contribution of "mechanical" problems to in-stent restenosis: An intravascular ultrasonographic analysis of 1090 consecutive in-stent restenosis lesions.* Am Heart J, 2001. **142**(6): . 970-974.

92. Ali, Z.A., et al., *The "Oculo-Appositional Reflex": Should Optical Coherence Tomography-Detected Stent Malapposition Be Corrected?* J Am Heart Assoc, 2019. **8**(7): Article . e012262.

93. Caixeta, A., V.C. Braga, and G.S. Mintz, *Very late stent thrombosis with bare-metal stent: identifying severe stent malapposition and underexpansion by intravascular ultrasound.* Einstein (Sao Paulo), 2013. **11**(3): . 364-366.

94. Ahn, J.M., et al., *Meta-analysis of outcomes after intravascular ultrasound-guided versus angiography-guided drug-eluting stent implantation in 26,503 patients enrolled in three randomized trials and 14 observational studies.* Am J Cardiol, 2014. **113**(8): 1338-1347.

95. Choi, S.Y., et al., *Intravascular ultrasound findings of early stent thrombosis after primary percutaneous intervention in acute myocardial infarction: a Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) substudy.* Circ Cardiovasc Interv, 2011. **4**(3): 239-247.

96. Araki, M., et al., *Optical coherence tomography in coronary atherosclerosis assessment and intervention.* Nat Rev Cardiol, 2022. **19**(10): 684-703.

97. Ali, Z.A. and G.S. Mintz, *Intravascular Imaging: Too Much or Too Little of a Good Thing?* JACC Case Rep, 2020. **2**(3): 516-517.

98. Canty, J.M., Jr., *FAME, ISCHEMIA and outcomes: Coronary physiology vs. plaque instability and myocardial infarction.* Trends Cardiovasc Med, 2022, Article https://doi.org/10.1016/j.tcm.2022.03.003; Manuscript_05855ef05b1cce25421dce7593fd591f .

99. Rahman, S., et al., *Diabetes-associated macrovasculopathy: pathophysiology and pathogenesis.* Diabetes Obes Metab, 2007. **9**(6): 767-80.

100. Abizaid, A., et al., *The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation.* J Am Coll Cardiol, 1998. **32**(3): . 584-589.

101. Kannan, A., et al., *Coronary Revascularization in Chronic and End-Stage Renal Disease: A Systematic Review and Meta-analysis.* Am J Ther, 2016. **23**(1): e16-28.

102. Amemiya, K., et al., *Chronic stent recoil in severely calcified coronary artery lesions. A serial optical coherence tomography study.* Int J Cardiovasc Imaging, 2020. **36**(9): 1617-1626.

103. Di Mauro, M., Fiorentini, V., Mistrilli, R, Venesiano, F.A., and Di Lucia, L. Acute coronary syndrome and renal implantment:a systemic review. Res Cardiovas. Med., 2022, 23(2): Article 49 (doi.org/10.31083/rcm2302049).

104. Chin, C.Y., et al., *Coronary Plaque Characteristics in Hemodialysis-Dependent Patients as Assessed by Optical Coherence Tomography.* Am J Cardiol, 2017, 119 (1): 1313-1319..

105. Lentine, K.L., et al., *Cardiac evaluation before kidney transplantation: a practice patterns analysis in Medicare-insured dialysis patients.* Clin J Am Soc Nephrol, 2008. **3**(4): p. 1115-24.

106. Amemiya, K., et al., *Effect of cutting balloon after rotational atherectomy in severely calcified coronary artery lesions as assessed by optical coherence tomography.* Catheter Cardiovasc Interv, 2019. **94**(7): 936-944.

107. Abizaid, A., et al., *Role of intravascular ultrasound and Doppler flow studies in coronary interventions.* Indian Heart J, 1998. 50 Suppl 1: 99-103.

108. Aksoy, A., et al., *Propensity-score-matched comparison of safety, efficacy, and outcome of intravascular lithotripsy versus high-pressure PTCA in coronary calcified lesions.* Int J Cardiol Heart Vasc, 2021. **37**: Article 100900.

109. Abizaid, A., et al., *Is intravascular ultrasound clinically useful or is it just a research tool?* Heart, 1997. **78** Suppl 2(Suppl 2): 27-30.

110. Zhang, M., et al., *Intravascular Ultrasound-Derived Calcium Score to Predict Stent Expansion in Severely Calcified Lesions.* Circ Cardiovasc Interv, 2021. **14**(10): Article e010296.

111. Yamamoto, M.H., et al., *Mechanisms of Orbital Versus Rotational Atherectomy Plaque Modification in Severely Calcified Lesions Assessed by Optical Coherence Tomography.* JACC Cardiovasc Interv, 2017. **10**(24): 2584-2586.

112. Hoffmann, R., et al., *Comparative early and nine-month results of rotational atherectomy, stents, and the combination of both for calcified lesions in large coronary arteries.* Am J Cardiol, 1998. **81**(5): 552-755.113. Balanescu, M. Fractional Flow Reserve Assessment of Coronary Artery Stenosis. Europ Cardiol. Rev.2016,11(2):77-82

APPENDIX 1

Curriculum Vitae of Candidate

Curriculum Vitae: Dr YASIR PARVIZ (July 2023)

Qualifications: MBBS, MRCP (UK), MRCP (Lon), CCT (medicine), CCT (cardiology), FACC, FRCP, MSc

Mobile and Email address: +971509698579
dr1yasir@hotmail.com /yasir.parviz@gmail.com

Personal Data:

Name: Yasir Parviz
D.O.B: 04.05.1979
Address: Home (Permanent),137 Bockinglane, Sheffie
Nationality: British

Certifications

Certificate of Completion of Training (CCT)	Cardiology	31/07/2015
Certificate of Completion of Training (CCT)	Internal Medicine	31/07/2015

Fellowships

08/2016 - 09/2017	Interventional Research Fellow	Columbia University Medical Centre. New York. Presbyterian Hospital. USA
01/2015- 12/ 2015	Interventional Fellow	The University of Western Ontario. London Health Sciences Centre. Canada
08/2011- 01/2015	Interventional Fellow	The Sheffield Hallam University. Sheffield Teaching Hospital. South Yorkshire. U. K

Scholarships and Awards

Gulf PCR-GIM 2017 Best Performing Clinician	Best Clinical Case Award
Academic Awards Year 1997-2002	Scholarships awarded by the University of Peshawar, for standing in "First Three" in all the Professional examinations.
Certificate of Merit Year 2002	Awarded for the best performance in internal medicine during the year 2002.
Academic Excellence Award	The 2nd Best graduate of the year 2002, by Ayub Medical College.

Career Plan

My career aim is to work in a cardiology centre, where I can continue to build on my experience and skills in the field of interventional cardiology. My goal is to excel in the challenging field of cardiology that would enable me to continue to improve my clinical skills, build up my research strengths, teach residents and medical students.

Professional Registration

The Society for Cardiac Angiography and Interventions
Royal College of Physicians, London UK
General Medical Council, UK

European Society of Percutaneous Intervention (EAPCI)
British Society of Cardiology, UK
The College of Physicians and Surgeons of Ontario (CPSO)
The Canadian Medical Protective Association
Medical Defence Unit

Professional Experience

Nov 2022- Present	Clemenceau Medical Centre Hospital Consultant Interventional Cardiologist
June 2021-Nov 2022	Kings College Hospital-Dubai-London Consultant Interventional Cardiologist Dubai
Dec 2017- June 2021	Director cardiac catheter labs Consultant Interventional Cardiologist Canadian Specialist Hospital Dubai UAE
October 2017 - December2017	Sherwood Hospitals NHs Trust Consultant Interventional Cardiologist

August 2016 - Sep2017	Imaging and Physiology Fellow New York Presbyterian Hospital & Columbia University Medical Centre. USA
January 2016- July 2016	Consultant Interventional Cardiologist. Northern Lincolnshire and Goole NHS Foundation Trust.UK
January 2015- January 2016	Advanced Interventional Fellow London Health Sciences Centre. Canada
August 2013- December 2014	Advanced interventional Fellow UK (Health Education Yorkshire and the Humber). Sheffield teaching Hospitals NHS Trust
August 2011- August 2013	Specialist registrar Cardiology (Health Education Yorkshire and the Humber). Sheffield teaching Hospitals NHS Trust
August 2010 - August 2011	Specialist registrar Cardiology (Health Education Yorkshire and the Humber).Chesterfield Royal Hospital NHS Trust
January2009-August 2010	Specialist registrar Cardiology (LAT) (Health Education Yorkshire and the Humber). Leeds General Infirmary

March 2008 –December 2008	Registrar in Cardiology University Hospitals of Morecambe Bay
August 2007 –March 2008	Clinical Registrar in Cardiology Heart of England NHS Trust
August 2006-August 2007	Registrar in Cardiology (Rotation) University Hospitals of Leicester NHS Trust
August 2005-August 2006	Senior House Officer, Critical Care. Good Hope Hospital. NHS Trust
November 2004 –August 2005	Senior House Officer, Medicine Birmingham Heartlands Hospital
February 2004 –November 2004	Clinical attachment Medicine Birmingham Heartlands Hospital
January 2003 –January 2004	House Officer, Medicine Reading Hospital, Peshawar Pakistan

Cath Lab Skills:

I have working experience as consultant interventional cardiologist as well as an interventional fellow in leading health care systems of UK, Canada, and the USA.

- I am fully trained in coronary angioplasty and have now been the first operator in over 5000PCIs.
- Radial-based approach (same day discharge) for Cardiac Cath procedures
- Emergency interventions for heart attack
- Multi-vessel disease management in patients where Bypass is turned down or declined.
- Interventions of vein graft cases and failures of CABG
- Intravascular lithotripsy or Shockwave therapy.
- Orbital atherectomy for severe calcification in coronary artery
- Rotational Atherectomy for complex disease
- Treatments for stent failures.
- Chronic total occlusions
- Right Heart catheterization.
- Pulmonary hypertension, evaluation, and assessment.

Expertise in the field of intracoronary imaging and physiology:

I have received dedicated training in coronary imaging and physiology from Columbia Medical Center and Cardiovascular Research Foundation (CRF).

I have developed the skills in the cutting-edge technology that in turn facilitates a better understanding of the mechanisms of coronary artery disease, coronary imaging, and physiology. I have gained competence in technical aspects of various imaging and coronary physiology techniques. These skills have consolidated my training, education and techniques in the field of coronary intervention and helping in future innovation and my research aspirations.

I am a teacher and trainer in the field and invited all over the world for talks and training in the field of imaging and physiology.

Expertise in interventions of patients with Diabetes and chronic kidney disease:

I have a particular interest in cardiovascular assessment of patients with chronic kidney disease. I have established the clinic database for cardiovascular assessment of patients undergoing renal, liver and pancreas transplant at Presbyterian Hospital, Columbia University Medical Centre, New York. This has helped us understand the cardiovascular outcomes in these complex cohort. I have pioneered the use of **zero contrast and ultra-low contrast PCI (ULPCI)** in high complex intervention using the IVUS co-registration/tri-registration technology (Philips) for patients with advanced kidney disease and low eGFR. I have helped in establishing the ULPCI program in the region.

I have Masters in the field of chronic kidney disease and cardiovascular implications from university of central Lancashire. UK.

Microvascular assessment: I have wide experience in performing and interpretation of coronary microvascular dysfunction (CFR / IMR) using the Coro ventis system (Abbott).

Complex coronary intervention: Extensive experience in performing advanced complex PCI including high risk and surgical turndown patients using rotational atherectomy, orbital atherectomy, shockwave lithotripsy, rota-tripsy technique, intracoronary imaging (IVUS/OCT), intra-coronary physiology and mechanical hemodynamic support.

Expertise in Renal Interventions:

I have dedicated training in the field of renal interventions and have particular interest in the renal denervation's therapy for treatment of hypertension.

Certification in Cardiac CT:

I have particular interest in cardiac CT and have attended dedicated training to gain expertise in the field.

Clinical Skills

Working as a consultant interventional cardiologist, I have full understanding of running a private clinic-based practise.

I have been actively practising cardiology in private setting for more than 5 years and have daily clinic appointments of patients requiring expertise in the field of cardiovascular medicine.

I have regular referrals from various other health care providers requiring expert cardiac care.

I have been actively involved in ward-based care and doing my own daily ward rounds and supervise the registrar and junior doctors in organising the ward rounds.

On call Commitments

I have experience of being on-call for regional cardiology centre as well as for district general hospital for Primary Percutaneous PCI (PPCI). My clinical outcomes are excellent as reflected by patient satisfaction.

Practical Skills

Invasive cardiology

Procedure	Number, N=	Competence, Level 3=independent
PCI	5000	Level 3
Coronary Angiogram	>3800	Level 3
Intravascular imaging (IVUS, OCT)	400	Level 3
Intracoronary physiology (FFR/IFR) Level 3	500	Level 3
Rotational atherectomy	30	Level 3
Right Heart catheterization	>200	Level 3
Temporary Pacing	>100	Level 3

Permanent Pacemaker	>100	Level 3
Reveal Devices	>30	Level 3
Peri cardiocentesis	>20	Level 3

Course	**Training Provider**	**Duration**	**Date Completed**
Canadian Cardiovascular Society Fellows Course (CCC)	CCC Toronto	2days	22/10/2015
Cardiovascular Research Foundation (CRF) Course	CRF USA	3days	22/05/2015
Trans Pennine PCI 2012.	Queens Hotel, Leeds	2 days	06/07/2012
East Midlands ACS Day	Derby Royal Hospital	1 day	13 /06/2012
Cath lab complications course	Derby Royal Hospital	1 day	04/07/2012
Bristol PCI course	Bristol Royal Infirmary	2 days	04/09/2011
Radial master class	University Hospital of Staffordshire	1 day	16/10/2012

Interventional trainees' course	Leeds	3 days	29/10/10
British cardiovascular Interventional society meeting	Manchester	1 day	07/05/2010
Coronary angiogram and PCI	Manchester Royal Infirmary	2 days	26/07/2009
BCS training Days	London	1day	06/12/2010
BCS training Days	Manchester	1 day	06/06/2010
ESC Congress	Munich, Germany	5days	03/09/2008
BCS Annual Scientific Conference	Manchester, UK	2 days	04/06/208
IMPACT Course	Hull Royal Infirmary	2days	27/09/ 2005
Clinical Radiology Course	Good Hope Hospital.	1 day	14/08/2005
ALS Course	Leeds General infirmary	2days	22/04/2014

Non –clinical courses:

Agent for change, Collaborating for quality	Kings Fund London	1 day	10/11/2010
Research skills &evidence-based medicine	Yorkshire Deanery	4 days	10/12/2009
Evidence -based medicine	Yorkshire Deanery	1 day	08/12/2009
Teaching and Presentation Skills Course	Yorkshire Deanery	3days	14/11/2009

Academic Experience:

Presentations:

A case of chest pain. Role of intracoronary imaging and physiology to diagnose anomalous coronary artery	Gulf PCR –GIM 2017
Role of intracoronary imaging and physiology in cardiac catheter lab	Dr Panjwani Centre for Molecular Medicine and Drug Research, Karachi, (Invited Lecture)
Feasibility, Safety, and Outcomes of Chronic Total Occlusion	TCT 2017, Denver

Revascularization in End-Stage Renal Disease	
External Elastic Lamina vs Luminal Diameter for Determination of Stent Diameter by Optical Coherence Tomography	TCT 2017, Denver
Revascularisation with Percutaneous coronary artery intervention	CCC Oct 2015, Toronto Canada
does not affect androgen status in males with chronic stable. angina pectoris	
Transfusion of stored RBCS have adverse impact on endothelial function	CCC Oct 2015, Toronto Canada
The effect of fresh versus old blood transfusion on endothelial function	ESC 2015, London UK
Myocardial protection: new strategies	The University of Western Ontario.
Clinical Presentation: Dyspnoea & Oedema	Yorkshire deanery regional teaching
Non-Invasive Investigation of Coronary Disease	Yorkshire deanery regional teaching
Blood Pressure control &Stroke prevention	National GP Forum
Herpes zoster Presentation for BHIVA	14th annual conference Belfast

Infective Endocarditis – Diagnosis & Management	Leicester General Hospital
Stroke in young patients – Diagnosis and management	Birmingham Heartlands Hospital
Phaeochromocytoma – Diagnosis & Management	Chesterfield Royal Hospital
Hyperthyroidism and Cardiovascular diseases	Chesterfield Royal Hospital

Invited speaker Faculty:

I am invited regularly on various conferences and meetings all over world.

Transcatheter Cardiovascular Therapeutics (TCT)

EuroPCR

Gulf PCR

Dr Panjwani Centre for Molecular Medicine and Drug Research, Karachi

Pakistan Cardiac Society

Pakistan interventional society

Pakistan Cardiac Society (Gulf Chapter).

Scientific Training Session, Abuja. Nigeria

Research Experience:

- I have a strong inclination towards research, as I believe it keeps one self-sharp in one's field and helps in learning the latest developments. Working on academic cardiovascular units has given me the opportunity to understand the basics of research methodology.
- I have experience of a dedicated research fellowship in the field of coronary physiology and coronary imaging at Columbia Medical Centre and Cardiovascular Research Foundation (CRF), one of leading organisation in the field of cardiovascular research.

- I was an investigator and collaborator of various studies at **Columbia University Medical Centre.**
- **ORACLE** (Comparison of Orbital versus Rotational Atherectomy Effects on Coronary Microcirculation in Percutaneous Coronary Intervention) (Protocol-noAAAQ9267).
- **OCT-IVUS-Dual-Imaging study** (Protocol- noAAAQ8295).
- **SIEMENS-FFR study** (Protocol-noAAAQ6857).
- **PERFORM (**Pressure Wire compared to microcatheter-based sensing technology for the evaluation of Coronary fractional flow reserve Measurements) (Protocol- noAAAQ1712).
- **ACIST FFR** (Protocol-noAAAQ2057).
- **Patients with Chronic kidney disease and CTO, feasibility, safety, and outcome study.**
- During my fellowship at **London Health Sciences Centre**, I build on to my research strengths and worked on "The effect of fresh versus old blood transfusion on endothelial Function".
- I have been involved in collaborative work with academic centres from **Turin and Edinburg** on the project of Frailty Assessment as a prognostic Tool in Elderly Acute Coronary Syndrome patients to Identify those approaching end-of-life: **FATE-ACS study**. This is a multicentre study, and I was lead from **Sheffield Teaching Hospital** and involved in the collection, compilation, and analysis of data. This experience was extremely useful in developing an understanding for the need of collaboration across the world to produce internationally competitive research.
- Worked in collaboration with world leading experts **Bertram Pitt and Faiez Zannad** about Mineralocorticoid Antagonism (MRA).
- Worked in **LIGHT institute in Leeds**, on the project of "First reported adherence vs non-adherence investigation (RANI 1)".
- Working at academic **Sheffield Teaching Hospital** involved in the recruitment of Project "Impact of Percutaneous Coronary Intervention on Testosterone Levels in Men with Chronic Stable Angina." STH Project Reference Number: STH 14219. Involved in various other research projects leading to peer-reviewed publications.
- To further enhance my skills, I have attended "Research skills &evidence-based medicine" course with Yorkshire deanery. Research skills Course, Code RES57- Nov 2009. Evidence- based

medicine 8th December 2009. Research in Cardiology: Why, When Where and How. 27th April 2012. Organised by BCIS Research & Development Committee.

Publications:

- Cellular and Molecular Approaches to Enhance Myocardial Recovery After Myocardial Infarction. **Yasir Parviz**, Mohammad Waleed, Sethumadhavan Vijayan, David Adlam, Shahar Lavi, Dr Arif Al Nooryani, Javaid Iqbal, Gregg W. Stone Ms. Cardiovasc Revas Med. 2018 Jun 2. pii: S1553-8389(18)30243-4. doi: 10.1016/j.carrev.2018.05.021.
- Pressure Wire Compared to Microcatheter Sensing for Coronary Fractional Flow Reserve: The PERFORM Study.Ali ZA, **Parviz Y**, Brinkman M, Matsumura M, Redfors B, Brogno DA, Corral MD, Fall KN, Mintz GS, Stone GW, Maehara A, Jeremias A, Kirtane AJ.
  Euro Intervention. 2018 May 15. pii: EIJ-D-18-00064. doi: 10.4244/EIJ-D-18-00064.
- Imaging and Physiology to Guide Venous Graft Interventions Without Contrast Administration in Advanced Renal Failure. **Yasir Parviz**, **MBBS, MRCP**, Khady Fall, MD, Gregg W. Stone, MD2; Akiko Maehara, MD, Ori Ben-Yehuda, MD, Gary S. Mintz, MD, Ziad A. Ali, MD, DPhil. J INVASIVE CARDIOL 2017;29(11): E163-E165.
- Utility of Intra Coronary Imaging in the Cardiac Catheterization laboratory: Comprehensive Evaluation with Intravascular Ultrasound and Optical Coherence Tomography
  Yasir Parviz, Evan Shlofmitz MD, Khady N Fall MD, Maayan Konigstein MD, Akiko Maehara MD, Allen Jeremias MD, Richard A Shlofmitz MD, Gary S Mintz MD, Ziad A Ali MD DPhil. Br Med Bull. 2018 Mar 1;125(1):79-90. doi: 10.1093/bmb/ldx049.
- A Review of Strategies for infarct size reduction during acute myocardial infarction **Parviz Y,** Sethumadhavan Vijayan, Lavi S. Cardiovascular Revascularization Medicine doi: 10.1016/j.carrev.2017.02.004.
- Using sound advice—intravascular ultrasound as a diagnostic tool. **Parviz Y,** Fall KN, Ali ZA J Thorac Dis 2016. doi: 10.21037/jtd.2016.10.64

- The effect of fresh versus standard blood transfusion on microvascular endothelial function. **Yasir Parviz,** Cyrus Hsia MD, Mistre Alemayehu MSc, Sabrina Wall BSc, Rodrigo Bagur MD, PhD, Nour Abu-Romeh BSc, Ian Chin-Yee, Shahar Lavi MD. Am Heart J. 2016 Aug: doi: 10.1016/j.ahj.2016.05.021
- Nitroglycerin-Derived Pd/Pa for the Assessment of Intermediate Coronary Lesions. Zeev Israeli, MD; Rodrigo Bagur ; Bogdan-Dorian Murariu, Sabrina Wall, Mistre Alemayehu, **Yasir Parviz**, , Pantelis Diamantouros, Shahar Lavi, J INVASIVE CARDIOL 2017 August 15
- Comparison of P2Y12 inhibitors for mortality and stent thrombosis in patients with acute coronary syndromes: single centre study of 10,793 consecutive 'real-world' patients. Rebecca Gosling, Momina Yazdani, **Yasir Parviz**, Ian R Hall, Ever D Grech, Julian P Gunn, Robert F Storey, Javaid Iqbal. CPLA-2016-0433.R1 Jan 2017 Platelets.
- Coronary Plaque Characteristics in Haemodialysis-Dependent Patients as Assessed by Optical Coherence Tomography American Journal of Cardiology. Chee Yang Chin; Mitsuaki Matsumura; Akiko Maehara, M.D.; Wenbin Zhang; Cheolmin T Lee; Myong Hwa Yamamoto; Lei Song; **Yasir Parviz**; Nishan Jhalani; Sumit Mohan; Lloyd E Ratner; David J Cohen; Ori Ben-Yehuda; Gregg W Stone; Richard A Shlofmitz; Tsunekazu Kakuta; Gary S Mintz; DOI: ttp://dx.doi.org/10.1016/j.amjcard.2017.01.022
- Emergency intervention in a case of an anomalous origin of the right coronary artery from the left anterior descending artery. **Parviz Y**, Rowe R, Rinze R. Am J Emerg Med. 2017 Jan 16. pii: S0735-6757(17)30017-7. doi: 10.1016/j.ajem.2017.01.017.
- Revascularization with percutaneous coronary intervention does not affect androgen status in males with chronic stable angina pectoris. Gosai JN, Charalampidis P, Nikolaidou T, **Parviz Y**, Morris PD, Channer KS, Jones TH, Grech ED. Andrology. 2016 Mar 29. doi: 10.1111/andr.12189.
- Percutaneous brachial artery access for coronary artery procedures: Feasible and safe in the current era **Yasir Parviz,** Rebecca Rowe, Sethumadhavan Vijayan, Javaid Iqbal, Allison C. Morton, EverD. Grech, Ian Hall, Julian Gunn.Doi: http://dx.doi.org/10.1016/j.carrev.2015.08.004
- Randomized Trial of Compression Duration Post Trans-Radial Cardiac Catheterization and Intervention. SHAHAR LAVI, ASIM N. CHEEMA, Andrew Yadegari, Zeev Israeli, Yaniv Levi,

Sabrina Wall, Mistre Alemayehu, **Yasir Parviz**, Bogdan-Dorian Murariu, Terry McPherson, Jaffer Syed, RODRIGO H. BAGUR DOI:10.1161/JAHA.116.005029

- Radiotherapy-induced Cardiac Implantable Electronic Device Dysfunction in Patients with Cancer.Rodrigo Bagur, MD, PhD. Mathilde Chamula, MD, Émilie Brouillard, MD, Caroline Lavoie, MD, Luis Nombela-Franco, MD, PhD, Anne-Sophie Julien, MSc, Louis Archambault, PhD, Nicolas Varfalvy, PhD, Valérie Gaudreault, MD, PhD, Sébastien X. Joncas, MD, Zeev Israeli, MD, **Yasir Parviz,** MBBS, Mamas A. Mamas, DPhil, Shahar Lavi, MD DOI: http://dx.doi.org/10.1016/j.amjcard.2016.09.036
- Emerging Cardiovascular Indications of Mineralocorticoid Receptors Antagonists. **Yasir Parviz**, Javaid Iqbal, Bertram Pitt, Sonal Mehra, David Adlam, Abdallah Al-Mohammad, Faiez Zannad DOI**:** http://dx.doi.org/10.1016/j.tem.2015.01.007
- Selection of a mineral corticoid receptor antagonist for patients with hypertension or heart failure. Iqbal J, Parviz Y, Pitt B, Newell-Price J, Al-Mohammad A, Zannad F. Eur J Heart Fail. 2014 Feb; 16(2):143-50. Doi: 10.1111/ejhf.31. Epub 2013 Dec 14
- Effect of eplerenone in PCI -treated post-myocardial infarction patients with left ventricular systolic dysfunction: a sub-analysis of the EPHESUS trial, Javaid Iqbal, Renaud Fay, David Adlam, Iain Squire, **Yasir Parviz**, Julian Gunn, Bertram Pitt, Faiez Zannad **Eur J** Heart Fail. 2014 Jun; 16(6):685-91. Doi: 10.1002/ejhf.88. Epub 2014 Apr 4
- Calculating the overall risk of within-stent restenosis after multilesion percutaneous coronary intervention. **Yasir Parviz**, Hannah Gul, Simon Smith, Ever D. Grech. Postep Kardiol Inter 2013; 9, 2 (32): 170–171. (Advances in Interventional Cardiology)
- Repeat coronary angiography with previously normal arteries: a futile exercise? Rebecca Rowe, **Yasir Parviz**, Javaid Iqbal, James Heppenstall, Dawn Teare Julian Gunn. Catheter Cardiovasc Interv. 2014 Jun 27. Doi: 10.1002/ccd.25589
- Giant saphenous vein graft aneurysm presenting as stridor. **Yasir Parviz**; William Parker; Peter Brown; John N. West European Heart Journal - Cardiovascular Imaging 2013; doi: 10.1093/ehjci/jet253

- Audit of cardiac catheterisation in a district general hospital: implications for training and patient safety. **Y Parviz**, A Rothman, C J Cooke. Volume 21 Issue 3 July–September 2014 the British Journal of Cardiology, *Br J Cardiol* 2014.
- Impact of frailty on outcomes after percutaneous coronary intervention: a prospective cohort study.Rachel Murali-Krishnan, Javaid Iqbal, Rebecca Rowe, Emer Hatem, **Yasir Parviz**, James Richardson, Ayyaz Sultan and Julian Gunn *Open Heart* 2015;2: doi:10.1136/openhrt-2015-000294
- "A 16-year-old boy with chest pain" Walker AM, **Parviz Y**, Heppenstall J, Best J, Grech ED.BMJ. 2014 Oct 15; 349: g6172. doi: 10.1136/bmj. g6172
- Prospective assessment of a palliative care tool to predict one-year mortality in patients with acute coronary syndrome. Moretti C, Iqbal J, Murray S, Bertaina M, **Parviz Y**, Fenning S, Quadri G, Gunn J, D'Ascenzo F, Marra S, Moiraghi C, Riccardini F, Veglio F, Gaita F, Denvir M. Eur Heart J Acute Cardiovasc Care. 2016 Feb 15. pii: 048872616633841
- "A case of chest pain, abnormal Electrocardiogram and Skin lesions" **Y Parviz**, NH Shah - JMC803W, J Med Cases • 2012; 3(6):358-360 Journal of Medical Cases, 2012 - journalmc.org
- "Left Atrial Myxoma with Concurrent Saddle Pulmonary Embolism and Duke's B Adenocarcinoma" Mehra, Sonal; **Parviz, Yasir**; Al-Mohammad, Abdallah JMC1243W,
- Incidence and predictors of stent thrombosis: a single Centre study of 5,833 consecutive patients undergoing coronary artery stenting. Euro intervention. Iqbal J, Sumaya W, Tatman V, **Parviz Y,** Morton A, Grech E, Campbell S, R, Gunn Euro Intervention. 2013 May 20;9(1):62-9. doi: 10.4244/EIJV9I1A10
- Acute coronary syndrome and anaesthesia/ AAGBI core topics in anaesthesia, book chapter. ISBN. 9781118777442, **Y Parviz**, R Orme, T Chico.
- Left ventricular free wall rupture complicating acute STEMI. Fent, Grech E, **Parviz Y**, Briffa N. Acute Card Care. 2016 Mar 16:1
- Imaging and Physiology to Guide Venous Graft Interventions without Contrast Administration in Advanced Renal Failure. **Yasir Parviz**, MBBS MRCP, Khady Fall MD, Gregg W Stone MD, Akiko Maehara MD, Ori Ben-Yehuda MD, Gary S. Mintz MD, Ziad A. Ali, MD DPhil. Journal of invasive cardiology. Accepted manuscript, Aug 2017.

- Mechanisms of Orbital Versus Rotational Atherectomy Plaque Modification in Severely Calcified Lesions Assessed by Optical Coherence Tomography. Myong Hwa Yamamoto, MD Akiko Maehara, MD, Keyvan Karimi Galougahi, MD, Gary S. Mintz, MD, Yasir Parviz, MD, Sung Sik Kim, MD, Kohei Koyama, MD, PhD, Kisaki Amemiya, MD, Song-Yi Kim, MD, Masaru Ishida, MD, Monica Losquadro, MS, Ajay J. Kirtane, MD, SM, Elizabeth Haag, RN, Fernando A. Sosa, MS, Gregg W. Stone, MD, Jeffery W. Moses, MD, Masahiko Ochiai MD, PhD, Richard A. Shlofmitz, MD, Ziad A. Ali, MD, DPhil. JACC Cardiovasc Interv. 2017, (in press).
- Pressure Wire Compared to Microcatheter-Based Sensing Technology for the Evaluation of Coronary Fractional Flow Reserve Measurements. Ziad A. Ali, MD, DPhil, **Yasir Parviz**, MBBS, Matthew Brinkman, MS, Mitsuaki Mitsumura, BS, Björn Redfors, MD, Keyvan Karimi Galougahi, MD, PhD, Tamim M. Nazif, MD, Jeffrey W. Moses, MD, David Brogno, MD, Manish A. Parikh, MD, Philip Green, MD, Dimitri Karmpaliotis, MD, PhD, Maria Corral, MD, Khady N. Fall MD, MPH, Gary S. Mintz, MD, Ori Ben-Yehuda, MD, Gregg W. Stone, MD, Martin B. Leon, MD, Akiko Maehara, MD, Allen Jeremias, MD, MSc, Ajay J. Kirtane, MD, SM. JACC Cardiovasc Interv. 2017, (in press).
- Cephalic Vein Access - A Feasible, Safe and Effective Method for Device Implantation. Khan HR, Shah N, Parviz Y.J Ayub Med Coll Abbottabad. 2017 Jul-Sep;29(3):514-515.

- Role Of Intra Coronary Imaging and Physiology In Diagnosis And Management of Coronary Artery Disease. **Yasir Parviz**, Kokab Awan, Sethumadhavan Vijayan, Ayyaz Sultan, Javaid Iqbal. April 2017 J Ayub Med Coll Abbottabad 2017;29(3):

Abstracts:

- Feasibility, safety, and outcomes of chronic total occlusion revascularization in end-stage renal disease. **Yasir Parviz** MBBS, Matthew Finn MD Nisha B Jhalani MD, Bharath G. Rathakrishnan MD, Keyvan Karimi Galougahi MD, Raja Hatem MD, Gary S. Mintz MD, Akiko Maehara MD, Ajay J. Kirtane MD SM, Ori Ben-Yehuda MD, Gregg W. Stone MD, Martin B. Leon MD, Mark A Hardy MD, Sumit Mohan MD, Jai Radhikrishnan MD, David J Cohen MD, Lloyd E Ratner

MD MPH, Emmanouil S Brilakis MD, Jeffrey W. Moses MD Dimitri Karmpaliotis MD PhD, Ziad A. Ali MD DPhil

- External elastic lamina vs luminal diameter for determination of stent diameter by optical coherence tomography. **Yasir Parviz***, Evan Shlofmitz*, Bjorn Redfors, Mitsuaki Matsumura, Khady N Fall, Akiko Maehara, Gary S Mintz, Allen Jeremias, Fernando Sosa, Elizabeth Haag, Keyvan Karimi Galougahi, Dimitri Karmpaliotis, Ajay Kirtane, Jeffrey Moses, Charles Simonton, Ori Ben-Yehuda, Gregg W Stone, Richard A Shlofmitz, Ziad A Ali
- Derivation and Validation of a Luminal Diameter Correction Factor for Determination of Stent Sizing by Optical Coherence Tomography: An ILUMIEN III sub-study. Evan Shlofmitz MD, **Yasir Parviz** MD, Richard A. Shlofmitz MD, Akiko Maehara MD, Franco Fabbiocchi MD, Tamim M. Nazif MD, Giulio Guagliumi MD, Perwaiz M. Meraj MD, Fernando Alfonso MD, Habib Samady MD, Takashi Akasaka MD, Eric B. Carlson MD, Massoud A. Leesar MD, Mitsuaki Matsumura BS, Melek Ozgu Ozan MS, Gary S. Mintz MD, Ori Ben-Yehuda MD, Charles Simonton MD, Gregg W. Stone MD, Ziad A. Ali MD for the ILUMIEN III: OPTIMIZE PCI Investigators
- U ltra-Low Contrast Coronary Angiography in Patients with Advanced Chronic Kidney Disease - Feasibility and Outcomes Compared to Standard Angiography Navdeep K Bhatti MD, Nisha B Jhalani MD, Keyvan Karimi Galougahi MD, **Yasir Parviz** MBBS, Bharath G. Rathakrishnan MD, Tamim M. Nazif MD, Jeffrey W. Moses MD, Susheel Kodali MD, Dimitri Karmpaliotis MD PhD, Gary S. Mintz MD, Akiko Maehara MD, Ajay J. Kirtane MD SM, Ori Ben-Yehuda MD, Gregg W. Stone MD, Martin B. Leon MD, Russell J. Crew MD, Geoffery Dube MD, Mark A Hardy MD, Sumit Mohan MD, Jai Radhikrishnan MD, David J Cohen MD, Lloyd E Ratner MD MPH, Ziad A. Ali MD DPhil
- Incidence and predictors of stent thrombosis: a single Centre study of 5,833 consecutive patients undergoing coronary artery stenting. Abstract EUROPCR 2013 Javaid Iqbal, Wael Sumaya, Victoria Tatman **Yasir Parviz**, Allison C Morton, Stephen Campbell, Robert F Storey, Julian Gunn

- Frailty assessment as a prognostic tool in elderly acute coronary syndrome patients to identify those approaching end –of –life: results from prospective multicentre FATE –ACS study. Eur Heart J (2013) 34 (supple 1): doi:10.1093/eurheartj/eht309.P3083
C.Moretti, S Fenning **Y. Parviz**, J. Gunn, F. D Ascenzo, F. Giusto, F Gaital, J Iqbal,
- Lower mortality and stent thrombosis rates associated with introduction of potent $P2Y_{12}$ inhibitors in patients with acute coronary syndromes. Javaid Iqbal*, Rebecca Rowe*, Yao-Jun Zhang, **Yasir Parviz**, Ever D Grech, Julian Gunn, Robert F Storey. Abstract AHA 2014
- "Initial HIV diagnosis and management, does site influence partner notification"?
Presented at the annual scientific BAASH meeting –May 2006.Published in Journal of STD &AIDS **Yasir Parviz**
- Radiotherapy-induced Cardiac Implantable Electronic Device Disorders In Cancer Patients. Abstracts 14945 AHA 2015M. Chamula: C.Lavoie: É.Brouillard:.S.Lavi . L. Nombela-Franco : A.Julien: L. Archambault: N. arfalvy: F. Turcotte-Gosselin: F. eaupré: S.X. Joncas: .V. Gaudreault: **Y. Parviz:** P.J. Teefy: R. Bagur
- The effect of fresh versus old blood transfusion on endothelial Function" abstract
ESC 2015. **Y. Parviz** , Doi. http://dx.doi.org/10.1016/j.cjca.2015.07.491.
- Revascularisation with Percutaneous coronary artery intervention does not effect androgen status in males with chronic stable angina pectoris, abstract CCC Oct2015 Toronto Canada J. Gosai, Parviz, Y. P., Chlarampidis, T. Nikolaidou, P. Morris, E .Grech, http://dx.doi.org/10.1016/j.cjca.2015.07.019
- Impact of Frailty on Length of Hospital Stay after Percutaneous Coronary Intervention. Murali-Krishnan R, Iqbal J, Rowe R, **Parviz Y**, Sultan A, Gunn J Heart. 2014 Jun; 100(Supple 3):A45. Doi: 10.1136/heartjnl-2014-306118.77.
- Non sustained rise of serum testosterone with PCI. Abstract for ACC 2013
- Non-invasive estimation of left ventricular filling pressure with MRI: preliminary experience Swift AJ, **Parviz Y**, Rothman A, Capener D and Al-Mohammad A. Abstract. Euro CMR 2016

- A prospective, randomized trial of short vs long radial arterial clamp duration following cardiac catheterization. Postcath Radial Arterial Clamp Time In the CAth Lab

(PRACTICAL)Shahar Lavi, Andrew Yadegari, Asim Cheema, Rodrigo Bagur, Nour Aburomeh, Yaniv Levi, **Yasir Parviz**, Zeev Israeli, Kokab Awan, Mistre Alemayehu, Dorian Murariu, Sabrina Wall, Terry McPherson, Jaffer Syed. Circulation. 2016;134: A14370

Audits:

- Audit of Diagnostic Cardiac Catheterization in a District General Hospital: Implications for Training and Patient Safety.
- An audit of clopidogrel prescribing according to guidelines.
- An audit of morbidity and mortality in tertiary cardiology centre.
- Repatriation of patients from tertiary cardiology centre.
- Incidence and predictors of stent thrombosis: a single centre study of 5,833 consecutive patients undergoing coronary artery stenting.

- **Director of the cardiac Audit, interventional cardiology research and Quality Improvement Projects:**

  I have been director of (QIP) at various teaching hospitals where I have practiced. I have special interest and wide experience in QIP, research, academia, developing/ improving policies, protocols and new services that help to deliver a high-quality service.

Management Experience:

- MSc (Advancing health care practice, in progress), Open University of UK.
- Postgraduate Certificate of Attainment at Improvement Practitioner level from NHS Institute for Innovation and Improvement. 20th March 2013. London UK.
- Represented Chesterfield Royal Hospital at Agent for change, Collaborating for the quality conference at Kings Fund London 2010.
- 3-day Management course, Organised by Health Education Yorkshire (H.E.Y) and Humber 29th to 31st October 2014.
- Chief Fellow at London Health Sciences Center for the year 2015-2016

- SpR representative at Sheffield teaching hospital NHS Trust DMT.
- Organiser for induction and placement of medical students from Sheffield University to the hospital.
- Reviewed the local clinical practice, and designed and implemented the new guidelines for the management of ACS at Airedale Hospital NHS trust.
- Organised PACES examinations at Leicester Royal infirmary and Leeds general Infirmary. Medical rota manager at Heart of England NHS trust.

Teaching Experience:

- I have been actively involved in the teaching of Master Programme (MED6052: Vascular Disease & Clinical Practice) at Sheffield Hallam university.
- Lectures to undergraduate medical students at the University of Sheffield on general cardiology.
- Formal teaching to foundation year doctors and SHO's on the management of a variety of cardiology conditions on regular basis.
- Formal teaching to SHO for PACES examination and actively involved in regional teaching for CMT trainees.
- Examiner for medical student OSCE at the University of Sheffield.
- Coordinator for phase-2 cardiovascular clinical skills teaching.
- Attended Teaching and Presentation Skills Course. Oct/Nov 2009 organised by Yorkshire deanery.
- Currently undertaking a post-graduation certificate in teaching and learning for the health care professional (TLHP) at University of Sheffield.

Additional Skills:

- Proficient in:
- Microsoft Word, Microsoft Excels and PowerPoint.
- Conducting literature review & Database.

- Passed European Computer Driving License Exam.

Personal interests:

- Enjoy cycling, running, and playing Hockey. I am passionate about cricket, and keenly follow the experiences of the Pakistani and English cricket teams.

References:
Will be provided as required.

APPENDIX 2

(All 16 Full Publications)

LIST OF SIXTEEN FULL PAPERS TO FORM PhD BY PUBLICATION AND CLASSIFIED INTO THREE CATAGORIES

A. Intracoronary imaging and physiology (10 papers)

1.Parviz, Y., Fall, K., Stone, G., Maehara, A., Ben-Yehuda, O., Mintz, G., and Ali, Z. (2017). Imaging and Physiology to Guide Venous Graft Interventions Without Contrast Administration in Advanced Renal Failure. The Journal of Invasive Cardiology, 29: E163-E165, **(Impact Factor 1.07 and 6 citations).**

2. Parviz, Y. (2017). Intra coronary imaging to detect mal apposition: Are We Seeing Too Much. Heart. (A BMJ Journal), 103 (9): Article 2017; 0- heartjnl-2015-307888v1) (**Impact Factor 5.42 and no citation).**

3. Parviz, Y., Evan, S., Khady N.F., Maayan K., Akiko, M., Allen, J., Richard, A.S., Gary, S.M., and Ziad A.A. (2017). Utility of intracoronary imaging in the cardiac catheterization laboratory: comprehensive evaluation with intravascular ultrasound and optical coherence tomography. British Medical Bulletin, 125(1):79-90. (doi: 10.1093/bmb/ldx049. **(Impact Factor: 3.045 and 18 citations).**

4. Parviz, Y., P., Khady N.F., and Ziad A.A (2016). Using sound advice—intravascular ultrasound as a diagnostic tool. Journal of Thoracic Diseases. 8(10): E1395-E1397. (doi: 10.21037/jtd.2016.10.64. 10.21037/jtd.2016.10.64, **(Impact Factor: 2.365 and 3 citations).**

5. Chin, C., Matsumura, M., Maehara, A., Zhang, W., Lee, C., Yamamoto, M., Song, L., **Parviz, Y.,** Jhalani, N., Mohan, S., Ratner, L., Cohen, D., Ben-Yehuda, O., Stone, G., Shlofmitz, R., Kakuta, T., Mintz, G., and Ali, Z. (2017). Coronary Plaque Characteristics in Haemodialysis-Dependent Patients as Assessed by Optical Coherence Tomography. The American Journal of

Cardiology. American Journal of Cardiology,119(9): 1313-1319. (doi: 10.1016/j.amjcard.2017.01.022. Epub 2017 Feb 9. **(Impact factor: 2.26 and no citation)**

6. **Parviz, Y.,** Awan, K., Vijayan, S., Sultan, A., and Iqbal, J. (2017). Role Of Intra Coronary Imaging and Physiology in Diagnosis And Management Of Coronary Artery Disease. Journal of Ayub Medical College, Abbottabad: JAMC. 29: 516-522. **(Impact Factor 0.481 and 515 citations).**

7.Yamamoto, M.H., Maehara, A., Karimi, G.K, Mintz, G.S., **Parviz. Y**., Kim, S.S., Koyama, K., Amemiya, K., Kim, S.Y., Ishida, M., Losquadro, M., Kirtane, A.J., Haag. E., Sosa, F.A., Stone, G.W., Moses, J.W., Ochiai, M., Shlofmitz, R.A., and Ali Z.A. (2017). Mechanisms of Orbital Versus Rotational Atherectomy Plaque Modification in Severely Calcified Lesions Assessed by Optical Coherence Tomography. JACC Cardiovascular Intervention, 10(24): 2584-2586. (doi: 10.1016/j.jcin.2017.09.031. PMID: 29268891), (**Impact Factor: 11.2 and no citation).**

8. Ali, Z., **Parviz, Y.,** Brinkman, M., Matsumura, M., Redfors, B., Brogno, D., Corral, M., Fall, K., Mintz, G., Stone, G., Maehara, A., Jeremias, A., and Kirtane, A. (2018). Pressure Wire Compared to Microcatheter Sensing for Coronary Fractional Flow Reserve: The PERFORM Study. Euro-Intervention: Journal of Euro-PCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 14(4): e459-e466. doi: 10.4244/EIJ-D-18-00064. **(Impact Factor 6.534 and 5 citations).**

9. Shlofmitz, E., Jeremias, A., **Parviz, Y.,** Karimi, G.K., Redfors, B., Petrossian, G., Edens, M., Matsumura, M., Maehara, A., Mintz, G., Stone, G., Shlofmitz, R., and Ali, Z. (2020). External elastic lamina vs. luminal diameter measurement for determining stent diameter by optical coherence tomography: an ILUMIEN III sub-study. European Heart Journal of Cardiovascular Imaging. 22(7):753-759. doi: 10.1093/ehjci/jeaa276 **(Impact Factor: 6.875 and no citation).**

10. Israeli, Z., Bagur, R., Murariu, D., Wall, S., Alemayehu, M., **Parviz, Y**., Diamantouros, P., and Lavi, Shahar. (2017). Nitro-glycerine-Derived Pd/Pa for the Assessment of Intermediate Coronary Lesions. The Journal of Invasive Cardiology. 29(12): E177-E183. **Impact Factor:1.07 and 1 citation).**

B. MR antagonism and cardiovascular diseases (3 Papers)

11. Iqbal, J., Parviz, Y., Pitt B, Newell-Price, J., Al-Mohammad, A., and Zannad, F. (2014). Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure. European Journal of Heart Failure, 16(2):143-150. (doi: 10.1111/ejhf.31. PMID: 24464876), **(Impact Factor of 15.534 and 52 citations).**

12. Iqbal, J., Fay, R., Adlam, D., Squire, I., **Parviz, Y.,** Gunn, J., Pitt, B., and Zannad, F. (2014). Effect of eplerenone in percutaneous coronary intervention-treated post-myocardial infarction patients with left ventricular systolic dysfunction: A sub-analysis of the EPHESUS trial. European Journal of Heart Failure, 16: 685–691, (16.10.1002/ejhf.88**. (Impact Factor 15.534 and 24 citations).**

13. Parviz, Y., Iqbal, J., Pitt, B., Adlam, D., Al-Mohammad, A., and Zannad, F. (2015). Emerging cardiovascular indications of mineralocorticoid receptor antagonists. Trends in Endocrinology and Metabolism, April 2015, Vol. 26 (4):201-211 (26.10.1016/j.tem.2015.01.007), **(Impact Factor: 12.015 and 31 citations).**

C. Infarct Size and endothelial function (3 Papers)

14. Parviz, Y., Vijayan, S., and Lavi, S. (2017). A Review of Strategies for infarct size reduction during acute myocardial infarction. Cardiovascular Revascularization Medicine, vol and Cardiovascular Revascularization Medicine, 18(5): 374-383. (doi: 10.1016/j.carrev.2017.02.004. (18. 10.1016/j.carrev.2017.02.004), (**Impact Factor: 1.168 and 15 citations).**

15. Parviz, Y., Waleed, M., Vijayan, S., Adlam, D., Lavi, S., Nooryani, A., Iqbal, J., and Stone, Gregg. (2018). Cellular and Molecular Approaches to Enhance Myocardial Recovery After Myocardial Infarction. Cardiovascular Revascularization Medicine. 20(4):351-364. (doi: 10.1016/j.carrev.2018.05.021. Epub, (**Impact Factor: 1.168 and 32 citation).**

16. Parviz, Y., Hsia, C., Alemayehu, M., Wall, S., Bagur, R., Abu-Romeh, N., Chin-Yee, I., and Lavi, S. (2016). The effect of fresh versus standard blood transfusion on microvascular endothelial function. American Heart Journa,181:156-161. (10.1016/j.ahj.2016.05.021. **(Impact Factor 4.749 and 1,315 citations).**

(A). First ten publications on intracoronary imaging and physiology

A) Intracoronary Imaging and Physiology

1. **Parviz, Y.,** Fall, K., Stone, G., Maehara, A., Ben-Yehuda, O., Mintz, G., and Ali, Z. (2017). Imaging and Physiology to Guide Venous Graft Interventions Without Contrast Administration in Advanced Renal Failure. The Journal of Invasive Cardiology, 29 (11): E163-E165, **(Impact Factor 1.07 and 6 citations).**

2. **Parviz, Y.** and Hanif, S. **(2017).** Intra coronary imaging to detect mal apposition: Are We Seeing Too Much. Heart. (A BMJ Journal), 103 (9): Article 2017; 0- heartjnl-2015-307888v1) **(Impact Factor 5.42 and no citation).**

3. **Parviz, Y.,** Shiofmitz, E., Fall, K.N., Konigstein, M., Maehara, A., M., Jerimias, A., Shlofmitz, R.A., A.S., Mintz, G.S., and Ali, Z.A.. (2018). Utility of intracoronary imaging in the cardiac catheterization laboratory: comprehensive evaluation with intravascular ultrasound and optical coherence tomography. British Medical Bulletin, 125(1):79-90. (doi: 10.1093/bmb/ldx049. **(Impact Factor: 3.045 and 18 citations).**

4. **Parviz, Y., P.,** Fall, K.N., , and Ali, ZA. (2016). Using sound advice—intravascular ultrasound as a diagnostic tool. Journal of Thoracic Disease. Journal of Thoracic Diseases. 8(10): E1395-E1397. (doi: 10.21037/jtd.2016.10.64. 10.21037/jtd.2016.10.64, **(Impact Factor: 2.365 and 3 citations).**

5. Chin, C., Matsumura, M., Maehara, A., Zhang, W., Lee, C., Yamamoto, M., Song, L., **Parviz, Y.,** Jhalani, N., Mohan, S., Ratner, L., Cohen, D., Ben-Yehuda, O., Stone, G., Shlofmitz, R., Kakuta, T., Mintz, G., and Ali, Z.A. (2017). Coronary Plaque Characteristics in Haemodialysis-Dependent Patients as Assessed by Optical Coherence Tomography. The American Journal of Cardiology. American Journal of Cardiology,119(9): 1313-1319. (doi: 10.1016/j.amjcard.2017.01.022. Epub 2017 Feb 9. **(Impact factor: 2.26 and no citation)**

6. **Parviz, Y.,** Awan, K., Vijayan, S., Sultan, A., and Iqbal, J. (2017). Role Of Intra Coronary Imaging and Physiology in Diagnosis And Management Of Coronary Artery Disease. Journal of Ayub Medical College, Abbottabad: JAMC. 29(3): 516-522. **(Impact Factor 0.481 and 515 citations).**

7. Yamamoto, M.H., Maehara, A., Karimi, G.K, Mintz, G.S., **Parviz. Y**., Kim, S.S., Koyama, K., Amemiya, K., Kim, S.Y., Ishida, M., Losquadro, M., Kirtane, A.J., Haag. E., Sosa, F.A., Stone, G.W., Moses, J.W., Ochiai, M., Shlofmitz, R.A., and Ali Z.A. (2017). Mechanisms of Orbital Versus Rotational Atherectomy Plaque Modification in Severely Calcified Lesions Assessed by Optical Coherence Tomography. JACC Cardiovascular Intervention, 10(24): 2584-2586. (doi: 10.1016/j.jcin.2017.09.031. PMID: 29268891), **(Impact Factor: 11.2 and no citation).**

8. Ali, Z., **Parviz, Y.,** Brinkman, M., Matsumura, M., Redfors, B., Brogno, D., Corral, M., Fall, K., Mintz, G., Stone, G., Maehara, A., Jeremias, A., and Kirtane, A. (2018). Pressure Wire Compared to Microcatheter Sensing for Coronary Fractional Flow Reserve: The PERFORM Study. Euro-Intervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 14(4): e459-e466. doi: 10.4244/EIJ-D-18-00064. **(Impact Factor 6.534 and 5 citations).**

9. Shlofmitz, E., Jeremias, A., **Parviz, Y.,** Karimi, G.K., Redfors, B., Petrossian, G., Edens, M., Matsumura, M., Maehara, A., Mintz, G.S, Stone, G. W., Shlofmitz, R. A., and Ali, Z. (2021). External elastic lamina vs. luminal diameter measurement for determining stent diameter by optical coherence tomography: an ILUMIEN III sub-study. European Heart Journal - Cardiovascular Imaging. European Heart Journal of Cardiovascular Imaging. 22(7):753-759. doi: 10.1093/ehjci/jeaa276 **(Impact Factor: 6.875 and no citation).**

10. Israeli, Z., Bagur, R., Murariu, B-D., Wall, S., Alemayehu, M., **Parviz, Y**., Diamantouros, P., and Lavi, S. (2017). Nitro-glycerine-Derived Pd/Pa for the Assessment of Intermediate Coronary Lesions. The Journal of Invasive Cardiology. 29(12): E177-E183. **Impact Factor:1.07 and 1 citation).**

Manuscript 1

Imaging and Physiology to Guide Venous Graft Interventions Without Contrast Administration in Advanced Renal Failure

Yasir Parviz, MBBS, MRCP[1]; Khady Fall, MD[1]; Gregg W. Stone, MD[1,2]; Akiko Maehara, MD[1,2]; Ori Ben-Yehuda, MD[1,2]; Gary S. Mintz, MD[3]; Ziad A. Ali, MD, DPhil[1,2]

J INVASIVE CARDIOL 2017;29(11):E163-E165.
KEY WORDS: PCI, chronic kidney disease, coronary artery bypass graft, intravascular ultrasonography, coronary physiology

Patients with previous coronary artery bypass grafting and advanced chronic kidney disease (CKD) are considered high risk for revascularization. In addition to native coronary artery angiography, additional contrast is required to visualize the bypass conduits, increasing the risk of contrast-induced nephropathy (CIN) and need for renal replacement therapy. As a result, despite the need for revascularization, these patients are frequently under-treated.[1] There is evidence in the literature that intravascular ultrasound (IVUS)-guided interventions reduce the amount of contrast and its associated risk of CIN.[2] We recently described intravascular imaging and physiology-guided percutaneous coronary intervention (PCI) without contrast administration in advanced CKD.[3] Here we describe step-by-step "zero-contrast" saphenous vein bypass graft (SVG) intervention using a modified technique.

- Ultra-low contrast angiography, defined as contrast volume/estimated glomerular filtration rate <1, is performed.
- The left ventricular end-diastolic pressure is used to guide hydration.
- Imaging- and physiology-guided PCI is performed 1 week after angiography.
- Guide-catheter engagement is confirmed by the entry of a workhorse guidewire into the SVG.
- A pressure wire capable of measuring pressure and flow is used to record the baseline fractional flow reserve (FFR) and coronary flow reserve (CFR).
- Near-infrared spectroscopy (NIRS)/IVUS (Infraredx) is used for assessment of reference vessel sizing, stent landing zones, and plaque composition with stent length based on the distance between the two reference areas, ensuring complete lesion coverage.
- The NIRS/IVUS catheter is re-advanced, manually marking the landing zones by "dry" cine angiograms for co-registration.
- An embolic protection device is considered for high lipid-core burden index (LCBI).[4,5] $LCBI_{4mm}$ is a quantitative summary metric of the total lipid-core plaques detected over any 4 mm segment of vessel relative to total length of the pullback.
- Following stent deployment, NIRS/IVUS identifies areas of under-expansion and postdilation is performed to optimize PCI results.
- Final FFR confirms resolution of ischemia and CFR the absence of slow flow with improved absolute flow.

References

1. Dangas G, Iakovou I, Nikolsky E, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol.* 2005;95:13-19.
2. Mariani J Jr, Guedes C, Soares P, et al. Intravascular ultrasound guidance to minimize the use of iodine contrast in percutaneous coronary intervention: the MOZART (Minimizing cOntrast utiliZation With IVUS Guidance in coRonary angioplasTy) randomized controlled trial. *JACC Cardiovasc Interv.* 2014;7:1287-1293.
3. Ali ZA, Karimi Galougahi K, Nazif T, et al. Imaging- and physiology-guided percutaneous coronary intervention without contrast administration in advanced renal failure: a feasibility, safety, and outcome study. *Eur Heart J.* 2016;37:3090-3095.
4. Goldstein JA, Maini B, Dixon SR, et al. Detection of lipid-core plaques by intracoronary near-infrared spectroscopy identifies high risk of periprocedural myocardial infarction. *Circ Cardiovasc Interv.* 2011;4:429-437.
5. Stone GW, Rogers C, Hermiller J, et al; FilterWire EXREI. Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. *Circulation.* 2003;108:548-553.

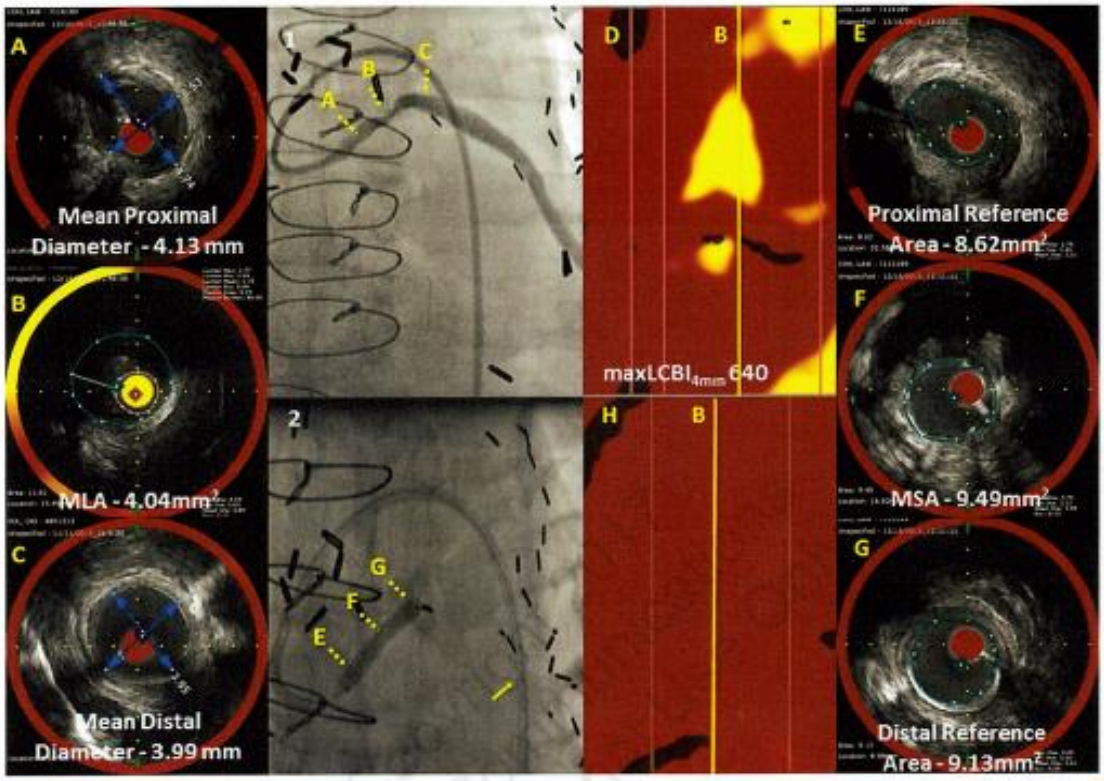


FIGURE 1. (1) Ultra-low contrast angiography identified a lesion in the proximal saphenous vein graft (SVG) to first obtuse marginal artery (fractional flow reserve 0.74; coronary flow reserve 1.8) in a patient with chronic kidney disease (CKD) stage V. Intravascular ultrasound (IVUS) marked the (A) proximal reference, (B) minimal luminal area, and (C) distal reference. (D) The block chemogram identified a large lipid core with max lipid core burden index ($LCBI_{4mm}$ 640), (2) based on which embolic protection device (EPD; yellow arrow) was deployed followed by stenting with a 3.50 x 20 mm drug-eluting stent (DES). Postdilation was performed with a non-compliant 3.75 x 15 mm balloon at 20 atm to areas of underexpansion identified by IVUS. Following PCI optimization, the (E) proximal reference area was found to be smaller than the (F) minimal stent area and (G) distal reference area confirming optimal stent expansion. (H) The block chemogram showed a significant reduction in the lipid burden (max $LCBI_{4mm}$ 120) and absence of yellow at the site of previous max LCBI consistent with lipid embolization, captured in the EPD (B). Improved fractional flow reserve (0.91) and coronary flow reserve (3.1) confirmed physiological improvement. *(continued)*

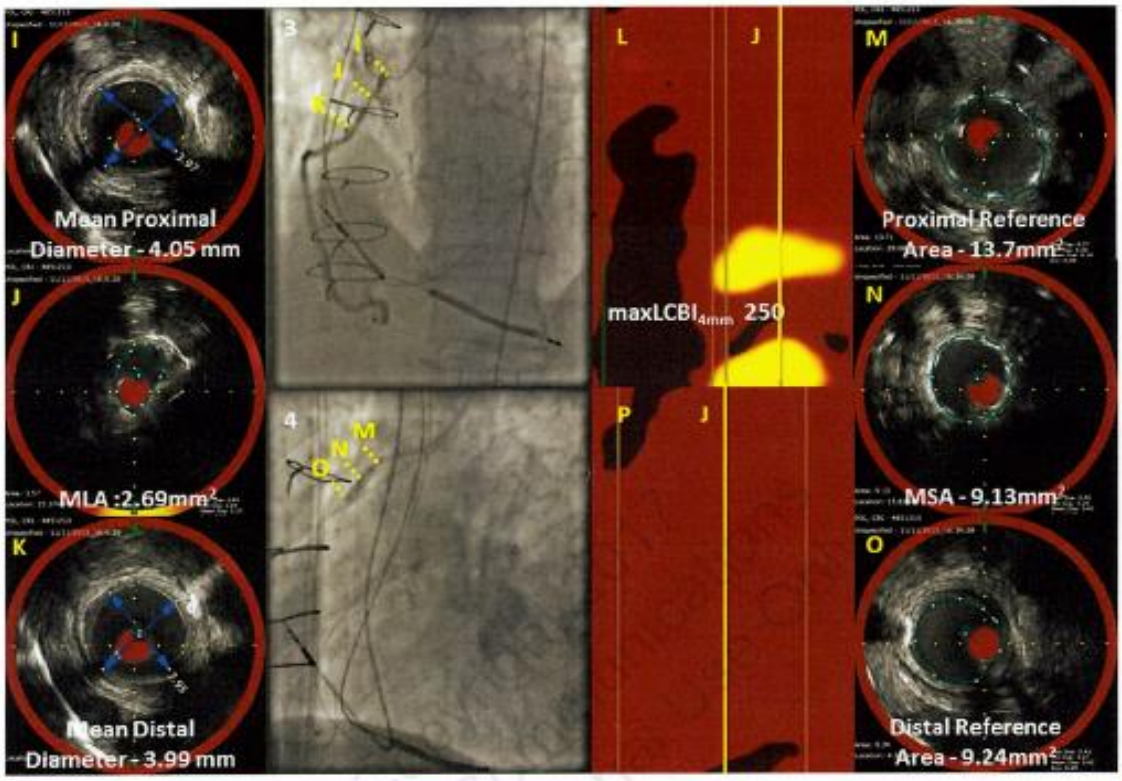


FIGURE 1 *(continued)*. [3] Ultra-low contrast angiography identified a lesion in the proximal SVG to posterior descending artery (fractional flow reserve 0.70; coronary flow reserve 1.1) in a patient with CKD stage V. IVUS marked the (I) proximal reference, (J) minimal luminal area, and (K) distal reference. (L) The block chemogram identified a lipid core with max $LCBI_{4mm}$ 250 corresponding with the minimal luminal area (J) and thus, no EPD was used. (4) Following stenting with a 3.5 x 15 mm DES, postdilation was performed with a non-compliant 3.75 x 12 mm balloon at 22 atm to areas of underexpansion identified by IVUS. Following PCI optimization, the (M) proximal reference area was larger than the (N) minimal stent area (9.13 mm²), as was the (O) distal reference area, confirming optimal stent expansion. (P) The block chemogram no longer identified significant lipid burden (max $LCBI_{4mm}$ 90). Improved fractional flow reserve (0.89) and coronary flow reserve (2.0) confirmed physiological improvement.

From the [a]Division of Cardiology, Center for Interventional Vascular Therapy, New York-Presbyterian Hospital & Columbia University, New York, New York; and the [b]Cardiovascular Research Foundation, New York, New York.

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Stone reports grants from the Cardiovascular Research Foundation, personal fees from Valvemedix, Toray, Matrizyme, Miracor, TherOx, Reva, V-wave, Vascular Dynamics, Ablative Solutions, Neovasc, Medical Development Technologies; equity/options from the MedFocus family of funds, Guided Delivery Systems, Micardia, Vascular Nanotransfer Technologies, Cagent, Qool Therapeutics, Caliber, Aria, the Biostar family of funds; consultant on prasugrel patent litigation paid for by Lupin Pharmaceuticals. Dr Maehara reports payment for independent CEC, core lab, and statistical analysis to the Cardiovascular Research Foundation. Dr Ben-Yehuda reports grant funds from St. Jude Medical. Dr Ali reports personal fees from St. Jude Medical, Acist Medical, and CSI; grant funds from St. Jude Medical. Dr Mintz reports grant funds from St. Jude and Boston Scientific; personal fees from Boston Scientific and Acist Medical. The remaining authors report no conflicts of interest regarding the content herein.

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Manuscript 2

BMJ JOURNALS

- HEART: Volume 103, Issue 9; 708 responses

Title of E-letter: Intra coronary imaging to detect mal-apposition: Are We Seeing Too Much!

E-letter ID: heartjnl_el;19674
Authors Name: Yasir
Parviz and Dr Sadia Hanif
Institution: Columbia University Medical Center
Occupation: Doctor
This letter is a response to: Alessandra Giavarini, Ismail Dogu Kilic, Alfredo Redondo Diéguez, Giovanni Longo, Isabelle Vandormael, Nilesh Pareek, Ritesh Kanyal, Ranil De Silva, Carlo Di Mario

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Main Text:
We would like to congratulate Giavarini A et al on this comprehensive, educational article on intracoronary imaging.1 Various modalities can be used to understand the mechanism of stent failure, and there is an ongoing debate on detection of stent mal-apposition, and whether this has any clinical impact. Acute stent mal-apposition on its own is not associated with adverse clinical events unless associated with under expansion or having inflow- outflow issues. Acute mal-apposition and its associated clinical events are possibly reduced due to negative remodelling.2 The clinically events are non-significant may be due to the fact that newer generation of stents and stronger antiplatelets are performing very well. There is limited literature evidence to support that acute mal-apposition is associated with stent thrombosis.3 Late acquired mal-apposition in combination with other contributing factors can be associated with stent failure. Most of the available literature looking into the mechanism of stent failure is from IVUS studies and newer technology, OCT due to superior resolution has the ability to detect a higher percentage of mal appositions. [Table 1] There is on-going research on to the clinical significance of these findings. Table 1. Detection of mal-apposition by IVUS /OCT and Clinical impact.(can provide in table form as well)

1) Im et al. Circ Cardiovasc Interv 2014;7: 88-96 356(n),62%(OCT), no impact.
2)Kubo et al. JACC Cardiovasc Imaging 2013;6:1095-104 100(n), 14%(IVUS), 39%(OCT), no impact
3) Kawamori et al. EHJ Cardiovasc Imaging 2013; 14:865-75 40(n), 65%(OCT), no impct

4) Bezerra et al. JACC Cardiovasc Interv 2013;6: 228-36 26(n), 42% (IVUS), 96%(OCT), no impact
5) Ali ZA et al Lancet. 2016 Nov 26;388(10060):2618-2628 304(n), 39% (IVUS), 41% OCT, no impact
6) Prati et al JACC Cardiovascular Imaging November 2015 2015;8: 1297- 832(n), 50%(OCT), no impact
7) Prati F et al Am Heart J. 2015 Feb;169(2):249-56.
63 (n), 52%(OCT), no impact
8) Hong et al, Circulation. 2006; 113:414-9 557(n), 12 %(IVUS), no impact
9) Steinberg et al J Am Coll Cardiol Intv 3:486-494 1,580 1580(n), 7-10%(IVUS), no impact
10) Soeda et al Circulation. 2015 Sep 15;132(11):1020-9 786(n), 39%(OCT), no impact
11) Kimura M Am J Cardiol. 2006;98: 436-442. 168(n) 77% (IVUS), no impact
12) Cook S Circulation. 2007;115: 2426-2434. 144(n),77%(IVUS) , had clinical impact.
13) Guo et al. Circulation 2010;122: 1077-84 241(n),35%(IVUS), no impact
14) Choi et al. Circ Cardiovasc Interv 2010; 122:1077-84 356(n),62% (IVUS), no impact

References.

1.Giavarini A, Kilic ID, Redondo Dieguez A, Longo G, Vandormael I, Pareek N, Kanyal R, De Silva R and Di Mario C. Intracoronary Imaging. Heart. 2017.

2. Guo N, Maehara A, Mintz GS, He Y, Xu K, Wu X, Lansky AJ, Witzenbichler B, Guagliumi G, Brodie B, Kellett MA, Jr., Dressler O, Parise H, Mehran R and Stone GW. Incidence, mechanisms, predictors, and clinical impact of acute and late stent mal-apposition after primary intervention in patients with acute myocardial infarction: an intravascular ultrasound sub-study of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. Circulation. 2010; 122:1077-84.

3. Alfonso F, Suarez A, Angiolillo DJ, Sabate M, Escaned J, Moreno R, Hernandez R, Banuelos C and Macaya C. Findings of intravascular ultrasound during acute stent thrombosis. Heart. 2004;90: 1455-9.

4. Ali ZA, Maehara A, Genereux P, Shlofmitz RA, Fabbiocchi F, Nazif TM, Guagliumi G, Meraj PM, Alfonso F, Samady H, Akasaka T, Carlson EB, Leesar MA, Matsumura M, Ozan MO, Mintz GS, Ben-Yehuda O, Stone GW and Investigators IIOP. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. Lancet. 2016;388:2618-2628.

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Invited Review

Utility of intracoronary imaging in the cardiac catheterization laboratory: comprehensive evaluation with intravascular ultrasound and optical coherence tomography

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Abstract

Background: Intracoronary imaging is an important tool for guiding decision making in the cardiac catheterization laboratory.

Sources of data: We have reviewed the latest available evidence in the field to highlight the various potential benefits of intravascular imaging.

Areas of agreement: Coronary angiography has been considered the gold standard test to appropriately diagnose and manage patients with coronary artery disease, but it has the inherent limitation of being a 2-dimensional x-ray lumenogram of a complex 3-dimensional vascular structure.

Areas of controversy: There is well-established inter- and intra-observer variability in reporting coronary angiograms leading to potential variability in various management strategies. Intracoronary imaging improves the diagnostic accuracy while optimizing the results of an intervention. Utilization of intracoronary imaging modalities in routine practice however remains low worldwide. Increased costs, resources, time and expertise have been cited as explanations for low incorporation of these techniques.

Growing points: Intracoronary imaging supplements and enhances an operator's decision-making ability based on detailed and objective lesion

assessment rather than a subjective visual estimation. The benefits of intravascular imaging are becoming more profound as the complexity of cases suitable for revascularization increases.

Areas timely for developing research: While the clinical benefits of intravascular ultrasound have been well validated, optical coherence tomography in comparison is a newer technology, with robust clinical trials assessing its clinical benefit are underway.

Key words: intravascular ultrasound, optical coherence tomography, percutaneous coronary intervention

Introduction

Coronary angiography is considered the gold standard for the assessment of coronary artery disease.[1] Cardiologists perform millions of coronary angiograms annually worldwide.[2] Angiography is a 2-dimensional lumenogram of a complex 3-dimensional arterial structure; therefore, it is limited in providing accurate diagnostic information. An angiogram using multiple orthogonal views with visual estimation can provide information about a patient's coronary artery anatomy; however, this approach has several limitations due to inherent operator variability, which can lead to wide differences in interpretation of stenosis severity obtained from angiography in comparison to non-invasive imaging, expert core lab assessment, computer assisted measurements and autopsy comparisons.[3,4] Though conventional coronary angiography is universally available and has good spatial and temporal resolution, it is limited in its ability to provide anatomical intravascular data and offers no insight into the physiologic correlation of the disease process.[1,5] These shortcomings are most obvious in challenging situations; for instance, coronary artery calcification is underdiagnosed with angiography in as many as half the cases compared to intravascular ultrasound (IVUS).[3]

Intracoronary imaging can help reduce the high intra- and inter-observer variability in the interpretation of stenosis severity and morphology of lesions that exists with angiographic assessment.[3] The technology provides precise and computerized measurements that help guide the decision-making process and reduces the variability in reporting.[6,7] Intravascular imaging (IVI) can provide detailed information about vessel anatomy, extent and severity of the disease process, plaque morphology and precise vessel sizing for stent selection (Fig. 1). This information helps guide decision making and facilitates revascularization with percutaneous coronary interventions (PCI). Modern advances with IVI have made the technology user-friendly and available for routine use in the cardiac catheterization laboratory.[8] Its use is of particular importance when treating complex higher risk indicated patients including for treatment decisions involving the left main stem and bifurcation disease.[4,5,9,10] Adjunctive IVI can help us understand the mechanisms underlying stent failures. Despite the well-established role of IVI and innovations in technology, the everyday use of these modalities remains low worldwide.[10]

IVUS

IVUS is a sound-based technology that uses a specially designed catheter with an ultrasound probe to visualize intracoronary anatomy.[11] IVUS has been in use for more than half a century; its clinical utility has been validated in multiple randomized trials, and there are ongoing studies demonstrating the role of IVUS in improving clinical outcomes.[12] Real-time 360° cross-sectional images are obtained with IVUS, providing additional information and enhancing what is known from the lumen contours obtained by angiography. Detailed information in regard to the lumen, vessel size and plaque morphology can be valuable in the decision-making process. IVUS has the capacity to provide information on perivascular structures (perivascular damage) due to higher penetration power.

