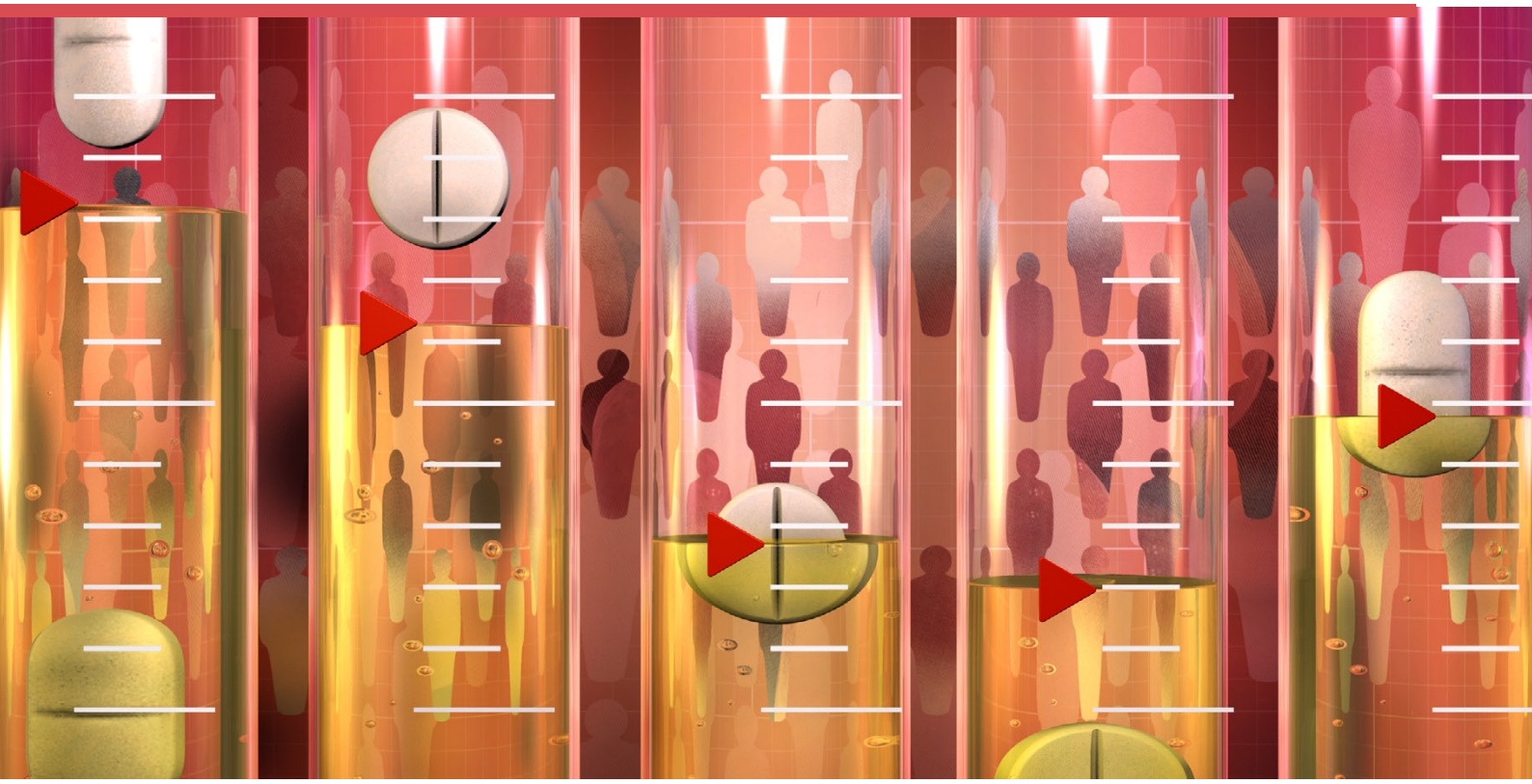


Prescribing statins to reduce cardiovascular risk

Lowering lipid levels should be viewed as one aspect of reducing a patient's overall cardiovascular disease risk. The aim of treatment is to achieve a reduction in lipid levels rather than meet a specific target. Statins remain the medicine of choice for lowering lipids, and should be prescribed at an appropriate potency and dose; atorvastatin is usually the first-line choice of statin.

