Carotid Intima-Media Thickness is Superior to other Non-Invasive Functional and Structural Vascular Assessments in Risk Stratification of Subjects with Established Cardiovascular Disease

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LAU ET AL.: ***Carotid Intima-Media Thickness is Superior to other Non-Invasive Functional and Structural Vascular Assessments in Risk Stratification of Subjects with Established Cardiovascular Disease.*** **Objective:** *In patients with known cardiovascular disease (CVD), risk scores based on traditional risk factors of atherosclerosis do not apply and alternative methods of risk stratification are needed. We aim to compare the prognostic values of a range of commonly used non-invasive vascular assessments in a group of patients with known CVD. Incremental values of surrogate markers used in combination would also be assessed.* **Methods:** *We determined the brachial endothelial function (flow-mediated dilatation (FMD), nitroglycerin-mediated dilatation (NMD)), carotid artery atheroma burden (carotid mean maximum intima-media thickness (mmIMT) and plaque), ankle-brachial index (ABI) and arterial stiffness (brachial-ankle pulse wave velocity (baPWV)) in 387 patients with known CVD or equivalent (139 patients with iscahemic stroke (ISS), 130 patient with coronary artery disease (CAD), 100 patients with diabetes without CAD or ISS and 19 patients with both CAD and ISS). Patients were followed-up at 25±6 months and presence of a major adverse cardiovascular event (MACE) was documented.* **Results:** *During the follow-up period, a total of 46 MACEs occurred. Carotid mmIMT was significantly greater in patients with MACEs (1.18±0.29 mm versus 1.07± 0.31 mm, P=0.027) but there were no significant differences in FMD, NMD, carotid plaque prevalence, ABI or baPWV in subjects with or without MACEs. Kaplan-Meier curve analysis revealed a significantly greater number of adverse events in patients with a mmIMT>1.2 mm (P<0.0001 by log rank test) or baPWV>1445 cm/s (P=0.005). Univariate analysis with Cox proportional hazards modeling identified mmIMT>1.2 mm, baPWV>1445 cm/s, ABI≤1.1, NMD≤13.5%, age and oral nitrate use as positive predictors of MACEs (all P<0.1). However, multivariate analysis revealed that out of all non-invasive vascular assessments, only mmIMT>1.2 mm (Hazards ratio 2.49, 95% confidence interval 1.15-5.39, P=0.020) was an independent predictor of MACEs. Furthermore, patients with a combined impairment of mmIMT and baPWV was associated with an increased risk of MACE compared with those with impairment of either marker alone (P=0.007 by log rank test) but did not provide significant incremental benefit for MACE prediction compared with mmIMT or baPWV alone (P=0.11 and P=0.053 by comparing 2 receiver operating characterisitic curves).* **Conclusions:** *Amongst a range of non-invasive vascular assessments of atherosclerosis, carotid IMT provides the best predictive value for MACEs in patients with established CVD or equivalent.*

Cardiovascular adverse event, carotid intima-media thickness, risk prediction

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摘要

目的：對心血管疾病患者，基於經典動脈粥樣硬化危險因素的危險評分並不適用，需要另類的危險程度分級方法。本文旨在比較心血管疾病患者中幾種常用非創傷性血管評估指標的診斷意義並評估替代標誌組合的增量價值。**方法：**測定387例確診心血管疾病或類似疾病患者（其中139例缺血性中風（ISS）、130例冠脈疾病（CAD）、100例無CAD或ISS的糖尿病、19例CAD合併ISS）的肱動脈內皮功能（流量介導的血管舒張功能FMD）、硝酸甘油介導的血管舒張（NMD）、頸動脈粥樣硬化負荷（頸動脈平均最高中層內膜厚度mmIMT和斑塊）、踝臂指數（ABI）及動脈硬度（肱動脈–踝動脈脈搏波傳導速度baPWV），並隨訪25±6月的主要不良心血管事件（MACE）。**結果：**隨訪期間共發生46次MACE。發生MACE組的頸動脈mmIMT明顯增加（1.18±0.29 mm versus 1.07±0.31 mm, P=0.027）。但有無MACE兩組間FMD、NMD、頸動脈斑塊發生率、ABD或baPWV皆無顯著差異。Kaplan-Meier 曲線分析顯示mmIMT>1.2 mm（時序檢驗P<0.0001）或 baPWV>1445 cm/s（P=0.005）患者發生不良事件的次數更多。Cox比率危險模型單因素分析定義mmIMT>1.2 mm、baPWV>1445 cm/s、 ABI≤1.1、NMD≤13.5%、年齡及口服硝酸鹽爲MACE 的正性預測因數（所有P < 0.1）。然而，多因素分析顯示所有非創傷性血管評價指標中，僅有mmIMT>1.2 mm 是MACE的獨立預測因數（危險比率 2.49, 95% 可信區間1.15-5.39, P=0.020）。此外，mmIMT 和baPWV同時減少患者較單一指標減少患者的MACE危險性增加（時序檢驗P=0.007），但是沒有證據表明兩者同時減少較單一指標減少對MACE預測具有顯著增值效益（兩組受者運行特徵曲線P=0.11、P=0.053）。**結論：**確診心血管疾病患者的非創傷性血管動脈粥樣硬化評價指標中，頸動脈IMT對MACE具有最佳預測意義。

