Who should be referred for a CT coronary calcium score? Introducing a simple patient risk questionnaire combining traditional and novel risk factors

Stephen M. Fenton[a], Millie Arora[b], Heidi Gransar[c], Daniel S. Berman[c] and Nathan D. Wong[b]

Background **Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of death. Coronary artery calcium (CAC) strongly predicts the risk of ASCVD. There is a need to know who would benefit most from CAC scanning.**

Objectives **We examined the utility of a new, simple, easy-to-use, and interactive patient risk questionnaire (PRQ), incorporating both traditional and non-traditional risk factors to identify those most likely to benefit from CAC scanning.**

Methods **Data from the EISNER Study was used to study the PRQ in relation to the extent of CAC and whether it added incremental value over the Pooled Cohort Risk Score (PCRS) for identifying CAC.**

Results **Among 1332 participants a mean PRQ score of 5.6 ± 1.7 was obtained. Negative scans ranged from 95.5% for PRQ scores of 0–1 to only 32.5% for those with a PRQ score of 8. A PRQ score of 3 or more was shown to be associated with a 54% prevalence of CAC. The frequency of a CAC score >=100 was 0 with PRQ = 0–1 and 36% in patients with PRQ = 8. The cNRI of the PRQ score over the PCRS in predicting the presence of CAC was 0.20 (95% CI, 0.09– 0.30; *P* = 0.0004), mainly due to down-stratifying risk**

Conclusions **A unique and simple PRQ identifies those most likely to have a positive CAC scan and may be useful to predict who will benefit most from CAC scanning, allowing for its use in those patients who are most appropriate.** *Coron Artery Dis* **33: 618–625**

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Keywords: ASCVD risk assessment, coronary artery calcium, CAC testing, heart attack risk

[a]Heart Initiative, Bligh Street Cardiology, Sydney, Australia, [b]Department of Medicine, Heart Disease Prevention Program, Division of Cardiology, University of California, Irvine and [c]Department of Imaging, Cedars-Sinai Medical Center, Los Angeles, California, USA

Correspondence to Dr.Stephen Fenton, MD, The Heart Initiative, Bligh Street Cardiology, Level 23, 25 Bligh St, Sydney, NSW, 2000, Australia
Tel: +61292237911; e-mail: stephen.fenton@blighstreetcardiology.com.au

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in men and women [1]. About half of patients with heart attacks die before they can make it to the hospital [2–4]; half of these have no warning symptoms [2–5]. An accurate risk assessment of ASCVD is essential to not only identify an individual's true risk of serious cardiovascular outcomes but also to effectively balance the benefits and risks of therapy. Overestimation of risk leads to unnecessary medication, unjustified patient anxiety and unwarranted family concern. Underestimation of risk, especially in younger patients, may result in dire and tragic clinical consequences [6–9]. Traditional risk assessment using risk scores such as the Pooled Cohort Risk Score (PCRS) [10] often can overestimate ASCVD risk. Coronary artery calcium (CAC) scanning is a simple, reliable and noninvasive test that measures calcified atherosclerosis and strongly improves risk prediction of ASCVD over traditional risk assessment in a graded fashion in age-appropriate patients [11–15]. But a major limitation of the clinical penetration of CAC scanning is a lack of agreement as to who would most benefit. We hypothesized that the addition of novel risk factors to traditional risk factors may improve risk discrimination and thereby better guide who will most benefit from referral for a CAC scan for a more accurate and personalized risk prediction. We examined the utility of a new simple interactive patient risk questionnaire (PRQ), incorporating both traditional and non-traditional risk factors to achieve this.

Methods

We examined data collected between May 2001 and May 2005 from 1332 participants (mean age 58.6 ± 8.5 years; 47% female) from the Early Identification of Subclinical Atherosclerosis by Non-invasive Imaging Research (EISNER) study who had risk factor measures as well as coronary calcium scores [16]. Figure 1 details the reasons for exclusion from the EISNER original patient sample to obtain our 1332 included patients. We extracted data into the PRQ (see Table 1) to provide a point-based sum score. The composite list of traditional (beyond age and sex) and novel (nontraditional) risk factors used in this study, together with other accepted 'risk enhancers', is

