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Title	Updates Regarding Prediction and Prevention of Sudden Cardiac Death
Type	Article
URL	https://clok.uclan.ac.uk/id/eprint/35074/
DOI	
Date	2019
Citation	Elkilany, Galaleldin Nagib, Allah, Sherif Baath, Elmaha, Mohammed, Singh, Jaipaul, Singh, Ram, Elkilany, Yomna and Nanda, Navin C (2019) Updates Regarding Prediction and Prevention of Sudden Cardiac Death. EC Cardiology, 6 (11). pp. 103-121.
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Updates Regarding Prediction and Prevention of Sudden Cardiac Death

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Abstract

Sudden cardiac death (SCD) remains a major public health problem globally, especially in the United States causing more than 300,000 deaths annually. SCD from cardiac arrest is the most common cause of death worldwide, accounting for >50% of all deaths from cardiovascular diseases (CVDs) and it is characterized by unexpected collapse due to an underlying cardiovascular cause. The condition usually results from an electrical disturbance in the heart that disrupts its pumping action, stopping blood flow to the body. When the heart stops, the lack of oxygenated blood can causes death or permanent brain damage within minutes. Time is extremely critical when someone or a clinician is helping an unconscious person who is not breathing. SCD represents a major challenge for the clinician because most episodes occur in individuals without previously known cardiac disease. Hence, an early prediction of individuals at risk of SCD is the holly-grail of all physicians. Because most individuals experiencing SCD currently are not identifiable as being at high risk, community-based public access to defibrillation programs is essential to save lives and more so to improve neurological and functional outcomes for cardiac arrest victims. In order to prevent SCD, it is imperative to impose an aggressive management of cardiovascular risk factors, including performing exercise regularly, educating patients about the dangers of CVDs, promoting a healthy diet, restricting consumption of sugar, saturated fat, salt and smoking cessation to promote a heart healthy behavior to all, young children in particular. Finally, a preclinical prediction of patients at risk of SCD and early detection of the disease is crucial for early intervention and definitely will reduce the incidence of sudden cardiac death dramatically.

Keywords: Heart Attack; Coronary Thrombosis; Sudden Death; Myocardial Infarction; Cardiac Imaging; Risk Factors; Exercise

A preview of SCD

Advances regarding the prediction, prevention and management of diseases and syndromes leading to cardiac arrest and SCD have progressed rapidly since the early 1960s. The incidence of SCD may be about 20% per year in patients with heart failure and those with markers of arrhythmias, compared with about 1 - 2% in the general population, i.e. subjects with no "known" preexisting heart disease. In order to identify patients at risk of SCD, a multidisciplinary approach is an option. There are standards, as well as emerging risk stratification strategies, for patients without prior cardiac events. Syncope may herald onset of ventricular dysrhythmias and it requires prompt evaluation. However, electrocardiogram (ECG) is useful to screen for potential primary or secondary electrical abnormalities. Risk markers are dynamic and they are changing rapidly. Thus, the clinician needs to update patients risk status over time, especially after intervening cardiac events, including myocardial infarction (MI) and congestive heart failure (CHF). Most cases of sudden cardiac arrest occur in

people who have coronary artery disease (CAD) and/or multiple risk factors for CAD**.** If a heart attack occurs, often as a result of acute coronary occlusion, it can trigger ventricular fibrillation and sudden cardiac arrest. Figure 1 shows prevalence of myocardial fibrosis and other risk factors for SCD in HCM patients with ICD who present high risk for sudden death [1].
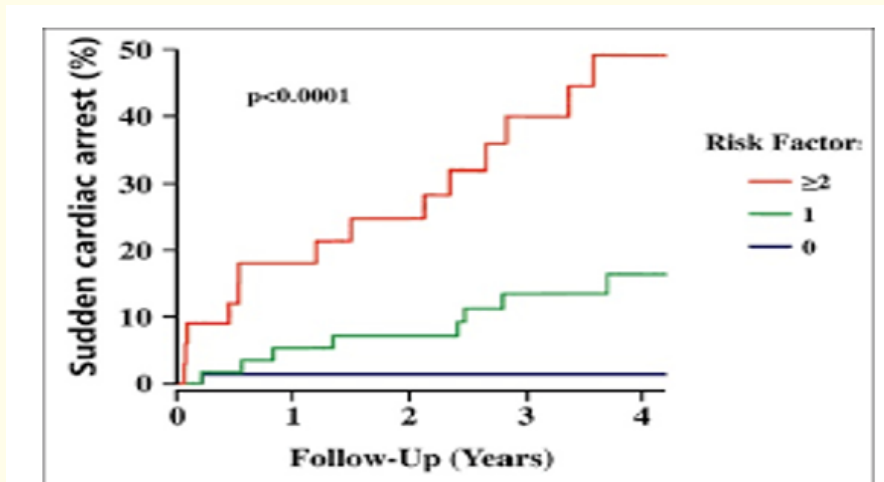

Figure 1: *Prevalence of myocardial fibrosis and other risk factors for SCD in HCM patients with ICD who present high risk for sudden death [1].*

In addition, cardiomyopathies (dilated, hypertrophic and restrictive type) and ion channelopathies (Long QT syndrome LQTS, Brugada syndrome, short QT syndrome SQTS and polymorphic ventricular tachycardia CPVT) can cause SCD as well. If not treated immediately, sudden cardiac arrest can lead to death. With fast, appropriate medical care, survival is possible. Giving cardiopulmonary resuscitation (CPR), using a defibrillator or even just giving compressions to the chest can improve the chances of survival until advanced life support and emergency workers arrive. Recent advances in cardiac imaging techniques as speckle tracking echocardiography, computed tomography and Cardiac Magnetic Resonance Imaging (CMRI) can help in the preclinical detection of patients at risk of serious cardiac arrhythmias and SCD.

In addition, multimodality approach to atherosclerosis imaging is in great progress to identify vulnerable atherosclerotic plaque liable to rupture. This is the leading cause of death in 50% or more of patients who died suddenly. Each modality offers unique measurements of disease severity. Together, this information can be used to determine anatomic and hemodynamic consequences of atherosclerosis, complimented by detail on plaque composition, overall disease burden and current metabolic activity acting within an individual patient.

Consequently, early detection of people at high risk of SCD is a must through a proper utilization of cardiovascular imaging tools. In experimental human hypertrophic cardiomyopathy (HCM), myocardial cell mechanical dysfunction precedes histopathological changes, such as myocyte disarray, fibrosis and hypertrophy. Several clinical reports have demonstrated that the majority of hypertrophic cardiomyopathy (HCM) genotype(+)/phenotype(-) subjects display myocardial functional or histopathological changes, such as reduced tissue Doppler imaging-derived systolic and diastolic velocities, abnormal ECG and cardiac magnetic resonance (CRM)-visualized myocardial crypts and evidence of a fibrotic state. Moreover, CRM can detect an increased type I procollagen synthesis by late gadolinium myocardial enhancement (Figures 2 and 4A). All these signs have been proposed as preclinical markers of HCM and those at risk of SCD. Late gadolinium enhancement (LGL) has been used to identify areas of myocardial fibrosis, which is arrhythmogenic in cardiomyopathy, right ventricular dysplasia and some cases of mitral valve prolapsed syndrome as well. Importantly, speckle tracking echocardiography (STE) is recently used as an important tool in the diagnosis of non STEMI in critical care departments, which can add greatly to the triage of diagnosis of ACS (acute coronary syndromes). Global longitudinal systolic strain speckle tracking echocardiography (STE) and Tissue

Doppler Imaging (TDI) are of crucial importance in the preclinical diagnosis of myocardial diseases specifically in HCM (+) genotype, diabetes- induced cardiomyopathy and in hypertensive heart disease.

