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Randomised clinical trial using Coronary Artery Calcium Scoring in Australian Women with Novel Cardiovascular Risk Factors (CAC-WOMEN Trial): study protocol

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ABSTRACT

Introduction Cardiovascular disease (CVD) is the leading cause of death in women around the world. Aboriginal and Torres Strait Islander women (Australian Indigenous women) have a high burden of CVD, occurring on average 10–20 years earlier than non-Indigenous women. Traditional risk prediction tools (eg, Framingham) underpredict CVD risk in women and Indigenous people and do not consider female-specific 'risk-enhancers' such as hypertensive disorders of pregnancy (HDP), gestational diabetes mellitus (GDM) and premature menopause. A CT coronary artery calcium score ('CT-calcium score') can detect calcified atherosclerotic plaque well before the onset of symptoms, being the single best predictor for future cardiac events. A CT-calcium score may therefore help physicians intensify medical therapy in women with risk-enhancing factors.

Methods and analysis This multisite, single-blind randomised (1:1) controlled trial of 700 women will assess the effectiveness of a CT-calcium score-guided approach on cardiovascular risk factor control and healthy lifestyle adherence, compared with standard care. Women without CVD aged 40–65 (35–65 for Aboriginal and Torres Strait Islander women) at low-intermediate risk on standard risk calculators and with at least one risk-enhancing factor (eg, HDP, GDM, premature menopause) will be recruited. Aboriginal and Torres Strait Islander women will be actively recruited, aiming for ~10% of the sample size. The 6-month coprimary outcomes will be low-density lipoprotein cholesterol and systolic blood pressure. Barriers and enablers will be assessed, and a health economic analysis performed.

Ethics and dissemination Western Sydney Local Health District Research Ethics Committee (HREC 2021/ETH11250) provided ethics approval. Written informed consent will be obtained before randomisation. Consent will be sought for access to individual participant Medicare Benefits Schedule, Pharmaceutical Benefits Scheme claims usage through Medicare Australia and linked Admitted Patient Data Collection. Study results will be disseminated via peer-reviewed publications and presentations at national and international conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised trial of a CT-calcium score-guided approach to cardiovascular risk factor control in women with female-specific, 'risk enhancing' factors of gestational diabetes, hypertensive disorders of pregnancy and/or premature menopause.
⇒ This is the first trial of CT-calcium scoring that will include a focused subgroup of Indigenous participants (Australian Aboriginal and Torres Strait Islander women).
⇒ Participants will include young to middle-aged women where the prevalence of CT-calcium score of zero (despite the presence of risk-enhancing factors) may limit the efficacy of a CT-calcium score-guided approach to cardiovascular risk factor control.
⇒ The 6-month follow-up time period and sample size means that the primary outcome will focus on blood pressure and lipid control, rather than major adverse cardiovascular events or deaths.

Trial registration number ACTRN12621001738819p.

INTRODUCTION

Cardiovascular disease (CVD) affects an estimated 275.2 million women worldwide and causes 8.94 million deaths per year.[1] While the incidence of coronary events has been falling, this rate of decline has been much slower in women than men.[2] Inequities in awareness, prevention and treatment of CVD in women have all been well documented.[3–10] However, prevention and treatment strategies that take into account female-specific risk factors for heart disease are needed if we are to narrow the gender gap. The Australian absolute cardiovascular disease risk calculator (ACDRC) and Framingham Risk Score are traditional risk prediction tools

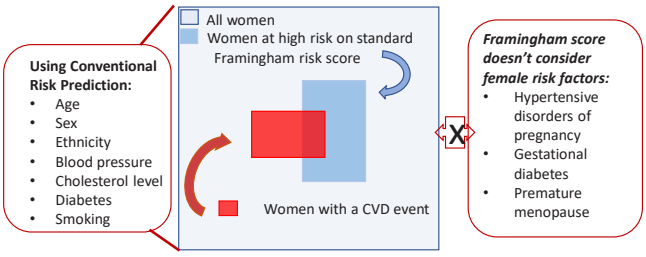

Figure 1 Classification of women's cardiovascular risk. CVD, cardiovascular disease.

that estimate 5 and 10-year CVD risk, respectively. Such calculators are heavily driven by age and sex, with almost all women under 65 years of age categorised as 'low' risk despite a >30% lifetime risk of CVD in most women.[11–13] In addition, conventional scores can misclassify risk—and this occurs more often in women than men, particularly Aboriginal and Torres Strait Islander women (Australian Indigenous women) (figure 1).[14 15] On average, CVD events occur 10–20 years earlier in Aboriginal and Torres Strait Islander women, and coronary heart disease is the single largest contributor to the 8-year gap in life expectancy, compared with non-Indigenous women.