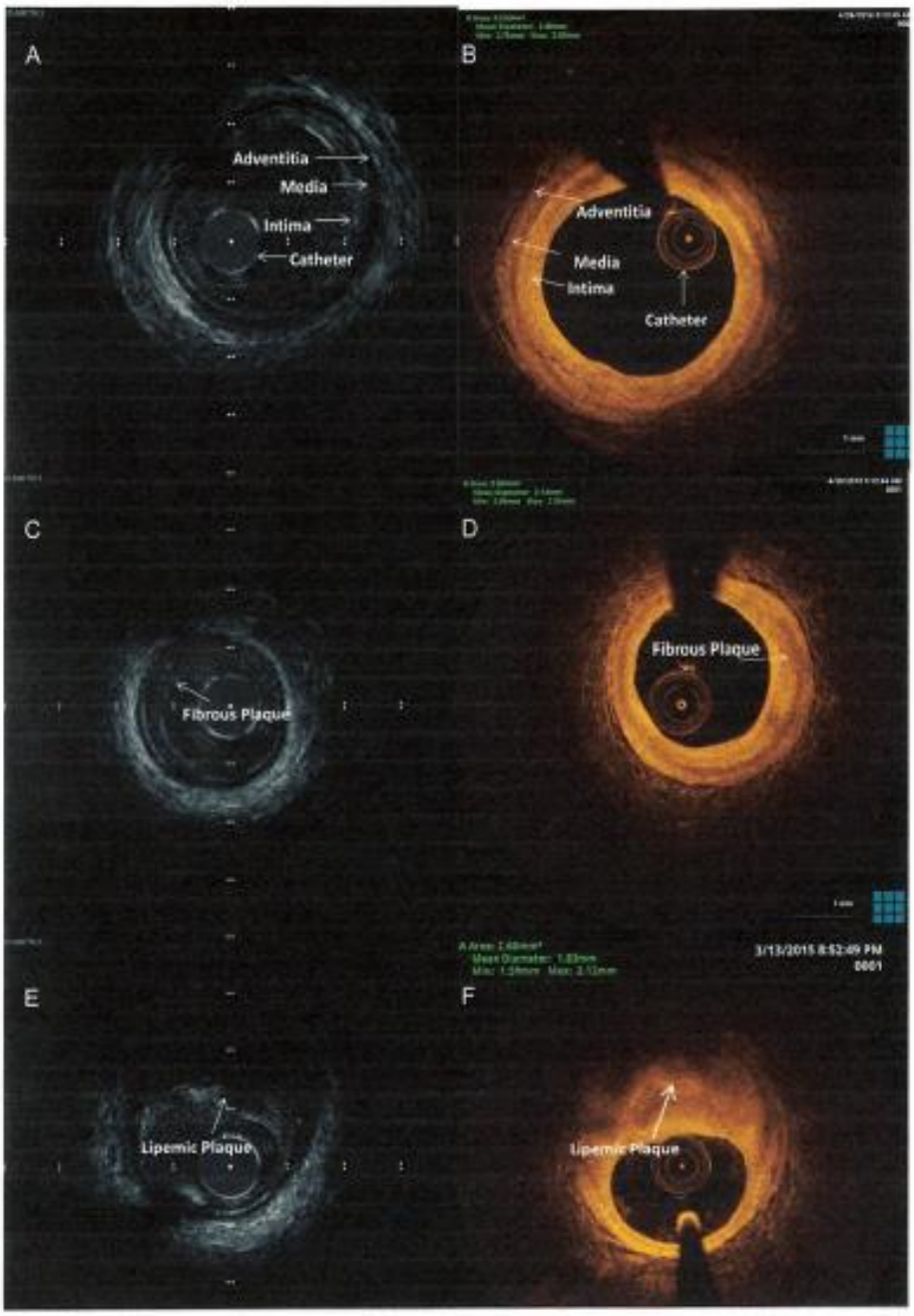

Fig. 1 Various plaque morphologies as seen by intravascular ultrasound (IVUS) (left) and optical coherence tomography (OCT) (right). (**A** and **B**) Normal characteristics of the vessel wall. (**C** and **D**) Eccentric fibrotic plaque. (**E** and **F**) Lipid plaque. The lipid component of the plaque is echolucent (IVUS) and also appears as a low signal (low light reflection, OCT). (**G** and **H**) Calcium creates a deep acoustic shadowing that hides the underlying structures (asterisk) and hampers the delineation of the external elastic membrane. The posterior boundary of the calcium deposit (asterisk) appears sharp and well visible with OCT (**H**). (**I** and **J**) Stented segments.

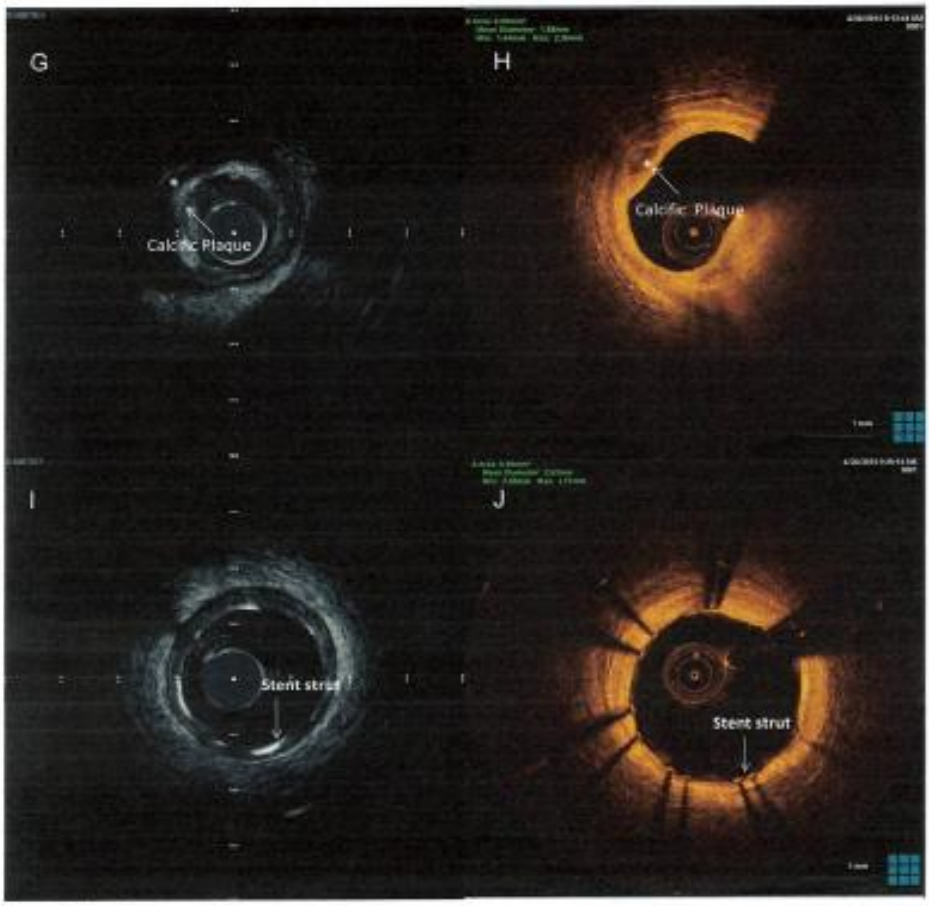

Fig. 1 *Continued*

IVUS can be used at any stage of the procedure. As part of a diagnostic assessment, IVUS can help to assess the plaque morphology, selecting the stent sizing based on lumen dimensions and selecting the precise length of a stent. During the procedure IVUS can confirm stent expansion and maximal luminal gain. Postprocedure imaging can help identify possible complications including dissections, under-expansion, malapposition, tissue protrusion and hematomas.

Large-scale data from randomized trials have demonstrated that an IVUS-guided revascularization strategy compared with angiography-guided PCI can lead to improved clinical outcomes.[13] The Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions (IVUS-XPL) randomized, multicenter trial was conducted in 1 400 patients with long coronary lesions (implanted stent ≥28 mm in length) and demonstrated that IVUS-guided everolimus-eluting stent implantation, compared with angiography-guided stent implantation, resulted in a significantly lower rate of the composite endpoint of major adverse cardiac events at 1 year.[14]

An in-depth review by Mintz. demonstrated the importance of imaging-guided revascularization in its review of nine randomized trials and 30 registry studies comparing IVUS-guided DES implantation with conventional angiographic guidance.[15] Specifically IVUS guidance was associated with a reduction in

adverse events in all of the nine meta-analyses to date on this topic and was a cost-effective strategy.

The Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study was a large study that included a pre-specified substudy that demonstrated the benefit of utilization of IVUS therapy in the 3349 (39%) patients treated with IVUS-guided PCI.[7] Utilization of IVUS changed the PCI strategy in 74% of cases. Not only did IVUS impact decision making at the time of PCI, but the changes led to improved clinical outcomes compared with angiographic guidance. At 1 year, there was a significant reduction in definite/probable stent thrombosis (0.52% versus 1.04%, $P = 0.003$) and MI (2.5% versus 3.7%, $P = 0.004$) as well as the composite of major adverse cardiac events (3.1% versus 4.7%, $P = 0.002$).

The utility of IVUS has been recognized by various cardiac societies and recommended in the decision-making process in the cardiac catheterization laboratory. The use of IVUS has been encouraged in the assessment of intermediate lesions, for guiding stent implantation, and for determining the cause of stent thrombosis (Table 1).

Guideline updates now include a new class IIa recommendation that supports using IVUS for the assessment of angiographically indeterminate left main coronary artery disease (Table 2). Table 2 Current guideline recommendations for use of intravascular ultrasound and optical coherence tomography.

Serial surveillance with IVUS to monitor intima-media thickness post-heart transplantation has also been included in the recommendations for 4–6 weeks post-cardiac transplant and at 1 year follow-up.[18] Another benefit of IVUS is with high-risk groups including patients with renal insufficiency undergoing percutaneous revascularization; in these patients, IVUS guidance can help reduce the volume of contrast administered.[19] IVUS-guided PCI has been used to develop a 'zero contrast' PCI strategy to treat patients at high risk of developing contrast-induced nephropathy.[20] IVUS can also be useful in cases of apparently normal coronary arteries on angiography. Patients presenting with chest pain and positive non-invasive testing with discordant findings on angiography should undergo further evaluation with IVUS to exclude the presence of occult disease or clinical significance of an anomalous origin of a coronary artery.[21] Lastly, in the setting of acute emergencies in patients presenting with acute chest pain, IVUS can facilitate the diagnoses of acute aortic and coronary dissections.[22]

Optical coherence tomography

Optical coherence tomography (OCT) is a newer intracoronary imaging modality in comparison to IVUS. Naohiro Tanno and James G. Fujimoto developed this technology during the 1990s with initial ophthalmologic applications that led to the first OCT-based imaging catheter used in a coronary artery, with the first in-man report published in 2001.[23] This light-based technology has differences in comparison to sound-based IVUS.[24] OCT has higher axial resolution of 10–15 μm in contrast to the 150–200 μm resolution achieved with conventional IVUS catheters.[25] The high resolution helps delineate the three layers of an arterial wall and can differentiate between different tissue characteristics, providing detailed assessment for dissection, tissue prolapse, thrombi and stent apposition.[26] While OCT has higher resolution, the penetration is lower compared with

Table 1 Comparison of angiography and intravascular imaging modalities

Angiography	Intravascular ultrasound/optical coherence tomography
2-Dimensional	360° View
Planar	Tomographic and sagittal
Shadow of lumen	Visualization of shape and location
Wall structure not imaged	Visualization of inner wall structures and morphology
Vessel is seen for short time period during the contrast injection	Confluent imaging; the whole vessel can be imaged
Quantitative coronary angiography analysis with mistakes	Spatial imaging precise assessment

Table 2 Current guideline recommendations for use of intravascular ultrasound and optical coherence tomography

ACCF/AHA/SCAI guidelines for PCI recommendations (2011)[15,16]	ESC guidelines in myocardial revascularization (2014)[17]
Intravascular ultrasound	
• IVUS is reasonable for the assessment of angiographically indeterminate left main coronary artery disease (Class IIa, Level of Evidence: B)	• IVUS to asses severity and optimize treatment of unprotected left main lesions (Class IIa, Level of evidence B)
• IVUS and coronary angiography are reasonable 4–6 weeks and 1 year after cardiac transplantation to exclude donor coronary artery disease, detect rapidly progressive cardiac allograft vasculopathy, and provide prognostic information (Class IIa, Level of Evidence: B)	• IVUS in selected patients to optimize stent optimization (Class IIa, Level of evidence B)
• IVUS is reasonable to determine the mechanism of stent restenosis (Class IIa, Level of Evidence: C)	• IVUS to assess mechanisms of stent failure (Class IIa, Level of evidence C)
• IVUS may be reasonable for the assessment of non–left main coronary arteries with angiographically intermediate coronary stenosis (50–70% diameter stenosis) (Class IIb, Level of Evidence: B)	
• IVUS may be considered for the guidance of coronary stent implantation, particularly in cases of left main coronary artery stenting (Class IIb, Level of Evidence: B)	
• IVUS may be reasonable to determine the mechanism of stent thrombosis (Class IIb, Level of Evidence: C)	
• IVUS for routine lesion assessment is not recommended when revascularization with PCI or CABG is not being contemplated (Class III, Level of Evidence: C)	
Optical coherence tomography	
• The appropriate role for optical coherence tomography in routine clinical decision making has not been established	• OCT should be considered in patients to understand the mechanism of stent failure (Class IIa, Level of evidence C)
	• OCT in selected patients to optimize stent implantation (Class IIb, Level of evidence C)

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; IVUS, intervascular ultrasound; OCT, optical coherence tomography; SCAI, Society for Cardiovascular Angiography and Interventions.

IVUS. To obtain images, OCT requires displacement of blood from the segment being evaluated during imaging acquisition. While initially achieved by proximal balloon occlusion with time-domain OCT, in contemporary practice this is routinely achieved by contrast injection using frequency domain-OCT.

The unique features of OCT offer the ability to identify a very thin fibrous cap covering the lipid core and can potentially be used to predict future coronary events by identifying vulnerable plaques.[27] Compared with IVUS, which uses ultrasound technology and cannot penetrate calcium, OCT can assess the depth of calcium in a coronary lesion.[28–31] This insight can alter patient management, as the operator can appropriately determine the need for lesion preparation and the use of atherectomy if indicated. OCT can improve PCI results with the precise and accurate information it provides, identifying the ideal landing zones for a stent and aiding the selection of appropriate stent sizing. One of the particular advantages of this technology is to provide detailed information during cases of stent failure to help understand the mechanism of failure.[32–34] Small thrombi that may be missed by angiography or IVUS can be detected by OCT. The

resolution of OCT can also provide detailed lesion assessment, identifying the etiology of restenosis, by helping to determine if restenosis is focal or diffuse, and detecting the presence of neo-intimal thickening, microvessels, stent under-expansion and intraluminal calcification.[32,33,35] Knowledge of the characteristics and morphology of in-stent restenosis influences the subsequent management, which can vary widely to include a change in antiplatelet therapy, laser atherectomy or brachytherapy.

The CLI-OPCI study demonstrated that an OCT-guided strategy changed the decision-making process in 35% of cases. OCT-guided stent implantation reduced mortality and MI at 1 year. The CLI-OPCI study also demonstrated that select patients with ST-elevation MI could be identified who could be treated with thrombus aspiration alone based on an OCT finding of plaque erosion rather than fibrous cap rupture.[36]

The clinical safety of OCT was demonstrated in the Does Optical Coherence Tomography Optimize Results of Stenting (DOCTORS) study, wherein 240 patients presenting with non-ST-elevation MI were randomized to either OCT-guided PCI or angiography-guided PCI. The DOCTORS study found that OCT did not increase periprocedural complications, type 4a MI or acute kidney injury. OCT-guided PCI was associated with higher postprocedure FFR than PCI guided by angiography alone.[37]

In the EROSION study, a proof of concept study, patients with residual stenosis <70% and plaque erosion identified on OCT in the setting of ACS, were treated with anti-thrombotic therapy without stenting. OCT imaging helped to determine in which patients stenting could safely be avoided.[38]

To determine the ideal OCT-based stent sizing strategy, the ILUMIEN III: OPTIMIZE PCI study randomized 450 patients to IVUS-guided, OCT-guided or angiography-guided PCI.[26] The ILUMIEN III trial found that an external elastic lamina-based stent optimization strategy was safe and resulted in similar minimum stent area to that of IVUS-guided PCI. There was a trend toward benefit of OCT over angiography guidance.

A number of inherent limitations of OCT technology exist, as it requires the displacement of blood for adequate visualization. There are some difficulties obtaining the optimal image quality in cases of large diameter or aneurysmal vessels and in aorto-ostial lesions. As contrast is traditionally used to displace blood, OCT is often avoided in patients with renal failure as there are risks of contrast-induced kidney injury. Alternative non-contrast based flush agents are being evaluated in clinical studies for this patient population.

OCT is a safe and effective intracoronary modality used in cardiac catheterization laboratory that has been studied in multiple large-scale studies with a favorable safety profile.[39] There are ongoing clinical trials to demonstrate the impact of this technology in improving long-term clinical outcomes.[26] As further data is published, insights into the economic impact of OCT can be ascertained.

We recommend an algorithmic approach with IVI for comprehensive evaluation of coronary lesions (Fig. 2). Use of IVI both pre- and post-PCI can optimize results. Pre-PCI lesion assessment can determine the plaque morphology and provide guidance on when lesion preparation is needed. IVI provides measurements of the lesion length and vessel dimensions guiding stent selection. This can result in fewer stents used as well as an increased likelihood of appropriate stent sizing.[7,26] Post-PCI imaging is critical to confirm adequate stent expansion and exclude the presence of significant edge dissections or hematomas. When cases of stent failure are encountered, IVI is particularly important to determine the mechanism of stent failure. Determining the etiology of stent failure will impact how the patient is subsequently treated.

Areas of controversy

Low utilization of IVI in routine practice is often explained by the following criticisms: (i) IVI is too complicated to obtain and interpret, (ii) results are already good enough with modern equipment and techniques, (iii) IVI is unlikely to significantly change patient management, (iv) IVI is too expensive, (v) IVI takes too much time and (vi) IVI involves excessive risk. These issues can all be overcome by an understanding of the different technologies available and interpretation of the images (Table 3).

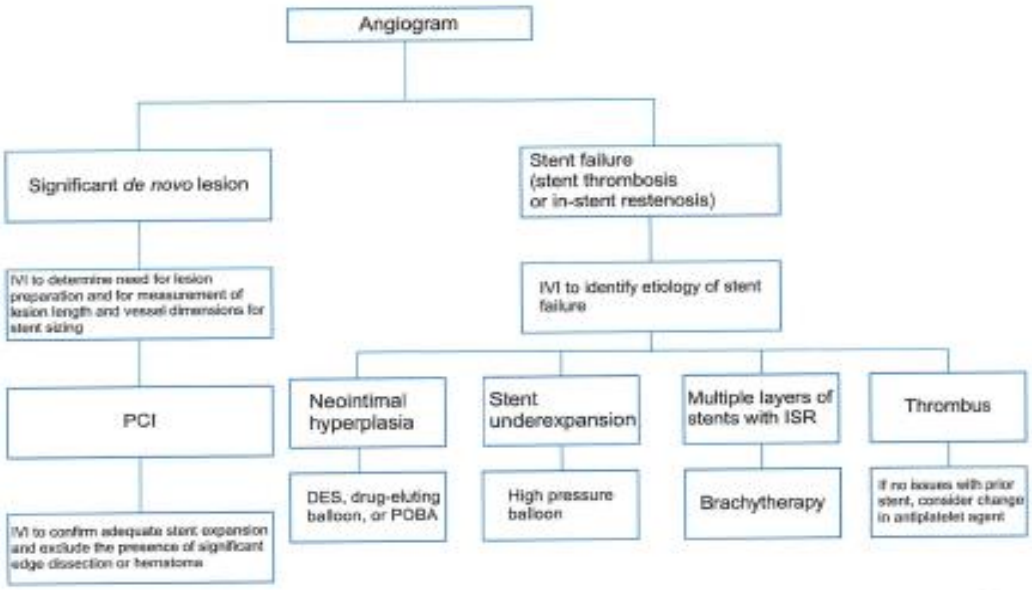

Fig. 2 Algorithmic approach for utilization of intracoronary imaging. DES = drug-eluting stent; ISR = in-stent restenosis; IVI = intravascular imaging; PCI = percutaneous coronary intervention; POBA = plain old ballon angioplasty.

An algorithmic approach can allow an interventional cardiologist to incorporate IVI into his or her daily practice while individualizing therapy and tailoring treatment to each patient.

Growing points

As costs decline for IVI tools with improved reimbursement, utilization may improve. Additionally, further availability and integration into existing catheterization laboratory systems can improve utilization. Software including co-registration with angiography can improve diagnostic accuracy and utility of the data obtained with IVI.

Areas timely for developing research

There is large-scale evidence for utility of IVUS in clinical practice with a large number of trials currently ongoing. Clinical research interest in OCT is profound as well, with clinical studies underway to assess how best to incorporate OCT to improve the clinical outcomes for patients. The beneficial clinical role of OCT-guided therapy for assessment of plaque morphology and stent optimization is planned to be evaluated in the ILUMIEN IV multicenter trial.

Studies currently in progress include OPTICO-ACS (NCT03129503), which will assess the *in vivo* characterization of the ACS-causing 'culprit lesion'; Optical Coherence Tomography Intravascular Ultrasound Dual Imaging (NCT02984891), which will compare IVUS and OCT; Optical Coherence Tomography Findings and Coronary Bifurcation Lesions (NCT03172845); 6-month Intracoronary Optical Coherence Tomography Evaluation of Three New Generation Drug Eluting Stent (CREBX-OCT) (NCT02850497); Optical Coherence Tomography to Improve Clinical Outcomes During Coronary Angioplasty (NCT02065102); Optical Coherence Tomography Assessment of Gender diVersity In Primary Angioplasty (OCTAVIA) (NCT02577965); Optical Coherence Tomography Morphologic and Fractional Flow Reserve Assessment in Diabetes Mellitus Patients (COMBINE) (NCT02989740),[63] and Evaluation of Statin-induced Lipid-rich Plaque

Table 3 Comparison of angiography, intravascular ultrasound and optical coherence tomography for various clinical scenarios

Clinical feature	Angiography	IVUS	OCT	Evidence
Assessment of left main coronary artery stenosis	†	†††	†	IVUS[40,41] vs OCT[42]
Assessment of non-left main coronary artery stenosis	††	††	†††	IVUS[43,44] vs OCT[26,39,45,46]
Localize the culprit lesion	†	††	†††	IVUS[47,48] vs OCT[48–50]
Identify a vulnerable plaque	0	†† (VH-IVUS)	†††	IVUS[48,51–53] vs OCT[27,48,50,54]
Determine the likelihood of distal embolization and periprocedural MI	0	††† (VH-IVUS)	††	IVUS[55,56] vs OCT[57,58]
Size the vessel undergoing stent implantation	††	†††	†††	IVUS[9,14,59,60] vs OCT[61]
Optimize stent results	†	†††	†††	IVUS[7,14] vs OCT[26,37]
Evaluate stent thrombosis or restenosis	†	††	†††	IVUS[62] vs OCT[32–35]

0, no evidence; † = some evidence; †† = moderate evidence; †††, strong evidence; IVUS, intravascular ultrasound; MI, myocardial infarction; OCT, optical coherence tomography.

Progression by Optical Coherence Tomography Combined With Intravascular Ultrasound (NCT01023607).

Conclusions

Modern x-ray angiography is a valuable tool in the cardiac catheterization laboratory to obtain images of coronary arteries. There are inherent limitations of this 2-dimensional technique and adjunctive intravascular techniques (IVUS and OCT) provide precise and detailed data of the 3-dimensional coronary artery tree. Hurdles of procedure-related cost and time are overcome by the benefits gained with IVI. A number of randomized trials are ongoing evaluating the impact of intracoronary imaging on long-term clinical outcomes. Combining an algorithmic approach to IVI with sound clinical judgment can improve the decision-making process and can help improve the clinical outcomes.

Conflict of interest statement

The authors have no potential conflicts of interest.

Disclosures

Evan Shlofmitz: Consultant – CSI. Akiko Maehara: Institutional grant support – Boston Scientific, St. Jude Medical; consultant – Boston Scientific, OCT Medical Imaging Inc.; speaker fee – St. Jude Medical. Allen Jeremias: Grants and personal fees – Philips/Volcano, Abbott Vascular. Richard A. Shlofmitz: Consultant – CSI. Gary S. Mintz: Consultant – Boston Scientific, ACIST; fellowship/grant support – Volcano, Boston Scientific, InfraReDx; honoraria - Boston Scientific, ACIST. Ziad A. Ali: Grants and personal fees – St. Jude Medical and CSI; personal fees from ACIST Medical Systems. Columbia University, his employer, receives royalties from Abbott Vascular for sale of the MitraClip. The rest of the authors have nothing to disclose.

Topic

Percutaneous transluminal coronary angioplasty, cardiology, stent, intravascular imaging, percutaneous coronary intervention, optical coherence tomography, revascularization, coronary arteriosclerosis, angiogram, coronary angiography

References

1. Shapiro TA, Herrmann HC. Coronary angiography and interventional cardiology. *Curr Opin Radiol* 1992;4:55–64.
2. Gerber Y, Rihal CS, Sundt TM 3rd, et al. Coronary revascularization in the community. A population-based study, 1990 to 2004. *J Am Coll Cardiol* 2007;50:1223–9.
3. Leape LL, Park RE, Bashore TM, et al. Effect of variability in the interpretation of coronary angiograms on

the appropriateness of use of coronary revascularization procedures. *Am Heart J* 2000;139:106–13.

4. Girasis C, Onuma Y, Schuurbiers JC, et al. and the meeting of the European Bifurcation C. Validity and variability in visual assessment of stenosis severity in phantom bifurcation lesions: a survey in experts during the fifth meeting of the European Bifurcation Club. *Catheter Cardiovasc Interv* 2012;79:361–8.
5. Tobis J, Azarbal B, Slavin L. Assessment of intermediate severity coronary lesions in the catheterization laboratory. *J Am Coll Cardiol* 2007;49:839–48.
6. Bashore TM, Balter S, Barac A, et al. ACCF Task Force Members. American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions expert consensus document on cardiac catheterization laboratory standards update: a report of the American College of Cardiology Foundation Task Force on Expert Consensus documents developed in collaboration with the Society of Thoracic Surgeons and Society for Vascular Medicine. *J Am Coll Cardiol* 2012;59:2221–305.
7. Witzenbichler B, Maehara A, Weisz G, et al. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. *Circulation* 2014;129:463–70.
8. Gutierrez-Chico JL, Alegria-Barrero E, Teijeiro-Mestre R, et al. Optical coherence tomography: from research to practice. *Eur Heart J Cardiovasc Imaging* 2012;13:370–84.
9. Jensen LO, Thayssen P, Mintz GS, et al. Comparison of intravascular ultrasound and angiographic assessment of coronary reference segment size in patients with type 2 diabetes mellitus. *Am J Cardiol* 2008;101:590–5.
10. Leesar MA, Masden R, Jasti V. Physiological and intravascular ultrasound assessment of an ambiguous left main coronary artery stenosis. *Catheter Cardiovasc Interv* 2004;62:349–57.
11. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001;37:1478–92.
12. Omoto R. Intracardiac scanning of the heart with the aid of ultrasonic intravenous probe. *Jpn Heart J* 1967;8:569–81.
13. Mintz GS. Intravascular ultrasound and outcomes after drug-eluting stent implantation. *Coron Artery Dis* 2017;28:346–52.
14. Hong SJ, Kim BK, Shin DH, et al. IVUS-XPL Investigators. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL Randomized Clinical Trial. *JAMA* 2015;314:2155–63.
15. Levine GN, Bates ER, Bittl JA, et al. ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* 2016;134:e123–55.
16. Levine GN, Bates ER, Blankenship JC, et al. ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2011;124:e574–651.
17. Windecker S, Kolh P, Alfonso F, et al. ESC/EACTS guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;35:2541–619.
18. Levine GN, Bates ER, Blankenship JC, et al. American College of Cardiology F, American Heart Association Task Force on Practice G, Society for Cardiovascular A and Interventions. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2013;82:E266–355.
19. Mariani J Jr., Guedes C, Soares P, et al. Intravascular ultrasound guidance to minimize the use of iodine contrast in percutaneous coronary intervention: the MOZART (Minimizing cOntrast utiliZation With IVUS Guidance in coRonary angioplasTy) randomized controlled trial. *JACC Cardiovasc Interv* 2014;7:1287–93.

20. Ali ZA, Karimi Galougahi K, Nazif T, et al. Imaging- and physiology-guided percutaneous coronary intervention without contrast administration in advanced renal failure: a feasibility, safety, and outcome study. *Eur Heart J* 2016;37:3090–5.
21. de Oliveira DM, Gomes V, Caramori P. Intravascular ultrasound and pharmacological stress test to evaluate the anomalous origin of the right coronary artery. *J Invasive Cardiol* 2012;24:E131–4.
22. Parviz Y, Fall KN, Ali ZA. Using sound advice-intravascular ultrasound as a diagnostic tool. *J Thorac Dis* 2016;8:E1395–97.
23. Brezinski ME, Tearney GJ, Bouma BE, et al. Optical coherence tomography for optical biopsy. Properties and demonstration of vascular pathology. *Circulation* 1996;93:1206–13.
24. Tenekecioglu E, Albuquerque FN, Sotomi Y, et al. Intracoronary optical coherence tomography: Clinical and research applications and intravascular imaging software overview. *Catheter Cardiovasc Interv* 2017;89:679–89.
25. Giavarini A, Kilic ID, Redondo Dieguez A, et al. Intracoronary imaging. *Heart* 2017;103:708–25.
26. Ali ZA, Maehara A, Genereux P, et al. ILUMIEN III OPTIMIZE PCI Investigators. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. *Lancet* 2016;388:2618–28.
27. Campos CM, Garcia-Garcia HM, Iqbal J, et al. Serial volumetric assessment of coronary fibroatheroma by optical frequency domain imaging: insights from the TROFI trial. *Eur Heart J Cardiovasc Imaging* 2017. doi:10.1093/ehjci/jew338.
28. Kimura S, Sagawa Y, Sugiyama T, et al. Progression of a lesion with nodular calcification: serial observations by optical coherence tomography and coronary angioscopy. *Coron Artery Dis* 2017;28:266–7.
29. Kataoka Y, Puri R, Hammadah M, et al. Spotty calcification and plaque vulnerability in vivo: frequency-domain optical coherence tomography analysis. *Cardiovasc Diagn Ther* 2014;4:460–9.
30. Yahagi K, Joner M, Virmani R. The mystery of spotty calcification: can we solve it by optical coherence tomography? *Circ Cardiovasc Imaging* 2016;9:e004252.
31. Mintz GS. Intravascular imaging of coronary calcification and its clinical implications. *JACC Cardiovasc Imaging* 2015;8:461–71.
32. Gonzalo N, Serruys PW, Okamura T, et al. Optical coherence tomography patterns of stent restenosis. *Am Heart J* 2009;158:284–93.
33. Prati F, Stazi F, Dutary J, et al. Detection of very early stent healing after primary angioplasty: an optical coherence tomographic observational study of chromium cobaltum and first-generation drug-eluting stents. The DETECTIVE study. *Heart* 2011;97:1841–6.
34. Souteyrand G, Amabile N, Mangin L, et al. and Investigators P. Mechanisms of stent thrombosis analysed by optical coherence tomography: insights from the national PESTO French registry. *Eur Heart J* 2016;37:1208–16.
35. Goto K, Takebayashi H, Kihara Y, et al. Appearance of neointima according to stent type and restenotic phase: analysis by optical coherence tomography. *EuroIntervention* 2013;9:601–7.
36. Prati F, Di Vito L, Biondi-Zoccai G, et al. Angiography alone versus angiography plus optical coherence tomography to guide decision-making during percutaneous coronary intervention: the Centro per la Lotta contro l'Infarto-Optimisation of Percutaneous Coronary Intervention (CLI-OPCI) study. *EuroIntervention* 2012;8:823–9.
37. Meneveau N, Souteyrand G, Motreff P, et al. Optical coherence tomography to optimize results of percutaneous coronary intervention in patients with Non-ST-elevation acute coronary syndrome: results of the multicenter, randomized DOCTORS Study (Does Optical Coherence Tomography Optimize Results of Stenting). *Circulation* 2016;134:906–17.
38. Jia H, Dai J, Hou J, et al. Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion (the EROSION study). *Eur Heart J* 2017;38:792–800.
39. Prati F, Cera M, Ramazzotti V, et al. Safety and feasibility of a new non-occlusive technique for facilitated intracoronary optical coherence tomography (OCT) acquisition in various clinical and anatomical scenarios. *EuroIntervention* 2007;3:365–70.
40. Kang SJ, Lee JY, Ahn JM, et al. Intravascular ultrasound-derived predictors for fractional flow reserve in intermediate left main disease. *JACC Cardiovasc Interv* 2011;4:1168–74.
41. Jasti V, Ivan E, Yalamanchili V, et al. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation* 2004;110:2831–6.
42. Parodi G, Maehara A, Giuliani G, et al. Optical coherence tomography in unprotected left main coronary artery stenting. *EuroIntervention* 2010;6:94–9.
43. de la Torre Hernandez JM, Lopez-Palop R, Garcia Camarero T, et al. Clinical outcomes after intravascular ultrasound and fractional flow reserve assessment of intermediate coronary lesions. Propensity score matching of large cohorts from two institutions with a differential approach. *EuroIntervention* 2013;9:824–30.
44. Nam CW, Yoon HJ, Cho YK, et al. Outcomes of percutaneous coronary intervention in intermediate coronary artery disease: fractional flow reserve-guided versus

intravascular ultrasound-guided. *JACC Cardiovasc Interv* 2010;3:812–7.
45. Pawlowski T, Prati F, Kulawik T, et al. Optical coherence tomography criteria for defining functional severity of intermediate lesions: a comparative study with FFR. *Int J Cardiovasc Imaging* 2013;29:1685–91.
46. Shiono Y, Kitabata H, Kubo T, et al. Optical coherence tomography-derived anatomical criteria for functionally significant coronary stenosis assessed by fractional flow reserve. *Circ J* 2012;76:2218–25.
47. Hong YJ, Jeong MH, Choi YH, et al. Differences in intravascular ultrasound findings in culprit lesions in infarct-related arteries between ST segment elevation myocardial infarction and non-ST segment elevation myocardial infarction. *J Cardiol* 2010;56:15–22.
48. Kubo T, Imanishi T, Takarada S, et al. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. *J Am Coll Cardiol* 2007;50:933–9.
49. Barlis P, Serruys PW, Gonzalo N, et al. Assessment of culprit and remote coronary narrowings using optical coherence tomography with long-term outcomes. *Am J Cardiol* 2008;102:391–5.
50. Jang IK, Tearney GJ, MacNeill B, et al. In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. *Circulation* 2005;111:1551–5.
51. Yamagishi M, Terashima M, Awano K, et al. Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before an acute coronary syndrome. *J Am Coll Cardiol* 2000;35:106–11.
52. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) study. *JACC Cardiovasc Imaging* 2011;4:894–901.
53. Stone GW, Maehara A, Lansky AJ, et al. and PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; 364:226–35.
54. Kini AS, Vengrenyuk Y, Yoshimura T, et al. Fibrous cap thickness by optical coherence tomography in vivo. *J Am Coll Cardiol* 2017;69:644–57.
55. Shibuya M, Okamura A, Hao H, et al. Prediction of distal embolization during percutaneous coronary intervention for unstable plaques with grayscale and integrated backscatter intravascular ultrasound. *Catheter Cardiovasc Interv* 2013;81:E165–72.
56. Uetani T, Amano T, Ando H, et al. The correlation between lipid volume in the target lesion, measured by integrated backscatter intravascular ultrasound, and post-procedural myocardial infarction in patients with elective stent implantation. *Eur Heart J* 2008;29: 1714–20.
57. Porto I, Di Vito L, Burzotta F, et al. Predictors of periprocedural (type IVa) myocardial infarction, as assessed by frequency-domain optical coherence tomography. *Circ Cardiovasc Interv* 2012;5:89–96, S1-6.
58. Stone GW, Maehara A, Muller JE, et al. and CANARY Investigators. Plaque characterization to inform the prediction and prevention of periprocedural myocardial infarction during percutaneous coronary intervention: the CANARY Trial (Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow). *JACC Cardiovasc Interv* 2015;8:927–36.
59. Zhang Y, Farooq V, Garcia-Garcia HM, et al. Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. *EuroIntervention* 2012;8:855–65.
60. Singh V, Badheka AO, Arora S, et al. Comparison of inhospital mortality, length of hospitalization, costs, and vascular complications of percutaneous coronary interventions guided by ultrasound versus angiography. *Am J Cardiol* 2015;115:1357–66.
61. Viceconte N, Chan PH, Barrero EA, et al. Frequency domain optical coherence tomography for guidance of coronary stenting. *Int J Cardiol* 2013;166:722–8.
62. Guo N, Maehara A, Mintz GS, et al. Incidence, mechanisms, predictors, and clinical impact of acute and late stent malapposition after primary intervention in patients with acute myocardial infarction: an intravascular ultrasound substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. *Circulation* 2010;122:1077–84.
63. Kennedy MW, Fabris E, Ijsselmuiden AJ, et al. Combined optical coherence tomography morphologic and fractional flow reserve hemodynamic assessment of non- culprit lesions to better predict adverse event outcomes in diabetes mellitus patients: COMBINE (OCT-FFR) prospective study. Rationale and design. *Cardiovasc Diabetol* 2016;15:144.

Manuscript 4

Commentary

Using sound advice—intravascular ultrasound as a diagnostic tool

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Intravascular ultrasound (IVUS) uses varying-frequency catheter-based transducers for assessment of blood vessel dimensions and morphology. Along with advances in the field of interventional cardiology, IVUS technology has progressed in the last two decades. Dedicated training centers in combination with enthusiasm from a new generation of cardiologists complemented by well-established evidence for simplicity, safety and efficacy of IVUS systems have led to increased routine use of this imaging modality. Currently available catheters use sound frequencies in the range of 20–70 MHz, moving from older grayscale IVUS to radiofrequency IVUS (RF-IVUS) and more recently high-definition IVUS (HD-IVUS) devices, some with the ability to differentiate plaque composition.

IVUS has the ability to provide a 360° cross-sectional view of the vasculature with real time images. With excellent tissue penetration, IVUS can provide detailed and valuable information on vessel lumen dimensions including large diameter arteries such as the left main coronary artery (LMCA) as well as atherosclerotic plaque morphology and burden. Compared to other intravascular imaging modalities such as optical coherence tomography (OCT), IVUS has the advantage of not requiring blood clearance, overcoming some of the limitations of two-dimensional lumenography by angiography (1,2). For instance, clinically significant high-grade stent edge dissections that may be missed on angiography can be identified on IVUS, with the utility of IVUS becoming more evident in treatment of complex coronary lesions, including interventions performed on the LMCA (3,4). Large registry data have indicated a reduction in mortality in IVUS-guided percutaneous coronary intervention (PCI) of unprotected LMCA compared to angiography alone (6.0% *vs.* 13.6%) (5).

By extrapolation, IVUS may also have utility in the emergency setting for pathologies involving the LMCA such as spontaneous or iatrogenic dissection. The incidence of spontaneous dissection in the LMCA has been reported to be ~1% of all epicardial coronary arteries (6,7). Similar to aortic dissection, a spontaneous dissection of the LMCA leads to generation of a false lumen and intramural hematoma with or without intimal tear that may propagate retrograde into the aorta. Additionally, a type A aortic dissection may extend into the LMCA antegrade. The acute coronary syndrome (ACS) associated with acute aortic dissection may be due to compression of the LMCA ostium by the false lumen, intimal flap causing ostial LMCA obstruction or extension of the dissection plane down the coronary tree and rarely due to avulsion of the coronary arteries from the sinuses of valsalva. The clinical presentation of dissection in the LMCA can be varied, spanning from a catastrophic cardiac emergency to ACS with varying degrees of underlying ischemia. Patients with type A aortic dissection can present with ACS, in which case the presentation may mandate early revascularization therapy, which may be done by PCI depending on the context. Coronary artery occlusion secondary to aortic dissection is infrequent, but in the cases where ST-segment elevation myocardial infarction is present, early revascularization with PCI should be considered without delaying for aortic imaging as supported by various guidelines (8).

In a recent issue of *JACC Cardiovascular Interventions*, Takahashi *et al.* (9) described a case of aortic dissection, presenting as ACS, involving the LMCA. Emergency angiography revealed left main stem closure and

to investigate the cause operators performed IVUS demonstrating a dissecting hematoma extending from aorta to left main. Based on IVUS it was concluded that the etiology was a type A aortic dissection, generating a hematoma that extended into the left main causing obstruction and this was confirmed by post procedure computed tomography (CT). The use of IVUS in this emergency setting helped in reaching the correct diagnosis and guided the appropriate strategy of stenting as a bridge to definitive cardiac surgery.

In these emergency instances, the first diagnostic test may be angiography and where there is a suspicion for dissection, particularly entry into the false lumen, IVUS should be considered to confirm the diagnosis as well as the luminal position of the guidewire. Indeed, IVUS has shown to be superior to other imaging modalities in cases of LMCA dissection (10,11). For instance, compared to OCT, IVUS does not require flush clearance of the coronary artery where, particularly in a large diameter artery like the LMCA, injection may lead to hydraulic extension of the dissection. Additionally, with high tissue penetration, IVUS can evaluate the external elastic lamina and entire dissection plane in the LMCA even in the presence of large intraluminal thrombi or intramural hematoma. Additionally, it may be feasible to differentiate spontaneous LMCA dissection, often visualized as hemorrhage in the outer third of the media or between the outer media and external elastic lamina that can lead to development of hematoma causing compression of the true lumen. The direction of spread of spontaneous dissection starts from within the arterial wall extending towards the lumen. In the cases of iatrogenic dissection as the result of wires or catheters, dissection may be visualized on IVUS from the lumen towards the media (12). Critically, differentiation of the true and false lumen on IVUS is feasible as the true lumen appears smaller with branches and a three layered appearance comprising the layers of the native vessel wall. The false lumen is more often larger and contains evidence of thrombus (13). Alongside this, IVUS can localize intimal tears and extent of intramural hematoma, the site of primary fenestration, with measurements of proximal normal aorta and even real time measurement of flow in the true and false lumens (14).

Various other non-invasive modalities like CT and Magnetic resonance imaging (MRI) are not able to provide 360-degree cross sectional views of vascular lumens at the resolution provided by IVUS. In a comparative study of IVUS with non-invasive imaging modalities, IVUS had an advantage at detecting visceral artery origin in cases of aortic dissection. The detection rate of visceral arteries by IVUS was 96.4%, higher than CT (70.2%) and digital subtraction angiography (DSA) (84.5%) (13). Lastly it is important to note that despite the use of multiple non-invasive imaging modalities as well as trans-esophageal echocardiography, the possibility of not recognizing aortic dissection is estimated at ~5% (15). It is thus recommended that in cases of high suspicion of aortic dissection other imaging modalities like aortography and IVUS strongly considered.

Conclusions

IVUS is highly recommended in cases of left main coronary dissection, to not only determine the etiology but also the extent of dissection and treatment plan. The routine use of IVUS is encouraged such that interventionalist's are confident using this modality including the emergency setting.

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Footnote

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References

1. Leesar MA, Masden R, Jasti V. Physiological and intravascular ultrasound assessment of an ambiguous left main coronary artery stenosis. Catheter Cardiovasc Interv 2004;62:349-57.
2. de la Torre Hernandez JM, Hernández Hernandez F, Alfonso F, et al. Prospective application of pre-

defined intravascular ultrasound criteria for assessment of intermediate left main coronary artery lesions results from the multicenter LITRO study. J Am Coll Cardiol 2011;58:351-8.
3. Jensen LO, Thayssen P, Mintz GS, et al. Comparison of intravascular ultrasound and angiographic assessment of coronary reference segment size in patients with type 2 diabetes mellitus. Am J Cardiol 2008;101:590-5.
4. Tobis J, Azarbal B, Slavin L. Assessment of intermediate severity coronary lesions in the catheterization laboratory. J Am Coll Cardiol 2007;49:839-48.
5. Park SJ, Kim YH, Park DW, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. Circ Cardiovasc Interv 2009;2:167-77.
6. Auer J, Punzengruber C, Berent R, et al. Spontaneous coronary artery dissection involving the left main stem: assessment by intravascular ultrasound. Heart 2004;90:e39.
7. DeMaio SJ Jr, Kinsella SH, Silverman ME. Clinical course and long-term prognosis of spontaneous coronary artery dissection. Am J Cardiol 1989;64:471-4.
8. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Catheter Cardiovasc Interv 2010;76:E43-86.
9. Takahashi K, Inaba S, Kikuchi K, et al. Intravascular Ultrasound-Diagnosed Acute Aortic Dissection Involving Left Main Closure. JACC Cardiovasc Interv 2016;9:1631-2.
10. Chun JH, Lee SC, Gwon HC, et al. Left main coronary artery dissection after blunt chest trauma presented as acute anterior myocardial infarction: assessment by intravascular ultrasound: a case report. J Korean Med Sci 1998;13:325-7.
11. Morocutti G, Spedicato L, Vendrametto F, et al. Intravascular echocardiography (ICUS) diagnosis of post-traumatic coronary dissection involving the common trunk. A case report and review of the literature. G Ital Cardiol 1999;29:1034-7.
12. Klein AJ, Hudson PA, Kim MS, et al. Spontaneous left main coronary artery dissection and the role of intravascular ultrasonography. J Ultrasound Med 2010;29:981-8.
13. Jiang JH, Wang YQ, Guo DQ, et al. The application of intravascular ultrasound imaging in identifying the visceral artery in aortic dissection. Zhonghua Yi Xue Za Zhi 2003;83:1580-2.
14. Maehara A, Mintz GS, Castagna MT, et al. Intravascular ultrasound assessment of spontaneous coronary artery dissection. Am J Cardiol 2002;89:466-8.
15. Svensson LG, Labib SB, Eisenhauer AC, et al. Intimal tear without hematoma: an important variant of aortic dissection that can elude current imaging techniques. Circulation 1999;99:1331-6.

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Manuscript 5

Coronary Plaque Characteristics in Hemodialysis-Dependent Patients as Assessed by Optical Coherence Tomography

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Coronary arteries in patients with chronic kidney disease (CKD) have been shown to exhibit more extensive atherosclerosis and calcium. We aimed to assess characteristics of coronary plaque in hemodialysis (HD)-dependent patients using optical coherence tomography (OCT). This was a multicenter, retrospective study of 124 patients with stable angina who underwent OCT imaging. Sixty-two HD-dependent patients who underwent pre-intervention OCT for coronary artery disease were compared 1:1 with a cohort of patients without CKD, matched for age, diabetes mellitus, gender, and culprit vessel. Baseline characteristics were comparable. Pre-intervention OCT imaging identified 62 paired culprit, 53 paired non-culprit, and 19 paired distal vessel lesions. Lesion length, minimum lumen area, and area stenosis were similar between groups. The HD-dependent group had greater mean calcium arcs in culprit (54.3° vs 26.4°, p = 0.004) and non-culprit lesions (34.3° vs 24.5°, p = 0.02) and greater maximum calcium arc in distal vessel segments (101.6° vs 0°, p = 0.03). There were no differences in lipid arcs between groups. There was a higher prevalence of thin intimal calcium, defined as an arc of calcium >30° within intima <0.5 mm thick, in patients in the HD-dependent group (41.9% vs 4.8%, p <0.001). There was a higher prevalence of calcified nodules in the HD-dependent group (24.2% vs 9.7%, p = 0.049) but no differences in medial calcification or thin-cap fibroatheroma. In conclusion, in this OCT study, HD-dependent patients, compared with matched patients without CKD, had more extensively distributed coronary calcium and uniquely, a higher prevalence of non-atherosclerotic thin intimal calcium. This thin intimal calcium may cause an overestimation of calcium burden by intravascular ultrasound and may contribute to the lack of correlation between increased coronary artery calcification scores with long-term outcomes in patients with CKD. **(Am J Cardiol 2017;■:■–■)**

Chronic kidney disease (CKD) is strongly associated with accelerated coronary artery disease (CAD). Accordingly, cardiovascular disease is the leading cause of morbidity and mortality in patients with hemodialysis (HD)-dependent end-stage renal disease (ESRD), with a mortality risk up to 20-fold greater than in an age- and gender-matched general population.[1–3] Autopsy and in vivo imaging studies by computed tomography and intravascular ultrasound (IVUS) have demonstrated significant associations between CKD and CAD severity and calcification.[4–8] Optical coherence tomography (OCT) provides high-resolution assessment of coronary plaque with the additional benefit over IVUS of penetration through calcium; however, its use in patients with CKD is limited by the need for additional contrast medium used for flush clearing the artery during OCT image acquisition. Consequently, understanding of coronary plaque characteristics by OCT in patients with CKD is limited. The aim of the present study was to use OCT to assess coronary plaque characteristics of patients with HD-dependent ESRD.

Methods

Patients across 3 sites (Columbia University Medical Center, New York, New York; St. Francis Hospital and Heart Center, Roslyn, New York; Tsuchiura Kyodo Hospital,

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See page 6 for disclosure information.

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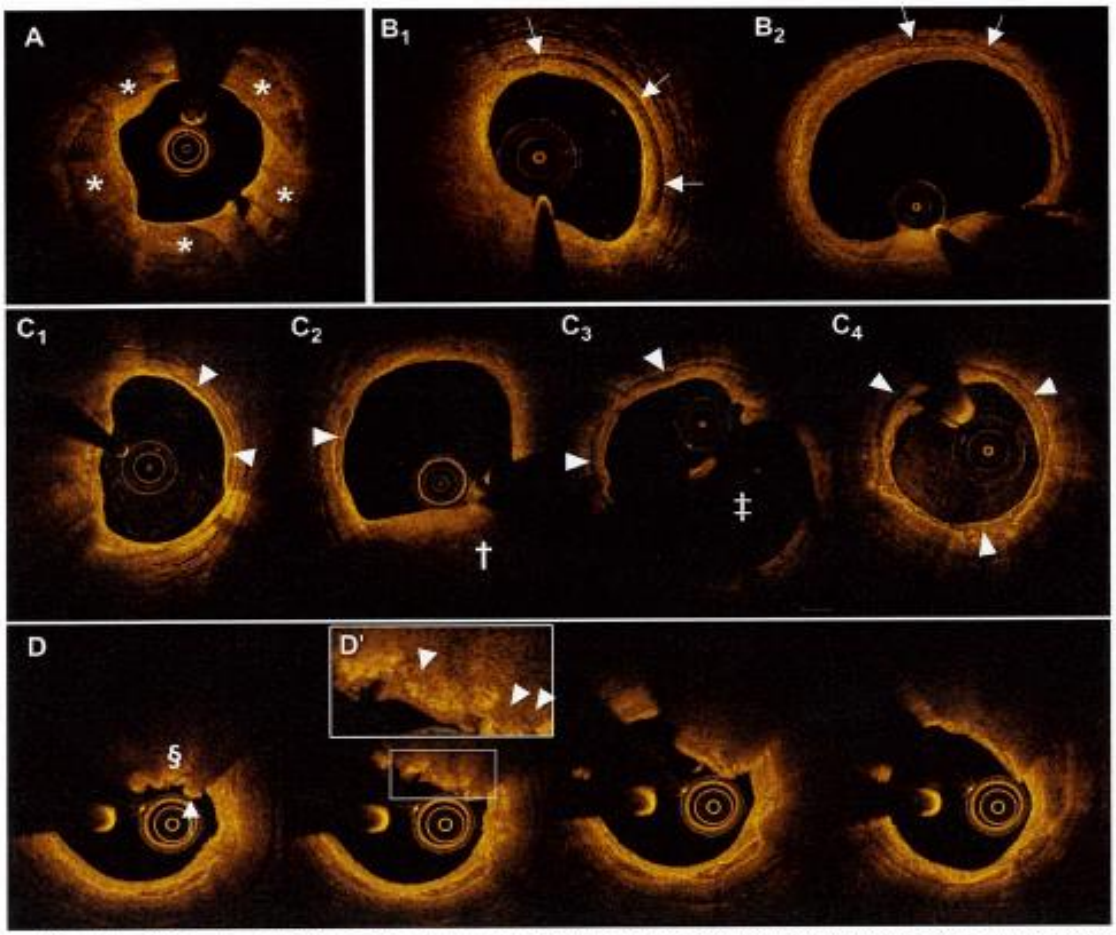

Figure 1. Qualitative OCT analyses. *(A)* Intimal calcific plaque, seen as bulky signal-poor regions (*) with sharply delineated borders. *(B_1, B_2)* Medial calcification, seen as a segment of well-defined media with borders more sharply delineated *(arrows)* than adjacent noncalcific media. *(C)* Thin intimal calcification, seen as a calcium arc >30° *(arrowheads)* within nonlipidic intima <0.5 mm thick, separated from the media, and located opposite classic intimal calcific plaque *(C_1)*, opposite a lipid pool *(C_2, †)*, opposite a ruptured plaque *(C_3, ‡)*, or circumferentially in a distal vessel segment *(C_4)*. *(D)* Calcified nodule (§) seen as an accumulation of small nodular calcifications *(D', arrowheads)* above a calcium plate, with attenuation because of platelet-rich thrombus *(D, arrow)* and fibrin.

Tsuchiura, Japan) who underwent OCT to guide CAD management from November 2008 to January 2016 were identified. From this pooled cohort, all HD-dependent patients were included in this study. These patients were compared 1:1 with a propensity score–matched cohort of patients without CKD, defined by an estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2 calculated using the Modification of Diet in Renal Disease study equation[9] and without clinical, imaging, tissue, or laboratory evidence of kidney damage. Matching criteria were (in order) age, diabetes mellitus, gender, and culprit vessel. The study was approved by the institutional review board at each center, and all patients provided signed written, informed consent.

OCT was performed using a commercially available frequency domain OCT system (ILUMIEN OPTIS or C7-XR FD-OCT System; St. Jude Medical, St. Paul, Minnesota; or Lunawave optical frequency domain imaging system; Terumo Corporation, Tokyo, Japan) or time domain OCT system (M2/M3 Cardiology Imaging System; Lightlab Imaging, Westford, Massachusetts). After diagnostic angiography, patients received 100 μg intracoronary nitroglycerin. For frequency domain OCT imaging, a 2.7Fr (Dragonfly Duo or Dragonfly OPTIS; St. Jude Medical) or 2.6Fr catheter (Fastview; Terumo Corporation) was advanced distal to the target lesion. Automated pullback was triggered using intracoronary contrast injection (3 to 4 ml/s, 12 to 14 ml total) with a motorized pullback speed of up to 25 mm/s (Dragonfly) or 40 mm/s (Fastview), a frame rate of 100 per second (Dragonfly) or 160 per second (Fastview), and a maximum scan length of 75 mm (Dragonfly) or

150 mm (Fastview). For time domain OCT imaging, a low-pressure occlusion balloon (Helios; Goodman, Nagoya, Japan) with distal flush ports was inflated proximal to the lesion, and the imaging wire was automatically pulled back at 1.0 to 3.0 mm/s during continuous saline infusion. All OCT images were de-identified and digitally stored. Only previously untreated segments were included. OCT images were analyzed by 2 independent investigators (CYC and MM) using St. Jude Medical Offline Review Workstation software (version E.0.2). In case of a disagreement, consensus was achieved with a third investigator (AM).

A culprit lesion was defined as the segment that was stented by comparing pre- and post-PCI OCT images. When post-PCI OCT was not performed, the stented segment was determined by co-registering the pre-PCI OCT pullback with the final coronary angiogram. When PCI was not performed, the culprit lesion was determined as the segment most likely to be causing ischemia, most commonly the segment containing the minimum lumen area (MLA). Nonculprit lesions were defined as any ≥10-mm-long segment adjacent to the culprit lesion.

Calibration was performed for each segment, and every frame was evaluated. Structures were classified according to established OCT reporting standards, and all arcs were measured relative to the center of mass of the lumen.[10] Area stenosis was calculated using the formula (1 − [MLA/mean reference lumen cross-sectional area]) and expressed as a percentage. The maximum calcium and lipid arcs for each culprit and nonculprit lesion were measured. Where superficial calcium was identified, this was classified as calcific plaque regardless of whether lipid was present deep to the calcium; as such, analyzed calcium and lipid arcs never overlapped. In addition, calcium and lipid arcs were measured at 1-mm intervals over the entire length of each lesion and were summed and divided by the number of 1-mm-interval frames analyzed to obtain the mean calcium and lipid arcs. Where the distal coronary artery segment, as defined angiographically,[11] was imaged by OCT, the maximum calcium arc was measured.

Calcific plaque had a low-backscatter signal with sharply delineated borders (Figure 1). Calcium present in the medial layer was classified as medial calcification (Figure 1). Calcium of arc >30° within a non-atherosclerotic intima <0.5 mm thick (lumen to internal elastic lamina) was classified as thin intimal calcium (Figure 1). A calcified nodule was an accumulation of multiple small nodular calcifications with superficial thrombus or fibrin above an underlying calcium plate, with or without significant luminal protrusion (Figure 1). Lipidic plaque had a signal-poor region with diffuse borders and high attenuation, consistently over at least 5 adjacent slices. OCT thin-cap fibroatheroma (OCT-TCFA) was a lipidic plaque with an overlying fibrous cap with a minimum thickness ≤65 μm. Side branches were assessed for the presence of ostial calcium. The intra- and interobserver κ-coefficients for thin intimal calcium were both 0.833 and for medial calcification were 0.833 and 0.667, respectively.

Only propensity score–matched pairs were included for statistical analysis. In patients with both a proximal and a distal nonculprit lesion analyzable, only the proximal lesion was used for quantitative analyses, whereas both proximal and distal lesions were included in qualitative analyses.

Table 1
Baseline characteristics

Variable	HD Group (n=62)	Non-CKD Group (n=62)	*P*-value
Age (years)	63.3±10.6	65.2±11.5	0.07
Female	20 (32%)	13 (21%)	0.19
Diabetes mellitus	38 (61%)	38 (61%)	1.00
Hypertension	58 (94%)	50 (81%)	0.08
Hyperlipidemia	41 (66%)	42 (68%)	1.00
Prior smoker	24 (39%)	37 (60%)	0.03
Statin use on admission	44 (71%)	49 (79%)	0.63
Total cholesterol (mg/dL)	148.8±35.2	156.6±38.7	0.14
Low-density lipoprotein cholesterol (mg/dL)	81.5±30.6	89.5±33.6	0.20
HD duration (months)	18.7 (10.5-37.2)	—	—
eGFR, mL/min/1.73m^2	—	78.5±15.4	—
Left ventricular ejection fraction (%)	57.5 (48.1-60)	55 (53-62)	0.86
OCT system used			
Time domain OCT	10 (16%)	4 (7%)	0.11
Frequency domain OCT	47 (76%)	50 (81%)	0.51
Optical frequency domain imaging	5 (8%)	8 (13%)	0.58

Values are mean ± standard deviation, n (%), or median (interquartile range).

eGFR = estimated glomerular filtration rate; HD = hemodialysis; LDL-C = low density lipoprotein; OCT = optical coherence tomography.

Categorical variables were compared by the McNemar test or the exact McNemar test for <25 discordant pairs. Continuous variables were compared by Student's *t* test (if normally distributed) or the Wilcoxon signed rank test (if not normally distributed). p Value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 18.0 (SPSS Inc.; IBM, Armonk, New York).

Results

A total of 124 patients were included in the study; 62 HD-dependent patients with analyzable pre-PCI OCT pullbacks were matched with 62 patients with eGFR >60 ml/min/1.73 m^2. Baseline characteristics were comparable between groups (Table 1). The median duration of HD in the HD group was 18.7 months (interquartile range 10.5 to 37.2 months). The mean eGFR in the non-CKD group was 78.5 ± 15.4 ml/min/1.73 m^2.

The culprit vessel location was similar between groups. Thirty-seven patients (59.7%) in the HD group and 29 patients (46.8%) in the non-CKD group had an analyzable distal vessel, of which 19 in each group were matched pairs (Table 2). Culprit lesion length, MLA, and area stenosis were similar between groups (124 matched culprits). Mean calcium arc (54.3° vs 26.4°, p = 0.004) and maximum calcium arc (179° vs 122°, p = 0.02) were greater in the HD group. There were no differences in mean and maximum lipid arcs between groups.

Among 106 matched nonculprit lesions, lesion length, MLA, and area stenosis were similar between groups. Mean calcium arc (34.3° vs 24.5°, p = 0.02) and maximum calcium arc (133° vs 90°, p = 0.02) were greater in the HD group. There were no differences in mean and maximum

Table 2
Quantitative optical coherence tomography findings

Variable	HD Group	Non-CKD Group	*P*-value
Culprit vessel location			
Left anterior descending	33 (53%)	41 (66%)	0.13
Left circumflex	11 (18%)	8 (13%)	0.55
Right coronary	18 (29%)	13 (21%)	0.38
Culprit lesion			
Matched lesions	62	62	—
Length (mm)	21.3 (15.5-30.8)	19.8 (13.9-33.8)	0.79
Minimum lumen area (mm^2)	1.68 (1.07-2.39)	1.66 (1.16-2.36)	0.46
Average reference lumen area (mm^2)	5.6 (4.67-7.54)	5.66 (4.63-7.17)	0.80
Minimum lumen diameter (mm)	1.27 (0.97-1.44)	1.24 (1.02-1.49)	0.26
Area stenosis (%)	73.1 (59.0-80.5)	70.9 (60.3-79.4)	0.67
Mean calcium arc (°)	54.3 (15.3-145.0)	26.4 (8.0-59.7)	0.004
Maximum calcium arc (°)	179 (104-344)	122 (71-213)	0.02
Mean lipid arc (°)	20.3 (6.1-43.3)	21.9 (9.8-52.4)	0.83
Maximum lipid arc (°)	113 (71-196)	105 (67-169)	0.40
Non-culprit lesion			
Matched lesions	53	53	—
Length (mm)	17.8 (12.8-24.4)	18.4 (13.6-26.8)	0.19
Minimum lumen area (mm^2)	4.43 (3.31-5.33)	4.60 (3.68-6.14)	0.41
Average reference lumen area (mm^2)	6.84 (5.36-9.16)	6.9 (5.37-9.17)	0.14
Minimum lumen diameter (mm)	2.07 (1.80-2.43)	2.78 (2.26-3.29)	0.48
Area stenosis (%)	29.6 (20.9-38.2)	30.3 (21.2-43.1)	0.73
Mean calcium arc (°)	34.3 (10.3-109.4)	24.5 (3.8-53.2)	0.02
Maximum calcium arc (°)	133 (63-240)	90 (33-142)	0.02
Mean lipid arc (°)	10.1 (0-39.1)	8.8 (0-31.0)	0.61
Maximum lipid arc (°)	86 (0-138)	77 (0-122)	0.27
Distal vessel segment			
Analyzable by optical coherence tomography	37 (60%)	29 (47%)	—
Matched segments	19	19	—
Maximum calcium arc (°)	101 (76-313)	0 (0-78)	0.03

Values are n (%) or median (interquartile range).
HD = hemodialysis.

lipid arcs between groups. The maximum calcium arc was greater in the distal segment of the coronary artery in the HD group (101.6° vs 0°, p = 0.03).

There was a significantly higher prevalence of thin intimal calcium in culprit vessels in the HD group (41.9% vs 4.8%, p <0.001) in both culprit (30.7% vs 3.2%, p <0.001) and nonculprit lesions (24.5% vs 1.9%, p <0.001) (Table 3). There was a higher prevalence of calcified nodules in the HD group (24.2% vs 9.7%, p = 0.049). There was a trend toward more medial calcification in culprit lesions in the HD group (p = 0.11), but no difference in TCFA or side branch ostial calcium between groups.

The quantitative and qualitative findings among patients in the HD group divided by tertiles of HD duration have been summarized in Table 4. The median HD duration in the first, second, and third tertiles were 5.3, 18.6, and 60.0 months, respectively. The mean calcium arc increased with increasing HD duration in both culprit (23.6° vs 30.8° vs 115.2°, p = 0.005) and non-culprit lesions (10.3° vs 24.5° vs 94.5°, p = 0.01). The prevalence of thin intimal calcium was significantly higher in patients in the highest HD duration tertile (35.0% vs 14.3% vs 76.2%, p <0.001).

Table 3
Qualitative optical coherence tomography findings

Variable	HD Group	Non-CKD Group	*P*-value
Entire vessel			
Thin intimal calcification	26 (42%)	3 (5%)	<0.001
Medial calcification	11 (18%)	4 (7%)	0.12
Calcified nodule	15 (24%)	6 (10%)	0.049
Thin-cap fibroatheroma	3 (5%)	1 (2%)	0.63
Sidebranch ostial calcium	11 (18%)	5 (8%)	0.21
Culprit lesion			
Thin intimal calcification	19 (31%)	2 (3%)	<0.001
Medial calcification	8 (13%)	2 (3%)	0.11
Calcified nodule	10 (16%)	3 (5%)	0.09
Non-culprit lesion			
Thin intimal calcification	13 (25%)	1 (2%)	<0.001
Medial calcification	5 (9%)	3 (6%)	0.73
Calcified nodule	7 (13%)	4 (8%)	0.51

Values are n (%).
HD = hemodialysis.

Discussion

We report comprehensive atherosclerotic plaque characteristics in HD-dependent patients by OCT. (1) Compared with patients without CKD, HD-dependent patients had CAD that contained greater mean and maximum calcium arcs in both culprit and nonculprit segments and greater distal vessel calcium arcs, consistent with overall increased calcium burden (Figure 2). (2) Among patients with ESRD, higher mean and maximum calcium arcs were associated with increasing duration on HD. (3) Compared with patients without CKD, patients with HD-dependent ESRD had a higher prevalence of calcium within non-atherosclerotic thin intima.

Pathology studies clearly illustrate a link between renal dysfunction and accelerated coronary atherosclerosis, calcification, and medial thickness.[4,5] By computed tomography, coronary calcification was identified in as many as 40% of asymptomatic patients with CKD, with a 2-year doubling of the calcification score in young patients with ESRD.[12,13] IVUS studies have further demonstrated correlations between renal dysfunction and coronary calcification across all ranges of CKD.[14–16] As opposed to IVUS, OCT uses light waves, which have superior calcium penetration. In patients with a large calcium burden, this allows for better assessment of calcified plaque thickness and structures deep to calcium; however, the use of OCT in patients with CKD is problematic for the risk of contrast-induced nephropathy. Although non–contrast-based media (e.g., dextran) are available, contrast remains the most widely available, used, and only approved flushing medium for OCT. As such, OCT studies of patients with CKD are rare. Kato et al[9] examined characteristics of non-culprit plaques in 37 patients with mild-to-moderate CKD and found a higher prevalence of calcium and a greater lipid burden compared with those without CKD; however, calcium was recorded only for its presence and was not quantified.

Table 4
Hemodialysis subgroup analysis by hemodialysis duration

Variable	Hemodialysis Duration			*P*-value
	Tertile 1 (n=20)	Tertile 2 (n=21)	Tertile 3 (n = 21)	
Hemodialysis duration (months)	5.3 (1.1-9.4)	18.6 (16-23)	60.0 (37.6-75.9)	—
Culprit				
Area stenosis (%)	74.1 (63.0-82.2)	77.1 (61.1-81.9)	72.8 (58.9-74.7)	0.83
Mean calcium arc (°)	23.6 (5.3-90.3)	30.8 (15.8-137.6)	115.2 (56.1-169.2)	0.005
Max calcium arc (°)	143 (87-220)	135 (91-315)	321 (198-360)	0.003
Mean lipid arc (°)	22.0 (10.7-37.4)	20.0 (2.0-44.8)	19.6 (9.0-36.4)	0.90
Max lipid arc (°)	104 (70-178)	111 (46-200)	117 (93-196)	0.88
Thin intimal calcification	4 (20%)	1 (5%)	14 (67%)	<0.001
Medial calcification	2 (10%)	2 (10%)	4 (19%)	0.60
Calcified nodule	4 (20%)	2 (10%)	4 (19%)	0.57
Non-Culprit				
Analyzable lesions	17	20	21	
Area stenosis (%)	34.0 (27.5-44.0)	25.7 (23.6-37.5)	30.1 (15.7-37.0)	0.53
Mean calcium arc (°)	10.3 (0-56.4)	24.5 (3.6-75.6)	94.5 (30.2-133.6)	0.01
Max calcium arc (°)	95 (0-188)	92 (45-213)	194 (115-242)	0.11
Mean lipid arc (°)	10.6 (0-36.4)	28.2 (0-58.6)	3.7 (0-20.3)	0.16
Max lipid arc (°)	70 (0-124)	123 (37-184)	74 (0-123)	0.21
Thin intimal calcification	4 (24%)	2 (10%)	8 (38%)	0.10
Medial calcification	1 (6%)	2 (10%)	3 (14%)	0.69
Calcified nodule	1 (6%)	2 (10%)	4 (19%)	0.44
Entire vessel				
Thin intimal calcification	7 (35%)	3 (14%)	16 (76%)	<0.001
Medial calcification	3 (15%)	2 (10%)	6 (296%)	0.26
Calcified nodule	5 (25%)	3 (14%)	7 (33%)	0.34
Thin-cap fibroatheroma	1 (5%)	2 (10%)	0 (0%)	0.24

Values are n (%), or median (interquartile range).

Our study compared HD-dependent patients with ESRD with a matched group of patients with eGFR >60 ml/min/1.73 m^2, using matching criteria shown to be independent predictors of coronary intimal and medial calcification.[7,17,18] Although it would have been insightful to have a third group of patients with moderate CKD, the number of these patients in our cohort was too small to be able to perform effective propensity score matching, primarily because of the risk of contrast-induced nephropathy. We studied only stable angina patients. First, most HD-dependent patients who underwent OCT interrogation at our centers presented with stable angina. This may be explained by the presence of more extensive coronary calcium, which may confer plaque stability.[19] Indeed, the incidence of TCFA in our cohort was low despite a high prevalence of diabetes mellitus. Second, plaque characteristics in patients with stable symptoms are more likely to reflect the natural history of calcification. Third, coronary arteries of stable patients were unlikely to contain thrombus that may obscure vessel wall structures by OCT.

The prevalence of CAD in patients with CKD is, in part, explained by the clustering of atherosclerotic risk factors in these patients.[20] Additionally, increased duration of HD, oxidative stress, inflammation, and metabolic imbalances, such as homocysteinemia, hyperphosphatemia, and hypercalcemia, are also postulated risk factors for atherosclerosis and calcification.[15,21–23]

The mechanism of classic intimal calcification is imperfectly understood but is currently considered to be an active process that may begin within lipid pools and involve apoptosis of smooth muscle cells and macrophages and the release of matrix vesicles that calcify in the extracellular environment.[24] The presence of bone proteins and cartilage in the vessel wall, and cells that display osteoblastic differentiation, supports the notion that vascular calcification shares processes similar to bone formation.[25] A uremic environment stresses inhibitory mechanisms of calcification, promoting further calcium deposition.[18,26] Calcified areas are mostly located around and proximal, rather than distal to a necrotic core.[27] As they progress, they enlarge to form calcified plates that are the hallmark of stable and fibrocalcific plaque. These plates may fracture and form nodular calcification, observed as small, rounded calcified fragments separated by fibrin that were also more common in the present study. Calcified nodules can cause discontinuity of overlying collagen and endothelium predisposing to acute thrombosis[24] and may be one reason for increased cardiovascular mortality in patients with ESRD.

Medial calcification occurs independently of intimal calcification and is strongly linked with CKD, age, and diabetes mellitus.[17,18,28] It is not associated with lipid deposition or inflammation and starts within elastic fibers and smooth muscle cells of the media.[24] These smooth muscle cells lose their contractile properties and gain osteochondrogenic markers, forming bands of calcium-rich deposits that extend deep into the inner layer of the media and may involve the circumference of the vessel.[17] At advanced stages, calcification progresses to form solid plates or sheaths, increasingly distorting the medial architecture and intruding on the intima. Studies show increased medial

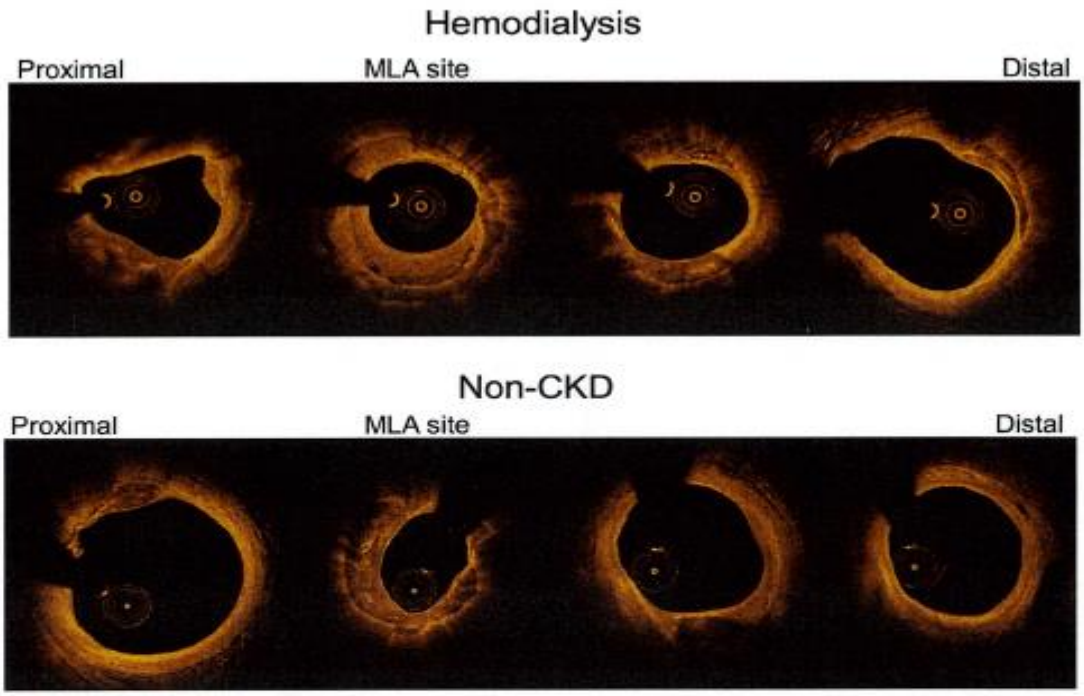

Figure 2. Distribution of calcification in representative cases. OCT frames of representative cases from the HD *(top panel)* and non-CKD *(bottom panel)* groups are compared. Both were left anterior descending arteries and contained effectively circumferential calcium at the MLA site. The main difference in calcium distribution between the 2 vessels was seen away from the MLA site where the vessel in the HD-dependent patient continued to contain greater calcification proximally and distally compared with the patient without CKD.

calcification in patients with CKD, with evidence of functional and prognostic relevance because of increased arterial stiffness.[29] The present study only showed a trend toward more medial calcification in culprit lesions in HD-dependent patients, likely owing to an overall underestimation of medial calcification because of the limited penetration of OCT through large calcific and lipidic plaques that were more common in the HD group.