KEY MESSAGES:

- 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
- Atorvastatin is the recommended statin for patients with known CVD or those with a five-year CVD risk > 20%. Patients at highest CVD risk tend to benefit the most from higher dose or higher potency statins.
- Atorvastatin is now often preferred to simvastatin for primary prevention for patients with a five-year CVD risk 10 – 20%
- There is some limited evidence of a small benefit of adding ezetimibe for secondary prevention, but little evidence for the use of other lipid-lowering medicines such as fibrates

Treat overall cardiovascular disease risk

One of the key changes to managing lipids in recent years is the shift in focus from treating hyperlipidaemia in isolation to an approach that aims to reduce a patient's overall cardiovascular disease (CVD) risk.[1, 2]

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. Depending on individual clinical need, lipid-lowering, blood pressure-lowering, glucose-lowering and antiplatelet medicines may also be required to reduce risk. Determining the degree of CVD risk using a risk calculator or chart provides a starting point for a discussion about recommended treatment and the patient's preference for intervention.

There is a large body of evidence that supports the use of statins for both primary and secondary prevention of CVD.[3, 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.[5–7]

At present, guidelines on CVD risk assessment and management for clinicians in New Zealand are based on the New Zealand Primary Care Handbook 2013 update.[1] However, the Ministry of Health, in conjunction with the Heart Foundation, is currently working on a new consensus statement for CVD risk assessment, based on risk equations that have been developed specifically for New Zealand populations.*[8]

* Current New Zealand Cardiovascular Risk Charts are adapted from the Framingham Cardiovascular risk charts and may under- or overestimate risk in some individuals.[1] It is expected that the planned 2017 consensus should address some of these concerns.

Discussing cardiovascular risk with patients

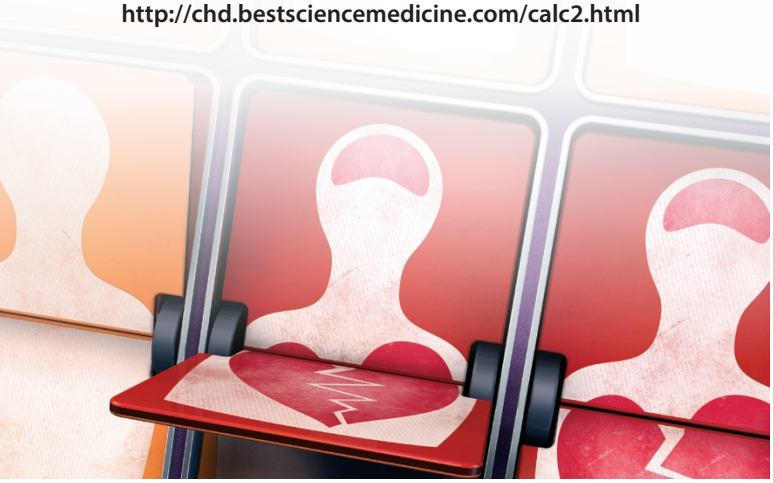
When considering cardiovascular risk reduction it is important to take into account the patient's point of view, including their:[9]

- 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; checking that the patient agrees with the plan and understands what has been discussed. Involving the patient in decisions about their health is likely to assist with attaining and sustaining lifestyle changes and to 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**

An example of an interactive web based cardiovascular risk/benefit calculator can be found at: **http://chd.bestsciencemedicine.com/calc2.html**



When should a statin be considered?

Current New Zealand recommendations on lipid management are primarily determined by the patient's level of cardiovascular risk:[1]

N.B. These recommendations will be updated as necessary when the Ministry of Health consensus statement is released.

CVD risk <10%

Patients should be encouraged to make healthy lifestyle decisions; the majority can be managed without the need for lipid-lowering medicines.

CVD risk 10 – 20%

Patients should be strongly encouraged to make healthy lifestyle changes. A discussion about the benefits and risks of medicines (both lipid and blood pressure lowering) to lower cardiovascular risk is recommended so that a shared decision on management can be reached. If lifestyle modifications have not reduced cardiovascular risk, e.g. after 6 – 12 months, recalculate cardiovascular risk and consider prescribing a statin following a discussion of the benefits and risks of treatment.

CVD risk >20% or known CVD

Lipid-lowering medicines, in addition to lifestyle changes and other medicines to reduce cardiovascular risk, depending on the patient's individual clinical circumstances, are strongly recommended.

