Risk treatment thresholds for initiating cardiovascular disease pharmacotherapy: Synthesis of international evidence to support guideline recommendations

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Background
A new Australian guideline for cardiovascular disease (CVD) risk assessment and management was published in 2023, including new risk treatment thresholds.

Objective
This article summarises the published peer-reviewed global evidence that informed guideline recommendations on risk treatment thresholds for initiating blood pressure- and lipid-lowering therapy for CVD primary prevention.

Discussion
Evidence from 13 meta-analyses, randomised controlled trials and modelling studies involving more than 515,700 patients showed that preventive pharmacotherapy reduced the number of CVD events at all risk levels. Findings informed the new risk treatment thresholds outlined in the 2023 Australian CVD risk assessment and management guideline, which recommends blood pressure- and lipid-lowering pharmacotherapy for people at high five-year risk (≥10% based on the new risk calculator) and consideration of therapy for those at intermediate risk (5% to <10%) and generally does not recommend preventive pharmacotherapy for those at low risk (<5%).

CARDIOVASCULAR DISEASES (CVDs) are a leading cause of death and morbidity globally.[1] An estimated 80% of CVDs are preventable through interventions that reduce risk, such as avoiding tobacco use, maintaining a healthy diet, engaging in regular physical activity, and taking prescribed blood pressure- and/or lipid-lowering medications.[2,3] In people without known atherosclerotic CVD, stratifying and treating according to their estimated risk of developing CVD underpins primary prevention in Australia and internationally. In July 2023, an updated Australian guideline on CVD risk assessment and management was published, including a new risk calculator and recommended thresholds for initiating blood pressure- and lipid-lowering therapy.[4]

Aim

This article summarises an evidence synthesis undertaken to inform recommendations on the risk level to commence pharmacotherapy under the new guideline on CVD risk assessment and management.[4] The review was commissioned by the National Heart Foundation of Australia on behalf of the Australian Chronic Disease Prevention Alliance. It involved reviewing CVD risk treatment thresholds recommended in major international prevention guidelines and the latest peer-reviewed literature. Evidence on the effects of initiating blood pressure- and lipid-lowering therapy at different levels of CVD risk on fatal and non-fatal CVD events was considered.

CVD risk treatment thresholds recommended in major international guidelines

Risk treatment thresholds recommended for initiating preventive pharmacotherapy vary internationally. Most guidelines recommend a five-year equivalent primary CVD risk range of >5–10% for considering pharmacotherapy use, although specific risk categories vary between countries (Table 1). Several guidelines vary recommendations across a gradient of risk. For example, in New Zealand, blood pressure- and lipid-lowering therapy is strongly recommended for those with a five-year risk ≥15%, with potential treatment for those with 5–15% risk following patient–doctor discussions. In both the USA and Canada, preventive medications are recommended for those at high risk (≥20% 10-year risk) of CVD and lower risk (≥7.5% in the USA and <20% in Canada) if risk-enhancing factors are present (Table 1).

Evidence synthesis methods

We undertook an evidence synthesis focusing on evidence published since the 2012 Australian guideline was released.[15] We used systematic review methods (PROSPERO: CRD42021260012),[16] searching

Table 1. Overview of CVD risk treatment thresholds for initiating pharmacotherapy as recommended in major international guidelines

Country/region	Guideline	Risk treatment threshold
Canada	2021 Canadian Cardiovascular Society guidelines for the management of dyslipidaemia for the prevention of CVD in adults[5]	Lipid-lowering therapy recommended at ≥20% 10-year risk. Considered for those at low (<10%) or intermediate (10.0–19.9%) risk if additional criteria are met
New Zealand	2018 CVD risk assessment and management for primary care[6]	Lipid- and blood pressure-lowering treatment strongly recommended for ≥15% 5-year risk Considered (benefits and harms discussed) for 5–15% risk
England and Wales	CVD: Risk assessment and reduction, including lipid modification (updated 2016)[7,8]	Lipid-lowering treatment (atorvastatin) offered at ≥10% 10-year risk
Scotland	Risk estimation and the prevention of CVD (2017)[9]	Lipid-lowering treatment (atorvastatin) recommended at ≥20% 10-year risk
Europe	2021 European Society of Cardiology guidelines on CVD prevention in clinical practice[10]	Treatment with blood pressure- and/or lipid-lowering therapy is dependent on age-specific treatment targets and age-specific 10-year risk thresholds: ≥7.5% for <50 years, ≥10% for 50–69 years, ≥15% for ≥70 years. Treatment considered at 2.5 to <7.5% for <50 years, 5 to <10% for 50–69 years, 7.5 to <15% for ≥70 years[A]
Norway	New guidelines for the prevention of CVD (2017)[11]	Age-specific 10-year risk thresholds for lipid- and/or blood pressure-lowering treatment: ≥5% for 45–54 years, ≥10% for 55–64 years, ≥15% for 65–74 years
USA	2019 American College of Cardiology and American Heart Association guideline on the primary prevention of CVD[12]	Lipid-lowering treatment at ≥20% 10-year risk with treatment considered for ≥7.5 to <20% if risk-enhancing factors are present (treatment discussed if risk is 5 to <7.5% and risk-enhancing factors are present)
Japan	Japan Atherosclerosis Society guidelines for prevention of atherosclerotic CVD 2017[13]	Lipid-lowering treatment considered for all risk categories if 3–6 months of behaviour modification is ineffective
Global	Prevention of CVD: Guidelines for assessment and management of cardiovascular risk (2007)[14]	>30% 10-year risk with lipid- and/or blood pressure-lowering treatment. Considered at 20–30% risk if behavioural strategies are inadequate

