Coronary artery calcium scoring in cardiovascular risk assessment of people with family histories of early onset coronary artery disease

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The known: Australian guidelines define intermediate risk of cardiovascular disease more restrictively than overseas guidelines. CT coronary artery calcium scoring can be used to re-classify patients at intermediate risk, but is not widely used in Australia.

The new: Overseas risk prediction tools were superior to the Australian cardiovascular disease risk calculator with respect to identifying people with family histories of early onset coronary artery disease who have coronary artery calcium.

The implications: CT calcium scoring could be used to identify a considerable number of people who could benefit from statin treatment as primary prevention, but are currently excluded by Australian guideline-directed treatment thresholds.

Abstract

Objectives: To assess the predictive value of the Australian absolute cardiovascular disease risk (ACVDR) calculator and other assessment tools for identifying Australians with family histories of early onset coronary artery disease (CAD) who have coronary artery calcification.

Design, setting, participants: People without known CAD were recruited at seven Australian hospitals, October 2016 – January 2019. Participants were aged 40–70 years, had a family history of early onset CAD, and a 5-year ACVDR of 2–15%.

Main outcome measures: CT coronary artery calcium score greater than zero (any coronary calcification) or greater than 100 (calcification warranting lipid therapy).

Results: 1059 participants were recruited; 477 (45%) had non-zero coronary artery calcium scores (median 5-year ACVDR, 4.8% [IQR, 2.9–7.6%]; median coronary artery calcium score, 41.7 [IQR, 8–124]); 582 (55%) did not (median 5-year ACVDR, 3.2% [IQR, 2.0–4.6%]). Of 151 participants with calcium scores of 100 or more, 116 (77%) were deemed to be at low cardiovascular risk by Australian guidelines, while 14 of 75 participants at intermediate risk (19%) had zero calcium scores. The sensitivity of the ACVDR calculator for identifying people with non-zero calcium scores (area under receiver operator curve [AUC], 0.674) was lower than that of the pooled cohort equation (AUC, 0.711; $P < 0.001$). ACVDR (10-year)- and Multi-Ethnic Study of Atherosclerosis (MESA)-predicted risk categories concurred for 511 participants (48%); classifications were concordant for 925 participants (87%) when the ACVDR was supplemented by calcium scores.

Conclusions: Coronary artery calcium scoring should be considered as part of the heart health check for patients at intermediate ACVDR risk and with family histories of early onset CAD. Alternative risk calculators may better select such patients for further diagnostic testing and primary prevention therapy.

Trial registration: Australian New Zealand Clinical Trials Registry, ACTRN 12614001294640; 11 December 2014 (prospective).

Fewer than 30% of people in Australia at high risk of a primary cardiovascular event receive guideline-recommended statin therapy.[1] This missed opportunity for preventing cardiovascular disease motivated introducing the Medical Benefits Scheme (MBS) item for heart health checks in early 2019 to encourage cardiovascular risk assessment and statin prescribing according to Australian primary prevention guidelines.[2,3] However, the National Vascular Disease Prevention Alliance (NVDPA) guidelines for managing absolute cardiovascular disease risk were most recently updated in 2012, and they differ in important details from overseas guidelines.[4] Firstly, the Australian absolute cardiovascular disease risk (ACVDR) calculator,[5] used to select patients for primary prevention statin therapy, is a locally calibrated version of the Framingham risk equation, which has been superseded in the United States by the pooled cohort equation (PCE).[6] Secondly, the definition of intermediate risk, the threshold for considering statin therapy, is lower in US guidelines (10-year risk, 7.5% – < 20%)[6] than in Australian guidelines (5-year risk, 10–15%).[3]

Further, the Australian guidelines do not mention computed tomography (CT) coronary artery calcium scoring. Coronary artery calcium is a sensitive marker of subclinical coronary atherosclerosis, and calcium scoring is an accepted re-classification tool for assessing risk in middle-aged people.[7] A zero calcium score indicates that the risk of cardiovascular disease is lower than 0.5% per year,[8,9] while the risk reduction achieved by statin therapy in asymptomatic people with calcium scores of 100 or more is similar to the benefit of statins prescribed as secondary prevention.[10,11] US guidelines include calcium scoring as a decision aid, recommending statin therapy for people over 55 with non-zero calcium scores and for anybody with scores of 100 or more (class IIa recommendation); they recommend not initiating statins for people with zero calcium scores.[6]

The high cost of coronary CT calcium scanning in Australia (it is not subsidised by the MBS) and the radiation exposure involved should influence referral decisions. These considerations are particularly pertinent for people with family histories of early onset coronary artery disease (CAD), for whom statin therapy should be considered if they have subclinical atherosclerosis, as their outcomes are poorer than for the general population.[9]

We compared the performance of the ACVDR calculator and other standard cardiovascular disease risk tools with respect to identifying people who have non-zero coronary artery calcium scores and may therefore benefit from statin therapy. We also assessed the value of calcium scoring for guiding treatment of people with a family history of early onset CAD.

