



High calcium scores in patients with a low Framingham risk of cardiovascular (CVS) disease: implications for more accurate CVS risk assessment in New Zealand

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Abstract

Aims New Zealand (NZ) patients are recommended to undergo an 'adjusted' Framingham score to assess their cardiovascular (CVS) risk. The current (2009) NZ CVS Risk Guideline does not recommend the use of a 'calcium score' as an additional risk tool, although it has been shown to be powerfully predictive of CVS events above the predictive power of traditional Framingham risk factors. Calcium scores of >400 are very strongly predictive of a future CVS event and give direct evidence of atheromatous disease in the coronary circulation. Identification of people with advanced, premature coronary atheroma would allow early treatment of those who may benefit from more vigorous preventative strategies, including statin therapy.

Methods Using a prospectively acquired, comprehensive database we audited the first 1000 patients (7 August 2006 to 28 November 2008) to undergo a 64-slice computed tomographic (CT) cardiac angiogram (GE Light Speed), which included a scan for a 'calcium score', at the Mercy Hospital, Auckland. We excluded 58 patients who had experienced one or more of a previous myocardial infarction (MI) (n=21), coronary artery bypass graft (CABG) surgery (n=15), percutaneous coronary intervention (PCI) (n=13) or stroke (n=21) and who therefore already had definite evidence of vascular disease and would be automatically placed in a high risk strata. We calculated each patient's Framingham risk from the original 'Anderson' equation, used by the 1996 NZ CVS risk Guideline, and the 'adjusted' Framingham 5-year CVS risk using the NZ Guidelines Group 2003/2009 recommendations, and then compared this with the observed calcium scores.

Results The mean patient age was 56 (SD 9) years; 364 (39%) patients were female, 82% patients were Caucasian. 41% were current (4.6%) or previous (36%) cigarette smokers, 35% had a history of hypertension, 44% hyperlipidaemia and 5.6% had diabetes mellitus. The percentage of patients at 'low' 5-Year CVS risk (0-10% 5-year risk), using the 1996 and 2003/2009 guideline methods, was 78% and 58% respectively. Of patients in these Framingham 'low-risk' groups, 10% and 8.8% had a calcium score of >400 Agatston units, indicating that they were actually at very high CVS risk, and 203 (28%) and 147 (27%) respectively had a calcium score of >100 Agatston units, indicating that they were actually at 'high risk' and not 'low risk'.

Conclusion Approximately 10% to 27% of patients with a low CVS risk as assessed by the established Framingham equation have a markedly increased calcium score and hence a significantly increased risk of a CVS event. Currently promoted methods of risk assessment may be inadvertently, falsely re-assuring these patients. Clinicians

managing patients may consider a calcium score as an additional tool to the standard risk assessment strategies.

The traditional method of assessing cardiovascular (CVS) risk has been to measure baseline factors in an intermediate-sized cohort of a general population and, after some years, to then estimate which factors are subsequently found to be predictive of CVS events.

The Framingham epidemiological study pioneered many of the methods commonly used in risk estimation,^{1,2} and these have been widely used for the assessment of CVS risk. The major and independent CVS risk factors demonstrated by Framingham are cigarette smoking, elevated blood pressure, elevated serum total cholesterol and low-density lipoprotein cholesterol, diabetes mellitus, male gender and advancing age³.

Other studies have been conducted using different population cohorts, such as the larger Prospective Cardiovascular Munster (PROCAM) project⁴ which enrolled German industrial employees and included additional potential risk factors. From these epidemiological studies, a variety of calculations have been developed to try to predict the risk of a CVS event.

Another important method of assessing CVS risk is to use an individual's family history of CVS disease, particularly a family history of 'premature' CVS disease (first degree relatives: male <55 years, females <65 years), which approximately doubles the risk for an individual.⁵ A range of 'biomarkers' have also been shown to help define CVS risk in a population, including, homocysteine levels and lipoprotein (a).⁶ Inflammatory markers, which recognise that atherosclerosis is an inflammatory disease⁶ are also useful at assessing risk, with the 'highly sensitive' C-reactive protein (CRP) being widely studied, to date.⁷

'Thrombogenic' risk factors have also been assessed, with the serum fibrinogen level being particularly predictive of CVS risk⁸. Ethnic characteristics have also been assessed outside of the Framingham study, who were largely of white European descent, with the absolute CVS risk of Indians and Pakistanis living in a western society being about twice that of the white European population.⁹ In addition, Māori age-specific rates of death from CVS disease are two to three times higher than non-Māori in those aged less than 75 years of age in the New Zealand population.¹⁰

Further, psychosocial factors have more recently been demonstrated to have a significant impact on the CVS risk of a population.¹¹ However, with all of these additional risk factors which have been modelled and validated in a variety of populations, there is, as yet, no general agreement as to how they should be included in the CVS risk stratification dataset for daily clinical use.

