

Future directions in cardiovascular disease risk prediction



CPD 

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Background

Although the National Vascular Disease Prevention Alliance (NVDPA) guidelines were published in 2012, many individuals at high risk of cardiovascular disease (CVD) are not prescribed preventive medication or have CVD risk factors recorded. Better use of CVD risk prediction tools and targeting of medication could reduce CVD.

Objective

The aim of this article is to review recent developments in CVD risk prediction, including calculators developed in the USA, UK and New Zealand, and non-traditional tests for cardiovascular risk assessment.

Discussion

The Framingham Risk Equation explains much of the risk variance in the population but overestimates risk for a contemporary Australian population. Newer risk calculators show improvement in calibration. Individuals vary greatly in terms of whether they will find the potential benefits of taking medication worthwhile, and shared decision-making tools can help to clarify decision making.

DIAGNOSING AND MANAGING risk factors for cardiovascular disease (CVD) is so routine in general practice that it is possible to underestimate its importance in reducing cardiovascular events. If cardiovascular deaths had remained at the levels seen at their peak in 1968 in Australia, there would have been approximately 200,000 additional deaths in 2015, a year in which there were 159,052 total deaths.¹ Much of the decline has been due to decreases in smoking, blood pressure and cholesterol levels even prior to medical interventions, but widespread use of blood pressure-lowering and lipid-lowering therapy has also played a significant part.²

Deaths and disability from CVD could be reduced even further by improved targeting of therapies. It is recommended that patients who are at high risk of CVD take both blood pressure-lowering and lipid-lowering medications.³ The current Australian guidelines produced by the National Vascular Disease Prevention Alliance (NVDPA) define high risk as a risk of >15% of a CVD event over the next five years. In 2017, the Pharmaceutical Benefits Advisory Committee removed restrictions on prescribing of statins to allow prescribing in accordance with the guidelines. Currently, only 25% of people aged 45–74 years who are at high risk are taking both types of medications, as are

only 35% of those aged >75 years.⁴ It is unknown how many of those not taking both types of medications had not been assessed and offered medication, and how many had been offered medication but did not want to take it or had stopped because of side effects. However, based on MedicineInsight data, only 17% of adults aged ≥45 years have all the risk factors recorded to calculate cardiovascular risk.⁵ A new Medicare Benefits Schedule (MBS) item became available in 2019 to further support the use of absolute risk assessment in general practice.

Being able to assess whether a patient is at high risk for CVD requires the use of a CVD risk calculator. Individual risk factors, such as blood pressure and lipid levels, are poor predictors of overall (or absolute) cardiovascular risk, and clinicians are not able to intuitively combine these factors accurately.⁶ Rod Jackson and his team in New Zealand developed one of the first ways to calculate cardiovascular risk, using coloured charts.⁷ In Australia, the NVDPA has developed a website that allows clinicians to calculate cardiovascular risk online (www.cvdcheck.org.au). The risk calculator is now also embedded in the software programs used by the majority of general practitioners (GPs) in Australia.

The risk calculator currently recommended by the NVDPA is based on

the Framingham Risk Equation.⁸ More than 360 other CVD risk equations have been developed,⁹ many incorporating risk factors not included in the Framingham Risk Equation. The objective of this review is to provide an update for Australian GPs on recent developments in cardiovascular risk calculators and their application, and suggest potential future directions.

The purpose of cardiovascular disease risk prediction

CVD risk calculators are used to determine an individual's risk of developing CVD in the short term, generally five or 10 years, to determine if the patient is at high risk. Prescription of preventive medication, generally both lipid-lowering and blood pressure-lowering medication, is recommended for individuals at high risk, for whom it is most likely that benefits will outweigh the harms.² CVD risk calculators should not be used to determine whether counselling and advice for lifestyle factors should be given to individuals, as this is recommended regardless of the CVD risk estimate. Patients who smoke or are obese or not physically active should be encouraged to adopt healthier lifestyles. Patients with very high blood pressure or lipid levels should also be prescribed medication to lower these, and patients with other conditions that are considered high risk for CVD should be treated with both medications, irrespective of estimated CVD risk (Table 1).²

The accuracy of cardiovascular disease risk prediction

The Framingham Risk Equation used in the NVDPA calculator is based on the Framingham Heart Study and the Framingham Offspring Study cohorts, who had baseline measures taken between 1968 and 1975.⁸ In addition to the age of the study and the limited number of potential risk factors evaluated, major limitations include the restricted geographic and socioeconomic diversity of the participants, and that 100% of participants were of European American ancestry. Despite this, the Framingham Risk Equation shows good

discrimination even in a recent Australian population (Table 1),¹⁰ and the traditional risk factors explain much of the risk variance in the population.