A unique finding of the present study, especially in patients with HD, was the observation of an arc of calcium within thin intima. We postulate this pattern of thin intimal calcification to be distinct from classic atherosclerotic intimal calcification that commonly occurs as patchy clusters near lipid pools. The significantly higher prevalence in patients with HD suggests a mechanism linked either to chronic renal impairment or to the hemodynamic effects of HD. A potential clinical implication of thin intimal calcium is an overestimation of calcium burden when assessed by IVUS. Thin intimal calcium may contribute to the lack of correlation between increased coronary artery calcification scores with obstructive CAD and long-term outcomes in patients with CKD. Coronary artery calcification scores, as derived by computed tomography, has been shown to be an unreliable marker of the degree of coronary stenosis in uremic patients, with a sensitivity and specificity significantly lower than in the general population.[30]

Our study has a number of limitations. This study was observational with discretionary use of OCT. In addition, because of the avoidance of contrast media in patients with non−HD-dependent CKD, we could not perform comparison with non-CKD or ESRD patients. Also, our use of lipid arc may have underestimated the amount of lipidic plaque. Importantly, OCT imaging did not include the entire coronary artery length and included only a single vessel. Finally, the study population comprised patients with stable angina warranting invasive coronary angiography; therefore, these data cannot be extrapolated to asymptomatic patients or those presenting with acute coronary syndromes.

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1. Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray D, Barre PE. Outcome and risk factors of ischemic heart disease in chronic uremia. *Kidney Int* 1996;49:1428–1434.
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296–1305.
3. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006;17:2034–2047.
4. Schwarz U, Buzello M, Ritz E, Stein G, Raabe G, Wiest G, Mall G, Amann K. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant* 2000;15:218–223.
5. Nakano T, Ninomiya T, Sumiyoshi S, Fujii H, Doi Y, Hirakata H, Tsuruya K, Iida M, Kiyohara Y, Sueishi K. Association of kidney function with coronary atherosclerosis and calcification in autopsy samples from Japanese elders: the Hisayama study. *Am J Kidney Dis* 2010;55:21–30.
6. Kato K, Yonetsu T, Jia H, Abtahian F, Vergallo R, Hu S, Tian J, Kim S-J, Lee H, McNulty I, Lee S, Uemura S, Jang Y, Park S-J, Mizuno K, Yu B, Jang I-K. Nonculprit coronary plaque characteristics of chronic kidney disease. *Circ Cardiovasc Imaging* 2013;6:448–456.
7. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, Ouyang P, Jackson S, Saad MF. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2005;111:1313–1320.
8. Moe SM, O'Neill KD, Fineberg N, Persohn S, Ahmed S, Garrett P, Meyer CA. Assessment of vascular calcification in ESRD patients using spiral CT. *Nephrol Dial Transplant* 2003;18:1152–1158.
9. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006;145:247–254.
10. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, Bouma B, Bruining N, Cho JM, Chowdhary S, Costa MA, de Silva R, Dijkstra J, Di Mario C, Dudek D, Falk E, Feldman MD, Fitzgerald P, Garcia-Garcia HM, Gonzalo N, Granada JF, Guagliumi G, Holm NR, Honda Y, Ikeno F, Kawasaki M, Kochman J, Koltowski L, Kubo T, Kume T, Kyono H, Lam CC, Lamouche G, Lee DP, Leon MB, Maehara A, Manfrini O, Mintz GS, Mizuno K, Morel MA, Nadkarni S, Okura H, Otake H, Pietrasik A, Prati F, Räber L, Radu MD, Rieber J, Riga M, Rollins A, Rosenberg M, Sirbu V, Serruys PW, Shimada K, Shinke T, Shite J, Siegel E, Sonoda S, Suter M, Takarada S, Tanaka A, Terashima M, Thim T, Uemura S, Ughi GJ, van Beusekom HM, van der Steen AF, van Es GA, van Soest G, Virmani R, Waxman S, Weissman NJ, Weisz G. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies. *J Am Coll Cardiol* 2012;59:1058–1072.
11. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975;51:5–40.
12. Russo D, Palmiero G, De Blasio AP, Balletta MM, Andreucci VE. Coronary artery calcification in patients with CRF not undergoing dialysis. *Am J Kidney Dis* 2004;44:1024–1030.
13. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000;342:1478–1483.
14. Gruberg L, Rai P, Mintz GS, Canos D, Pinnow E, Satler LF, Pichard AD, Kent KM, Waksman R, Lindsay J, Weissman NJ. Impact of renal function on coronary plaque morphology and morphometry in patients with chronic renal insufficiency as determined by intravascular ultrasound volumetric analysis. *Am J Cardiol* 2005;96:892–896.
15. Ogita M, Funayama H, Nakamura T, Sakakura K, Sugawara Y, Kubo N, Ako J, Ishikawa S, Momomura S. Plaque characterization of non-culprit lesions by virtual histology intravascular ultrasound in diabetic patients: impact of renal function. *J Cardiol* 2009;54:59–65.
16. Baber U, Stone GW, Weisz G, Moreno P, Dangas G, Maehara A, Mintz GS, Cristea E, Fahy M, Xu K, Lansky AJ, Wennerblom B, Mathey DG, Templin B, Zhang Z, Serruys PW, Mehran R. Coronary plaque composition, morphology, and outcomes in patients with and without chronic kidney disease presenting with acute coronary syndromes. *JACC Cardiovasc Imaging* 2012;5:S53–S61.
17. Lanzer P, Boehm M, Sorribas V, Thiriet M, Janzen J, Zeller T, St Hilaire C, Shanahan C. Medial vascular calcification revisited: review and perspectives. *Eur Heart J* 2014;35:1515–1525.
18. Shanahan CM. Mechanisms of vascular calcification in CKD—evidence for premature ageing? *Nat Rev Nephrol* 2013;9:661–670.
19. Ehara S, Kobayashi Y, Yoshiyama M, Shimada K, Shimada Y, Fukuda D, Nakamura Y, Yamashita H, Yamagishi H, Takeuchi K, Naruko T, Haze K, Becker AE, Yoshikawa J, Ueda M. Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. *Circulation* 2004;110:3424–3429.
20. Uhlig K, Levey AS, Sarnak MJ. Traditional cardiac risk factors in individuals with chronic kidney disease. *Semin Dial* 2003;16:118–127.
21. Moe SM, Chen NX. Pathophysiology of vascular calcification in chronic kidney disease. *Circ Res* 2004;95:560–567.
22. Madore F. Uremia-related metabolic cardiac risk factors in chronic kidney disease. *Semin Dial* 2003;16:148–156.
23. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, Chertow GM. Cardiac calcification in adult hemodialysis patients: a link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 2002;39:695–701.
24. Otsuka F, Sakakura K, Yahagi K, Joner M, Virmani R. Has our understanding of calcification in human coronary atherosclerosis progressed? *Arterioscler Thromb Vasc Biol* 2014;34:724–736.
25. Demer LL, Tintut Y. Vascular calcification: pathobiology of a multifaceted disease. *Circulation* 2008;117:2938–2948.
26. Kirsch AH, Kirsch A, Artinger K, Schabhüttl C, Goessler W, Klymiuk I, Gülly C, Fritz GA, Frank S, Wimmer R, Brodmann M, Anders HJ, Pramstaller PP, Rosenkranz AR, Eller K, Eller P. Heterogeneous susceptibility for uraemic media calcification and concomitant inflammation within the arterial tree. *Nephrol Dial Transplant* 2015;30:1995–2005.
27. Burke AP, Kolodgie FD, Farb A, Weber D, Virmani R. Morphological predictors of arterial remodeling in coronary atherosclerosis. *Circulation* 2002;105:297–303.
28. Amann K. Media calcification and intima calcification are distinct entities in chronic kidney disease. *Clin J Am Soc Nephrol* 2008;3:1599–1605.
29. London GM. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003;18:1731–1740.
30. Sharples EJ, Pereira D, Summers S, Cunningham J, Rubens M, Goldsmith D, Yaqoob MM. Coronary artery calcification measured with electron-beam computerized tomography correlates poorly with coronary artery angiography in dialysis patients. *Am J Kidney Dis* 2004;43:313–319.

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COMMENTARY

ROLE OF INTRA CORONARY IMAGING AND PHYSIOLOGY IN DIAGNOSIS AND MANAGEMENT OF CORONARY ARTERY DISEASE

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Background: Coronary artery disease (CAD) is the leading cause of death in the Indo-Pakistan subcontinent as well as globally. Coronary angiography is considered the gold standard test for the diagnosis of CAD. Therefore, an accurate interpretation of coronary angiography is of paramount importance in decision-making to treat patients with CAD. Coronary angiography has the inherent limitation of being a two-dimensional X-Ray lumenogram of a complex three-dimensional vascular structure. Visual assessment of angiogram can lead to both inter- and intra-observer variability in the assessment of the severity and extent of the disease which can lead to differences in management strategies. This issue becomes even more relevant when assessing left main stem (LMS), bifurcations, diffuse coronary artery disease or situations involving complex coronary morphology. Interventional cardiology has been revolutionised by recent advances in techniques, and innovative technologies in the catheterisation laboratory. Today, a modern catheterisation laboratory is equipped with adjunctive technologies, such as Quantitative Coronary Angiography (QCA), Fractional Flow Reserve (FFR), Intra-Vascular Ultra-Sonography (IVUS), and Optical Coherence Tomography (OCT), to help clinicians make a well-informed decision based on detailed anatomical and physiological assessment of a coronary artery rather than judgement based solely on visual assessment. In this article, we have briefly described the utility and evidence behind these adjunctive modalities and have provided examples of clinical cases to highlight their use in aiding physicians to make a well-informed treatment decision.

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INTRODUCTION

Invasive coronary angiography is considered the gold standard test for assessing the severity and extent of coronary artery disease (CAD).[1] Coronary angiography has been in use for over 70 years. We have seen significant developments and innovations in the technology in recent years and currently it is routinely used in clinical practice all over the world.[2] Millions of coronary angiograms are performed annually worldwide to obtain critical information about the coronary anatomy which along with clinical presentation helps physicians to make treatment plans for patients suffering with CAD. Despite the fact that X-ray angiography is believed to be gold standard to diagnose epicardial coronary disease, one needs to bear in mind that it only provides a two-dimensional lumenogram of a complex three-dimensional arterial structure. Modern X-ray equipment in the cardiac catheterisation laboratory with flat panel detectors and advanced image enhancement algorithms, provide excellent angiographic images with good spatial and temporal resolution. Nevertheless, decisions based solely on X-ray angiography are prone to error, both in deciding whether a particular lesion is significant or not, and making a strategy for the treatment of a particular lesion that is causing ischemia. Cardiologists, often need more information about a particular disease process like, vessel anatomy, extent and severity of the lesion, plaque characteristics such as calcification, fibrosis, plaque rupture, and precise vessel sizing to plan the interventional strategy in a particular case.

There is ample evidence in the literature to suggest that when a particular lesion is viewed by different operators, they can assign various degrees of the stenosis to that specific lesion if based solely on visual estimation.[3] Therefore, from very early on, it was felt that there is a need to reduce or eliminate this inter-observer variability in assessing the degree of stenosis and in the last few decades emergence of newer techniques and technology used both inside and outside the catheterisation laboratory have revolutionized the field of invasive cardiology. Several adjunctive techniques have emerged to improve the diagnostic accuracy and help guide the decision-making process to improve the clinical outcomes.[4] In the era of modern interventional cardiology, cardiologists are performing increasingly complex and challenging cases.[5] A modern catheterisation laboratory is now equipped with adjunctive modalities such as quantitative coronary angiography (QCA), fractional flow reserve (FFR), intravascular ultrasound (IVUS), and optical coherence tomography (OCT). Use of these adjunctive technologies is of great help when

assessing borderline lesions (i.e diameter stenosis of 40–70%), complex left main stem[6, 7] and bifurcation disease[8].

In this article, we provide a brief overview of how the decision-making process has evolved from simple 'eye-balling' of coronary angiogram to one that employs intra-coronary imaging techniques and coronary physiology assessment. These modalities which were predominantly research tools in the past, are now used on daily basis to help make decisions in critical clinical scenarios. In addition to the modalities mentioned in this paper, several other are in development or in clinical use e.g. Near-Infrared Spectroscopy (NIRS), Index of micro-circulatory resistance, (IMR) and are beyond the scope of this paper.

Visual assessment based on Coronary Angiography (CA):

X-ray angiography is widely available and relatively cheap and easy to perform. It has good spatial and temporal resolution and remains the gold standard for diagnosing CAD. Traditionally, the CAD severity is assessed by visual estimates that are based upon multiple views of a coronary artery obtained during an angiogram. Several studies have shown that there is a significant difference in visual estimation of a particular lesion when reported by a physician at different time intervals, or in comparison with other colleagues.[3,8] Despite the potential harmful implications of visual estimation techniques, it still remains the most commonly used form of lesion evaluations and is still widely practised.[9] Although in the majority of cases, it provides diagnostic information, it is not very good at assessing physiological significance of intermediate lesions. Further, X-ray angiography provides limited information about microvascular status. There are many factors that independently contribute to decreased blood flow across a stenosed area (eg, diastolic pressure time, microvascular resistance and effective luminal area.[10] Visual assessment of the CA does not provide this information that is critical to making the decision for patients' care. The interventional community has been well aware of these limitations of CA and many adjunctive modalities, as mentioned earlier, have been developed to overcome these shortcomings of angiography.

Quantitative Coronary Angiography (QCA):

The clinical importance of a coronary narrowing is dependent upon the degree of narrowing, shape, length, eccentricity, number of side branches involved and the presence of subsequent stenosis in a given artery[11,12], Therefore, when coronary luminal effective area is reduced and an attempt is made to estimate the coronary area by simple visual estimation, there is inherent tendency to make mistakes and these limitations were realized in the very early days of coronary angiography and as such attempts at improving this assessment were made. QCA technique is probably the earliest technique to angiographically quantify the degree of stenosis. QCA was done for the first time by Brown and his companions and they were able to manually trace the arterial tree.[13] Then computer programming was used to digitally construct a 3-D representation of the arterial segment and calculate not only the degree of stenosis but also obtain physiological data. The QCA measurements have shown good correlation with visual estimates from cine–film and with haemodynamic significance as depicted by various test for assessment of ischemia.[14]

Although this technique is a well-validated tool for accurately and reproducibly defining coronary lesion severity, it requires additional time and effort. Furthermore, since QCA indirectly defines the anatomy of the vascular wall through inference about the lumen, it may not accurately report the variable and diffuse nature of the atherosclerotic lesion, a finding confirmed by post-mortem studies as well as by IVUS imaging techniques.[15–17] Furthermore, QCA has methodological limitations in assessing bifurcation lesions.[18] Finally, several studies have shown that endovascular techniques such as IVUS, OCT and angioscopy are better at delineating vascular features that accompany unstable ischemic syndromes alongside plaque morphology.[19]

In our opinion estimation of coronary stenosis based on QCA is a simple and low-cost tool with easy learning and should be used routinely, particularly in health care settings where other imaging and physiology based assessments are difficult to access and implement.

Intra-vascular Ultra-Sonography (IVUS):

Intra vascular ultrasound (IVUS) was first introduced by a Japanese group to study intra-cardiac structures in the 1960s.[20] It is now widely used as an intravascular imaging modality to visualise coronary anatomy from the inside of a coronary artery and has excellent penetration power to better delineate and highlight a diseased segment. It has the ability to provide 360° detailed information about an artery with real-time images. This technique yields unique point-of-view pictures, generated in real time, providing information that is far superior to simple angiography or QCA.[21] IVUS can help in the detailed assessment of lumen, vessel size, extent and distribution of plaque. The information obtained by IVUS can help the cardiologist to understand the detailed anatomy of the lesion. Advanced techniques

employing spectral analysis of ultrasound has enabled the development of Virtual histology intravascular ultrasound (VH-IVUS), which can provide further tissue characterization of plaques.

The utility of IVUS is more evident in the treatment of complex coronary lesions, particularly interventions performed on the LMS.[6,7] IVUS can be useful in the diagnosis of dissections spontaneous or iatrogenic.[22] The efficacy and usefulness of IVUS has been validated in several studies.[23,24] The potential utility of IVUS has been recognized by various cardiac societies and recommended in decision-making process in the cardiac catheterization laboratory. The use of IVUS has been particularly encouraged in the assessment of intermediate lesions, guiding stent implantation, and for understanding the mechanisms of stent failure. (Table-1)

IVUS as a modality has been useful particularly in the assessment of cardiac transplant patients.[25,26] Some institutions have used this modality to develop a 'Zero contrast PCI program' to treat patients at high risk of developing contrast-induced nephropathy.[27] IVUS is also a useful tool in the setting of acute emergencies and can help diagnose acute aortic and coronary dissections.[28] IVUS is an excellent modality to optimize the results for various stent based techniques and has shown to improve outcomes compared with angiography-based treatment.[23,24]

The concerns related to cost of this modality have been addressed and it has been demonstrated that although it is associated with higher initial cost, the IVUS guided procedures are more cost effective incomparision to angiography based decisions.[29] We would highly recommend IVUS particularly for assessment of LMS, and large calibre coronary arteries due to excellent penetration power. IVUS is a preferable intracoronary imaging modality in patients with renal disease as it requires no additional contrast. IVUS should be used for optimizing the stents to get the best possible results for patients to minimize the chances of stent failure. This will be cost saving for a system with minimal health care resources.

Table-1: Current guidelines recommendations for use of FFR/IVUS /OCT

Modality	ACC/AHA/SCAI guidelines (2011)	ESC guidelines (2014)
FFR	Recommended to use in intermediate lesions (Level of Evidence A)	1. Recommended to use in intermediate lesions (Level of evidence 1A) and 2. to help decide PCI in multi-vessel disease (Level of evidence 2A)
IVUS	1. Assessment of left main stem disease (Level of Evidence B) 2. Assessment of moderate coronary artery lesions (Level of Evidence B) 3. To guide coronary stent implantation especially (Level of Evidence B) 4. Understanding the mechanism of stent failure (Level of Evidence C) 5. For assessment of cardiac transplant patients. (Level of Evidence B)	1. Assessment and treatment of LMS (Level of evidence 2A) and 2. To optimise stent implantation (Level of evidence 2A)
OCT	The routine use of optical coherence tomography is not established yet. [NB Guidelines are from 2011/2014 and there has been good literature supporting these modalities in recent years and we expect an update in coming years.]	Can be used to understand the mechanism of stent failure and also to optimise the stent results [Level of evidence 2B).

Optical Coherence Tomography (OCT):

Optical coherence tomography (OCT) is another technique to image the coronary artery. OCT evolved from the pioneering work done by Tanno and Fujimoto during the 1990s.[30] It uses light[31], and has the advantage of the higher axial resolution of 10–15 μm, compared to 150–200 μm for IVUS.[32] OCT clearly delineates the three layers of an arterial wall. The excellent resolution of OCT gives detailed information about tissue characteristics and plaque morphology. Information after the implantation of stents like stent apposition, intraluminal thrombi (red and white), dissection, tissue prolapse, can be studied by OCT.[33] OCT has the ability to identify vulnerable plaques and can potentially help treat them even before an event occurs.[34] Moreover, OCT can precisely measure the length and vessel diameter during the PCI that is useful in optimising the size of balloons and stents. OCT, with its superior resolution compared to IVUS, can also help identify the angle and location of the dissection flap more accurately,tissue prolapse, stent edge dissection, and stent malapposition.[35] OCT is particularly useful in understanding the potential mechanism of stent failure. Current OCT techniques require the replacement of the blood in the vessel with a contrast agent and this causes limitation of technology, when assessing vessels of

large diameter or lesions at ostia of coronary arteries.

The safety of OCT technology has been well documented in large-scale clinical trials[36]; However, routine clinical use of OCT still requires further clinical trials to validate the technology, establish standard protocols and to test its safety and efficacy in improving clinical outcomes.[33] Cost remains an important factor in the world-wide uptake of this technology.

We would suggest using OCT in cases where the mechanism of acute coronary syndrome presentation is not clear and this technology can help in the quantification of plaque morphology, and tissue characterization. OCT is an extremely useful tool when an operator is not sure about post procedure dissection, thrombus, stent expansion and apposition. Whenever there is a case of stent failure OCT should be used to understand the mechanism of restenosis and stent thrombosis.

Fractional Flow Reserve (FFR):

Intra-coronary imaging modalities like IVUS and OCT provide a detailed anatomical assessment of coronary lesions, but give limited information about the functional severity of these lesions. Fractional flow reserve (FFR) measurement goes one step further in determining the lesion severity as it calculates the ratio between the maximum achievable blood flow in the stenosed segment of the artery and the theoretical maximum flow in a normal segment of the same artery.[37] FFR can be measured by using a coronary guidewire or a microcatheter (MC) equipped with a pressure sensor that first measures the pressure distal to the stenotic segment of the artery and then measures the aortic pressure under conditions of maximum myocardial hyperaemia. In general, if this FFR ratio is lower than 0.80, and then it is generally considered to be associated with myocardial ischemia. The concept of measuring the blood flow across a stenotic lesion is as old as coronary angioplasty itself. FFR technique has further been validated and evaluated to reduce mortality and morbidity associated with the treatment of intermediate coronary lesions.[38-40] The FAME and FAME II studies have examined the role of FFR in the assessment of multi-vessel CAD, and there is strong evidence now that a revascularization strategy using FFR yields much better clinical outcomes in patients with stable angina and multi-vessel CAD compared to optimal medical treatment alone.[40-42] Current, AHA/ESC guidelines have encouraged the use of this technology to further assess angiographic intermediate coronary lesions (50%-70% diameter stenosis) and its use can be beneficial when making revascularization decisions in patients with stable ischemic heart disease.

Despite the clinical utility and cost-effectiveness of FFR as a modality, it is surprising to note that uptake of FFR is still low with only 6–10% of patients in the United States receiving physiologic FFR assessment prior to percutaneous coronary intervention (PCI).[33,43]

Contrary to the perception that physiology based intervention increases the cost of the procedure, there is evidence that physiology based interventions actually can reduce the cost to half over a period of one-year due to minimising the cost of medications and inappropriate stenting.[44] This can be of particular benefit in a country like Pakistan, where patients and public are struggling to meet the health care costs associated with stent-related procedures.

We would recommend as per guidelines that whenever there is a moderate lesion with stenosis of (40–70%), FFR should be used to make the decision about PCI.

Summary:

Modern X-ray equipment in the catheterisation laboratory provides diagnostic coronary angiograms of excellent quality and resolution. However, a decision based on a simple visual assessment of angiogram can lead to erroneous and sometimes devastating consequences. Thus, an operator must utilise the adjunctive techniques and tools available at his/her disposal to make an informed and well-planned treatment choice. The use of these adjunct techniques like QCA, IVUS, OCT and FFR require the operator to be well trained in their use. Other limiting factors that must be overcome, especially in developing countries, include initial cost, procedure duration, education and training. However, the first step in this journey is for the interventional community to recognise the limitations of angiography.

CASE-1

A coronary angiography of right coronary artery (RCA) demonstrating a lesion in distal RCA. The severity of lesion is assessed differently in different views. The lesion appears significant in (LAO 17.70-Caudal 25.30) (Figure-1A) and non-significant in (LAO 7-Cranial 23.30) (Figure-1B). To assess the functional severity of this lesion an FFR was performed and it demonstrated a functionally non-significant (FFR=0.90) lesion, (Figure-1C, Figure-1 D). Based on this information patient was treated with medical therapy and avoided unnecessary stenting of the coronary artery. The case highlights the limitations of visual estimation of CAD in a single angiographic view and use of FFR to help guide the treatment strategy.

Figure-1: Discrepancy in angiography and physiology measurements.

CASE-2

Angiographic and IVUS measurement discrepancy is highlighted in the following case. Angiogram panel (A) shows a lesion in LMCA but IVUS (A1) demonstrated that lesion is non-significant with an MLA of 8.6 mm^2. Another angiogram (B) shows possible lesion in LMCA and IVUS (B1) showed it to be significant with MLA of 4.6 mm^2.

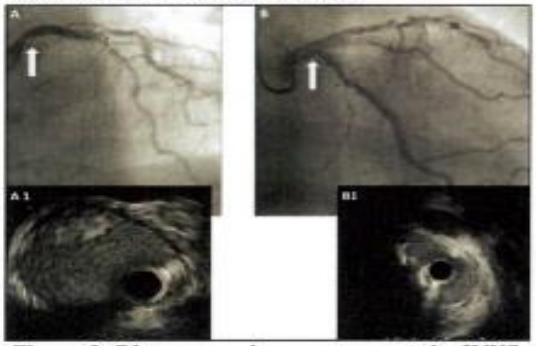

Figure-3: Discrepancy in measurements by IVUS and Angiography

CASE-3

A patient presented with Non- ST elevation myocardial infarction (NSTEMI), and coronary angiography of right coronary artery (RCA) demonstrated three mild to moderate lesions in mid region, (White and red arrows). Based on angiography it was not clear which one is culprit lesion and a decision was made to image the lesions with IVUS and OCT. The Proximal and distal lesions (white arrows) were non-significant (non–culprit) and middle lesion (red arrows) demonstrated plaque rupture with superimposed thrombus.

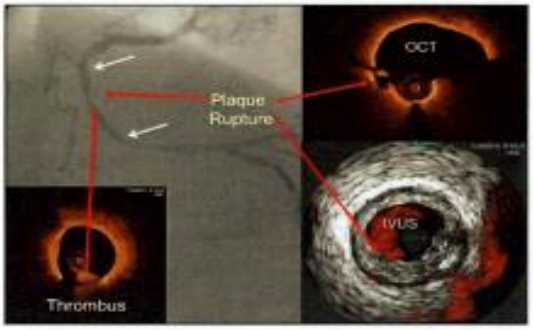

Figure-3: Role of OCT in helping to decide the mechanism of acute coronary syndrome.

REFERENCES

1. Shapiro TA, Herrmann HC. Coronary angiography and interventional cardiology. Curr Opin Radiol 1992;4(4):55–64.
2. Proudfit WL, Shirey EK, Sones FM Jr. Selective cine coronary arteriography. Correlation with clinical findings in 1,000 patients. Circulation 1966;33(6):901–10.
3. Leape LL, Park RE, Bashore TM, Harrison JK, Davidson CJ, Brook RH. Effect of variability in the interpretation of coronary angiograms on the appropriateness of use of coronary revascularization procedures. Am Heart J 2000;139(1 Pt 1):106–13.
4. Bashore TM, Balter S, Barac A, Byrne JG, Cavendish JJ, Chambers CE, *et al*. 2012 American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions expert consensus document on cardiac catheterization laboratory standards update: A report of the American College of Cardiology Foundation Task Force on Expert Consensus documents developed in collaboration with the Society of Thoracic Surgeons and Society for Vascular Medicine. J Am Coll Cardiol 2012;59(24):2221–305.
5. Iqbal J, Serruys PW, Taggart DP. Optimal revascularization for complex coronary artery disease. Nat Rev Cardiol 2013;10(11):635–47.
6. Jensen LO, Thayssen P, Mintz GS, Egede R, Maeng M, Junker A, *et al*. Comparison of intravascular ultrasound and angiographic assessment of coronary reference segment size in patients with type 2 diabetes mellitus. Am J Cardiol 2008;101(5):590–5.
7. Tobis J, Azarbal B, Slavin L. Assessment of intermediate severity coronary lesions in the catheterization laboratory. J Am Coll Cardiol 2007;49(8):839–48.
8. Girasis C, Onuma Y, Schuurbiers JC, Morel MA, van Es GA, van Geuns RJ, *et al*. Validity and variability in visual assessment of stenosis severity in phantom bifurcation lesions: a survey in experts during the fifth meeting of the European Bifurcation Club. Catheter Cardiovasc Interv 2012;79(3):361–8.
9. Fleming RM, Fleming DM, Gaede R. Training physicians and health care providers to accurately read coronary arteriograms. A training program. Angiology 1996;47(4):349–59.
10. Marcus ML, Skorton DJ, Johnson MR, Collins SM, Harrison DG, Kerber RE. Visual estimates of percent diameter coronary stenosis: "a battered gold standard". J Am Coll Cardiol 1988;11(4):882–5.

11. Fleming RM, Harrington GM. Quantitative coronary arteriography and its assessment of atherosclerosis. Part II. Calculating stenosis flow reserve from percent diameter stenosis. Angiology 1994;45(10):835–40.
12. Feldman RL, Nichols WW, Pepine CJ, Conti CR. Hemodynamic significance of the length of a coronary arterial narrowing. Am J Cardiol 1978;41(5):865–71.
13. Tuinenburg JC, Koning G, Hekking E, Zwinderman AH, Becker T, Simon R, *et al*. American College of Cardiology/European Society of Cardiolgoy International Study of Angiographic Data Compression Phase II: the effects of varying JPEG data compression levels on the quantitative assessment of the degree of stenosis in digital coronary angiography. Joint Photographic Experts Group. J Am Coll Cardiol 2000;35(5):1380–7.
14. Gottsauner-Wolf M, Sochor H, Moertl D, Gwechenberger M, Stockenhuber F, Probst P. Assessing coronary stenosis. Quantitative coronary angiography versus visual estimation from cine-film or pharmacological stress perfusion images. Eur Heart J 1996;17(8):1167–74.
15. Arnett EN, Isner JM, Redwood DR, Kent KM, Baker WP, Ackerstein H, *et al*. Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings. Ann Intern Med 1979;91(3):350–6.
16. Dietz WA, Tobis JM, Isner JM. Failure of angiography to accurately depict the extent of coronary artery narrowing in three fatal cases of percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1992;19(6):1261–70.
17. Nissen SE, Gurley JC, Grines CL, Booth DC, McClure R, Berk M, *et al*. Intravascular ultrasound assessment of lumen size and wall morphology in normal subjects and patients with coronary artery disease. Circulation 1991;84(3):1087–99.
18. Grundeken MJ, Ishibashi Y, Généreux P, LaSalle L, Iqbal J, Wykrzykowska JJ, *et al*. Inter-core lab variability in analyzing quantitative coronary angiography for bifurcation lesions: a post-hoc analysis of a randomized trial. JACC Cardiovasc Interv 2015;8(2):305–14.
19. Ambrose JA. Prognostic implications of lesion irregularity on coronary angiography. J Am Coll Cardiol 1991;18(3):675–6.
20. Omoto R. Intracardiac scanning of the heart with the aid of ultrasonic intravenous probe. Jpn Heart J 1967;8(6):569–81.
21. Leesar MA, Masden R, Jasti V. Physiological and intravascular ultrasound assessment of an ambiguous left main coronary artery stenosis. Catheter Cardiovasc Interv 2004;62(3):349–57.
22. Klein AJ, Hudson PA, Kim MS, Cleveland JC Jr, Messenger JC. Spontaneous left main coronary artery dissection and the role of intravascular ultrasonography. J Ultrasound Med 2010;29(6):981–8.
23. Abizaid AS, Mintz GS, Abizaid A, Mehran R, Lansky AJ, Pichard AD, *et al*. One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. J Am Coll Cardiol 1999;34(3):707–15.
24. Witzenbichler B, Maehara A, Weisz G, Neumann FJ, Rinaldi MJ, Metzger DC, *et al*. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. Circulation 2014;129(4):463–70.
25. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, *et al*. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58(24):e44–122.
26. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, *et al*. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv 2013;82(4):E266–355.
27. Ali ZA, Karimi Galougahi K, Nazif T, Maehara A, Hardy MA, Cohen DJ, *et al*. Imaging- and physiology-guided percutaneous coronary intervention without contrast administration in advanced renal failure: a feasibility, safety, and outcome study. Eur Heart J 2016;37(40):3090–5.
28. Parviz Y, Fall KN, Ali ZA. Using sound advice-intravascular ultrasound as a diagnostic tool. J Thorac Dis 2016;8(10):E1395–7.
29. Mueller C, Hodgson JM, Schindler C, Perruchoud AP, Roskamm H, Buettner HJ. Cost-effectiveness of intracoronary ultrasound for percutaneous coronary interventions. Am J Cardiol 2003;91(2):143–7.
30. Brezinski ME, Tearney GJ, Bouma BE, Izatt JA, Hee MR, Swanson EA, *et al*. Optical coherence tomography for optical biopsy. Properties and demonstration of vascular pathology. Circulation 1996;93(6):1206–13.
31. Tenekecioglu E, Albuquerque FN, Sotomi Y, Zeng Y, Suwannasom P, Tateishi H, *et al*. Intracoronary optical coherence tomography: Clinical and research applications and intravascular imaging software overview. Catheter Cardiovasc Interv 2017;89(4):679–89.
32. Giavarini A, Kilic ID, Redondo Diéguez A, Longo G, Vandormael J, Pureek N , *et al*. Intracoronary Imaging. Heart 2017;103(9):708–25.
33. Ali ZA, Maehara A, Généreux P, Shlofmitz RA, Fabbiocchi F, Nazif TM, *et al*. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. Lancet 2016;388(10060):2618–28.
34. Campos CM, García-García HM, Iqbal J, Muramatsu T, Nakatani S, Dijkstra J, *et al*. Serial volumetric assessment of coronary fibroatheroma by optical frequency domain imaging: insights from the TROFI trial. Eur Heart J Cardiovasc Imaging 2017.
35. Guo N, Maehara A, Mintz GS, He Y, Xu K, Wu X, *et al*. Incidence, mechanisms, predictors, and clinical impact of acute and late stent malapposition after primary intervention in patients with acute myocardial infarction: an intravascular ultrasound substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. Circulation 2010;122(11):1077–84.
36. Prati F, Cera M, Ramazzotti V, Imola F, Giudice R, Albertucci M. Safety and feasibility of a new non-occlusive technique for facilitated intracoronary optical coherence tomography (OCT) acquisition in various clinical and anatomical scenarios. EuroIntervention 2007;3(3):365–70.
37. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J Koolen JJ, *et al*. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334(26):1703–8.
38. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, *et al*. Fractional flow reserve-guided PCI for

stable coronary artery disease. N Engl J Med 2014;371(13):1208–17.
39. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, *et al*. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367(11):991–1001.
40. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, *et al*. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360(3):213–24.
41. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, *et al*. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 2010;55(25):2816–21.
42. Fearon WF, Tonino PA, De Bruyne B, Siebert U, Pijls NH. Rationale and design of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study. Am Heart J 2007;154(4):632–6.
43. Messenger JC, Ho KK, Young CH, Slattery LE, Draoui JC, Curtis JP, *et al*. The National Cardiovascular Data Registry (NCDR) Data Quality Brief: the NCDR Data Quality Program in 2012. J Am Coll Cardiol 2012;60(16):1484–8.
44. Fearon WF, Shilane D, Pijls NH, Boothroyd DB, Tonino PA, Barbato E, *et al*. Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. Circulation 2013;128(12):1335–40.

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Letter

Research Correspondence

Mechanisms of Orbital Versus Rotational Atherectomy Plaque Modification in Severely Calcified Lesions Assessed by Optical Coherence Tomography

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Rotational atherectomy (RA) and orbital atherectomy (OA) are designed to ablate calcified plaque, but differences in their mechanisms of action in vivo are not well described 1, 2, despite the importance of atherectomy in treating complex coronary artery disease.

This was a retrospective observational study comparing the effects of OA (n = 30) versus RA (n = 30) on severely calcified lesions (maximum calcium angle by OCT >270°) followed by stenting from March 2014 to August 2016 at 3 centers (NewYork-Presbyterian Hospital, New York, New York: n = 6 [RA], n = 6 [OA]; Showa University Northern Yokohama Hospital, Yokohama, Japan: n = 24 [RA]; St. Francis Hospital, Roslyn, New York: n = 24 [OA]). OCT images were acquired with the ILUMIEN OPTIS system (St. Jude Medical, St. Paul, Minnesota) and the Dragonfly Duo or Dragonfly OPTIS imaging catheter (Abbott Vascular, Santa Clara, California) or the Lunawave optical frequency domain imaging system and FastView coronary catheter (Terumo, Tokyo, Japan). OCT was performed pre-intervention (if possible), post-atherectomy (RA or OA), and post-stenting.

Calcium cross-sectional area (CSA) at the maximum calcium ablation site was identified by comparing pre- and post-atherectomy images and measured by manual segmentation. Calcium angle and lumen CSA were measured every 1 mm throughout the calcified plaque in the post-atherectomy image. Calcium modification was identified as a round, concave, polished lumen

surface (Figure 1). Noncalcified plaque modification was a round shape of the noncalcified plaque surface post-atherectomy. Stent malapposition (distance between stent strut and lumen surface >0.2 mm), asymmetry index (1 – minimum/maximum stent diameter irrespective of location), and eccentricity index (minimum/maximum stent diameter at same location) were evaluated. Calcium fracture was defined as discontinuity of the luminal surface in the calcified plaque.

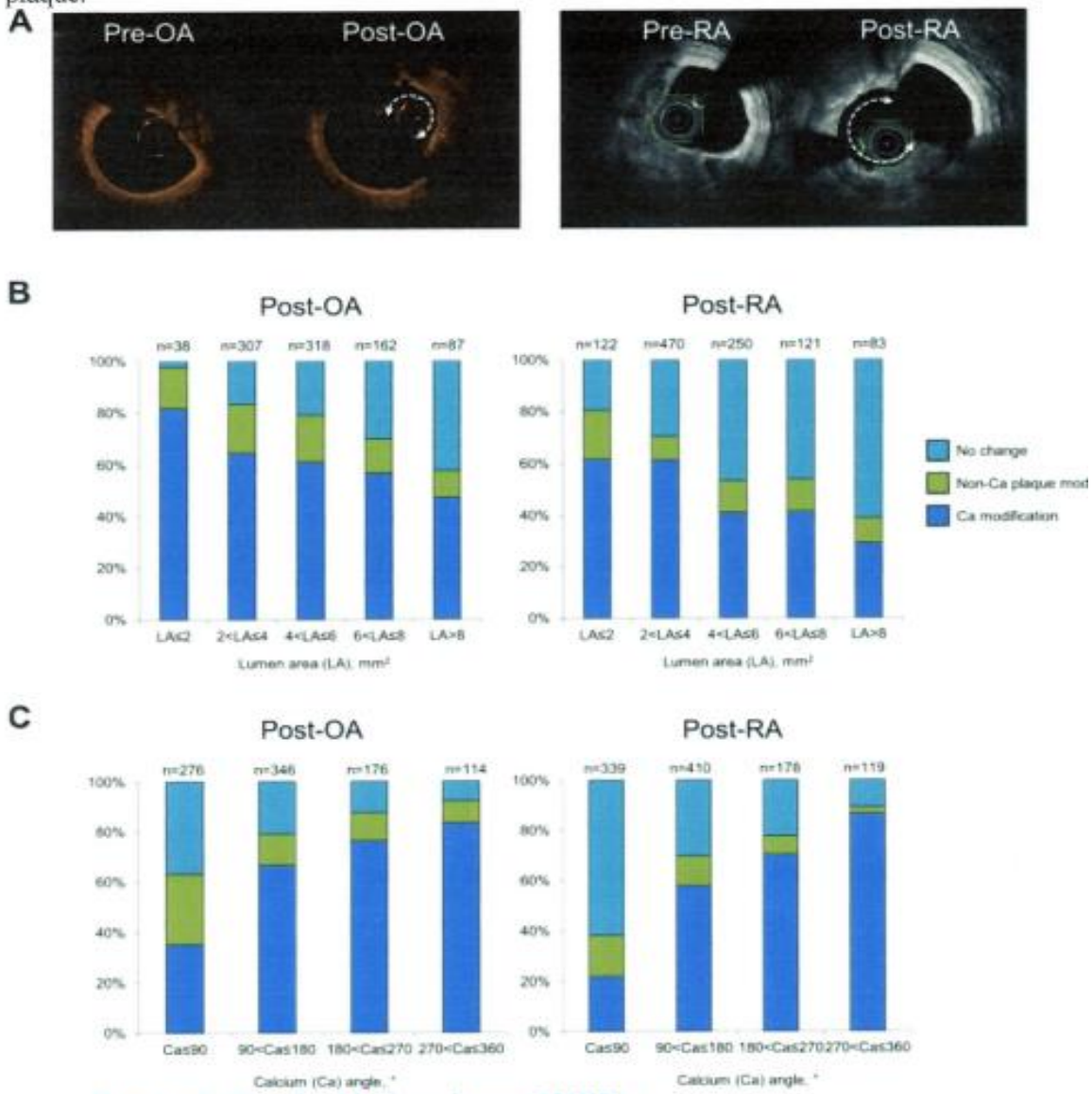

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Figure 1. Representative Image and Prevalence of Calcium Modification

(A) Comparing pre- and post-procedure in both orbital atherectomy (OA) and rotational atherectomy (RA), calcium modification (a round, concave, polished lumen surface; **dotted double-headed arrow**) was seen. The prevalence of calcium or noncalcified plaque modification as a function of **(B)** lumen area and **(C)** calcium angle. Compared with RA, OA

creates more calcium modification, especially in a larger lumen area and more noncalcified plaque modification.

Median patient age was 69 (interquartile range [IQR]: 62 to 75) years, 65% were men, and 18% were on hemodialysis; lesions were in the left anterior descending artery in 72%, with angiographic severe calcification in 58% (no difference between OA and RA). Pre-procedural OCT imaging was performed in 33 lesions (18 OA; 15 RA). At the maximum calcium modification site, calcium CSA pre-atherectomy (OA 3.6 [IQR: 3.1 to 5.0] mm^2 vs. RA 4.5 [IQR: 3.0 to 6.5] mm^2; p = 0.33), post-atherectomy (OA 2.9 [IQR: 2.4 to 4.6] mm^2 vs. RA 3.8 [IQR: 2.7 to 5.9] mm^2; p = 0.33), and the decrease in calcium CSA from pre- to post-atherectomy (OA 0.56 [IQR: 0.38 to 0.76] mm^2 vs. RA 0.60 [IQR: 0.45 to 0.79] mm^2; p = 0.49) were not different between devices.

After either OA or RA, calcium and noncalcified plaque modification was colocalized at the site of the OCT imaging catheter. Among all analyzed slices, noncalcified plaque modification post-atherectomy (OA: 1,067 slices; RA: 1,389 slices) was more frequent in the OA group vs. the RA group (16.9% [IQR: 8.4% to 23.8%] vs. 10.0% [IQR: 6.4% to 14.0%] of slices per lesion; p = 0.01). Among slices with any OCT-defined calcium (OA: 912 slices; RA: 1,046 slices), there was a trend toward more post-atherectomy calcium modification after OA versus RA (63.6% [IQR: 43.6% to 71.3%] vs. 51.8% [IQR: 39.9% to 63.3%] of slices per lesion; p = 0.09), particularly at sites with a post-atherectomy lumen CSA >4 mm^2 (53.0% [IQR: 43.5% to 76.9%] vs. 35.0% [IQR: 0% to 52.2%] of slices per lesion; p = 0.001), but not ≤4 mm^2 (71.4% [IQR: 51.7% to 85.7%] vs. 66.7% [IQR: 50.0% to 85.8%] of slices per lesion; p = 0.81). Calcium modification was greater in slices with a smaller lumen CSA and a larger angle of calcium in both devices (Figure 1).

Comparing OA versus RA, minimum stent CSA (5.3 [IQR: 3.8 to 6.2] mm^2 vs. 5.0 [IQR: 4.6 to 6.1] mm^2; p = 0.86), stent expansion (67.4% [IQR: 55.0% to 80.5%] vs. 66.7% [IQR: 61.8% to 88.9%]; p = 0.61), asymmetry (0.35 [IQR: 0.26 to 0.41] vs. 0.34 [IQR: 0.24 to 0.34]; p = 0.49), and eccentricity (0.75 [IQR: 0.66 to 0.79] vs. 0.76 [IQR: 0.70 to 0.80]; p = 0.29) were similar. Although malapposition was frequent in both groups (OA: 96.7% vs. RA: 90%; p = 0.61), maximum malapposition CSA was limited (1.5 [IQR: 0.9 to 2.3] mm^2 vs. 1.1 [IQR: 0.8 to 1.8] mm^2; p = 0.31). Overall, calcium fracture behind stent was frequent (82%), with similar prevalence and length (OA: 4.5 [IQR: 1.9 to 7.9] mm vs. RA: 3.0 [IQR: 1.9 to 5.2] mm; p = 0.38). There was no coronary perforation.

Potentially due to the lack of randomization, patients undergoing OA had vessels with larger diameter (OA: 2.67 [IQR: 2.50 to 3.05] mm vs. RA: 2.49 [IQR: 2.30 to 2.92] mm; p = 0.10) and less severe narrowing (OA: 57.7% [IQR: 49.1% to 66.7%] vs. RA: 66.3% [IQR: 63.5% to 72.6%]; p = 0.004) in pre-procedural quantitative coronary analysis, thus a bias in device selection cannot be excluded.

With both RA and OA, guidewire bias contributes to and directs plaque modification. Compared with RA, OA creates more calcium modification in lesions with larger lumen area as well as more noncalcified plaque modification; the effect in lesions with smaller lumen area is similar between devices. Importantly, final stent expansion was similar after plaque modification with either device.

References

1. 1

A.S. Kini, Y. Vengrenyuk, J. Pena. *et al.*
Comparison of rotational atherectomy vs. orbital atherectomy for the treatment of heavily calcified coronary plaques

Catheter Cardiovasc Interv, 86 (2015), pp. 1024-1032
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2. 2

M.S. Lee, K.W. Park, E. Shlofmitz, R.A. Shlofmitz

Comparison of rotational atherectomy vs. orbital atherectomy for the treatment of heavily calcified coronary plaques

Am J Cardiol, 119 (2017), pp. 1320-1323

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- Comparison of Coronary Intravascular Lithotripsy and Rotational Atherectomy in the Modification of Severely Calcified Stenoses
  2023, American Journal of Cardiology

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  2023, JACC: Asia

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- Intravascular lithotripsy for the treatment of severely calcified coronary artery disease: A DISRUPT CAD III intravascular ultrasound substudy
  2023, Cardiovascular Revascularization Medicine

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- A State-of-the-Art Review: The Percutaneous Treatment of Highly Calcified Lesions
  2022, Heart Lung and Circulation

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  Following both technologies, intravascular imaging should be performed to assess plaque morphology. OA appears to provide greater calcified and non-calcified plaque modification on OCT, particularly in larger vessels [64]. Otherwise, outcomes between the technologies are comparable with shorter fluoroscopy times using OA but similar complication rates [65].

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Manuscript 8

Pressure wire compared to microcatheter sensing for coronary fractional flow reserve: the PERFORM study

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KEYWORDS

- fractional flow reserve
- percutaneous coronary intervention
- stable angina

Abstract

Aims: Among technologies used to assess FFR, a monorail, sensor-tipped micro pressure catheter (PC) may be advantageous for delivery and re-assessment. We sought to determine whether the larger cross-sectional area of the PC influences FFR measurements compared to the pressure wire.

Methods and results: PERFORM was a single-centre, prospective study designed to determine the precision and accuracy of the PC compared with the pressure wire (PW) for measurement of FFR. Eligible patients had native coronary artery target lesions with visually estimated diameter stenosis of 40-90%. The independently adjudicated primary endpoint was the difference in hyperaemic PW-determined minimal FFR with and without the PC distal to the stenosis. Seventy-four patients (95 lesions) were prospectively analysed between December 2015 and December 2016. Median hyperaemic FFR was 0.84 (IQR 0.78, 0.89) with the PW and 0.79 (IQR 0.73, 0.85) with the PC distal to the stenosis ($p<0.001$). Such differences led to clinical discordance, whereby the PC decreased the hyperaemic PW-determined FFR from >0.80 to ≤0.80 in 17 of 95 measurements (19%). Median resting Pd/Pa was lower following introduction of the PC compared with the PW alone (0.93 [IQR 0.90, 0.97] versus 0.90 [IQR 0.86, 0.95], $p<0.001$). Median pressure drift was not different between the PW and the PC (0.01 [IQR −0.01, 0.05] versus 0.01 [IQR 0.00, 0.02], $p=0.38$).

Conclusions: Introduction of the PC reduced both hyperaemic FFR and resting Pd/Pa compared with the PW alone, leading to re-classifying physiological significance to below the clinical threshold in one out of five assessments. ClinicalTrials.gov Identifier: NCT02648230

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Abbreviations

FFR	fractional flow reserve
IQR	interquartile range
MLD	minimum lumen diameter
Pa	aortic pressure
PC	pressure catheter
Pd	distal pressure
PW	pressure wire
QCA	quantitative coronary angiography
RVD	reference vessel diameter

Introduction

Fractional flow reserve (FFR) measurements in randomised clinical outcomes trials were made using a 0.014" coronary hypotube with a piezo-resistive sensor near its tip[1-3]. However, the presence of electrical connections, and more recently optical fibre, within the shaft of these "wires" limits their torqueability in comparison to workhorse wires. A new FFR technology with an optical pressure sensor mounted at the tip of a monorail microcatheter (Navvus®; ACIST Medical Systems, Eden Prairie, MN, USA) has been developed to counter some of the limitations of the wire-based FFR measurement. While a microcatheter system facilitates multiple advancement and withdrawal over the operator's guidewire of choice, the larger diameter of the catheter may also influence coronary haemodynamics across the target lesion. The degree to which this may occur in practice is unknown.

The PrEssure wiRe Compared to Microcatheter-based Sensing Technology For the Evaluation of FFR Measurements (PERFORM) study was designed to determine the precision and accuracy of the Navvus pressure catheter (PC) compared with the pressure wire (PW) among an unselected group of patients undergoing FFR assessment for routine clinical indications.

Methods

STUDY DESIGN

PERFORM was a prospective, single-centre study conducted at Columbia University Medical Center (New York, NY, USA) comparing the PW (Aeris™; St. Jude Medical, St. Paul, MN, USA) and the PC (Navvus). The institutional review board approved the study protocol. The trial was registered at ClinicalTrials.gov: NCT02648230.

PARTICIPANTS

Patients undergoing coronary angiography based on clinical indication were considered for enrolment. Eligible patients had one or more target lesions located in a native coronary artery with visually estimated diameter stenosis of 40-90% and planned use of FFR for clinical decision making[4]. Left main or ostial right coronary artery stenosis, bypass graft stenoses, and chronic total occlusions were excluded.

PROCEDURES

Coronary angiography was performed via femoral or radial access, and anticoagulation, dual antiplatelet therapy and other medications were administered per local standard of care. A minimum 6 Fr guiding catheter was used.

Following angiography, performed in a view that would allow optimal quantitative coronary angiography (QCA), physiological assessments were performed **(Figure 1)**. Briefly, the PC was loaded onto the PW, and the aortic pressure transducer, PC, and PW all equilibrated to zero pressure outside of the body. With the PC used as an introducer, the PW alone was advanced to the aorto-ostial junction where PW equalisation was performed after ensuring the presence of an appropriate aortic waveform, with guide disengagement performed if necessary. The PW was then advanced across the lesion with the sensor located at least 3 cm distal to the lesion and preferably in the distal third of the artery. Following administration of intracoronary nitroglycerine and saline flush, the guide catheter was disengaged, the position of the PW was recorded on cine angiography, and the lowest basal distal pressure/aortic pressure (Pd/Pa) was recorded. The preloaded PC was then advanced from outside the body to the aorto-ostial junction where PC equalisation was performed, again ensuring the presence of the appropriate aortic waveform. The PC was then advanced just proximal to the PW sensor, and the lowest basal Pd/Pa of both the PC and PW was recorded simultaneously. To induce hyperaemia, intravenous adenosine was infused at 140 µg/kg/min. At maximal hyperaemia, the FFR was recorded on both the PW and the PC. The PC was then slowly pulled back, making note of pressure step-ups across the lesion, and the PC drift was recorded at the aorto-ostial junction. Subsequently, the PC was completely removed, and the FFR was recorded again with the PW alone. The PW was then slowly pulled back, making note of pressure step-ups across the lesion, and the pressure again recorded at the aorto-ostial junction. Pd/Pa, FFR, and pressure drift of each device were also recorded in real time using time-stamped still photography. Revascularisation was guided by hyperaemic FFR measured by the PW alone.

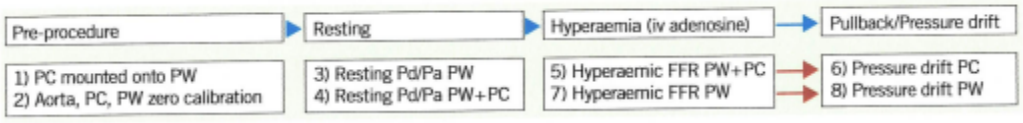

Figure 1. *Protocol for physiologic assessment using a pressure wire and a pressure catheter. FFR: fractional flow reserve; IV: intravenous; PC: pressure catheter; PW: pressure wire*

OUTCOMES

The primary endpoint of the study was the difference in hyperaemic PW-determined minimal FFR with and without the presence of the PC distal to the stenoses. Secondary endpoints included device success (the ability to cross the lesion and record a hyperaemic FFR), the difference in PW-determined resting Pd/Pa with and without the PC distal to the stenosis, PW and PC pressure drift, and discordance in physiological significance (hyperaemic FFR ≤0.80 by one modality versus >0.80 with the other modality and hyperaemic FFR ≤0.75 by one modality versus >0.80 with the other modality). Other outcomes assessed were the proportion of lesions with a mean hyperaemic FFR difference ≥0.05 and ≥0.10, and a sensitivity analysis for resting Pd/Pa and hyperaemic FFR comparing measurements made using the PW versus the PC when both devices were in the distal coronary artery.

DATA ANALYSIS

Primary and secondary imaging and physiology endpoints were independently performed in the angiography and physiology core laboratories at the Cardiovascular Research Foundation (New York, NY, USA). Offline QCA analyses to determine percentage diameter stenosis, reference artery diameter, and lesion level characteristics were performed by an independent core lab (Cardiovascular Research Foundation) using automated software (QAngio; Medis, Leiden, the Netherlands). Haemodynamic data were analysed by an independent physiology core lab (Cardiovascular Research Foundation). Tracing from the PW and the PC were scrambled in the core laboratory such that measurements did not undergo paired analysis, avoiding bias.

STATISTICAL ANALYSIS

The sample size was calculated assuming a difference of 0.02 between PC- and PW-determined FFR with a standard deviation of 0.065[5,6]. At an α of 0.025 (one-sided), 85 lesions would be required to reject the null hypothesis that there was no difference between PC- and PW-measured FFR with 80% power. Normal distribution of parameters was assessed using the Kolmogorov-Smirnov test, and homogeneity of variance was assessed using Levene's test. Continuous values were summarised using median and interquartile range (IQR), and differences were compared using the Mann-Whitney U test. Systematic errors of measurement induced by the PC were assessed using Pearson correlation and Bland-Altman analysis. The univariate association between the PW and PC difference in measurements (ΔFFR) and patient or lesion characteristics was assessed using the Student's t-test (binary parameters) or Pearson correlation (continuous parameters). The adjusted association between the ΔFFR and patient and lesion characteristics was determined using multivariable linear regression. P-values <0.05 were considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

PATIENTS AND PROCEDURES

Between December 2015 and December 2016, 74 patients with 95 lesions had successful PW measurements and were enrolled in the study. Patient data and angiographic lesion characteristics are presented in **Table 1**.

STUDY ENDPOINTS

Device success in crossing the lesion was 100% with the PW and 95% with the PC (p=0.02). FFR was available with both the PW and the PC for 89 lesions (94%), and resting Pd/Pa was available with both the PW and PC for 88 lesions (93%). Resting Pd/Pa measured on the PW decreased significantly from 0.93 (IQR 0.90, 0.97) to 0.90 (IQR 0.86, 0.95), following advancement of the PC distal to the stenosis (p<0.001) **(Table 2)**. While the PW and PC assessments of resting Pd/Pa were closely correlated **(Figure 2A)**, the PC led to overestimation of the pressure gradient. Bland-Altman analysis did not identify systematic differences between PW and PC measurements of the resting Pd/Pa **(Figure 2B)**. The distribution of the differences in Pd/Pa is shown in **Figure 2C**.

Table 1. Patient and procedural characteristics.

Patient-level characteristics (N=74)		
Age, years		64±11
Male		54 (73)
Weight, kg		83±18
Height, cm		171±10
Diabetes		53 (72)
Hypertension		71 (96)
Hypercholesterolaemia		73 (99)
Former smoker		38 (51)
Current smoker		12 (16)
History of heart failure		43 (58)
Ejection fraction, %		55±13
Lesion-level characteristics (N=95)		
Target vessel	Left anterior descending	47 (49)
	Left circumflex	23 (24)
	Right	25 (26)
Eccentric lesion		64 (67)
Thrombus		1 (1)
Tortuosity		32 (34)
Calcification		51 (54)
Aneurysmal lesion		5 (5)
Ectasia present		12 (13)
Bifurcation		21 (22)
Interpolated reference vessel diameter, mm		2.84±0.58
Distal reference vessel diameter, mm		2.66±0.58
In-segment minimum lumen diameter, mm		1.61±0.48
Diameter stenosis (by quantitative coronary angiography), %		44±10
Diameter stenosis (visual), %		66±10
Lesion length, mm		12.2±7.3
Lesion angle, °		26.5±10.3

Values are mean±standard deviation or n (%).

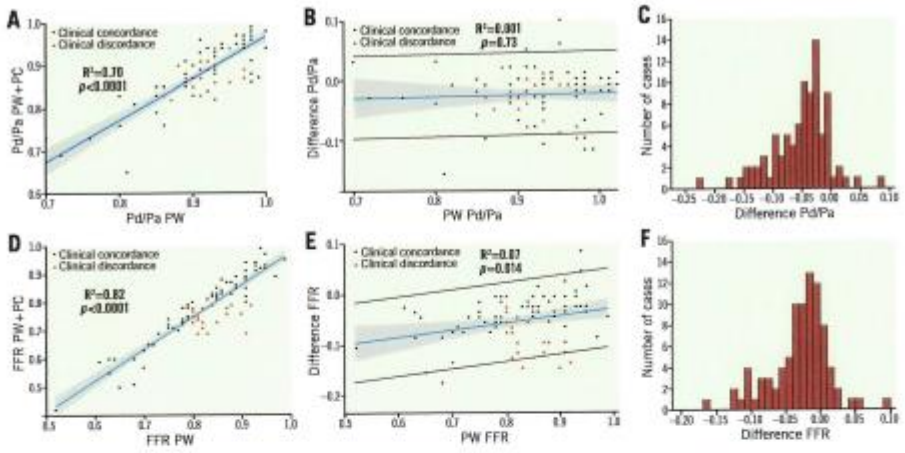

Figure 2. *Correlation between resting Pd/Pa and hyperaemic fractional flow reserve between pressure catheter and pressure wire. Correlation between the pressure catheter (PC) and pressure wire (PW) (A) and Bland-Altman analysis of agreement (B) for resting Pd/Pa. Distribution of the difference in Pd/Pa between PC and PW (C). Correlation between the PC and PW (D) and Bland-Altman analysis of agreement (E) for hyperaemic fractional flow reserve (FFR). Distribution of the difference in FFR between PC and PW (F).*

Following the introduction of the PC distal to the target lesion, hyperaemic FFR measured on the PW decreased significantly from 0.84 (IQR 0.78, 0.89) to 0.79 (IQR 0.73, 0.85) (p<0.001) **(Table 2)**. While the PW and PC assessments of hyperaemic FFR were well correlated (R2=0.82, p<0.0001) **(Figure 2D)**, introduction of the PC distal to the stenosis led to overestimation of the severity of the pressure gradient. Moreover, the difference between PW and PC measurements increased with decreasing FFR values **(Figure 2E)**, indicating that FFR overestimation by the PC occurs more frequently in more severe lesions. The introduction of the PC resulted in a decrease in FFR compared with the PW alone by ≥0.10 in 13 (15%) lesions and by ≥0.05 in 35 (39%) lesions. These differences led to discordance in ascribing physiologic significance in a number of lesions, with the PC measuring FFR ≤0.80 in 17 lesions (19%) for which the FFR measured by the PW was >0.80 **(Table 2)**, and with the PC measuring FFR ≤0.75 in eight lesions (9%) for which the PW was >0.80. There were no instances of the PW measuring FFR ≤0.80 and the PC >0.80. The distribution of the differences in FFR is shown in **Figure 2F**.

Sensitivity analyses identified no difference in resting Pd/Pa (0.90 [IQR 0.86, 0.95] versus 0.91 [IQR 0.87, 0.96], p=0.054) or hyperaemic FFR (0.79 [IQR 0.73, 0.85] versus 0.80 [IQR 0.73, 0.86], p=0.44) measured by the PW or PC when both devices were simultaneously in the distal coronary circulation. Pressure drift was not different between the PC and the PW (0.01 [IQR -0.01, 0.05] versus 0.01 [IQR 0.00, 0.02], p=0.38).

Among patients with ΔFFR (difference between FFR measured by PC and PW), lesion location in the right coronary artery, interpolated reference vessel diameter (RVD), distal RVD, in-segment minimum lumen diameter (MLD), and lesion length were significantly associated with the ΔFFR in univariate analyses **(Table 3)**. Discordance between PW and PC measurements was observed more often in vessels with small distal RVD and longer lesion length with differences pronounced in different ranges of FFR values **(Figure 3)**. In multivariable analyses only distal RVD and lesion length were identified as independent predictors of ΔFFR **(Table 4)**.

Table 2. Physiological parameters.

Parameter	Pressure wire	Pressure catheter	p-value
FFR	0.84 [0.78, 0.89]	0.79 [0.73, 0.85]	<0.001
Clinically discordant (FFR from >0.80 to ≤0.80)	–	17 (19)	<0.001
FFR underestimated by ≥0.05, %*	2 (2)	35 (39)	<0.001
FFR underestimated by ≥0.10, %*	0 (0)	13 (15)	<0.001
Pd/Pa	0.93 [0.90, 0.97]	0.90 [0.86, 0.95]	<0.001
Pressure drift	0.01 [–0.01, 0.05]	0.01 [0.00, 0.02]	0.38

*Versus the other device. Values are median (interquartile range).
FFR: fractional flow reserve; Pa: aortic pressure; Pd: distal pressure

Discussion

PERFORM was a direct comparison of the PW and the PC for physiologic assessment of moderate coronary artery stenosis, which aimed to determine whether the larger cross-sectional area of the

Table 3. Univariate associations between patient/lesion characteristics and the difference in fractional flow reserve measured with the pressure wire versus pressure catheter.

Observed difference in fractional flow reserve according to the presence versus absence of a characteristic				
Patient/lesion characteristic		ΔFractional flow reserve		*p*-value
		Characteristic present	Characteristic absent	
Male (men vs. women)		–0.03 (–0.05, –0.02)	–0.03 (–0.08, –0.01)	0.63
Diabetes (yes vs. no)		–0.03 (–0.08, 0.00)	–0.03 (–0.07, –0.02)	0.46
Hypertension (yes vs. no)		–0.03 (–0.13, –0.02)	–0.03 (–0.06, –0.01)	0.16
History of heart failure (yes vs. no)		–0.04 (–0.09, –0.02)	–0.03 (–0.05, 0.00)	0.12
Previous cerebrovascular accident (yes vs. no)		–0.06 (–0.09, –0.02)	–0.03 (–0.05, 0.00)	0.053
Former smoker (yes vs. no)		–0.03 (–0.05, –0.01)	–0.04 (–0.08, –0.02)	0.40
Current smoker (yes vs. no)		–0.03 (–0.08, –0.02)	–0.03 (–0.04, –0.01)	0.43
Non-smoker (yes vs. no)		–0.03 (–0.06, –0.02)	–0.03 (–0.11, –0.01)	0.80
Target vessel	LAD (yes vs. no)	–0.03 (–0.06, –0.02)	–0.04 (–0.08, –0.02)	0.35
	LCx (yes vs. no)	–0.03 (–0.05, –0.02)	–0.04 (–0.09, –0.02)	0.30
	RCA (yes vs. no)	–0.04 (–0.08, –0.02)	–0.03 (–0.04, 0.00)	0.033
Eccentric lesion (yes vs. no)		–0.03 (–0.06, –0.02)	–0.04 (–0.08, –0.02)	0.32
Tortuosity (yes vs. no)		–0.04 (–0.06, –0.02)	–0.04 (–0.09, –0.02)	0.23
Calcification (yes vs. no)		–0.04 (–0.07, –0.02)	–0.04 (–0.08, –0.02)	0.74
Ulcerated lesion (yes vs. no)		–0.04 (–0.08, –0.02)	–0.07 (–0.08, –0.03)	0.46
Aneurysmal lesion (yes vs. no)		–0.04 (–0.07, –0.02)	–0.04 (–0.04, –0.02)	0.93
Ectasia present (yes vs. no)		–0.04 (–0.07, –0.02)	–0.05 (–0.08, –0.02)	0.69
Bifurcation (yes vs. no)		–0.04 (–0.07, –0.02)	–0.04 (–0.09, –0.01)	0.88

Correlation between continuous variables and the observed difference in fractional flow reserve			
Patient/lesion characteristic	ΔFractional flow reserve		*p*-value
	Mean±standard deviation	Correlation coefficient	
Age, years	63.90±10.66 (89)	0.10 (–0.11, 0.30)	0.36
Weight, kg	81.73±18.07 (89)	0.11 (–0.11, 0.31)	0.33
Height, cm	170.18±9.55 (89)	0.10 (–0.11, 0.30)	0.35
Ejection fraction, %	55.10±13.23 (60)	0.14 (–0.12, 0.38)	0.30
Interpolated reference vessel diameter, mm	2.84±0.59 (89)	0.31 (0.11, 0.49)	0.003
Distal reference vessel diameter, mm	2.66±0.59 (89)	0.35 (0.16, 0.52)	<0.001
In-segment minimum lumen diameter, mm	1.61±0.50 (89)	0.27 (0.06, 0.45)	0.01
Diameter stenosis (by QCA), %	43.92±10.45 (89)	–0.08 (–0.29, 0.13)	0.43
Diameter stenosis (visual), %	65.84±10.34 (89)	–0.16 (–0.36, 0.05)	0.13
Lesion length, mm	12.10±7.22 (89)	–0.23 (–0.42, –0.03)	0.027
Lesion angle, °	26.47±10.20 (89)	–0.09 (–0.29, 0.13)	0.43

Values are median (interquartile range) or mean±standard deviation (N) and correlation coefficient (95% confidence interval). LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; QCA: quantitative coronary angiography; RCA: right coronary artery

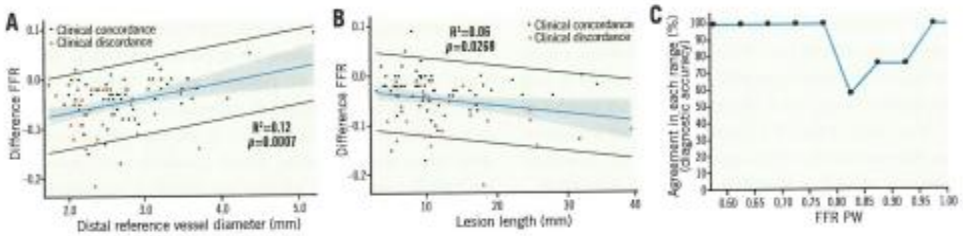

Figure 3. *Relationship between ΔFFR and distal reference vessel diameter (A), lesion length (B) and agreement by FFR range (C). FFR: fractional flow reserve; PC: pressure catheter; PW: pressure wire*

the PW and the PC, especially in values around the 0.8 ischaemia threshold **(Figure 2B)**, exists. We did, however, identify a systematic and proportional difference in the FFR, finding a greater difference between devices the lower the FFR values were **(Figure 2B)**. Univariate analysis identified a number of factors associated with the ΔFFR between devices. Nonetheless, in multivariable analysis, only distal RVD and lesion length were identified as independent predictors of ΔFFR. These data suggest that operators need to pay close attention to placement of the PC during physiological assessment, perhaps placing the PC distal to the stenosis, but not in the very distal coronary artery, or interpreting the PC-based FFR measurements in smaller vessels with caution.

Study limitations

Our study has a number of important limitations. First, our study was conducted in a single centre with significant experience in physiological assessment using FFR, which may limit its generalisability. Nevertheless, no pressure tracings were rejected by the physiology core laboratory, highlighting a potential advantage of a single centre where both physician training and trial monitoring are closely regulated and uniform. Second, our study was not randomised. The IMPACT study randomised physiological assessment by PC or PW, changing the order of use of the devices by random allocation[16]; however, measurements in our study were performed during a single administration of intravenous adenosine as an infusion and thus may be less prone to the error introduced by intracoronary bolus adenosine administration in the IMPACT study[16]. Third, a larger sample size may have been able to provide greater power to detect specific patient or lesion characteristics associated with the ΔFFR. Fourth, we compared the PC to a specific PW from a single manufacturer. Although similar findings between the PC and other PWs may be inferred, our study can neither confirm nor refute this possibility. Finally, a new iteration of the PC is available with 33% less cross-sectional area, probably impacting on our findings.

Conclusions

In conclusion, introduction of the larger cross-sectional area PC reduced device success and both resting Pd/Pa and hyperaemic FFR compared with the PW, with no difference in drift. Compared with the PW, the PC led to re-classifying physiological significance to below the clinical threshold in one out of five assessments, particularly in vessels with small distal reference vessel diameters and long lesions, where PC measurements may be less reliable due to the larger cross-sectional profile of the PC.

Impact on daily practice

The results of the current study are consistent with others evaluating the haemodynamic effect of the larger diameter PC across intermediate coronary stenoses. While varying marginally in the magnitude of the difference, the PC does introduce a decrease in the hyperaemic FFR.

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Conflict of interest statement

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References

1. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, Maccarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med.* 2012;367:991-1001.

2. Pijls NH, Van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, Van't Veer M, Bär F, Hoorntje J, Koolen J, Wijns W, De Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol.* 2007;49:2105-11.

3. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, Maccarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* 2009;360:213-24.

4. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol.* 2010;55:2816-21.

5. De Bruyne B, Pijls NH, Barbato E, Bartunek J, Bech JW, Wijns W, Heyndrickx GR. Intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. *Circulation.* 2003;107:1877-83.

6. Johnson NP, Johnson DT, Kirkeeide RL, Berry C, De Bruyne B, Fearon WF, Oldroyd KG, Pijls NHJ, Gould KL. Repeatability of Fractional Flow Reserve Despite Variations in Systemic and Coronary Hemodynamics. *JACC Cardiovasc Interv.* 2015;8:1018-27.

7. Daniels DV, Van't Veer M, Pijls NH, Van Der Horst A, Yong AS, De Bruyne B, Fearon WF. The impact of downstream coronary stenoses on fractional flow reserve assessment of intermediate left main disease. *JACC Cardiovasc Interv.* 2012;5:1021-5.

8. Rimac G, Fearon WF, De Bruyne B, Ikeno F, Matsuo H, Piroth Z, Costerousse O, Bertrand OF. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: A systematic review and meta-analysis. *Am Heart J.* 2017; 183:1-9.

9. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. *JACC Cardiovasc Interv.* 2016;9:1022-31.

10. Banerjee RK, Peelukhana SV, Goswami I. Influence of newly designed monorail pressure sensor catheter on coronary diagnostic parameters: an in vitro study. *J Biomech.* 2014;47:617-24.

11. Verberne HJ, Meuwissen M, Chamuleau SA, Verhoeff BJ, Van Eck-Smit BL, Spaan JA, Piek JJ, Siebes M. Effect of simultaneous intracoronary guidewires on the predictive accuracy of functional parameters of coronary lesion severity. *Am J Physiol Heart Circ Physiol.* 2007;292:H2349-55.

12. Pouillot C, Fournier S, Glasenapp J, Rambaud G, Bougrini K, Vi Fane R, Geyer C, Adjedj J. Pressure wire versus microcatheter for FFR measurement: a head-to-head comparison. *EuroIntervention.* 2018;13:e1850-6.

13. Masdjedi K, Van Mieghem NM, Diletti R, Van Geuns RJ, De Jaegere P, Regar E, Zijlstra F, Van Domburg RT, Daemen J. Navvus FFR to reduce CONTRAst, Cost and radiaTion (CONTRACT): insights from a single-centre clinical and economical evaluation with the Rxi Rapid-Exchange FFR device. *Int J Cardiol.* 2017;233:80-4.

14. Fearon WF, Chambers JW, Seto AH, Sarembock IJ, Raveendran G, Sakarovitch C, Yang L, Desai M, Jeremias A, Price MJ; ACIST-FFR Study Investigators. ACIST-FFR Study (Assessment of Catheter-Based Interrogation and Standard Techniques for Fractional Flow Reserve Measurement). *Circ Cardiovasc Interv.* 2017 Dec;10(12).

15. Menon M, Jaffe W, Watson T, Webster M. Assessment of coronary fractional flow reserve using a monorail pressure catheter: the first-in-human ACCESS-NZ trial. *EuroIntervention.* 2015;11:257-63.

16. Wijntjens GW, Van De Hoef TP, Kraak RP, Beijk MA, Sjauw KD, Vis MM, Madera Cambero MI, Brinckman SL, Plomp J, Baan J Jr, Koch KT, Wykrzykowska JJ, Henriques JP, De Winter RJ, Piek JJ. The IMPACT Study (Influence of Sensor-Equipped Microcatheters on Coronary Hemodynamics and the Accuracy of Physiological Indices of Functional Stenosis Severity). *Circ Cardiovasc Interv.* 2016 Dec;9(12).