The development of CT cardiac angiography (CTCA) has been a significant, recent medical development which now allows for direct, non-invasive imaging of an individual's coronary arteries. This ability to assess both the lumen, and also the degree of calcification and atheroma within the walls of the coronary arteries has brought a new dimension to CVS risk assessment. Intuitively, it would seem that there would be a major advantage in being able to determine the amount of atheroma which is *actually* present in an individual's coronary arteries, and with this, a better ability to predict risk.

The amount of calcification in the coronary artery walls, as assessed by the Agatston 'calcium score'¹² has been shown to be highly predictive of CVS risk. A calcium score of ≥ 100 conferred a 10-fold increase in risk, in the St Francis Heart study of 4,613 asymptomatic people followed for 4.3 years compared with a calcium score of 0.¹³ Further, the coronary calcium score alone was superior to the Framingham Risk Score at predicting CVS events (area under the receiver-operating characteristic [ROC] curve of 0.79 ± 0.03 vs 0.69 ± 0.03 , $p=0.0006$), and enhanced the stratification of those falling into the Framingham categories of low, intermediate, and high risk ($p < 0.0001$).

We reviewed the first 1000 patients undergoing a CT cardiac angiogram, which included a calcium score, at the Mercy Hospital in Auckland. We wished to calculate patients' baseline 'CVS risk', as assessed by the previous [1996¹⁴] and current [2003/2009^{15,16}] New Zealand Guideline recommendations, and the patients' actual calcium score, to determine if some apparently 'low risk' patients were actually 'high-risk', and were inadvertently being falsely reassured about their personal CVS risk.

Methods

Data collection—A prospective audit of all patients presenting for computed tomographic (CT) cardiac angiogram was performed. Data were prospectively collected by a practice nurse using a standardised data collection sheet from 07 August 2006 until 28 November 2008.

The data collection form recorded patient demographics, personal and family history, medication use and the results from the CT cardiac angiogram and the calcium score. Referrals from cardiologists in Auckland were of patients principally with equivocal exercise test changes, and/or equivocal symptoms.

All CT cardiac angiograms, including the calcium score, were performed by one of three radiographers using a standardised procedure for the 64-slice CT machine (GE Light Speed). The calcium score was derived according to the method of Agatston,¹² with these details incorporated into the CT machine.

All patients gave informed consent to undergo the clinical investigation as a part of their clinical management. As an audit of current practice, individual patient consent was not required for this study.¹⁷

Framingham CVS Risk Scores—The 5-year risk of a CVS event was calculated using two models. The first model was the basic model of Anderson^{1,2} developed using data from the Framingham study with the equation then used in the 1996 New Zealand Guidelines.¹⁴ This model was significantly extended for New Zealand conditions by the New Zealand Guideline Group (NZGG) in 2003¹⁵ and minimally changed again in 2009.¹⁶

For the basic model, in 1990^{1,2} Anderson et al used data from 5573 subjects in the original and 'offspring' Framingham Heart Study, aged 30 to 74 years. Requirements for inclusion were 1) age 30 to 74 years at the time of baseline examination (from 1968 through 1975); 2) measurements were available for systolic blood pressure (SBP), diastolic blood pressure (DBP), cigarette smoking status, total and high-density lipoprotein (HDL) cholesterol, and the diagnosis (yes or no) of diabetes mellitus, and electrocardiogram (ECG) criteria for left ventricular hypertrophy (LVH); and 3) freedom from CVS disease (stroke, transient ischaemic attack (TIA), coronary heart disease (CHD) [angina pectoris, unstable angina, myocardial infarction (MI), and sudden CHD death], congestive heart failure, and peripheral vascular disease (intermittent claudication) until the time of risk factor measurement.

These criteria were also the CVS 'endpoints' used in Framingham. The basic Framingham equation used to predict these events incorporated patients' age, gender, total and HDL-cholesterol, SBP, DBP, smoking, diabetes, and ECG-LVH. The equation allowed CVS risk to be determined from 4 to 12 years into the future.