People with an existing cardiovascular condition or who have had a previous CVD event are regarded as "very high risk" and can be automatically allocated to this category without having to calculate CVD risk. Also included in the very high risk group are people with genetic lipid disorders, e.g. familial hypercholesterolaemia, and those with diabetes who have nephropathy or other renal disease resulting in renal impairment (eGFR ≤ 60 ml/min/1.73m^2).

For full details of the CVD risk assessment update from 2013, see: **www.health.govt.nz/system/files/documents/publications/cardiovascular-disease-risk-assessment-updated-2013-dec13.pdf**

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:[9]

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

There is good evidence that statin treatment results in beneficial CVD risk reduction, such as:[3]

- Statins reduce cardiovascular risk in each year of continued treatment
- Statins can reduce LDL cholesterol by >50% in people who have a pre-treatment LDL cholesterol level of ≥4 mmol/L
- Every 1 mmol/L decrease in LDL cholesterol 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 cardiovascular risk
- If 10,000 patients took an effective dose of a statin for *primary* prevention for five years, resulting in a decrease in LDL cholesterol 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, resulting in a decrease in LDL cholesterol of 2 mmol/L, major vascular events would be prevented in approximately 1000 (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 cardiovascular 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.[16] An informed discussion about potential adverse effects of statins and how these can be managed (see "Managing adverse effects of statins"), 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 provide benefits for older people for both primary and secondary prevention, therefore age alone is not a reason to decide against a statin, or to stop a statin.[6] A recent subgroup analysis of data from two trials (JUPITER and HOPE-3) has confirmed that there is some evidence of benefit of a statin for primary prevention in people aged ≥70 years for non-fatal stroke or myocardial infarction and cardiovascular death, but a non-significant reduction in all-cause mortality.[17] However, it should be noted that the numbers of older people in these trials were small and that both trials had initial support from the pharmaceutical industry.[17]

Providing a definite age cut-off at which a statin should not be prescribed is difficult due to the varying health of older people and the fact that CVD risk scores are estimates only,

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.[4, 9–11] Changes were made because of the increase in evidence showing that better outcomes could be achieved, especially in primary prevention, by the management of absolute CVD risk rather than management of single risk factors.[2,12,13] 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.[6]

The majority of international guidelines now follow a similar approach, including that:

- Lipid management should be viewed as one aspect of reducing cardiovascular risk rather than in isolation
- There is a focus on prescribing a statin of an appropriate intensity and titrating to the maximum tolerated dose for each patient
- There remains an emphasis on intensifying lifestyle modifications to reduce CVD risk for all patients
- At their time of publication, the evidence for non-statin medicines, such as fibrates or ezetimibe, was lacking and these medicines were not recommended, however, a recent trial has shown some benefit in adding ezetimibe to a statin for secondary prevention[14]

Variations between the major guidelines, include:[12, 15]

- The way in which CVD risk is determined (which tool is used) and how it is expressed, e.g. five versus ten years
- 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

and also because risks and benefits do not "change overnight" when a person reaches a certain age, e.g. 75 years.[7, 9]

The decision to initiate a statin in an older patient for primary prevention should therefore be individualised, taking into account factors such as frailty, co-morbidities, life-expectancy, polypharmacy, the potential for adverse effects and interactions and the patient's view on taking preventative medicines.[6, 7, 9, 17]

Whether a statin should be de-prescribed in an older person also depends on individual factors. The decision may be straightforward in a patient with a limited life expectancy or 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.[18, 19]

For further information, see: "A guide to deprescribing – general information" and "A guide to deprescribing – statins", available from: **www.cpsedu.com.au/resources**

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").

Currently, best advice is:[1, 9, 20]

- For primary prevention for people with a five-year CVD risk of 10–20%*: 20 mg atorvastatin
- For primary prevention for people with a five-year CVD risk >20%: 20–40 mg atorvastatin
- For secondary prevention for people with known CVD: 20–80 mg atorvastatin (aim for maximum tolerated dose)

* A statin in this risk group should be considered after a discussion with the patient about lifestyle measures and the benefits and risks of medicines

Statin intensity

Statins can be classified by the percentage they can reduce LDL-cholesterol levels, referred to as the intensity, which may help in determining equivalent doses if switching between statins due to intolerance (Table 1).[4] Rosuvastatin (not subsidised) is the most potent statin available in New Zealand, followed by atorvastatin, simvastatin then pravastatin.[20]

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, 20]

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.[22] Statins with a longer half-life, such as atorvastatin and rosuvastatin, can be taken in the morning or at night with equivalent efficacy.[22] 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.

