Title	Incremental predictive value of vascular assessments combined with the Framingham Risk Score for prediction of coronary events in subjects of low-intermediate risk
Author(s)	Lau, KK; Chan, YH; Yiu, KH; Tam, S; Li, SW; Lau, CP; Tse, HF
Citation	Postgraduate Medical Journal, 2008, v. 84 n. 989, p. 153-157
Issued Date	2008
URL	http://hdl.handle.net/10722/57513
Rights	Creative Commons: Attribution 3.0 Hong Kong License

Incremental predictive value of vascular assessments combined with the Framingham Risk Score for prediction of coronary events in subjects of low intermediate risk

K-K Lau, Y-H Chan, K-H Yiu, S Tam, S-W Li, C-P Lau and H-F Tse

Postgrad. Med. J. 2008;84;153-157
doi:10.1136/pgmj.2007.064089

Incremental predictive value of vascular assessments combined with the Framingham Risk Score for prediction of coronary events in subjects of low–intermediate risk

K-K Lau,[1] Y-H Chan,[1] K-H Yiu,[1] S Tam,[2] S-W Li,[3] C-P Lau,[1] H-F Tse[1]

[1] Cardiology Division, Department of Medicine, University of Hong Kong, Hong Kong, China; [2] Department of Clinical Biochemistry Unit, Queen Mary Hospital, Hong Kong, China; [3] Department of Medicine, Tung Wah Hospital, Hong Kong, China

Correspondence to: Dr H-F Tse, Cardiology Division, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, China; hftse@hkucc.hku.hk

Received 15 August 2007
Accepted 23 January 2008

ABSTRACT

Background: In patients with low–intermediate risk, the use of the Framingham Risk Score (FRS) may not allow accurate prediction of the occurrence of coronary events.

Objective: To determine whether non-invasive vascular sonographic assessments add value to the FRS for prediction of coronary events.

Methods: Brachial artery flow-mediated dilatation (FMD), carotid intima–media thickness (IMT) and the presence of carotid plaque in 70 male subjects (mean (SD) age 62 (9) years) with a low–intermediate FRS who presented with a recent coronary event were evaluated and compared with those in 35 male controls matched for age (mean age 60 (9) years).

Results: Patients with a recent coronary event had a significantly higher FRS than controls. They had a significantly lower FMD (3.56 (2.41)% vs 5.18 (2.69)%, $p = 0.003$) and significantly higher prevalence of carotid plaque (67% vs 40%, $p = 0.008$), but there was no significant difference in mean maximum IMT between the two groups (1.01 (0.28) vs 0.96 (0.14) mm, $p = 0.32$). Multivariate analysis revealed that FMD $\leqslant 4.75\%$ was an independent predictor of an acute coronary event. Of the three vascular markers, FMD $\leqslant 4.75\%$ and presence of carotid plaque provided the best diagnostic accuracy for a coronary event, with area under the curve (AUC) of 0.70 and 0.64 ($p = 0.001$ and $p = 0.033$), respectively, based on receiver operating characteristic curve analysis. Furthermore, incorporating carotid plaque or FMD $\leqslant 4.75\%$ into the FRS (AUC = 0.72 and AUC = 0.78) provided incremental benefit in risk stratification over FRS alone (AUC = 0.66) ($p = 0.008$ and $p = 0.007$, for comparison of difference in two receiver operating characteristic curves).

Conclusions: Incorporating a measure of FMD or carotid plaque burden with FRS significantly increases the accuracy of predicting coronary events in subjects of low–intermediate risk and hence should be considered as additional investigations to improve coronary risk assessment.