Methods

Study design and participants

We analysed screening data from the Coronary Artery calcium score: Use to Guide management of Hereditary Coronary Artery Disease (CAUGHT-CAD) trial (ACTRN 12614001294640), a randomised controlled trial assessing the utility of coronary artery calcium scoring for guiding risk evaluation and primary prevention statin therapy in patients with family histories of early onset CAD.[12] Briefly, participants aged 40–70 years and free of clinical cardiovascular disease at baseline were recruited from the community at the Royal Hobart Hospital, Royal Perth Hospital, Royal Adelaide Hospital, the Baker Heart and Diabetes Institute and Austin Hospital (Melbourne), the Sunshine Coast University Hospital, and Ipswich Hospital during 1 October 2016 – 31 January 2019. Self-reported family history of early onset CAD was defined as having a first degree relative under 60 years of age or a second degree relative under 50 with CAD. Inclusion criteria were a 5-year ACVDR predicted risk of 2–15%, never having received statin therapy, total cholesterol not exceeding 6.5 mmol/L, and low-density lipoprotein cholesterol below 5.0 mmol/L. Exclusion criteria included Pharmaceutical Benefits Scheme eligibility for statin therapy (Box 1), major systemic illness, impaired renal function, atrial fibrillation, and high risk of statin-induced myopathy, as well as contraindications for CT scanning.

All participants underwent baseline clinical and standard pathology assessments, including lipid profile. Coronary artery calcium was measured with low-dose (1 mSv), electrocardiogram-gated, non-contrast, dual-source 128-slice CT machines, and reported as Agatston scores according to the area and density of visually identified coronary calcium lesions.

Risk score calculation

We calculated risk scores for our participants with seven cardiovascular risk models cited in guidelines and with publicly available risk algorithms[14–21] (Box 2), and compared their

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1 Pharmaceutical Benefits Schedule (PBS) statin therapy eligibility criteria at the commencement of our study (2016)[13,*]

Category	Eligibility criteria (any)
Diabetes mellitus	• 60 or more years old • Aboriginal or Torres Strait Islander Australian • Microalbuminuria: urinary albumin excretion rate > 20 μg/min or urinary albumin:creatinine ratio > 2.5 (men) or 3.5 (women) • Total cholesterol > 5.5 mmol/L
Hypertension	• Total cholesterol > 6.5 mmol/L • Total cholesterol > 5.5 mmol/L and high-density lipoprotein cholesterol < 1 mmol/L
Aboriginal or Torres Strait Islander	• Total cholesterol > 6.5 mmol/L • Total cholesterol > 5.5 mmol/L and high-density lipoprotein cholesterol < 1 mmol/L
Family history of symptomatic coronary heart disease[†]	• Low-density lipoprotein cholesterol > 5 mmol/L • Total cholesterol > 6.5 mmol/L • Total cholesterol > 5.5 mmol/L and high-density lipoprotein cholesterol < 1 mmol/L

* The PBS indication for statin therapy for primary prevention has since been extended to all people over 60 years of age with diabetes and to people of any age with systolic blood pressure of 180 mmHg or more or diastolic blood pressure of 110 mmHg or more, and also includes other people excluded from our study (eg, people with chronic kidney disease or a 5-year risk of cardiovascular disease greater than 15%).[13] † First degree relative under 60 or second degree relative under 50 years of age. ◆

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identification of people with non-zero calcium scores (as a measure of subclinical atherosclerosis) with that of the 5-year ACVDR calculator. We also calculated 10-year ACVDR risk to compare risk assignment with the Multi-Ethnic Study of Atherosclerosis (MESA).[18] We calculated both fatal coronary event risk (SCORE-CAD) and combined fatal coronary event and stroke risk with the European Systematic Coronary Risk Evaluation (SCORE) tool.[17] ASSIGN (Scotland)[14] and PREDICT (New Zealand)[16] include postcode-based measures of socio-economic status (Scottish Index of Multiple Deprivation [SIMD]; New Zealand Index of Socioeconomic Deprivation). We derived corresponding scores for our participants by inverting the 2016 Index of Relative Advantage and Disadvantage (IRSAD) rankings (Australian Bureau of Statistics).[26] The SIMD scores for Australian postcodes were derived from the 2012 SIMD dataset.

