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COMMENTARY

Should Coronary Calcium Scoring Be Used as the Central Tool for Cardiac Risk Assessment?

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When an asymptomatic person is screened for cardiovascular disease, we are asking if they are at a significant risk of cardiovascular events or death and in addition, will this information lead to clinical benefits from more appropriate pharmacologic therapy or investigations? Accurate answers to these questions will provide targeted treatment options, more cost-effective use of health dollars, and reduce cardiovascular events and premature death.

There are many possible approaches to screening including risk factor scores, coronary calcification score (CACS), carotid imaging, stress testing and biomarkers such as high sensitivity cRP. The current Australian National Vascular Disease Prevention Alliance (NVDPA) guidelines for Absolute Cardiovascular Disease Risk (ACDR) [1] separates people into three groups based on their predicted risk of cardiovascular disease (CVD) within 5 years – high (>15%), moderate (10-15%) and low (<10%). They recommend that all ''high risk'' and certain ''moderate risk'' persons should be treated with pharmacologic therapy and considered for further screening. They do not recommend further testing in ''low risk'' persons and do not endorse antihypertensive therapy in these people unless their blood pressure (BP) is persistently ≥160/100. It has been noted [2] that ''below the age of 45 years, almost all patients will be low risk''.

It is valid to ask questions about this scoring system:

a. Have these risk factor scores or tables been validated to determine an individual's cardiovascular risk?

The NVDPA risk score employs the Framingham Risk Equation (FRE), which employs age, diabetes, smoking, blood pressure and total/HDL cholesterol to estimate risk. The guideline statement admits that it may underestimate risk in Aboriginal and Torres Strait Islander peoples, adults with diabetes aged between 45 and 60 years, adults with socioeconomic deprivation or depression and adults aged over 74 years. They also state that this equation has not been specifically assessed in adults who are overweight or obese (63% of Australians in 2014) [3]. The FRE has been abandoned by the American Heart Association/American College of Cardiology (AHA/ACC), which now employ the New Pooled Cohort atherosclerotic cardiovascular disease (ASCVD) Risk Equation and is not used by the European Society of Cardiology (ESC) who employ the Systematic COronary Risk Evaluation (SCORE) algorithm, but even these updated risk scores overestimate risk [4,5]. In fact, no risk factor score has ever been formally validated in randomised controlled trials with clinical events as outcomes.

Of those with heart attack, 62% of men and 53% of women have none or only one coronary risk factor [6] and yet 63% of the population have only one coronary risk factor [7]. Thirteen per cent of people with fatal myocardial infarction have no coronary risk factors [8]. Almost all individuals with none or one coronary risk factor are considered ''low risk'' and do not qualify for lipid lowering therapy [9]. In four major studies, more than 75% of all hard coronary events occurred in persons classified as low or intermediate risk [10–13], and the majority of persons classed as high risk had no coronary events. Not only are risk factors poor at predicting outcomes they are also poor at motivating patients to participate in preventative strategies.

The current NVDPA recommendation to withhold BP lowering therapy from ''low risk'' persons unless their BP is ≥160/100 is not consistent with the 2017 ACC/AHA guidelines [14] which recommend pharmacotherapy for low risk persons if they have a BP ≥140/90.

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b. Are there a significant number of ''low risk'' persons who are misclassified and having major CV events or dying and could pharmacotherapy improve their outcome?

Epidemiologist, Geoffrey Rose, made an essential observation about preventative medicine when he stated that ''the greatest number of deaths from CVD occur in lower risk patients because there are many more of them'' [15]. This has been confirmed, when in pooled data from the follow-up of almost 110,000 people aged greater than 40 years, more than one-half of the cardiovascular disease (CVD) deaths occurred in the portion of the population traditionally estimated to be ''low risk,'' or <10% CVD death risk [16].

More recent Australian data have shown that 20% of myocardial infarctions occur in the young [17]. Coronary atheroma is well documented in young adults [18,19] and 19% of young men aged 30–34 years who underwent autopsy after a violent death had a 40% coronary lesion [20] with lesions correlated with obesity and traditional risk factors. Seventy-five per cent of younger patients presenting with ST-elevation myocardial infarction were considered low risk the day before their event [21].

