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Trial Design Paper

Rationale and Design of a Trial to Personalize Risk Assessment in Familial Coronary Artery Disease

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Abstract

Background: The lifetime risk of coronary artery disease (CAD) is doubled in people with a family history (FHx) of premature disease, yet this risk is not captured in most 5 or 10-year risk assessment algorithms. Coronary artery calcium scoring (CCS) is a marker of subclinical CAD risk, which has been shown in observational studies to provide prognostic information that is incremental to clinical assessment, is relatively inexpensive and performed with a small radiation dose. However, the use of CCS in guiding prevention is not strongly supported by guidelines. Showing definitive evidence of the efficacy and cost-effectiveness of CCS is therefore of importance.

Study design: The proposed randomized controlled trial (RCT) of the use of CCS, will be targeted to 40-70 year old 1st degree relatives of patients with CAD onset <60 years old, or 2nd degree relatives of patients with onset <50 years old. Control patients will undergo standard risk scoring and be blinded to CCS results. In the intervention group, primary prevention in patients undergoing CCS will be informed by this score. At three years, effectiveness will be assessed on change in plaque volume at CT coronary angiography (CTCA), the extent of which has been strongly linked to outcome.

Summary: The CAUGHT-CAD trial will provide evidence to inform the guidelines regarding the place of CCS in decision-making regarding primary prevention of patients with a FHx.

Keywords. Coronary calcium score, prevention, family history, coronary artery disease.

Rationale

The frequency of all ischemic heart disease endpoints is increased in relatives of patients with documented CAD. In the Framingham study, a family history of premature CAD (FHx) doubled the odds of CAD (1), and among 5347 asymptomatic individuals in the Multi-Ethnic Study of Atherosclerosis (MESA), the odds of a coronary calcium score (CCS) >0 was increased 1.94 times (95% CI, 1.64 to 2.29 odds) by FHx, independent of age, gender, and race (2). However, FHx has not been included in most CAD risk scores (3), with few exceptions (4), for a variety of reasons. First, the need for parsimony in risk assessment algorithms – although FHx is associated with co-exposure to treatable risks (such as poor diet choices or passive smoking) within the family environment, and also potentially accounts for genetic contributions to the other classical risk factors. Second, the scores have focused on 5 and 10–year risk, while FHx seems to have most impact on lifetime risk (5). Third, there has been a focus on traditional risk factors (smoking, hyperlipidemia, diabetes, and hypertension), which together with abdominal obesity, psychosocial factors, and diet and physical activity account for 90% or more of population-attributable risk of myocardial infarction (6). Fourth, the reclassification of risk with FHx has been considered of borderline value in the population context (7); environment-based risk factors outweighing the contribution of genetic risk factors in population attributable risk (8).

Failure to incorporate FHx in risk assessment may lead to under-treatment of those with a FHx at intermediate risk - and overtreatment of similar subjects with no FHx (9). In this situation, CCS may be a useful additional risk marker (10), especially in individuals deemed at low risk by existing assessment measures (1). A meta-analysis of 32 studies linking measures of subclinical atherosclerosis recently showed a significant relationship between these markers and FHx of CAD, independent of traditional risk factors (11). These features support a more active approach in patients with a FHx. There are two ways of addressing this. First, to compensate for the effect of FHx, guidelines in some jurisdictions have proposed lower treatment thresholds, which is consistent with an approach of tailoring the intensity of primary prevention strategies to the risk of coronary events (12). The problem is that there is no consensus on treatment thresholds – which currently range from a 10

year absolute risk as low as 7.5% in the most recent US guidelines (3), through to 20% in the UK guidelines (13) and 30% in New Zealand (14). This variation reflects various degrees of enthusiasm for treating an intermediate risk group (2–10% 5-year risk) in whom pharmacological or lifestyle interventions may show only modest returns (15).

Another way of resolving the conundrum of FHx would be to seek evidence of subclinical atherosclerosis in order to further stratify risk levels (16). Detection of subclinical CAD using coronary calcium score (CCS) is feasible and reliable, has been extensively studied in risk evaluation in primary prevention, and is more predictive of outcome than alternative tests such as carotid intima-medial thickness (17). However, CCS has not been incorporated as a routine in the guidelines, and most young patients with a positive CCS score do not satisfy criteria for lipid-lowering therapy by global risk scoring. In 2611 asymptomatic participants aged 30-65 years in the Dallas Heart Study, the use of non-invasive atherosclerosis imaging resulted in bidirectional reclassification of eligibility for lipid-lowering therapy, with 6.3% of subjects being reclassified as being not at goal and 2.7% as being at goal (18). In a median follow-up of 7.6 years in the MESA study, 55% of incident events (myocardial infarction, angina resulting in revascularization, resuscitated cardiac arrest, stroke, CV death) occurred in the 21% of participants with CCS ≥100, even though 65% of events occurred in participants with 0 or 1 lipid abnormalities (7). This evidence supports the role of CCS for predicting risk, but the evidence in favor of CCS providing an outcome benefit is currently limited. Accordingly, we developed a randomized controlled trial (RCT) to demonstrate whether the use of CCS to select intermediate-risk subjects with a FHx for primary prevention, altered the progression and outcome of CAD.