In the past, clinical prediction of cardiovascular disease has mainly relied on evaluation of its risk factors. On the basis of multivariate statistical models of an individual's cardiovascular risk factors, different risk scores have been developed to improve the prediction of coronary risk.[1–3] The Framingham Risk Score (FRS) is one of the most common scoring systems used to stratify subjects into low, intermediate or high risk of developing a future coronary event.[1 4 5] However, this method stratifies a large and heterogeneous population of subjects into the low–intermediate risk category, in whom the decision to initiate primary prevention remains unclear.[6 7] Therefore, in such subjects, additional methods for risk stratification of cardiovascular disease are needed. Previous studies have already shown that use of the Coronary Calcium Score (CCS) determined by using cardiac CT has incremental benefit when used in conjunction with the FRS for risk prediction, especially in patients in the intermediate-risk category.[8 9] However, measurement of the CCS has a number of drawbacks, including a high test cost, limited availability and risk of exposure to radiation.

In contrast, vascular ultrasonography would be a much more accessible tool in the primary care setting. Various vascular ultrasonographic assessments, such as brachial endothelial function, carotid intima–media thickness (IMT) and detection of carotid plaque have already been shown to independently predict the presence of coronary artery disease (CAD).[10–12] However, the clinical value of these assessments above clinical risk scores for prediction of future cardiovascular risk has not been determined. Therefore, the purpose of this study was to investigate the potential added benefits of different non-invasive vascular assessments (brachial endothelial function, carotid IMT and carotid plaque detection) in conjunction with the FRS for coronary risk prediction.

MATERIALS AND METHODS

Subjects

The study population comprised 70 consecutive male patients with a low–intermediate coronary risk (<10% in 10 years as determined by the FRS), who were discharged from hospital after an acute coronary event (including myocardial infarction and unstable angina). Myocardial infarction was defined as the presence of two or three of the following: prolonged chest pain, diagnostic evolutionary ECG changes, and an increase in serum creatine kinase activity to twice the upper limit of normal. Unstable angina was defined as the presence of chest pain prompting hospital admission together with ischaemic ECG changes and normal serum creatine kinase activity. All patients had significant CAD detected by coronary angiogram and had received successful coronary revascularisation with percutaneous coronary intervention before discharge. Patients with pre-existing diabetes mellitus were considered to be

CAD equivalent and were not included in this analysis. Furthermore, patients with a clinical history of myocardial infarction, coronary revascularisation and angina, who died or developed heart failure after hospitalisation, were excluded.

The control group consisted of 35 age-matched male subjects recruited from a health screening programme. All subjects had neither symptoms of angina nor a history of cardiovascular disease, stroke or diabetes mellitus and had a CCS of <10 as detected by multi-slice cardiac CT.

All subjects were recruited between 1 July 2005 and 30 June 2006. The study was approved by the institutional review board, and all subjects gave written informed consent.

Study design

This is a case–control study involving a Chinese patient cohort, with or without hypertension, with an estimated low–intermediate risk of a coronary event. The objective of the study was to determine the value of the FRS, brachial endothelial function and carotid ultrasound assessment, used alone or in combination, for prediction of coronary events. In this study, the FRS was calculated using a recalibrated version of the risk score that has been validated for Chinese.[13]

Baseline demographic data, cardiovascular risk factors and cardiovascular drugs being used at the initial presentation of patients with CAD were documented. Cardiovascular risk factors, including tobacco smoking, diabetes mellitus, hypercholesterolaemia, hypertension, body mass index and history of cardiovascular disease 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 mm Hg at two different times or taking medication. Diabetes mellitus was defined as a serum fasting glucose of ≥7.1 mmol/l or taking medication. Hypercholesterolaemia was defined as a fasting total serum cholesterol concentration of ≥4.9 mmol/l or taking medication. Body mass index was calculated as weight in kilograms divided by the square of the height in metres. Smoking status was recorded as either smoker (past and current) or non-smoker. Fasting serum glucose and lipid concentrations were determined in controls and in patients within 24 h of their initial presentation of the acute coronary event.

