Association of cardiovascular health and risk prediction algorithms with subclinical atherosclerosis identified by carotid ultrasound

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BACKGROUND The requirement for laboratory tests to assess conventional cardiovascular disease (CVD) risk may be a barrier to the early detection and management of atherosclerosis in some population groups. A simpler risk assessment could facilitate detection of CVD.

OBJECTIVES The association of the Fuster-BEWAT Score (FBS), Framingham Risk Score (FRS), and Pooled Cohort Equation (PCE) with the presence of carotid plaque was investigated, with the intention of developing a stepped screening process for the primary prevention of CVD.

METHODS Asymptomatic participants with a family history of premature CVD had an absolute cardiovascular disease risk (ACVDR) score calculated using the FBS, FRS, and PCE risk equations. This risk classification was compared with the presence or absence of carotid plaque on ultrasound. Prediction of carotid plaque presence by risk scores and risk factors was assessed by logistic regression and area under the curve (AUC) for discrimination and diagnostic performance. A classification and regression-tree (CART) model was obtained for stratification of risk assessment.

RESULTS Risk score calculation and ultrasound scanning were performed in 1031 participants, of whom 51 had carotid plaques. Participants with plaque and male sex showed higher risk (higher PCE and FRS and lower FBS, as higher scores of FBS indicate better cardiovascular health). Participants ≤50 years of age showed the FBS was a significant predictor; there was a reduced likelihood of plaque presence with a higher score (OR 0.54, 95% CI 0.39–0.75, $P < .01$). Higher ACVDR (evidenced by higher PCE and FRS scores and lower FBS score) was associated with an increased likelihood of carotid plaque; however, the FBS and the addition of risk factors not included in the equation showed the highest AUC (AUC = 0.76, $P < .001$). CART modeling showed that participants with FBS between 6 and 9 would be recommended for further risk stratification using the PCE, whereupon a PCE score ≥5% conferred an increased risk and greater possibility for plaque. Validation of the model using a different cohort showed similar risk stratification for plaque presence according to level of risk by CART analysis.

CONCLUSION FBS was able to identify the presence of carotid plaque in asymptomatic individuals. Its use for initial risk delineation might improve the selection of patients for more specific and complex assessment, reducing cost and time.

KEYWORDS Subclinical atherosclerosis; Carotid plaque; Cardiovascular risk factors; Primary prevention; Screening; Risk scores

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Introduction

Notwithstanding the advances in technology, diagnostic tools, and patient management,[1] cardiovascular disease (CVD) remains the leading cause of death worldwide.[2] CVD continues to be a significant public health concern in developed countries, but mortality is also increasing rapidly in low- and middle-income countries (LMICs). In these countries, most of the population, particularly in rural and low socioeconomic areas, do not have ready access to primary health care and pathology services for lipid assessment are limited.[3–6] This is a problem for the most widely used CVD risk scores, such as the Framingham Risk Score (FRS)[7] and the Pooled Cohort Equation (PCE),[8] which require lipid concentrations for calculation. However, the Fuster-BEWAT score (FBS; blood pressure, exercise, weight, alimentation, and tobacco) is a simple measurement based on lifestyle and risk factors (RFs) of CVD that does not rely on laboratory testing.[9]

The most cost-effective strategies to reduce the burden of CVD in LMICs involve both population- and individual-based approaches. These include a refocus toward preventive action to encourage individuals to seek early consultation, opportunistic screening of CVD risk, efficient management, and structured follow-up of those with increased risk of chronic disease with a focus within primary care to engage the population at risk. In this context, an accessible CVD

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KEY FINDINGS

- The Fuster-BEWAT Score (FBS), a non-pathology-based cardiovascular risk score, is a significant predictor of carotid plaque in participants ≤50 years of age.
- If FBS is used for pathology-independent screening, a score between 6 and 9 should be recommended for further risk stratification using the pooled cohort equation (PCE). In this setting, a PCE score ≥5% conferred an increased risk and greater possibility for plaque.
- The use of FBS for initial risk delineation might improve the selection of patients for more specific and complex assessment, reducing cost and time.

risk assessment tool to improve the identification of subclinical atherosclerosis should be investigated, with key consideration of the limitations and the feasibility for effective implementation in LMICs.[10,11] Asymptomatic atherosclerosis is a prelude to CVD events[12] and therefore is a good intermediate endpoint for the comparison of risk scores. The purpose of this study was to compare the association of the FBS, FRS, and PCE risk scores with the presence of carotid plaque in asymptomatic individuals with the intention of developing a staged screening process for primary prevention.

Textbox 1
Variables included in the PCE, FRS, and FBS

PCE	FRS	FBS
Age (years)	Age (years)	Blood pressure: SBP and/or DBP (mm Hg)
Sex (male/female)	Sex (male/female)	Exercise
Ethnicity (White/other)	HDLC (mmol/L)	Weight (BMI)
SBP (mm Hg)	TC (mmol/L)	Alimentation (fruits and vegetables)
DBP (mm Hg)	SBP (mm Hg)	Smoking (>1 pack per day, <1 pack per day, nonsmoker)
TC (mmol/L)	Hypertension treatment (yes/no)	
HDLC (mmol/L)	Smoking status (yes/no)	
LDLC (mmol/L)	Diabetes mellitus (yes/no)	
Diabetes mellitus history (yes/no)		
Smoking history (current/former/never)		
Hypertension treatment (yes/no)		

BMI = body mass index; DBP = diastolic blood pressure; FBS = Fuster-BEWAT Score; FRS = Framingham Risk Score; HDLC = high-density lipoprotein cholesterol; LDLC = low-density lipoprotein cholesterol; PCE = Pooled Cohort Equation; SBP = systolic blood pressure; TC = total cholesterol.