Hypertensive disorders of pregnancy (HDP) such as pre-eclampsia, gestational diabetes mellitus (GDM) and premature menopause all confer a twofold, and in the case of early-onset pre-eclampsia an eightfold, higher independent risk of CVD.[16–19] Yet, awareness of these female-specific, risk-enhancing factors, among patients and healthcare practitioners, remains low.[5] Cardiology guidelines currently tell health providers to '*consider*' these female-specific conditions as '*risk enhancing*' for CVD, yet give no clear guidance on what this means in practical terms; for example, *should women with these female-specific risk factors receive more aggressive lipid and blood pressuring lowering medications?* We need a way to decide which women, with these risk-enhancing factors, should receive aggressive primary CVD prevention.

A CT-coronary artery calcium score ('CT-calcium score') directly measures calcified coronary plaque in asymptomatic individuals. The presence of coronary calcium is the single best predictor of future cardiac events in women and men, across ages and ethnicities.[12 20] Furthermore, CT-calcium scoring is widely available, simple (takes <5 min) and non-invasive, and confers minimal radiation (~1 mSv, less than a standard mammogram). A CT-calcium score is endorsed by the American, European and Australian guidelines to help reclassify CVD risk and guide medical therapy. A CT-calcium score provides individualised risk and can help treatment decisions and encourage healthy lifestyle adherence.[21]

In women with risk-enhancing factors, a CT-calcium score could be of benefit—where it can be used to guide initiation or uptitration of medical therapies such as statins and antihypertensives. Yet, to date, there are no trials that have looked at a CT-calcium score-guided approach to preventive care in women with risk-enhancing factors. In addition, CT-calcium scoring has been little tested in Indigenous populations, who have been severely under-represented in clinical trials and cohort studies.[22 23] CT-calcium scoring remains underused in clinical practice, often confers a cost to the patient and implementation research is needed to improve its uptake.

The aim of this trial is to assess a CT-calcium score-guided approach to cardiovascular (CV) risk factor control and healthy lifestyle adherence in women with risk-enhancing factors, who would otherwise be deemed at low-intermediate risk and not qualify for intensive medical therapy. It is anticipated that a high proportion of women with risk-enhancing factors will have premature coronary artery disease (CAD) detected by CT scanning. We hypothesise that CT-calcium score-guided approach in women will significantly improve CV risk factor control through intensification of medical therapy (initiation or uptitration of statin and blood pressure (BP)-lowering medications), improved adherence to this medical therapy and healthy lifestyle changes motivated by the intervention, compared with standard care. In addition, we will assess the implementation of a CT-calcium score-guided approach in clinical practice, including enablers and barriers and cost-effectiveness.