Introduction

The syndrome of SCD represents one of the most frequent causes of death in patients with diabetes mellitus (DM), CAD and CHF [2]. SCD has not been significantly reduced, despite improvements in the treatment of acute coronary syndromes (ACSs), including acute myocardial infarction (AMI) and during long-term treatment of CVDs as well as DM [2]. Sudden cardiac arrest signs and symptoms are immediate and drastic and include sudden collapse, no pulse, no breathing and loss of consciousness. Sometimes other signs and symptoms occur before sudden cardiac arrest. These might include chest discomfort, shortness of breath, weakness, palpitations and history of syncope or pre syncope. But sudden cardiac arrest often occurs with no warning [3]. The patient should ask for immediate doctor consultation or call for emergency medical help if he or she develops episodes of chest pain or discomfort, heart palpitations, unexplained wheezing, shortness of breath, fainting or near fainting and lightheadedness or dizziness. If someone is seen unconscious and not breathing normally, then it is of paramount importance to call the emergency number for immediate help and if possible, start immediately with cardiopulmonary resuscitation (CPR) [3].

How to perform CPR?

Quickly check the breathing of the subject. If the person is not breathing normally, then begin CPR. The procedure involves pushing hard and faster on the person's chest at the rate of 100 to 120 compressions a minute. With some training in CPR, it is possible to check the person's airway and deliver rescue breaths after every 30 compressions. Allow the chest to rise completely between compressions. Keep doing this until a portable defibrillator is available or emergency workers arrive on the scene to help the patient.

Use a portable defibrillator

It is very important to continue chest compressions while the defibrillator is charging. Once ready, deliver one shock if advised by the device (i.e. if the rhythm is ventricular fibrillation) and then immediately resume CPR, starting with chest compressions, for about two minutes. Amiodarone intravenous bolus should be given to improve responsiveness to next DC shock [3]. It is also important to check the person's heart rhythm at the same time and if necessary, applied another shock to the patient with the defibrillator. It is also important to repeat this cycle until the person is recovered with consciousness or until emergency workers arrive at the scene to take over. Portable automated external defibrillators (AEDs) should be available in many places, including airports, casinos and shopping malls. They are programmed to allow a shock only when appropriate [3].

Pathophysiology

Ventricular fibrillation is the mechanism underlying most sudden cardiac arrest episodes. Survival chance declines by ≈10% per minute for patients in ventricular fibrillation. This underscores the critical importance of early and definitive intervention with defibrillation. Other events such as cardiac tachycardias, bradycardias or pulseless electric activity can also result in cessation of cardiac mechanical activity with absence of signs of circulation. Other cardiovascular causes of SCD include stroke, pulmonary embolism and aortic rupture. Cardiac arrest typically arises suddenly in an individual with the appropriate anatomic or electrophysiological substrate without an identifiable trigger. Although the current paradigm for the pathophysiology of SCD includes an abnormal myocardial substrate and transient factors that trigger the cardiac arrest. (Figure 3). The community approaches to resuscitation and care after out-of-hospital cardiac arrest is crucial for better outcomes of such patients population [2,3].

Risk factors

Sudden cardiac arrest is often linked with coronary artery disease (CAD). Moreover, the same factors which place the patient at risk of CAD can also lead to the risk of sudden cardiac arrest. Some of these risk factors include a family history of CAD, smoking, hypertension, high blood cholesterol, obesity, magnesium deficiency, DM and sedentary lifestyle (Figures 1). Other factors that might increase the risk of sudden cardiac arrest include a previous history of syncope, episodes of cardiac arrest, family history of other forms of heart disease or heart rhythm disorders, congenital heart defects, heart failure and cardiomyopathy, all of which can increase risk of SCD as well (Figure 1 and 4B) [3,13,19].
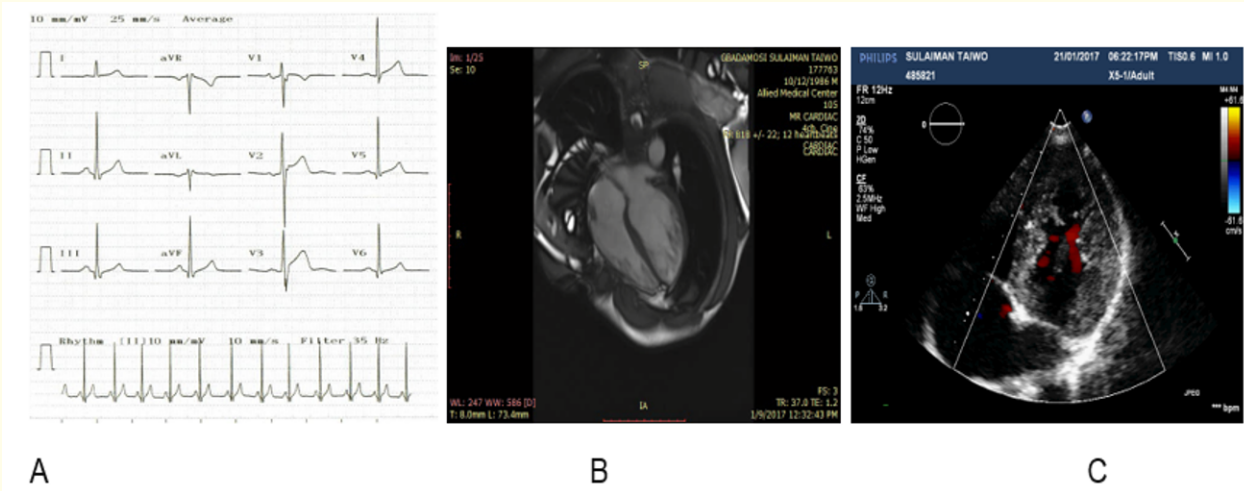
Figure 2: *(A)- Typical electrocardiogram (ECG) recordings of a patients who came with palpitation and who were diagnosed by cardiac magnetic resonance imaging (CMR) and echocardiography as Left Ventricular Non-Compaction (LVNC). The ECG traces showed a notch at up sloping of S wave in anterior chest leads (new finding in early LVNC). (B) The same patient CRM and Echocardiography (C) a scan showing 3 apical trabeculations which are exceeding 3:1 non compact to compact layer of the myocardium (with an abnormal deflection at S wave upstroke in EKG) which is a definite diagnosis of early non- compaction left ventricle (LVNC).This was first recognized by Elkilany et al in 2018 :Cardiomyopathies at risk of SCD (XXIV World Congress of Echocardiography and Allied Techniques , Albina , Bulgaria 2018).*
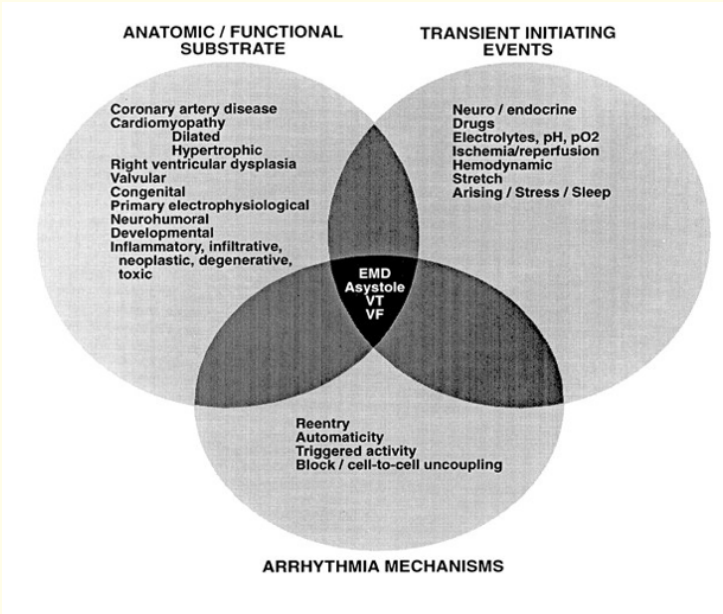

