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Atherosclerosis: Open Access

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Review Article Open Acces

Advanced Carotid Atherosclerosis and the Risk of Subsequent Major Cardiovascular Events: Carotid Ultrasound Study

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Abstract

Introduction: Very little is known about the role of atherosclerotic carotid plaque morphology, vulnerability, and Total Plaque Area (TPA) in the development of Major Cardiovascular Events (MCVE).

Aim of this study: To assess the role of carotid atherosclerosis and the plaque morphology in the prediction of MCVE.

Importance of the study: A better understanding of the role of detection of atherosclerosis and unstable plaque morphology can help to improve strategies for prevention of Acute Cardiovascular Events (ACVE) worldwide.

Methods: This study analyzed the medical records of 452 patients with 2.5-years follow-up. The primary outcomes were the composite of first occurrence of stroke, cardiovascular death, and Acute Coronary Syndromes (ACS) hospitalization.

Results: The results show that carotid atherosclerosis was present in 44% of patients (n=103) and this was associated with increasing conventional cardiovascular risk factors and extent of symptomatic vascular disease. During 2.5 years follow-up, 10% of patients experienced ≥ 2 MCVE. After adjustment for cardiovascular risk factors, the risk of ACS and stroke increased by 23% (95% Confidence Interval [CI]), and 45% (95% confidence interval), respectively in patients with carotid ultrasonic (US) evidence of advanced carotid atherosclerosis in comparison to control (P<0.001). The relative increase of cerebrovascular events was 22% in patients with carotid US evidence of vulnerable plaque morphology versus benign morphology. The high risk for all-cause and cardiovascular death of these patients remained significant after adjustment for various established cardiovascular risk factors in multivariable regression analysis (adjusted hazard ratio 2.4, P<0.001; compared to patients without (US) evidence of advanced carotid atherosclerosis features).

Conclusion: It is concluded that carotid TPA and features of vulnerability were associated with an increased risk of MCVE.

Keywords: Carotid atherosclerosis; Carotid ultrasound; Cardiovascular events; Plaque morphology

Introduction

The presence of carotid plaque reflects overall atherosclerotic burden and may predict major cardiovascular events. This study examined the association among carotid atherosclerosis (plaque volume and morphology), history of athero-thrombotic events, and risk of cardiovascular events following Reduction of Athero-thrombosis for Continued Health (REACH) registry protocol. This study recruited 452 (United Arab Emitrates) patients who were included in the clinic registry and information on carotid atherosclerosis of 231 patients were analyzed at baseline. The primary outcome was focused on the composite of first occurrence of cardiovascular events, death, myocardial infarction or coronary hospitalization [1].

Atherosclerotic plaques begin as endothelial dysfunction and focal thickenings of the intimal layers of the arterial wall and subsequently, progress with lipid deposition. Damage to the arterial wall leads to hypertrophy, thickening, arterial stiffness and dysfunction can increase the risk of plaque formation [1]. Measures of atherosclerotic plaque in the carotid arteries and thickness of the Carotid Intima-Media (cIMT) are readily obtained using carotid US techniques [1]. Both types of measurements improve risk prediction for ischemic heart disease and ischemic stroke independently of major cardiovascular risk factors, but measures of plaque are stronger predictors than cIMT [1-3]. In previous large studies on the role of carotid atherosclerosis in ischemic stroke, several authors have not collected information and not investigated the role of carotid atherosclerosis- plaque morphology and their association between cardiovascular risk factors and ischemic stroke subtypes [4-6] (Figure 1).

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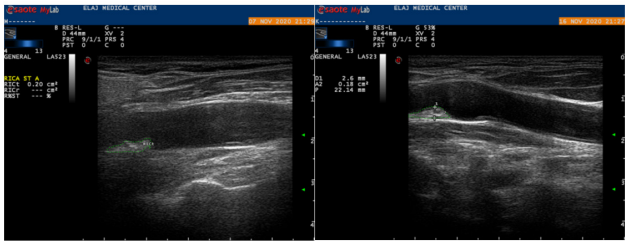
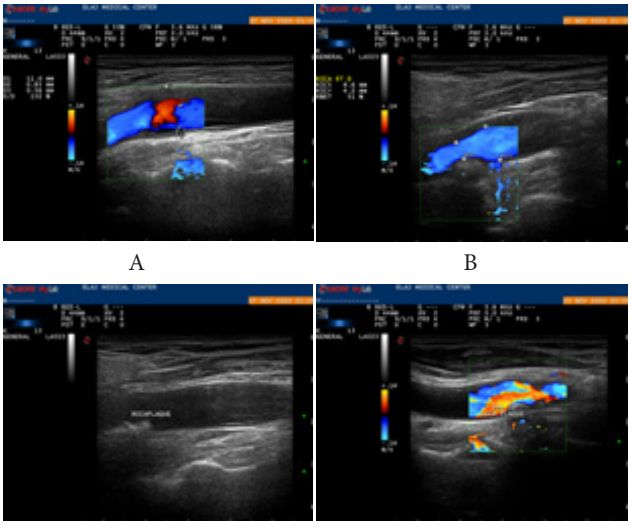