Many new factors have been shown to increase the relative risk of CVD. Showing increased relative risk, however, is not sufficient to show that a risk factor is useful for inclusion in CVD risk prediction. Since risk factors tend to cluster, they do not always add predictive value. For example, body mass index (BMI) does not add predictive value to models that include blood pressure and cholesterol.¹¹

Ideally, new tests and factors would be evaluated in randomised controlled trials. However, given the size and duration of trials required to do this, an approach that evaluates how the risk factor improves CVD risk prediction is often required. The addition of a risk factor is deemed to better identify who to treat if it improves: 1) discrimination, 2) classification and 3) calibration, and if the overall expected benefits of testing and treatment outweigh the harms.¹² Discrimination is most often evaluated using the C statistic (or the closely related area under the receiver operating curve). A test that perfectly discriminates between those who have a disease and those who do not has a C statistic of 1. The net reclassification index is the sum of the proportions of people who are correctly and incorrectly reclassified as low and high risk because of the addition of the risk factor, and it has a maximum value of 2. Calibration measures whether predictions systematically overestimate or underestimate the actual probability of an event. A substantial proportion of contemporary populations are treated with blood pressure-lowering or lipid-lowering medications, causing older risk calculators such as the Framingham Risk Equation to overestimate the observed risk of events. Evaluations of the calibration of a risk calculator need to take treatment frequency in the population into account, as their purpose is to predict cardiovascular events (and therefore potential benefits of treatment) for an untreated patient.

Three important risk calculators have been developed recently in the USA

(Pooled Cohort Equation – atherosclerotic CVD [PCE-ASCVD]),¹¹ the UK (QRISK, recently updated to QRISK3)¹³ and New Zealand (PREDICT-1).¹⁴ The main features of these risk equations and the Framingham Risk Equation currently recommended by the NVDPA, including estimates of their accuracy and calibration, are shown in Table 1. Note that the estimated accuracy of the QRISK3 and PREDICT-1 equations may be overstated, as they are tested using the same population cohort as was used for development. Notably, the three new equations include a number of new risk factors, particularly ethnicity and measures of socioeconomic deprivation.

Other risk factors were considered when developing these newer models but were not included in the final models. As an example, the PCE-ASCVD model does not include family history, BMI or waist circumference as these factors did not improve discrimination beyond the traditional risk factors in a French risk model or in the development of the PCE-ASCVD equation.¹⁵

Individualising risk prediction

The current NVDPA guidelines recommend that the traditional risk factors be used for assessment, but additional risk factors can be used to guide decision making for an individual. For example, medication can be recommended to patients from high-risk ethnic groups who are assessed as being at moderate risk by the calculator.

CVD risk calculators estimate risk on the basis of population estimates. Substantial numbers of people need to be treated to prevent a cardiovascular event, many of whom would never have had an event even without treatment, while a significant proportion of people classified as low risk will subsequently have a cardiovascular event (Table 2). It would be ideal to use tests that can more accurately assess the cardiovascular risk for an individual patient.

The United States Preventive Services Task Force has recently reviewed the evidence for some tests that are potential candidates for this: ankle-brachial index,

