The Cardiac Society of Australia and New Zealand

Coronary Artery Calcium Scoring – Position Statement

Development of this position statement was coordinated by Christian Hamilton-Craig (co-chair), Gary Liew (co-chair), Jonathan Chan, Clara Chow, Michael Jelinek, Niels van Pelt and John Younger.
No authors have any relevant Conflict of Interest to disclose.

It was reviewed by the Quality Standards Committee and ratified at the CSANZ Board meeting held on Friday, 26th May 2017.

Coronary Artery Calcium Scoring (CAC) is a non-invasive quantitation of coronary artery calcification using computed tomography (CT). It is a marker of atherosclerotic plaque burden and an independent predictor of future myocardial infarction and mortality.

CAC provides incremental risk information beyond traditional risk calculators (eg. Framingham Risk Score). Its use for risk stratification is confined to primary prevention of cardiovascular events, and can be considered as "individualized coronary risk scoring" for those not considered to be of high or low risk. Medical practitioners should carefully counsel patients prior to CAC. CAC should only be undertaken if an alteration in therapy including embarking on pharmacotherapy is being considered based on the test result.

Patient groups to consider Coronary Calcium Scoring

1. CAC is of most value in intermediate risk patients (absolute 10-year cardiovascular risk of 10-20%) who are asymptomatic, do not have known coronary artery disease and aged 45 – 75 years, where it has the ability to reclassify patients into lower or higher risk groups.

2. It may also be considered for lower risk patients (absolute 10-year cardiovascular risk 6-10%) particularly in those where traditionally risk scores under estimate risk e.g. especially in context of family history of premature CVD and possibly in patients with diabetes aged 40 to 60 years old.

Patient groups in whom Coronary Calcium Scoring should not be considered

CAC is not recommended for patients who are:

1. At very low risk (<5% absolute 10 year risk); or,

2. High risk (>20% absolute 10 year risk) - as testing is unlikely to alter the recommended management. This includes some patients who are automatically considered to be high risk (eg. diabetics over 60 years old or diabetics with albuminuria, chronic kidney disease (eGFR < 45 mL/min), BP > 180/110, familial hypercholesterolaemia and cholesterol > 7.5 mmol/L) and therefore should be managed aggressively with optimal medical therapy; or

3. Symptomatic or previously documented coronary artery disease.

Interpretation of CAC

CAC = 0.	A zero score confers a **very low** risk of death, <1% at 10 years.
CAC = 1-100.	**Low risk**, <10%
CAC = 101-400.	**Intermediate** risk, 10-20%
CAC = 101-400 & >75th centile.	**Moderately high** risk, 15-20%
CAC > 400.	**High** risk, >20%

Management recommendations based on CAC

Optimal diet and lifestyle measures are encouraged in all risk groups and form the basis of primary prevention strategies. Patients with moderately-high or high risk based on CAC score are *recommended* to receive preventative medical therapy such as aspirin and statins. The evidence for pharmacotherapy is less robust in patients at intermediate levels of CAC 100-400, with modest benefit for aspirin use; though statins maybe *reasonable* if they are above 75th centile. Aspirin and statins are generally not recommended in patients with CAC < 100.

Repeat CAC testing

In patients with a CAC of 0, a repeat CAC may be considered in 5 years but not sooner.
In patients with positive calcium score, routine re-scanning is not currently recommended. However, an annual increase in CAC of >15% or annual increase of CAC >100 units are predictive of future myocardial infarction and mortality.

Cost effectiveness of CAC based primary prevention recommendations

There is currently no data in Australia & New Zealand that CAC is cost-effective in informing primary prevention decisions. Given the cost of testing is currently borne entirely by the patient, discussion regarding the implications of CAC results should occur before CAC is recommended and undertaken.

INTRODUCTION

Coronary Artery Calcium Scoring (CAC) is a technique of measuring the amount of calcium in the coronary arteries using ECG-gated non-contrast computed tomography (CT) scan of the heart. Its main clinical application is to predict the risk of a future cardiac event in an asymptomatic individual in the setting of primary prevention. The scan acquisition is relatively quick (less than 10 seconds), has low radiation exposure (~ 1mSv) and does not require intravenous contrast or special preparation.

The development of atherosclerotic plaque has been well studied. As atheroma develops, it may form lipid pools, fibrous tissue and calcium at later stages.[1] Calcification does not occur in normal vessel wall; it often represents the 'tip of the iceberg' in atherosclerosis with a component of non-calcified plaque which is not visible on non-contrast CT scan. CAC is a surrogate measure of total atherosclerotic plaque burden but it is not specific for luminal obstruction. As CAC and plaque burden increase, there is proportionate rise in the risk of cardiovascular disease (CVD) events.

Currently in Australia, Medicare does not regulate or reimburse for CAC testing. Furthermore, there has not been guidance from national bodies on indications, patient population, scanning techniques and reporting standards. The literature continues to evolve and is not conclusive with respect to certain aspects of CAC interpretation and subsequent clinical management. This document will attempt to provide some background information, rationale and guidance on these matters so that the test is used appropriately and a high standard maintained for practice in Australia & New Zealand.

DEVELOPMENT OF CAC

The ability to image calcification within coronary arteries was recognised from the earliest days of x-ray technology in the 1920s.[2] Coronary calcification was linked to atherosclerosis before the end of the 1950s and calcium seen on fluoroscopy carried prognostic significance.[3, 4] In the late 1980s it was shown that early CT scanners were more sensitive than fluoroscopy for detecting calcium (62% versus 35%) but the images were affected by motion artefact.[5]

A new era in cardiac imaging arrived in 1990s with the development of ultrafast computed tomography, later known as electron beam computed tomography (EBCT). These scanners were developed primarily for cardiac applications but were never commercially available in Australia. They could generate 3mm thick slices with a scan time (temporal resolution) of 100 milliseconds, gated to the diastolic phase of the cardiac cycle. This allowed the heart to be examined in a single breath hold with minimal movement artefact.

Arthur Agatston (cardiologist), Warren Janowitz (radiologist) and David King (Engineer - Imatron, manufacturer of EBCT), devised a scoring system which later became known as the Agatston score.[6] Calcium appears bright on a CT image, meaning that it has a high CT number, or Hounsfield unit (HU). It was decided that the cut-off should be 130HU for lesions to be considered calcified. The area of all coronary lesions with HU above this number would be calculated and summed. Lesions with dense calcification would be brighter and a weighting factor between 1 and 4 was applied based upon the peak density (as assessed in HU) of the lesion.[7] The Agatston score was the product of the calcified area by the weighting factor.

Other methods for both imaging and quantifying coronary calcium have been proposed, including thicker slices and scores based upon the number, mass or volume of the lesions.[8-10] However it is still the original Agatston score that is most commonly used both in trials and clinical practice.

Improvements in multi-detector CT (MDCT) technology (predominantly temporal resolution and z-axis coverage) have made it possible to perform CAC reliably in the last decade. Early MDCT scanners showed significant variability in the calcium score depending upon the image reconstruction and scoring algorithm and were not equivalent to EBCT.[11] However agreement between calcium scores obtained on MDCT and EBCT has since been established.[12, 13]

Following acquisition of the CT images, calcium scores are calculated using commercially available software packages. The software usually highlights areas with HU>130 and the trained reader manually identifies coronary lesions. The software calculates HU and area which provides the Agatston score. Calcification of the mitral annulus, aortic root, pericardium and streak or beam hardening artefact near the inferior wall of the heart can make interpretation of the images more challenging. Therefore, care must be taken by the reader to identify coronary calcification correctly.