(A) (B)

Figure 1: Carotid ultra-sound (US) showing in (A) The typical features of vulnerable [unstable] carotid atherosclerotic plaque (Irregular surface) in right common carotid artery and (B) Image shows a large carotid atherosclerotic plaque after the bulb of LCCA ; total plaque area (TPA)= 22mm. These images are consistent with plaque instability in the form of irregular surface (A) and Hypo echoic area appears clearly just beneath the cap (B).

The carotid plaque is defined as "a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima-media thickness or demonstrated a thickness of greater than or equal to 1.5 mm" [7]. For the clinician, there is a need to characterize "vulnerable plaque", i.e., the plaque susceptible to rupture, which can give rise to clinical complications, from embolization to thrombosis leading to symptoms, myocardial infarction, stroke and death. The vulnerability features are only weakly related to plaque size and stenosis but are related mainly to plaque morphology and histologic content including plaque size matters, but shape and content of the plaque also matter. Vulnerable, high-risk plaque is histologically different from stable, benign, clinically asymptomatic plaque. This is related mainly to its higher content of lipid with necrotic cores due to invasion of lipid pools by macrophages and other inflammatory cells, and to a lesser extent by larger plaque burden [7,8] (Figure 2).

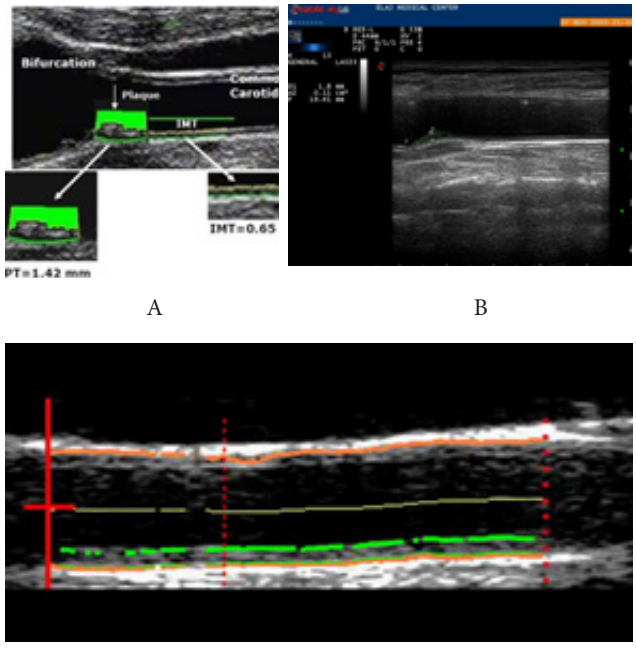


A B

C D

Figure 2: PIllustrative carotid atheroma of different morphologies. (A) and (B) show the ultra-sound (US) features of stable (uncomplicated smooth atheromatous plaque) whereas (C) and (D) reveal US features of vulnerable plaque morphology (undulation and low echogenicity (soft).

A thrombotic occlusion of the vessel fed by ruptured coronary atherosclerotic plaque may result in ACS such as unstable angina, myocardial infarction or even death. In contrast, embolization from a vulnerable atherosclerotic unstable plaque in carotid arteries may result in transient ischemic attack or stroke. The atherosclerotic plaque is susceptible to such clinical events which are termed high-risk or vulnerable plaque, and its identification in humans by carotid US before it becomes symptomatic is of great clinical importance (Figure 3). Ultrasonic tissue characterization of the atherosclerotic plaque is possible with different techniques such as vascular, virtual histology and intravascular ultrasound [9]. This sub-study now illustrates the US features of atherosclerotic plaques prone to develop MCVE among a symptomatic population. As such, the purpose of the study was to investigate carotid ultrasound evaluation of plaque burden and vulnerability which have been used for risk stratification and for the future clinical application of anti-atherosclerotic therapies. Increasing evidence indicates that measuring plaque burden and its morphology are superior to conventional risk factors for ACS, cerebrovascular disease progression, and death. This study also investigated the atherosclerotic Total Plaque Volume (TPV) and criteria of plaque vulnerability as predictors of cardiovascular outcomes for comparison.