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.[23] 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).[3]

Observational studies report a wider range of adverse effects and appear to be more in step with "real world"

Table 1: Daily doses of differing intensities of statin treatment.[4, 9]

High intensity On average, lowers LDL cholesterol by ≥ 50%	**Moderate intensity** On average, lowers LDL cholesterol by 30–50%	**Low intensity** On average, lowers LDL cholesterol by <30%
Rosuvastatin 20-40 mg	Rosuvastatin 5–10 mg	Simvastatin: 10 mg
Atorvastatin: 40–80 mg	Atorvastatin: 10–20 mg	Pravastatin: 10–40 mg
Simvastatin: 80 mg†	Simvastatin: 20–40 mg	

† Simvastatin 80 mg, daily, may be associated with an increased risk of muscle-related adverse effects[5, 21]

experiences of people taking statins. The lack of consensus on whether statins are actually causative has led to the use of the term statin-associated symptoms.[24, 25] It is estimated that statin-associated muscle symptoms, e.g. muscle aches and weakness, not necessarily accompanied by a rise in creatinine kinase, affect 7% to 29% of people taking statins.[24] 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.[25, 26] This is when patients expect to experience adverse effects based on information from the media, other people or even from their clinician.[25, 26] A recent study found that patients were more likely to report muscle-related symptoms when the patient and the clinician were aware that a statin was being taken than when use of a statin was blinded.[27]

* Statins can cause usually asymptomatic elevations in liver function tests particularly early in treatment, however, hepatotoxicity is very rare[3]

An approach to managing statin-associated symptoms

When a patient taking a statin reports symptoms, a suggested approach is to:[24, 25, 31]

- Assess for "true" intolerance, e.g. check for a rise in creatinine kinase if there is muscle pain or check liver function tests if hepatotoxicity is suspected
- Review the patients other medicines to check for interactions
- Reassure the patient about the safety and effectiveness of statin treatment
- Stop the statin
- Check for resolution of symptoms (suggested timeframe two to four weeks)
- If symptoms have resolved try reinstating the statin

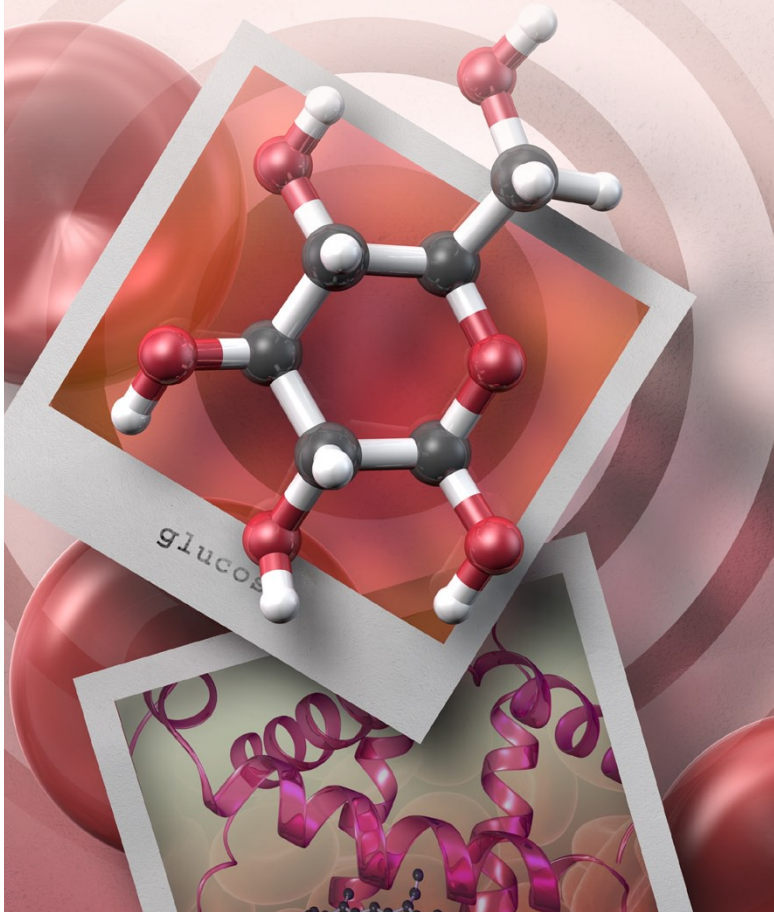
Current expert advice and limited trial evidence supports the view that any statin is better than no statin, and patients should be encouraged to persist with treatment at whatever dose and frequency they can tolerate.[32] If symptoms recur when the statin is recommenced consider options such as dose reduction, alternate day dosing, or switching to another statin.[32] Some patients may tolerate low dose pravastatin (the least potent statin), others may prefer to take atorvastatin intermittently, e.g. twice a week, as this will still provide some benefit. If the symptoms recur gradually but are initially tolerable some patients may find "pulse dosing" a useful strategy. This is where