Methods

Participant characteristics

Participants were selected from an asymptomatic adult population with a family history of premature CVD, enrolled in the Intima-Media Thickness Guidance of Primary Prevention in Relatives of Individuals with Early Onset Atherosclerosis Study (IMPRESS). At baseline, participants were assessed for eligibility and selected according to inclusion and exclusion criteria across 3 study sites in Australia: Baker Heart and Diabetes Institute (Melbourne), Princess Alexandra Hospital-University of Queensland, and the Australian National University (Canberra). The study was conducted in individuals between 40 and 65 years of age, free of CVD or diabetes, who had a first-degree relative with premature atherosclerotic CVD (occurring before the age of 65 years), including coronary artery disease/acute myocardial infarction, ischemic stroke, and peripheral vascular disease.

The study (protocol version 4.0; May 2011) was approved by the Human Research Ethics Committees of the Alfred Hospital (Project No: 16/10); the Metro South Health Service District on behalf of Prince Alexandra Hospital and the University of Queensland (Project no: HREC/09/QPAH/202); and ACT Health (11-09357/1).

Assessment of CVD risk factors

Baseline assessment included collecting data on demographic profile (age and sex), clinical status (body mass index, systolic blood pressure and diastolic blood pressure, vital signs, and past/current cardiac and noncardiac disease states), physical activity (categorized as low, moderate, or high as assessed via the International Physical Activity Questionnaire[13]), daily fruit and vegetable intake (daily servings), and smoking (current, former, never).

Point-of-care blood testing included lipid profile (total cholesterol [TC], high-density lipoprotein cholesterol [HDLC], low-density lipoprotein cholesterol [LDLC], and triglycerides), and fasting blood glucose via the Cholestech LDX (Abbott, Abbott Park, IL). LDLC was imputed in 343 participants and calculated according to TC, HDLC, and triglyceride levels (LDLC = TC – HDLC – (triglycerides / 5)).[14] The validity of these results was confirmed in a random sample of 5% (n = 56) of the total study population by comparison with the LDLC test results using Bland-Altman analysis. The accuracy of the imputed LDLC showed a mean difference of -0.0073 (± 0.03) in this population.

Risk level assessment

Participants attended a baseline clinic visit for eligibility assessment. Level of risk for future CVD was initially determined by the FRS using a computerized tool according to recommended guidelines.[7,15] The FRS estimates the 5-year CVD risk in individuals with no previous history of disease.[15] Risk calculation was additionally assessed using the PCE and FBS. The PCE is a sex- and race-specific tool for estimating 10-year absolute rates of atherosclerotic cardiovascular disease events in a primary prevention population between 20 and 79 years of age. Similar to the FRS, the PCE categorized risk by a combination of traditional

Table 1 Participant characteristics

Characteristics	Overall (N = 1031)	Carotid plaque		*P* value
		Absent (n = 980)	Present (n = 51)	
Age (years), mean ± SD	53.1 ± 6.9	53.0 ± 6.9	55.9 ± 6.2	.003*
Female sex, n (%)	632 (61%)	604 (62%)	28 (55%)	.336
Premature CVD				
Parents, n (%)	936 (91%)	890 (91%)	46 (91%)	.805
Siblings, n (%)	315 (31%)	298 (30%)	17 (33%)	.660
Ethnicity				
White, n (%)	936 (91%)	892 (91%)	44 (86%)	.220
Physical activity intensity				
Low, n (%)	387 (38%)	369 (38%)	18 (35%)	.800
Intermediate, n (%)	501 (48%)	474 (48%)	27 (53%)	
Intense, n (%)	143 (14%)	137 (14%)	6 (12%)	
Alimentation (number of daily servings)				
Fruit, mean ± SD	1.6 ± 1.2	1.6 ± 1.2	1.8 ± 1.2	.316
Vegetable, mean ± SD	2.4 ± 1.4	2.4 ± 1.4	2.2 ± 1.4	.135
Smoking				
Never, n (%)	579 (56%)	558 (57%)	21 (41%)	.060
Current, n (%)	81 (8%)	74 (8%)	7 (14%)	.069
Ex-smoker, n (%)	371 (36%)	348 (35%)	23 (45%)	.426
Clinical features				
History of hypertension, n (%)†	295 (29%)	273(28%)	22 (43%)	.019*
History of elevated cholesterol, n (%)†	401 (39%)	376 (38%)	25 (49%)	.128
SBP (mm Hg), mean ± SD	131.6 ± 16.1	131.4 ± 16.0	134.9 ± 17.4	.132
DBP (mm Hg), mean ± SD	81.9 ± 10.1	81.8 ± 10.1	83.9 ± 9.0	.159
BMI (kg/m^2),‡ mean ± SD	27.9 ± 5.2	28.0 ± 5.3	27.5 ± 4.3	.567
Laboratory tests				
TCH (mmol/L),‡ mean ± SD	5.1 ± 1.1	5.1 ± 1.1	5.0 ± 1.1	.602
HDLC (mmol/L),‡ mean ± SD	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	.320
LDLC mmol/L),‡ mean ± SD	3.0 ± 1.1	3.0 ± 1.1	3.0 ± 1.1	.838
TG (mmol/L),‡ mean ± SD	1.5 ± 0.9	1.5 ± 0.9	1.2 ± 0.5	.091
Fasting blood glucose (mmol/L),‡ mean ± SD	5.1 ± 0.9	5.1 ± 0.9	4.8 ± 0.7	.008*
Risk scores				
PCE,‡ mean ± SD	4.4 ± 4.4	4.3 ± 4.3	6.1 ± 4.8	.004*
FRS,‡ mean ± SD	4.3 ± 3.7	4.3 ± 3.7	5.6 ± 4.2	.015*
FBS,‡ mean ± SD	7.89 ± 2.6	7.9 ± 2.6	6.9 ± 2.8	.008*

BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; FBS = Fuster-BEWAT Score; FRS = Framingham Risk Score; HDLC = high-density lipoprotein cholesterol; LDLC = low-density lipoprotein cholesterol; PCE = Pooled Cohort Equation; SBP = systolic blood pressure; TCH = total cholesterol; TG = triglycerides.

*Asterisk indicates statistically significant values.

†Collected via self-report.

‡Missing values: BMI = 2, TCH = 7, HDLC = 11, LDLC = 11, TG = 313, blood glucose = 8, PCE = 11, FRS = 3, FBS = 1.

cardiovascular RFs and providing a risk category based on percentage of risk.[16,17] A higher score in the FRS and the PCE represents a higher risk of CVD, whereas a lower FBS represents increased CVD risk. Differing from the other scores, the FBS measures ideal cardiovascular health (ie, the higher the score, the healthier the individual) using a combination of RFs.[18] The FBS does not consider blood tests, age, race, or sex as part of the risk calculation. Textbox 1 describes each variable included in the 3 absolute CVD risk (ACVDR) scores.

Vascular ultrasonography

Carotid arteries were scanned at baseline using a high-frequency (6–13 MHz bandwidth) transducer with a standard commercial ultrasound machine (Vivid I; General Electric, Milwaukee, WI). The right and left carotid arteries were assessed in 3 longitudinal images (anterior, lateral, and posterior) and in the short axis for plaque identification. Imaging was performed by expert personnel (trained research nurses) to ensure accuracy and reproducibility. Baseline images were assessed for presence of carotid plaque, defined as a focal echogenic wall thickening that encroached on the arterial lumen, with a carotid intima-media thickness >1.5 mm.[19]

Statistical analysis

Mean and standard deviation was calculated for continuous variables, and frequency and percentage for categorical variables. For each risk equation, mean computed scores (PCE, FRS, and FBS) were compared with carotid plaque (presence or absence) by analysis of variance for differences between groups. Risk scores and the presence or absence of carotid plaque were also stratified by sex and age category. For age category, a dichotomous variable was constructed based on

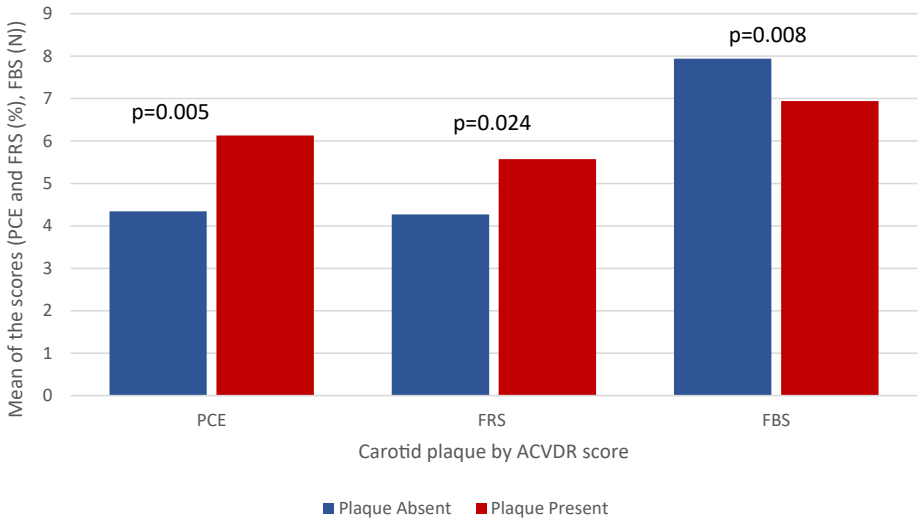

Figure 1 Mean scores for cardiovascular risk (Pooled Cohort Equation [PCE], Framingham Risk Score [FRS], and Fuster-BEWAT Score [FBS]) in participants with and without carotid plaque. ACVDR = absolute cardiovascular disease risk.

the change of decade closest to the mean age of the study population (≤50 and ≥51 years).

Univariate and multivariate logistic regression analyses (with calculation of odds ratios [ORs] and 95% confidence intervals [CIs]) were conducted to assess the relationship of each risk score with the presence of carotid plaque. Traditional RFs that were not measured by the scores were included in each analysis (for example, the FBS does not include lipids, diabetes, age, sex, ethnicity, or medications, so these RFs were added as variables in the logistic regression model), to assess the variation of prediction of the scores. Receiver operating characteristic (ROC) curves were created to assess the performance of the regression models in correctly discriminating risk. The area under the curve (AUC) obtained from the analyses of the 3 scores for prediction of the presence of carotid plaque were compared for statistical difference,[20] initially between the scores only and subsequently with the inclusion of traditional RFs. The Youden index was calculated to assess the effectiveness and optimal cut-off point for predicting the likelihood of plaque presence. Finally, a classification and regression tree (CART) analysis was conducted to analyze the FBS and PCE scores to best fit the model of carotid plaque risk categorization. The CART analysis is used as an alternative to linear regression analyses to build a decision tree to determine the benefits of further risk assessment for the presence of carotid plaque.

