An update on STATINS

Key concepts

- The decision to initiate a statin should be based upon an individual's risk of CVD, the likely benefit of treatment and potential adverse effects
- Targets are generally not necessary in primary prevention, where any reduction in lipid levels results in a reduction in CVD risk
- In secondary prevention, lipid levels should be viewed as a guide to management rather than targets to achieve
- Simvastatin 20 – 40 mg is a reasonable starting dose for many people, although individual patient factors influence the choice of statin and intensity of treatment - people at highest CVD risk tend to benefit the most from higher doses or higher potency statins
- After initiating statin treatment, creatine kinase should be checked when there are unexplained muscular symptoms, however no other monitoring is routinely required
- Lipid-lowering agents other than statins may be considered for those who require additional lipid-lowering, when statins alone are not adequately controlling dyslipidaemia, or in cases of statin intolerance

Current recommendations for statin use in New Zealand and international guidelines

New evidence is continually emerging on the use of statins, particularly in relation to their role in primary prevention of cardiovascular disease (CVD), specific dose regimens and treatment targets. This information, both in the lay press and medical literature, prompts reflection on current cardiovascular guidelines and consideration of whether there is anything new that represents a significant shift from current practice for primary care clinicians.

New Zealand Guidelines Group cardiovascular guidelines

The New Zealand guidelines for the use of lipid lowering agents as part of CVD risk management recommend the following:[1]

- Treatment should be based on an individual's five-year CVD risk
- Statin treatment should be initiated for people with known CVD or at high CVD risk
- Starting doses:

  For people with a five-year CVD risk of 15 – 20%, simvastatin 20 mg (titrate if needed)

  For people with known CVD or a CVD risk > 20%, simvastatin 40 mg
- Lowering of LDL-cholesterol is the primary indicator of optimum lipid management. Targets include total cholesterol < 4.0 mmol/L and LDL-cholesterol < 2.0 mmol/L.
- If LDL-cholesterol targets are not met, options include increasing simvastatin to 80 mg, substituting simvastatin for atorvastatin or combining simvastatin with nicotinic acid or ezetimibe.

For full details of the New Zealand Guidelines Group (NZGG) Cardiovascular Guideline, visit: **www.nzgg.org.nz**

United Kingdom NICE cardiovascular guidelines

The National Institute for Health and Clinical Excellence (NICE) guidance on lipid modification is presented in terms of primary and secondary prevention and recommendations are based on the ten-year risk of CVD. The following recommendations are given:[2]

- Statin treatment for primary prevention is recommended when the CVD ten-year risk reaches 20%
- For both primary and secondary prevention the recommended initial dose for simvastatin is 40 mg

Comparison between Guidelines

A key difference between NZGG and NICE Guidelines is in the use of cholesterol targets. The NICE guidance recognises that more than half the patients will be unable to achieve traditional targets such as LDL-cholesterol < 2 mmol/L. Targets are now regarded as levels that can guide increases in dose or intensity of treatment in patients at greatest risk i.e. for secondary prevention. Measurement of lipid levels is considered unnecessary in lower risk patients i.e. for primary prevention.

It may appear that patients can be started on statin treatment at lower CVD risk in the United Kingdom. However recent risk/outcome data (which are still accumulating) indicate that CVD risk in New Zealand may be overestimated by up to 5%.[3] This means that a patient calculated to have a 15% five-year CVD risk, is more likely to have a risk closer to 10%. If it is assumed that a 10% five-year CVD risk is equivalent to a 20% ten-year CVD risk, then it can be concluded that New Zealand recommendations are similar to United Kingdom recommendations.

When should statin treatment be initiated?

New Zealand guidelines recommend the use of a statin in the primary prevention of cardiovascular disease when the five-year CVD risk reaches 15–20%.[1]

Increasingly people are being considered for statin treatment for primary prevention of CVD. The potential benefit of statins for primary prevention was highlighted by the landmark West of Scotland Coronary Prevention Study (WOSCOPS) which found a 31% reduction in coronary events with pravastatin compared with placebo.[4] A recent meta-analysis of primary prevention trials concluded that statins improve survival and reduce the risk of major cardiovascular and cerebrovascular events in people without established cardiovascular disease.[5]

Included in this analysis was the JUPITER trial (see sidebar) which has caused much subsequent debate. This trial demonstrated that rosuvastatin reduced the rate of adverse cardiovascular events in people with increased CVD risk.[6] However the patients included in the study had normal LDL-cholesterol levels to begin with and the CVD risk was defined by increased levels of high sensitivity CRP, a controversial surrogate marker of CVD risk.

