1. PROTOCOL TITLE: **C**oronary **A**rtery calcium score: **U**se to **G**uide management of **H**eredi**t**ary **C**oronary **A**rtery **D**isease – (CAUGHT-CAD)

2. CHIEF INVESTIGATOR DETAILS AND QUALIFICATIONS

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3. PURPOSE OF STUDY

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 ([1]).

This spectre has motivated efforts to reduce the risk of individuals without defined disease. The lifetime risk of CAD is doubled in people with a family history of premature CAD, yet this risk is not captured in most 5 or 10-year risk assessment algorithms. A promising marker of subclinical risk is coronary artery calcium scoring (CCS). This has been shown in observational studies to provide prognostic information that is incremental to the clinical assessment of CV risk, is relatively inexpensive and performed with a small radiation dose. However, use of CCS in guiding prevention is not incorporated in Australian guidelines. Definitive evidence of the efficacy and cost-effectiveness of CCS is therefore of primary importance.

The proposed study will be the first randomized controlled trial (RCT) of the use of CCS, and 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 but have blinded CCS results. In the intervention arm, treatment will be initiated based on CCS, applying the new ACC/AHA prevention guidelines. At three years, the effectiveness of intervention will be assessed on change in plaque volume at CT coronary angiography (CTCA), the extent of which has been strongly linked to outcome. The results will provide high-level evidence to inform the guidelines regarding the place of CTCA in risk assessment, specifically in patients with a family history of premature CAD.

AIMS AND HYPOTHESES

This RCT will compare clinical risk evaluation with and without CCS in asymptomatic relatives of patients with (CAD). This information will be used to implement a risk reduction program in “at risk” patients, based on detection of subclinical atherosclerosis. This program will be a community-based primary prevention program that will include combined pharmacologic and lifestyle intervention.

Primary Aim:

To determine whether therapy based on CCS leads to lower plaque burden at a median follow-up of 3 years

Secondary Aims:

1. To assess cost-effectiveness of CCS-based preventive strategy
2. To identify whether CCS improves adherence to therapy
3. To determine change in MACE after risk assessments
4. To identify if cardiac and carotid ultrasound can be used to facilitate selection for CT imaging (thus reducing population exposure to radiation).

Primary Hypotheses:

CCS-based preventive strategy in subjects with a family history of CAD will reduce coronary plaque burden at 3-year follow-up (a marker of subsequent risk)

Secondary hypotheses:

The use of CCS in subjects with a CAD family history will

a) Improve adherence to therapy

b) Provide cost-effective management in the Australian setting

4. BACKGROUND AND PRELIMINARY STUDIES

Rationale for study

Family history doubles the lifetime risk of CAD. Epidemiological studies have shown that the frequency of all ischemic heart disease (IHD) endpoints is increased in relatives of patients with documented CAD. In the Framingham study, a family history of premature CAD doubled the odds of CAD ([2]). In the Multi-Ethnic Study of Atherosclerosis (MESA), the age, gender, and race-adjusted odds ratio for CCS >0 *with* versus *without* a family history of premature CAD was 1.94 (95% CI, 1.64 to 2.29) in 5347 asymptomatic individuals (47% men; age 62±10 years) ([3]). However, family history has not been included in most CAD risk scores ([4]), with few exceptions ([5]), for a variety of reasons. First, it reflects the need for parsimony in risk assessment algorithms. Second, the scores have focussed on 5 and 10–year risk, while family history seems to have most impact on lifetime risk ([6]). Third, there has been a focus on traditional risk factors (smoking, hyperlipidemia, diabetes, and hypertension), which are present in 80% of patients after myocardial infarction ([7]). Fourth, the reclassification of risk with family history has been considered of borderline value in the population context ([8]), environment-based risk factors outweighing the contribution of genetic risk factors in population attributable risk ([9]). Nonetheless, recent guidelines recommend family history as a useful additional risk marker ([10]), as it potentially accounts for the genetic contributions to the other classical risk factors, as well as for the association of treatable risks within the family environment. Importantly, the independent effects of family history may be most important in individuals who otherwise are rated at low risk by existing assessment measures ([2]). A meta-

analysis of 32 studies linking measures of subclinical atherosclerosis (coronary artery calcium, carotid intima thickness, vascular function, and inflammatory markers) recently showed a significant relationship between these markers and family history of CAD, independent of traditional risk factors ([11]). *These features suggest the predominant link between family history and cardiovascular events is vascular disease and support a more aggressive approach in patients with a family history of premature CAD.*

Utility of imaging in detecting subclinical atherosclerosis and risk stratification

The use of primary prevention strategies in subjects at high risk for cardiac events (eg. >3%/year) is widely accepted, but there remains an intermediate risk group (0.4–3%/year) in whom pharmacological or lifestyle interventions may show only modest returns ([19]). In these individuals, a clue as to whether patients are already showing subclinical atherosclerosis may help to further stratify risk levels ([20]). Detection of subclinical CAD can be pursued through several means including coronary CT. Coronary CT may be performed without contrast to obtain CCS, or with higher doses of radiation and contrast to obtain CT coronary angiography (CTCA) (Figure 1).