Table 1. Description of commonly used cardiovascular risk predictors

	NVDPA³	PCE-ASCVD¹¹	QRISK3¹³	PREDICT-1¹⁴
Diseases predicted	<ul style="list-style-type: none"> • MI • Stroke • Heart failure • Peripheral vascular disease • CHD death 	<ul style="list-style-type: none"> • MI • Stroke • CHD death 	<ul style="list-style-type: none"> • MI • Angina • Ischaemic stroke • TIA • CVD death 	<ul style="list-style-type: none"> • MI • Angina • Stroke • Heart failure • Peripheral vascular disease • CVD death
Treatment threshold	>15% over five years for both BP-lowering drugs and statins (approximately >20% over 10 years)	Recommend shared decision making for statins for >7.5% over 10 years and BP-lowering drugs for >10% over 10 years	Recommend for >10% over 10 years	Strong recommendation for >15% over five years, shared decision making for 5–15%
Derivation cohort	Framingham Heart and Framingham Offspring	Framingham Heart and Framingham Offspring, ARIC, Cardiovascular Health, Cardia	UK general practices	NZ general practices
Age of derivation cohort (size)	30–74 years (5,573)	40–79 years (24,626)	25–84 years (7,890,000)	30–74 years (401,752)
Factors included	<ul style="list-style-type: none"> • Age • Sex • Smoking status • Diabetes status • SBP (ideally SBP prior to BP treatment) • TC and HDL • Presence of LV hypertrophy 	<ul style="list-style-type: none"> • Age • Separate models for males and females • Smoking status • Diabetes status • SBP and whether they are taking BP-lowering medication • TC and HDL • Ethnicity (two categories) 	<ul style="list-style-type: none"> • Age • Separate models for males and females • Smoking status (five categories) • Diabetes status (type 1 or 2) • SBP and whether they are taking BP-lowering medication and BP variability • TC and HDL • Townsend score of socioeconomic status • Ethnicity (nine categories) • Family history of premature CVD • Atrial fibrillation, rheumatoid arthritis, chronic kidney disease (stages 3–5), migraine, systemic lupus erythematosus, severe mental illness, erectile dysfunction • Corticosteroid use • Atypical antipsychotic use 	<ul style="list-style-type: none"> • Age • Separate models for males and females • Smoking status (three categories) • Diabetes status (also separate model) • SBP and whether they are taking BP-lowering medication • TC and HDL, and whether they are taking lipid-lowering medication • New Zealand Index of Socioeconomic Deprivation (five categories) • Ethnicity (five categories) • Family history of premature CVD (men only) • Atrial fibrillation • Antithrombotic medication
Additional indications for statin therapy for primary prevention	<ul style="list-style-type: none"> • Diabetes and age >60 years • Diabetes with micro-albuminuria • Moderate or severe CKD • Familial hypercholesterolaemia, TC >7.5 mmol/L 	<ul style="list-style-type: none"> • LDL \geq4.9 mmol/L • Diabetes and LDL \geq1.8 mmol/L 	<ul style="list-style-type: none"> • Type 1 diabetes • CKD 	<ul style="list-style-type: none"> • TC:HDL >8.0 • Moderate or severe CKD³⁴

Table 1. Description of commonly used cardiovascular risk predictors (cont'd)

	NVDPA ³	PCE-ASCVD ¹¹	QRISK3 ¹³	PREDICT-1 ¹⁴
Additional indications for blood pressure lowering therapy for primary prevention	<ul style="list-style-type: none"> Diabetes and age >60 years Diabetes with micro-albuminuria Moderate or severe CKD BP ≥140/90 mmHg if moderate absolute risk, BP ≥160/100 mmHg if low risk³⁵ 	<ul style="list-style-type: none"> BP >140/90 mmHg Diabetes or renal disease and BP >130/80 mmHg³⁶ 	<ul style="list-style-type: none"> ABPM or HBPM >150/95 mmHg Diabetes or renal disease and ABPM or HBPM >135/85 mmHg ABPM or HBPM >135/85 mmHg and age <60 years to consider medication³⁷ 	<ul style="list-style-type: none"> BP >160/100 mmHg³⁴
C statistic – women	0.80 (0.76, 0.84) (Australia) ¹⁰	0.84 (0.80, 0.87) (Australia) ¹⁰ 0.74 (0.71, 0.76) (USA) ³⁸ 0.71 (0.70, 0.72) (NZ) ¹⁴	0.88 (0.88, 0.88) (UK) ¹³	0.73 (0.72, 0.73) (NZ) ¹⁴
C statistic – men	0.74 (0.71, 0.78) (Australia) ¹⁰	0.77 (0.74, 0.80) (Australia) ¹⁰ 0.65 (0.62, 0.68) (USA) ³⁸ 0.71 (0.70, 0.72) (NZ) ¹⁴	0.86 (0.86, 0.86) (UK) ¹³	0.73 (0.72, 0.73) (NZ) ¹⁴
Calibration	Overestimated risk for Australian population ¹⁰	Overestimated risk for Australian ¹⁰ and NZ populations ¹⁴	Well calibrated for UK population ¹³	Well calibrated for NZ population ¹⁴