Study design and objectives

Design. The CAUGHT-CAD study (Coronary Artery calcium score: Use to Guide management of HerediTary CAD); ACTRN 12614001294640, https://www.anzctr.org.au/) is an RCT that seeks to evaluate the utility of CCS in intermediate-risk subjects with a FHx who do not satisfy current

Australian guidelines for primary prevention. The primary endpoint will be change of coronary plaque volume at 3 years, and the secondary endpoint will be outcome after 9 years.

Support. The CAUGHT-CAD trial (Coronary Artery calcium score: Use to Guide management of Hereditary Coronary Artery Disease) is supported in part by a Project Grant from the National Health and Medical Research Council, Canberra, Australia. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Patient selection. Asymptomatic subjects age 40-70 years old with a FHx of CAD involving an index patient <60y (1st degree) or <50y (2nd degree) who are not already on statins, who have a total cholesterol (TC) ≤6.5 mmol/L and LDLC <5 mmol/L, and who have a 5 year risk >2% using the Australian risk calculator. This calculates absolute 5-year risk of coronary heart disease and stroke (in contrast to 10 year coronary risk from the Framingham calculator) from age, sex, smoking status, blood pressure, total and high-density lipoprotein cholesterol, diabetes mellitus and ECG evidence of left ventricular hypertrophy (http://www.cvdcheck.org.au/), using an equation based on data from the Framingham Study.

Subjects are excluded if they are already on statins (or intolerant to statins), or have symptomatic vascular disease (for which statins would be indicated), pre-existing muscle disease (as this may be confused with myalgia from statins), atrial fibrillation (which interferes with CTCA), or chronic kidney disease on hemodialysis (because of vascular calcification). Groups unable to provide informed consent, or with major systemic illness limiting life expectancy are excluded, as are women of child-bearing potential. Of note, statins are prescribed as "usual care" for Australian patients with diabetes mellitus (DM) in the presence of total cholesterol >5.5 mmol/L, age ≥60 years old, microalbuminuria or of Aboriginal or Torres Strait Islander origin, and consequently patients in these categories are excluded – however, all other patients with DM are eligible for randomization.

In all cases, the first step is a standard clinical history (19) and risk evaluation using the Australian risk calculator. Low (<2% 5-year risk) and high risk patients (>10% 5-year risk) are excluded and referred for management. The remainder undergo CCS.

Clinical evaluation. Baseline measures include a survey of health behavior, chronic illnesses and medications and socio-demographic factors; measures of health-related and CVD-specific quality of life, depression and anxiety (5,20); a 6 minute walk test; BMI and waist circumference measures, and systolic and diastolic BP. The following investigations are undertaken at baseline profiling; fasting lipid profile, glucose, high-sensitive C-reactive protein, creatinine, creatine kinase, liver function tests and full blood count.

Coronary CT. CCS are performed on a dual source 128 slice CT machines, equipped with radiation dose reduction systems and appropriate reconstruction algorithms. Images are performed at a temporal resolution of 330msec and spatial resolution 0.24mm. The estimated radiation dose for calcium score is approximately 1mSv (dose length product 90mGycm). The Agatston score, performed on standard commercial workstations, is used to stratify groups with CCS >0 and <100 and 100-400 (Figure 1).

Eligible patients (CCS >0 and <400) undergo a CTCA (for baseline plaque volume and exclusion of serious CAD). Excellent image quality is essential for plaque volume measurement. Acquisitions are not performed at heart-rates >65/minute (the target is <60/minute). Patients are prepared with oral metoprolol, and additional oral and/or intravenous beta-blockade may be administered to further lower the heart rate. In patients intolerant of beta blockers, verapamil or ivabradine are used. CTCA will also be performed on the same CT system, with temporal resolution reduced to 165 msec during CTCA acquisition. The estimated radiation dose for full CTCA varies according to patient size and heart rate, but is routinely ~2 mSv (21).

After CT, patients with a score of 0 (low risk, who do not require specific therapy) are excluded, as are those with a score >400 (who are at risk of significant coronary stenosis), or with serious obstructive disease by CTCA (Figure 1).

Randomisation. Subjects are centrally randomized using the Data Management Centre, with a 1:1 ratio of CCS-guided and usual care (CCS blinded). As CCS may be a determinant of progression and risk, randomization as stratified by groups with CCS<100 and 100-400 (Figure 1).