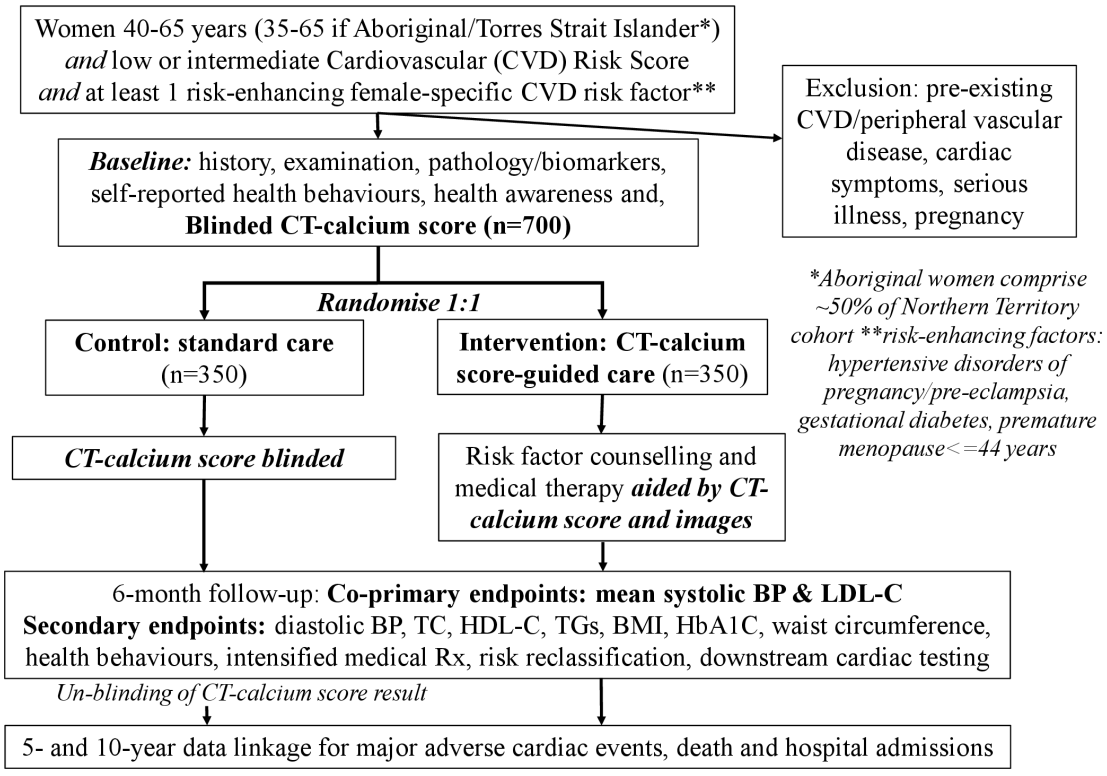

Figure 2 Study flow chart. BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

METHODS AND ANALYSIS

Study design

The Coronary Artery Calcium Scoring in Australian Women with Novel Cardiovascular Risk Factors (CAC-WOMEN Trial) will be a multisite randomised controlled trial (RCT) assessing the effectiveness of a CT-calcium score-guided CV prevention intervention on CV risk factor control and healthy lifestyle adherence, compared with usual care. The trial is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621001738819p) and the Standard Protocol Items: Recommendations for Interventional Trials checklist for randomised clinical trial protocols was completed.[24] Women will undergo blinded CT-calcium scoring followed by 1:1 randomisation to intervention (CT-calcium score-guided care) or control (standard care) and followed for 6 months (figure 2).

Patient and public involvement

Consumer consultation and engagement has been integral to the study design. This includes consumer endorsement by the Australian and New Zealand Alliance for Cardiovascular Trials with acceptance of each study measure and by the Diabetes across the Lifecourse: Northern Australia Partnership's Aboriginal and Torres Strait Islander Advisory Group (represented by SG on this manuscript), whose members are all Aboriginal women from the Northern Territory (NT) including Aboriginal community members, consumers, clinicians and researchers.[25] We will sustain our existing community engagement through regular phone/email communication with our established networks of community contacts, community newsletters and regular stakeholder meetings. The Aboriginal and Torres Strait Islander Advisory Group has already been established and will provide continual feedback and help build relationships and capacity within organisations to improve health and well-being in the community. Throughout the study, we will build research capacity in the NT focusing on Aboriginal and Torres Strait Islander research, ensuring the benefits of the results are translatable to other regions and sustainable.

A steering committee will meet quarterly and oversee all aspects of the clinical trial and will include all chief investigators, relevant clinicians, stakeholders, a consumer and a member/s of the Aboriginal and Torres Strait Islander Advisory Group. The trial will begin enrolment in August 2022, with anticipated ~2.5 years for enrolment and final study follow-up complete by February 2025.