ABPM, ambulatory blood pressure monitoring; ARIC, Australian Research Integrity Committee; BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HBPM, home blood pressure monitoring; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; MI, myocardial infarction; NVDPA, National Vascular Disease Prevention Alliance; NZ, New Zealand; PCE-ASCVD, Pooled Cohort equation – atherosclerotic cardiovascular disease; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischaemic attack

coronary artery calcium scoring, high-sensitivity C-reactive protein¹⁶ and exercise electrocardiography (ECG).¹⁷ A summary of their findings is shown in Table 3. Coronary artery calcium scoring has also been assessed in a relatively small randomised controlled trial, randomising individuals to scanning or not prior to assessment of traditional risk factors. The trial of 2137 patients followed for four years found no evidence of a difference in clinical outcomes (ie myocardial infarction, cardiac death, all-cause mortality).¹⁸ A greater number of patients who had undergone scanning commenced blood pressure medication (presumably because of increased classification of patients as being high risk), with a subsequent improvement in blood pressure levels; however, there was no change in medication adherence for those taking medication. Two small randomised controlled trials have assessed exercise ECG in patients at high risk and found no evidence of a difference in health

outcomes, although the trials were also limited by their small sizes.¹⁷ To date, there is no convincing evidence for the use of these non-traditional tests in routine risk assessment.

Another potential avenue is the use of genetic testing, such as polygenic risk scores. The UK Biobank project contains genetic information for more than half a million individuals and has identified 1.7 million genetic variants contributing to the risk of coronary artery disease. However, improvement in risk prediction beyond that of the traditional risk factors was very modest, improving the C statistic from 0.670 to 0.696.¹⁹

Aboriginal and Torres Strait Islander population

While the Framingham Risk Equation overestimates CVD risk in the general Australian population, it underestimates risk in the Aboriginal and Torres Strait Islander population by approximately

one-third.²⁰ Until a specific model for this population is developed or better calibrated, it is important that clinicians are aware of this underestimation and upwardly adjust estimates of CVD risk if they are using a CVD risk calculator for this population. It is also recommended that assessment begins earlier (eg at the age of 18 years),²¹ with particular consideration given to other conditions not covered by the Framingham Risk Equation that have been shown to place an individual at high risk of CVD.

Use in the elderly

The decision of whether to prescribe (or to continue to prescribe) lipid-lowering and blood pressure-lowering medication for the elderly is complex. The risk of a CVD event greatly increases with age, increasing the potential benefits of treatment; however, the risk of harmful side effects also increases, as do comorbidities and competing causes

of mortality. A recent study using an intervention to improve the alignment between the health priorities of elderly patients who have multimorbidities with their clinical care led to three times as many patients stopping cardiovascular medication than usual care.²²

Communication

Since CVD prevention involves prescribing medication to healthy, asymptomatic individuals, a shared decision-making

approach is essential.²³ Reviews have concluded that communicating baseline absolute risk and how treatment can modify this risk is the best way to help patients understand their own risk and consider action to reduce this, including lifestyle change or medication.²⁴ This is particularly important for individuals at lower levels of risk, where the potential benefit of treatment is smaller. Many individuals require evidence of a substantial reduction in risk before they consider it worthwhile to take daily

medication.²⁵ However, Australian GPs have identified communication as one of the barriers to conducting risk assessments in general practice, particularly for patients with perceived low health literacy.²⁶ Reviews of decision support tools for CVD risk communication have noted that a wide range of resources are available online.²⁷ Unfortunately, few met criteria to meet the needs of most people, particularly those with low health literacy.²⁸

GPs can address this by explaining CVD risk using simple frequencies to explain both the risk and benefit of medication.²⁹ For example, a patient with 10% risk could be told: ‘Out of 100 people like you, approximately 10 will have a heart attack or stroke in the next five years. If all 100 take a statin, approximately two heart attacks or strokes could be prevented. Approximately one person will have muscle aches and pains, but if this happens we can stop the medication.’ Recent calculators have generally used a 10-year time frame, and this may be more effective for conveying risk and motivating lifestyle changes.³⁰