EBCT routinely delivered very low doses during calcium scoring between 0.7 and 1.3 milliSieverts (mSv). Radiation from MDCT was initially higher with some early studies reporting doses between 3 and 4 mSv.[14, 15] Guidelines for minimizing radiation exposure during calcium scoring with MDCT have been published and the dose should now average between 0.5 and 1.5 mSv on most modern scanners using prospective ECG-gated technique.[16] This is similar to 2 breast mammograms.

The HU of any tissue will vary depending upon the energy of the X-Ray used to obtain the image ie. kiloVolt (kV) setting. A study comparing 100kV to 120kV for CAC found the threshold in defining calcified lesions had to be set higher at 147 HU for 100kV rather than traditional 130 HU.[17] Although CT coronary angiogram studies are now routinely performed at low radiation doses using 100kV or even 80kV protocols, calcium scoring should be performed at 120kV and reconstructed at 3mm slice thickness in order to derive a conventional Agatston score. Radiation can be minimized by adjusting other scanner settings, particularly scan length and tube current.

Estimates of coronary calcium scores can be obtained from standard non-ECG gated CT chest scans, from contrast enhanced CT coronary angiograms and from gated calcium scans acquired at different kV protocols.[18-20] The equivalence of these techniques with an Agatston score is still being studied and their utility remains controversial.

Recommendations: Technique

- Multi-detector CT (preferably 16 detectors or greater)
- Prospective ECG-gated non-contrast scan; single breath hold.
- Use of 120kV and reconstructed at 3mm slice thickness
- Limit scan length to region of interest

CLINICAL RISK PREDICTION

A comprehensive review of clinical risk prediction strategies and biomarkers is beyond the scope of this document. The Heart Foundation as part of the National Vascular Disease Prevention Alliance (NVDPA) has published guidelines on absolute CVD risk (http://www.heartfoundation.org.au/SiteCollectionDocuments/guidelines-Absolute-risk.pdf). However, we will cover key concepts and describe the role of CAC in context.

Prevention of cardiovascular disease is important in maintaining a healthy productive population and reducing the cost of healthcare in the long term. The intensity of any intervention should be commensurate to the degree of baseline risk of an individual or population. This principle should achieve the best balance between clinical outcomes, cost and safety. The challenge has always been to identify individuals at higher risk who may derive greater benefit from early detection and treatment. As a consequence, various tools or calculators have been developed from large studies (Framingham, PROCAM, SCORE) to estimate an individual's absolute risk in a 5 or 10-year period.[21]

In Australia, the NVDPA has developed a tool based on Framingham Risk Score (www.cvdcheck.org.au). Clinicians in New Zealand should refer to the New Zealand Guidelines Group, New Zealand Primary Care Handbook 2012 (updated 2013).[22] The recommendation is that all patients from 45-75 years old be actively assessed in general practice. We acknowledge that every tool has its short-comings and therefore of varying accuracy. There are small differences between the NVDPA tool and Framingham Risk Score (FRS). Traditional FRS has cutoffs on 10-year risk at <10%, 10-20% and >20% in classifying low, intermediate and high risk groups respectively

(http://cvdrisk.nhlbi.nih.gov/calculator.asp). However the NVDPA uses 5-year risk of <10%, 10-15% and >15% for the same groups. Although it may not translate to 10-year risk of <20%, 20-30% and >30% precisely, an individual deemed to be at intermediate risk (10-20%) according to FRS may be low risk when calculated using NVDPA tool. We are unable to provide in-depth analysis or reconciliation between these two tools and acknowledge that NVDPA has been developed in the Australian context. However, the vast majority of research trials involving CAC have used FRS as the default risk prediction tool. There are no studies to date using NVDPA and CAC with outcomes data. This document will use the traditional FRS as the basis for our discussion involving CAC.

There are certain populations which are automatically deemed to be high-risk for development of CVD (see NVPDA website). They include diabetics over 60 years old or diabetics with albuminuria, chronic kidney disease (eGFR < 45 mL/min), BP > 180/110, familial hypercholesterolaemia and cholesterol > 7.5 mmol/L. Therefore, no further risk assessment is required and they should be treated aggressively with optimal medical management. Age and gender remain the most important factors when determining risks. It is also important to note that most risk calculators including FRS and NVDPA do not account for family history.

The FRS was developed in context of predominantly Caucasian population of north-eastern USA and its accuracy in risk prediction may be different when applied to other populations and ethnicities across the world. It is reassuring that the landmark 'Multi-Ethnic Study of Atherosclerosis' (MESA) study found no variation in risk prediction of CAC when applied to gender and to four broad racial groups of Caucasian, African-American, Hispanic and Chinese.[23] In Australia, we acknowledge that certain sub-groups of Aboriginals and Torres Straits Islanders have poorer health outcomes and remain at higher risk.[24]

A key concept is that CAC provides direct visual evidence of coronary atherosclerosis that is present in an individual patient whereas risk calculators are reliant on antecedent risk factors. Local studies have demonstrated that patients at "low-intermediate risk" by the NZ Framingham equation can have markedly increased calcium scores at increased risk of CV events[25], and in this scenario the FRS risk may be falsely reassuring compared to risk as demonstrated on CAC scoring.

PREDICTION OF CVD EVENTS AND MORTALITY

There have been a number of large scale prospective studies published in the literature that have proven the prognostic value of CAC in asymptomatic patients, especially in the subgroup at intermediate cardiovascular risk profile.[23, 26-28] The relationship between calcium score and major adverse cardiovascular events including all-cause mortality, cardiovascular events and non-fatal myocardial infarction, has been established in a number of studies. A large prospective study involving 25,253 patients in USA with a mean follow-up of 6.8 years showed the calcium score was associated with survival (Figure 1).[27]

A large study of 9715 patients in Tennessee, USA with the longest follow-up period of 15 years has recently been published.[29] The all-cause mortality rate at 15 years according to CAC results are as follows: CAC 0: 3%, CAC 1-100: 6-9%, CAC 101-399: 14%, CAC 400-999: 21%, CAC ≥ 1000: 28%.

The 2007 ACC/AHA consensus document on CAC provided a pooled analysis of studies and found a commensurate rise in annual myocardial infarction or cardiac death rate. [30] This approximates the event rate of traditional FRS 10-year risk groups of low, intermediate and high. Table 1 outlines the annual event rate and relative risk according to CAC result.

The usefulness of a new risk marker is assessed by its ability to provide new information, which improves upon current risk calculators or markers. One measure is improving the accuracy of predicting cardiovascular events or mortality, which is often expressed as the area under a receiver operating characteristic curve (AUC) where 1.0 indicates perfect prediction.

Many studies have reported the improvement in AUC for predicting CVD events when CAC is added to traditional risk factors from approximately 0.6 to > 0.7.[26, 31, 32] Yeboah et al, in a MESA study of

6814 patients, compared the ability of different risk markers (CAC, high-sensitivity CRP, ankle-brachial index, brachial FMD, carotid IMT, family history) in improving the ability to predict CVD events when added to FRS.[33] They found CAC resulted in the highest improvement of AUC from 0.62 to 0.78. Family history was the next best marker at AUC 0.67 with the other markers resulting in only modest improvements over FRS or not at all.

RECLASSIFICATION OF PATIENT RISK

A relatively new concept is Net Reclassification Improvement (NRI) where individuals with and without clinical events are correctly reclassified to higher or lower risk groups.[34]

The Heinz Nixdorf Recall study was a prospective cohort study of 4,129 patients aged 45-75 without known CVD undergoing CAC with a median follow-up of 5 years.[35] Addition of CAC to FRS improved the AUC from 0.68 to 0.75. In FRS intermediate risk group, CAC was able to reclassify 24% of patients into higher risk and 19% into lower risk groups.