The results were then validated using data from the Childhood Determinants of Adult Health (CDAH) study,[21] a longitudinal, prospective population-based cohort study in

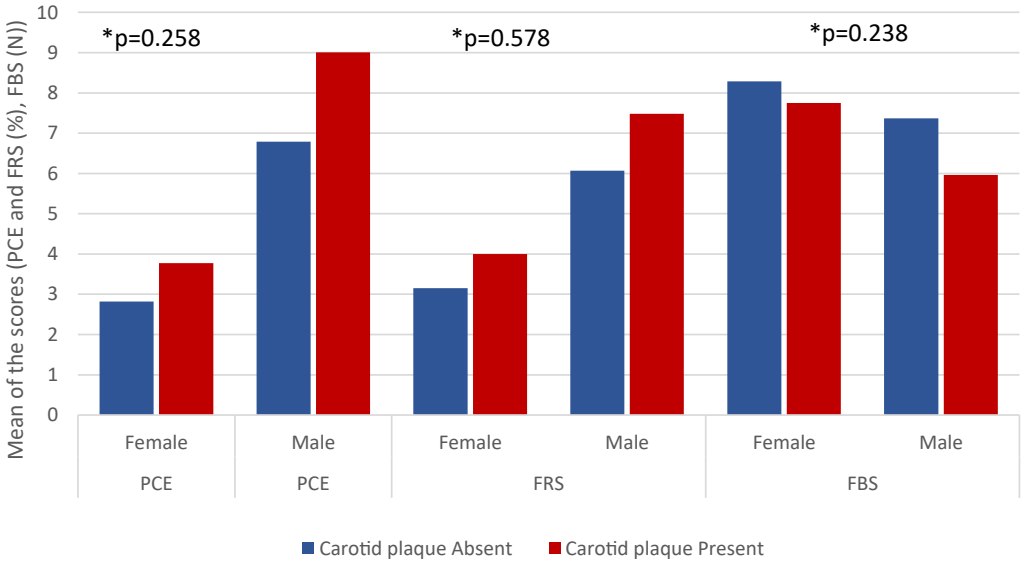

Figure 2 Mean scores for cardiovascular risk (Pooled Cohort Equation [PCE], Framingham Risk Score [FRS], and Fuster-BEWAT Score [FBS]) in participants with and without carotid plaque, by sex.

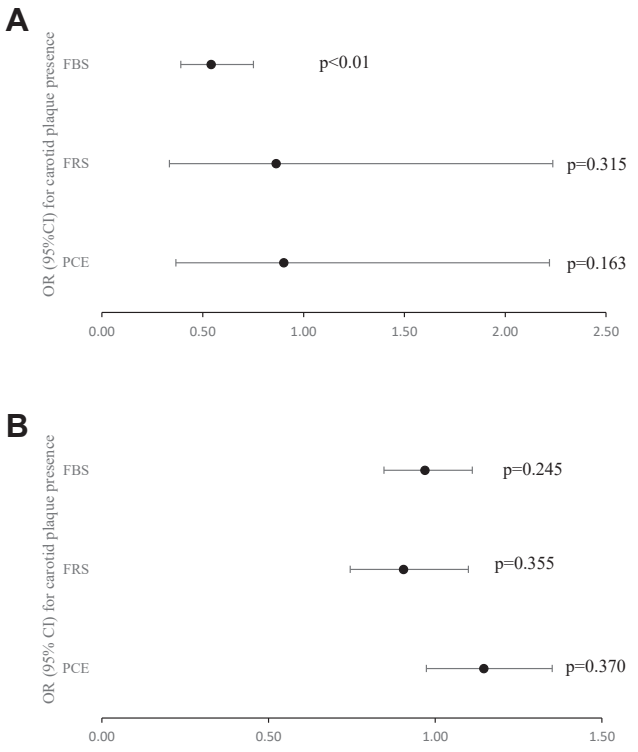

Figure 3 Association of risk scores (odds ratios and 95% CI) with carotid plaque: **A:** in participants ≤50 years of age; **B:** in participants ≥51 years of age. FBS = Fuster-BEWAT Score); FRS = Framingham Risk Score; PCE = Pooled Cohort Equation).A) Participants ≤50 years of age B) Participants ≥51 years of age

Australia, Finland, and the United States that aimed to examine childhood predictors of adult CVD and diabetes. The AUC curve of the FBS was obtained, followed by a Youden index calculation and a CART analysis.

All statistical analyses were conducted in SPSS, version 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) and Stata, version 17 (Stata Corp. 2021. Stata Statistical Software: Release 17. College Station, TX: Stata Corp LLC).

Results

Participant characteristics

After baseline profiling of 1352 individuals screened for eligibility, 1070 participants were identified as eligible to participate in the study. Table 1 shows the population characteristics at baseline comparing participants with and without carotid plaque. After exclusion of 39 owing to missing images, 1031 (61% female, 53 ± 6.9 years of age) participants were included. Of these, 51 participants (5%; 55% female) had carotid plaque. Participants with carotid plaque were on average older (56 ± 6.2 years) than those without plaque (53 ± 6.9 years), with a mean age differential of 3 years between the 2 groups. A higher proportion of those with carotid plaque had comorbid hypertension (43% vs 28%) and had a lower blood glucose than those without plaque. Moreover, participants with carotid plaque showed on average higher PCE and FRS and lower FBS scores of at least 1 point of mean difference in comparison to those without plaque.

