



Prescribing statins to reduce cardiovascular risk

Lowering lipid levels should be viewed as one aspect of reducing a patient's overall cardiovascular disease risk, and treatment decisions are based on this. Statins remain the medicine of choice for lowering lipids and should be prescribed at an appropriate potency and dose; atorvastatin is the first-line choice of statin.

KEY PRACTICE POINTS:

- Statins are the recommended first-line lipid-lowering medicine in New Zealand and international guidelines
- The decision to initiate a statin should be based on individual cardiovascular disease (CVD) risk, the likely benefit of treatment and the risk of adverse effects
- Five-year CVD risk > 15% or TC/HDL-C ratio ≥ 8: lipid-lowering treatment recommended with LDL-C target ≤ 1.8 mmol/L
- Five-year CVD risk 5 to 15%: consider benefits and risks of statin treatment. Aim for LDL-C target reduction of ≥ 40% if statin treatment is commenced.
- Five-year CVD risk < 5%: recommend lifestyle interventions only
- Atorvastatin is the first-line choice of statin treatment
- There is some evidence of benefit of adding ezetimibe for secondary prevention of CVD in selected groups of people
- Fibrates are no longer routinely used in New Zealand


Treat overall cardiovascular disease risk: a summary


There has recently been a shift in focus from treating hyperlipidaemia in isolation to an approach that aims to reduce a patient's overall cardiovascular disease (CVD) risk.¹ Risk calculators based on New Zealand PREDICT equations are now incorporated into decision support software for clinicians to begin discussions with patients. In addition, an interactive tool is available on the Heart Foundation website to aid patients' awareness and understanding of their CVD risk. New Zealand Primary Prevention Equations are designed for men and women aged 30–74 years; separate equations are used for people with or without diabetes.

Lifestyle modifications to reduce CVD risk are appropriate for everyone; this includes a healthy diet, regular exercise, weight management, limiting alcohol consumption and smoking cessation. Substituting saturated dietary fat with mono and polyunsaturated fats is most effective in reducing LDL-C whilst improving HDL-C from a dietary standpoint, based on current recommendations.¹

For patients with a five-year CVD risk $\geq 15\%$, lipid-lowering and blood pressure-lowering medicines are recommended, as their risk is equivalent to the risk for people with prior CVD. Aspirin should also be considered in some groups (see: <https://www.health.govt.nz/publication/cardiovascular-disease-risk-assessment-and-management-primary-care>).¹

There is a large body of evidence that supports the use of statins for both primary and secondary prevention of CVD.^{2–4} However, there is still debate in the medical literature on the place of statins for primary prevention in people aged over 75 years, mainly due to a lack of quality evidence.^{5–9}

 A CVD risk assessment tool is available via bestpractice Decision Support on your patient management system. If your practice does not have access to this, contact BPAC Clinical Solutions: <https://bpacsolutions.co.nz/contact/>; alternatively, an online CVD risk calculator, with the option of using the PREDICT data, is available from: <http://chd.bestsciencemedicine.com/calc2.html>

 The Heart Foundation interactive tool for patients is available here: www.heartfoundation.org.nz/your-heart/my-heart-check

Discussing cardiovascular risk with patients

Discussions about CVD risk reduction should begin with consideration of the patient's point of view, including their:¹¹

- Current knowledge about their CVD risk and what this means to them

- Thoughts and beliefs regarding their health in the future
- Readiness to make (and sustain) lifestyle changes
- Feelings about taking long-term medicines to reduce risk

Sometimes a clinician will have to guide a patient to a more realistic view of their risk and help them to understand the implications of having an event, such as a stroke. An individualised plan for future management can be developed, based on current evidence and practice; check that the patient agrees with the plan and understands what has been discussed. Actively engaging the patient in decisions about their health means they are more likely to take responsibility and assist with attaining and sustaining lifestyle changes and may improve adherence to medicines if required.

 For further information on communicating cardiovascular risk with patients, see: www.bpac.org.nz/BPJ/2014/September/cvrisk.aspx

When should a statin be considered?

Current New Zealand recommendations on lipid management are primarily determined by the patient's level of cardiovascular risk with some exceptions, e.g. those with a TC/HDL-C ratio ≥ 8 :¹

Pharmacological treatment is not recommended for people at low risk (< 5%)

Lipid-lowering medicines are generally not recommended for patients with a five-year CVD risk less than 5%; lifestyle interventions should be encouraged.