In 1996, the New Zealand Guidelines group developed the CVS risk stratification charts which simplified access to the Framingham risk calculation by the (now familiar) coloured, graphical approach.¹⁴ Although the 1993 New Zealand dyslipidaemia guidelines¹⁸ used a '10-year' CVS risk

period (along with most International Guidelines), a 5-year CVS risk figure was subsequently adopted in 1996

In 2003, in response to criticism that the New Zealand 1996 Framingham equation did not account for individuals that were obviously at high risk, a set of additional risk factors was formed (Table 1) which permitted a one off 5% increase in the risk estimate in those individuals which had at least one of these risk factors¹⁵. Very minor changes were then made by the New Zealand Guidelines group in 2009¹⁶, with the CVS risk assessment being the same, except that 'metabolic syndrome' was removed from the 'additional risk factors' which could give an extra 5% risk, and diastolic blood pressure values were no longer a feature of the coloured charts (the systolic blood pressure was always the parameter actually used in the equation). The NZGG still opted for a 5-year CVS risk time scale.

Table 1. Variables included in CVS risk prediction models

Variables	Framingham Anderson	NZGG Framingham Ad Hoc Adjustment
Guideline Publication	1996	2003/2009
Age	Yes	Yes
Gender	Yes	Yes
Diabetes	Yes	Yes
Smoking Status	Yes	Yes
Total Cholesterol/HDL Cholesterol	Yes	Yes
Systolic blood pressure	Yes	Yes
LVH	Yes	No
A 'one off' 5% increase if one of the following is present		
Family history of premature coronary heart disease or ischaemic stroke in a first-degree male relative before the age of 55 years OR a first-degree female relative before the age of 65 years		Yes
Māori OR Pacific* OR people from the Indian subcontinent		Yes
People with both diabetes and microalbuminuria		Yes
People who have had type 2 diabetes for more than 10 years OR who have an HbA1c consistently greater than 8%		Yes
People with the metabolic syndrome		Yes
IF Total Cholesterol >8 then risk >15%		Yes
IF Total Cholesterol/ HDL >8 then risk >15%		Yes
IF BP consistently >170/100 then risk 15%		Yes

* Mostly of Samoan, Tongan, Niuean, or Cook Islands origin.

Statistics—Continuous data are summarised as median and interquartile range or mean and standard deviation as appropriate. Differences in frequencies were tested using Chi-squared procedures or Fisher's exact test as appropriate and differences between groups in continuous variables using the Wilcoxon independent groups test. SAS software (SAS Institute Inc, v9.1) was used to perform the analyses. All tests were two-tailed and a 5% significance level was used.

Results

We examined the first 1,000 patients undergoing CT cardiac angiography and a calcium score at Mercy Radiology, Auckland. We excluded 58 patients with one or more prior CVS events [previous MI (n=21), CABG surgery (n=15), PCI (n=13) or stroke (n=21)], and assessed 942 patients for their CVS risk.

Patient demographics—The mean patient age was 56 (SD 8.9) years, 364 (39%) patients were female, 82% were Caucasian. 381 (40%) were current (4.6%) or

previous (36%) smokers, 35% had a history of hypertension, 44% hyperlipidaemia and 5.6% had diabetes mellitus (Table 2).

Table 2. Baseline patient demographic data (n=942)

Variables	Values
Mean age [years] (SD)	56 (8.9)
Sex (female)	364 (39%)
Ethnicity	
Caucasian	776 (82%)
Māori	16 (1.7%)
Pacific	11 (1.2%)
Indian	45 (4.8%)
Asian	27 (2.9%)
Not reported	30 (3.2%)
Others	37 (3.9%)
Smoking	
Current	43 (4.6%)
Previous	338 (36%)
Never	559 (59%)
Not reported	2 (0.2%)
Hyperlipidaemia	416 (44%)
Hypertension	326 (35%)
Diabetes mellitus	53 (5.6%)
Family history of 1st-degree relative with CVS disease	449 (48%)

The distribution of total calcium scores is shown in Figure 1. 319 patients (34%) had a coronary circulation free from calcium, using the Agatston technique (12). 112 patients (12%) had scores >400 and are considered to both have considerable calcium deposition in the coronary circulation and to be at 'very high' risk of a vascular event.