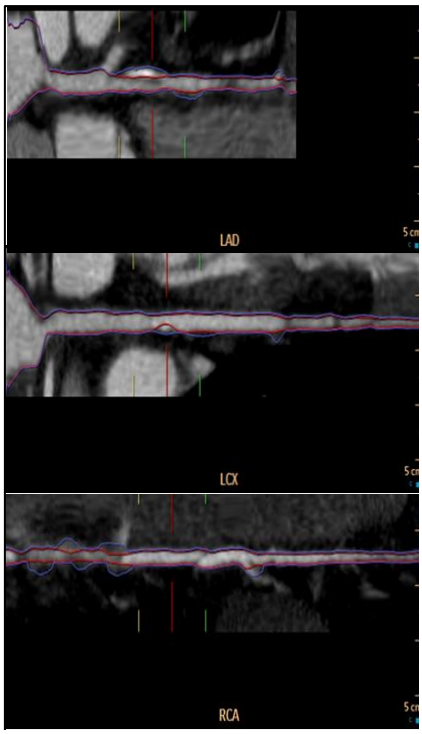

Figure. 1 CT coronary angiography of LAD, LCX and RCA images, together with use of multiplanar reconstruction to quantify plaque volume in each vessel. This 66 yo woman with a positive family history had CCS 65 with plaque volume 54mm^3

Although CTCA identifies plaque volume (which we will use to characterize the effect of therapy, see below), this test is not appropriate for screening ([21]). CCS is very 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 ([22]). In a study of 25,523 consecutive asymptomatic subjects (Figure 2), CCS was associated with outcome, irrespective of other risk factors ([23]). 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 ([24]). 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. CCS ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity has been proposed to use to facilitate decisions regarding lipid-lowering management in intermediate-risk subjects ([4]).

Most young patients with a positive CCS score do not satisfy criteria for lipid-lowering therapy by global risk scoring or PBS guidelines. In 2611 asymptomatic participants aged 30 to 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 ([25]). In a median follow-up of 7.6 years in the MESA study, 55% of incident events (myocardial infarction, angina resulting in revascularisation, 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 ([8]).

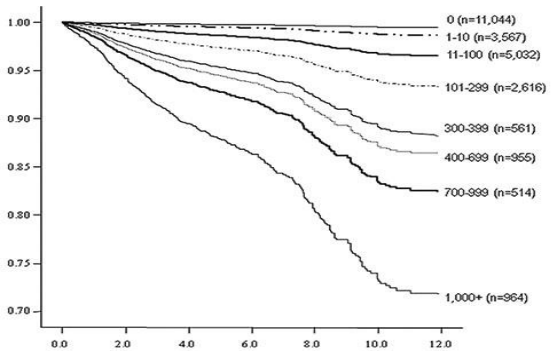

Figure 2. Association of CCS with all-cause mortality. X axis: Cumulative Survival. Y axis: Time to Follow-Up (yrs). p < 0.0001 overall and for each subset

Using CCS to provide an outcome benefit.

The preceding evidence supports the role of CCS for predicting risk. However, the evidence in favour of CCS providing an outcome benefit is currently limited. This could be achieved in two ways – by facilitating selection for preventive therapy, and by facilitating adherence with preventive therapy. Showing subjects their CCS is strongly associated with subjects initiating therapy ([26]) 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 ([27]) found that subjects with evidence of atherosclerosis showed better perception of cardiovascular risk and improved adherence to lifestyle advice. In four RCTs (n=709), screening did not influence risk factor status, with the exception, in one study, of improved smoking cessation (18% vs. 6%, p=0.03). The results of one RCT may be particularly instructive. Although it showed no benefit overall ([28]), in a post hoc analysis, it showed that targeted intervention in patients with a family history of CAD improved event-free survival in 1000 patients (age 59±6 years) with follow-up over 4.3 years ([29]). The findings support the role of patient selection in screening, and hint at a specific indication for patients with a family history of CAD. Indeed, the appropriate use criteria for cardiac CT list the use of CCS in low risk patients with a family history as being appropriate ([30]).