Table 2 Determinants of carotid plaque presence prediction according to all risk scores and risk factors not included in the risk scores

Carotid plaque presence prediction by PCE and RFs				
		95% CI		*P* value
Variables	OR	Lower	Upper	
PCE	1.10	1.04	1.16	.001*
Family history parents	1.05	0.35	3.13	.933
Family history siblings	1.15	0.58	2.30	.683
Blood glucose	0.55	0.39	0.78	.001*
Fruit >5 serves daily	1.18	0.94	1.48	.156
Vegetable >5 serves daily	0.82	0.64	1.03	.090
Physical activity	1.00	1.00	1.00	.886
BMI	0.99	0.93	1.05	.626
Carotid plaque presence prediction by FRS and RFs				
FRS	1.09	1.02	1.17	.017*
Blood glucose	0.56	0.39	0.79	.001*
Fruit >5 serves daily	1.22	0.97	1.54	.088
Vegetable >5 serves daily	0.80	0.63	1.01	.062
Physical activity	1.00	1.00	1.00	.829
DBP	1.01	0.98	1.05	.388
LDLC	1.01	0.75	1.36	.956
Carotid plaque presence prediction by FBS and RFs				
FBS	0.85	0.75	0.97	.012*
Age	1.08	1.03	1.13	.001*
Sex	1.32	0.68	2.54	.415
History of Hypertension	1.63	0.87	3.05	.131
Family history parents	1.02	0.34	3.08	.968
Family history siblings	1.02	0.51	2.06	.951
Ethnicity	1.13	0.33	3.94	.846
TCH	0.50	0.18	1.40	.189
HDLC	1.69	0.53	5.43	.377
LDLC	2.19	0.78	6.15	.137
Blood glucose	0.48	0.33	0.69	<.001*

*Asterisk indicates statistically significant values.

BMI = body mass index; CI = confidence interval; FBS = Fuster-BEWAT score; FRS = Framingham Risk Score; HDLC = high-density lipoprotein cholesterol; LDLC = low-density lipoprotein cholesterol; OR = odds ratio; PCE = Pooled Cohort Equation; RFs = risk factors; TC = total cholesterol.

Association of scores with subclinical atherosclerosis

Figure 1 shows that the PCE and FRS were significantly higher, and the FBS significantly lower, in those with carotid plaque detected compared to no carotid plaque at baseline ($P < .05$). Figure 2 highlights that males had higher PCE and FRS and lower FBS compared to females (all main effects $P < .001$) and the relationship between higher ACVDR scores in those with carotid plaque occurred for both males and females (all interaction effects $P > .05$). Figure 3 compares the association of risk level (according to the PCE, FRS, and FBS results) with carotid plaque presence in participants ≤50 years of age (panel A) and ≥51 years of age (panel B). The likelihood of plaque was reduced with higher FBS in individuals ≤50 years of age (OR 0.54, 95% CI 0.39–

