

**Role of Simultaneous Carotid Ultrasound in Patients
Undergoing Stress Echocardiography for Assessment of
Chest Pain with No Previous History of Coronary Artery
Disease**

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Abstract

Background: Stress echocardiography (SE) is utilised to assess new onset chest pain. While a negative study infers absence of flow-limiting coronary artery disease (FL-CAD), it does not verify non-flow limiting CAD (where plaque rupture is common, resulting in myocardial infarction (MI) and death). This can be indirectly assessed by carotid ultrasound, detecting carotid plaque (CP). In large epidemiological studies in asymptomatic population, CP was associated with CAD and MI beyond traditional risk factors, but no outcome data on combining SE (functional) and CP (anatomical) in symptomatic patients.

Methods: 591 consecutive patients, referred for SE, underwent simultaneous carotid ultrasound. Composite end-point of major adverse event (MAE) (all-cause mortality, MI and later than 3 months, unplanned, coronary angioplasty) was assessed.

Results: While 67 (11%) patients had abnormal SE, CD was detected in 415 (70%). While both abnormal SE and CP were independent predictors of FL-CAD, pre-test probability had no significant association on multivariate analysis. The positive predictive value of SE for the detection of FL-CAD improved from 56% to 70% when CP was present. Pre-test probability of CAD, abnormal SE, and CPB predicted MAE, both in medium- (3 years) and long-term (7.2 years) follow up. MAE rates per year increased in a step-by-step fashion: CP-ve and SE-ve, CP+ve and SE-ve, CP-ve and SE+ve versus CP+ve and SE+ve, both in medium- and long-term ($p<0.0001$).

Absence of CPBurden in females with abnormal SE ruled out flow-limiting CAD on coronary

angiography in 93% versus 57% in males. CPB was the only independent predictor of MAE in females, whereas in males both SE and CPB remained significant.

Discussion: A combined assessment of functional and anatomical assessment of patients with new onset chest pain infers incremental prognostic information, beyond pre-test probability and SE alone. These findings have implications for routine use of carotid ultrasound during SE.

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DECLARATION OF ORIGINALITY

I declare that I am the sole author of this thesis, that all data presented is my work and that any contributions from third parties are appropriately acknowledged and referenced.

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Publications Arising From This Thesis

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2. Long-Term Prognostic Value of Simultaneous Assessment of Atherosclerosis and Ischaemia in Patients with Suspected Angina: Implications for Routine Use of Carotid Ultrasound during Stress Echocardiography. **Ahmadvazir S**, Pradhan J, Khattar RS, Senior R. *J Am Soc Echocardiogr*. 2020 May;33(5):559-569. doi: 10.1016/j.echo.2019.11.019.
3. Incremental Prognostic Value of Simultaneous Stress Echocardiography and Carotid Ultrasound in Patients with Suspected Coronary Artery Disease: A Prospective Study. **Ahmadvazir S**, Shah BN, Zacharias K, Senior R. *JACC Cardiovasc Imaging*. 2018 Feb;11(2 Pt 1):173-180. doi: 10.1016/j.jcmg.2016.12.020.
4. Role of Simultaneous Carotid Ultrasound in Patients Undergoing Stress Echocardiography for Assessment of Chest Pain with no Previous History of Coronary Artery Disease. **Ahmadvazir S**, Shah BN, Pabla JS, Zacharias K, Senior R. *Am Heart J*. 2014 Aug;168(2):229-36. doi: 10.1016/j.ahj.2014.04.016. Epub 2014 May 15.

Presentations Arising From This Thesis

Oral Presentations:

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2- British Cardiovascular Society (BCS) Annual Conference, Manchester, 2019

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Poster Presentations:

1- European Society of Cardiology (ESC) Annual Scientific Congress, Munich, 2012.

Ahmadvazir S, Kinsey C, Zacharias K, Pabla J, Shah BN & Senior R. Higher prevalence of carotid disease compared to myocardial ischaemia in patients undergoing stress echocardiography for suspected coronary artery disease.

2- European Society of Cardiology (ESC), Annual Scientific Congress, Amsterdam, 2013.

Ahmadvazir S, Zacharias K, Pabla JS, Gani F, Shah BN & Senior R. Carotid plaque provides incremental information for predicting presence of coronary artery disease in patients evaluated for suspected coronary artery disease by stress echocardiography.

- 3- **British Cardiovascular Society (BCS)** Annual Conference, Manchester, **2016**. **Ahmadvazir S**, Zacharias K, Shah BN, Kinsey C, Young G, Senior R. Synergistic value of simultaneous stress echocardiography and carotid ultrasound performed in patients with suspected angina without known coronary artery disease for the prediction of outcome.
- 4- **American College of Cardiology (ACC)**, Annual Scientific Congress, Chicago, 2016. Senior R, Shah BN, Zacharias K, Kinsey C, Young G, **Ahmadvazir S**. Simultaneous carotid ultrasonography provides incremental Prognostic value beyond clinical and stress echocardiography data in patients with suspected angina without known coronary artery disease: a prospective study.
- 5- **European Society of Cardiology (ESC)**, Annual Scientific Congress, Paris, 2019. **Ahmadvazir S**, J Pradhan, R Khattar, R Senior. *Poster Presentation-* Long-term Prognostic Value of Simultaneous Assessment of Atherosclerosis and Ischaemia in Patients with Suspected Angina: Implications for Routine Use of Carotid Ultrasound during Stress Echocardiography.

List of Abbreviations

ACEi	Angiotensin converting enzyme inhibitor
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
BMI	Body mass index
BP	Blood pressure
CACS	Coronary artery calcium scoring
CAD	Coronary artery disease
CD	Carotid artery disease
CHD	Coronary heart disease
CI	Confidence interval
C-IMT	Carotid intima-media thickness
CMR	Cardiac magnetic resonance imaging
CP	Carotid (artery) plaque
CPB	Carotid (artery) plaque burden
CTCA	Computerised tomography coronary angiography
CU	Carotid ultrasound
CVD	Cardiovascular disease
ECG	Electrocardiogram
ExECG	Exercise ECG
FFR	Fractional flow reserve
FL-CAD	Flow-limiting coronary artery disease
FRS	Framingham risk score
IMT	Intima-media thickness
KM	Kaplan-Meier

MAE	Major adverse events
MACE	Major adverse cardiac events
MCE	Myocardial contrast echocardiography
MVD	Microvascular disease
NPV	Negative predictive value
NRI	Net reclassification improvement
PET	Positron emission tomography
PPV	Positive predictive value
PTP	Pre-test probability
pWTSI	Peak wall thickening scoring index
SPECT	Single photon emission computerised tomography
SE	Stress echocardiography
TIA	Transient ischemic attack
TRF	Traditional (cardiovascular) risk factor
US	Ultrasound

PART I – BACKGROUND, OBJECTIVES & METHODS

Chapter 1. Investigation of Symptomatic Patient for Suspected Coronary Artery Disease

Chest pain is a common medical problem; 20-40% of all adults experience chest pain at some point during their life-time (1-2); it accounts for 1-2% of all adult consultations in the primary care (3).

However, chest pain is often not cardiac in origin and a final diagnosis of coronary artery disease (CAD) (stable angina or acute coronary syndrome) only account for 8-15% of patients (4). Although an invasive coronary angiography is considered as gold standard diagnostic test for CAD, it is associated with potential complications, including risk of mortality (5). Therefore, its routine use cannot be justified in all patients with chest pain. On the other hand, Bayes' theorem states the probability of a patient having disease, after a test is performed, will be the product of disease probability before the test and the probability that the test provided a true result. Both the European (6) and the American (7) guidelines support estimating the pre-test probability (PTP) of CAD to guide further evaluation and treatment; a concept first introduced in 1979 by Diamond and Forrester (8). All the subsequent PTP tools rely on Diamond and Forrester principal idea of integrating age, sex and chest pain characteristics. Typical angina has three characteristics: 1) sub-sternal chest discomfort with a characteristic quality and duration that is 2) provoked by exertion or emotional stress and 3) relieved by rest or nitroglycerin. However, when only two are met, the pain is described as atypical angina, and if only one or none are present, then it is defined as non-cardiac pain.

Different PTP estimation tools, with inherent differences in their accuracies, often result in a wide group deemed to have intermediate PTP (9). To complicate the matter further, there is no agreement on the definition of low, intermediate and high risk groups based on PTP and what investigation each group should have. The American guideline (7), while recognising that the intermediate cut-off is rather arbitrary, endorses employing 10% to 90%, whereas the European guideline (6) classifies patients with PTP of 15% to 85% as intermediate. In the U.K., the 2010 National Institute for Health and Care Excellence (NICE) guidance on new onset chest pain guidance adapted the 10% to 90% definition of intermediate group based on its own tool (10). The aforementioned international guidelines and the 2010 NICE guidance recommended patients with intermediate PTP, which constitute a large group of patients, should undergo further investigation. However, there is no agreement over the type of investigation among guidelines and it has been suggested that PTP estimation tools often result in an over-estimation of the likelihood of CAD (11-15), especially in women (11).

In PROMISE study, 97% of patients referred for computed tomography coronary angiography (CTCA) had intermediate PTP (mean 41%); however, the prevalence of FL-CAD (>50% stenosis) in this group was 14% (15). CONFIRM study also reported significant over-estimation of PTP (14), where prevalence of FL-CAD based on CTCA was significantly less than those predicted by guideline probabilities (18% versus 51%, $p < 0.001$). These studies faced significant criticism of their methodology by Diamond (16), who pointed out in CONFIRM one third of participants were asymptomatic, and therefore, PTP algorithm do not apply. Equally, breathlessness was the main complaint in more than one tenth of participants. He reminded their original Diamond and Forester PTP method, and subsequent tools based on their principal, have not been validated in these patients, yet in CONFIRM breathlessness was categorised as atypical angina. He also high-lighted PTP algorithms were validated

against invasive coronary angiography, not CTCA outcomes. Despite such valid points, NICE removed reliance on PTP tools from its 2016 revised guideline (10).

Previously, the 2013 ESC endorsed CAD consortium method of estimating PTP (17), which offered a good discrimination for FL-CAD, based on the multi-centre SCOT-HEART study (18), a large clinic-based cohort of stable symptomatic patients, investigated with CTCA. However, the most recent ESC guideline on “chronic coronary syndrome” (6) modified its PTP algorithm, adopting the PTP table based on pooled data from 3 large cohort studies, including CONFIRM and PROMISE (19). In this study, contrary to SCOT-HEART, PTP of significant CAD across symptomatic patient categories was reported to be substantially lower than the 2013 ESC guideline PTP method, and therefore resulting in over-estimation of CAD. It should be pointed out that the arguments by Diamond (16) remain applicable to this new approach. Sub-sequent small and large studies have suggested an under-estimation of CAD prevalence, when employing the new ESC table of PTP, against CTCA outcome (20-21).

1.1 Functional non-invasive investigations

The ischaemic cascade (22) (Figure 1.1) proposes the sequence of events that happen progressively during myocardial oxygen supply–demand mismatch, starting with changes of perfusion (detectable by myocardial perfusion scan and positron emission tomography (PET) scan, and more recently by cardiac magnetic resonance imagining (CMR) and myocardial contrast echocardiography (MCE)), and metabolic abnormality, which in turn causes diastolic abnormalities (detectable on echocardiography, for example by Doppler derived mitral inflow). If the ischaemia continues, it will lead to abnormal systolic function (detectable on echocardiography, first on Doppler tissue imaging/strain and then wall thickening

abnormality), followed by ECG abnormalities and finally manifest itself with chest pain. When the reduction in coronary flow is brief, these abnormalities disappear, not necessarily in a reverse order and when the ischaemia is prolonged, it leads to myocardial stunning, infarction and necrosis. The ischemic cascade concept suggests modalities that detect ischemia earlier are likely to have better sensitivity, which is not supported by clinical studies. Therefore, such a cascade has been questioned by some investigators, and instead “constellation of myocardial events” has been proposed, arguing the events do not necessarily occur in the order described (23).

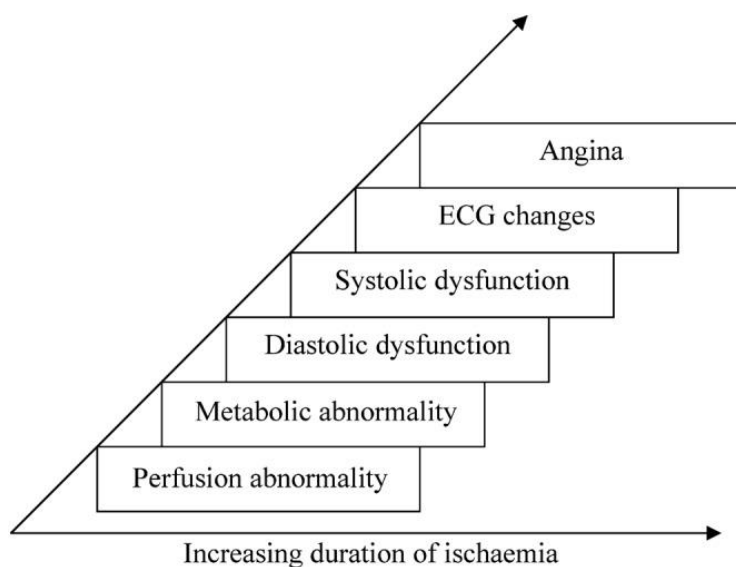


Figure 1.1. Ischaemic cascade. The presence of coronary artery stenosis leads to myocardial hypoperfusion, followed by metabolic abnormalities, diastolic dysfunction, systolic dysfunction, and ECG abnormalities, culminating in chest pain. Reprinted from Pakkal M, et al. *Br J Radiol.* 2011; 84(Spec Iss 3):S280–S295.

1.1.1 Exercise tolerance test

Although exercise ECG (ExECG) is the most widely available technique and by far the safest functional investigation, risk of serious complications such as myocardial infarction and even death still applies. Overall cardiac complication rate is estimated at 0.8:10,000 (95% confidence intervals (CI) of 0.3-1.9) (18).

ExECG is commonly performed using by treadmill or bicycle ergometer. When treadmill is employed, Bruce protocol is the most commonly used protocol, where during graded increase in speed and slope, ECG is continuously monitored and blood pressure and heart rate recorded. During bicycle ergometer, patients are required to maintain a cycling rate (usually at 50 revolutions per minute) in order to keep the work rate constant, the latter is calculated in watts (W). Subjects commence exercise at 50 watts workload, which is increased by 25 watts every 3 minutes. Similar to treadmill, ECG is continuously monitored and blood pressure and heart rate recorded. During the test, there should be appropriate blood pressure and heart rate increase to graded exercise. Maximum heart rate is estimated as 220-age, and achieving 85% of this is an anticipated level. A normal response is recorded in the absence of symptoms, appropriate blood pressure and heart rate response, without ECG changes suggestive of ischaemia and no ventricular arrhythmias.

1.1.1.1 Contra-indications

Common absolute and relative contra-indications (25) of ExECG are summarised below.

Absolute	Relative
- Acute myocardial infarction (within 2 days) - Unstable angina not previously stabilised by medical therapy - Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise - Symptomatic severe aortic stenosis - Uncontrolled symptomatic heart failure - Acute pulmonary embolus or pulmonary infarction - Acute myocarditis or pericarditis - Acute aortic dissection	- Known obstructive left main coronary stenosis - Electrolyte abnormalities - Severe arterial hypertension (>200 mm Hg and/or diastolic blood pressure of >110 mm Hg) - Tachyarrhythmias or bradyarrhythmias - Hypertrophic cardiomyopathy and other forms of outflow tract obstruction with severe resting gradient - Mental or physical impairment leading to inability to exercise adequately - High-degree atrioventricular block

1.1.1.2 End-points and interpretation

The followings are common absolute and relative indications to terminate the test (25):

Absolute indications	Relative indications
- Drop in systolic blood pressure of >10 mmHg from baseline blood pressure despite an increase in work load, when accompanied by other evidence of ischaemia - Moderate to severe angina - Increasing nervous system symptoms (eg, ataxia, dizziness, or nearsyncope) - Signs of poor perfusion (cyanosis or pallor) - Technical difficulties in monitoring ECG or systolic blood pressure	- Drop in systolic blood pressure of ≥ 10 mm Hg from baseline blood pressure despite an increase in workload, in the absence of other evidence of ischaemia - ST or QRS changes such as excessive ST depression (>2 mm of horizontal or downsloping ST-segment depression) or marked axis shift - Arrhythmias other than above, including multifocal or triplets pre-mature ventricular contracture, supraventricular tachycardia, heart block, or

- Subject's desire to stop - Sustained ventricular tachycardia - ST elevation (≥ 1.0 mm) in leads without diagnostic Q-waves (other than V1 or aVR) - Occurrence of supraventricular tachycardia or atrial fibrillation with a high heart rate response	- bradyarrhythmias - Fatigue, shortness of breath, wheezing, leg cramps, or claudication - Development of bundle branch block or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia - Increasing chest pain - Hypertensive response (systolic blood pressure of ≥ 250 mm Hg and/or a diastolic blood pressure of ≥ 115 mm Hg).
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Most common definition of a positive result is developing horizontal or downsloping ST-segment depression of >1 mm, 0.08 seconds after J point, in at least two consecutive ECG leads; developing ST elevation is a rare occurrence, but indicative of more significant CAD. ExECG also provides the physician with invaluable information about functional capacity as well as blood pressure and heart rate respond to exercise. Current treatment with anti-anginal medication therapy, especially beta-blockers and rate-limiting calcium channel blockers, significantly affects the diagnostic accuracy of all forms of stress; therefore, such medications should be withheld to avoid a false-negative result.

1.1.1.3 Diagnostic accuracy

ST segment depression as a marker of ischaemia in symptomatic women undergoing ExECG has a lower sensitivity and specificity of 61% and 70%, respectively (26), compared with a sensitivity and specificity of 68% and 77% in males, respectively (27). In women, positive predictive value of ST-segment depression is significantly lower for detection of FL-CAD

(defined as luminal diameter stenosis >50%) compared with men (47% versus 77%, respectively; $p < 0.05$) (28); however, negative results in women have better negative predictive value. Conversely, in women, there is no relationship between ST-segment depression during ExECG and cardiovascular mortality or all-cause mortality, and therefore is not of prognostic significance (29).

1.1.1.4 Limitations

The most common limitation of ExECG is an abnormal resting ECG, such as left bundle branch block, ECG changes due to left ventricular hypertrophy or ventricularly paced rhythm, as in such patients interpreting the ECG changes will be challenging. Another limitation is the inability of significant number of patients to exercise or to achieve 85% of age-predicted heart rate. In a small study, 17% of those who could exercise did not achieve 85% of age-predicted heart rate (30).

Despite these, the American (7) guideline has endorsed its use as an initial test in patients with intermediate PTP of CAD, unless the ECG is uninterpretable, noting its wide availability and years of experience of use in frontline cardiology. The European (6) and the UK NICE (10) guidelines, however, advise against using ExECG, and endorse using an imaging modality as the initial investigation of intermediate-risk group.

1.1.2 Stress Echocardiography

This method combines echocardiography with a physical, pharmacological, or electrical stress, aiming to detect systolic regional wall thickness abnormality especially during demand stress. When stress echocardiography is performed with exercise (treadmill or ergometric

bicycle), it also offers a functional assessment similar to ExECG. In patients who are unable to exercise, a pharmacological stressor is used. There are two groups of stressors: 1- Dobutamine, which is a β -adrenergic agonist, with both positive chronotropic and inotropic effects resulting in increase of myocardial work and oxygen demand and 2- vasodilators such as adenosine or dipyridamole, which act by inducing heterogeneity in myocardial perfusion by increasing blood flow to normal arteries while decreasing perfusion to stenotic vessels as the myocardium supplied by a diseased coronary artery has a reduced perfusion reserve. Another mechanism is myocardial capillary de-recruitment, where the coronary artery pressure distal to the stenosis decreases during hyperaemia (31). However, as myocardial oxygen demand is lower than inotropic stress (due to lack of significant heart rate response), sensitivity of the test is lower. The electrical stress is achievable in patients with a permanent pacemaker, capable of pacing up to at least 85% of age-predicted target heart rate, where the device can be externally programmed to increase the heart rate.

Stress echocardiography has the advantage of rapid performance and immediate result availability. As SE employs ultrasound, the imaging component is very safe, and any risk is related to the stress modality and left ventricular opacification with contrast echocardiography, if required. For the latter, ultrasound microbubbles have been used and the second generation ultrasound microbubbles have an excellent safety profile (32-33).

1.1.2.1 Contraindications

Contraindications are similar to that of stand-alone ExECG. Vasodilator stress is contraindicated in patients with significant reactive airway disease, severe sinus bradycardia (heart rate <40bpm), greater than first-degree heart block or sick sinus syndrome, without a

pacemaker. Certain medications, such as beta-blockers, should be withheld prior to stress echocardiography. Methylxanthines such as caffeine and theophylline competitively block adenosine receptors and must be avoided for 24 hours prior to vasodilator SE.

1.1.2.2 End-points and interpretation

The end-points of ExECG remain applicable in all types of SE, apart from asymptomatic reduction in blood pressure during Dobutamine SE, which can be observed in 20% of patients and is not of diagnostic or prognostic significance (34). When using pharmacological stressor, severe hypotension (systolic blood pressure <80mmHg) should result in stopping the test. Vasodilators should be stopped if patient develops persistent second-degree or sign of third-degree atrioventricular or sino-atrial block, wheezing or severe chest pain.

The hallmark of myocardial ischaemia during SE is the occurrence of regional wall thickening abnormality, detected qualitatively by expert readers.

1.1.2.3 Diagnostic Accuracy

In a meta-analysis (35), exercise, dobutamine, dipyridamole, and adenosine echocardiography showed sensitivity of 83, 81, 72, and 79%, respectively, and specificity of 84, 84, 95, and 91%, respectively, for the detection of flow-limiting CAD (FL-CAD) (defined as major coronary artery luminal diameter stenosis >50%). A negative exercise SE has a cardiac event rate (cardiac death or acute myocardial infarction) per person-year of 0.9% for the next three years (36). However, an abnormal SE carries a higher event rate, regardless of presence or

absence of FL-CAD on subsequent coronary angiography (37). In a study of 1477 patients, those with a “false-positive” SE result, during a follow-up period of 2.4 ± 1.0 years, had similar all-cause mortality rate to the ones with “true-positive” results which suggested that myocardial ischemia can occur due to other factors, such as microcirculation abnormalities.

1.1.2.4 Limitations

The primary limitation of SE is the inherent dependence on expert interpretation, with a negative impact on reproducibility and reliance on sonographer and interpreter skill and experience. The advent of harmonic imaging, tissue Doppler imaging (TDI) and speckle tracking have raised possibilities of quantitative assessment; however, these methods are yet to translate from research labs to clinical practice in SE.

Image quality, especially poor endocardial delineation, has a significant impact on feasibility and diagnostic accuracy of stress echocardiography. The latter can be addressed by utilising left ventricular opacification with ultrasound microbubble, which has been shown to improve image quality, the interpretability and diagnostic yield of stress echocardiography (32-33), especially in patients with intermediate coronary lesions (38). While lack of ionisation would make SE an ideal test in women, its efficacy is challenged by low prevalence of FL-CAD in these groups (39-40) and higher occurrence of coronary microvascular disease (MVD) (40-41) resulting in a lower predictive value of SE for detection of FL-CAD, leading to unnecessary referral for invasive coronary angiography (42). In women, it also has lower ability to detect single vessel CAD (43).

1.1.3 Myocardial perfusion imaging

There are a number of techniques that assess myocardial perfusion, such as myocardial perfusion scintigraphy (MPS) with single photon emission computed tomography (SPECT), positron emission tomography (PET), myocardial contrast echocardiography (MCE), and stress cardiac magnetic resonance (CMR). Among these, MPS with SPECT is the most common myocardial perfusion test in clinical practice to evaluate new-onset chest pain; therefore, we will discuss MPS with SPECT in further detail.

SPECT involves intravenous injection of gamma-emitting radioisotope and gamma ray camera to reconstruct images which show their cardiac uptake, proportional to blood flow of myocardium, at rest and at maximum hyperaemia. The two most commercially available nuclear agents are technetium-99m (^{99m}Tc) labelled radiopharmaceuticals (sestamibi and tetrofosmin) and thallium-201 (Tl-201) chloride. Similar to SE, SPECT can be performed pharmacologically or physically; with the latter being the preferred modality, achievable by treadmill or ergonomic bicycle. Pharmacological stress agents are also similar to SE, with Regadenoson also employed as a vasodilator. Dobutamine is usually reserved for patients with restrictive airway disease who cannot exercise, as it is not as potent as vasodilators in achieving maximal coronary blood flow and therefore has lower sensitivity.

1.1.3.1 Interpretation considerations

A combined approach, consisting of reviewing the raw data, qualitative-visual analysis, quantitative-software analysis, and evaluation of motion and function, is recommended.

Review of raw data helps to recognise and eliminate motion and soft-tissue attenuation. Quantitative assessments have been shown to have similar reproducibility to visual assessment (44), although sensitivity and diagnostic accuracy appears to be similar to visual assessment and specificity lower than visual assessment (45).

1.1.3.2 Diagnostic accuracy

In a recent large meta-analysis, comprising 114 studies, the sensitivity was 88% but the specificity was much lower at 61% (46). Whereas in another smaller meta-analysis of 8 studies, when SPECT was compared with invasive fractional flow reserve (FFR), the sensitivity was 74% and the specificity was 77% (47). A normal MPS SPECT has a low hard cardiac event rate (<1% per year) (48).

1.1.3.3 Limitations

Apart from quality limitations, such as motion and soft-tissue attenuation (especially breast attenuation in females) artefact, presence of left bundle branch block (LBBB) and asymmetrical septal thickness in hypertrophic cardiomyopathy can lead to false-positive results. While quantification softwares have been developed to assist with SPECT interpretation, reporting is still largely based on expert visual assessment, which can be affected by the aforementioned quality limitations.

It has been suggested that women have higher false positive SPECT, possibly due to breast attenuation artefact and a smaller average heart size, as observed in smaller studies (49),

although no statistically significant difference in sensitivity and specificity was noted in a meta-analysis (50).

A clinically important limitation is “balanced” ischaemia, in which the radiotracer uptake by different myocardial regions becomes homogenously distributed secondary to global hypoperfusion in all myocardial segments in the presence of significant three vessels CAD or a combination of left main and multi-vessel CAD. Markers such as transient ischemic dilation or reduction in left ventricular ejection fraction are indicators of balanced ischaemia (46, 51).

Perhaps the most important consideration is radiation to self, relatives and staff. The amount of effective radiation exposure, expressed in millisieverts (mSv), to the patient depends on the type of radiotracer, equipment, protocols and patient body habitus. It is estimated that typical values range from 2.2 to 31.5 mSv; the most commonly performed rest-stress ^{99m}Tc Sestamibi study averages 11.3 mSv (52). For comparison, annual background radiation exposure in the UK is 2.7 mSv (53), and an invasive coronary angiography involves a typical value of 7 mS radiation exposure (52).

1.1.3.4 Other myocardial perfusion modalities

While perfusion PET has a sensitivity of 93% and a specificity of 92% for detection of FL-CAD (54), due its complexity of methodology and high costs, as well as limited availability, it is used less frequently in clinical practice, and more frequently as a research tool.