Risk reduction

Although clinical practice is often based on the use of specific cut-offs to treat individual risk factors, the tendency of multiple risk factors to compound the subsequent risk of an event makes this process rather difficult. For example, while it is reasonable that the current Pharmaceutical Benefits Scheme (PBS) guidelines for statins ([12]) will not support treatment for a 40-year-old non-smoker with a total cholesterol (TC) 6 mmol/litre and low HDL (absolute risk 0.5-1%/yr), their failure to support treatment for a 60-year-old normotensive smoker with the same TC (cardiac event risk 2-4%/yr) is more concerning. Even with these restrictions, the prescription of statins for primary prevention is increasing, and forming a significant burden on the PBS. An alternative strategy, supported in new AHA guidelines ([4]) and by the Heart Foundation ([13]), is the assessment of absolute risk. This approach enables the aggressiveness of prevention strategies to be tailored to the risk of coronary events, as proposed by the 27th Bethesda Conference ([14]). Various treatment thresholds have been proposed – ranging from as low as a 7.5% 10 year absolute risk in the most recent US guidelines ([4]), through to 20% in the UK guidelines ([15]) and 30% in New Zealand ([16]). Although absolute risk is mentioned as a means of selecting therapy in the Australian guidelines ([17]), this approach has failed to gain wide acceptance, possibly reflecting the use of lipid levels in the PBS ([12]). The consequence is under treatment of those at the highest absolute risk - and probably overtreatment of low-risk subjects ([18]). *An alternative approach proposed in this study is to identify "at risk" individuals, and then to initiate treatment based upon the presence of subclinical vascular disease. Subjects with a family history of CAD represent a group where this may be beneficial.*

Preliminary data

In preliminary data in 140 asymptomatic subjects undergoing CCS to elucidate primary prevention decisions, 66 were evaluated because of a CAD family history. Of these, 15 (23%) had a score of 0, but 38 (58%) had a score >10 and 12 (15%) had a score >100, which confers event-rates similar to secondary prevention populations, irrespective of lipid status ([8]). Subjects with a score of <10 was present in 13%, and these patients warrant standard lifestyle guidance but can otherwise be reassured (Figure 2). Of the reminder, approximately half had a CCS <100 and the rest were >100. Plaque volume (89±81ml) was calculated in all subjects, being 57mm^3 and 138mm^3 in lower and upper CCS groups, respectively.

5. PARTICIPANTS

Selection and recruitment of study subjects

Entry of patients into the study will be from the community, from hospital cardiology departments and from general practice. Newspaper advertisements and flyers will be placed to seek the involvement of subjects with a family history of CAD. Therefore, subjects will enter

the study based on response to advertisement or contact with an index hospital patient.

Inclusion Criteria:

1. Asymptomatic subjects age 40-70y with a family history of CAD involving an index patient <60y (1st degree) or <50y (2nd degree)
2. Statin naïve
3. TC ≤ 6.5 mmol/L and LDLC <5 mmol/L, and
4. 5 year Australian risk ≥2%.

Exclusion criteria:

1. Symptomatic coronary, cerebrovascular, or peripheral vascular disease
2. Intolerance of statins or currently on statins for any length of time
3. Pre-existing muscle disease (eg polymyositis, fibromyalgia) - this may be confused with myalgia from statins
4. Patients on drugs that increase the risk of myopathy/rhabdomyolysis such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV/hepatitis C protease inhibitors)
5. Atrial fibrillation (interferes with CTCA)
6. Chronic kidney disease on haemodialysis (because of vascular calcification) or GFR <50ml/min per 1.73m^2 using the Modification of Diet in Renal Disease (MDRD) formula
7. Inability to provide informed consent
8. Major systemic illness eg. malignancy; rheumatoid arthritis
9. Women of child bearing potential (due to performance of CT)
10. Poorly controlled hypertension: SBP> 200 and or DBP > 100
11. Severe psychiatric disorder (eg bipolar depression; psychosis)
12. Patients eligible for treatment based on current Australian guidelines (5 year risk >15%)
13. Patients eligible for treatment based on current PBS thresholds TC >7.5 mmol/l and other criteria (Table 1).

Table 1. PBS-eligible patients excluded from the study

Diabetes mellitus	• ≥60 years old • Aboriginal or Torres Strait Islander patients • microalbuminuria (urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females) • TC >5.5 mmol/L

Hypertension	TC >6.5 mmol/L TC >5.5 mmol/L and HDL <1 mmol/L
Aboriginal or Torres Strait Islander	TC > 6.5 mmol/L TC > 5.5 mmol/L and HDL <1 mmol/L
Family history of symptomatic CHD; <50 years in >1 2nd degree and <60 years in >1st degree relatives	LDLC >5mmol/L TC >6.5mmol/L TC > 5.5 mmol/L with HDLC < 1 mmol/L

Withdrawal Criteria

Reasons for withdrawal from study may include, *but are not limited to*, the following:

- Investigator's request, for safety reasons, such as severe adverse reactions to drugs used in study i.e. statin intolerance and beta –blockers for heart rate management during CTCA
- Investigator's request, for other reasons, such as subject non-compliance
- Subject's request, for tolerability reasons
- Subject's request, for other reasons, such as withdrawal of informed consent

Discontinuation of statin use alone does not constitute discontinuation or withdrawal from the study. Subjects should continue to be followed as though they had completed the treatment phase. Subjects who prematurely discontinue study medication are to be followed for the remainder of their follow-up period and should undergo all subsequent visit evaluations whenever possible.