A study of 3043 patients aged 32–46 years undergoing coronary artery calcium scoring (CACS), a measure of coronary atheromatous burden, found that 10.2% had positive scores, which increased to 20.1% 5 years later. Any positive score led to a five-fold increase in fatal and non-fatal coronary heart disease (CHD) events over 12 years of follow-up, with hazard ratios of 2.6, 5.8 and 9.8 for CACS strata of 1–19, 20–99 and >100 respectively. A score of >100 led to an almost four-fold risk of total death compared to those without any calcification [22].

Do many low risk or young patients need to be screened with CACS to find those at increased risk? In those with 10-year Framingham Risk Score estimates of 5% to 7.5%, 7.5% to 10%, 10% to 15%, and 15% to 20%, the prevalence of CACS ≥100 was 18%, 25%, 33%, and 41%, respectively, translating into a number needed to screen (NNS) of 5.5, 4, 3, and 2.5 to detect a CACS ≥100 [23]. Amongst young people aged 33–45 years, 19% of patients with a risk score of 5% to 10% had some CAC (NNS ≈ 5), and 17% of persons with an FRS >10% already had a CACS of ≥100 (NNS ≈ 6). In other words, CACS screening less than six ''low risk'' people will identify one person with a CAC which is clinically significant and may be prognostic and change that person's management. The NVDPA guidelines do not recommend statin therapy in ''low risk'' patients, but as demonstrated above [23], many ''low risk'' persons have a significant CACS and are not low risk. Coronary artery calcium scoring has been shown to be predictive of CHD events in persons with low, low density lipoprotein (LDL) levels [24] and also in ''low risk'' women [25]. Doctors and the general public have an over reliance on ''normal'' lipid levels being protective of heart attack, yet a study of over 136,000 patients hospitalised with CAD, showed that most had ''normal'' lipid levels (77% had LDL < 3.36, 45% had HDL > 1.0, and 62% had triglycerides <1.7 mmol/l) [26]. The Dallas Heart Study comprised a young population (mean age 44 yrs.) and demonstrated that CAC significantly improved both the C-statistic and net reclassification index above the traditional risk score model [27].

Does lipid-lowering therapy alter their outcome? An underpowered double-blind randomised controlled trial of patients with CACSs >80th percentile for age and sex showed a non-significant reduction in events in the overall trial but a significant reduction in CVD events in that subset with a CACS >400 treated with atorvastatin 20 mg (NNT ≈ 14) [28]. A large trial randomising people with high CAC scores to placebo or a statin may not be performed for ethical reasons.

It has been shown that statin therapy is most efficacious in reducing risk in low risk patients. In the Cholesterol Treatment Trialists meta-analysis [29] of 27 randomised statin trials (>170,000 research participants) for a 40 mg/dl reduction in LDL-C, relative risk reduction for major vascular events for high-risk patients was approximately 21%, 31% for those at a baseline risk of 5% to <10%, and greatest at 39% at the lowest risk (<5% baseline risk). The investigators of this meta-analysis predicted that generic statin interventions were ''likely to be cost-effective in individuals at an annual vascular disease risk down to about 1%''. Aspirin therapy was examined in the Multi-Ethnic Study of Atherosclerosis (MESA) study and was found to be beneficial in those with a CACS > 100, not beneficial in those with CACS of zero, and there was clinical equipoise in those with CACS of 1-99 [30]. Although a Poly Pill strategy could be used across entire sections of the population, calcium scoring would most accurately determine those where both statins and aspirin would be most useful and cost-effective.

We are therefore missing an opportunity in correctly identifying and treating young or ''low-risk'' people who are dying prematurely from coronary disease. There is, therefore, a strong case for screening younger patients with CACS and lower cut-offs for treatment than older patients should be considered.

c. Are there a significant number of ''high risk'' persons who are misclassified and being administered pharmacotherapy or investigations, which may be unnecessary or harmful?

In those at higher risk with 10-year Framingham Risk Score (FRS) estimates of 10% to 15%, 15% to 20%, and >20% the prevalence of a CAC = 0 was 36%, 27%, and 17% respectively [31]. A pooled study of over 70,000 people demonstrated a mortality rate of 0.5% at 4.2 years when CAC = 0 [32].

A pooled study of three US studies showed that 31% of elderly people had zero CACS [33], many of whom were deemed ''high risk'' and treated inappropriately. Major cost savings may be made by ''de-risking'' these patients, thereby avoiding statins, aspirin or downstream testing and their complications. It has been estimated that a CACS reclassifies about 50% of patients who are not eligible for statin drugs [34]. Conversely, the presence of any calcium in the arteries implies risk and this knowledge can help individuals with high scores adopt healthier lifestyles and begin medical

therapy such as statin drugs and aspirin, to improve their odds of long-term survival.