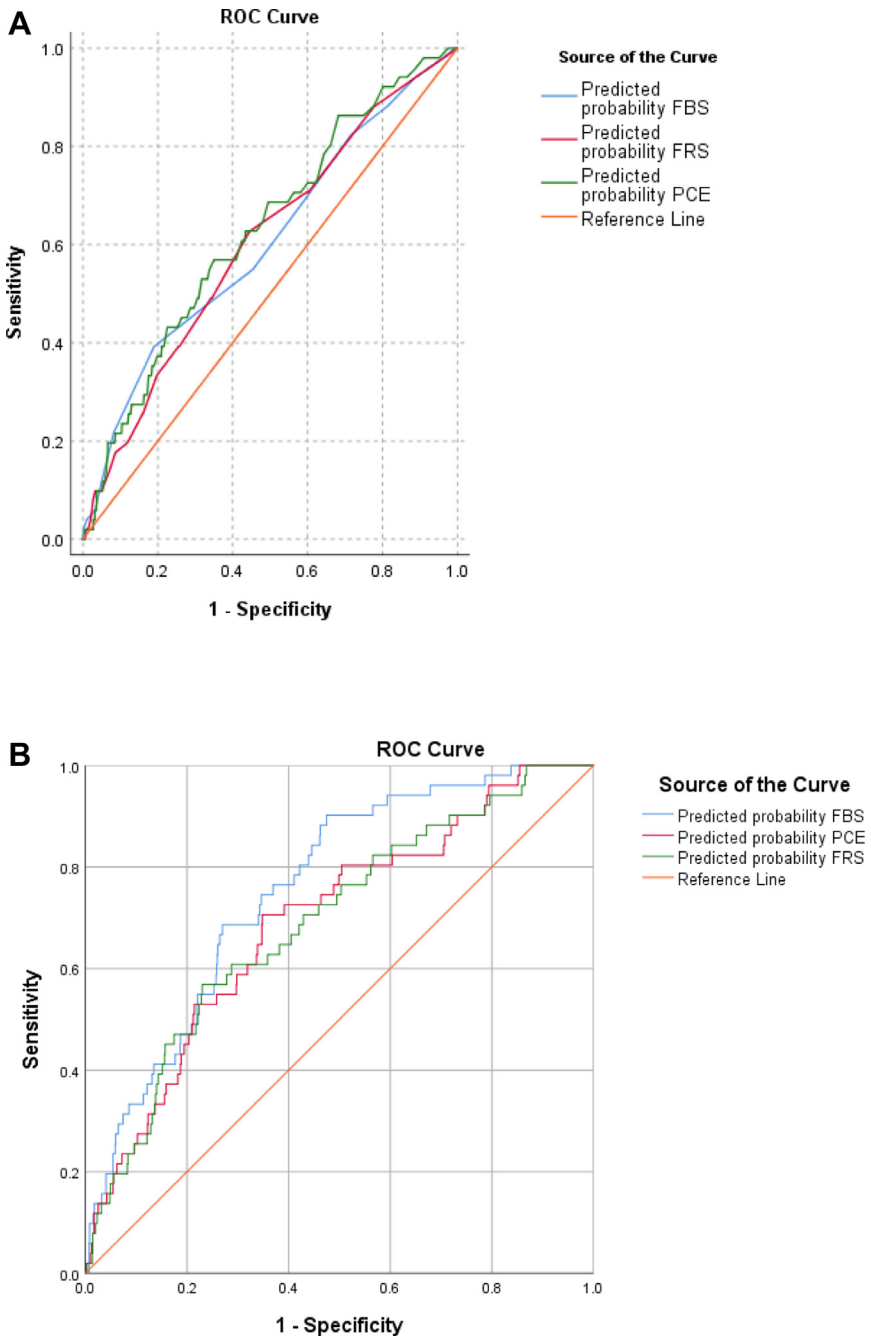

Figure 4 Discrimination of the risk score models. **A:** Area under the receiver operator characteristic (ROC) curve is shown for Pooled Cohort Equation (PCE), Framingham Risk Score (FRS), and Fuster-BEWAT Score (FBS). **B:** Area under the curve of PCE, FRS, FBS when adding risk factors not included in the scores.4A 4B

0.75, $P < .01$). All other scores did not show significant difference in the OR of carotid plaque presence by age category.

Probability of presence of carotid plaque by risk score level

In univariate logistic regression analyses (data not shown) all 3 scores were significantly associated with the presence of carotid plaque (all $P < .05$). A higher PCE (OR 1.07, 95% CI 1.02–1.13) and FRS (OR 1.07, 95% CI 1.01–1.14) increased the odds of carotid plaque being present, whereas the odds of carotid plaque were reduced for increases in FBS score (OR 0.86, 95% CI 0.77–0.96).

Table 2 shows the logistic regression of models including the 3 scores and individual CVD RFs not considered in the calculation of each score. A model that included PCE, family history of premature CVD, fasting blood glucose (mmol/L), number of fruit and vegetable serves per day, body mass index (kg/m^2), and physical activity intensity per week showed that the PCE and fasting blood glucose only remained

Table 3 Area-under-the-curve analysis of Fuster-BEWAT Score and risk factors not included in the equation

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)
Age	1.07 (1.02, 1.12)	1.07 (1.02, 1.12)	1.07 (1.02, 1.12)	1.07 (1.02, 1.12)	1.08 (1.03, 1.14)
Male sex	1.25 (0.69, 2.25)	1.20 (0.66, 2.18)	1.19 (0.63, 2.24)	1.27 (0.70, 2.28)	1.39 (0.76, 2.52)
Ethnicity	0.56 (0.24, 1.31)	0.55 (0.23, 1.29)	0.56 (0.24, 1.31)	0.56 (0.24, 1.32)	0.46 (0.20, 1.10)
FBS	0.87 (0.77, 0.98)	0.87 (0.77, 0.97)	0.87 (0.77, 0.98)	0.87 (0.77, 0.98)	0.84 (0.74, 0.95)
TC		0.90 (0.69, 1.16)			
HDLC			0.84 (0.40, 1.79)		
LDLC				0.97 (0.74, 1.27)	
Blood glucose					0.50 (0.35, 0.71)
	C-statistic=0.67 (0.60, 0.74)	C-statistic=0.67 (0.60, 0.74)	C-statistic=0.67 (0.61, 0.74)	C-statistic=0.67 (0.60, 0.74)	C-statistic=0.73 (0.66, 0.79)
In comparison to model 1	REF	$P = .98$	$P = .79$	$P = .52$	$P = .015$

CI = confidence interval; FBS = Fuster-BEWAT Score; HDLC = high-density lipoprotein cholesterol; LDLC = low-density lipoprotein cholesterol; OR = odds ratio; TC = total cholesterol.

significant. For every 1% increase in the PCE score, the odds of plaque presence also increased by 10% ($P < .001$).

In a model including the FRS, the score was adjusted with blood glucose (mmol/L), fruit and vegetable serves daily, physical activity intensity per week, diastolic blood pressure (mm Hg), LDLC (mmol/L), and ethnic background. Only blood glucose and the FRS were significant predictors of plaque presence. There was a 9% increase in the odds of carotid plaque presence for every 1% increase in the FRS ($P = .017$).

The model that included the FBS adjusted for age, sex, history of hypertension, family history of premature CVD, ethnic background, lipid profile (TC, HDLC, and LDLC [mmol/L]), and blood glucose (mmol/L) showed that FBS, age, and blood glucose were significant determinants of carotid plaque presence ($P < .01$). For every 1-point increase in the FBS the odds of plaque presence decreased by 15% ($P = .012$).