關鍵詞：心血管不良事件　頸動脈中層內膜厚度　危險預測

Introduction

Various types of risk assessment scores, such as the Framingham Risk Score have been used for risk stratification of subjects without established cardiovascular diseases (CVD). However, these risk scores are not applicable for patients with established CVD. Recently, various types of surrogate markers of atherosclerosis, including vascular endothelial function, carotid intima-media thickness (IMT) and plaque burden, ankle-brachial index (ABI) and arterial stiffness have been increasingly used for the prediction of cardiovascular events. Several studies have shown that these markers correlate with the extent and degree of atherosclerosis,[1-10] and have prognostic values in the prediction of cardiovascular-related events.[11-18] Indeed, recent clinical guidelines have recommended the use of these markers for risk stratification of asymptomatic subjects.[19,20] However, the relative clinical values of these different surrogate markers in patients with established CVD or equivalent remain unclear.

The purpose of this study was to compare the prognostic implications of several surrogate markers of vascular assessment including brachial endothelial function, carotid atheroma burden, ABI and arterial stiffness in the prediction of cardiovascular events. Furthermore, the potential incremental prognostic values of these surrogate makers used in combination will be assessed.

Materials and Methods

Subjects

The study population comprised of 387 consecutive patients with a known history of coronary artery disease (CAD), ischaemic stroke (ISS) or diabetes mellitus (DM) (CAD equivalent).[21] The presence of CAD was defined by a documented history of an acute coronary event (myocardial infarction or unstable angina), previous percutaneous coronary intervention, coronary artery bypass grafting surgery or positive myocardial perfusion scan. ISS was defined as a neurological deficit of sudden onset that persisted for more than 24 hours, corresponded to a vascular territory in the absence of primary haemorrhage, was not explained by other causes (trauma, infection, vasculitis), and was confirmed by computerised axial tomography or magnetic resonance imaging of the brain. Patients with haemorrhagic stroke, suspected cardioembolic

stroke and stroke due to other causes were excluded. DM was defined as a serum fasting glucose of ≥7.1 mmol/L or on oral hypoglycaemic agents or insulin injection therapy. The study was approved by the institutional review board, and all subjects gave written informed consent.

Study Design

All patients were prospectively recruited between July 2005 and June 2006 from our medical outpatient clinics. Baseline demographic data, cardiovascular risk factors and cardiovascular medications at the time of recruitment were documented. Cardiovascular risk factors, including tobacco smoking, DM, hypercholesterolaemia, hypertension, body-mass index and family history of CVD in first-degree relatives younger than 55 years of age were assessed. Hypertension was defined as either resting systolic or diastolic blood pressure ≥140/90 mmHg at two different times or on anti-hypertensive medications. Hypercholesterolaemia was defined as a fasting total serum cholesterol level of ≥4.9 mmol/L or on lipid-lowering medications. Body-mass index was calculated as weight in kilograms divided by the square of height in metres. Smoking status was recorded as either smoker (past and current) or non-smoker.

Vascular Assessments

Vascular ultrasound examinations for brachial endothelial function, carotid IMT and presence of carotid plaque were evaluated through a standard B-mode ultrasound examination with the use of a 7.5 MHz linear array transducer and a high resolution ultrasound system (Agilent Sonos 5500, Philips, Andover, Massachusetts, USA) as described previously.[22,23] Measurements of ABI and arterial stiffness were performed using a commercially available device based on oscillometric method (VP-2000, Colin Corporation, Komaki, Japan).