Discuss the use of medicines for people with a 5–15% five-year intermediate risk

The benefits and harms of lipid-lowering medicines should be clearly presented and discussed with all patients with a five-year CVD risk of 5–15% to allow an individualised decision about the initiation of pharmacological treatment. However, the benefit of lipid-lowering treatment is likely to outweigh harm for most people in this risk category.

Lipid-lowering medicines are recommended for patients with existing CVD or a $\geq 15\%$ five-year risk

All patients with known CVD or with a five-year risk $\geq 15\%$ should be prescribed lipid-lowering treatment along with advice on lifestyle interventions.


Lipid-lowering medicines are recommended for patients with TC/HDL-C ratio ≥ 8 regardless of CVD risk

If a patient has a TC/HDL-C ratio of ≥ 8 despite lifestyle interventions, lipid-lowering medicines are recommended, regardless of their calculated CVD risk.

Key practice points from the Cardiovascular Disease Risk Assessment and Management for Primary Care: 2018 consensus – a reminder


In 2018 a consensus statement on CVD was published by the Ministry of Health and the Heart Foundation. Important changes from the previous New Zealand Primary Care Handbook: 2013 update included:¹⁰

- New Zealand Primary Prevention Equations were developed from the New Zealand PREDICT study rather than using Framingham equations which did not consider unique aspects of the New Zealand population
- Māori, Pacific and South Asian population screening now starts earlier at age 30 and 40 years for men and women, respectively
- Screening from age 25 years is recommended for those with severe mental illness due to high-risk categorisation
- New classification of clinical high-risk groups (heart failure, eGFR < 30 mL/min/1.73 m² and diagnosis of asymptomatic carotid or coronary disease)
- > 15% CVD risk or TC/HDL-C ratio ≥ 8, classified as high-risk, lipid-lowering treatment recommended
- 5–15% CVD risk classified as intermediate risk, benefits/harms to be discussed about whether to initiate treatment
- < 5% CVD risk, no pharmacotherapy, lifestyle improvement recommended
- Introduction of 'targets' for lipid management. High-risk individuals are recommended to aim for a LDL-C target of 1.8 mmol/L or lower. Intermediate-risk individuals taking statin treatment, are recommended to aim for a LDL-C target reduction of 40% or greater.

 For further information, see: "2018 Cardiovascular Disease Risk Assessment and Management Series" available at bpac.org.nz/2018/cvd.aspx or for information on specific subgroups, see: CVD Consensus Statement Updates – Heart Foundation, available from: www.heartfoundation.org.nz/professionals/health-professionals/cvd-consensus-summary

People with very high triglycerides need special consideration

Patients with very high triglyceride levels (> 11 mmol/L) may benefit from lipid-lowering medicines, independent of their estimated CVD risk as they are at increased risk of pancreatitis. Advice on lifestyle interventions and appropriate management of co-morbidities, e.g. diabetes, is strongly recommended and may successfully reduce triglyceride levels. If triglyceride levels remain high in these patients despite lipid-lowering treatment, consider discussion with a cardiologist.

 For full details of the CVD risk assessment and management for primary care, see: "Cardiovascular Disease Risk Assessment and Management for Primary Care", available from: www.health.govt.nz/publication/cardiovascular-disease-risk-assessment-and-management-primary-care

Discuss risks and benefits before prescribing a statin

If a patient's CVD risk indicates that a statin may be appropriate, consider the following discussion points:^{1, 11}

- How successful lifestyle changes have been
- Patient preference
- Co-morbidities
- Other medicines currently being prescribed
- General frailty
- Life expectancy

There is satisfactory evidence that statin treatment results in beneficial effects for CVD risk reduction, such as:²¹

- Statins through each mmol/L reduction in LDL-C, reduce relative CVD risk by 25% over five years
- Statins can reduce LDL cholesterol by > 50 % in people who have a pre-treatment LDL-C level of ≥ 4 mmol/L
- Every 1 mmol/L decrease in LDL-C produces a reduction in major vascular events of approximately 25% and reduction in coronary mortality of at least 20% in patients at differing levels of CVD risk
- If 10,000 patients took an effective dose of a statin for primary prevention for five years which resulted in a LDL-C reduction of 2 mmol/L, major vascular events would be prevented in approximately 500 (5%)
- If 10,000 patients took an effective dose of a statin for secondary prevention for five years which resulted in a LDL-C reduction of 2 mmol/L, major vascular events would be prevented in approximately 1,000 (10%)

The risks of statin treatment include potential adverse effects (see: "Managing adverse effects of statins"), medicine interactions, polypharmacy and "pill burden".