Figure 3: *Venn diagram illustrating the interaction of various anatomic/functional and transient factors that modulate potential arrhythmogenic mechanisms capable of causing sudden cardiac death (Taken from Douglas P. Zipes, and Hein J. J. Wellens Circulation. 1998;98:2334-2351).*
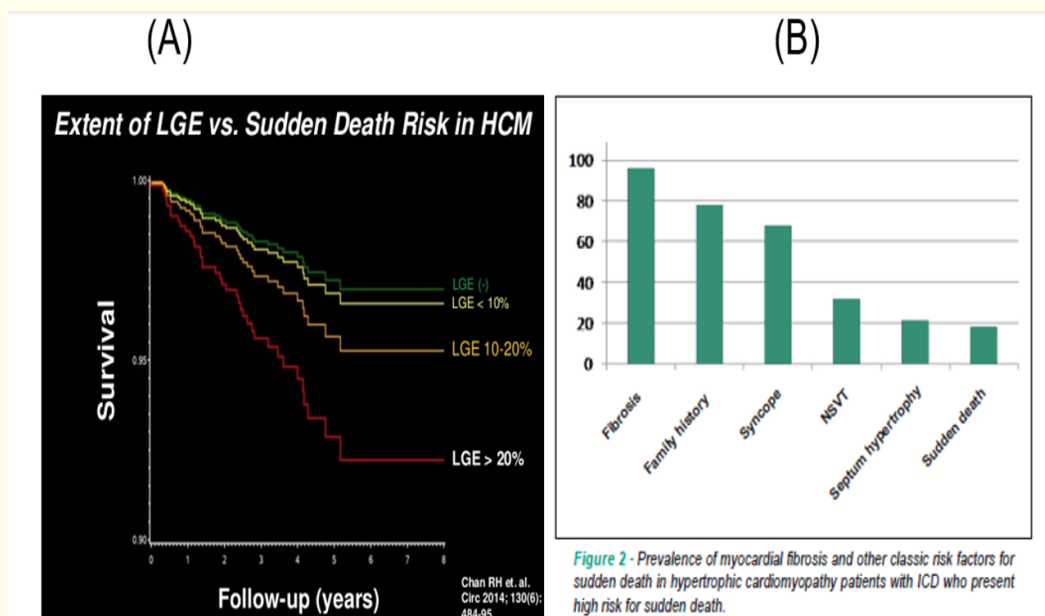
Figure 4: (A) Prognostic value of late gadolinium enhancement in clinical outcomes of SCD for hypertrophic cardiomyopathy [52]; (B) bar charts showing fibrosis and other classical risk factors for SCD in hypertrophic cardiomyopathy [52].

Preclinical detection of SCD

According to the available worldwide data of increasing incidence of SCD among general population who are at low risk of sudden death, certain emerging imaging modalities are crucial to identify such patients population. Currently, speckle tracking echocardiography is much helpful in identifying certain categories of patients presumably considered at low risk of SCD. Speckle tracking echocardiography (STE) could identify early abnormalities in left ventricle function in idiopathic left ventricular hypertrophy and during screening of hypertrophic cardiomyopathy families. Certain HCM cases did not show either any ECG abnormalities or left ventricular hypertrophy by conventional 2-dimensional echocardiography. However, they showed depressed global longitudinal peak systolic strain STE (Figure 5) [4,5].

The early clinical abnormalities in global longitudinal peak systolic strain STE (systolic dysfunction) and diminished E annular velocity (diastolic dysfunction) during tissue Doppler study can be demonstrated in apparently a symptomatic diabetic and hypertensive population [4-5]. Moreover, it was found also that two dimensional strain (2DS) was more sensitive than conventional two dimensional echocardiography (2DE) in detecting preclinical left ventricle doxorubicin-induced cardiac toxicity in children [6]. Because diabetic patients are at high risk of CAD, heart failure and SCD, novel diagnostic imaging techniques, specially tissue Doppler imaging (TDI) and systolic strain STE could identify cardiac impairment in diabetic patients earlier before the development and progression to heart failure [7]. Nevertheless, the development of more targeted therapeutic strategies will definitely improve the outcome in patients with diabetes induced- left ventricular dysfunction [7,8].

In diabetes mellitus (DM), functional alternations (diastolic and then systolic dysfunction and failure) correlate with glycemic control. These functional alterations are preceded by a variety of structural, molecular and cellular changes, many of which are present in asymptomatic diabetic individuals and experimental models of diabetes [7,8]. Moreover, alterations to myocardial and vascular integrity appear to be initiated during a pre diabetic stage. Although the etiology of diabetic cardiomyopathy is complex and multi factorial, it is of paramount importance to map a molecular, structural and functional basis for this condition [7,8].

Screening the general population for the risk of SCD, vigilance for electrocardiographic (ECG) and echocardiographic signs of inheritable arrhythmogenic diseases seems to be an important part of clinical practice and this can be can contributed to the early identification
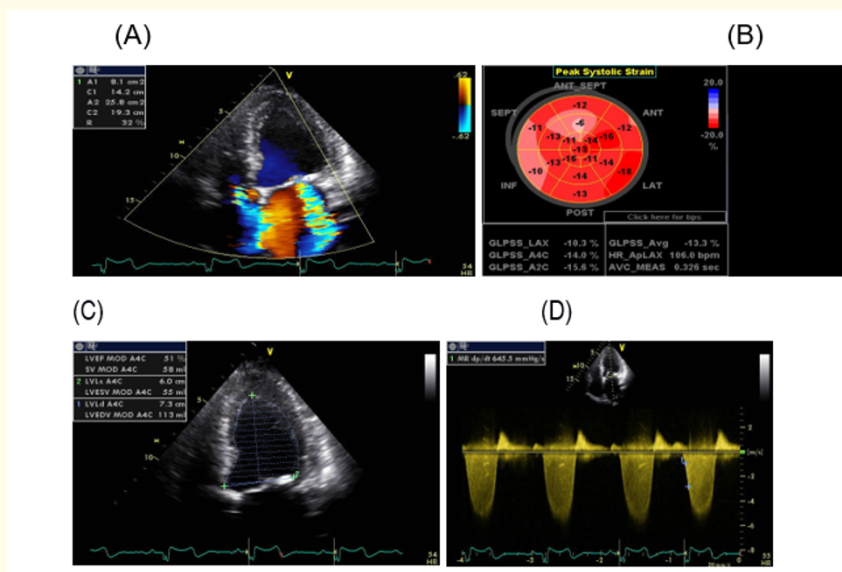
Figure 5: Bulls eye technique of automated function imaging(AFI) generated from apical 2,3 and 4 chamber views illustrated the impaired global longitudinal peak systolic strain (GLPSS) of -13% in patient with significant mitral incompetence but normal ejection fraction EF = 51%) (A) Apical 4 chambers view showed mitral incompetence (MR) grade II/IV , (B)Global longitudinal peak systolic strain -13% (normal values < -17%), (C)showed normal EF (Ejection Fraction by 2dimensional echocardiography)and (D) Rate of pressure development (MR)+dp/dt =645mmhg/s (Normal>1000-1200mmhg) which showed positive correlation to GLPSS but not with EF, Euro Echo 2009 , Spain , Madrid , Author Galal E. Nagib Elkilany ,MD [4,5].

of patients at risk of SCD. Whether such a careful approach should be extended to mass screening in populations at risk of sudden death is still unclear. Italy and Japan have implemented ECG screening systems, which may identify symptomatic patients with inheritable arrhythmogenic diseases [9]. At present, consensus exists among experts in Europe and the United States (US) which support pre-participation screening in athletes (an approach that has been endorsed by the International Olympic Committee) [10-12].

Unfortunately, there are no clear data to support the benefit of broad screening programs in the general population. Narain., *et al*. [13] screened 12,000 unselected healthy individuals 14 - 35 years of age. Screening was performed through a 12-lead ECG and consultation with a cardiologist. Individuals with abnormalities underwent a transthoracic echocardiogram. Although the screening identified only a few patients with either inheritable channelopathies or cardiomyopathies (4/12000), the authors concluded that the cost to identify individuals at increased risk of SCD might still support a mass-screening program. Consequently, it is now possible to support the existing recommendations for pre-participation screening in athletes as well as screening family members of SCD victims. The diagnosis of an inheritable arrhythmogenic disorder is established in up to 50% of families with a sudden arrhythmic death syndrome (SADS) victim, especially those with channelopathies [e.g. LQTS, Brugada syndrome and CPVT] and occasionally subtle forms of cardiomyopathy [HCM and arrhythmogenic right ventricular cardiomyopathy (ARVC) in particular]. First-degree relatives of the victim should be informed of the potential risk of similar events to themselves and should undergo cardiac evaluation. A family history of recurrent premature sudden unexpected deaths (SUDS) or inheritable heart disease represents a 'very high risk category' that makes familial evaluation strongly recommended [14].