Therapy. In *usual care*, subjects will undergo standardized education about CAD prevention and risk management will be undertaken by the patient's physician, blinded to the evaluation of CCS. This will involve weight control, treatment of dysglycemia and hypertension to target, and lipid management in accordance with current national criteria. In some instances, statins may be started – based on the physician's evaluation of risk – but this is expected to be uncommon.

In *CCS-guided care*, all participants will undergo tailored health profiling to define individual modifiable risk factors and the delivery of clearly articulated health care goals. This standardized intervention will include: *supporting lifestyle and risk modification* (individualized nutrition, weight and physical activity goals), *encouraging active self-management of risk* (one-on-one counseling and education, including use of the CCS image to facilitate discussion) and *improving coordination of care* between subjects' healthcare providers (e.g. primary care, pharmacists etc) to achieve individual goals for optimal risk and disease management.

In the CCS-guided arm, participants with a CCS>0 are treated with atorvastatin 40 mg/d, based on the recommendation of moderate-high intensity statin in patients with >7.5% 10-year risk in the guidelines (3), and are not treated to target. Given the planned screening measures, intolerance (eg. myalgia) at this dose was expected to be <5%. In the presence of myalgia, the dose is reduced to 20 mg, and if unsuccessful, by a switch to rosuvastatin or pravastatin, with dose reduction if necessary. If all steps are unsuccessful, the drug is stopped and the subject retained in the trial with follow-up on grounds of intention to treat. Other therapy indicated by standard primary prevention guidelines (e.g. anti-hypertensives) will also be initiated. Follow-up is arranged at one month (phone or e-mail according to preference) to review the efficacy of the self-care plan and prescribed statin therapy. A face-to-face meeting at three months reviews longer-term risk management.

Endpoints. The primary end-point is *absolute change in total coronary plaque volume* after 36 months after CCS, assessed by an independent core laboratory.

Baseline and follow-up plaque volume studies will be blindly compared in the core laboratory using a workstation for 3-dimensional image analysis. Volume rendering and curved multi-planar reformats are used to evaluate the coronary vessels. Vessels $\geq$2 mm diameter will be assessed for the presence of plaque. Images undergo semi-automated image extraction using proprietary software. After

identifying the plaque area, we use an automated plaque detection tool to quantify plaque volume on both baseline and follow-up scans (22,23). The automated software detects outer vessel wall and lumen and the intervening plaque, but in each case, we manually adjust borders of the vessel wall and lumen to optimize and confirm software estimates. In cases of mixed plaque phenotype, we also manually adjust the borders to correctly separate calcified from non-calcified components. The software then provides volume of both components of mixed plaques. Low attenuation plaque is identified as plaque with attenuation <30 HU. This technique has been previously published (24). Inter- and intra-observer variability has been published previously, but will be assessed on 10% of scans.

Secondary endpoints will be: MACE (death, myocardial infarction, stroke) after 9 years, symptom status, health-related quality-of-life (health state utility values), health resource consumption, including hospitalization and data-linkage to administrative data. These data will inform a model to assess cost-effectiveness.

Safety. Every opportunity will be taken to ensure that significant CAD is actioned - the study will be restricted to CCS≤400 and the presence of left main involvement at CTCA will lead to notification of the subject's physician and appropriate investigation. Extracardiac findings will also be investigated in all subjects. However, no other cardiac interventions are planned in control patients. CT findings will be made available to all subjects at the end of the study.

Radiation safety is an important consideration. The use of prospective gating has permitted a radiation dose of 2mSv, analogous to a year's background radiation in Australia, and a fatal cancer risk (assuming linearity of risk) of 1:10,000.

The main anticipated side-effect of statin therapy is myalgia. Adverse events (AEs) and serious adverse events (SAEs) are identified at follow-up. A Data Safety and Monitoring Board, led by an experienced clinician, will review the safety findings at the end of each year. All endpoints will be blindly adjudicated (including determination of probable causality). While it is unlikely that there will be events in the study time-frame that justify stopping, we will use the Haybittle-Peto stopping rule at a p=0.001.

Data Collection and Management. Standardized data acquisition is obtained using Case Report Forms. Data capture, analyses and archiving are coordinated through a secure web-based database and electronic capture of paper-based CRFs. Assessments will be undertaken at a series of mandatory time-points with a window of one month either side of the scheduled visit to permit flexible scheduling (Table 1). Independent study monitors will verify 5% of study data against source documents.

Statistical Analyses All data will be pooled and summarized with respect to demographic and baseline characteristics. Exploratory data analyses will be performed using descriptive statistics.