Outcomes

The primary outcome was coronary artery calcification (ie, non-zero calcium score), interpreted as a marker of CAD risk.[8] The secondary outcome was a calcium score of 100 or more (calcification warranting lipid therapy). Predicted 10-year risk in the MESA model (which incorporates calcium scoring and has been validated with respect to cardiovascular events)[18] was used as an independent surrogate measure of true cardiovascular risk.

Statistical analysis

Values for continuous variables are summarised as means with standard deviations (SDs) or medians with interquartile ranges (IQRs); categorical variables are summarised as numbers and proportions, with confidence intervals (CIs) calculated with the binomial method. The statistical significance of differences between proportions by calcium score group or test classification were assessed in χ^2 or McNemar tests (categorical variables) and t or rank sum tests (continuous variables). Areas under the receiver operator curves (AUCs) for prediction models were compared using the Hanley–McNeil method.[27] The optimal cut-points of risk were determined according to the Youden J statistic (sensitivity + specificity – 1; this optimises discrimination when sensitivity and specificity are equally weighted[28]); we also estimated the cut-points needed for achieving 80% sensitivity.

The effect of coronary artery calcium scoring for adjusting predicted ACVDR or PCE risk (as independent variables) was assessed in multivariable linear regression models, with the MESA score as the dependent variable. We then assessed changes in risk classification in models comparing the combination of ACVDR or PCE and calcium score with the MESA score. The association of age of CAD onset in relatives with subclinical disease was assessed by univariable logistic regression. Risk classification performance was based on US guideline 10-year risk categories: low/borderline (< 7.5%), intermediate (7.5% to less than 20%), and high risk (≥ 20%). Statistical analyses were conducted in Stata 15.1 and with the *ROCR* package in R 3.5.1.

Ethics approval

Our study was approved by the Tasmanian Human Research Ethics Committee (reference, 14-281) and by all participating institutions. All participants provided written informed consent.

Results

Coronary artery calcium was measured in 1059 participants; 477 had non-zero Agatston scores (45%; median score, 41.7; IQR, 8–124), including 151 with scores of 100 or more (14%). The

2 Characteristics of the cardiovascular disease risk prediction models discussed (adapted from reference 4)

Characteristic	SCORE[4,17]	Framingham risk score (FRS)[20,22]	ASSIGN-SCORE[14,23]	Pooled cohort equation[6,19]	PREDICT[16,24]	CUORE[21,25]	MESA[18]	ACVDR[3,15]
Age range (years)	40–65	30–75	30–74	20–79	30–74	35–69	45–85	Indigenous Australians: 35–74; Non-Indigenous Australians: 45–74
Sex	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total cholesterol	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
High-density lipoprotein cholesterol	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statin therapy	No	No	No	No	Yes	No	Yes	No
Smoking	Yes	Yes	Cigarettes per day	Yes	Non-, ex-, current smoker	Yes	Yes	Yes
Systolic blood pressure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Treatment for hypertension	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Diabetes mellitus	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country	Yes (high/low risk)	USA	Scotland	USA	New Zealand	Italy	USA	Australia
Socio-economic status	No	No	Yes (SIMD)	No	Yes	No	No	No
Family history	No	No	Yes (first-degree relative under 60)	No	Yes	No	Yes	No
Other	No	No	No	Ethnic background	Ethnic background, atrial fibrillation, anti-thrombotic therapy	No	Coronary artery calcium score	Electrocardiography: left ventricular hypertrophy
Study date	2003	2008	2008	No	2018	2007	2015	2009
Study data	12 pooled prospective studies	Framingham Heart and Offspring Studies	SHHEC prospective study	4 pooled prospective studies	Single prospective cohort study	Prospective (fixed Italian cohort of 12 random samples)	Prospective MESA study; validated: HNR, DHS	Based on Australian disease rates
Sample size	117 098 men; 88 080 women	3969 men; 4522 women	6540 men; 6757 women	10 745 men; 13 881 women	226 053 men; 175 699 women	7056 men; 12 574 women	6814 participants	Calibrated with FRS
Time course	10 years	10 years	10 years	10 years	5 years	10 year	10 years	5 years
Outcome	Cardiovascular disease mortality (coronary artery disease- and stroke-specific mortality)	Fatal and non-fatal cardiovascular events (coronary, coronary insufficiency, angina, stroke, peripheral artery disease, heart failure)	Fatal and non-fatal major coronary and stroke events, any hospital discharge diagnosis of coronary heart disease or coronary interventions	Fatal and non-fatal myocardial infarction, coronary artery disease death, fatal or non-fatal stroke	Fatal and non-fatal cardiovascular disease, including stroke, peripheral vascular disease and heart failure; coronary insufficiency, angina	Fatal and non-fatal major coronary and stroke events; revascularisation included, but not angina	Incident hard coronary heart disease (myocardial infarction, cardiac arrest, fatal coronary heart disease, revascularisation for prior or concurrent angina)	Based on FRS: fatal and non-fatal cardiovascular disease, including peripheral artery disease, stroke, renovascular disease, heart failure, angina, coronary insufficiency
Risk categories	Low: < 1%; Moderate: 1–5%; High: > 5%	Low: < 10%; Moderate: 10–19%; High: ≥ 20%	Low: < 20%; High: ≥ 20%	Low: < 5%; Borderline: 5–7.5%; Moderate: 7.5–< 20%; High: ≥ 20%	Low: < 5%; Moderate: 5–15%; High ≥ 15%	Low: < 3%; Moderate: 3–20%; High: > 20%	Not stated	Low: < 10%; Moderate: 10–15%; High: > 15%