A multidisciplinary approach of family members of SCD victims should be followed, as recently recommended [15-17]. Various protocols have been proposed for screening family members of sudden death victims [18-19] These protocols usually follow a stepwise approach, starting with lower-cost and higher-yield investigations and moving on to further examinations based on both the initial findings

and the history [19]. Whenever a diagnosis is suspected and based on the presence of either structural or electrical abnormalities, the standard procedure for the diagnosis of the suspected disease should be followed.

Accurate history taking is the first step to reach a post-mortem diagnosis. Age is very important (before or after 35 - 40 years) when the victim is young, the focus should be on cardiomyopathies and ion channelopathies. The evaluation of premonitory cardiac symptoms including syncope, palpitation or epilepsy. For older victims (> .40 years of age), the presence of risk factors for CAD should be assessed (e.g. active or passive smoking, dyslipidemia, hypertension or diabetes). In addition, a complete three-generation pedigree should be created, recording all sudden deaths and cardiac diseases [8,18,19]. Family members with symptoms suggestive of the presence of a cardiac condition, such as syncope, palpitations or chest pain, should be prioritized for evaluation. In the absence of a definite diagnosis in the family, very young children should be screened at least with a baseline ECG and an echocardiogram. Asymptomatic and adults can be discharged from care unless symptoms appear or new information from the family becomes available. When an inheritable arrhythmogenic disease is suspected, DNA samples from the victim are the best source of information when performing a molecular autopsy. If there is a positive result, family members should be offered the opportunity to undergo predictive genetic screening, in a cascade fashion. Targeted molecular screening in first-degree relatives may be considered when there is the suspicion of the presence of an inheritable disease in family members. Conversely, genetic screening of a large panel of genes should not be performed in either sudden unexpected death survivors [SUDS] or sudden arrhythmogenic death syndrome (SADS) in relatives without clinical clues for a specific disease after clinical evaluation [18,19].

Screening patients with documented or suspected ventricular arrhythmias (VAs)

Clinical history of palpitations, pre-syncope and syncope are the three most important symptoms that require a thorough clinical history taking and possibly further investigations to rule out a relation to ventricular arrhythmias (VAs). Palpitations related to ventricular tachycardia (VT) are usually of a sudden onset/offset pattern and may be associated with pre syncope and/or syncope. Syncope occurring during strenuous exercise, while sitting or in the supine position should always raise the suspicion of a cardiac cause, while other situational events may indicate vasovagal syncope or postural hypotension [20]. Symptoms related to underlying structural heart diseases, as chest discomfort, dyspnoea and fatigue may also be present and CAD and cardiac function should be sought. Thorough investigation of family history of SCD and drugs used, must be included in the evaluation of patients suspected of having a VA. A positive family history of SCD is a strong independent predictor of susceptibility to VA and SCD [21]. Although physical examination can seldom reveal dysfunction, it may sometimes give valuable clues.

During diagnostic approach for family members of sudden unexplained death syndrome or SADS, the victims should be included in addition to personal history and family history. In addition, baseline 12-lead ECG with standard and high precordial leads, 24-hour ambulatory ECG, exercise stress test, signal-averaged ECG. provocative test (when Brugada syndrome is suspected) and cardiac imaging with real time 2DE and/or CMR (with or without contrast) must also be investigated. Genetic testing targeted molecular testing and genetic counseling should be applied as well if there is the clinical suspicion of a disease [16,21].

A standard resting 12-lead ECG may reveal signs of inherited disorders associated with VAs and SCD such as ion channelopathies (LQTS, SQTS, Brugada syndrome, CPVT) and cardiomyopathies (ARVC, LVNC and HCM). Other ECG parameters can identify underlying structural disease including bundle branch block, atrioventricular (AV) block, ventricular hypertrophy and Q waves consistent with ischemic heart disease (IHD) or infiltrative cardiomyopathy. Electrolyte disturbances and the effects of various drugs may result in repolarization abnormalities and/or prolongation of the QRS duration. Exercise ECG or SPECT imaging is most commonly applied to detect silent ischaemia in adult patients with ventricular VAs. Exercise testing in adrenergic-dependent rhythm disturbances, including monomorphic ventricular tachycardia (VT) and polymorphic VT such as CPVT, is useful for diagnostic purposes and in evaluating response to therapy. Exercise testing should be performed where resuscitation equipment and trained personnel are immediately available. [22].

Either continuous or intermittent ambulatory recording techniques can aid in relating symptoms to the presence of the arrhythmia. Silent myocardial ischemic episodes may also be detected. A 24- to 48-h continuous Holter recordings appropriate whenever the arrhythmia is known or suspected to occur at least once a day. Implantable subcutaneous devices that continuously monitor the heart rhythm and record events over a timeframe measured in years can record patient activation or automatically for pre-specified criteria. They may be very useful in diagnosing serious tachyarrhythmias and bradyarrhythmias in patients with life-threatening symptoms such as syncope.

Signal-averaged ECG(SA-ECG) improves the signal: noise ratio of a surface ECG so that low-amplitude (microvolt level) signals, referred to as 'late potentials', can be identified at the end of the QRS complex. Late potentials indicate regions of abnormality of the myocardium with slow conduction, a substrate abnormality that may allow for re-entrant ventricular tachyarrhythmias. SAECG is recommended for differential diagnosis of structural heart disease, such as CAD and ARVC, in patients with VAs [21,22]. It should be emphasized here that SAECG is of low positive and negative predictive values to identify patients at risk of VAs and SCD.

Echocardiography is the most commonly used imaging technique, when compared to cardiac magnetic resonance (CMR) and cardiac computed tomography (CT). Echocardiography with strain and STE are inexpensive, readily available, real time and can provide accurate evaluation of myocardial structure and function and congenital heart disorders associated with VA and SCD [23]. Therefore, echocardiography is recommended for patients with VAs and who are suspected of having structural heart disease and in the subset of patients at high risk of the developing serious VA or SCD (Figure 2 and 5).

The combination of echocardiography with exercise or pharmacological stress is applicable to a selected group of patients who are suspected of having VAs triggered by ischemia and who are unable to exercise or have resting ECG abnormalities that limit the accuracy of the ECG for ischemia detection [3,23].

Advances in cardiac magnetic resonance imaging (CMR) have made it possible to evaluate both the structure and function of the heart. This is of particular value to patients with suspected ARVC, in whom CMR provides excellent assessment of RV size, function and regional wall motion. Furthermore, extensive LGE late Gadolinium enhancement (LGE) by CMR can identify high-risk HCM patients. This is an independent predictor of SCD. Quantitative assessment of myocardial fibrosis by LGE can thus be a clinically useful tool to help risk stratify patients with HCM [24].

On the other hand, computed tomography (CT) allows precise quantification of LV volumes, ejection fraction, calcium scoring and coronary anomalies evaluation. In addition, it can provide clear images of the coronary arteries from which the extent of calcification and severity of CAD can be quantified. Cardiac CT can be used in selected patients in whom evaluation of cardiac structures is not feasible with echocardiography and CMR. CT coronary angiography is of high specificity and sensitivity in the diagnosis of CAD. However, radiation stochastic effects should be considered before requesting such important noninvasive diagnostic test.

Myocardial perfusion single-photon emission computed tomography (SPECT) using exercise or pharmacological agents is applicable for a selected group of patients who are suspected of having VA triggered by ischemia and who are unable to exercise or have resting ECG abnormalities that limit the accuracy of the ECG for ischemia detection. Accurate quantification of LVEF is possible with gated radionuclide angiography (multiple-gated acquisition scan) and may be helpful in patients for whom this measurement is not available with echocardiography. SPECT imaging is an excellent quantitative test which can measure with very high accuracy, the amount of myocardium at jeopardy, but nevertheless, the radioactive isotopes hazards should be considered as well [18,19]. Similarly, coronary angiography plays an important diagnostic role in establishing or excluding the presence of significant obstructive CAD in patients with life-threatening VAs or in survivors of SCD [19-21].