The primary analysis will compare the 3-year coronary plaque volume in CCS-guided and usual care subjects. We will use linear mixed models to correct for coincidental between-group differences despite randomization, and to obtain the effect size of CCS-based management, independent of age, sex and baseline risk. The same methods will be used for the secondary end-points. The primary analysis will be on grounds of intention-to-treat (ITT), but we will also perform a per-protocol analysis.

Events are expected to be very rare. Nonetheless, differences between groups with respect to the number and/or timing of events will be assessed using survival curves for all-cause and event-free survival. Cox-Proportional Hazards Models will be used to examine the independent effect of treatment and risk factors on outcomes.

Sample size calculations. Power calculations have been based on the following observations. Prior observational studies have suggested that the difference between statin treated and untreated patients with regard to change in coronary plaque volume is in the range of 40-60 mm^3. In a CAD screening population, approximately 50% of whom had a FHx of CAD, baseline noncalcified plaque was in the range of 315 mm^3 and low attenuation plaque of 95 mm^3, statins reduced noncalcified plaque volume by 47±72 mm^3 (vs control 14±77, $p<0.001$) and low attenuation plaque by 12±19 mm^3 (vs control 6±23, $p<0.0001$) over 12 months (24). In contrast, a virtual histology-intravascular ultrasound study of 172 CAD patients showed atheroma volumes of 152±132 mm^3 with CCS=0, 171±114 mm^3 with CCS 1-100, and 195±149 mm^3 with CCS 101-400. Respective low attenuation plaque volumes were 15±18, 20±19 and 23±19 (25). Accordingly, we have powered this study for a delta plaque volume of

20 mm^3, to allow for smaller differences in progression rates between the groups than in prior observational reports (Table 2). Previous work has shown CCS exclusion criteria (0 and >400) in 30% of intermediate risk patients with FHx of CAD (2). We have therefore determined that 638 patients will need to undergo serial imaging to have 80% power to detect a difference between the groups of 20 mm^3, with a standard deviation of 90 mm^3 (two-sided α=0.05). Assuming that 15% of subjects will drop out or not have evaluable imaging at both time points, 734 subjects will be randomized over the 1st 18 months of the study, to provide a minimum 3 year follow-up. Other scenarios (involving larger change in plaque volume or smaller variances) may enable appropriate analysis to be performed with a smaller sample size (Table 2).

Based on a previous non-randomized study of patients with FHx and CC (29), we expect 9 year event rates of 14 vs 25%, and 540 patients would have a 90% power to show a difference at p=0.05.

Cost-effectiveness analysis. An economic analysis will be undertaken to assess the cost-effectiveness of CCS guided primary prevention of CVD from a health care payer's perspective. The incremental cost-effectiveness ratio (ICER) for CCS guided prevention compared with routine care will be calculated based on a Markov Model. The model will be informed by observed transition probabilities between health states, and costs and health state utility values assessed during the trial. Uncertainty will be assessed through a Monte Carlo simulation, enabling the calculation of a confidence interval for the ICER.

Preliminary data.

The most common source of recruitment has been direct from the community – especially large workplaces – and in response to media advertisements seeking the involvement of asymptomatic subjects with a FHx. Smaller numbers have originated from family members of patients with premature CAD attending inpatient or outpatient clinics, from lipid specialists and primary care – including searches of electronic health records.

The first 500 scanned patients had a mean age of 59±8 years, 53% were women, and the 5 year risk was 5±3%) (Table 3). From 40-70 year-old subjects with a family history, and without exclusion criteria, there was a screening failure rate of 51%. The most common causes were

low risk (24%), high risk (17%), or because the participant decided not to proceed with recruitment, including because of radiation safety concerns (10%).

CCS ranged from 0 to >2000; 51% had a score of 0, but few had a score >400. Subjects with a score of <100 accounted for >50% of those randomized (Figure 2). Plaque volume (89±81ml) was calculated in all subjects, being 57mm^3 and 138mm^3 in lower and upper CCS groups, respectively. CCS>0 was associated with age, but not age of onset in the patient's relative, BP, lipid profile or BMI (Table 4).

These findings emphasize that half of *a priori* intermediate-risk, middle-aged subjects with a FHx of premature CAD have a CCS=0, conferring low risk *a posteriori*. This finding suggests that the current guidance regarding lower threshold for primary prevention intervention may not be beneficial in the majority of patients with a FHx.

Context

The CAUGHT-CAD trial seeks to define the value of assessing CCS in patients with a FHx and *a priori* intermediate-risk of CAD as a means of identifying a subclinical subgroup that would preferentially benefit from primary preventative therapy. The primary outcome is change in plaque volume, but we will study the impact of CT-based intervention on outcomes over a decade.