In the MESA study, the AUC for prediction of cardiac events improved from 0.76 to 0.81 when CAC was added to risk factors.[32] More importantly it was able to reclassify more than half of intermediate risk patients into higher risk (16%) and lower risk (39%). Similarly in the Rotterdam Study, just over 50% of intermediate risk patients were correctly reclassified based on CAC results with follow-up of 9 years.[36]

Absence of coronary calcification – "the power of zero"

There have been multiple studies examining the low event rates in patients with CAC of zero.[37-39] In a study of 44,052 patients, 45% had a zero score and cardiovascular mortality at 10 years was just under 1%.[38] Risk factors did influence mortality rate amongst those with CAC = 0, with 10-year mortality in diabetics of 3.7%, smokers 3.3% and hyperlipidaemia 1.7%. Patients with a family history of IHD also had a slightly higher mortality of 1.6%. However, a MESA sub-study found CAC was the overriding factor in predicting outcomes.[40] Patients with CAC > 300 but no risk factors had an event rate 3.5 times higher than patients with CAC = 0 with 3 or more risk factors.

In a large study of 4864 patients with follow-up of 15 years, a CAC = 0 conferred an annual mortality rate of < 0.5%.[41] The overall mortality at 15 years was 4.7% but was non-linear with most events occurring after 12th year. It provided incremental value beyond FRS and was able to reclassify nearly 60% of patients into either lower or higher risk groups. However, in high-risk patients as determined by FRS, the warranty period for CAC of zero was shorter at 6 years.

Normal CAC distribution for age and gender

Reference values of CAC for specific age groups and gender have been derived from previously large observational studies which contain self-referred patients or heterogeneous risk factors.[42, 43] Hoffmann et al. set out to define normal distributions of CAC using 1586 Framingham Heart Study patients without known CVD and no cardiac risk factors.[44] Table 2 outlines the distribution of calcium according to age and gender. They also used the 90th percentile of CAC as the cut-off value for disease and applied it to a larger Framingham cohort with cardiac risk factors. This resulted in 14% more patients in the larger Framingham cohort as having significantly increased CAC.

Table 3 demonstrates the distribution of the larger Framingham cohort with risk factors according FRS risk-groups and CAC groups.[44] No results shown for women with high FRS due to small sample size. In the FRS intermediate-risk group, 32% of men and 24% of women had CAC > 100 who may potentially benefit from therapy.

INDICATIONS AND PATIENT POPULATION

The main use of CAC is to predict future cardiovascular risk in asymptomatic patients. In essence, it is a targeted screening tool and we would take into consideration some principles of population health screening. The target population needs to be identified, the tool should be affordable / cost-effective and

widely available, relatively safe, able to detect pathology in an early stage and intervention with treatment should lead to an improved outcome.
The 2010 American guidelines on cardiac risk assessment have recommended CAC in asymptomatic patients deemed to be at intermediate risk of 10-20% (Class IIa, Level B evidence).[21] They have also suggest that CAC may be reasonable for those who have a 6-10% 10-year risk (Class IIb, Level B) but not in individuals with <6% risk (Class III, Level B).

Although some cohorts from which risk calculators (FRS, SCORE, PROCAM) are derived have patients as young as 30 years-old, the majority of the evidence is in patients aged 40-75 years old.[21] However, in large trials of CAC, there are a wide range of age groups. The MESA study enrolled patients between 45-84 years.[23] The Cooper Clinic study had patients between 22-96 years.[28] Current recommendation from NVDPA is to assess absolute risk of adults starting at the age of 45 in Australia. Therefore, individuals aged 45-75 years are probably the most appropriate to undergo CAC as the majority of evidence is derived from that group.

In a large observational study, Raggi et al. found patients with **diabetes** have a higher mortality compared to non-diabetics across all categories of CAC with the exception of CAC of zero.[31] Addition of CAC to FRS improved the accuracy of predicting CVD events from AUC of 0.72 to 0.79. Patients with diabetes have a higher risk for CVD which develops earlier compared with nondiabetic patients.[45] CAC could be considered in diabetic patients without known CVD aged 40 to 60 years. Diabetics over 60 years are considered to be high risk and should receive optimal medical therapy.

Women have traditionally lower risk than men given the same age and risk factors.[21] However, in a study of 2447 women undergoing CAC, FRS frequently underestimates their risk even in presence of CAC > 100 or CAC > 75th percentile.[46] A MESA sub-study of FRS 'low risk' women found 6% had CAC >100 and 4% had CAC > 300.[47] High CAC was predictive of CVD events even in this 'low risk' group of women with an adjusted hazard ratio of 8.3. As most women under 60 years would be classified as 'low risk' by FRS, perhaps CAC is appropriate for those with 6-10% 10-year risk.

Recommendation: Asymptomatic patients suitable for CAC

- Aged 45-75 years with intermediate cardiovascular risk (10-20%)
- There is a possible role for CAC in those aged 45-75 years with lower cardiovascular risk (6-10%) as defined by FRS in:
    - Those with a strong family history of premature CHD
    - Diabetics aged 40 – 60 years old.
    - Indigenous patients (Aboriginals, Maori and Pacific Island patients) >40 years old.

CAC in Symptomatic Patients

Performance of CAC was popular as an adjunct just prior to coronary CTA in symptomatic patients. It provided an estimate of plaque burden and in some cases with very high CAC > 800, it was predictive of non-diagnostic CCTA studies due to blooming artefact.[48, 49] The additional radiation of 1-2 mSv was consider innocuous compared to traditional retrospective techniques of CCTA which resulted in 7-12 mSv.[50] However, with prospective scanning techniques, iterative reconstructions and wide volume scanners, CCTA can often be performed with < 2mSv.[51] Therefore, adding CAC to CCTA can sometimes double the radiation dose. The argument for not proceeding with CCTA when CAC is high for fear of non-diagnostic scan is less convincing now when the radiation involved is similar to that of a CAC in the first place.

Although high CAC has been predictive perfusion defects on functional studies, by itself is not sufficient to exclude severe stenosis in a patient with chest pain.[52] In a large study of 2115 patients undergoing CAC and coronary angiography, a positive CAC had overall sensitivity of 99% but specificity of only 28% for obstructive disease.[53] Using CAC > 100, sensitivity was 87% and specificity of 79%. In symptomatic patients, a CAC = 0 does not mean an absence of plaque. Approximately 0.6% had obstructive lesions due to non-calcified plaque but all most all were in young patients <45 years-old.[53]

A study of 4338 patients followed for 2.3 years found routine CAC in addition to coronary CTA did not add value in prediction of CVD events.[54] Recently, a sub-study of ROMICAT II trial of using coronary CTA in emergency department found CAC does not provide incremental value over CCTA nor can it exclude acute coronary syndrome.[55]

In the assessment of symptomatic patients, CAC should not be the sole test used. We recommend coronary CTA, functional testing or invasive coronary angiography where appropriate.

INTERPRETATION & MANAGEMENT BASED ON CAC

Table 4 summarizes the 10-year mortality risk and our suggested management strategy according to CAC results. It is important to advocate a healthy diet and lifestyle for all risk groups and discuss the risk and benefits of any pharmacotherapy.

The ability of CAC to provide incremental risk predictive information beyond FRS and to appropriately re-classify individuals into higher or lower risk groups has been discussed in this document. It is also apparent that with increasing CAC, there is increased risk of future CVD events. Our recommendation for management in any given category of CAC results lies with the 10-year risk group which it represents. Currently, there are no large scale prospective randomized trials comparing outcomes based on treatments guided by CAC to traditional risk assessment tools alone. Most studies have estimated the impact of treatment strategies from relative risk reductions observed from clinical trials and applied to risk associated with CAC result.