Electrophysiological study (EPS) has been used to document the inducibility of VT, to guide ablation, to assess the risks of recurrent VT or SCD, to evaluate loss of consciousness in selected patients with arrhythmias suspected as a cause and to assess the indications for implantable cardiovertor defibrillator (IDC) therapy. Moreover, EPS may be used to document the arrhythmic cause of syncope and should be used to complete a full syncope workup. It is most useful in patients with CAD and LV dysfunction. The diagnostic yield depends greatly on the selected patient populations and is low in the absence of structural heart disease or abnormal ECG [25].

Pharmacotherapy for ventricular arrhythmia and prevention of sudden cardiac death

The selection of appropriate therapy for the management of VA and for the prevention of SCD should not be focused on arrhythmia alone and should be multidisciplinary including the associated medical conditions (substrate of arrhythmia) that may contribute to and/or exacerbate arrhythmia, the risk posed by arrhythmia and the risk–benefit aspects of potential therapy. Management of a manifest arrhythmia alone without looking for the original disease failed to improve outcome which was evident in CAST trial [26]. As such, management of VA may involve discontinuation of offending pro-arrhythmic drugs and appropriate therapy of the original disease (beta blockers, statins, dual antiplatelet therapy or revascularization in critical CAD). In the absence of correctable heart disease (such as CAD, valvular

heart disease or congenital heart defects), anti-arrhythmic therapy with drugs, implantable devices, ablation or surgery could be of great help. Anti-arrhythmic drugs, with the exception of beta-blockers, have not been shown in randomized clinical trials (RCTs) to be effective in the primary management of patients with life-threatening VAs or in the prevention of SCD. Occasional studies with amiodarone have shown positive results, but this is not a consistent finding [27]. Recently, however, it has been demonstrated that some sodium current blockers (predominantly class IB like mexiletine and class IC like flecainide) actively inhibit both the peak sodium current and the late component of the sodium current which may induce an abbreviation of the QT interval in patients with LQTS type 3. For this reason, these drugs may be considered to abbreviate the QT interval in patients with type 3 LQTS [28].

Beta-blockers are effective in suppressing ventricular ectopic beats and arrhythmia as well as in reducing SCD in a spectrum of cardiac disorders in patients with and without heart failure (HF). Beta-blockers are effective and generally safe anti-arrhythmic agents that can be considered as the main stay of anti-arrhythmic drug therapy in the management of VA and the prevention of SCD but should not be used in acute heart failure or impending shock state [29].

Amiodarone has a broad spectrum of action that includes blockade of depolarizing sodium currents and potassium channels that conduct repolarizing currents; these actions may inhibit or terminate VAs by influencing automaticity and reentry. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) trial showed a lack of survival benefit for treatment with amiodarone vs. placebo in patients with LVEF ≤ 35% [30].

Sotalol is a rapid delayed rectifier potassium current inhibitor with beta-blocker properties and it is very effective in suppressing VA. Sotalol can be used safely in patients with CAD unless they have HF [31].

Generally, anti-arrhythmic drug therapy has never been clearly shown to reduce sudden arrhythmic death in patients who have already suffered a life-threatening VA. However, in patients fitted with an ICD, amiodarone, especially in conjunction with betablockers, significantly reduces ICD interventions [32].

Electrolytes administration of potassium to restore normal blood levels can favorably influence the substrate involved in VA. Magnesium administration can specifically help to suppress cardiac arrhythmias. Electrolyte disturbances are common in patients with HF, particularly those using high-doses of potassium-sparing diuretics. Recently, a data-base study including 38,689 patients with acute myocardial infarction showed the lowest risk of VF, cardiac arrest or death with potassium concentrations of 3.5–4.5 mmol/L [33].

Other drug therapy which improve survival and reduce SCD

Cardiac enlargement and adverse remodeling occurs in the ventricle following myocardial infarction or in association with non-ischemic cardiomyopathy. These structural changes, as well as associated ion-channel alterations, can exacerbate the potential for VA. Several drugs, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs), can improve survival and reduce rates of SCD through their reverse remodeling effect [34]. Also, anticoagulants and/or anti platelets may be helpful for reducing the frequency of coronary thrombotic occlusions in high-risk patients [35]. Furthermore, findings indicate that statins may reduce the occurrence of life-threatening VAs in high-risk patients [36].

Device therapy for SCD Prevention

Implantable cardioverter defibrillator (ICD) have been used in patients for 30 years. Most clinical trials normally support the use of ICD therapy in survivors of either VF or aborted cardiac arrest. Later trials demonstrated a benefit of defibrillator therapy in patients at risk of sudden death (primary prevention), specifically those patients with depressed left ventricular ejection fraction (LVEF < 30 - 35%).

ICD therapy prevents SCD and prolongs life in patients at high risk of sudden arrhythmic death, provided that the patient does not suffer from other conditions that limit life expectancy to, 1–2 years [37]. Long-term studies have demonstrated the efficacy of ICDs [38] and cardiac resynchronization therapy defibrillators (CRT-Ds) [39] over a mean follow-up of 8 and 7 years, respectively. On the other hand, defibrillators may cause complications, including in appropriates shocks, device-related infection and lead failure which are especially frequent in children [40]. Despite the indications for ICD therapy in post-myocardial infarction patients with reduced ejection fraction, which is strongly supported by evidence-based data, a clear gap exists between guidelines and clinical practices in several countries.

Secondary prevention of sudden cardiac death

Several important trials [Antiarrhythmic drugs Versus Implantable Defibrillator (AVID) [41], Canadian Implantable Defibrillator Study (CIDS) [42] and Cardiac Arrest Study Hamburg (CASH) [43] have been conducted in patients who had suffered a cardiac arrest or life-threatening VA (hemodynamically unstable ventricular arrhythmia with syncope) in which treatment with an ICD was compared with anti-arrhythmic drug therapy, predominantly amiodarone. Although only one showed a statistically significant reduction in the rate of total mortality, the ICD reduced the rates of arrhythmic mortality in both the AVID and CASH trials. A meta-analysis of the three trials demonstrated that ICD therapy was associated with a 50% reduction in arrhythmic mortality and a 28% reduction in total mortality. An analysis of the AVID trial results clearly demonstrated that the benefit was confined primarily to patients with an LVEF (left ventricular ejection fraction) between 20 and 34% [41]. The guidelines for use of ICDs for secondary prevention have been generally accepted by clinicians.

An external defibrillator with leads and electrodes attached to a wearable vest has been shown to successfully identify and interrupt VT and VF. No prospective randomized clinical trials (RCTs) evaluating this device have been reported, but there are many case reports, case series and registries that have reported the successful use of the wearable cardioverter defibrillator (WCD) in a relatively small proportion of patients at risk of potentially fatal VAs. Recently, Epstein., *et al.* [44] reported that 133 of 8,453 (1.6%) patients received 309 appropriate shocks and 91% were resuscitated from a VA. Thus, this device can save lives in vulnerable patients, but its efficacy has not been validated. In patients with transient impaired LVEF, the WCD can be used temporarily until LV function has recovered sufficiently, following insults such as myocardial infarction, post-partum cardiomyopathy, myocarditis or interventions such as revascularization associated with transient LV dysfunction. Public access defibrillation linked with cardiopulmonary resuscitation has been shown to be more effective than cardiopulmonary resuscitation alone and public access defibrillation is now well established, especially in locations where crowds and stress are common and particularly where trained volunteers can be readily available [45].