Table 1 Clinical characteristics and vascular assessment variables of the study population

Characteristic	CAD (n = 70)	Controls (n = 35)	p Value
Age (years)	62.4 (8.5)	59.5 (8.9)	0.11
Male	70 (100%)	35 (100%)	1.00
Body mass index (kg/m^2)	25.1 (3.3)	24.0 (3.1)	0.12
Blood pressure (mm Hg)			
Systolic	126.3 (16.6)	122.6 (16.1)	0.28
Diastolic	74.0 (8.9)	75.1 (9.4)	0.58
Hypertension	42 (60%)	9 (26%)	0.001
Hypercholesterolaemia	58 (83%)	19 (54%)	0.002
Smoking	38 (54%)	15 (43%)	0.27
Family history of cardiovascular disease	9 (13%)	1 (3%)	0.10
FRS (%)	3.29 (2.23)	2.06 (1.21)	0.003
Biochemistry analysis			
Total cholesterol (mmol/l)	4.80 (1.00)	4.93 (0.70)	0.50
LDL (mmol/l)	2.92 (0.83)	3.08 (0.68)	0.33
HDL (mmol/l)	1.14 (0.25)	1.27 (0.31)	0.031
Triglyceride (mmol/l)	1.58 (1.24)	1.24 (0.48)	0.13
Blood glucose (mmol/l)	5.27 (0.86)	5.04 (0.42)	0.13
Drugs			
Anti-hypertensives	62 (89%)	10 (29%)	<0.001
Lipid-lowering therapy	55 (79%)	1 (3%)	<0.001
Vascular assessment variables			
FMD (%)	3.56 (2.41)	5.18 (2.69)	0.003
mmIMT (mm)	1.01 (0.28)	0.96 (0.14)	0.32
Carotid plaque	47 (67%)	14 (40%)	0.008

Values are mean (SD) or number (%).
CAD, coronary artery disease; FMD, flow-mediated dilatation; FRS, Framingham Risk Score (10-year calculated risk of developing a coronary event); HDL, high-density lipoprotein; LDL, low-density lipoprotein; mmIMT, mean maximum intima–media thickness.

Vascular ultrasound studies

Vascular ultrasound examinations were performed within 3 weeks of initial presentation in patients with CAD. 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.[14–16] A single experienced operator, who was blinded to the identity of the study subjects, performed all the vascular ultrasound examinations.

Brachial endothelial function

Patients were studied in the fasting state, and vasoactive drugs were withheld for 12 h before the scans. Longitudinal brachial artery diameter was obtained at rest, and then during flow-mediated dilatation (FMD), induced by inflation of a pneumatic tourniquet placed on the forearm to a pressure of 50 mm Hg above systolic blood pressure for 5 min. The cuff was then released, and serial images of the brachial artery were recorded for 5 min. Finally, brachial artery diameter was measured again at 4 min after administration of 400 μg sublingual nitroglycerine spray. FMD was defined as the percentage change in brachial artery diameter between 1 min after cuff deflation and baseline. All digital images were stored on optical diskettes for subsequent off-line analysis using a computer workstation (EchoPAC; GE Medical Systems, Milwaukee, Wisconsin, USA). The brachial artery diameter was measured by a single operator, and the mean of three consecutive measurements was calculated. The intra-observer correlation coefficient for FMD was 0.90 (two repeated measurements in 20 randomly chosen subjects).

Carotid IMT

Carotid IMT was determined by measuring manually the distance between the lumen–intima and media–adventia border of the vascular wall using electronic callipers. 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 in 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 IMT of >1.5 mm.[17] The intra-observer coefficient of variation and correlation coefficient for mmIMT were 4.2% and 0.97, respectively (two repeated measurements in 20 randomly chosen subjects).

Cardiac CT CCS

Cardiac CT was performed in all control subjects from the base of the heart to the apex in one breath-hold in the supine

