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Primary prevention of cardiovascular disease: new guidelines, technologies and therapies

Mark R Nelson
MB BS(Hons), FRACGP, PhD, Professor and Chair[1]

Jennifer A Doust
BM BS, FRACGP, PhD, Professor of Clinical Epidemiology[2]

1 Discipline of General Practice, University of Tasmania, Hobart, TAS.

2 Centre for Research in Evidence-Based Practice, Bond University, Gold Coast, QLD.

Mark.Nelson@utas.edu.au

doi: 10.5694/mja12.11054

Summary

- A trend in primary prevention of cardiovascular disease (CVD) has been a move away from managing isolated risk factors, such as hypertension and dyslipidaemia, towards assessment and management of absolute CVD risk.
- In Australian guidelines, absolute CVD risk is calculated as the probability of a stroke, transient ischaemic attack, myocardial infarction, angina, peripheral arterial disease or heart failure occurring within the next 5 years.
- Absolute CVD risk should be regularly assessed in patients aged 45 years or older (35 years or older in Aboriginal and Torres Strait Islander people) using the Australian absolute CVD risk calculator (http://www.cvdcheck.org.au).
- For patients currently taking a blood pressure (BP)-lowering or lipid-lowering agent, pretreatment values should be used to calculate risk.
- Patients at high absolute risk of CVD (>15% over 5 years) should be treated with both BP-lowering and lipid-lowering agents, unless contraindicated or clinically inappropriate.
- For patients at moderate absolute risk of CVD (10%–15%) treatment with a BP-lowering and/or a lipid-lowering agent should be considered if the risk remains elevated after lifestyle interventions, BP is ⩾160/100 mmHg, there is a family history of premature CVD, or the patient is of South Asian, Middle Eastern, Maori, Pacific Islander, Aboriginal or Torres Strait Islander ethnicity.
- BP measurements taken using an oscillometric device can be used to approximate mean daytime ambulatory BP.

A continuing trend in primary prevention of cardiovascular disease (CVD) in general practice has been the move away from managing isolated CVD risk factors, such as hypertension and dyslipidaemia, towards assessment and management of these factors under the banner of absolute CVD risk.[1] This has been underscored by the publication of guidelines for assessment and management of absolute risk.[2,3] These guidelines seek to consolidate various individual disease and risk factor guidelines, recognising CVD as a common end-disease pathway and, therefore, the benefit of taking a common absolute risk-based approach. The rationale behind adopting this approach can be summarised as follows:

- Medication is best initiated in those most likely to benefit from it, and who therefore have a favourable risk-to-benefit ratio.
- It is more cost-effective than intervention for single risk factors.
- It avoids medicalisation of the low-risk population.
- It better identifies those most likely to have covert CVD, avoiding costly additional investigations.
- Beneficial therapeutic agents can be initiated at a level above the ideal rather than at an arbitrary cut point.
- Due attention is paid to CVD risk, which might otherwise be subsumed within a particular chronic disease management strategy (eg, diabetes and blood glucose levels)[4] (see example in Box 1).

Here, we provide information for general practitioners on new approaches to clinical management of CVD risk factors in patients without overt disease, and new technologies and therapies to assess and manage them.

The Australian absolute CVD risk guidelines

In the Australian National Vascular Disease Prevention Alliance (NVDPA) guidelines for assessing absolute CVD risk, absolute risk is calculated as the probability of a stroke, transient ischaemic attack, myocardial infarction, angina, peripheral arterial disease or heart failure occurring within the next 5 years.[2] Absolute risk is categorised, and can be communicated to patients, as low (<10%), moderate (10%–15%) or high (>15%). Medication is recommended for individuals at high risk and sometimes for those at moderate risk if additional risk factors are at play (eg, Aboriginal or Torres Strait Islander status or a family history of premature CVD).