Figure 1. Frequency distribution of total calcium scores (n=942)

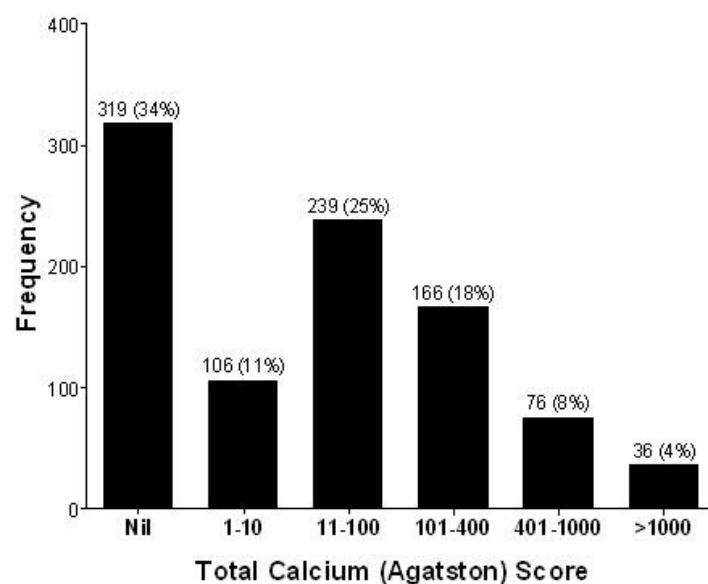
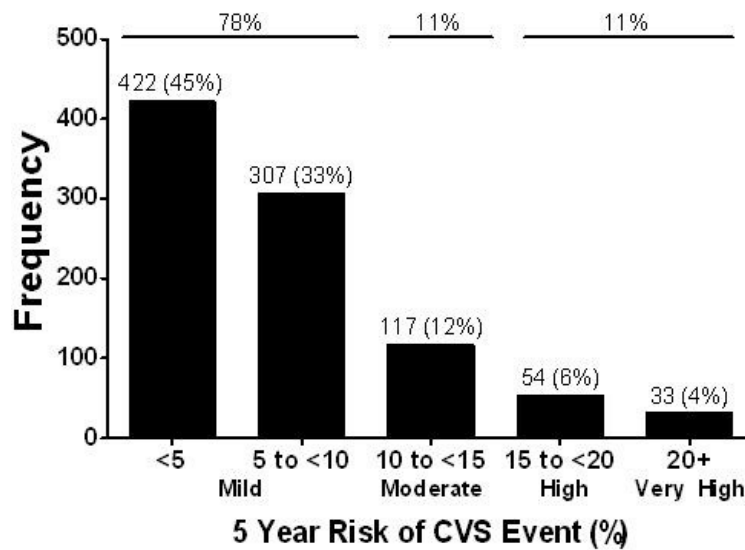
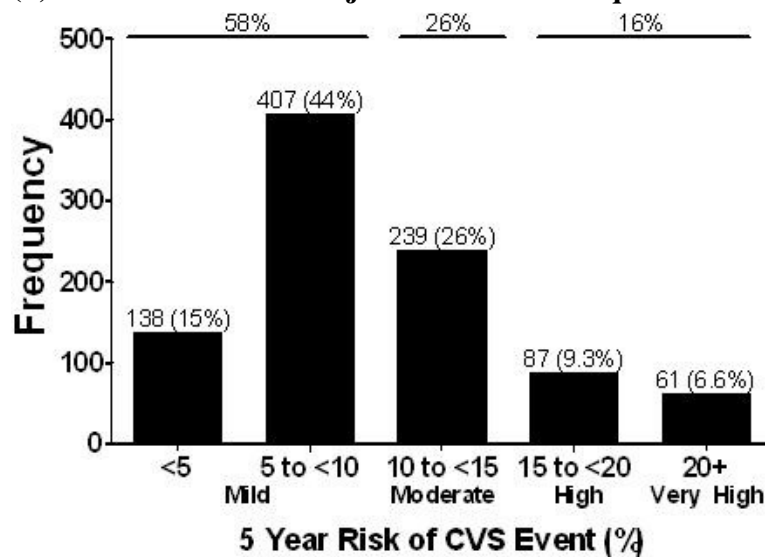


Figure 2. Framingham Risk Scores of Cohort (n=942):
(a) 1996 NZGG original Anderson equation