CCS and primary prevention. CCS is known to be an important predictor of outcome in primary prevention. For example, a classic study of >25,000 consecutive asymptomatic subjects, showed the association of CCS with outcome, irrespective of other risk factors (26). Indeed, the addition of CCS to traditional risk factors improved the area under the ROC curves, from 0.61 to 0.81 ($p<0.0001$), a finding confirmed in other studies (27). A score of zero was identified in 44% of individuals, who had an event rate of 0.6% over 12-years - a finding also independent of other risk factors. A CCS ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity has been proposed to facilitate decisions regarding lipid-lowering management in intermediate-risk subjects (3).

However, it remains unproven that this risk assessment strategy *changes* outcome. This could be achieved in two ways – by facilitating selection and/or facilitating adherence with preventive therapy.

Showing subjects their CCS is strongly associated with subjects initiating therapy (28) and in a systematic review of eight non-randomised studies (n=2,994) evaluating the use of CCS in improving adherence to therapy, Rodondi et al (29) found that subjects with evidence of atherosclerosis showed better perception of cardiovascular risk and improved adherence to lifestyle advice. However, in four RCTs (n=709), screening did not influence risk for poorer outcomes, with the exception, in one study, of improved smoking cessation (18% vs. 6%, p=0.03). The results of one negative RCT may be particularly instructive (30); in a post hoc analysis, it suggested that *targeted intervention* in patients with a FHx improved event-free survival in 1000 patients (age 59±6 years) with follow-up over 4.3 years (31). The findings support the role of patient selection in screening, and hints at a specific indication for patients with a FHx. Indeed, the appropriate use criteria for cardiac CT lists the use of CCS in low risk patients with a FHx as being appropriate (32).

Identifying response. The long-term benefits of CCS-guided therapy are likely to be attributable to reduction of plaque volume by appropriate therapy. The progression of coronary atherosclerotic burden measured by intravascular ultrasound (IVUS) is linked to adverse cardiovascular events (33); each standard deviation increase in change in percent atheroma volume was associated with a 1.20-fold greater risk for MACE. The use of coronary CT to measure total plaque burden has been well validated. In a recent meta-analysis of 42 studies (n=1360, 75% men; mean 59 years), no significant difference was found between CTCA and IVUS measurements of vessel lumen cross-sectional area, plaque area, percentage of area stenosis, or plaque volume. CTCA had 93% sensitivity and 92% specificity for the detection of any plaque compared with IVUS. The same was true in eight studies of plaque volume in studies using automated measurement techniques (34). However, while CCS acts as the trigger for therapy, because of the cofounding effects of statins on CCS this is not itself a suitable endpoint.

Coronary lesions associated with a large plaque burden and a small luminal area are the most likely to be associated with acute events (35). In a study of 1584 patients with suspected CAD undergoing CTCA, and followed for a median 5.5 years, non-obstructive lesions were associated with a 2.5-fold increased hazard (similar to that of 1- and 2-vessel stenosis) with 35 of 794 (4%) patients having events (36). Similarly, in 347 among 20,000 patients with suspected CAD in the international

CONFIRM (Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry who died over a median follow-up of 2.3 years, the CTCA parameters most associated with outcome were proximal mixed or calcified plaques and stenoses >50% (37).

Limitations. The exclusion of participants with CCS=0 means that the study is limited to patients with calcified plaque. An alternative protocol would have been to include patients with a CCS=0, which would have captured patients with noncalcified plaque. We decided against this design as it would have required performance of CTCA for plaque burden in more than twice as many patients – which would have increased the cost of the trial and as well as the radiation burden to a degree that we found hard to justify in the context of the very low risk in this group and the infrequent finding of noncalcified plaque with CCS=0. However, we will follow all patients for endpoints at 9 years.

Conclusion. Coronary artery disease (CAD) remains a major cause of premature death and disability, and cost-effective primary prevention depends on accurately evaluating CAD risk. Although most new presentations with CAD involve new symptoms (eg. angina), >20% of initial presentations are with a sudden catastrophic event such as infarction, stroke or even sudden cardiac death (38). This study will be the first randomized trial of the value of CCS as assessed by CTCA for facilitating decision-making to optimize the control of atherosclerosis in asymptomatic individuals at intermediate risk and with a FHx of CAD.

The CAUGHT-CAD clinical investigators.