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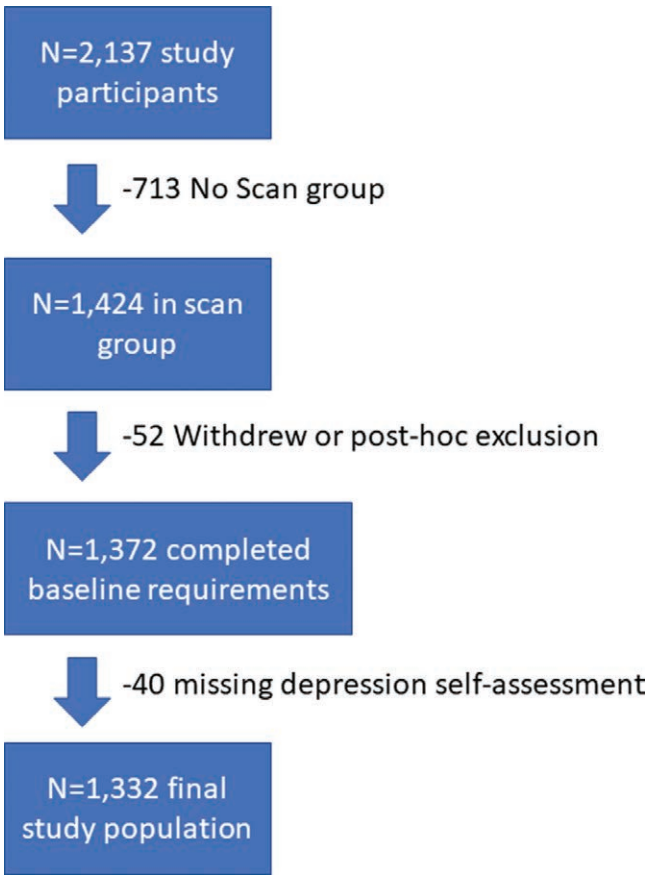
listed below in Table 1. The EISNER study received institutional review board approval by Cedars-Sinai Medical Center and all patients provided informed consent. The EISNER study population included persons of intermediate ASCVD risk where CAC scoring is recommended by guidelines and is thus an appropriate target population for use of the PRQ where the range of scores will adequately identify the presence and extent of CAC.

Figure 2 shows the PRQ score algorithm. Traditional risk factors (TRF) included were age, sex, smoking, high blood pressure, high cholesterol and diabetes. For age and sex, 3 points were allocated to males aged 50 years or over and females 60 years and over, 2 points to males aged 45–49 years and females 55–59 years and 1 point to males aged 40–44 years and females 50–54 years. Males under 40 years and females under 50 years received zero points for age. The gender-based age difference utilized is based on strong evidence that the extent of subclinical atherosclerosis in men is similar to that in women 5–10 years older [3]. Nontraditional risk factors included a family history of premature coronary disease (male first-degree relative of 55 or less or female first-degree relative 65 or less) with weighting for multiple members (such inclusion of weighting for family history has not been a consideration in any previous scoring system), being overweight or sedentary, life-long exposure to a high saturated diet, history of obstructive sleep apnea, gout or high uric acid, psychosocial factors (including the history of depression, high stress, social isolation or Type A personality) or current or past marathon running or other high-endurance long-distance sports (e.g. cycling or ocean swimming). South Asian ancestry is also included as a factor consistent with it being a risk-enhancing factor in guidelines [10].

The PRQ provided a summation of the above factors, where data were available, which was tested in relation to the extent of CAC (proportion with scores of 0, 1–99, 100–299 and 300 and higher) using Pearson's chi-square test. We also examined the robustness of the PRQ without age and sex present (which are strongly related to CAC) to identify the presence and extent of CAC. In addition, the 10-year risk of ASCVD was calculated

Fig. 1



Summary of patient population selection from EISNER study database. EISNER, Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research.

Table 1 Composite list of 'traditional' 'non-traditional' risk factors

(Count 1 point for each factor)
Smoking - past history or current (2+ years of over 10/day)
High blood pressure (over 140/90 mmHg) or on treatment
High cholesterol levels (total >6.2 mmol/L (= 240 mg/dL); LDL >3.6 mmol/L (= 140 mg/dL)
Diabetes (on medication or diet-controlled)
One, two or three or more first degree relatives (parent or sibling) with premature heart disease (male under 55 years; female under 60 years) 1, 2 or 3 points depending on number
Being overweight (BMI over 25)
Being sedentary (not exercising for at least 30 mins 3× a week)
Life-long exposure to a high saturated fat diet (e.g. many years of high intake of meat, dairy, lard and deep-fried)
History of obstructive sleep apnea
History of gout or high uric acid
History of depression, high stress or social isolation
Type A personality (being very driven)
Other lipid abnormalities if known high Lp(a) >125nmol/L(50 mg/dL), low HDL (<0.9 mmol/L or
39 mg/dL or high triglycerides >2.0 mmol/L (≥180 mg/dL)
Marathon runner or similar high endurance activity (triathlete; ocean swimming and cyclist)
History of chronic kidney disease
History of chronic inflammatory conditions (psoriasis, rheumatoid arthritis, lupus, HIV/AIDS)
Being of South Asian ancestry
History in pregnancy of pre-eclampsia or gestational diabetes
History of premature menopause (younger than 40 years)