The Investigator must carefully document all premature study discontinuations, withdrawals and their causes.

A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the final protocol procedures. The Investigator must determine the primary reason for discontinuation. Withdrawal due to an adverse event should be distinguished from withdrawal due to other reasons. A discontinuation due to a serious adverse event must be reported immediately to investigator and appropriate HREC. The Investigator will record the reason for study discontinuation, provide or arrange for appropriate follow up for such subjects, and document the course of the subject's condition during the appropriate follow up period on the follow up contact Case Report Form (CRF).

Subjects who withdraw consent and refuse to return for subsequent visits, if consent to, will be contacted by telephone 30 days following last visit to assess their current health status. It is imperative that all subjects are accounted for at the conclusion of the trial.

6. STUDY PLAN AND DESIGN

This is an RCT to evaluate the utility of CCS in **intermediate-risk subjects with a family history of premature CAD** who do not satisfy current PBS guidelines for the prescription of statins. Recruitment will also select CCS that most require intervention (Figure 3). Patients with a score of 0 (low risk, who do not require specific therapy) will be excluded, as with those with a score >400 (who are at risk of significant coronary stenosis). Eligible patients will undergo a CTCA (for baseline plaque volume and exclusion of serious CAD). Then recruitment will be stratified into groups with CCS >0-100 and 101-400, and randomized to therapy.

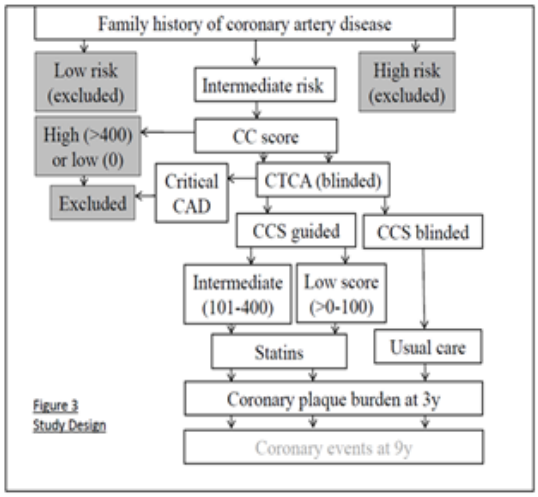

Figure 3: Study Design

Randomisation

Subjects will be centrally randomised using the Menzies Institute for Medical Research Data Management Centre (using a computerised protocol supervised by CIH) with a 1:1 ratio of CCS reporting to usual care (CCS blinded). We will block-randomise for the five participating centres and randomisation will be stratified according to risk level (low or intermediate risk groups)

Initial screening

Entry of patients into the study will be by initial contact by their treating clinician from within hospital cardiology departments, by lipid specialists and general practice. In hospitals, index cases of myocardial infarction <60y will be approached to ask their 1st degree relatives to undergo screening, and index cases of myocardial infarction <50y will be approached to ask their 1st and 2nd degree relatives to undergo evaluation. If the patient's relative is interested in undergoing screening or hearing further about the study, they will attend a visit and be informed by the Clinician about the project.

In general practices, the EMR will be searched for people with premature CAD or family history of premature CAD and newspaper advertisements seeking the involvement of subjects with a family history of CAD will be utilised. Study nurses ([35]) will assess future CV risk starting with a standard clinical history ([36]). Patients with symptoms of existing CV disease will be excluded and referred appropriately if already not under treatment.

Subjects will enter the study based on response to advertisement or contact with the index patient from the family. All subjects will undergo risk evaluation using the Australian risk calculator. Low (<2% 5 year risk) and high risk patients (>15% 5 year risk) will be excluded from study entry and referred for management. The remainder will undergo CCS.

Baseline measures

1. Survey and assessment of health behaviour, chronic illnesses, medications and socio-demographic factors
2. Measures of health-related quality of life (AQoL, EQ-5D) and depression and anxiety (PHQ-9 , GAD) ([6, 37]) (Patients that are found to have scores on the depression and anxiety scale (PHQ-9 , GAD) that are suboptimal, will be referred to their GP for further assessment.
3. Assessment of kidney and liver function using GFR (<50ml/min per 1.73m^2 using the Modification of Diet in Renal Disease (MDRD) formula) and LFT's to ensure ALT or AST is < 3 times upper limit of normal
4. 6 minute walk test
5. BMI and waist circumference measures
6. Systolic and diastolic BP
7. FBC, Blood biochemistry and Lipid profile

Accredited laboratories with standard reference ranges will undertake pathology tests. The following investigations will be undertaken as part of baseline profiling of study participants; fasting lipid profile (total cholesterol, HDL, LDL and triglycerides), glucose (to identify undiagnosed diabetes), high-sensitive C-Reactive Protein (hs-CRP), creatinine (related to exclusion with CKD), CK (related to exclusion with myopathy), FBC (regarding anaemia exclusion).