Doctors can reliably estimate relative risk — that is, the risk level of an individual with a risk factor compared with someone who does not have that risk factor.[5] The problem with relative risk is that it tells you that a smoker is at greater risk than a non-smoker but does not convey what that risk actually is. The absolute CVD risk calculator recommended by the NVDPA (http://www.cvdcheck.org.au) is based on the Framingham Heart Study.[2,6,7] It has good predictive value for subsequent CVD events in untreated individuals and has been validated in the Australian population aged 30–74 years.[8]

1 Case example: how the absolute risk approach better targets therapy

Joe is a 64-year-old man who smokes but does not have diabetes or known cardiovascular disease (CVD). His blood pressure is 136/82 mmHg, total cholesterol level is 5.4 mmol/L and high-density lipoprotein (HDL) cholesterol level is 1.0 mmol/L.

Jane is a 46-year-old woman who does not smoke and does not have diabetes or known CVD. Her blood pressure is 142/82 mmHg, total cholesterol level is 6.5 mmol/L and HDL cholesterol level is 1.4 mmol/L.

Using the isolated risk factor approach, other than smoking, Joe has no elevated individual risk factors that would warrant treatment with medication. Jane, on the other hand, has hypercholesterolaemia and hypertension that would see her taking lifelong antihypertensive and lipid-lowering therapy.

However, using the absolute risk approach, Joe's absolute risk is high (21%) and Jane's is low (3%). Joe requires medication in addition to lifestyle changes, while Jane needs attention paid to her antecedent risk behaviour rather than medication. ◆

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2 Conditions conferring a high risk of cardiovascular disease*

- Diabetes and age > 60 years
- Diabetes with microalbuminuria (> 20 µg/min or urinary albumin : creatinine ratio > 2.5 mg/mmol for males, > 3.5 mg/mmol for females)
- Moderate or severe chronic kidney disease (persistent proteinuria or estimated glomerular filtration rate < 45 mL/min/1.73 m^2)
- A previous diagnosis of familial hypercholesterolaemia
- Systolic blood pressure ⩾ 180 mmHg or diastolic blood pressure ⩾ 110 mmHg
- Serum total cholesterol level > 7.5 mmol/L

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If a patient has manifest CVD (eg, past history of stroke or myocardial infarction) or already has a condition that places him or her at high risk of CVD (Box 2), then no risk assessment is required before commencing blood pressure (BP)-lowering and/or lipid-lowering therapy. The NVDPA assessment guidelines recommend that all other adults aged 45–74 years should be assessed for cardiovascular risk.[2] Below the age of 45 years, almost all patients will be at low risk. For people older than 74 years, the guidelines recommend entering their age as 74 in the calculator, to provide a minimum estimate of risk.

All attempts at recalibrating calculators for Aboriginal or Torres Strait Islander peoples have so far failed, with recognition that risk is underestimated in this population.[9] Assessment should commence in Aboriginal or Torres Strait Islander adults at the age of 35 years (in deference to the reduced life expectancy in this population) and the score used as a minimum estimate of risk.

Barriers to uptake of the absolute risk approach, such as acceptability, feasibility and effectiveness in the primary care context, need to be overcome.[10] Depending on the clinical context, treatment on the basis of elevated single risk factors may still be appropriate. For example, atrial fibrillation has a well recognised thromboembolic stroke risk, which warrants a disease-specific stroke and bleeding risk assessment for anticoagulant or antiplatelet therapy.

Recommended changes to clinical practice from the 2012 management guidelines

The 2012 NVDPA guidelines for managing absolute CVD risk recommend both BP-lowering and lipid-lowering agents for all patients at high absolute risk of CVD, unless contraindicated or clinically inappropriate.[3] For patients at moderate risk, treatment with a BP-lowering and/or lipid-lowering agent should be considered if the risk remains elevated after lifestyle interventions, BP is ⩾ 160/100 mmHg, there is a family history of premature CVD, or the patient is of South Asian, Middle Eastern, Maori, Pacific Islander, Aboriginal or Torres Strait Islander ethnicity. The guideline authors recommend that people with a BP of ⩾ 160/100 mmHg be treated for their BP regardless of their absolute risk level. The 2012 guidelines have also revised and simplified BP targets to aim for with BP-lowering treatment and lifestyle measures: for the general population or those with a reduced glomerular filtration rate, the target is ⩽ 140/90 mmHg; and for people with microalbuminuria, macroalbuminuria or diabetes, the target is ⩽ 130/80 mmHg.