Perfusion CMR has been shown to be an effective tool for investigating wall thickening in response to stress due to its high temporal and spatial resolution, without the limitations

associated with poor echo windows. When compared with FFR, it has a sensitivity of 89% and a specificity of 87% (55). However, it is less commonly used as the initial tool to assess new onset chest pain due to lower availability and associated cost.

Similar to SE, MCE can be performed with exercise or pharmacologically, but it differs in using either an infusion or boluses of ultrasound microbubbles, which disperse when exposed to high energy ultrasound impulse, with infusion being the preferred method. Therefore, MCE can assess both myocardial thickening and perfusion; the latter is investigated by the rate of microbubble replenishment. MCE with vasodilator has a sensitivity of 83%, and specificity of 79%, whereas MCE with dobutamine/exercise has sensitivity of 88% and specificity of 77% (56). While MCE is a rapid bedside method for assessing myocardial perfusion, its wider clinical uptake has been slow, mainly due to the number of trained physicians.

1.2 Anatomical assessment

1.2.1 Computed tomography coronary angiography and calcium scoring

Computed tomography coronary angiography (CTCA) (57-58) has been regarded as a paradigm shift in the investigation of CAD; prior to this technical achievement, visualisation of coronary anatomy required invasive coronary angiography. While 64-slice scanners are now common-place, more advanced 256- and 320-slice scanners allow single beat acquisition: imaging entire heart in one phase, rather than stitching them together.

1.2.1.1 Coronary artery calcium score

Coronary artery calcium score (CACS) is commonly used to quantify coronary artery calcific burden, usually given as a number called Agatston score, reflecting the density of the calcium. A calcium score of zero is indicative of a low annual incidence of adverse events (all-cause mortality, nonfatal myocardial infarction, and unstable angina) of 0.4% (CI 0.1% to 1.3%) in asymptomatic population studies (59).

In asymptomatic population, CACS has been shown to be an independent predictor of all-cause mortality, where risk-adjusted relative risk values for coronary calcium were 1.64, 1.74, 2.54, and 4.03 for scores of 11-100, 101-400, 401-1,000, and greater than 1,000, respectively ($P < 0.001$ for all values) (60).

While incremental value of CACS above traditional risk factors (TRFs) and the Framingham Risk Score (FRS) in asymptomatic population has been demonstrated (61-62), in symptomatic patients CONFIRM registry indicates CACS provides no incremental prognostic information to CTCA (63).

Furthermore, in symptomatic patients with a CACS of zero, both non-flow limiting (NFL-CAD) and flow limiting-CAD (FL-CAD) can still be present, both of which are associated with increased cardiovascular events. This was demonstrated in the large CONFIRM registry (63), where 13% of patients with a CACS of zero had NFL-CAD and 3.5% had FL-CAD on CTCA. Patients with CACS of zero, but evidence of NFL-CAD, had a composite (all-cause mortality, myocardial infarction, or late coronary revascularisation) event rate of 3.9%, compared with 0.8% in those with CACS of zero and no CAD on CTCA.

1.2.1.2 Computed tomography coronary angiography

The diagnostic accuracy of CTCA depends on the technology employed, with the 64-slice scanner being the most commonly used and studied. The sensitivity of 64-slice scanners for detecting patients with significant CAD is ranging from 81 to 99%, and specificity from 64 to 93%, with a positive predictive value ranging from 64 to 92%, and a negative predictive value ranging between 83 and 99% (64). While the negative predictive value in the low- and intermediate PTP groups is reported at nearly 100% (64), making CTCA a very helpful tool for exclusion of CAD in such patients, the positive predictive value remains a challenge, even with 320 slice scanners (65), as CTCA tends to over-estimate significance of coronary lesions (64, 66), which can then lead to unnecessary downstream coronary angiography.

1.2.1.3 Limitations

The largest limitation of CTCA in the UK is perhaps its availability; the British Society of Cardiac Imaging estimated that in 2017 there was a UK-wide shortfall of 43%, to implement the 2016 NICE guidance (67).

The second limitation is the difference between accurately identifying CAD and determining whether the detected anatomic lesion is responsible for the reported symptom. While CTCA can identify anatomical lesions, their very presence is not necessarily indicative that the perceived symptom was cardiac, nor it depicts any information about its functional significance. In fact multiple comparative studies of CTCA and MPS SPECT show that only 30–50% of significant stenosis (>50%) are associated with reversible perfusion defects.

Another limitation is radiation exposure. The effective dose, expressed in millisieverts (mSv), depends on multiple factors, including the volume of acquisition, the duration of the scan, and the radiation energy level used. While with the newer generations of CT-scanners and sophisticated acquisition techniques, CTCA can be performed with significantly low radiation dose of less than 1 mSv (69), CTCA with conventional 64-slice CT scanners involves 12 to 18 mSv radiation exposure (64). Corresponding doses are 7 mSv for invasive angiography (52), 11.3 mSv for rest–stress Sestamibi MPS (52), and 2.7 mSv from yearly background radiation exposure in the UK (53).

Lastly, 64-slice CT scanners require a slow heart rate of less than 70 beats per minute. In order to achieve this, patients are given beta-blockers prior to the scan; patients with asthma receive Ivabradine instead. Rapid heart rate, atrial fibrillation and ectopic beats can reduce image quality and may make the study uninterpretable. CTCA, like any other contrast-based investigation, carries the risk of allergic reaction and contrast-induced nephropathy. The latter limits its utility in patients with significant kidney dysfunction. Incidental non-cardiac findings pose a mix of opportunity of early detection of diseases at an early stage as well as causing anxiety and over investigation for an otherwise benign finding.

Nonetheless, NICE has endorsed CTCA as the initial test for all patients with new onset chest pain in its 2016 revision (10).

1.2.2 Conventional invasive coronary angiography

Conventional invasive coronary angiography remains as the “gold standard” in the diagnosis of coronary artery disease (6). However, it is an invasive procedure and unacceptable as a

first line investigation, unless the pre-test probability is high (6). This is due to several potential complications, most importantly mortality = 0.08%, myocardial infarction = 0.06% for single vessel CAD, vascular complications = 0.2% and contrast-induced nephropathy (ranging between 3.3% to 16.5%) (5). Moreover, it provides only a “luminogram” that does not necessarily impart information about plaque presence. While interpreting the result remains largely qualitative, there are tools that enable quantitative assessment, although even these have failed to accurately predict the functional significance of coronary lesions (70). Several large registries have shown that significant number of patients, who undergo invasive coronary angiography, have no obstructive CAD, nearly two-thirds of women and a third of men (71-72).

1.3 Hybrid anatomical and functional approach

In order to improve stand-alone anatomical or functional coronary assessments, integration of the two methods has been proposed. These include integrated CACS and MPS SPECT (73), CTCA and MPS SPECT (73), CTCA and CT-derived functional flow ratio (FFR) (74), and finally routine, rather than selective, invasive FFR during angiography.

It has been shown that patients with matched CTCA and MPS SPECT findings have higher composite major adverse cardiac events (MACE) and mortality compared with unmatched and normal studies, with annual MACE of 21.8% vs. 9.0% vs 2.4%, respectively (75).

It has been demonstrated that visual assessment of coronary artery with invasive coronary angiography can over- or under- estimate lesion significance, not only when they are estimated to be intermediate, but also when they are deemed none-significant (<30%) or

significant (>70%). This was demonstrated in the RIPCORDER study, where 47% of the lesions graded as significant, turned out to be FFR negative; whereas, 13% of lesions graded as non-significant, were FFR positive (76). Therefore, it has been suggested that each coronary angiography, should contain a routine hybrid FFR assessment, especially if intervention is intended.

The CT-FFR is a rather new technology which applies computational flow modelling to images acquired for CTCA to assess the significance of coronary lesions. CT-FFR is reportedly superior to CTCA alone as gate-keeper to the invasive catheterisation. In ADVANCE study, CT-FFR changed management in almost two thirds of participants when lesions were 30-90% based on CTCA (77). However, in the recently published FORECAST study (78), a strategy of CTCA followed by CT-FFR in lesions deemed $\geq 40\%$, did not significantly reduce overall cardiac costs within 9 months compared to routine assessment. There were no differences in secondary endpoints such as a composite of major adverse cardiac and cerebrovascular events and revascularisation either. There was, however, a 22% reduction of invasive coronary angiography in the CT-FFR arm compared with routine care ($p = 0.01$). It is noticeable that even in the routine arm, CTCA was used in 61.4% of patients, which could have skewed the cost analysis, as it can lead to down-stream further assessment due to over-estimation of coronary artery disease.

1.4 Further considerations

A negative functional test, as the name implies, while reassuring, does not exclude presence of coronary artery disease, it only assesses its functional significance. Therefore, patients

with a negative SE may still have coronary atherosclerosis, experience myocardial infarction from a non-flow limiting CAD and plaque rupture. In fact, it is more likely for a patient to suffer from a myocardial infarction from a plaque rupture of non-flow limiting atherosclerosis than from heavily calcified flow-limiting CAD (79). This also explains why patients with abnormal functional test, may suffer from AMI in a territory different to the territory that ischaemia was demonstrated. On the other hand, an abnormal SE carries a higher event rate, regardless of presence or absence of flow-limiting CAD on subsequent coronary angiography, as demonstrated by Form et al. (37); patients with “false-positive” SE result had similar all-cause mortality rate compared with “true-positive” results, which has been contributed to presence of micro-vascular disease and hypertensive response, as well as atherosclerotic non-flow limiting CAD.

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Chapter 2. Use of Carotid Ultrasound to Identify Subclinical Cardiovascular Disease

Cardiovascular disease (CVD) (which consists of coronary artery disease (CAD), cerebrovascular disease, peripheral vascular disease and atherosclerotic-aneurysmal disease of the aorta) remains the leading cause of mortality and morbidity worldwide (1). Over the past five decades mortality rate from CVD has been falling in the UK: In 1961, more than half of all deaths in the UK were attributed to CVD; whereas in 2017 it has fallen to 28 per cent (2). There are 7.4 million people living with CVD, leading to £9 billion annual healthcare cost and £19 billion annual cost to the UK economy (2). Of the 170,000 CVD deaths in 2017, CAD was responsible for 64,000. The decline in mortality has been attributed to reductions in major risk factors (particularly smoking and adopting healthy life style), developments in pharmacological primary preventative therapies, recognition of cardiac risk factors and their modification, as well as revascularisation procedures for acute myocardial infarction and secondary preventative measures (3).

The current practice in preventing the occurrence of clinical cardiovascular events has evolved around identifying individuals deemed to be at high-risk of future CAD events. Algorithms, such as the Framingham Risk Score (FRS) (4) or Systematic COronary Risk Evaluation (SCORE) (5), reflect the overall burden of traditional risk factors (gender, age, blood pressure, diabetes, cholesterol, smoking and family history), where risk factor modification therapy is reserved for those deemed to have a high (>20%) 10-year risk of suffering a clinical event. However, such risk-scoring algorithms are imperfect (6) and often

poorly applied by physicians (7). Although levels of traditional cardiovascular risk factors are associated with the extent and severity of atherosclerosis, there is substantial variation in the amount of atherosclerosis for every level of risk factor exposure. Also, high-risk groups contain only a fraction of the individuals that will ultimately suffer a clinical cardiovascular event; in the Prospective Cardiovascular Munster (PROCAM) study (8), the minority were classified as high risk (7.7%) and the majority as low risk (77.3%). However, at 10 years, 36.9% of myocardial infarctions occurred in the high-risk group, 31.7% in the intermediate- and 31.4% in the low-risk group (Figure 2.1).

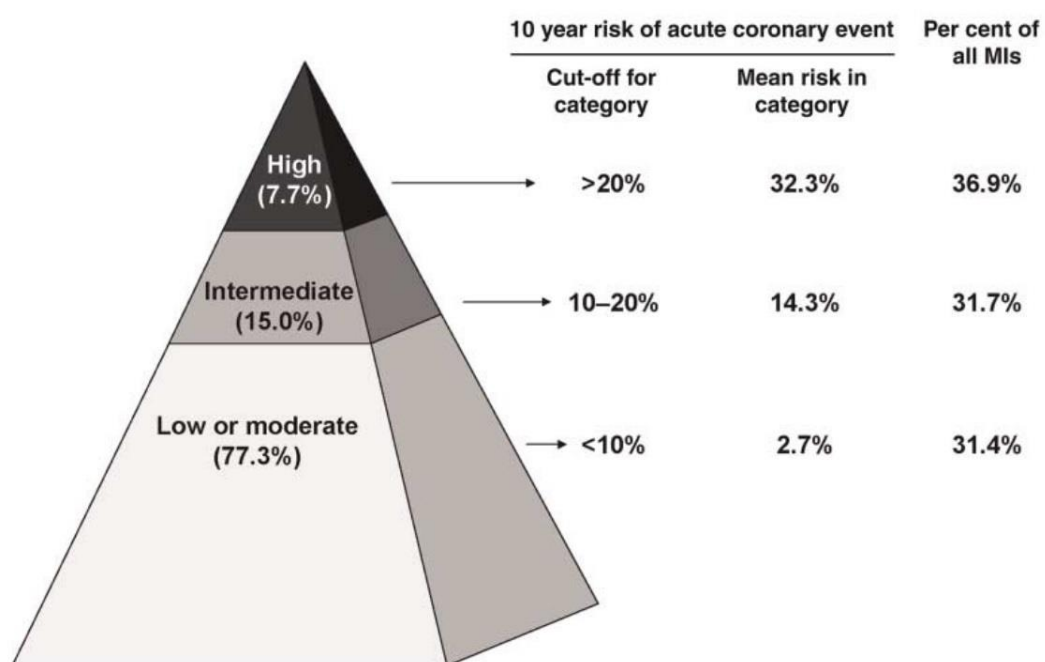


Figure 2.1. Prevalence of acute coronary events within categories stratified for cardiovascular risk within the Prospective Cardiovascular Munster (PROCAM) cohort.

MI: Myocardial infarction. Reprinted from Assmann G, *Eur Heart J Suppl*, Vol 7, Issue suppl_F, 2005, Pages F9–F14

This is explained by the low-risk group being very large, with at least 30% of those who went on to suffer an event, not having any traditional cardiovascular risk factors. Therefore, a “detection gap” exists, which may be defined as the difference between CAD cases or events currently detected and the total burden of disease or events among the population (9).

The European Society of Cardiology has endorsed CVD risk stratification using Systematic COronary Risk Evaluation (SCORE) (5), where the predictors are age, sex, smoking, systolic blood pressure, and total cholesterol, in subjects between the age of 40 and 65. This tool is based on examination carried out as far back as 1967, with the latest performed in 1991, and did not include diabetes as a predictor. Its strong-point, estimating a hard-endpoint of 10-year risk of CVD mortality, is arguably also its weakest point, as it does not predict the natural history of CVD and developing symptoms, which often pre-dates mortality. Whereas offering medication to those at high risk of developing symptomatic CVD, such as non-fatal myocardial infarction, hence improving quality of life, is of equal importance. SCORE is, however, easily applicable due to its clear end-point, which has been used to re-calibrate it for each European country based on national cause-specific mortality rates from a single year. The re-calibration, conversely, is likely to lead to over-estimation of mortality risk, as national databases include patients that were excluded from the original SCORE, such as those with previous CVD, diabetes or familial hyperlipidaemia.

Cardiovascular Risk Score (QRISK) was developed in the UK, from the databases of general practice attendees. It estimates 10-year risk of developing CVD, based on not only TRF, but also body mass index, family history of cardiovascular disease, Townsend deprivation index, and use of antihypertensive treatment (QRISK1). The second version added ethnicity, type 2 diabetes, treated hypertension, rheumatoid arthritis, renal disease, and atrial fibrillation. While it has many

advantages, such as annual update and wide age-coverage (25-84 years), its database has several inherent limitations; data is not a random representative sample of the population, subject's risk factors were documented at scatter times during the data acquisition period, with missing information imputed rather than deleted. The proportion with missing data for some of the risk factors in the derivation cohorts was substantial, (>70% for ethnicity; >60% for cholesterol). There was also no data on risk-modifying medication use, such as statins or platelet inhibitors.

Framingham risk score (FRS) estimates a patient's 10-year risk for myocardial infarction and cardiac death based on gender, age, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, and cigarette use (10). FRS does not contain family history of premature coronary disease and diabetes as risk factors. While the latter group are recommended to be considered as high risk, FRS results in underestimation of risk in patients with significant family history. FRS has also been criticised for over-estimation of high-risk individuals and European populations (11). Conversely, FRS underestimates risk in younger patients at risk of developing CVD, as demonstrated in the study by Akosah et al (12), where nearly 70% of first myocardial infarction in males younger than 55 years and females younger than 65 years, occurred in patients who were classified as low risk.

In the UK, at the time our research protocol was developed, the National Institute for Health and Clinical Excellence (NICE) recommended using Framingham equation to estimate 10 year risk of CVD (13). However, in 2014, NICE changed its position and endorsed the use of QRISK2 (14).

2.1. Enhancing coronary artery disease risk prediction

The poor predictive value of traditional risk factors and limitations of current risk calculator tools has encouraged research into subclinical CVD to help improve risk prediction. This approach essentially represents a form of disease “screening”, as in other areas of medicine allowing the detection and modification of a potential clinical entity at its earliest stages. Technological developments have made the quantification of subclinical disease processes more feasible and accurate, providing detailed information that relates directly to pathology. These advances that can identify an individual’s vulnerability to future CVD events include arterial structural imaging modalities (that can detect sub-clinical atherosclerosis), arterial functional modalities (which measure the effects of disease processes, such as hypertension or diabetes, upon vascular function) and blood biomarkers (Figure 2.2).

2.2 Imaging subclinical cardiovascular disease: Carotid Ultrasound

Imaging techniques can detect subclinical CVD by directly visualising the anatomical presence of arterial disease. Ultrasonography is an attractive modality for this purpose: it is non-invasive, involves no ionising radiation, and is more readily available compared with CT or MRI. As arterial disease is rarely confined to one vascular bed, ultrasonography of carotid or femoral artery, offers a “pan arterial” assessment that represents subclinical peripheral, cerebro- and coronary vascular disease. In clinical cardiology, carotid ultrasonography is most frequently utilised to risk stratify patients prior to coronary artery by-pass grafting. The incidence of coexisting flow limiting coronary and carotid artery disease varies from 2-14% (15) with the incidence of significant (>50%) carotid artery stenosis reported as high as 22% in patients undergoing CABG (16). Similarly, patients with carotid artery disease are likely to

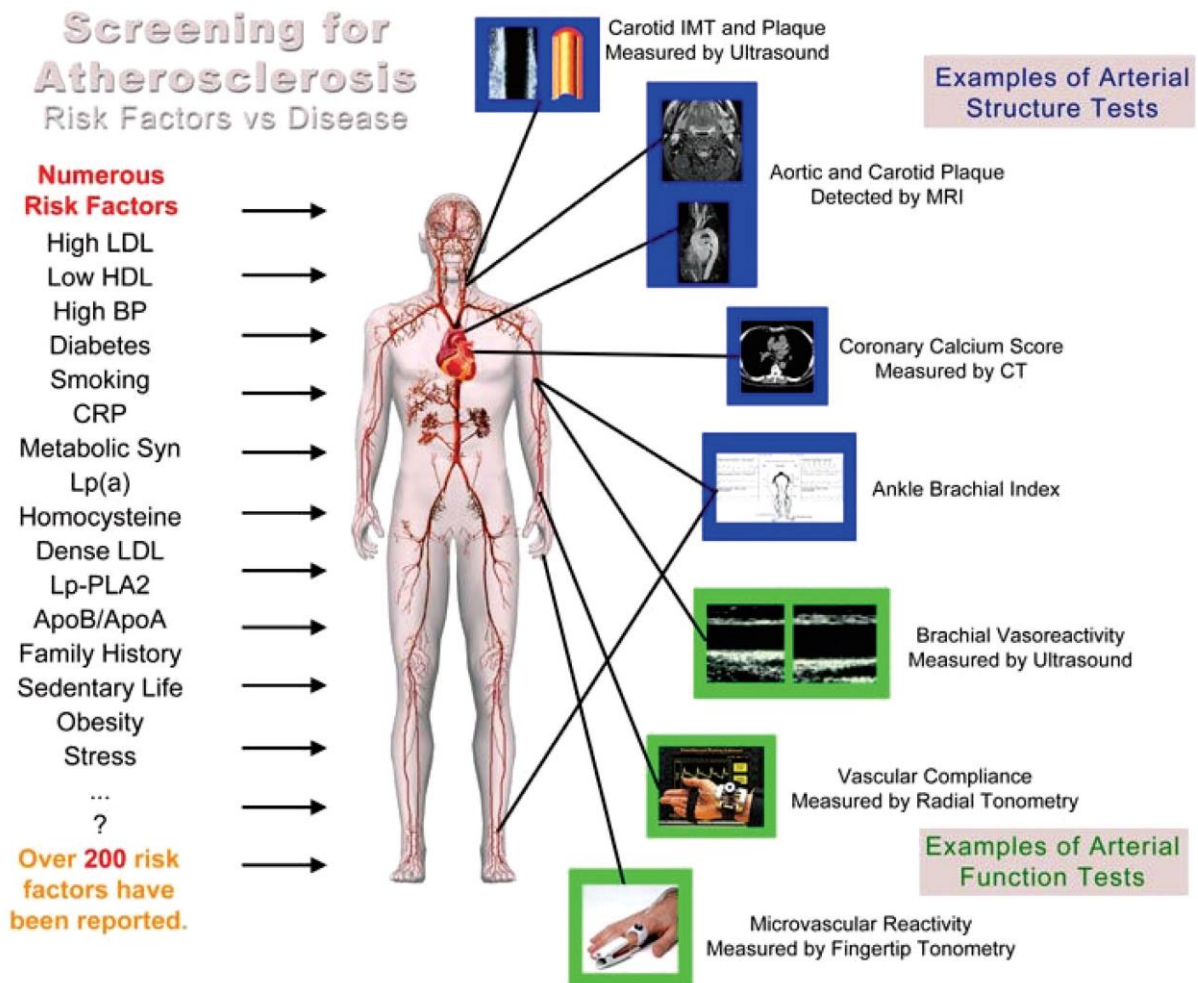


Figure 2.2. Screening for atherosclerosis. Screening for subjects at risk for cardiovascular complications: blood biomarkers/risk factors and/or markers of subclinical disease. Apo indicates apolipoprotein; BP, blood pressure; CT, computed tomography; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; Lp(a), lipoprotein a; Lp-PLA2, lipoprotein-associated phospholipase A2; MRI, magnetic resonance imaging; and Syn, syndrome. Reprinted from Naghavi M et al. *Am J Cardiol.* 2006;98(suppl):2H–15H.

have coronary artery disease, with the atherosclerotic burden in a carotid artery and coronary artery being the same as between any two coronary arteries (10). Subclinical carotid artery disease includes abnormal intima-media thickness and presence of carotid plaque.

2.3 Carotid intima-media thickness

Carotid intima-media thickness (C-IMT), which is the combined thickness of the carotid artery intima and media, can be measured with high-resolution ultrasonography (Figure 2.3), and has been extensively used as a research tool in epidemiological studies as an outcome variable (18-19) or in trials of disease intervention as a surrogate end-point (20).

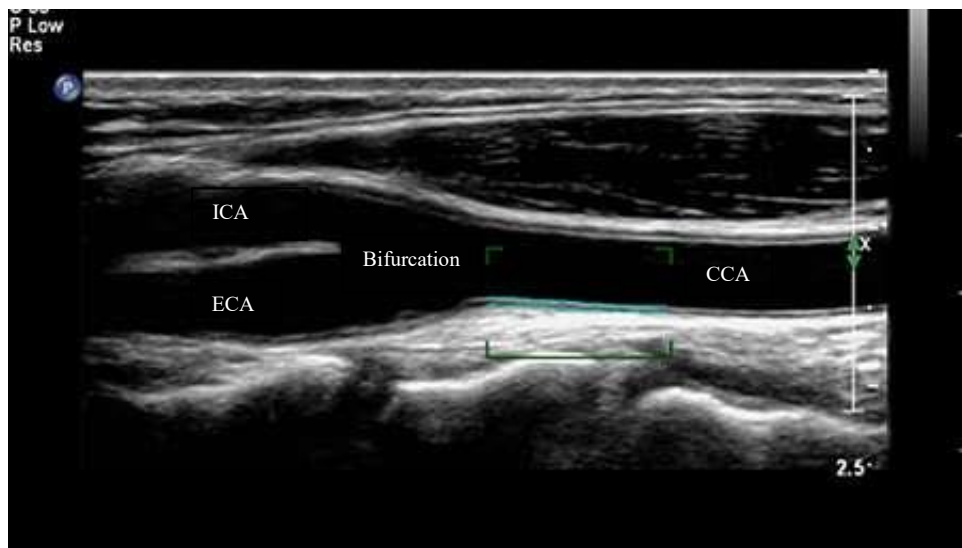


Figure 2.3. An ultrasound image of a normal carotid artery, demonstrating common carotid artery (CCA), its bifurcation into the internal (ICA) and external (ECA) carotid arteries. Intima-media thickness, detected as two green lines, is measured using Philips Qlab software, by placing one centimetre detection box over the selected segment by operator. Figure courtesy of Philips, available from: [QLAB Cardiac Analysis Cardiovascular ultrasound quantification software | Philips Healthcare](#)

Pignoli and colleagues (21), using B-mode ultrasound, identified IMT as a double-line on the far wall of the common carotid artery and showed a good correlation with histological specimen, which in turn has been found to correlate with atherosclerosis in other vascular beds (22). Increased C-IMT is associated with cardiovascular risk factors (23-24), prevalent cardiovascular disease (26-27), and the presence and extent of angiographically determined coronary atherosclerosis (28-30). Several studies show that increased C-IMT is predictive of cardiovascular events in asymptomatic individuals including myocardial infarction, stroke and death (18-19, 23, 30-32).

2.3.1 Limitations of carotid intima-media thickness

Carotid intima-media thickness is dominated by “media”, both at health and when diseased (around 97% at health and 80% with atherosclerosis); when diseased there is significant smooth muscle hypertrophy and/or hyperplasia, with age and hypertension as primary contributors; whereas, carotid plaque initiates by intima thickening (33-34).

C-IMT suffered from significant heterogeneity of definition, as demonstrated in Figure 2.4, there was even no agreement on the definition of common carotid artery, its bifurcation and internal carotid artery (18). The first Mannheim consensus was published in 2004 in an attempt in unifying C-IMT ultrasound protocols (36), by which time many research groups have completed multiple large scale studies, using various protocols: measuring IMT at different walls, sides, sites and insonation angles; during different cardiac cycle phases; reporting it as a mean or maximum; not separating IMT and plaque; employing predefined figures for upper-limit of normal for C-IMT regardless of age, sex or race.