A single experienced operator, who was blinded to the identity of the study subjects performed all the vascular ultrasound examinations. Another experienced operator, also blinded to the identity of the study subjects, operated on the VP-2000 and obtained the ABI and arterial stiffness parameters.

Brachial Endothelial Function

Patients were studied in the fasting state and vasoactive medications were withheld for 12 hours before the scans. Longitudinal brachial artery diameter was obtained at rest, and then during flow-mediated dilation (FMD), induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 50 mmHg above systolic blood pressure for 5 minutes. The cuff was then released and serial imaging of the brachial artery was recorded for 5 minutes. After another 5 minutes of rest, 400 μg of sublingual nitroglycerin via a spray was administered. The brachial artery diameter was measured again, 4 minutes after administration of nitroglycerin. FMD was defined as the percentage change in brachial artery diameter between 1 minute after cuff deflation and that on the baseline scan. Nitroglycerin-mediated dilatation (NMD) was defined as the percentage change in brachial artery diameter 4 minutes after administration of nitroglycerin and that on the baseline scan. All digital images were stored on optical diskettes for subsequent off-line analysis using a computer workstation (EchoPAC, GE Medical, Wisconsin, USA). The brachial artery diameter was measured by a single operator and an average value from three consecutive measurements was calculated. The intra-observer correlation coefficient for FMD was 0.90 and the intra-observer correlation coefficient for NMD was 0.86 (2 repeated measurements in 20 randomly chosen subjects).

Carotid Intima-Media Thickness and Plaque

Carotid IMT was determined by measuring manually the distance between the lumen-intima and media-adventia border of the vascular wall using electronic calipers. Each ultrasonic scan was performed in the anterior, lateral and posterior projections of the right and left carotid arteries. Three IMT measurements were made on the near and far wall of the common carotid arteries, carotid bifurcation and internal carotid arteries. The mean maximum IMT (mmIMT) was used for analysis and was calculated by averaging the values of maximum IMT measured from 12 pre-selected segments of the carotid arteries. Presence of carotid plaque was defined as an endoluminal protrusion of the arterial lumen of at least 0.5 mm or 50% of the

surrounding IMT value or demonstrates an IMT of >1.5 mm.[24] The intra-observer correlation coefficient for mmIMT was 0.97 (2 repeated measurements in 20 randomly chosen subjects).

Ankle-Brachial Index and Arterial Stiffness

Subjects were studied under supine resting conditions in a quiet and temperature-controlled room for the measurements of ABI and arterial stiffness. Pneumatic pressure cuffs with oscillometric pressure sensors were wrapped tightly around both arms and both ankles. Electrocardiographic electrodes were attached onto both wrists and a phonocardiogram was placed at the left second intercostal space, at the margin of the sternum. After ensuring that the patients have rested for 15 minutes, a fully automatic data acquisition would begin. Pressure waveforms of the brachial and posterior tibial arteries were recorded. Based on the height of the patient, the device estimated the path lengths from the brachial artery to posterior tibial artery. Brachial-ankle PWV (baPWV) was calculated as the path length divided by the corresponding time interval (cm/s). The right and left baPWV were averaged and the resulting value selected as the representative baPWV.

The pneumatic pressure cuffs over the arms and ankles enabled simultaneous measurement of systolic blood pressure of the 4 limbs. The right-and left-sided ABI were calculated as the ankle systolic blood pressure divided by the brachial systolic blood pressure measured from right and left side, respectively. The right and left ABI were averaged and the resulting value selected as the representative ABI.

The intra-observer correlation coefficient for ABI was 0.85 and the intra-observer correlation coefficient for baPWV was 0.98 (2 repeated measurements in 20 randomly chosen subjects).

Clinical Outcome

All patients were followed-up in our clinic every 3-4 months. Clinical data of all patients were retrieved from the medical records and subsequently during the most recent clinic visit. Major adverse cardiovascular event (MACE) was defined as death due to cardiovascular causes, acute coronary syndrome, heart failure hospitalisation, symptom driven revascularisation procedures (carotid endarterectomy, percutaneous coronary intervention or coronary artery bypass graft surgery) or ISS. Cardiovascular death was defined as death due to lethal cardiac arrhythmias, myocardial infarction, heart failure, fatal stroke or unexplained sudden death. Myocardial infarction was defined as the presence of chest pain and/or elevation of creatine kinase >2 times the upper limit of normal, with or without new ST-segment elevation (>0.1 mV) in at least 2 contiguous leads. Unstable angina was defined as hospitalisation because of angina pectoris that occurred at rest and that was associated with ECG changes. ISS was defined as clinical and radiological evidence of stroke without intracranial haemorrhage. Heart failure hospitalisation was defined as hospitalisation because of heart failure as diagnosed by using the modified Framingham criteria.[25,26]