Aspirin and other antiplatelet agents are no longer routinely recommended for use in primary prevention of CVD, including for people with diabetes or high absolute CVD risk. Previous recommendations for people with diabetes were based on the assumption of equivalent CVD risk to those with established CVD but without diabetes.[11] However, recent primary prevention trials in patients with diabetes have not shown benefit for aspirin.[12,13] Harm–benefit analyses of antiplatelet drugs for primary prevention assume that risk of CVD rises with age but risk of adverse effects does not. While it is true that CVD risk is largely determined by age, the risk of adverse effects is also likely to be higher in older people.[14] An ongoing clinical trial, Aspirin in Reducing Events in the Elderly (ASPREE), is being conducted in Australian general practice to examine whether the benefits of routine aspirin outweigh the harms in patients aged 70 years or older.[15]

Lifestyle interventions

Regardless of a patient's risk level, the advice in the 2012 NVDPA guidelines remains that treatment should always begin with lifestyle interventions, such as smoking cessation; reducing intake of dietary salt, fat, high-calorie drinks and overall calories; and increasing exercise. Most people at moderate absolute risk should be given the opportunity to reduce their risk by following lifestyle advice, with drug therapy only considered if their risk does not reduce in 3–6 months or if they have specific additional risk factors, such as Aboriginal or Torres Strait Islander status or a family history of premature CVD.

Smoking is the most important modifiable risk factor, and action on smoking is always the highest-priority lifestyle intervention. Smoking cessation reduces the risk of CVD substantially and sustainably, and it also reduces all-cause mortality.[16] Health professional advice, nicotine replacement therapy and medication are effective smoking cessation interventions.[17-19]

Weight loss is important in that it reduces the risk of elevated BP and lipid levels and diabetes. Even modest weight loss (5%–10% of initial weight) can improve health.[20] There are no simple answers to the question of which diet will achieve weight loss. Whichever diet is chosen, it needs to be sustainable to be effective. There is some evidence that low-carbohydrate–high-protein diets, such as the CSIRO (Commonwealth Scientific and Industrial Research Organisation) diet, have greater weight loss and lower attrition rates in the short term, but longer-term evidence is lacking.[21]

Weight-loss medications available to date have been disappointing because of the lack of sustained weight loss and the risk of side effects. Several weight-loss medications have been withdrawn from market due to harmful effects, the most recent being sibutramine.[22] In addition, weight loss achieved using medication is unlikely to have the same health benefits as weight loss achieved by diet and exercise, with all their associated benefits for health and wellbeing. The draft National Health and Medical Research Council *Clinical practice guidelines for the manage-*

ment of overweight and obesity in adults, adolescents and children in Australia[23] recommend orlistat as an agent with proven effectiveness in adults,[24] although its use will be limited by the acceptability of side effects, such as flatulence and anal leakage.

Weight-loss surgery has shown promise for patients with significant obesity. The Swedish Obese Subjects study found average weight loss from various types of bariatric surgery of 14%–25% over 10 years, and a reduction in all-cause mortality, diabetes and CVD.[25] However, this was not a randomised controlled trial, and the intensity of monitoring and follow-up of patients may influence the generalisability of the study results. Weight-loss surgery is recommended if a patient has a body mass index > 40 kg/m^2, or > 35 kg/m^2 with comorbidity.[26]

Regular physical activity reduces CVD risk and individual CVD risk factors and protects against other diseases.[3] Health benefits are achieved with around 150–300 minutes of moderate-intensity activity or 75–150 minutes of vigorous activity each week.[3,23]

How do guideline recommendations align with prescribing criteria for lipid-lowering drugs?