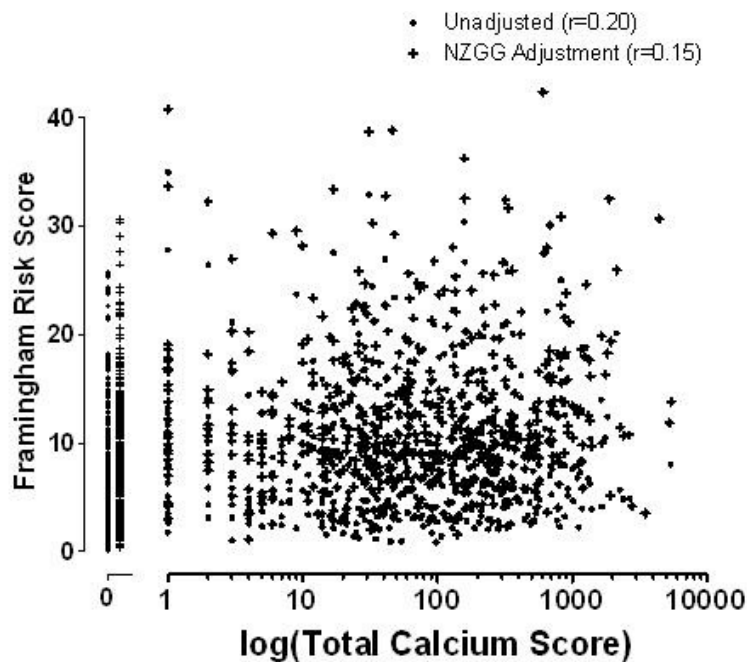
(b) 2003/2009 NZGG 'adjusted' Anderson equation



The distribution of CVS risk scores (Figure 2a) shows that 45% of patients were predicted to be at 'very low' (<5%) and 4% of patients at 'very high' (>20%) CVS risk within 5 years, using the 1996¹⁶ NZGG method, and 15% and 6.6% respectively using the 2003/2009 NZGG adjustments (Figure 2b).

Agreement between risk predictors and total calcium score is shown in Figure 3. There is a statistically significant ($P < 0.0001$), although poor correlation (Spearman) between total calcium score and the NZGG (1996) unadjusted ($r = 0.20$) and NZGG (2003/2009) 'adjusted' ($r = 0.15$) Framingham 5-year CVS event risk.

Figure 3. Correlation between Framingham risk score ('Anderson' NZGG 1996 unadjusted, and with NZGG 2003/2009 adjustments) and total calcium score