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External elastic lamina vs. luminal diameter measurement for determining stent diameter by optical coherence tomography: an ILUMIEN III substudy

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Aims Optical coherence tomography (OCT)-guided external elastic lamina (EEL)-based stent sizing is safe and as effective as intravascular ultrasound in achieving post-procedural lumen dimensions. However, when compared with automated lumen diameter (LD) measurements, this approach is time-consuming. We aimed to compare vessel diameter measurements and stent diameter selection using either of these approaches and examined whether applying a correction factor to automated LD measurements could result in selecting similar stent diameters to the EEL-based approach.

Methods and results We retrospectively compared EEL-based measurements vs. automated LD in reference segments in 154 OCT acquisitions and derived a correction factor for stent sizing using the ratio of EEL to LD measurements. We then prospectively applied the correction factor in 119 OCT acquisitions. EEL could be adequately identified in 100 acquisitions (84%) at the distal reference to allow vessel diameter measurement. Vessel diameters were larger with EEL-based vs. LD measurements at both proximal (4.12 ± 0.74 vs. 3.14 ± 0.67 mm, $P < 0.0001$) and distal reference segments (3.34 ± 0.75 vs. 2.64 ± 0.65 mm, $P < 0.0001$). EEL-based downsizing led to selection of larger stents vs. an LD-based upsizing approach (3.33 ± 0.47 vs. 2.70 ± 0.44, $P < 0.0001$). Application of correction factors to LD [proximal 1.32 (IQR 1.23–1.37) and distal 1.25 (IQR 1.19–1.36)] resulted in discordance in stent sizing by >0.25 mm in 63% and potentially hazardous stent oversizing in 41% of cases.

Conclusion EEL-based stent downsizing led to selection of larger stent diameters vs. LD upsizing. While applying a correction factor to automated LD measurements resulted in similar mean diameters to EEL-based measurements, this approach cannot be used clinically due to frequent and potentially hazardous stent over-sizing.

Keywords optical coherence tomography • stent sizing • intravascular imaging

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Introduction

When compared with intravascular ultrasound (IVUS), that enables visualization of the external elastic lamina (EEL) behind most atherosclerotic lesions, the limited penetration depth of light emitted in optical coherence tomography (OCT) results in frequent loss of visualization of EEL.[1,2] Thus, in contrast to IVUS, most studies of OCT-guided percutaneous coronary intervention (PCI) have used luminal dimensions in lieu of the 'true' vessel size, i.e. EEL-based diameter, for selection of stent diameters. This approach has resulted in selecting smaller stent diameters and thereby smaller final minimum stent areas (MSA) compared with either IVUS- or angiography-guided stenting.[1,3,4] Since post-PCI MSA is a critical determinant of freedom from early and late major adverse cardiovascular events (MACE) after stenting,[5–12] smaller lumen dimensions measured on OCT may be a major limitation of this imaging modality, possibly offsetting benefits afforded by its superior resolution in guiding PCI procedures.

The ILUMIEN III randomized trial demonstrated that OCT-guided EEL-based stent sizing was feasible, safe, and as effective in achieving similar MSA as IVUS, and led to greater minimal and mean stent expansion compared with angiography, and the least number of untreated procedural complications.[13] Nevertheless, EEL-based measurements on OCT are performed manually, are time-consuming, and require specific training and experience. In contrast, automated mean lumen diameter (LD) measurement is a simple, readily available feature on commercial OCT systems, yet it has the aforementioned limitation of leading to selection of undersized stents.

We sought to determine the magnitude of difference between the EEL- and automated LD-based selection of stent diameters. We also examined whether deriving and applying a correction factor for LD (LD_{Corr}) may provide guidance in selecting stent diameters that are similar to the EEL-based measurements, thus obviating the need to manually search for and measure the EEL-based diameter.

Methods

Study design and participants

In a retrospective set of 154 OCT acquisitions from the ILUMIEN III study, we manually measured the mean EEL to EEL diameter at the proximal and distal reference segments where at least 180° of reference vessel EEL could be visualized. Greater than 180° of EEL could be visualized at either reference segment in 85% of cases, 69% at the proximal reference vessel and 77% at the distal reference. We then recorded the proximal and distal reference mean LD from the OCT automated measurements at the exact same location. We undertook hypothetical stent sizing by using the distal reference vessel measurements (i) rounding down the mean distal EEL reference diameter to the nearest device size for EEL-based stent sizing and (ii) rounding up the mean distal LD to the nearest device size for LD-based stent sizing. Using the reference vessel EEL and LD measurements, we derived a correction factor for vessel sizing by calculating the ratio of EEL to LD measurements (LD_{Corr}) at both the proximal and distal references. For validation of LD_{Corr}, we prospectively scanned 119 consecutive patients undergoing OCT for clinical indication at two centers (Columbia University Medical Center, New York, NY, USA and St. Francis Hospital, Roslyn, NY, USA). Greater than 180° of EEL could be visualized at either reference segment in 92 (77%) cases, but in 100 acquisitions (84%) at the distal reference. We applied the LD_{Corr} in the validation cohort by multiplying the respective proximal- and distal-derived correction factors to the mean LD of the proximal and distal reference vessels. We then compared these calculations to the actual EEL-based measurements of the reference segments (LD_{Corr} vs. EEL). We subsequently undertook hypothetical stent sizing by using the distal reference vessel measurements (i) rounding down the mean distal EEL reference diameter to the nearest device size for EEL-based stent sizing and (ii) rounding up the LD to the nearest device size for LD-based stent sizing (*Figures 1* and *2*). We then compared the stent sizing based on the calculated vs. actual EEL-based reference diameters: i.e. we compared the LD_{Corr} × mean distal LD rounded down to ~0.25 mm with the EEL-based distal diameter rounded down to ~0.25 mm.

Procedures

We performed pre-PCI OCT after administration of intracoronary nitroglycerin through a guiding catheter (≥6F). We performed OCT via femoral or radial access using unfractionated heparin or bivalirudin anticoagulation per the operator preference. We acquired the OCT images using the Dragonfly OPTIS Imaging Catheter (Abbott Vascular, Santa Clara, CA, USA). The EEL-based measurements were independently performed by two cardiologists with extensive experience in OCT analysis (Y.P. and E.S.).

Statistical analysis

Statistical analyses were performed with SPSS version 20.0 (IBM, Armonk, NY, USA). Normally distributed continuous variables are reported as mean with SD and compared with the Student's *t*-test; continuous variables not exhibiting normal distribution are reported as median with first and third quartiles and compared with the Mann–Whitney *U* test. Categorical variables are summarized as numbers (percentages) and compared using χ^2 statistics or Fisher's exact test, as appropriate. The 95% confidence interval (CI) was calculated for the difference in proportions between groups. A *P*-value <0.05 was considered statistically significant.

Results

Baseline demographic, procedural and OCT characteristics of the derivation and validation cohorts are presented in *Table 1*.

Derivation cohort

While the mean LD highly correlated with the EEL-based diameter at the proximal reference ($R^2 = 0.74$, $P < 0.0001$), the mean LD was significantly smaller than the EEL-based diameter (3.14 ± 0.67 vs. 4.12 ± 0.74, $P < 0.0001$; *Figure 3A*), with an absolute difference of 0.96 ± 0.32 mm, 95% CI 0.89–1.02. Similarly, at the distal reference, the mean LD also highly correlated with the EEL-based diameter ($R^2 = 0.74$, $P < 0.0001$), and the mean LD was smaller than the EEL-based diameter (2.64 ± 0.65 vs. 3.34 ± 0.76, $P < 0.0001$; *Figure 3B*), with an absolute difference of 0.71 ± 0.43 mm, 95% CI 0.63–0.79. Accordingly, stent sizing based on the distal reference mean LD upsized to the nearest device size led to selection of significantly smaller stent diameters compared with EEL-based downsizing to the nearest device size (2.70 ± 0.44 vs. 3.33 ± 0.47, $P < 0.0001$; *Figure 3C*). Mean LD-based stent selection led to stent under-sizing in 91% of cases compared with the EEL-based measurement.

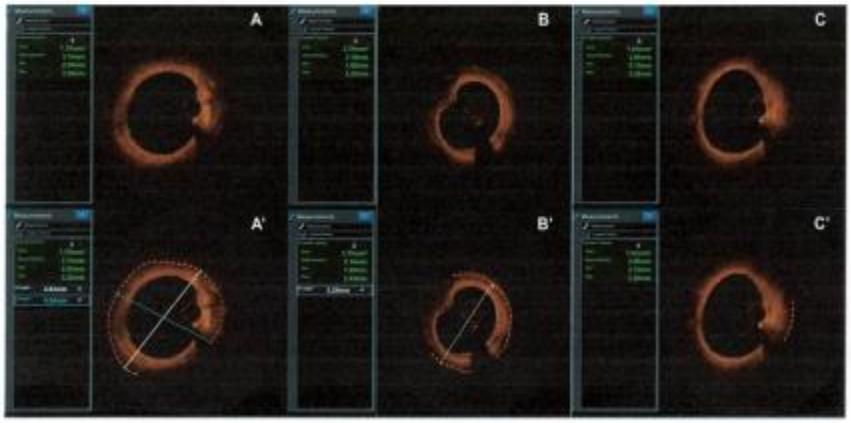

Figure 1 EEL vs. lumen-based device sizing. (*A*) OCT cross-section shows an automated minimal and maximal lumen diameters of 2.99 and 3.36 mm, respectively, with mean lumen diameter of 3.15 mm. Using a lumen-based sizing strategy, rounding up leads to the choice of a 3.25 mm device. (*A'*) The EEL (yellow dashed line) is visible for >270° allowing measurement of EEL minimal and maximal diameters of 4.34 and 4.83 mm respectively. The mean EEL-EEL diameter is 4.59 mm. Using an EEL-based sizing strategy, rounding down leads to the choice of a 4.5 mm device. The difference in device size choice based on the lumen vs. EEL is 1.25 mm. (*B*) OCT cross-section shows an automated minimal and maximal lumen diameters of 1.80 and 2.43 mm, respectively, with mean lumen diameter of 2.18 mm. Using a lumen-based sizing strategy, rounding up leads to the choice of a 2.25 mm device. (*B'*) The EEL (yellow dashed line) is visible for <270° allowing measurement of a single EEL diameter of 3.25 mm. Using an EEL-based sizing strategy, leads to choice of a 3.25 mm device. The difference in device size choice based on the lumen vs. EEL is 1 mm. (*C*) OCT cross-section shows an automated minimal and maximal lumen diameters of 2.72 and 3.28 mm, respectively, with mean lumen diameter of 2.98 mm. Using a lumen-based sizing strategy, rounding up leads to the choice of a 3.0 mm device. (*C'*) The EEL (yellow dashed line) is visible for <90° not allowing measurement of EEL vessel diameters. EEL, external elastic lamina; OCT, optical coherence tomography.

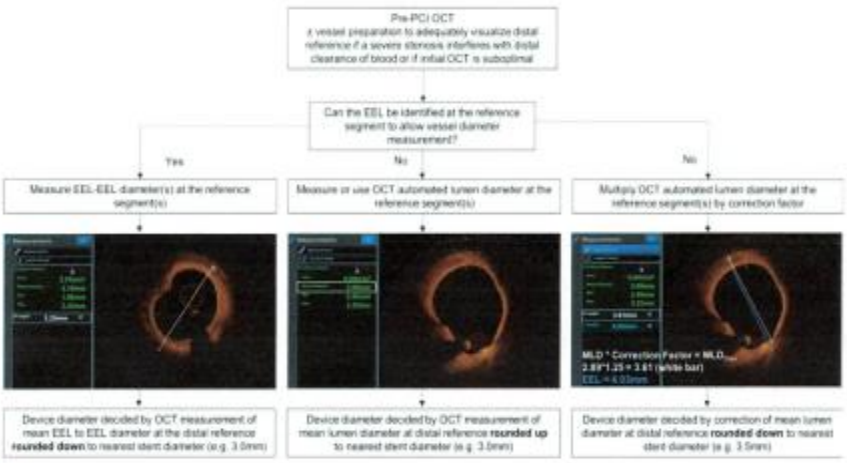

Figure 2 Methods to determine device size using EEL, lumen, and LD_{corr}. (*A*) Greater than 180° of EEL are visible. The EEL–EEL diameter measures 3.25 mm (white bar). The mean EEL diameter rounded down determines the device size (3.0 mm). (*B*) Less than 180° of EEL are visible, thus the OCT mean lumen diameter is used to determine device diameter. The mean lumen diameter is 2.89 mm. The mean lumen diameter rounded up determines the device size (3.0 mm). (*C*) Less than 180° of EEL are visible. The OCT mean lumen diameter is multiplied by the respective correction factor (in this case distal, thus 1.25) and used to determine the device diameter. The mean lumen diameter is multiplied by the correction factor to mimic EEL sizing, and rounded down to determine the device size (3.5 mm). Note that the MLD_{corr} (white bar—3.61 mm) is still smaller than the true EEL-EEL diameter (4.03 mm). EEL, external elastic lamina; MLD_{Corr}, minimal lumen diameter—corrected; OCT, optical coherence tomography.

Table 1 Demographic and procedural characteristics

	Derivation, (*n* = 154)	Validation (*n* = 100)	*P*-value
Demographic			
Age (years)	65.5 ± 9.3	64.4 ± 11.0	0.49
Male	109 (69)	66 (66)	0.62
Hypertension	124 (78)	83 (83)	0.37
Dyslipidaemia	115 (73)	73 (73)	0.97
Diabetes	52 (33)	42 (42)	0.14
Prior coronary artery bypass grafting	3 (1.9%)	5 (5)	0.16
Silent ischaemia	6 (4)	4 (4)	0.99
Stable angina	54 (34)	31 (31)	0.60
Unstable angina	72 (46)	43 (43)	0.87
NSTEMI	20 (13)	16 (16)	0.43
STEMI	6 (3.8)	6 (6.0)	0.55*
Procedural			
Target vessel			
Left anterior descending	80 (51)	63 (63)	0.048
Left circumflex	43 (27)	22 (22)	0.39
Right	35 (22)	15 (15)	0.12
OCT			
Proximal EEL (mm)	4.12 ± 0.74	4.08 ± 0.66	0.89
Proximal LD (mm)	3.14 ± 0.67	3.14 ± 0.61	0.93
Distal EEL (mm)	3.34 ± 0.75	3.44 ± 0.58	0.75
Distal LD (mm)	2.64 ± 0.66	2.68 ± 0.53	0.81

Values are n (%) or mean ± SD.
EEL, external elastic lamina; LD, lumen diameter; NSTEMI, non-ST-elevation myocardial infarction; OCT, optical coherence tomography; STEMI, ST-elevation myocardial infarction.

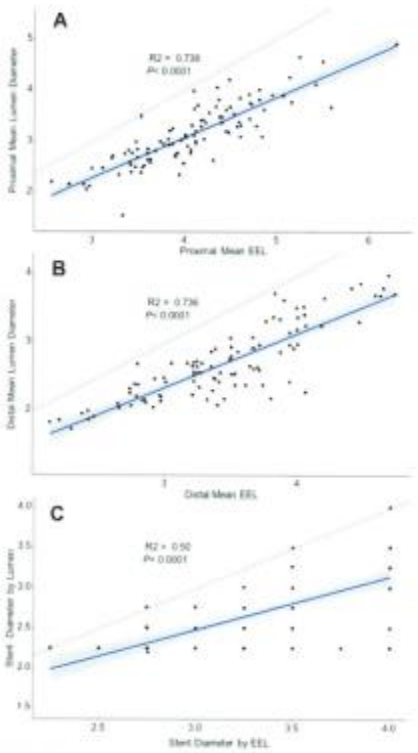

Figure 3 Scatterplot comparing mean lumen diameter with external elastic lamina-derived measurements and stent sizing. Scatterplot comparing (*A*) the proximal reference mean lumen diameter with external elastic lamina-derived measurements, (*B*) the distal reference mean lumen diameter with external elastic lamina-derived measurements, and (*C*) the stent diameter by lumen-derived measurements with the stent diameter by external elastic lamina-derived measurements. The line of best fit is in blue with the associated shaded error bands in grey.

The magnitude of differences between the mean LD and EEL-based diameters at the proximal and distal reference segments and in stent sizing is shown in *Table 2*. The mean EEL-based size was larger by ~1 mm in the proximal reference and 0.75 mm in the distal reference. When hypothetical stent sizing was performed based on distal EEL-based downsizing vs. LD-based upsizing, the stent diameters were undersized by LD-based measurement in the majority of the cases, by ≥0.25 mm in 10%, by ≥0.50 mm in 34%, by ≥0.75 mm in 31%, and by 1 mm in 16% of the reference segments, with the selected stent diameters being equal with either of the strategies in only 9% of the reference segments. LD_{Corr} was calculated to be 1.32 (IQR 1.23–1.37) in the proximal reference and 1.25 (IQR 1.19–1.36) in the distal reference.

Validation cohort

There was no significant difference in the LD or EEL-based measurements in the proximal or distal reference segments between the derivation and validation cohorts (*Table 1*). When the proximal correction factor was applied to the proximal LD in the validation cohort, mean vessel diameter was similar between the EEL-based measurements and the corrected LD (4.08 ± 0.66 vs. 4.14 ± 0.80, $P = 0.56$; $R^2 = 0.74$, $P < 0.0001$; *Figure 4A*). Similarly, applying the correction factor to the distal LD resulted in corrected LDs that were similar to the EEL-based diameters (3.44 ± 0.58 vs. 3.34 ± 0.67, $P = 0.29$; $R^2 = 0.74$, $P < 0.0001$; *Figure 4B*). However, stent sizing based on corrected LD led to discordance of the chosen stent size when compared with EEL-based sizing by at least 0.25 mm in 63% of cases ($P < 0.001$). Furthermore, using the corrected LD led to stent oversizing in 41% of cases (by 0.25 mm in 22%, 0.50 mm in 13%, 0.75 mm in 3%, and 1.0 mm in 3%; $P < 0.001$; *Figure 4C*).

Discussion

In the current study, we investigated the differences between the mean LD and EEL-based measurements by OCT and how these

Table 2 Lumen vs. external elastic lamina-based measurements

	Lumen ($n = 100$)	External elastic lamina ($n = 84$)	*P*-Value
Proximal reference			
Mean vessel diameter (mm)	3.14 ± 0.67	4.12 ± 0.74	<0.0001
Distal reference			
Mean vessel diameter (mm)	2.64 ± 0.65	3.34 ± 0.76	<0.0001
Stent diameter			
Mean lumen diameter (mm)	2.70 ± 0.44	3.33 ± 0.47	<0.0001
Undersized by ≥0.25 mm	10 (10)	0 (0)	<0.0001
Undersized by ≥0.50 mm	34 (34)	0 (0)	<0.0001
Undersized by ≥0.75 mm	31 (31)	0 (0)	<0.0001
Undersized by ≥1.00 mm	16 (16)	0 (0)	<0.0001

Values are n (%) or mean ± SD.

differences may impact stent sizing. We report a number of clinically relevant findings. First, at the proximal reference segment, the mean difference between the mean LD and EEL-based diameters was ~1 mm, while at the distal reference segment the mean difference was ~0.75 mm. Secondly, as opposed to the LD-based stenting, EEL-based stent sizing led to the selection of a larger diameter stent in >90% of cases; on average this difference was >0.5 mm. Thirdly, while using a corrected LD-based measurement is a practical approach, potentially obviating the need for manual EEL-based measurement, its application led to discordance in stent sizing in more than half of the cases, with potentially hazardous oversizing in 41% of cases.

While OCT provides high-resolution cross-sectional images of the plaque microarchitecture, the penetration depth of OCT is limited, potentially limiting visualization of the entire vessel wall. As a result, a perception has prevailed that measurements requiring visualization of the EEL—including vessel diameter, area, and plaque burden—cannot be reliably performed with OCT. This perception has led to a widespread adoption of the lumen-based stent sizing by OCT. The consequence of such a strategy is a smaller post-PCI MSA compared with both angiography and IVUS. In the ILUMIEN I study, angiography guidance during PCI led to a larger MSA compared with lumen-based OCT guidance.[9] Subsequently, multiple studies have shown that IVUS-guided PCI, based on vessel wall measurements, leads to larger MSAs compared with lumen-based measurements with OCT guidance during PCI.[1,14,15] Given that the MSA is the most consistent and strongest predictor of PCI outcomes,[11,12,16–22] OCT may be disadvantaged compared with IVUS due to differences in stent sizing strategy. Nevertheless, a specific OCT-guided EEL-based stent optimization strategy in the randomized ILUMIEN III trial was safe and resulted in similar MSA to that of IVUS-guided PCI with a trend towards larger MSA compared with angiography guidance and the least number of untreated PCI complications.[13] Critically, despite the aforementioned perceptions, there was no difference in the ability to identify >180° of EEL between OCT (84%) and IVUS (83%) in the ILUMIEN III study.

In the current study, we show that the EEL-based diameter is consistently larger than the mean LD at both the proximal and distal reference segments. While this finding in and of itself is rather obvious, it is the magnitude of the difference that has the potential to impact PCI strategy. At the proximal reference, the difference between the EEL-based diameter and mean LD was ~1 mm and at the distal reference ~0.75 mm. These large differences translate directly into meaningful differences in the choice of stent size, with a direct impact on the final MSA. Indeed, even when employing a strategy of upsizing from the mean LD measurements compared with downsizing from the EEL-based measurements at the distal reference to guide the choice of the stent diameter, the mean difference in stent size was well >0.5 mm in diameter.

Despite the positive results of the ILUMIEN III trial, the OCT-guided EEL-based sizing strategy has not been widely adopted, with concerns regarding the ability to consistently visualize the EEL at reference segments, lack of automated measurements, and effects on workflow quoted as the likely reasons. As such, utilizing a lumen-based correction factor has the potential to significantly improve the workflow and eliminate operator errors in measurement. Unfortunately, our data suggest that a correction factor applied to the automated LD cannot safely estimate the EEL-based dimensions for stent sizing. We therefore recommend following the algorithmic OCT-guided EEL-based stent sizing strategy as described in the ILUMIEN III trial.[23] The long-term benefits of applying this strategy are currently being assessed in the ongoing ILUMIEN IV: OPTIMAL PCI trial (NCT03507777).

Based on the current study, in practice, EEL-based measurements should be used wherever possible for stent sizing (expected to be feasible in majority, i.e. >80%, of cases) and LD-based measurements with rounding up only used when EEL-based measurements are not feasible. After measurement of stent diameter and length, the angiographic co-registration function should be utilized for positioning stents at the intended segments to improve placement precision and reduce geographic miss. If OCT angiography co-registration is not available, a cine angiogram must be acquired during the OCT pullback so that the OCT frames can be correlated with the angiogram with the help of the fiduciary landmarks (e.g. side branches, calcium deposits, and previous stents).

Limitations

The prospective component of this a study was conducted at two high-volume institutions by experienced OCT operators. As a small number of patients were included in this study, large-scale

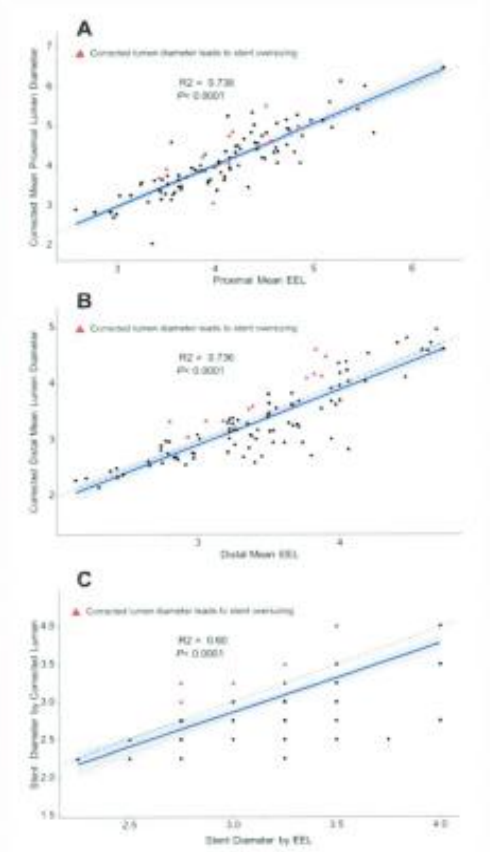

Figure 4 Scatterplot comparing the corrected mean lumen diameter with the external elastic lamina-derived measurements and stent sizing. Scatterplot comparing (*A*) the corrected mean lumen diameter with the external elastic lamina-derived measurements at the proximal reference, (*B*) the corrected mean lumen diameter with the external elastic lamina-derived measurements at the distal reference, and (*C*) the stent diameter by corrected lumen-derived measurements with the stent diameter by external elastic lamina-derived measurements. The line of best fit is in blue with the associated shaded error bands in grey.

prospective randomized trials would be needed to demonstrate that EEL-based stenting is practical in a clinical setting and leads to improved clinical outcomes. Future studies need to assess the incidence and impact of intravascular imaging on stent under- and oversizing. Alternative more sophisticated algorithms to generate a correction factor were not attempted and may have improved the predictive performance. In the future, artificial intelligence-based algorithms may be able to automatically detect the EEL where visible, thus obviating the need for a correction factor.

Conclusions

The application of an EEL-based stent sizing strategy results in larger stent size selection compared with a mean LD-guided stent sizing strategy. A universally applicable correction factor for LD cannot be recommended to replace OCT-guided EEL-based measurements for stent sizing.

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Conflict of interest: E.S. is a consultant: Abbott Vascular and Opsens. M.M. is a consultant: Terumo Corporation. A.M. received grant support from Abbott Vascular and Boston Scientific, consultant for Conavi Medical Inc. G.S.M. is a honoraria: Boston Scientific, Philips, Terumo, and Medtronic. A.J. received Institutional grant support and consultant: Philips/Volcano and Abbott Vascular. G.W.S. received research grants: Abbott; speaker honoraria: Terumo, Amaranth, and Novartis; consultant: Shockwave, Valfix, TherOx, Reva, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Matrizyme, Miracor, Neovasc, V-wave, Abiomed, Claret, Sirtex, MAIA Pharmaceuticals, SpectraWave, and Ancora; and equity/options: Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, MedFocus family of funds, SpectraWave, Orchestra Biomed, and Aria. Z.A.A. received Institutional research grants to Columbia University: Abbott and Cardiovascular Systems Inc.; consultant: Abbott, Amgen, Astra Zeneca, and Boston Scientific; and equity: Shockwave Medical. Other authors report no conflict of interest.

Data availability

The data underlying this article are available in the article.

References

1. Habara M, Nasu K, Terashima M, Kaneda H, Yokota D, Ko E et al. Impact of frequency-domain optical coherence tomography guidance for optimal coronary stent implantation in comparison with intravascular ultrasound guidance. *Circ Cardiovasc Interv* 2012;**5**:193–201.
2. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 2012;**59**:1058–72.
3. Wijns W, Shite J, Jones MR, Lee SW-L, Price MJ, Fabbiocchi F et al. Optical coherence tomography imaging during percutaneous coronary intervention impacts physician decision-making: ILUMIEN I study. *Eur Heart J* 2015;**36**:3346–55.
4. Kubo T, Shinke T, Okamura T, Hibi K, Nakazawa G, Morino Y et al. Optical frequency domain imaging vs. intravascular ultrasound in percutaneous coronary intervention (OPINION trial): Study protocol for a randomized controlled trial. *J Cardiol* 2016;**68**:455–60.
5. Zhang Y-J, Pang S, Chen X-Y, Bourantas CV, Pan D-R, Dong S-J et al. Comparison of intravascular ultrasound guided versus angiography guided drug eluting stent implantation: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2015;**15**:153.
6. Jang J-S, Song Y-J, Kang W, Jin H-Y, Seo J-S, Yang T-H et al. Intravascular ultrasound-guided implantation of drug-eluting stents to improve outcome: a meta-analysis. *JACC Cardiovasc Interv* 2014;**7**:233–43.
7. Witzenbichler B, Maehara A, Weisz G, Neumann F-J, Rinaldi MJ, Metzger DC et al. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. *Circulation* 2014;**129**:463–70.
8. Elgendy IY, Mahmoud AN, Elgendy AY, Bavry AA. Outcomes with intravascular ultrasound-guided stent implantation: a meta-analysis of randomized trials in the era of drug-eluting stents. *Circ Cardiovasc Interv* 2016;**9**:e003700.
9. Ahn J-M, Kang S-J, Yoon S-H, Park HW, Kang SM, Lee J-Y et al. Meta-analysis of outcomes after intravascular ultrasound-guided versus angiography-guided drug-

eluting stent implantation in 26,503 patients enrolled in three randomized trials and 14 observational studies. *Am J Cardiol* 2014;**113**:1338–47.
10. Hong S-J, Kim B-K, Shin D-H, Nam C-M, Kim J-S, Ko Y-G, for the IVUS-XPL Investigators *et al.* Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL Randomized Clinical Trial. *JAMA* 2015;**314**:2155–63.
11. Song H-G, Kang S-J, Ahn J-M, Kim W-J, Lee J-Y, Park D-W *et al.* Intravascular ultrasound assessment of optimal stent area to prevent in-stent restenosis after zotarolimus-, everolimus-, and sirolimus-eluting stent implantation. *Cathet Cardiovasc Interv* 2014;**83**:873–8.
12. Prati F, Romagnoli E, Burzotta F, Limbruno U, Gatto L, La Manna A *et al.* Clinical impact of OCT findings during PCI: the CLI-OPCI II Study. *JACC Cardiovasc Imaging* 2015;**8**:1297–305.
13. Ali ZA, Maehara A, Généreux P, Shlofmitz RA, Fabbiocchi F, Nazif TM *et al.* Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. *Lancet* 2016;**388**:2618–28.
14. Maehara A, Ben-Yehuda O, Ali Z, Wijns W, Bezerra HG, Shite J *et al.* Comparison of stent expansion guided by optical coherence tomography versus intravascular ultrasound: the ILUMIEN II Study (observational study of optical coherence tomography [OCT] in patients undergoing fractional flow reserve [FFR] and percutaneous coronary intervention). *JACC Cardiovasc Interv* 2015;**8**:1704–14.
15. Otake H, Kubo T, Takahashi H, Shinke T, Okamura T, Hibi K *et al.* Optical frequency domain imaging versus intravascular ultrasound in percutaneous coronary intervention (OPINION Trial): results from the OPINION Imaging Study. *JACC Cardiovasc Imaging* 2018;**11**:111–23.
16. Choi S-Y, Witzenbichler B, Maehara A, Lansky AJ, Guagliumi G, Brodie B *et al.* Intravascular ultrasound findings of early stent thrombosis after primary percutaneous intervention in acute myocardial infarction: a Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) substudy. *Circ Cardiovasc Interv* 2011;**4**:239–47.
17. Doi H, Maehara A, Mintz GS, Yu A, Wang H, Mandinov L *et al.* Impact of post-intervention minimal stent area on 9-month follow-up patency of paclitaxel-eluting stents: an integrated intravascular ultrasound analysis from the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent Trials. *JACC Cardiovasc Interv* 2009;**2**:1269–75.
18. Fujii K, Carlier SG, Mintz GS, Yang Y-M, Moussa I, Weisz G *et al.* Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol* 2005;**45**:995–8.
19. Kang S-J, Ahn J-M, Song H, Kim W-J, Lee J-Y, Park D-W *et al.* Comprehensive intravascular ultrasound assessment of stent area and its impact on restenosis and adverse cardiac events in 403 patients with unprotected left main disease. *Circ Cardiovasc Interv* 2011;**4**:562–9.
20. Liu X, Doi H, Maehara A, Mintz GS, de Ribamar Costa J, Sano K *et al.* A volumetric intravascular ultrasound comparison of early drug-eluting stent thrombosis versus restenosis. *JACC Cardiovasc Interv* 2009;**2**:428–34.
21. Moussa I, Moses J, Di Mario C, Albiero R, De Gregorio J, Adamian M *et al.* Does the specific intravascular ultrasound criterion used to optimize stent expansion have an impact on the probability of stent restenosis? *Am J Cardiol* 1999;**83**:1012–7.
22. Soeda T, Uemura S, Park S-J, Jang Y, Lee S, Cho J-M *et al.* Incidence and clinical significance of poststent optical coherence tomography findings: one-year follow-up study from a multicenter registry. *Circulation* 2015;**132**:1020–9.
23. Shlofmitz E, Shlofmitz RA, Gallogahi KK, Rahim HM, Virmani R, Hill JM *et al.* Algorithmic approach for optical coherence tomography-guided stent implantation during percutaneous coronary intervention. *Interv Cardiol Clin* 2018;**7**:329–44.

ORIGINAL CONTRIBUTION

Manuscript 10

Nitroglycerin-Derived Pd/Pa for the Assessment of Intermediate Coronary Lesions

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ABSTRACT: Objectives. To assess the predictive value of Pd/Pa after nitroglycerin administration [Pd/Pa[N]] as compared with standard fractional flow reserve [FFR]. **Methods.** Consecutive patients with intermediate coronary lesions assessed by FFR between January 2014 and October 2015 were included. We measured Pd/Pa at baseline, Pd/Pa [N], and Pd/Pa after incremental doses of intracoronary adenosine. **Results.** A total of 134 patients [27% females; mean age, 65 years] were included. The diagnostic performance of Pd/Pa[N] and identification of cut-off value for Pd/Pa [N] compared with FFR threshold of 0.8 using receiver-operating characteristic [ROC] area under the curve analysis was between 0.98 [95% confidence interval, 0.95-1.00; *P*<.05] for 48 µg and 0.86 [95% confidence interval, 0.79-0.94; *P*<.05] for 240 µg adenosine. Pd/Pa[N] ≤0.8 had 100% positive predictive value. Pd/Pa[N] ≥0.94 provided 100% negative predictive value with a high sensitivity [>92%]. Optimal diagnostic accuracy of Pd/Pa[N] was achieved for values ≤0.84. The Pearson's correlation between Pd/Pa[N] and FFR varied between 0.89 for 24 µg adenosine and 0.77 for 240 µg [*P*<.01]. **Conclusion.** Pd/Pa[N] values can be used for diagnosis of hemodynamically significant lesions. Pd/Pa[N] correlates well with standard FFR. Pd/Pa[N] cut-off of ≤0.8 can be considered significant without need for adenosine injection. The value of using adenosine whenever Pd/Pa[N] is >0.94 is limited.

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KEY WORDS: fractional flow reserve, local drug delivery

Fractional flow reserve (FFR), defined as the ratio of maximal blood flow in a stenotic artery to maximum blood flow in the absence of stenosis, emerged as an important tool in clinical decision making and is recommended by current guidelines.[1,2] FFR is calculated based on the assumption that there is a linear relationship between driving pressure and myocardial blood flow during maximal hyperemia. Therefore, since its introduction, the standard method for FFR measurement is achieving maximal hyperemia.

The achievement of maximal vasodilation of the two components of coronary circulation (epicardial and microvascular arteries), is enhanced by various stimuli.[3,4] A bolus of intracoronary (IC) nitrate aims to prevent any vasospasm in the epicardial vessels and is recommended as a standard[3] prior to the administration of adenosine, which is used for microvascular dilatation and can be administered intravenously (IV) or IC. IV adenosine was initially recommended and is used by many laboratories, but requires a large venous access and a larger amount of adenosine compared to the IC dose, resulting in higher cost. Its short-term effect, ease of use, and safety made IC adenosine the drug of choice in many laboratories.[5]

There is no widely accepted IC adenosine dose, although recent data suggest that administration of 100 µg for the right coronary artery and 200 µg for the left might be sufficient.[6] Often, incremental doses are used to avoid side effects that are more common with higher doses. A failure to produce maximal hyperemia was reported in 10%–15% of the initial FFR studies when low doses of adenosine were used (8–12 µg for the right coronary and 15–18 µg for the left).[7] Submaximal hyperemia may lead to an underestimation of the lesion's hemodynamic significance. A dose-response relationship for IC adenosine doses as high as 100 µg has been demonstrated in animals and humans.[8,9] More recently, experience with the administration of very high adenosine doses (up to 720 µg) has been reported with mixed results.[10-12]

Although injecting incremental doses of IC adenosine is feasible, it is also time and resource consuming. Furthermore, positive FFR values are often obtained with lower adenosine dose or with administration of other vasodilators.

Based on our experience with FFR studies, we noticed that post-nitroglycerin Pd/Pa (Pd/Pa[N]) could predict the hemodynamic significance of coronary lesions prior to IC adenosine injection. Therefore, the aim of this study is to assess the predictive value of Pd/Pa(N), as compared with standard IC-FFR and the impact of incremental doses of IC adenosine.

Methods

The study protocol was approved by the Western University Research Ethics Board. The authors have conformed to institutional guidelines and those of the American Physiological Society. Due to the nature of this study, informed consent was not required. As part of a quality improvement

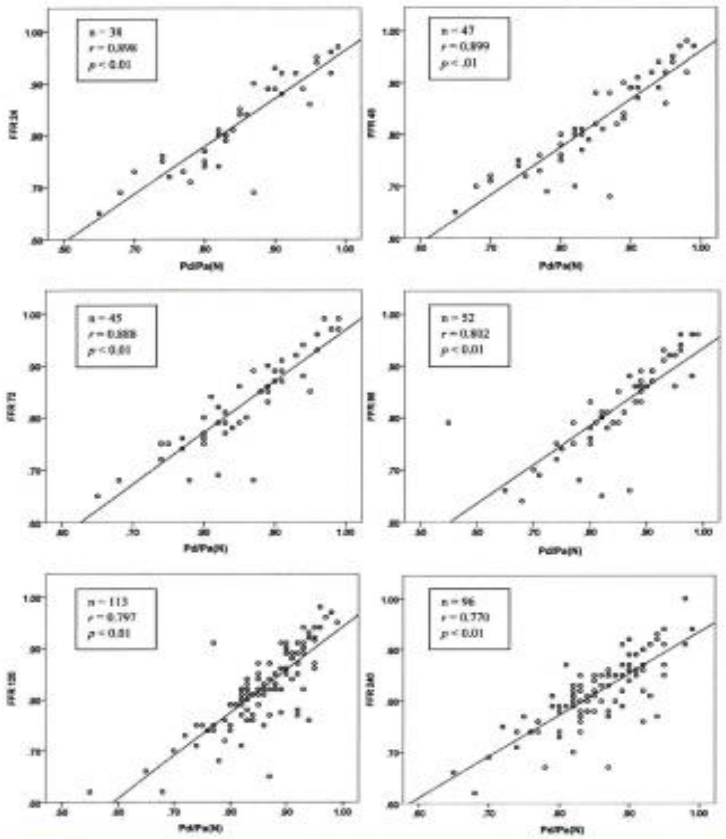

FIGURE 1. Pd/Pa(N) and fractional flow reserve (FFR) correlation. Scatter plots and Pearson's correlation coefficients between Pd/Pa readings post nitroglycerin and FFR readings taken after various dosages of adenosine.

project, data were collected from all FFR studies performed at London Health Sciences Center between January 2014 and October 2015. Incremental doses of adenosine for IC injection ranging from 24 µg to 360 µg were recommended but not mandatory for the operators. Exclusion criteria for this study were either lack of nitroglycerin injection prior to adenosine administration or injection of a single adenosine dose.

The FFR measurement protocol at our center after coronary angiography includes a 0.014" high-fidelity pressure-recording PrimeWire Prestige Plus guidewire (Philips Volcano Corporation) or PressureWire Aeris (Abbott Vascular) introduced through a 5 or 6 Fr guiding catheter into the coronary artery. The guidewire was calibrated and then advanced to the distal tip of the catheter, followed by equalization. The pressure wire was subsequently advanced into the coronary artery with the pressure sensor placed beyond the lesion site. Pressure distal to the stenotic lesion (Pd) and aortic pressure (Pa) were recorded. A single dose of IC nitroglycerin was given (50–200 µg depending on patient blood pressure, mean dose of 113 µg) followed by a saline flush. Pd/Pa(N) corresponds to the lowest Pd/Pa determination post nitroglycerin administration, usually within 10 seconds. Incremental doses of adenosine ranging from 24 to 360 µg were given. Baseline Pd/Pa values, post Pd/Pa(N) values, and post-adenosine FFR values were recorded.

Each dose was given only after the effect of the previous dose wore off and Pd/Pa returned to baseline value. Drift was excluded at the end of each FFR study by pulling back the pressure wire to the distal tip of the catheter. Maximal drift of 0.02 was accepted.

Statistical analysis. Descriptive statistics for the study population are presented as mean ± standard deviation for continuous variables and number (%) for categorical variables. For the assessment of the relationship between Pd/Pa(N) and standard FFR, Pearson's correlation coefficient (r) was used. Estimation of the diagnostic performance of Pd/Pa(N) and identification of cut-off value for Pd/Pa(N) compared with FFR threshold of 0.8 was conducted using receiver-operating characteristic (ROC) and area under the curve (AUC) analysis. Sensitivity, specificity, and negative and positive predictive values with corresponding 95% confidence intervals (CIs) were calculated. All statistical tests were considered statistically significant when a *P*-value was <.05. Data analyses were performed using Statistical Package for Social Sciences (SPSS) v. 20 (IBM, Inc).

Results

Baseline patient characteristics are described in Table 1. A total of 310 FFR studies were performed during the above-mentioned time frame; 134 studies met the inclusion criteria. Table 2 provides a list of the studied lesions and their locations. Procedural success for advancing the pressure wire distal to the stenosis was 100%.

The Pearson's correlation between Pd/Pa(N) and FFR was studied for all administered doses and was overall good, with superior correlation for the lower doses – varying between 0.89 for 24 µg and 36 µg adenosine and 0.77 for 240 µg (*P*<.01). Figure 1 shows scatter plots and positive Pearson's

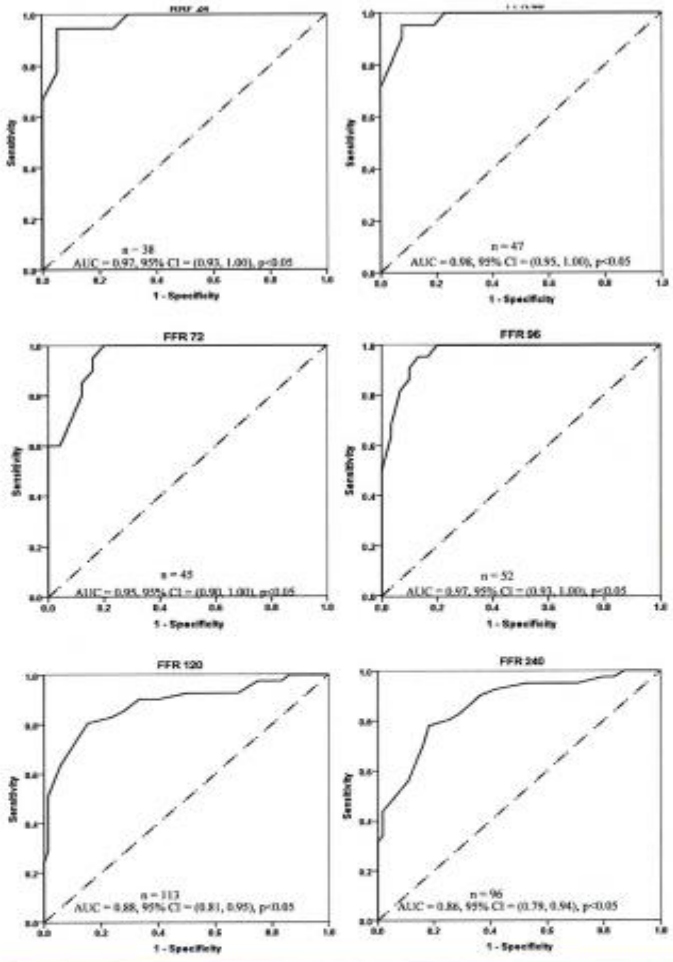

FIGURE 2. Pd/Pa(N) receiver operating characteristic curves and and area under the curve (AUC) for each dosage of adenosine. A classification cut-off of 0.80 was used for each adenosine dosage. The test variable was post-nitroglycerin Pd/Pa readings. CI = confidence interval.

correlation for each adenosine dose. Figure 2 shows ROC curves for the Pd/Pa(N) using a FFR value of 0.8 as the reference (standard) variable. AUC was between 0.98 (95% CI, 0.95–1.00; $P<.05$) for 48 μg adenosine and 0.86 (95% CI, 0.79–0.94; $P<.05$) for 240 μg adenosine. Table 3 summarizes the cases and demonstrates the number of available values for each of the adenosine doses.

According to available and missing values and to avoid potential bias, the Pd/Pa(N), FFR 120, and FFR 240 values were used in the subsequent analysis. Tables 4 and 5 demonstrate the classification accuracy for the two selected doses, respectively. For both, Pd/Pa(N) ≥0.94 provided 100% negative predictive value (NPV) with a high sensitivity (>92%). The optimal diagnostic accuracy of Pd/Pa(N) was achieved for values ≥0.84, which resulted in accuracy of 83.2% and 68.1% for 120 μg adenosine and 240 μg adenosine, respectively.

Pd/Pa (N) values as predictor of final FFR values and clinical decision.

Pd/Pa (N) ≥0.8. Twenty-four patients (18%) had a Pd/Pa(N) ≥0.8. For these studies, adenosine injections, regardless of dose administered or number of injections, FFR remained positive and therefore would not have changed the operator's treatment strategy.

Pd/Pa (N) >0.8. Seventy-five patients (54%) with a Pd/Pa(N) >0.8 were further evaluated with adenosine doses of 120 μg and 240 μg. Of these, 55 studies were negative for the 120 μg. Only 4 out of 55 studies turned out positive when tested with increasing dose of 240 μg.

Discussion

The results of this study suggest that Pd/Pa(N) can be used for diagnosis of hemodynamically significant lesions. Pd/Pa(N) correlates well with FFR. Pd/Pa(N) cutoff of ≤0.8 can be considered significant with no need for adenosine injection. The value of using adenosine whenever Pd/Pa(N) is above 0.94 is limited.

Our findings extend recent observations,[13] which indicate a good correlation of Pd/Pa(N) with FFR results. Moreover, a high negative predictive value for Pd/Pa(N)- >0.88 to exclude lesion significance was established, potentially reducing the need for adenosine in a significant number of patients.[13] Baseline Pd/Pa values prior to hyperemia were also studied[14] and showed good correlation to FFR. However, Pd/Pa(N) was shown to correlate better with FFR than baseline Pd/Pa.[13]

The administration of IV adenosine as a means of achieving maximal hyperemia is considered by some the gold standard, but its widespread use in the catheterization laboratory is limited by some drawbacks, including length of time during drug application to achieve a steady-state and the

Table 1. Baseline demographics.

Characteristic	(N = 134)
Female	37 (27.6%)
Mean age (years)	65 ± 10.2
Baseline hemodynamic data	
Heart rate (beats/min)	66.5 ± 13.0
Blood pressure - systole (mm Hg)	125 ± 23.2
Blood pressure - diastole (mm Hg)	66 ± 10.4
Associated medical conditions	
History of coronary artery disease	62 (50.6%)
Hypertension	98 (71.7%)
Hyperlipidemia	99 (74.3%)
Smoking	
Never	83 (62.0%)
Current	15 (11.2%)
Former	36 (26.8%)
Diabetes	35 (26.1%)
Clinical indication for the study	
Angina, chest pain, or equivalent	84 (62.7%)
Non-ST elevation acute coronary syndrome	32 (23.8%)
ST-elevation MI (non-culprit vessel)	9 (6.7%)
Congestive heart failure	3 (2.2%)
Other (syncope, arrhythmia, positive stress test, valvular heart disease)	6 (4.6%)

Data presented as number (%) or mean ± standard deviation.
MI = myocardial infarction.

Table 2. Studied vessels.

Vessel	Number of Cases
LMCA to LAD	3
LAD	95
Proximal	34
Middle	57
Distal	4
Diagonal	4
RCA[1]	14
Proximal	1
Middle	9
Distal	4
PRL	1
PDA	1
LCX	11
Proximal	4
Middle	7
Marginal	3
Ramus	2

LAD = left anterior descending; LMCA = left main coronary artery; RCA = right coronary artery; PRL = posterolateral branch; PDA = posterior descending artery; LCX = left circumflex.

Table 3. Summary of cases.

FFR Score*	Number of Cases (n = 134)	Missing Cases
Pd/Pa(B)	134	0 (0%)
Pd/Pa(N)	134	0 (0%)
FFR 24	38	96 (71.6%)
FFR 36	2	132 (98.5%)
FFR 48	47	87 (64.9%)
FFR 60	17	117 (87.3%)
FFR 72	45	89 (66.4%)
FFR 96	52	82 (61.2%)
FFR 120	113	21 (15.7%)
FFR 144	2	132 (98.5%)
FFR 180	8	126 (94.0%)
FFR 192	3	131 (97.8%)
FFR 240	96	38 (28.4%)
FFR 360	1	133 (99.3%)

Data presented as number or number (%).
*Pd/Pa was measured at baseline (B), post nitroglycerin (N), or at various increasing adenosine doses from 24 µg to 360 µg.

higher occurrence of systemic adverse reactions,[15,16] making the IC adenosine injection a more appealing alternative.

However, even the use of IC adenosine is time and resource consuming, and therefore FFR is often underused. Current data from the United States CathPCI registry indicates that only 6.1% of patients with moderate coronary lesions were assessed with FFR prior to PCI.[17] Data from a Swedish registry[18] showed utilization of FFR in 0.2% and 10% of patients in Iceland and Sweden, respectively.

For these reasons, the search for a simplified, quicker, and even adenosine-free alternative is ongoing. Instantaneous wave-free ratio (iFR) has been proposed as an index of stenosis severity that is independent of hyperemia and can be measured without the need for adenosine.[19] The diagnostic accuracy of iFR and resting Pd/Pa compared with standard FFR was studied and found to be 80% for both indices.[20] Others demonstrated a lower diagnostic accuracy for iFR when compared with FFR.[21]

Recently, the effect of IC contrast injection on Pd/Pa was reported.[22,23] It showed higher diagnostic accuracy of contrast as compared with resting Pd/Pa or iFR.[24] However, earlier works demonstrated that contrast-induced hyperemia is inferior compared with hyperemia achieved by other means[25] and the excessive use of contrast for that purpose must be balanced with the potential low risk of contrast-induced acute kidney injury.

When Pd/Pa(N) values are near normal (defined in this study by values ≥0.94), Pd/Pa(N) has an excellent NPV and a very high sensitivity. Therefore, based on our findings, the physician might opt to skip any adenosine injection since the chances of a positive FFR are very low.

Alternatively, injection of very high adenosine doses (and foregoing any doses lower than 240 µg that were tested in the current study) may be considered to rule out an FFR-positive lesion. It is likely that such negative Pd/Pa(N)- positive standard FFR results will be in the gray zone. The clinical significance of gray-zone FFR (0.8>FFR≥0.75) is not yet clear. In patients with stable coronary artery disease and gray-zone FFR followed for approximately 2 years, medically treated

Table 4. Classification accuracy based on increasing cut-off values for post-nitroglycerin Pd/Pa, using post adenosine 120 µg fractional flow reserve with 0.80 cut-off as reference.

Criterion for Pd/Pa[N]	Positive Cases [n]	Negative Cases [n]	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]	Diagnostic Accuracy [%]	Youden's Index
≤0.80	20	93	46.3	98.6	95.0	76.3	79.6	0.45
≤0.81	22	91	51.2	98.6	95.5	78.0	81.4	0.50
≤0.82	30	83	63.4	94.4	86.7	81.9	83.2	0.58
≤0.83	40	73	75.6	87.5	77.5	86.3	83.2	0.63
≤0.84[a]	44	69	80.5	84.7	75.0	88.4	83.2	0.65
≤0.85	51	62	82.9	76.4	66.7	88.7	78.8	0.59
≤0.86	55	58	85.4	72.2	63.6	89.7	77.0	0.58
≤0.87	61	52	90.2	66.7	60.7	92.3	75.2	0.57
≤0.88	66	47	90.2	59.7	56.1	91.5	70.8	0.50
≤0.89	74	39	92.7	50.0	51.4	92.3	65.5	0.43
≤0.90	82	31	92.7	38.9	46.3	90.3	58.4	0.32
≤0.91	87	26	92.7	31.9	43.7	88.5	54.0	0.25
≤0.92	94	19	97.6	25.0	42.6	94.7	51.3	0.23
≤0.93	100	13	97.6	16.7	40.0	92.3	46.0	0.14
≤0.94	103	10	92.7	13.9	39.8	100.0	45.1	0.07
≤0.95	108	5	100.0	6.9	38.0	100.0	40.7	0.07
≤0.96	110	3	100.0	4.2	37.3	100.0	38.9	0.04
≤0.97	111	2	100.0	2.8	36.9	100.0	38.1	0.03
≤0.98	112	1	100.0	0.0	36.6	100.0	37.2	0.00
≤0.99	113	0	100.0	0.0	36.3	–	36.3	0.00
≤1.00	113	0	100.0	0.0	36.3	–	36.3	0.00

Data presented as number or percentage. PPV = positive predictive value; NPV = negative predictive value. [a]Post-nitroglycerin Pd/Pa was associated with the highest diagnostic accuracy when compared to a 0.80 cut-off for fractional flow reserve after 120 µg adenosine dosage.

patients had a lower event rate and no difference in presence of angina when compared with patients who were revascularized.[36] When followed for 4.5 ± 2.1 years, patients with deferred revascularization had similar need for intervention whether their FFR was 0.75 to 0.80 or 0.81 to 0.85.[37] The DEFER trial did not show clinical benefit for revascularization for lesions with FFR >0.75 as compared with medical therapy.[38] A threshold of 0.8 was subsequently adopted.[21] It seems that a true cut-off for FFR lesions does not exist and a gradual relation between degree of ischemia and outcome is more likely.[30,31] Taken together, the clinical benefit of using high-dose adenosine to rule out true positive lesions is currently unknown. Further studies are needed to determine if an FFR-negative lesion that turned out to be positive only after high-dose adenosine should be revascularized.

Study limitations. The present study has several limitations. The main one lies within the small number of patients and the non-randomized nature, which may introduce selection bias. Moreover, the lack of protocol-driven nitroglycerin dosage might limit the reproducibility of our findings. The absence of comparator group for IV adenosine infusion and the low number of non-left anterior descending coronary artery FFR studies are other important limitations. Yet, we have demonstrated good correlation between Pd/Pa(N) and a wide spectrum of IC adenosine doses and the clinical importance of lesions diagnosed by very high-dose adenosine is unclear.

Conclusion

We demonstrated that Pd/Pa(N) correlates well with FFR results. When Pd/Pa(N) is ≤0.8, there is no need for adenosine injection. When Pd/Pa(N) is ≥0.94, there is a high probability of an FFR-negative lesion. Pd/Pa(N)-based strategy may be integrated into the hemodynamic assessment of borderline lesion.

References

1. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol. 2011;58:e44-e122.
2. Hau WK. Routine pressure-derived fractional flow reserve guidance: from diagnostic to everyday practice. J Invasive Cardiol. 2006;18:240-245.

Table 5. Classification accuracy based on increasing cut-off values for post-nitroglycerin Pd/Pa, using post-adenosine 240 µg fractional flow reserve with 0.80 cut-off as reference.

Criterion for Pd/Pa(N)	Positive Cases (n)	Negative Cases (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic Accuracy (%)	Youden's Index
≤0.80	19	77	43.9	98.2	94.7	70.1	63.7	0.42
≤0.81	21	75	46.3	96.4	90.5	70.7	63.7	0.43
≤0.82	29	67	56.1	89.1	79.3	73.1	63.7	0.45
≤0.83	38	58	70.7	83.6	76.3	79.3	66.4	0.54
≤0.84*	42	54	78.0	81.8	76.2	83.3	68.1	0.60
≤0.85	47	49	80.5	74.5	70.2	83.7	65.5	0.55
≤0.86	50	46	82.9	70.9	68.0	84.8	64.6	0.54
≤0.87	57	39	90.2	63.6	64.9	89.7	63.7	0.54
≤0.88	61	35	92.7	58.2	62.3	91.4	61.9	0.51
≤0.89	68	28	95.1	47.3	57.4	92.9	57.5	0.42
≤0.90	74	22	95.1	36.4	52.7	90.9	52.2	0.31
≤0.91	78	18	95.1	29.1	50.0	88.9	48.7	0.24
≤0.92	84	12	97.6	20.0	47.6	91.7	45.1	0.18
≤0.93	86	10	97.6	16.4	46.5	90.0	43.4	0.14
≤0.94	89	7	95.1	12.7	46.1	100.0	42.5	0.08
≤0.95	93	3	100.0	5.5	44.1	100.0	38.9	0.05
≤0.96	93	3	100.0	5.5	44.1	100.0	38.9	0.05
≤0.97	93	3	100.0	5.5	44.1	100.0	38.9	0.05
≤0.98	95	1	100.0	0.0	43.2	100.0	37.2	0.00
≤0.99	96	0	100.0	0.0	42.7	–	36.3	0.00
≤1.00	96	0	100.0	0.0	42.7	–	36.3	0.00

Data presented as number or percentage. PPV = positive predictive value; NPV = negative predictive value. *Post-nitroglycerin Pd/Pa was associated with the highest diagnostic accuracy when compared to a 0.80 cut-off for fractional flow reserve after 120 µg adenosine dosage.

3. Pijls NH, Sels JW. Functional measurement of coronary stenosis. *J Am Coll Cardiol.* 2012;59:1045-1057.
4. McGeoch RJ, Oldroyd KG. Pharmacological options for inducing maximal hyperaemia during studies of coronary physiology. *Catheter Cardiovasc Interv.* 2008;71:198-204.
5. Casella G, Leibig M, Schiele TM, et al. Are high doses of intracoronary adenosine an alternative to standard intravenous adenosine for the assessment of fractional flow reserve? *Am Heart J.* 2004;148:590-595.
6. Adjedj J, Toth GG, Johnson NP, et al. Intracoronary adenosine: dose-response relationship with hyperemia. *JACC Cardiovasc Interv.* 2015;8:1422-1430.
7. Jeremias A, Whitbourn RJ, Filardo SD, et al. Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. *Am Heart J.* 2000;140:651-657.
8. Di Segni E, Higano ST, Rihal CS, Holmes DR Jr, Lennon R, Lerman A. Incremental doses of intracoronary adenosine for the assessment of coronary velocity reserve for clinical decision making. *Catheter Cardiovasc Interv.* 2001;54:34-40.
9. Murtagh B, Higano S, Lennon R, Mathew V, Holmes DR Jr, Lerman A. Role of incremental doses of intracoronary adenosine for fractional flow reserve assessment. *Am Heart J.* 2003;146:99-105.
10. De Luca G, Venegoni L, Iorio S, Giuliani L, Marino P. Effects of increasing doses of intracoronary adenosine on the assessment of fractional flow reserve. *JACC Cardiovasc Interv.* 2011;4:1079-1084.
11. Lopez-Palop R, Carrillo P, Frutos A, et al. Comparison of effectiveness of high-dose intracoronary adenosine versus intravenous administration on the assessment of fractional flow reserve in patients with coronary heart disease. *Am J Cardiol.* 2013;111:1277-1283.
12. Rother J, Achenbach S, Trobs M, et al. Comparison of standard- and high-dose intracoronary adenosine for the measurement of coronary fractional flow reserve (FFR). *Clin Res Cardiol.* 2016;105:1003-1010.
13. Martin-Reyes R, de la Torre Hernandez JM, Franco-Pelaez J, et al. The use of the acute Pd/Pa drop after intracoronary nitroglycerin infusion to rule out significant FFR: CANICA [can intracoronary nitroglycerin predict fractional flow reserve without adenosine?] multicenter study. *Catheter Cardiovasc Interv.* 2016;87:262-9. Epub 2015 Jul 25.
14. Kim JS, Lee HD, Suh YK, et al. Prediction of fractional flow reserve without hyperemic induction based on resting baseline Pd/Pa. *Korean Circ J.* 2013;43:309-315.
15. Schlundt C, Bietau C, Klinghammer L, et al. Comparison of intracoronary versus intravenous administration of adenosine for measurement of coronary fractional flow reserve. *Circ Cardiovasc Interv.* 2015;8(5).
16. Leone AM, Porto I, De Caterina AR, et al. Maximal hyperemia in the assessment of fractional flow reserve: intracoronary adenosine versus intracoronary sodium nitroprusside versus intravenous adenosine: the NASCI (Nitroprussiato versus Adenosina nelle Stenosi Coronariche Intermedie) study. *JACC Cardiovasc Interv.* 2012;5:402-408.

17. Dattilo PB, Prasad A, Honeycutt E, Wang TY, Messenger JC. Contemporary patterns of fractional flow reserve and intravascular ultrasound use among patients undergoing percutaneous coronary intervention in the United States: insights from the National Cardiovascular Data Registry. *J Am Coll Cardiol.* 2012;60:2337-2339.
18. Gudnason T, Gudnadottir GS, Lagerqvist B, et al. Comparison of interventional cardiology in two European countries: a nationwide Internet based registry study. *Int J Cardiol.* 2013;168:1237-1242.
19. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol.* 2012;59:1392-1402.
20. Jeremias A, Maehara A, Genereux P, et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *J Am Coll Cardiol.* 2014;63:1253-1261.
21. Berry C, van 't Veer M, Witt N, et al. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients. *J Am Coll Cardiol.* 2013;61:1421-1427.
22. Spagnoli V, Amabile N, Dillinger JG, et al. Myocardial fractional flow reserve measurement using contrast media as a first-line assessment of coronary lesions in current practice. *Can J Cardiol.* 2016;32:739-746. Epub 2015 Sep 25.
23. Schampaert E, Mansour S, Palisaitis DA. Can we just rely on contrast? *Can J Cardiol.* 2016;32:717-719.
24. Johnson NP, Jeremias A, Zimmermann FM, et al. Continuum of vasodilator stress from rest to contrast medium to adenosine hyperemia for fractional flow reserve assessment. *JACC Cardiovasc Interv.* 2016;9:757-767.
25. Nolte F, van de Hoef TP, de Klerk W, et al. Functional coronary stenosis severity assessed from the mean pressure gradient-velocity relationship obtained by contrast medium-induced submaximal hyperaemia. *EuroIntervention.* 2014;10:320-328.
26. Lindstaedt M, Halilcavusogullari Y, Yazar A, et al. Clinical outcome following conservative vs revascularization therapy in patients with stable coronary artery disease and borderline fractional flow reserve measurements. *Clin Cardiol.* 2010;33:77-83.
27. Depta JP, Patel JS, Novak E, et al. Outcomes of coronary stenoses deferred revascularization for borderline versus nonborderline fractional flow reserve values. *Am J Cardiol.* 2014;113:1788-1793.
28. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. *J Am Coll Cardiol.* 2007;49:2105-2111.
29. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* 2009;360:213-224.
30. Lavi S, Rihal CS, Yang EH, et al. The effect of drug-eluting stents on cardiovascular events in patients with intermediate lesions and borderline fractional flow reserve. *Catheter Cardiovasc Interv.* 2007;70:525-531.
31. Adjedj J, De Bruyne B, Flore V, et al. Significance of intermediate values of fractional flow reserve in patients with coronary artery disease. *Circulation.* 2016;133:502-508.

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(B). Three research papers (11-13) on MR antagonism and cardiovascular diseases

B) Mineralocorticoid (MR) Antagonism and cardiovascular diseases

11. Iqbal, J., Parviz, Y., Pitt B, Newell-Price, J., Al-Mohammad, A., and Zannad, F. (2014). Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure. European Journal of Heart Failure, 16(2):143-150. (doi: 10.1111/ejhf.31. PMID: 24464876), **(Impact Factor of 15.534 and 52 citations).**

12. Iqbal, J., Fay, R., Adlam, D., Squire, I., **Parviz, Y.,** Gunn, J., Pitt, B., and Zannad, F. (2014). Effect of eplerenone in percutaneous coronary intervention-treated post-myocardial infarction patients with left ventricular systolic dysfunction: A sub-analysis of the EPHESUS trial. European Journal of Heart Failure, 16: 685–691, (16.10.1002/ejhf.88. **(Impact Factor 15.534 and 24 citations).**

13. Parviz, Y., Iqbal, J., Pitt, B., Adlam, D., Al-Mohammad, A.,and Zannad, F.. (2015). Emerging cardiovascular indications of mineralocorticoid receptor antagonists. Trends in Endocrinology and Metabolism, 26 (4):201-211 (doi.26.10.1016/j.tem.2015.01.007), **(Impact Factor: 12.015 and 31 citations).**

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REVIEW

Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure

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Clinical trials have demonstrated morbidity and mortality benefits of mineralocorticoid receptor antagonists (MRAs) in patients with heart failure. These studies have used either spironolactone or eplerenone as the MRA. It is generally believed that these two agents have the same effects, and the data from studies using one drug could be extrapolated for the other. National and international guidelines do not generally discriminate between spironolactone and eplerenone, but strongly recommend using an MRA for patients with heart failure due to LV systolic dysfunction and post-infarct LV systolic dysfunction. There are no major clinical trials directly comparing the efficacy of these two drugs. This article aims to compare the pharmacokinetics and pharmacodynamics of spironolactone and eplerenone, and to analyse the available data for their cardiovascular indications and adverse effects. We have also addressed the role of special circumstances including co-morbidities, concomitant drug therapy, cost, and licensing restrictions in choosing an appropriate MRA for a particular patient, thus combining an evidence-based approach with personalized medicine.

Keywords Aldosterone • Spironolactone • Eplerenone • Heart failure

Introduction

Mineralocorticoid receptor antagonists (MRAs) improve outcomes in patients with chronic heart failure (CHF) caused by LV systolic dysfunction (LVSD).[1–3] Eplerenone and spironolactone (or its metabolite, potassium canrenoate) are the currently licensed MRAs for clinical use. Clinical studies show the benefit of MRAs, but there are limited data on direct comparison of these MRAs. It is generally believed that the benefits of different MRAs represent a 'class effect'. National and international guidelines including those from the American Heart Association (AHA) and European Society of Cardiology (ESC) do not discriminate between spironolactone and eplerenone, but strongly recommend using these for patients with CHF and post-infarct LVSD.[4,5]

Spironolactone and eplerenone differ in their molecular structure, pharmacokinetics, and pharmacodynamics (Table 1). Spironolactone is a non-specific MRA and, due to its structural similarity to progesterone,[6] has affinity for progesterone, androgen, and glucocorticoid receptors. Eplerenone is chemically different,[7] and substitution of the 17-α-thioacetyl group of spironolactone with a carbomethoxy group in eplerenone provides greater selectivity for mineralocorticoid receptors (MRs) and minimal binding to progesterone and androgen receptors.[6] Spironolactone has substantially greater affinity for MRs than eplerenone, which is important to consider when comparing similar doses of these two drugs. Spironolactone and eplerenone differ in their metabolism and half-life.[6,8] Eplerenone produces more consistent inhibition of the rapid non-genomic effects of aldosterone (including coronary vasoconstriction, increased systemic vascular resistance, and potentiation of the vasoconstrictor effect of angiotensin II in coronary arteries) than spironolactone.[7,8] Based on these biochemical and pharmacological differences, this review aims to

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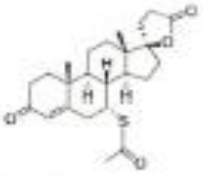
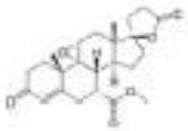
Table 1 Comparison of biochemical and pharmacological properties of spironolactone and eplerenone

	Spironolactone	Eplerenone
Chemical structure		
Chemical formula	$C_{24}H_{32}O_4S$	$C_{24}H_{30}O_6$
Mode of action	Competitive MR antagonism	Competitive MR antagonism
MR affinity	High	10- to 20-fold lower
MR selectivity	Non-selective (also binds to glucocorticoid, progesterone, and androgen receptors)	Higher selectivity for MR
Inhibition of non-genomic MR effects	No	Yes
Onset/offset of action	Slow	Quicker
Bioavailability	60–90%	Absolute bioavailability unknown
Volume of distribution	Unknown	43–90 L
Protein binding	90% bound to plasma proteins	50% bound to plasma proteins
Metabolism	Hepatic metabolism to active metabolites	Hepatic metabolism by CYP3A4 to inactive metabolites
Half-life of drug	1–2 h	4–6 h
Active metabolites	Yes	No
Elimination half-life of drug and metabolites	10–35 h	4–6 h

MR, mineralocorticoid receptor.

compare systematically the available data to evaluate whether spironolactone and eplerenone can be substituted for each other for their cardiovascular indications.

Mineralocorticoid receptor antagonists for systemic hypertension

Mineralocorticoid receptor antagonists are effective in reducing blood pressure (BP) when used as monotherapy[10,11] or in combination regimens.[11–13] MRAs have been shown to be as effective as ACE inhibitors or ARBs in lowering BP.[14] Furthermore, it has also been suggested that MRAs can reduce BP as effectively as calcium channel blockers and, additionally, may have a more potent effect on reducing microalbuminuria.[11] Eplerenone has been shown to be better tolerated than the widely used calcium channel blocker amlodipine, with comparable reductions in systolic BP.[15] MRAs have also been shown to prevent end-organ damage in both pre-clinical[17] and clinical studies.[18,19] Furthermore, in the EPHESUS trial, eplerenone-associated reduction in all-cause mortality was significantly greater in those with a history of systemic hypertension.[3] The use of MRAs as anti-hypertensive agents, however, remains low. Current guidelines consider MRAs as fourth-line therapy for essential hypertension (except for patients with hypertension secondary to hyperaldosteronism, where it is first line),[20] which effectively limits their use to resistant hypertension only. Further large-scale studies showing efficacy, safety, and end-organ protection are warranted before MRAs can be moved higher up in the treatment algorithm for essential hypertension.[21]

The two MRAs have been directly compared in a few trials of systemic hypertension. A multicentre, double-blind, placebo-controlled trial in >400 patients with mild to moderate essential hypertension evaluated the efficacy, safety, and tolerability of the two MRAs over an 8-week treatment period and found that the magnitude of reduction in BP with eplerenone (100 mg daily) was 25% less than that with a similar dose of spironolactone, suggesting that spironolactone may have a more potent effect on BP.[12] The antihypertensive effect of spironolactone has also been shown to be greater than that of eplerenone in systemic hypertension associated with primary aldosteronism; a multicentre, double-blind, parallel-group, randomized, controlled trial showed that spironolactone (25–225 mg once daily) had almost a two-fold greater BP-lowering effect than eplerenone (100–300 mg once daily).[22] Another randomized, open-label, blinded-endpoint study compared spironolactone (25 mg twice a day) and eplerenone (25 mg twice a day) in patients with idiopathic hyperaldosteronism, and found that an equal proportion of patients achieved normal BP in both groups.[24] However, the BP-lowering effect of spironolactone was greater than that of equal doses of eplerenone.[24] The more potent and prolonged effect of spironolactone in lowering BP may be due to the longer half-life of its active metabolites, as compared with eplerenone.[6,8]

These data suggest that spironolactone is more effective than eplerenone when used at the same doses and, although there is no dose equivalence between the two drugs, spironolactone could be

used as first-choice MRA in the treatment of essential or secondary hypertension. However, if patients develop spironolactone-related adverse effects, then it may be worth switching to eplerenone, probably at a higher dose.

Mineralocorticoid receptor antagonists for heart failure

National and international guidelines recommend MRAs for patients with CHF caused by LVSD,[4,5] based on morbidity and mortality benefits seen in three landmark trials (RALES, EPHESUS, and EMPHASIS-HF).[1–3] These trials are not, however, directly comparable due to considerable differences in patient populations and trial design.[22] The RALES trial consisted of patients with advanced CHF, the EPHESUS trial included patients with LVSD after acute myocardial infarction (AMI), and the EMPHASIS-HF trial enrolled CHF patients with mild (NYHA II) symptoms.[1–3] Baseline drug therapy, especially the use of beta-blockers and ACE inhibitors, also differed markedly among these trials and could partially account for the observed differences in mortality reduction in these trials. Based on these differences, caution is warranted in directly comparing the results of these trials. Chatterjee *et al.* have recently carried out an 'indirect pooled analysis' of 13 studies using spironolactone (or canrenone) and eplerenone, and suggested that eplerenone was outperformed by other MRAs (15% vs. 26% reduction in all-cause mortality and 17% vs. 25% reduction in cardiac mortality).[23] However, this comparison is misleading for a variety of reasons. This analysis included some small trials with <100 subjects or short follow-up of 2–3 months duration, which may not be relevant to measure mortality or safety endpoints. Without these limitations, only three studies (EPHESUS, EMPHASIS-HF, and RALES) drove the results. However, these three trials cannot be directly compared due to differences in trial population and design (*Table 2*). We believe that available data have to be analysed at patient and trial level to decide on evidence-based use of the two MRAs. We will compare the use of these drugs for different forms of heart failure separately.