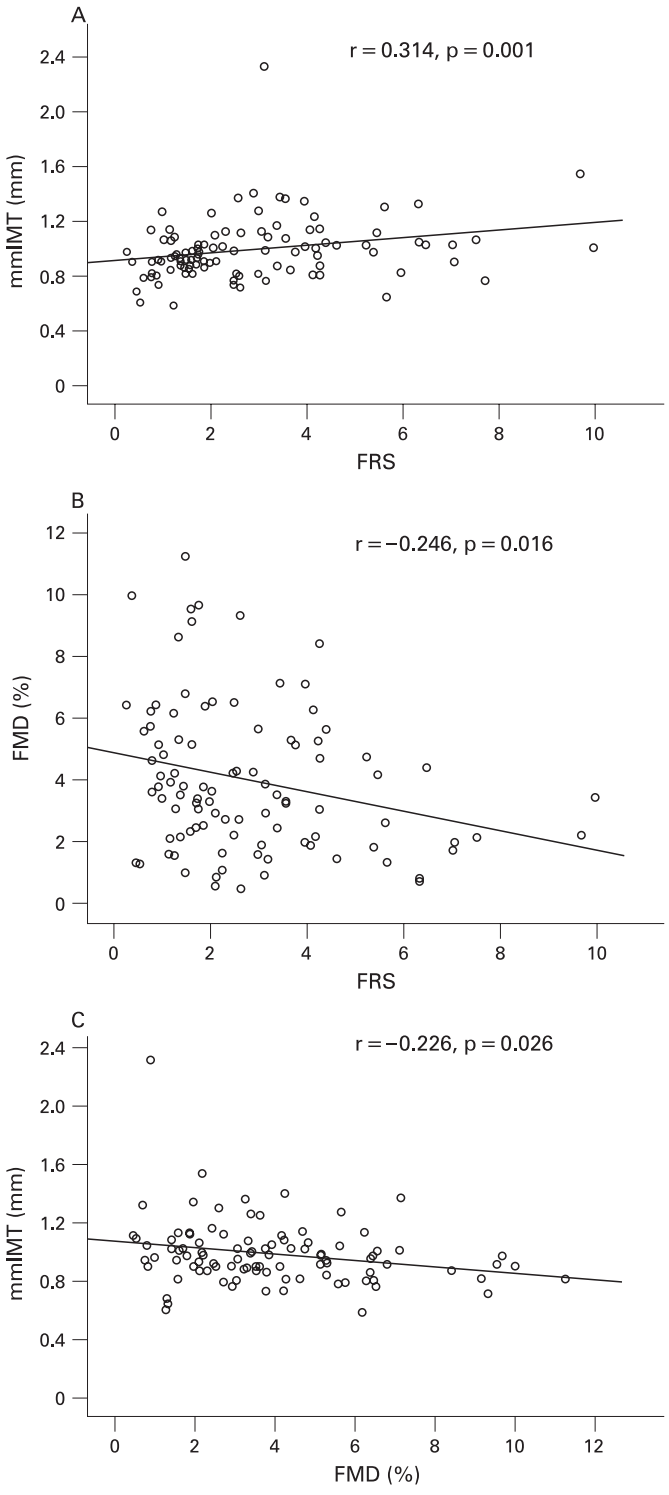

Figure 1 Correlations between (A) mean maximum carotid intima–media thickness (mmIMT) and Framingham Risk Score (FRS), (B) flow-mediated dilatation (FMD) and FRS, and (C) FMD and mmIMT.

position using a Light speed (LX16) General Electric (GE) CT scanner (GE Medical Systems). Scan parameters included slice thickness 2.5 mm (eight images collected simultaneously), cine scan mode, 0.05 s cine time interval, 120 Kv, 300 mAs (0.5 s per rotation), and cardiac gating with prospective triggering. Data were transferred to Advantage Workstation 4.2 for post-processing, and calculation of the CCS was performed using GE cardiac software.

Statistical analysis

For power calculation, we required 62 subjects to ensure that the true value lay within 0.2 of our estimate to determine the true sensitivity and specificity of 0.5 with 5% significant level and 80% power.