ACVDR = Australian absolute cardiovascular disease risk calculator; DHS = Dallas Heart Study; HNR = Heinz Nixdorf Recall Study; MESA = Multi-Ethnic Study of Atherosclerosis; SCORE = European Systematic Coronary Risk Evaluation; SIMD = Scottish Index of Multiple Deprivation; SHHEC = Scottish Heart Health Extended Cohort Study. ◆

median age of participants with non-zero scores was higher than for the 582 (55%) with zero scores; the proportions who were men (60% *v* 39%) or receiving anti-hypertension therapy (21% *v* 15%) were also larger. The median 5-year ACVDR was higher for participants with non-zero than for those with zero scores (4.8%; IQR, 2.9–7.6% *v* 3.2%; IQR, 2.0–4.6%). Smoking rates, lipid profiles, and prevalence of diabetes were similar in the two groups (Box 3).

Classifying risk: Australian and United States guidelines

Of the 477 participants with non-zero calcium scores, Australian criteria[3] classified 61 as being at intermediate 5-year risk (13%; 95% CI, 10–16%), whereas the US criteria[6] classified 190 as being at intermediate 10-year risk (40%; 95% CI, 36–44%). Were non-zero calcium score the criterion for statin therapy, the US guidelines appropriately guided management — that is, recommended statins for patients with non-zero scores and not for patients with zero calcium scores — for 706 of 1059 participants (67%); the Australian guidelines did so for 629 of 1059 (59%) (Box 4).

The median ACVDR for the 151 participants with calcium scores of 100 or more was 6.0% (IQR, 3.6–9.8%); 116 of these participants (77%) were deemed to be at low cardiovascular risk by Australian guidelines. Were a calcium score of 100 Agatston units the criterion for statin therapy, the 5-year ACVDR threshold of 10% would be appropriate for 903 of 1059 participants (85%) (Box 4).

Applying US calcium scoring-based guidelines[6] would increase the number of participants eligible for statin therapy, from 75 at intermediate ACVDR risk to a total of 397 participants, an increase of 322 (116 with calcium scores of 100 or more and 206 participants aged 55 or more with non-zero calcium scores below 100). The median 10-year MESA risk for the 322 statin-eligible participants was 6.5% (IQR, 4.4–10%).

Optimal risk thresholds for identifying people with coronary artery calcium

The optimal risk thresholds for identifying people with non-zero calcium scores (sensitivity and specificity equally weighted) were 4.8% for 5-year ACVDR (sensitivity, 51%; specificity, 77%) and 6.1% for PCE 10-year risk (sensitivity, 50%; specificity, 82%). Treating all patients with 5-year ACVDR of 5% or more would increase the proportion of patients with non-zero calcium scores receiving appropriate treatment (from 61 [13%] to 219 of 477 [46%]), but would also increase the proportion of people at intermediate risk with zero calcium scores receiving statin treatment from 14 of 75 (19%) to 118 of 337 (35%). With a 5-year ACVDR threshold of 5%, the number needed to scan to identify one person with a non-zero calcium score (inverse of the positive predictive value) was 1.5; at this threshold, all 20 participants with a MESA risk of 20% or more would be identified (Box 8). With the PCE 10-year risk threshold of 7.5%, 66 of 256 patients at intermediate risk (26%) had zero calcium scores (Box 4). The 5-year ACVDR threshold needed to capture 80% of participants with non-zero calcium scores would be 2.6% (data not shown).

The optimal risk threshold for identifying people with calcium scores of 100 or more was 6.6% for both 5-year ACVDR (sensitivity, 49%; specificity, 84%) and PCE 10-year risk (sensitivity, 60%; specificity, 76%). Numbers needed to scan to identify one person with a calcium score of 100 of more were 7.0 with an ACVDR risk threshold of 2%, 3.9 at a threshold of 5%, and 2.1 at a threshold of 10%.