Statistical Analysis

Continuous variables were presented as mean±1 standard deviation. Categorical data were presented as frequencies and percentages. Statistical comparisons between groups were performed with Student's t test for continuous variables and Chi-squared test for categorical variables. Correlations between vascular assessment variables were evaluated by calculating the Pearson's correlation coefficient. Receiver operating characteristic (ROC) curves were constructed and the areas under the curve (AUC) as well as the cut-off values of the vascular assessments with optimal sensitivity and specificity were obtained. The standard error (SE) of the AUC was quoted. Cumulative event rates were calculated according to Kaplan-Meier method and log rank test. Cox regression analysis was used to determine the clinical predictors of MACE. Variables with $P<0.1$ in the univariate analysis were entered into a multivariate analysis model to identify the independent predictors for MACE.

All calculations were performed with use of SPSS 15.0 software with the exception of construction and comparison of the ROC curves which were calculated using the MedCalc 8.2.1.0 software. A P value <0.05 was considered to be statistically significant.

Results

Clinical Characteristics

The clinical characteristics of the study population are summarised in Table 1. Their mean age was 66.4±10.4 years and 251 were men (65%). Among them, 139 patients (36%) had ISS, 130 (34%) had CAD, 100 (26%) had DM without CAD or ISS, and 18 (5%) had both CAD and ISS. Furthermore, 268 (69%) patients had hypertension, 210 (54%) had DM and 245 (63%) had hypercholesterolaemia.

Relationships between Vascular Assessment Parameters

As shown in Table 2, there were only weak correlations among different vascular assessment parameters. Parameters of endothelial function including FMD and NMD were negatively correlated with carotid mmIMT (r=-0.12 and r=-0.21 respectively) and baPWV (r=-0.14 and r=-0.17 respectively) (all *P<0.05*). Carotid mmIMT was negatively correlated with ABI (r=-0.31) and positively correlated with baPWV (r=0.20) (all *P<0.001*).

Table 1. Clinical characteristics of the study population

Characteristic	All (N=387)	With MACE (N=46)	Without MACE (N=341)	P-value
Age, years	66.4±10.4	72.0±7.2	65.6±10.6	<0.0001
Males, n (%)	251 (65)	30 (65)	221 (65)	0.92
Body-mass index, kg/m^2	25.4±3.6	25.8±3.5	25.4±3.6	0.43
Blood pressure, mmHg				
Systolic	138.5±20.4	144.0±22.8	137.7±20.0	0.093
Diastolic	76.1±10.1	77.5±12.2	76.0±9.8	0.46
Hypertension, n (%)	268 (69)	33 (72)	235 (69)	0.38
DM, n (%)	210 (54)	29 (63)	181 (53)	0.20
Hypercholesterolaemia, n (%)	245 (63)	31 (67)	214 (63)	0.14
Smoking, n (%)	167 (43)	21 (46)	146 (43)	0.36
Family history of CVD, n (%)	23 (6)	3 (7)	20 (6)	0.87
Biochemistry analysis				
Total cholesterol, mmol/L	4.62±0.90	4.59±1.05	4.62±0.89	0.86
LDL, mmol/L	2.64±0.77	2.57±0.94	2.65±0.76	0.60
HDL, mmol/L	1.33±0.35	1.34±0.32	1.32±0.35	0.69
Triglyceride, mmol/L	1.43±0.82	1.47±0.84	1.43±0.82	0.79
Blood glucose, mmol/L	6.13±2.04	6.71±2.77	6.08±1.93	0.18
Medications				
Beta-blocker, n (%)	130 (34)	20 (43)	110 (32)	0.17
Calcium channel blocker, n (%)	117 (30)	15 (33)	102 (30)	0.94
ACEI/ARB, n (%)	190 (49)	25 (54)	165 (48)	0.27
Nitrate, n (%)	98 (25)	20 (43)	78 (23)	0.001
Aspirin, n (%)	229 (59)	25 (54)	204 (60)	0.32
Statin, n (%)	214 (55)	28 (61)	186 (55)	0.75

Abbreviations: MACE=major adverse cardiovascular event; DM=diabetes mellitus; CVD=cardiovascular disease; LDL=low-density lipoprotein; HDL=high-density lipoprotein; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker

Clinical Outcomes

During a mean follow-up of 25±6 months (range 1 month-30 months), 46 MACE were observed in 46 patients (11.9%), including 6 cardiovascular deaths, 6 acute coronary syndromes (2 unstable angina, 3 non-ST elevation myocardial infarctions and 1 ST elevation myocardial infarction), 7 heart failure hospitalisations, 14 revascularisation procedures (all percutaneous coronary interventions) and 13 ISS.