Description of the intervention

At baseline, a CT-calcium score, a physical examination including weight, waist circumference and BP, as well as fasting pathology for basic renal function, full blood count, liver function, lipids and diabetic markers will be performed. A CT-calcium score will be done using low-dose, ECG-gated non-contrast multidetector CT machines at each recruiting site. The CT scan is performed during a breath hold and takes <5 min to complete. No intravenous cannula or contrast is required. The images are reconstructed at >3 mm slice thickness and reported as an Agatston score as per standard practice. Any non-cardiac incidental findings (anticipated to be <5%) are

reported by the local radiologist and conveyed to the treating general practitioner (GP). Incidental findings will be minimised by limiting scan length to the region of interest. Radiation exposure from a CT-calcium score is negligible, ~1 mSv, less than background radiation levels and equivalent or less than a standard mammogram. Consumer feedback has shown high acceptability of the CT scan in women with and without Aboriginal and Torres Strait Islander backgrounds.

Women in the intervention group will have a private, one-on-one CVD risk factor counselling session (telehealth will be used where possible, or in person if this is the participant's preference, for up to 45 min) aided by the recent CT-calcium score result where relevant (within a week). The risk factor counselling will be based on the European Society of Cardiology 2021 guidelines[26] and Cardiac Society of Australia guidelines.[27] Interpreters will be used for those of non-English-speaking backgrounds as needed. The CT-calcium score report will be discussed, including the CT-calcium score and age and sex-matched percentiles, and visual images of the woman's coronary arteries shown. The presence of any coronary calcium, as constituting premature coronary atherosclerosis, that is, coronary heart disease (as all women are ≤65 years of age), will be imparted and discussed in the context of each participant's individual risk factors. For CT-calcium score of 0, it will be imparted that this equates to a very low 5-year risk of CV events but that uncontrolled CVD risk factors need to be addressed due to impact on lifelong CVD risk. Women will receive a telehealth follow-up counselling session (or telephone where telehealth is unavailable), expected to take 5–10 min, by the study nurse at 1 and 3 months, to monitor risk factor modification. Women will be encouraged to follow-up with their GP to discuss their risk factors, with a letter provided to the participant to take to their GP. For those women where it is deemed necessary (eg, CT-calcium score >99 or ≥75% age/sex matched, uncontrolled BP or cholesterol levels requiring medications), a consultation with a study doctor in the CT-calcium score clinic at each site will be performed (telehealth will be used where possible). The CT images will be used by the study doctor to facilitate discussion with the following medical recommendations: (a) for coronary artery calcium (CAC) score=0; patient-led discussion regarding cessation of statins, if there is no history of low-density lipoprotein cholesterol (LDL-C) >4.9 mmol/L or alternate statin indications; (b) CAC score=1–99 and <75% age/sex matched; lifestyle modifications emphasised with consideration for lipid-lowering (statins) and BP-lowering medications; (c) CAC score >99 or ≥75% age/sex matched; initiation of lipid-lowering[13 20 28] and BP-lowering medications for systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic BP ≥90 mm Hg will be strongly encouraged (with BP targets of 130/80 for women with diabetes or with renal impairment/microalbuminuria). Primary prevention aspirin is generally not recommended. Statins will be started at a moderate-intensity dose, for example, start with rosuvastatin 10 mg or atorvastatin 20 mg or simvastatin 40 mg and uptitrate as needed, with recommendations to retest lipid levels in 3 months. If there is a history of statin-related side effects, a low-dose statin will be recommended with uptitration to a moderate dose after 2–4 weeks. BP-lowering medication will be started and uptitrated after 2–4 weeks if necessary to meet BP targets. If BP targets are not met with monotherapy, changing to a combined dose BP medication will be recommended. Prior to commencement of statins and/or BP-lowering medications, counselling regarding pregnancy and contraception use will be undertaken for any woman of childbearing age. Further doctor consultations will be arranged by the study nurse/coordinator as needed to monitor initiation of new medications or uptitration of medications. In the intervention group, the details of the CT-calcium scores and recommendations will be provided in letter form to the participant's GP.

Women in the control group remain under the care of their GP and are blinded to the CT-calcium score result for the 6-month study period. The participants are provided with a letter detailing the results of the baseline examination and pathology and are encouraged to see their GP for a discussion of CVD risk factor treatment in accordance with current national recommendations/guidelines. Following the 6-month trial period, the woman and their GP will be provided with the written CT-calcium score report and the opportunity provided to discuss the result with the study nurse/coordinator at each site via telephone. If there is a detection of very high CT-calcium score (ie, >400) in the blinded CAC control group, which is expected to be very low (<5%), the patient and the doctor will be immediately notified to ensure there is no delay in preventive therapy.