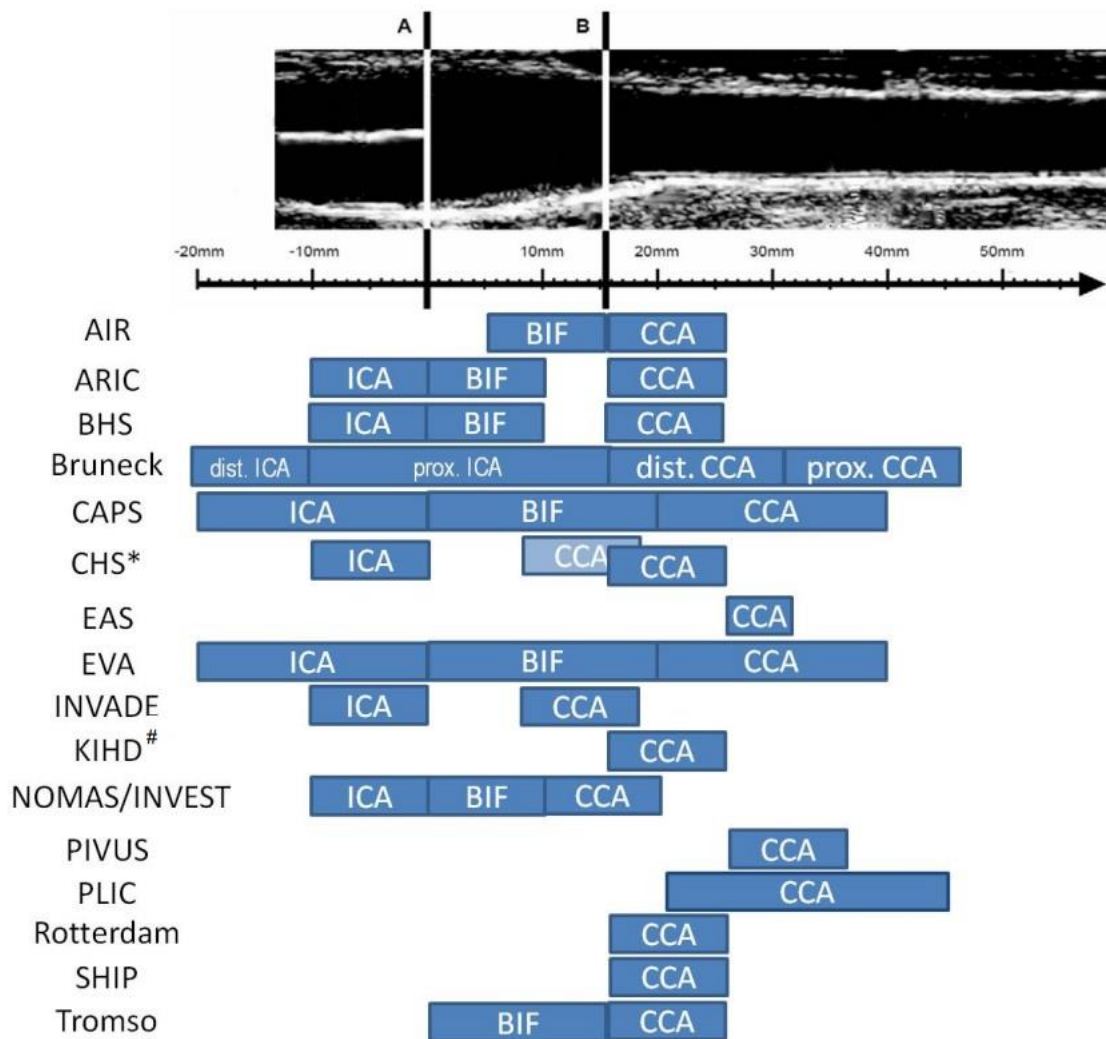


Figure 2.4. Variations in the definition of common carotid artery, its bifurcation and internal carotid artery in large-scale epidemiological studies

AIR: Atherosclerosis and Insulin Resistance, ARIC: Atherosclerosis Risk in Communities Study, BIF: Bifurcation, BHS: Bogalusa Heart Study, CAPS: Carotid Atherosclerosis Progression Study, CCA: Common carotid artery, CHS: Cardiovascular Health Study, Dist: Distal, EAS: Edinburgh Artery Study, EVA: Etude sur le vieillissement artériel, ICA: Internal carotid artery, INVADF: Interventionsprojekt zerebrovaskuläre Erkrankungen und Demenz im Landkreis Ebersberg, KIHD: Kuopio Ischemic Heart Disease Study, NOMAS/INVEST: Northern Manhattan Study/The Oral Infections and Vascular Disease Epidemiology Study, PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors, PLIC: Progression of Lesions in the Intima of the Carotid, Prox: Proximal, SHIP: Study of Health in Pomerania. Reprinted from Lorenz MW et al *Lancet* 2012;379:2053-62, supplementary appendix

2.4 Carotid plaque

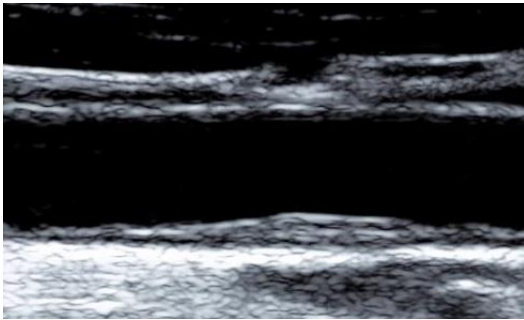
Whilst C-IMT and carotid plaque are strongly correlated, and increased thickness of IMT is a strong predictor of future occurrence of a new plaque (36), they are not the same phenomenon. C-IMT measurement needs to be interpreted in the context of the individual's age, gender and ethnicity, whereas presence of plaque reflects atherosclerosis (37-40), and therefore is always abnormal. From a pathological perspective, plaque initiates with intimal thickening, leading to focal thickening of the arterial wall with protrusion into the lumen, with development of lipid-pools with macrophages, extracellular lipid accumulation, and fibrous cap (34, 41).

Carotid plaque is associated with TRFs (age, male sex, hypertension, smoking, hyperlipidemia, type II diabetes and body-mass index) (42-47) and CAD (22, 48-49), and its detection improves cardiac outcome prediction beyond TRF (40, 50) and FRS (51).

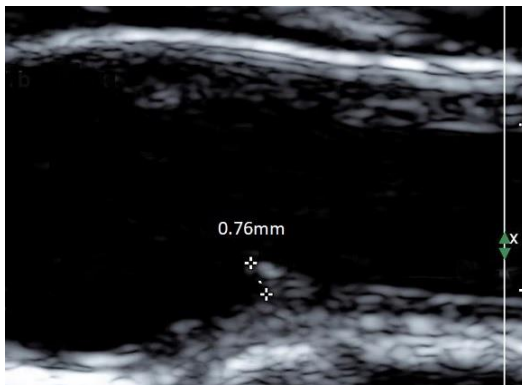
2.4.1 Ultrasound detection and definition of carotid plaque

Ultrasound detection of carotid plaque (CP) had similar drawbacks to C-IMT: lack of definition conformity, which resulted in multiple epidemiological studies either measuring IMT in a segment with plaque and reporting it as abnormal IMT or ignoring it. In fact, the first Mannheim consensus offered no definition of CP (32). The most recent Mannheim consensus (52) defined CP as “a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness >1.5 mm as measured from the intima-lumen interface to the media-adventitia interface” (Figure 2.5).

A. Intima-media thickness more than 50% of adjacent segment



B. Protrusion more than 0.5mm



C. Thickness exceeding 1.5mm



Figure 2.5. Carotid plaque according to Mannheim consensus. Figure “A” depicts a segment of carotid artery, where the IMT thickness is >50% of the surrounding segments (measurements not shown), which meets plaque definition.

While these cut-offs are rather arbitrary, it should reduce the variability that exists in ultrasound detection of carotid plaque.

Carotid plaque burden (CPB), defined as the number of detected plaques, is a simple method of quantifying carotid plaque and has several advantages: as the angle or plane of image acquisition is not as critical as others, obtaining images is easier, and counting the number of plaques does not require advanced quantification software or training, and it is associated with cardiac outcomes. In the Multi-Ethnic Study of Atherosclerosis (MESA) (50), among the 2673 asymptomatic participants with a CACS of zero at the time of recruitment, prevalence of carotid plaque was 36%. During 16 years of follow up CP and its burden were independently associated with coronary heart disease (CHD) events (cardiac mortality, cardiac arrest resuscitation and myocardial infarction). In another study of 367 asymptomatic elderly men (mean age 78 ± 4) (40), while presence of CP was associated with a 3.5-fold increased all-cause mortality risk, CPB offered better risk stratification. The risk increased 2.9-fold with 1 to 2 plaques, 3.1-fold with 3 to 4, and 4.7-fold when 5 or more plaques were present. CPB was an independent predictor of all-cause mortality, after correction for TRF and medication. In BioImage Study (53), CPB measured from 'cross-sectional sweep' video ultrasound acquisition and divided into tertiles, with cut-offs of 4.3 mm^2 , 169.4 mm^2 and 536.6 mm^2 , showed association with major adverse cardiac events (cardiac mortality, MI and ischemic stroke) during 3 years follow up. While hazard ratio of first and second tertiles crossed one, third tertile HR was 2.36 (95% CI 1.13–4.92).

Carotid plaque can be further assessed and quantified using other ultrasound methods, such as grey-scale characteristics (54-55), 3-dimensional plaque volume (56) and intra-plaque

neovascularisation (57). While these methods infer more information, they are more complex and make the transition to clinical practice more demanding.

2.4.3 Ultrasound imaging of carotid plaque compared with CT- derived Coronary Artery Calcium Score (CACS)

In a systemic review, ability of CP and CACS in prediction of risk for developing fatal or non-fatal cardiovascular events were evaluated. Added predictive value of CP over traditional prediction models in subjects with intermediate cardiovascular risk, ranged from 0.01 to 0.05 compared with 0.05 to 0.13 for CACS and the net reclassification improvement (NRI) ranged from 8% to 11% for CP compared with 14% to 25% for CACS (58). In another publication from the MESA (57), both CPB and CACS predicted future CHD events and improved prediction of CHD events compared to TRFs: CACS had hazard ratio (HR) of 2.09 (95% CI, 1.84 – 2.38; P <0.001) while CPB had a HR of 1.35 (95% CI, 1.21 – 1.51; P <0.001). In BioImage Study (58), also a large epidemiological research programme, investigators compared levels of CACS (0, 1-100, 101-400, >400) and 3-dimensional ultrasound derived CPB, defined as the sum of 3-dimensional plaque areas, categorised into no plaque, <2.58 cm², 2.58 - 4.21 cm², >4.21 cm², in their ability to predict a composite end-point of cardiovascular death, myocardial infarction, and ischemic stroke. They demonstrated adding CACS or 3D-CPB to TRFs improves risk prediction and reclassification to a similar degree, in a step-wise fashion, with lowest events noted in patients without CPB or CACS, and the highest in the third CPB tertile or CACS >400.

Ultrasound detection of CP is radiation free, relatively inexpensive, feasible in all patients and perhaps represents atherosclerosis at an earlier stage (50); whereas CACS requires

radiation exposure, hence increased risk of cancer, it is not available at bed-side and perhaps represents a later stage of atherosclerosis (50, 61).

2.5 Role of ultrasound detection of carotid intima-media thickness versus carotid plaque

In order to overcome the inherent problem with inconsistency in the definition of C-IMT, and therefore outcomes of such studies, pooled data from 14 large epidemiological studies, concentrating on common carotid IMT measurement and FRS was analysed in The USE Intima-Media Thickness (USE-IMT) collaboration study in 2012 (19). Adding C-IMT to FRS in overall cohort resulted in a 0.8% (95% confidence interval 0.1% - 1.6%) net reclassification improvement (NRI). In subjects with intermediate risk (FRS = 5% - 20%), the majority (88%) remained in the same risk group after adding C-IMT to FRS. Authors concluded “the addition of common C-IMT measurements to the FRS was associated with small improvement in 10-year risk prediction of first-time myocardial infarction or stroke, but this improvement is unlikely to be of clinical importance.”

In the Atherosclerosis Risk in Communities Study (ARIC) study (51) risk prediction of addition of C-IMT and plaque to TRF was assessed in subjects with no known CVD, for a composite end point of CHD death, MI and coronary revascularisation. A model of C-IMT plus plaque added to TRF, resulted in 23% reclassification and a 9.9% net reclassification index (NRI) for prediction of CHD, although the majority (62%) of NRI was a result of downgrading from intermediate to low risk.

Inaba et al. (49) in their meta-analysis of eleven epidemiological studies, compared diagnostic accuracy of C-IMT and carotid plaque in prediction of CAD and future MI. While carotid plaque had higher diagnostic accuracy than C-IMT for the detection of CAD, it failed to reach statistical significance after adjusting for covariates ($p = 0.21$). However, presence of carotid plaque was more strongly associated with incident myocardial infarction, compared to C-IMT ($p = 0.04$) and retained significance even after adjusting for covariates on multivariate analysis ($p = 0.046$).

While incremental value of carotid ultrasonography, detecting carotid plaque, in risk prediction has been demonstrated, to convincingly demonstrate the value of carotid atherosclerosis imaging, it will require a prospective, randomised study, comparing a strategy of imaging-guided risk factor modification to standard TRFs modification alone. In this regard, randomised data showing the efficacy of any atherosclerosis imaging strategy is scant.

Ultrasound measurement of C-IMT for cardiovascular risk assessment in asymptomatic individuals at intermediate risk, was given a Class IIa recommendation (level of evidence B) in the 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults (62) [pre-dating the USE-IMT collaboration]; however, it made no reference to carotid plaque assessment.

2.6 Combination of Carotid Ultrasound and Stress Echocardiography

The only published study, which evaluated carotid disease in symptomatic patients undergoing stress testing prior to this study, was the work of Kanwar et al. (63). They

investigated usefulness of carotid ultrasonography in 50 symptomatic patients scheduled for coronary angiography, who were also evaluated with different types of stress imaging (SE and SPECT). CP was seen in 76% of patients and was more prevalent among those with abnormal stress imaging (83% versus 34%, $p = 0.006$). While 24% had an abnormal stress result, the majority had an equivocal stress result (64%). In the equivocal/negative group, the ten patients who had no CP, also did not have FL-CAD, therefore absence of CP, had a 100% negative predictive value; whereas, in the 12 patients with an abnormal SE, 9 also had CP, out of whom 8 had FL-CAD.

Another study, conducted by Sachpekidis et al. (published in 2011, after we have started recruitment), evaluated whether 3-dimensional left atrial volume index and/or carotid plaque, defined as a 1.2mm thickness, would improve diagnostic accuracy of dobutamine SE. They recruited 130 patients, however, only 39% had new onset chest pain; 38% were known CAD. CP was seen in 78% of patients, with no similar prevalence in patients with normal and abnormal SE (76% versus 89%, respectively, $p = 0.1$) (64).

Recently impact of assessing carotid plaque neovascularisation in patients undergoing stress echocardiography was investigated (65). In this study, of the 216 patients with known or suspected CAD (with a mixed indication for SE, such as dyspnoea, chest pain, pre-operative assessment), the 185 patients (86%) with carotid plaque were recruited and underwent carotid ultrasound with microbubble contrast before SE. Out of this patients, 69 (32%) had an abnormal SE, while 112 (61%) had plaque neovascularisation. After a median follow up of 31 months, 26 cardiovascular events, including cardiac death, myocardial infarction, unstable angina, and transient ischemic attack (TIA) or stroke were reported. While TRF, SE result

and number of the plaques failed to achieve univariate association with outcome, plaque neovascularisation, plaque echolucency and previous CAD showed association ($p = 0.04$, 0.006 and 0.06 , respectively). However, on Multivariate Cox proportional-hazard analysis, only plaque neovascularisation maintained association ($p = 0.02$). While this study offers interesting insights into association of plaque vulnerability detected by presence of neovascularisation, there are several methodological considerations that affect its results: inclusion of patients with a history of CVD (64% of the participants), mixed indications for SE (more than one third were not symptomatic, with another 18% investigated for dyspnoea without chest pain), as well as inclusion of stroke and TIA in the composite endpoint. While TRFs are associated with stroke and TIA, SE is neither performed nor designed to predict such outcome and their inclusion leads to bias towards carotid atherosclerosis. As many of the patients had a history of CVD, it is not surprising that a high proportion had abnormal SE; one third had a fixed defect, and another one third had mix of resting wall motion abnormality and ischemia, indicative of previous coronary event. Such two groups form a different cohort of patients, compared with those who have no resting wall motion abnormality.

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Chapter 3. Thesis Objectives, Method and Personal Contribution

3.1. Objectives

Primary hypothesis is whether a combined assessment of myocardial ischaemia with stress echocardiography (SE) (functional) and carotid artery atherosclerosis with ultrasound (carotid ultrasound = CU) (anatomic) confers a more accurate risk stratification of patients with new onset of chest pain without known CAD, than SE alone, for a composite end-point of all-cause mortality, non-fatal myocardial infarction and coronary revascularisation after three months from SE (and therefore not a direct consequence of SE result) during follow up.

Secondary hypothesis is whether detection of carotid artery disease with ultrasonography provides additive risk stratification beyond FRS, by improving net reclassification index (NRI). This would support and generate the hypothesis of initiating primary preventative therapies, such as statin, in patients with normal SE but with significant carotid atherosclerosis.

3.2 Method

Consecutive eligible patients, aged between 35 and 85, who were referred for SE by the attending cardiologists between August 2009 and February 2012, were approached to participate in the study. All participants provided written informed consent and the research was conducted in accordance with the declaration of Helsinki. All patients had new onset chest pain. The principal exclusion criteria were: age <35 or >85 years, known CAD (known

FL-CAD, previous myocardial infarction or coronary revascularisation), presence of resting wall motion/thickness abnormality, significant valve disease or hypertrophic cardiomyopathy, and prior stroke/TIA and/or carotid artery intervention (stenting or surgical endarterectomy). All patients underwent clinical assessment including a full history, including details of chest pain characteristics, traditional cardiovascular risk factor profile, current medication, and physical examination finding as well as ECG result were documented. SE was performed first, followed by carotid ultrasound in the same sitting. The referring cardiologists were notified of the SE results, who retained subsequent management of the patients as part of standard clinical practice. Carotid ultrasound results were not declared unless >70% carotid artery stenosis was detected.

The study was supported by Northwick Park Cardiac Research Fund and approved by the local research ethical committee. No extramural funding was used to support this work.

3.2.1 Power calculations (Mr. Paul Bassett, Medical Statistician)

To compare the proportion of actual events that are detected between the two methods (SE and CU), we shall compare their sensitivity. SE has a sensitivity of 81-83% (dobutamine and exercise, respectively) (1). Given an event that is predicted using SE, is very likely to be predicted using the two method in combination, we assume 12% of responses to be discordant. To increase the two tests sensitivity from 80% to 90%, with 5% significance level and 80% power, 92 events will be required.

In the catchment area of Northwick Park Hospital, a 6.4% hard end point (all-cause mortality and non-fatal myocardial infarction) was observed after a median of 28 months in patients assessed by SE for chest pain (2). During a mean of 28 months, 10.9% late revascularisation was reported in patients who underwent SE for chest pain in another institute (3). These figures result in a total of 17.3% event rate (10.9% + 6.4%). Therefore, it can be calculated that 532 ($92/17.3$) subjects are required. We calculated that in order to compensate for a possible 10% drop-out during follow up, we required a total of 591 ($532/0.9$) subjects.

3.2.2 Cardiac risk estimation

Pre-test probability (PTP) of CAD was calculated employing two methods. We used the method endorsed at the time by the UK National Institute for Health and Care Excellence (NICE) (4), which incorporates age, sex, character of chest pain, diabetes, cholesterol and smoking status. Patients were categorised into low (<10%), intermediate (10% - 90%) and high (>90%) PTP of CAD.

The second method was based on the 2013 European Society of Cardiology (ESC) guideline, which endorsed CAD consortium method (5), which incorporates sex, age, pain characteristics and cardiac risk factors (diabetes mellitus, smoking history, systemic hypertension and total cholesterol). PTP <15%, 15% to 85%, and >85% were defined as low, intermediate, and high, respectively.

At the time of recruitment, as NICE endorsed estimating likelihood of future CHD event based on Framingham Risk Score (FRS) (6), we also adopted FRS Algorithm (7) using the

Framingham Heart Study online calculator (8), which incorporates age, gender, smoking status, and history of hypertension. Framingham Risk Score (FRS) of <5%, 5% to 20%, and >20% were defined as low, intermediate, and high 10-year risk of coronary event, respectively.

3.2.3 Stress echocardiography

SE was performed in accordance with British Society of Echocardiography (BSE) guideline (9). Standard SE methodology, endpoints and contraindication were adhered to, as discussed in detail in Sections 1.1.2, 1.1.2.1 and 1.1.2.2. Patients were advised to stop rate-limiting medication for at least 24 hours. Treadmill exercise was the preferred stress modality; parasternal long-axis, short-axis and apical 4-, 2-, and 3-chamber images were obtained before and immediately after exercise (within 60-90 seconds) (Philips iE33, Philips Medical Systems, Best, Holland). In patients unable to exercise, Dobutamine was infused peripherally in 3-minute stages of 10, 20, 30 and 40mcg/kg/min. Atropine, in increments of 300mcg, up to 1.2 mg, was given whenever indicated.

When endocardial border definition was not well delineated in at least two consecutive segments, an intravenous micro-bubble agent was administered (Sonovue, Bracco, Milan, Italy). Peak and rest B-mode images were displayed digitally side-by-side for each view and analysed by a single experienced reader (Professor Senior), blinded to patient data, using 17 segments model and scored using 4-point scale (1 = normal; 2 = hypokinesis; 3 = akinesis; and 4 = dyskinesis). Stress echocardiography studies were reported as *normal* (no wall thickening abnormality at peak stress) or *abnormal* (inducible wall thickening abnormality in at least two segments). As the resting wall motion score of all segments was one in all

patients, peak wall thickness scoring index (pWTSI) was calculated as the sum of 17 segments score divided by 17. Abnormality at peak stress of just one segment was regarded as normal for the purpose of this study; however, it was reported and its clinical significance left to the discretion of the referring physician.

3.2.4 Carotid ultrasonography

Carotid ultrasonography was conducted in accordance with Mannheim guideline (10) using a high-resolution, non-harmonic B-mode ultrasound system (Philips iE33, Philips Medical Systems, Best, Holland) with a linear array 3- to 11-Mhz transducer, in both longitudinal and transverse axis. The left and right carotid arteries were systematically interrogated first in short- and then long-axis views for detection of atherosclerotic plaque formation. Images of the right and left common carotid arteries, their bifurcations (segment between flow divider and increase in diameter of CCA), internal and external carotid arteries were captured.

C-IMT measurements were taken at the far wall of CCA and bifurcation at end-diastole using a semi-automated edge detection algorithm (QLAB version 8; Philips Medical Systems, Best, Holland). A region of interest, one cm in length, was placed parallel to the vessel wall, allowing the software to detect the luminal-intimal and medial-adventitial interfaces, enabling determination of the IMT (Figure 2.5A). Three readings at each segment were made. Therefore, values for composite mean C-IMT were derived from 24 measurements in total, from the left and right carotid arteries. If there was evidence of carotid plaque formation, care was taken not to include the plaque in the IMT measurement. Whenever image quality or presence of plaque impeded measurement of C-IMT, mean C-IMT was calculated as the average of

obtainable measurements. C-IMT 75th age- and sex-specific percentile values were obtained from Northwick Park's healthy reference cohort (11). Carotid disease was defined as presence of abnormal C-IMT (C-IMT >75th age and sex-specific percentile) and/or presence of carotid plaque (a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value, or a thickness >1.5 mm as measured from the intima-lumen interface to the media-adventitia interface) per Mannheim consensus (10). A simplified definition of plaque, defined as focal structure intruding into the arterial lumen by ≥ 0.5 mm or >1.5 mm in thickness (therefore no C-IMT measurement) was also examined.

All carotid images were analysed by a single reader (S.A.), blinded to clinical details and SE outcomes. Carotid ultrasound results were not reported to the referring physician, unless there was evidence of flow-limiting stenosis ($\geq 70\%$). After completing patient recruitment, 40 patients were selected in random and C-IMT measurements were re-reported. Kappa statistic was performed, which indicated substantial intra-observer agreement ($k = 0.82$, $p < 0.0001$).

3.2.5 Coronary angiography and revascularisation

The decision to proceed to coronary angiography and revascularisation was taken by the attending cardiologist in consideration with the SE result. Standard techniques were used during angiography, with CAD defined qualitatively as $\geq 50\%$ luminal narrowing in ≥ 1 epicardial arteries or their major branches (≥ 2.5 mm in diameter).

3.2.6 Ascertainment of Events:

Primary outcome measure was major adverse events (MAEs), defined as all-cause mortality, non-fatal acute myocardial infarction (AMI) and unplanned coronary revascularization (>3 months after SE). The latter was performed on clinical grounds by the attending physician in the context of ongoing angina, despite optimal medical therapy or presentation with unstable angina/AMI, and was not as a direct consequence of the SE result.

Secondary outcomes were:

- 1) Major adverse cardiac events (MACE): cardiac mortality, non-fatal AMI and unplanned coronary revascularisation.
- 2) Hard events: all-cause mortality and non-fatal AMI.
- 3) Cardiac hard events: cardiac death and non-fatal AMI.

Patients were contacted at 28 months from the recruitment of the last patient, to gather short-term outcome information, and after 5 years from the recruitment of last patient, to gather long-term outcome data.

Mortality was identified from the U.K. National Health Service database; a copy of the death certificate was obtained to document the reported cause of death. Non-deceased participants were contacted directly and the incidence of events including definite or probable AMI (indicated by angina-type symptoms, abnormal electrocardiogram and positive blood markers), as well as coronary angiography and revascularisation were evaluated by obtaining their medical records. Stroke data was neither collected nor included in the end-points, as the

SE is neither performed nor designed to predict such outcome and its inclusion could lead to a bias towards carotid atherosclerosis.

3.3 Personal contribution to the study

I wrote the proposal under the supervision of Professor Senior and received approval from the local ethical committee. While I was working on the proposal, I underwent didactic carotid ultrasonography training at Northwick Park Hospital by attending the carotid ultrasound department (stroke/transient ischemic attack department), to learn general carotid ultrasonography. I then underwent further training in sub-clinical carotid ultrasonography at the cardiovascular research department by Professor Senior, advanced cardiac ultrasound physiologists, and my predecessor research fellows. I received formal training on using the Philips Qlab software by Philips representative to analyse carotid studies offline. I also expanded my knowledge and ability in performing and interpreting exercise and Dobutamine stress echocardiography at the cardiovascular research department.

From August 2009, I was personally responsible for recruitment of all the participants into this study, ensuring they fulfil the inclusion criteria and have no exclusion criteria, and obtaining their informed consent. Approximately 600 subjects were recruited from August 2009 to February 2012, when I finished recruiting 591 patients. Some of the patients that agreed to participate were removed due to findings of baseline echocardiographic images, such as resting wall thickness abnormalities or significant valve disease.

I personally performed all carotid ultrasounds for this study and analysed them, blinded to the patient data. I also acquired the majority of SE images, and supervised the rest. All SE images were reported off-line by Professor Senior, blinded to their clinical data.

At 28 months and 5 years intervals after the last patient recruitment, I co-ordinated and supervised data collection of outcome data by first checking participants' vital status on the NHS database and obtained a copy of death certificate whenever appropriate, in order to verify the cause of death. I then oversaw posting an approved questionnaire, in a prepaid envelope, to participants who were alive. Those who failed to respond were contacted directly over the phone. Finally, patients who were not responding and could not be contacted, their general practitioners (GP) were contacted and relevant medical events were verified. Whenever patients presented to another institute, copies of medical notes were obtained.