Imaging

i) Coronary calcium scoring

Calcium scoring will be performed on a dual source 128 slice CT machine, equipped with adaptive CTCA package, radiation dose reduction systems and appropriate reconstruction algorithms. The CCS images will be 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); in Australia the average background radiation dose is about 2.0 mSv per year. Calcium scoring will be performed on the Extended Brilliance workstation using the HeartBeat CS Calcium Scoring package (Philips, Best, Netherlands). Agatston parameters will be used to produce an Agatston score. At baseline, patients will be categorised

as having minimal risk if they have CCS 0, and high resolution calcium scores will be obtained in follow-up.

ii) CT coronary angiography

Excellent image quality is essential for plaque volume measurement. Acquisitions will not be performed at >65bpm (the target is <60bpm). Patients are prepared with oral metoprolol 50mg the night before, first thing in the morning, and 1.5 hours prior to study. Additional oral and/or IV beta blocker at time of study may be administered to further lower the heart rate. If patients are significantly asthmatic or intolerant of beta blockers, the same regimen is followed with oral verapamil 80mg or oral ivabradine 7.5mg. 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. Prospective ECG gating and adaptive reconstruction will be performed. Radiation doses in our labs are routinely ~2 mSv, less than previously reported ([38]). Detection of prognostically-important *obstructive* disease (>70% left main, expected to be rare) is an exclusion criterion (Figure 4).

iii) Echocardiography

Standard transthoracic echocardiography will be performed at the time of enrolment. Studies will be performed using standard ASE criteria: assessment of LV mass, 2D assessment of LV volumes and ejection fraction, transmitral flow, tissue Doppler imaging and LA volumes to calculate LV diastolic function and grade.

- Transmitral flow will be measured using pulsed-wave Doppler at the leaflet tips, aligned with the direction of LV filling. Mitral E and A waves, and medial and lateral mitral annular velocities (e') will be measured. The class of diastolic dysfunction was determined using the E/e', LA size and age-predicted normal range for E wave deceleration time as follows: class I – delayed relaxation; class II – pseudonormal filling (normal deceleration time for age in the presence of LA enlargement); and class III – restrictive filling (short deceleration time).
- Left atrial volume will be calculated from the apical 4- and 2-chamber views using the Simpson's rule method.
- Measurement of longitudinal strain: The three apical views will be acquired at increased frame-rate (50-70frames/second). Cine-loops of 5 cardiac cycles will be analyzed offline, to allow Doppler-independent strain and strain rate to be assessed using offline semi-automated speckle tracking techniques (Echopac, GE Medical Systems). Timing of the aortic valve opening and closure will be obtained using single-gated pulsed wave Doppler traces. The three apical views will be used to obtain an average global peak

systolic longitudinal strain and peak systolic longitudinal strain rate, with systole manually defined by aortic valve closure. After initial tracing of the endocardial border and software processing, the operator will confirm adequate tissue tracking. Segments unable to be adequately tracked will be excluded

iv) Carotid ultrasonography

3-Dimensional bilateral carotid ultrasound will be performed to assess carotid intimal thickness and plaque volume as a further marker of atherosclerotic risk incremental to CCS. A 3D-transducer will be translated along the neck of the patient and video frames captured and stored digitally. Plaque volume will then be manually calculated by tracing of the cross-sectional area at 1-2mm intervals.

Two plaque volume studies will be compared in the core lab, using a workstation for 3-dimensional image analysis. Studies will be blinded to the analyser. Volume rendering and curved multi-planar reformats will be used to evaluate the coronary vessels. Vessels 2 mm or larger in diameter will be assessed for the presence of plaque. The data will be transferred for semi-automated vessel extraction using proprietary software. After identifying the plaque area, we will use an automated plaque detection tool to quantify plaque volume on both baseline and follow up scans as previously published ([42,43]). The automated software detects outer vessel wall and lumen and the intervening plaque. In each case, we manually modify the linings of the vessel wall and lumen to optimise and confirm software estimates. In cases of mixed plaque phenotype, we also manually adjust the linings to correctly separate calcified components from the 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 ([44]). Interobserver and intraobserver variability has been published previously, but will be repeated on 10% of scans.