based on the PCRS [10] and utilizing the continuous PCRS and continuous PRQ, the continuous net reclassification improvement (cNRI) from adding the PRQ over the PCRS to predict the presence of CAC was calculated [17]. This tests the ability of the PRQ to improve reclassification of the likelihood of having CAC over the PCRS (not the other way around, because the PCRS is the first step in recommended ASCVD risk assessment according to guidelines). The cNRI identifies the proportion of persons with or without CAC that would be correctly identified from the addition of the PRQ scores assessed as a continuous variable over the PCRS measured continuously alone. The cNRI provides for more useful clinical interpretation (e.g. proportion of persons whose risk is reclassified) as compared to other metrics (e.g. c-statistic).

All data were analyzed using STATA version 14 (StataCorp LP, College Station, Texas, USA) for Windows.

Results

Table 2 shows descriptive statistics of our sample of 1332 participants, with a mean age of 58.6 ± 8.5 years; 47% female) and mean PRQ score of 5.6 ± 1.7 (range 0–11). Figure 3 shows the prevalence of CAC categories (0, 1–99, 100–299 and >=300) across PRQ scores. As the PRQ score increases, the prevalence of negative scans decreases sharply from 95.5% for PRQ scores of 0–1, to only 32.5% for those with a PRQ of 8. Furthermore, as demonstrated in Fig. 4, a patient with a PRQ score of 3 or more is associated with a 54% prevalence of any CAC, compared to <10% for those with a PRQ score of 0–2. A PRQ score of 6 or more was associated with a 29% prevalence of a CAC score of 100 or greater and a 64% prevalence of any CAC. The frequency of CAC scores >=100 was 0 in patients with PRQ = 0–1, and 36% in those with PRQ = 8. The cNRI of the PRQ score over the PCRS in predicting the presence of CAC was 0.20 (95% CI, 0.09–0.30; P = 0.0004), due to 25% of those without CAC being correctly down-classified minus 5% of those with CAC being incorrectly down-classified, indicating fewer patients would be identified as suitable for CAC scoring from using the PRQ over the PCRS. Figure 5 demonstrates the robustness of the PRQ showing persisting increases of CAC prevalence with increases in PRQ score increases despite the removal of age and sex, with a >50% prevalence of CAC reached on the PRQ score is 3 or greater. The Appendix provides examples of how the PRQ can be used.

Discussion

Current approaches for cardiovascular risk assessment rely on the use of the PCRS or other global risk assessment approaches, which are often inaccurate for estimating true risk, followed by subjective assessment of risk-enhancing factors, which may or may not be available, before deciding whether to perform CAC screening to further assess the ASCVD risk. Our study shows how a simple patient-administered health risk questionnaire can identify the likelihood of any or significant subclinical atherosclerosis as measured by a coronary calcium CT scan, thus more directly and efficiently assessing the appropriateness and need for a CAC scan. Our PRQ shows a score of 3 or greater to be associated with a >50% prevalence of having any CAC, which may be an appropriate cut point for indicating a patient should have a scan. Moreover, a PRQ score of 6 or greater indicates not only a >60% likelihood of having any CAC but also a>25% likelihood of having a significant CAC score of 100 or greater, which has been considered an indication for statin therapy according to recent cholesterol guidelines [10]. Finally, we showed the PRQ to result in significant risk reclassification over the PCRS for assessing the 10-year ASCVD risk [10], mainly identifying those less likely to have CAC resulting in potentially fewer CAC scans needing to be done than those identified by the PCRS.

Our study shows the following profiles of patients who may most benefit from CAC screening:

(1) All males at or above age 50 years, or females at or above age 60 years, (2) Males in the age range 45–49 years, or females age range 55–59 years who have 1 point or more on the composite risk table, (3) Males in the age range 40–44 years, or females age range 50–54 years who have 2 points or more on the composite risk table and (4) Males in the age range 35–39 years, or females age range 45–49 years who have 3 points or more on the composite risk table.