Continuous variables are presented as mean (SD). Categorical data are presented as frequencies and percentages. Statistical comparisons between groups were performed with the Student t test for continuous variables and χ^2 test for categorical variables. Correlations between variables were evaluated by calculating the Spearman correlation coefficient, as mmIMT and FMD did not follow normal distribution. A univariate binary logistic regression model was used to identify risk factors associated with a coronary event, then stepwise forward multivariate binary logistic was used to identify independent predictors of a coronary event. Receiver operating characteristic (ROC) curves were constructed, and the areas under the curve (AUC) as well as the sensitivities, specificities, positive and negative predictive values of the diagnostic test were obtained. Calculations were performed with use of SPSS V13.0 software, and the difference in AUC between two ROC curves was calculated with MedCalc 8.2.1.0 software. $p<0.05$ was considered to be significant.

RESULTS

Clinical characteristics

As shown in table 1, patients with CAD and controls were matched by age; all were male. Patients with CAD had a higher prevalence of hypertension ($p = 0.001$) and hypercholesterolaemia ($p = 0.002$) than controls. Furthermore, patients had significantly lower high-density lipoprotein than controls ($p = 0.031$). However, there were no differences in prevalence of smoking ($p = 0.27$), family history of cardiovascular disease ($p = 0.10$) or body mass index between the two groups ($p = 0.12$). For the 10-year predicted risk of developing a coronary event calculated from the FRS, patients with CAD had a significantly higher risk score than controls ($p = 0.003$). As expected, patients were more likely to have received drugs for treatment of hypertension and hypercholesterolaemia (both $p<0.001$).

Vascular assessment variables

Patients with CAD had a significantly lower brachial FMD than controls (3.56 (2.41)% vs 5.18 (2.69)%, $p = 0.003$). They also had a significantly higher prevalence of carotid plaque than controls (67% vs 40%, $p = 0.008$), but there was no significant difference in mmIMT between the two groups (1.01 (0.28) vs 0.96 (0.14) mm, $p = 0.32$).

As shown in fig 1, there was a modest but significant positive correlation between mmIMT and FRS ($r = 0.314$, $p = 0.001$), and negative correlation between FMD and FRS ($r = -0.246$, $p = 0.016$). Furthermore, FMD correlated inversely with mmIMT ($r = -0.226$, $p = 0.026$).

Table 2 summarises the diagnostic and optimal cut-off values of the FRS and individual vascular assessment variables for coronary event prediction obtained from ROC curve analysis. The FRS was identified to have moderate diagnostic value for coronary event prediction with an AUC of 0.66 ($p = 0.007$). Of the vascular assessment variables, FMD had the best diagnostic accuracy, with an AUC of 0.70 ($p = 0.001$). Presence of carotid plaque was also shown to have moderate diagnostic value, with an AUC of 0.64 ($p = 0.033$), but mmIMT was identified to be a poor diagnostic test, with an AUC of 0.54 ($p = 0.49$).

Table 2 Diagnostic values of the Framingham Risk Score and vascular assessment variables according to specified cut-off values

Marker	AUC (SD)	p Value	Cut-off values	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value
FRS	0.66 (0.06)	0.007	⩾2.50	56.7 (44.0 to 68.8)	74.3 (56.7 to 87.5)	80.9	47.3
FMD	0.70 (0.06)	0.001	⩽4.75	81.5 (70.0 to 90.1)	60.0 (42.1 to 76.1)	79.1	60.0
Carotid plaque	0.64 (0.05)	0.033		67.1 (54.9 to 77.9)	60.0 (42.1 to 76.1)	77.0	47.7
mmIMT	0.54 (0.06)	0.492	⩾1.05	34.8 (23.7 to 47.2)	82.9 (66.3 to 93.4)	80.0	39.2
FRS + FMD ⩽4.75	0.78 (0.05)	0.000	–	76.2 (63.8 to 86.0)	68.6 (50.7 to 83.1)	81.4	61.5
FRS + carotid plaque	0.72 (0.05)	0.000	–	83.6 (72.5 to 91.5)	62.9 (44.9 to 78.5)	81.2	66.7
FRS + mmIMT ⩾1.05	0.69 (0.05)	0.000	–	69.7 (57.1 to 80.4)	68.6 (50.7 to 83.1)	80.7	54.5
FRS + FMD ⩽4.75+ carotid plaque	0.75 (0.05)	0.000	–	81.0 (69.1 to 89.7)	68.6 (50.7 to 83.1)	82.3	66.7
FRS + carotid plaque + mmIMT ⩾1.05	0.73 (0.05)	0.000	–	75.8 (63.6 to 85.5)	71.4 (53.7 to 85.3)	83.3	61.0

AUC, area under curve; FMD, flow-mediated dilatation; FRS, Framingham Risk Score; mmIMT, mean maximum intima–media thickness.