As shown in Table 1, patients with MACE were significantly older (72.0±7.2 years versus 65.6±10.6 years, *P<0.0001*) and were more likely to be treated with an oral nitrate (43% versus 23%, P=0.001). There was nonetheless no significant differences in the two groups in terms of gender, proportion with hypertension, hypercholesterolaemia or DM, smoking or family history of CVD (all *P>0.05*).

Results from different vascular assessment parameters are shown in Table 3. Patients with MACE had significantly greater mmIMT (1.18±0.29 mm versus 1.07±0.31 mm, *P=0.027*) than those without MACE. However, there were no significant differences in FMD, NMD, carotid plaque prevalence, ABI nor baPWV between patients with or without MACE.

ROC curves were constructed to obtain the diagnostic values as well as optimal cut-off values of the different vascular assessment parameters (Table 4). All these parameters had good negative predictive values (90-98%) but poor positive predictive values (13-23%). These cut-off points were then used for subsequent Kaplan-Meier and Cox regression analysis. Kaplan-Meier analysis revealed that subjects with a raised mmIMT>1.2 mm (*P<0.0001*, Figure 1a) and increased baPWV>1445 cm/s (*P=0.005*, Figure 1b) were associated with the occurrence of MACE during follow-up. In contrast, FMD>2.1% (*P=0.10*), impaired

Table 2. Pearson correlation coefficients between vascular assessment parameters

	FMD	NMD	mmIMT	ABI
NMD	0.41**			
mmIMT	-0.12*	-0.21*		
ABI	0.10	0.10	-0.31**	
baPWV	-0.14*	-0.17**	0.20**	-0.10

Abbreviations: FMD=flow-mediated dilatation; NMD=nitroglycerin-mediated dilatation; mmIMT=mean maximum intima-media thickness; ABI=ankle-brachial index; baPWV=brachial-ankle pulse wave velocity
* *P<0.05*, ** *P<0.001*

Table 3. Vascular assessment parameters of study population

Vascular assessment parameters	All (N=387)	With MACE (N=46)	Without MACE (N=341)	P-value
FMD, %	2.94±2.47	3.25±2.12	2.90±2.53	0.34
NMD, %	13.76±6.49	12.16±5.29	14.00±6.63	0.053
mmIMT, mm	1.09±0.31	1.18±0.29	1.07±0.31	0.027
Carotid plaque, n (%)	239 (62)	30 (65)	209 (62)	0.25
ABI	1.08±0.10	1.06±0.13	1.08±0.10	0.18
baPWV, cm/s	1771±414	1845±410	1764±416	0.27

Abbreviations: MACE=major adverse cardiovascular event; FMD=flow-mediated dilatation; NMD=nitroglycerin-mediated dilatation; mmIMT=mean maximum intima-media thickness; ABI=ankle-brachial index; baPWV=brachial-ankle pulse wave velocity

NMD≤13.5% (*P=0.052*), the presence of carotid plaque (*P=0.43*) and decreased ABI≤1.1 (*P=0.062*) were not associated with the occurrence of MACEs.