Based on current evidence it may be appropriate to view lipid lowering treatment with statins as an intervention that can reduce relative cardiovascular risk (by approximately 20% to 30%) regardless of baseline LDL-cholesterol. The absolute benefit of treatment is proportional to the underlying absolute risk.[7]

Determining when the benefits of treatment outweigh its disadvantages (cost and adverse effects) requires estimation of the patient's underlying cardiovascular risk. Once a patient's cardiovascular risk is assessed, together with their doctor, they can decide whether a 20% to 30% relative risk reduction translates into an absolute risk reduction, large enough to be worth the cost and potential adverse effects of daily statin therapy.[7]

For example:

A 45-year-old non-smoking, non-diabetic, normotensive woman has a total cholesterol of 6.2 mmol/L and a HDL-cholesterol of 1.1 mmol/L. Her five-year risk of a cardiovascular event is assessed to be less than 2.5%. This could potentially be reduced by 0.5 to 0.75% if she were to be treated with a statin.

The GP and patient decide against the use of a statin as the absolute benefit of treatment is minimal (less than 1%) and does not warrant exposing the patient to the potential adverse effects of long-term statin therapy.

Acknowledging the limitations of CVD risk assessment

The calculation of CVD risk is limited by factors specific to individual patients. For example, using the charts in the New Zealand Cardiovascular Handbook may underestimate CVD risk for those who have:

- Total cholesterol ≥ 8 mmol/L
- Total cholesterol : HDL-cholesterol ratio ≥ 8
- Blood pressure consistently ≥ 170/100
- Diabetes with microalbuminuria for 10 years or with HbA_{1c} consistently ≥ 8%
- Family history of premature coronary heart disease or ischaemic stroke in a first-degree relative (father or brother < 55 years, mother or sister < 65 years)

And those who are:

- Māori, Pacific or from the Indian subcontinent
- Aged ≥ 75 years
- Aged < 35 years with known CVD risk factors
- Aged 20–34 years with diabetes
- Overweight
- High consumers of alcohol

For patients with these risk factors especially, lipid lowering drug treatment should be combined with advice on diet and lifestyle measures such as exercise, weight management, alcohol consumption and smoking cessation. Other risk factors should also be appropriately

addressed such as lowering raised blood pressure and managing diabetes.[1, 2]

For example:
A 52-year-old man has an estimated five-year CVD risk of 10–15% (calculated from the CVD risk tables). He reveals that he has a family history of premature coronary heart disease.

The GP decides that this patient should be moved up a risk category to >15% on the basis of his family history and therefore a statin is indicated.

How important are target lipid levels?

New Zealand guidelines recommend the following optimal lipid levels (targets) for people with known cardiovascular disease, cardiovascular risk > 15% or diabetes:[1]

Total cholesterol < 4.0 mmol/L
LDL cholesterol < 2.0 mmol/L
HDL cholesterol ≥ 1.0 mmol/L
Triglycerides < 1.7 mmol/L

The traditional view on lipid levels is "the lower, the better", which is technically correct from a disease-based point of view. However this view does not take into account how the treatment used to achieve this intervention will affect patient outcomes.[9]

Although specific target levels are recommended in New Zealand Guidelines, it is now widely agreed that it is not necessary to treat to target lipid levels in primary prevention of CVD. Many patients are unable to achieve target lipid levels, potentially leading to lack of motivation and non-compliance with treatment.[10]

The JUPITER Study

When results were first reported in 2008, the Justification for the use of statins in primary prevention: an intervention trial evaluating rosuvastatin (JUPITER) study was regarded by some as an important development in statin research. The results suggested that statins were beneficial in people with no history of CVD but assessed as being at increased CVD risk.[6] However, since this time the JUPITER study has received much criticism.

One of the most controversial aspects of JUPITER was that trial participants had no known CVD and had cholesterol levels within normal ranges but were designated to be at increased CVD risk due to elevated high sensitivity C-reactive protein (hsCRP) levels. The use of hsCRP as a surrogate marker for CVD risk is debatable.

The absolute effect size of the study was relatively modest – for every 1000 patients who received rosuvastatin for one year, roughly six fewer primary-endpoint events (first major cardiovascular event including unstable angina, myocardial infarction, stroke and arterial revascularisation) and three fewer deaths occurred. Therefore a large number of people with low-CVD risk would have to be treated in order for any benefit to be derived.