CAC AND STATIN THERAPY

High CAC > 400

The St Francis Heart study was a prospective double-blinded randomized control trial of atorvastatin 20mg/day, vitamin C and vitamin E against placebo in 1005 patients with elevated CAC followed-up for 4 years.[56] It was an underpowered study with a substantial population at low risk. It failed in its primary endpoint of reducing composite CVD events (6.9% v 9.9%; p=0.08). However, in a sub-population of patients with CAC > 400, there was a significant reduction in CVD events (8.7% v 15%; p = 0.046).

In patients with CAC>400, some studies have raised the concept of whether further functional assessment should be done as the risk of obstructive disease may be higher.[57, 58] Indeed the 2008 American guidelines on stress echocardiography deemed it ‘appropriate’ with a score of 7 out of 9 in patients with CAC > 400.[59] However, it is uncertain if further functional testing results in an overall benefit or influences revascularization in an otherwise asymptomatic individual. Functional testing should therefore be considered on an individual basis.

Intermediate CAC 101 - 400

The estimated 10-year risk for intermediate CAC group is approximately 10%-20% with previous pooled analysis observing an annual event rate of 1.3%.[30] The new American lipid guidelines (2013 ACC/AHA) have expanded indication for treatment with statins to include individuals (40-75 years old) with LDL > 1.8 mmol/L and a calculated 10-year risk of >7.5% for primary prevention (Class I indication, Level A evidence).[60] Furthermore they have recommended that statins be considered when CAC > 300 or above 75th percentile (Class IIb indication, Level C evidence). They have also advised on moderate to intensive dose statins achieving >30-50% reduction of LDL rather than traditional treat to LDL target strategy. However, there have been criticisms about possible over-estimation of CVD risk using the new algorithm by as much as 100% and subjecting a significant population to statin therapy which may be unnecessary.[61]

In Australia & New Zealand, we are yet to adopt these measures and the most recent NVDPA guidelines from 2012 suggests a target LDL < 2.0 mmol/L for all risk groups from consensus based recommendations (http://www.cvdcheck.org.au/pdf/Absolute_CVD_Risk_Full_Guidelines.pdf). It is

important to note that both 2013 ACC/AHA and NVDPA guidelines are different to Australian Pharmaceutical Benefit Schemes criteria for subsidized lipid therapies which were formulated in 2006 and have much higher thresholds (http://www.pbs.gov.au/info/healthpro/explanatory-notes/gs-lipid-lowering-drugs).

Blaha et al. investigated the ability of CAC to further risk stratify a cohort of MESA patients who would otherwise derive benefit from statins based on results of the JUPITER trial.[62] Raised high-sensitivity CRP was used as a marker for treatment in patients with LDL < 3.4 mmol/L in the JUPITER trial.[63] Blaha et al found nearly half of MESA JUPITER population to have CAC = 0 and calculated a 5-year NNT of 549 for statin therapy. Conversely about 25% of the population had CAC > 100 and estimated the 5-year NNT was only 24 for statin therapy.[62]

In patients with **CAC < 400 but >75th percentile**, there is less evidence about risk re-stratification. In this scenario other contextual factors could be taken into consideration. For example consideration maybe given to whether the patient is from a sub-group that Framingham-based risk scores generally under-estimates risk e.g. younger, female or has a family history of premature CHD. Age is a main driver of vascular risk, a younger person with a CAC >75th percentile is likely to have a 5 or 10 year absolute risk which may not be raised in absolute terms, their lifetime risk of a CV event or their potential life-years lost however is likely to be high.[64] Therefore, these patients may be reclassified as "high risk", and more aggressive therapies considered.

Low CAC 1-100

Although they have a relative risk of approximately 2-fold in comparison to patients with no CAC, the evidence for pharmacotherapy is weak. We would advocate a healthy diet and lifestyle in for maintaining a low 10-year risk, unless other clinical factors are present (eg strong family history of premature infarction <50 years of age in a first degree relative).

COST-EFFECTIVENESS

The EISNER study was a prospective randomized trial of 2137 volunteers without previous CVD to undergo CAC or no scan before risk factor counselling.[65] They were followed-up at 4 years and the primary endpoint was change in risk profiles / FRS and secondary endpoints were costs, downstream testing and adverse events. The CAC group had better risk factor control (BP, lipid profiles, weight) and FRS without increase in downstream cost. Medications and downstream testing increased proportionately with increasing CAC. However, as 50% of patients have a CAC = 0 and only 8% of patients have CAC > 400, there was a significant reduction in medication and procedural cost in patients with CAC = 0 compared to the no scan group which also incurred increased interventions. Hence, performing CAC was able to appropriately utilize resources where required. It should be noted that cost-effectiveness studies have not been conducted in an Australian setting.

Calcium Score, Dyslipidaemia and Statin Therapy

There is emerging evidence that statins stabilizes plaque, slows plaque progression and improve outcomes in patients with non-obstructive coronary plaques. Intravascular ultrasound studies have demonstrated plaque stabilization and even regression with statin therapy.[66, 67] A recent study utilizing coronary CTA found the presence and extent of non-obstructive plaque (stenosis < 50%) predicted mortality and treatment with statins reduced mortality with a hazard ratio of 0.39.[68] However, the CONFIRM registry (over 27,000 patients) did not find coronary CTA to provide additional predictive value over CAC in asymptomatic patients.[69] Therefore, coronary CTA is generally not recommended in asymptomatic individuals.

In a study of 5534 patients examining the relationship between dyslipidaemia and CAC, Martin et al. found CAC had a greater predictive value of events than any combination of lipid abnormalities eg. LDL > 3.3 mmol/L, cholesterol to HDL ratio > 4.8.[70] Patients with zero CAC but multiple lipid abnormalities had 5.9 events per 1000 person-years compared with 22.7 events in patients with CAC > 100 but no lipid abnormalities. The 5-year number needed to treat (NNT5) was 30 for patients with CAC

> 100 but without dyslipidaemia compared with a NNT5 of 154 in those with CAC = 0 with dyslipidaemia. Therefore, CAC could potentially guide statin therapy in the future.
A recent study of Framingham patients, found a very low cardiac event rate of 1.6% at 9 years in patients who qualify for statin therapy based on 2013 ACC/AHA guidelines but have CAC of zero.[71] They found using CAC = 0 as an ineligible criterion for statin did not result in an increase in cardiac events. Hence, there may be a potential cost savings in with-holding statin therapy for these very low risk patients identified by CAC who would otherwise have been treated according to guidelines.

The MESA study group conducted a cost-effectiveness analysis of utilizing CAC in FRS intermediate risk patients to guide statin therapy.[72] They compared treatment based on CAC results with that based on ATP III guidelines, assuming the modelling of annual statin cost of USD$1000 and a threshold of $100,000 to prevent one event. Treating patients with CAC > 100 was more cost-effective than ATP III strategies provided CAC costs less than USD$235 per test.

Another study of 2608 patients reported improved compliance with statin therapy and increased weight loss with increasing CAC over a 4-year period.[73]

CAC and Aspirin

Routine use of aspirin in general population for primary prevention is not recommended based on trials showing a decreased rate of CVD events but a similar increased rate of bleeding.[74-76] As the majority of the population in these trials is low-risk, the challenge is to identify individuals at higher risk where potentially the benefit of aspirin may outweigh the risk. The 2009 US Preventative Services Task Force (USPSTF) guidelines recommend that aspirin be considered for men 45-79 and women 55-79 according to baseline risk.[77] The 10-year baseline risk where benefits outweigh the risks for aspirin is >4% in men 45-59 years and >9% in men 60-69 years; >3% in women 55-59 years and >8% in women 60-69 years. Therefore, aspirin could be considered in FRS intermediate and high-risk individuals for primary prevention.