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1. Lloyd-Jones DM, Nam BH, D'Agostino RB, Sr. et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. JAMA 2004;291:2204-11.
2. Nasir K, Budoff MJ, Wong ND et al. Family history of premature coronary heart disease and coronary artery calcification: Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;116:619-26.
3. Stone NJ, Robinson J, Lichtenstein AH 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 2013.
4. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation 2008;118:2243-51, 4p following 2251.
5. Bachmann JM, Willis BL, Ayers CR, Khera A, Berry JD. Association between family history and coronary heart disease death across long-term follow-up in men: the Cooper Center Longitudinal Study. Circulation 2012;125:3092-8.
6. Khot UN, Khot MB, Bajzer CT et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003;290:898-904.
7. Sivapalaratnam S, Boekholdt SM, Trip MD et al. Family history of premature coronary heart disease and risk prediction in the EPIC-Norfolk prospective population study. Heart 2010;96:1985-9.
8. Yusuf S, Hawken S, Ounpuu S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937-52.
9. Heeley EL, Peiris DP, Patel AA et al. Cardiovascular risk perception and evidence--practice gaps in Australian general practice (the AusHEART study). Med J Aust 2010;192:254-9.
10. Goff DC, Jr., Lloyd-Jones DM, Bennett G et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013.
11. Pandey AK, Pandey S, Blaha MJ et al. Family history of coronary heart disease and markers of subclinical cardiovascular disease: where do we stand? Atherosclerosis 2013;228:285-94.
12. Fuster V, Gotto AM, Libby P, Loscalzo J, McGill HC. 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 1. Pathogenesis of coronary disease: the biologic role of risk factors. J Am Coll Cardiol 1996;27:964-76.
13. Anon. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease 2013.
14. Anon. New Zealand Cardiovascular Risk Charts.
15. Greenland P, Abrams J, Aurigemma GP et al. Prevention Conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. Circulation 2000;101:E16-22.
16. Taylor AJ, Merz CN, Udelson JE. 34th Bethesda Conference: Executive summary--can atherosclerosis imaging techniques improve the detection of patients at risk for ischemic heart disease? J Am Coll Cardiol 2003;41:1860-2.
17. Folsom AR, Kronmal RA, Detrano RC et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease

incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med 2008;168:1333-9.
18. See R, Lindsey JB, Patel MJ et al. Application of the screening for Heart Attack Prevention and Education Task Force recommendations to an urban population: observations from the Dallas Heart Study. Arch Intern Med 2008;168:1055-62.
19. Engbers LH, van Poppel MN, Chin APMJ, van Mechelen W. Worksite health promotion programs with environmental changes: a systematic review. Am J Prev Med 2005;29:61-70.
20. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ 1998;316:736-41.
21. Einstein AJ, Moser KW, Thompson RC, Cerqueira MD, Henzlova MJ. Radiation dose to patients from cardiac diagnostic imaging. Circulation 2007;116:1290-305.
22. Hamirani YS, Kadakia J, Pagali SR et al. Assessment of progression of coronary atherosclerosis using multidetector computed tomography angiography (MDCT). Int J Cardiol 2011;149:270-4.
23. Hamirani YS, Zeb I, Pagali SR et al. Normalization of automatic plaque quantification in cardiac computed tomography (CCT). Int J Cardiol 2011;146:282-90.
24. Zeb I, Li D, Nasir K et al. Effect of statin treatment on coronary plaque progression - a serial coronary CT angiography study. Atherosclerosis 2013;231:198-204.
25. Choi YH, Hong YJ, Park IH et al. Relationship between coronary artery calcium score by multidetector computed tomography and plaque components by virtual histology intravascular ultrasound. J Korean Med Sci 2011;26:1052-60.
26. Budoff MJ, Shaw LJ, Liu ST 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.
27. 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.
28. Nasir K, McClelland RL, Blumenthal RS et al. Coronary artery calcium in relation to initiation and continuation of cardiovascular preventive medications: The Multi-Ethnic Study of Atherosclerosis (MESA). Circ Cardiovasc Qual Outcomes 2010;3:228-35.
29. Rodondi N, Auer R, de Bosset Sulzer V, Ghali WA, Cornuz J. Atherosclerosis screening by noninvasive imaging for cardiovascular prevention: a systematic review. J Gen Intern Med 2012;27:220-31.
30. 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.
31. Mulders TA, Sivapalaratnam S, Stroes ES, Kastelein JJ, Guerci AD, Pinto-Sietsma SJ. Asymptomatic individuals with a positive family history for premature coronary artery disease and elevated coronary calcium scores benefit from statin treatment: a post hoc analysis from the St. Francis Heart Study. JACC Cardiovasc Imaging 2012;5:252-60.
32. Taylor AJ, Cerqueira M, Hodgson JM et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the

American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol 2010;56:1864-94.

33. Nicholls SJ, Hsu A, Wolski K et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol 2010;55:2399-407.
34. Fischer C, Hulten E, Belur P, Smith R, Voros S, Villines TC. Coronary CT angiography versus intravascular ultrasound for estimation of coronary stenosis and atherosclerotic plaque burden: a meta-analysis. J Cardiovasc Comput Tomogr 2013;7:256-66.
35. Stone GW, Maehara A, Lansky AJ et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226-35.
36. Hadamitzky M, Taubert S, Deseive S et al. Prognostic value of coronary computed tomography angiography during 5 years of follow-up in patients with suspected coronary artery disease. Eur Heart J 2013;34:3277-85.
37. Hadamitzky M, Achenbach S, Al-Mallah M et al. Optimized prognostic score for coronary computed tomographic angiography: results from the CONFIRM registry (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry). J Am Coll Cardiol 2013;62:468-76.
38. Dalager-Pedersen S, Ravn HB, Falk E. Atherosclerosis and acute coronary events. Am J Cardiol 1998;82:37T-40T.