The JUPITER study was terminated early, after only 1.9 years, instead of the planned four years, due to strong evidence of benefit in the treatment group. Early termination for benefit can provide an inflated estimate of benefit and understate harm.[8] There was also no indication about the long-term safety of the very low LDL-levels which were achieved in the study.

The results of the JUPITER study were taken into account when the New Zealand Cardiovascular Guidelines Handbook was revised in 2009 by the New Zealand Guidelines Group. However the Group did not think it justified any change in practice.

Additional reasons for not using lipid level targets in primary prevention include:[10]

- Clinical trial evidence is based on using specific doses of specific medicines to treat people, rather than using medicines to achieve specific targets
- The majority of studies that recruited selected populations did not find statin therapy reduced LDL-cholesterol below 2 mmol/L
- Targets do not take into account the distribution of cholesterol levels in the population prior to commencement of treatment, nor differing responses or adherence to treatment
- The adoption of targets may encourage indiscriminate use of either high-dose statins or combination lipid therapy

Target lipid levels are appropriate for guiding treatment in secondary prevention and for people with conditions that carry very high risk, such as those with familial hypercholesterolaemia.

Which statin and what dose should be prescribed?

The New Zealand guidelines recommend the following starting doses:[1]

- For people with five-year CVD risk of 15–20% – simvastatin 20 mg (titrate if needed)
- For people with known CVD or CVD risk >20% – simvastatin 40 mg

Statins available in New Zealand

There are three statins currently listed on the Pharmaceutical Schedule in New Zealand – simvastatin, atorvastatin and pravastatin (refer to the Pharmaceutical Schedule for prescribing criteria). N.B. The access criteria for atorvastatin have recently been widened (see page 55).

At comparable doses, statins are therapeutically equivalent in reducing LDL-cholesterol.[11] The HDL-cholesterol elevating and triglyceride lowering effects are also similar among different statins at equivalent doses. While there are some pharmacokinetic differences between statins, choice can generally be guided by patient tolerability and cost. If high intensity statin treatment is indicated atorvastatin may be better tolerated than simvastatin.

Simvastatin

- Current guidelines, availability criteria and cost mean simvastatin is the most commonly prescribed statin in New Zealand

Atorvastatin

- Consider when more intensive statin therapy is required
- Can be used in people with impaired renal function as no dose adjustment is required

Pravastatin

- Has the lowest potential for drug interactions as it is not extensively metabolised by cytochrome P450 isoenzymes

Initiating a statin

For primary prevention, the starting dose of a statin ranges from 20 – 40 mg. Table 1 outlines some specific scenarios in which a different dose or type of statin may be more appropriate.

Tolerance to dose and adverse effects

Moderate to high doses of statins are often used to ensure maximum LDL-cholesterol reductions. However, it is important to remember that most of the effect of a statin occurs at less than the maximum dose.[12] For each doubling of the statin dose e.g. from 20 mg to 40 mg simvastatin, there is only a small, additional absolute reduction in cardiovascular events. In addition, higher doses are associated with greater adverse effects.

Table 1: Recommended statin doses

Situation	Prescribing solution
Primary prevention of CVD (CVD risk ≥ 15%)	Simvastatin 20 – 40 mg
Patient with known CVD	Simvastatin 40 mg
Simvastatin not tolerated	Reduce dose if appropriate OR trial atorvastatin
Patient with severe renal insufficiency (creatinine clearance less than 30 mL/min)	Simvastatin 10 mg (use doses above 10 mg with caution) OR Consider changing to atorvastatin (no dose adjustment required in impaired renal function)
Risk of drug interactions e.g. amiodarone, verapamil, diltiazem, warfarin or combination with other lipid lowering agents	Consider switching to pravastatin (less potential for interactions, special authority criteria apply)
Intensive therapy required e.g. familial hypercholesterolemia, very high CVD risk	The maximum dose of simvastatin is 80 mg, with an increased risk of adverse effects and interactions at this level Consider switching to atorvastatin

For those patients who are unable to tolerate higher doses, or if there is the potential for drug interactions, lower doses may be safer and still provide worthwhile benefits.

If a patient experiences adverse effects with one particular statin, the dose can be lowered or the patient can be switched to another statin.[12]

Adverse effects of statin therapy are usually minor (Table 2). Asymptomatic elevation of transaminase levels can occur. However for some patients, adverse effects are more severe, sometimes leading to discontinuation of treatment.