After recruiting all the patients, I undertook a quality control and data validation exercise, crosschecking outlier variables, to ensure internal integrity of the data. I attended medical statistics course and performed all statistical analyses using SPSS versions 21.0 and 22.0 (IBM Corporation, USA), with the assistance of a medical statistician (Mr Paul Bassett). After completing patient recruitment, I assessed intra-observer agreement by selecting 40 cases in random and re-reported the carotid ultrasound, the kappa was indicative of an almost perfect agreement ($k = 0.82$, $p < 0.0001$).

I wrote all the drafts of subsequent papers and finalised them with the help and input of other authors, submitted the final version to journals, and carried out proof reading.

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PART II – STUDIES AND RESULTS

Chapter 4. Study I - Role of Simultaneous Carotid Ultrasound in Patients Undergoing Stress Echocardiography for Assessment of Chest Pain with no Previous History of Coronary Artery Disease

4.1 Abstract

Background: We prospectively explored prevalence of carotid disease (CD), its independent association with coronary artery disease (CAD) and outcome, as well as potential impact on management, in patients undergoing stress echocardiography (SE) for new onset chest pain without known CAD.

Methods: Accordingly, 591 consecutive patients referred for SE underwent carotid ultrasound. CD was defined as carotid intima-media thickness (C-IMT) >75th percentile for age and sex, and/or presence of plaque.

Results: Myocardial ischaemia was demonstrated in only a minority (11%) but there was a high prevalence of CD (70%). Incidence of CD was similar in patients with and without ischaemia (76% vs. 69%, $p = 0.26$). Carotid data led to reclassification of Framingham risk score (FRS) categories in 65% of patients, as well as more than a third of negative SE patients potentially benefitting from primary prevention therapy. Of the 83 patients undergoing coronary arteriography, 59 (71%) demonstrated coronary atherosclerosis (any atheroma) and 33 (40%) CAD. Positive predictive value (PPV) of SE for CAD was 56%, but presence of carotid plaque improved it to 70%. Whilst both CD and plaque showed association with CAD and revascularisation, after adjustment for conventional risk factors,

only carotid plaque maintained significant association ($p = 0.024$ and $p = 0.023$, respectively).

Conclusions: There is significantly higher prevalence of CD compared to myocardial ischaemia in patients undergoing SE and carotid ultrasound for suspected CAD. This can lead to significant FRS reclassification with important primary prevention implications. Carotid plaque is superior to clinical assessment for the prediction of CAD and improves PPV of SE for CAD in these patients.

4.2 Introduction

Stress echocardiography (SE) is a well-established tool for risk stratifying patients with new onset chest pain (1-4). However, it only identifies patients with flow-limiting coronary artery disease (CAD) and does not detect presence of non-flow limiting atherosclerosis. Therefore, a negative SE, whilst reassuring and indicative of good prognosis in the short-term, may not be benign in the long-term (5). Conversely, wall motion abnormalities during SE can occur in absence of epicardial CAD (for example due to microvascular dysfunction, endothelial dysfunction, coronary spasm) and may thus reduce the positive predictive value of an abnormal SE for CAD (4).

Carotid disease (CD) (defined as carotid intima-media thickness (C-IMT) >75th percentile for age and sex, and/or presence of plaque (6)) is associated with CAD (7-8) and predicts myocardial infarction, stroke and death (9-10), beyond traditional risk factors and the Framingham Risk Score (FRS) in asymptomatic populations (11-15). CD can be assessed at the time of SE by performing carotid ultrasonography using the same equipment. Although the role of carotid ultrasonography in asymptomatic populations is established in epidemiological studies, its potential utility in symptomatic patients undergoing SE is currently unknown. Therefore, we devised this study to answer two questions; firstly, to determine whether carotid ultrasonography data, in combination with SE in symptomatic patients without a prior history but suspected CAD, can improve the prediction of CAD and future events and, secondly, to determine whether carotid ultrasonography provide additive clinical information – in particular the potential to initiate primary prevention therapies – in patients with normal SE but with significant atherosclerosis.

4.3 Methods

4.3.1 Participants

Consecutive consenting patients with recent onset chest pain who were referred for a clinically indicated SE underwent carotid ultrasonography. The principal exclusion criteria were: age <35 or >85 years, known CAD (documented CAD, history of myocardial infarction or coronary revascularisation), presence of resting wall motion abnormality, significant valve disease or hypertrophic cardiomyopathy, and prior carotid artery intervention (stenting or surgical endarterectomy). Chest pain character, cardiovascular risk factor profile, medication, and physical examination findings were documented.

The study was supported by Northwick Park Cardiac Research Fund and approved by the local research ethical committee. No extramural funding was used to support this work.

4.3.2 Clinical risk stratification

The 2010 NICE guidance endorsed method of PTP estimation was used (Section 3.2.2).

4.3.2 Stress echocardiography

This was discussed in detail under Section 3.2.3

4.3.3 Carotid ultrasonography

This was discussed in detail under Section 3.2.4

4.3.5 Coronary angiography

This was discussed in detail under Section 3.2.5

4.3.6 Statistical analysis

Continuous variables were expressed as mean $\pm$ SD and categorical variables as percentages. Differences between continuous and categorical variables were compared using the Student's t-test and χ^2 test, respectively. C-IMT $>75^{\text{th}}$ age- and sex-specific percentile values were obtained from our institute's healthy reference cohort (18). Forward stepwise multiple logistic regression analyses were used to identify independent predictors of CAD and revascularisation. In the logistic regression model, criterion for entry of variables was set on $p \leq 0.1$. The difference in risk was expressed as the odds ratio with the corresponding 95% confidence intervals (CI).

A p value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 21.0 (IBM Corp., USA). The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the paper and its final contents.

4.4 Results

A total of 591 patients with a mean age of 59 ± 11 years (range 35-85), 46% men, and no history of CVD, participated in the study. Their demographic and clinical characteristics are depicted in Table 4.1. The majority of patients (74%) had an intermediate pre-test probability of CAD; similarly higher proportion of patients (53%) had intermediate FRS risk score.

Table 4.1. Baseline patient characteristics (n = 591)

Age (years), mean $\pm$ SD	59 $\pm$ 11
Male (%)	269 (46)
Ethnicity	
Asian (%)	326 (55)
Caucasian (%)	207 (35)
Afro-Caribbean (%)	53 (9)
Southeast Asia (%)	5 (1)
Body Mass Index, mean $\pm$ SD, kg/m ²	28 $\pm$ 5
Hypertension (%)	322 (55)
Diabetes mellitus (%)	142 (24)
Hypercholesterolemia (%)	341 (58)
Smoker (current or within last year) (%)	71 (12)
FH of premature CAD (%)	202 (34)
Drug History	
Aspirin (%)	168 (29)
Beta-blocker (%)	73 (12)
ACEi/ARB (%)	207 (35)
Statins (%)	240 (41)
Pre-test probability of CAD, mean $\pm$ SD	40 $\pm$ 30
Low (<10%)	117 (20)
Intermediate (10-90%)	436 (74)
High (>90%)	38 (6)
FRS categories (%)	
Low (<5%)	68 (11)
Intermediate (5-20%)	313 (53)
High (>20%)	210 (36)

ACEi: Angiotensin converter inhibitor, ARB: Angiotensin receptor blocker, CAD: Coronary artery disease, FH: Family history, FRS: Framingham risk score, SD: Standard deviation

Myocardial ischaemia was demonstrated in 67 (11%) patients. A higher number of patients underwent exercise (62%) compared to pharmacological SE (Table 4.2.). There was no major complication during SE. Four patients did not achieve $\geq 85\%$ target heart rate. One patient in dobutamine group achieved 84% despite maximum doses of dobutamine and atropine. Of the remaining 3 patients who were in the exercise stress group, two achieved 83% and the other one achieved 84%. All were reported as negative for prognostically significant CAD (i.e. $\geq 50\%$ left main or $\geq 70\%$ proximal left anterior descending disease). The referring physicians opted not to arrange further tests.

Table 4.2. Stress echocardiography and carotid ultrasound findings

Parameters	N (%)
Exercise SE	364 (62)
Contrast for LV opacification	291 (49)
Abnormal SE	67 (11)
Carotid IMT $> 75^{\text{th}}$ percentile for age and sex	228 (39)
Carotid Plaque	347 (59)
- CCA	113 (33)
- Bifurcation	314 (90)
- ICA	93 (27)
Carotid disease	415 (70)

CCA: Common carotid artery, ICA: Internal carotid artery, IMT: Intima-media thickness, LV: Left ventricle, SE: Stress echocardiography

4.4.1 Carotid ultrasonography

In contrast to SE results, majority of carotid ultrasonographies were abnormal (Table 4.2.); 415 (70%) patients had CD, mostly in the form of plaque [347 patients (59%)]. Plaque was most commonly observed at the bifurcation (90%). C-IMT was measurable in all but one patient (due to extensive plaques). In 5 patients ICA image quality precluded assessment and/or plaque detection.

Table 4.3 summarises the main demographic and clinical characteristics of the cohort according to their carotid status. Patients with CD were more likely to be older, male, hypertensive, hyperlipidemic and treated with a statin. There was no difference in prevalence of abnormal C-IMT between male and female participants ($p = 0.23$); therefore, the higher prevalence of CD in males ($p = 0.002$) was driven by carotid plaque ($p < 0.0001$).

There was no difference in prevalence of carotid disease [51 versus 364 (76% versus 69%), $p = 0.26$], carotid plaque [44 versus 303 (66% versus 58%), $p = 0.22$], abnormal C-IMT [28 versus 200 (42% versus 38%), $p = 0.57$] or mean C-IMT [$0.67 \pm 0.12\text{mm}$ vs. $0.70 \pm 0.12\text{mm}$, $p = 0.092$] in patients with and without abnormal SE, respectively (Figure 4.1).

Table 4.3. Carotid ultrasound outcome according to characteristics

	Carotid disease (N=415) (70%)	Normal carotid (N=176) (30%)	P value
Age (years), mean $\pm$ SD	61 $\pm$ 10.9	55 $\pm$ 10.8	<0.0001
Male (%)	206 (50)	63 (36)	0.002
BMI, mean $\pm$ SD	27.9 $\pm$ 5.1	28.1 $\pm$ 4.9	0.598
Hypertension (%)	252 (61)	70 (40)	<0.0001
Hypercholesterolemia (%)	255 (61)	86 (49)	0.01
Diabetes mellitus (%)	100 (24)	42 (24)	0.95
FH of premature CAD (%)	135 (33)	67 (38)	0.36
Smoker (%)	53 (13)	18 (10)	0.38
Statins (%)	185 (45)	55 (31)	0.003
Pre-test probability of CAD, mean $\pm$ SD	44 $\pm$ 30	30 $\pm$ 28	<0.0001
Low (%)	56 (13)	61 (35)	
Intermediate (%)	326 (79)	110 (62)	
High (%)	33 (8)	5 (3)	
FRS, mean $\pm$ SD	17.7 $\pm$ 9.2	12.3 $\pm$ 8.2	<0.0001
Low (%)	29 (7)	39 (22)	
Intermediate (%)	209 (50)	104 (59)	
High (%)	177 (43)	33 (19)	
Abnormal Stress Echocardiography (%)	51 (12)	16 (9)	0.26

BMI = body mass index; CAD = coronary artery disease; SD = standard deviation

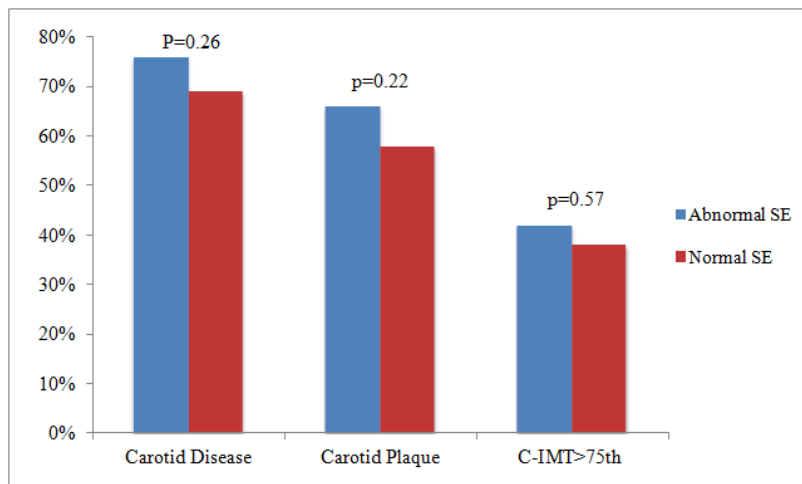


Figure 4.1. Prevalence of carotid abnormalities in patients with positive versus negative stress echocardiography. C-IMT: carotid intima-media thickness, SE: Stress echocardiography

4.4.2 FRS categories reclassification and implication on primary prevention

FRS categories in the negative SE cohort (524 patients) were up- or downgraded based on the presence or absence of CD, respectively (Table 4.4.). This led to a significant reclassification; 41% were up-graded and 24% were down-graded.

Table 4.4. Reclassification of Framingham Risk Score Categories after addition of Carotid data in patients with normal stress echocardiography (n = 524)

Original FRS	Reclassified FRS		
	<5%	5-20%	>20%
<5%	64 →	28	
5-20%	95 ←	284 →	189
>20%		29 ←	176

In total 180 patients (including 74 re-classified to intermediate FRS and 56 to high FRS), free from diabetes mellitus and not currently on primary preventative medication, had ultrasonographic evidence of carotid atherosclerosis and would potentially benefit from primary preventative treatment such as statins. This equates to 30% of the total cohort and 34% of the negative SE group.

4.3.3 Prediction of CAD

A total of 83 patients underwent coronary angiography (Table 4.5); this included all the patients with abnormal SE except one (who made an informed decision against), as well as a very small proportion (3%) of patients with normal SE (at the discretion of referring physician). CAD was demonstrated in 37 patients with abnormal SE, resulting in a positive predictive value (PPV) of 56%. CAD was seen in just two patients with normal SE who underwent coronary angiography (0.4% of normal SE cohort).

Table 4.5. Relationship between coronary angiography, stress echocardiography and carotid disease

	Abnormal SE (n = 67)		Normal SE (n = 524)	
	Without CD	With CD	Without CD	With CD
Normal Coronary Angiography	7	8	3	6
Atheroma and/or <50% CAD	4	10	1	5
Flow-limiting ($\geq$ 50%) CAD	4	33	1	1
Coronary angiography not performed	0	1	155	352

CAD= Coronary artery disease; CD= Carotid disease; SE= Stress echocardiography

Prevalence of CD increased with increasing degree of coronary atherosclerosis (Table 4.6). Of the 66 patients with abnormal SE undergoing CA, 44 also had carotid plaque, with 70% having significant CAD on CA. Therefore, addition of carotid plaque to the SE result significantly improved PPV of SE from 56% to 70%.

The greatest impact of carotid data was seen in patients with <10% pre-test probability of CAD. In this group, 8 patients had a positive SE but only one patient demonstrated CAD, who was the only patient with CD (the other 7 patients with abnormal SE had normal carotids and no significant CAD). In patients with >10% pre-test probability of CAD, PPV of SE was 62% (36/58) and presence of plaque improved it to 70% (30/43).

Male gender, hyperlipidemia, pre-test probability of CAD, FRS, abnormal SE, carotid plaque and disease were associated with CAD in 83 patients who underwent coronary angiography (Table 4.6). As the pre-test probability and FRS already include gender and lipid status, only pre-test probability, FRS, SE and carotid data (plaque and CD separately) were entered into the multivariable regression model. Carotid plaque and SE result were the only factors that maintained significance ($p = 0.024$ and $= 0.005$, respectively). Confidence interval of “pre-test probability” included null value, despite $p < 0.05$.

Table 4.6. Predictors of flow-limiting coronary artery disease (n = 83)

Variable	Univariable P value	Multivariable P value	Odds Ratio	95% CI
Age	0.15			
Male gender	0.01			
Hypertension	0.68			
Diabetes mellitus	0.88			
Smoker	0.82			
Hypercholesterolemia	0.02			
FH of premature CAD	0.4			
BMI	0.97			
Pre-test probability of CAD	0.035	0.047	1.018	1.000 - 1.036
FRS category	0.025			
Abnormal stress echocardiography	0.001	0.005	10.17	2.03 - 50.89
Carotid IMT>75 th percentile	0.805			
Carotid Plaque	0.002	0.024	3.35	1.06 - 10.55
Carotid Disease	0.024			

BMI= body mass index; CAD = coronary artery disease; FH = family history; FRS= Framingham risk score; IMT= intima-media thickness.

4.4.4 Coronary intervention

Of the 39 patients who had CAD, 32 (82%) patients underwent revascularisation. Whilst male gender, hyperlipidemia, abnormal SE, carotid plaque and carotid disease were all associated with revascularisation (Table 4.7.), carotid plaque was the only independent predictor of revascularisation ($p = 0.023$).

Table 4.7. Predictors of coronary intervention (n = 39)

Variable	Univariable P value	Multivariable P value	Odds Ratio	95% CI
Age	0.996			
Male gender	0.011			
Hypertension	0.501			
Diabetes mellitus	0.844			
Smoker	0.378			
Hypercholesterolemia	0.032			
FH of premature CAD	0.754			
BMI	0.382			
Pre-test probability of CAD	0.132			
FRS	0.189			
Abnormal stress echocardiography	<0.0001			
Carotid IMT >75 th percentile	0.252			
Carotid Plaque	0.003	0.023	4.11	1.21 - 13.93

BMI: body mass index, CAD: coronary artery disease, FH: family history, FRS: Framingham risk score, IMT: intima-media thickness.

4.5 Discussion

This is the first large prospective study to assess the prevalence of carotid disease in symptomatic patients without a history of cardiovascular disease, undergoing SE for evaluation of myocardial ischaemia and its implication on primary preventive therapy. The study demonstrated that in this population with a pre-test probability of CAD of 40%, the prevalence of CD was 70% whereas the prevalence of myocardial ischaemia was only 11%.

In the subset of patients who underwent coronary angiography, in which the pre-test probability of CAD was higher (55%), the prevalence of CAD was 47% and CD was 81%. CD was an independent predictor of CAD beyond that predicted by the pre-test probability of CAD and independent of SE data. In combination with SE data, carotid ultrasonography results improved PPV of SE significantly, especially in the low pre-test probability group. Finally, presence of CD was the only independent predictor of revascularisation in this study. This study also demonstrated that 65% of FRS categories underwent reclassification when carotid data was considered in normal SE cohort, which has implications for primary preventive therapy in nearly a quarter of them.

It is well known that atherosclerotic disease precedes development of flow-limiting lesions and ischemic symptoms. Indeed, severe atherosclerotic lesions may be present without manifest disease due to positive arterial remodeling (19) and the first event could thus be death or an acute ischemic event (20). This explains the significantly greater prevalence of carotid atherosclerosis than myocardial ischaemia in the present population. CD has been shown to predict future adverse CV events in large epidemiological studies of asymptomatic individuals (9, 15) and also shown to reflect presence and severity of CAD (7-8). The present study extends these findings by demonstrating, for the first time in a cohort of *symptomatic* patients, strong association between CD and CAD, beyond its clinical manifestation, and CD is widely prevalent in such patients, irrespective of SE result. Furthermore, as myocardial ischaemia on stress testing can occur due to causes other than flow-limiting CAD, the presence of carotid atherosclerosis indicates a high likelihood of CAD and thereby improves prediction of CAD in presence of abnormal SE.

The PPV of SE in this study was 56%, which is lower than previously reported in some studies. However, we excluded patients with known CAD, a group with a higher pre-test probability of flow-limiting CAD, and who have usually been included in other studies where higher PPV has been reported.

The independent association of CD with revascularisation, beyond traditional cardiac risk factors and myocardial ischaemia, supports its potential ability to predict spontaneous outcome as shown in studies in asymptomatic patients. Very limited studies, with small patient numbers, have previously evaluated CD in symptomatic patients undergoing stress testing. Kanwar et al. (21) utilised carotid ultrasonography in 50 symptomatic patients who were scheduled for coronary angiography, following stress imaging. Their study, unlike ours, only assessed patients already listed for coronary angiography. Similar to our findings; carotid plaque was an independent predictor of CAD. However, in addition, the pre-test probability of CAD and hypertension were also independent predictors. More importantly, they demonstrated incremental value of carotid ultrasonography in patients with equivocal/negative stress tests for predicting significant CAD. However, their patients had different types of stress imaging.

Another study assessed 130 subjects undergoing dobutamine SE with a view to establish whether three-dimensional left atrial volume assessment and/or presence of carotid plaque can predict the outcome of SE (22). However, the majority of these patients, unlike our population, had known CAD. In such a cohort, they also did not show a difference in the prevalence of carotid plaque in those with normal versus abnormal SE result.

Our approach of complementing an ischemic study (functional) by probing for evidence of atherosclerosis (anatomic), mirrors integrated positron emission tomography (PET) myocardial perfusion imaging with computed tomography (CT) coronary calcium scoring (23). While both anatomical additions have the potential of improving the prognostic value of functional imaging, the ultrasound approach is more cost-effective, easily and widely available (even at bed-side) and is radiation-free.

4.5.1 Clinical Implications

Whilst traditional risk factors and pre-test probability of CAD were significant in predicting CAD, the presence of carotid plaque provided incremental information in patients with chest pain but with no history of prior CAD disease. Carotid assessment improved the post-test probability of CAD following SE. Conversely, absence of CD in patients without manifest ischaemia, which was seen in a quarter of patients in our study, will be even more reassuring. Large scale, well-conducted population studies of asymptomatic individuals (9-15) have reported the findings of long-term follow-up and demonstrated the ability of carotid ultrasonography findings to re-classify risk as well as predict future CV events. This has led to a Class IIa American College of Cardiology/American Heart Association recommendation for carotid ultrasonography in risk stratification of asymptomatic patients with intermediate risk (24). Our study confirms that symptomatic patients also frequently have atherosclerosis despite not meeting criteria for primary prevention therapies using clinical risk markers. FRS reclassification in population studies using C-IMT and plaque data has been shown to offer a small, but significant, improvement in 10-year risk prediction of myocardial infarction and stroke (12, 15). However, in these studies impact of CD on reclassification of FRS categories was rather weak. In a recent meta-analysis (14), adding C-IMT data had no influence on FRS

categories in more than 90% of patients. Whereas in our cohort of symptomatic patients, majority were in fact upgraded (41%) and only 35% underwent no change. Based on the presence of CD, a significant proportion of the negative SE cohort (34%) would potentially benefit from pharmaceutical intervention such as statins. They were, otherwise, not candidates for such treatment based on clinical profile only. Whilst implementing this approach can improve long-term health and is economically sound (25), to date this has not been verified in a randomised controlled trial (RCT). Nevertheless, primary prevention is currently common practice in patients deemed high risk despite lack of RCT derived evidence. There are, however, studies showing regression of C-IMT and atherosclerosis by introduction of statin (26) and one may extrapolate that such intervention is of benefit in the presence of abnormal CD, given its correlation with CAD and cardiovascular events.

4.5.2 Study Limitations

Not all subjects underwent coronary angiography and there is a referral bias for those who did. However, coronary angiography was requested on clinical grounds, as is usual practice. Performing invasive coronary angiography in all patients with normal SE is not ethical. SE data, on the basis of which most patients underwent coronary angiography, was used in the models predicting CAD and revascularisation. However, CD remained an independent predictor of CAD and revascularisation when SE data was excluded (data not presented). We however, acknowledge that number of coronary interventions may be marginally low to optimally assess associations with factors. FRS was originally derived from a predominantly Caucasian population and its use, while common practice, is not validated in subjects from Indian sub-continent, who made the majority of our cohort. However, FRS has been successfully applied to many other ethnic groups (27). FRS reclassification with event

outcome would have helped to support or dispute this approach by allowing for net reclassification index calculation. This data collection is currently ongoing.

4.5.3 Conclusion

This prospective study revealed that carotid ultrasound in symptomatic patients referred for clinically indicated SE, can identify early atherosclerosis that may necessitate primary preventive therapy despite reassuring SE result. Simultaneous carotid ultrasound further improved the prediction of CAD by SE and identified patients at high risk of revascularisation. Thus, carotid ultrasonography is a simple, rapid and accurate bedside method for enhancing the diagnostic value with potential for improving risk assessment of SE.

4.6 References

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Chapter 5. Study II - Incremental Prognostic Value of Simultaneous Stress Echocardiography and Carotid Ultrasound in Patients with Suspected Coronary Artery Disease: A Prospective Study

5.1 Abstract

Background: The clinical significance of atherosclerosis assessment by carotid US in patients undergoing stress echocardiography (SE) in such patients is unknown.

Methods Consecutive patients with suspected angina but no history of CAD underwent simultaneous SE and US prospectively to assess myocardial ischaemia and CPB, respectively. Patients were followed up for major adverse events (MAEs): all-cause mortality, nonfatal myocardial infarction, and unplanned coronary revascularisation.

Results: Of 591 recruited patients, 580 (men, 46%; mean age 59 ± 11 years) patients were available for follow-up. SE demonstrated myocardial ischaemia in 12%, but prevalence of carotid plaques was 59%. During a median follow-up of $1,117 \pm 361$ days, 40 first MAEs occurred. In the multivariable regression model, pre-test probability (PTP) of CAD ($p = 0.001$), abnormal SE ($p < 0.0001$), and CPB ($p < 0.0001$) predicted MAEs. MAE rates per year increased from 0.9% versus 1.97% versus 4.3% versus 9.7% in patients with no carotid plaque and normal SE versus patients who had plaque and normal SE versus those with no plaque and abnormal SE versus patients with plaque and abnormal SE, respectively ($p < 0.0001$). In hierarchical analysis, CPB provided incremental prognostic value over PTP of CAD and SE; likewise, SE was incremental to PTP-CAD and CPB ($p < 0.0001$ for both).

Conclusions: In patients with suspected stable angina without known CAD, simultaneous SE (for ischaemia) and US (for atherosclerosis) provided incremental prognostic value.

5.2 Introduction

When patients without a history of coronary artery disease (CAD) present with recent onset suspected angina, they may undergo functional non-invasive tests for detection of myocardial ischaemia, both for diagnostic and risk stratification purposes. Although a negative test for ischaemia reduces the probability of flow-limiting CAD, it does not exclude the presence of non-flow limiting CAD, which can adversely affect prognosis (1). Preventative pharmacological measures such as aspirin and statins in these patients may improve outcome, despite the absence of ischaemia. Conversely, presence of ischaemia may occur in the absence of epicardial CAD (e.g. microvascular dysfunction, endothelial dysfunction, and coronary spasm) and may portend different outcomes compared with those with obstructive atherosclerotic disease. A combination of single-photon emission computed tomography (SPECT) or positron emission tomography (PET), and computed tomography coronary angiography (CTCA) has been proposed for the detection of myocardial ischaemia and atherosclerotic disease, respectively, for optimal management of such patients (2-3). However, high ionising radiation burden, limited availability, and the prohibitive cost of these tests limit their combined use.

Stress echocardiography (SE) is widely used for the diagnosis and risk stratification of patients with recent onset chest pain. Similarly, carotid ultrasound (CU), which can detect atherosclerosis and is closely associated with CAD, has also been shown to predict cardiac mortality and acute myocardial infarction (AMI) beyond clinical risk factors in asymptomatic patients (4). SE and CU can be performed at the bedside simultaneously without ionising radiation and are relatively inexpensive. We hypothesised that combined SE and CU in patients with recent onset suspected stable angina but without history of CAD may provide

incremental prognostic information beyond clinical risk factors. If shown to do so, this would have clinical implications for daily clinical practice. Accordingly, we conducted a large prospective study in such patients referred for SE who also underwent CU.