The balance of benefit and risk will differ for each patient. For example, people at the highest CVD risk will benefit the most from taking a statin, with larger reductions in absolute risk, and any potential harms from statin treatment likely to be perceived as a lower risk. In contrast, people at a lower level of CVD risk receive less benefit from taking a statin but have the same risk of harms, therefore may feel that the risk of taking a statin outweighs the benefit.¹ An informed discussion about potential adverse effects of statins and how these can be managed (see below), and reassurance about any “myths” about statins, may help in this decision process.

Age alone is not a reason to decline a statin

There is increasing evidence that statins benefit older people for both primary and secondary prevention, therefore age alone is not a reason to decide against or to stop a statin (see: “The benefits of using statins among older people”).⁵ The decision to initiate a statin in an older patient for primary prevention should take into account factors such as frailty, comorbidities, life-expectancy, polypharmacy, the potential for adverse effects and interactions as well as the patient’s view on taking preventative medicines.^{5, 11, 22, 23}

Providing a definite age cut-off at which a statin should not be prescribed is difficult due to the physical heterogeneity of older people, and also because risks and benefits do not “change overnight” when a person reaches a certain age, e.g. 75 years.^{11, 23} Current New Zealand Primary Prevention Equations have not been validated for people aged 75 years and older and as such are estimates only; equation estimates can still be a useful indicator or starting point in CVD management.¹

Whether a statin should be de-prescribed in an older person also depends on individual factors. A study recently found from 18 international guidelines that discontinuation among older adults was primarily due to health status and statin intolerance.²⁴ The decision may be straightforward in a patient with limited life expectancy or a poor functional status, but is likely to be more complicated in those who are well and independent, or those at very high risk of recurrent cardiovascular events where there is evidence of continued benefit.^{25, 26}

 For further information, see: “A guide to deprescribing - general information” and “A guide to deprescribing – statins”, available from: <http://www.cpsedu.com.au/resources>

International guidelines on lipid-lowering

There have been a number of new or updated international guidelines on dyslipidaemia and CVD risk reduction over the last few years.^{3, 11–17} Changes were made due to evidence indicating that better outcomes could be achieved, especially in primary prevention, by the management of absolute CVD risk rather than management of single risk factors.^{3, 18, 19} There has been some criticism of this risk-based approach because it widens the number of people who would “qualify” for treatment with a statin, yet other authors feel that statins are underused.⁵

The majority of international guidelines now follow a similar approach, including that:^{1, 3, 9, 12–16, 18, 19}

- Lipid management should be viewed as one aspect of reducing CVD risk rather than in isolation
- There remains an emphasis on intensifying lifestyle modifications to reduce CVD risk for all patients, particularly smoking cessation, weight optimisation, exercise and healthy diet
- There is shared decision making and comprehensive discussions with patients
- There is a focus on prescribing a statin of appropriate intensity and titrating to the maximum tolerated dose for each patient to reflect risk level

- LDL-C is used as a tool for monitoring effectiveness and change
- Sub-optimal LDL-C despite maximum tolerated dose of statin and lifestyle, allows for non-statin treatments to be considered in high-risk adults
- Ezetimibe may be considered for secondary prevention in certain circumstances such as people with statin intolerance and/or familial hypercholesterolaemia
- Fibrates are not generally recommended

Variations between the major guidelines, include:^{9, 16, 19, 20}

- The way in which CVD risk is determined (which tool is used) and how it is expressed, e.g. five versus ten years
- Definition of high-risk populations and their subsequent management
- Risk modifiers such as blood pressure or diabetes
- The CVD risk threshold at which treatment with a statin is recommended
- Whether or not a specific reduction in lipid levels is recommended
- The use of fasting or non-fasting lipid levels

Choice and dose of statin

Atorvastatin is the first-line choice of statin for most patients. If it is not tolerated, consider lowering the dose or changing to another statin (see: "An approach to managing statin-associated symptoms").