Statin intolerance

Statin intolerance is defined as "the presence of clinically significant adverse effects that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised".[10]

Table 2: Adverse effects related to statin use[10]

Common	Gastrointestinal disturbance (abdominal pain, constipation, flatulence, acid reflux) Headache Myalgia
Less common	Sleep disturbances, including insomnia and nightmares Memory loss Sexual dysfunction Depression
Rare	Serious muscular effects e.g. myopathy, rhabdomyolysis Peripheral neuropathy Interstitial lung disease Skin rashes and hair loss

Statin intolerance is common and is thought to affect approximately 5 to 10% of people taking statins.[10] A recent study found that a regimen of 2.5 mg simvastatin, taken every other day and titrated upward, was tolerated in more than 50% of previously statin intolerant patients, with satisfactory lipid lowering efficacy.[13] Studies have also shown that low dose atorvastatin is tolerated and efficacious in people with previous statin intolerance.[13]

What monitoring is required when prescribing a statin?

The New Zealand guidelines recommend that creatine kinase is checked in symptomatic patients taking statins. No other monitoring is routinely required.[1]

Before initiating a statin:

- Measure baseline liver enzymes (ALT only required). The risk to the liver from statin treatment is negligible. Statins should not be withheld in patients with mildly raised baseline levels. However, do not initiate a statin if the ALT level is three or more times the upper limit of normal.
- A baseline creatine kinase level is not necessary. Awareness of risk and monitoring for symptoms is more important.

Monitoring during statin treatment:[1]

- It is not necessary to routinely monitor liver function during treatment
- Monitoring of creatine kinase is not required in people who are asymptomatic. If there is unexplained muscle pain, tenderness or weakness, statin treatment should be stopped and creatine kinase levels checked.

For more information on monitoring, see "Liver Function Testing in primary care" (bpac^nz, July 2007).

Statin induced myopathy

The risk of myopathy in people using statins is usually related to the dose they are taking, with higher risk associated with higher doses. Elderly people and people taking combination lipid-lowering treatments are also at greater risk.

Other risk factors for statin induced myopathy include:[14]

- Underlying muscle disorders
- Past history of myopathy with any lipid-lowering drug
- Renal or liver impairment
- Multisystem diseases e.g. diabetes
- Untreated hypothyroidism
- Major surgery or trauma
- Co-prescription of drugs that inhibit cytochrome P450 (CYP3A4) e.g. fibrates, nicotinic acid, calcium channel blockers, ciclosporin, amiodarone, macrolide antibiotics, azole antifungals, protease inhibitors, warfarin
- Vigorous exercise
- Alcohol misuse
- Excessive consumption of grapefruit juice

Management

For muscle pain without an elevated creatine kinase level, reduce the dose of the statin or trial a different statin. If symptoms do not resolve, discontinuation of the statin may be required.

If there are symptoms and the creatine kinase level is elevated between three to ten times normal, reduce the dose of the statin and monitor symptoms and creatine kinase level weekly. If symptoms do not resolve or creatinine kinase levels do not return to normal, discontinuation of the statin may be required.

If there are symptoms and the creatine kinase level is elevated greater than ten times normal, the statin should be discontinued immediately.[1]

When should other lipid lowering agents be considered?

The New Zealand guidelines recommend that simvastatin is the first-line medicine of choice for lipid reduction.[1]

Evidence from clinical trials strongly supports the use of statins in preference to other lipid lowering agents. Statins reduce the risk of major coronary events, revascularisation rates and stroke, regardless of the initial lipid levels.[9] In contrast to statins, the evidence of benefit to patient outcomes for other treatments is variable, ranging from reasonable evidence for nicotinic acid to no supportive evidence for ezetimibe (of long-term reduction in morbidity and mortality).[9]

Combination lipid-lowering treatment should generally be supervised by a specialist due to the increased risk of serious adverse effects such as rhabdomyolysis. Monitoring of liver function and creatine kinase should also be considered.[15]

For patients who require intensive lipid lowering treatment, combination treatment is considered to be no more effective than high-dose statin monotherapy, for improving clinical outcomes.[16]

Nicotinic acid

Nicotinic acid (also known a niacin or vitamin B3) has a long history of use for treating lipid disorders. It is particularly useful for increasing HDL-cholesterol levels. Nicotinic acid can be used alone or in combination with other lipid lowering medicines.