5.3 Methods

A complete description of the patient selection, SE, CU, clinical risk stratification, and coronary angiography was previously described (5). In summary, consecutive patients investigated because of new-onset stable chest pain, but who did not have a history of CAD or coronary intervention and who were referred for SE on clinical grounds, were enrolled in the study and provided written consent. Ethical and institutional review board approvals were obtained to perform this study.

5.3.1 Pre-test probability of CAD

This was calculated based on the U.K. National Institute for Health and Clinical Excellence (NICE) guideline (7), as discussed in detail under Section 3.2.2

5.3.1. Stress echocardiography

This was discussed in detail under Section 3.2.3

5.3.2 Carotid ultrasonography

This was discussed in detail under Section 3.2.4

5.3.4 Coronary angiography and revascularisation

This was discussed in detail under Section 3.2.5

5.3.5 Ascertainment of events

This was discussed in detail under Section 3.2.6

5.3.6. Statistical analysis

Baseline patient characteristics, CU, and SE results were compared across various outcomes using chi-square and Student t-test, as appropriate. The predictors of a first MAE were studied by Cox proportional-hazard regression to evaluate the independent relationship between each parameter and the respective outcome, resulting in identification of univariable predictors, with $p \leq 0.10$. This is known as univariable screening, which was performed to ensure avoidance of a low event per variable ratio. Plaque was tested as both a categorical (present versus absent) and a continuous variable as CPB, based on the number of plaques identified, in separate models. Kaplan-Meier survival curves were constructed to plot time-to-event outcomes, which were compared using the log-rank test. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed with SPSS version 22.0 (IBM, Armonk, New York).

5.4 Results

Of 591 patients recruited, 580 (98%) were available for follow-up. Their demographic characteristics, SE, and carotid data are listed in Table 5.1.

Table 5.1. Baseline patient characteristics, SE and Carotid Ultrasound findings of the follow-up cohort (n = 580)

Age (years), mean $\pm$ SD	60 $\pm$ 11
Male (%)	264 (46%)
Body Mass Index, mean $\pm$ SD, kg/m ²	28 $\pm$ 5%
Hypertension (%)	315 (54%)
Diabetes mellitus (%)	138 (24%)
Hypercholesterolemia (%)	336 (58%)
Smoker (current or within last year) (%)	67 (12%)
FH of premature CAD (%)	195 (34%)
Aspirin (%)	164 (28%)
Beta-blocker (%)	73 (13%)
ACEi/ARB (%)	205 (35%)
Statins (%)	233 (40%)
Pre-test probability of CAD, mean $\pm$ SD	40.3% $\pm$ 30.2%
- low PTP (%)	114 (20%)
- intermediate PTP (%)	428 (74%)
- high PTP (%)	38 (6)
Exercise SE (%)	356 (61%)
Contrast for opacification (%)	285 (49%)
Abnormal SE (%)	67 (12%)
Carotid Plaque (%)	343 (59%)
- Common carotid artery (%)	110 (32%)
- Bifurcation (%)	307 (90%)
- Internal carotid artery (%)	92 (27%)
C-IMT, mean $\pm$ SD, mm	0.68 $\pm$ 0.13

ACEi: Angiotensin convertor enzyme inhibitor, ARB: Angiotensin receptor blocker, CAD: Coronary artery disease, FH: Family history, SD: Standard deviation, C-IMT: carotid intima-media thickness, PTP: Pre-test probability, SE: Stress echocardiography

An abnormal SE was reported in 12%, whereas 59% had plaque. Prevalence of plaque was 34% and 64% in patients with low ($n = 114$) and intermediate PTP ($n = 428$), respectively. Seven patients had flow-limiting carotid disease ($>70\%$ stenosis, 5 in the common carotid artery and 3 in the internal carotid artery), none of whom had an abnormal SE.

Of 513 patients with normal SE, 299 (58%) patients had plaque, 164 (55%) of whom were not on statins, which constituted 28% of the whole population.

5.4.1 Follow-up

During median follow-up of 36.7 ± 11.9 months ($1,117 \pm 361$ days), there were a total of 40 MAEs (12 all-cause mortalities, 9 nonfatal AMIs, and 19 unplanned revascularisations), 32 MACEs (4 cardiovascular mortalities, 9 nonfatal AMI, and 19 unplanned revascularisations), and 13 hard cardiac events (4 cardiovascular mortalities and 9 nonfatal AMIs).

Time to first unplanned revascularisation ranged between 346 and 1,684 days; therefore, it was unlikely to be affected by SE result. The annual hard event rate in this population was 2.3%/year, which reflected a high prevalence of intermediate PTP of CAD. No event was reported in patients with significant ($>70\%$) carotid disease.

5.4.2 Cox regression analysis

Because PTP incorporated chest pain characteristics, age, sex, diabetes mellitus, and smoking status, these components were used collectively. Systemic hypertension, stain therapy, peak rate–pressure product, early revascularisation, SE result, and CPB were included. While PTP,

abnormal SE, and CPB predicted MAEs ($p = 0.001$, $p < 0.0001$, $p < 0.0001$, respectively) and MACEs ($p = 0.004$, $p < 0.0001$, $p < 0.0001$, respectively), only CPB retained significance in multivariable analysis for the prediction of hard cardiac events ($p < 0.0001$), with SE retaining borderline significance ($p = 0.06$) (Table 5.2).

Table 5.2. Cox regression analysis for the prediction of events

A. major adverse events (MAE)

	Univariable Analysis	Multivariable Analysis	HR	95% CI
	p value	p value		
Statin	0.028	0.072		
PTP	<0.0001	0.001	3.13	1.57-6.27
SE result	<0.0001	<0.0001	4.41	2.31-8.43
CPB	<0.0001	<0.0001	1.26	1.13-1.40

B. major adverse cardiac events (MACE)

	Univariable Analysis	Multivariable Analysis	HR	95% CI
	p value	p value		
Statin	0.028	0.12		
PTP	<0.0001	0.004	3.17	1.44-6.89
SE result	<0.0001	<0.0001	6.71	3.30-13.64
CPB	<0.0001	<0.0001	1.32	1.17-1.49

C. hard cardiac events: cardiac mortality + acute myocardial infarction

	Univariable Analysis	Multivariable Analysis	HR	95% CI
	p value	p value		
Hypertension	0.021	0.23		
PTP	0.017	0.22		
SE result	0.028	0.06		
CPB	<0.0001	<0.0001	1.53	1.27-1.84

CI: Confidence interval, CPB: Carotid plaque burden, HR: Hazard ratio, PTP: pre-test probability, SE: Stress echocardiography

When only intermediate PTP group (74% of patients) was considered, in whom investigation is deemed most appropriate, SE and CPB retained their significance in Cox regression analysis for prediction of MAEs (SE: $p < 0.0001$; CPB: $p < 0.0001$), MACEs (SE: $p < 0.0001$; CPB: $p < 0.0001$), and hard cardiac events (SE: $p = 0.033$; CPB: $p < 0.0001$) (Table 5.3).

Table 5.3. Cox regression analysis in patients with intermediate pre-test probability of coronary artery disease for the prediction of events

A. major adverse events (MAE)

	Univariable Analysis p value	Multivariable Analysis p value	HR	95% CI
SE result	<0.0001	<0.0001	4.51	2.17 - 9.41
CPB	<0.0001	<0.0001	1.27	1.12 - 1.45

B. major adverse cardiac events (MACE)

	Univariable Analysis p value	Multivariable Analysis p value	HR	95% CI
Statin	0.028	0.12		
SE result	<0.0001	<0.0001	6.64	2.97 - 14.83
CPB	<0.0001	<0.0001	1.36	1.18 - 1.56

C. hard cardiac events: cardiac mortality + acute myocardial infarction

	Univariable Analysis p value	Multivariable Analysis p value	HR	95% CI
SE result	0.003	0.033	4.15	1.12 - 15.34
CPB	<0.0001	<0.0001	1.59	1.28-1.97

CI: Confidence interval, CPB: Carotid plaque burden, SE: Stress echocardiography

5.4.3 Survival analysis: events in SE subgroups based on KM survival curves

Patients with an abnormal SE had significantly higher rates of MAEs, MACEs, and hard cardiac events compared with normal SE ($p < 0.0001$, < 0.0001 , and $= 0.02$, respectively). (Table 5.4).

Table 5.4. Incidence of adverse events in patients with normal vs. abnormal stress echocardiography based on Kaplan-Meier survival curves

	Normal SE (n=513)	Abnormal SE (n=67)	P value
MAE	24 (4.7%)	16 (24%)	< 0.0001
MACE	16 (3.1%)	16 (24%)	< 0.0001
Hard cardiac events	9 (1.75%)	4 (6%)	0.022

MACE: Major adverse cardiac event, MAE: Major adverse event, SE: Stress echocardiography

In patients with normal SE, combined hard cardiac event rates were 0.57% per year versus 1.95% per year with an abnormal SE (Figure 5.1).

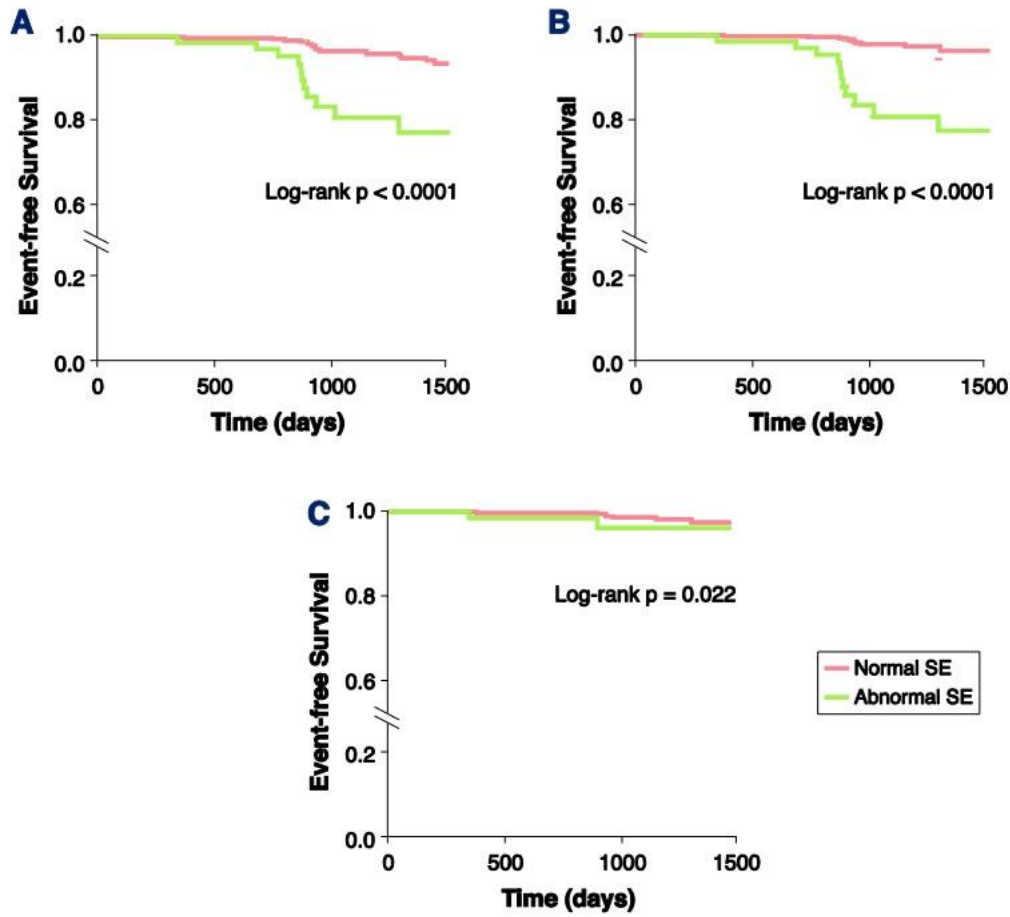


Figure 5.1. Kaplan-Meier curves based on SE results for the prediction of: A. major adverse events (MAE), B. major adverse cardiac events (MACE), C. hard cardiac adverse events.

SE: Stress echocardiography

5.4.4 Survival analysis: events in carotid plaque subgroups based on KM survival curves

Patients with CP had significantly higher rates of MAEs, MACEs, and hard cardiac events compared with those with no CP (Table 5.5.).

Table 5.5. Incidence of adverse events in patients with presence vs. absence of carotid plaque based on Kaplan-Meier survival curves

	Plaque absent (n = 237)	Plaque present (n = 343)	P value
MAE	9 (3.7%)	31 (9%)	0.009
MACE	6 (2.5%)	26 (7.6%)	0.005
Hard cardiac events	1 (0.4%)	12 (3.5%)	0.01

MACE: Major adverse cardiac event, MAE: Major adverse event

In patients with no CP, combined hard cardiac event rates were 0.13% per year versus 1.14% per year in those with CP (Figure 5.2).

5.4.5 Survival analysis: combined SE and plaque outcome based on KM survival curves

KM survival curves for the predictions of MAE, MACE and hard cardiac events demonstrate a significant stepwise increase in events across all combinations in patients with no plaque and normal SE vs. plaque and normal SE vs. no plaque and abnormal SE vs. plaque and abnormal SE, respectively (Table 5.6. and Figure 5.3).

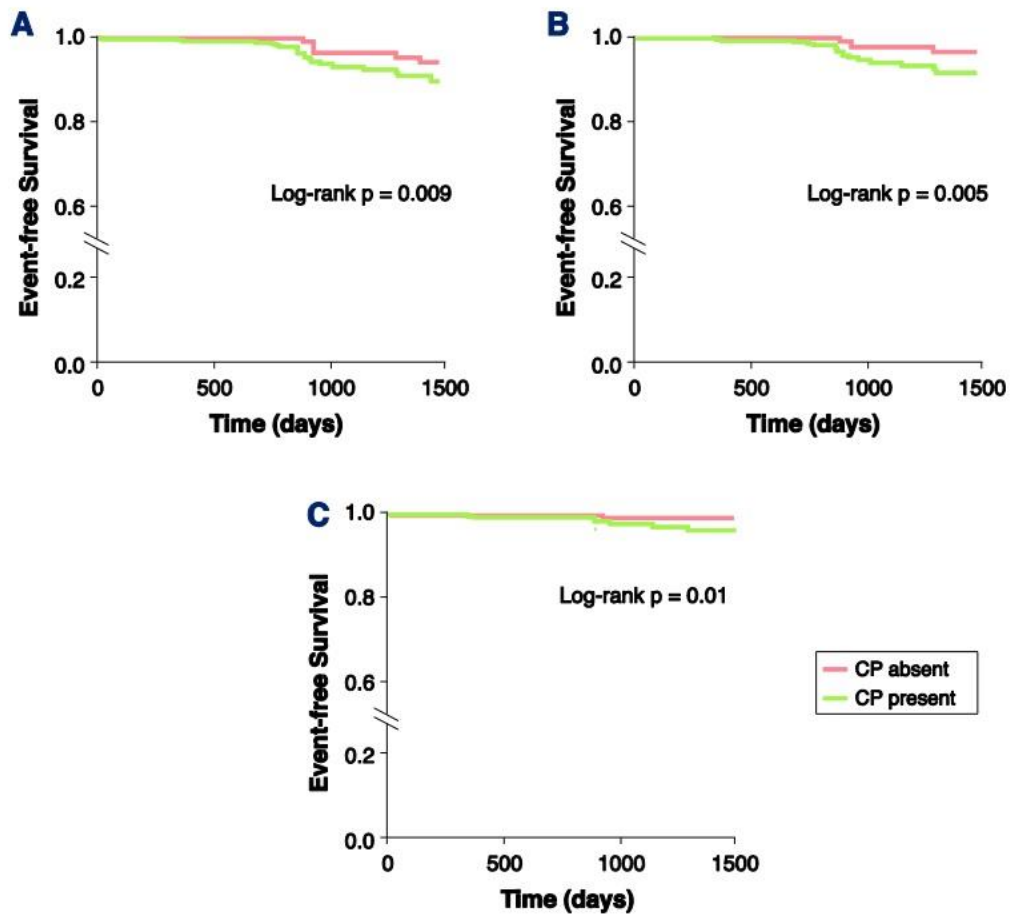


Figure 5.2. Kaplan-Meier curves based on carotid ultrasound results for the prediction of (A) major adverse events, (B) major adverse cardiac events, and (C) hard cardiac events.

CP: Carotid plaque

Table 5.6. Incidence of adverse events with combined stress echocardiography and carotid plaque results

	Normal SE, plaque absent	Normal SE, plaque present	Abnormal SE, plaque absent	Abnormal SE, plaque present	P value
MAE	6/214 (2.8%)	18/299 (6.0%)	3/23 (13%)	13/44 (29.5%)	<0.0001
Annualised MAE	0.9%	1.97%	4.3%	9.7%	
MACE	3/214 (1.4%)	13/299 (4.3%)	3/23 (13%)	13/44 (29.5%)	<0.0001
Annualised MACE	0.46%	1.42%	4.3%	9.7%	
Hard cardiac events	1/214 (0.5%)	8/299 (2.7%)	0/23(0%)	4/44 (9%)	0.022
Annualised hard cardiac events	0.15%	0.88%	0%	2.97%	

MACE: Major adverse cardiac event, MAE: Major adverse event, SE: Stress echocardiography

MAE rate/year increased from 0.9% versus 1.97% versus 4.3% versus 9.7% in patients with no plaque and normal SE vs. presence of plaque and normal SE vs. no plaque and abnormal SE vs. presence of plaque and abnormal SE, respectively (Table 5.6). Similar incremental effect was seen with MACE. Hard cardiac events were 0.15% versus 0.88% versus zero versus 2.97% respectively.

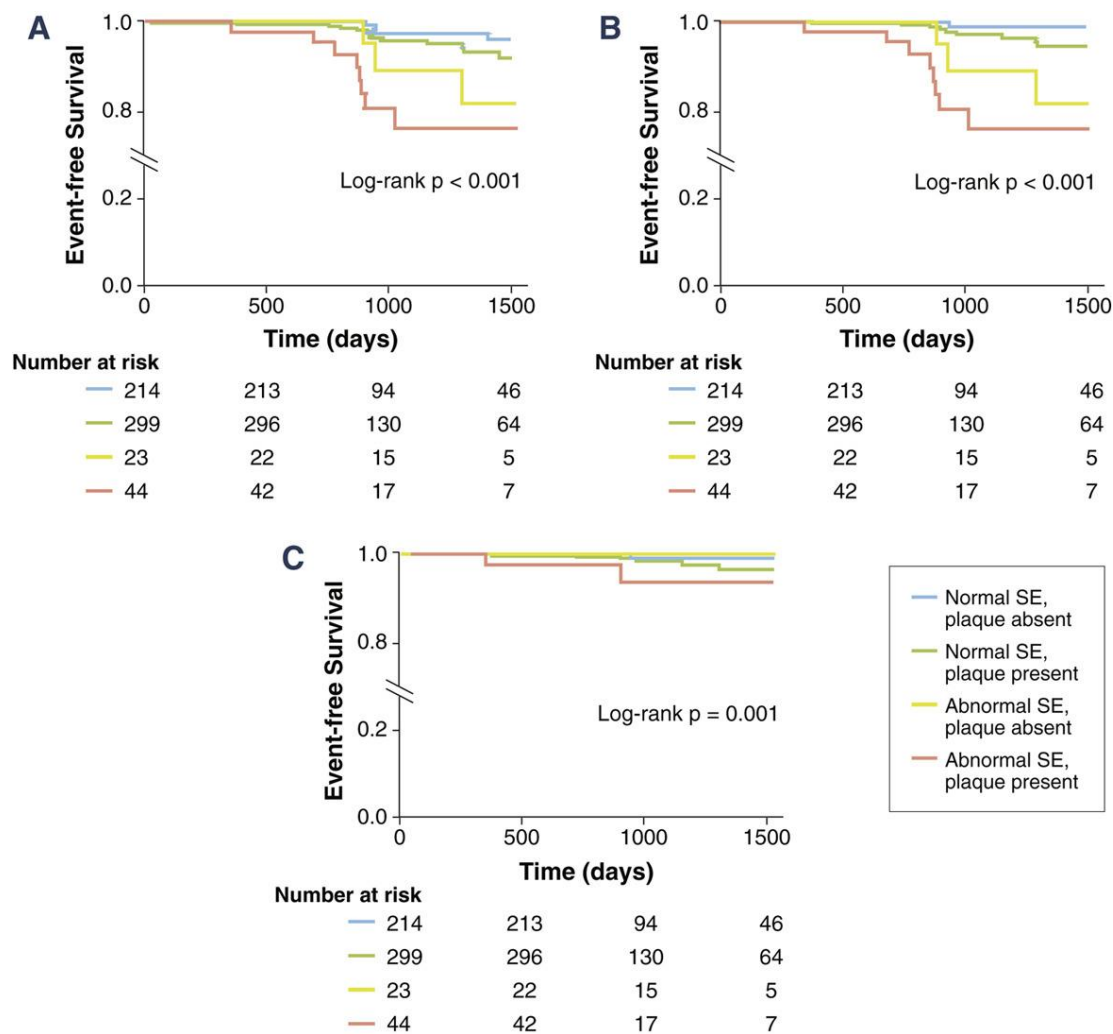


Figure 5.3. Kaplan-Meier curves based on SE and carotid plaque results.

(A) major adverse events, (B) major adverse cardiac events, and (C) hard cardiac events.
 SE: Stress echocardiography.

When prognosis was assessed in a hierarchical manner as done clinically (PTP followed by SE and CPB), it showed significant increment in global Chi-square for the prediction of MAE (Figure 5.4A), MACE (Figure 5.5A) and hard cardiac events (Figure 5.6A). Similar increments in global chi squares were observed when CPB was assessed after PTP followed by SE for MAE (Figure 5.4B), MACE (Figure 5.5B) and hard cardiac events (Figure 5.6B).

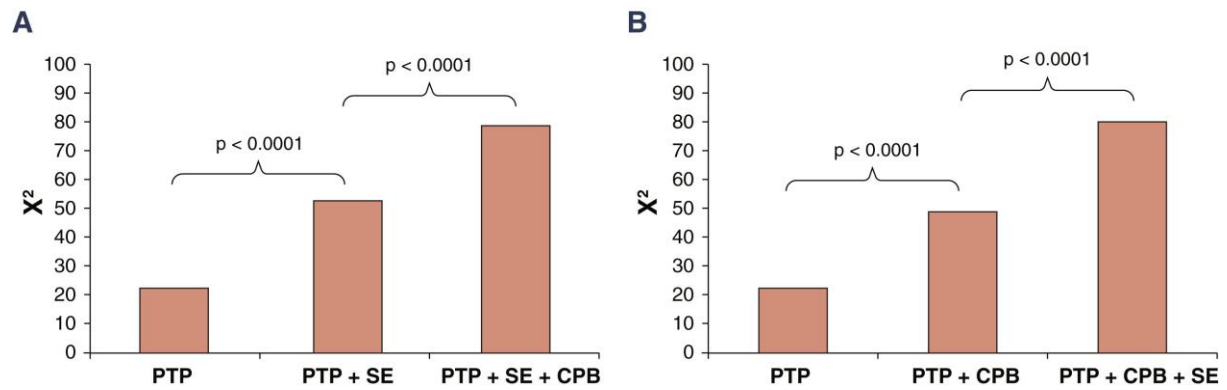


Figure 5.4. Incremental value of PTP-CAD, SE, and CPB: MAE

A. When prognosis was assessed in a hierarchical manner as done clinically (pre-test probability [PTP] followed by stress echocardiography [SE] and carotid plaque burden [CPB]), it showed significant increment in the global chi-square for the prediction of a major adverse event. B. Similar increments in the global chi-square were observed when CPB was assessed after PTP followed by SE.

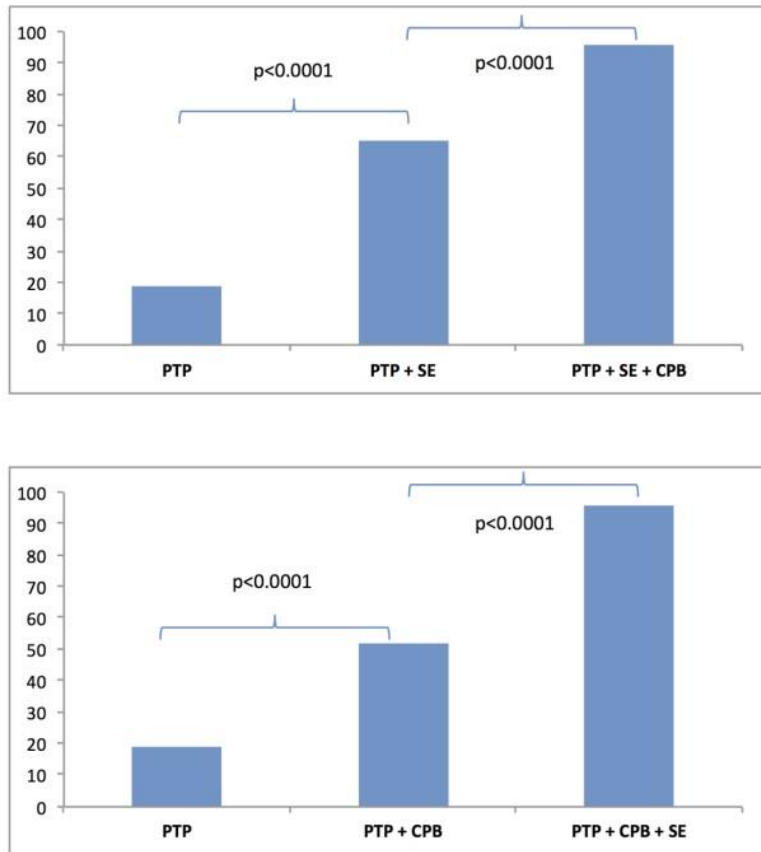


Figure 5.5. Incremental value of PTP-CAD, SE and CPB: MACE

A. When prognosis was assessed in a hierarchical manner as done clinically (pre-test probability [PTP] followed by stress echocardiography [SE] and carotid plaque burden [CPB]), it showed significant increment in the global chi-square for the prediction of a major cardiac adverse event. B. Similar increments in the global chi-square were observed when CPB was assessed after PTP followed by SE.