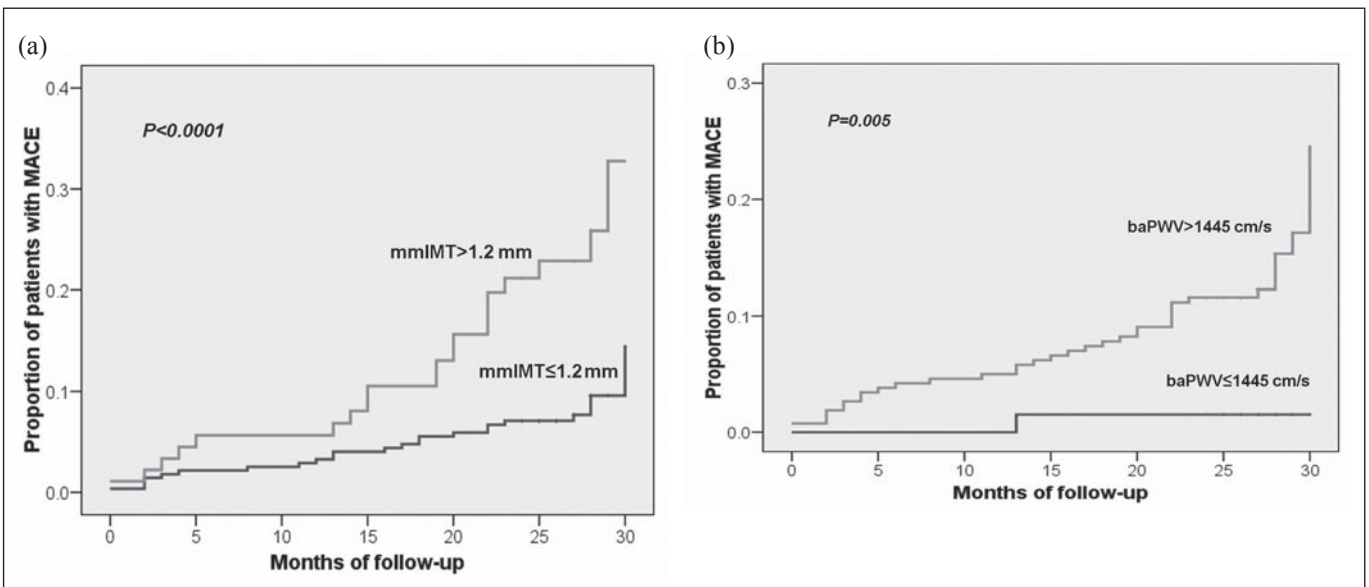
Univariate Cox regression analysis calculated that NMD≤13.5%, mmIMT>1.2 mm, ABI≤1.1, baPWV>1445 cm/s, age and oral nitrate use were positive predictors of MACE (Table 5, all *P<0.1*). Multivariate Cox regression analysis then revealed that mmIMT>1.2 mm (Hazards ratio [HR] 2.49, 95% confidence interval [CI] 1.15-5.39, *P=0.020*) and oral nitrate use (HR 2.37, 95% CI 1.14-4.94, *P=0.021*) were independent predictors for MACE.

The incremental value of using mmIMT and baPWV together for prediction of MACE was examined.

Table 4. Diagnostic values of various vascular assessments according to specified cut-off values

Marker	AUC (SE)	P-value	Cut-off values	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive predictive value, %	Negative predictive value, %
FMD	0.56±0.05	0.27	>2.1%	72.5 (56.1-85.4)	41.5 (35.9-47.2)	14.0	92.0
NMD	0.58±0.05	0.10	≤13.5%	71.8 (55.1-85.0)	43.8 (38.0-49.6)	14.4	92.2
mmIMT	0.63±0.05	0.005	>1.2 mm	46.5 (31.2-62.3)	78.9 (74.1-83.2)	22.5	91.8
Carotid plaque	0.53±0.05	0.54	-	69.8 (53.9-82.8)	36.1 (30.9-41.6)	12.6	90.1
ABI	0.56±0.05	0.20	≤1.1	85.7 (71.4-94.5)	30.2 (25.1-35.7)	14.3	93.9
baPWV	0.55±0.05	0.32	>1445 cm/s	97.2 (85.4-99.5)	21.4 (16.8-26.5)	13.1	98.4

Abbreviations: AUC=area under curve; SE=standard error; CI=confidence interval; FMD=flow-mediated dilatation; NMD= nitroglycerin-mediated dilatation; mmIMT=mean maximum intima-media thickness; ABI=ankle-brachial index; baPWV= brachial-ankle pulse wave velocity



Abbreviations: MACE= major adverse cardiovascular event; mmIMT= mean maximum imtima-media thickness; baPWV= brachial-ankle pulse wave velocity

Figure 1. *Kaplan-Meier curves for the development of MACE in patients with (a) mmIMT>1.2 mm or ≤1.2 mm and (b) baPWV> 1445cm/s or ≤1445cm/s*