The recommended dose is:³⁰

- Five-year CVD risk 5–15%: 10–20 mg atorvastatin (max 80 mg daily)
- Five-year CVD risk > 15% (including those with known CVD): 10–40 mg atorvastatin (max 80 mg daily)

It is recommended to monitor non-fasting lipids every six-to-twelve months until the desired target is reached. Once achieved, annual monitoring is appropriate.¹

Statin intensity

Statin intensity can be classified by the percentage that they can reduce LDL-C levels, referred to as the intensity, which may help in determining equivalent doses if switching between statins due to intolerance (Table 1).¹⁴ Rosuvastatin (not funded) is the most potent statin available in New Zealand, followed by atorvastatin, simvastatin then pravastatin.³⁰

N.B. The maximum recommended dose for simvastatin is 80 mg, however, doses of simvastatin above 40 mg should be used with caution due to the increased risk of myopathy and in most cases patients should be prescribed atorvastatin if higher doses are required.^{4,30}

Timing of administration

Cholesterol biosynthesis peaks overnight, therefore statins with a short half-life, such as simvastatin and pravastatin, should be taken in the evening.³¹ Statins with a longer half-life, such as atorvastatin and rosuvastatin, can be taken in the morning or at night with equivalent efficacy.³¹ Being able to take a statin at their preferred time of the day is likely to improve a patient's adherence to treatment and reduce discontinuation.

Table 1: Statin potency table: approximate equivalence.¹

Treatment Intensity	Pravastatin	Rosuvastatin	Atorvastatin	Simvastatin	%↓LDL-C
Low	20 mg			10 mg	30%
Medium	40 mg		10 mg	20 mg	38%
Medium	80 mg	5 mg	20 mg	40 mg	41%
High		10 mg	40 mg	80 mg [†]	47%
High		20 mg	80 mg		55%
Very High		40 mg			63%

[†] Simvastatin 80 mg, daily, may be associated with an increased risk of muscle-related adverse effects⁵

The benefits of using statins among older people

Data from JUPITER and HOPE-3 trials began discussions on statin use among older people; use of statins for primary prevention in those aged 70 years and older was supported based on evidence of benefit for non-fatal stroke, myocardial infarction and cardiovascular death, but there was a non-significant reduction in all-cause mortality.²² However, it should be noted that the proportion of older participants in these trials were small, and that both had initial support from the pharmaceutical industry.

Since then further benefits in older people have been reported such as:

- In patients aged 75 years and older, lipid-lowering treatments were found to be as effective in reducing CVD events as in those aged less than 75 years²⁷
- Statin treatment for primary prevention of CVD in people aged 50 to 75 years with a life expectancy of at least 2.5 years was found to reduce CVD events²⁸
- A systematic review and meta-analysis found no additional prevalence of muscle-related symptoms, adverse effects or treatment cessations attributable to statin treatment among older adults without CVD²⁹

A systematic review comparing international guidelines supported the use of statins for primary prevention in this population.⁷

Managing adverse effects of statins

Most patients tolerate statin treatment well. Serious adverse effects are rare and most emerge in the first three months of use.³² A recent systematic review of evidence from randomised controlled trials reported that the only adverse effects that have been reliably proven to be caused by statins were myopathy (muscle pain or weakness with a rise in creatinine kinase), an increased risk of the development of type 2 diabetes (see: “Statin use and diabetes”) and an increase in haemorrhagic stroke (although this is outweighed by the decreased risk of ischaemic stroke).²¹ Depending on the concentration of the statin (influenced by co-morbidities), rhabdomyolysis can occur; although rare, this can lead to significant kidney problems.³³

Adverse effects with long-term statin treatment:¹

- For every 10,000 people treated for five years, five cases of myopathy would result
- For every 10,000 people treated per year, additional muscle related problems would occur in every 10–20 cases. Of those, only one case would be expected to have significantly elevated creatine kinase levels.
- For every 10,000 people treated for five years, 50–100 new cases of diabetes would result

“Statin-associated symptoms”

Observational studies report a wider range of adverse effects and appear to be more in step with “real world” experiences of people taking statins. The lack of consensus on whether