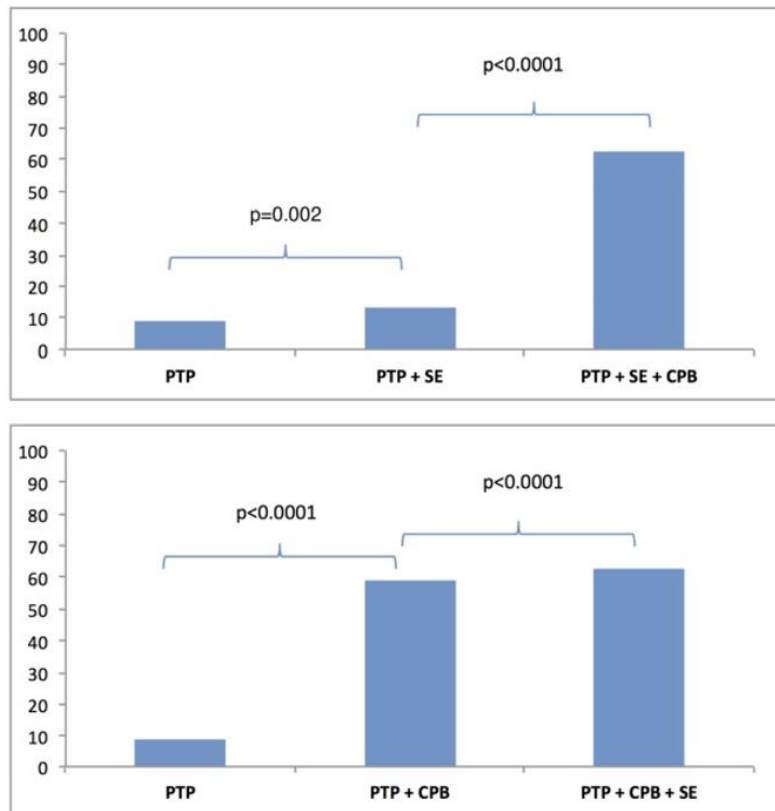


Figure 5.6. Incremental value of PTP-CAD, SE and CPB: Hard event

A. When prognosis was assessed in a hierarchical manner as done clinically (pre-test probability [PTP] followed by stress echocardiography [SE] and carotid plaque burden [CPB]), it showed significant increment in the global chi-square for the prediction of a hard event. B. Similar increments in the global chi-square were observed when CPB was assessed after PTP followed by SE

5.5 Discussion

This large prospective study was the first to demonstrate the incremental value of myocardial ischaemia and atherosclerosis assessment using US (SE and carotid US, respectively), for the prediction of MAEs in patients presenting with recent onset suspected stable angina, but who did not have a history of CAD. The study demonstrated that abnormal SE and CPB were powerful independent predictors of outcome. When clinical and imaging information for

ischaemia (SE) and atherosclerosis (US) were used in a hierarchical manner as performed clinically (clinical + SE + US), it provided stepwise incremental prognostic information. US followed by SE showed similar results confirming the incremental prognostic value of the 2 tests. The results were also replicated in the intermediate PTP group, in which testing was most warranted. In the whole cohort, MAE rates per year was 0.92% versus 1.97% versus 4.3% versus 9.7% in patients with no plaque and normal SE versus those with plaque and normal SE versus patients with no plaque and abnormal SE versus those with plaque and abnormal SE, respectively. A similar trend was observed when MACEs and hard cardiac events were assessed.

Atherosclerotic disease precedes development of flow-limiting lesions that give rise to ischemic symptoms. However, severe atherosclerotic lesions may be present without manifest disease due to positive arterial remodelling (8), and the first event could thus be death or an acute ischemic event (9). This was clearly shown in our study, that although a normal SE predicted a low annual hard cardiac event rate of approximately 0.57%, the presence of CP increased the event rate by 1.5 times, and the absence of plaque in patients with normal SE reduced it 4 times. Furthermore, because myocardial ischaemia on stress testing can occur due to causes other than flow-limiting CAD, the presence of carotid atherosclerosis indicated a high likelihood of CAD compared with those without plaque but who had ischemic SE. This study supported this concept because the presence of plaques more than doubled the cardiac event rate in patients with ischemic SE compared with those without plaques and ischemic SE.

Carotid disease, especially plaque, has been shown to predict future adverse cardiovascular events in large epidemiological studies of asymptomatic individuals (4, 10-12), and has also

been shown to reflect the presence and severity of CAD (13). The present study extended these findings by demonstrating, for the first time in a cohort of symptomatic patients, that CPB is a powerful predictor of MAEs. Although as a group, it is the plaque burden rather than mere presence of plaque that is the strongest predictor of outcome, on a per patient basis, detection of plaque appeared to define risk. For example, in this study, the hard cardiac event rate was only 0.4% in patients without plaques, but the presence of any plaque increased risk 8-fold.

The studied population was late middle-aged with no history of CAD, but this is typical in routine clinical practice. In a previous publication on the same population, we showed a strong association between the presence of CP and CAD, independent of all known risk factors (5). In a similar population evaluated with CTCA, the authors showed the prevalence of coronary atherosclerosis in 70% of patients; a finding that was similar to the present study in terms of carotid atherosclerosis (14). This study also showed that presence of noncalcified plaque in ≥ 2 coronary segments was an independent predictor of outcome.

The present study demonstrated the prognostic value of myocardial ischaemia detected by SE. The annualised hard cardiac event rate in patients with normal SE was 0.57%, which conferred a low risk, in keeping with a recent meta-analysis (15). Presence of ischaemia increased the hard cardiac event rate nearly 4-fold to approximately 2%, placing patients in the intermediate risk group, which warrants medical intervention. SE predicts spontaneous cardiac events such as death and AMI through rupture of plaques that are not necessarily at the site of coronary artery subtending the ischemic myocardium, but that are also subtending nonischemic segments (16). However, as discussed previously, coronary plaque disease may be present without the presence of myocardial ischaemia, and these plaques may be unstable.

Hence, even in the absence of ischaemia, the cardiac event rate increased 1.5 times when CP was present and decreased 4-fold when it was absent.

Similar data were obtained in an identical patient population using computed tomography coronary angiography (CTCA) for atherosclerosis assessment and SPECT for myocardial ischaemia (14). This study also showed that atherosclerosis was more prevalent than myocardial ischaemia. The presence of noncalcified coronary plaque improved prediction of outcome beyond clinical data, myocardial ischaemia, and even beyond presence of flow-limiting CAD (>50% luminal narrowing on CTCA). Furthermore, similar to our study, they showed an incremental prognostic effect when atherosclerosis data were incorporated with myocardial ischaemia assessment in the symptomatic population. In another study that combined CTCA with SPECT in a predominantly asymptomatic population, in whom stress SPECT was carried out appropriately, the authors demonstrated superior prognostication by atherosclerosis assessment over perfusion (17).

5.5.1 Clinical implications

Both the present study and previously published data (5) suggest that simultaneous assessment of myocardial ischaemia and atherosclerosis in patients presenting with suspected stable angina provide incremental prognostic information. Detection of CP is likely to have therapeutic implications. For example, if the test for myocardial ischaemia is negative, but the patient has evidence of atherosclerosis, then it could be hypothesised that such patients might benefit from aspirin and statin therapy (18-19), although a randomised prospective study to examine this theory in such patients is required. In our cohort, 28% of patients who had no

myocardial ischaemia on SE did have carotid atherosclerosis and were not on any primary preventative therapy.

The data on atherosclerosis and myocardial ischaemia that provide incremental prognostic benefit have, hitherto, been confined to patients undergoing computed tomography (CT)/SPECT or CT/PET. However, both combination modalities are costly, with a prohibitive ionising radiation dose, and both modalities are not widely available. This was the first study to show that contemporary SE (harmonic imaging with contrast use where required) and simultaneous US can not only provide similar prognostic information as radiation-based techniques, but was feasible in all patients, free of any ionizing radiation, significantly less costly, and ubiquitously available. Furthermore, unlike CT/SPECT or PET, the data of atherosclerosis and myocardial ischaemia could be provided instantly at the bedside.

5.5.2 Study limitations

This was a single centre study in which both SE and carotid images were analysed by a single (but different) reader. Although SE was reported qualitatively by an expert, US data were analysed by a recently trained operator, and the excellent inter-observer variability supported its translational outlook. The study did not assess the effects of primary prevention therapy in patients with normal SE but who had CPs. Hence, no firm conclusions could be drawn regarding the outcome of primary preventative therapy in this group of patients. The number of hard events was low (although they consisted of 50% of the primary events on which the power calculation was based). Because of relatively low mortality, this endpoint could not be individually assessed. Although 20% of patients belonged to the low PTP group, excluding

this group did not alter the data. The strength of the study was that it was large, prospective, and performed in patients who were clinically referred for SE. Carotid US was performed simultaneously. SE data were available for clinical decision making but not the carotid US result, because the latter was analysed several months later by a separate reader who did not read SE.

5.5.3 Conclusions

In patients with suspected stable angina but without known CAD, simultaneous SE (for ischaemia) and carotid US (for atherosclerosis) provided incremental prognostic value. This study supported performance of carotid US in such patients referred for SE for assessment of myocardial ischaemia because it has both prognostic importance and implications for primary prevention.

5.6 References

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Chapter 6. Study III – Long-Term Prognostic Value of Simultaneous Assessment of Atherosclerosis and Ischaemia in Patients with Suspected Angina: Implications for Routine Use of Carotid Ultrasound during Stress Echocardiography

6.1 Abstract

Background: While impact of carotid plaque on cardiovascular event is well investigated in asymptomatic epidemiological studies, long-term clinical impact of carotid plaque and its burden (CPB) in patients with new onset suspected stable angina with no history of coronary artery disease (CAD) beyond stress echocardiography (SE) is not known. We sought to investigate this with a prospective study, where patients were followed up for adverse events.

Methods: Consecutive patients referred for SE, underwent simultaneous carotid ultrasonography to assess CPB, defined as the total number of carotid plaques per patient. SE was reported off-line using 17-segments model and 4-points scale wall thickening scoring. Peak wall thickening scoring index (pWTSI) was the sum of scores of each segment divided by 17.

Results: Of the 591 patients, 573 (age 59 ± 11 , 45% male) had follow-up data. During median 7.2 years follow up, 85 patients had first MAE (all-cause mortality and acute myocardial infarction: 68 (hard events) and 17 unplanned revascularisation). On multivariate Cox regression analysis, pre-test probability of CAD ($p = 0.048$), pWTSI ($p < 0.0001$) and CPB ($p < 0.0001$) predicted major adverse events (MAE); however, only CPB retained significance

for both hard events and hard cardiac events ($p = 0.001$ and <0.0001 , respectively). MAE and hard events were least in patients with normal SE and absent carotid plaque (annualised event rate: 1.1% and 1.02%, respectively), with significant increase in normal SE and carotid plaque disease (2.4% and 2.05%, $p = 0.004$ and $p = 0.01$, respectively). Presence of plaque did not impact on these outcomes in abnormal SE cohort.

Conclusions: In patients with suspected stable angina without previous history of cardiovascular disease, carotid atherosclerosis and myocardial ischaemia detected by ultrasound provided synergistic information for the long-term prediction of events, but atherosclerosis predicted hard events beyond myocardial ischaemia, particularly in patients with a normal stress echocardiography.

6.2 Introduction

Patients presenting with suspected stable angina without prior coronary artery disease (CAD) should undergo clinical evaluation to determine the likelihood of CAD (1). An assessment of chest pain characteristics and the presence of coronary risk factors, provide pre-test probability (PTP) of CAD and future risk. Following clinical assessment, patients are considered for further testing for CAD (1). Assessment of such patients with stress echocardiography (SE) is a recognised approach to uncover myocardial ischaemia – a marker of flow limiting coronary stenosis (1). SE, through the assessment of the intensity and extent of ischaemia, also predicts risk. However, SE does not detect atherosclerosis directly, and might be normal in the absence of flow limiting CAD.

Coronary artery calcium scoring (CACS) (2-3), carotid plaque detection by ultrasound (4-6) and measurement of serum bio-markers of atherosclerosis (7) have been used in largely asymptomatic populations and shown to provide additive risk information beyond clinical risk markers, such as Framingham Risk Scores (FRS). Similar to SE, carotid ultrasound (CU) is a widely available low-cost technique, which can be performed at the bedside, and is free from ionising radiation. As there is a close association between CAD and carotid disease (8-9), the European Society of Cardiology (ESC) guideline gives CU a class 2B indication for risk stratification in patients presenting with new-onset suspected stable angina (1). While our group has published on the short-term synergistic impact of adding CU to SE (10), there is a paucity of long-term outcome data particularly related to hard events. Therefore, the aim of this study was to determine whether simultaneous CU detection of atherosclerosis could add to SE data in the prediction of long-term outcome in patients with suspected stable angina with no previous history of cardiovascular disease.

6.3 Methods

6.3.1 Study design

Consecutive consenting eligible patients, aged between 35 and 85, who were referred for SE by the attending cardiologists, were enrolled in the study (11). Ethical and institutional review board approvals were obtained. All patients underwent clinical assessment including a full history, clinical examination and ECG, followed by SE and then CU. The referring cardiologists were notified of the SE results, who retained subsequent management of the patients as part of standard clinical practice. CU results were not declared to the referring physician unless >70% carotid artery stenosis was detected.

6.3.2 Cardiac risk estimation

Pre-test probability (PTP) of CAD was calculated using clinical CAD consortium method (1), as discussed in detail under Section 3.2.2

6.3.3 Stress echocardiography

This was discussed in detail under Section 3.2.3

6.3.4 Carotid ultrasonography

This was discussed in detail under Section 3.2.4. A simplified definition of plaque, defined as focal structure intruding into the arterial lumen by ≥ 0.5 mm or > 1.5 mm in thickness

(therefore no C-IMT measurement required) was also examined.

6.3.5 Coronary angiography and revascularisation

This was discussed in detail under Section 3.2.5

6.3.6 Ascertainment of events

This was discussed in detail under Section 3.2.6

6.3.8 Statistical analysis

Variables were compared using Chi-square and Student's t-test as appropriate. Multivariable Cox regression analysis was performed to determine the independent predictors of outcome, incorporating variables with a p value ≤ 0.10 in the univariable analysis. Carotid plaque burden (CPB) defined as the number of individual plaques identified on ultrasound imaging, was used in the analysis. Kaplan-Meier (KM) survival curves were constructed to plot time-to-event outcomes, which were compared using the log-rank test. The effect of adding CPB to FRS for the prediction of cardiac hard events was evaluated quantitatively using the net reclassification improvement (NRI) (14). P values < 0.05 were considered statistically significant. Statistical analysis was performed with SPSS 22.0 (Armonk, NY: IBM Corp).

6.4 Results

Of the 591 enrolled patients, follow-up data of 573 (97%) was available. Their demographic parameters and carotid findings are summarised in Table 6.1.

Table 6.1. Baseline patient characteristics and carotid ultrasound findings of the follow-up cohort (n = 573)

Variable	
Age (years), mean $\pm$ SD	59 $\pm$ 11
Male (%)	259 (45)
Body Mass Index, mean $\pm$ SD, kg/m ²	28 $\pm$ 5
Cardiac Risk Factors	
Hypertension (%)	314 (55)
Diabetes mellitus (%)	139 (24)
Hypercholesterolemia (%)	309 (54)
Smoker (current or within last year) (%)	67 (12)
FH of premature CAD (%)	197 (34)
Drug History	
Aspirin (%)	162 (28)
Beta-blocker (%)	72 (13)
ACEi/ARB (%)	205 (35)
Statins (%)	236 (41)
Chest pain characteristics	
Non-cardiac	308 (54)
Atypical	117 (20)
Typical	147 (26)
Clinical pre-test probability of CAD, mean $\pm$ SD	19 $\pm$ 18.6
Low (%)	319 (56)
Intermediate (%)	251 (44)
High (%)	2 (<1%)

Framingham Risk Score, mean $\pm$ SD	16 $\pm$ 9.3
Low (<5%)	65 (11)
Intermediate (5-20)	303 (53)
High (>20)	205 (36)
Carotid US	
Plaque (%)	337 (59)
- Common carotid artery (%)	107 (32)
- Bifurcation (%)	299 (89)
- Internal carotid artery (%)	87 (23)
C-IMT, Mean of means	0.674 $\pm$ 0.127 mm
pWTSI	Min 1.0, Max 2.412
LV opacification	49%

ACEi: Angiotensin convertor enzyme inhibitor, ARB: Angiotensin receptor blocker, CAD: Coronary artery disease, C-IMT: carotid Intima-media thickness, FH: Family history, mm: Millimetre, SD: Standard deviation, pWTSI: Peak wall thickening scoring index

SE was abnormal in 67 (12%), whereas carotid plaque was noted in 337 (59%) of patients. Employing simplified plaque definition made no difference to plaque prevalence. CCA and bifurcation were imaged in all patients; however, in 5 patients ICA image quality precluded any measurements. Carotid plaque was most prevalent at the bifurcation (88.7% of all plaques observed). Amongst the 184 (32.1%) patients who were older than 65, plaque prevalence increased to 76% (140 patients) and abnormal SE also increased to 13.5% (25 patients). During a median follow-up of 7.2 years (2617 ± 469 days, range 17 – 3740 days), there were 85 first MAE (consisted of 68 hard-events: 36 all-cause mortality and 32 AMI, and 17 unplanned revascularisation) and 54 first MACE (5 cardiac mortality, 32 AMI and 17 unplanned revascularisation). Of the patients with abnormal SE, 32 of them had flow-limiting

CAD ($\geq 50\%$ stenosis). These patients underwent planned early revascularisation, apart from one patient who was managed medically and did not represent. Positive predictive values (PPV) of abnormal SE and presence of carotid plaque were 33% and 18.7%, respectively, for MAE, and 30% and 13% for MACE. Whereas negative predictive values (NPV) of normal SE and absence of carotid plaque were 87% and 90%, respectively, for future MAE, and 93% and 95%, respectively, for future MACE.

6.4.1 Event associations and Cox regression analysis

Traditional risk factors, age, sex, type of chest pain, clinical PTP, family history of CAD, drug therapy, planned early revascularisation (≤ 3 months), pWTSI and CPB were investigated in the univariable analysis. Any variable with $p \leq 0.1$ was entered in the multivariable Cox-regression analysis; however, when clinical PTP was a significant univariable, its components (sex, age, chest pain type and cardiac risk factors) were removed from further analysis to avoid bias. The results are shown in Table 6.2A-D.

Table 6.2. Cox regression analysis for the prediction of events

A. Major adverse events

	Univariable Analysis, p value	Multivariable Analysis, p value	HR	95% CI
PTP of CAD	<0.0001	0.048	1.628	1.003 – 2.643
Aspirin	<0.0001	0.122	1.440	0.907 – 2.287
Statin	0.002	0.395	1.230	0.764 – 1.979
CPB	<0.0001	<0.0001	1.195	1.101 – 1.298
pWTSI	<0.0001	<0.0001	4.367	2.312 – 8.250

B. Major adverse cardiac events

	Univariable Analysis, p value	Multivariable Analysis, p value	HR	95% CI
PTP of CAD	<0.0001	0.130	1.011	0.997 – 1.025
Aspirin	0.006	0.319	1.345	0.751 – 2.409
Statin	0.005	0.342	1.333	0.737 – 2.413
CPB	<0.0001	<0.0001	1.271	1.160 – 1.393
pWTSI	<0.0001	<0.0001	9.414	3.669 – 24.154
Early revascularisation	0.043	0.211	0.410	0.101 – 1.657

C. Hard events

	Univariable Analysis, p value	Multivariable Analysis, p value	HR	95% CI
PTP of CAD	<0.0001	0.018	1.015	1.003 – 1.027
Aspirin	<0.0001	0.182	1.911	0.917 – 2.548
Statin	0.004	0.310	1.312	0.777 – 2.215
CPB	0.001	0.001	1.176	1.072 – 1.290
pWTSI	0.045	0.182	1.911	0.738 – 4.946

D. Cardiac hard events

	Univariable Analysis, p value	Multivariable Analysis, p value	HR	95% CI
PTP of CAD	0.001	0.195	1.011	0.994 – 1.028
Aspirin	0.014	0.371	1.371	0.686 – 2.738
Statin	0.007	0.246	1.532	0.745 – 3.152
CPB	<0.0001	<0.0001	1.283	1.152 – 1.429
pWTSI	0.030	0.096	2.636	0.842 – 8.247

CAD: coronary artery disease, CI: Confidence interval, CPB: Carotid plaque burden, HR: Hazard ratio, PTP: Pre-test probability, pWTSI: Peak wall thickening scoring index

pWTSI and CPB were independent predictors of MAE ($p < 0.0001$ for both) and MACE ($p < 0.0001$ for both), which mainly consisted of hard events. When hard events or cardiac hard events were considered, while both pWTSI and CPB were univariable predictors for both (pWTSI: $p = 0.045$ and $p = 0.03$, CPB: $p = 0.0001$ and $p < 0.0001$, respectively), only CPB retained significance in the multivariable analysis (hard events $p = 0.008$, and cardiac hard events $p = 0.001$). Similar results were demonstrated with simplified plaque definition. PTP was an independent predictor of MAE and hard events, but not the coronary related events (MACE and hard cardiac events). Exclusion of patients with low PTP did not alter the results; pWTSI and CPB were independent predictors of MAE and MACE (SE: $p = 0.002$ and 0.001 , respectively, CPB: $p < 0.0001$ for both). CPB remained an independent predictor for hard events and cardiac hard events ($p = 0.001$ and $p < 0.0001$ respectively).

Bifurcation only plaque was more prevalent ($n = 143$, 67%) compared with non-bifurcation plaque ($n = 70$, 33%). The non-bifurcation plaque consisted of 44 CCA only, 12 ICA only and 14 patients with both CCA and ICA plaques. Patients with plaque in non-bifurcation segments experienced higher MAE compared with those with bifurcation only plaque [16/70 (23%) versus (16/143 (11%), respectively, $p = 0.025$]. CPB was not statistically different in these two sub-groups ($p = 0.75$).

We also examined SE modality (treadmill versus Dobutamine) as a univariate predicting events. Except for MACE, patients who had Dobutamine SE, had significantly higher events (MAE: $p = 0.002$, MACE: $p = 0.092$, Hard event: $p = 0.001$, cardiac hard event: $p = 0.045$). This, perhaps, reflects frailty and general status of those unable to exercise. We, therefore, did not enter SE modality in Cox-regression multivariable models.

6.4.2 Event rate and survival analysis

We assessed the value of combining SE and ultrasound results for the prediction of events (Table 6.3).

Table 6.3. Event rates and annualised event rate based on stress echocardiography and carotid ultrasound results

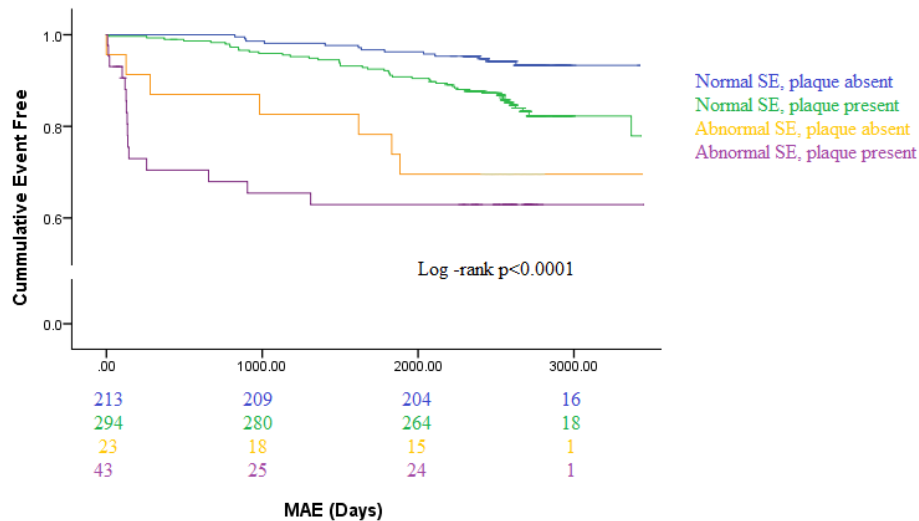
	Both normal	SE normal - plaque present	SE abnormal - plaque absent	Both abnormal	P value
MAE	16/212	47/294	7/23	15/44	<0.0001
Annualized MAE (%)	1.1	2.4	4.5	5	
MACE	6/212	28/294	5/23	15/44	<0.0001
Annualized MACE (%)	0.4	1.4	3.2	4.9	
Hard events	15/212	42/294	4/23	7/43	0.031
Annualized hard events (%)	1.02	2.05	2.50	2.34	
Cardiac hard events	5/212	23/294	2/23	7/43	0.001
Annualized cardiac hard events (%)	0.34	1.12	1.25	2.34	

MACE: Major adverse cardiac event, MAE: Major adverse event, SE: Stress echocardiography

The Patients were divided into four groups: normal SE and no evidence of plaque, normal SE with plaque present, abnormal SE and no plaque, abnormal SE and plaque present. For both MAE and MACE, there was a stepwise increase in event rates, annualised event rate changed from 1.1% to 2.4% to 4.5% to 5%, respectively ($p < 0.0001$) for MAE and from 0.4% to 1.4%

to 3.2% to 4.9%, respectively ($p < 0.0001$) for MACE. This is also shown in the Kaplan-Meier (KM) survival analysis (Figure 6.1).

A: Major adverse event (MAE)



B. Major cardiac adverse event (MACE)

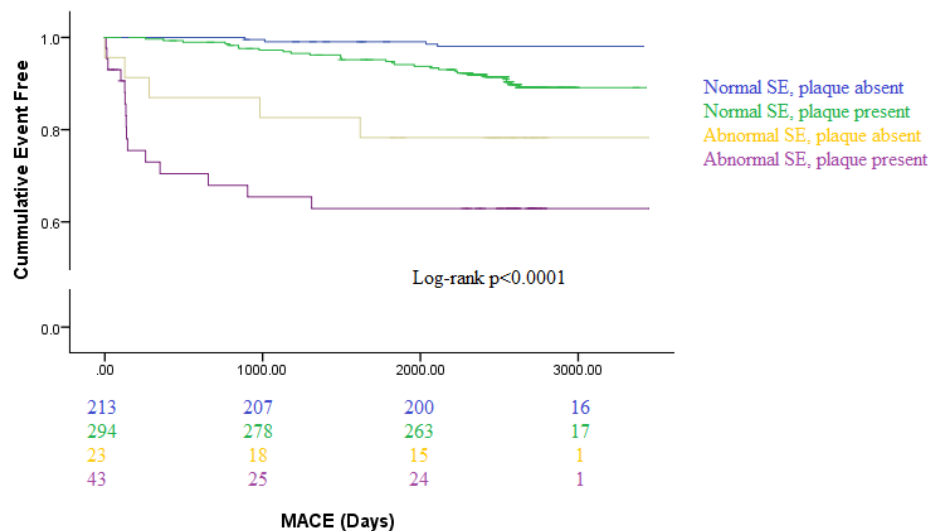
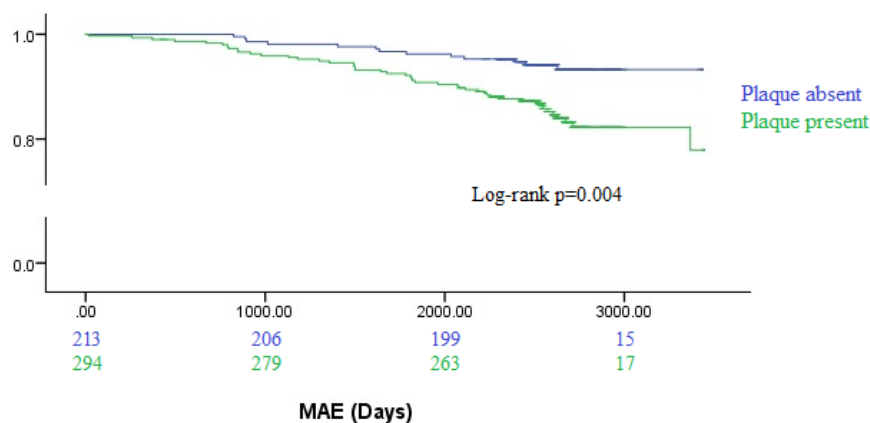


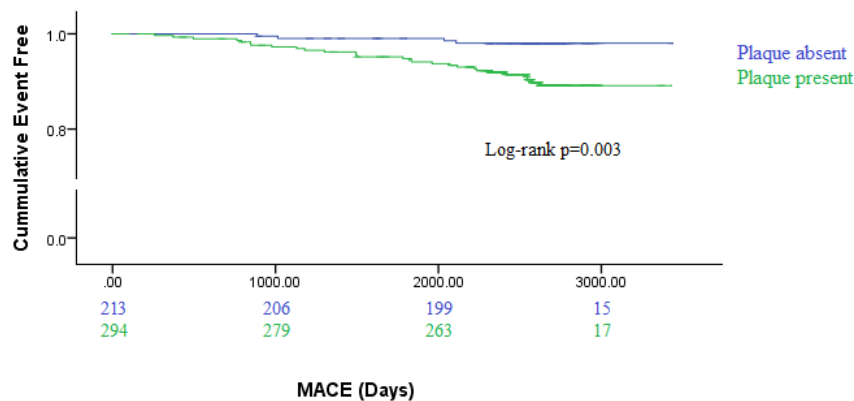
Figure 6.1. Kaplan-Meier (KM) survival analysis, according to stress echocardiography and carotid plaque status

The greatest impact of plaque was observed in patients with a normal SE, where presence of plaque increased event rates by more than two fold for MAE and by almost four fold for MACE (Table 6.3, and Figure 6.2 KM curves, $p = 0.004$ and $= 0.003$, respectively). Similar incremental values were observed in patients with a normal SE and presence of plaque for predicting hard events and cardiac hard events (Table 6.3, and Figure 6.2C-D KM curves, $p = 0.01$ and $= 0.007$, respectively). However, when SE was abnormal, plaque presence did not have a significant impact for any event categories (Figure 6.3A-D).