Sensitivity of risk score models for identifying people with coronary artery calcium

The sensitivity of the ACVDR (AUC, 0.674) for identifying people with non-zero calcium scores was lower than that of

3 Baseline characteristics of the 1059 study participants, by coronary artery calcium score

	Coronary artery calcium score		
	Zero	Non-zero	*P*
Number of participants	582	477	
Age (years), median (IQR)	54 (48–59)	59 (54–63)	< 0.001
Age of relative at CAD onset (years), median (IQR)*	52 (48–57)	52 (48–57)	0.55
Sex (men)	228 (39%)	286 (60%)	< 0.001
Total cholesterol (mmol/L), median (IQR)	5.5 (5.0–6.0)	5.6 (5.1–6.0)	0.41
High-density lipoprotein cholesterol (mmol/L), median (IQR)	1.5 (1.2–1.8)	1.4 (1.2–1.7)	0.15
Smoking			0.38
Non-smoker	344 (60%)	269 (56%)	
Ex-smoker	203 (35%)	182 (38%)	
Weekly smoker	9 (2%)	4 (1%)	
Daily smoker	20 (4%)	22 (5%)	
Systolic blood pressure (mmHg), mean (SD)	130 (14)	130 (13)	0.76
Treated for hypertension	87 (15%)	101 (21%)	0.011
Diabetes mellitus	8 (1%)	9 (2%)	0.68
IRSAD, median (IQR)	1029 (985–1072)	1034 (985–1073)	0.52
5-year ACVDR, median (IQR)	3.2% (2.0–4.6%)	4.8% (2.9–7.6%)	< 0.001

ACVDR = Australian Absolute Cardiovascular Disease Risk; CAD = coronary artery disease; IQR = interquartile range; IRSAD = Index of Relative Social Advantage and Disadvantage; SD = standard deviation. * Age of the youngest relevant relative; first degree preferred to second degree relative when both eligible. ◆

4 Cardiovascular risk thresholds in Australia and the United States, and coronary artery calcification

	Australia: 5-year risk		US: 10-year risk
	ACVDR: ≥ 10% (intermediate)	ACVDR: ≥ 5%	PCE: ≥ 7.5% (intermediate)
Number of participants	75	337	256
Coronary calcium score > 0	61	219	190
Accuracy (of risk tool)*	629/1059 (59%)	683/1059 (65%)	706/1059 (67%)
Sensitivity	61/477 (13%)	219/477 (46%)	190/477 (40%)
Specificity	568/582 (98%)	464/582 (80%)	516/582 (89%)
Positive predictive value	61/75 (81%)	219/337 (65%)	190/256 (74%)
Negative predictive value	568/984 (58%)	464/722 (64%)	516/803 (64%)
Coronary calcium score ≥ 100	35	86	80
Accuracy (of risk tool)	903/1059 (85%)	743/1059 (70%)	812/1059 (77%)
Sensitivity	35/151 (23%)	86/151 (57%)	80/151 (53%)
Specificity	868/908 (96%)	657/908 (72%)	732/908 (81%)
Positive predictive value	35/75 (47%)	86/337 (26%)	80/256 (31%)

ACVDR = Australian absolute cardiovascular risk; PCE = pooled cohort equation. * Accuracy = (true positives + true negatives)/total population, whereby "true positive" is defined as concurrence of the respective risk level being reached and the presence of coronary calcium, and "true negative" as the concurrence of the respective risk level not being reached and the absence of coronary calcium. ◆

the PREDICT (AUC, 0.697; v ACVDR: P = 0.005), CUORE (AUC, 0.704; P < 0.001), SCORE (AUC, 0.706; P = 0.003), PCE (AUC, 0.711; P < 0.001), and SCORE-CAD tools (AUC, 0.712; P < 0.001). All tools were better at identifying people with calcium scores of 100 or more, but the PCE (AUC, 0.728, P = 0.026) and SCORE-CAD (AUC, 0.733; P = 0.05) were superior to the ACVDR (AUC, 0.709). Tools that included family history as a predictor (ASSIGN, PREDICT) were not superior to other risk models (Box 5).
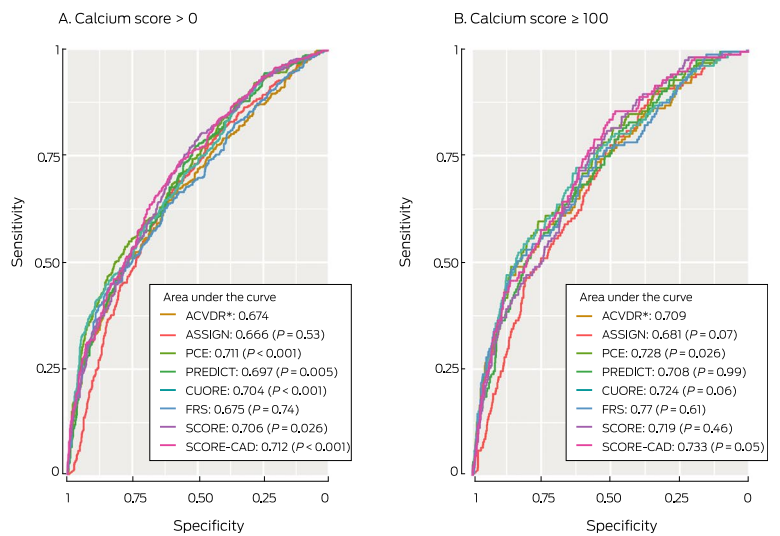
Associations between subclinical atherosclerosis and age of CAD onset in the index family member or the closeness of the relationship were not statistically significant (Box 6).