A B

C

Figure 3: Carotid ultra-sound (US) showing in (A) The typical features of vulnerable [unstable] carotid atherosclerotic plaque (Irregular surface) in right common carotid artery and (B) Image shows a large carotid atherosclerotic plaque after the bulb of LCCA ; total plaque area (TPA)= 22mm. These images are consistent with plaque instability in the form of irregular surface (A) and Hypo echoic area appears clearly just beneath the cap (B).

Literature Review

Patients and methods

In brief, this study is prospective, observational registry designed to provide up to 30 months of clinical follow-up of 452 out patients from 3 centers in (United Arab Emitrates).

Patients and definitions

Patients aged ≥ 45 years with ≥ 2 risk factors for atherosclerosis or established CAD, or Cerebrovascular Disease (CVD) were enrolled during 2017–2018 and followed-up until November 2020. Risk factors were diabetes mellitus, arterial hypertension, high LDL cholesterol, smoking, chronic kidney disease, asymptomatic carotid stenosis ≥ 50%, presence of ≥ 1 carotid plaque, systolic

blood pressure ≥ 130 mmHg, and age ≥ 65 years (men) or ≥ 70 years (women). Documented CAD consisted of ≥ 1 of the following: stable angina; history of unstable angina; history of percutaneous coronary intervention; history of coronary artery bypass grafting; or previous MI. Documented Cerebrovascular Disease (CVD) consisted of a neurologist/hospital report with the diagnosis of ischemic stroke or Transient Ischemic Attack (TIA).

Methods of investigation

From the 452 recruited patients, there were 221 asymptomatic control group without evidence of carotid atherosclerosis or CAD. The patients were examined by the carotid US and also for conventional risk factors for CAD. This investigation analyzed the medical records of the 452 patients with 2.5-years follow-up and 231 of them with information on carotid atherosclerosis at baseline. The primary outcome was the composite of first occurrence of stroke (or TIA), cardiovascular death, Myocardial Infarction (MI), or Acute Coronary Syndrome (ACS) hospitalization (Figures 4 and 5).

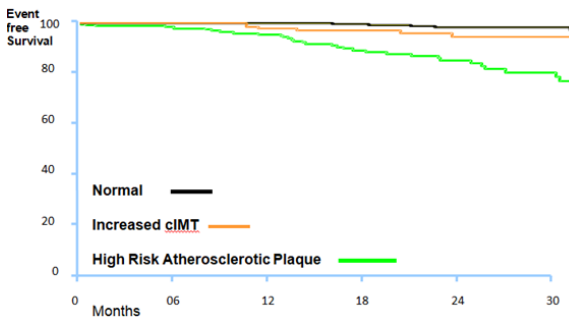
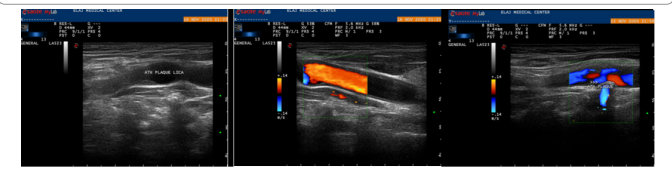


Figure 4: Kaplan-Meier log rank P<0.001.The patients with carotid atherosclerotic plaque showing significant increase of cardiovascular events; the risk of AMI , stroke , TIA, and death increased by 23% (95% confidence interval [CI]) during 30 Months follow up, in comparison to control subjects . In comparison, cIMT did not show significant increase of cardiovascular events during follow up.



(A) (B) (C)

Figure 5: (A) Show stable smooth outlines of a small atherosclerotic plaque in LICA. (B) Illustrate how color flow mapping (CFM) can improve the resolution of the cIMT and properly visualize the carotid plaque morphology. (C) Revealed the important role of Power Doppler technique in better plaque visualization

Asymptomatic persons underwent assessment of conventional risk factors and imaging by carotid ultrasound. Carotid plaque burden (TPA) and plaque morphology (features of vulnerable plaque) were measured. All participants were followed up for 30 months, and Major Cardiovascular Events (MACE) was collected and adjudicated. All data were available for 452 participants.