Study population

Women from the community will be eligible if they are aged 40–65 years (35–65 years if Aboriginal and/or Torres Strait Islander background), are low or intermediate risk for CVD based on conventional risk scores (eg, Australian absolute CV risk score) and have at least one risk-enhancing factor, namely HDP, gestational hypertension or pre-eclampsia, GDM, premature menopause (surgical/natural age ≤44 years) and/or Aboriginal and/or Torres Strait Islander background. The younger age cut-off of 35 years for Aboriginal and Torres Strait Islander women is due to CVD events that generally occur 10–20 years earlier in the Aboriginal and Torres Strait Islander population. Guidelines recommend in Australia that Aboriginal and Torres Strait Islander people should undergo CVD risk screening from a younger age.

Women will not be eligible if they are at very low risk for CVD or are at high/very high risk for CVD based on an Australian ACDRC (https://www.cvdcheck.org.au). Women must be able to provide and understand the informed consent with language assistance provided if required. Women who are aged 60 or over with diabetes mellitus (this automatically equates to a high-risk score

>15%), have pre-existing CVD (cardiac, cerebrovascular or peripheral vascular disease), have known statin intolerance, on dialysis (as this can affect coronary calcium scoring), currently pregnant or breast feeding or plan for future pregnancies, or have limited life expectancy of less than 5 years will also be excluded. Women currently taking statins can be considered for recruitment and assessed on a case-by-case basis depending on other risk factors and the knowledge that CAC=0 does not change an individual's lifetime risk for CVD in the presence of other risk factors.[29]

Randomisation and blinding

The secure REDCap database web application will be used for the women's registration and data collection, and will implement a 1:1 allocation ratio to intervention or control with permuted blocks of sizes 2 and 4 using a randomisation list generated by the statistician using the randomizeR package in R,[30] stratifying by site and aboriginal status. Balance of age categories (35–49, 50–59 and 60–65 years) and presence/absence of diabetes in each group will be monitored. To maintain blinding, the personnel performing the CT-calcium scan will be told not to reveal the results of the scan to the women in the study.

Recruitment

Women will be recruited from the community via online advertisements, flyers distributed in large workplaces, GP and specialist practices (eg, endocrinology, obstetrics, gastroenterology practices) and public hospitals. Media advertisements via television, newsletters/papers and radio will also be employed. All eligible women receive free CT-calcium scans and vouchers for study completion. Each site has a large obstetric department and past medical records can be obtained to identify women with a history of gestational risk factors of pre-eclampsia and GDM. In the NT Top End, 30% of the population are Aboriginal and/or Torres Strait Islander people, and there are existing study cohorts of women with GDM to help with recruitment. A research nurse/study coordinator at each site will recruit and follow-up participants, deliver the risk factor counselling sessions and coordinate the medical consultations. The NT site will, in addition, have an Aboriginal and/or Torres Strait Islander healthcare study worker with the ability to communicate in language to help recruit in remote settings and will be supported by the Diabetes across the Lifecourse: Northern Australia Partnership's Aboriginal and Torres Strait Islander Advisory Group. We recognise the importance of maintaining strong relationships with participants in this study. We want to show the participants that we value their time and dedication to this research and want to acknowledge the ongoing contributions of Aboriginal and Torres Strait Islander people to research.

Outcomes

To address the question of efficacy of CT-calcium score-guided care on objectively measured, modifiable CV risk factors, the coprimary outcomes are SBP (mm Hg) and serum LDL-C (mmol/L). Secondary outcomes are diastolic BP, high-density lipoprotein cholesterol, triglyceride levels, body mass index, glycosylated haemoglobin, waist circumference, meeting physical activity[31] recommendations and heart-healthy dietary guidelines measured at 6 months.[32 33] Secondary outcomes also include the incidence of CAD as assessed by a CT-calcium score at baseline in all women, women's awareness of their risk of CVD and total mortality/major adverse cardiovascular events (MACE) at 5 and 10 years, as measured by data linkage (see postrandomisation phase below). Details of data collection are shown in table 1. Patients may withdraw any time.