Differences between tools in 10-year risk classification

Ten-year risk classification with the PCE was lower than with the ACVDR for 497 of 1059 participants (47%); the median calcium score for the 420 participants classified as intermediate risk by the ACVDR but as low risk by the PCE was 0 (IQR, 0–13) (Box 7; Supporting Information, table 1). Of 582 participants with zero calcium scores, the PCE classified 516 (88%) and the ACVDR 264 (45%) as being at low risk. Ten-year risk classification with the MESA was lower than with the ACVDR for 530 (50%) and higher for 18 participants (2%).

The median 10-year risk for all 1059 participants was 2.9% (IQR, 2.0–6.0%) with MESA, 4.2% (IQR, 2.1–7.3%) with the PCE, and 9.4% (IQR, 6.0–14%) with the ACVDR. The PCE- and MESA-predicted risk categories concurred for 831 participants (78.5%); the ACVDR- (10-year) and MESA-predicted risk categories concurred for 511 participants (48.3%) (Box 8; Supporting Information, table 1). After combining the ACVDR (10-year) with

5 Sensitivity of risk prediction models with respect to including people with non-zero coronary calcium scores: receiver operator characteristic curves

A. Calcium score > 0

Area under the curve
ACVDR*: 0.674
ASSIGN: 0.666 (P = 0.53)
PCE: 0.711 (P < 0.001)
PREDICT: 0.697 (P = 0.005)
CUORE: 0.704 (P < 0.001)
FRS: 0.675 (P = 0.74)
SCORE: 0.706 (P = 0.026)
SCORE-CAD: 0.712 (P < 0.001)

B. Calcium score ≥ 100

Area under the curve
ACVDR*: 0.709
ASSIGN: 0.681 (P = 0.07)
PCE: 0.728 (P = 0.026)
PREDICT: 0.708 (P = 0.99)
CUORE: 0.724 (P = 0.06)
FRS: 0.77 (P = 0.61)
SCORE: 0.719 (P = 0.46)
SCORE-CAD: 0.733 (P = 0.05)

ACVDR = Australian absolute cardiovascular disease risk calculator; AUC = area under the receiver operator curve; FRS = Framingham risk score; PCE = pooled cohort equation; SCORE = European Systematic Coronary Risk Evaluation. * Reference for comparison with other models. ◆

calcium scores, concordance with MESA-predicted risk categories rose to 87.3% (925 participants), mainly by reclassifying people at intermediate risk as being at low risk (Box 8).

In the multivariable linear model, performance of the PCE and the ACVDR calculator was similar before (PCE, R^2 = 0.40; ACVDR, R^2 = 0.39) and after adding coronary artery calcium score to the clinical score (PCE, R^2 = 0.82; ACVDR, R^2 = 0.83). The β coefficient was greater for the PCE than for the ACVDR

6 Associations between coronary artery calcium score and the age and proximity of index relatives: odds ratios with 95% confidence intervals

Characteristic of index relative	Coronary artery calcium score	
	Non-zero	100 or more
Age: 40 years or less (v older than 40 years)	0.93 (0.63–1.37)	0.97 (0.54–1.65)
Age: 50 years or less (v older than 50 years)	0.98 (0.77–1.25)	0.95 (0.67–1.34)
First (v second) degree relative	1.30 (0.83–2.09)	0.97 (0.53–1.90)