Outcomes

The primary outcome for this analysis was the composite of first occurrence of cardiovascular events, cardiovascular death, MI, or coronary hospitalization. A secondary pre specified outcome was defined as the first occurrence of MI (fatal or nonfatal). Endpoints were not adjudicated. Cardiovascular deaths included fatal stroke, fatal MI, or other cardiovascular death (other death of cardiac origin; pulmonary embolism; any sudden death, including unobserved and unexpected death (eg, while sleeping) unless proven otherwise by autopsy; death after a vascular operation, vascular procedure; death attributed to heart failure; death after a visceral or limb infarction; and any other death that could not be definitely attributed to a nonvascular cause or hemorrhage). Any MI or stroke followed by a death, irrespective of the cause, in the next 28 days was considered to be a fatal MI or fatal stroke. Coronary hospitalization consisted of hospitalization for unstable angina, coronary artery bypass grafting, or coronary angioplasty/stenting.

Statistical analysis

To assess the selection bias related to missing information on carotid atherosclerosis, we compared the baseline characteristics between the included and non-included patients using Student's t-test test for continuous variables and the $\chi 2$ test for categorical variables. We also estimated the absolute standardized differences (expressed as percentages of pooled standardized differences) to identify the most important differences (Figure 6).

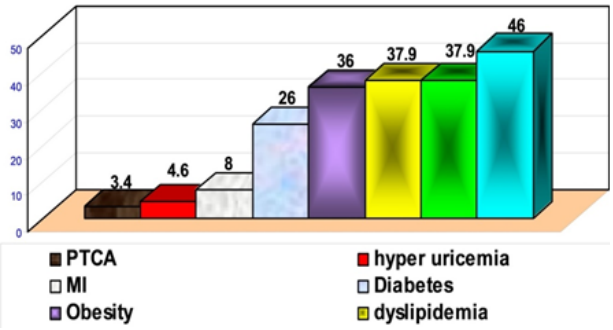


Figure 6: Conventional risk factors in the studied groups (PTCA: Percutaneous Trans-Luminal Angioplasty, MI: Myocardial Infarction).

We also calculated and compared the age- and sex-adjusted prevalence rates of carotid atherosclerosis across baseline characteristics using logistic regression analysis. The difference in prevalence according to number of symptomatic arterial disease locations was tested using the test for trend in the multiple logistic models. We further investigated the impact of the presence of carotid atherosclerosis on 2.5-years cardiovascular risk and death from ACVE through the calculation of Hazard Ratios (HRs) and Kaplan Meier curve. Cox proportional hazard models were further adjusted on pre specified confounding variables, including cardiovascular risk factors (diabetes mellitus, hypertension, hypercholesterolemia, current smoking, Chronic Kidney Disease (CKD), and hs CRP (C-reactive protein) c. The proportional hazard assumptions were checked using the log–log survival plots and by introducing a time-dependent variable into models. Adjusted event rates were calculated using the corrected group prognosis method; adjustment for age was made using the quartile values. Our first analyses concerned the entire study group. Further analyses were performed for 2 subsets (patients with ≥ 2 risk factors only and those with CAD and CVD,) and were stratified according to the number of symptomatic arterial disease locations. Finally, to assess whether patients with ischemic stroke and carotid atherosclerosis were at similar risk as patients with CAD, we calculated and compared the carotid atherosclerosis–specific rates of coronary events in patients enrolled with ischemic stroke but no history of MI and those enrolled with MI but no history of ischemic stroke. Statistical testing was performed at the 2-tailed α level of 0.05.

Data were analyzed using the SAS software package (Table 1).