Postrandomisation phase

Data linkage with government repositories (National Death Index, Admitted Patient Data Collection, Emergency Department Data Collection, Medical Benefits Scheme and Pharmaceutical Benefits) with consent will be done to correlate abnormal CT-calcium score with long-term events including total mortality and MACE at 5 and 10 years.

Sample size

Based on local control data and previous studies[34 35] as well as data specifically in Aboriginal and Torres Strait Islander women,[36] we aim to detect a clinically meaningful difference in SBP of 4 mm Hg (SD 14 mm Hg) and difference in LDL-C of 0.25 mmol/L (SD 0.9 mmol/L). We estimate that with 87%–89% power and two-sided α of 0.025 to account for the two primary endpoints, an overall 20% dropout (that allows for a 10% dropout overall and a 30% dropout rate in the NT based on experience in Aboriginal and Torres Strait Islander health research), we will need a total sample size of 700 to detect an effect on either of the coprimary endpoints. Aboriginal and Torres Strait Islander women will comprise ~50% of the recruited women in the NT, but ~2% elsewhere, with an expected overall proportion of ~10% of the study population. We are not able to power our study for this subgroup, with these data being hypothesis generating.

Statistical analysis

The analysis will follow the intention-to-treat principle. The two groups will be compared using independent t-tests or χ^2 tests as appropriate. Regression analysis, adjusting for the baseline level of each primary outcome and secondary outcomes, will be used to assess the treatment effect using p value <0.025 as significant for primary outcome and p value <0.05 for secondary outcomes. Dichotomous variables will be created using recommended targets for each individual CVD risk

Table 1 Data collection details

	Screening	Baseline	Telehealth (1 week)	Telehealth (1 month)	Telehealth (3 months)	Visit 2 (6 months)	5 years	10 years
Visit week	–1	0	1	2	3	4	Data linkage	
General								
Medical history	X							
Cardiovascular risk assessment*	X	X						
Informed consent		X						
Randomisation		X						
Medical history and physical assessment								
Demographics		X						
Medical and surgical history		X						
Hormonal therapy and allergies		X						
Non-traditional risk factor assessment†		X						
Systolic/diastolic blood pressure‡		X				X		
BMI, height, weight, waist/hip circumference		X				X		
Smoking, quit attempts (self-reported)		X						
Cardiometabolic medication use and adherence (self-reported)		X						
Fasting blood test§		X				X		
Urine albumin to creatinine ratio (ACR)¶		X				X		
Clinical procedure								
CT-calcium score		X						
Questionnaires								
Physical activity**		X				X		
Dietary intake††		X				X		
Quality of life, EQ-5D-3L		X				X		
Risk perceptive survey		X						
Other								
Risk factor counselling (intervention group only)‡‡			X					
Risk factor modification monitoring (intervention group only)				X	X			
Major cardiac events (MI and stroke) and hospitalisations		X				X	X	X

*Eligibility will be conducted over the telephone. Women's age (criterion 1) and presence of at least one risk-enhancing factor will be confirmed (criterion 3). In order to determine the eligibility for criterion 2 (being at low or intermediate risk for CVD), pragmatic questions will be asked as not all women will have recent lipids or blood pressure measurements. Women will first be asked if they have had their blood pressure and/or cholesterol levels checked in the past year, and if they are aware of these results then an Australian absolute risk score will be calculated using the Australian absolute cardiovascular disease risk calculator (http://www.cvdcheck.org.au) to determine low to intermediate risk group.
†Pregnancy-related conditions, premature menopause, chronic inflammatory conditions (such as lupus, rheumatoid arthritis, arthropathies) and polycystic ovarian syndrome.
‡Three resting, sitting, digital recordings, mean of last two readings, measured by research nurse.
§Full blood count, liver function, renal function and electrolytes, lipids (TC, LDL-C, HDL, TG, lipoprotein(a), apo(B)), markers of diabetes (FBGL, HbA1c, fasting insulin) and biomarkers (high-sensitivity (hs) troponin, C-reactive protein (CRP) (high-sensitivity CRP ideally) and brain natriuretic peptide (BNP)).
¶Urinary albumin-to-creatinine ratio in women with diabetes and/or background renal impairment. If fasting bloods were performed with lipids and diabetic markers within 3 months of study enrolment, tests do not need to be repeated. Additional tests are to be requested as necessary as per protocol.
**Self-reported—adapted from General Physical Activity Questionnaire and self-reported exercise in the past 7 days.
††Self-reported—adapted from WHO steps instrument and short-item diet quality assessment and self-reported diet consumed in the past 7 days.
‡‡Conducted in person, but can be via telehealth when deemed necessary, for instance, due to COVID-19-related restrictions or rural location of participant.
BMI, body mass index; CVD, cardiovascular disease; EQ-5D-3L, EuroQoL 5 Dimensions 3 Level Version; FBGL, fasting blood glucose level; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol; TG, triglyceride.