Patients with end-stage renal disease (ESRD) are at higher risk for cardiac events but risk stratification is difficult and coronary risk factors are common. The FRE does not include renal function, and pooled analyses from large studies have shown the poor predictive value of risk score models in patients with chronic kidney disease (CKD) [35]. The NVDPA guidelines classify all patients with ''moderate or severe CKD (persistent proteinuria or estimated glomerular filtration rate <45 mL/min/1.73 m^2)'' to be high risk, but is this correct? Four papers have demonstrated improved risk prediction with CACS in patients with CKD [36–39] as well as its incremental accuracy when added to myocardial perfusion imaging [40–42] and have shown very low risk in those ESRD patients with a CACS of zero [41].

Similarly, the NVDPA classifies all patients with diabetes and age >60 years or with microalbuminuria as high risk, but is this correct? In the MESA study, the annual coronary event rate in diabetics without coronary calcification was very low (<1%) [43]. In the Diabetes Heart Study [44], CACS provided a dramatic reclassification of risk of patients with type II diabetes aged 34–86 years. Using multivariate analysis, the odds ratios (95% CI) for CVD mortality using CAC 0–9 as the reference group were, CAC 10–99: 2.93 (0.74–19.55); CAC 100–299: 3.17 (0.70–22.22); CAC 300–999: 4.41 (1.15–29.00); and CAC ≥1,000: 11.23 (3.24–71.00). In these patients a CACS = 0 was a reliable indicator of low risk. The authors concluded in diabetics, ''that CAC is a more reliable indicator of CVD risk than the established cardiovascular risk factors''. The warranty period for diabetics however, may be shorter for diabetics than non-diabetics [45], and it has been suggested [46] that ''adequate intervals for observation for subclinical CAD may be 5 years in patients with diabetes mellitus and 15 years in those without''. It was recommended that ''every diabetic patient has a CAC scan before initiating statin therapy and if the score is 0, do not start statin medications, but repeat the test in 5 years to reassess the need for this therapy''.

d. Is Coronary Calcium Scoring a better approach to risk stratification and determining pharmacotherapy and downstream testing?

Variables associated with good prognosis were analysed in the MESA study, including CACS = 0, carotid intima thickness, brachial flow mediated dilatation, ABI >0.9, hsCRP <2 mg/l, homocysteine <10 mmol/l, NT proBNP <100, no microalbuminuria, no family history of CAD, absence of metabolic syndrome and healthy lifestyle. CACS = 0 was the strongest negative risk marker for events at 10 years [47]. An asymptomatic individual with a calcium score of 0 has a minimal risk of death from any cause over the next 15 years [48]. The Heinz Nixdorf Recall Study [49] also demonstrated the excellent prognosis of those with CACS = 0 with an event rate of only 0.16%/year; with CACS showing significantly better results for c-statistics than traditional risk factors for both men and women.

The FRS, CACS, treadmill testing and stress myocardial perfusion imaging (SPECT) were assessed and followed for 7 years in 988 people [50] and CACS significantly improved long-term risk stratification beyond all other modalities across the entire spectrum of clinical risk. Risk scores do not take into account genetics, epigenetics, unmeasured risk factors such as second hand tobacco exposure, air pollution, adverse dietary factors, depression and other psychosocial issues. In contrast, CACS measures the end result of the lifelong influence of all known and unrecognised factors leading to coronary atherosclerosis and provides a quantitative measure of atheromatous burden that is strongly correlated with cardiovascular events and death.

Coronary artery calcium scoring outperforms risk factor scores for predicting cardiac events [51,52]. A recent analysis of pooled data from three large US studies showed that replacing risk factors with CAC scoring and retaining age, significantly improved the C statistic for coronary heart disease events (0.740 v 0.703, difference +0.037; 95% confidence interval of difference 0.012-0.062) [33], but not for stroke. It is of great importance that CAC outperformed the combined group of risk factors in predicting coronary risk. In addition, as lipid-lowering therapy has larger benefits in reducing coronary events than stroke events, CAC scoring should be preferred over risk factor scores in guiding the need for statins.

A 2014 review [53] concluded ''Although risk factors have proven to be useful therapeutic targets, they are poor predictors of risk'' and ''coronary calcium scoring is at the present time, superior to any combination of risk factors and serum biomarkers''. A 2009 study of long-term follow-up (15-20 yrs) of the Coronary Artery Risk Development in Young Adults (CARDIA) and MESA studies demonstrated that young adults with low ''short-term'' (10 year) risk will have a high ''lifetime risk'' when they have a high baseline CAC score [54].