Basic and advanced life support activities have led to the generation of protocols to guide responders. These documents have been published by the European Resuscitation Council and the International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care [46]. It is now well established that implantable cardioverter defibrillator (ICD) can effectively decrease death from ventricular arrhythmias in highly selected patients who are at risk of SCD. Unfortunately, risk of inappropriate shocks, mortality from frequent therapy, chance of failing in abortion of arrhythmias despite having a defibrillator and our inability to recognize which of several hundreds of thousands of patients at risk for sudden death but do not meet current criteria for defibrillator, limit ICD effectiveness.
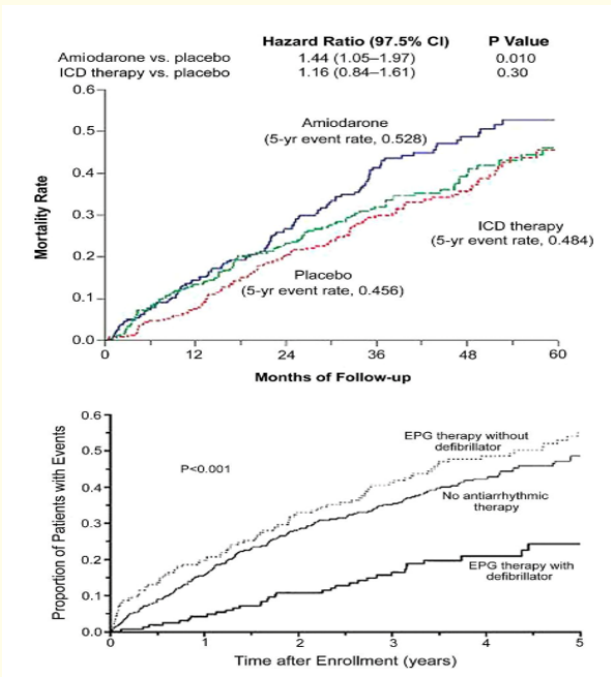

Figure 6: Time course graphs over five years showing sudden cardiac death (mortality rates; top figure) and the proportion of patients with events leading to sudden cardiac death (taken from Hurts, The Heart, chapter 91: sudden cardiac death 14th edition), Jonathan W. Waks and Mark E. Josephson.

Figure 6 illustrates mortality rates (above) and proportion of patients with events. Several limitations of the ICD device have been recognized. For example, even though they are highly effective in abortion of ventricular arrhythmias, ICDs do not prevent recurrent VT episodes and furthermore, the underlying arrhythmogenic substrate remains unchanged or may even progress over time.

All randomized ICD trials indicated an ICD-unresponsive SCD rate of 5%. Unfortunately, the retrospective post-hoc analyses have not revealed any distinguishing causes or characteristics of those who have had ICD-unresponsive events.
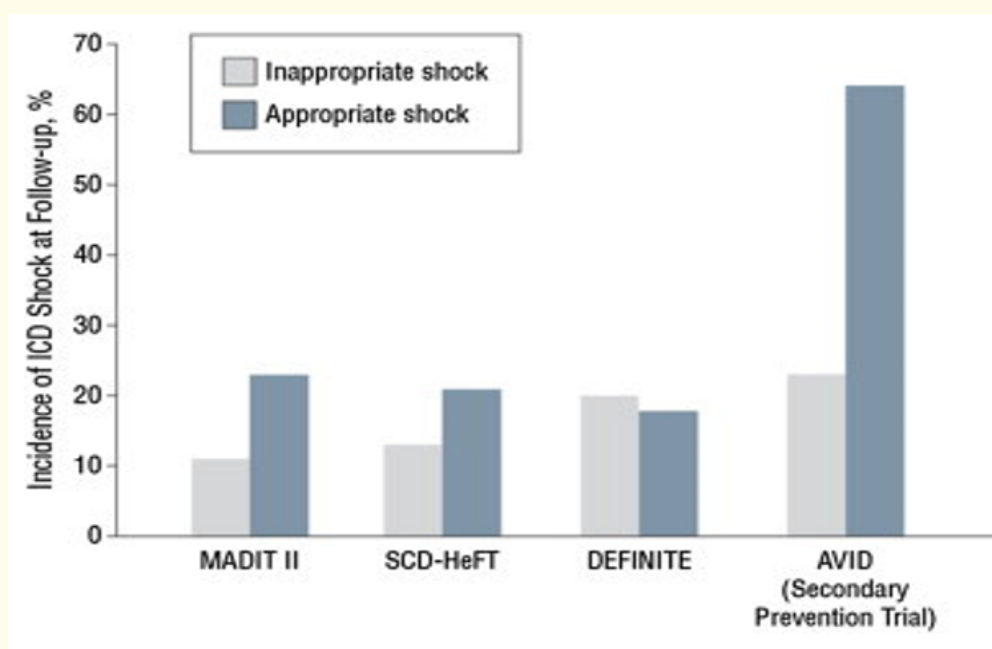

Figure 7: *Bar charts showing the incidence of in appropriate shocks versus appropriate shocks in major trials of ICD implantation for prevention of SCD in the mega multicenter trials [36].*

Figure 8 below shows the different studies which evaluated the effectiveness of ICD in mortality. For example, the Oregon Sudden Un-expected Death Study found that among ICD patients with SCD, 17% of patients had VT/VF, suggesting failure of ICD therapy to abort the lethal rhythm [47]. Similarly, Vest prevention of early sudden death trial indicated that a WCD failed to reduce SCD up to 90 days among patients with moderate to severe LV dysfunction immediately post myocardial infarction compared with controls [48].

Interventional therapy

Catheter ablation has evolved into an important treatment option for patients with scar-related heart disease presenting with either VT or ventricular fibrillation (VF). Data from two prospective randomized multi-centre trials on outcome in patients with ischemic heart disease demonstrated that catheter ablation for VT decreases the likelihood of subsequent ICD shocks and prevents recurrent episodes of VT [49]. Moreover, catheter ablation is often used to control incessant VT or electrical storms (i.e. recurrent VT/VF with frequent appropriate ICD firing) and to reduce or prevent recurrent episodes of sustained VT [49]. While ICDs can effectively terminate VT in patients with either ischemic or non-ischemic cardiomyopathy, they may not prevent arrhythmia recurrence. Although catheter ablation is an accepted treatment option for a wide range of VT substrates, there is a lack of evidence from prospective, randomized trials that catheter ablation reduces mortality.

In patients without overt structural heart disease, VT is most commonly eliminated from either the RV or LV outflow tracts. The 12-lead surface ECG demonstrates a LBBB, morphology if VT arises from the right ventricular outflow tract (RVOT) or a RBBB inferior axis
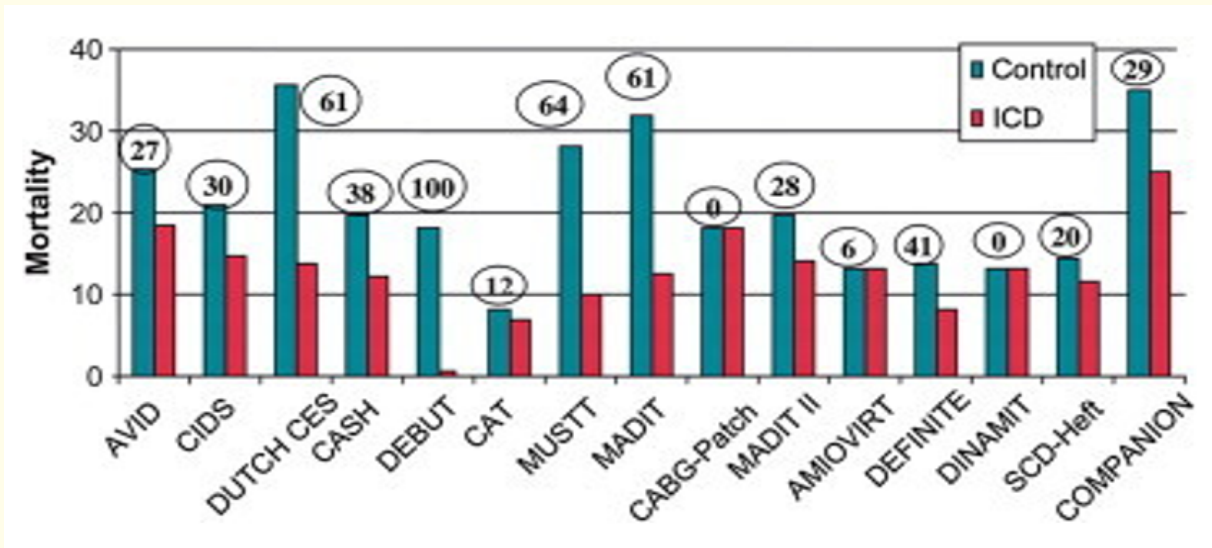
Figure 8: *Bar charts showing the different studies which evaluated the effectiveness of ICD in mortality in different clinical trials. For example, Definite trial evaluated implantable cardioverter defibrillators (ICDs) versus none in patients with non-ischemic cardiomyopathies, EF < 35% and premature ventricular contractions or non-sustained ventricular tachycardia [30,36,38,41].*

morphology if arising from the left ventricular out flow tract (LVOT). Triggered activity is the most common underlying pathophysiological mechanism targeting the earliest site of activation during catheter ablation results in a high rate of procedural success.