Table 2 Differences in RALES, EPHESUS, and EMPHASIS-HF trials

	RALES	EPHESUS	EMPHASIS-HF
Patient number	1663	6632	2737
Drug	Spironolactone	Eplerenone	Eplerenone
Mean drug dose (mg)	26	44	39
NYHA class	III–IV	I–IV	II
LVEF (%)	26	33	26
Ischaemic aetiology (%)	55	100	70
ACE inhibitor/ARB (%)	95	86	94
Beta-blockers (%)	11	78	87
Diuretics (%)	100	60	84
Years of recruitment	1995–96	1999–2001	2006–10
Mean follow-up (months)	24	16	21
Mortality in placebo group at 1 year (%)	27	14	7

Chronic heart failure due to left ventricular systolic dysfunction

RALES and EMPHASIS-HF have evaluated the efficacy of the two MRAs in CHF due to LVSD, showing that both drugs were effective in reducing mortality. In RALES, spironolactone produced a 30% relative reduction in mortality during an average follow-up of 24 months.[1] In EMPHASIS-HF, there was a 24% reduction in cardiovascular death and a 42% reduction in hospitalization for heart failure.[3] Based on individual trial design, it could be suggested to use spironolactone for advanced CHF and eplerenone for CHF with mild symptoms. However, it is counterintuitive to believe that these drugs will be effective in patients with only severe or mild symptoms, respectively. It may be tempting to think that either of these two drugs could be used in CHF due to LVSD. One possible limitation to this 'class effect' reasoning is the concern about dosing. In the 'real world', spironolactone is being used overwhelmingly, even in mild to moderate CHF, at doses used in the RALES trials. Several observational studies, inherently of less value than prospective randomized trials, have raised concerns that MRAs (mainly spironolactone) may not be as effective and safe as suggested by the results of the three main randomized trials.[27] This could possibly be due to off-label usage in higher risk groups, inappropriate dosing, or lack of careful monitoring, factors which are seldom seen in the settings of a clinical trial. Based on good evidence-base practice, one can expect the benefit–risk ratio shown in individual trials only when using the same drugs and dosages as used in corresponding trials. Therefore, until further data are available, it might be prudent to use the MRA and dosing regimens proven to be safe and effective in the major randomized trials, i.e. spironolactone 12.5–50 mg/day in patients with severe CHF due to LVSD and eplerenone 25–50 mg/day in patients with CHF due to LVSD and mild symptoms. Indeed, this approach has been adopted in some of the guidelines.[28,29]

Left ventricular systolic dysfunction after myocardial infarction

Both spironolactone and eplerenone have been shown to improve LV pressure recovery following ischaemia and reperfusion in pre-clinical studies.[30] Spironolactone has not been studied in clinical trials for this indication. In the landmark EPHESUS trial, a mean dose of 43 mg of eplerenone produced 15% reduction in all-cause mortality, 17% reduction in cardiovascular mortality, and 21% reduction in sudden cardiac death (SCD).[2]

Although lack of clinical data does not mean that spironolactone has no effect in post-infarct LVSD, the evidence-based approach suggests that eplerenone, and not spironolactone, should be recommended for post-infarct LVSD patients, as suggested by the National Institute for Health and Clinical Excellence (NICE), UK. Furthermore, patients with MI are frequently treated with PCIs, and eplerenone (but not spironolactone) may also prevent in-stent restenosis.[31] Spironolactone was shown to inhibit post-angioplasty restenosis in rabbits.[32] However, these results could not be reproduced in a porcine coronary angioplasty model[33] or in a clinical trial.[34] However, eplerenone has shown promising results in many pre-clinical models.[31,34,35] This differential effect of eplerenone

could possibly be due to substantial (&65%) reduction in collagen content in the neointima and media, which spironolactone has not been shown to reduce.[31] Furthermore, whilst eplerenone is selective for MRs, spironolactone may also block progesterone receptors (progesterone has been shown to have antiatherosclerotic and antirestenotic properties by inhibiting foam cell formation).[36] The efficacy of eplerenone for this indication has not been formally tested in a clinical trial. However, in the EPHESUS trial, 24% of patients received PCI as a treatment for AMI and, although there was no statistically significant interaction, the magnitude of beneficial effects of eplerenone, as compared with placebo, was greater in PCI-treated patients compared with patients who did not have PCI.[7] There are currently two ongoing trials to test MRAs in an AMI population: ALBATROSS (NCT-01059136) and REMINDER (NCT-01176968) testing spironolactone and eplerenone, respectively. Both agents will be administered within 24 h of an AMI. These trials may help understand potential similarities and differences between the two MRAs.

Prevention of sudden cardiac death in heart failure

Mineralocorticoid receptor antagonists, in addition to standard therapy, reduced the incidence of SCD in the RALES, EPHESUS, and EMPHASIS-HF trials.[1–3] Spironolactone has been shown to improve electrophysiological parameters such as QT interval dispersion.[37] Furthermore, spironolactone, in combination with ACE inhibitors, reduced arrhythmias in post-MI patients.[38] MRAs acutely improve cardiac vagal control, irrespective of any diuretic effects, which may partially explain their beneficial effects.[39] Wei et al. performed a meta-analysis of MRA trials to evaluate their role in the prevention of SCD in heart failure patients.[40] This meta-analysis included seven trials with a total of 8635 patients. All eplerenone data were derived from the EPHESUS trial. The majority of the spironolactone data came from the RALES trial, whilst the other five trials (all with spironolactone) contributed only 340 patients in this meta-analysis. Both MRAs significantly reduced the risk of SCD, ventricular tachycardia, and episodes of ventricular premature complexes (Table 3).[40]

In summary, both drugs have a potential, and similar, role in prevention of ventricular arrhythmias and SCD in CHF patients. Hence, this indication does not affect the choice of which MRA should be used. Thus, the choice continues to be based on the severity of symptoms and the circumstances of heart failure (post-infarct or not).

Heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction (HF-PEF) or diastolic heart failure (DHF) is pathophysiologically different from heart failure due to LVSD.[41] Hence, the data from studies evaluating the effects on patients with heart failure due to LVSD should not be directly extrapolated to diastolic dysfunction.

Mineralocorticoid receptor activation leads to LV hypertrophy and collagen deposition, which reduces compliance.[42] Eplerenone has been shown to attenuate collagen turnover in patients with DHF[43,44] and to improve the echocardiographic measures of diastolic function.[44] There was, however, no significant improvement in 6 min walk distance.[44] Furthermore, any benefit of eplerenone on morbidity and mortality in HF-PEF remains to be demonstrated.

Table 3 Mineralocorticoid receptor antagonists for prevention of sudden cardiac death

	Spironolactone	Eplerenone
Dose (mg/day)	25	25–50
Patient number	1663	6632
NYHA class	III or IV	II
LVEF	≤35%	≤40%
Follow-up	24	16
VA hospitalization	Spironolactone 2.8% vs. control 2.8%, $P = 0.9$	Eplerenone 1.6% vs. control 1.6%, $P = 0.8$
Sudden cardiac death	Spironolactone 10% vs. control 13%, $P = 0.03$	Eplerenone 4.9% vs. control 6.1%, $P = 0.03$

VA, ventricular arrhythmias.

A few studies have assessed the effect of spironolactone on diastolic dysfunction. Spironolactone (25 mg/day) in combination with ACE inhibitors improved myocardial function, reduced LV hypertrophy, and reduced markers of collagen turnover in patients with metabolic syndrome and already receiving ACE inhibitors.[45] Aldo-DHF randomized 422 patients with DHF (NYHA II/III, EF ≥50% and echocardiographic evidence of diastolic dysfunction) to receive either spironolactone (25 mg/day) or placebo for a period of 12 months and revealed no improvement in exercise capacity or quality of life, despite improved biochemical and echocardiographic features in the spironolactone group.[46] TOPCAT is a large (n = 3445) multicentre, randomized, double-blind, placebo-controlled trial of spironolactone in patients with DHF.[47] The trial results were presented at AHA Scientific Sessions, November 18, 2013. During an average follow-up of 3.3 years, there was no difference in the primary endpoints (the rate of cardiovascular mortality, aborted cardiac arrest, or heart failure hospitalization) between the spironolactone and placebo groups (18.6% vs. 20.4%; HR 0.89, 95% CI 0.77–1.04). The rate of heart failure hospitalization was, however, significantly reduced in the spironolactone group (12% vs. 14.2%, HR 0.83, 95% CI 0.69–0.99).

In summary, for HF-PEF there is no current indication for either agent. However, spironolactone can potentially be used for reduction in heart failure hospitalization in this challenging group of patients with limited therapeutic options.

Right heart failure and pulmonary arterial hypertension

Plasma aldosterone levels have been shown to correlate with progression of pulmonary arterial hypertension (PAH).[48] Conversely, MR blockade reduces the proliferation of pulmonary arterial smooth muscle cells.[49] Both spironolactone and eplerenone have

been shown to prevent or reverse pulmonary vascular remodelling and improve cardiopulmonary haemodynamics in murine models of PAH.[30]

To date, no studies have evaluated the role of MRAs in patients with PAH and right heart failure. The use of MRAs in the treatment of PAH and right heart failure is, therefore, not licensed at the moment (except as part of diuretic therapy), due to lack of clinical evidence. However, the pre-clinical data appear promising and clinical trials are warranted.

Other potential factors in choosing a mineralocorticoid receptor antagonist

Gender

Spironolactone can produce endocrine sexual side effects. It can interfere with 17-hydroxylase activity (causing a decrease in testosterone synthesis) and peripheral metabolism of testosterone (causing changes in the testosterone to oestradiol ratio), resulting in gynaecomastia,[31] which is reported in 10–20% of the men taking spironolactone.[1,32] Hypertensive trials have directly compared spironolactone and eplerenone, and suggest that eplerenone causes fewer endocrine side effects, including gynaecomastia.[12–14] As a significant proportion of men are likely to be affected with this side effect, it is reasonable to offer eplerenone as an alternative long-term therapy in male patients affected by gynaecomastia on spironolactone or who elect not to be given spironolactone for fear of developing that complication. In female patients, spironolactone is likely to be better tolerated than in male patients and should remain as first-line therapy. However, it must be kept in mind that women receiving spironolactone can also develop mastodynia and menstrual irregularities,[12,33] and may require switching to eplerenone, a manoeuvre that usually ameliorates these symptoms.[34]

Heart failure with diabetes mellitus

Spironolactone and eplerenone are equally effective in CHF patients with or without diabetes.[12] However, spironolactone has been shown to impair endothelial function, as measured by acetylcholine-mediated vasodilatation, in patients with type 2 diabetes, possibly due to the worsening of glycaemic control and an increase in plasma angiotensin II.[35] In contrast, eplerenone could improve coronary circulatory function (adenosine-stimulated myocardial perfusion reserve) and endothelial function in diabetic patients already receiving ACE inhibitors.[36] Furthermore, spironolactone can increase HbA_{1c} (glycated haemoglobin) levels in patients with type 2 diabetes with or without nephropathy or poorly controlled hypertension.[10,37] In a study of 107 patients with mild CHF, spironolactone increased HbA_{1c} and cortisol levels and reduced adiponectin levels over 4 months, findings which might be expected to herald an increased risk of developing diabetes.[38] However, eplerenone has no such effects, suggesting the possibility of a differential effect, depending on the selectivity of MR blockade.[36] Therefore, it could be argued that eplerenone is the preferred MRA for diabetics. However, it must be noted that there are opposing reports on the relationship of HbA_{1c} levels and outcomes in patients with CHF.[37,38] Therefore, caution is warranted in interpreting the differences between eplerenone and spironolactone in patients with diabetes in the absence of direct comparative outcome trials.

Table 4 Comparison of adverse events in spironolactone and eplerenone chronic heart failure with left ventricular systolic dysfunction trials

	Spironolactone	Eplerenone
Main trial	RALES	EMPHASIS-HF
Mean drug dose (mg)	26	39
Gynaecomastia (%)	9	0.5
Breast pain (%)	2	0.5
Adverse event (%)	82	72
Serious hyperkalaemia (K^+ >6 mmol)	1.2% in placebo and 1.7% in spironolactone group ($P < 0.001$)	1.9% in placebo and 2.5% in eplerenone group ($P = 0.3$)
Discontinuation due to adverse event	5% higher than placebo group	2.4% less than placebo group

Hyperkalaemia

Both drugs can cause hyperkalaemia, and the incidence of serious hyperkalaemia is likely to be higher in real life than in clinical trials.[1,2,39] There are no direct comparative data to differentiate between the two agents in terms of risk of hyperkalaemia. However, the available evidence suggests that the risk of hyperkalaemia may be lower with eplerenone (Table 4). In view of the greater affinity of spironolactone for MRs, as well as its longer half-life, the risk of hyperkalaemia may be greater with 25 mg of spironolactone than with 25 mg of eplerenone, the starting doses of these drugs in the landmark trials. Furthermore, if hyperkalaemia develops with MRA treatment, it is likely to take a longer time to obtain normokalaemia with spironolactone in view of its longer half-life.

Other co-morbidities

Spironolactone is also used for non-cardiac indications including hyperaldosteronism, cirrhosis with ascites and portal hypertension, and nephrotic syndrome. There have been no major placebo-controlled, randomized trials comparing the relative efficacy of the two drugs in the management of these conditions and, until more data become available, it is reasonable to start with spironolactone in these co-morbid conditions and switch to eplerenone if side effects are limiting.

Concomitant therapy

Caution is warranted for patients on multiple drugs to avoid potential drug interaction and altered metabolism of drugs.[28] Eplerenone is metabolized primarily by cytochrome P450 3A4 (CYP3A4); therefore, it should be avoided in patients receiving

potent inhibitors of this enzyme, such as ketoconazole (may induce a five-fold increase in eplerenone levels). Closer monitoring may be needed when eplerenone is used with less potent inhibitors of CYP3A4, such as verapamil, erythromycin, fluconazole, and protease inhibitors. Conversely, the CYP3A4 inducer, St John's Wort, may reduce eplerenone levels by 30%.

Licensing restrictions

The licensing restrictions may have implications on which agent can be prescribed in different geographical and ethnic groups. Spironolactone is widely licensed for treatment of hypertension and heart failure. In Europe and Canada, eplerenone is indicated for patients with CHF and post-infarct LVSD, but not for the treatment of essential hypertension.[40] In the USA, eplerenone is indicated for all these conditions, whilst in some Asian countries eplerenone is indicated only for hypertension.[12,41,42]

Cost implications

Treatment with an MRA is cost-effective for the management of CHF due to LVSD.[43] In the absence of a randomized controlled trial, it is difficult to establish the cost benefit of one agent over the other. Although spironolactone is substantially cheaper, eplerenone causes fewer side effects and may potentially be more cost-effective in the management of post-infarct LVSD.[44] The incremental cost-effectiveness ratio of eplerenone, compared with that of standard care alone (and not spironolactone), is £4457 and £7893 for each additional quality-adjusted life year (QALY) when 2-year and lifetime treatment duration is assumed, respectively.[44] These figures are well below the £20 000 threshold accepted as good value by NICE, UK. The results of these health economic analyses are based on higher relative effectiveness estimated for eplerenone compared with spironolactone from the meta-regression. However, if a 'class effect' is considered more plausible than the results of an evidence synthesis model, spironolactone is the most cost-effective treatment.

Cost-effectiveness analysis of the EMPHASIS-HF trial was recently presented at the ESC Conference, showing that eplerenone is cost-effective in CHF patients with mild symptoms, by improving quality of life and reducing hospitalization (John McMurray, ESC 2012). In addition to standard care, eplerenone prescription increased lifetime direct costs by £3822 for the UK, and €7239 for Spain, with additional quality-adjusted life expectancy of 1.22 QALYs (UK, discount rate 3.5%) and 1.33 years (Spain, discount rate 3%). Mean lifetime costs were £3140 per QALY in the UK, €4812 per QALY in Greece, and €5442 per QALY in Spain. Probabilistic sensitivity analysis suggested a 100% likelihood of eplerenone being regarded as cost-effective at a willingness to pay threshold of £20 000 per QALY (UK) or €30 000 per QALY (Spain). Therefore, by currently accepted standards of value for money, the addition of eplerenone to optimal medical therapy for patients with CHF and mild symptoms is likely to be cost-effective.

Future directions

Head-to-head trial to evaluate side effects

It would be difficult, if not impossible, to conduct a head-to-head trial of these two drugs, due to the reasons already outlined. However, as both drugs appear effective for many cardiovascular indications and the main factor in decision-making relates to side effect profile, it should be possible to conduct a small-scale trial focusing on side effects, and not the efficacy, of these two drugs.

Personalized medicine

In the absence of direct comparative evidence, it should remain perfectly acceptable (and preferable) to recommend one agent or the other based on an individual patient's profile, including gender, co-morbidities, etc. This approach allows combining evidence-based with personalized medicine.

Non-steroidal mineralocorticoid receptor antagonists

Both spironolactone and eplerenone are steroidal compounds. There are a few non-steroidal MRAs at various stages of development.[45,46] It would be interesting to see if these compounds

Table 5 A suggested approach to select mineralocorticoid receptor antagonists for cardiovascular indications

Indication	First-line MRA	Selection of MRA
Hypertension	Spironolactone	Consider gender (eplerenone for male patients)* and licensing restrictions
Chronic heart failure and LVSD	Either	Consider eplerenone for mild heart failure and male patients and spironolactone for females or those with severe heart failure
LVSD post-MI	Eplerenone	
Diastolic heart failure	Potentially spironolactone	Consider eplerenone for male patients and switch to eplerenone for all patients with side effects
PAH/RHF	Neither	Convincing pre-clinical data exist clinical trials

LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; PAH, pulmonary arterial hypertension; RHF, right heart failure.
*There are limited data supporting a gender-based approach in selecting MRAs and it could be argued to give eplerenone to male patients only if/when sexual side effects occur.

show similar efficacy, but have fewer side effects. Being non-steroidal, it is envisaged that these compounds will have fewer endocrine side effects. It is also being suggested that these compounds may have higher affinity for cardiac MRs, rather than renal MRs, and, therefore, potentially less tendency for hyperkalaemia. BAY 94-8862 (Bayer Pharma, Germany) is currently being tested in ARTS (minerAlocorticoid Receptor antagonist Tolerability Study; NCT01345656) trial, and the results of this study will be of major interest.[44]

Summary

There is a paucity of direct comparative data for spironolactone and eplerenone. It may not be appropriate to compare trials using spironolactone or eplerenone in heart failure directly due to vast differences in patient population and trial design. Choice of a specific agent could be based on clinical indications (such as the nature of heart failure), individual patient factors (such as gender, co-morbidities, occurrence of side effects), geographical licensing restriction, and community-level cost–benefit analysis. Based on the data available, we have suggested a simple approach to select a particular MRA for various cardiovascular indications (Table 5). Further comparative studies and cost–benefit analyses are warranted.

Conflict of interest: B.P. has received honoraria from Pfizer and serves on the advisory boards for Pfizer and Novartis. A.A.M. was advisor to NICE (UK) for CHF guidelines and heart failure Quality Standards, and is a member of the NICE group on Acute Heart Failure NICE guidelines. F.Z. has received honoraria from Pfizer, Novartis, Roche, Servier, AstraZeneca, and Takeda. All other authors have no conflicts of interest to declare.

References

1. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;**341**:709–717.
2. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.
3. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
4. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;**119**:1977–2016.
5. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803–869.
6. de Gasparo M, Joss U, Ramjoue HP, Whitebread SE, Haenni H, Schenkel L, Kraehenbuehl C, Biollaz M, Grob J, Schmidlin J. Three new epoxy-spirolactone derivatives: characterization in vivo and in vitro. *J Pharmacol Exp Ther* 1987;**240**:650–656.
7. Struthers A, Krum H, Williams GH. A comparison of the aldosterone-blocking agents eplerenone and spironolactone. *Clin Cardiol* 2008;**31**:153–158.
8. Gardiner P, Schrode K, Quinlan D, Martin BK, Boreham DR, Rogers MS, Stubbs K, Smith M, Karim A. Spironolactone metabolism: steady-state serum levels of the sulfur-containing metabolites. *J Clin Pharmacol* 1989;**29**:342–347.
9. Michea L, Delpiano AM, Hitschfeld C, Lobos L, Lavandero S, Marusic ET. Eplerenone blocks nongenomic effects of aldosterone on the Na+/H+ exchanger, intracellular Ca2+ levels, and vasoconstriction in mesenteric resistance vessels. *Endocrinology* 2005;**146**:973–980.
10. Jeunemaitre X, Chatellier G, Kreft-Jais C, Charru A, DeVries C, Plouin PF, Corvol P, Menard J. Efficacy and tolerance of spironolactone in essential hypertension. *Am J Cardiol* 1987;**60**:820–825.
11. Croom KF, Perry CM. Eplerenone: a review of its use in essential hypertension. *Am J Cardiovasc Drugs* 2005;**5**:51–69.
12. Sternon J. Spironolactone and altizide in systolic hypertension: ambulatory multicenter study. *Am J Cardiol* 1990;**65**:24K–27K.
13. Chapman N, Dobson J, Wilson S, Dahlof B, Sever PS, Wedel H, Poulter NR. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 2007;**49**:839–845.
14. Flack JM, Oparil S, Pratt JH, Roniker B, Garthwaite S, Kleiman JH, Yang Y, Krause SL, Workman D, Saunders E. Efficacy and tolerability of eplerenone and losartan in hypertensive black and white patients. *J Am Coll Cardiol* 2003;**41**:1148–1155.
15. White WB, Duprez D, St Hillaire R, Krause S, Roniker B, Kuse-Hamilton J, Weber MA. Effects of the selective aldosterone blocker eplerenone versus the calcium antagonist amlodipine in systolic hypertension. *Hypertension* 2003;**41**:1021–1026.
16. Hollenberg NK, Williams GH, Anderson R, Akhras KS, Bittman RM, Krause SL. Symptoms and the distress they cause: comparison of an aldosterone antagonist and a calcium channel blocking agent in patients with systolic hypertension. *Arch Intern Med* 2003;**163**:1543–1548.
17. Brilla CG, Matsubara LS, Weber KT. Anti-aldosterone treatment and the prevention of myocardial fibrosis in primary and secondary hyperaldosteronism. *J Mol Cell Cardiol* 1993;**25**:563–575.
18. Sato A, Suzuki Y, Saruta T. Effects of spironolactone and angiotensin-converting enzyme inhibitor on left ventricular hypertrophy in patients with essential hypertension. *Hypertens Res* 1999;**22**:17–22.
19. Savoia C, Touyz RM, Amiri F, Schiffrin EL. Selective mineralocorticoid receptor blocker eplerenone reduces resistance artery stiffness in hypertensive patients. *Hypertension* 2008;**51**:432–439.
20. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A. 2007 ESH-ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Blood Press* 2007;**16**:135–232.
21. Zannad F. Aldosterone antagonist therapy in resistant hypertension. *J Hypertens* 2007;**25**:747–750.
22. Weinberger MH, Roniker B, Krause SL, Weiss RJ. Eplerenone, a selective aldosterone blocker, in mild-to-moderate hypertension. *Am J Hypertens* 2002;**15**:709–716.
23. Parthasarathy HK, Menard J, White WB, Young WF Jr, Williams GH, Williams B, Ruilope LM, McInnes GT, Connell JM, MacDonald TM. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. *J Hypertens* 2011;**29**:980–990.
24. Karagiannis A, Tziomalos K, Papageorgiou A, Kakafika AI, Pagourelias ED, Anagnostis P, Athyros VG, Mikhailidis DP. Spironolactone versus eplerenone for the treatment of idiopathic hyperaldosteronism. *Expert Opin Pharmacother* 2008;**9**:509–515.
25. Zannad F, Gattis Stough W, Rossignol P, Bauersachs J, McMurray JJ, Swedberg K, Struthers AD, Voors AA, Ruilope LM, Bakris GL, O'Connor CM, Gheorghiade M, Mentz RJ, Cohen-Solal A, Maggioni AP, Beygui F, Filippatos GS, Massy ZA, Pathak A, Pina IL, Sabbah HN, Sica DA, Tavazzi L, Pitt B. Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integrating evidence into clinical practice. *Eur Heart J* 2012;**33**:2782–2795.
26. Chatterjee S, Moeller C, Shah N, Bolorunduro O, Lichstein E, Moskovits N, Mukherjee D. Eplerenone is not superior to older and less expensive aldosterone antagonists. *Am J Med* 2012;**125**:817–825.
27. Hernandez AF, Mi X, Hammill BG, Hammill SC, Heidenreich PA, Masoudi FA, Qualls LG, Peterson ED, Fonarow GC, Curtis LH. Associations between aldosterone antagonist therapy and risks of mortality and readmission

among patients with heart failure and reduced ejection fraction. JAMA 2012;308:2097–2107.
28. Krum H, Jelinek MV, Stewart S, Sindone A, Atherton JJ. 2011 update to National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. Med J Aust 2011;194:405–409.
29. McKelvie RS, Moe GW, Cheung A, Costigan J, Ducharme A, Estrella-Holder E, Ezekowitz JA, Floras J, Giannetti N, Grzeslo A, Harkness K, Heckman GA, Howlett JG, Kouz S, Leblanc K, Mann E, O'Meara E, Rajda M, Rao V, Simon J, Swiggum E, Zieroth S, Arnold JM, Ashton T, D'Astous M, Dorian P, Haddad H, Isaac DL, Leblanc MH, Liu P, Sussex B, Ross HJ. The 2011 Canadian Cardiovascular Society heart failure management guidelines update: focus on sleep apnea, renal dysfunction, mechanical circulatory support, and palliative care. Can J Cardiol 2011;27:319–338.
30. Chai W, Garrelds IM, de Vries R, Danser AH. Cardioprotective effects of eplerenone in the rat heart: interaction with locally synthesized or blood-derived aldosterone? Hypertension 2006;47:665–670.
31. Ward MR, Kanellakis P, Ramsey D, Funder J, Bobik A. Eplerenone suppresses constrictive remodeling and collagen accumulation after angioplasty in porcine coronary arteries. Circulation 2001;104:467–472.
32. Van Belle E, Bauters C, Wernert N, Hamon M, McFadden EP, Racadot A, Dupuis B, Lablanche JM, Bertrand ME. Neointimal thickening after balloon denudation is enhanced by aldosterone and inhibited by spironolactone, and aldosterone antagonist. Cardiovasc Res 1995;29:27–32.
33. Karaahmetoglu H, Iyisoy A, Amasyali B, Celik T, Ozturk C, Kose S, Isik E. Spironolactone does not prevent restenosis after coronary stenting in humans. Ann Acad Med Singapore 2004;33:769–774.
34. Wakabayashi K, Suzuki H, Sato T, Iso Y, Katagiri T, Takeyama Y. Eplerenone suppresses neointimal formation after coronary stent implantation in swine. Int J Cardiol 2006;107:260–266.
35. Iqbal J, Macdonald LJ, Low L, Seckl JR, Yau CW, Walker BR, Hadoke PW. Contribution of endogenous glucocorticoids and their intravascular metabolism by 11β-HSDs to postangioplasty neointimal proliferation in mice. Endocrinology 2012;153:5896–5905.
36. Cheng W, Lau OD, Abumrad NA. Two antiatherogenic effects of progesterone on human macrophages; inhibition of cholesteryl ester synthesis and block of its enhancement by glucocorticoids. J Clin Endocrinol Metab 1999;84:265–271.
37. Yee KM, Pringle SD, Struthers AD. Circadian variation in the effects of aldosterone blockade on heart rate variability and QT dispersion in congestive heart failure. J Am Coll Cardiol 2001;37:1800–1807.
38. Beck L, Blanc-Guillemaud V, Cherif OK, Javier B, Davy JM. Effects of spironolactone and losinopril on the spontaneous and chronic ventricular arrhythmias in a rat model of myocardial infarction. Cardiology 2001;96:85–93.
39. Fletcher J, Buch AN, Routledge HC, Chowdhary S, Coote JH, Townend JN. Acute aldosterone antagonism improves cardiac vagal control in humans. J Am Coll Cardiol 2004;43:1270–1275.
40. Wei J, Ni J, Huang D, Chen M, Yan S, Peng Y. The effect of aldosterone antagonists for ventricular arrhythmia: a meta-analysis. Clin Cardiol 2010;33:572–577.
41. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J 2011;32:670–679.
42. Ramires-Gil JF, Delcayre C, Robert V, Wassef M, Trouve P, Mougenot N, Charlemagne D, Lechat P. In vivo left ventricular function and collagen expression in aldosterone/salt-induced hypertension. J Cardiovasc Pharmacol 1998;32:927–934.
43. Mak GJ, Ledwidge MT, Watson CJ, Phelan DM, Dawkins IR, Murphy NF, Patle AK, Baugh JA, McDonald KM. Natural history of markers of collagen turnover in patients with early diastolic dysfunction and impact of eplerenone. J Am Coll Cardiol 2009;54:1674–1682.
44. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the randomized aldosterone antagonism in heart failure with preserved ejection fraction trial (RAAM-PEF). J Card Fail 2011;17:634–642.
45. Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H, Mysiak A, O'Moore-Sullivan T, Marwick TH. A randomized study of the beneficial effects of aldosterone antagonism on LV function, structure, and fibrosis markers in metabolic syndrome. JACC Cardiovasc Imaging 2011;4:1239–1249.
46. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Loffler M, Dungen HD, Tschope C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B. Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA 2013;309:781–791.
47. Desai AS, Lewis EF, Li R, Solomon SD, Assmann SF, Boineau R, Clausell N, Diaz R, Fleg JL, Gordeev I, McKinlay S, O'Meara E, Shaburishvili T, Pitt B, Pfeffer MA. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. Am Heart J 2011;162:966–972.e10.
48. Maron'yuk TVCI, Masenko VP, Volkov VN, Belenkov Iu N. Activity of renin–angiotensin–aldosterone system (RAAS) and vasopressin level in patients with primary pulmonary hypertension. Ter Arkh 1998;70:31–36.
49. Yamanaka R, Otsuka F, Nakamura K, Yamashita M, Otani H, Takeda M, Matsumoto Y, Kusano KF, Ito H, Makino H. Involvement of the bone morphogenetic protein system in endothelin- and aldosterone-induced cell proliferation of pulmonary arterial smooth muscle cells isolated from human patients with pulmonary arterial hypertension. Hypertens Res 2010;33:435–445.
50. Maron BA, Zhang YY, White K, Chan SY, Handy DE, Mahoney CE, Loscalzo J, Leopold JA. Aldosterone inactivates the endothelin-B receptor via a cysteinyl thiol redox switch to decrease pulmonary endothelial nitric oxide levels and modulate pulmonary arterial hypertension. Circulation 2012;126:963–974.
51. Rose LI, Underwood RH, Newmark SR, Kisch ES, Williams GH. Pathophysiology of spironolactone-induced gynecomastia. Ann Intern Med 1977;87:398–403.
52. Preiss D, van Veldhuisen DJ, Sattar N, Krum H, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, Zannad F, McMurray JJ. Eplerenone and new-onset diabetes in patients with mild heart failure: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). Eur J Heart Fail 2012;14:909–915.
53. Davies JI, Band M, Morris A, Struthers AD. Spironolactone impairs endothelial function and heart rate variability in patients with type 2 diabetes. Diabetologia 2004;47:1687–1694.
54. Joffe HV, Kwong RY, Gerhard-Herman MD, Rice C, Feldman K, Adler GK. Beneficial effects of eplerenone versus hydrochlorothiazide on coronary circulatory function in patients with diabetes mellitus. J Clin Endocrinol Metab 2007;92:2552–2558.
55. Swaminathan K, Davies J, George J, Rajendra NS, Morris AD, Struthers AD. Spironolactone for poorly controlled hypertension in type 2 diabetes: conflicting effects on blood pressure, endothelial function, glycaemic control and hormonal profiles. Diabetologia 2008;51:762–768.
56. Yamaji M, Tsutamoto T, Kawahara C, Nishiyama K, Yamamoto T, Fujii M, Horie M. Effect of eplerenone versus spironolactone on cortisol and hemoglobin A(1)(c) levels in patients with chronic heart failure. Am Heart J 2010;160:915–921.
57. Gerstein HC, Swedberg K, Carlsson J, McMurray JJ, Michelson EL, Olofsson B, Pfeffer MA, Yusuf S. The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Arch Intern Med 2008;168:1699–1704.
58. Tomova GS, Nimbal V, Horwich TB. Relation between hemoglobin a(1c) and outcomes in heart failure patients with and without diabetes mellitus. Am J Cardiol 2012;109:1767–1773.
59. Tamirisa KP, Aaronson KD, Koelling TM. Spironolactone-induced renal insufficiency and hyperkalemia in patients with heart failure. Am Heart J 2004;148:971–978.
60. Böhm M, Ruilope LM, Bramlage P, Pitt B, Zannad F. Clinical efficacy of aldosterone-blocking agents. Eur Heart J Suppl 2011;13(Suppl B):B34–B39.
61. Burgess ED, Lacourcière Y, Ruilope-Urioste LM, Oparil S, Kleiman JH, Krause S, Roniker B, Maurath C. Long-term safety and efficacy of the selective aldosterone blocker eplerenone in patients with essential hypertension. Clin Ther 2003;25:2388–2404.
62. Saruta T, Kageyama S, Ogihara T, Hiwada K, Ogawa M, Tawara K, Gatlin M, Garthwaite S, Bittman R, Patrick J. Efficacy and safety of the selective aldosterone blocker eplerenone in Japanese patients with hypertension: a randomized, double-blind, placebo-controlled, dose-ranging study. J Clin Hypertens 2004;6:175–183; quiz 184–185.
63. McKenna C, Burch J, Suekarran S, Walker S, Bakhai A, Witte K, Harden M, Wright K, Woolacott N, Lorgelly P, Fenwick L, Palmer S. A systematic review and economic evaluation of the clinical effectiveness and cost-effectiveness of aldosterone antagonists for postmyocardial infarction heart failure. Health Technol Assess 2010;14:1–162.
64. McKenna C, Walker S, Lorgelly P, Fenwick E, Burch J, Suekarran S, Bakhai A, Witte K, Harden M, Wright K, Woolacott N, Palmer S. Cost-effectiveness of aldosterone antagonists for the treatment of post-myocardial infarction heart failure. Value Health 2012;15:420–428.
65. Fagart J, Hillisch A, Huyet J, Barfacker L, Fay M, Pleiss U, Pook E, Schafer S, Rafestin-Oblin ME, Kolkhof P. A new mode of mineralocorticoid receptor antagonism by a potent and selective nonsteroidal molecule. J Biol Chem 2010;285:29932–29940.
66. Pitt B, Filippatos G, Gheorghiade M, Kober L, Krum H, Ponikowski P, Nowack C, Kolkhof P, Kim SY, Zannad F. Rationale and design of ARTS: a randomized, double-blind study of BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease. Eur J Heart Fail 2012;14:668–675.

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Effect of eplerenone in percutaneous coronary intervention-treated post-myocardial infarction patients with left ventricular systolic dysfunction: a subanalysis of the EPHESUS trial

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Aims EPHESUS was a multicentre, double-blind clinical trial in which 6632 patients with acute myocardial infarction (AMI) complicated by LV systolic dysfunction (LVSD) were randomized to receive eplerenone (*n* = 3319) or placebo (*n* = 3313). A total of 1580 EPHESUS patients were treated with PCI, which is now the standard treatment for AMI. This EPHESUS substudy examined the effects of eplerenone upon cardiovascular outcomes in PCI-treated patients.

Methods and results EPHESUS patients were divided into PCI-treated and non-PCI-treated cohorts, and the effect of eplerenone upon mortality and other major adverse cardiovascular outcomes was assessed in each cohort. The PCI-treated patients (*n* = 1580) were younger, and had better renal function and fewer co-morbidities than non-PCI-treated patients (*n* = 5052). Cardiovascular mortality was significantly lower in PCI-treated patients as compared with non-PCI-treated patients (7% vs. 16%, $P < 0.0001$). However, the incidence of non-fatal events was similar in PCI-treated and non-PCI-treated cohorts. There was no statistical difference between the PCI-treated and non-PCI-treated cohorts in the primary or secondary outcomes of the trial. Eplerenone administration, compared with placebo, in the PCI-treated cohort did not affect PCI-related clinical outcomes, including recurrence of angina, the occurrence of acute coronary syndromes, or the need for further revascularization.

Conclusions The beneficial effects of eplerenone in the EPHESUS trial exist for both PCI- and non-PCI-treated AMI patients with LVSD. Eplerenone has minimal, if any, effect upon reducing PCI-related adverse events in the PCI-treated cohort.

Keywords Eplerenone • Heart failure • Angioplasty • Myocardial infarction

Introduction

Acute myocardial infarction (AMI) and consequent LV systolic dysfunction (LVSD) are the leading causes of morbidity and mortality. Mineralocorticoid receptor (MR) antagonism with eplerenone has been shown to improve survival and reduce hospitalization due to cardiovascular events in patients with AMI and LVSD in the landmark EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trial.[1] In this trial, a mean dose of 43 mg of eplerenone produced a significant reduction in

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all-cause and cardiovascular mortality compared with placebo.[1] National and international guidelines therefore strongly recommend using MR antagonists for patients with post-infarct LVSD.[2,3]

In contemporary practice, patients with AMI are usually treated with PCI, involving balloon angioplasty and stent implantation.[4,5] However, only a quarter of patients in the EPHESUS trial received PCI for treatment of AMI while others were treated with thrombolysis, coronary artery bypass grafting (CABG), or conservative medical treatment.[1] Therefore, application of the EPHESUS data to current practice can be questioned. We aimed to evaluate the impact of eplerenone administration in heart failure among patients managed with PCI.

Experimental data have suggested that eplerenone may improve the PCI outcomes by reducing neointimal proliferation[6] and accelerating endothelial regeneration.[7,8] While pre-clinical studies support these hypotheses,[9–11] there has been no study investigating this potential benefit of eplerenone in humans. Although the EPHESUS trial did not have a pre-specified aim to examine PCI outcomes, and there was no routine angiographic follow-up, surrogate clinical markers were systematically recorded. The second objective of this study was to evaluate the impact of eplerenone upon PCI-related adverse clinical outcomes, including recurrence of angina, the occurrence of acute coronary syndromes, and the need for repeat revascularization.

Methods

EPHESUS trial

EPHESUS was a large multicentre, double-blind randomized controlled clinical trial that assessed the impact of eplerenone upon clinical outcomes in patients with LVSD after AMI.[1] Patients ($n = 6632$) were randomized to receive eplerenone ($n = 3319$) or placebo ($n = 3313$). Eplerenone was initiated at 25 mg/day at ~7 days after AMI and titrated at 4 weeks to 50 mg/day, if serum potassium was <5 mmol/L. About 24% patients in the EPHESUS trial received PCI as a treatment of AMI while others were treated with thrombolysis (27%), CABG (11%), or conservative medical treatment (48%). Patients were followed-up for an average of 16 months.

EPHESUS PCI substudy

This substudy evaluated the effect of eplerenone administration in the PCI-treated subgroup of patients in the EPHESUS trial. We analysed the PCI-treated ($n = 1580$) vs. non-PCI-treated ($n = 5052$) patients. Furthermore, we compared the baseline characteristics and clinical outcomes in PCI-treated patients in the eplerenone- ($n = 799$) and placebo- ($n = 781$) treated groups.

Statistical analysis

Data are presented as mean ± SD or proportion and percentage, as indicated. Continuous variables were analysed using the Mann–Whitney test and categorical variables with the χ^2 test. Multivariate analyses were performed using the Cox regression method. Hazard ratios (HRs) along with the 95% confidence interval (CI) are presented. *P*-values <0.05 were considered significant. All statistical analyses were performed using SAS® 9.2 software (SAS Institute, Cary, NC, USA).

Results

The EPHESUS PCI cohort is different from the non-PCI cohort

The baseline demographic and clinical characteristics of PCI-treated ($n = 1580$) and non-PCI-treated ($n = 5052$) patients in the EPHESUS trial are shown in Table 1. The PCI-treated patients were younger, and had better renal function, fewer co-morbidities, and higher prescription of evidence-based medication including beta-blockers, ACE inhibitors, and statins. Cardiovascular mortality was significantly lower in PCI-treated patients as compared with non-PCI-treated patients (7% vs. 16%, $P < 0.0001$), but the incidence of non-fatal events was similar in the two groups (Table 1).

Eplerenone improves outcomes in both the PCI-treated and the non-PCI-treated cohort

Eplerenone treatment was similarly effective in reducing mortality, cardiovascular events, and hospitalization in both PCI-treated and non-PCI-treated AMI patients with LVSD (*Figure 1*). On multivariate Cox regression analysis, with eplerenone and PCI as co-variables, both PCI and eplerenone administration were independently associated with better clinical outcomes (*Table 2*).

Baseline characteristics of the EPHESUS PCI cohort

The baseline characteristics of the EPHESUS PCI cohort treated with placebo or eplerenone were similar (*Table 3*). The mean age of the patients was 60 years, with 77% male patients. The two groups were similar in terms of age, gender, ethnicity, LV function, co-morbidities, and prescription of medication at discharge (*Table 3*). There was no significant difference in adverse events between the eplerenone- or placebo-treated EPHESUS PCI cohort: hyperkalaemia (2.4% vs. 3.3%, $P = 0.33$), hypokalaemia (1.7% vs. 0.8%, $P = 0.10$), gynaecomastia in men (0.6% vs. 0.6%, $P = 1.00$), and renal dysfunction (3.2% vs. 2.0%, $P = 0.13$).

Eplerenone does not affect PCI-related clinical outcomes

Eplerenone, compared with placebo, in the PCI cohort did not impact upon the incidence of sudden cardiac death, non-fatal MI, or stroke (Table 4). Although there was a statistically significant reduction in events related to heart failure and hospital admissions, there was no effect upon PCI-related adverse outcomes, including recurrence of angina pectoris, unstable angina, AMI, or need for further revascularization (*Table 4*).

Discussion

This substudy analysis of the EPHESUS trial has highlighted that eplerenone is effective in patients with AMI and LVSD whether

Table 1 Baseline comparison of PCI-treated and non-PCI-treated EPHESUS patients

Characteristic	Non-PCI treated, n = 5052 (76%)		PCI treated, n = 1580 (24%)		P-value
	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	
Demographics					
Age (years)	5052	65 ± 11	1580	61 ± 12	<0.0001
Caucasian		4589 (91%)		1395 (88%)	0.003
Male		3491 (69%)		1223 (77%)	<0.0001
Time from AMI to randomization (days)	5051	7.4 ± 2.9	1580	6.7 ± 3.0	<0.0001
Clinical					
Blood pressure (mmHg)					
Systolic	5050	120 ± 17	1580	116 ± 16	<0.0001
Diastolic	5050	73 ± 11	1580	70 ± 11	<0.0001
LV ejection fraction (%)	5041	33 ± 6	1576	33 ± 6	0.85
Previous hospitalization for HF		452 (9%)		60 (4%)	<0.0001
Symptoms of heart failure		4047 (80%)		1232 (79%)	<0.0001
Potassium (mmol/L)	5029	4.28 ± 0.45	1566	4.21 ± 0.43	<0.0001
Creatinine (μmol/L)	5026	102 ± 29	1568	95 ± 25	<0.0001
eGFR (MDRD, mL/min/1.73 m²)	4888	67 ± 19	1493	74 ± 19	<0.0001
Medical history	5052		1580		
Previous MI		1462 (29%)		336 (21%)	<0.0001
Diabetes mellitus		1658 (33%)		484 (31%)	0.10
Heart failure		853 (17%)		122 (8%)	<0.0001
Hypertension		3159 (63%)		848 (54%)	<0.0001
Medications	5052		1580		
ACEI/ARB		4318 (85%)		1433 (91%)	< 0.0001
Beta-blockers		3641 (72%)		1320 (84%)	< 0.0001
Diuretics		3172 (63%)		812 (51%)	< 0.0001
Aspirin		4377 (87%)		1493 (94%)	< 0.0001
Anticoagulants		934 (18%)		174 (11%)	< 0.0001
Statins		2026 (40%)		1069 (68%)	< 0.0001
Outcomes	5052		1580		
Cardiovascular mortality		784 (16%)		106 (7%)	<0.0001
Non-fatal events (ACS/revascularization)		1073 (21%)		339 (21%)	0.85

ACEI, ACE inhibitor; ACS, acute coronary syndrome; AMI, acute myocardial infarction; eGFR, estimated glomerular filtration rate [Modification of Diet in Renal Disease (MDRD) formula]; HF, heart failure; PCI, percutaneous coronary intervention.

treated with or without PCI. However, there is no evidence that eplerenone has any impact upon PCI-related outcomes including recurrence of angina, AMI, and repeat revascularization.

Eplerenone improved outcomes in both the PCI-treated and non-PCI-treated population

Mineralocorticoid receptor antagonists are strongly recommended for patients with LVSD and symptoms of heart failure,[11,13] based on morbidity and mortality benefits seen in three landmark trials: RALES, EPHESUS, and EMPHASIS-HF.[1,14,15] The RALES trial consisted of patients with advanced heart failure, the EPHESUS trial included patients with LVSD after AMI, and the EMPHASIS-HF trial enrolled patients with heart failure and mild (NYHA class II) symptoms.[1,14–16] In RALES, spironolactone produced 30% relative reduction in mortality during an average follow-up of 24 months.[14] In EMPHASIS-HF, eplerenone was associated with a 24% reduction in cardiovascular death and a 42% reduction in hospitalization for heart failure.[15] Only the EPHESUS trial specifically examined patients with LVSD after an AMI and showed that eplerenone produced 15% reduction in all-cause mortality, 17% reduction in cardiovascular mortality, and 21% reduction in sudden cardiac death.[1] In contemporary practice, most patients with AMI receive PCI treatment.[4] Our data show that eplerenone confers similar benefit in patients with AMI and LVSD whether or not they are treated with PCI. The outcomes observed in the PCI subgroup were similar to those reported in the full EPHESUS cohort.[1] Our analysis shows that PCI itself was associated with a major reduction in adverse outcomes in AMI patients, consistent

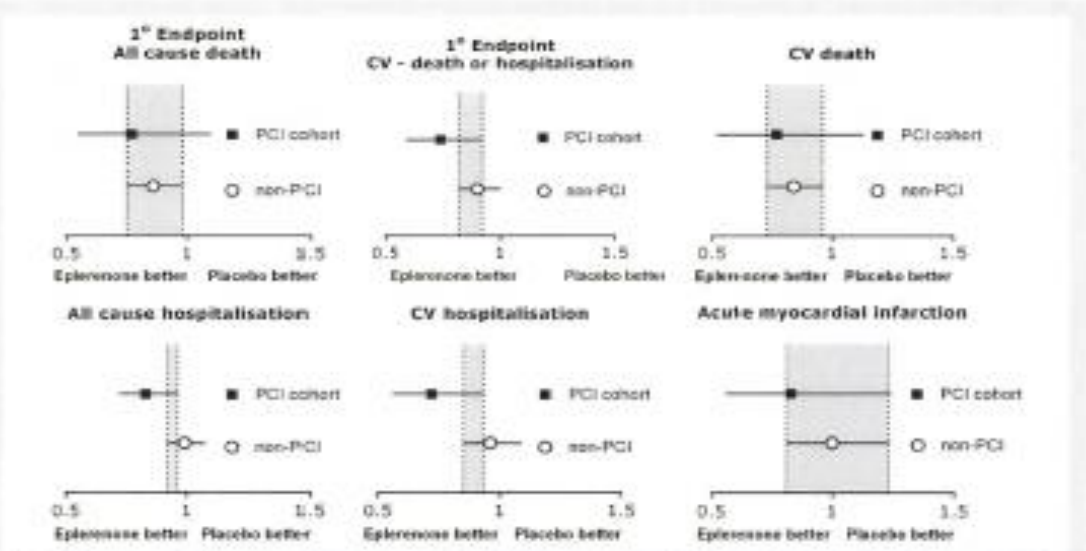

Figure 1 Outcomes in PCI-treated and non-PCI-treated EPHESUS patients. Outcomes for both cohorts are shown as the hazard ratio (HR) with the 95% confidence interval (CI). The 95% CI for all HR values between PCI-treated and non-PCI-treated EPHESUS patients overlap with each other (shown in grey shade). CV, cardiovascular; PCI, percutaneous coronary intervention.

Table 2 Association of outcomes with eplerenone and PCI in EPHESUS patients in multivariable Cox regression analysis with eplerenone and PCI as covariables

	Eplerenone, yes vs. no		PCI, yes vs. no	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Primary outcomes				
All-cause death	0.85 (0.75–0.96)	0.008	0.41 (0.35–0.51)	<0.0001
Cardiovascular death or hospitalization	0.87 (0.80–0.95)	0.003	0.62 (0.55–0.70)	<0.0001
Secondary outcomes				
All-cause death or any hospitalization	0.92 (0.86–0.99)	0.017	0.91 (0.84–0.99)	0.022
Cardiovascular death	0.83 (0.73–0.95)	0.005	0.41 (0.33–0.50)	<0.0001
Sudden death from cardiac causes	0.79 (0.64–0.97)	0.027	0.49 (0.36–0.65)	<0.0001
Acute myocardial infarction	0.82 (0.61–1.11)	0.20	0.34 (0.20–0.56)	<0.0001
Heart failure	0.80 (0.62–1.04)	0.099	0.35 (0.23 – 0.53)	<0.0001
Stroke	0.91 (0.56–1.56)	0.73	0.37 (0.16–0.87)	0.023
Any hospitalization	0.95 (0.89– 1.02)	0.18	1.00 (0.92–1.09)	1.00
Cardiovascular hospitalization	0.91 (0.82– 1.02)	0.098	0.73 (0.64–0.84)	<0.0001
Acute myocardial infarction	0.96 (0.80–1.16)	0.67	0.81 (0.65–1.02)	0.069
Heart failure	0.86 (0.75–0.98)	0.029	0.67 (0.56–0.80)	<0.0001
Stroke	1.18 (0.87–1.62)	0.29	0.48 (0.25–0.64)	0.0002
Ventricular arrhythmia	0.95 (0.65–1.39)	0.79	0.62 (0.37–1.03)	0.066
Acute myocardial infarction or unstable angina	1.01 (0.89–1.14)	0.92	0.96 (0.83–1.11)	0.60

CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention.

Table 3 Baseline comparison of placebo- or eplerenone-treated patients in the EPHESUS-PCI group

Characteristic	Placebo, n = 781 (49%)		Eplerenone, n = 799 (51%)		P-value
	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	
Age (years)	781	61 ± 12	799	60 ± 11	0.05
Caucasian		688 (88%)		707 (88%)	0.81
Male gender		591 (76%)		632 (79%)	0.10
Blood pressure (mmHg)					
Systolic	781	116 ± 16	799	115 ± 15	0.43
Diastolic	781	70 ± 11	799	70 ± 10	0.65
LV ejection fraction (%)	779	33 ± 6	797	33 ± 6	0.83
Time from AMI to randomization (days)	781	6.6 ± 3.0	799	6.8 ± 3.0	0.23
Previous hospitalization for HF		34 (4%)		26 (3%)	0.25
Symptoms of heart failure		615 (79%)		617 (78%)	0.37
Potassium (mmol/L)	771	4.21 ± 0.43	795	4.21 ± 0.43	0.85
Creatinine (μmol/L)	768	94 ± 25	790	95 ± 25	0.23
eGFR (MDRD, mL/min/1.73 m^2)	737	74 ± 19	756	73 ± 19	0.45
Medical history	781		799		
Previous MI		161 (21%)		175 (22%)	0.53
Diabetes mellitus		240 (31%)		244 (31%)	0.93
Heart failure		66 (8%)		56 (7%)	0.28
Hypertension		423 (54%)		425 (53%)	0.70
Medications	781		799		
ACEI/ARB		708 (91%)		725 (91%)	0.95
Beta-blockers		648 (83%)		672 (84%)	0.54
Diuretics		406 (52%)		406 (51%)	0.64
Aspirin		739 (95%)		754 (94%)	0.82
Anticoagulant agents		82 (10%)		92 (12%)	0.52
Statins		537 (69%)		532 (67%)	0.36

Symptoms of heart failure: Killip's class > I.
ACEI, ACE inhibitor; AMI, acute myocardial infarction; eGFR, estimated glomerular filtration rate [four-variable Modification of Diabetes in Renal Disease (MDRD) formula]; HF, heart failure; PCI, percutaneous coronary intervention.

Table 4 Effect of eplerenone on angioplasty-related outcomes in the EPHESUS-PCI cohort

	Eplerenone (n = 799)	Placebo (n = 781)	HR (95% CI)	P-value
Repeat revascularization (PCI/CABG)	51 (6%)	44 (6%)	1.13 (0.75–1.69)	0.56
Angina pectoris	24 (3%)	24 (3%)	0.97 (0.55–1.70)	0.90
Unstable angina	84 (11%)	82 (10%)	1.00 (0.73–1.35)	0.98
Acute myocardial infarction	45 (6%)	53 (7%)	0.83 (0.56–1.24)	0.37
Sudden cardiac death	21 (3%)	30 (4%)	0.67 (0.39–1.17)	0.16
Heart failure	60 (8%)	86 (11%)	0.66 (0.47–0.91)	0.012
Cardiovascular hospitalization	108 (14%)	140 (18%)	0.72 (0.56–0.93)	0.011

CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio.

with numerous other reports.[17,18] However, eplerenone administration was also an independent factor associated with improved outcomes, emphasizing the importance of MR antagonism in LVSD after AMI, including patients treated with primary PCI. Therefore, prescribing eplerenone to patients with AMI and LVSD remains beneficial in patients treated with and without PCI.

Whilst the EPHESUS trial included patients with all forms of AMI [unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), and STEMI] and there was a delay in commencing eplerenone, a recently reported clinical trial (REMINDER: impact of eplerenone on cardiovascular outcomes in patients post myocardial infarction NCT-01176968) has shown that early use of eplerenone can improve the outcome of patients presenting with acute STEMI without heart failure.[19] Over 1000 patients were randomized (n = 506/group) to initiation of eplerenone or placebo within 12–24 h of STEMI. Eplerenone 25 or 50 mg/day (89% patients received 50 mg/day) produced a significant reduction

(HR 0.58, 95% CI 0.45–0.75, $P < 0.0001$) in the primary endpoint (a composite of cardiovascular mortality, ventricular arrhythmia, clinical or subclinical heart failure at 1 month) at a mean follow-up of 10.5 months.[19] ALBATROSS (Aldosterone blockade early after acute myocardial infarction; NCT-01659136) is an ongoing multicentre, open-labelled, randomized trial to assess the effects of MR blockade with a 200 mg i.v. bolus of potassium canrenoate followed by 25 mg/day spironolactone for 6 months in 1600 patients with STEMI or high risk NSTEMI.[20]

Eplerenone did not affect PCI-related outcomes

Mineralocorticoid receptors are widely distributed in the vascular system, including endothelial cells, endothelial progenitor cells (EPCs), vascular smooth muscle cells (VSMCs), and intact vessels.[8,21,22] These receptors also influence vascular function and remodelling.[8,23] MR activation has been shown to increase proliferation of VSMCs[8] and to impair differentiation and proliferation of EPCs.[7] These characteristics suggest that MR activation is a potential stimulus for neointimal proliferation and restenosis. In humans, elevated baseline plasma aldosterone levels directly correlate with risk of restenosis[24] and inversely correlate with circulating EPCs and endothelial colony-forming units.[8] Mineralocorticoid receptor antagonists reduce atherosclerosis,[23,25] prevent adverse vascular remodelling,[26] and attenuate post-angioplasty neointimal proliferation in experimental animals.[9,11,27]

Spironolactone has been shown to inhibit neointimal proliferation after balloon angioplasty of iliac arteries in rabbits.[27] However, these results could not be reproduced in a porcine coronary angioplasty model,[9,28] which is the gold standard pre-clinical model for restenosis. Additionally, a single-centre clinical trial failed to show any effect of spironolactone in reducing restenosis.[29] Nevertheless, promising experimental data have been obtained with eplerenone.[9–11] Our data suggest that, like spironolactone, eplerenone does not appear to affect PCI-related clinical outcomes. Therefore, eplerenone cannot currently be recommended for patients undergoing PCI without co-existing AMI or LVSD.

Study limitations

This study has several limitations. It is a post-hoc analysis with inherent shortcomings of any such study. Patients in the EPHESUS PCI cohort did not have routine angiographic follow-up to document any effect of eplerenone on angiographic restenosis; however, our assessment of clinical events is perhaps more relevant than angiographic outcomes.

Conclusion

The beneficial effects of eplerenone on heart failure events and hospitalization seen in the EPHESUS trial are similar for both PCI-treated and non-PCI-treated AMI patients with LVSD. There is no evidence that eplerenone reduces the risk of recurrent ischaemia-related events including recurrence of angina or the need for repeat revascularization. Use of eplerenone is strongly recommended in AMI patients with LVSD.

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References

1. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.
2. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009;**53**:e1–e90.
3. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008;**10**:933–989.
4. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**61**:e78–e140.
5. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J* 2010;**31**:2501–2555.
6. Ishizawa K, Izawa Y, Ito H, Mori C, Miyata K, Fujita Y, Kawamatsu T, Tsushima K, Tamaki T, Nishiyama A, Yoshizumi M. Aldosterone stimulates vascular smooth muscle cell proliferation via big mitogen-activated protein kinase 1 activation. *Hypertension* 2005;**46**:1046–1052.
7. Thum T, Schmiedeke K, Fommer F, Weidemann Y, Dietrich B, Widder JD, Jankowski V, Hübner S, Erd G, Bauersachs J. Impairment of endothelial progenitor cell function and vasculogenesis capacity by aldosterone in mice and humans. *Eur Heart J* 2011;**32**:1275–1286.
8. Wu VC, Lo SC, Chen YL, Huang PH, Tsai CT, Liang CJ, Kao CC, Kuo TT, Lee BC, Wu EL, Jin YH, Sun YY, Lin SL, Chen JW, Lin SJ, Wu KD. Endothelial progenitor cells as primary aldosteronism: a biomarker of severity for aldosterone vasculopathy and prognosis. *J Clin Endocrinol Metab* 2011;**96**:3176–3183.
9. Wajed MR, Kandalaft P, Ramsey D, Pundir J, Bobik A. Eplerenone suppresses constrictive remodelling and collagen accumulation after angioplasty in porcine coronary arteries. *Circulation* 2001;**104**:467–472.
10. Watanabayashi R, Suzuki H, Saito T, Ito Y, Katagiri T, Takeyama Y. Eplerenone suppresses neointimal formation after coronary stent implantation in swine. *Int J Cardiol* 2006;**107**:260–266.
11. Iqbal J, Macdonald LJ, Esler L, Senkal JB, Yau CW, Walker BR, Hadoke PW. Contribution of endogenous glucocorticoids and their interconversion to postangioplasty neointimal proliferation in mice. *Endocrinology* 2012;**153**:5096–5105.

12. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;**119**:1977–2016.
13. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803–869.
14. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717.
15. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
16. Iqbal J, Parviz Y, Pitt B, Newell-Price J, Al-Mohammad A, Zannad F. Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure. *Eur J Heart Fail* 2014;**16**:143–150.
17. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**:13–20.
18. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, Wheatley DJ, Pocock SJ. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet* 2002;**360**:743–751.
19. Montalescot G, Pitt B, Lopez-de-Sa E, Hamm CW, Flather M, Verheugt F, Shi H, Turgonyi E, Orri M, Vincent J, Zannad F. Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure. ACC, San Francisco, 10 March, 2013.
20. Beygui F, Vicaut E, Ecollan P, Machecourt J, Van Belle E, Zannad F, Montalescot G. Rationale for an early aldosterone blockade in acute myocardial infarction and design of the ALBATROSS trial. *Am Heart J* 2010;**160**:642–648.
21. Hadoke PW, Iqbal J, Walker BR. Therapeutic manipulation of glucocorticoid metabolism in cardiovascular disease. *Br J Pharmacol* 2009;**156**:689–712.
22. Kayes-Wandover KM, White PC. Steroidogenic enzyme gene expression in the human heart. *J Clin Endocrinol Metab* 2000;**85**:2519–2525.
23. Suzuki J, Iwai M, Mogi M, Oshita A, Yoshii T, Higaki J, Horiuchi M. Eplerenone with valsartan effectively reduces atherosclerotic lesion by attenuation of oxidative stress and inflammation. *Arterioscler Thromb Vasc Biol* 2006;**26**:917–921.
24. Amano T, Matsubara T, Izawa H, Torigoe M, Yoshida T, Hamaguchi T, Ishii H, Miura M, Hayashi Y, Ogawa Y, Murohara T. Impact of plasma aldosterone levels for prediction of in-stent restenosis. *Am J Cardiol* 2006;**97**:785–788.
25. Keidar S, Hayek T, Kaplan M, Pavlotzky E, Hamoud S, Coleman R, Aviram M. Effect of eplerenone, a selective aldosterone blocker, on blood pressure, serum and macrophage oxidative stress, and atherosclerosis in apolipoprotein E-deficient mice. *J Cardiovasc Pharmacol* 2003;**41**:955–963.
26. Endemann DH, Touyz RM, Iglarz M, Savoia C, Schiffrin EL. Eplerenone prevents salt-induced vascular remodeling and cardiac fibrosis in stroke-prone spontaneously hypertensive rats. *Hypertension* 2004;**43**:1252–1257.
27. Van Belle E, Bauters C, Wernert N, Hamon M, McFadden EP, Racadot A, Dupuis B, Lablanche JM, Bertrand ME. Neointimal thickening after balloon denudation is enhanced by aldosterone and inhibited by spironolactone, and aldosterone antagonist. *Cardiovasc Res* 1995;**29**:27–32.
28. Bacchetta MD, Salemi A, Mills F, Hong MK, Tio F, Zhou Y, Chun R, Southard E, Lee LY, Mack CA, Krieger KH, Isom OW, Ko W, Borer JS, Catanzaro DF. Low-dose spironolactone: effects on artery-to-artery vein grafts and percutaneous coronary interventions. *Am J Ther* 2009;**16**:204–214.
29. Kursaklioglu H, Iyisoy A, Amasyali B, Celik T, Ozturk C, Kose S, Isik E. Spironolactone does not prevent restenosis after coronary stenting in humans. *Ann Acad Med Singapore* 2004;**33**:769–774.

Review

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Emerging cardiovascular indications of mineralocorticoid receptor antagonists

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Mineralocorticoid receptor (MR) antagonism is a well-established treatment modality for patients with hypertension, heart failure, and left ventricular systolic dysfunction (LVSD) post-myocardial infarction (MI). There are emerging data showing potential benefits of MR antagonists in other cardiovascular conditions. Studies have shown association between MR activation and the development of myocardial fibrosis, coronary artery disease, metabolic syndrome, and cerebrovascular diseases. This review examines the preclinical and clinical data of MR antagonists for novel indications including heart failure with preserved ejection fraction (HFPEF), pulmonary arterial hypertension (PAH), arrhythmia, sudden cardiac death, valvular heart disease, metabolic syndrome, renal disease, and stroke. MR antagonists are not licensed for these conditions yet; however, emerging data suggest that indication for MR antagonists are likely to broaden; further studies are warranted.

Introduction

The mineralocorticoid receptor (MR; see Glossary) is a cytosolic steroid receptor that binds mineralocorticoids and glucocorticoids [1]. MR is expressed in many tissues including kidney and heart. In epithelial tissues, MR activation and nuclear translocation results in increased expression of proteins that regulate sodium/potassium homeostasis, with concomitant sodium reabsorption and increase in extracellular volume, increased blood pressure, and potassium excretion. Inhibition of MR results in reduced sodium resorption in the kidneys and reduced urinary potassium excretion [1].

Landmark trials including RALES (Randomized ALdactone Evaluation Study), EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), and EMPHASIS-HF (Eplerenone in Mild

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Glossary

Acute myocardial infarction (AMI): necrosis of heart muscles usually caused by lack of blood supply due to occlusion of a coronary artery. It is further divided into ST elevation MI (STEMI) and non-ST elevation MI (NSTEMI) based on presence or absence of ST segment elevation on electrocardiogram (ECG).
ALBATROSS: Aldosterone blockade early after acute myocardial infarction clinical trial.
Angiotensin converting enzyme (ACE) inhibitors: pharmaceutical drugs that are used to treat hypertension and congestive heart failure. Their mode of action is via the inhibition of the angiotensin-converting enzyme of the RAAS.
Angiotensin receptor blockers (ARBs): pharmaceutical drugs that are used to treat hypertension and heart failure.
Aldo-DHF: Aldosterone Receptor Blockade in Diastolic Heart Failure clinical trial.
ARIES: Ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy study.
ALCHEMIST: ALdosterone Antagonist Chronic HEModialysis Interventional Survival trial.
Brain natriuretic peptide (BNP): a peptide secreted by the heart in response to changes in pressure that occur during heart failure and used for diagnosis of heart failure. The N terminus of prohormone BNP (NT-proBNP) may have higher sensitivity and specificity for diagnosing heart failure.
DOHAD: Dialysis Outcomes Heart Failure Aldactone Study.
EPHESUS Trial: Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study.
EMPHASIS-HF Trial: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure.
Heart failure with preserved ejection fraction (HFPEF): symptoms and signs of heart failure with normal or preserved ejection fraction. This is also known as diastolic dysfunction.
Left ventricular systolic dysfunction (LVSD): defined as an ejection fraction less than 40% in the EPHESUS trial.
Mineralocorticoid receptor (MR): also known as the aldosterone receptor, is a receptor that binds mineralocorticoids and glucocorticoids with equal affinity. Activation of the receptor results in signal translocation and target gene expression.
MIRAcle: Mineralocorticoid Receptor Antagonists in End Stage Renal Disease study.
OPTIMIZE-HF: Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure study.
Pulmonary arterial hypertension (PAH): a condition whereby the blood pressure in the arteries of the lungs is abnormally high, affecting the function of the right side of the heart.
Renin–angiotensin–aldosterone system (RAAS): an endocrine system and signaling pathway that is responsible for regulating blood pressure and systemic vascular resistance.
RALES Trial: Randomized ALdactone Evaluation Study.
REMINDER Trial: Impact eplerenone on cardiovascular outcomes in patients post myocardial infarction.
SPIR AF: Effect of combined spironolactone-β-blocker + amiodarone treatment on occurrence of symptomatic atrial fibrillation (AF) episodes in patients with a history of paroxysmal AF.
Sudden Cardiac Death (SCD): Unexpected death which is presumed to be cardiac in origin and usually secondary to ventricular arrhythmias.
TOPCAT Trial: Treatment of Preserved Cardiac function with an Aldosterone antagonist trial.

Patients Hospitalization and Survival Study in Heart Failure) have demonstrated that MR antagonists (spironolactone or eplerenone) have beneficial effects in patients with heart failure and LVSD. However, MR antagonists also have potential effects on vascular inflammation, macrophage activation, oxygen free radical formation, endothelial dysfunction, and myocardial fibrosis, and hence may provide more widespread benefits on cardiovascular disease states. These effects are mediated by a variety of signaling mechanisms and mediators, outlined in Figure 1 and reviewed in detail elsewhere [2]. This review briefly describes the existing indications of MR antagonists and critically evaluates potential indications of MR antagonists for the treatment of HF-PEF, PAH, cardiac arrhythmias, valvular heart disease, metabolic syndrome, renovascular diseases, and cerebrovascular diseases.

Current and emerging MR antagonists

Eplerenone and spironolactone (and its metabolite, potassium canrenoate) are the currently licensed MR antagonists for clinical use. Spironolactone is a high affinity but nonspecific MR antagonist and, due to its structural similarity to progesterone, binds also to progesterone, androgen, and glucocorticoid receptors, but with reduced affinity [3]. Eplerenone is also a steroidal compound with greater selectivity for MR and minimal binding to progesterone and androgen receptors [3]. Spironolactone and eplerenone differ in their metabolism and half-life [3,4]. There are also a few non-steroidal MR antagonists (e.g., Finerenone, BR-4628) at various stages of development [5–7]. These emerging MR antagonists have the potential to deliver similar efficacy, but with less endocrine side effects, such as estrogenic side effects, including impotence and gynecomastia in men and menstrual irregularity in women, due to their non-steroidal structure. These compounds may also have higher affinity for cardiac MR, rather than renal MR, and therefore, potentially a reduced tendency for hyperkalemia than currently licensed agents. A comparison of MR antagonists is given in Table 1.

Currently licensed cardiovascular indications of MR antagonists

Chronic heart failure due to LVSD

RALES and EMPHASIS-HF trials have proven the efficacy of MR antagonists in chronic heart failure due to LVSD. In the RALES study, spironolactone showed a 30% relative reduction in mortality at 24-month follow-up [8]. In EMPHASIS-HF, there was a 24% reduction in cardiovascular death, and a 42% reduction in hospitalization for heart failure [9]. However, both spironolactone and eplerenone can potentially cause hyperkalemia, raising concerns about use of MR antagonist in patients with renal impairment [8,10]. It is worth noting that in patients with LVSD and moderate renal impairment, a newer non-steroidal MR antagonist, Finerenone (BAY 94-8862), decreased biomarkers of hemodynamic stress equivalent to spironolactone, but with lower incidence of hyperkalemia and worsening renal function [11]. Such newer compounds could potentially be safer alternatives to current MR antagonists for the existing cardiovascular indications.

LVSD after MI

In the EPHESUS trial, eplerenone administered 3–4 days after an acute myocardial infraction (AMI) in patients with clinical heart failure and LVSD, produced a 15% reduction in all-cause mortality, a 17% reduction in cardiovascular mortality and a 21% reduction in sudden cardiac death [10]. It was recently reported in the REMINDER trial that early administration of eplerenone within 24 hours of symptom onset can improve the outcome of patients with ST segment elevation myocardial infarction (STEMI), a type of heart attack, without clinical heart failure [12]. Eplerenone produced a significant reduction in the primary endpoint (composite of cardiovascular mortality,

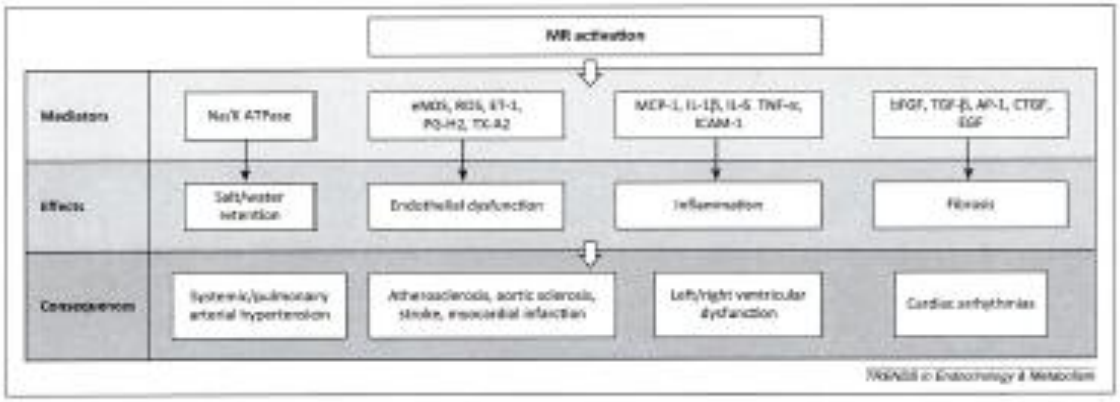
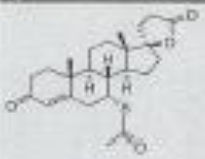
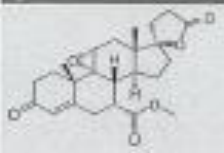
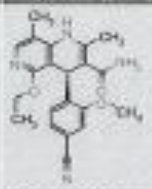


Figure 1. Mineralocorticoid receptor (MR) activation: pathophysiological effects and cardiovascular disease association. MR activation can lead to adverse cardiovascular outcomes via a number of potential pathways and mediators affecting electrolyte balance, inflammation, endothelial function, and fibrosis. Abbreviations: Na/K ATPase, sodium/potassium adenosine triphosphatase; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; ET-1, endothelin-1; PG-H2, prostaglandin H2; TX-A2, thromboxane A2; MCP-1, monocyte chemotactic protein-1; IL-1β, interleukin 1-beta; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha; ICAM-1, intercellular adhesion molecule 1; bFGF, basic fibroblast growth factor; TGF-β, transforming growth factor-beta; AP-1, activator protein 1; CTGF, connective tissue growth factor; EGF, epidermal growth factor.

Table 1. Comparison of current and emerging MR antagonists

	Spironolactone	Eplerenone	Finerenone (BAY 94-8862)
Chemical structure			
Chemical group	Steroid	Steroid	Non-steroidal
Mode of action	Competitive MR antagonism	Competitive MR antagonism	Competitive MR antagonism
MR affinity	+++	+	+++
MR selectivity	+	+++	+++
Inhibition of nongenomic MR effects	No	Yes	Unknown
Onset/offset of action	Slow	Quicker	Unknown
Bioavailability	60–90%	Absolute bioavailability unknown	Unknown (94% in rats)
Volume of distribution	Unknown	43–60 liters	Unknown
Protein binding	98% bound to plasma proteins	93% bound to plasma proteins	Unknown
Metabolism	Hepatic metabolism to active metabolites	Hepatic metabolism by CYP3A4 to inactive metabolites	Unknown
Half-life of drug	1–2 hours	4–6 hours	Unknown (8.5 hours in rats)
Active metabolites	Yes	No	Activity of metabolites not known
Elimination half-life of drug and metabolites	10–35 hours	4–6 hours	Unknown

ventricular arrhythmia, clinical or subclinical heart failure at 1 month, as determined by an ejection fraction less than 40% or elevation in brain natriuretic peptide (BNP) or N terminus of prohormone BNP (NT-BNP); heart rate (HR) 0.58, 95% confidence interval (CI) 0.45–0.75, $P < 0.0001$], at a mean follow-up of 10.5 months [12]. This improvement in primary endpoint was driven by a reduction in brain natriuretic peptide (BNP) levels (HR 0.58, 95% CI 0.44–0.77, $P < 0.0001$); the study was not able/powered to demonstrate effects on cardiac mortality (HR 0.52, 95% CI 0.05–5.99, P = ns), hospitalization (HR 0.56, 95% CI 0.20–1.54, P = ns), and ejection fraction (HR 1.08, 95% CI 0.58–2.00, P = ns) [12]. Spironolactone has not been assessed for this indication. However, ALBATROSS (Aldosterone blockade early after acute myocardial infarction; NCT-01059136) is an ongoing multicenter, open-labelled, randomized trial to assess the effects of MR blockade. The trial will assess a 200-mg intravenous bolus of potassium canrenoate followed by 25 mg/day spironolactone for 6 months, in 1600 patients with STEMI or high-risk NSTEMI [13]. In summary, the best current available evidence supports eplerenone in the treatment of LVSD after MI [4].

Systemic hypertension

MR antagonists are used as monotherapy and as an add-on therapy for hypertension [14,15]. These agents are as effective in lowering blood pressure as the currently recommended first-line anti-hypertensive agents – angiotensin converting enzyme (ACE) inhibitors [16] or angiotensin receptor blockers (ARBs) [17]. Eplerenone is better tolerated than amlodipine, a widely used calcium channel blocker, with similar reduction in systolic blood pressure [18]. MR antagonists have also been shown to prevent hypertension-induced end organ damage in both preclinical [19] and clinical studies [16,20]. However, MR antagonists are still used infrequently and considered as fourth-line therapy (for patients with resistant hypertension), in national and international guidelines [21]. The underuse of MR antagonists is due to relative paucity of long-term clinical outcome data, compared with other antihypertensive drugs. Therefore, potential future roles of MR antagonists in hypertension will be guided by further population-level data, but there is scope for wider acceptance in the treatment of hypertension.