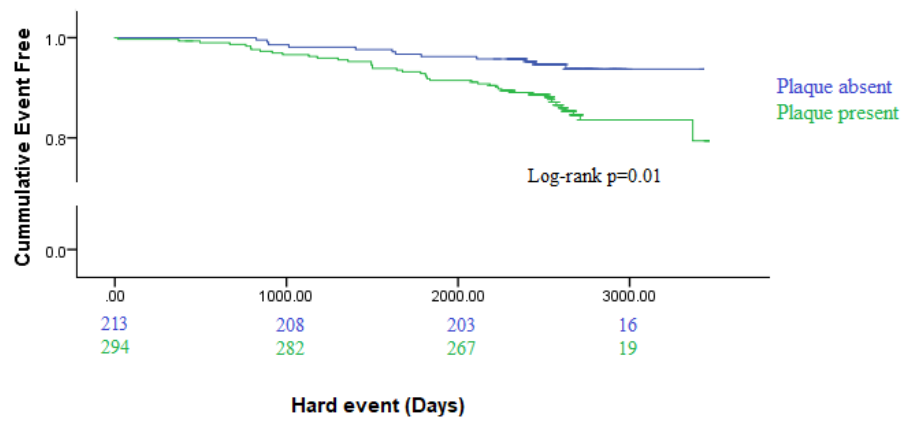
A. Major adverse event (MAE)



B. Major cardiac adverse event (MACE)



C. Hard events



D. Cardiac hard event

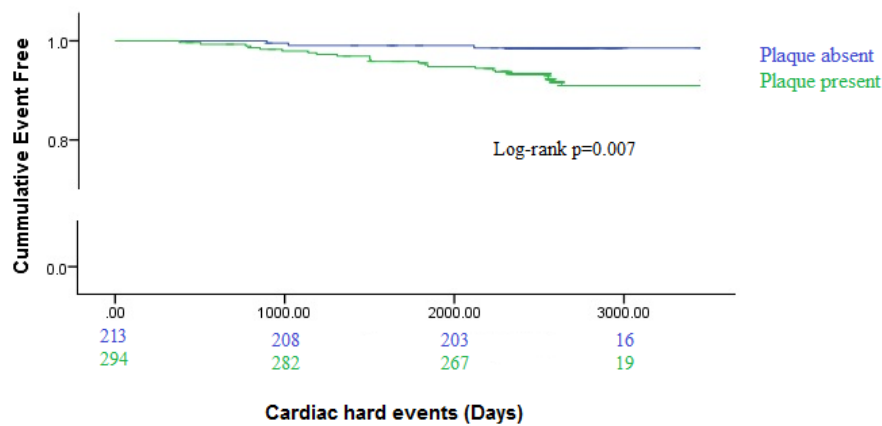
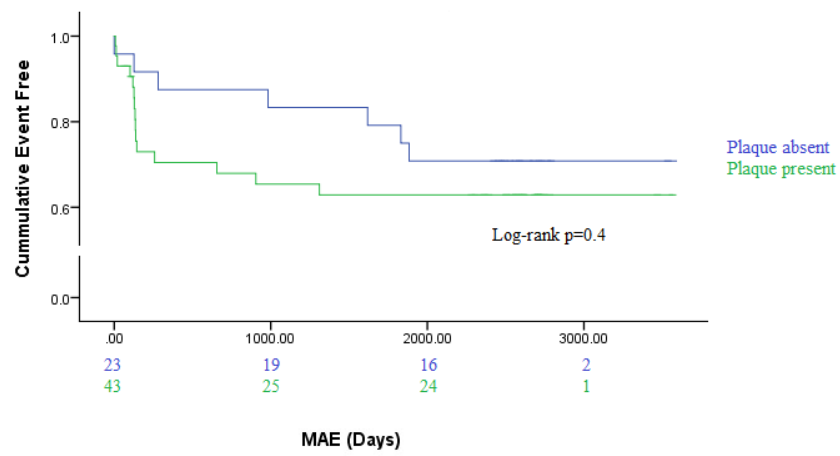
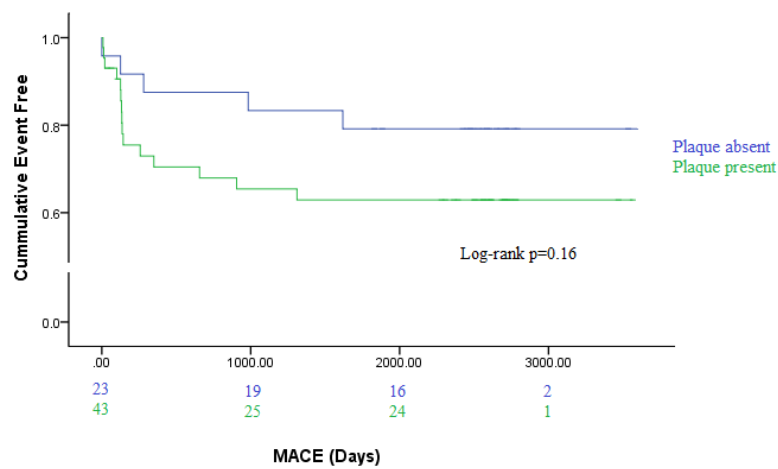


Figure 6.2. Kaplan-Meier curves. The impact of carotid plaque presence in patients with normal stress echocardiography

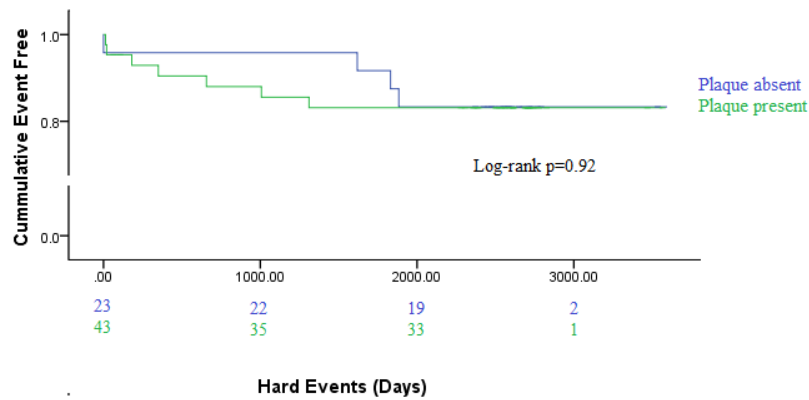
A. Major adverse event (MAE)



B. Major cardiac adverse event (MACE)



C. Hard event



D. Cardiac hard event

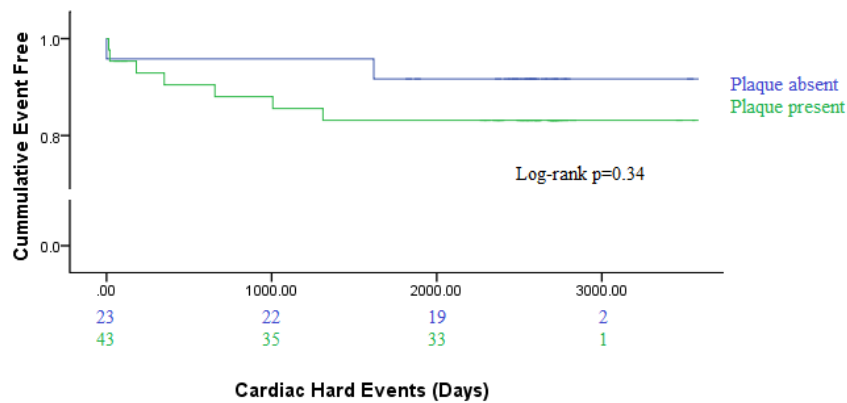


Figure 6.3. Kaplan-Meier curves. The impact of carotid plaque presence in patients with abnormal stress echocardiography

6.4.3 Relationship between increasing plaque burden and outcome

Patients were then divided into three groups (Table 6.4): Group A - no evidence of plaque (236 patients, 34.8%), Group B - between one and four plaques (282 patients, 52.5%), and Group C – five or more plaques (55 patients, 12.7%).

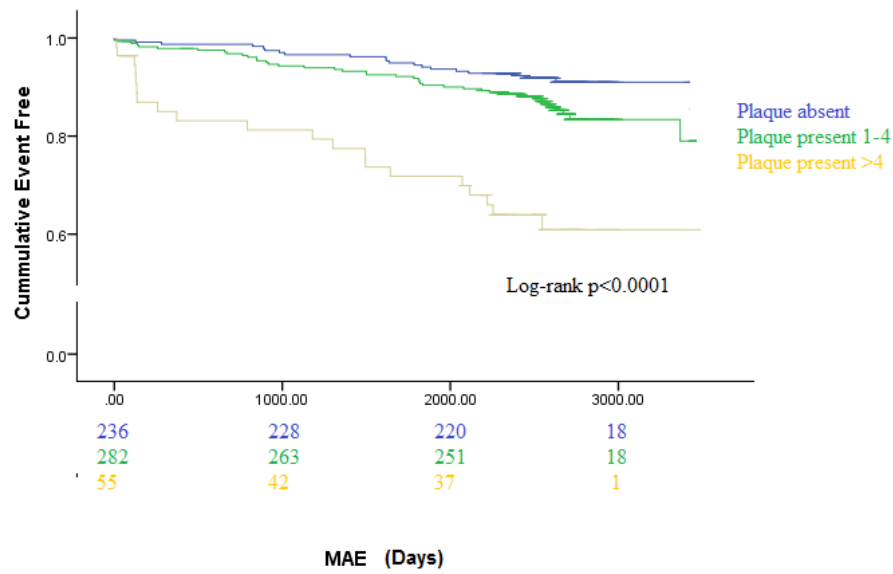
Table 6.4. Outcomes and annualised event rates in patients according to carotid plaque burden

	No plaque	Between 1-4 plaques	More than 4 plaques	P value
MAE	23/236 (10%)	42/282 (15%)	20/55 (36%)	<0.0001
Annualised MAE	1.4%	2.2%	5.4%	
MACE	11/236 (5%)	26/282 (9%)	17/55 (31%)	<0.0001
Annualised MACE	0.6%	1.4%	4.6%	
Hard events	19/236 (8%)	34/282 (12%)	15/55 (27%)	<0.0001
Annualised hard events	1.2%	1.7%	3.9%	
Hard cardiac events	7/236 (3%)	18/282 (6%)	12/55 (22%)	<0.0001
Annualised hard cardiac events	0.4%	0.9%	3.1%	

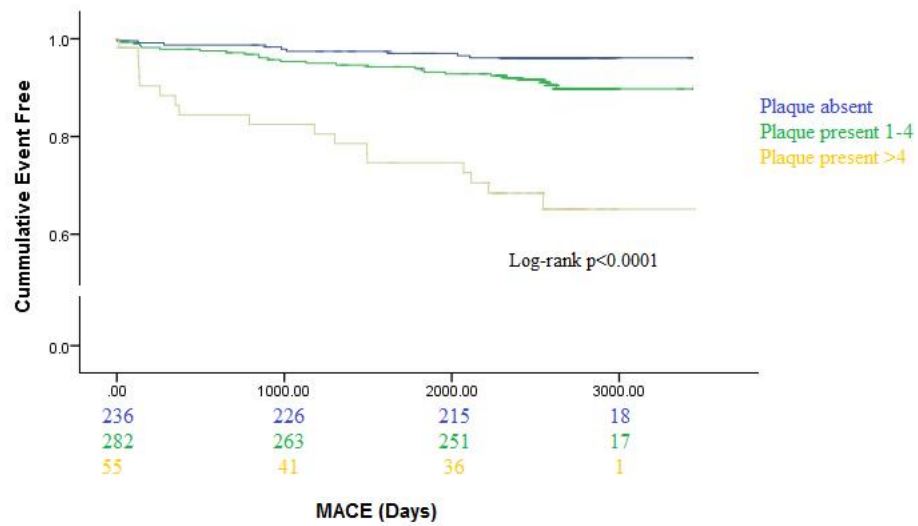
MACE: Major adverse cardiac event, MAE: Major adverse event

KM analysis (Figure 6.4) showed that patients with ≥ 5 plaques were most likely to experience MAE, MACE, hard events or cardiac hard events, compared to those with 1-4 plaques or no plaque (Log-rank $p < 0.0001$ for all).

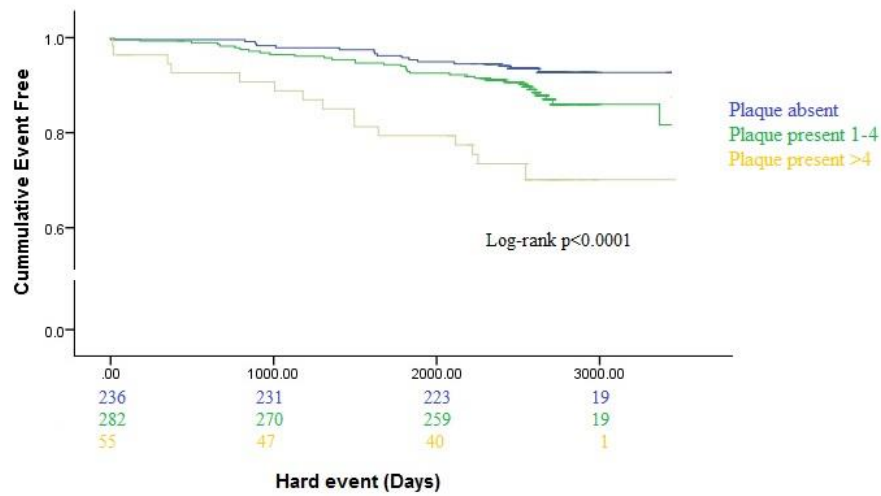
A. Major adverse event (MAE)



B. Major cardiac adverse event (MACE)



C. Hard event



D. Cardiac hard event

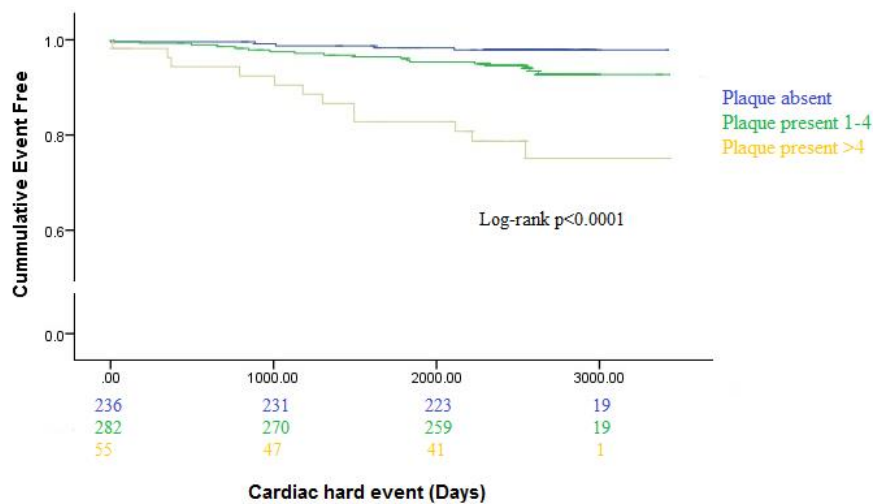


Figure 6.4. Kaplan-Meier curves depicting impact of CPB on outcomes

6.4.4 Net reclassification improvement (NRI)

Since FRS is validated for the prediction of cardiac hard events; plaque burden was assessed against FRS for only cardiac hard events by matching it with the observed outcomes, as

outlined in Table 6.5. NRI_{event} was 0.24 in patients with cardiac events and $NRI_{\text{non-event}}$ was 0.02 in patients without events. Therefore, the overall NRI was 0.26 or 26%.

Table 6.5. Reclassification of FRS categories after addition of CPB for the prediction of cardiac hard events

Original FRS	<i>Reclassified[§]</i> <i>Non-Events</i>		
	<5%	5-20%	>20%
<5%*, n	50	14	0
5-20%†, n	134	140	13
>20%‡, n	0	45	140

Original FRS	<i>Reclassified[§]</i> <i>Events</i>		
	<5%	5-20%	>20%
<5%*, n	1	0	0
5-20%†, n	5	10	3
>20%‡, n	0	1	19

* No plaque made no change, 1-4 and >4 plaques resulted in upgrade

† No plaque resulted in downgrade, 1-4 plaques made no change and >4 plaques upgrade

‡ No plaque resulted in downgrade, 1-4 and >4 plaques made no change

§ model containing Framingham risk score and Carotid plaque burden

CPB: Carotid plaque burden, FRS: Framingham risk score, NRI: Net reclassification improvement

6.4.5 FRS versus CPB in primary prevention

The relationship between FRS, CPB and preventative therapy is depicted in Table 6.6. Plaque was most prevalent in high FRS patients where 57.6% had 1-4 plaques and 20% had 5 or

more plaques. Despite low FRS in 65 patients, 21.5% had 1-4 plaques but none had ≥ 5 plaques. Most patients were not on statin or aspirin. Similarly, 49.5% of participants with intermediate FRS had 1-4 plaques and 4.6% had >4 plaques; whereas, 45.9% had no plaque. In the intermediate patients who had ≥ 5 plaques, 42.9% and 71.4% did not receive statin or aspirin therapy, respectively. Conversely, many patients in the high FRS group were treated with statin and aspirin for primary prevention with no evidence of plaque (50% and 58.7%, respectively).

Table 6.6. Relationship between FRS, carotid plaque burden and preventive therapy

	No plaque	Between 1-4 plaques	More than 4 plaques
FRS <5 (n=65)	51	14	0
Not on Statin	42	11	0
Not on Aspirin	48	13	0
FRS = 5-20 (n=303)	139	150	14
Not on Statin	99	80	6
Not on Aspirin	111	113	10
FRS >20 (n=205)	46	118	41
Not on Statin	23	59	17
Not on Aspirin	27	67	22

FRS: Framingham risk score

6.5 Discussion

To our knowledge, this is the first study in patients with new onset chest pain, without known

CAD, who underwent simultaneous stress echocardiography (for myocardial ischaemia) and carotid ultrasound (for atherosclerosis) to demonstrate that both predicted MAE and MACE over more than 7 years follow-up period. However, carotid plaque, but not abnormal SE, predicted hard end points independent of clinical history and cardiac risk factors. These results were also true in the cohort with intermediate PTP, where testing is deemed most appropriate. The lowest event rates across all categories of events were noted in patients with a normal SE and without carotid plaque, whereas presence of myocardial ischaemia conferred the worst outcome. There was a graded increase in all categories of events with increasing CPB.

Myocardial ischaemia occurs due to flow-limiting CAD. However, coronary atherosclerosis process begins long before the development of significant stenosis. The risk prediction of SE is similar to the anatomical techniques that detect flow-limiting CAD (15). However, the anatomy based computerised tomographic coronary angiography (CTCA) is also capable of detecting non-flow limiting plaques and, therefore, provide incremental value for risk prediction in the absence of inducible myocardial ischaemia. Spontaneous coronary events, like AMI and coronary death, can occur due to rupture of a coronary plaque preceding the onset of coronary stenosis, and usually there is a higher prevalence of non-flow-limiting plaques than coronary stenosis. This phenomenon was shown in the sub-analysis of the PROMISE study, where patients with chest pain without known CAD, were randomised into CTCA versus stress testing (15). The predictive value of hard events was superior by CTCA compared to stress testing. However, both CTCA and stress testing were found to have similar predictive values in patients with flow-limiting stenosis. The present study showed very similar findings, with carotid plaque, a marker of atherosclerosis. Carotid atherosclerosis, detected by ultrasound, was superior to SE for the prediction of hard events,

including cardiac events. However, the major prognostic impact of carotid plaque was seen in patients with no evidence of inducible myocardial ischaemia by SE. In patients without myocardial ischaemia, the hard event and cardiac hard event rates increased >2 fold and >3 fold, respectively, when plaque was detected. In patients with myocardial ischaemia, the presence or absence of carotid atherosclerosis had minor impact on risk prediction. It can be argued that participants with an abnormal SE were started on medication or existing treatment intensified, which in part, might have contributed to reduction in events in this group off-setting the predictive value of carotid plaque in patients with abnormal SE. It is also likely that participants with abnormal SE and no carotid plaque had detectable plaque(s) in other vessels, such as iliofemoral, where plaque is more prevalent (16-17). Generally, plaque presence had lower PPV than SE for both MAE and MACE, probably because myocardial ischaemia represented significant coronary stenosis and higher atherosclerosis burden. Absence of plaque had comparable NPV with normal SE for both MAE and MACE.

In patients with intermediate grade stenosis on CTCA, often further investigation, such as a functional test, is required to determine its haemodynamic significance. This may be achieved as a hybrid technique using SPECT or PET (18), which not only increases cost, but also non-ionising radiation burden and requires significantly longer time in terms of scanning and interpretation. On the contrary, carotid ultrasound can be performed simultaneously with SE in the same sitting with very little increase in time and cost. The present study, with hybrid SE and carotid ultrasound, is very similar to the data obtained from CT/SPECT for the prediction of outcome (18).

We observed higher event rate in a non-bifurcation plaque position. This is likely to be due to the diversity of biomechanical effects between formation, progression and rupture of plaque in different positions, for example higher wall shear stress and lower wall tensile stress in the bifurcation (19). It has been asserted that plaque formation in CCA is indicative of more advanced atherosclerotic disease, than bifurcation and proximal ICA, which are sites of non-laminar turbulent flow (6). However, our data should be approached as hypothesis generating and further studies are required to examine this finding in more details.

In CACS studies, a low event rate was demonstrated in patients with zero CACS, with graded increase when CACS was 1-400 and >400 (2-3). Similar finding was observed in our symptomatic cohort, where zero carotid plaque had a low annualized hard cardiac event rate of 0.4%, which rose >2-fold with 1-4 carotid plaques and rose further >3-fold with 5 or more plaques. However, carotid ultrasound has the benefit of being inexpensive, more readily available and free from ionising radiation. Carotid plaque is more readily detectable using the simplified definition, removing the need for special software and post-processing, which should streamline translation into clinical arena. Therefore, our data supports performing carotid ultrasound as part of patient evaluation and risk stratification, and in the event of plaque absence, highly reassuring, especially when coupled with normal SE.

We have previously reported the short-term incremental prognostic impact of carotid plaque over SE in the same cohort but the assessment of its prognostic impact on hard outcome was limited by the occurrence of only few events (10). Longer follow-up resulted in the accumulation of significantly higher hard events, which enabled us to determine the value of both carotid atherosclerosis and SE for the prediction of hard events. In this study, carotid plaque but not SE predicted hard outcomes. Because of the higher event rates, more detailed

analysis of the impact of number of carotid plaques and its location on outcome could be performed with interesting findings. Higher cardiac events rate also allowed us to investigate the effect of carotid atherosclerosis on FRS against primary prevention, which was not possible in the short-term study. Finally, the present study with larger number of events confirmed the short-term follow-up data that carotid atherosclerosis and SE provided synergistic information for the prediction of major adverse events in patients with suspected angina but without cardiac history seen even long-term which made this observation robust. Kanwar et al. were the first to report their experience of employing carotid ultrasound in symptomatic patients without known CAD, assessed by SE. However, the study population was small - 50 patients, with no follow-up data (20).

6.5.1 Clinical implications

Our study suggested that symptomatic patients with suspected CAD, following initial clinical evaluation, may first undergo SE to establish the presence of myocardial ischaemia as the cause of chest pain, as patients with an abnormal SE carry the highest risk, regardless of the presence or absence of carotid atherosclerosis. It has also been shown that patients with an abnormal SE have higher event rates, irrespective of extent of CAD (21).

However, patients with normal SE should undergo carotid ultrasound, as the presence of atherosclerosis significantly increased risk. Absence of atherosclerosis in these patients confers >3 fold decrease in coronary risk and >2 fold decrease for all risk. Those patients with no demonstrable ischaemia but with carotid atherosclerosis may benefit from primary prevention therapy. Studies have shown survival benefit when primary prevention therapies,

such as statin and aspirin, were introduced in patients with detectable atherosclerosis (22-23). For example, in one study, treatment with Atorvastatin 20 mg/day in patients with CACS >400, resulted in significant reduction in absolute risk of composite cardiovascular events (22). In our study carotid ultrasound resulted in more than a quarter increase of NRI, when compared to the traditional risk factor profiling FRS. The greatest benefit was observed in the intermediate FRS group, where 50% of patients would have benefitted from primary prevention therapy. Conversely, a significant proportion of high FRS patients had no evidence of carotid atherosclerosis but receiving such medications. However, larger adequately powered randomized studies would be required to establish the benefit or lack of benefit of treating patients with intermediate FRS and carotid atherosclerosis versus high FRS and absent carotid atherosclerosis.

6.5.2 Strengths and limitations

The strengths of this study include its prospective nature, long-term follow up (which is necessary to show the prognostic benefit of atherosclerosis versus ischaemia), and fairly large patient cohort with a sufficient number of events to allow us to draw meaningful conclusions. However, it is a single centre study. We assessed carotid plaque utilising 2-dimensional ultrasound, whereas 3-dimensional volumetric assessments could have provided a more accurate evaluation (24). We also did not analyse plaque characteristics such as echolucency and plaque neorevascularisation; the latter is clinically feasible, using ultrasound contrast agents (25), which were used in nearly half of our SE. Carotid plaque assessment employing grey-scale to detect calcium has shown significant association with flow-limiting CAD and prediction of cardiovascular event (26). However, the simplicity of carotid plaque assessment

in this study can easily be incorporated into routine clinical practice compared to more complex methodologies. We also did not assess plaques in other important arterial regions, such as the iliofemoral region.

Measuring C-IMT can be more challenging and time consuming; however, even a more simplified definition of plaque, limiting it to $\geq 0.5\text{mm}$ intrusion and thickness $>1.5\text{mm}$, offered similar outcome. This finding has similarities to the study by Polak et al (27), where several definitions of carotid plaque were assessed, including far wall IMT $>1.5\text{ mm}$ in the common carotid artery and ICA, which were incremental to FRS for the prediction of coronary artery disease events.