Miedema et al, used data from the large MESA study to estimate the benefit vs. risk of aspirin according to CAC result.[78] The authors calculated the 5-year number needed to harm from aspirin 442 for major bleeding, and the number needed to treat (NNT) was in favour of Aspirin when the CAC score was above 100 Agatston units. Thus, patients with **CAC > 100** derive net benefit from aspirin regardless of their traditional risk factors: FRS <10% risk, NNT was 173; FRS > 10%, NNT was 92. Conversely, patients with CAC = 0, the NNT was 808 for patients with FRS >10%. Results for patients with CAC 1-99 were mixed and aspirin could not be routinely recommended. Therefore, this study showed the potential of CAC results guiding aspirin therapy in patients who are low to intermediate risk by FRS, and recommends that patients with CAC>100 will benefit from aspirin

Serial or Follow-up CAC

One of the most common questions faced by clinicians and patients after an initial CAC is if or when another is needed. Currently there are no studies which show a regression of calcium scores on subsequent scans. Therefore, the result can either remain the same or more likely worsen with time. There are several definitions of CAC progression and evaluation may be in continuous or categorical fashion.[79]

Min et al, studied the determinants of calcium conversion from a normal scan (CAC = 0) to a positive one (CAC > 0).[80] They followed 422 patients with CAC = 0 who had yearly calcium scans for 5 years and found that 25% became positive; mean time to conversion was 4.1 ± 0.9 years. This was touted as the ‘warranty period’ of a normal calcium score. They found the rate of conversion was non-linear with the highest rate occurring in the fifth year. Therefore, there was little value in performing another scan for at least 4-5 years. Significant factors which influenced conversion included age, diabetes and smoking. However, no individual risk factor accelerated the conversion from normal to abnormal. Hence, one could not advocate a sub-group eg. diabetic patients in undergoing more frequent CAC.

In a larger study from the MESA cohort, approximately 36% of 3112 patients who were initially normal returned a positive scan in 6.1 years.[81] The median CAC was 7.1 when first positive with 52% patients

in CAC 1-10, 44% in CAC 11-99 and 4% in CAC > 100. Appearance of calcium tends to be in a single vessel (72%), with left anterior descending artery the most common site.

The rate of change has also been studied in patients with baseline CAC > 0. In a study of 495 patients by Raggi et al, an annual increase in CAC by >15% was an independent predictor of myocardial infarction and carried a 17-fold increased risk compared to patients who did not progress.[82] Budoff et al, studied 4609 patients and found an annual increase of CAC > 15% independently predicted mortality with a hazard ratio of 2.98.[83] In the MESA cohort of 6778 patients followed for 7.6 years, the mean time to a second scan was 2.5 years.[84] In patients with baseline CAC > 0, an adjusted absolute change in CAC per year carried a hazard ratio of 1.3 per 100 unit change for myocardial infarction and mortality. They showed CAC progression predicted cardiac events even after adjusting for risk factors and baseline score.

Currently, factors which cause an acceleration of CAC progression have not been determined conclusively. One small study found insulin resistance to be an independent predictor.[85] It is apparent from studies of CAC progression, the baseline calcium score is an important predictor.[85, 86] A 15% increase in CAC for someone with a score of 10 probably carries a lower risk than the same increase in someone with a score of 300.[84] Whilst a high baseline CAC itself may be a confounder, it represents patients with higher plaque burden, some of which is non-calcified plaque which will calcify in future. Furthermore, the cost-effectiveness of repeated CAC, at what intervals and determinants on clinical outcomes are uncertain.

There are many questions that remain about CAC progression and further research is needed. Patients with high CAC > 400 should already be treated aggressively and repeat scans may not alter management. Patients with low CAC 1-100 may derive some benefit from repeat CAC, assuming a significant progression warrants some change in therapy even if their CAC remains < 100 at follow-up. It would be reasonable for patients with diabetes or those with CAC 101-400 to undergo repeat CAC at 3 years based upon our discussion above.[84, 85] However, we currently do not have good evidence that we can halt CAC progression with some trials finding statin therapy did not make a difference to progression.[56, 86, 87] One theory is the conversion of non-calcified plaque to calcium by statins, but the role of calcium in vulnerable plaques is beyond our scope.[88] It remains to be seen if longer duration or more intensive statin therapy along with vigorous control of diabetes, hypertension and other risks may slow CAC progression. Therefore, we are unable to provide firm recommendations on which sub-populations should undergo serial CAC and at what intervals. Annual CAC would seem excessive and unwarranted by current literature.

REPORTING STANDARDS

It is preferable that specialists reporting CAC should hold appropriate credentialing (Level A or B) from the Australian New Zealand Conjoint Committee for the Recognition of Training in CT Coronary Angiography.

We **recommend** the following minimum information to be included in a CAC report:

- Patient name, age / date of birth, gender
- Indication
- Date of scan, technique (eg. Prospective, 120kV, 3mm slice reconstructions) and equipment
- Radiation exposure eg. *DLP* and effective dose *mSv*
- Total Agatston score
- Distribution of calcium according to each of major coronary arteries eg. Total CAC is 120; Left anterior descending 60, Left circumflex 10, Right coronary artery 50.
- Centile: based on patient age and gender – this is derived from vendor specific software or manually obtained from MESA website (http://mesa-nhlbi.org/Calcium/input.aspx.)
- Other non-coronary findings eg. Pericardial thickness, hiatus hernia, lung mass, etc.

Optional information which may be included in a report:

- Calculated vascular age based on CAC from MESA website. (http://www.mesa-nhlbi.org/calcium/arterialage.aspx)
- Reference range for CAC and indication of 10-year risk of a cardiovascular event (*table 4*).

It is **not appropriate** to comment upon the likelihood of coronary artery stenosis based on CAC alone. A non-contrast CT scan does not provide such anatomical information (as opposed to Coronary CT Angiography) and the presence of dense calcification on 3mm slice reconstructions does not equate to severe stenosis at that site.

CONCLUSION

Coronary Artery Calcium Scoring is a robust and reproducible way of detecting coronary atherosclerosis and to estimate future risk of cardiac events. It has incremental benefit beyond traditional risk prediction tools and biomarkers. It can be easily performed using current multi-detector CT with very low radiation. It is of greatest benefit when applied to asymptomatic individuals between ages 45 to 75 years old who are at intermediate risk as determined by Framingham Risk Score or similar calculators. It has the ability of re-classify many into either lower risk, with potential cost-savings in minimizing therapy or into higher risk group where appropriate therapies may improve outcomes.