True and accurate risk assessment of atherosclerotic vascular disease is essential for its optimal management, appropriate use of medication and resources and the prevention of its potentially tragic consequences. The

Fig. 2

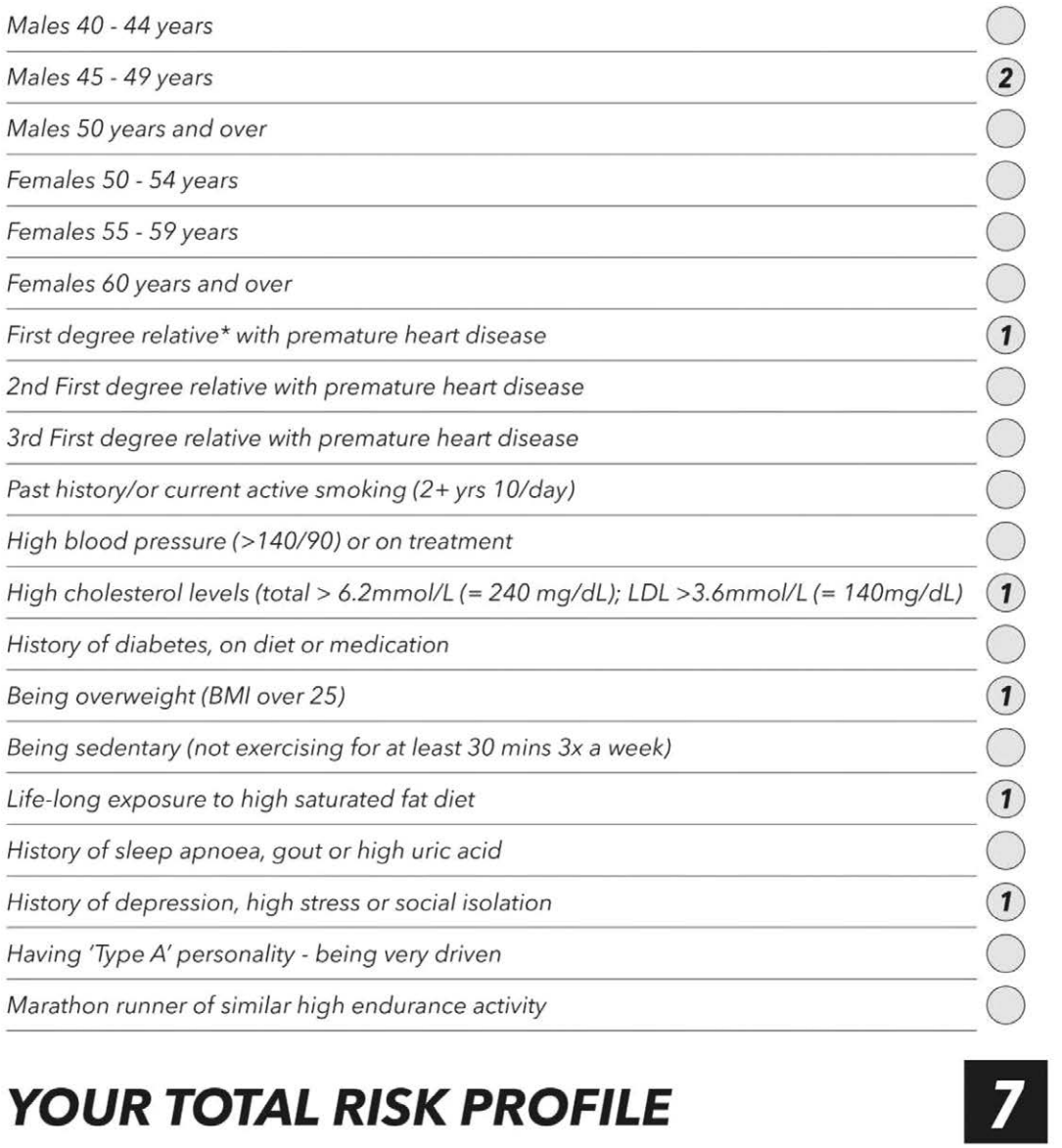


Table 1 Example of PRQ in 2 male patients aged 48 with near identical risk profiles and PRQ scores of 7. Each had a father having had heart attack at 50 years, grew up with a high saturated fat diet, had a high cholesterol (LDL of 3.5mmol/L or 136 mg/dL) and history of depression. Based on 7 points a CAC was strongly recommended.