7 Comparison of predicted 10-year cardiovascular risk by the Australian absolute cardiovascular disease risk (ACVDR) calculator and the pooled cohort equation, and coronary artery calcium scores
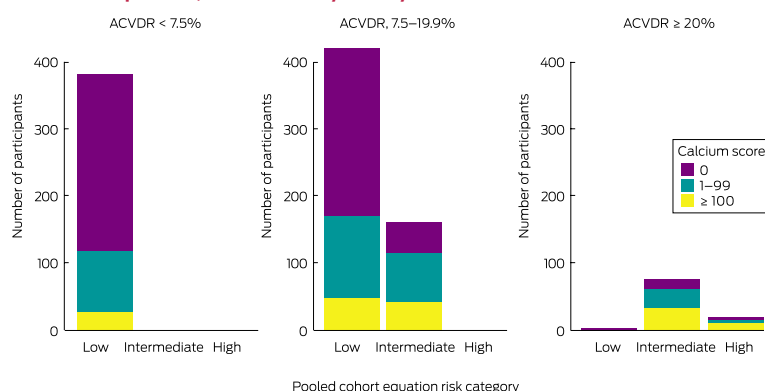
8 Comparison of predicted 10-year cardiovascular risk by the Australian absolute cardiovascular disease risk (ACVDR) calculator* and the pooled cohort equation with Multi-Ethnic Study of Atherosclerosis (MESA) risk classification
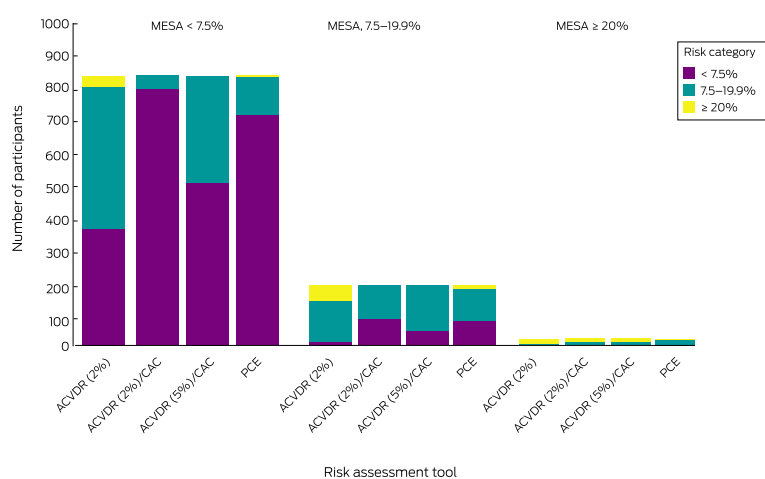
CAC = coronary artery calcium scoring. * The results of two inclusion ACVDR risk level thresholds for scanning are shown: 2% (with and without calcium scoring) and 5% (with calcium scoring). Numbers of participants by MESA risk group: < 7.5%: 851; 7.5–19.9%, 188; ≥ 20%, 20. ◆

both before (PCE, 0.66; 95% CI, 0.62–0.72; ACVDR, 0.48; 95% CI, 0.44–0.51) and after standardisation and adjustment for calcium score (PCE, 0.36; 95% CI, 0.33–0.39; ACVDR, 0.28; 95% CI, 0.25–0.30) (Supporting Information, table 2).

Discussion

We have identified two problems with the assessment of cardiovascular disease risk according to Australian guidelines. First, the statin treatment threshold (5-year risk of 10%) is higher than overseas and excludes many patients with both family histories of early onset CAD and subclinical atherosclerosis. Second, all the cardiovascular risk tools examined were moderately sensitive for identifying people with coronary artery calcium, but the ACVDR calculator was among the least sensitive in this regard.

Comparison of the performance of the ACVDR and other risk estimation tools

The various risk models are based on different populations, algorithms, risk factors, and predicted cardiovascular outcomes. While we did not compare the prognostic performance of the ACVDR in Australian patients with that of other tools, we found that it tends to rate coronary risk in Australian patients higher than most overseas models.

The CUORE, PCE, and SCORE models were better at discriminating between people with and without subclinical atherosclerosis than the locally calibrated ACVDR and more comprehensive models that include family history and social deprivation as factors (PREDICT, ASSIGN). The PCE, CUORE and SCORE models are based on different risk algorithms and study populations. The endpoints for the PCE, CUORE and SCORE are limited to major cerebrovascular and coronary events. In contrast, the Framingham model and its derivatives, the ACVDR and PREDICT, include softer endpoints, such as elective revascularisation, angina pectoris, peripheral artery disease, renovascular disease, and heart failure; the ASSIGN model endpoints include any hospital discharge diagnosis of coronary heart disease or coronary artery intervention (Box 2). These endpoints entail more subjective clinician decisions and are therefore less reliable, perhaps explaining the lower specificity of these models for identifying subclinical disease. Further, we did not find an association between postcode-based socio-economic status (IRSAD) and subclinical atherosclerosis, in contrast to other studies.[29] These differences in endpoints and the inclusion of risk factors not independently associated with subclinical disease in our sample may also explain the tendency of some tools to generate higher risk estimates, one of the motives for developing the PCE.[19] While prediction models validated in local cohorts can perform better than those validated overseas with respect to symptomatic CAD,[30] local calibration may be insufficient to overcome deficiencies in the parent model.