		CAD group(n=128)	Carotid atherosclerosis	Control (n=221)	P value
		46%	(n=103) 44%		
		%	%	%	
Cardiac biomarkers	POS	91.80%	55.60%	---	<0.001
	NEG	8.20%	44.40%	---	
HTN	NEG	39.20%	55.60%	79.30%	<0.001
	POS	60.80%	44.40%	20.70%	
DM	NEG	50.50%	63.90%	79.30%	0.013
	POS	49.50%	36.10%	20.70%	
Smoking	NEG	47.40%	63.90%	82.80%	0.002
	POS	52.60%	36.10%	17.20%	
Hyperlipidemia	NEG	56.70%	69.40%	89.70%	0.002
	POS	43.30%	30.60%	10.30%	
ECG(LAD)	POS	24.40%	23.30%	0.00%	0.004
	NEG	75.60%	76.70%	100.00%	
ECG(RCA)	POS	19.30%	26.70%	0.00%	0.004
	NEG	80.70%	73.30%	100.00%	
ECG (Cx)	POS	23.90%	6.70%	0.00%	0.008
	NEG	76.10%	93.30%	100.00%	
hs CRP	Mean ± SD	3mg/L	5 mg/L	0.6 mg/L	<0.001
Creatinine	Mean ± SD	30.72	21.4	21.71	0.003

Table 1: Sowing the conventional risk factors for cardiovascular diseases, the mean renal function test and the ECG among the different groups. [Coronary Artery Disease (CAD), Arterial Hypertension (HTN), Diabetes Mellitus (DM), High sensitivity C Reactive Protein (hs CRP), Pos. (Positive), Neg. (Negative), ECG (Electrocardiogram), LAD (Left Anterior Descending Coronary Artery). RCA (Right Coronary Artery), CX (Circumflex coronary artery)].

This research project had the relevant ethical clearance from the Ethics Committees from Masafi Hospital, Al-Fujairah, DMUH, Dubai, and Elaj Medical Centre, Ajman, (United Arab Emitrates).

Results

The patients had a mean (SD) age of 55.6 (± 10.0) years, and 250 (55.3%) were men and 202 were women. In this study, the results show that hypo-echoic (low echogenicity) or dis-homogeneous plaques, with spotty micro-calcification and large plaque burden, surface irregularities and plaque neovascularization by contrast-enhanced ultrasound were found to be more prone to clinical complications than hyper-echoic, extensively calcified, homogeneous plaques with limited plaque burden, smooth luminal plaque surface and absence of neovascularization .The lower-target (no evidence of carotid atherosclerosis) group consisted of 221 subjects and the higher-target (presence of carotid atheroma) group consisted of 231 subjects. The median follow-up was 30 months. TPA predicted stroke, death or TIA (Kaplan-Meier log rank P<0.001) and stroke/death/TIA/myocardial infarction (any cardiovascular event) (P<0.001). In Cox regression, TPA remained a significant predictor of events after adjustment for conventional coronary risk factors (P=0.001).

After adjustment for Blood Pressure (BP), age, gender, smoking, diabetes, CKD and cholesterol level, the features of vulnerable carotid atherosclerotic plaque had a strong association with probable TIA and stroke (OR, 1.4; 95% CI, 1.2-1.6). Interestingly, high sensitivity C Reactive Protein (hs CRP) had a higher risk ratio of 1.35 than that of arterial hypertension (risk ratio of 1.3) compared to total cholesterol risk ratio of 1.2.

The US features of carotid plaque vulnerability include one or more of the followings: Hypo echoic or dis-homogeneous plaques, with spotty micro-calcification, surface irregularities and plaque neovascularization by contrast-enhanced ultrasound (These typical features of plaque instability. In addition, the present study revealed that Color Flow Mapping (CFM) and power Doppler can improve the image resolution of the intima, cIMT and proper plaque visualization. Therefore, early carotid atherosclerosis can be detected in a sub clinical stage of the disease.

Among the entire study population during 2.5-year follow up, coronary event rates were higher among patients with versus without carotid atherosclerosis (age- and sex adjusted). In multivariable analysis, including all cardiovascular risk factors, the greatest difference between-group was observed for nonfatal MI (HR, 1.5; 95% CI, 1.30–1.7) when carotid atherosclerosis was present. This observation of an association of positive carotid artery remodeling and ACS (unstable angina, NSTEMI and STEMI), suggesting that plaque vulnerability may be a systemic phenomenon. Furthermore, plaque neovascularization by contrast-enhanced ultrasound points to high risk advanced atherosclerotic plaque liable to rupture [10-13].