Statin use and type 2 diabetes

Statins as a class can increase the risk of developing hyperglycaemia and insulin resistance which eventually can lead to the development of type 2 diabetes, possibly due to the raised activity of LDL receptors allowing more cholesterol to enter pancreatic cells.²¹ People most at risk of developing diabetes while taking a statin are those who already have risk factors such as impaired fasting glucose, elevated HbA_{1c}, increased BMI or advanced age.²¹ Meta-analyses from randomised controlled trials report that the risk of developing diabetes ranges from approximately 4–12%, but if observational studies are included, much higher figures are quoted, e.g. 44% increase in risk.^{38–40} More recently, a study reported a 38% increased risk of type 2 diabetes associated with statin use.⁴¹ Preventative strategies such as weight management and dietary control can be used to minimise type 2 diabetes risk prior to statin treatment.

Pravastatin (lowest potency statin) is associated with the lowest risk of developing new onset diabetes mellitus, atorvastatin has moderate risk and rosuvastatin (highest potency) has the highest risk.³³ As well as the dose-dependent risk, there is also a time-dependent risk of developing type 2 diabetes.⁴² The evidence also suggests that statin treatment should not be withheld in people at risk of diabetes or if diabetes develops, as the expected decrease in major vascular events when taking a statin is greater than the increased CVD risk with statin-induced diabetes.²¹


The possibility of this adverse effect should be discussed with patients prior to prescribing a statin, especially those with pre-existing risk factors for diabetes.



statins are actually causative has led to the use of the term statin-associated symptoms.^{16, 18, 34, 35} It is estimated that statin-associated muscle symptoms (e.g. muscle aches and weakness, not necessarily accompanied by a rise in creatinine kinase) affect 10–15% of people taking statins.¹⁸ Other reported statin-associated symptoms include effects on cognitive function primarily memory loss and confusion, but also effects on sleep and mood, and changes in hepatic* and renal function. While there is a lack of evidence that these symptoms are actually caused by statins, they are clinically important as they contribute to the way people feel about taking statins and can result in poor adherence and cessation.

The nocebo effect (the opposite of the placebo effect) can also influence a patient's decision to start, or continue, a statin.³⁵ This is when patients expect to experience adverse effects based on information from the media, other people or even from their clinician.^{35, 36} Whether statin-associated muscle symptoms are caused by a pharmacological effect or nocebo effect remains controversial.³²

* Statins can cause usually asymptomatic elevations in liver function tests particularly early in treatment, however, hepatotoxicity is very rare.²¹

 For further information, see: "The nocebo effect: what is it, why is it important and how can it be reduced?", available from: <https://bpac.org.nz/2019/nocebo.aspx>

An approach to managing statin-associated symptoms

When a patient taking a statin reports symptoms, a suggested approach is to:^{1, 34, 35}

- Review the patient's other medicines to check for interactions and evaluate risk factors


- Check creatine kinase (CK) levels only in those with symptomatic muscle pain, tenderness or weakness. Request liver function tests only if hepatotoxicity is suspected.
- Reduce dose or discontinue the statin for muscle pain without a rise in CK. Reconsider statin once symptoms have subsided.
- Monitor symptoms and CK weekly along with dose reduction or discontinuation with a CK rise three to ten times above normal
- Discontinue statin immediately with a rise in CK of more than ten times above normal with symptoms


Current expert advice and limited trial evidence supports the view that any statin is better than no statin, and patients should be encouraged to persist with treatment at whatever dose and frequency they can tolerate.³⁵ If symptoms recur when the statin is recommenced consider options such as dose reduction, alternate day dosing, or switching to another lipid-lowering treatment.³⁵ Alternative day dosing has been found to be better tolerated than every day dosing for myalgia, however the CVD benefit has not yet been demonstrated.³⁵ Some patients may tolerate low dose pravastatin (the least potent statin), others may prefer to take atorvastatin intermittently, e.g. twice a week. If the symptoms recur gradually but are initially tolerable some patients may find "pulse dosing" a useful strategy. This is where the statin is taken for a specified time followed by a break and then repeating on a continuing cycle (e.g. statin for three months, stop for one month and then restart pattern).³⁶

It is important to identify those who are truly statin intolerant to avoid unnecessary discontinuation of the beneficial treatment.