1) Patient A had a CAC result of zero. The management recommendations were for optimisation of risk factors and reassessment for plaque by CAC in 3 years.

2) Patient B had a CAC of 260 placing him in the 97th percentile and therefore at very high risk. Review by a preventative cardiologist and aggressive risk factor management is indicated.

Patient Risk Questionnaire (PRQ)

demonstration and quantification of atherosclerosis if present would seem fundamental to the accurate risk assessment of atherosclerotic disease. Indeed, clinical studies now involving thousands of patients consistently demonstrate a near-linear relationship between the extent of coronary atherosclerotic disease burden and the risk of myocardial infarction and death [18,19]. This clear risk continuum indicates we are currently missing the opportunity to provide effective preventive measures to millions of patients with nonobstructive coronary heart disease including many young adults [20,21].

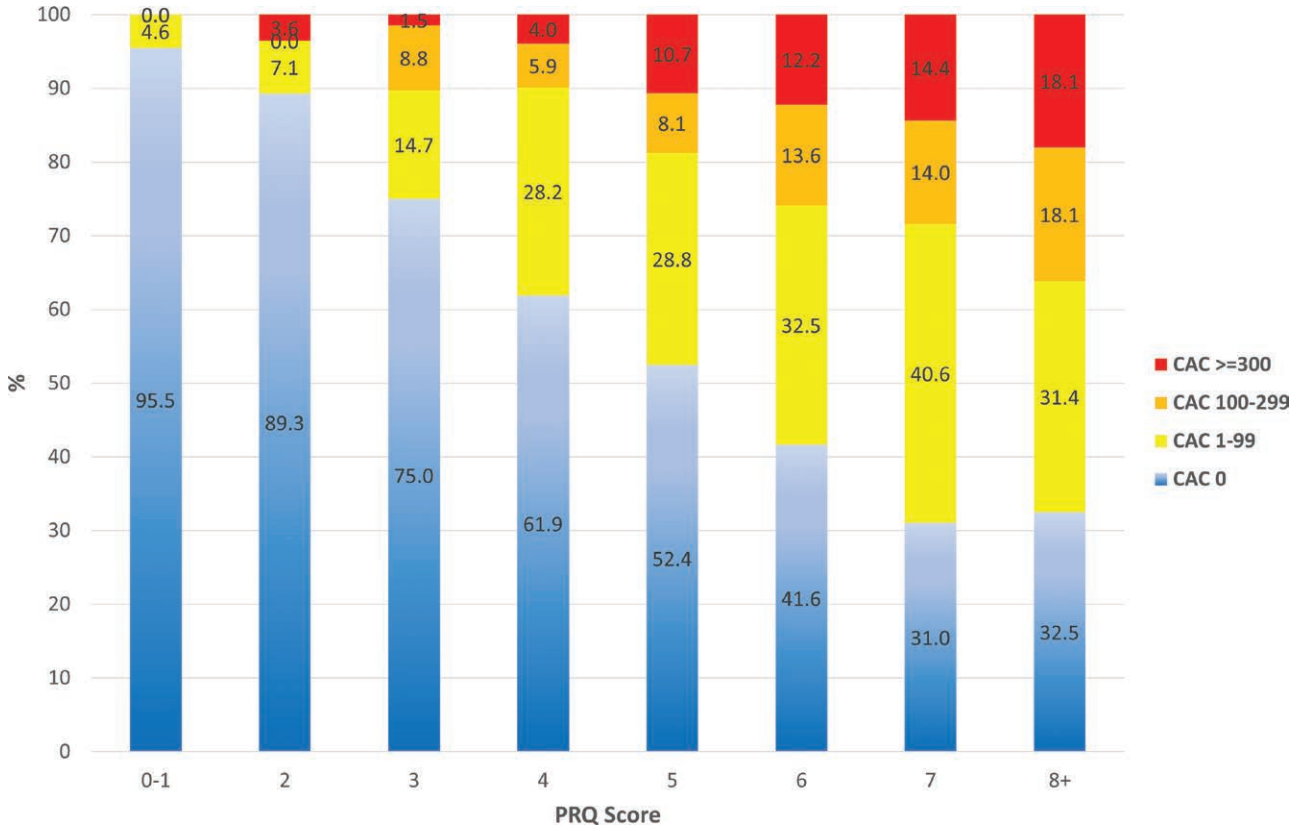
While guidelines have generally indicated the 'intermediate risk' patient to be suitable for CAC screening, further refining those most likely to have CAC by the use of appropriate strategies such as the use of a PRQ as we have proposed may help in better targeting those who could benefit most from resulting preventive strategies. It is widely recognized that CAC testing is a simple, well-tolerated, inexpensive and widely available tool to assess the presence and quantification of coronary atherosclerosis in asymptomatic patients and is cost-effective across a broad range of baseline risk [8,22]. However, its clinical penetration is limited by a consensus on who would benefit most from referral for a CAC scan [22–24].