REFERENCES

[1] Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W, Jr., et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation. 1995;92:1355-74.
[2] Lenk R. Röntgendiagnose der Koronarsklerose in vivo. Fortschr Geb Rontgenstrahlen. 1927;35:1265-8.
[3] Blankenhorn DH, Stern D. Calcification of the coronary arteries. Am J Roentgenol Radium Ther Nucl Med. 1959;81:772-7.
[4] Margolis JR, Chen JT, Kong Y, Peter RH, Behar VS, Kisslo JA. The diagnostic and prognostic significance of coronary artery calcification. A report of 800 cases. Radiology. 1980;137:609-16.
[5] Reinmuller R, Lipton MJ. Detection of coronary artery calcification by computed tomography. Dynamic Cardiovasc Imaging. 1987;1:139-45.
[6] Schmermund A. The Agatston calcium score: a milestone in the history of cardiac CT. J Cardiovasc Comput Tomogr. 2014;8:414-7.
[7] Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15:827-32.
[8] Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. Radiology. 1998;208:807-14.
[9] Callister T, Janowitz W, Raggi P. Sensitivity of two electron beam tomography protocols for the detection and quantification of coronary artery calcium. AJR Am J Roentgenol. 2000;175:1743-6.
[10] Moselewski F, O'Donnell CJ, Achenbach S, Ferencik M, Massaro J, Nguyen A, et al. Calcium concentration of individual coronary calcified plaques as measured by multidetector row computed tomography. Circulation. 2005;111:3236-41.
[11] Mahnken AH, Wildberger JE, Sinha AM, Flohr T, Truong HT, Krombach GA, et al. Variation of the coronary calcium score depending on image reconstruction interval and scoring algorithm. Invest Radiol. 2002;37:496-502.
[12] Becker CR, Kleffel T, Crispin A, Knez A, Young J, Schoepf UJ, et al. Coronary artery calcium measurement: agreement of multirow detector and electron beam CT. AJR Am J Roentgenol. 2001;176:1295-8.
[13] Detrano RC, Anderson M, Nelson J, Wong ND, Carr JJ, McNitt-Gray M, et al. Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility--MESA study. Radiology. 2005;236:477-84.
[14] Morin RL, Gerber TC, McCollough CH. Radiation dose in computed tomography of the heart. Circulation. 2003;107:917-22.
[15] Mahnken AH, Wildberger JE, Simon J, Koos R, Flohr TG, Schaller S, et al. Detection of coronary calcifications: feasibility of dose reduction with a body weight-adapted examination protocol. AJR Am J Roentgenol. 2003;181:533-8.
[16] Voros S, Rivera JJ, Berman DS, Blankstein R, Budoff MJ, Cury RC, et al. Guideline for minimizing radiation exposure during acquisition of coronary artery calcium scans with the use of multidetector computed tomography: a report by the Society for Atherosclerosis Imaging and Prevention Tomographic Imaging and Prevention Councils in collaboration with the Society of Cardiovascular Computed Tomography. Journal of cardiovascular computed tomography. 2011;5:75-83.
[17] Nakazato R, Dey D, Gutstein A, Le Meunier L, Cheng VY, Pimentel R, et al. Coronary artery calcium scoring using a reduced tube voltage and radiation dose protocol with dual-source computed tomography. J Cardiovasc Comput Tomogr. 2009;3:394-400.
[18] Kirsch J, Buitrago I, Mohammed TL, Gao T, Asher CR, Novaro GM. Detection of coronary calcium during standard chest computed tomography correlates with multi-detector computed tomography coronary artery calcium score. Int J Cardiovasc Imaging. 2012;28:1249-56.

[19] Otton JM, Lonborg JT, Boshell D, Feneley M, Hayen A, Sammel N, et al. A method for coronary artery calcium scoring using contrast-enhanced computed tomography. Journal of cardiovascular computed tomography. 2012;6:37-44.
[20] Deprez FC, Vlassenbroek A, Ghaye B, Raaijmakers R, Coche E. Controversies about effects of low-kilovoltage MDCT acquisition on Agatston calcium scoring. Journal of cardiovascular computed tomography. 2013;7:58-61.
[21] Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010;56:e50-103.
[22] Guidelines N. New Zealand Primary Care Handbook 2012. Wellington: New Zealand Guidelines Group. 2012;3rd Edition.
[23] Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008;358:1336-45.
[24] Wang Z, Hoy WE. Is the Framingham coronary heart disease absolute risk function applicable to Aboriginal people? The Medical journal of Australia. 2005;182:66-9.
[25] Ellis CJ, Legget ME, Edwards C, Van Pelt N, Ormiston JA, Christiansen J, et al. High calcium scores in patients with a low Framingham risk of cardiovascular (CVS) disease: implications for more accurate CVS risk assessment in New Zealand. N Z Med J. 2011;124:13-26.
[26] Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. Jama. 2004;291:210-5.
[27] Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol. 2007;49:1860-70.
[28] LaMonte MJ, FitzGerald SJ, Church TS, Barlow CE, Radford NB, Levine BD, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. American journal of epidemiology. 2005;162:421-9.
[29] Shaw LJ, Giambrone AE, Blaha MJ, Knapper JT, Berman DS, Bellam N, et al. Long-Term Prognosis After Coronary Artery Calcification Testing in Asymptomatic Patients: A Cohort Study. Ann Intern Med. 2015;163:14-21.
[30] Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol. 2007;49:378-402.
[31] Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. J Am Coll Cardiol. 2004;43:1663-9.
[32] Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. Jama. 2010;303:1610-6.
[33] Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. Jama. 2012;308:788-95.
[34] Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Statistics in medicine. 2008;27:157-72; discussion 207-12.
[35] Erbel R, Mohlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol. 2010;56:1397-406.

[36] Elias-Smale SE, Proenca RV, Koller MT, Kavousi M, van Rooij FJ, Hunink MG, et al. Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. J Am Coll Cardiol. 2010;56:1407-14.
[37] Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffmann U, Cury RC, et al. Diagnostic and prognostic value of absence of coronary artery calcification. JACC Cardiovasc Imaging. 2009;2:675-88.
[38] Blaha M, Budoff MJ, Shaw LJ, Khosa F, Rumberger JA, Berman D, et al. Absence of coronary artery calcification and all-cause mortality. JACC Cardiovasc Imaging. 2009;2:692-700.
[39] Shareghi S, Ahmadi N, Young E, Gopal A, Liu ST, Budoff MJ. Prognostic significance of zero coronary calcium scores on cardiac computed tomography. J Cardiovasc Comput Tomogr. 2007;1:155-9.
[40] Silverman MG, Blaha MJ, Krumholz HM, Budoff MJ, Blankstein R, Sibley CT, et al. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. European heart journal. 2014;35:2232-41.
[41] Valenti V, B OH, Heo R, Cho I, Schulman-Marcus J, Gransar H, et al. A 15-Year Warranty Period for Asymptomatic Individuals Without Coronary Artery Calcium: A Prospective Follow-Up of 9,715 Individuals. JACC Cardiovasc Imaging. 2015.
[42] Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol. 2001;87:1335-9.
[43] McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2006;113:30-7.
[44] Hoffmann U, Massaro JM, Fox CS, Manders E, O'Donnell CJ. Defining normal distributions of coronary artery calcium in women and men (from the Framingham Heart Study). Am J Cardiol. 2008;102:1136-41, 41 e1.
[45] Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation. 2007;115:114-26.
[46] Michos ED, Nasir K, Braunstein JB, Rumberger JA, Budoff MJ, Post WS, et al. Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. Atherosclerosis. 2006;184:201-6.
[47] Lakoski SG, Greenland P, Wong ND, Schreiner PJ, Herrington DM, Kronmal RA, et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the multi-ethnic study of atherosclerosis (MESA). Arch Intern Med. 2007;167:2437-42.
[48] Chao SP, Law WY, Kuo CJ, Hung HF, Cheng JJ, Lo HM, et al. The diagnostic accuracy of 256-row computed tomographic angiography compared with invasive coronary angiography in patients with suspected coronary artery disease. European heart journal. 2010;31:1916-23.
[49] Gitsioudis G, Hosch W, Iwan J, Voss A, Atsiatorme E, Hofmann NP, et al. When do we really need coronary calcium scoring prior to contrast-enhanced coronary computed tomography angiography? Analysis by age, gender and coronary risk factors. PLoS One. 2014;9:e92396.
[50] Hausleiter J, Martinoff S, Hadamitzky M, Martuscelli E, Pschierer I, Feuchtner GM, et al. Image quality and radiation exposure with a low tube voltage protocol for coronary CT angiography results of the PROTECTION II Trial. JACC Cardiovasc Imaging. 2010;3:1113-23.
[51] Hosch W, Stiller W, Mueller D, Gitsioudis G, Welzel J, Dadrich M, et al. Reduction of radiation exposure and improvement of image quality with BMI-adapted prospective cardiac computed tomography and iterative reconstruction. European journal of radiology. 2012;81:3568-76.
[52] Chang SM, Nabi F, Xu J, Peterson LE, Achari A, Pratt CM, et al. The coronary artery calcium score and stress myocardial perfusion imaging provide independent and complementary prediction of cardiac risk. J Am Coll Cardiol. 2009;54:1872-82.