Discussion

The results show that the patients were in their working age and there was almost equal number of men and women. Plaque characterization in the patients supports aggressive and intensive medical therapy as well as interventional procedures, including bypass arterial graft or stenting. This is the first study to provide a comprehensive understanding of the field of carotid ultrasonic vascular morphology together with plaque burden and their role in cardiovascular events in both men and women in their working age. This paper presents fundamental and advanced ultrasonic methods for analyzing plaque volume and morphology. However, very little is known about the arterial mechanics of plaque buildup, arterial fibrous cap rupture and the role of plaque neo-vascularization. In the present study, US echogenicity characteristics and morphological characterization of carotid plaque types have been shown to have clinical utility in prediction of stroke risks and acute cardiovascular events.

A recent trial has undertaken measurements of the carotid US plaque burden (derived from number and maximum size of carotid artery plaques) and first ischemic stroke during follow-up. The results revealed strong associations between cardiovascular risk factors, carotid plaque burden and ischemic stroke subtypes. The investigators in this mega trial suggested that carotid artery atherosclerosis is an important risk factor chiefly for large artery and lacunar stroke. By contrast, arterial hypertension is an important risk factor both for atherosclerosis and for all ischemic stroke subtypes. Alternatively, the current findings in our study revealed the potential role of carotid

artery imaging in the early prediction of MCVE through accurate measurements of total plaque area and definite evaluation of the morphology of vulnerable atherosclerotic plaque.

A large-scale study is highly required to distinguish the underlying pathophysiologic characteristics of ischemic stroke subtypes. Moreover, MCVE and data from such imaging may lead to a better understanding of the potential benefits of different drug treatments for the prevention of different subtypes of ischemic stroke and ACS. Similar data on plaque volume evaluation were reported before by Wannarong et al. These authors studied the relationship between the TPV and total plaque area and their correlation to cardiovascular events, although, plaque morphology and carotid US features of atherosclerotic plaque vulnerability were not included in their important study.

Cardiovascular syndromes include ACS (unstable angina, non ST elevation MI (NSTEMI) and ST elevation MI (STEMI) or Sudden Cardiac Death (SCD), as well as advanced atherosclerosis of the carotid and cerebral arteries which can progress to Transient Ischemic Attacks (TIA) or ischemic stroke. The etiology of these complexes is blood thrombosis which forms on the surface of the damaged endothelium of the atherosclerotic coronary or carotid arteries, most frequently in the internal carotid artery. Pathophysiological studies have shown that the most common cause of formation of a blood clot is rupturing of the (unstable) atherosclerotic fibrous cap. This can be confirmed and visualized by Intravascular US (IVUS), Virtual histology (VH-IVUS), Optical Coherence Tomography (OCT) and Magnetic Resonance Imaging (MRI) [12]. The wide spread use of statin drugs, especially atorvastatin, simvastatin and rosuvastatin and lifestyle changes have resulted in a better control of inflammatory changes ongoing inside the atherosclerotic plaque. This, in turn, results in reduction in the incidence of strokes and ACS. On the other hand, carotid US can demonstrate easily the carotid plaque thickness, morphology and plaque burden, which can definitely predict the future of cardiovascular events in asymptomatic adults. Interestingly, the present study demonstrated that the magnitude of independent risk of cerebrovascular events is associated predominantly with features of carotid unstable atherosclerotic plaque and hs CRP (C-reactive protein).

Clinical perspectives

Despite advances in treatment for Atherosclerotic Cardiovascular Disease (ASCVD), atherosclerosis and its complications (MCVE) remain the leading cause of morbidity and mortality, being the source of the greatest health-care costs in the Western world. Although the underlying pathogenesis of atherosclerosis is well understood, predicting who will become affected and suffer clinical disease is not fully understood, despite much knowledge about risk factors. In fact, risk prediction derived from risk factors for ASCVD has been shown to perform rather poorly. An alternative approach for predicting symptomatic ASCVD is based on the identification of subclinical atherosclerosis in presumably healthy people. Prediction of major cardiovascular events can be improved using imaging such as ultrasound assessment of carotid plaque. This study analyzed the predictive value of carotid ultrasound measures of carotid plaque size (TPA) and morphology (features of vulnerable plaque).

Conclusion

The simpler TPA and US evidence of vulnerable atherosclerotic plaques can predict cardiovascular events. These techniques may be employed as simple useful measures for the prediction of future MCVE in asymptomatic cardiovascular diseases.

Limitations

Multi-center trials are pre-request before clinical application of carotid US for prediction of the risk of MCVE. Moreover, there is an urgent need for the initiation of anti-atherosclerotic and anti -platelets therapy, in such asymptomatic patients with US evidence of advanced features of carotid atherosclerosis.

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