We have established that a unique and simple PRQ which includes both important self-reported TRFs together with novel, non-traditional risk factors and a unique weighting for family history, provides a personal

Table 2 Descriptive statistics of study population

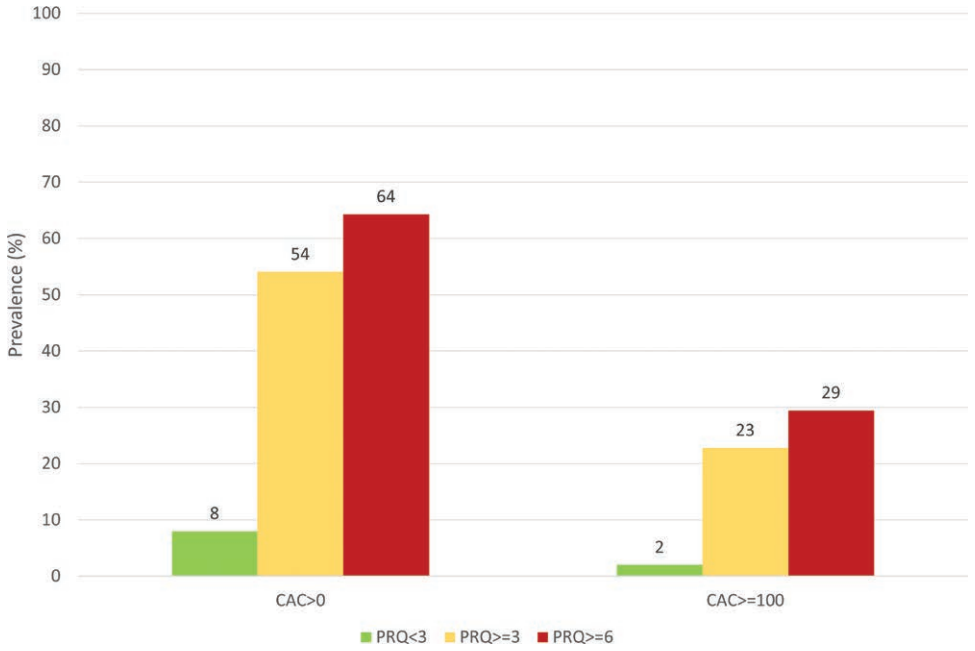
Mean (sd) age (years)	58.6±8.5
Female	625 (46.9%)
Family history of premature CHD *Family History of CAD males<55 (male relative), females<65 (female relative)*	370 (27.8%)
Current smoking	80 (6.0%)
Past smoking	554 (41.6%)
Hypertension (%) (*history of high blood pressure OR medication OR BP>=140/90 (sbp, dbp)*	775 (58.2%)
Hyperlipidemia *(history of high cholesterol OR cholesterol medication OR LDL>=140 OR TC>=240*	915 (68.7%)
Diabetes (*history of diabetes OR diabetes medication OR fasting glucose>=126 OR non- fasting glucose>=200)*	113 (8.5%)
Mean (sd) BMI	27.5±5.2
BMI≥25 kg/m^2	890 (66.8%)
Regular physical activity (*at least 3 times a week for at least 30 minutes each time)*	726 (54.5%)
High saturated fat diet (self-reported)	113 (8.5%)
Depression (self-reported diagnosis)	136 (10.2%)

Fig. 3



Extent (%) of CAC by PRQ cumulative Score ($P<0.001$ across score categories). CAC, coronary artery calcium; PRQ, patient risk questionnaire.