[53] Knez A, Becker A, Leber A, White C, Becker CR, Reiser MF, et al. Relation of coronary calcium scores by electron beam tomography to obstructive disease in 2,115 symptomatic patients. Am J Cardiol. 2004;93:1150-2.
[54] Kwon SW, Kim YJ, Shim J, Sung JM, Han ME, Kang DW, et al. Coronary artery calcium scoring does not add prognostic value to standard 64-section CT angiography protocol in low-risk patients suspected of having coronary artery disease. Radiology. 2011;259:92-9.
[55] Pursnani A, Chou ET, Zakroysky P, Deano RC, Mamuya WS, Woodard PK, et al. Use of coronary artery calcium scanning beyond coronary computed tomographic angiography in the emergency department evaluation for acute chest pain: the ROMICAT II trial. Circ Cardiovasc Imaging. 2015;8.
[56] Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. J Am Coll Cardiol. 2005;46:166-72.
[57] He ZX, Hedrick TD, Pratt CM, Verani MS, Aquino V, Roberts R, et al. Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. Circulation. 2000;101:244-51.
[58] Moser KW, O'Keefe JH, Jr., Bateman TM, McGhie IA. Coronary calcium screening in asymptomatic patients as a guide to risk factor modification and stress myocardial perfusion imaging. J Nucl Cardiol. 2003;10:590-8.
[59] Douglas PS, Khandheria B, Stainback RF, Weissman NJ, Peterson ED, Hendel RC, et al. ACCF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for stress echocardiography: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, American Society of Echocardiography, American College of Emergency Physicians, American Heart Association, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance: endorsed by the Heart Rhythm Society and the Society of Critical Care Medicine. Circulation. 2008;117:1478-97.
[60] Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2889-934.
[61] Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. Lancet. 2013;382:1762-5.
[62] Blaha MJ, Budoff MJ, DeFilippis AP, Blankstein R, Rivera JJ, Agatston A, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. Lancet. 2011;378:684-92.
[63] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195-207.
[64] Blaha MJ, Silverman MG, Budoff MJ. Is there a role for coronary artery calcium scoring for management of asymptomatic patients at risk for coronary artery disease?: Clinical risk scores are not sufficient to define primary prevention treatment strategies among asymptomatic patients. Circ Cardiovasc Imaging. 2014;7:398-408; discussion
[65] Rozanski A, Gransar H, Shaw LJ, Kim J, Miranda-Peats L, Wong ND, et al. Impact of coronary artery calcium scanning on coronary risk factors and downstream testing the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. J Am Coll Cardiol. 2011;57:1622-32.
[66] Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. Jama. 2006;295:1556-65.
[67] Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol. 2010;55:2399-407.

[68] Chow BJ, Small G, Yam Y, Chen L, McPherson R, Achenbach S, et al. Prognostic and therapeutic implications of statin and aspirin therapy in individuals with nonobstructive coronary artery disease: results from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter registry) registry. Arteriosclerosis, thrombosis, and vascular biology. 2015;35:981-9.
[69] Cho I, Chang HJ, Sung JM, Pencina MJ, Lin FY, Dunning AM, et al. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM Registry (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry). Circulation. 2012;126:304-13.
[70] Martin SS, Blaha MJ, Blankstein R, Agatston A, Rivera JJ, Virani SS, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis. Circulation. 2014;129:77-86.
[71] Pursnani A, Massaro JM, D'Agostino RB, Sr., O'Donnell CJ, Hoffmann U. Guideline-Based Statin Eligibility, Coronary Artery Calcification, and Cardiovascular Events. Jama. 2015;314:134-41.
[72] Roberts ET, Horne A, Martin SS, Blaha MJ, Blankstein R, Budoff MJ, et al. Cost-effectiveness of coronary artery calcium testing for coronary heart and cardiovascular disease risk prediction to guide statin allocation: the Multi-Ethnic Study of Atherosclerosis (MESA). PLoS One. 2015;10:e0116377.
[73] Kalia NK, Cespedes L, Youssef G, Li D, Budoff MJ. Motivational effects of coronary artery calcium scores on statin adherence and weight loss. Coron Artery Dis. 2015;26:225-30.
[74] Antithrombotic Trialists C, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849-60.
[75] Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. Jama. 2006;295:306-13.
[76] Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med. 2012;172:209-16.
[77] Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;150:405-10.
[78] Miedema MD, Duprez DA, Misialek JR, Blaha MJ, Nasir K, Silverman MG, et al. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the multi-ethnic study of atherosclerosis. Circ Cardiovasc Qual Outcomes. 2014;7:453-60.
[79] Paixao AR, Chakravorty R, Khera A, Leonard D, DeFina LF, Barlow CE, et al. Disagreement Between Different Definitions of Coronary Artery Calcium Progression. JACC Cardiovasc Imaging. 2015;8:743-4.
[80] Min JK, Lin FY, Gidseg DS, Weinsaft JW, Berman DS, Shaw LJ, et al. Determinants of coronary calcium conversion among patients with a normal coronary calcium scan: what is the "warranty period" for remaining normal? J Am Coll Cardiol. 2010;55:1110-7.
[81] Alluri K, McEvoy JW, Dardari ZA, Jones SR, Nasir K, Blankstein R, et al. Distribution and burden of newly detected coronary artery calcium: Results from the Multi-Ethnic Study of Atherosclerosis. J Cardiovasc Comput Tomogr. 2015;9:337-44 e1.
[82] Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. Arteriosclerosis, thrombosis, and vascular biology. 2004;24:1272-7.
[83] Budoff MJ, Hokanson JE, Nasir K, Shaw LJ, Kinney GL, Chow D, et al. Progression of coronary artery calcium predicts all-cause mortality. JACC Cardiovasc Imaging. 2010;3:1229-36.
[84] Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2013;61:1231-9.
[85] Lee KK, Fortmann SP, Fair JM, Iribarren C, Rubin GD, Varady A, et al. Insulin resistance independently predicts the progression of coronary artery calcification. American heart journal. 2009;157:939-45.

[86] Wong ND, Kawakubo M, LaBree L, Azen SP, Xiang M, Detrano R. Relation of coronary calcium progression and control of lipids according to National Cholesterol Education Program guidelines. Am J Cardiol. 2004;94:431-6.
[87] Raggi P, Davidson M, Callister TQ, Welty FK, Bachmann GA, Hecht H, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). Circulation. 2005;112:563-71.
[88] Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. J Am Coll Cardiol. 2015;65:1273-82.