Incremental benefit of vascular markers for coronary risk prediction

As shown in fig 2, the combination of FRS with either carotid plaque (AUC = 0.72) or FMD ⩽4.75% (AUC = 0.78) provided significant incremental benefit for coronary event prediction compared with FRS alone (AUC = 0.66, comparison with FRS + carotid plaque, p = 0.008; comparison with FRS + FMD ⩽4.75%, p = 0.007, for comparison of two ROC curves). However, the combination of mmIMT ⩾1.05 mm with FRS did not provide any incremental benefit (AUC = 0.69, p = 0.18 for comparison with ROC curve of the FRS). The combination of both carotid plaque and FMD ⩽4.75% with the FRS achieved an AUC of 0.75 (p<0.001) but did not provide further improvement compared with the use of either vascular marker alone (comparison with FRS + FMD ⩽4.75%, p = 0.34, comparison with FRS + carotid plaque p = 0.060).

Univariate analysis revealed that the FRS, hypertension, hypercholesterolaemia, impaired FMD and presence of carotid plaque predicted the occurrence of coronary events (table 3). Multivariate analysis showed that FRS (odds ratio (OR) 1.45, 95% CI 1.03 to 2.05, p = 0.034), hypercholesterolaemia (OR 4.80, 95% CI 1.67 to 13.65, p = 0.003) and impaired FMD (OR 7.97, 95% CI 2.69 to 23.59, p = 0.000) were independent predictors of a coronary event, but hypertension and presence of carotid plaque were not.

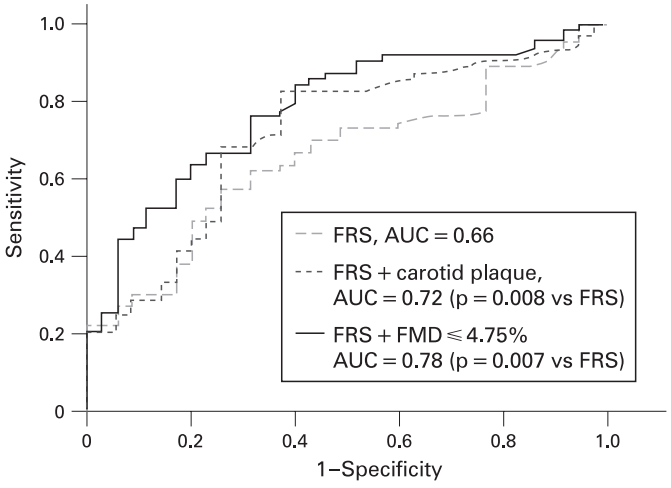

Figure 2 Receiver operating characteristic (ROC) curves to illustrate the incremental benefit achieved by adding presence of carotid plaque or an impaired flow-mediated dilatation (FMD) of ⩽4.75% to the Framingham Risk Score (FRS) for coronary risk prediction. AUC, area under the curve.

DISCUSSION

The results of this study show that the use of various vascular assessments improved risk stratification in low–intermediate risk patients as determined by the FRS. Of the different vascular assessment variables, brachial FMD was superior to the FRS, carotid IMT or the presence of carotid plaque for predicting coronary events. Furthermore, impaired FMD was an independent predictor of coronary events beyond the information provided by the FRS. However, the combination of both brachial FMD and presence of carotid plaque with the FRS did not further improve the predictive value. Used independently, an impaired brachial FMD or identification of carotid plaque provided added value to risk stratification when used together with the FRS. This finding therefore raises the potential of using vascular markers for coronary risk stratification in the future.