factor. The relative risks and associated 95% CIs will be presented from a log binomial model.

Economic analysis

Economic analysis will take the perspective of the healthcare funder. Healthcare costs, including the cost of the intervention, using a CT-calcium score as a screening test and downstream healthcare resources, for example, use of medical services (GP, specialists, hospital and non-hospital diagnostic tests), prescribed pharmaceutical costs of medications, cardiac investigations and inpatient/outpatient healthcare, will be compared between treatment groups. A within-trial economic evaluation will estimate the incremental cost per additional person achieving a clinically meaningful improvement in LDL-C and in SBP. Bootstrapping will be used to estimate a distribution around costs and health outcomes,

and to calculate the CIs around the incremental cost-effectiveness ratios. One-way sensitivity analysis will be conducted around key variables and a probabilistic sensitivity analysis will estimate uncertainty in all parameters. A cost-effectiveness acceptability curve will be plotted to provide information about the probability that the intervention is cost-effective at various levels of willingness to pay for outcomes. Additionally, using data on the prevalence of CAD, sensitivity, specificity, positive predictive value, costs of screening and downstream healthcare costs, modelling will estimate the cost-effectiveness of the intervention using incremental cost per CV event/death prevented.

Process and feasibility evaluation

An evaluation of a CT-calcium score-guided prevention approach will focus on identifying the enablers, barriers, reach, effectiveness, acceptability and sustainability of implementing the intervention into current clinical services. Using the Reach x Efficacy-Adoption, Implementation, and Maintenance (RE-AIM) framework,[37] a mixed methods process evaluation will involve (1) quantitative and survey data related to primary and secondary outcomes, participant attendance and dropout rates, and (2) qualitative data including interviews with participants and relevant stakeholders. This process and feasibility evaluation will focus on the site/s recruiting Aboriginal and Torres Strait Islander women where acceptability and sustainability are paramount to changing clinical practice.

DISCUSSION

On top of barriers to accurate risk prediction of CVD in women in primary care practice, female patients are less likely to receive preventive medications than men.[38] These issues are even more pronounced in Aboriginal and Torres Strait Islander women, who have a life expectancy of 8 years younger than women without an Aboriginal and Torres Strait Islander background. This significantly higher risk for CVD in Aboriginal and Torres Strait Islanders is largely driven by a high burden of CVD risk factors at a younger age.[39 40] Conventional CVD risk scores can underestimate risk in younger women, and particularly in Aboriginal and Torres Strait Islander women.[14] However, we need to get the balance right—we want to ensure the right women are targeted to receive more intensive preventive pharmacotherapy for CVD.

The absence of CAC (CAC=0) confers a <1% 10-year risk of CV death, whereas an abnormal CT-calcium score >1 or >100 confers an approximately fourfold and 10-fold higher risk of CV mortality, respectively.[12 20 41 42] The value of a CT-calcium score in predicting CVD is more marked in women than men: the same CT-calcium score in a woman more than doubles the risk of a coronary event, compared with a man with the same score.[43] Abnormal coronary calcium detected on CT scanning is also common in women. In younger women (aged 45–54 years), women at very low CVD risk (<6% 10-year risk) or in women with a single risk-enhancing factor (eg, premature menopause), abnormal CT-calcium scores have been reported in 16%–25%.[12 13 42 44] In middle-aged women with at least one traditional CV risk factor, an abnormal CT-calcium score (>0) is seen in 40%–57% of women, with a CT-calcium score >99 in approximately 14%.[23 45] In addition, in a few small studies, female-specific risk-enhancing factors (such as HDP or premature menopause) have been shown to correlate with higher CT-calcium score.[46 47] CT-calcium scoring has the additional value of being an effective tool to guide medical therapy. Women with abnormal CT-calcium score meet the guideline recommendations for statin therapy.[20 28] Furthermore, knowledge of an individual's CT-calcium score empowers both the treating doctor and the patient: when an individual is shown a visual image of their atherosclerotic plaque, adherence to both lifestyle changes and medications improves.[21] A CT-calcium score provides individualised risk, and gives treating doctors an objective 'decision tool' rather than a prediction tool.