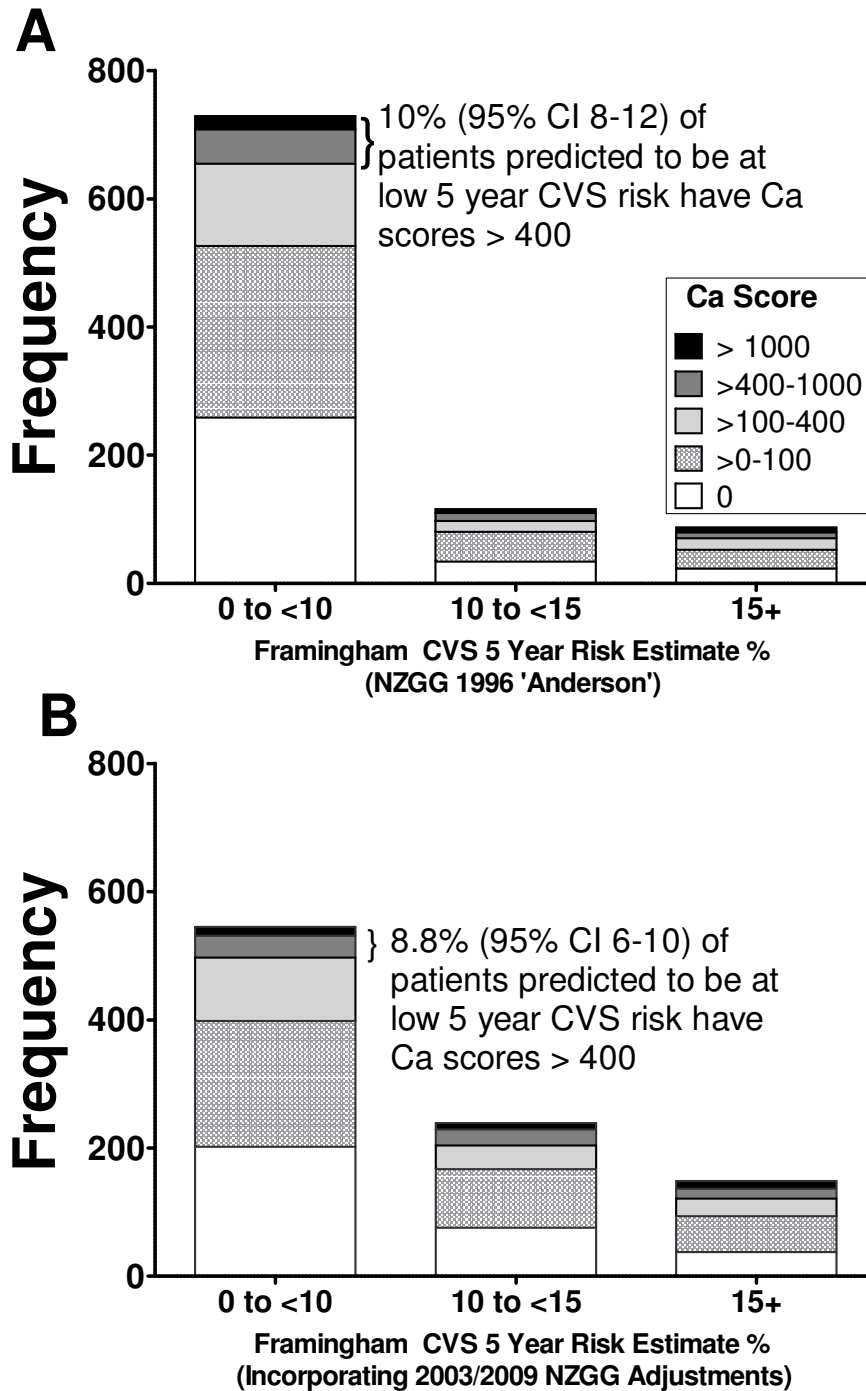


There is a wide spectrum of Framingham CVS risk scores in those with a total calcium score of zero. Similarly of the 110 patients with total calcium scores >400, 83 patients had an adjusted Framingham risk score <15% (including 48 patients <10% and 10 patients <5%). Reducing the unadjusted five year risk estimates to bands of risk: low (0-10%), moderate (10-15%) and high risk (>15%) showed 10% of patients calculated to be at low risk of a CVS event in five years to have total calcium scores in excess of 400, indicating very high risk (Figure 4). Application of the NZGG (2003/2009) adjustment reduced this to 8.8%.

Hoff¹⁹ has provided age and gender-specific percentiles for total calcium score. In our patient group of 942 patients, 109 (12%) had total calcium scores above the 90th percentile for their age and gender, placing them at increased CVS risk, yet they had the same median adjusted Framingham risk score (9.0 [IQR 7.2, 12.0] v 8.7 [IQR 6.2, 12.7 P=0.35]).

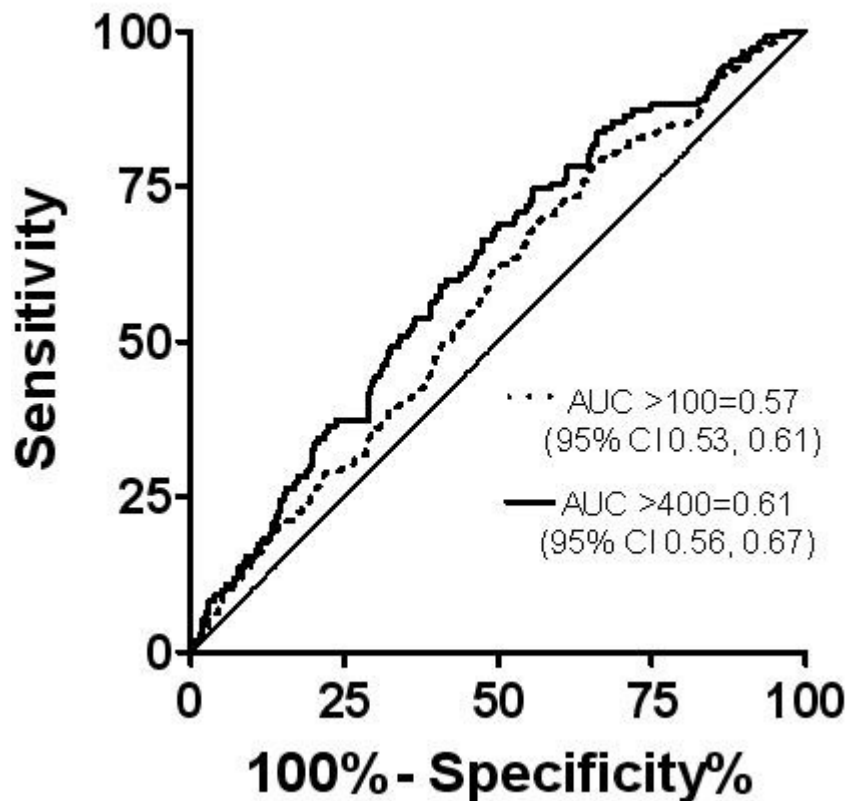
For patients calculated by the NZGG 1996 and 2003/2009 CVS risk guidelines to be at 'low risk' (0-10%), 14% and 9.1% respectively actually had a calcium score above the 90th percentile for this age and gender matched population, indicating that they were, in fact, at very high risk.