This was a single centre study with the inherent limitation of applying the findings more widely. A large, multi-centre study, where participants with normal SE and carotid plaque are randomised to treatment with statins or placebo will be required to further verify these findings.

6.5.3 Conclusions

In patients with suspected stable angina without previous history of cardiovascular disease, carotid atherosclerosis and myocardial ischaemia detected by ultrasound provided synergistic information for the long-term prediction of events, but carotid atherosclerosis predicted hard events beyond myocardial ischaemia, particularly in patients with a normal SE.

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Chapter 7. Study IV – Gender Based Impact of Carotid Plaque in Chest Pain Patients Undergoing Stress Echocardiography

7.1 Abstract

Background: Women with suspected angina without history of coronary artery disease (CAD) less frequently have flow-limiting stenosis (FL-CAD) and more often have microvascular disease, affecting predictive accuracy of stress echocardiography (SE) for detection of FL-CAD. We postulated that carotid plaque burden (CPB) assessment would improve detection of FL-CAD and risk stratification.

Methods: Consecutive consenting patients assessed by SE on clinical grounds for new onset chest pain also underwent simultaneous carotid ultrasound. Patients were followed for major adverse events (MAE): all-cause mortality, non-fatal myocardial infarction and unplanned revascularisation. Carotid plaque presence and burden (CPB) were assessed.

Results: After a median follow up of 7.2 years, of the 591 recruited patients, 573 (97%) outcome data (314 females) was obtainable. Despite lower pre-test probability of CAD in females versus males (14.9 ± 0.8 versus 20.5 ± 1.3 , respectively, $p < 0.0001$), prevalence of myocardial ischaemia was similar ($p = 0.08$). Females also had lower prevalence of both carotid plaque ($p < 0.0001$) and FL-CAD ($p < 0.05$). CPB improved positive predictive value of SE for detection of FL-CAD (from 34.5% to 60%) in females, but not in males. Absence of CPB in females with myocardial ischaemia ruled out FL-CAD in 93% versus 57% in

males. CPB was the only independent predictor of MAE ($p = 0.012$) in females, whereas in males both SE ($p < 0.0001$) and CPB ($p = 0.003$) remained significant.

Conclusion: In females with new-onset stable angina without a history of cardiovascular disease, carotid plaque burden improved predictive accuracy of myocardial ischaemia for flow-limiting CAD. However, carotid plaque burden provided incremental risk stratification in both sexes.

7.2 Introduction

Females presenting with suspected stable angina are less likely to have flow-limiting coronary artery disease (FL-CAD) compared with males (1-2) but have a higher incidence of microvascular disease (MVD) (2-4). These lead to lower predictive values of stress tests for detection of FL-CAD in women (5).

Carotid ultrasound (CU), a rapid non-invasive technique, can detect carotid plaque and its burden (CPB), which is closely associated with CAD (6). We have previously shown that combination of stress echocardiography (SE) and CPB improves prediction of CAD and provides synergistic prognostic information in patients with suspected stable angina but without any history of CAD (7-8) and even during longer follow-up (9). We postulated that the presence of CPB would enhance predictive value of SE for detection of FL-CAD in females with differential impact on major adverse events (MAE) - the primary end-point.

7.3 Method

Consecutive consenting patients with recent onset chest pain, who were referred for SE, were recruited (cross-sectional data previously published (7)) and followed-up long-term (8-9). Patients with known CAD, resting wall thickness abnormality, and previous carotid artery intervention were excluded. Local research ethical committee approved the study, which was funded by Northwick Park Cardiovascular Research. There was no patient involvement in the design or conduct of this research.

7.3.1 Risk assessment

Pre-test probability (PTP) of CAD was calculated using CAD consortium method, as discussed in detail under Section 3.2.2

7.3.2 Stress echocardiography

This was discussed in detail under Section 3.2.3

7.3.2 Carotid ultrasonography

This was discussed in detail under Section 3.2.4

7.3.3 Coronary angiography and revascularisation

This was discussed in detail under Section 3.2.5

7.3.4 Composite end-point

This was discussed in detail under Section 3.2.6

7.3.5 Statistical analysis

Continuous variables were expressed as mean ($\pm$ standard deviation) and categorical variables as percentages. Differences between continuous and categorical variables were compared using Student's t-test and χ^2 test, respectively. Cox-regression analysis was used to identify independent predictors of MAE. In Cox-regression model, criterion for entry of

variables was $p \leq 0.1$. The difference in risk was expressed as hazard ratio (HR) with corresponding 95% confidence intervals. Statistical significance was considered present at $p < 0.05$. Statistical analysis was performed using SPSS version 23.0 (IBM Corporation, USA).

7.4 Results

Of the 591 patients recruited, MAE data was obtainable in 573 (314 females (55%)) over a follow-up period of 7.2 years (2617 ± 469 days, range 17 – 3740), as outlined in Table 7.1. All patients had diagnostic SE and CU images. Females were older ($p = 0.009$), with more frequent family history of CAD ($p=0.02$) but less smoking habit ($p < 0.0001$). Typical angina tended to be higher in females. Other cardiac risk factors were similar. PTP of CAD was significantly higher in males than females ($p < 0.0001$), mainly driven by sex.

7.4.1 Stress echocardiography and carotid plaque burden

While there were no sex differences in incidence and extent of ischaemia, CPB was significantly lower in females (Tables 7.2. and 7.3.).

Table 7.1. Demographics of 573 participants

Variable	Male n=259 (45%)	Female n=314 (55%)	P value
Age, year $\pm$ SD	58 $\pm$ 11.8	60.5 $\pm$ 10.8	0.009
Race			0.43
Asian	154 (59.5%)	167 (53%)	
Caucasian	86 (33.2%)	112 (35.7%)	
Afro-Caribbean	19 (7%)	31 (10%)	
South Asian	1 (<1%)	4 (1.3%)	
Body Mass Index, kg/m ² $\pm$ SD	27.5 $\pm$ 4.5	28.2 $\pm$ 5.3	0.69
Hypertension	138 (53%)	176 (56%)	0.51
Diabetes mellitus	60 (24%)	79 (25%)	0.58
Hypercholesterolemia	146 (56%)	163 (52%)	0.29
Smoker	49 (19%)	18 (6%)	<0.0001
Family history of premature CAD	76 (29%)	121 (39%)	0.02
Drug History			
Aspirin	74 (29%)	88 (28%)	0.89
Beta-blocker	30 (12%)	42 (13%)	0.52
ACEi/ARB	88 (34%)	115 (37%)	0.7
Statins	117 (45%)	119 (38%)	0.09
Chest pain characteristics			0.08
Non-cardiac	150 (58%)	158 (50%)	
Atypical	55 (21%)	62 (20%)	
Typical	55 (21%)	94 (30%)	
Pre-test probability of CAD			
Basic	19 $\pm$ 1.2	13.3 $\pm$ 0.8	<0.0001
Clinical	20.5 $\pm$ 1.3	14.9 $\pm$ 0.8	<0.0001

ACEi: Angiotensin-converting-enzyme inhibitor, ARB: Angiotensin receptor blocker, CAD:

Coronary artery disease, SD: Standard deviation

Table 7.2. Results of Stress Echocardiography and Carotid Ultrasound

	Male N=259	Female N=314	P value
Abnormal stress echocardiography	37 (14%)	30 (10%)	0.08
Peak wall thickness scoring index	1.05±0.17	1.05±0.19	0.72
Carotid plaque	173 (67%)	164 (52%)	<0.0001

Table 7.3. Carotid plaque burden in females and males (p value <0.0001 for all)

	No plaque	1-4 plaque	More than 4
Female	150	143	21
Male	86	139	34

7.4.2 Composite outcome

During a median follow-up of 7.2 years, there were 86 first MAE: 36 all-cause mortalities, 32 AMI (68 hard events) and 18 unplanned revascularisations (Table 7.4.), without sex-differences in MAE ($p = 0.79$). While similar number of males and females underwent coronary angiography (62 versus 56, $p = 0.06$), fewer females had coronary intervention (19 versus 31, $p = 0.01$), reflecting lower FL-CAD prevalence in females ($p < 0.05$).

Table 7.4. Outcome breakdown

	Male N=259	Female N=314	P value
Major Adverse Event	40 (15.4%)	46 (14.6%)	0.79
Death	12 (4.6%)	24 (7.6%)	0.14
Acute	18 (9.5%)	14 (4.6%)	0.2
Coronary Angiography	62 (24.3%)	56 (17.8%)	0.061
FL-CAD	35 (13.5%)	21 (6.7%)	0.047
Revascularisation			
Any	31 (12%)	19 (6%)	0.012
Late	20 (7.7%)	13 (4.1%)	0.067

FL-CAD: Flow limiting coronary artery disease

7.4.3 Relationship between stress echocardiography, carotid plaque burden and coronary angiography

Similar proportion of two sexes underwent coronary angiography throughout follow-up (Table 7.4 and 7.5). Ischaemia was reported in 29 females, out of which 10 had FL-CAD (Table 7.5); therefore, positive predictive value (PPV) of SE was 34%. However, 15 of them had CP, out of which 9 patients had FL-CAD, PPV of 60%. On the other hand, in males 37 patients had ischaemia, 22 of them had FL-CAD (PPV = 59%), the latter only improved to 64% when CP was detected in 18 of them. Of the 29 females with ischaemia, 14 patients had no evidence of CP, of which only one patient had FL-CAD - a negative predictive value of 92.9%; whereas in males, this was only 56%. Majority of patients had no ischaemia (285

female and 222 male), of whom 27 (9.5%) females and 25 (11%) males underwent coronary angiography. FL-CAD was detected in 10 (37%) females versus 11 (44%) male patients.

Table 7.5. Results of stress echocardiography versus carotid ultrasound versus coronary angiography in males and females

Sex	SE versus Carotid Plaque			
	Normal SE, Plaque Absent	Normal SE, Plaque Present	Abnormal SE, Plaque absent	Abnormal SE, Plaque Present
Female	136	149	14	15
Angiography Normal Results	4	5	11	4
Atheroma	5	2	2	2
$\geq 50\%$	1	10	1	9
Total	10	17	14	15
Male	77	145	9	28
Angiography Normal Results	2	6	1	7
Atheroma	1	3	4	3
$\geq 50\%$	2	11	4	18
Total	5	20	9	28

SE: Stress echocardiography

7.4.4 Relationship between stress echocardiography, carotid plaque and major adverse events

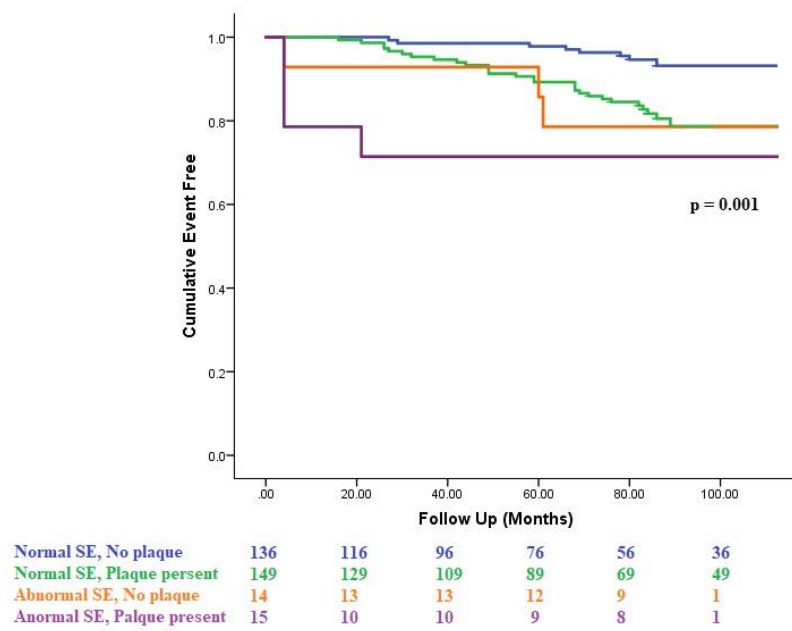
In both males and females, normal SE and no carotid plaque had similar outcome rates, and detection of carotid plaque provided comparable incremental prognostic information (Table 7.6). In both sexes, abnormal SE increased annual MAE rates, but more so in males than females. Carotid plaque was more prevalent in males patients with myocardial ischaemia versus no ischaemia ($p = 0.01$), but there was no difference in females ($p = 0.49$). However, in the presence of ischaemia, detection of carotid plaque did not influence outcome in both sexes. Proportion of males with CPB was also significantly higher compared with females in patients with myocardial ischaemia ($p = 0.04$) (Table 7.6). Kaplan-Meier curves of combination of SE result and plaque detection (Figure 7.1) demonstrate two different patterns: while in males ischaemia has the biggest impact on survival, in females it is the combination of the two methods.

Table 7.6. Major adverse event according to sex, SE and carotid ultrasound

	Normal SE, plaque absent	Normal SE, plaque present	Abnormal SE, plaque absent	Abnormal SE, plaque present	P value
Female					
MAE	11/136 (8%)	28/149 (19%)	3/14 (21%)	4/15(27%)	0.013
Annualised Rate	1.2%	2.7%	3.1%	3.8%	
Male					
MAE	5/77 (6%)	20/145 (13%)	4/9 (44%)	11/28 (39%)	<0.0001
Annualised Rate	1%	2.1%	6.8%	6%	

MAE: Major adverse event, SE: stress echocardiography

A. Females



B. Males

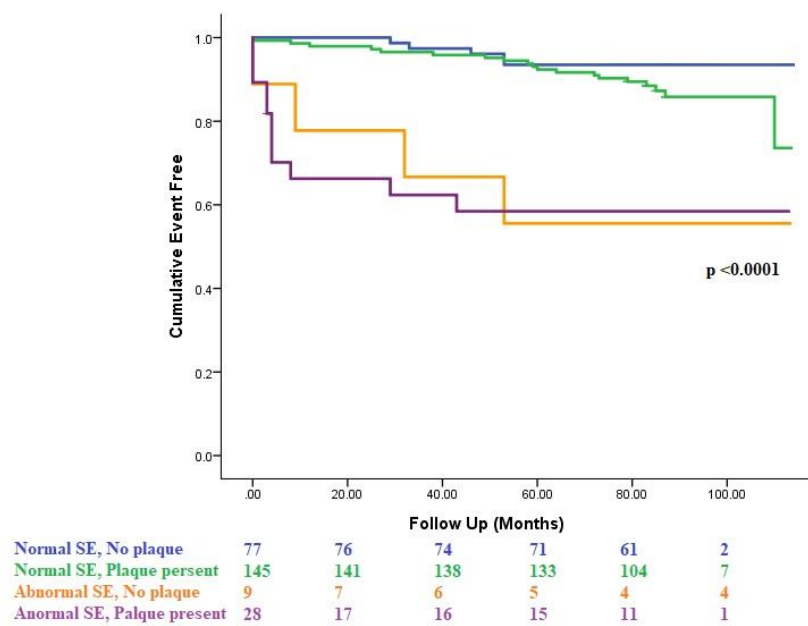


Figure 7.1. Kaplan-Meier survival event-free curves for major adverse events of females and males according to stress echocardiography versus carotid plaque results. MAE:

Major adverse event, SE: Stress echocardiography

In both sexes, current treatment with aspirin and statin, PTP of CAD, pWTSI, and CPB showed association (defined as $p \leq 0.1$) with MAE (Table 7.7). While in females, CPB was the only independent predictor of MAE ($p = 0.012$), in males ischaemia ($p < 0.0001$), CPB ($p = 0.003$), alongside treatment with aspirin ($p = 0.018$) retained significance.

Table 7.7. Cox-regression analysis of MAE in females and males

A. Females

	Univariate P value	Multivariate P value	Hazard ratio	95% CI
ASA	0.012	0.87	1.06	0.56-2.01
Statin	0.005	0.16	1.59	0.84-3.03
PTP of CAD	<0.0001	0.075	1.02	0.99-1.04
pWTSI	0.032	0.11	2.25	0.83-6.09
CPB	<0.0001	0.012	1.87	1.15-3.05

B. Males

	Univariate P value	Multivariate P value	Hazard ratio	95% CI
ASA	0.001	0.018	2.34	1.16-4.72
Statin	0.09	0.92	1.04	0.51-2.09
PTP of CAD	<0.0001	0.23	1.01	0.99-1.03
pWTSI	<0.0001	<0.0001	24.76	8.07-75.92
CPB	0.003	0.003	2.15	1.30-3.54

ASA: Aspirin, CAD: Coronary artery disease, CI: Confidence interval, CPB: Carotid plaque burden, pWTSI: Peak wall thickness scoring index, PTP: Pre-test probability.

7.5 Discussion

This is the first long-term prospective follow-up study comparing the prevalence and the clinical impact of CPB in relation to sex in patients with suspected angina undergoing SE for ischaemia assessment in patients without a history of CAD. Despite higher prevalence of family history of CAD and tendency towards higher prevalence of typical angina, females had both lower prevalence and lower extent of CPB and FL-CAD. Consequently, despite similar incidence of presence and extent of myocardial ischaemia, PPV for detection of FL-CAD was significantly lower in females versus males. Presence of CPB significantly improved prediction of FL-CAD in females but not in males. Conversely, when CPB was absent in females with myocardial ischaemia prevalence of FL-CAD was virtually absent (approximately 7%). Finally, in females CPB provided prognostic information beyond myocardial ischaemia, while in males both myocardial ischaemia and CPB provided synergistic prognostic information. The observations can be explained based on two facts- lower prevalence of atherosclerotic disease and higher occurrence of MVD in females (1-4). Lower prevalence of atherosclerosis in females accounted for lower predictive value of ischaemia for the detection of FL-CAD. Presence of CPB was associated with increased prevalence of CAD and hence improved the PPV, whilst its absence decreased probability of CAD. In males prevalence of atherosclerosis was high, thus CPB did not contribute significantly in enhancing the predictive accuracy of myocardial ischaemia for the detection of FL-CAD. The lower prevalence of FL-CAD in females also explains the fact that myocardial ischaemia in females was not an independent predictor of outcome as the majority of ischaemia was not due to CAD but likely to be due to MVD. It has been shown that patients with MVD has compromised outcome compared to a normal population but FL-CAD has the worst outcome (12). However, detection of CPB predicted outcome beyond

ischaemia in females, as it represented patients with atherosclerotic CAD. CPB was equally powerful for the prediction of outcome in males, but so was myocardial ischaemia- the latter because of higher prevalence of CAD in males.

The relative benign prognosis in females with ischaemia versus males was also shown in our study where the proportion of patients with CPB was lower in females versus males with ischaemia. This particular association in women and atherosclerosis for prediction of outcome better than ischaemia alone detected by functional tests has also been shown using Coronary Computed Tomography Angiography versus functional testing in the sub analysis of PROMISE trial (13).

7.5.1 Clinical implications

In our population, both prevalence of ischaemia and long-term MAE were low, which is similar to large studies such as PROMISE (13) and SCOT-Heart (14), where event rate were low to intermediate. The investigation modality utilised to assess such patients should also be a low-risk test, and ultrasound-based techniques have the lowest risks. This study hypothetically suggests that females should undergo simultaneous SE and carotid ultrasound. In the presence of ischaemia and CPB, one may proceed directly to coronary angiography. In the absence of CPB but abnormal SE, females can be medically managed; whereas males should undergo coronary angiography when ischaemia is detected irrespective of carotid status. However, in both females and males, presence of CP should alert the physicians to consider preventative therapy, regardless of ischaemia. However, doubtless, a larger study would be required to verify these findings and its clinical implications.

7.5.2 Limitations

This is a single-centre prospective observational study, not primarily performed to address sex-based differences. It was thus not sufficiently powered to address hard outcomes. Furthermore only 21% underwent coronary angiography but this reflected real world practice in a population where the majority demonstrated no inducible ischaemia.

7.5.3 Conclusion

In patients presenting with new-onset stable angina without a history of cardiovascular disease carotid plaque assessment improved the predictive accuracy of myocardial ischaemia for the detection of obstructive CAD in females. However, carotid plaque assessment provided incremental risk stratification in both sexes.

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PART III – DISCUSSION, CONCLUSION & FUTURE

WORK

Chapter 8. Discussion, Conclusions and future work

This thesis explored the impact of imaging carotid atherosclerosis by ultrasound in a large cohort of symptomatic individuals, who were assessed by stress echocardiography referred for new onset chest pain suspected of angina, without previous history of coronary artery disease. The hypothesis was ultrasound detection of carotid atherosclerosis (which is a marker of global atherosclerosis, including coronary arteries) will improve risk stratification beyond stress echocardiography derived myocardial ischemia assessment (especially in patients with a normal SE, as it does not exclude existence of non-obstructive CAD - the most frequent cause of coronary events).

Although carotid artery disease, which consists of abnormal C-IMT and carotid plaque, is associated with cardiovascular events, the performance of C-IMT as a prognosticator in epidemiological studies has been inconsistent. Carotid plaque, on the other hand, is a better marker of atherosclerotic burden as demonstrated in asymptomatic epidemiological cohorts compared with C-IMT. This thesis confirmed this assertion in a cohort of symptomatic patients based on prediction of adverse events; despite an association between C-IMT and prevalence of CAD, C-IMT failed to retain significance in relation to outcomes. Therefore, this study does not support C-IMT measurement on its own or as part of carotid artery disease definition in clinical practice.

While both abnormal SE and CPB were independently associated with major adverse events, both in medium- and long- term, carotid ultrasonography was incremental to SE, and it out-

performed SE in long-term for the prediction of hard events. Stress echocardiography detects ischaemia due to flow-limiting CAD, whereas presence of carotid plaque is associated with CAD, both flow-limiting and non-flow limiting. It is well documented that most coronary events occur due to rupture of such non-flow limiting plaques mostly because of its high prevalence compared to flow-limiting lesions.

This thesis also demonstrated significant proportion of patients, despite normal SE, have evidence of carotid disease and thus are at higher risk of future events. However, many of these patients, based on their Framingham risk score (FRS), would not receive primary preventative medication. Risk calculators such FRS, are population-based global risk assessment tools, whereas the result of carotid ultrasound enables physicians to make patient-specific treatment decisions, offering maximum benefit and avoiding unnecessary treatment. The 2018 American multi-society guideline on cholesterol management (1) has endorsed the use of coronary artery calcium score to guide statin therapy in people at intermediate risk: a CAC score of 0, confers a “no statin” approach (in the absence of diabetes mellitus, active smoking, or family history of premature coronary heart disease), when the score is 1 - 99, initiating statin for patients ≥ 55 years of age is reasonable and with a score of more than 100, starting statin is advocated. The present study demonstrated that the patients with no carotid plaque are at low risk; whereas, those with more than 4 plaques are at higher risk of future events, and those with 1-4 plaques are at intermediate risk. Whether by initiating primary preventative therapy, such as statin, in the two latter groups, the risk would be mitigated, and in those without carotid plaque, statin therapy can be safely avoided, requires a separate study.

The gender study advances our understanding of differences between females and males, investigated with chest pain. Though the prevalence of myocardial ischemia was similar between the two groups, fewer patients demonstrated CAD in females. In females, detection of carotid plaques added to the diagnostic accuracy of SE for the detection of CAD and improved risk stratification. However, in males, carotid plaques did not improve detection of CAD but SE and carotid plaque demonstrated synergistic effect on outcome, the impact of abnormal SE was more prominent. In females, absence of carotid plaque indicated that despite an abnormal SE outcome, most patients have no flow limiting lesion on coronary angiography. In females microvascular disease is prevalent and likely to lead into an abnormal SE and a carotid study is likely to help distinguish abnormal SE due to flow limiting CAD versus microvascular disease.

This work indicates patients with suspected stable angina, who are investigated by SE for the detection of myocardial ischaemia, benefit from carotid ultrasound to look for evidence of sub-clinical atherosclerosis: patients with abnormal SE and high CPB, are at highest risk and should be offered aggressive treatment to reduce risk, patients with a normal SE, can guide physicians to offer patient-specific risk stratification, whereas in females with abnormal SE, absence of carotid plaque, should encourage physicians to consider alternative diagnosis.

The significance of our studies has been acknowledged by the latest American Society of Echocardiography guideline (2) on the ultrasound assessment of carotid arterial plaque as demonstrated in these statements and stated: *“Recent studies suggest that carotid plaque imaging in patients with normal stress tests provides improved prognostic information: patients without plaque have an excellent prognosis, whereas patients with a normal imaging*

test for myocardial ischaemia, but atherosclerotic plaques in the carotid artery, may benefit from more aggressive medical treatment. (3-7)

The combination of carotid plaque assessment with stress testing is a promising area offering enhanced risk stratification. Further multicentre confirmation will allow for consideration of practice recommendations in the future. The writing panel calls for further development and study of application tools for the integration of carotid plaque assessment into existing risk stratification algorithms and testing.”

To translate these findings from research arena into clinical practice, echo laboratories need to invest in staff training, equipment, and software for carotid ultrasound, although cost and infrastructural change implications will be minimal.

8.1 Proposed future work

8.1.1 Quantification of Carotid Plaque

We employed a consensus definition of carotid plaque, using two-dimensional ultrasound imaging, based on presence versus absence, as well as number (carotid plaque burden). However, carotid plaque can be further analysed using more sophisticated definitions, such as grey-scale characteristic and plaque area (8-9), which can be performed using the existing acquisitions.

Prognostic impact of combining SE with carotid plaque neovascularisation and 3D-derived plaque volume assessment can be studied in new study, where patients with new onset chest pain and no history of CVD are recruited and followed up for a composite outcome of cardiac end-points.

8.1.2 Speckle Tracking Analysis of Stress Echocardiography

Stress echocardiography is often criticised for its reliance on expert opinion. Speckle tracking, a novel technique in quantitative assessment of cardiac function, has been employed to assess regional and global left ventricular function (10). While it has been employed in reporting stress echocardiography (11-12), there is paucity of data in regards to follow up data. One obstacle has been the use of micro-bubble contrast. However, it has been shown that use of contrast has no impact on speckle tracking and may even improve image quality for speckle tracking (13). In our cohort, such enhancement was used in under 50% of the subjects. This would form a sizable database, one group with and another without contrast, allowing analysis of stress echocardiography quantitatively and investigating its association with outcome measures, on its own, as well as together with carotid atherosclerosis.

8.1.3 Hypothesis Generating for future studies

In this study, there was more than a quarter increase of net reclassification index (NRI) when carotid ultrasound result was added to Framingham Risk Score (FRS). The greatest benefit was detected in patients with intermediate FRS, where 50% of patients perhaps would have benefitted from primary prevention therapy. However, an adequately powered randomised

study would be required to investigate the impact of treating patients with intermediate FRS and evidence of carotid atherosclerosis and high carotid plaque burden.

It was also observed that in females, absence of carotid plaque, despite abnormal stress echocardiography, significantly reduces the likelihood of flow limiting CAD. This observation can be further investigated in a large study and if proven, will aid physicians to avoid unnecessary downstream invasive investigation.

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Part IV – Appendix

Chapter 9. Editorial

1. Editorial of Study II, Chapter 5: Stress Echocardiography, Carotid Arteries, and More: Its Versatility for Our Imaging Times
2. Editorial of Study III, Chapter 6: “Sound” Advice - Let’s “Stress” the Importance of Prevention: Combining Carotid Ultrasound and Stress Echocardiography for Cardiovascular Risk Assessment

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