There is increasing interest in ‘heart age’ calculators, which have been promoted around the world including in Australia, New Zealand and the UK.³¹ While there are claims that giving patients an ‘older’ heart age can motivate them

Table 2. Classification of patients using Framingham and PCE-ASCVD risk calculators*

	NVDPA	PCE-ASCVD 2013
Proportion of women aged 40–74 years without CVD classified as high risk by risk equation	2% (Australia) ¹⁰	18% (Australia) ¹⁰ 20% (USA) ³⁸
Proportion of men aged 40–74 years without CVD classified as high risk by risk equation	17% (Australia) ¹⁰	46% (Australia) ¹⁰ 26% (USA) ³⁸
Proportion of women aged 40–74 classified as low risk who have a CVD event within 12 years	3% (Australia) ¹⁰	1% (Australia) ¹⁰
Proportion of men aged 40–74 classified as low risk who have a CVD event within 12 years	7% (Australia) ¹⁰	3% (Australia) ¹⁰

*These estimates are based on the risk calculator alone and do not include the proportion who are classified as high risk by other clinical factors, such as the presence of chronic kidney disease. CVD, cardiovascular disease; NVDPA, National Vascular Disease Prevention Alliance; PCE-ASCVD, Pooled Cohort Equation – atherosclerotic cardiovascular disease

Table 3. Review of non-traditional risk factors for cardiovascular disease risk assessment by United States Preventive Services Task Force

	Discrimination	Reclassification	Harms
Ankle-brachial index ¹⁶	No change when added to PCE-ASCVD	NRI not statistically significant when added to PCE-ASCVD	Very limited data
Coronary artery calcium ¹⁶	Improved discrimination of PCE-ASCVD from 0.74 to 0.76 in Multi-Ethnic Study of Atherosclerosis (MESA) cohort (USA)	NRI of 0.12 when added to PCE-ASCVD (mostly due to correctly reclassifying patients with events from low to high risk; somewhat offset by incorrect reclassification of patients without events from low to high risk)	Radiation exposure <2 mSv (chest X-ray 0.1 mSv), possible increase in flow-on testing, particularly cardiac imaging
High-sensitivity C-reactive protein ¹⁶	No change when added to PCE-ASCVD	NRI not statistically significant when added to PCE-ASCVD	Very limited data
Resting or exercise ECG ¹⁷	Five studies, improved C statistic by 0.02–0.03 when added to Framingham Risk Equation or PCE-ASCVD	Improvement in reclassification varying between 0.036 and 0.030, but using previous threshold levels for treatment decisions	Very limited data

ECG, electrocardiography; NRI, net reclassification index; PCE-ASCVD, Pooled Cohort Equation – atherosclerotic cardiovascular disease

to change their lifestyles, a review of biological age formats found no evidence that this is more effective than absolute risk formats.³² Anecdotally, New Zealand GPs find this to be a useful communication tool to get people interested in their CVD risk and lifestyle change, but absolute risk must be used when considering medication.³³ This is important not only to determine who is at high risk and likely to benefit from medication, but also to enable a shared, informed decision with the patient.

Conclusion

More recent CVD risk calculators improve CVD risk prediction, particularly those with included measures of ethnicity and socioeconomic deprivation. Much research is being conducted into potential new measures for CVD risk prediction, such as machine learning techniques, genetics and more sophisticated imaging. However, to date these techniques have not shown a greater ability to predict CVD than risk calculators built using more traditional clinical factors.

The current threshold for recommended treatments in Australia means that a substantial proportion of individuals who subsequently develop CVD are currently classified as low risk (Table 2). Lowering the recommended threshold would improve access to preventive treatment and lower the incidence of CVD, but would also result in a large proportion of the population being recommended treatment with both blood pressure-lowering and lipid-lowering medication. Some individuals would be happy to take daily medication to reduce this risk, but others would not. It is important that any decision is in line with the patient's values regarding their healthcare and that the decision is reviewed as the patient's circumstances change.

Many patients at high risk of CVD, even using the current threshold, are not being assessed for their risk of CVD and therefore are missing out on potential treatment. It is important that GPs use the new MBS heart health check item numbers or other systematic approaches to ensure that their patients are being

assessed and reviewed, and offered treatment where appropriate.

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