Figure 4. Agatston calcium score by band of 5-year CVS risk estimated by: (A) the original Anderson equation (NZGG 1996) (B) with the NZGG 2003/2009 'adjusted' Anderson equation



Since an elevated calcium score has been recognised as a potential risk factor for a CVS event and is direct evidence of coronary atherosclerosis, we examined the ability of the NZGG (2003/2009) adjusted Framingham risk score to discriminate those patients with total calcium >100 and >400 Agatston units. Patients with scores >100 or >400 were not well predicted by the adjusted Framingham score with only a moderate ability to discriminate as assessed by the area under the ROC curve (0.57 and 0.61 respectively (Figure 5).

Figure 5. Receiver operating characteristics of the 5-year risk of a CVS event from the Framingham score (with NZGG 2003/2009 adjustments) to discriminate people with total Agatston calcium scores of >100 and >400



Discussion

We have assessed the CVS 5-year risk of a selected New Zealand population, as promoted by the current 2009 NZ Guideline Groups methodology¹⁶. Within this population who are estimated to be at 'low risk' (0-10%), approximately 10% have a calcium score which at >400 Agatston units actually places them at 'very high' risk of a CVS event, up to 30 times the risk of a population with a calcium score of zero Agatston units²⁰.

Further, approximately 25% of this population have a calcium score of >100 Agatston units, which actually places them at 'high' risk of a CVS event, possibly up to 10 times the risk of the population with a calcium score of <100 Agatston units¹³.

This finding is of considerable concern, as the currently promoted methods of CVS risk assessment may, inadvertently, be falsely reassuring 10 to 25% of the 'low-risk' population. Hence, this finding sharply questions the currently employed method of CVS risk assessment in our New Zealand population.

With the new ability to accurately image the coronary arteries, both for calcium and for soft, mixed and fibrous atheromatous plaque, there is the potential to far more accurately assess CVS risk based upon the knowledge of how the very many 'risk factors' *actually result* in premature atheroma within the coronary arteries.

There has always been something incongruous about the epidemiological methods of CVS risk assessment, as currently promoted. If a clinician wishes to detect a colon cancer, a colonoscopy is undertaken, or a mammogram to identify a breast cancer as he 'looks for disease'. However, if the premature development of coronary atheroma is to be determined, we have been encouraged to view charts of some major risk factors for the condition. Intuitively, the ability to visualise the degree of an individuals *actual* coronary atheromatous burden would seem to have the potential for more accurate, CVS risk assessment.

Although early studies comparing the prognostic accuracy of coronary calcium measurement by CT vs the Framingham Score alone, or risk factors alone, yielded conflicting results, subsequent larger reports have conclusively demonstrated the predictive value of a calcium score in CVS risk assessment.²⁰⁻²⁴ Budoff et al have published the largest cohort (25,253 patients) with the longest mean follow up (6.8±3 years) to date²⁴. Using the end-point of all cause mortality, a calcium score of >10 predicted increased risk, with risk-adjusted relative risk ratios of 2.2 to 12.5 with calcium scores of 11 to 100 through to >1,000.

Ten-year survival (after adjustment for risk factors, including age) was 99.4% for a calcium score of 0 and worsened to 87.8% for a score of >1,000 (p<0.0001). In the St. Francis Heart Study¹³, in which over 4,500 patients were followed for 4.3 years, a calcium score of >400 was associated with a 30-fold increased risk for myocardial infarction or coronary artery disease death (coronary death, nonfatal myocardial infarction (MI), surgical or percutaneous coronary revascularization procedures, non-hemorrhagic stroke, and peripheral vascular (i.e., arterial) surgery).

In the Prospective Army Coronary Calcium Project, in which younger patients were evaluated with a calcium score and followed prospectively, the calcium score was associated with a 12-fold increased risk for hard coronary heart disease events (p=0.004), even after controlling for the Framingham risk score²².

A recent prospective European study²³ enrolled 510 uncomplicated type-2 diabetic patients who underwent a calcium score assessment. The ROC analysis for CVS risk prediction showed that a calcium score had the best area under the curve (0.92), significantly better than the United Kingdom Prospective Diabetes Study (UKPDS) risk score (0.74) and Framingham score (0.60) (p<0.0001). The relative risk (RR) to predict a CVS event for a calcium score of 101 to 400 was 10.1 and increased to 58.1 for scores >1000 (p <0.0001).