Be aware of medicine interactions with statins

Statins can have serious interactions with some other medicines; in particular, be aware of the interaction between simvastatin and potent CYP3A4 inhibitors such as erythromycin, clarithromycin, azole antifungals (e.g. itraconazole, ketoconazole) and ciclosporin, which can result in rhabdomyolysis.

 For further information, see: Simvastatin and atorvastatin: beware of potential CYP3A4 interactions when prescribing other medicines, available from: <http://www.bpac.org.nz/BPJ/2014/April/news.aspx>

 Check for medicine interactions prior to prescribing a statin to reduce the risk of adverse effects: www.nzf.org.nz



Should other lipid-lowering medicines be considered?

Some international guidelines recommend the use of non-statin medicines for the primary or secondary prevention of CVD, such as ezetimibe and alirocumab, both of which are available in New Zealand (only ezetimibe is funded).^{3, 14–16, 18} A non-statin medicine, e.g. ezetimibe may be considered in high-risk patients such as those who have had a CVD event in addition to a statin, if lifestyle measures and optimal statin treatment (maximally tolerated dose and potency of statin) has not produced a sufficient response, or as monotherapy if a statin is intolerable or contraindicated.¹⁴

Ezetimibe

Ezetimibe inhibits the absorption of dietary cholesterol in the small intestine resulting in LDL-C reductions.³⁰ Most guidelines now recommend that ezetimibe be considered in patients with familial hypercholesterolaemia as a monotherapy if statins are intolerable or contraindicated, or added to a statin if the patient's lipid levels are not adequately controlled despite optimal statin treatment.^{3, 15–18}

Evidence from IMPROVE-IT show ezetimibe when added to simvastatin reduces cardiovascular events in patients with previous acute coronary syndrome. When stratified by diabetes, the benefit of the combination treatment was enhanced in patients with diabetes and those high-risk patients without diabetes.⁴³ A meta-analysis found ezetimibe reduces the risk of myocardial infarction and stroke by 13.5% and 16%, respectively, and its use has since been recommended in combination with a PCSK9 inhibitor, should the maximum tolerated dose of a statin not achieve LDL-C goals.^{18, 44} A 2020 study found ezetimibe plus a statin to be more effective in reducing LDL-C than doubling the dose of the statin; in accordance with those results, a meta-analysis and systematic review found treatment with ezetimibe and a statin produced a modest LDL-C reduction compared to a statin alone. Furthermore, atorvastatin and ezetimibe together have been found to have the best therapeutic effect.⁴⁵

Other non-statin medicines

Alirocumab: This is a PCSK9 inhibitor which enhances LDL-C uptake by increasing the number of LDL-receptors.³⁰ Although an approved medicine in New Zealand, it is not subsidised on the community pharmaceutical schedule and given it is a monoclonal antibody-based treatment, is expensive. Since 2019, alirocumab has been included in the ESC/EAS guidelines for dyslipidaemia due to efficacy advancements in this class.¹⁸ PCSK9 inhibitors in addition to statins or ezetimibe, are effective for people intolerant of other treatments or for those who are unable to meet their LDL-C goals despite optimal use of other medicines.¹⁸ Recent results demonstrate alirocumab

taken every other week significantly reduces ischaemic events, with the majority of patients on a high potency and high dose statin.⁴⁶ However, there is minimal evidence on safety or use in place of a statin, so it is first recommended to try other lipid-lowering treatments.⁴⁶

Fibrates

Fibrates primarily lower triglycerides and increase HDL-C. They are no longer routinely recommended for reducing CVD risk for either primary or secondary prevention due to a lack of strong evidence in the reduction of cardiovascular morbidity, mortality and LDL-C.^{9, 36} Gemfibrozil has now been discontinued leaving bezafibrate as the only fully funded fibrate available in New Zealand.

Bezafibrate, although not routinely recommended and advised against in some guidelines, may be used in conjunction with statin treatment in patients with a high CVD risk where lifestyle changes and a maximally tolerated dose of statin have not produced reasonable reductions in lipid levels.¹¹ This combination increases the risk of myopathy; to minimise this risk it is suggested that the fibrate is taken in the morning and the statin in the evening.

N.B. Nicotinic acid is no longer recommended as a lipid-lowering treatment, either as monotherapy or in combination with a statin.¹¹

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