Therapeutic arms of study

i) **Usual care:** Subjects with a family history who are randomised to usual care will undergo standard risk evaluation, weight control, treatment of dysglycemia and hypertension to target, and lipid management in accordance with current PBS criteria.

ii) **Randomised to CCS:** The primary intervention is targeted CCS-guided primary prevention. All participants will undergo tailored health profiling to define individual modifiable risk factors and the delivery of clearly articulated health care goals. This standardised intervention will include:

- Supporting lifestyle and risk modification: individualised nutrition, weight and physical activity goals to facilitate positive health outcomes in the longer-term.
- Encouraging active self-management of risk via one-on-one counselling and education.
- Improving coordination of care between subjects' healthcare providers (e.g. GP, Pharmacists etc) to achieve individual goals for optimal risk and disease management.

Pharmacological therapy: The two groups that are most closely related in the guidelines ([4]) are patients with symptomatic disease (recommended high-intensity statin), and patients with >7.5% 10-year risk (recommended moderate-high intensity statin). Participants will therefore be treated with atorvastatin with concomitant liver function test monitoring. Dose is started at 40 mg/d however intolerance (eg. myalgia) at this dose is expected in <5%. In the event of intolerance the dose will be reduced to 20 mg, and if still unsuccessful the medication would be switched to rosuvastatin. LFT will be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose upto 40md/d, and semi-annually thereafter. Should an increase in ALT or AST of >3 times upper limit of normal persists, reduction of dose is performed and if still unresolved drug is wwithdrawn. If all steps are unsuccessful, the drug will be stopped and the subject retained in the trial with follow-up on grounds of intention to treat. Consistent with the guidelines, there will be no treatment to target. Other therapy indicated by standard primary prevention guidelines (e.g. anti-hypertensives) will also be initiated. Follow-up will be arranged at one month and 3 months (phone or e-mail according to preference) to review the efficacy of their self-care plan and prescribed statin therapy.

Table 2. Timing of study measures

Study Procedures (month)	**Screening**	**Initiation**	**4 wks**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**108**
Informed consent	X										
CT Imaging	CCS/CTCA								CTCA		
Echocardiogram	X									X	
Carotid Ultrasound	X									X	
Clinical Review -Medical history -Risk assessment -Concomitant medications -Vital signs (BP, HR) -Physical exam -12 Lead ECG -F/up phone call review	 X X X X X X	 X X	 X X	 X	 	 X X	 	 X X	 	 X X	Data linkage

-6 minute walk test	X										
Pregnancy test (if applicable)	X									X	
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	
Blood test	X	X	X		X	X	X	X	X	X	
Dispense study drug		X			X	X	X	X	X	X	
Medication compliance (pill counts)	X	X				X		X		X	
QoL measures	X									X	
Resource use questionnaires						X		X		X	

8. OUTCOMES

The CIs have expertise in cohort follow-up and data linkage, and the patients recruited to this study will certainly be followed for major events. However, the required timeframe for outcome events exceeds the duration of this grant, and there is a need to guide the existing ad hoc use of CCS in the interim. Coronary calcium scores are performed in Australia and internationally in the selection of patients for primary prevention, but on the basis of observational data only. This will be the first randomized trial of the benefits of this approach, and the first to perform an economic analysis. This topic is extremely significant - current primary prevention of atherosclerosis involves treatment of <u>many</u> individuals with traditional risk factors but low overall risk and is associated with much non-adherence to treatment and wasted resources. CCS could be a more effective, more efficient way of screening for CAD in patients with a family history of CAD, helping people to manage their risk of CAD and therefore have significant economic long term benefit to the health care system for the prevention and treatment of heart disease. If the study is successful, a targeted preventative strategy in patients with a family history of CAD has the potential to provide a practical, economically efficient, and sustainable means to deliver maximal gains from a population-based approach.

The study team is well positioned to translate the study results into daily practice through the usual processes of conferences and publication, as well as social engagement through the Heart Foundation. The team are well placed to influence position statements and guidelines, having previously been involved in a number of national and international guidelines panels.

The primary end-point will be determined by the absolute change in coronary total and non-calcified plaque volume after a minimum of 36 months after CCS. This will address the primary aim of showing the efficacy of CCS-based therapy.

The secondary endpoints will be assessed by:

1) Symptom status and health resource consumption, including hospitalisation. These assessments will be obtained using a follow-up questionnaire, as well as consent to re-contact the patient in follow-up. These data will inform the model to assess cost-effectiveness, which is a secondary aim of the study.

2) Tablet counts and lipid profile, reflecting adherence to therapy. These data will inform the 2nd secondary aim of identifying whether CT improves adherence to therapy.

MACE (death, myocardial infarction, stroke) after 5 years will be a secondary endpoint (not covered by this grant). In order to analyse for confounders and competing risks, the following cardiac events will be considered: a) sudden death; b) death resulting from a cardiac cause; c) overt heart failure requiring hospitalisation; d) life-threatening arrhythmias requiring treatment.