The single-centre St Francis Heart Study randomised patients to CT-calcium score-guided statin use, but lacked power to show this reduced the primary endpoint of MACE (p=0.08).[48] The Early Identification of Subclinical Atherosclerosis by Non-invasive Imaging Research RCT (2011) in a single New York centre randomised patients to CT-calcium scan, or no scan (2:1 randomisation) with ~50% of their cohort women, and abnormal coronary calcium found in 57%. They found a CT-calcium score-guided approach to risk factor counselling significantly reduced BP, lipid levels and waist circumference, and improved healthy lifestyle adherence. However, this was in a largely Caucasian, highly educated American population.[23] The National Health and Medical Research Council-funded Australian Coronary Artery calcium score: Use to Guide management of Hereditary Coronary Artery Disease (CAUGHT-CAD) trial will assess a CT-calcium score-guided primary prevention approach in low-risk patients (mean 5-year Australian CVD risk score of ~4%) with a family history of CAD on a primary endpoint of CT-measured coronary plaque. To date, 1000 patients have undergone CT-calcium scoring, with abnormal scores (>0) in 45%, with these patients then randomised to statins or no statins. The final results of this trial testing the efficacy of statins on coronary plaque burden in a low-risk population with a family history are expected in 2022.[49]

Limitations

Participants will include young to middle-aged women where the prevalence of CT-calcium scores of zero (despite the presence of risk-enhancing factors) may limit the efficacy of a CT-calcium score-guided approach to CV risk factor control. A CT-calcium score does not identify non-calcified plaque, which may be more evident in younger patients and women and portend elevated CV risk even in the absence of coronary calcification. A recent Danish study showed that in younger patients, a

lack of calcified plaque did not rule out the presence of non-calcified plaque or obstructive coronary disease.[29] The 6-month follow-up time period and sample size means that the primary outcome will focus on BP and lipid control, rather than MACE or deaths. LDL-C and SBP are well validated as surrogate markers for CVD. Reductions in both LDL-C and SBP closely and linearly correlate with reductions in MACE and death. While a trial outcome of MACE/death would be ideal, this is not feasible as previous analyses have demonstrated such trials would require extremely large sample sizes (approximately 30 000 patients).[50]

CONCLUSION

This multisite, single-blind RCT will be the first to assess a CT-calcium score-guided approach to CV care and prevention in women with female-specific risk-enhancing factors. If positive, the trial could pave the way for widespread implementation of CT-calcium scores to guide preventive care, and therefore reduce the burden of CVD in women in Australia and around the world.

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Contributors SM was involved in the design, methodology and statistical analysis approach, and wrote the original manuscript. SZ conceptualised the idea and was a contributor to the methodology, review and editing of the protocol, and funding acquisition, and accepts the responsibility as the paper guarantor. CC contributed to the conceptualisation, methodology, and review and editing of the protocol. LM-B contributed to the methodology and review and editing of the protocol, and provided the engagement and consultation with NT Aboriginal women and communities. SG contributed to the methodology and review and editing of the protocol, and is the chair of Diabetes across the Lifecourse: Northern Australia Partnership's Aboriginal and Torres Strait Islander Advisory Group, and will help prioritise the recruitment of Aboriginal women in the Darwin site and encourage engagement, and will be in constant consultation and provide feedback from the NT Aboriginal women and communities. SJN, AB, AW, AI and EW-L contributed to the methodology and review and editing of the protocol. AVH contributed to the economic data collection and methodology. All authors read and approved the final manuscript.

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