Emerging cardiovascular indications of MR antagonists

HF-PEF

MR activation may cause left ventricular hypertrophy (LVH) and collagen deposition, which reduces LV compliance, a characteristic of HF-PEF. MR antagonists have therefore been investigated as potential therapeutic agents (Table 2). Although eplerenone has been shown to attenuate collagen turnover in patients with HF-PEF [22,23] and improve echocardiographic measures of diastolic function, this did not correlate with functional improvement [23]. After 6 months of treatment, no differences in 6-minute walk distance were noted in the eplerenone and placebo groups. However, this small study (n = 40) was underpowered to demonstrate functional outcomes. A sub-study of the OPTIMIZE-HF trial compared 492 patients with HF-PEF receiving MR antagonists with 457 propensity matched patients not receiving MR antagonists [24]. During the mean follow-up of 2.4 years, the primary composite endpoint of all-cause mortality or HF hospitalization occurred in 392 (81%) and 393 (81%)

Table 2. Summary of studies investigating MR antagonists for HF PEF

Study name	Study design	Drug (dose)	No. of patients	Eligibility criteria[a]	Primary endpoints	Follow-up	Outcomes	Refs
RAAM-PEF	Single-center, randomized, double blind, placebo-controlled trial	Eplerenone (50 mg/day)	44	Clinical HF with NYHA Class II or III symptoms, EF ≥ 45% and BNP levels ≥ 100 pg/ml	6-minute walk distance	6 months	No significant difference in the change in 6-minute walk test between the eplerenone and placebo arms; however, improvement in diastolic function and reduced collagen turnover	[23]
OPTIMIZE-HF	Matched patients from a registry	Any MR antagonist	574	EF ≥ 40%, no renal impairment, not using ACE-I/ARB	All-cause mortality, HF hospitalization, all-cause hospitalization	2.4 years	No impact on all-cause mortality or HF hospitalization	[24]
Kosmala et al.	Prospective, blinded, parallel-group, placebo-controlled trial	Spironolactone (25 mg/day)	88	Patients with DHF and metabolic syndrome already receiving ACE-I/ ARB	Echocardiographic indices of LV systolic and diastolic function, and serum markers of collagen turnover	6 months	Spironolactone improved LV function and reduced markers of collagen turnover	[25]
Aldo-DHF	A multicenter, prospective, randomized, double-blind, placebo-controlled trial	Spironolactone (25 mg/day)	422	HF symptoms with NYHA class II or III or evidence of diastolic heart failure (grade ≥ II on echocardiography	Exercise capacity, peak VO_2, diastolic function	1 year	No improvement in exercise capacity or quality of life; however, improved myocardial function, reduced LVH, and reduced markers of collagen turnover	[26]
TOPCAT	Multicenter, randomized, double blind, placebo-controlled trial	Spironolactone (15–45 mg/day)	3445	HF with EF > 45%, controlled BP, serum K⁺ < 5.0	CV mortality, aborted cardiac arrest, HF hospitalizations	3.4 years	No reduction in primary end-points but reduction in HF hospitalization	[27]

[a]Abbreviations: HF, heart failure; NYHA, New York Heart Association; EF, ejection fraction; BNP, brain natriuretic peptide; MR antagonist, mineralocorticoid receptor antagonist; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DHF, diastolic heart failure; LVH, left ventricular hypertrophy; BP, blood pressure.

patients receiving and not receiving MR antagonists, respectively (HR 0.97, 95% CI 0.84–1.11, $P = 0.63$).

Kosmala *et al.* ($n = 90$) have shown that spironolactone improved myocardial function and reduced markers of collagen turnover at 6 months, compared to placebo, in patients with metabolic syndrome already receiving ACE inhibitors [25]. The Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) trial ($n = 422$) also demonstrated an improvement in left ventricular diastolic function on echocardiography with spironolactone, but failed to show any significant benefit on exercise capacity or quality of life at 1-year follow-up [26]. TOPCAT (Treatment of Preserved Cardiac function with an Aldosterone antagonisT), the largest trial so far for this indication, randomized 3345 patients with HF-PEF to spironolactone or placebo, and failed to show any significant effect on the primary composite endpoint of cardiovascular mortality, aborted cardiac arrest, and heart failure hospitalization (HR 0.89, 95% CI 0.77–1.04, $P = 0.14$), at 3.3 year follow-up [27] (Table 2). However, there was a significant reduction in HF hospitalization (HR 0.83, 95% CI 0.69–0.99, $P = 0.042$). Moreover, subgroup analyses suggested that spironolactone appeared to have beneficial effects in patients enrolled in the trial, based on high baseline BNP, rather than those included on the basis of a hospitalization for heart failure symptoms. Furthermore, a post-hoc analysis suggested that there might be geographic differences in the outcomes [27]. These hypothesis-generating analyses suggest there may be merit in further investigations in high-risk patients with more stringent diagnostic criteria for HF-PEF.

PAH

Pulmonary hypertension is a condition with raised blood pressure in the pulmonary vasculature leading to strain on the right side of the heart and consequent right heart failure.

Elevated plasma aldosterone levels have been associated with the progression of PAH [28]. MR blockade reduces the proliferation of pulmonary arterial smooth muscle cells [29]. Both spironolactone and eplerenone have been shown to prevent or reverse pulmonary vascular remodeling, and improve cardiopulmonary hemodynamics in murine models of PAH [30].

The data from ARIES (Ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy study) evaluated ambrisentan (an endothelin receptor antagonist) against a placebo. A sub-analysis identified 21 patients (out of the 67 randomized to ambrisentan alone) with a combination of ambrisentan and spironolactone for the treatment of PAH. The results showed that combination treatment resulted in an improvement in World Health Organization (WHO) functional class by ≥ 1 ($P = 0.08$), 6-minute walking distance by 94% ($P = 0.11$), with a drop in BNP levels ($P = 0.08$) [31].

The use of MR antagonists in the treatment of PAH and right heart failure is not licensed currently (except as part of diuretic therapy in patients with right-sided heart failure). There are minimal clinical data at present, but preclinical data appear promising and have led to a number of clinical studies, which will address this indication more definitively (Table 3).

Atrial arrhythmias/fibrillation

There are emerging data, mainly from preclinical studies, on the role of MR antagonists in atrial arrhythmias. MR activation may have direct effects (changes in myocyte electrical properties, abnormal repolarization, ion channel abnormalities, nitric oxide availability, atrial dysfunction, and myocardial fibrosis), and indirect effects mediated by control of hypertension and heart failure and prevention of hypokalemia.

Increased MR expression and associated fibrosis of the left atrial tissue has been reported in human atrial fibrillation (AF) and a cellular model of AF [32,33]. MR activation is a potential substrate for atrial arrhythmias characterized by atrial fibrosis, myocyte hypertrophy, and conduction disturbances [34]. Plasma aldosterone levels are raised in patients with AF [35] and patients with primary aldosteronism have a 12-fold higher risk of developing AF compared with blood pressure-matched controls [36].

Spironolactone has been shown to prevent atrial fibrosis in preclinical studies [36]. Pre-treatment with spironolactone in a ventricular tachy-pacing AF model in dogs reduced the amount of atrial fibrosis and inducibility of AF [37]. Spironolactone also prevented AF-related changes in atrial structure and function *in vivo* in a canine model of persistent AF; reduced apoptotic cell death, myolysis, and mitochondrial swelling; and maintained left atrial ejection fraction [38]. Eplerenone has also been shown to suppress fibrosis and inducible AF in a canine model [39].

The clinical data also suggest that MR antagonists may have a beneficial effect in patients with AF. A small retrospective study in 83 patients with AF, including 23 who were treated with spironolactone for ≥ 3 months, has shown that the spironolactone group had significantly fewer AF-related hospitalizations or need for electrical cardioversion [40]. MR antagonism has also been shown to improve maintenance of sinus rhythm after radiofrequency catheter ablation in patients with persistent AF. In a study examining 161 patients with persistent AF who underwent ablation, eplerenone was used in 55 patients and not used in the remaining 106 patients [41]. Other conventional pharmacologic agents, including ACE inhibitors or ARBs, were used equally in the two groups. After 24 months of follow-up, the rate of freedom from AF recurrence was significantly greater in the eplerenone group (60%) than in the non-eplerenone group (40%) ($P = 0.011$). In a multivariate cox regression analysis, eplerenone therapy was an independent predictor of maintenance of sinus rhythm [41]. New onset AF was an adjudicated, pre-specified secondary endpoint in the EMPHASIS-HF trial and was significantly reduced by eplerenone [42]. At the mean follow-up of 2 years, new onset AF occurred in 25/911 (2.7%) of the patients in the group randomized to eplerenone, versus 40/883 (4.5%) in the group randomized to placebo (HR 0.58, 95% CI 0.35–0.96, $P = 0.034$). Similar findings were reported in SPIR-AF trial ($n = 164$ patients); at the 12-month follow-up,

Table 3. Summary of ongoing studies investigating MR antagonists for newer indications[a]

Study	NCT	Design	Phase	n	Condition	Study drug (dose)	Eligibility criteria	Primary endpoints	Secondary endpoints	Expected results
Aldosterone Antagonism and Microvascular Function	01697119	Randomized, double blind trial	4	60	Metabolic syndrome	Eplerenone (50 mg/day)	40–65 years, Caucasian with metabolic syndrome	Change in capillary recruitment	Microvascular blood volume in skeletal muscle of the forearm	2015
Comparison of Effects of Eplerenone Versus Spironolactone in Heart Failure Patients With Glucose Intolerance or Type 2 Diabetes (SNOW)	01586442	Randomized double blind trial	3	62	Metabolic syndrome	Eplerenone (25–50 mg/day) vs. Spironolactone (12.5–25 mg/day)	Patients > 18 years with NYHA class II–IV, impaired glucose tolerance or type 2 diabetes, LVEF ≤ 40%, on ACE inhibitor (or ARB) and beta-blockers	HbA_{1c}	Fasting glucose, lipid profile, insulin, cortisol, adiponectin, NT-proBNP levels	2014
Early Mineralocorticoid Receptor Antagonist Treatment to Reduce Myocardial Infarct Size (MINIMISE STEMI)	01882179	Randomized double blind trial	3	150	Myocardial infarction	Potassium Canrenoate, followed by Spironolactone 25–50 mg/day	Patients > 18 years with acute STEMI and K^+ < 5 mmol/l	Myocardial infarct size, as assessed by cardiac MRI	Cardiac biomarkers, TIMI flow, ST resolution, microvascular obstruction	2015
ALdosterone Antagonist Chronic Hemodialysis Interventional Survival Trial (ALCHEMIST)	01848639	Randomized, double blind trial	3	835	Chronic kidney disease	Spironolactone (25 mg/day)	Age > 18 years old, on hemodialysis for at least 6 months for end-stage renal disease regardless of the etiology	Time to onset of the first incident: nonfatal MI or HF hospitalization or nonfatal stroke or cardiovascular death	Cumulate rate of nonfatal MI, hospitalization for heart failure, nonfatal stroke or CV death	2016
Mineralocorticoid Receptor Antagonist in End Stage Renal Disease (MiRE3Da)	01651053	Randomized, double blind trial	2	120	Chronic kidney disease	Spironolactone (50 mg/day)	Age > 18 years, on hemodialysis for 3+ months, and having 3 dialysis sessions per week	Left Ventricular Mass Index as assessed by cardiac MRI	Cardiac function, 24-hour BP, NYHA class, 6-minute walk test, vascular function assessment	2014
MR Antagonist and Kidney Allograft Histology	01510795	Open label, non-randomized study	4	40	Chronic kidney disease	Spironolactone (25-50 mg/day)	Renal transplant, K^+ < 5 mmol/l, eGFR > 30 ml/min and not on ACE inhibitor or ARB	Changes in chronic Banff scores	eGFR, urinary protein/creatinine ratio and urinary albumin/creatinine ratio	Unknown
EPLIBerause In CsA-Treated Recipients (EpleCsAT)	01834768	Open label, single-group assignment study	2	Not stated	Chronic kidney disease	Eplerenone (25 mg/day)	Patient >18 years with a functional kidney allograft, on cyclosporine A, GFR 30–60 ml/min/1.73 m^2	Adverse event requiring discontinuation of eplerenone		2011
Mineralocorticoid Antagonism and Endothelial Dysfunction in Autosomal Dominant Polycystic Kidney Disease (ADPKD)	01853553	Randomized, double blind trial	4	60	Chronic kidney disease	Spironolactone (25 mg/day)	Age 60–79 years, with ADPKD, eGFR ≥ 60 ml/min, BP > 130/80 on ACE inhibitor or ARB, free from anticoagulants and alcohol dependence	Flow-mediated dilation at 6 months	Vascular stiffness, aortic pulse wave velocity, carotid compliance at 6 months	2016
Spironolactone for Pulmonary Arterial Hypertension	01712620	Randomized, double blind trial	1–2	70	PAH	Spironolactone (25 mg/day)	WHO Group 1 PH patients	6-minute walk distance	VO_2 max, right heart function, biomarkers of vascular inflammation	2015
Effects of Spironolactone on Collagen Metabolism	01488571	Randomized, double-blind,	4	50	PAH	Spironolactone (50 mg/day)	WHO Group 1 PH patients	Biomarker level	Adverse events, 6-minute walk test,	2015/16

Table 3 (Continued)

Study	NCT	Design	Phase	n	Condition	Study drug (dose)	Eligibility criteria	Primary endpoints	Secondary endpoints	Expected results
in Patients With Pulmonary Arterial Hypertension		cross-over study							functional class, clinical worsening	
Safety and Efficacy Study of RAYA-6862 in Subjects With Worsening Chronic Heart Failure and Left Ventricular Systolic Dysfunction and Either Type 2 Diabetes Mellitus With or Without Chronic Kidney Disease or Chronic Kidney Disease Alone (ARTS-HF)	01807221	Randomized, double-blind trial	2b	1060	Heart Failure	Finerenone (BAY 94-8862)	Worsening Chronic Heart Failure and Left Ventricular Systolic Dysfunction and Either Type 2 Diabetes Mellitus With or Without Chronic Kidney Disease or Chronic Kidney Disease Alone	KIT-proBNP	Potassium levels, heart rate, BP	2015

*Abbreviations: STEMI, ST segment elevation myocardial infarction; TBR, thrombolysis in myocardial infarction; PFO, primary aldosteronism or coronary intervention; ADPKD, autosomal dominant polycystic kidney disease; PAH, pulmonary arterial hypertension; HF, heart failure; NYHA, New York Heart Association; BP, systolic blood pressure; BNP, brain natriuretic peptide; MR antagonist, mineralocorticoid receptor antagonist; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CHF, chronic heart failure; LVH, left ventricular hypertrophy; BP, blood pressure; MVD, microvascular dysfunction.

spironolactone-treated groups had a significant ($P < 0.001$) reduction in the incidence of AF episodes compared to the comparator non-spironolactone groups [43].

In summary, MR antagonists may have a role in the prevention of atrial arrhythmias, especially AF, and further randomized controlled trials are warranted.

Ventricular arrhythmias and sudden cardiac death

Mineralocorticoids may play a potential role in ventricular arrhythmias and sudden cardiac death (SCD). Overexpression of cardiac MR in murine models has been shown to result in severe ventricular arrhythmias and death [44]. This conditional cardiac-specific MR overexpression resulted in ion channel remodeling and prolonged ventricular repolarization, without systemic aldosterone access. Conversely, MR blockade, in addition to the standard therapy, reduced the incidence of sudden cardiac death in the RALES, EPHESUS, and EMPHASIS-HF trials [8–10]. A recent meta-analysis has shown that MR antagonists reduce the risk of SCD in patients with LVSD [45]. Both spironolactone and eplerenone significantly reduced ventricular premature complexes, ventricular tachycardia, and SCD [45]. Additionally, spironolactone in combination with ACE inhibitors reduced arrhythmias in post-MI patients [46].

In summary, the larger studies of MR antagonists in LVSD have confirmed a reduction in ventricular arrhythmias and SCD; however, the role of MR antagonists in patients with risk of ventricular arrhythmias and SCD without LVSD needs further evaluation in clinical studies.

Reno-vascular and chronic kidney disease

The kidney and renal vasculature are potential targets of aldosterone-mediated pathology. The spontaneously hypertensive stroke-prone rats, characterized by activation of the renin–angiotensin–aldosterone system (RAAS), develop severe hypertension, cerebral hemorrhage, and renal pathology. Spironolactone has been shown to protect against the development of malignant nephrosclerotic and cerebrovascular lesions in this model, independent of its blood pressure lowering effect [47]. MR activation has also been implicated in the cardiac hypertrophy observed in uremic rats, and spironolactone has been shown to attenuate cardiac hypertrophy and prevented oxidative stress in this model [48].

In dialysis patients, the efficacy and safety of MR antagonists have been reported in a few small clinical studies, reviewed elsewhere [49]. DOHAS (Dialysis Outcomes Heart Failure Aldactone Study), a prospective, multicenter, randomized, controlled, open-label trial ($n = 309$), has shown that spironolactone (25 mg/day) may substantially reduce cardiovascular and cerebrovascular morbidity and mortality in patients on hemodialysis [50]. Spironolactone has also been reported to be safe in patients with early stages of chronic kidney disease with a strict monitoring of renal function and electrolytes over the first month of treatment, followed by standard surveillance [51]. However, further large-scale, multicenter, randomized, double-blind, placebo-controlled trials in patients with different stages of renal insufficiency are needed [52]. ALCHEMIST (ALdosterone Antagonist Chronic HEModialysis Interventional Survival

Trial; NCT01848639) and MiREnDa (Mineralocorticoid Receptor Antagonists in End Stage Renal Disease; NCT01691053) are currently ongoing (Table 3) and will provide further data needed before definitive treatment recommendations can be made. The non-steroidal MR antagonist, Finerenone (BAY 94-8862), is also being tested in clinical trials for heart failure patients with chronic kidney disease and in patients with diabetic nephropathy (Table 3).

Other possible cardiovascular indications of MR antagonists

Metabolic syndrome and coronary artery disease

Aldosterone plays a central role in linking obesity, dyslipidemia, insulin resistance, renal dysfunction, hypertension, and other features of metabolic syndrome. Obesity is known to be associated with a reduced level of adiponectin and increases in proinflammatory adipokines. Guo *et al.* have shown that in a diabetic mouse model, MR blockade reduces the expression of proinflammatory and prothrombotic factors in adipose tissue and increases expression of adiponectin in heart and adipose tissue [53]. Armani *et al.* have shown that spironolactone can prevent glucose impairment, body weight gain, and expansion of white fat in high-fat-fed mice [54]. MR blockade may also improve the detrimental endocrine and vascular abnormalities that characterize the metabolic syndrome by increasing pancreatic insulin release, improving utilization of glucose, as well as increasing vasorelaxation of the endothelium [55]. Therefore, it can be hypothesized that MR blockade might reduce the risk of coronary artery disease in patients with a metabolic syndrome. Aldosterone has been shown to accelerate atherosclerosis in preclinical studies and to promote a rupture-prone inflammatory plaque phenotype [56]. Plasma aldosterone is also associated with progression of atherosclerosis in humans [57]. However, there have been concerns that spironolactone may impair glycemic control and endothelial function in patients with type 2 diabetes [53,55,58]. Eplerenone may have no such adverse effects [58] and actually may improve coronary circulatory function (adenosine-stimulated myocardial perfusion reserve) and endothelial function in diabetic patients already receiving ACE- inhibitors [59]. In the ongoing SNOW trail (comparison of Effects of Eplerenone Versus Spironolactone in Heart Failure Patients With Glucose Intolerance or Type 2 Diabetes; NCT01586442), investigators will examine whether the selectivity of eplerenone for the MR will translate into a better glucose and metabolic profile, compared to spironolactone in patients with heart failure, with glucose intolerance, or type 2 diabetes.

Aldosterone has also been linked to the development of prothrombotic conditions. Hypertensive subjects with an increased renin–sodium profile are at increased risk for MI [60]. It is plausible that this deleterious role of the RAAS system is via interaction with the homeostatic balance of prothrombotic and fibrinolytic systems. Brown *et al.* have reported that aldosterone correlates with plasminogen activator inhibitor-1 (PAI-1) levels in patients [61]. MR antagonism can also limit infarct size during AMI, and this potential role is currently being studied in MINIMISE-STEMI, a trial where patients with STEMI receive intravenous potassium canrenoate prior to coronary angioplasty followed by 3 months of oral spironolactone (Table 3).

In summary, there are encouraging early data and further clinical studies are needed to help elucidate the possible role of MR antagonists in primary or secondary prevention of coronary athero-thrombotic disease.

Post-angioplasty remodeling

MR antagonists have a potentially beneficial impact on post-angioplasty constrictive remodeling. Eplerenone has been shown to attenuate constrictive remodeling and in-stent restenosis after coronary artery angioplasty in experimental animals [62]. This benefit seems to be due to reduction in collagen accumulation. Spironolactone has been shown to inhibit neointimal proliferation after balloon-angioplasty in rabbits [63]. However, these results could not be reproduced in a porcine coronary angioplasty model [62] or in a clinical trial [64]. Eplerenone has shown promising results in many preclinical models [62,65,66]. However, the efficacy of eplerenone for this indication has not been tested in a dedicated clinical trial. A post-hoc analysis of the EPHESUS trial studied 1580 EPHESUS patients treated with percutaneous coronary intervention (PCI). Eplerenone administration, compared with placebo, in the PCI-treated EPHESUS cohort did not affect PCI-related clinical outcomes, including recurrence of angina, the occurrence of acute coronary syndromes, or the need for further revascularization [67]. Therefore, use of an MR antagonist cannot be recommended to prevent restenosis in patients undergoing PCI who have no other indication for these drugs. However, further prospective studies to evaluate angiographic outcomes with eplerenone may provide a definitive answer.

Aortic valve disease

In theory, MR activation can promote aortic sclerosis and aortic stenosis, due to its effect on inflammation and fibrosis. Once aortic valve disease has been established, the pressure or volume overload may induce left ventricular dysfunction, which can be potentially prevented or treated with MR antagonists.

A clinical trial randomized 65 patients with asymptomatic moderate to severe aortic stenosis to eplerenone (100 mg) or a placebo, and followed up for an average of 19 months. Cardiac magnetic resonance imaging, echocardiography, and NT-proBNP were performed at baseline and follow-up. Eplerenone did not affect the progression of aortic stenosis (change in aortic valve area -0.11 ± 0.22 vs. -0.18 ± 0.24 cm^2 per year, $P = 0.2$), the development of left ventricular hypertrophy (change in LV mass index -0.3 ± 14.6 vs. $+6.1 \pm 15$ g/m^2 per year, $P = 0.3$), and the onset of systolic (change in LV ejection fraction $+0.0 \pm 5.7\%$ vs. $+0.8 \pm 5.7\%$ per year, $P = 0.9$) or diastolic dysfunction (change in E/E' $+0.49 \pm 0.7$ vs. $+1.32 \pm 2.0$ per year, $P = 0.4$) [68]. However, this study used a small patient group who were asymptomatic, and therefore further studies with a larger cohort of asymptomatic and symptomatic patients randomized to placebo, spironolactone, or eplerenone are needed

before completely ruling out any utility of MR antagonists for this indication.

There is currently no strong clinical evidence for the use of MR antagonists in medical management for aortic regurgitation. Preclinical data have suggested that the RAAS may play a role in mediating LV hypertrophy, and that MR blockade may maintain normal systolic function in aortic regurgitation. Zendaoui *et al.* looked at the effect of spironolactone in adult rats with severe aortic regurgitation compared to non-treated and sham-operated rats over 6 months [69]. Spironolactone decreased myocardial fibrosis with decreased heart weight and LV expression of atrial natriuretic peptide mRNA, resulting in a protective effect against volume-overload cardiomyopathy [69]. However, there has been no clinical study to date to investigate the effect of MR antagonism on the progression of aortic regurgitation or prevention of its consequences on LV function.

In summary, the data for use of MR antagonists for aortic valve disease is sparse and further clinical studies to confirm or refute this potential indication are needed.

Stroke

Cerebrovascular events, alongside other cardiovascular events, are more common in patients with primary aldosteronism, independent of hypertension [36]. Preclinical and clinical evidence suggest that MR activation leads to worse outcome after stroke [70]. Experimental data have shown that MR antagonism reduces the incidence/size of stroke, and improves survival in an experimental model of stroke-prone spontaneously hypertensive rats maintained on a 1% saline and stroke-prone diet [47,71]. It has also been shown that pre-treatment with eplerenone reduces stroke size in a mouse model of middle cerebral artery occlusion [72]. A study by Frieler *et al.* explored the mechanism of action of MR at the cellular level, and demonstrated that MR expressed in myeloid cells (i.e., non-lymphocytic leukocytes) is potentially involved in post stroke outcome, by showing that myeloid-specific MR knockout mice had 65% reduction in infarct volume ($P = 0.005$) after middle cerebral artery occlusion [73]. Clinical studies have shown a strong association of increased level of aldosterone with risk of stroke and death [74]. Further large-scale randomized control trials are required to explore the beneficial effects of MR antagonists in the prevention and treatment of stroke.

Concluding remarks and future perspectives

The beneficial effects of MR antagonism have been robustly demonstrated for patients with hypertension and heart failure due to LVSD. Recently, an MR antagonist was shown to reduce the hospitalization rate in patients with HF-PEF. However, the emerging data suggests that MR antagonists may also have a role in the treatment of other cardiac and vascular conditions including atrial fibrillation, pulmonary hypertension, renal failure, and stroke. The beneficial effects of MR antagonists in these conditions have been shown in pre-clinical or small-scale clinical studies; adequately powered randomized trials are warranted to confirm these findings. It is also prudent to highlight that the non-steroidal MR antagonists currently in development may have less endocrine side effects and hyperkalemia (due to their bio-distribution properties), thereby improving efficacy and reducing side effects. It is, therefore, plausible that the clinical indications for both novel and existing MR antagonists will be extended in the future.

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References

1 Funder, J.W. (2005) Mineralocorticoid receptors: distribution and activation. *Heart Fail. Rev.* 10, 15–22
2 Fuller, P.J. and Young, M.J. (2005) Mechanisms of mineralocorticoid action. *Hypertension* 46, 1227–1235
3 Struthers, A. *et al.* (2005) A comparison of the aldosterone-blocking agents eplerenone and spironolactone. *Clin. Cardiol.* 31, 153–158
4 Iqbal, J. *et al.* (2004) Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure. *Rev. J. Heart Fail.* 16, 143–150
5 Fagart, J. *et al.* (2005) A new mode of mineralocorticoid receptor antagonism by a potent and selective nonsteroidal molecule. *J. Biol. Chem.* 280, 29432–29440
6 Pitt, B. *et al.* (2012) Rationale and design of ARTS: a randomized, double-blind study of BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease. *Eur. J. Heart Fail.* 14, 668–675
7 Martin-Fernandez, B. *et al.* (2014) Beneficial effects of prostacyclin in the cardiac alterations induced by aldosterone in rat heart through mineralocorticoid receptor blockade. *PLoS ONE* 9, e111184 Published online October 29, 2014. http://dx.doi.org/10.1371/journal.pone.0111184
8 Pitt, B. *et al.* (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N. Engl. J. Med.* 341, 709–717
9 Zannad, F. *et al.* (2011) Eplerenone in patients with systolic heart failure and mild symptoms. *N. Engl. J. Med.* 364, 11–21
10 Pitt, B. *et al.* (2003) Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N. Engl. J. Med.* 348, 1309–1321
11 Pitt, B. *et al.* (2013) Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur. Heart J.* 33, 2463–2473
12 Montalescot, G. *et al.* (2013) Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: the Randomized Double-Blind Reminder Study. *Eur. Heart J.* 35, 2295–2302 Published online April 29, 2014. http://dx.doi.org/10.1093/eurheartj/ehu164
13 Bergmann, F. *et al.* (2011) Rationale for an early aldosterone blockade in acute myocardial infarction and design of the ALBATROSS trial. *Ann. Heart J.* 161, 642–648
14 Croom, K.F. and Perry, C.M. (2005) Eplerenone: a review of its use in essential hypertension. *Am. J. Cardiovasc. Drugs* 5, 51–69
15 Chapman, N. *et al.* (2007) Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 49, 839–845
16 Pitt, B. *et al.* (2003) Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. *Circulation* 108, 1831–1838
17 Flack, J.M. *et al.* (2010) Efficacy and tolerability of eplerenone and losartan in hypertensive black and white patients. *J. Am. Coll. Cardiol.* 41, 1349–1355
18 Hallenberg, N.K. *et al.* (2003) Symptoms and the distress they cause: comparison of an aldosterone antagonist and a calcium channel

blocking agent in patients with systolic hypertension. Arch. Internal Med. 165, 1543–1548
19 Brilla, C.G. et al. (1993) Anti-aldosterone treatment and the prevention of myocardial fibrosis in primary and secondary hyperaldosteronism. J. Mol. Cell Cardiol. 25, 563–575
20 Sato, A. et al. (1999) Effects of spironolactone and angiotensin-converting enzyme inhibitor on left ventricular hypertrophy in patients with essential hypertension. Hypertens. Res. 22, 17–22
21 Mancia, G. et al. (2007) 2007 ESH-ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press 16, 135–232
22 Mak, G.J. et al. (2009) Natural history of markers of collagen turnover in patients with early diastolic dysfunction and impact of eplerenone. J. Am. Coll. Cardiol. 54, 1674–1682
23 Deswal, A. et al. (2011) Results of the Randomized Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction Trial (RAAM-PEF). J. Card. Fail. 17, 634–642
24 Patel, K. et al. (2013) Aldosterone antagonists and outcomes in real-world older patients with heart failure and preserved ejection fraction. JACC Heart Fail. 1, 40–47
25 Kosmala, W. et al. (2011) A randomized study of the beneficial effects of aldosterone antagonism on LV function, structure, and fibrosis markers in metabolic syndrome. JACC Cardiovasc. Imaging 4, 1239–1249
26 Edelmann, F. et al. (2010) Rationale and design of the 'aldosterone receptor blockade in diastolic heart failure' trial: a double-blind, randomized, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in patients with symptomatic diastolic heart failure (Aldo-DHF). Eur. J. Heart Fail. 12, 874–882
27 Pitt, B. et al. (2014) Spironolactone for heart failure with preserved ejection fraction. N. Engl. J. Med. 370, 1383–1392
28 Martyniuk, T.V. et al. (1998) [Activity of renin-angiotensin-aldosterone system (RAAS) and vasopressin level in patients with primary pulmonary hypertension]. Ter. Arkh. 70, 33–38
29 Yamanaka, R. et al. (2010) Involvement of the bone morphogenetic protein system in endothelin- and aldosterone-induced cell proliferation of pulmonary arterial smooth muscle cells isolated from human patients with pulmonary arterial hypertension. Hypertens. Res. 33, 435–445
30 Maron, B.A. et al. (2012) Aldosterone inactivates the endothelin-B receptor via a cysteinyl thiol redox switch to decrease pulmonary endothelial nitric oxide levels and modulate pulmonary arterial hypertension. Circulation 126, 963–974
31 Maron, B.A. et al. (2013) Effectiveness of spironolactone plus ambrisentan for treatment of pulmonary arterial hypertension (from the [ARIES] study 1 and 2 trials). Am. J. Cardiol. 112, 720–725
32 Pei, H.A. et al. (2007) [Study on expression of mineralocorticoid receptor in human atria during atrial fibrillation]. Zhonghua Xin Xue Guan Bing Za Zhi 35, 114–116
33 Lavall, D. et al. (2014) The mineralocorticoid receptor promotes fibrotic remodeling in atrial fibrillation. J. Biol. Chem. 289, 6656–6668
34 Reil, J.C. et al. (2012) Aldosterone promotes atrial fibrillation. Eur. Heart J. 33, 2098–2108
35 Goette, A. et al. (2001) Effect of successful electrical cardioversion on serum aldosterone in patients with persistent atrial fibrillation. Am. J. Cardiol. 88, 906–909 A8
36 Milliez, P. et al. (2005) Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J. Am. Coll. Cardiol. 45, 1243–1248
37 Yang, S.S. et al. (2008) Effects of spironolactone on electrical and structural remodeling of atrium in congestive heart failure dogs. Chinese Med. J. 121, 38–42
38 Zhao, J. et al. (2010) Effects of spironolactone on atrial structural remodelling in a canine model of atrial fibrillation produced by prolonged atrial pacing. Br. J. Pharmacol. 159, 1584–1594
39 Shroff, S.C. et al. (2006) Selective aldosterone blockade suppresses atrial tachyarrhythmias in heart failure. J. Cardiovasc. Electrophysiol. 17, 534–541
40 Williams, R.S. et al. (2011) Effect of spironolactone on patients with atrial fibrillation and structural heart disease. Clin. Cardiol. 34, 415–419
41 Ito, Y. et al. (2013) Effect of eplerenone on maintenance of sinus rhythm after catheter ablation in patients with long-standing persistent atrial fibrillation. Am. J. Cardiol. 111, 1012–1018
42 Swedberg, K. et al. (2012) Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) study. J. Am. Coll. Cardiol. 59, 1598–1603
43 Dabrowski, R. et al. (2010) Effect of combined spironolactone-beta-blocker +/− enalapril treatment on occurrence of symptomatic atrial fibrillation episodes in patients with a history of paroxysmal atrial fibrillation (SPIR-AF study). Am. J. Cardiol. 106, 1609–1614
44 Ouvrard-Pascaud, A. et al. (2005) Conditional mineralocorticoid receptor expression in the heart leads to life-threatening arrhythmias. Circulation 111, 3025–3033
45 Wei, J. et al. (2010) The effect of aldosterone antagonists for ventricular arrhythmia: a meta-analysis. Clin. Cardiol. 33, 572–577
46 Beck, L. et al. (2001) Effects of spironolactone and fosinopril on the spontaneous and chronic ventricular arrhythmias in a rat model of myocardial infarction. Cardiology 96, 85–90
47 Rocha, R. et al. (1998) Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rats. Hypertension 31, 451–458
48 Michea, L. et al. (2008) Mineralocorticoid receptor antagonism attenuates cardiac hypertrophy and prevents oxidative stress in uremic rats. Hypertension 52, 295–300
49 Chua, D. et al. (2010) Spironolactone use in heart failure patients with end-stage renal disease on hemodialysis: is it safe? Clin. Cardiol. 33, 604–608
50 Matsumoto, Y. et al. (2014) Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. J. Am. Coll. Cardiol. 63, 528–536
51 Edwards, N.C. et al. (2012) The safety and tolerability of spironolactone in patients with mild to moderate chronic kidney disease. Br. J. Clin. Pharmacol. 73, 447–454
52 Pitt, B. and Rossignol, P. (2014) Mineralocorticoid receptor antagonists in patients with end-stage renal disease on chronic hemodialysis. J. Am. Coll. Cardiol. 63, 537–538
53 Guo, C. et al. (2008) Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. Circulation 117, 2253–2261
54 Armani, A. et al. (2014) Mineralocorticoid receptor antagonism induces browning of white adipose tissue through impairment of autophagy and prevents adipocyte dysfunction in high-fat-diet-fed mice. FASEB J. 28, 3745–3757
55 Briet, P. et al. (2011) Role of the renin-angiotensin system and aldosterone on cardiometabolic syndrome. Int. J. Hypertens. 2011, 685238 Published online June 23, 2011. http://dx.doi.org/10.4061/2011/685238
56 McGraw, A.P. et al. (2013) Aldosterone increases early atherosclerosis and promotes plaque inflammation through a placental growth factor-dependent mechanism. J. Am. Heart Assoc. 2, e000018 Published online February 22, 2013. http://dx.doi.org/10.1161/JAHA.112.000018
57 de Rita, O. et al. (2012) Effects of aldosterone on human atherosclerosis: plasma aldosterone and progression of carotid plaque. Can. J. Cardiol. 28, 706–711
58 Yamaji, M. et al. (2010) Effect of eplerenone versus spironolactone on cortisol and hemoglobin A1(c) levels in patients with chronic heart failure. Am. Heart J. 160, 915–921
59 Joffe, H.V. et al. (2007) Beneficial effects of eplerenone versus hydrochlorothiazide on coronary circulatory function in patients with diabetes mellitus. J. Clin. Endocrinol. Metab. 92, 2552–2558
60 Alderman, M.H. et al. (1991) Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. N. Engl. J. Med. 324, 1098–1104
61 Brown, N.J. et al. (1998) Effect of activation and inhibition of the renin-angiotensin system on plasma PAI-1. Hypertension 32, 965–971
62 Ward, M.R. et al. (2001) Eplerenone suppresses constrictive remodeling and collagen accumulation after angioplasty in porcine coronary arteries. Circulation 104, 467–472
63 Van Belle, E. et al. (1995) Neointimal thickening after balloon denudation is enhanced by aldosterone and inhibited by

spironolactone, and aldosterone antagonists. Cardiovasc. Res. 29, 27–32
64 [illegible], H. et al. (2004) Spironolactone does not prevent restenosis after coronary stenting in humans. Ann. Acad. Med. Singapore 33, 769–774
65 Wakabayashi, K. et al. (2006) Eplerenone suppresses neointimal formation after coronary stent implantation in swine. Int. J. Cardiol. 107, 260–266
66 Iqbal, J. et al. (2012) Contribution of endogenous glucocorticoids and their intravascular metabolism by 11beta-HSDs to postangioplasty neointimal proliferation in mice. Endocrinology 153, 5896–5905
67 Iqbal, J. et al. (2014) Effect of eplerenone in percutaneous coronary intervention-treated post-myocardial infarction patients with left ventricular systolic dysfunction: a subanalysis of the EPHESUS trial. Eur. J. Heart Fail. 16, 685–691
68 Stewart, R.A. et al. (2008) A randomized trial of the aldosterone-receptor antagonist eplerenone in asymptomatic moderate-severe aortic stenosis. Am. Heart J. 156, 348–355
69 Zendaoui, A. et al. (2012) Effects of spironolactone treatment on an experimental model of chronic aortic valve regurgitation. J. Heart Valve Disease 21, 478–486
70 Menard, J. (2004) The 45-year story of the development of an anti-aldosterone more specific than spironolactone. Mol. Cell. Endocrinol. 217, 45–52
71 Dorrance, A.M. et al. (2001) Spironolactone reduces cerebral infarct size and EGF-receptor mRNA in stroke-prone rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 281, R944–R950
72 Iwanami, J. et al. (2007) Pretreatment with eplerenone reduces stroke volume in mouse middle cerebral artery occlusion model. Eur. J. Pharmacol. 566, 153–159
73 Frieler, R.A. et al. (2011) Myeloid-specific deletion of the mineralocorticoid receptor reduces infarct volume and alters inflammation during cerebral ischemia. Stroke 42, 179–185
74 Tomaschitz, A. et al. (2010) Plasma aldosterone levels are associated with increased cardiovascular mortality: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Eur. Heart J. 31, 1237–1247

(C). Three research papers (14-16) on Infarct Size and endothelial function

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2. **Parviz, Y.,** Waleed, M., Vijayan, S., Adlam, D., Lavi, S., Nooryani, A., Iqbal, J., and Stone, Gregg. (2018). Cellular and Molecular Approaches to Enhance Myocardial Recovery After Myocardial Infarction. Cardiovascular Revascularization Medicine. 20(4):351-364. (doi: 10.1016/j.carrev.2018.05.021. Epub , (**Impact Factor: 1.168 and 32 citation).**

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A review of strategies for infarct size reduction during acute myocardial infarction☆

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ABSTRACT

Advances in medical and interventional therapy over the last few decades have revolutionized the treatment of acute myocardial infarction. Despite the ability to restore epicardial coronary artery patency promptly through percutaneous coronary intervention, tissue level damage may continue. The reported 30-day mortality after all acute coronary syndromes is 2 to 3%, and around 5% following myocardial infarction. Post-infarct complications such as heart failure continue to be a major contributor to cardiovascular morbidity and mortality. Inadequate microvascular reperfusion leads to worse clinical outcomes and potentially strategies to reduce infarct size during periods of ischemia–reperfusion can improve outcomes. Many strategies have been tested, but no single strategy alone has shown a consistent result or benefit in large scale randomised clinical trials. Herein, we review the historical efforts, current strategies, and potential novel concepts that may improve myocardial protection and reduce infarct size.

1. Introduction

Risk factor modification, in combination with prompt revascularization and optimal medical therapy, has led to a reduction in the morbidity and mortality associated with myocardial infarction (MI) [1]. However, one-month mortality following an infarct is still in the order of 2.5 to 5% and post-infarct conditions (e.g. myocardial dysfunction and heart failure) continue to be major contributors of morbidity and mortality and impact on health care economics worldwide [1,2]. Irrespective of strategies aimed at prompt revascularization of occluded epicardial arteries in the catheterization laboratory, thrombosis, embolization and release of harmful substances to the myocardium persist in the peri-infarct period. The associated reperfusion injury can result in further harm and adversely affect the long-term prognosis after MI by increasing the infarct size [1,2].

The microvascular status remains a strong prognostic marker [3]. Infarct size correlates with left ventricular (LV) systolic dysfunction, presence of arrhythmias, morbidity, and mortality following an acute MI [4]. The importance of infarct size and increase in LV volumes has been shown in acute ST-elevation MI (STEMI) treated with reperfusion therapy [4]. Various strategies can be used to measure the infarct size such as bio-markers, technetium-99 m sestamibi single-photon emission computed tomography (SPECT) myocardial perfusion imaging, and cardiac magnetic resonance imaging (CMR) [5]. Strategies to reduce infarct size during periods of ischemia–reperfusion can lead to improved LV function [6,7].

Herein, we review the currently available therapies for myocardial protection (i.e., for the prevention of injury associated with an acute MI and reperfusion), while highlighting novel and cost-effective strategies to reduce infarct size.

2. Pathogenesis

2.1. Ischemic cascade

The myocardial territory supplied by the infarct-related artery (IRA) undergoes biochemical changes at the cellular level. Myocardial cells enter a state of ischaemia, switching the metabolism to anaerobic form, which leads to accumulation of lactate, cellular acidosis, increased intracellular calcium, and production of reactive oxygen species (ROS), all contributing to apoptosis.

2.2. Microvascular obstruction

Microvascular obstruction (MVO) is the inability of a previously ischemic myocardium to be reperfused despite having achieved patency of the epicardial vessel supplying the region of myocardium [8].

The incidence of MVO can be as high as 67% in patients presenting with STEMI and treated with primary percutaneous coronary intervention (PPCI), despite achieving thrombolysis in myocardial

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infarction grade 3 (TIMI 3) flow in the epicardial coronary artery [9]. MVO is associated with major adverse cardiac events (MACE) rates of 30% at 1 month and 60% at 12 months [10–12]. MVO results from a combination of an inflammatory state, endothelial dysfunction, apoptotic cell death, and associated vasoconstriction in the myocardial bed [13,14].

2.3. Reperfusion injury

Reperfusion injury may occur during the restoration of flow in occluded coronary arteries. This injury is thought to be due to free radicals, calcium build-up, acidosis, inflammation and accumulation of neutrophils. All these changes lead to the opening of the mitochondrial permeability transition pore (MPTP) and cell death.

The reperfusion era has seen great strides in the therapeutic strategies leading to improved survival of patients presenting with an acute MI [10,11] and there are continued efforts to reduce the reperfusion-associated injury.

2.4. No-reflow phenomenon

No-reflow phenomenon is defined as inadequate myocardial perfusion through a given segment of the coronary circulation without angiographic evidence of mechanical vessel obstruction [15]. No-reflow is possibly due to MVO alongside other mechanisms such as myocardial stunning, ischaemia–reperfusion injury, autonomic dysfunction and microvascular constriction, free radical-induced myocardial injury as well as neutrophil and platelet micro-aggregates causing luminal obstruction of the microvasculature [16]. No-reflow phenomenon has been linked to larger infarct size and poorer outcomes [17].

3. Assessing infarct size

An electrocardiogram is the earliest and perhaps the easiest way to gain information regarding infarct size. Infarct size can be estimated from the extent of ST-segments deviations (elevation and depression) as well from the number of leads affected. ECG can be used to assess the efficacy of various reperfusion therapies. However, this is imprecise and has been shown not to correlate well with imaging studies [18,19]. Attempts at quantifying final infarct size by using formulae to calculate the myocardium at risk, such as Aldrich score was employed in the thrombolytic era [20]. Infarct size can be measured using biomarkers or imaging. Peak levels of creatine kinase isoenzyme MB (CK-MB) and troponin have been studied [21–25]. Although biomarkers are useful in giving a rough estimate of the infarct size, their use is limited because of reperfusion affecting the enzyme kinetics and difficulty in determining peak values [5]. There is a significant correlation between individual time-point, peak, and area-under time-concentration curve (AUC) of these biomarkers determined infarct size in comparison with SPECT. The AUC and peak levels of troponin I at 72 h have strong predictive correlation as compared to troponin T [26]. It is important to note that it is less practical to generate AUC curves from troponins, as opposed to CK, as they are elevated for a longer time and hence a peak value of a troponin measured at a specific time can be a more useful in in daily practice [27]. A single point measurement can be as useful in infarct size estimation as compared to a measurement derived from the area under the curve.

Imaging modalities such as Tc99 Sestamibi SPECT imaging and CMR have been widely studied [28–30]. SPECT Sestamibi imaging has been used as endpoints in several randomized trials [31,32]. It is good at detecting transmural infarcts. However, CMR with superior spatial resolution has improved ability to detect smaller, sub-endocardial infarcts and has emerged as the gold standard in assessing infarct size [33,34]. CMR is also able to evaluate other useful parameters such as microvascular obstruction (MVO), salvaged myocardium, and myocardium at risk and predict ventricular dysfunction [35,36]. In addition CMR indices have been shown to provide independent prognostic information [37]. Echocardiographic assessment of global and regional left ventricular function can be used but these are indirect measurements and influenced by variety of factors [38]. Advanced echocardiographic techniques such as global longitudinal strain by 2D speckle tracking and wall motion score index have been studied and shown to correlate with infarct size of CMR [39,40]. These techniques may prove to be quick and easy methods to assess infarct size and predict prognosis at the bedside. The various methods commonly employed to assess infarct size has been summarized in Table 1.

The index of microcirculatory resistance (IMR) was developed as an invasive measure of microvascular status, utilizing a pressure and temperature sensitive guidewire [41,42]. In a recently published trial involving 283 STEMI patients, IMR greater than 40 was associated with larger infarct size on CMR [43]. This may be a useful tool to risk stratify patients in the cardiac catheterization laboratory.

4. Therapies for infarct size reduction

There are various potential strategies for infarct size reduction [Figure 1]. Efforts to minimize the myocardial damage can be started even before the patients' presentation to hospital, and various mechanical and pharmacological agents can be tried during the hospital stay and continued even after discharge to have best clinical outcomes. These efforts for emerging therapies are ongoing, and large-scale randomized clinical trials are needed to investigate the clinical applicability of various strategies.

4.1. Mechanical interventions

4.1.1. Primary angioplasty and timing of stenting

Primary percutaneous coronary intervention (PPCI) is the current gold standard worldwide for the treatment for STEMI, with strong evidence supporting the benefits of PPCI over thrombolysis [44]. When compared to fibrinolysis, PPCI leads to better ST segment elevation resolution, arterial patency, and reduced infarct size [45]. However, PCI of an athero-thrombotic lesion during STEMI, can lead to distal embolization of debris, further augmenting MVO, infarct size, and other harmful sequelae [46]. Therefore, various interventions can be used in an attempt to reduce this risk.

In order to minimize the damage associated with stenting, a strategy of delaying the stenting tested. There were initial results from a small study showing benefit in a delayed stenting strategy in patients with the patent infarct related artery [47]. This was followed by the larger randomized DEFER-STEMI study (Randomized Trial of Deferred Stenting Versus Immediate Stenting to Prevent No- or Slow-Reflow in Acute ST-Segment Elevation Myocardial Infarction), which also supported a strategy of deferred stenting with lesser no-reflow/slow flow, fewer thrombotic events and increased myocardial salvage [48]. However, the Danish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: DEFER and the Mechanical Intervention Approach in Acute ST-Segment-Elevation Myocardial Infarction: The MIMI Study failed to show the benefit of such strategy [49,50]. The Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3–DEFER) study was a large open-label randomized controlled trial that randomized patients to immediate and delayed stenting strategies. This study also failed to show any difference in the occurrence of death, heart failure, myocardial infarction, or repeat revascularization [51].

More recently, the INNOVATION Study (Impact of Immediate Stent Implantation Versus Deferred Stent Implantation on Infarct Size and Microvascular Perfusion in Patients With ST-Segment–Elevation Myocardial Infarction) randomized 114 patients to immediate stenting or deferred stenting. The overall infarct size and MVO were not significantly different between the groups [52]. However, in anterior wall MI,

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deferred stenting strategy seemed to have beneficial effects on infarct size and MVO.

MVO assessed by CMR after MI has been shown to be related to ischaemic time (time between symptom onset and successful restoration of blood flow) as opposed to the mode of reperfusion therapy, highlighting the importance of early reperfusion in reducing MVO [53].

There is convincing evidence that early revascularization with primary PCI helps in infarct size reduction. A strategy of deferred stenting cannot be recommended at this stage.

4.1.2. Distal protection devices

Embolic protection devices (EPD) are intended to capture and remove debris generated during the various interventional procedures, with the ultimate aim of reducing myocardial damage. Various EPDs have been used in an attempt to reduce adverse distal embolization [54–61]. In contrast to their benefit in vein graft interventions, the evidence regarding the utility of these devices in preserving myocardium viability during STEMI has been disappointing [Table 2].

4.1.3. Thrombectomy

Thrombectomy during acute MI has shown conflicting results. There is some evidence that manual thrombectomy can reduce infarct size and preserve microvascular integrity as assessed by CMR [62]. On the other hand, a meta-analysis suggested that it may be associated with harm [63]. The Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction (INFUSE-AMI) trial showed no benefit in infarct size reduction [64]. Initially, there was much enthusiasm with the publication of the TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) trial that showed benefits of using routine thrombus aspiration, not only in improving reperfusion as assessed by TIMI blush grade, but also in reducing mortality [65,66]. It led to changes in guideline recommendation in favor of mechanical thrombectomy. Later, the larger TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) trial showed no improvement in both 30-day and 1-year mortality with routine aspiration thrombectomy [67]. Finally, TOTAL (Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI) trial proved that routine manual thrombectomy in STEMI patients did not improve clinical outcomes [68]. A sub-study of TOTAL demonstrated that routine thrombectomy during PPCI has no beneficial impact on myocardial blush grade or post-PCI TIMI flow grade. There was reduced distal embolization associated with thrombectomy group in comparison to PCI alone group [69].

TAPAS trial was a relatively small single centre trial with the very high use of GP2b3a inhibitors. It was underpowered to detect differences in the secondary endpoints. Some of the differences between the three trials are summarized in Table 3.

The contradictory findings between TAPAS and the other two trials may be due to some of the differences such as the use of GP2b3a inhibitors, direct stenting and use of balloon predilatation. TASTE and TOTAL trials were conducted in different eras with significant differences in anti-thrombotic pharmacotherapies, increased use of radial access for PCI and improved stent technology. Ultimately, the discrepancy between the trials underscore the importance of performing clinical trials with sufficient power, once smaller trials suggest an effect of intervention or medication.

Recently, a meta-analysis using individual patient level data from TAPAS, TASTE and TOTAL trials, concluded that routine thrombus aspiration did not improve clinical outcomes [70]. However, in those patients with highest thrombus burden, thrombus aspiration was associated with reduced cardiovascular death at the expense of higher risk of stroke or transient ischaemic attack (TIA).

There are clear limitations to the current technology available in aspiration thrombectomy, such as iatrogenic thrombus embolization during the crossing of the lesion with a guide wire, difficulty in treating large organized thrombi, potential displacement of thrombi into other vessels and systemic circulation during removal of the aspiration catheter. It is possible that as technology improves, especially if the risk of stroke is mitigated, mechanical thrombectomy may prove a useful strategy in infarct size reduction.

The use of mechanical and aspiration thrombectomy has limited impact on infarct size reduction and is not recommended for routine use.

4.1.4. M guard stents

Polyethylene terephthalate micronet mesh-covered stent (M guard, Inspire-MD, Israel) was designed to prevent distal embolization by facilitating the capture of thrombus behind the mesh covering the stent. M guard has shown superior rates of epicardial coronary flow and complete ST-segment resolution in comparison to bare metal stent [71].

However, one trial revealed higher target lesion revascularization (TLR) rates associated with M guard stents, raising questions about their long-term safety profile [72]. Nonetheless, there is compelling evidence from clinical trials as well as registries showing improved outcomes in acute MI patients treated with this stent [73].

Table 1
Methods to assess infarct size. ECG– electrocardiogram, SPECT– single photon emission computed tomography.

Method	Advantage	Disadvantage
ECG	Easily available. Available in an emergency.	It provides an indirect measure of infarct size that can be quantitative by utilization of various scores.
Biomarkers	Easily available. Available in an emergency	Need for repeated sampling for peak levels, affected by reperfusion. True troponin AUC is not a practical approach.
Echocardiographic techniques	Easily available. Available in emergency	Operator dependent; not widely used outside the research setting
Tc-99 Sestamibi SPECT imaging	Can assess full thickness infarcts. Not available in an emergency	The low spatial resolution, hence misses sub-endocardial infarcts; need for radioactive tracer with limited shelf life and use of ionizing radiation.
Cardiac MRI	Current gold standard; high spatial resolution; can detect sub-endocardial infarcts better. not available in an emergency	Not widely available, cannot be used in patients with metal implants or those who have claustrophobia. Not available in the emergency setting.
Index of micro-circulatory resistance (IMR)	The numerical value for myocardial resistance Correlates with infarct size on CMR. Useful for prompt decision-making in the catheterization laboratory.	Invasive technique Requires adenosine to induce hyperaemia.

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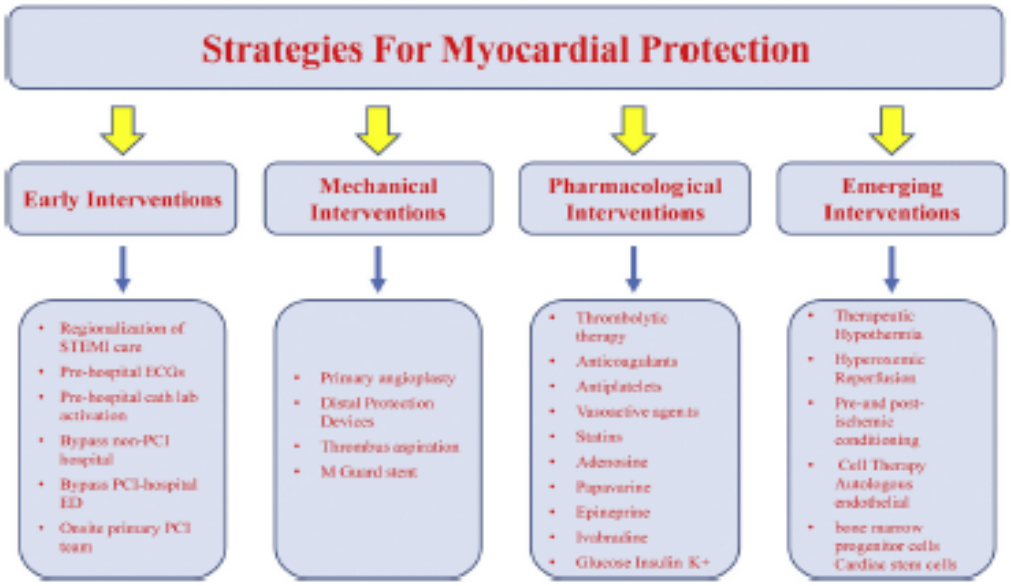

Fig. 1. Various potential strategies for infarct size reduction.

Further trials are needed to test the concept of covered stent platforms in STEMI.

4.2. Pharmacological therapies

4.2.1. Thrombolytic therapy

Although thrombolysis is a well validated and widely used therapy, it restores coronary perfusion in only 60–80% of cases [74,75].

Large-scale clinical trials have demonstrated infarct size reduction and improvement in regional and global LV function in patients where intravenous thrombolytic therapy has been successful [76]. It has been reported that intracoronary thrombolysis with primary PCI leads to improved myocardial perfusion and TIMI blood flow as shown in data from a pilot study [77] and a randomized trial demonstrating that intracoronary streptokinase administration immediately after PCI significantly improves infarct size and left ventricular volumes and function [78].

There is convincing evidence that a timely administration of intravenous thrombolytic therapy can help reduce the infarct size. Further studies are needed to test the effect of intracoronary fibrinolysis.

4.2.2. Anticoagulant therapy antiplatelet therapy

A wide variety of anti-coagulant and antiplatelet agents have been used in the treatment of acute myocardial infarction.

These agents have a potential role in infarct size reduction by having an impact on the no-reflow phenomenon and MVO, associated with embolization of particles during acute MI. There is a combination of fibrin and blood cells in the formation of these thrombi and hence logically we need a combination of antiplatelet and anticoagulants. The thrombi formation is a combination of activation of blood coagulation cascade as well as platelets. These mechanisms are linked to each other in a vicious cycle as, thrombin, is an enzyme generated by blood coagulation that leads to platelet activation.

The thrombo-embolic state during no reflow is composed of platelet aggregates with associated fibrin strands [79–81].

Different antiplatelet agents with their potential role in infarct size reduction are listed in Table 4. A high loading dose (600 mg) of clopidogrel has been shown to be more effective than low dose (300 mg) in reducing the CMR measured infarct size in patients undergoing PPCI for STEMI [82]. In a small study, upstream treatment with clopidogrel compared to those clopidogrel loading after reaching the catheterization laboratory was noted to have reduced MVO

Table 2
Trials of embolic protection devices.

Trial (year)	Number	Device	Findings
EMERALD (2005) [56]	501	Guard wire plus	No reduction in infarct size.
MICADO (2007) [55]	154	Guide wire	Better TIMI perfusion grade
ASPIRAGUS (2007) [56]	341	Guide wire plus	No reduction in infarct size
PRIMEAR (2007) [57]	140	Spider X	No benefit on myocardial perfusion /ejection fraction.
PROMISE (2005) [58]	200	Filter wire-EX	No improvement in perfusion
UPFLOW (2007) [59]	100	Filter wire-EX	No improvement in perfusion
DEDICATION (2008) [60]	626	Filter wire-EZ & Spider X	No improvement in perfusion
PREPARE (2009) [61]	284	Proxis embolic protection system	Rapid ST segment resolution. No difference in myocardial reperfusion.

The data suggest that distal protection devices have no clear beneficial role in infarct size reduction.

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Table 3
Differences between major thrombectomy trials.

Characteristic	TAPAS	TASTE	TOTAL
Number of patients randomized	1071	7244	10,732
Study design	Single-centre RCT	Swedish multicentre RCT	Multi-national multicentre RCT
Direct stenting	62%	15%	17%
GP2b3a use	92%	17%	40%
Primary end point	Post-procedural myocardial blush grade of 0 or 1	All-cause mortality at 30 days	CV death, recurrent MI, cardiogenic shock or NYHA IV heart failure at 180 days
Secondary endpoint	TIMI flow grade of 3, complete resolution of ST-segment elevation, the absence of persistent ST-segment deviation, TVR, reinfarction, death & MACE at 30 days	30-day rate of hospitalization for recurrent MI, stent thrombosis, TVR, TLR, and the composite of all-cause mortality or recurrent MI and during index admission, complications of PCI, stroke, heart failure, and length of stay in the hospital	Stent thrombosis or TVR within 180 days and cardiovascular death within 180, safety outcome of stroke within 30 days
Reperfusion	Improved	Not reported	Improved
Stroke at 30 days	Not reported	No difference	Increased
1-year mortality	Reduced	No difference	No difference
1-year recurrent MI, Stent thrombosis, TVR	No difference	No difference	No difference

RCT – randomized controlled trial, MI – Myocardial infarction, TVR – target vessel revascularisation, TLR – target lesion revascularisation, MACE – major adverse cardiac events, CV – cardiovascular.

although the infarct sizes were not different [83]. The newer generation of antiplatelet agents has shown promising results in clinical studies. The recently published CV-TIME trial randomized 76 STEMI patients to receiving clopidogrel or ticagrelor loading doses prior to Primary PCI. The index of microcirculatory resistance (IMR) measured immediately afterwards, wall motion score index assessed by echocardiography and peak cardiac enzyme (CK) levels were assessed, all of which were in favor of ticagrelor [84]. A post hoc analysis of the Complete Versus Lesion-Only PRImary PCI Trial-CMR (CvLPRIT-CMR) substudy found that newer antiplatelet agents (ticagrelor and prasugrel) were associated with reduced infarct size compared with clopidogrel in patients undergoing primary PCI [85]. Animal studies suggest that the benefit seen with ticagrelor as compared to clopidogrel was dependent on adenosine-receptor activation with downstream upregulation of endothelial nitric oxide synthase and Cyclo-oxygenase-2 activity [86]. Ticagrelor is also thought to have potential protective effects against ischemia–reperfusion injury, which is mediated by adenosine, due to its action on the adenosine transporter type 1 equilibrative nucleoside transporter (ENT1) leading to increased concentration of adenosine, particularly at sites of ischemia and tissue injury [87]. The ability of chronic ticagrelor use in reducing infarct size has been tested in a pre-clinical setting in comparison to clopidogrel [88]. The clinical benefits seen in the PLATO (The multicenter, randomized, placebo-controlled Platelet inhibition and patient Outcomes) trial [89] could potentially be due to cardio protective properties of ticagrelor. Prasugrel has less data supporting its role in infarct size reduction. There is evidence that prasugrel inhibits platelet–leukocyte interactions and may reduce platelet-mediated inflammatory responses [90].

There is conflicting evidence for the potential role of various anticoagulant therapies in infarct size reduction [91–94]. Newer antiplatelet agents, in particular ticagrelor seem to reduce infarct size as compared to clopidogrel.

4.2.3. Vasoactive agents

Vasoactive agents have shown potential in infarct size reduction by having an impact on the acute ischemic injury. These vasoactive agents can decrease the myocardial oxygen demand and increase the oxygen supply, and thereby have an impact on anaerobic metabolism and enhance the supply of nutrient agents at the site of ischemia and reperfusion [95,96].

Nitrates have potential to limit or prevent the vasoconstrictive impacts of various chemicals at the site of inflammation and myocardial injury. The potential antiplatelet effects of nitrates can prevent re-occlusion and re-thrombosis [97].

Calcium channel blockers have vasodilator properties as well as cyto-protective impact by reducing the impact of calcium into the damaged myocardial cells [98].

Beta blockers are thought to reduce the reperfusion associated injury. These agents reduce the myocardial oxygen demand and have a potential beneficial role in the supply–demand imbalance of severe myocardial ischaemia leading to infarction. There is limited evidence for the use of vasodilators such as alpha blockers, beta blockers, calcium channel blockers and nitrates/nitrite donors in reducing the infarct size [Table 4].

4.2.4. Statin therapy

Statin (HMG-CoA reductase inhibitor) therapy has been shown to be cardio-protective by reducing inflammation and atherosclerosis via cholesterol-dependent pathways as well as other pleiotropic effects independent of its cholesterol lowering properties [113]. One of the potential mechanisms is by increasing the NO synthetase and hence potential to reduce atherosclerosis [114]. Statin therapy has shown to inhibit the endothelial exocytosis and hence they have a beneficial effect on protecting the myocardium and reducing the infarct size [115].

The ability to reduce the infarct size and cardio-protection is demonstrated in various animal models as well in clinical settings [116–118]. Statin therapy has acute cardio-protective benefits that are independent of its cholesterol lowering properties. This acute impact may be decreased during chronic use; however chronic statin therapy still plays cardio protective roles by lowering the lipid load. Statins have been reported to exert beneficial effects on the nitric oxide pathway and reduce cardiac cell death in a number of cardiovascular disease states. It has also been suggested that simvastatin reduces no-reflow by activating the mitochondrial K(ATP) channel [119].

There is convincing clinical evidence confirming the cardio protective effect of statin pre-treatment in patients undergoing PCI [120,121].

HMG-CoA reductase inhibitor therapy has shown a reduction in infarct size in preclinical as well as in clinical settings.

4.2.5. Adenosine and A2A receptor agonists

There is conflicting evidence regarding the role of adenosine as a myocardial protection agent during STEMI [122]. Adenosine has been shown to reduce infarct size, if given early (within 120 min) [123],

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Table 4
Anti-thrombotic and vasoactive pharmacological agents tested in myocardial protection in both pre-clinical and clinical studies.

Agents	Preclinical evidence	Clinical evidence	Number of subjects	Findings
Anticoagulants				
UFH	–	HORIZON AMI HORIZON AMI CMRI sub-study	51	No difference in infarct size, MVO, LVEF, or LV volume in comparison to bivalirudin [91] Infarct size reduction when used in addition to bivalirudin [92]
Enoxaparin	Dog model	–	71	Significant reduction in infarct size [93]
Rondaparinux	–	OASIS 5	20,078	Non-inferior to enoxaparin in prevention of cardiac death, and MI [94]
Bivalirudin	–	HORIZON AMI CMRI sub-study	51	No benefit in infarct size reduction as compared to Heparin [91]
Anti-platelet agents				
Aspirin /NCX4016 (NO-aspirin)	Pig model	–	19	NCX4016 (nitro-derivative of aspirin), reduces the extent of myocardial injury following ischaemia and reperfusion Aspirin has no beneficial role in infarct size reduction [99]
Thromboxane synthetase inhibitors, Benzylimidazole and OKY-046	Dog model	–	72	Reduced infarct size [100]
Clopidogrel	–	Observational study	198	High dose (600 mg) reduced myocardial infarct size and improved myocardial salvage compared with a 300-mg loading dose [82]
Ticagrelor	Rat model	–	32	Ticagrelor protects against reperfusion injury [88]
Cangrelor	Monkey model	–	31	Significantly decreased infarct size by an amount equivalent to that seen with ischemic post conditioning [101].
Prasugrel	–	INFUSE AMI	452	Showed better, TIMI 3 flow, lower corrected TIMI frame counts, and lower infarct size [102]
Abciximab	–	Prospective randomized trial	200	Improved recovery of microvascular perfusion and myocardium at risk [103].
		RELAX MI	210	Improved ventricular function recovery [104].
Tirofiban	–	On-TIME2	984	Improved ST-segment resolution and clinical outcomes. [105]
Vaso-active agents				
Alpha blockers				
Urapidil/Phentolamine	–	Multicentre, prospective, non-randomized trial	40	Attenuates vasoconstriction and post ischemic LV dysfunction [106]
Beta blockers				
Metoprolol	–	MITOCARD-CNIC	270	Reduced infarct size and improved left ventricular ejection. [107,108]
	–	COMMIT	45,852	Reduces the risks of reinfarction and ventricular fibrillation [109]
Calcium channel blockers				
Diltiazem (Intracoronary)	Dog model	–	25	Increases the salvage of myocardium [110]
Nitrates/Nitrite/NO donors				
Sodium nitrite	–	NAMI Trial	229	No benefit in infarct size reduction [111]
Tilarginine	–	TRIUMPH	398	No benefit in infarct size reduction [112]

whereas late administration (after 3 h) was not beneficial [124]. AMISTAD and AMISTAD II (A randomized, double-blinded, placebo-controlled multicentre trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction) trials have shown infarct size reduction after administration of adenosine [125]. As an adjunct to PCI, there is some evidence that adenosine given prior to PCI reduces the 'no-reflow' phenomenon [126]. As previously described, ticagrelor has pleotropic effects on adenosine receptors and is thought to exert protective effects independent of the anti-platelet activity.

There is evidence that adenosine and related substances help in reducing the infarct size.

4.2.6. Papaverine

Papaverine is an opiate derivative that vasodilates by direct relaxation of arteriolar smooth muscle and coronary arteriolar bed [127]. Intracoronary administration of papaverine attenuated angiographic no-reflow better than nitro-glycerine [128].

4.2.7. Epinephrine

Intracoronary administration of epinephrine has shown improvement in TIMI flow without serious adverse hemodynamic or chronotropic effects [129].

4.2.8. Ivabradine

Ivabradine acts on the I_f ion current, expressed in the sinoatrial node, and has shown benefit in preclinical and clinical settings. The infarct size reduction is independent of bradycardia, and we need to explore this pleiotropic action in future trials [130].

Papaverine, Epinephrine and Ivabradine has limited evidence in infarct size reduction.

4.2.9. Glucose, insulin, potassium (GIK)

The GIK has no beneficial role in myocardial protection [131]. The OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes-6) trial showed no beneficial impact [132]. The combined OASIS-6 and CREATE-ECLA trial had similar negative results. A meta-

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Table 5
Miscellaneous pharmacological agents used for infarct size reduction.

Agents	Evidence/Mechanisms
AdipoRon [145]	Protection against myocardial injury
Adiponectin [146]	Anti-inflammatory, anti-oxidant and anti-apoptotic
Apr Aliskiren [147]	Increases bradykinin and kallikrein levels
Bradykinin [148]	Inhibits apoptosis
BAY58 (guanylyl cyclase activator) [149]	Protection through post conditioning
Capsaicin [150]	Hypothermia induced protection
CTRP9 [151]	Reduction of adiponectin receptor 1
Cytochrome P450 inhibitors [152]	Role in Myocardial ischemia/reperfusion injury
Dark chocolate receptors [153]	Acts via-opioid receptor to produce cardiac protection
Epicatechin [154]	Improves mitochondrial function
Erythropoietin [155]	Renal nerve-mediated renal protection
Leptin [156]	Anti-inflammatory
Late sodium channel blockade [157]	Evidence in myocardial protection
Protein kinase C [158]	Ischemic post conditioning
Resveratrol [159]	Antioxidant activity and upregulation of NO production
Sildenafil- mediated [160]	Up-regulating VEGF and Ang-1 system
Sevoflurane [27]	Infarct size reduction in cases of anterior MI.
Tadalafil [161]	Attenuates ischemic cardiomyopathy

analysis of 16 randomized trials did not reveal any mortality benefit for STEMI patients [133].

There is no role of GIK infusion in infarct size reduction.

4.2.10. Ischaemic conditioning

Ischaemic conditioning is a fascinating concept where intermittent occlusion of coronary arteries (local ischaemic conditioning) [134–136] or arteries to another part of the body or organ, commonly the upper limbs (remote conditioning) can lead to improved outcomes after myocardial injury. Remote ischaemic conditioning can be performed before an expected ischaemic insult (pre conditioning), during the evolution of an ischaemic insult (per-conditioning) or soon after the completion of an ischaemic insult (post conditioning) [137]. Although experts have proposed various theories, the exact mechanism is not fully known [137]. Remote ischaemic pre-conditioning has been shown to reduce infarct size in small trials [138,139] and larger trials and underway. A more recent meta-analysis also concluded that remote ischaemic pre-conditioning is effective and may reduce long-term clinical events [140]. There is, however, conflicting results from a large trial in patients undergoing CABG, where remote ischaemic pre-conditioning did not improve outcomes [141]. A trial studying post conditioning immediately after stenting during PCI did not show reduction in the incidence of peri-procedural myocardial injury or effect on long term outcome [142,143]. A recent systematic review and meta-analysis looking at a large body of evidence from a variety of clinical settings found that, the evidence does not support a clinically significant effect of ischaemic conditioning on all-cause mortality. Although, there was a suggestion that ischaemic conditioning may reduce myocardial ischaemia, stroke, and acute kidney injury, the authors concluded that the results were uncertain and that ischaemic conditioning cannot be recommended for routine use [144].

Ischaemic conditioning cannot be recommended as a strategy at present and large clinical trials are ongoing.

4.2.11. Miscellaneous agents used for infarct size reduction

A number of less commonly used pharmacotherapies have been tried in pre-clinical and clinical studies for infarct size reduction. They are summarized in Table 5.

4.3. Emerging strategies for infarct size reduction

There are continuous efforts and advances to help reduce the infarct size. Various emerging strategies [Fig. 1] have been evaluated in preclinical as well as in clinical settings with the potential to reduce the infarct size. A large number of these agents are in development and the list of potential strategies is likely to broaden. There are also experimental strategies being evaluated for prevention of adverse LV remodeling such as injectable bio-absorbable cardiac matrix. [162,163]

5. Summary

Numerous cardio-protective strategies have been tried to help reduce the infarct size. Although various agents have shown benefit in small proof of concept studies, identifying a single therapy specifically designed for infarct size reduction in large clinical studies has been unsuccessful so far. Keeping in view the available evidence in this field, clinicians can use their clinical acumen with evidence and can potentially employ a combination of various therapies tailored to individual high-risk patients to reduce the infarct size [164].

Further comparative, large scale, clinical studies and cost–benefit analysis are warranted to evaluate various cardio-protective strategies.

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References

[1] Roe MT, Messenger JC, Weintraub WS, Cannon CP, Fonarow GC, Dai D, et al. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. J Am Coll Cardiol 2010;56:254–63.
[2] Rosamond WD, Chambless LE, Heiss G, Mosley TH, Coresh J, Whitsel E, et al. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987–2008. Circulation 2012;125:1848–57.
[3] Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 1998;97:765–72.
[4] Burns RJ, Gibbons RJ, Yi Q, Roberts RS, Miller TD, Schaer GL, et al. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. J Am Coll Cardiol 2002;39:30–6.
[5] Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. J Am Coll Cardiol 2004;44:1533–42.
[6] Ibanez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. J Am Coll Cardiol 2015;65:1454–71.
[7] Jaffe R, Dick A, Strauss BH. Prevention and treatment of microvascular obstruction-related myocardial injury and coronary no-reflow following percutaneous coronary intervention: a systematic approach. JACC Cardiovasc Interv 2010;3:695–704.
[8] Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. J Am Coll Cardiol 2009;54:281–92.
[9] van't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle myocardial infarction study group. Circulation 1998;97:2302–6.
[10] Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I investigators. Circulation 1995;91:1659–68.
[11] Stone GW, Grines CL, Browne KF, Marco J, Rothbaum D, O'Keefe J, et al. Predictors of in-hospital and 6-month outcome after acute myocardial infarction in the reperfusion era: the primary angioplasty in myocardial infarction (PAMI) trail. J Am Coll Cardiol 1995;25:370–7.
[12] Bolognese L, Carrabba N, Parodi G, Santoro GM, Buonamici P, Cerisano G, et al. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute myocardial infarction. Circulation 2004;109:1121–6.
[13] Saraste A, Pulkki K, Kallajoki M, Henriksen K, Parvinen M, Voipio-Pulkki LM. Apoptosis in human acute myocardial infarction. Circulation 1997;95:320–3.
[14] Maxwell SR, Lip GY. Reperfusion injury: a review of the pathophysiology, clinical manifestations and therapeutic options. Int J Cardiol 1997;58:95–117.
[15] Reffelmann T, Kloner RA. The coronary no-reflow phenomenon: a review of mechanisms and therapies. Eur Heart J 2001;22:729–39.
[16] Bouleti C, Mewton N, Germain S. The no-reflow phenomenon: state of the art. Arch Cardiovasc Dis 2015;23:00180–1.