In 2006, the Pharmaceutical Benefits Advisory Committee (PBAC) revised the Pharmaceutical Benefits Scheme (PBS) *General statement for lipid-lowering drugs prescribed as pharmaceutical benefits*.[27] This revision aimed to bring the PBS prescribing criteria for lipid-lowering drugs more in line with the absolute risk approach, while recognising that, at the time, a lack of widespread access to a CVD risk calculator was a barrier to using absolute risk as a prescribing criterion. Conditions considered in the NVDPA guidelines[2,3] to confer a high risk of CVD that are not currently included in the PBS criteria are: moderate or severe chronic kidney disease; total cholesterol level > 7.5 mmol/L in males who are less than 35 years old and in premenopausal women; and systolic BP ⩾ 180 mmHg and total cholesterol level < 6.5 mmol/L, or total cholesterol level < 5.5 mmol/L and high-density lipoprotein cholesterol level > 1.0 mmol/L.

To date, what has not been presented to the PBAC for consideration is the effectiveness and cost-effectiveness of lipid-lowering treatments for patients at high (or moderate) absolute risk with "normal" lipid levels. From our previous analysis of the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) cohort, about 90% of patients at high absolute risk who do not meet the current PBS criteria for prescription of lipid-lowering drugs are in this category.[28]

How frequently should absolute CVD risk be monitored?

Once management decisions have been made, absolute risk should be monitored according to the recommendations in Box 3. The reassessment of absolute risk in the absence of a trigger such as initiation of smoking or diabetes diagnosis may be conducted at longer intervals than currently recommended, especially in low-risk individuals, as reclassification (ie, moving from low to moderate or moderate to high risk), which would lead to management changes, is likely to be an infrequent phenomenon.[29] If a patient is already being treated for elevated BP or lipid levels, the pretreatment values should be used to calculate absolute risk.

3 Recommended frequency of monitoring for absolute cardiovascular disease (CVD) risk*

Regular review of absolute CVD risk is recommended at intervals according to the initial assessed risk level:

- Regular review of absolute CVD risk is recommended at intervals according to the initial assessed risk level:
- Low (< 10% risk of cardiovascular event within 5 years): review every 2 years
- Moderate (10%–15% risk of cardiovascular event within 5 years): review every 6–12 months
- High (> 15% risk of cardiovascular event within 5 years): review according to clinical context

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Is there evidence for the absolute CVD risk approach?

Using the absolute risk approach, patients who have isolated elevated risk factors, but low absolute risk, will generally not be treated with medication. Because age is such a strong predictor of risk, this means that younger patients with isolated elevated risk factors will in general not be treated with BP-lowering or lipid-lowering agents. Many clinicians may be uncomfortable with this approach, as they feel that delaying treatment until it reaches a particular risk threshold can allow irreparable damage to occur. It is unlikely that there will be a randomised controlled trial of the absolute risk approach versus the isolated risk factor approach to test this, because of the sample size and time that would be required.

However, previously conducted trials support the absolute risk approach. Individual patient data (IPD) meta-analyses of both BP-lowering and lipid-lowering drug trials have shown that the relative risk reduction of cardiovascular events is consistent regardless of baseline BP or lipid levels. The IPD meta-analysis of BP-lowering drug trials showed that the relative risk reduction was constant down to the lowest BP levels observed in the trials (110 mmHg systolic and 70 mmHg diastolic), and that results were consistent in trials of patients with a prior history of coronary heart disease or stroke and those with no prior history of vascular disease.[30] The same result has been observed in cohort studies.[31] Similarly, the recently updated IPD meta-analysis of lipid-lowering drug trials by the Cholesterol Treatment Trialists' Collaboration confirms that the relative risk reduction is consistent in patients with or without pre-existing CVD and is independent of the baseline cholesterol level.[32] This study provided further empirical evidence to support the absolute risk approach, by showing a constant relative risk reduction regardless of the baseline risk of a cardiovascular event, and therefore increasing benefits from treatment in patients with increased absolute risk of CVD.