Recent clinical guidelines have recommended the incorporation of CCS, carotid IMT and carotid plaque as "atherosclerosis tests" to risk-stratify the presence of CAD in apparently healthy subjects.[18] However, studies have revealed a weak correlation between carotid IMT and the extent of CAD.[19] Carotid plaque, in contrast, has been shown to be superior to CCS and carotid IMT for prediction of significant CAD and hence a better surrogate marker for predicting coronary events.[20] In this study, there was no significant difference in carotid mmIMT between patients with CAD and controls, but as expected, patients with CAD had a significantly higher prevalence of carotid plaque. On the other hand, our results have shown that the brachial

What is already known on this topic

- Coronary calcium score has incremental benefit when used in conjunction with the Framingham Risk Score (FRS) for coronary risk prediction, especially for subjects of intermediate risk.
- Various non-invasive vascular sonographic assessments (brachial flow-mediated dilatation (FMD), carotid intima–media thickness and carotid plaque) independently predict the presence of coronary artery disease.

What this study adds

Non-invasive vascular sonographic assessments (brachial FMD and carotid plaque detection) provide incremental value when used with the FRS in risk stratification of developing a coronary event in low–intermediate risk subjects.

Table 3 Univariate and multivariate predictors of an acute coronary event

	Univariable		Multivariable	
Risk variable	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
FRS	1.50 (1.13 to 2.00)	0.006	1.45 (1.03 to 2.05)	0.034
Hypertension	4.33 (1.77 to 10.62)	0.001		
Hypercholesterolaemia	5.28 (2.20 to 12.68)	0.000	4.80 (1.67 to 13.65)	0.003
Smoking	1.58 (0.70 to 3.59)	0.27		
FMD $\leqslant$4.75	6.63 (2.64 to 16.66)	<0.001	7.97 (2.69 to 23.59)	<0.001
mmIMT $\geqslant$1.05	2.58 (0.94 to 7.07)	0.066		
Carotid plaque	3.07 (1.32 to 7.10)	0.009		

FMD, flow-mediated dilatation; FRS, Framingham Risk Score; mmIMT, mean maximum intima–media thickness.

Suggestions for future studies on this topic

Larger scaled prospective studies to confirm the potential of vascular sonographic assessments in coronary risk stratification.

endothelial function test is superior to the FRS, carotid IMT or plaque detection for predicting coronary events. This finding suggests that vascular endothelial function is more important than the extent of atherosclerosis or overall clinical risk profile in determining the risk of acute coronary events in a low–intermediate risk population.

Previous studies have shown that FMD and carotid atherosclerosis provide distinct independent information about atherosclerosis.[21 22] Whereas FMD identifies abnormalities of the endothelial function preceding development of an anatomical lesion, carotid IMT and plaque formation indicate the presence of a histological abnormality, suggestive of a more advanced stage of atherosclerosis. Furthermore, FMD is most closely correlated to cardiovascular risk factors and estimated 10-year coronary heart disease risk in subjects at a low risk of a coronary event.[23] Consistent with these findings, we have shown that, of the surrogate markers tested, FMD has the best predictive value and provides incremental value when used with the FRS in risk stratification of developing a coronary event in low–intermediate risk patients, in the presence or absence of hypertension.

There are several limitations in this study. This was a retrospective study which consisted of a small number of patients who presented with acute coronary events. Only male Chinese subjects were studied, hence our results might not be applicable to women or other ethnic groups. Therefore, the clinical prediction values of different non-invasive vascular sonographic assessments need to be confirmed by future prospective studies in a larger patient cohort with low–intermediate FRS involving subjects of both genders.

Acknowledgements: We thank Ms Patsy Chau, Department of Community Medicine, University of Hong Kong for her support with the statistical analysis.

Funding: This study was supported by the CRCG Small Project Funding of the University of Hong Kong (Project No 200507176137).

Competing interests: None.