Fig. 4



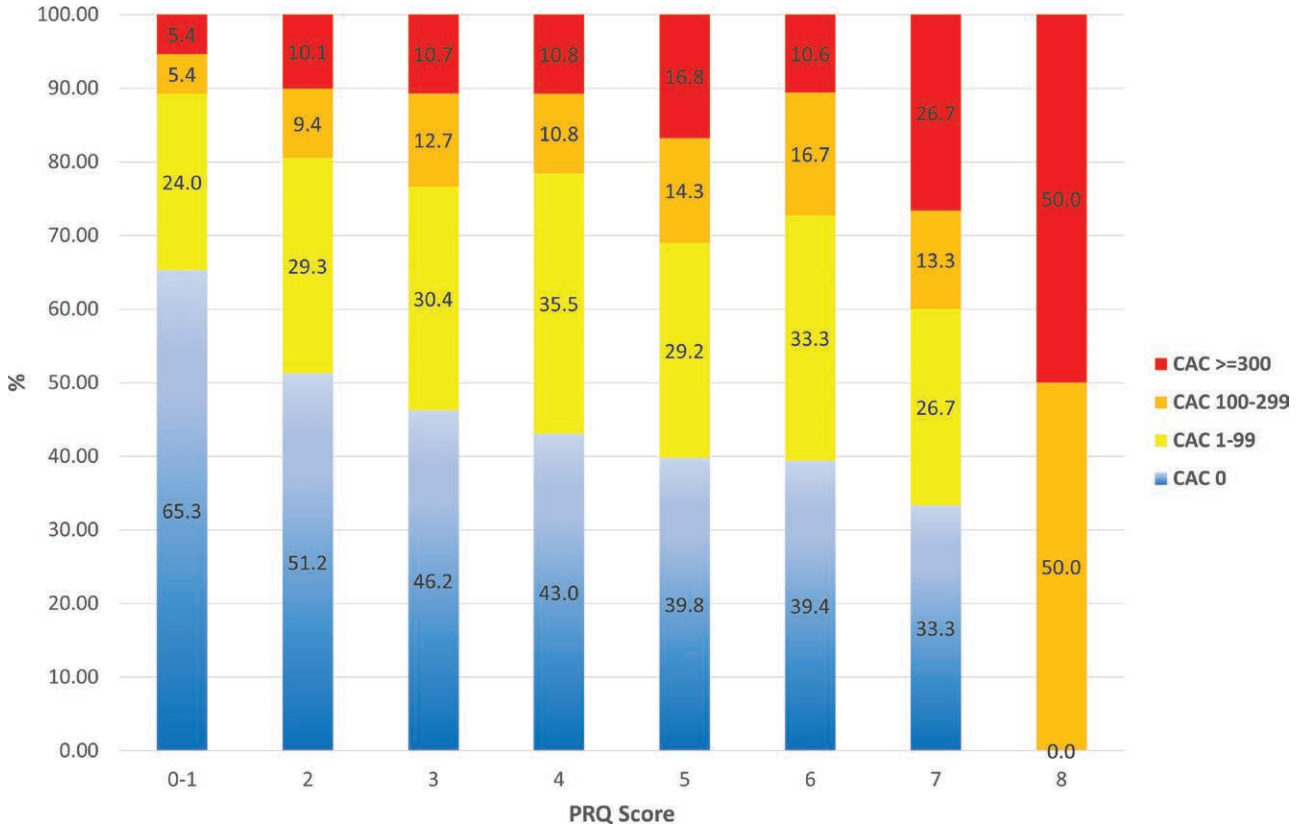
Prevalence of CAC versus PRQ score ranges (n=1332). CAC, coronary artery calcium; PRQ, patient risk questionnaire.

risk profile that shows a relation between the number of self-reported risk factors and CAC burden. The findings support the importance of including novel risk factors in addition to TRFs. This approach provides a useful new algorithm for risk assessment in primary prevention suggesting the first step could be a personal risk-profile calculation, as described, to guide who will benefit most from having a CAC scan. The demonstration of the presence and quantification of coronary atherosclerosis by the CAC scan in turn can be used to predict the more accurate cardiovascular risk. This approach may thereby allow appropriate utility and broader penetration of such CAC testing in the community resulting in improved risk stratification and effective targeted management. Our 20% cNRI being due mainly to down stratification of risk indicates the utility of the PRQ in identifying fewer persons who might benefit from having a CAC scan than the PCRS, although does not account for the further clinician-patient risk discussion and consideration of other risk enhancing factors not assessed in the PRQ that might further inform the appropriateness of CAC scanning.