Advances in screening of patients at high risk of SCD: The crucial role of ECG and Cardiac Imaging modalities in SCD prevention
Cardiac magnetic resonance (CMR)

CRM imaging may facilitate non-invasive identification of the arrhythmic substrate in either patients with a history of myocardial infarction or in patients presenting with epicardial VT [50]. Polymorphic VT is defined as a continually changing QRS morphology often associated with acute myocardial ischemia, acquired or inheritable ion channelopathies or ventricular hypertrophy. Non-invasive imaging of cardiac structure, best done by magnetic resonance imaging, can be used to plan and guide ablation procedures for VT [50]. A three-dimensional electro-anatomical mapping system may aid in localization of abnormal ventricular tissue and permits substrate ablation without induction of VT that may harm the patient.

Patients with hypertrophic cardiomyopathy (HC) are reported to have annual mortality rate of about 1.0% and those patients without sudden death risk factors and with either no or mild symptoms are generally considered to have a benign clinical presentation. On the other hand, extensive late gadolinium enhancement (LGE) by CMR can identify high-risk HCM patients and this is considered an independent predictor of SCD. Quantitative assessment of myocardial fibrosis by LGE is a useful diagnostic tool to help risk stratify patients with HCM [51]. Interestingly, a scar burden identified with MRI has been found to be more sensitive and specific marker for arrhythmic risk than EF in HCM as illustrated in figure 8 [51]. In addition, a meta-analysis by Green., *et al*. [52] showed significant associations between the presence of LGE and cardiovascular mortality, HF death and all-cause mortality in HCM.

Electrocardiogram (ECG)

ECG can target the general population including athletes, all adults with any risk factor, syncope, family history of inherited arrhythmia syndrome or/and structural heart disease through a proper illustration of QT duration, morphology of T wave, QRS duration, QRS fragmentation, hypertrophy pattern, repolarization abnormalities and Brugada syndrome characteristic features. In the Oregon Sudden Unexpected Death Study, the Risk of SCD associated with ≥ 4 ECG abnormalities (Heart rate > 75 bpm, QRS duration > 110ms, prolonged QTc,T peak- T end > 89 ms, QRS-T angle >90, delayed QRS transition zone, ECG strain pattern of LVH type) remained significant after

multivariable adjustment (hazard ratio 4.84; 95% CI 2.34–9.99); $P < 0.001$ [47].This novel cumulative ECG risk score was independently associated with SCD and was particularly effective for LVEF >35% where risk stratification is currently unavailable [47].

Echocardiography and deformation imaging role in preclinical detection of cardiac dysfunction

Preclinical diagnosis of (HCM) normally refers to the detection of either functional or histopathological abnormalities in subjects who carry any HCM-causing gene mutation, before or even without the development of left ventricular hypertrophy. Myocardial cell mechanical dysfunction precedes histopathological changes, such as myocyte disarray, fibrosis and hypertrophy. The majority of HCM genotype (+) /phenotype (-) subjects display either myocardial functional or histopathological changes, such as reduced tissue Doppler imaging-derived systolic and diastolic velocities, abnormal electrocardiogram, cardiac magnetic resonance-visualized myocardial crypts/ scar. Figure 9 shows tissue Doppler (left diagram; A) revealing reduced Ea (mitral annular septal velocity) in one member of families of HCM in the absence of any echocardiographic or ECG abnormalities, whereas the right diagram (B) illustrates an example of GLS Speckle tracking echocardiography which is able to detect early subtle systolic dysfunction among patients with different forms of cardiomyopathies [4,5,53].
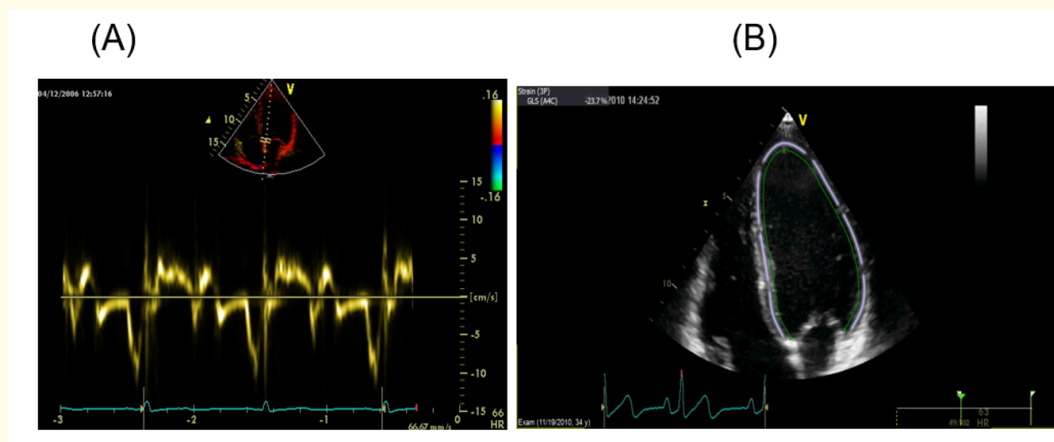

Figure 9: Tissue Doppler (left; A) showed reduced Ea velocity in one member of families of HCM in the absence of any echocardiographic or ECG abnormalities. On the right (B) is GLS Speckle tracking echocardiography which can detect any early subtle systolic dysfunction among patients with different forms of cardiomyopathies [4,5,53].

Predicting and Preventing Sudden Cardiac Death in CAD

Multiple strategies have evolved to predict and prevent SCD. One strategy receiving recent emphasis is primordial prevention of CAD [54]. This approach stresses the importance of prevention of the development of risk factors for CVDs and stroke, as represented in the term primordial prevention. Optimization of blood pressure, weight, glucose (HBA1c), cholesterol, smoking, diet and physical activity, through lifestyle interventions are the focus of this approach [54]. The primary prevention of SCD with risk stratification and intervention in those individuals with established CVDs disease place them at high risk. This in turn is another strategy to improve outcomes [54,55]. Risk factors for SCD include advanced age, male sex, cigarette smoking, hypertension, sedentary life style, diabetes mellitus, hypercholesterolemia, obesity and family history of CAD [55]. These risk factors for SCD are also predictors of CAD–related death and all-cause of mortality [54]. Impaired left ventricular function, as well as multiple other genetic, anatomic and electrophysiological risk factors for sudden death, have been identified [54,55]. Although risk stratification is useful to identify populations of individuals at risk for SCD, current techniques to identify high-risk individuals lack sufficient predictive value to have clinical utility because of the relatively low event rates or absolute risk [54,55]. Accordingly, carotid artery ultrasound, which measures carotid intima media thickness (cIMT) can detects atheromatous plaques (Figure 10). This is a strong indicator of overall vascular health. cIMT is well recognized and also an accepted marker to predict cardiovascular disease. Figure 10 shows typical examples of ultrasound image of carotid arteries with (A) increased intima thickness and (B) non-obstructive atherosclerotic plaque [56].
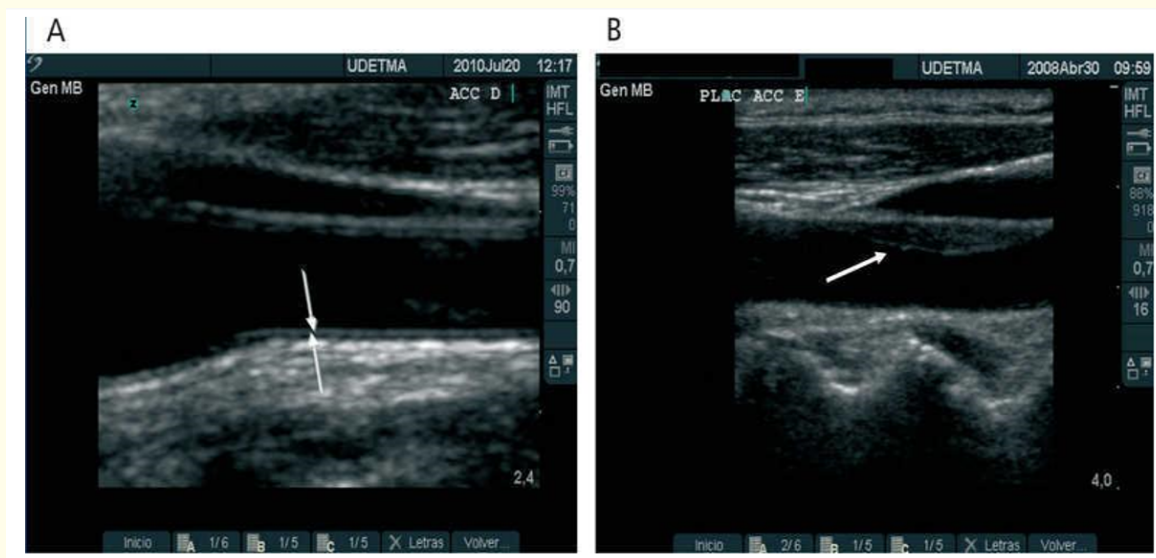
Figure 10: Ultrasound image of carotid arteries showing (A) increased intima thickness and (B) non-obstructive atherosclerotic plaque [56].