Fig 1. Study design

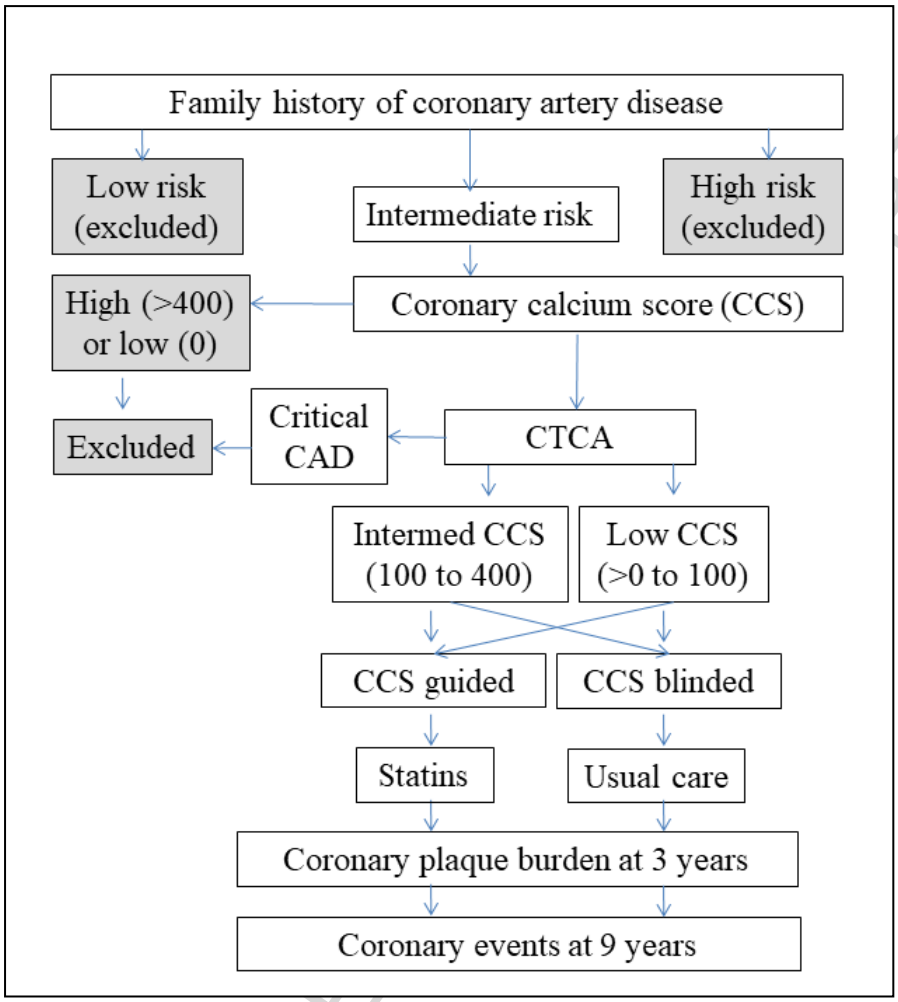

Figure 2. CT coronary angiography of LAD, LCX and RCA images, together with use of multiplanar reconstruction to quantify plaque volume in each vessel. This 66 year old woman with a positive FHx had CCS 65 with plaque volume of 54mm^3.