Table 5. Cox regression analyses for MACE in patients with CVD

Risk variable	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
FMD>2.1%	1.74 (0.87-3.50)	0.12		
NMD≤13.5%	1.97 (0.98-3.97)	0.058	1.17 (0.54-2.55)	0.69
mmIMT>1.2 mm	2.88 (1.58-5.25)	0.001	2.49 (1.15-5.39)	0.020
Carotid plaque	1.30 (0.68-2.49)	0.43		
ABI≤1.1	2.23 (0.94-5.30)	0.069	1.14 (0.43-3.04)	0.79
baPWV>1445 cm/s	10.04 (1.37-73.4)	0.023	6.76 (0.90-50.67)	0.063
Age	1.07 (1.03-1.10)	<0.0001	1.03 (0.99-1.08)	0.16
Male gender	1.09 (0.59-2.00)	0.78		
Body-mass index	1.04 (0.96-1.12)	0.39		
Hypertension	1.43 (0.68-2.98)	0.35		
DM	1.63 (0.88-3.01)	0.12		
Smoking	1.28 (0.70-2.34)	0.43		
Family history of CVD	1.01 (0.31-3.27)	0.98		
Beta-blocker	1.70 (0.91-3.16)	0.10		
Calcium channel blocker	1.29 (0.68-2.46)	0.43		
ACEI/ARB	1.44 (0.78-2.74)	0.27		
Nitrate	1.97 (1.08-3.61)	0.008	2.37 (1.14-4.94)	0.021
Aspirin	0.84 (0.44-1.60)	0.59		
Statin	1.15 (0.63-2.08)	0.65		

Abbreviations: MACE=major adverse cardiovascular event; CVD=cardiovascular disease; HR=hazards ratio; CI=confidence interval; FMD=flow-mediated dilatation; NMD=nitroglycerin-mediated dilatation; mmIMT=mean maximum intima-media thickness; ABI=ankle-brachial index; baPWV=brachial-ankle pulse wave velocity; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker

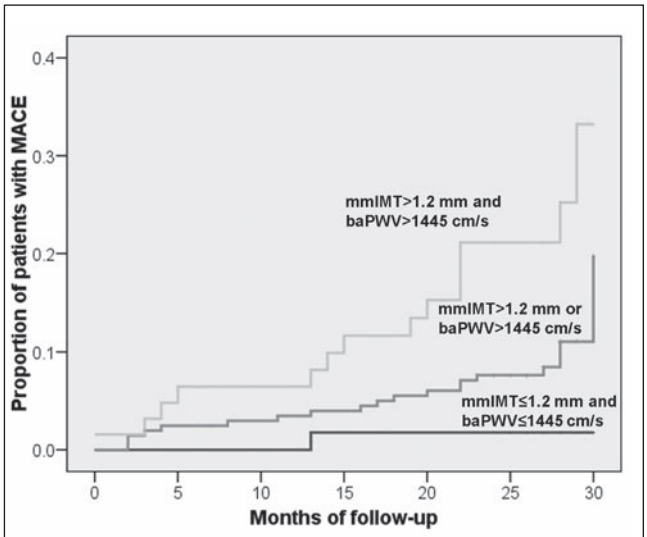
In Kaplan-Meier analysis, either increased mmIMT or baPWV was associated with an increase risk of MACE compared with patients with a normal mmIMT and baPWV (*P=0.045*, Figure 2). Furthermore, patients with both increased mmIMT and baPWV were associated with a further increase risk of MACE compared with those with increased either marker alone (*P=0.007*, Figure 2). Nevertheless, the combination of mmIMT and baPWV (AUC=0.67) did not provide significant incremental benefit for MACE prediction compared with mmIMT (AUC=0.63, *P=0.11*) or baPWV (AUC=0.55, *P=0.053*) alone.

Discussion

The results of this study demonstrated that in a population with established CVD or equivalent, increased mmIMT or baPWV were associated with increased risk of MACEs upon follow-up. However, multivariate analysis revealed that only an increased mmIMT>1.2 mm was an independent predictor for MACE and that subjects with mmIMT>1.2 mm were associated with a 2.5-fold increased risk of developing MACEs. In contrast, parameters of brachial endothelial function (including FMD and NMD) and ABI did not

have significant prognostic values. Although patients with both increased mmIMT and baPWV had a significantly greater risk of developing MACEs, the combined use of both parameters did not significantly increase the prediction value for adverse clinical outcome.