The largest study of cost effectiveness of statin therapy for people with CAC > 1, or CAC > 100 compared with guideline based treatment or statins for all intermediate risk persons [55]. It found the CAC strategies were more effective and particularly cost-effective when the cost of the procedure was less than US $150 and those treated with CAC > 100 had a greater net gain in QALYs. It has also been proven that low dose computed tomographic (CT) screening reduces mortality from lung cancer in those with a 30-pack year smoking history [56] and cost effectiveness is further improved if two major diseases are screened with one test. I have personally discovered two early lung cancers and a breast cancer with CACS. Finally, a study of long-term compliance to statin therapy in patients having CAC scoring, showed that patients in the top quartile of CAC score had 91% compliance at 1 to 3 years, compared with only 44% compliance in those in the lowest quartile [57].

The 2013 AHA/ACC guidelines [58] recommend CACS in intermediate (class IIa) and those at low-intermediate risk (class IIb). It specifically recommends statins in those with either CACS ≥300 or CACS ≥75th percentile for age, sex, and ethnicity. This latter recommendation implies a lower cut-off

for treatment in younger people. New NZ guidelines now include CACS >400 as a high-risk variable. In comparison, the current NVDPA guidelines [1] state, ''There is no current support for the use of ancillary cardiac imaging such as coronary CT angiography to refine FRE based risk assessment and decisions to initiate therapy". The new Cardiac Society of Australia and New Zealand (CSANZ) position statement on CACS [59] describes the benefits of screening, but misses a great opportunity by only recommending its use only in ''intermediate risk" people. The debate elsewhere has now shifted to screening those who are younger and ''low risk" [22,60,61] and I have provided evidence of its utility in de-risking ''high risk" people.

Critics of CACS raise concern over radiation exposure, but validated low (0.37 mSv) and standard dose (0.73 mSv) CACS, are at a level below or similar to that of mammography (0.7 mSv) [62]. In addition, mammography is often performed annually, whereas CACS may only be required once or twice in a lifetime. Coronary artery calcium scoring is easily performed, widely available, takes about 5 seconds and is inexpensive (Aust $100–$150).

Conclusions

Medical screening should be cheap, safe, non-invasive, accessible, accurately detect early disease, and facilitate early and effective treatment. Risk factor algorithms misclassify a large number of people in all three risk categories, frequently misdirect treatment and are poor at motivating lifestyle changes. In contrast, CACS meets all these criteria, more accurately classifies those at greatest risk of death and coronary events, guiding those who benefit from statin therapy, aspirin or require more cardiac investigations and more effectively motivates lifestyle modification. Coronary artery calcium scoring ''de-risks" wrongly classified high-risk people, and for the first time, a single screening test, truly identifies those at truly low risk – those with CACS = 0. A risk factor algorithm that includes obesity, could be used for determining the age at which CACS is performed and calculating the ''warranty period" after a CACS = 0 is measured when further testing may be required. For example, a single CACS is performed in most people at age 40 years and, if zero, repeated 15 years later. In diabetics and those with multiple risk factors, CACS might be performed at an earlier age, and repeated every 5 years, if the score remains zero. CACS referrers should also ask for a lung assessment in persons with a significant smoking history.

I contend that the current NVDPA guidelines are obsolete and that risk factor scoring should be downgraded and CACS, which has a higher C-statistic, used as the central pillar of risk prediction. As clinicians, we have an obligation to our patients to provide them with the best contemporary advice regarding their individual health risks, particularly, the commonest cause of death and disability. Risk factors should remain strongly in focus as therapeutic targets and not employed for risk prediction.

Risk factor algorithms can be misleading to doctors and dangerous for their patients whereas CAC scoring provides more accurate individualised risk assessment. In my opinion, consideration should be given to:

1. Changes to the NVDAP guidelines with CACS as the major tool for screening those without known coronary disease
2. Utilisation of CACS at least once in all patients 40-75 years, or in younger patients with adverse risk factors
3. Lower cut-offs for CACS risk in younger patients
4. A revision to the PBAC guidelines for CACS guided statin use in primary prevention
5. Government subsidy of CACS screening
6. CACS screening promotion with public education programs
7. Education of doctors regarding CACS screening, interpretation and management

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