3) Cross-sectional comparison of ultrasound of the heart and carotids with results of CT, to see if ultrasound could be used to facilitate selection for CT scanning (thereby potentially limiting population exposure to radiation).

9. ETHICAL CONSIDERATIONS

Detection of significant *left main* disease [>50% stenosis] is expected to be rare, but these subjects are at intermediate risk with a family history, so the risk of undiagnosed CAD is not trivial. Thus, every opportunity will be taken to ensure that significant CAD is actioned - the study will be restricted to CCS<400 and CTCA will be checked for left main involvement. 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. Additionally, the participant would be withdrawn if they meet the criteria for the commencement of statin therapy or if their Australian Risk Calculator score puts them in a higher category as assessed by the investigator and referred for management.

9. SPECIFIC SAFETY CONSIDERATIONS

Risk with radiation: Radiation safety is an important consideration; the radiation dose of 4mSv per scan which is done at screening and at 36 months of study. 2mSv is analogous to a year's background radiation in Australia, and a fatal cancer risk (assuming linearity of risk) of 1:10,000 – compared to a lifetime cancer risk of 1:5, according to the FDA. Subjects will be excluded if they have already reached their yearly limit of radiation. Women of child bearing potential are enrolled into the study only if they have no intent of pregnancy during the course of the study. They are informed of the potential hazards of the medication and

radiation on pregnancy. In the unlikely event of a pregnancy the patient is withdrawn from study and referred for management. All women of child-bearing potential are screened at all time points requiring radiation exposure.

Risk with medications in the study: In addition to the goals of the study, these at-risk subjects will be provided information on their coronary risk status. The main anticipated side effect of statin therapy is expected to be myalgia and altered liver function, which are assessed by ensuring that AST and ALT levels are <3 times upper limit of normal. Similarly beta-blockers are used in the study to achieve heart rate < 60beats/min during the scans, however, risks with this medication are minimum to nil considering the short duration of therapy under physicians guidance at time of administration. Adverse events (AEs) and serious adverse events (SAEs) will be identified at follow-up (table 2). This study will have a Data and Safety and Monitoring Board, led by an experienced clinicians, who 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 time frame of the study that justify stopping, when necessary we will use the Haybittle-Peto stopping rule at a p=0.001.

Table 3. Data and Safety Monitoring Board (DSMB)	
A/Prof Phil Roberts-Thomson, Hobart	DSMB Chair
Prof Joseph Selvanayagam, Flinders	DSMB Member
Prof Garry Jennings, Melbourne	DSMB Member
Petr Otahal	DSMB Biostatistician

Standard risks with blood collection: Usually one attempt at drawing blood is enough, however additional attempts may be necessary if first is unsuccessful. The collection of blood may cause some discomfort, bruising, minor infection or bleeding. In even rarer cases a nerve maybe damaged inducing long lasting abnormal sensations (parasthesia), impaired sensation of touch and persistent pain. Events such as dizziness, discomfort, bruising, minor infection or bleeding can be easily treated.

Risks from ECG: This is a test that looks at the electrical activity of your heart by putting small sticky patches on certain area of your body while you are lying down. These patches have small wires that connect to a machine, which will read and print a report. The test takes about 5 minutes. The patches that stick to your chest may irritate your skin and cause itching and redness. The study staff may need to shave your chest hair so that the patches stick to your skin. When they remove the sticky pads, it might sting for a few seconds.

10. DRUGS

Supply of atorvastatin has been negotiated with local suppliers at each of the sites. At hospital sites, they may be dispensed through the Pharmacy

Study drug is available for the duration of the study only. If the study is positive, subjects will be so informed, but if they wish to continue, will need to source the drug themselves. We will make it clear that even if the study is positive, this strategy will not be in the guidelines. Generic costs are less than a standard PBS script, but still ~$20/month. If the study is negative, patients will be so informed and advised about the lack of evidence to continue taking the drug.

11. ANALYSIS AND REPORTING OF RESULTS

Data collection and management

Study data capture, analyses and archiving will be coordinated through a secure web-based database or electronic capture of paper-based CRFs at Menzies Institute for Medical Research. 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 2). Standardised data acquisition will be obtained using Case Report Forms. Participants will be reminded of the need to adhere to the study schedule, with appointment cards and reminder phone calls and/or letters to minimise loss to follow-up. Errors or omissions will be recorded on Data Query Forms that will be returned to the investigational site for resolution. Independent study monitors will verify 5% of study data against source documents.