Level of discrimination of the risk score models

The areas under the ROC curve comparing the ACVDR scores only (Figure 4A) and the ACVDR risk scores with the addition of RFs not included in each of the equations (Figure 4B) are represented. The 3 scores alone showed a similar c-statistic; the PCE showed the highest AUC of 0.63 (95% CI, 0.55–0.71; $P = .001$), followed by the FBS with an AUC of 0.61 (95% CI, 0.52–0.69; $P = .015$) and the lowest AUC from the FRS (0.60 [95% CI, 0.52–0.68; $P = .011$). When the models included the ACVDR scores and the RFs not considered in each score (Figure 4B), there was a significant increase of the AUC in all models. The most significant increase was in the model including the FBS/RFs, which showed an AUC of 0.76 (95% CI, 0.70–0.82; $P < .001$). The PCE/RFs had an AUC of 0.69 (95% CI, 0.62–0.77; $P < .001$). Similarly, the model including the FRS/RFs showed an AUC of 0.69 (95% CI, 0.62–0.76; $P < .001$).

More comprehensive analyses of the FBS and RFs not included in the equation were explored (Table 3). Model 1 (Reference model) included the FBS, age, male sex, and ethnicity (c-statistic = 0.67 [95% CI, 0.60–0.74]). Models 2–5 included the addition of 1 biochemical RF to each model. Model 5, which included the addition of blood glucose, showed the highest increase in c-statistic (0.73 [95% CI, 0.66–0.79, $P = .015$]).

Figure 5 shows the CART analysis of a decision tree developed using the 2 ACVDR scores that showed the highest AUC (FBS and PCE) results in our population. According

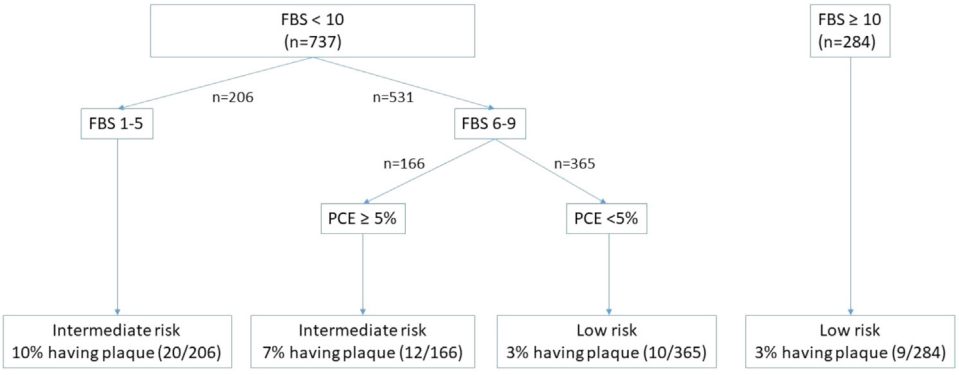

Figure 5 Classification and regression-tree model for risk stratification using the 2 absolute cardiovascular disease risk scores that showed the highest area under the curve (Fuster-BEWAT Score [FBS] and Pooled Cohort Equation [PCE]) results in our population.

to the model partition, participants with an FBS ≥10 were classified as low risk (n = 284); only 9 (3%) participants in this category had carotid plaques. Participants with an FBS of 6–9 (n = 531) were indicated to benefit with subsequent classification according to the ACVDR PCE assessment. In those with a PCE <5% (n = 365), only 3% (n = 10) had carotid plaque and these were deemed to be low risk. Participants with a PCE ≥5% were indicated as intermediate risk (n = 166), of whom 7% (n = 12) had carotid plaque. Of the 206 participants with the lowest FBS (1–5), 10% (n = 20) had carotid plaques, making this group an automatic higher-risk group without the need for further stratification by PCE results.

Validation of CART analysis

To validate the findings of the CART analysis, the same procedure was applied in a population with similar characteristics as the population in our study. The CDAH study had a younger population free of CVD, with a mean age of 44 ± 3 years (52% female).[21] The validation analysis included 1140 participants and carotid plaque was detected in 13%. The AUC in predicting carotid plaque was slightly lower than in our study (0.65 [95% CI, 0.60–0.71]) and with each increasing point of the FBS, there was a 10% reduction in odds of carotid plaque presence (OR = 0.90 [95% CI, 0.85–0.96]). The Youden index showed that using the FBS cut-off of 8 identified 68% higher odds in participants with FBS <8 than those with FBS ≥8 (OR = 1.68 [95% CI, 1.01–2.83]). Finally, we applied the IMPRESS classification tree to the CDAH study. The CART analysis showed that 27.3% of participants of the CDAH study with FBS 1–5 (intermediate risk) had carotid plaque and only 11.4% in those with FBS ≥10 (low risk). In participants with FBS between 6 and 9, the PCE showed that 30% of participants with scores ≥5% (intermediate risk) had carotid plaque and 15.5% with PCE <5% (low risk) had plaque.

Discussion

In this relatively young cohort of asymptomatic individuals with a family history of CVD, we demonstrated that the FBS was superior in predicting subclinical atherosclerosis compared with the FRS and PCE, both of which require biochemical parameters. Of the 3 ACVDR scores, the FBS showed the highest discrimination accuracy. The addition of blood glucose was consistently found to improve risk prediction; however, this finding should be interpreted with caution. In addition, age improved the predictive ability to the FBS and could be considered as an additional variable, which has not previously been demonstrated.[18] The FBS was shown to be significant in the detection of subclinical atherosclerosis in younger adults (≤50 years of age), which might improve the early detection of atherosclerosis at younger ages. Finally, a CART decision tree suggested a strategy for incorporation of FBS into CVD risk assessment in resource-constrained settings. These results show that the highest (≥10) and lowest (1–5) FBS can be directly classified into low- and intermediate-risk, while further pathology testing for calculation of PCE seems to be most useful among participants with an FBS of 6–9.