[A]Recommendations are for healthy people. Different recommendations apply to people with established cardiovascular disease (CVD), diabetes, chronic kidney disease or familial hypercholesterolaemia.

PubMed and the Cochrane Library using a combination of terms (ie cardiovascular disease, vascular disease, drug therapy, treatment, statins, primary prevention and prevention) for studies published between January 2012 and July 2021. We included systematic reviews and meta-analyses, randomised controlled trials (RCTs) and modelling studies (where treatment effects were derived from RCTs) reporting the effects on fatal and non-fatal CVD outcomes of initiating blood pressure- and/or lipid-lowering treatments at different levels of risk estimated using risk prediction equations. We also reviewed citation lists of included publications and citations in international CVD guidelines updated since 2012. We assessed the quality of the included articles using published tools but were unable to evaluate the quality of meta-analyses due to a lack of appropriate published tools.[17–20]

Evidence on the clinical effects of initiating blood pressure-lowering medication at different CVD risk levels

We identified six studies (two meta-analyses,[21,22] three single-blinded RCTs[23–25] and one modelling study[26]) reporting on the effects of blood pressure-lowering treatment at different baseline levels of CVD risk.

The two largest studies, both of which were primarily restricted to people with high blood pressure, were a 2014 meta-analysis[22] (68 trials; n=245,870; proportion with existing CVD not reported) and a 2018 meta-analysis of individual participant data from the Blood Pressure Lowering Treatment Trialists' Collaboration[21] (BPLTTC; 11 trials; n=47,872; 35,671 [75%] without prevalent CVD and 12,201 [25%] with prior CVD). The results outlined below are for all participants (those with and without CVD), as neither trial provided relevant results stratified by CVD status at baseline.

Both meta-analyses showed that blood pressure-lowering medication reduces the risk of CVD events across all levels of

estimated risk,[21,22] with results from the BPLTTC analysis showing a risk reduction of around 18–22% for major CVD, even at lower levels of risk.[21] Data indicated that initiating treatment in those with a five-year risk >10% would treat a similar number of people as initiating treatment in those with systolic blood pressure ≥160 mmHg.[21] Under the 2012 Australian CVD guideline, treatment was recommended for those with blood pressure persistently ≥160/100 mmHg.[15] The number needed to treat (NNT) for five years to avoid one CVD event varied by type of CVD outcome but typically increased gradually with decreasing CVD risk level, with the exception of the lowest CVD risk category in the 2014 meta-analysis, where treating those at <5% 10-year CVD risk required a much larger NNT (ranging from 152 for a composite outcome of stroke, coronary heart disease and heart failure to 806 for heart failure only) than other risk categories.[22] For a broad composite CVD outcome, around 28 people needed to be treated at >15% five-year risk to avoid one CVD event, while the NNT was approximately 33 at >10%, 38 at >7.5% and 46 at >5% five-year risk.[21]

All other studies had small sample sizes (n<5000), except for a modelling study, which only included data for China and India.[26] The only Australian study available was an RCT with limited power, reporting hazard ratios for a single type of blood pressure treatment (chlorothiazide) across five-year CVD risk treatment thresholds (low risk <6.1%; moderate risk 6.1–17.0%; high risk >17.0%) that were not comparable to those used in other studies or the 2012 Australian guideline.[25]

Evidence on the clinical effects of initiating lipid-lowering medication at different CVD risk levels

We identified one meta-analysis[2] and six modelling studies[27–32] examining lipid-lowering therapies at different levels of CVD risk.