Pharmacological interventions have been very successful in reducing the risk of sudden cardiac arrest in patients with impaired left ventricular systolic function from either coronary disease or cardiomyopathy employing β-blockers, angiotensin-converting enzyme inhibitors, ARBS, dual antiplatelet therapy and statins [34-35].

Device therapy

Multiple clinical trials randomizing several thousand patients have demonstrated that the ICD prevents SCD and significantly reduces overall mortality among patients with left ventricular dysfunction in dilated non-ischemic cardiomyopathy and ischemic heart disease [30,36,38,41,57]. Secondary prevention refers to clinical intervention in patients who have survived a prior cardiac arrest or sustained ventricular tachycardia. In such patients, the ICD has proven superior to antiarrhythmic drug therapy for prolonging survival [57].

Multimodality approaches to atherosclerosis imaging

Each modality offers unique measurements of coronary artery disease severity. Together, multimodality imaging can be used beneficially to determine anatomic and hemodynamic consequences of atherosclerosis, complimented by detail on plaque composition, overall disease burden and current metabolic activity acting within an individual patient. A lipid-rich coronary plaque displaying thin overlying fibrous cap and indicative of thin-cap fibro atheroma is liable to rupture and progress subsequently to un stable plaque and acute coronary occlusion which are the main causes of SCD in adult population. Figure 11 illustrates examples of multimodal approach to atherosclerosis imaging [58]**.**

Conclusion

In conclusion, sudden cardiac death is still a major health problem despite the great progress in drug and device therapies. In this manuscript, we focused on the crucial role of **e**arly prediction and prevention of SCD which are the holy grail of all physicians worldwide. A multidisciplinary approach is essential in order to identify those patients who are at risk of SCD. There are standard as well as emerging risk stratification strategies for patients without prior cardiac events. The initial step is to assess the risk score for each patient which should include his/her age, sex, family history of CAD or SCD, smoking history, life style habits including physical activity, diets, dyslipidemia, DM, hypertension and obesity. Syncope may herald onset of ventricular dysrhythmias and requires prompt evaluation starting by ECG measurements (holter or loop recorder for arrhythmia monitoring) which are very useful to screen for potential primary or second-
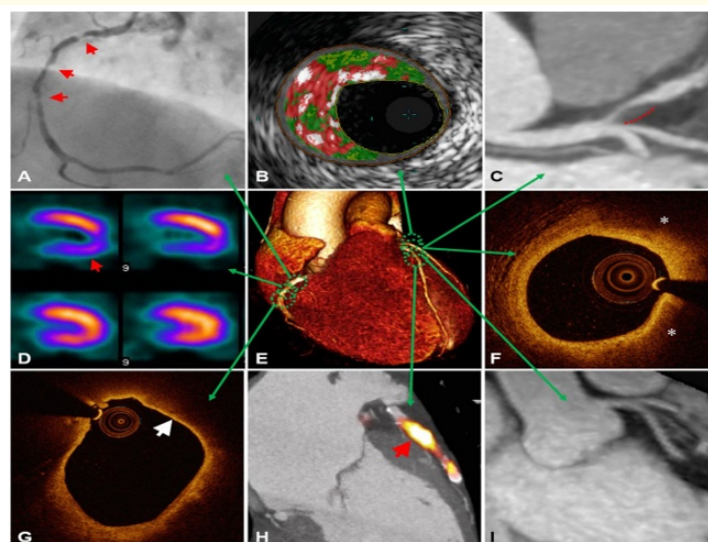
Figure 11: *Multimodal approach to atherosclerosis imaging. A, X-ray angiography showing multiple right coronary artery atherosclerotic lesions (arrows) resulting in significant luminal narrowing; B, virtual histology intravascular ultrasound (VH-IVUS) demonstrating coronary plaque with high content of necrotic core (red), as well as dense calcium (white) and fibro-fatty regions (dark/ light green); C, Computed tomographic (CT) angiography showing non calcified plaque in the left anterior descending artery with positive remodelling (dashed line); D, single-photon emission computed tomography (SPECT) myocardial perfusion scan with stress-induced perfusion defect (arrow); E, 3D volume rendered CT whole-heart image; F, optical coherence tomography (OCT) image of a coronary plaque showing lipid , characterized as signal-poor regions with poorly demarcated borders; G, OCT image of a lipid-rich coronary plaque displaying thin overlying fibrous cap (arrow), indicative of thin-cap fibro atheroma; H, Fused ^{18}F-NaF positron emission tomography (PET)-CT image showing high left anterior descending artery tracer uptake (arrow) revealing active plaque micro calcification; I, 3-T magnetic resonance (MR) contrast-angiography performed with dual ECG and respiratory navigator gating showing clear delineation of the proximal left-sided coronary vessels [58].*

ary electrical abnormalities. The clinician needs to update patients risk status over time, especially after intervening cardiac events (MI and CHF).

For the evaluation of CAD, the physician must recommend either stress EKG or stress echocardiography. Myocardial perfusion imaging (MPI) at rest and stress is an option for patients with poor echocardiography window and for quantitative and definite diagnosis of ischemia and scar. Furthermore, echocardiography and deformation imaging (Strain and SRI) should be used as a screening tool in all families who have a history of dilated cardiomyopathy, HCM and syncope or SCD. Computed tomography (MSCT) should be indicated for definite diagnosis of CAD in moderate to high risk population. Coronary angiography should be reserved for high risk patients in the presence of acute angina type chest pain, an abnormal ECG or/and high cardiac biomarkers highly suggestive of severe CAD or acute myocardial ischemia. On the other hand, CMR is of crucial importance in certain group of patients who are at high risk of SCD when echocardiographic examination is insufficient and to risk stratify certain categories of high risk patients (HCM, RVCM and non-compaction of left ventricle).

In addition, recent data revealed that targeted molecular screening in first-degree relatives should be considered in DCM and HCM families as well as in families of unexplained SCD. Prevention of SCD should be initiated by public awareness of all major risk factors for CAD and all preventive measures which can include drugs (β-blockers, angiotensin-converting enzyme inhibitors, dual antiplatelet therapy and statins) or/and devices (ICD) that demonstrated significant reduction of mortality. Finally, education programs are recommended at an early stage in life about the risk factors of CVDs and how these diseases can reduce the quality of life of the patients if the risks are not prevented or reduced during their life time.

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