Tools that performed better than the ACVDR included markers of cumulative exposure to risk factors, such as treatment for hypertension, that may help identify established subclinical disease.[31] The median risk estimate in our study was 50% lower with the PCE than that with the ACVDR (4.2% v 9.4%), and the PCE risk classification was lower for about half of our participants. This is important for people with family histories of early onset CAD; absolute coronary risk may be their primary concern

and the proportional reduction in absolute risk achievable with statin therapy is central to management discussions with their clinicians.

Risk thresholds for statin therapy

Risk thresholds for statin therapy in Australian guidelines are higher than in more recent US and European guidelines that may better reflect falling drug prices and greater evidence of clinical benefit.[3,6] As cardiovascular event rates for people with family histories of early onset CAD and coronary calcification exceed those associated with US guideline-defined intermediate risk thresholds, our findings suggest that Australian patients are undertreated by international standards.[9] However, the ACVDR identifies people with coronary artery calcium poorly, so that lowering the treatment threshold alone would lead to unnecessary treatment for a considerable number of patients.

Coronary artery calcium scoring

More than one-half of our participants, despite family histories of early onset CAD and other risk factors, had zero calcium scores. Further, calcium scores could inform decisions about statin therapy and risk factor control in 430 participants (41%): statins might be considered for 416 below the 10% ACVDR 5-year risk threshold with non-zero calcium scores (only 61 of 477 people with non-zero scores were identified by this threshold), but their use reconsidered for 14 treatment-eligible participants with zero scores. Our data support the Cardiac Society of Australia and New Zealand position statement that calcium scores are most helpful in patients at intermediate 10-year risk (10–20%).[32] We propose a 5-year ACVDR risk of 5% as a suitable threshold for coronary artery calcium scoring for patients with family histories of early onset CAD: in our study, this threshold identified all participants with a MESA risk exceeding 20%, and would minimise the proportion of scans yielding zero calcium scores.

ACVDR performance data are limited, but it has been reported that overestimation of 10-year risk in an Australian population was greater with the 1991 and 2008 Framingham risk tools than with the PCE.[33] In our study, the β coefficient for predicting the coronary risk-specific MESA score was smaller for the ACVDR than the PCE, probably reflecting the inclusion of non-coronary endpoints by the ACVDR. Further, the proportions of participants re-classified at low 10-year risk after including coronary artery calcium score were similar for the ACVDR and PCE. Improved ACVDR risk prediction may affect the cost-effectiveness of systematic coronary calcium score testing. The numbers needed to scan to identify people with 5-year ACVDR risk of 5% with calcium scores above zero (1.5) or 100 (3.9) could assist discussions about referring patients with family histories of early onset CAD for calcium scoring.

Limitations

Risk was based on a single clinical assessment of dynamic variables (blood pressure, lipid profile). Socio-economic status inputs for PREDICT and ASSIGN risk scores were based on the Australian Bureau of Statistics IRSAD, which may not be an appropriate substitute for the original markers. Family history was self-reported and ethnic background not routinely recorded for our participants, which may affect risk calculations, particularly with the PREDICT model, which includes these factors. As our data were derived from a randomised controlled trial (CAUGHT-CAD), selection bias may affect the generalisability of our findings. As CT coronary artery calcium scanning was performed at various imaging services, inter-observer variability and mis-classification are possible. We assessed only risk models with publicly available algorithms.

We used the MESA tool as an external comparator because the prediction and management of coronary risk (rather than other events) is the main driver of clinical decision making in familial CAD and coronary artery calcium is a powerful predictor of coronary risk. The addition of calcium scoring may personalise the application of the ACVDR calculator, but the MESA tool has not been validated in an Australian population, and further outcome studies will be needed before changes to risk assessment and statin treatment thresholds in Australia can be recommended.

Conclusion

Risk estimation is central to primary prevention of cardiovascular disease. Australian guidelines for statin therapy minimise overtreatment, but can also lead to not treating patients with family histories of early onset CAD. The ACVDR is inferior to the PCE, SCORE, and CUORE models with respect to identifying people with non-zero calcium scores. Coronary artery calcium scores could be used to re-classify risk in one-half of our sample, and could change decisions about statin treatment in 41%. A 5-year predicted ACVDR of 5% for symptomatic atherosclerotic disease may be a suitable threshold for referring patients for coronary artery calcium scoring.

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Supporting Information

Additional Supporting Information is included with the online version of this article.