Statin use and type 2 diabetes

Statins as a class can increase the risk of developing type 2 diabetes, possibly due to the raised activity of LDL receptors allowing more cholesterol to enter pancreatic cells.[3] 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} or an increased BMI.[3] Meta-analyses of data from previous 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.[28–30]

However, 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 increase in CVD risk with statin-induced diabetes.[3]

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.



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.[26]

For further information on assessing myalgia, see: "Investigating myalgia in patients taking statins". **www.bpac.org.nz/BT/2014/August/myalgia.aspx**

Be aware of medicine interactions

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, ketaconazole) 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: **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?

Most international guidelines do not recommend the use of non-statin medicines for the primary or secondary prevention of cardiovascular disease.[1, 4, 9] At the time the major guidelines were being developed it was felt that there was a lack of evidence to support a beneficial effect on patients' cardiovascular outcomes.[9, 33]

A non-statin medicine may be considered in high risk patients, e.g. 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 entirely intolerable or contraindicated.[4]

Fibrates

Fibrates primarily lower triglycerides and increase HDL-cholesterol. However, they have not been reliably shown, when prescribed as either monotherapy or combination therapy, to reduce cardiovascular morbidity or mortality and produce only minor decreases in LDL-cholesterol.[9, 34] They are therefore no longer routinely recommended for reducing CVD risk for primary or secondary prevention.

On an individual basis, some experts may recommend that bezafibrate* is trialled in conjunction with statin treatment in patients with a high level of cardiovascular risk where lifestyle changes and a maximally tolerated dose of statin have not produced reasonable reductions in lipid levels. However, this approach is not consistently recommended; NICE guidelines (UK) do not recommend routine treatment with a fibrate, and advise against using a fibrate in combination with statin treatment.[9] The combination of a statin and a fibrate increases the risk of myopathy.[11] If prescribed it is suggested that the risk may be minimised by taking the fibrate in the morning and the statin in the evening.[11]

Fibrates should not be the first-line medicine for the treatment of people with familial hypercholesterolaemia; a high intensity statin should be prescribed.[35] A statin is also the first choice of treatment in patients with high triglycerides and/or low HDL.[11] An exception to this, however, would be in a patient with marked hypertriglyceridaemia to reduce the risk of pancreatitis that is associated with very high levels of triglycerides.[36]

* Use of gemfibrozil with a statin is contraindicated due to the high risk of rhabdomyolysis[11, 20]

Ezetimibe

Ezetimibe inhibits the absorption of dietary cholesterol in the small intestine resulting in reductions in LDL-cholesterol.[37] Most current guidelines do not routinely recommend ezetimibe for lipid-lowering for primary or secondary prevention because at the time of their publication there was a lack of available evidence showing that it could improve clinical outcomes. There has been some recent evidence largely based on the IMPROVE-IT trial reporting that ezetimibe may result in a small reduction in rates of myocardial infarction and stroke when added to simvastatin treatment in patients with a previous acute coronary syndrome.[14, 38] However, when compared to monotherapy with a high intensity statin, it is thought that ezetimibe is unlikely to result in lower all-cause mortality or any differences in deaths due to cardiovascular disease.[38]

NICE guidelines (UK) recommend that ezetimibe be considered in patients with familial hypercholesterolaemia as 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.[35]

N.B. Nicotinic acid is no longer recommended as a lipid-lowering treatment, either as monotherapy or in combination with a statin.[9]

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This article is available online at: **www.bpac.org.nz/2017/statins.aspx**

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