REFERENCES

1. **Wilson PW,** D'Agostino RB, Levy D, *et al*. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;**97**:1837–47.
2. **De Backer G,** Ambrosioni E, Borch-Johnsen K, *et al*. European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2003;**10**:S1–10.
3. **British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; Stroke Association**. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;**91**(Suppl 5):v1–52.
4. **Kannel W,** Dawber T, Kagan A, *et al*. Factors of risk in development of coronary heart disease: six year follow-up experience. The Framingham Study. *Ann Intern Med* 1961;**55**:35–50.
5. **Wilson P,** Castelli W, Kannel W. Coronary risk prediction in adults (The Framingham Heart Study). *Am J Cardiol* 1987;**59**:91–4G.
6. **Khot UN,** Jia G, Moliterno DJ, *et al*. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA* 2003;**290**:898–7.
7. **Ridker PM,** Rifai N, Rose L, *et al*. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;**347**:1557–65.
8. **Greenland P,** LaBree L, Azen SP, *et al*. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004;**291**:210–15.
9. **Arad Y,** Goodman KJ, Roth M, *et al*. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: The St Francis Heart Study. *J Am Coll Cardiol* 2005;**46**:158–65.
10. **O'Leary DH,** Polak JF. Intima-media thickness: a tool for atherosclerosis imaging and event prediction. *Am J Cardiol* 2002;**90**:18L–21L.
11. **Fathi R,** Haluska B, Isbel N, *et al*. The relative importance of vascular structure and function in predicting cardiovascular events. *J Am Coll Cardiol* 2004;**43**:616–23.
12. **Fathi R,** Haluska B, Isbel N, *et al*. Prognostic value of brachial artery endothelial function and wall thickness. *J Am Coll Cardiol* 2005;**46**:1006–10.
13. **Liu J,** Hong Y, D'Agostino RB Sr, *et al*. Predictive value for the Chinese population of the Framingham CHD Risk Assessment tool compared with the Chinese multiprovincial cohort study. *JAMA* 2004;**291**:2591–9.
14. **Corretti MC,** Anderson TJ, Benjamin EJ, *et al*. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002;**39**:257–65.
15. **Ip MS,** Tse HF, Lam B, *et al*. Endothelial function in obstructive sleep apnea and response to treatment. *Am J Respir Crit Care Med* 2004;**169**:348–53.
16. **Lau KK,** Chan YH, Yiu KH, *et al*. Burden of carotid atherosclerosis in patients with stroke: relationships with circulating endothelial progenitor cells and hypertension. *J Hum Hypertens* 2007;**21**:445–51.
17. **Touboul PJ,** Hennerici MG, Meairs S, *et al*. Mannheim carotid intima-media thickness consensus (2004–2006). *Cerebrovasc Dis* 2007;**23**:75–80.
18. **Naghavi M,** Falk E, Hecht HS, *et al*. From vulnerable plaque to vulnerable patient. Part III. Executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. *J Am Coll Cardiol* 2006;**98**:2–15H.
19. **Spence J.** Ultrasound measurement of carotid plaque as a surrogate outcome for coronary artery disease. *Am J Cardiol* 2002;**89**:10–16B.
20. **Brook RD,** Bard RL, Patel S, *et al*. A negative carotid plaque area test is superior to other noninvasive atherosclerosis studies for reducing the likelihood of having underlying significant coronary artery disease. *Arterioscler Thromb Vasc Biol* 2006;**26**:656–62.
21. **Amir O,** Jaffe R, Shiran A, *et al*. Brachial reactivity and extent of coronary artery disease in patients with first ST-elevation acute myocardial infarction. *Am J Cardiol* 2006;**98**:754–7.
22. **Yan RT,** Anderson TJ, Charbonneau F, *et al*. Relationship between carotid artery intima-media thickness and brachial artery flow-mediated dilation in middle-aged healthy men. *J Am Coll Cardiol* 2005;**45**:1980–6.
23. **Witte DR,** Westerink J, de Koning EJ, *et al*. Is the association between flow-mediated dilation and cardiovascular risk limited to low-risk populations? *J Am Coll Cardiol* 2005;**45**:1987–93.