APPENDIX A:

Development process:

This position statement was developed by members of the Society of Cardiovascular Computed Tomography (SCCT) International Regional Committee for Australia & New Zealand and appointed members of the Imaging Council of the Cardiac Society of Australia & New Zealand. Included are members with population health expertise and non-imaging backgrounds to provide a balanced view. The document was then reviewed by the Imaging Council of CSANZ, the Clinical and Preventative Cardiology Council, and the Quality and Standards Committee before being ratified by the Board of CSANZ.

Conflicts of interest /Disclosures:

Dr Liew has no disclosures.
Dr Chow has no disclosures.
Dr van Pelt has no disclosures.
Dr Younger has no disclosures.
Dr Jelenik has no disclosures.
Dr Chan has no disclosures.
Dr Hamilton-Craig has received research grants from Abbott, Siemens, and the Smart Futures Fellowship, Queensland Government.

APPENDIX B:

Figure 1

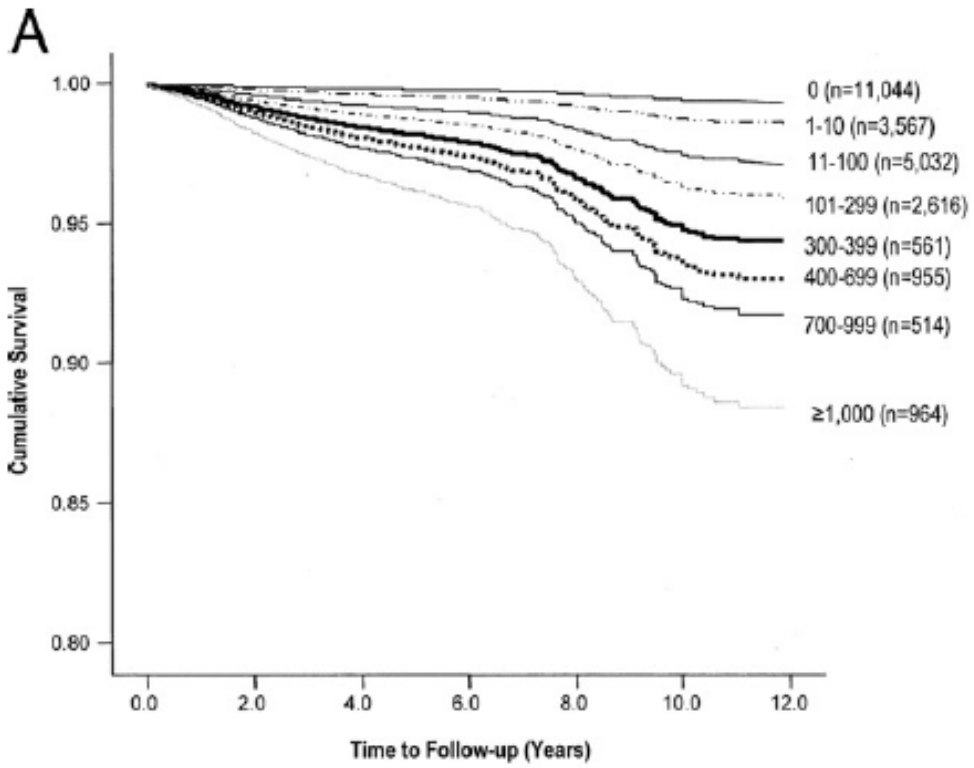

Fig 1. Increasing CAC predicts mortality (Budoff et al, JACC 2007).

Figure 2

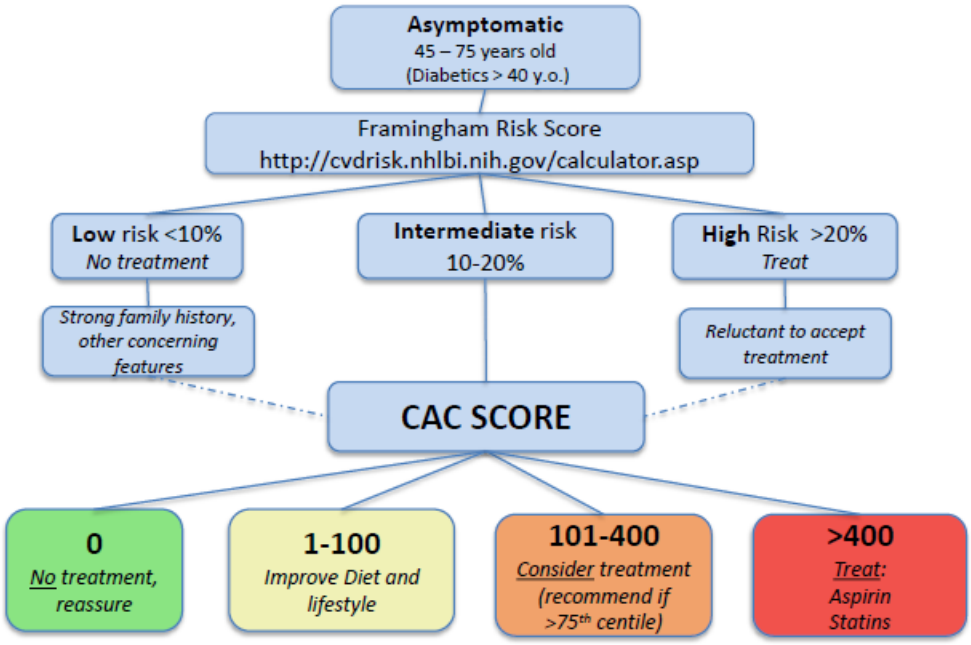

Fig 2. Suggested algorithm for use of CAC scoring.

Table 1: Annual rate of myocardial infarct or death, and relative risk according to CAC. (Adapted from Greenland, JACC 2007).

	Annual event rate	Relative Risk (cf. CAC = 0)
CAC 1-99	0.4%	1.9
CAC 100-399	1.3%	4.3
CAC ≥ 400	2.4%	7.2

Table 2: Normal CAC distribution in healthy cohort without risk factors (Adapted from Hoffmann, AJC 2008)

	Men				Women			
Age	<45	45-54	55-64	65-74	<45	45-54	55-64	65-74
Percentile								
25th	0	0	0	40	0	0	0	0
50th	0	0	30	173	0	0	0	4
75th	0	21	162	585	0	0	17	43
90th	8	108	315	1230	0	1	91	212

Table 3: General Framingham patients stratified by FRS risk groups and CAC. (Adapted from Hoffmann, AJC 2008)

FRS 10-year risk	Men (n = 1652)			Women (n = 1576)	
	Low (<6%)	Intermediate (6-20%)	High (>20%)	Low (<6%)	Intermediate (6-20%)
Patients *n* (%)	741 (44.9%)	798 (48.3%)	113 (6.8%)	1197 (76%)	379 (24%)
CAC = 0	68%	33%	10%	77%	42%
CAC 1-100	25%	35%	22%	17%	34%
CAC 101-400	5%	18%	21%	4%	17%
CAC >400	2%	14%	47%	2%	7%

Table 4: Suggested management based on CAC results for asymptomatic patients

CAC	**10-year risk**	**Guidance**
0	Very Low (< 1%)	Reassure; maintenance of healthy diet and lifestyle.
1-100	Low (<10%)	Maintenance of healthy diet and lifestyle
101 - 400	Moderate (10-20%)	Aspirin **recommended** Statins **considered reasonable**
101 – 400 & >75th centile	Moderately High (15-20%)	Reclassify as high risk; Aspirin **recommended** Statins **considered reasonable**
>400	High (>20%)	Aspirin **recommended** Statin **recommended**, to achieve target LDL < 2.0 mmol/L Consider functional assessment.