New technologies for CVD risk factors and risk assessment

New technologies that are currently having an impact on BP management in general practice are ambulatory BP

devices and oscillometric BP devices (for both clinic and home use).[33,34] These devices permit an estimation of BP that is more representative of usual BP and associated CVD risk, through a combination of reducing "white coat" effects and observer error, allowing systematic collection of multiple BP recordings and, for measures made outside the clinic, identification of masked hypertension. Ambulatory BP monitoring involves measuring BP at regular intervals over a 24-hour period while patients undergo normal daily activities, including sleep. Home BP monitoring is a validated method for monitoring and managing a patient's BP, which can be readily incorporated into practice. Where barriers to ambulatory and home BP monitoring exist, oscillometric devices can be used to approximate mean daytime ambulatory BP.[35] This "automated office BP" measurement has three basic principles: multiple BP readings are taken; an automated device is used; and measurements are taken while the patient rests quietly alone. The oscillometric device distributed by the High Blood Pressure Research Council of Australia can be used in this way. The machine can be set to automatically record three BP measures at 5-minute intervals. The patient is then left to sit alone for 15 minutes in a room or a screened area, and the BP value displayed after this time is the average of all recordings. These devices can also be used as a screening device for peripheral arterial disease.[36] Users should be aware that BP levels measured this way are generally 5 mmHg lower than clinic measures.[37]

Multiple clinical, biomarker and imaging tests have been proposed as methods for identifying patients at high risk of CVD. Of most clinical use would be tests that could more effectively discriminate moderate-risk patients who are actually at high or low risk of a cardiovascular event. A series of recent reviews has shown that many of the studies aiming to improve identification of patients at increased risk by using non-traditional risk factors, such as C-reactive protein (CRP) and fibrinogen, had methodological flaws and that, on the evidence to date, these factors were unlikely to improve the discrimination of risk.[38] Similarly, using apolipoproteins A and B reclassifies less than 1% of patients beyond the classification based on traditional risk factors.[39] The cost, inconvenience to patients and potential harm mean that calls for these tests to be used more widely are premature. Biomarkers already in use in general practice, such as CRP, add very little to current risk algorithms.[40] The use of computed tomography coronary angiography to screen patients needs careful evaluation of cost and radiation risk before implementation.[41] Coronary artery calcium scoring may have a future role in reclassification for individuals found to be at moderate risk using routine risk stratification.[42]

New therapies for CVD risk factors

People who regularly consume fish have lower CVD event rates than non-consumers.[43,44] However, intervention trials of fish oils are less convincing. A meta-analysis of 48 randomised controlled trials showed no benefit of omega-3 fats on mortality or cardiovascular events in patients with or without existing coronary heart disease.[45] Therefore, in primary prevention, it is justified to recommend the consumption of fish as part of a healthy diet, without the need to use fish oil supplements.

Denervation of the kidney using minimally invasive devices has BP-lowering effects in the majority of treated individuals, but it may also have benefits for glucose metabolism, renal impairment, left ventricular hypertrophy, and other conditions.[46] This method is still early in its development and availability.

Conclusion

The move to an approach based on absolute risk for the primary prevention of CVD is likely to improve the effectiveness and cost-effectiveness of treatment, and the 2009 and 2012 NVDPA guidelines support this approach. The absolute risk approach targets the patients who are most likely to benefit from medication, and reduces the medicalisation of patients at low risk. The increasing availability of cardiovascular risk calculators, either on the internet or as standalone software, also removes one of the barriers to implementing the absolute risk approach. New technologies have varying evidence of utility, but oscillometric BP devices can be readily adopted. The role of coronary artery calcium scoring and other biomarkers in risk stratification is yet to be established.

Competing interests: Mark Nelson is a member of the NVDPA, which produced the absolute CVD risk assessment and management guidelines. Jennifer Doust is a member of the PBAC, which produced the statin prescribing criteria.

Provenance: Commissioned; externally peer reviewed.

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