Our results showed significant interactions between the FBS and other RFs. The age of our cohort might play a role in risk classification, as it has been considered a key determinant of CVD risk in most traditional risk scores. Regarding age difference, participants who were ≤50 years of age had less risk of carotid plaque presence and had better results of the FBS score, whereas the PCE and the FRS were not significantly different between participants with and without plaque. Nonetheless, the 3 scores were significantly different between younger and older people, showing an increased association of plaque presence and worse scores in older participants. Although our analysis did not show significance between male sex and FBS scores for plaque presence, the FBS scores were lower in male than in female participants. Previous studies have shown that males have an increased risk of subclinical atherosclerosis and increased risk assessed by CVD risk scores, confirming that sex-specific profiling might be a significant step to consider.[18,23]

Finally, our study showed a significant interaction between the FBS and blood glucose inversely associated with plaque presence, which is an anomalous finding. Further studies might be needed to offer a better interpretation of this finding.

Previous experience of the FBS

The FBS is a simple tool that includes lifestyle risk variables to assess ideal cardiovascular health with a simple score calculation.[9] The current study is not the first to demonstrate the effectiveness of FBS in predicting subclinical atherosclerosis. In a study conducted in a Cuban population, the FBS showed high concordance with the Ideal Cardiovascular Health Score (ICHS) when assessing CVD risk.[6] The ICHS, similar to the PCE and the FRS, is a popular risk score that combines clinical and laboratory (serum cholesterol and fasting blood glucose) parameters.[18]

Similarly, the Progression of Early Subclinical Atherosclerosis study showed that participants with ideal FBS and ICHS, both recommended for primary prevention, had lower adjusted ORs for plaque presence and coronary artery calcium score than those with lower scores (denoting increased CVD risk).[18] In this study, the AUC showed similar discrimination as the ICHS for carotid plaque presence and coronary artery calcium score.[18] In our study, the FBS showed a better predictive accuracy and higher AUC than the PCE and FRS.

Clinical application of FBS

The importance of risk prediction and the use of risk scores have been widely studied and reported.[24,25] Although of pivotal importance in primary prevention of CVD,[24] they have shown some limitations, such as misclassification of risk in younger populations, women, and different ethnic groups.[26–28] Both the FRS and the PCE have shown overestimation of risk and the need of calibration when

assessing a multiethnic population.[29] Access to pathology and laboratory analyses in LMICs is a significant barrier to traditional cardiovascular risk score algorithms. Despite recent significant improvements, cost and availability remain barriers to testing in primary care settings.[4,10] The advantage of the FBS score is that it does not need blood tests and can be easily assessed in any health care setting without access to laboratories.

By conducting an ROC analysis, we found that the FBS was better associated with the presence of carotid plaque in our population. The Youden index helped to adjust the cut-off risk to improve the predictive value for risk of subclinical atherosclerosis. A further CART analysis improved the selection of individuals likely to require additional screening in a 2-stage screening process. The first stage showed that participants with FBS $\geq$10 could be directly classified as low risk, and no further subclinical atherosclerosis screening is needed. On the other hand, participants with FBS between 1 and 5 are classified as intermediate risk. This group of participants might benefit from further subclinical atherosclerosis studies, such as carotid ultrasound for plaque detection.

After the first stage of initial risk classification by the FBS, a second stage is required for a reduced number of individuals (ie, those with FBS between 6 and 9) who will need laboratory tests to further classify the risk level by including the PCE. This second stage classified the population into 2 groups: Participants with PCE $<$5% were classified as low risk and discarding the need for further screening tests, whereas those with PCE $\geq$5% were classified as intermediate risk, requiring further ultrasound screening testing.

When the stratification of risk proposed in our study was applied in the CDAH study population,[21] the findings were consistent with the IMPRESS study. Although the population was younger, the FBS showed slightly lower AUC (0.65 vs 0.73), and the prevalence of plaque was higher in the CDAH study, both studies showed similar results in the classification of risk and the presence of carotid plaque, with similar CART analysis result, and favored further screening of those at intermediate risk.

Strengths and limitations

The outcomes included in this study are an intermediate point (presence or absence of plaque) in the development of atherosclerotic CVD and not cardiovascular events. The primary aim of this study was to improve risk stratification to identify subclinical atherosclerosis in relatively younger adults aged 40–65 years. Therefore, the number of participants with plaque detected is just the right outcome of this study.

We considered including other scores, such as the INTERHEART risk score.[22] However, it was not feasible owing to different methods to measures some of the variables, such as psychosocial factors and diet.

Conclusion

The FBS is a simple score to measure cardiovascular health risk without laboratory or imaging testing. The score showed good discrimination of participants with carotid plaque, and thereby the prediction of CVD risk. The use of the FBS for risk stratification may be useful in regions where access to laboratory tests is limited in populations who do not engage with primary care (eg, young adults) or to better identify those who might need more advanced testing (eg, of lipid levels).

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Disclosures

The authors declare no conflicts of interest.

Availability of Data and Material

All data is available upon request.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Ethics Statement

The study (protocol version 4.0; May 2011) was approved by the Human Research Ethics Committees of the Alfred Hospital (Project No: 16/10); the Metro South Health Service District on behalf of Prince Alexandra Hospital and the University of Queensland (Project no: HREC/09/QPAH/202); and ACT Health (11-09357/1).

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