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[17] Resnic FS, Wainstein M, Lee MKY, Behrendt D, Wainstein RV, Ohno-Machado L, et al. No-reflow is an independent predictor of death and myocardial infarction after percutaneous coronary intervention. Am Heart J 2003;145:42–6.
[18] Christian TF, Clements IP, Behrenbeck T, Huber KC, Chesebro JH, Gersh BJ, et al. Limitations of the electrocardiogram in estimating infarction size after acute reperfusion therapy for myocardial infarction. Ann Intern Med 1991;114:264–70.
[19] Barbagelata A, Di Carli MF, Califf RM, Garg J, Birnbaum Y, Grinfeld L, et al. Electrocardiographic infarct size assessment after thrombolysis: insights from the acute myocardial infarction STudy ADenosine (AMISTAD) trial. Am Heart J 2005;150:659–65.
[20] Aldrich HR, Wagner NB, Boswick J, Corsa AT, Jones MG, Grande P, et al. Use of initial ST-segment deviation for prediction of final electrocardiographic size of acute myocardial infarcts. Am J Cardiol 1988;61:749–53.
[21] Licka M, Zimmermann R, Zehelein J, Dengler TJ, Katus HA, Kübler W. Troponin T concentrations 72 hours after myocardial infarction as a serological estimate of infarct size. Heart 2002;87:520–4.
[22] Arruda-Olson AM, Roger VL, Jaffe AS, Hodge DO, Gibbons RJ, Miller TD. Troponin T levels and infarct size by SPECT myocardial perfusion imaging. JACC Cardiovasc Imaging 2011;4:523–33.
[23] Roberts R, Henry PD, Sobel BE. An improved basis for enzymatic estimation of infarct size. Circulation 1975;52:743–54.
[24] Hackel DB, Reimer KA, Ideker RE, Mikat EM, Hartwell TD, Parker CB, et al. Comparison of enzymatic and anatomic estimates of myocardial infarct size in man. Circulation 1984;70:824–35.
[25] Tanaka H, Abe S, Yamashita T, Arima S, Saigo M, Nakao S, et al. Serum levels of cardiac troponin I and troponin T in estimating myocardial infarct size soon after reperfusion. Coron Artery Dis 1997;8:433–9.
[26] Chia S, Senatore F, Raffel OC, Lee H, Wackers FJ, Jang IK. Utility of cardiac biomarkers in predicting infarct size, left ventricular function, and clinical outcome after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2008;1:415–23.
[27] Luvi S, Bainbridge D, D'Alfonso S, Diamantouros P, Syed J, Jablonsky G, et al. Sevoflurane in acute myocardial infarction: a pilot randomized study. Am Heart J 2014;168:776–83.
[28] Gibbons RJ, Verani MS, Behrenbeck T, Pellikka PA, O'Connor MK, Mahmarian JJ, et al. Feasibility of tomographic 99mTc-hexakis-2-methoxy-2-methylpropyl-isonitrile imaging for the assessment of myocardial area at risk and the effect of treatment in acute myocardial infarction. Circulation 1989;80:1277–86.
[29] Medrano R, Lowry RW, Young JB, Weilbaecher DG, Michael LH, Afridi I, et al. Assessment of myocardial viability with 99mTc sestamibi in patients undergoing cardiac transplantation. A scintigraphic/pathological study. Circulation 1996;94:1010–7.
[30] Hillenbrand HB, Kim RJ, Parker MA, Fieno DS, Judd RM. Early assessment of myocardial salvage by contrast-enhanced magnetic resonance imaging. Circulation 2000;102:1678–83.
[31] Mahaffey KW, Puma JA, Barbagelata NA, DiCarli MF, Leesar MA, Browne KF, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the acute myocardial infarction STudy of ADenosine (AMISTAD) trial. J Am Coll Cardiol 1999;34:1711–20.
[32] Kopecky SL, Aviles RJ, Bell MR, Lobl JK, Tipping D, Frommell G, et al. A randomized, double-blinded, placebo-controlled, dose-ranging study measuring the effect of an adenosine agonist on infarct size reduction in patients undergoing primary percutaneous transluminal coronary angioplasty: the ADMIRE (AmP579 delivery for myocardial infarction REduction) study. Am Heart J 2003;146:146–52.
[33] Kitagawa K, Sakuma H, Hirano T, Okamoto S, Makino K, Takeda K. Acute myocardial infarction: myocardial viability assessment in patients early thereafter comparison of contrast-enhanced MR imaging with resting (201)Tl SPECT. Single photon emission computed tomography. Radiology 2003;226:138–44.
[34] Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. Lancet 2003;361:374–9.
[35] de Waha S, Desch S, Eitel I, Fuernau G, Zachrau J, Leuschner A, et al. Impact of early vs. late microvascular obstruction assessed by magnetic resonance imaging on long-term outcome after ST-elevation myocardial infarction: a comparison with traditional prognostic markers. Eur Heart J 2010;31:2660–8.
[36] Larose E, Rodés-Cabau J, Pibarot P, Rinfret S, Proulx G, Nguyen CM, et al. Predicting late myocardial recovery and outcomes in the early hours of ST-segment elevation myocardial infarction traditional measures compared with microvascular obstruction, salvaged myocardium, and necrosis characteristics by cardiovascular magnetic resonance. J Am Coll Cardiol 2010;55:2459–69.
[37] Eitel I, de Waha S, Wöhrle J, Fuernau G, Lurz P, Pauschinger M, et al. Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. J Am Coll Cardiol 2014;64:1217–26.
[38] Califf RM, Harrelson-Woodlief L, Topol EJ. Left ventricular ejection fraction may not be useful as an end point of thrombolytic therapy comparative trials. Circulation 1990;82:1847–53.
[39] Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K, Hol PK, et al. Strain echocardiography and wall motion score index predicts final infarct size in patients with non–ST-segment–elevation myocardial infarction. Circ Cardiovasc Imaging 2010;3:187–94.
[40] Mistry N, Beitnes JO, Halvorsen S, Abdelnoor M, Hoffmann P, Kjeldsen SE, et al. Assessment of left ventricular function in ST-elevation myocardial infarction by global longitudinal strain: a comparison with ejection fraction, infarct size, and wall motion score index measured by non-invasive imaging modalities. Eur J Echocardiogr 2011;12:678–83.
[41] Aarnoudse W, van den Berg P, van de Vosse F, Geven M, Rutten M, Van Turnhout M, et al. Myocardial resistance assessed by guidewire-based pressure–temperature measurement: in vitro validation. Catheter Cardiovasc Interv 2004;62:56–63.
[42] Fearon WF, Balsam LB, Farouque HM, Caffarelli AD, Robbins RC, Fitzgerald PJ, et al. Novel index for invasively assessing the coronary microcirculation. Circulation 2003;107:3129–32.
[43] Carrick D, Haig C, Ahmed N, Carberry J, Yue May VT, McEntegart M, et al. Comparative prognostic utility of indexes of microvascular function alone or in combination in patients with an acute ST-segment-elevation myocardial infarction. Circulation 2016;134:1833–47.
[44] Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.
[45] Berrocal DH, Cohen MG, Spinetta AD, Ben MG, Rojas Matas CA, Gabay JM, et al. Early reperfusion and late clinical outcomes in patients presenting with acute myocardial infarction randomly assigned to primary percutaneous coronary intervention or streptokinase. Am Heart J 2003;146:E22.
[46] Mauri L, Rogers C, Baim DS. Devices for distal protection during percutaneous coronary revascularization. Circulation 2006;113:2651–6.
[47] Meneveau N, Seronde MF, Descotes-Genon V, Dutheil J, Chopard R, Ecarnot F, et al. Immediate versus delayed angioplasty in infarct-related arteries with TIMI III flow and ST segment recovery: a matched comparison in acute myocardial infarction patients. Clin Res Cardiol 2009;98:257–64.
[48] Carrick D, Oldroyd KG, McEntegart M, Haig C, Petrie MC, Eteiba H, et al. A randomized trial of deferred stenting versus immediate stenting to prevent no- or slow-reflow in acute ST-segment elevation myocardial infarction (DEFER-STEMI). J Am Coll Cardiol 2014;63:2088–98.
[49] Kelbaek H, Høfsten DE, Køber L, Helqvist S, Kløvgaard L, Holmvang L, et al. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial. Lancet 2016;387:2199–206.
[50] Belle L, Motreff P, Mangin L, Rangé G, Marcaggi X, Marie A, et al. Comparison of immediate with delayed stenting using the minimalist immediate mechanical intervention approach in acute ST-segment–elevation myocardial infarction: the MIMI study. Circ Cardiovasc Interv 2016;9:e003388.
[51] Kelbaek H, Høfsten DE, Køber L, Helqvist S, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, De Backer O, Bang LE, Kofoed KF, Lønborg J, Ahtarovski K, Vejlstrup N, Bøtker HE, Terkelsen CJ, Christiansen EH, Ravkilde J, Tilsted H-H, Villadsen AB, Aarøe J, Jensen SE, Raungaard B, Jensen LO, Clemmensen P, Grande P, Madsen JK, Torp-Pedersen C, Engstrøm T, et al. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial. Lancet 2016;387:2199–206.
[52] Kim JS, Lee HJ, Woong Yu C, Kim YM, Hong SJ, Park JH, et al. INNOVATION study (Impact of immediate stent implantation versus deferred stent implantation on infarct size and microvascular perfusion in patients with ST-segment–elevation myocardial infarction). Circ Cardiovasc Interv 2016;9.
[53] Khan JN, Razvi N, Nazir SA, Singh A, Masca NG, Gershlick AH, et al. Prevalence and extent of infarct and microvascular obstruction following different reperfusion therapies in ST-elevation myocardial infarction. J Cardiovasc Magn Reson 2014;16:16–38.
[54] Stone GW, Webb J, Cox DA, Brodie BR, Qureshi M, Kalynych A, et al. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. JAMA 2005;293:1063–72.
[55] Matsuo A, Inoue N, Suzuki K, Nakamura R, Fujita H, Miki S, et al. Limitations of using a GuardWire temporary occlusion and aspiration system in patients with acute myocardial infarction: multicenter investigation of coronary artery protection with a distal occlusion device in acute myocardial infarction (MICADO). J Invasive Cardiol 2007;19:132–8.
[56] Muramatsu T, Kozuma K, Tsukahara R, Ito Y, Fujita N, Suwa S, et al. Comparison of myocardial perfusion by distal protection before and after primary stenting for acute myocardial infarction: angiographic and clinical results of a randomized controlled trial. Catheter Cardiovasc Interv 2007;70:677–82.
[57] Cura FA, Escudero AG, Berrocal D, Mendiz O, Trivi MS, Fernandez J, et al. Protection of distal embolization in high-risk patients with acute ST-segment elevation myocardial infarction (PREMIAR). Am J Cardiol 2007;99:357–63.
[58] Gick M, Jander N, Bestehorn HP, Kienzle RP, Ferenc M, Werner K, et al. Randomized evaluation of the effects of filter-based distal protection on myocardial perfusion and infarct size after primary percutaneous catheter intervention in myocardial infarction with and without ST-segment elevation. Circulation 2005;112:1462–9.
[59] Guetta V, Mosseri M, Shechter M, Matetzky S, Assali A, Almagor Y, et al. Safety and efficacy of the FilterWire EZ in acute ST-segment elevation myocardial infarction. Am J Cardiol 2007;99:911–5.
[60] Kelbaek H, Terkelsen CJ, Helqvist S, Lassen JF, Clemmensen P, Kløvgaard L, et al. Randomized comparison of distal protection versus conventional treatment in primary percutaneous coronary intervention: the drug elution and distal protection in ST-elevation myocardial infarction (DEDICATION) trial. J Am Coll Cardiol 2008;51:899–905.
[61] Haeck JD, Koch KT, Bilodeau L, Van der Schaaf RJ, Henriques JP, Vis MM, et al. Randomized comparison of primary percutaneous coronary intervention with combined proximal embolic protection and thrombus aspiration versus primary percutaneous coronary intervention alone in ST-segment elevation myocardial

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infarction: the PREPARE (PRoximal embolic protection in acute myocardial infarction and resolution of ST-elevation) study. JACC Cardiovasc Interv 2009;2:934–43.
[62] Sardella G, Mancone M, Canali E, Di Roma A, Benedetti G, Stio R, et al. Impact of thrombectomy with EXPort catheter in infarct-related artery during primary percutaneous coronary intervention (EXPIRA trial) on cardiac death. Am J Cardiol 2010;106:624–9.
[63] Tamhane UU, Chetcuti S, Hameed I, Grossman PM, Moscucci M, Gurm HS. Safety and efficacy of thrombectomy in patients undergoing primary percutaneous coronary intervention for acute ST elevation MI: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 2010;10:10.
[64] Brener SJ, Maehara A, Dizon JM, Fahy M, Witzenbichler B, Parise H, et al. Relationship between myocardial reperfusion, infarct size, and mortality: the INFUSE-AMI (intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction) trial. JACC Cardiovasc Interv 2013;6:718–24.
[65] Svilaas T, Vlaar PJ, van der Horst IC, Diercks GF, de Smet BJ, van den Heuvel AF, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008;358:557–67.
[66] Vlaar PJ, Svilaas T, van der Horst IC, Diercks GFH, Fokkema ML, de Smet BJGL, van den Heuvel AFM, Anthonio RL, Jessurun GA, Tan E-S, Suurmeijer AJH, Zijlstra F, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. Lancet 2008;371:1915–20.
[67] Fröbert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med 2013;369:1587–97.
[68] Jolly SS, Cairns JA, Yusuf S, Meeks B, Pogue J, Rokoss MJ, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. N Engl J Med 2015;372:1389–98.
[69] Sharma V, Jolly SS, Hamid T, Sharma D, Chiha J, Chan W, et al. Myocardial blush and microvascular reperfusion following manual thrombectomy during percutaneous coronary intervention for ST elevation myocardial infarction: insights from the TOTAL trial. Eur Heart J 2016;37:1891–8.
[70] Jolly SS, James SK, Dzavik V, Cairns JA, Mahmoud KD, Zijlstra F, et al. Thrombus aspiration in ST elevation myocardial infarction: an individual patient meta-analysis. Circulation 2016;9:025371.
[71] Stone GW, Abizaid A, Silber S, Dizon JM, Merkely B, Costa RA, et al. Prospective, randomized, multicenter evaluation of a polyethylene terephthalate micronet mesh-covered stent (MGuard) in ST-segment elevation myocardial infarction: the MASTER trial. J Am Coll Cardiol 2012;28:04506–8.
[72] Fernandez-Cisnal A, Cid-Alvarez B, Alvarez-Alvarez B, Cubero-Gomez JM, Ocaranza-Sanchez R, Lopez-Otero D, et al. Real world comparison of the MGuard stent versus the bare metal stent for ST elevation myocardial infarction (the REWARD-MI study). Catheter Cardiovasc Interv 2015;85:17.
[73] Dudek D, Brener SJ, Rakowski T, Dziewierz A, Abizaid A, Silber S, et al. Efficacy of an embolic protection stent as a function of delay to reperfusion in ST-segment elevation myocardial infarction (from the MASTER trial). Am J Cardiol 2014;114:1485–9.
[74] Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis in myocardial infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987;76:142–54.
[75] Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;348:771–5.
[76] Morgan CD, Roberts RS, Haq A, Baigrie RS, Daly PA, Gent M, et al. Coronary patency, infarct size and left ventricular function after thrombolytic therapy for acute myocardial infarction: results from the tissue plasminogen activator: Toronto (TPAT) placebo-controlled trial. TPAT study group. J Am Coll Cardiol 1991;17:1451–7.
[77] Sezer M, Oflaz H, Goren T, Okcular I, Umman B, Nisanci Y, et al. Intracoronary streptokinase after primary percutaneous coronary intervention. N Engl J Med 2007;356:1823–34.
[78] Sezer M, Cimen A, Aslanger E, Elitok A, Umman B, Bugra Z, et al. Effect of intracoronary streptokinase administered immediately after primary percutaneous coronary intervention on long-term left ventricular infarct size, volumes, and function. J Am Coll Cardiol 2009;54:1065–71.
[79] Baumgartner HR. The role of blood flow in platelet adhesion, fibrin deposition, and formation of mural thrombi. Microvasc Res 1973;5:167–79.
[80] Badimon L, Badimon JJ. Mechanisms of arterial thrombosis in nonparallel streamlines: platelet thrombi grow on the apex of stenotic severely injured vessel wall. Experimental study in the pig model. J Clin Invest 1989;84:1134–44.
[81] Lassila R, Badimon JJ, Vallabhajosula S, Badimon L. Dynamic monitoring of platelet deposition on severely damaged vessel wall in flowing blood. Effects of different stenoses on thrombus growth. Arteriosclerosis 1990;10:306–15.
[82] Song YB, Hahn JY, Gwon HC, Chang SA, Lee SC, Choe YH, et al. A high loading dose of clopidogrel reduces myocardial infarct size in patients undergoing primary percutaneous coronary intervention: a magnetic resonance imaging study. Am Heart J 2012;163:500–7.
[83] de Waha S, Eitel I, Desch S, Fuernau G, Lurz P, Schuler G, et al. Association of upstream clopidogrel administration and myocardial reperfusion assessed by cardiac magnetic resonance imaging in patients with ST-elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care 2014;3:110–7.
[84] Park SD, Lee MJ, Baek YS, Kwon SW, Shin SH, Woo SI, et al. Randomised trial to compare a protective effect of clopidogrel versus Ticagrelor on coronary microvascular injury in ST-segment elevation myocardial infarction (CV-TIME trial). EuroIntervention 2016;12:e964–71.
[85] Khan JN, Greenwood JP, Nazir SA, Lai FY, Dalby M, Curzen N, et al. Infarct size following treatment with second- versus third-generation P2Y12 antagonists in patients with Multivessel coronary disease at ST-segment elevation myocardial infarction in the CvLPRIT study. J Am Heart Assoc 2016;5:003403.
[86] Nanhwan MK, Ling S, Kodakandla M, Nylander S, Ye Y, Birnbaum Y. Chronic treatment with ticagrelor limits myocardial infarct size: an adenosine and cyclooxygenase-2-dependent effect. Arterioscler Thromb Vasc Biol 2014;34:2078–85.
[87] Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of Ticagrelor: evidence and potential clinical relevance. J Am Coll Cardiol 2014;63:2503–9.
[88] Ye Y, Birnbaum GD, Perez-Polo JR, Nanhwan MK, Nylander S, Birnbaum Y. Ticagrelor protects the heart against reperfusion injury and improves remodeling after myocardial infarction. Arterioscler Thromb Vasc Biol 2015;35:1805–14.
[89] Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet 2010;375:283–93.
[90] Totani L, Dell'Elba G, Martelli N, Di Santo A, Piccoli A, Amore C, et al. Prasugrel inhibits platelet-leukocyte interaction and reduces inflammatory markers in a model of endotoxic shock in the mouse. Thromb Haemost 2012;107:1130–40.
[91] Wöhrle J, Merkle N, Kunze M, Cristea E, Mehran R, Rottbauer W, et al. Effect of bivalirudin compared with unfractionated heparin plus abciximab on infarct size and myocardial recovery after primary percutaneous coronary intervention: the horizons-AMI CMRI substudy. Catheter Cardiovasc Interv 2012;79:1083–9.
[92] Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218–30.
[93] Liberman D, Khalil A, Dagenais P, Quan E, Delorme F, Uzan A, et al. The low molecular weight heparin, enoxaparin, limits infarct size at reperfusion in the dog. Cardiovasc Res 1998;37:656–66.
[94] Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 2006;354:1464–76.
[95] Maroko PR, Kjekshus JK, Sobel BE, Watanabe T, Covell JW, Ross Jr J, et al. Factors influencing infarct size following experimental coronary artery occlusions. Circulation 1971;43:67–82.
[96] Maseri A, L'Abbate A, Chierchia S, Parodi O, Severi S, Biagini A, et al. Significance of spasm in the pathogenesis of ischemic heart disease. Am J Cardiol 1979;44:788–92.
[97] Gavin JB, Maxwell L, Edgar SG. Microvascular involvement in cardiac pathology. J Mol Cell Cardiol 1998;30:2531–40.
[98] Nayler WG, Ferrari R, Williams A. Protective effect of pretreatment with verapamil, nifedipine and propranolol on mitochondrial function in the ischemic and reperfused myocardium. Am J Cardiol 1980;46:242–8.
[99] Wainwright CL, Miller AM, Work LM, Del Soldato P. NCX-4016 (NO-aspirin) reduces infarct size and suppresses arrhythmias following myocardial ischaemia/reperfusion in pigs. Br J Pharmacol 2002;135:1882–8.
[100] Mullane KM, Fornabaio D. Thromboxane synthetase inhibitors reduce infarct size by a platelet-dependent, aspirin-sensitive mechanism. Circ Res 1988;62:668–78.
[101] Yang XM, Liu Y, Cui L, Yang X, Tandon N, Kambayashi J, et al. Two classes of anti-platelet drugs reduce anatomical infarct size in monkey hearts. Cardiovasc Drugs Ther 2013;27:109–15.
[102] Brener SJ, Oldroyd KG, Maehara A, El-Omar M, Witzenbichler B, Xu K, et al. Outcomes in patients with ST-segment elevation acute myocardial infarction treated with clopidogrel versus prasugrel (from the INFUSE-AMI trial). Am J Cardiol 2014;113:1457–60.
[103] Neumann FJ, Blasini R, Schmitt C, Alt E, Dirschinger J, Gawaz M, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation 1998;98:2695–701.
[104] Maioli M, Bellandi F, Leoncini M, Toso A, Dabizzi RP. Randomized early versus late abciximab in acute myocardial infarction treated with primary coronary intervention (RELAx-AMI trial). J Am Coll Cardiol 2007;49:1517–24.
[105] Van't Hof AW, Ten Berg J, Heestermans T, Dill T, Funck RC, van Werkum W, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537–46.
[106] Gregorini L, Marco J, Kozakova M, Palombo C, Anguissola GB, Marco I, et al. Alpha-adrenergic blockade improves recovery of myocardial perfusion and function after coronary stenting in patients with acute myocardial infarction. Circulation 1999;99:482–90.
[107] Mateos A, García-Lunar I, García-Ruiz JM, Pizarro G, Fernández-Jiménez R, Huertas P, et al. Efficacy and safety of out-of-hospital intravenous metoprolol administration in anterior ST-segment elevation acute myocardial infarction: insights from the METOCARD-CNIC trial. Ann Emerg Med 2015;65:318–24.
[108] García-Ruiz JM, Fernández-Jiménez R, García-Alvarez A, Pizarro G, Galán-Arriola C, Fernández-Friera L, et al. Impact of the timing of metoprolol administration during STEMI on infarct size and ventricular function. J Am Coll Cardiol 2016;67:2093–104.
[109] Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1622–32.
[110] Higginson L, Tang A, Knoll G, Calvin J. Effect of intracoronary diltiazem on infarct size and regional myocardial function in the ischemic reperfused canine heart. J Am Coll Cardiol 1991;18:868–75.
[111] Siddiqi N, Neil C, Bruce M, MacLennan G, Cotton S, Papadopoulou S, et al. Intravenous sodium nitrite in acute ST-elevation myocardial infarction: a randomized controlled trial (NIAMI). Eur Heart J 2014;35:1255–62.

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[112] Alexander JH, Reynolds HR, Stebbins AL, Dzavik V, Harrington RA, Van de Werf F, et al. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. JAMA 2007;297:1657–66.
[113] Jones SP, Gibson MF, Rimmer III DM, Gibson TM, Sharp BR, Lefer DJ. Direct vascular and cardioprotective effects of rosuvastatin, a new HMG-CoA reductase inhibitor. J Am Coll Cardiol 2002;40:1172–8.
[114] Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998;97:1129–35.
[115] Yamakuchi M, Greer JJ, Cameron SJ, Matsushita K, Morrell CN, Talbot-Fox K, et al. HMG-CoA reductase inhibitors inhibit endothelial exocytosis and decrease myocardial infarct size. Circ Res 2005;96:1185–92.
[116] Wayman NS, Ellis BL, Thiemermann C. Simvastatin reduces infarct size in a model of acute myocardial ischemia and reperfusion in the rat. Med Sci Monit 2003;9:BR155–9.
[117] Ueda Y, Kitakaze M, Komamura K, Minamino T, Asanuma H, Sato H, et al. Pravastatin restored the infarct size-limiting effect of ischemic preconditioning blunted by hypercholesterolemia in the rabbit model of myocardial infarction. J Am Coll Cardiol 1999;34:2120–5.
[118] Matsuki A, Igawa A, Nozawa T, Nakadate T, Igarashi N, Nonomura M, et al. Early administration of fluvastatin, but not at the onset of ischemia or reperfusion, attenuates myocardial ischemia–reperfusion injury through the nitric oxide pathway rather than its antioxidant property. Circ J 2006;70:1643–9.
[119] Zhao JL, Yang YJ, Cui CJ, You SJ, Gao RL. Pretreatment with simvastatin reduces myocardial no-reflow by opening mitochondrial K(ATP) channel. Br J Pharmacol 2006;149:243–9.
[120] Herrmann J, Lerman A, Baumgart D, Volbracht L, Schulz R, von Birgelen C, et al. Preprocedural statin medication reduces the extent of periprocedural non-Q-wave myocardial infarction. Circulation 2002;106:2180–3.
[121] Briguori C, Colombo A, Airoldi F, Violante A, Focaccio A, Balestrieri P, et al. Statin administration before percutaneous coronary intervention: impact on periprocedural myocardial infarction. Eur Heart J 2004;25:1822–8.
[122] Claeys MJ, Bosmans J, De Ceuninck M, Beunis A, Vergauwen W, Vorlat A, et al. Effect of intracoronary adenosine infusion during coronary intervention on myocardial reperfusion injury in patients with acute myocardial infarction. Am J Cardiol 2004;94:9–13.
[123] Pitarys II CJ, Virmani R, Vildibill Jr HD, Jackson EK, Forman MB. Reduction of myocardial reperfusion injury by intravenous adenosine administered during the early reperfusion period. Circulation 1991;83:237–47.
[124] Babbitt DG, Virmani R, Vildibill Jr HD, Norton ED, Forman MB. Intracoronary adenosine administration during reperfusion following 3 hours of ischemia: effects on infarct size, ventricular function, and regional myocardial blood flow. Am Heart J 1990;120:808–18.
[125] Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW. A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). J Am Coll Cardiol 2005;45:1775–80.
[126] Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. Circulation 2000;101:2154–9.
[127] Wilson RF, White CW. Intracoronary papaverine: an ideal coronary vasodilator for studies of the coronary circulation in conscious humans. Circulation 1986;73:444–51.
[128] Ishihara M, Sato H, Tateishi H, Kawagoe T, Shimatani Y, Kurisu S, et al. Attenuation of the no-reflow phenomenon after coronary angioplasty for acute myocardial infarction with intracoronary papaverine. Am Heart J 1996;132:959–63.
[129] Skelding KA, Goldstein JA, Mehta L, Pica MC, O'Neill WW. Resolution of refractory no-reflow with intracoronary epinephrine. Catheter Cardiovasc Interv 2002;57:305–9.
[130] Heusch G, Skyschally A, Schulz R. Cardioprotection by ivabradine through heart rate reduction and beyond. J Cardiovasc Pharmacol Ther 2011;16:281–4.
[131] Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005;26:650–61.
[132] Diaz R, Goyal A, Mehta SR, Afzal R, Xavier D, Pais P, et al. Glucose–insulin–potassium therapy in patients with ST-segment elevation myocardial infarction. JAMA 2007;298:2399–405.
[133] Mamas MA, Neyses L, Fath-Ordoubadi F. A meta-analysis of glucose–insulin–potassium therapy for treatment of acute myocardial infarction. Exp Clin Cardiol 2010;15:e20–4.
[134] Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986;74:1124–36.
[135] Deutsch E, Berger M, Kussmaul WG, Hirshfeld Jr JW, Herrmann HC, Laskey WK. Adaptation to ischemia during percutaneous transluminal coronary angioplasty. Clinical, hemodynamic, and metabolic features. Circulation 1990;82:2044–51.
[136] Yellon DM, Alkhulaifi AM, Pugsley WB. Preconditioning the human myocardium. Lancet 1993;342:276–7.
[137] Vanezis AP, Rodrigo GC, Squire IB, Samani NJ. Remote ischaemic conditioning and remodelling following myocardial infarction: current evidence and future perspectives. Heart Fail Rev 2016;21:635–43.
[138] Botker HE, Kharbanda R, Schmidt MR, Bottcher M, Kaltoft AK, Terkelsen CJ, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. Lancet 2010;375:727–34.
[139] Rentoukas I, Giannopoulos G, Kaoukis A, Kossyvakis C, Raisakis K, Driva M, et al. Cardioprotective role of remote ischemic periconditioning in primary percutaneous coronary intervention: enhancement by opioid action. JACC Cardiovasc Interv 2010;3:49–55.
[140] Le Page S, Bejan-Angoulvant T, Angoulvant D, Prunier F. Remote ischemic conditioning and cardioprotection: a systematic review and meta-analysis of randomized clinical trials. Basic Res Cardiol 2015;110:015–0467.
[141] Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, et al. Remote ischemic preconditioning and outcomes of cardiac surgery. N Engl J Med 2015;373:1408–17.
[142] Lavi S, D'Alfonso S, Diamantouros P, Camuglia A, Garg P, Teefy P, et al. Remote ischemic postconditioning during percutaneous coronary interventions: remote ischemic postconditioning-percutaneous coronary intervention randomized trial. Circ Cardiovasc Interv 2014;7:225–32.
[143] Lavi S, Abu-Romeh N, Wall S, Alemayehu M, Lavi R. Long-term outcome following remote ischemic postconditioning during percutaneous coronary interventions-the RIP-PCI trial long-term follow-up. Clin Cardiol 2017.
[144] Sukkar L, Hong D, Wong MG, Badve SV, Rogers K, Perkovic V, et al. Effects of ischaemic conditioning on major clinical outcomes in people undergoing invasive procedures: systematic review and meta-analysis. BMJ 2016;355:i5599.
[145] Zhang Y, Zhao J, Li R, Lau WB, Yuan YX, Liang B, et al. AdipoRon, the first orally active adiponectin receptor activator, attenuates postischemic myocardial apoptosis through both AMPK-mediated and AMPK-independent signalings. Am J Physiol Endocrinol Metab 2015;309:2.
[146] Nanayakkara G, Kariharan T, Wang L, Zhong J, Amin R. The cardio-protective signaling and mechanisms of adiponectin. Am J Cardiovasc Dis 2012;2:253–66.
[147] Kold SS, Zogar J, Campbell DJ. Aliskiren reduces myocardial ischemia–reperfusion injury by a bradykinin B2 receptor- and angiotensin AT2 receptor-mediated mechanism. Hypertension 2014;63:768–73.
[148] Sheng Z, Yao Y, Li Y, Yan F, Huang J, Ma G. Bradykinin preconditioning improves therapeutic potential of human endothelial progenitor cells in infarcted myocardium. PLoS One 2013;8.
[149] Methner C, Lukowski R, Grube K, Loga F, Smith RA, Murphy MP, et al. Protection through postconditioning or a mitochondria-targeted S-nitrosothiol is unaffected by cardiomyocyte-selective ablation of protein kinase G. Basic Res Cardiol 2013;108:013–0337.
[150] Dow J, Simkhovich BZ, Hale SL, Kay G, Kloner RA. Capsaicin-induced cardioprotection. Is hypothermia or the salvage kinase pathway involved? Cardiovasc Drugs Ther 2014;28:295–301.
[151] Kambara T, Ohashi K, Shibata R, Ogura Y, Maruyama S, Enomoto T, et al. CTRP9 protein protects against myocardial injury following ischemia–reperfusion through AMP-activated protein kinase (AMPK)-dependent mechanism. J Biol Chem 2012;287:18965–73.
[152] Granville DJ, Tashakkor B, Takeuchi C, Gustafsson AB, Huang C, Sayen MR, et al. Reduction of ischemia and reperfusion-induced myocardial damage by cytochrome P450 inhibitors. Proc Natl Acad Sci U S A 2004;101:1321–6.
[153] Panneerselvam M, Tsutsumi YM, Bonds JA, Horikawa YT, Saldana M, Dalton ND, et al. Dark chocolate receptors: epicatechin-induced cardiac protection is dependent on delta-opioid receptor stimulation. Am J Physiol Heart Circ Physiol 2010;299:10.
[154] Yamazaki KG, Andreyev AY, Ortiz-Vilchis P, Petrosyan S, Divakaruni AS, Wiley SE, et al. Intravenous (−)-epicatechin reduces myocardial ischemic injury by protecting mitochondrial function. Int J Cardiol 2014;175:297–306.
[155] Oba T, Yasukawa H, Nagata T, Kyogoku S, Minami T, Nishihara M, et al. Renal nerve-mediated erythropoietin release confers cardioprotection during remote ischemic preconditioning. Circ J 2015;79:1557–67.
[156] Xu TT, Liu SP, Wang XS. Amelioration of myocardial ischemia/reperfusion injury by leptin pretreatment and ischemic preconditioning in mouse. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2010;22:105–8.
[157] Strasser R, Vogt A, Schaper W. Myocardial protection by preconditioning. Experimental and clinical significance. Z Kardiol 1996;85:79–89.
[158] Zhong GQ, Tu RH, Zeng ZY, Li QJ, He Y, Li S, et al. Novel functional role of heat shock protein 90 in protein kinase C-mediated ischemic postconditioning. J Surg Res 2014;189:198–206.
[159] Shen M, Jia GL, Wang YM, Ma H. Cardioprotective effect of resvaratrol pretreatment on myocardial ischemia–reperfusion induced injury in rats. Vasc Pharmacol 2006;45:122–6.
[160] Koneru S, Varma Penumathsa S, Thirunavukkarasu M, Vidavalur R, Zhan L, Singal PK, et al. Sildenafil-mediated neovascularization and protection against myocardial ischaemia reperfusion injury in rats: role of VEGF/angiopoietin-1. J Cell Mol Med 2008;12:2651–64.
[161] Salloum FN, Chau VQ, Hoke NN, Kukreja RC. Tadalafil prevents acute heart failure with reduced ejection fraction in mice. Cardiovasc Drugs Ther 2014;28:493–500.
[162] Leor J, Tuvia S, Guetta V, Manczur F, Castel D, Willenz U, et al. Intracoronary injection of in situ forming alginate hydrogel reverses left ventricular remodeling after myocardial infarction in swine. J Am Coll Cardiol 2009;54:1014–23.
[163] Rao SV, Zeymer U, Douglas PS, Al-Khalidi H, White JA, Liu J, et al. Bioabsorbable intracoronary matrix for prevention of ventricular remodeling after myocardial infarction. J Am Coll Cardiol 2016;68:715–23.
[164] Zhou SS, Tian F, Chen YD, Wang J, Sun ZJ, Guo J, et al. Combination therapy reduces the incidence of no-reflow after primary per-cutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction. J Geriatr Cardiol 2015;12:135–42.

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Cellular and molecular approaches to enhance myocardial recovery after myocardial infarction

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ABSTRACT

Reperfusion therapy has resulted in significant improvement in post-myocardial infarction morbidity and mortality in over the last 4 decades. Nonetheless, it is well recognized that simply restoring patency of the epicardial artery may not stop or reverse damage at microvascular level, and myocardial salvage is often suboptimal. Numerous efforts have been undertaken to elucidate the mechanisms underlying extensive myonecrosis to facilitate the discovery of therapies to provide additional and incremental benefits over current therapeutic pathways. To date, conclusively effective strategies to promote myocardial recovery have not yet been established. Novel approaches are investigating the foundational cellular and molecular bases of myocardial ischemia and irreversible injury. Herein, we review the emerging concepts and proposed therapies that may improve myocardial protection and reduce infarct size. We examine the preclinical and clinical evidence for reduced infarct size with these strategies, including anti-inflammatory agents, intracellular ion channel modulators, agents affecting the reperfusion injury salvage kinase (RISK) and nitric oxide signaling pathways, modulators of mitochondrial function, anti-apoptotic agents, and stem cell and gene therapy. We review the potential reasons of failures to date and the potential for new strategies to further promote myocardial recovery and improve prognosis.

Contents

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1. Introduction

The success achieved over the last 4 decades in reducing the morbidity and mortality associated with acute myocardial infarction (AMI) has been attributed to a combination of timely reperfusion strategies and adjunctive medical therapies [1]. Although primary percutaneous coronary intervention (PCI) has significantly improved mortality and morbidity in patients with ST-elevation myocardial infarction (STEMI), myocardial dysfunction and heart failure resulting from AMI is still distressingly frequent. Despite timely restoration of epicardial coronary artery patency by PCI, myocardial recovery is often suboptimal resulting in extensive myonecrosis. As such, new approaches are needed to enhance myocardial function after STEMI [2,3]. Effective therapies must be addressed to the underlying mechanisms determining infarct size after early reperfusion, including microvascular dysfunction and release of reactive oxygen species (ROS) and other cellular and humoral mediators.

2. Pathophysiology of post reperfusion myocardial injury

The determinants of myocardial injury post reperfusion in STEMI are incompletely understood, and are likely to be multifactorial. Acute thrombotic occlusion of an epicardial coronary artery leads to myocardial ischaemia which if not reversed quickly results in myonecrosis. Reperfusion using fibrinolytic agents or primary PCI can reestablish blood flow and theoretically halt the wavefront of myonecrosis that spreads from the subendocardium to the subepicardium. However, atherothrombotic material can embolise to the distal microvasculature and cause microvascular obstruction (MVO), impairing myocardial recovery. Restoration of blood flow itself may also directly extend the degree of myonecrosis, a phenomenon termed 'myocardial reperfusion injury'. Reperfusion injury accounts for up to 50% of the final infarct size in animal studies [4]. Reperfusion injury involves a variety of complex cellular and molecular mechanisms including activation of free radicals, intracellular calcium accumulation, acidosis, inflammation and neutrophil infiltration [5,6]. As a consequence of these metabolic alterations, the mitochondrial permeability transition pores (mPTP) opens and the process of apoptosis is initiated [7].

Antioxidants in the human body serve as defence mechanisms to preserve homeostasis [8]. During AMI and after reperfusion these endogenous agents are less effective and there is accumulation of various substances including xanthine oxidase, hypoxanthine and others. Restoration of flow (either spontaneously through endogenous fibrinolysis or through reperfusion therapy) with increased downstream oxygen delivery leads to formation of reactive oxygen species (ROS) [9]. A potentially important target of ROS is the tetrahydrobiopterin–eNOS complex, which may be dissociated by oxidation, resulting in peroxynitrite formation and reduced NO availability [10]. These alternations can potentially damage DNA, proteins, carbohydrates, and lipids.

Although the process of cell death starts from within the cardiac myocyte, the microvasculature, inflammatory cells, and platelets all play a role in promoting (or preventing) cell death [6,11]. The sequence of events and role of MPTP opening during reperfusion injury and its relationship to sarcolemmal rupture, calpain activation, high oscillating Ca^{2+} in the presence of ATP and development of contracture, leading to apoptosis, are not well understood (Fig. 1).

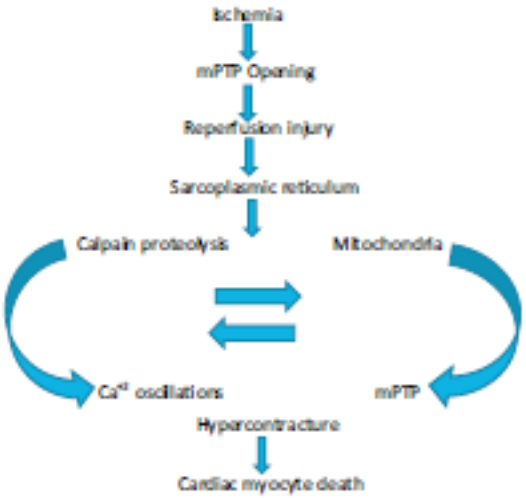

Fig. 1. Pathophysiology of reperfusion injury.

In this review, we provide an overview of novel concepts and therapies based on cellular and molecular disturbances in STEMI that may be applied to reduce infarct size (Fig. 2). We also describe the possible reasons why many promising therapies have thus far failed, and why future approaches may succeed.

3. Agents to reduce inflammation

Vascular inflammation is thought to play an important role in coronary artery plaque initiation, progression, rupture and thrombosis [12]. The Prospective Physicians Health Study (PHS) demonstrated that men with high baseline levels of C-reactive protein (CRP) measured with a high sensitivity assay are more likely to develop adverse cardiac events than those with normal levels [13]. It is also well established that during the acute inflammatory state that accompanies AMI chemokines and neutrophils are released into circulation [14, 15]. Thus, agents targeting the inflammatory cascade may reduce infarct size (Table 1). A variety of anti-inflammatory agents have been studied for this purpose but despite promising results in experimental studies, most agents have failed to demonstrate reductions in infarct size or improved clinical outcomes in human trials (Table 1) [16, 17].

3.1. Specific anti-inflammatory agents studied to reduce infarct size

3.1.1. Pexelizumab

The activation of the complement system may increase the extent of myonecrosis after coronary artery thrombosis [23]. Pexelizumab is a monoclonal antibody that binds the complement component 5 (C5). Anti-C5 therapy in the setting of MI has shown to inhibit cell apoptosis and necrosis leading to reduction in infarct size in the preclinical setting [18]. In the small COMMA (COMplement inhibition in Myocardial infarction treated with Angioplasty) trial, pexelizumab failed to reduce infarct size, but was associated with a reduction in mortality [18]. Conversely, in the large scale Apex-AMI trial (Pexelizumab for Acute ST-Elevation Myocardial Infarction in Patients Undergoing Primary Percutaneous Coronary Intervention), pexelizumab reduced infarct size at 90 days and improved left ventricular ejection fraction (LVEF) in a cardiac magnetic resonance imaging (CMRI) sub-study, but did not reduce mortality [16,19]. As a result of these conflicting results, and given the negative clinical results of the pivotal Apex-AMI trial, pexelizumab development for AMI has not progressed [24].

3.1.2. Fibrin-Derived Peptide, FX06

Fibrin-Derived Peptide, FX06 is a naturally occurring peptide derived from human fibrin that competes with E1 fragments of fibrin for binding to an endothelial specific molecule, VE-cadherin. FX06 has been shown to have anti-inflammatory properties, and decreased myocardial infarct size in animal models by mitigating reperfusion injury [25, 26]. Unfortunately, no difference in infarct size as measured by CMRI or troponin-I levels was evident with its use in the FIRE (Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury) trial [17].

3.1.3. Colchicine

Colchicine, an anti-inflammatory agent, was evaluated in STEMI patients for infarct size reduction [20]. A colchicine regimen of 1.5 mg followed by 0.5 mg 1 h later and 0.5 mg twice daily for 5 days was evaluated with infarct size assessed by CMRI. There was no benefit in infarct size reduction in the colchicine group [20]. Additionally, in a small study colchicine failed to demonstrate a reduction in peak CRP values post-acute MI as compared to placebo [27, 28].

Fig. 2. Emerging strategies for myocardial protection.

Table 1
Anti-inflammatory agents investigated to reduce infarct size.

Agent	Clinical evidence	Time of infarct size assessment	Primary endpoints	Secondary endpoints	Findings	n
Pexelizumab	COMMA trial	90 days	Infarct size	Composite of death, new or worsening heart failure, shock or stroke.	No major impact on infarct size [18]	960
	Apex-AMI trial	3–5 days and 90 days	Infarct size	left ventricular ejection fraction(LVEF), median peak creatine kinase(CK), thrombolysis in Myocardial Infarction (TIMI) flow, death, heart failure or shock.	Reduced infarct size at 90 days and improved LVEF in the cardiac magnetic resonance (CMR) sub-study [16, 19]	5745
FX06	FIRE trial	5 and 40 days	Infarct size	Size of necrotic core zone and MVO, infarct size at 4 months, left ventricular function, troponin I levels, and safety.	No major impact on infarct size [17]	234
Colchicine	Pilot Study	5 days	Creatine kinase-MB (CKMB); In subgroups – absolute myocardial infarct volume, determined by LGE, was the primary outcome.	Maximal high-sensitivity troponin T.	Smaller infarct size by both CMR and biomarker levels [20,21]	151
IL-1 Inhibitors	MRC-ILA Heart Study	14 days	High-sensitivity C-reactive protein level; levels of von Willebrand factor (vWF) and IL-6, troponin; infarct size estimated by CMR; and burden of ischaemia by continuous ECG monitoring		No reduction in infarct size [22]	

COMMA trial, (COMplement Inhibition in Myocardial Infarction treated with Angioplasty), Apex-AMI trial, (Pexelizumab for Acute ST-Elevation Myocardial Infarction in Patients Undergoing Primary Percutaneous Coronary Intervention), FIRE trial, (Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury) Trial, MRC-ILA Heart Study (Investigation of the effect of interleukin-1 receptor antagonist (IL-1ra) on markers of inflammation in non-ST elevation acute coronary syndromes).

Studies of colchicine in MI were not powered to for clinical outcomes. The ongoing Colchicine and Spironolactone in Patients with STEMI/SYNERGY Stent: CLEAR-SYNERGY (OASIS-9) trial is designed to detect an effect on clinical outcomes in an adequately powered trial involving 4000 patients (NCT03048825).

3.1.4. Interleukin-1 (IL-1)

Myocardial infarction has a well-established inflammatory component. [29, 30] Interleukin-1 (IL-1) is a cytokine released from macrophages and monocytes and plays an important role in the inflammatory cascade [31]. Interleukin-1 has been detected in human coronary arteries with atherosclerosis [32, 33] and also been found in high concentration after coronary intervention. It is a potential target to reduce neointimal proliferation [34]. IL-1 is an early mediator of the inflammatory cascade and is actively involved in mobilisation of various components of inflammation. Alongside these inflammatory components glucocorticoids are released, playing a vital role in the stress response during myocardial infarction. [35, 36]

IL-1 is expressed in the coronary arteries of patients with coronary artery disease [37]. IL-1 has been shown to drive the rise in CRP in acute coronary syndromes(ACS) [22]. Inhibitors of IL-1 have reduced infarct size in both preclinical and some clinical studies [38, 39]. In a mouse model, treatment with an IL-1β blocking monoclonal antibody prevented further deterioration in LV function after acute MI [38]. A randomized controlled trial in a pig model demonstrated significant infarct size reduction and preservation of LV function with MCC950 treatment, a selective NLRP3-inflammasome inhibitor [40]. In the randomized MRC-ILA Heart Study (Investigation of the effect of Interleukin-1 receptor antagonist (IL-1ra) on markers of inflammation in non-ST elevation acute coronary syndromes), a recombinant IL-1 receptor antagonist resulted in increased rates of recurrent MI within 12 months [22]. However this trial was underpowered and a larger study evaluating longer term IL-1 inhibition is ongoing [41].

3.2. Carbon monoxide

Carbon monoxide (CO) is a toxic substance given its ability to bind haemoglobin thereby displacing oxygen [42, 43]. While CO poisoning is associated with cardiovascular complications, including myocardial necrosis [44, 45]; there is some evidence that CO in small doses may have cardioprotective effects [46–48]. At low levels, CO inhibits the expression of pro-inflammatory cytokines (including TNF-α, IL-1β, MIP-1β) and increases the expression of the anti-inflammatory cytokine IL-10 through a MAP kinase pathway [49, 50].

Various CO-releasing molecules (CORM) have been developed for infarct size reduction [51, 52, 53]. CORM administration reduced infarct size in mice without any effect on arterial blood pressure, heart rate and carboxyhaemoglobin levels [54]. CORMs have also been shown to favourably influence post-infarction LV remodelling in a mouse model of LAD ligation [55]. In another experiment pre-treating mice with CORM-3, 24–72 h prior to coronary occlusion reduced infarct size [56]. These data support a potential role for CORMs in limiting ischaemic myocardial damage after coronary occlusion and reperfusion, warranting further development of these agents.

3.3. Possible reasons for failure of anti-inflammatory agents

Anti-inflammatory agents have reduced infarct size in preclinical studies but have thus far failed to show benefit in clinical trials. It may be that the pathophysiologic and cellular processes of AMI in mice, rodents and rabbit models differ substantially from humans. Preclinical studies mostly involve healthy and young animals without atherosclerosis that mounts a robust inflammatory response, unlike some patients with chronic comorbidities.

One possible reason that therapies for infarct size reduction have failed in humans is that their targets were often non-specific. Specific agents targeting individual molecules may be more effective. Such targets may be identified from human genome-wide associated studies (HGWAS) [57]. In this regard coronary artery disease and AMI are associated with abnormal metabolic pathways that are often genetically regulated [58, 59]. The lessons learned from gene-targeted cancer therapies can be translated to applications to reduce the infarct size [60]. Diagnostic imaging modalities such as FDG-PET may be used to develop goal-directed therapies [61]. A number of pre-clinical efforts in this regard are already underway and may translate to human patients in the near future [62].

3.4. Regulation of intracellular ion channels

3.4.1. mPTP inhibitors and cyclosporine

Opening of the mitochondrial permeability transition pore (mPTP) has been shown to be centrally involved in reperfusion injury, and inhibitors of mPTP opening may prevent or reduce apoptosis and myonecrosis and enhance the cellular recovery (Fig. 3) [63, 64]. The immunosuppressive agent cyclosporine is one such inhibitor of mPTP

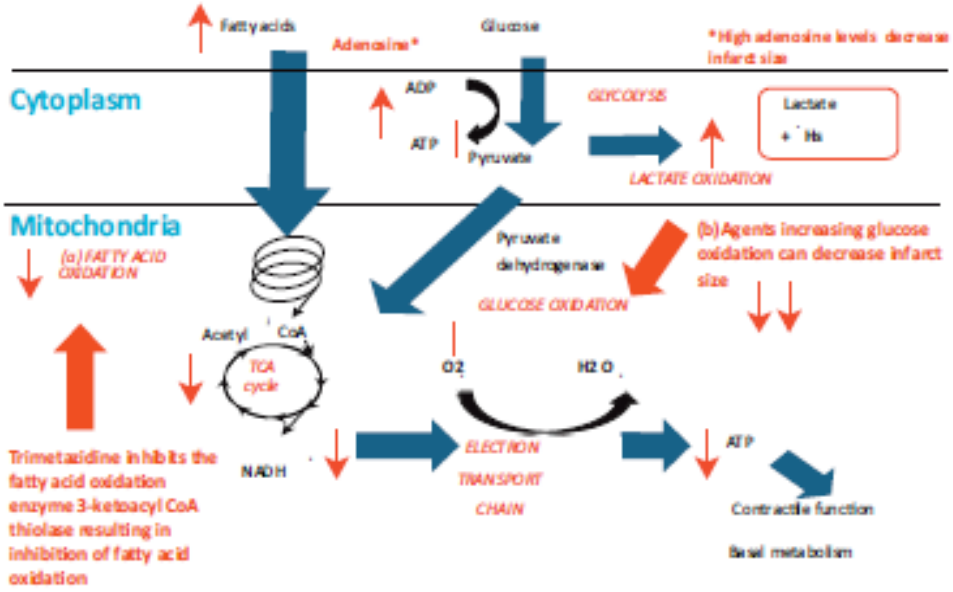

Fig. 3. Mechanisms of agents affecting fatty acid and glucose oxidation.

opening. Small-scale studies have shown that cyclosporine therapy at the time of acute MI reperfusion may reduce infarct size and mitigate pathologic LV remodelling [21,65]. In a meta-analysis of 20 in vivo experimental studies in animal models (involving four species), cyclosporine was found to be beneficial in reducing infarct size. However, a beneficial response was not present in porcine models raising concerns in regards to the cardioprotective potential in humans [66].

In the randomized CIRCUS (Does Cyclosporine Improve Clinical Outcome in ST-Elevation Myocardial Infarction Patients) trial, intravenous cyclosporine (2.5 mg/kg Ciclomulsion) failed to reduce infarct size or improve event-free survival [67]. It was hypothesized that the negative results of this study may have been due to the formulation of cyclosporine used (CicloMulsion, NeuroVive Pharmaceuticals). However, the CYCLE (CYClosporinE A in Reperfused Acute Myocardial Infarction) trial, in which the alternative formulation (Sandimmune, Novartis) was given as a single intravenous bolus before primary PCI in anterior STEMI patients, also was negative, demonstrating no effect on ST-segment resolution, infarct size, LV remodelling or clinical outcomes [68].

mPTP is a non-selective pore and cyclosporine A is not specific for cyclophilin D, also binding cytosolic cyclophilin A [69]. Argaud et al. demonstrated that the specific mPTP inhibitor NIM811, a remodelling derivative devoid of activity on calcineurin, increased the resistance of mPTP to Ca^{2+} overload and limited infarct size when given at the time of reflow [70]. Clinical studies are thus required to determine whether specific inhibitors of the mPTP will more consistently reduce infarct size and improve outcomes [71]. CAPRI (Ciclosporin to Reduce Reperfusion Injury in Primary PCI) trial is a single centre, double-blind randomized trial, currently recruiting patients for the study and aiming to evaluate the effectiveness of IV Ciclosporin on reducing reperfusion injury in patients undergoing primary PCI.

3.4.2. Na^+/H^+ exchange (NHE1) inhibitors

In experimental models reducing intracellular Calcium (Ca^{2+}) overload by blocking the sarcolemmal Ca^{2+} ion channel, the mitochondrial Ca^{2+} uniporter, or the sodium-hydrogen exchanger decreases myocardial infarct size [72]. Cariporide, a specific benzoyl-guanidine Na^+/H^+ exchange (NHE1) inhibitor, has been shown to have cardioprotective effects [73]. Specific inhibition of Na^+/H^+ exchange using HOE-642 can potentially retard myocardial remodelling and improve diastolic function [74]. However, clinical benefits of cariporide in humans were not present in the ESCAMI (evaluation of the safety and cardioprotective effects of eniporide in acute myocardial infarction) and CASTEMI (CAlfarat in ST-elevation Myocardial Infarction) trials [75,76]. At this time there is limited evidence that agents regulating intracellular ions and cytosolic calcium may reduce infarct size or improve clinical outcomes (Table 2).

3.4.3. Potential reasons for failure of modulators of intracellular ions

Various agents (e.g. cyclosporine, TRO40303 and MTP-131) reported benefit in pre-clinical models but not in human clinical trials. Most of these molecules were tested before validation of molecular and cellular targets. These agents were also administered to patients treated with antiplatelet agents which may themselves have cardioprotective properties [80,81]. Delivering the compound at the right time and at the right dose to achieve adequate therapeutic levels also remains a challenge. Compounds with better bioavailability may improve outcomes through regulation of intracellular ions and cytosolic calcium. Intracoronary administration may be more effective than systemic administration.

3.5. Agents impacting the reperfusion injury salvage kinase pathway

In preclinical studies the reperfusion injury salvage kinase (RISK) pathway has been shown to have a significant cardioprotective effect. This is achieved by a variety of pathways that includes the activation of mPTP as well.

A variety of agents have shown to activate the RISK pathway and potentially reduce infarct size (Table 3).

3.5.1. Opioids

Morphine has been tested as a cardioprotective agent in preclinical as well as in clinical studies [118,119]. In a prospective randomized trial, intracoronary morphine failed to reduce infarct size as assessed

Table 2
Agents with cellular targets to reduce infarct size.

AGENTS	Cellular target	Clinical evidence	Time line for assessment of infarct size	Primary endpoints	Secondary endpoints	Findings	n
Cyclosporine	mPTP	CIRCUS study	1 year	A composite of all cause death, worsening of heart failure during the initial hospitalization, rehospitalization for heart failure, or adverse left ventricular remodelling at 1 year.		Did not prevent adverse left ventricular remodelling.No reduction in infarct size. [67]	791
		CYCLE trial	60 min, 4 days and 6 months	Incidence of ≥70% ST-segment resolution 60 min after TIMI flow grade 3	High-sensitivity cardiac troponin T (hs-cTnT) on day 4, left ventricular (LV) remodelling, and clinical events at 6-month follow-up.	No reduction in infarct size [68].	410
TRO40303	Indirect mPTP inhibitor	MITOCARE	3 days	Infarct size	Infarct size and clinical safety outcomes.	No significant infarct size reduction [77].	163
Bendavia	Mitochondria-targeting peptide	EMBRACE-STEMI	72 h and 4 + −1 days	Infarct size.	Infarct size.	No reduction in infarct size by biochemical analysis [78].	297
Cariporide	Na^+/H^+ exchange (NHE) inhibitor	Rupprecht, Hans-Jürgen, et al.				Reduces reperfusion injury [73].	100
Eniporide	Specific NHE1 inhibitors	ESCAMI	0–72 h	Infarct size, area under the curve [AUC] (0 to 72 h). Clinical outcomes death, cardiogenic shock, heart failure, life-threatening arrhythmia.		No reduction in infarct size [75].	
Caldaret	NHE1 inhibitors	CASTEMI	7 and 30 days	Infarct size, area under the concentration–time curve (AUC) for total creatine kinase (CK) and its MB isoenzyme (CK-MB) to 72 h; for troponin T (TnT) and lactate dehydrogenase		Lack of cardio protection [76].	
Delcasertib	Inhibitor of delta Protein Kinase C(PKC)	PROTECTION - AMI	3 months	Infarct size	Infarct size, electrocardiographic ST-segment recovery, AUC or time to stable ST recovery, or LVEF.	No reduction in infarct size [79].	1010

CIRCUS study, Does Cyclosporine Improve Clinical Outcome in ST-Elevation Myocardial Infarction Patients trial, CYCLE trial, CYCLosporinE A in Reperfused Acute Myocardial Infarction, MITOCARE, Multicenter Multicentre, randomized, double-blind, placebo-controlled study to assess safety and efficacy of TRO40303 for reduction of reperfusion injury in STEMI patients undergoing primary PCI, NA, Not Available, EMBRACE-STEMI, Evaluation of the Myocardial Effects of Bendavia for Reducing Reperfusion Injury in Patients With Acute Coronary Event re-STEMI, ESCAMI, evaluation of the safety and cardioprotective effects of eniporide in acute myocardial infarction, CASTEMI, CAldaret in ST-elevation Myocardial Infarction, PROTECTION – AMI, Inhibition of d-Protein Kinase C for Reduction of Infarct Size in Acute Myocardial Infarction, REVEAL, Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction.

by CMRI. There was also no difference in myocardial salvage ST – segment resolution or peak CK-MB levels compared with control [120].

3.5.2. Volatile anaesthetics

Volatile anaesthetic agents may reduce infarct size by affecting the potassium ATP (KATP) channel, mitochondrial permeability transition pore (mPTP), reactive oxygen species (ROS) production, cytoprotective Akt and extracellular signal kinases (ERK) pathways. The evidence in regards to the cardioprotective role of these agents is controversial, although isoflurane, desflurane, and sevoflurane have demonstrated some cardioprotective potential [121–123]. A comparison of various agents during on-pump cardiac surgery has shown no significant difference in infarct size reduction [82]. Randomized clinical trials are required to examine whether these agents have meaningful cardioprotective effects in humans.

3.5.3. Erythropoietin

In animals studies erythropoietin administration before ischemic reperfusion injury conveyed significant myocardial protection through mechanisms involving reduction of caspase-3 activity and up-regulation of Bcl-2 in association with enhanced ERK-induced GATA-4 stability [104]. However, the cardioprotective effect of erythropoietin was not replicated in a clinical trial, REVEAL (The Reduction of Infarct Expansion and Ventricular Remodelling With Erythropoietin After Large Myocardial Infarction) [88].

3.5.4. Natriuretic peptides (Atrial (ANP) and B- type natriuretic peptide (BNP))

There is some preclinical as well as clinical evidence that natriuretic peptides may reduce infarct size. Pre-clinical studies in rabbits have shown encouraging results when ANP was administered prior to myocardial reperfusion [110]. In the Japan-Working groups of acute myocardial Infarction for the reduction of Necrotic Damage by ANP (J-WIND-ANP) trial, an ANP analogue (Carperitide) was administered intravenously as an adjunct to primary PCI to patients with STEMI. Infarct size was reduced by 15% as assessed by 72 h AUC total CK [96]. These results warrant further human randomized trials.

3.5.5. GLP1 (Glucagon-like peptide) inhibitors

The glucagon-like peptide-1 (GLP-1) may have cardioprotective effects via regulation of blood glucose. These chemicals have insulin-like properties and affect glucose uptake, not needing administration of glucose in this regard. There is preclinical as well as clinical evidence for the use of GLP1 inhibitors to reduce infarct size. An IV infusion of exenatide started at least 15 min before primary PCI and continued for 6 h after primary PCI in STEMI reduced infarct size by 23% as demonstrated by

Table 3
Potential agents acting on RISK pathway and other cellular targets for infarct size reduction.

AGENTS	Cellular target	Clinical evidence	Time Frame for assessment of infarct	Primary end points	Secondary end point	Findings	n
Remifentanil infusion		During CABG				The possible beneficial impact on biomarkers of injury [82,83].	200
Fentanyl		During CABG				Reduction in enzyme release in the treatment group [84].	150
Isoflurane		During CABG				Significant reduction in peak cTnI up to 36 h postoperatively in the isoflurane group [85, 86].	45
Exenitide	GLP 1	Lonborg et al.				Some beneficial effect of reducing the infarct size [87].	
Erythropoietin		REVEAL	2–6 days and 12 ± 2 weeks	Infarct size.		No significant reduction in infarct size [88]	
Adenosine		AMISTAD-I	6 ± 1 days	Infarct size	Myocardial salvage index and a composite of in-hospital clinical outcomes (death, reinfarction, shock, congestive failure or stroke).	Significant reduction in infarct size [89]	222
Adenosine		AMISTAD- II				Significant reduction in infarct size [90]	
		Ross Flaherty et al.	30 to 60 min. 30 days			No effect on enzymatic infarct size. [91]	
Nitrite therapy		NIAMI trial	6–8 days. 6 months.	Infarct size	Plasma troponin I and CK area under the curve, left ventricular volumes (LV), and LVEF.	No reduction in infarct size [92].	
		Jones et al.	2 days	Infarct size.	Infarct size	No evidence of reduction in infarct size [93]	
		NOMI study				No beneficial effect on the infarct size. NCT01968304	
Magnesium		ISIS-4-A				No clinical benefit in infarct size reduction [94, 95]	
ANP/BNP		J-WIND-ANP	3 days and 6–12 months.	Infarct size		Some reduction in infarct size [96]	
Nicorandil		J-WIND-KATP	3,6 days. 12 months.	Infarct size.		No significant reduction in infarct size [96]	

AMISTAD trial, In Acute Myocardial Infarction STady of Adenosine. NA, Not available. ISIS-4-A, 4th International Study of Infarct Survival. NIAMI trial, Intravenous sodium nitrite in acute ST-elevation myocardial infarction. NOMI study, Nitric Oxide for inhalation to reduce reperfusion injury in acute ST-elevation Myocardial Infarction. J-WIND-ANP, Japan-Working groups of acute myocardial Infarction for the reduction of Necrotic Damage by ANP.

CMRI, and increased myocardial salvage [87, 124]. Subcutaneous exenatide prior to primary PCI in STEMI resulted in a 52% reduction in infarct size assessed by CMRI at 1 month [125]. However, these results were not replicated in a large double-blind, placebo-controlled randomized trial [126]. These conflicting results may be due to differences in the patient populations studied and/or different doses used in the varying trails. Further clinical trials with GLP-1 agents are warranted to investigate their potential to reduce infarct size and improve prognosis in STEMI.

3.56. Nicorandil

In J-WIND-KATP (Japan-Working groups of acute myocardial Infarction for the reduction of Necrotic Damage by ANP) trial, 545 patients were randomized to a 0.067-mg/kg bolus followed by 24-h infusion of 1.67 g/kg/min of nicorandil or placebo [96]. Nicorandil administration showed no difference in infarct size as measured by CK-MB release.

3.57. HMG-CoA reductase inhibitors

Statins have been shown to be cardioprotective with their effects not solely related to LDL reduction [100]. Increasing the availability of NO synthetase by statins may reduce the myocardial injury and hence may be cardioprotective [127, 128]. A beneficial role of statin therapy in infarct size reduction has been demonstrated in preclinical studies [111, 129]. To date, the acute use of statins to reduce infarct size and improve prognosis independent of their favourable effects on cholesterol metabolism has not been demonstrated.

3.58. Adenosine

During myocardial ischemia, adenosine is produced in cardiac myocytes by dephosphorylation of adenosine monophosphate (AMP); within seconds of ischemia the level of interstitial adenosine rises and causes arteriolar vasodilatation [130, 131]. Clinical studies with adenosine have reported conflicting results for infarct size reduction. In the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial, adenosine given as an adjunct to thrombolytic therapy resulted in a 33% relative reduction in infarct size [89]. In the AMISTAD- II trial, intravenous adenosine (50 microgram/kg/min and 70 microg/kg/min doses) in patients with anterior STEMI receiving thrombolysis or primary PCI was associated with reduced infarct size, particularly with the high-dose [90]. However, a clinical benefit was not observed. Moreover, high dose intracoronary adenosine during primary PCI in AMI did not reduce enzymatic infarct size in another study [91]. Further studies with adenosine or adenosine analogues are warranted, especially at higher doses.

3.59. Magnesium

Neither regional nor systemic magnesium reduced infarct size in animal models [116]. Conflicting results of magnesium on infarct size reduction have been reported from small studies [132]. Some studies suggested magnesium sulfate may reduce infarct size when given before or at the time of reperfusion, rather than after coronary reperfusion [133]. However, in a large clinical trial magnesium sulfate provided no clinical benefit in infarct size reduction or survival [94].

3.6. Agents acting via nitric oxide signaling pathways

Nitrites and nitric oxides (NO) offer the potential to salvage jeopardized myocardium, and many NO donors have been tested for their ability to reduce infarct size. In experimental models, sodium nitrite has shown efficacy in reducing infarct size when used either pre occlusion or as a peri-conditioning agent [101, 102, 134]. In the randomized NIAMI (Intravenous sodium nitrite in acute ST-elevation myocardial infarction) trial, intravenous sodium nitrite failed to reduce infarct size in comparison to placebo [92]. The negative results may be attributable due to the fact that >90% of patients had received nitro-glycerine prior to reperfusion. Also, whether a higher dose or longer duration of infusion would have been effective.

In another trial, a 10 ml bolus of intracoronary sodium nitrite (1.8 μmol) was administered to patients undergoing primary PCI versus placebo just before balloon inflation. There was no evidence of a reduction in infarct size as assessed by creatine kinase and troponin T release and by CMRI measured on day two, although by chance total ischemia time was longer in the treatment group [93]. However, in a post hoc analysis of 66 patients with TIMI flow ≤ I, nitrite administration was associated with a statistically significant reduction in infarct size and MACE and an improved myocardial salvage index. These findings need to be replicated in a larger randomized trial.

In the NOMI study (NCT01398384) inhaled nitric oxide at 80 ppm (parts per million) initiated prior to primary PCI and administered for 4 h did not reduce the primary endpoint of infarct size as assessed by CMRI at 48–72 h. Whether this negative effect is due to patient selection factors or prior dosing with intracoronary or intravenous nitro-glycerine or lack of effectiveness is speculative. Further clinical trials are warranted to explore the potential beneficial effect of administering intracoronary nitrites while the culprit artery is still occluded.

3.7. Strategies targeting mitochondrial function

During myocardial ischemia, there is a switch of mitochondrial energy metabolism; oxidation is decreased and glycolysis becomes the predominant source of energy production. Fatty acids are the principal substrate for residual oxidative metabolism. The increase in glycolysis and decrease in glucose oxidation results in the production of both lactate and hydrogen ions. Therapeutic agents to increase glucose oxidation can potentially decrease ischemic injury (Fig. 4). Various agents which target mitochondrial function have been studied in both pre-clinical and clinical setting to examine their potential to reduce infarct size.

3.7.1. Trimetazidine

Trimetazidine is an anti-ischemic agent that enhances mitochondrial glucose metabolism and inhibits fatty acid metabolism [135, 136]. It has an inhibitory action on the β-oxidation of fatty acids by blocking long-chain 3-ketoacyl-coenzyme A thiolase (LC 3-KAT), which enhances glucose oxidation.

Some preclinical and clinical evidence supports the potential cardioprotective role of trimetazidine [136, 137]. The anti-ischemic effects of Trimetazidine has been demonstrated in a small, randomized, double-blind study where it decreased the maximum ST-segment shift and delayed its onset in comparison to placebo treatment [138]. Trimetazidine in combination with PCI decreased cardiac troponin I release in comparison to placebo [139]. In another study trimetazidine improved symptoms, exercise capacity and reduced ischemia as assessed by SPECT (single photon emission computed tomography) [140].

In a large prospective, randomized, double-blind EMIP-FR (European Myocardial Infarction Project – Free Radical) trial, 19,725 patients with AMI within 24 h were enrolled, there was no difference between trimetazidine and placebo for the main endpoint of 35-day mortality [141, 142]. Thus, although there is some evidence that trimetazidine delays the onset of ischemia and may reduce infarct size, this agent has not shown to be of clinical benefit in large-scale trials.

3.7.2. Delcasertib

Delcasertib is a peptide inhibitor of delta protein kinase C (PKC), a major mediator of the mitochondrial apoptotic pathway. Although delcasertib showed promise in preclinical studies, it was ineffective

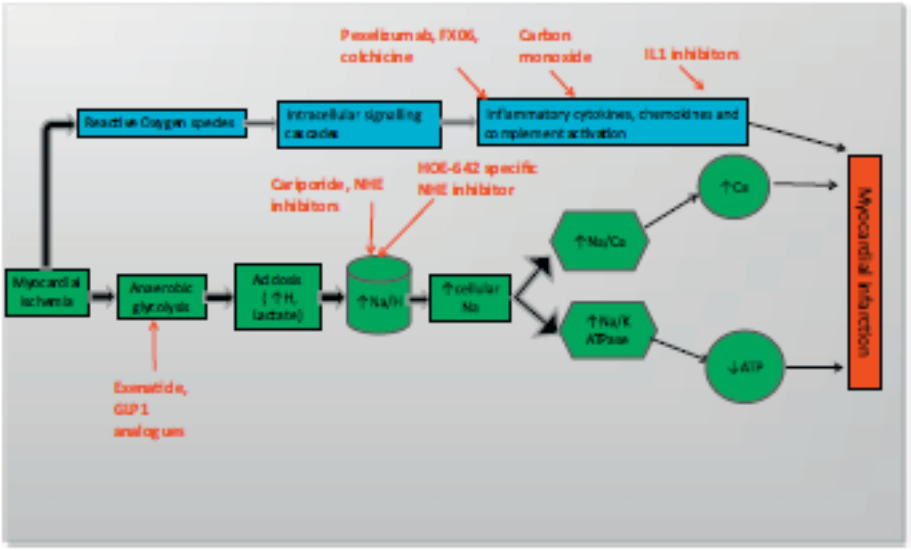

Fig. 4. Various agents and potential mechanisms to reduce infarct size.

Table 4
Various types of stem cells and studies assessing their impact on LV function.

Cell type	Trial	Participants (treatment/control)	Evidence of changes in LV function
BMMC	Strauer	10	No significant difference in LVEF [146].
BMMC/CPC	TOPCARE-MI	59	Some improvement in LVEF [147].
BMMC	Fernandez-Aviles	20	Some improvement in LVEF [148].
CD133-BMMC	Bartunek	16/19	Some improvement in LVEF [149].
MSC	Chen et al.	34/35	Some improvement in LVEF. [150]
BMMC	BOOST	30/30	Some improvement in LVEF [151].
BMMC	Janssens et al.	34/33	No significant improvement in LVEF [152]
BMMC	ASTAMI	50/47	No significant improvement in LVEF. [153]
BMMC	REPAIR-AMI	102/102	Some improvement of LVEF [154].

BMMC, Bone marrow mononuclear cells CPC, circulating progenitor cells. MSC, Mesenchymal stem cell. LVEF, Left Ventricular Ejection Fraction. TOPCARE-AMI, Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction. ASTAMI, Autologous Stem-Cell Transplantation in Acute Myocardial Infarction. BOOST, Bone Marrow Transfer to Enhance ST-elevation Infarct Regeneration. LVEF, left ventricular ejection fraction. REPAIR-AMI, Reinfusion of Enriched Progenitor Cells and Infarct Remodelling in Acute Myocardial Infarction.

in the PROTECTION–AMI (Inhibition of delta-protein kinase C by delcasertib as an adjunct to primary percutaneous coronary intervention for acute anterior ST-segment elevation myocardial infarction) trial [79] [Table 2] The reasons for the neutral study may relate to patient selection, as 30%–40% of patients had TIMI flow of >1 before primary PCI. In addition, it may take up to 30 min for delcasertib to reach steady state. It is also possible that the dosing was inadequate, as lack of signs of toxicity raised the question of whether the dose used was sufficient.

3.7.3. TRO40303

TRO40303 is an indirect inhibitor of the mitochondrial permeability transition pore (mPTP) and has shown beneficial impact on infarct size reduction in preclinical settings. Conversely, in a large scale trial, MITOCARE (Multicentre, randomized, double-blind, placebo-controlled study to assess safety and efficacy of TRO40303 for reduction of reperfusion injury in STEMI patients undergoing primary PCI), no reduction in infarct size was present with TRO40303 treatment. [Table 2] There may be multiple reasons why this trial was negative. The sample size was small and the groups were imbalanced (higher initial mean CK, fewer patients with baseline TIMI 0 flow, more patients with TIMI 0/1 flow post-PCI, and older age in the TRO40303 group). Dosing may also have been inadequate.

Table 5
Various animal models and agents tested for infarct size reduction.