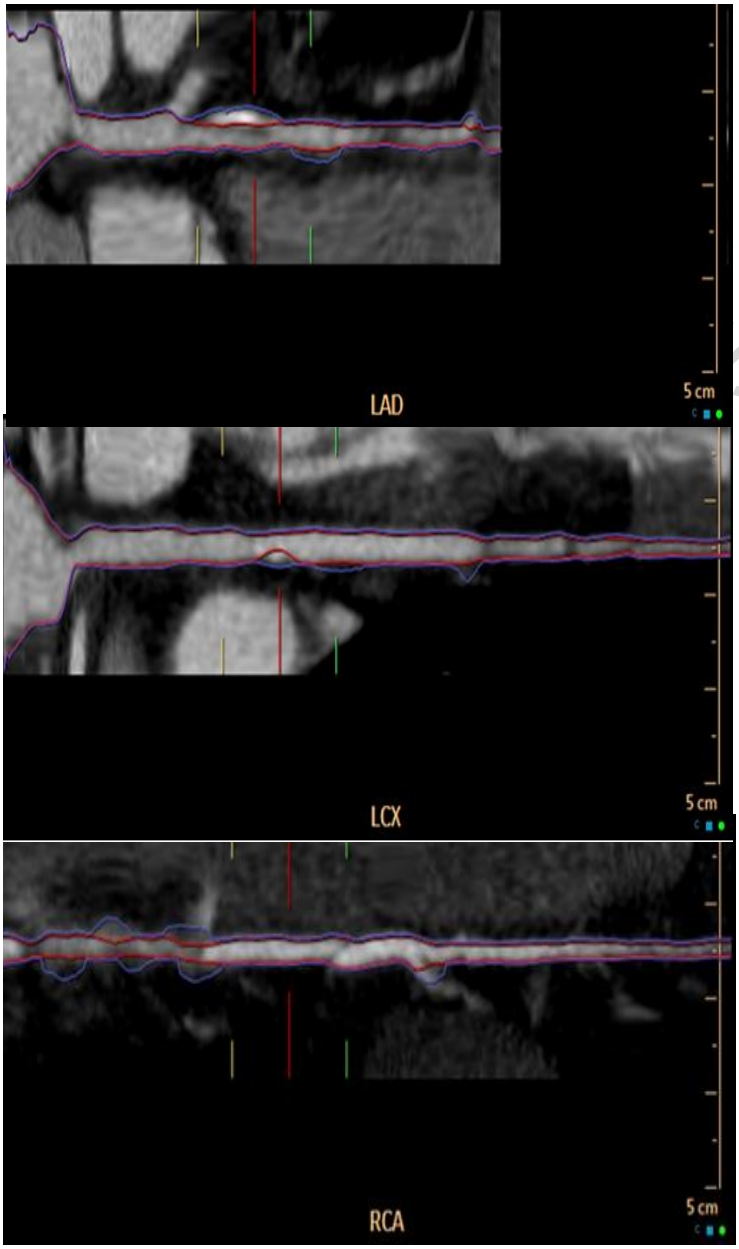

Table 1. Timing of study measures

Study Procedures (month)	Screening	Initiation	12m	24m	36m	108m
Informed Consent	X					
CT imaging	CCS/CTCA				CCS/CTCA	
Clinical review - Medical History	X					Data linkage
- Risk assessment	X					
- Concomitant Medications	X	X	X	X	X	
- Vital Signs (BP, HR)	X	X	X	X	X	
- Physical Exam	X					
- 12 Lead ECG	X					
Pregnancy Test (if applicable)	X					
AE/SAE Assessment	X	X	X	X	X	
Labs (listed above)	X	X*	X*	X*	X*	
Dispense Study Drug		X*	X*	X*	X*	
Medication Compliance (pill counts)	X	X*	X*	X*	X*	
QoL Measures	X		X	X	X	
Resource Use Questionnaire			X	X	X	

*treated patients

Table 2. Sample size (80% power, alpha 0.05, 15% dropout) for anticipated scenarios, based on different expected averages and variances of changes in plaque volume.

Scenario	Δplaque volume	SD of Δplaque volume	n required	n allowing for droput
1	20	90	638	734
2	30	90	286	330
3	20	70	388	450
4	30	70	174	200

Table 3. Clinical characteristics of recruited patients.

	n (%) or mean±SD
Age (years)	59±8
Female gender	266 (53%)
Age of relative with CAD (years)	51±7
Medical therapy	
- ACEi/ARB	67 (13%)
- Beta blockers or calcium channel blockers	9 (2%)
Risk factors	
- Hypertension (SBP >140 or on therapy)	100 (20%)
- Systolic blood pressure	126±16 mmHg
- Current smoker	18 (3.6%)
- Known dyslipidemia	66 (13%)
- Total cholesterol (mmol/l)	5.5±0.7
- LDL cholesterol (mmol/l)	3.4±0.7
- CRP mg/L	3.0±6.0
Australian risk calculator score (5 year risk) %	4.8±2.9
Comorbidity	
- Chronic kidney disease	12 (2%)
- Depression	60 (12%)
- Obesity	79 (16%)
Calcium score	
- 0	275
- 0-100	144
- 100-400	59
- >400	22

To convert from mmol/L to mg/dL for total, HDL, and LDL cholesterol multiply mmol/L by **38.67**. e.g. 3.5 mmol/L = 3.5 mmol/L * **38.67** = **135** mg/dL.

Table 4. Factors associated with CCS of 0.

Risk	OR (95%CI)	p
Age	0.90 (0.87-0.93)	<0.001
Age of onset in relative	1.02 (0.99-1.06)	0.21
SBP	0.99 (0.98-1.01)	0.22
LDLC	0.74 (0.52-1.05)	0.09
BMI	0.98 (0.93-1.03)	0.51