Our study had some limitations. Nontraditional risk factors in this study were limited allowing for a lack of data available, but it is logical and entirely reasonable to extend the list to include well-accepted other so-called 'risk-enhancers' recognized to be associated with a higher incidence of premature atherosclerotic disease and risk, as utilized in the PCRS and prevention guidelines, notwithstanding that their utility there is aimed at 'shared decision making' over 'who should be prescribed a statin' [24]. In addition, PRQ risk factors are given a value of 1 and are not continuous variables. However, the score is not intended as a risk predictor but as a personal risk-profiling tool to guide who should best be referred for a CAC which itself provides more accurate risk prediction. Furthermore, the approach using metrics in relation to CAC scoring has been previously validated, clearly establishing a difference between a population with a less favorable cardiovascular health profile compared to a healthier one [25]. There is no intention to suggest these factors have equal importance in their atherogenicity or should undermine clinical judgment, but rather, by their consideration, to assist clinicians and indeed patients in providing a 'wide net' and high sensitivity to those, especially younger patients, who may unknowingly be at risk and benefit from plaque testing. Also, information about some of the risk factors in the EISNER study was not available in our study; for example, history was not fully available re life-long exposure to a high saturated diet. In such a case, it may have 'upscored' the patient say from 2 to 3 and have increased the validity of the results.

This is the first evidence-based clinical approach and algorithm utilizing a consideration of a composite of both traditional and novel risk factors to determine who will benefit most from coronary plaque testing by using a CT coronary calcium score. Importantly, and uniquely, it is the first published clinical approach that provides a weighting

Fig. 5



Extent (%) of CAC by PRQ cumulative Score without age and sex. CAC, coronary artery calcium; PRQ, patient risk questionnaire.

for the strength of an individual's family history as a risk factor. The algorithm also gives sex-appropriate weighting for age. This removes the need for an absolute age cutoff 'for all' for a CAC scan recommendation (e.g. 'do a CAC for all patients above 40 or 45 years'), which has been proposed elsewhere and may seem over-zealous. However, even if a nominal target down to say 'age 40 years' were adopted, it would still miss some very high-risk patients in their 30s while this new clinical algorithm will still allow their capture. Further clinical studies to evaluate and confirm this approach will be helpful.

In summary, this simple PRQ approach can trigger an appropriate CAC scan to identify a wider and younger population of patients at potential but underestimated risk with previously unrecognized significant atherosclerosis and its clinical consequences. In addition, alternatively, this approach can reassure those others, especially older patients in whom the PCRS and other TRF-based risk scores have overestimated individual risk.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

Appendix Here are examples of how the personal risk-profile approach can be used.

(1) 55-year-old male executive. Used to smoke for several years. Grew up with a very high saturated fat diet, work-related stress overweight and sedentary.Based on age alone, but also noting other risk factors, a CAC scan is strongly recommended.

(2) 38-year-old male musician. Father died of a heart attack at the age of 45 years. An elder brother has had coronary artery bypass surgery at the age of 43 years. High cholesterol levels on recent testing. History of obstructive sleep apnoea using a mouth splint.Based on the above this patient has two family members with premature disease and also a high cholesterol as well as obstructive sleep apnea. These four risk factors mean he would qualify (only 3 required) so a CAC scan is strongly recommended.

(3) 58-year-old female schoolteacher. Mother died of a heart attack aged 68 years. Recent diagnosis of diabetes on medication. History of depression on medication. Mostly sedentary because of back pain.Based on the above this patient does not receive a point for family history (premature disease is defined as female below

age 65 years), but diabetes and depression as well as being sedentary all score a point which means three additional points. Therefore, a CAC scan is indicated.

(4) A 48-year-old female chef is worried about her cardiac risk because a good friend's husband died suddenly aged 50 years. She is very healthy with a low normal cholesterol number and has no points on the above scale except perhaps for having a 'Type A personality' as she is quite driven to achieve in her work which she loves.Based on the above this patient would at most have 1 point added at most for the Type A personality. At her current age of 48 years, a CAC is not indicated. The recommendation is for a healthy diet and lifestyle approach and a reevaluation of the need for CAC scanning using this approach in 3 years. (Unless something were to change, she will not need a CAC in 3 years. But a 'reevaluation' in 3 years is advisable in case something does change e.g. she may develop high blood pressure and become overweight. At that age of 51 years these 1 or 2 additional risk factors could change recommendation for a CAC scan.)

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