Responding to these overwhelming data, that in asymptomatic patients there is an incremental prognostic value of a calcium score, an American College of Cardiology/American Heart Association clinical Expert Consensus Panel²⁵ and the National Cholesterol Education Program (NCEP) Adult Treatment Panel 3²⁶ have recommended coronary artery calcium score assessment in patients at intermediate risk (10% to 20% risk prediction at 10 years) to refine the risk assessment and adjust the intensity of treatment accordingly.

Other recommendations have been published by Hecht et al.²⁷, and by the Screening for Heart Attack Prevention and Education (SHAPE) guidelines²⁸; particularly from the latter, the Texas State legislature has mandated insurance coverage for coronary artery calcium scoring for the intermediate-risk population²⁹.

Interest has also been given to patients who are calculated by the Framingham score to be at high CVS risk, but are found to have a low calcium score. The potential to reassign these patients to a lower risk has been discussed, and may have particular relevance to an older population, whose CVS risk in current epidemiological-based risk equations has been largely driven by their advanced age³⁰.

The concept that the degree of atherosclerosis *actually found* in the coronary arteries, rather than using a patient's age as a surrogate for this finding, has also been suggested.³¹ In our cohort, using the 2003/2009 NZGG, we found 26% of an apparently 'high risk' (5-year CVS event risk ≥ 15) cohort with a calcium score of zero, which would place them in a low risk (although clearly not a 'no risk') category.

The advantage of using the calcium score to improve on CVS risk prediction has been reviewed in the Multi-Ethnic Study of Atherosclerosis (MESA)³². During a median follow-up of 5.8 years, a final cohort of 5878 participants experienced 209 coronary heart disease (CHD) events of which 122 were myocardial infarction, death from CHD, or resuscitated cardiac arrest.

The 'net reclassification index', which reflects the ability of a 'new' risk factor to predict risk over the established methods, was measured for calcium score at a high 25%^{32,33}. In contrast, the widely reported inflammatory marker: CRP^{34,35} has been less able to independently predict CVS events after correction for other risk factors.¹³

One limitation to our study is the fact that some patients were offered a CTCA based on atypical symptoms, or had equivocal stress tests, whereas Framingham patients were reported to be asymptomatic. Therefore the Framingham risk assessment tool may underestimate the risk in our study population. However, these patients did not have clinical angina, as they would not have been offered a CTCA, which is very much used as a 'rule out' coronary disease procedure; the negative predictive power of the CTCA being its major clinical benefit.³⁶

In an editorial article in the Journal of the American College of Cardiology in 2007, Alan Guerci stated that there was "a consistent record of incremental prognostic value of the coronary calcium score, which (then) comprised of more than 300,000 patient years of observation"³⁷. He felt that it was time to 'move on' to the "remaining important questions about calcified coronary plaques, prognostic accuracy in minorities, the effect of screening on outcomes, and cost-effectiveness".

Our New Zealand cohort mimics the overseas experience, and with particular reference to our local methods of assessing risk, there are clearly issues of inaccuracy and false reassurance of significant numbers of the population, which could potentially be alleviated by the use of a coronary calcium score.

Conclusions

Approximately 10% to 25% of patients with a low CVS risk as assessed by the traditional Framingham equation, have a markedly increased calcium score and hence, actually, a significantly increased risk of a CVS event. Clinicians managing patients may consider a calcium score as an additional tool to the standard risk assessment.

Further work needs to be done to determine the relationship between standard risk factors and the total calcium score, and the utility of these tests alone, or in combination, to predict future CVS events in a New Zealand population. Indeed 26% of patients classified as high risk by the Framingham model have calcium score of zero suggesting a potentially lower 'true' risk.

This study has highlighted that the traditional CVS risk assessment based on age, gender, blood pressure, diabetes, a cigarette smoking history and blood lipids does not concord well with measured coronary calcium scores. In particular CT calcium scoring can identify a group of patients who are at a high likelihood of significant vascular events yet who may have inadvertently been falsely reassured by a low calculated Framingham CVS risk score.

Potential Conflicts of Interest: CE, ML, CEEd, NvP, JO, JC, HW and MO all received payment for reporting of Cardiac CT scans, from the 'Auckland Heart Group' private cardiology practice, or for working at the Mercy Radiology Cardiac CT scanner. As a part of their private cardiology practice CE, ML, CEEd, NvP and JO have a share-holding in the 'Auckland Heart Group', which itself has a minority share in the ownership of the Mercy Radiology Cardiac CT scanner.

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