The meta-analysis used individual participant data from 174,149 people (69,959 without a history of vascular disease) from 27 trials contributing to the Cholesterol Treatment Trialists' Collaboration, conducted before the end of 2009.[2] When restricted to participants without a history of vascular disease, overall, a 1.0-mmol/L reduction in low-density lipoprotein (LDL) cholesterol was associated with a 25% reduction in the likelihood of a major vascular event (rate ratio [RR]: 0.75; 95% confidence interval [CI]: 0.70–0.80).[2] There was some evidence that the relative risk reduction of major vascular events differed across levels of CVD risk (test for trend, $P<0.01$), although the RRs in the lowest two risk categories (<5% and 5% to <10%) were at least as large as those observed within the highest risk categories (RRs for major vascular event: 0.61 [95% CI: 0.45–0.81] for <5% five-year risk, 0.66 [95% CI: 0.57–0.77] for 5% to <10% risk and 0.83 [95% CI: 0.58–1.18] for ≥30% risk).[2]

Among participants with and without vascular disease, a 1.0-mmol/L LDL reduction with statin treatment was estimated to prevent six major vascular events per 1000 treated over five years for those with <5% five-year risk, 15 for 5% to <10% five-year risk and 31 for 10–20% five-year risk.[2] NNTs were not reported.

Only one of the six modelling studies included data relevant to Australia and was assessed as high quality.[30] The modelling suggested age- and sex-specific 10-year CVD risk treatment thresholds for Australia where benefits outweighed harms, ranging from 11% for men aged 40–49 years (approximately equivalent to 5–6% five-year risk) to 17% for those aged 70–75 years (an approximate 8–9% five-year risk) and from 15% 10-year risk for women aged 40–49 years (an approximate 7–8% five-year risk) to 18% for those aged 70–75 years (an approximate 9% five-year risk).[30]

Overall, the international evidence demonstrates that lipid-lowering treatment decreases the relative risk of major CVD outcomes by approximately 25% in those without a history of vascular disease, and there is little evidence that this relative reduction differs across risk category. However, there is little contemporary data available and very little data specific to Australia's context.

Conclusion

The current available global evidence indicates that both blood pressure- and lipid-lowering therapy are effective at reducing CVD events across all levels of CVD risk and that a five-year risk treatment threshold of around 6–10%, consistent with recommendations in major international guidelines, is associated with a modest NNT to prevent one CVD event. For example, for blood pressure-lowering medication, 33 people need to be treated to prevent one CVD event at a five-year risk level of >10%, while for lipid-lowering therapy, a 1.0-mmol/L reduction in LDL cholesterol would prevent approximately 15–31 major vascular events per 1000 treated for those with a five-year CVD risk of 5–20%.

Our review did not explicitly consider adverse events and the included studies did not comprehensively report on potential treatment harms. Limitations of the evidence synthesised included limited contemporary and Australian data; differences in definitions of CVD outcomes hampering between-study comparisons; most studies contributing to the included blood pressure-lowering meta-analyses being restricted to people with high blood pressure; lack of reporting on risk equation calibration, which influences the level at which the risk treatment threshold should be set; and most studies lacking statistical comparison of outcomes between different CVD risk levels.

Our review informed the 2023 Australian guideline recommendations for initiating preventive pharmacotherapy for those at high risk (≥10% five-year risk based on the new calculator), consideration of treatment for those at intermediate risk (5% to <10% five-year risk) and generally not offering pharmacotherapy to those at low risk (<5% five-year risk).[4] The Guideline Expert Steering Group considered evidence from this review as well as consensus on safety of medicines, contextual factors around medicine availability, affordability, and patient values and preferences.

Key points

- This article outlines methods and evidence used to inform risk treatment threshold recommendations for CVD primary prevention in Australia.
- This work was commissioned by the National Heart Foundation of Australia, on behalf of the Australian Chronic Disease Prevention Alliance, as part of the

2023 update of the Australian CVD risk assessment and treatment guideline.

- The NNT with blood pressure-lowering treatment for five years to avoid one CVD event increased gradually with lower CVD risk levels (ie 28 NNT at >15% five-year risk, 38 at >7.5% and 46 at >5%).
- For lipid-lowering therapy, a 1.0-mmol/L reduction in LDL cholesterol would prevent approximately six major vascular events per 1000 treated for those with <5% five-year risk, with 15 and 31 events prevented for those at 5% to <10% and 10–20% five-year risk, respectively.
- International evidence supports a 6–10% five-year risk treatment threshold for initiating pharmacotherapy for primary prevention of CVD events.

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