Animal model	Agents	Findings
Mice studies	IL-1 Inhibitors	Preservation of LV function [38]
	Carbon monoxide	Reduced infarct size [54]
	Cyclosporine	Improved survival Improved LVEF [97]
	Delcasertib	Some reduction in infarct size [98, 99]
	Rosuvastatin	Some reduction in myocardial necrosis [100].
	Nitrite	Some reduction in infarct size [101, 102].
Rat studies	Pexelizumab	Reduction in infarct size [18].
	Fluvastatin	Significant reduction in infarct size [103].
	Erythropoietin	Significant myocardial protection under moderate hyperglycemic condition [104]
	Morphine	Significant reduction in infarct size [105].
	Morphine	Potential cardio protective role [106].
	Tramadol	May reduce the myocardial infarct size [107].
Rabbit studies	Simvastatin	Some reduction in infarct size [108]
	Adenosine	Reduction in infarct size [92, 109].
	ANP/BNP	Some reduction in infarct size [110]. Some reduction in infarct size [111].
	Esiporide	Some cardio protective effect [112].
	Bendavia	Reduced myocardial infarct size by ~50% when administered for either 1 or 3 h of reperfusion [113].
	NIM811	Some reduction in infarct size [70].
	Cyclosporine	Reduced infarct size. Apoptotic cell death reduced [114]
Dog studies	Adenosine	Significant reduction in myocardial perfusion injury [115]
	Magnesium	No significant reduction in infarct size [116].
Pig studies	FXN06	Infarct size reduction [25, 26]
	IL-1 Inhibitor	Reduction in infarct size [40]
	Cariporide	Significantly reduced infarct size [117]

Interleukin-1 receptor inhibitors (IL-1 inhibitors), Atrial (ANP) and B- type Natriuretic peptide (BNP), Fibrin-Derived Peptide, FXN06.

3.7.4. Bendavia

Bendavia is another mitochondria-targeting peptide and similarly failed to replicate favourable preclinical results in clinical trials such as the EMBRACE-STEMI (Evaluation of Myocardial Effects of Bendavia for Reducing Reperfusion Injury in Patients With Acute Coronary Events) trial, in which treatment with MTP-131 was not associated with a decrease in myocardial infarct size as assessed by AUC_{0-72} of CK-MB [143]. In comparison to the MITOCARE study, EMBRACE-STEMI limited the inclusion of patients with only large anterior STEMI and administered the investigational drug for a prolonged time to ensure therapeutic effect. Despite these adjustments, MPT-131 did not show a reduction in infarct size. Thus, there is no current evidence supporting the use of mitochondrial function modulators for infarct size reduction.

3.7.5. *Strategies to inhibit apoptosis (anti-apoptotic agents)*

Apoptosis may play a crucial role in the pathophysiology of myocardial infarction, and inhibition of apoptosis in the early stages of reperfusion may reduce infarct size.

3.7.6. *SB239063 and insulin*

In experimental studies treatment with SB239063 and insulin markedly decreased myocardial apoptosis (10.6 ± 1.5% and 7.9 ± 0.9% respectively, $P < 0.01$ vs. vehicle) and significantly reduced infarct size (43 ± 3.6% and 35 ± 2.9%, respectively, $P < 0.01$ vs. vehicle) [144].

3.7.7. *MicroRNA-24 (miR-24)*

The effects of MicroRNA-24 (miR-24) in inhibiting LV remodelling by suppressing cellular apoptosis via the phosphatase and tensin homolog (PTEN) have been studied in AMI rat models [145]. These studies suggest that Ad-miR-214 may protect against reperfusion injury and decrease myocardial cell apoptosis through a PTEN-mediated mechanism.

However, whether apoptosis is a primary or secondary event in the pathophysiology of AMI is controversial. Methods to assess apoptosis are also suboptimal. Currently available methods utilizing the terminal deoxynucleotidyl-transferase-mediated dUTP nick end-labelling (TUNEL) cannot differentiate the cell type that is undergoing apoptosis in a tissue sample comprising multiple types of cells. Ultimately, clinical trials will be required to determine whether anti-apoptotic agents provide beneficial effects in reducing infarct size and improving prognosis.

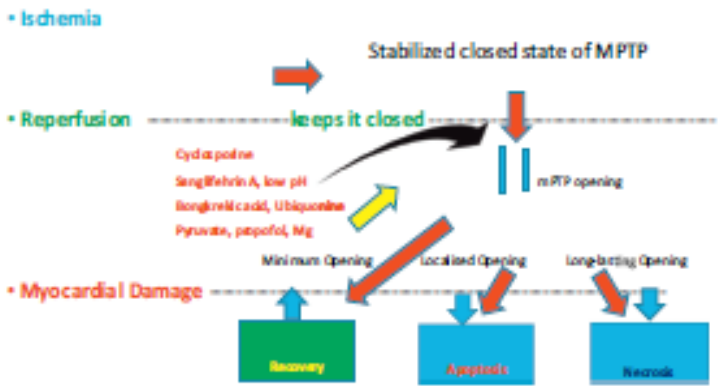

Fig. 5. Various agents acting on mPTP channels and mechanisms to reduce infarct size.

3.8. Stem cell and gene therapy to reduce infarct size

3.8.1. Stem cell therapy

Stem cell therapy to improve myocardial function after large STEMI has been extensively studied in phase I and II trials [Table 4].

Early experimental studies in animals suggested improvement in LV systolic function following cell therapy with bone marrow-derived mononuclear cells (BMMC) although with no effect on infarct size [155]. The BOOST (The Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration Trial) suggested that intracoronary transfer of autologous bone marrow cells after acute MI could improve LV systolic function, a finding that was not supported by the Leuven trial [151,152]. The REPAIR-AMI (Reinfusion of Enriched Progenitor Cells and Infarct Remodelling in Acute Myocardial Infarction) trial reported a greater absolute increase in LVEF in the BMMC group than in the placebo group (2.5%; 95% CI, 0.5 to 4.5; P = 0.01) [154].

Allogeneic mesenchymal precursor cells (MPCs) have been safely delivered into the intra-coronary milieu after AMI in sheep, and improved myocardial function [156]. There is some evidence that a combination of human cardiac stem cells (hCSC) and bone marrow mesenchymal stem cells (hMSC) may reduce scar after MI and enhance restoration of systolic and diastolic function after MI [157].

However, clinical outcomes with stem cell therapy have been conflicting, likely explained by differences in patient characteristics and the cell type, number, timing and route of administration. Large-scale phase III trials are required to determine if this approach can durably improve LV function and prognosis after large MI.

3.8.2. Gene therapy

Gene therapy to enhance cardiac function is challenging due to the need for vectors and gene transcription and translation. Turunen MP et al. used "lentiviral" in vivo for delivery of small hairpin RNA (shRNA) into hearts in a murine infarction model. shRNA complementary to the promoter of vascular endothelial growth factor (VEGF-A) was able to up-regulate endogenous VEGF-A expression [158]. Infarct size reduction was noted in histological, multiphoton microscopic and MRI studies. Clinical studies are required to advance these preclinical observations.

4. Summary and future directions

Although numerous agents have been shown to reduce infarct size in preclinical models [Table 5], there is limited clinical evidence of benefit to date (Fig. 5) [159]. Emerging strategies effecting valid molecular and cellular targets require further study in humans. Rather than a "one size fits all" approach, individualized tailored therapies may be required for patients with select clinical, myocardial or genetic/cellular characteristics. Further study is also required to determine why beneficial animal studies have not translated into human effectiveness. Despite the numerous setbacks to date, there is a great clinical need to enhance myocardial recovery and LV function in patients with large MI to reduce the burden of heart failure and improve survival.

References

[1] Roe MT, Messenger JC, Weintraub WS, Cannon CP, Rosenow GC, Dai D, Chen AY, Klein LW, Masoudi FA, McKay C, Hewitt K, Brindis RG, Peterson ED, Rumsfeld JS. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. J Am Coll Cardiol 2010;56:254–63.
[2] Hausenloy DJ, Yellon DM. Myocardial protection: is primary PCI enough? Nat Clin Pract Cardiovasc Med 2009;6:12–3.
[3] Parviz Y, Vijayan S, Lavi S. A review of strategies for infarct size reduction during acute myocardial infarction. Cardiovasc Revasc Med 2017;18(5):374–83. https://doi.org/10.1016/j.carrev.2017.02.004.
[4] Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med 2007;357:1121–35.
[5] Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest 2013;123:92–100.
[6] Heusch G, Kleinbongard P, Skyschally A, Levkau B, Schulz R, Erbel R. The coronary circulation in cardioprotection: more than just one confounder. Cardiovasc Res 2012;96:237–45.
[7] Ong SB, Dongworth RK, Cabrera-Fuentes HA, Hausenloy DJ. Role of the MPTP in conditioning the heart – translatability and mechanism. Br J Pharmacol 2015;172:2074–84.
[8] Jackson MJ. An overview of methods for assessment of free radical activity in biology. Proc Nutr Soc 1988;58:1001–6.
[9] Granger DN. Role of xanthine oxidase and granulocytes in ischemia-reperfusion injury. Am J Physiol 1988;255:H1269–75.
[10] Inserte J, Hernando V, Vilardosa U, Abad E, Poncelas-Nozal M, Garcia-Dorado D. Activation of cGMP/protein kinase G pathway in postconditioned myocardium depends on reduced oxidative stress and preserved endothelial nitric oxide synthase coupling. J Am Heart Assoc 2013;2:e005975.
[11] Ruiz-Meana M, Inserte J, Fernandez-Sanz C, Hernando V, Miro-Casas E, Barba I, Garcia-Dorado D. The role of mitochondrial permeability transition in reperfusion-induced cardiomyocyte death depends on the duration of ischemia. Basic Res Cardiol 2011;106:1259–68.
[12] Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature 2011;473:317–25.
[13] Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–9.
[14] Nahrendorf M, Pittet MJ, Swirski FK. Monocytes: protagonists of infarct inflammation and repair after myocardial infarction. Circulation 2010;121:2437–45.
[15] Swirski FK, Nahrendorf M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. Science 2013;339:161–6.
[16] Armstrong PW, Granger CB, Adams PX, Hamm C, Holmes Jr D, O'Neill WW, Todaro TG, Vahanian A, Van de Werf F. Pexelizumab for acute ST-elevation myocardial infarction in patients undergoing primary percutaneous coronary intervention: a randomized controlled trial. JAMA 2007;297:43–51.
[17] Atar D, Petzelbauer P, Schwitter J, Huber K, Rensing B, Kaprzak JD, Butter C, Grip L, Hansen PR, Slagboek T, Clemmensen PM, Martin-Gallan A, Grudelis B, Buser PT. Effect of intravenous IV.06 as an adjunct to primary percutaneous coronary

intervention for acute ST-segment elevation myocardial infarction: results of the F.I.R.E. (efficacy of FX06 in the prevention of myocardial reperfusion injury) trial. J Am Coll Cardiol 2009;53:720–9.
[18] Granger CB, Mahaffey KW, Weaver WD, Theroux P, Hochman JS, Filloon TG, Rollins S, Todaro TG, Nicolau JC, Ruzyllo W, Armstrong PW. Pexelizumab, an anti-C5 complement antibody, as adjunctive therapy to primary percutaneous coronary intervention in acute myocardial infarction: the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial. Circulation 2003;108:1184–90.
[19] Patel MR, Worthley SG, Stebbins A, Dill T, Rademakers FE, Valeti US, Barsness GW, Van de Werf F, Hamm CW, Armstrong PW, Granger CB, Kim RJ. Pexelizumab and infarct size in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: a delayed enhancement cardiac magnetic resonance substudy from the APEX-AMI trial. JACC Cardiovasc Imaging 2010;3:52–60.
[20] Deftereos S, Giannopoulos G, Angelidis C, Alexopoulos N, Filippatos G, Papoutsidakis N, Sianos G, Goudevenos J, Alexopoulos D, Pyrgakis V, Cleman MW, Manolis AS, Tousoulis D, Lekakis J. Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. Circulation 2015;132:1395–403.
[21] Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol 2013;61:404–10.
[22] Morton AC, Rothman AM, Greenwood JP, Gunn J, Chase A, Clarke B, Hall AS, Fox K, Foley C, Banya W, Wang D, Flather MD, Crossman DC. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. Eur Heart J 2015;36(6):377–84. https://doi.org/10.1093/eurheartj/ehu272.
[23] Crawford MH, Grover FL, Kolb WP, McMahan CA, O'Rourke RA, McManus LM, Pinckard RN. Complement and neutrophil activation in the pathogenesis of ischemic myocardial injury. Circulation 1988;78:1449–58.
[24] Gibson CM, Pride YB. Myocardial infarct size reduction with Pexelizumab: the role of chance is patently clear. J Am Coll Cardiol Img 2010;3:61–3.
[25] Roesner JP, Petzelbauer P, Koch A, Mersmann J, Zacharowski PA, Boehm O, Reingruber S, Pasteiner W, Mascher D, Wolzt M, Barthuber C, Nöldge-Schomburg GE, Scheeren TW, Zacharowski K. The fibrin-derived peptide Bbeta15–42 is cardioprotective in a pig model of myocardial ischemia-reperfusion injury. Crit Care Med 2007;35:1730–5.
[26] Zacharowski K, Zacharowski PA, Friedl P, Mastan P, Koch A, Boehm O, Rother RP, Reingruber S, Henning R, Emeis JJ, Petzelbauer P. The effects of the fibrin-derived peptide Bbeta(15–42) in acute and chronic rodent models of myocardial ischemia-reperfusion. Shock 2007;27:631–7.
[27] Akodad M, Lattuca B, Nagot N, Georgescu V, Buisson M, Cristol JP, Leclercq F, Macia JC, Gervasoni R, Cung TT, Cade S, Cransac F, Labour J, Dupuy AM, Roubille F. COLIN trial: value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response. Arch Cardiovasc Dis 2017;3 (30232-1).
[28] Hemkens LG, Ewald H, Gloy VL, Arpagaus A, Olu KK, Nidorf M, Glinz D, Nordmann AJ, Briel M. Cardiovascular effects and safety of long-term colchicine treatment: Cochrane review and meta-analysis. Heart 2016;102:590–6.
[29] Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol 2012;32:2045–51.
[30] Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. N Engl J Med 2002;347:5–12.
[31] Dinarello CA, Simon A, van der Meer JW. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Nat Rev Drug Discov 2012;11:633–52.
[32] Galea J, Armstrong J, Gadsdon P, Holden H, Francis SE, Holt CM. Interleukin-1 beta in coronary arteries of patients with ischemic heart disease. Arterioscler Thromb Vasc Biol 1996;16:1000–6.
[33] Sutherwaite G, Francis SE, Suvarna K, Blakemore S, Ward C, Wallace D, Braddock M, Crossman D. Differential gene expression in coronary arteries from patients presenting with ischemic heart disease: further evidence for the inflammatory basis of atherosclerosis. Am Heart J 2005;150:488–99.
[34] Chamberlain J, Evans D, King A, Dewberry R, Dower S, Crossman D, Francis S. Interleukin-1beta and signaling of interleukin-1 in vascular wall and circulating cells modulates the extent of neointima formation in mice. Am J Pathol 2006;168:1396–403.
[35] Dunn AJ. Role of cytokines in infection-induced stress. Ann N Y Acad Sci 1993;697:189–202.
[36] Korneva EA, Rybakina EG, Orlov DS, Shamova OV, Shanin SN, Kokryakov VN. Interleukin-1 and defensins in thermoregulation, stress, and immunity. Ann N Y Acad Sci 1997;813:465–73.
[37] Galea J, Armstrong J, Gadsdon P, Holden H, Francis SE, Holt CM. Interleukin-1β in coronary arteries of patients with ischemic heart disease. Arterioscler Thromb Vasc Biol 1996;16:1000–6.
[38] Toldo S, Mezzaroma E, Bressi E, Marchetti C, Carbone S, Sonnino C, Van Tassell BW, Abbate A. Interleukin-1beta blockade improves left ventricular systolic/diastolic function and restores contractility reserve in severe ischemic cardiomyopathy in the mouse. J Cardiovasc Pharmacol 2014;64:1–6.
[39] Grothusen C, Hagemann A, Attmann T, Braesen J, Broch O, Cremer J, Schoettler J. Impact of an interleukin-1 receptor antagonist and erythropoietin on experimental myocardial ischemia/reperfusion injury. ScientificWorldJournal 2012;2012:737585.
[40] van Hout GP, Bosch L, Ellenbroek GH, de Haan JJ, van Solinge WW, Cooper MA, Arslan F, de Jager SC, Robertson AA, Pasterkamp G, Hoefer IE. The selective NLRP3-inflammasome inhibitor MCC950 reduces infarct size and preserves cardiac function in a pig model of myocardial infarction. Eur Heart J 2017;38(11):828–36. https://doi.org/10.1093/eurheartj/ehw247.
[41] Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1beta inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). Am Heart J 2011;162:597–605.
[42] Chance B, Erecinska M, Wagner M. Mitochondrial responses to carbon monoxide toxicity. Ann N Y Acad Sci 1970;174:193–204.
[43] Coburn RF. Mechanisms of carbon monoxide toxicity. Prev Med 1979;8:310–22.
[44] Satran D, Henry CR, Adkinson C, Nicholson CI, Bracha Y, Henry TD. Cardiovascular manifestations of moderate to severe carbon monoxide poisoning. J Am Coll Cardiol 2005;45:1513–6.
[45] Sloan EP, Murphy DG, Hart R, Cooper MA, Turnbull T, Barreca RS, Ellerson B. Complications and protocol considerations in carbon monoxide-poisoned patients who require hyperbaric oxygen therapy: report from a ten-year experience. Ann Emerg Med 1989;18:629–34.
[46] Johnson RA, Kozma F, Colombari E. Carbon monoxide: from toxin to endogenous modulator of cardiovascular functions. Braz J Med Biol Res 1999;32:1–14.
[47] Caumartin Y, Stephen J, Deng JP, Lian D, Lan Z, Liu W, Garcia B, Jevnikar AM, Wang H, Cepinskas G, Luke PP. Carbon monoxide-releasing molecules protect against ischemia–reperfusion injury during kidney transplantation. Kidney Int 2011;79:1080–9.
[48] Wei Y, Chen P, de Bruyn M, Zhang W, Bremer E, Helfrich W. Carbon monoxide-releasing molecule-2 (CORM-2) attenuates acute hepatic ischemia reperfusion injury in rats. BMC Gastroenterol 2010;10:42.
[49] Otterbein LE, Bach FH, Alam J, Soares M, Tao Lu H, Wysk M, Davis RJ, Flavell RA, Choi AM. Carbon monoxide has anti-inflammatory effects involving the mitogen-activated protein kinase pathway. Nat Med 2000;6:422–8.
[50] Goebel U, Mecklenburg A, Siepe M, Roesslein M, Schwer CI, Pahl HL, Priebe HJ, Schlensak C, Loop T. Protective effects of inhaled carbon monoxide in pig lungs during cardiopulmonary bypass are mediated via an induction of the heat shock response. Br J Anaesth 2009;103:173–84.
[51] Motterlini R, Clark JE, Foresti R, Sarathchandra P, Mann BE, Green CJ. Carbon monoxide-releasing molecules: characterization of biochemical and vascular activities. Circ Res 2002;90:E17–24.
[52] Foresti R, Bani-Hani MG, Motterlini R. Use of carbon monoxide as a therapeutic agent: promises and challenges. Intensive Care Med 2008;34:649–58.
[53] Clark JE, Naughton P, Shurey S, Green CJ, Johnson TR, Mann BE, Foresti R, Motterlini R. Cardioprotective actions by a water-soluble carbon monoxide-releasing molecule. Circ Res 2003;93:e2–8.
[54] Guo Y, Stein AB, Wu WJ, Tan W, Zhu X, Li QH, Dawn B, Motterlini R, Bolli R. Administration of a CO-releasing molecule at the time of reperfusion reduces infarct size in vivo. Am J Physiol Heart Circ Physiol 2004;286:H1649–53.
[55] Wang G, Hamid T, Keith RJ, Zhou G, Partridge CR, Xiang X, Kingery JR, Lewis RK, Li Q, Rokosh DG, Ford R, Spinale FG, Riggs DW, Srivastava S, Bhatnagar A, Bolli R, Prabhu SD. Cardioprotective and antiapoptotic effects of heme oxygenase-1 in the failing heart. Circulation 2010;121:1912–25.
[56] Stein AB, Guo Y, Tan W, Wu WJ, Zhu X, Li Q, Luo C, Dawn B, Johnson TR, Motterlini R, Bolli R. Administration of a CO-releasing molecule induces late preconditioning against myocardial infarction. J Mol Cell Cardiol 2005;38:127–34.
[57] Wellcome Trust Case Control C. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–78.
[58] Lusis AJ, Fogelman AM, Fonarow GC. Genetic basis of atherosclerosis: part I: new genes and pathways. Circulation 2004;110:1868–73.
[59] CAD Consortium, Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, König IR, Cazier JB, Johansson A, Hall AS, Lee JY, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K, Lundmark P, Lyytikäinen LP, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E, Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Altshuler D, Balmforth AJ, Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R, Consortium D, Consortium C, Doney AS, El Mokhtari N, Eriksson P, Fischer K, Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G, Han BG, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J, Langenberg C, Langford C, Leander K, Lokki ML, Lundmark A, MI McCarthy, Meisinger C, Melander O, Mihailov E, Maouche S, Morris AD, Muller-Nurasyid M, Mu TC, Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schafer A, Sivananthan M, Song C, Stewart AF, Tan ST, Thorgeirsson G, van der Schoot CE, Wagner PJ, Wellcome Trust Case Control C, Wells GA, Wild PS, Yang TP, Amouyel P, Arveiler D, Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F, Cupples AL, de Faire U, Dehghan A, Diemert P, Epstein SE, Evans A, Ferrario MM, Ferrieres J, Gauguier D, Go AS, Goodall AH, Gudnason V, Hazen SL, Holm H, Iribarren C, Jang Y, Kähönen M, Kee F, Kim HS, Klopp N, Koenig W, Kratzer W, Kuulasmaa K, Laakso M, Laaksonen R, Lee JY, Lind L, Ouwehand WH, Parish S, Park JE, Pedersen NL, Peters A, Quertermous T, Rader DJ, Salomaa V, Schadt E, Shah SH, Sinisalo J, Stark K, Stefansson K, Trégouët DA, Virtamo J, Wallentin L, Wareham N, Zimmermann ME, Nieminen MS, Hengstenberg C, Sandhu MS, Pastinen T, Syvänen AC, Hovingh GK, Dedoussis G, Franks PW, Lehtimäki T, Metspalu A, Zalloua PA, Siegbahn A, Schreiber S, Ripatti S, Blankenberg SS, Perola M, Clarke R, Boehm BO, O'Donnell C, Reilly MP, März W, Collins R, Kathiresan S, Hamsten A, Kooner JS, Thorsteinsdottir U, Danesh J, Palmer CN, Roberts R, Watkins H, Schunkert H, Samani NJ. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet 2013;45:25–33.
[60] Greco O, Dachs GU. Gene directed enzyme/prodrug therapy of cancer: historical appraisal and future prospectives. J Cell Physiol 2001;187:22–36.

[61] Herrero P, Kisrieva-Ware Z, Dence CS, Patterson B, Coggan AR, Han DH, Ishii Y, Eisenbeis P, Gropler RJ. PET measurements of myocardial glucose metabolism with 1-11C-glucose and kinetic modeling. J Nucl Med 2007;48:955–64.
[62] Rzhetsky A, Wajngurt D, Park N, Zheng T. Probing genetic overlap among complex human phenotypes. Proc Natl Acad Sci U S A 2007;104:11694–9.
[63] Ravenscroft D, Kunst G, Boston-Griffiths E, Kolvekar S, Chaubey S, Johnson L, Desai J, Yelken D. The effect of cyclosporin-a on peri-operative myocardial injury in adult patients undergoing coronary artery bypass graft surgery: a randomised controlled clinical trial. Heart 2014;100:544–9.
[64] Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, Elbelghiti R, Cung TT, Bonnefoy E, Angoulvant D, Macia C, Raczka F, Sportouch C, Gahide G, Finet G, André-Fouët X, Revel D, Kirkorian G, Monassier JP, Derumeaux G, Ovize M. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. N Engl J Med 2008;359:473–81.
[65] Mewton N, Croisille P, Gahide G, Rioufol G, Bonnefoy E, Sanchez I, Cung TT, Sportouch C, Angoulvant D, Finet G, André-Fouet X, Derumeaux G, Piot C, Vernhet H, Revel D, Ovize M. Effect of cyclosporine on left ventricular remodeling after reperfused myocardial infarction. J Am Coll Cardiol 2010;55:1200–5.
[66] Lim WY, Meerkin CM, Berry C. Cyclosporin variably and inconsistently reduces infarct size in experimental models of reperfused myocardial infarction: a systematic review and meta-analysis. Br J Pharmacol 2012;165:2034–43.
[67] Cung TT, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, Bonnefoy-Cudraz E, Guerin P, Elbaz M, Delarche N, Coste P, Vanzetto G, Metge M, Aupetit JF, Jouve B, Motreff P, Tron C, Labeque JN, Steg PG, Cottin Y, Range G, Clerc J, Claeys MJ, Coussement P, Prunier F, Moulin F, Roth O, Belle L, Dubois P, Barragan P, Gilard M, Piot C, Colin P, De Poli F, Morice MC, Ider O, Dubois-Rande JL, Unterseeh T, Le Breton H, Beard T, Blanchard D, Grollier G, Malquarti V, Staat P, Sudre A, Elmer E, Hanssen M, Berger C, Ben Hadda I, Jouan C, Derumeaux G, Mewton N, Ovize M. Cyclosporine before PCI in patients with acute myocardial infarction. N Engl J Med 2015;373:1021–31.
[68] Omani F, Latini R, Staszewsky L, La Vecchia L, Locuratolo N, Sicuro M, Masson S, Barlera S, Milani V, Lombardi M, Contaldo F, Mollichelli N, Santarelli A, De Cesare N, Sganzerla P, Bolognese L, Maggioni AP, Limbruno U, Investigators C. Cyclosporine a in Reperfused myocardial infarction: The Multicenter, Controlled, Open-Label CYCLE Trial. J Am Coll Cardiol 2016;67:305–14.
[69] Brenner C, Moulin M. Physiological roles of the permeability transition pore. Circ Res 2012;111:1237–47.
[70] Argaud L, Gateau-Roesch O, Raisky O, Loufouat J, Robert D, Ovize M. Postconditioning inhibits mitochondrial permeability transition. Circulation 2005;111:194–7.
[71] Bucundo HT, Kowalowski AJ. Letter regarding article by Argaud et al, "postconditioning inhibits mitochondrial permeability transition". Circulation 2005;111:e462 (author reply e462).
[72] Kevelaitis E, Qureshi AA, Mosaic C, Marotte F, Kavelaitiene S, Avkiran M, Menasche P. Na^+/H^+ exchange inhibition in hypertrophied myocardium subjected to cardioplegic arrest: an effective cardioprotective approach. Eur J Cardiothorac Surg 2005;27:111–6.
[73] Rapprecht HJ, Vom Dahl J, Terres W, Seyfarth KM, Richardt G, Schultheiss HP, Bartorelli AL, Sheehan FH, Drexler H. Cardioprotective effect of the Na^+/H^+ exchange inhibitor cariporide in patients with acute anterior myocardial infarction undergoing direct PTCA. Circulation 2000;101:2892–8.
[74] Seki SI, Galanopoulos PT, Kashihara H, Talling DN, Leblanc JG, Tibbits GF. Na^+/H^+ exchange inhibition with HOE 642 improves recovery of the injured neonatal rabbit heart. Can J Cardiol 2003;19:1515–9.
[75] Zeymer U, Suryapranata H, Monassier JP, Opolski G, Davies J, Rasmanis G, Linssen G, Tebbe U, Schroder R, Tiemann R, Machnig T, Neuhaus KL, Investigators E. The Na^+/H^+ exchange inhibitor eniporide as an adjunct to early reperfusion therapy for acute myocardial infarction. Results of the evaluation of the safety and cardioprotective effects of eniporide in acute myocardial infarction (ESCAMI) trial. J Am Coll Cardiol 2001;38:1644–50.
[76] Bar FW, Tzivoni D, Dirksen MT, Fernandez-Ortiz A, Heyndrickx GR, Brachmann J, Reiber JH, Avanthy N, Tatsuno J, Davies M, Hibberd MG, Kracoff MW. Results of the first clinical study of adjunctive CAldaret (MCC-135) in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: the randomized multicentre CASTEMI study. Eur Heart J 2006;27:2516–23.
[77] Atar D, Arheden H, Berdeaux A, Bonnet JL, Carlsson M, Clemmensen P, Cuvier V, Danchin N, Dubois-Rande JL, Engblom H, Erlinge D, Fjrat H, Halvorsen S, Hansen HE, Hauke W, Heiberg E, Koul S, Larsen AI, Le Corvoisier P, Nordrehaug JE, Paganelli F, Pruss RM, Rousseau H, Schuller S, Soman G, Traneb V, Veje J, Vicaut E, Jensen SE. Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: MITOCARE study results. Eur Heart J 2015;36:112–9.
[78] Chakrabarti AK, Feeney K, Abueg C, Brown DA, Cayc E, Tendera M, Janosi A, Giugliano RP, Kloner RA, Weaver WD, Bode C, Godlewski J, Merlocy B, Gibson CM. Rationale and design of the EMBRACE STEMI study: a phase 2a, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability and efficacy of intravenous Bendavia on reperfusion injury in patients treated with standard therapy including primary percutaneous coronary intervention and stenting for ST-segment elevation myocardial infarction. Am Heart J 2013;165:508–14.
[79] Lincoff AM, Roe M, Aylward P, Gallo J, Rynkiewicz A, Guetta V, Zeiher M, Kleiman N, White H, McErlean E, Erlinge D, Laine M, Dos Santos Pereira JM, Goodman S, Mehta S, Atar D, Suryapranata H, Jensen SE, Ferrer T, Fernandez-Ortiz A, Schoos D, Radice P, Bell C, Brennan D, Bell G, Kracoff M. Inhibition of delta-protein kinase C by delcasertib as an adjunct to primary percutaneous coronary intervention for acute anterior ST-segment elevation myocardial infarction: results of the PROTECTION AMI randomized controlled trial. Eur Heart J 2014;35:2516–23.
[80] Ye Y, Birnbaum GD, Perez-Polo JR, Nanhwan MK, Nylander S, Birnbaum Y. Ticagrelor protects the heart against reperfusion injury and improves remodeling after myocardial infarction. Arterioscler Thromb Vasc Biol 2015;35:1805–14.
[81] Totani L, Dell'Elba G, Martelli N, Di Santo A, Piccoli A, Amore C, Evangelista V. Prasugrel inhibits platelet-leukocyte interaction and reduces inflammatory markers in a model of endotoxic shock in the mouse. Thromb Haemost 2012;107:1130–40.
[82] De Hert S, Vlasselaers D, Barbe R, Ory JP, Delcogel D, Donnadonni R, Demeere JL, Muller J, Wouters P. A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery. Anaesthesia 2009;64:953–60.
[83] De Hert SG, Van der Linden PJ, Cromheecke S, Meeus R, Nelis A, Van Reeth V, ten Broecke PW, De Blier IG, Stockman BA, Rodrigus IE. Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. Anesthesiology 2004;101:299–310.
[84] Tritapepe L, Landoni G, Guarracino F, Rompel F, Crivellari M, Maselli D, De Luca M, Fochi O, D'Avolio S, Bignami E, Calabro MG, Zangrillo A. Cardiac protection by volatile anaesthetics: a multicentre randomized controlled study in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Eur J Anaesthesiol 2007;24:323–31.
[85] Tempe DK, Datta D, Garg M, Minhas H, Tomar A, Virmani S. Myocardial protection with isoflurane during off-pump coronary artery bypass grafting: a randomized trial. J Cardiothorac Vasc Anesth 2011;25:59–65.
[86] Amr YM, Yassin IM. Cardiac protection during on-pump coronary artery bypass grafting: ischemic versus isoflurane preconditioning. Semin Cardiothorac Vasc Anesth 2010;14:205–11.
[87] Lonborg J, Kelbaek H, Vejlstrup N, Botker HE, Kim WY, Holmvang L, Jorgensen E, Helqvist S, Saunamaki K, Terkelsen CJ, Schoos MM, Kober L, Clemmensen P, Treiman M, Engstrom T. Exenatide reduces final infarct size in patients with ST-segment-elevation myocardial infarction and short-duration of ischemia. Circ Cardiovasc Interv 2012;5:288–95.
[88] Najjar SS, Rao SV, Melloni C, Raman SV, Povsic TJ, Melton I, Ilarraza GW, Prather K, Heitner JF, Kilaru R, Gruberg L, Harrabiad V, Greenhaus mAB, Patel M, Kim RJ, Talan M, Bernard L, Longo DL, Lakatta EG, Harrington RA. Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction: REVEAL: a randomized controlled trial. JAMA 2011;305:1863–72.
[89] Mahaffey KW, Puma JA, Barhaghpaka NR, Dicarli MF, Lesnar MA, Browne KF, Stuenberg BR, Bolli R, Casas AC, Molina-Viamonte V, Orlandi C, Blevins R, Gibbons RJ, Califf RM, Granger CB. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. J Am Coll Cardiol 1995;34:1711–20.
[90] Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW, Investigators A-I. A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). J Am Coll Cardiol 2005;45:1775–80.
[91] Foldenma MI, Vlaar PJ, Vogelzang M, Gu YL, Kamp inga MA, deSmet BJ, Jessurun GA, Anthonio RL, van den Heuvel AF, Tan ES, Zijlstra F. Effect of high-dose intracoronary adenosine administration during primary percutaneous coronary intervention in acute myocardial infarction: a randomized controlled trial. Circ Cardiovasc Interv 2009;2:323–9.
[92] Siddiqi IN, Nelli C, Bruce M, MacLennan G, Corron S, Papadopoulou S, Pavlinch M, Bunce N, Lim PO, Hildick-Smith D, Shirwitz J, Madhani M, Boon N, Dawson D, Karki JC, Freemeaux M. Intravenous sodium nitrite in acute ST-elevation myocardial infarction: a randomized controlled trial (NAMI). Eur Heart J 2014;35:1255–62.
[93] Jones DA, Pellaton C, Velmurugan S, Rathod KS, Andiapen M, Antoniou S, van Eijl S, Webb AJ, Westwood MA, Rumar MK, Mathur A, Ahluwalia A. Randomized phase 2 trial of intracoronary nitrite during acute myocardial infarction. Circ Res 2015;116:437–47.
[94] ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet 1995;345:669–85.
[95] Tan K, Salie N, Taub N, Sowton E. Clinical and lesion morphologic determinants of coronary angioplasty success and complications: current experience. J Am Coll Cardiol 1995;25:855–65.
[96] Kitakaze M, Asakura M, Kim J, Shintani Y, Asanuma H, Hamasaki T, Seguchi O, Myoishi M, Minamino T, Ohara T, Nagai Y, Nanto S, Watanabe K, Fukuzawa S, Hirayama A, Nakamura N, Kimura K, Fuji K, Ishihara M, Saito Y, Tomoike H, Kitamura S, Investigators JW. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. Lancet 2007;370:1483–93.
[97] Gomez L, Thibault H, Gharib A, Dumont JM, Vuagniaux G, Scalbro F, Derumeaux G, Ovize M. Inhibition of mitochondrial permeability transition improves functional recovery and reduces mortality following acute myocardial infarction in mice. Am J Physiol Heart Circ Physiol 2007;293:H1654–61.
[98] Ikeno F, Inagaki K, Renaee M, Mochly-Rosen D. Impaired perfusion after myocardial infarction is due to reperfusion-induced deltaPKC-mediated myocardial damage. Cardiovasc Res 2007;73:699–709.
[99] Inagaki K, Chen L, Ikeno F, Lee FH, Imahashi K, Bouley DM, Renaee M, York PG, Murphy E, Mochly-Rosen D. Inhibition of delta-protein kinase C protects against reperfusion injury of the ischemic heart in vivo. Circulation 2003;108:2306–7.
[100] Jones SP, Gibson MF, Rimmer 3rd DM, Gibson TM, Sharp BR, Teiler DJ. Direct vascular and cardioprotective effects of rosuvastatin, a new HMG-CoA reductase inhibitor. J Am Coll Cardiol 2002;40:1172–8.
[101] Darhuilian C, Shiva S, Aleksenyenko A, Pendyal A, Beiser DG, Munasinghe JP, Anderson SA, Chesley CF, Vanden Hoek TL, Gladwin MT. Nitrite therapy after

cardiac arrest reduces reactive oxygen species generation, improves cardiac and neurological function, and enhances survival via reversible inhibition of mitochondrial complex I. Circulation 2009;120:897–905.
[102] Hendgen-Cotta UB, Merx MW, Shiva S, Schmitz J, Becher S, Klare JP, Steinhoff HJ, Goedecke A, Schrader J, Gladwin MT, Kelm M, Rassaf T. Nitrite reductase activity of myoglobin regulates respiration and cellular viability in myocardial ischemia-reperfusion injury. Proc Natl Acad Sci U S A 2008;105:10256–61.
[103] Zhou R, Xu Q, Zheng P, Yan L, Zheng J, Dai G. Cardioprotective effect of fluvastatin on isoproterenol-induced myocardial infarction in rat. Eur J Pharmacol 2008;586:244–50.
[104] Jun JH, Jun NH, Shim JK, Shin EJ, Kwak YL. Erythropoietin protects myocardium against ischemia-reperfusion injury under moderate hyperglycemia. Eur J Pharmacol 2014;745:1–9.
[105] Dorsch M, Behmenburg F, Raible M, Blase D, Grievink H, Hollmann MW, Heinen A, Huhn R. Morphine-induced preconditioning: involvement of protein kinase a and mitochondrial permeability transition pore. PLoS One 2016;11:e0151025.
[106] Small BA, Lu Y, Hsu AK, Gross GJ, Gross ER. Morphine reduces myocardial infarct size via heat shock protein 90 in rodents. Biomed Res Int 2015;2015:129612.
[107] Zhang LZ, Guo Z. Tramadol reduces myocardial infarct size and expression and activation of nuclear factor kappa B in acute myocardial infarction in rats. Eur J Anaesthesiol 2009;26:1048–55.
[108] Iliodromitis EK, Andreadou I, Prokovas E, Zoga A, Farmakis D, Fotopoulou T, Ioannidis K, Paraskevaidis IA, Kremastinos DT. Simvastatin in contrast to postconditioning reduces infarct size in hyperlipidemic rabbits: possible role of oxidative/nitrosative stress attenuation. Basic Res Cardiol 2010;105:193–203.
[109] Thornton JD, Liu GS, Olsson RA, Downey JM. Intravenous pretreatment with A1-selective adenosine analogues protects the heart against infarction. Circulation 1992;85:659–65.
[110] Yang XM, Philipp S, Downey JM, Cohen MV. Atrial natriuretic peptide administered just prior to reperfusion limits infarction in rabbit hearts. Basic Res Cardiol 2006;101:311–8.
[111] Wayman NS, Ellis BL, Thiemermann C. Simvastatin reduces infarct size in a model of acute myocardial ischemia and reperfusion in the rat. Med Sci Monit 2003;9:BR155–.
[112] Scholz W, Albus U, Counillon L, Gogelein H, Lang HJ, Linz W, Weichert A, Scholkens BA. Protective effects of HOE642, a selective sodium-hydrogen exchange subtype 1 inhibitor, on cardiac ischaemia and reperfusion. Cardiovasc Res 1995;29:260–8.
[113] Brown DA, Hale SL, Baines CP, del Rio CL, Hamlin RL, Yueyama Y, Kijtawornrat A, Yeh ST, Frasier CR, Stewart LM, Moukdar F, Shaikh SR, Fisher-Wellman KH, Neufer PD, Kloner RA. Reduction of early reperfusion injury with the mitochondria-targeting peptide bendavia. J Cardiovasc Pharmacol Ther 2014;19:121–32.
[114] Argaud L, Gateau-Roesch O, Muntean D, Chalabreysse L, Loufouat J, Robert D, Ovize M. Specific inhibition of the mitochondrial permeability transition prevents lethal reperfusion injury. J Mol Cell Cardiol 2005;38:367–74.
[115] Pitarys 2nd CJ, Virmani R, Vildibill Jr HD, Jackson EK, Forman MB. Reduction of myocardial reperfusion injury by intravenous adenosine administered during the early reperfusion period. Circulation 1991;83:237–47.
[116] Thurner V, Grunert S, Bier F, Schlack W. Effect of magnesium on infarct size after coronary occlusion. Animal experiment studies. Herz 1997;1:35–9.
[117] Kupatt C, Hinkel R, Horstkotte J, Deiss M, von Bruhl ML, Bilber M, Boekstegers P. Selective retroinfusion of GSH and cariporide attenuates myocardial ischemia-reperfusion injury in a preclinical pig model. Cardiovasc Res 2004;61:530–7.
[118] Gross ER, Hsu AK, Gross GJ. Opioid-induced cardioprotection occurs via glycogen synthase kinase beta inhibition during reperfusion in intact rat hearts. Circ Res 2004;94:960–6.
[119] Obame FN, Plin-Mercier C, Assaly R, Zini R, Dubois-Rande JL, Berdeaux A, Morin D. Cardioprotective effect of morphine and a blocker of glycogen synthase kinase 3 beta, SB216763 [3-(2,4-dichlorophenyl)-4(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione], via inhibition of the mitochondrial permeability transition pore. J Pharmacol Exp Ther 2008;326:252–8.
[120] Gwag HB, Kim EK, Park TK, Lee JM, Yang JH, Song YB, Choi JH, Choi SH, Lee SH, Chang SA, Park SJ, Lee SC, Park SW, Jang WJ, Lee M, Chun WJ, Oh JH, Park YH, Choe YH, Gwon HC, Hahn JY. Cardioprotective effects of intracoronary morphine in ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: a prospective, randomized trial. J Am Heart Assoc 2017;6.
[121] Warltier DC, Pagel PS, Kersten JR. Approaches to the prevention of perioperative myocardial ischemia. Anesthesiology 2000;92:253–9.
[122] Lavi S, Alemayehu M, McCarty D, Warrington J, Lavi R. One-year outcome of the sevoflurane in acute myocardial infarction randomized trial. Can J Anaesth 2015;62:1279–86.
[123] Takahata O, Ichihara K, Ogawa H. Effects of sevoflurane on ischaemic myocardium in dogs. Acta Anaesthesiol Scand 1995;39:449–56.
[124] Lonborg J, Vejlstrup N, Kelbaek H, Botker HE, Kim WY, Mathiasen AB, Jorgensen E, Helqvist S, Saunamaki K, Clemmensen P, Holmvang L, Thuesen L, Krusell LR, Jensen JS, Kober L, Treiman M, Holst JJ, Engstrom T. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. Eur Heart J 2012;33:1491–9.
[125] Woo JS, Kim W, Ha SJ, Kim JB, Kim SJ, Kim WS, Seon HJ, Kim KS. Cardioprotective effects of exenatide in patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of exenatide myocardial protection in revascularization study. Arterioscler Thromb Vasc Biol 2013;33:2252–60.
[126] Bernink FJ, Timmers L, Beek AM, Diamant M, Roos ST, Van Rossum AC, Appelman Y. Progression in attenuating myocardial reperfusion injury: an overview. Int J Cardiol 2014;170:261–9.
[127] Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998;97:1129–35.
[128] Yamakuchi M, Greer JJ, Cameron SJ, Matsushita K, Morrell CN, Talbot-Fox K, Baldwin 3rd WM, Lefer DJ, Lowenstein CJ. HMG-CoA reductase inhibitors inhibit endothelial exocytosis and decrease myocardial infarct size. Circ Res 2005;96:1185–92.
[129] Matsuki A, Igawa A, Nozawa T, Nakadate T, Igarashi N, Nonomura M, Inoue H. Early administration of fluvastatin, but not at the onset of ischemia or reperfusion, attenuates myocardial ischemia-reperfusion injury through the nitric oxide pathway rather than its antioxidant property. Circ J 2006;70:1643–9.
[130] Berne RM. The role of adenosine in the regulation of coronary blood flow. Circ Res 1980;47:807–13.
[131] Dole WP, Yamada N, Bishop VS, Olsson RA. Role of adenosine in coronary blood flow regulation after reductions in perfusion pressure. Circ Res 1985;56:517–24.
[132] Christensen CW, Rieder MA, Silverstein EL, Gencheff NE. Magnesium sulfate reduces myocardial infarct size when administered before but not after coronary reperfusion in a canine model. Circulation 1995;92:2617–21.
[133] Magnesium in Coronaries Trial I. Early administration of intravenous magnesium to high-risk patients with acute myocardial infarction in the magnesium in coronaries (MAGIC) trial: a randomised controlled trial. Lancet 2002;360:1189–96.
[134] Gonzalez FM, Shiva S, Vincent PS, Ringwood LA, Hsu LY, Hon YY, Aletras AH, Cannon 3rd RO, Gladwin MT, Arai AE. Nitrite anion provides potent cytoprotective and antiapoptotic effects as adjunctive therapy to reperfusion for acute myocardial infarction. Circulation 2008;117:2986–94.
[135] Gambert S, Vergely C, Filomenko R, Moreau D, Bettaieb A, Opie LH, Rochette L. Adverse effects of free fatty acid associated with increased oxidative stress in postischemic isolated rat hearts. Mol Cell Biochem 2006;283:147–52.
[136] Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res 2000;86:580–8.
[137] Liu YC, Li L, Su Q, Liu T, Tang ZL. Trimetazidine pretreatment inhibits myocardial apoptosis and improves cardiac function in a Swine model of coronary microembolization. Cardiology 2015;130:130–6.
[138] Kober G, Buck T, Sievert H, Vallbracht C. Myocardial protection during percutaneous transluminal coronary angioplasty: effects of trimetazidine. Eur Heart J 1992;13:1109–15.
[139] Bonello L, Sbragia P, Amabile N, Com O, Pierre SV, Levy S, Paganelli F. Protective effect of an acute oral loading dose of trimetazidine on myocardial injury following percutaneous coronary intervention. Heart 2007;93:703–7.
[140] El-Kady T, El-Sabban K, Gabaly M, Sabry A, Abdel-Hady S. Effects of trimetazidine on myocardial perfusion and the contractile response of chronically dysfunctional myocardium in ischemic cardiomyopathy: a 24-month study. Am J Cardiovasc Drugs 2005;5:271–8.
[141] Effect of 48-h intravenous trimetazidine on short- and long-term outcomes of patients with acute myocardial infarction, with and without thrombolytic therapy; A double-blind, placebo-controlled, randomized trial The EMIP-FR group European myocardial infarction project—free radicals. Eur Heart J 2000;21:1537–46.
[142] Grynberg A. The EMIP-FR study: the evolution of scientific background as a non-controlled parameter. Eur Heart J 2001;22:975–7 [author reply 978].
[143] Gibson CM, Giugliano RP, Kloner RA, Bode C, Tendera M, Janosi A, Merkely B, Godlewski J, Halaby R, Korjian S, Daaboul Y, Chakrabarti AK, Spielman K, Neal BJ, Weaver WD. EMBRACE STEMI study: a Phase 2a trial to evaluate the safety, tolerability, and efficacy of intravenous MTP-131 on reperfusion injury in patients undergoing primary percutaneous coronary intervention. Eur Heart J 2016;37:1296–303.
[144] Gao F, Tao L, Yan W, Gao E, Liu HR, Lopez BL, Christopher TA, Ma XL. Early anti-apoptosis treatment reduces myocardial infarct size after a prolonged reperfusion. Apoptosis 2004;9:553–9.
[145] Qin Y, Yu Y, Dong H, Bian X, Guo X, Dong S. MicroRNA 21 inhibits left ventricular remodeling in the early phase of rat model with ischemia-reperfusion injury by suppressing cell apoptosis. Int J Med Sci 2012;9:413–23.
[146] Strauer BE, Brehm M, Zeus T, Kostering M, Hernandez A, Sorg RV, Kogler G, Wernet P. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation 2002;106:1913–8.
[147] Assmus B, Schachinger V, Teupe C, Britten M, Lehmann R, Dobert N, Grunwald F, Aicher A, Urbich C, Martin H, Hoelzer D, Dimmeler S, Zeiher AM. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). Circulation 2002;106:3009–17.
[148] Fernandez-Aviles F, San Roman JA, Garcia-Frade J, Fernandez ME, Penarrubia MJ, de la Fuente L, Gomez-Bueno M, Cantalapiedra A, Fernandez J, Gutierrez O, Sanchez PL, Hernandez C, Sanz R, Garcia-Sancho J, Sanchez A. Experimental and clinical regenerative capability of human bone marrow cells after myocardial infarction. Circ Res 2004;95:742–8.
[149] Bartunek J, Vanderheyden M, Vandekerckhove B, Mansour S, De Bruyne B, De Bondt P, Van Haute I, Lootens N, Heyndrickx G, Wijns W. Intracoronary injection of CD133-positive enriched bone marrow progenitor cells promotes cardiac recovery after recent myocardial infarction: feasibility and safety. Circulation 2005;112:I178–83.
[150] Chen SL, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, Zhang JJ, Chunhua RZ, Liao LM, Lin S, Sun JP. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. Am J Cardiol 2004;94:92–5.
[151] Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, Fichtner S, Korte T, Hornig B, Messinger D, Arseniev L, Hertenstein B, Ganser A, Drexler H. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet 2004;364:141–8.

[152] Janssens S, Dubois C, Bogaert J, Theunissen K, Deroose C, Desmet W, Kalantzi M, Herbots L, Sinnaeve P, Dens J, Maertens J, Rademakers F, Dymarkowski S, Gheysens O, Van Cleemput J, Bormans G, Nuyts J, Belmans A, Mortelmans L, Boogaerts M, Van de Werf F. Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. Lancet 2006;367:113–21.

[153] Lunde K, Solheim S, Aakhus S, Arnesen H, Abdelnoor M, Egeland T, Endresen K, Ilebekk A, Mangschau A, Fjeld JG, Smith HJ, Taraldsrud E, Grogaard HK, Bjornerheim R, Brekke M, Muller C, Hopp E, Ragnarsson A, Brinchmann JE, Forfang K. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med 2006;355:1199–209.

[154] Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Holschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Suselbeck T, Assmus B, Tonn T, Dimmeler S, Zeiher AM. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med 2006;355:1210–21.

[155] Moelker AD, Baks T, van den Bos EJ, van Geuns RJ, de Feyter PJ, Duncker DJ, van der Giessen WJ. Reduction in infarct size, but no functional improvement after bone marrow cell administration in a porcine model of reperfused myocardial infarction. Eur Heart J 2006;27:3057–64.

[156] Houtgraaf JH, de Jong R, Kazemi K, de Groot D, van der Spoel TI, Arslan F, Hoefer I, Pasterkamp G, Itescu S, Zijlstra F, Geleijnse ML, Serruys PW, Duckers HJ. Intracoronary infusion of allogeneic mesenchymal precursor cells directly after experimental acute myocardial infarction reduces infarct size, abrogates adverse remodeling, and improves cardiac function. Circ Res 2013;113:153–66.

[157] Williams AR, Hatzistergos KE, Addicott B, McCall F, Carvalho D, Suncion V, Morales AR, Da Silva J, Sussman MA, Heldman AW, Hare JM. Enhanced effect of combining human cardiac stem cells and bone marrow mesenchymal stem cells to reduce infarct size and to restore cardiac function after myocardial infarction. Circulation 2013;127:213–23.

[158] Turunen MP, Husso T, Musthafa H, Laidinen S, Dragneva G, Laham-Karam N, Honkanen S, Paakinaho A, Laakkonen JP, Gao E, Vihinen-Ranta M, Liimatainen T, Yla-Herttuala S. Epigenetic upregulation of endogenous VEGF-A reduces myocardial infarct size in mice. PLoS One 2014;9.

[159] Zhou SS, Tian F, Chen YD, Wang J, Sun ZJ, Guo J, Jin QH. Combination therapy reduces the incidence of no-reflow after primary per-cutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction. J Geriatr Cardiol 2015;12:135–42.

The effect of fresh versus standard blood transfusion on microvascular endothelial function

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Background The duration of red blood cell (RBC) storage may have a negative impact on endothelial nitric oxide bioavailability. We tested the hypothesis that transfused fresh blood will have a more favorable effect on microvascular endothelial function as compared to older standard issue blood.

Methods Participants requiring chronic RBC transfusions were enrolled in a crossover design study to receive fresh (<7 days of storage) or standard (up to 42 days of storage) blood on 2 separate visits. Endothelial function was assessed by reactive hyperemia peripheral arterial tonometry that was measured before and after transfusions. For each participant, the difference between endothelial function pretransfusion and posttransfusion was assessed in relation to blood storage time.

Results Twenty-one patients (71 ± 16 years, 52% females) were enrolled. Mean age of fresh blood was 5.5 days (±1.0), and that of standard blood was 24.5 days (±7.9 days). The pretransfusion hemoglobin was 83.1 ± 2.5 g/L; and posttransfusion, 98.9 ± 2.6 g/L. An average of 2 U of packed RBCs was transfused. Microvascular endothelial function decreased more frequently after transfusion of standard blood compared to fresh blood. Standard issue blood transfusion was associated with decrease in reactive hyperemia peripheral arterial tonometry index (−0.25 ± 0.63) compared to fresh blood (+0.03 ± 0.49); $P = .026$.

Conclusion Transfusions of standard issue blood are associated with less favorable effect on microvascular endothelial function as compared to fresh blood. (Am Heart J 2016;181:156-61.)

Blood transfusion laboratories play a central role in ensuring an adequate and safe supply of blood products needed for various medical conditions.[1] Red blood cells (RBCs) are usually processed as a concentrated preparation, packed RBC (pRBC), from whole blood by removing the plasma. Packed RBC transfusion is a common therapeutic intervention worldwide, and it is the number 1 discharge code diagnosis of admitted patients in the United States[2] with approximately 85 million units of RBCs transfused annually.[3] Storage of RBC products for up to 42 days has greatly facilitated the ability of transfusion services to meet the ever-growing demands for transfusion.[4] Current evidence indicates that storage of RBCs in nutrient media for up to 42 days maintains adequate RBC 2,3-diphosphoglycerate and ATP levels and a 24-hour posttransfusion survival of at least 75% of transfused RBCs in the circulation.[5]

Prolonged storage of RBCs ex vivo, however, is associated with a number of well-described changes to RBC and the storage medium collectively referred to as the storage lesion which have been shown to have negative impact in animal models.[6]

During storage, RBCs undergo progressive structural and functional changes that reduce oxygen-transport capacity and viability, leading to hemolysis and release of microparticles, free hemoglobin, heme, and iron into the circulation.[7,8] These degradation products can actively scavenge nitric oxide (NO) via deoxygenation reaction, leading to reduced NO and subsequent vasoconstriction and endothelial dysfunction.[9] There is an ongoing debate surrounding the relationship between length of storage of RBCs and outcomes of transfused patients.[10-13]

Several recent randomized controlled trials did not detect a difference in outcomes between patients transfused with fresh and older stored blood.[12,14,15] However, with so many variables that may affect clinical outcomes, these

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studies raise as many questions as answers. It is not clear what mechanism(s) primarily underlie the RBC storage lesion and whether any of these alterations lead to potential adverse clinical outcomes that can be measured such as an effect on vascular function.

Studies in diabetic mice with endothelial dysfunction demonstrate that transfusing pRBCs stored for 14 days induces systemic vasoconstriction and inflammation as compared to fresh pRBCs stored for no longer than 48 hours.[16] The preclinical relationship between blood transfusion and associated endothelial derived factors could have potential clinical implications.[17] The aim of this study was to test the hypothesis that transfused standard issue RBCs have a negative impact on microvascular endothelial function compared to fresh RBCs.

Methods

This is an observational, case crossover, prospective, single-center study of patients attending the London Health Sciences Centre's IV Therapy Clinic.

The study was approved by the Research Ethics Board of Western University, and all participants provided written informed consent before enrollment. The study is registered at www.clinicaltrials.gov (identifier NCT02161042).

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

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Patients

Participants older than 18 years requiring chronic recurrent pRBC transfusions were enrolled to receive "fresh," defined as 7 days or less pRBC, and "standard issue" blood with storage duration up to 42 days on "first in, first out basis," on a second separate visit date. The experimental conditions were standardized at the 2 visits. All tests were performed in a relaxed calm atmosphere. Patients received the same background medications around the time of the 2 visits. They were instructed to refrain from smoking, alcohol, caffeine, and food rich in polyphenols for at least 12 hours before the study. Medications that could affect vascular reactivity were held. Each visit date lasted approximately 5 hours. Patients were allowed to have a very light breakfast at home as well as water and snack while receiving the blood transfusion. The first EndoPAT test at each visit was performed in the morning. After blood transfusion and a rest period, the second EndoPAT test at each visit was performed in the early afternoon. Participants were blinded to the type of blood transfused. The first 10 patients (group A) received standard issue blood on their first visit and fresh blood on the second visit. This sequence was reversed for the next 8 patients (group B). The last 3 patients were included in group A and received standard issue blood first (Figure 1). This order was not randomly assigned. Participants with latex allergy, life expectancy of <6 months, history and evidence of drug or alcohol abuse in the last 12 months, and any medical condition subjecting the participants to be at a higher risk for transfusion were excluded.

Endothelial function assessment

A fingertip pulse amplitude tonometry (peripheral arterial tonometry [PAT]) was used before and after blood transfusion to assess the peripheral vasodilator response, using the EndoPAT device (Itamar Medical, Inc, Caesarea, Israel). The EndoPAT has been validated as a method of microvascular endothelial function assessment in various studies.[17,18] The device uses unique biosensors placed on the tip of the index finger of each hand to measure pressure. Endothelial function is measured via a reactive hyperemia-peripheral arterial tonometry index (Rh-PAT index). The protocol for measurement of reactive hyperemia involved a baseline measurement for 5 minutes. On the test arm (nondominant arm), a blood pressure cuff was inflated 60 mm Hg above the baseline for 5 minutes. After deflation of the cuff, the PAT tracing was recorded for 5 minutes. The ratio of measured PAT signals in comparison to baseline measurements was calculated through a proprietary computer algorithm automatically normalizing for baseline signal and indexed to the contralateral arm. The calculated ratio, the Rh-PAT index, reflects the degree of endothelial function. Endothelial function was assessed at baseline and immediately after the transfusion of blood, using the EndoPAT to calculate the Rh-PAT index as described. The arm opposite to the test arm was used for blood transfusions.

Statistical analysis

Continuous variables are summarized by mean and SD or median (25th, 75th percentiles) if not normally distributed, and categorical variables are presented as counts/percentages. Comparisons between continuous variables were performed using the Student t test, paired t test, or Wilcoxon rank sum test when appropriate. Categorical variables were compared with the Pearson χ^2 test. Pearson correlation coefficients were used to quantify the univariate linear relationship between variables. P values are 2 tailed, and statistical significance was defined as $P < .05$.

Results

During the study period, 21 participants were enrolled and had transfusion of fresh and standard blood on 2 separate occasions with concomitant assessment of endothelial function. The mean age of participants was 71 ± 16 years, and 52% were females. All patients were transfusion dependent. The median duration of transfusion dependence with 25th to 75th percentiles was 1,578 days (221-3,510 days). The number of prior transfusions was 39 (18-181). The last transfusion was received 24.4 ± 11.8 days before study participation. The time interval between visits 1 and 2 was

Figure 1

Study flow diagram. All EndoPAT studies were standardized. Days reported are median.

Table I. Baseline characteristics and associated medical conditions

Characteristic	n = 21
Sex (female) (N)	11 (52%)
Age (y)	71 ± 16
Weight (kg)	73 ± 16.6
Height (m)	1.66 ± 0.10
Pretransfusion Hb (g/L)	83.1 ± 2.4
Posttransfusion Hb (g/L)	98.8 ± 2.6
Biochemical profile	
Creatinine (μmol/L)	85.5 ± 30.8
Fasting glucose (mmol/L)	7.1 ± 3.2
WBC (10⁹/L)	6.9 ± 7.17
Cholesterol (mmol/L)	3.6 ± 1.0
Triglycerides (mmol/L)	1.6 ± 1.3
HDL (mmol/L)	1.0 ± 0.4
LDL (mmol/L)	1.8 ± 0.9
Total cholesterol:HDL ratio	3.9 ± 1.4
Associated medical conditions	
Stable angina	6 (28%)
Prior myocardial infarction	2 (9.5%)
Heart failure	4 (19%)
Hypertension	9 (43%)
Hypercholesterolemia	7 (33%)
Smoking	
Former	7 (33%)
Current	4 (19%)
Never	10 (48%)
Diabetes	6 (29%)
Previous CVA/TIA	3 (14%)

Hb, Hemoglobin; WBC, white blood cell; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CVA/TIA, cerebrovascular accident/transient ischemic attack.

27 days (21-56 days). There was no significant difference between groups in any of these parameters. Concomitant medical conditions included diabetes (29%), hypertension (43%), and hypercholesterolemia (33%). The demographic and clinical characteristics of all the patients are described in Table I. Myelodysplastic syndrome (MDS) was the most frequent (57%) indication for blood transfusion (Table II). Medications used are described in Table III.

Mean age of fresh pRBCs was 5.5 ± 1.04 days, and that of standard pRBCs was 24.5 ± 7.9 days. The average pretransfusion hemoglobin was 83.09 ± 2.46 g/L, and posttransfusion value was 98.86 ± 2.64 g/L. An average of 2 U of pRBCs were transfused. There was a similar increase in hemoglobin levels by 14.0 ± 11.4 g/L after fresh blood transfusion and by 14.5 ± 8.4 g/L after standard issue blood transfusion ($P = .89$).

At baseline, patient heart rate was 71 ± 13 beats/min. Systolic and diastolic blood pressures were 119 ± 19 mm Hg and 61 ± 8 mm Hg, respectively. Posttransfusion heart rate was 69 ± 11 beats/min. Systolic and diastolic blood pressures were 121 ± 22 mm Hg and 63 ± 9 mm Hg, respectively. Hemodynamics were very similar between the first and second visits.

Baseline Rh-PAT index for the first visit (before standard or fresh transfusion) was 2.27 ± 0.74; and at the second visit, 2.28 ± 0.58 ($P = .69$).

Baseline Rh-PAT index before standard blood transfusion was 2.41 ± 0.68 and decreased posttransfusion to 2.16 ± 0.75 ($P = .08$). The Rh-PAT index at baseline before fresh blood transfusion was 2.18 ± 0.55; and post-fresh blood transfusion, 2.21 ± 0.7 ($P = .78$). There was no significant difference between Rh-PAT index at the baseline visit for standard transfusion and the baseline visit for fresh transfusion ($P = .34$).

Baseline EndoPAT values were 2.1 ± 0.22 for patients with MDS and 2.48 ± 0.23 for patients with other hematologic conditions ($P = .21$).

The baseline EndoPAT measurements were significantly correlated with body mass index (BMI) ($P = .018$). There

Table II. Different indications for transfusion

Indications of blood transfusion	n = 21
MDS	12
Myelofibrosis	1
Red cell aplasia	1
B-cell lymphoproliferative disorders including chronic lymphocytic leukemia	2
Chronic liver disease	1
Diamond-Blackfan anemia	1
Microcytic anemia	3

Table III. Concomitant medications

Medications	%
Aspirin	9.5
Warfarin	14.3
β-Blocker	19
ACE inhibitor or ARB	33.3
Spironolactone	9.5
Lipid-lowering agent	28.6
Insulin	7.1
Oral hypoglycemic agent	28.6
Ca-channel agonists	23.8
Glyceryl trinitrate	23.8

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker.

was no significant correlation with the presence of other risk factors.

Microvascular endothelial function decreased more often after transfusion of standard pRBCs, with a decrease in Rh-PAT index (−0.25 ± 0.63) compared to minimal change on average with fresh pRBCs (+0.03 ± 0.49) ($P = .026$) (Figure 2).

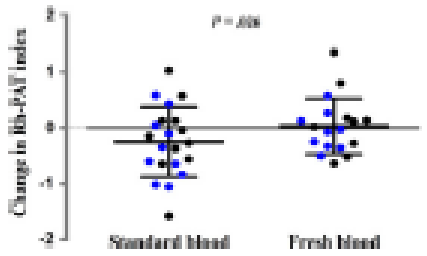
Discussion

The present study demonstrates that transfusion of standard blood may have a negative acute impact on microvascular endothelial function as compared to the transfusion of fresh blood.

The negative effect on Rh-PAT index as seen in our study is likely due to physiological changes in pRBC related to storage time.[15] Reductions in NO availability after transfusion of stored blood has been described.[4]

Standard issue blood transfusion leads to shedding of microparticles that actively scavenge NO due to deoxygenation reaction and leads to endothelial dysfunction. Indeed, a randomized trial of fresh (<14 days) versus standard issue blood (>21 days) demonstrated that NO-mediated vasodilation was reduced after transfusion of old stored blood as compared to fresh blood.[19] Our study extends this observation by its cross-over design. Endothelial dysfunction is associated with decreased NO availability and can cause vasospasm, vasoconstriction, thrombus formation, and abnormal vascular proliferation

Figure 2



Change in endothelial function. Absolute change in Rh-PAT values post transfusion compared to baseline. Blue indicates patients with MDS; black, all other patients.

leading to increased atherogenesis and enhancing the cardiovascular risks.[20]

We have not tested circulating biomarkers to further assess endothelial function. Measurement of circulating levels of nitrites and nitrosylated proteins could help in estimation of endothelial generation of NO but may not always represent endothelial NO production. Inflammatory cytokines and adhesion molecules such as E-selectin might have also been measured in the circulation.[21]

Patients with atherosclerosis often demonstrate evidence of oxidative stress and endothelial dysfunction.[22] It is unclear what the effect of blood transfusion is on such interaction and if a change in certain biomarker level is a cause or a result of endothelial dysfunction. The degradation products formed in pRBC can scavenge NO which may result in endothelial dysfunction.[9]

Endothelial dysfunction is an independent predictor of cardiovascular events.[17,18] There are different methods for assessment of endothelial function. It can be performed in the coronary arteries[26] or noninvasively in the peripheral circulation.[17,25] Two common noninvasive methods that are used are the brachial flow-mediated dilation (FMD) which assesses conduit vessel endothelial function[25] and the EndoPAT which reflects more the microcirculation.[17] These 2 tests have some degree of correlation with coronary endothelial function but measure different aspects of the vascular system, and results of both tests have been shown to correlate with clinical outcome.[26] Although FMD is a well-accepted method for assessment of endothelial function, it has limitations and is not well standardized.[26,27] The results of FMD are affected by probe position, technique for image acquisition, arterial edge detection, and software used.[25,26,28] We chose to use the EndoPAT for this study being less operator dependent, more standardized compared to brachial FMD and highly reproducible.[29] The EndoPAT results correlated with BMI but not with other risk factors. This finding is in accordance with previous studies demonstrating that the EndoPAT results are associated with metabolic risk factors such as diabetes mellitus and BMI

and less with traditional risk factors.[26,30,31] The EndoPAT results seem to provide additive information beyond traditional risk factors and thus useful in risk assessment beyond Framingham risk score.[17,31]

Blood transfusions may have an impact on endothelial dysfunction and potentially lead to worse cardiovascular outcomes. The participants in our study required repeat blood transfusions and therefore are potentially at risk due to recurrent blood transfusion effects on endothelial dysfunction.

We assessed microvascular endothelial function once following each transfusion, and therefore, our study does not provide information regarding the duration of the effect on endothelial function. Although abnormal EndoPAT results are a predictor of worse outcomes,[17,32] studies using EndoPAT often chose a single cutoff separating patients into dichotomous groups with normal or abnormal endothelial function. It is unknown if the small transient change in Rh-PAT with blood transfusion observed in our patients is clinically important. Although it is unknown if the effect of a single blood transfusion on endothelial function in participants with cardiac disease is harmful, a small-scale randomized trial showed that a liberal approach of blood transfusions was associated with increased mortality, recurrent myocardial infarction, and heart failure as compared to more restrictive use of blood transfusions in patients with acute myocardial infarction.[33] The effect of blood transfusion in patients presenting with myocardial infarction will be further assessed in the MINT trial (NCT02619136).

In a cardiac surgery cohort, blood transfusion is associated with more infections and ischemic postoperative morbidity, hospital stays, increased early and late mortality, and hospital costs.[34] A negative impact was also observed in a review of 9 studies that included patients from cardiac surgery, trauma, and intensive care.[11] A study from Cleveland clinic demonstrated that administration of standard blood (15-42 days of storage) as compared to fresher units (14 days of storage) to patients undergoing heart surgery was associated with acute negative effect including increase in in-hospital mortality and renal failure as well as increase in 1-year mortality.[35] Our study extends those observations and demonstrates acute negative impact on microvascular endothelial function which may in part account for some of the morbidity ascribed to transfusion of older stored blood in cardiac patients.

Numerous observational studies have shown conflicting results and at least 6 randomized controlled trials underway or recently completed have shown no difference in clinical outcomes due to RBC storage duration.[12,14,15] Specifically, 3 large multicenter randomized controlled trials in the critically ill,[15] cardiac patients,[12] and premature infants[14] did not identify any advantage in clinical outcomes of fresh versus older stored RBC products. It remains uncertain which of the myriad of RBC product changes during storage is important or whether any of the observed ex vivo changes has any measureable adverse clinical outcomes. Given the complexity of the RBC storage lesion and potential host disease variabilities in the population studied, even large randomized trials may be limited in their ability to provide a firm conclusion.[36]

Limitations

Our study was small in size, and therefore, the results may be impacted by intervariability and intravariability of the EndoPAT test. We limited the study to patients with hematology disorders. Therefore, it cannot be generalized to patients with other conditions including patients with cardiovascular disorders requiring blood transfusions. The long-term impact of repeat blood transfusions has not been studied.

The measurements obtained by the EndoPAT reflect the microcirculation, and therefore, the results of our study do not reflect effect of blood transfusion on conduit vessel endothelial function.

In conclusion, transfusion of standard issue blood product had a negative acute impact on microvascular endothelial function.

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References

1. Hess JR. Conventional blood banking and blood component storage regulation: opportunities for improvement. Blood Transfus 2010;8(Suppl 3):s9-15.
2. Pfuntner A, Wier LM, Stocks C. *Most frequent procedures performed in U.S. hospitals, 2010. Healthcare Cost and Utilization Project 2013.*
3. Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline from the AABB*. Ann Intern Med 2012;157(1):49-58.
4. Bennett-Guerrero E, Veldman TH, Doctor A, et al. Evolution of adverse changes in stored RBCs. Proc Natl Acad Sci U S A 2007;104(43): 17063-8.
5. Roback JD, Combs MR, Grossman BJ, Hillyer CD. *AABB technical manual. 16th ed. Maryland, USA: American Association of Blood Banks; 2008.*
6. Hess JR. Measures of stored red blood cell quality. Vox Sang 2014;107(1):1-9.
7. Donadee C, Raat NJ, Kanias T, et al. Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesion. Circulation 2011;124(4):465-76.
8. Berra L, Coppadoro A, Yu B, et al. Transfusion of stored autologous blood does not alter reactive hyperemia index in healthy volunteers. Anesthesiology 2012;117:56-63.
9. Reiter CD, Wang X, Tanus-Santos JE, et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. Nat Med 2002;8(12): 1383-9.

10. Edgren G, Kamper-Jorgensen M, Eloranta S, et al. Duration of red blood cell storage and survival of transfused patients (CME). Transfusion 2010;50(6):1185-95.
11. Tinmouth A, Fergusson D, Yee IC, et al. Clinical consequences of red cell storage in the critically ill. Transfusion 2006;46(11):2014-27.
12. Steiner ME, Ness PM, Assmann SF, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. N Engl J Med 2015;372(15):1419-29.
13. Chin-Yee I, Arya N, d'Almeida MS. The red cell storage lesion and its implication for transfusion. Transfus Sci 1997;18(3):447-58.
14. Fergusson DA, Hebert P, Hogan DL, et al. Effect of fresh red blood cell transfusion on clinical outcomes in premature, very low birth weight infants: the ARIPI randomized trial. JAMA 2012;308(14):1443-51.
15. Lacroix J, Hebert PC, Fergusson DA, et al. Age of transfused blood in critically ill adults. N Engl J Med 2015;372(15):1410-8.
16. Yu B, Lei C, Baron DM, et al. Diabetes augments and inhaled nitric oxide prevents the adverse hemodynamic effects of transfusing syngeneic stored blood in mice. Transfusion 2012;52(7):1410-22.
17. Rubinshtein R, Kuvin JT, Soffler M, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. Eur Heart J 2010;31(9):1142-8.
18. Kuvin JT, Mammen A, Mooney P, et al. Assessment of peripheral vascular endothelial function in the ambulatory setting. Vasc Med 2007;12(1):13-6.
19. Neuman R, Hayek S, Rahman A, et al. Effects of storage-aged red blood cell transfusions on endothelial function in hospitalized patients. Transfusion 2014.
20. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101(16):1899-906.
21. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation 2007;115(10):1285-95.
22. Lavi S, Yang EH, Prasad A, et al. The interaction between coronary endothelial dysfunction, local oxidative stress, and endogenous nitric oxide in humans. Hypertension 2008;51(1):127-33.
23. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003;23(2):168-75.
24. Lavi S, Prasad A, Yang EH, et al. Smoking is associated with epicardial coronary endothelial dysfunction and elevated white blood cell count in patients with chest pain and early coronary artery disease. Circulation 2007;115(20):2621-7.
25. Lavi S, Thorpe K, Lucas MC, et al. Inhibition of sPLA2 and endothelial function: a substudy of the SPIDER-PCI trial. Can J Cardiol 2012;28(2):215-21.
26. Flammer AJ, Anderson T, Celermajer DS, et al. The assessment of endothelial function: from research into clinical practice. Circulation 2012;126(6):753-67.
27. Bots ML, Westerink J, Rabelink TJ, et al. Assessment of flow-mediated vasodilatation (FMD) of the brachial artery: effects of technical aspects of the FMD measurement on the FMD response. Eur Heart J 2005;26(4):343-8.
28. Donald AE, Charakida M, Falaschetti E, et al. Determinants of vascular phenotype in a large childhood population: the Avon Longitudinal Study of Parents and Children (ALSPAC). Eur Heart J 2010;31(12):1502-10.
29. Selamet Tierney ES, Newburger JW, Gauvreau K, et al. Endothelial pulse amplitude testing: feasibility and reproducibility in adolescents. J Pediatr 2009;154(6):901-5.
30. Hamburg NM, Keyes MJ, Larson MG, et al. Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study. Circulation 2008;117(19):2467-74.
31. Hamburg NM, Palmisano J, Larson MG, et al. Relation of brachial and digital measures of vascular function in the community: the Framingham heart study. Hypertension 2011;57(3):390-6.
32. Akiyama E, Sugiyama S, Matsuzawa Y, et al. Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol 2012;60(18):1778-86.
33. Cooper HA, Rao SV, Greenberg MD, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). Am J Cardiol 2011;108(8):1108-11.
34. Murphy GJ, Reeves BC, Rogers CA, et al. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007;116(22):2544.
35. Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008;358(12):1229-39.
36. Chin-Yee IH, Chin-Yee BH, Pereira A. Clinical trials and the age of blood: ABLE but still wanting. Transfus Med 2015;25(5):349-50.