Carotid IMT has been shown to be one of the most promising non-invasive surrogate markers of predicting clinical outcomes in patients with CVD. Indeed, both the American Heart Association and the Society for Heart Attack Prevention and Eradication have recommended the use of carotid IMT as a surrogate marker for risk stratification in asymptomatic subjects.[19,27] A recent meta-analysis which included 37,000 individuals also concluded that carotid IMT was a strong predictor of future vascular events.[14] The results of the present study confirmed this finding and demonstrated that carotid IMT has the best prognostic value among different vascular surrogate makers in a patient cohort with established CVD. Whilst previous studies have identified an increased mmIMT>1 mm as a predictor for CVD events in the general population,[5] the optimal cut-off value of mmIMT in the prediction of MACE identified in the present study was >1.2 mm. This is likely because of the patient population included in this study had underlying CVD and thus their baseline IMT values would be expectedly much higher than the general population. As a result, a higher cut-off value of >1.2 mm for carotid mmIMT was required to identify patients at greatest risk of developing a recurrent major cardiovascular event.



Abbreviations: MACE= major adverse cardiovascular event; mmIMT= mean maximum imtima-media thickness; baPWV= brachial-ankle pulse wave velocity

Figure 2. *Kaplan-Meier curves for the development of MACE in patients with 1) both mmIMT>1.2 mm and baPWV>1445 cm/s, 2) either mmIMT>1.2 mm or baPWV>1445 cm/s and 3) both mmIMT≤1.2 mm and baPWV≤1445 cm/s.*

Previous studies have shown that the presence of carotid plaque is also a good predictor for CVD.[28] Based on the definition of carotid plaque from the Mannheim Carotid Intima-media Thickness Consensus,[24] we failed to demonstrate the predictive value of the presence of carotid plaque for MACE in patients with CVD. A more detailed assessment of carotid plaque by measuring the plaque area or even plaque volume may provide a more sensitive and better assessment of the burden of atherosclerosis, and thus improve its prognostic value.[29,30]

Arterial stiffness, as measured by baPWV has been suggested as a promising marker to predict adverse events in a high risk population. Previous studies have shown that increased arterial stiffness was associated with an increased risk of CAD and stroke.[31-34] Furthermore, increased arterial stiffness has been identified as an independent predictor of all-cause and cardiovascular mortality in hypertensive patients.[17] It has been postulated that an increased arterial stiffness is closely correlated with left ventricular hypertrophy, arterial wall thickening and atherosclerosis which could potentially contribute to the higher risk of adverse clinical outcomes in patients with CVD.[35-37] In this study, patients with higher baPWV had a significantly increased risk of MACEs. However, multivariate analysis failed to demonstrate baPWV as an independent predictor for MACEs in patients with CVD. The use of ABI, another structural assessment of the peripheral vascular system, also did not predict the occurrence of MACEs in this study. Indeed, the use of ABI as a surrogate marker is rather complicated as both low

(<1.0) or high (>1.4) ABI are associated with the presence of peripheral vascular disease.[38] Therefore, ABI is a less sensitive marker to predict MACEs in patients with established CVD as such subjects might have both low and high ABI values.

Endothelial dysfunction represents an early phenomenon of atherosclerosis preceding structural changes and clinical manifestations.[39] In low risk subjects without established CVD, the presence of endothelial dysfunction have been shown to predict the occurrence of adverse clinical events.[23,40] However, assessment of endothelial function appeared to have limited prognostic value in high risk subjects and patients with established CVD.[20,41,42] The results of this study supported these findings and demonstrated that brachial FMD did not predict MACEs in our patient cohort with established CVD or DM. In contrast, NMD, a marker which reflects the ability of vascular smooth muscle relaxation, has previously been shown to be impaired in subjects with cardiovascular risk factors as well as in patients with established CAD.[43,44] In this study, patients with an impaired NMD was associated with an increased risk of developing MACEs. Nevertheless, impaired NMD was not an independent predictor for MACE. On the other hand, the use of oral nitrate was shown to be an independent predictor for MACE. Although the reason remains unclear, it is possible that oral nitrate was more likely prescribed in patients with more severe CAD or it may be related to the potential adverse effects attributed to the long-term use of oral nitrate.[45]

Conclusions

The results of this study suggested that the measurement of carotid IMT as a non-invasive structural marker of atherosclerosis provides the best predictive value for MACEs in patients with established CVD or equivalent, and the combined use of vascular surrogate markers did not further improve their predictive value. Nevertheless, whether the regression of carotid IMT in those higher risk patients can reduce the risk of MACEs remains unclear.

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