The investigators own the data and results. Allocation of manuscript tasks will be allocated by the CIs on the NHMRC grant. Data are collected using scannable CRFs ("teleforms") and recorded into a database at the Clinical Trials Centre of the Menzies Institute for Medical Research. Datasheets, questionnaires and other relevant material are provided. The investigators will have access to research data. Once analysis has been completed, the material will be published and shared with study participants via the website. Recorded data will be stored on a physically-secure and password-protected database at the Menzies Institute for Medical Research.

Statistical Analysis

All data will be pooled and summarised 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 regression to correct for coincidental between-group differences despite randomisation, 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), ie. inclusion of all patients having taken part in baseline and final evaluation. 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.

Power calculations.

Power calculations are made from 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 mm3. The group of Budoff et al (39) have shown statins to reduce noncalcified plaque volume by 47±72 mm3 (vs control 14±77, p<0.001) and low attenuation plaque by 12±19 mm3 (vs control 6±23, p < 0.0001) over 12 months in a CAD screening population, approximately 50% of whom had a family history of CAD. These were generally at low risk although 20% had chest pain, but nonetheless, baseline noncalcified plaque was in the range of 315 mm3 and low attenuation plaque of 95 mm3. In contrast, Choi et al (40) reported the relationship between CCS and plaque components assessed by virtual histology-intravascular ultrasound in 172 CAD patients. In patients with CCS=0, atheroma volume with CCS=0 was 152±132 mm3, compared with 171±114 mm3 with CCS 1-100, and 195±149 mm3 with CCS 101-400. Respective low attenuation plaque volumes were 15±18, 20±19 and 23±19. However, the fundamental comparison in this study (CCS-guided vs usual care) is not a pure comparison of statin vs no statin, because a CCS score of 0 and >400 will be excluded. Previous work has shown these thresholds in 30% intermediate risk patients with family history of CAD (3).

Accordingly, this study is powered for a delta plaque volume of 20 mm3, which is reduced from the Budoff paper. Accordingly, the difference in progression rates between the groups will be less than prior observational reports. 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 mm3, with a standard deviation of 90 mm3 (two-sided α=0.05). This represents scenario 1 in the chart. Assuming that 15% of subjects will drop out or not have evaluable imaging at both time points, 734 subjects will be randomised over the 1st 18 months of the study, to provide a minimum 3 year follow-up. The involvement of 5 sites will require each to scan ~100 patients/year.

Cost-effectiveness analysis

An economic analysis will be undertaken to assess the cost effectiveness of CCS guided primary prevention of CVD in individuals of intermediate risk with a family history 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 constructed in Treeage© by CIs-G and A, with future transition

probabilities between health states, to be based on coronary plaque volume and observed events, and costs and health state utility values for the included health states to be preferentially derived from the trial data for each alternative. Within the trial health state utility values will be assessed using the EQ-5D (41) and AQoL (45). Resource use and costs will be assessed by patient contact at longterm follow-up. Individual patient permission for data linkage will be sought. A 10-year and overall lifetime horizon will be modelled separately, and will be used in our planned follow-up analysis after the completion of this grant. Death and the onset of high risk status will represent absorbing states. If the model predicts that a death has occurred, the discounted years lived, quality-adjusted life-years (QALYs) and associated health sector costs will be calculated as of that cycle; otherwise outcomes will be calculated based on event history at the completion of 10 or 40 cycles. Uncertainty will be assessed through probabilistic sensitivity analysis, Monte Carlo simulation enabling the calculation of a confidence interval for the ICER. A simple trial-based cost utility analysis based on individual patient-level utility and cost data will also be undertaken.

Reporting of results

Results of the study will be presented at conferences and published in peer reviewed journals. The Investigators intend to engage the Heart Foundation to influence guidelines. If the study is successful, a targeted preventative strategy in patients with a family history of CAD has the potential to provide a practical, economically efficient, and sustainable means to deliver maximal gains with a population-based approach.

OUTCOMES AND SIGNIFICANCE

Coronary calcium scores are performed in Australia and internationally in the selection of patients for primary prevention, but **on the basis of observational data only. This will be the first randomized trial of the benefits of this approach, and the first to perform an economic analysis.** This topic is extremely significant - current primary prevention of atherosclerosis involves treatment of many individuals with traditional risk factors but low overall risk and is associated with much non-adherence to treatment and wasted resources. CCS could be a more effective, more efficient way of screening for CAD in patients with a family history of CAD, helping people to manage their risk of CAD and therefore have significant economic long term benefit to the health care system for the prevention and treatment of heart disease. If the study is successful, a targeted preventative strategy in patients with a family history of CAD has the potential to provide a practical, economically efficient, and sustainable means to deliver maximal gains from a population-based approach.

Our team is also well positioned to **translate the study results into daily practice** through the usual processes of conferences and publication, as well as social engagement through the Heart Foundation. CIs A-C and E are well-placed to influence position statements and guidelines, having previously been involved in a number of national and international guidelines panels.

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