The addition of nicotinic acid to statin treatment significantly increases HDL-cholesterol and leads to additional LDL-cholesterol lowering along with lowering triglycerides and lipoprotein (a).[17] Nicotinic acid increases HDL-cholesterol between 15% to 35%, compared to between 5% to 15% with statin treatment.[17]

There is some evidence that combination nicotinic acid and statin treatment has the potential to result in reductions in risk for adverse cardiovascular events. However, large-scale clinical outcome trials are needed to confirm this.[17]

There has been concern that nicotinic acid treatment may lead to worsening of glucose control in people with diabetes. Studies have shown that the use of nicotinic acid may increase fasting glucose levels, possibly requiring adjustment of the patient's antihyperglycaemic regimen.[17]

The use of nicotinic acid is often limited by poor tolerability. At standard doses (1.5 to 4.5 g/day), flushing occurs in 80% of patients and pruritus, paresthesias and nausea each occur in about 20%.[18] A combination product (Tredaptive) has now been developed, which combines extended release nicotinic acid (1000 mg) with a prostaglandin inhibitor laropiprant (20 mg). This combination has been shown to reduce flushing compared to placebo. Tredaptive is not funded and costs approximately $100 per month.

See. "Nicotinic acid/laropiprant (Tredaptive®) now available in New Zealand" (BPJ 24, Nov 2009) .

Bottom line: Nicotinic acid could be considered in combination with a statin for those who require additional lipid-lowering, when statins alone are not adequately controlling dyslipidaemia. It may also be used as monotherapy for people who are intolerant of statins.

Ezetimibe

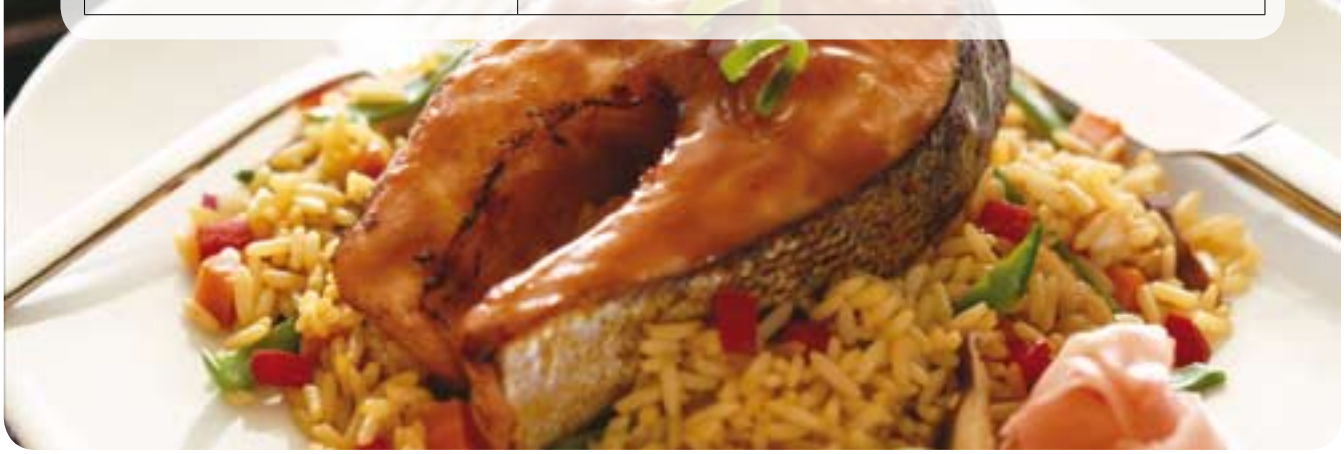
Ezetimibe is a cholesterol absorption inhibitor that reduces intestinal absorption of both dietary and biliary cholesterol.[19] The precise role of ezetimibe relative to other lipid lowering drugs is unclear. A recent trial found that ezetimibe in combination with a statin is less effective than nicotinic acid combined with a statin.[20] In addition the clinical benefits of ezetimibe, alone or in combination with a statin, on cardiovascular morbidity and mortality have not been established.[21]

Lifestyle interventions for lipid lowering

Lifestyle interventions, including dietary modification, exercise and weight management are an essential component for all people who require of lipid lowering,[22] and should accompany any pharmacological therapy.

Lifestyle advice should promote "healthy heart" foods and an active lifestyle. In general the following lifestyle advice can be discussed:[1]

Dietary advice "Small changes in eating habits can make a big difference"	Adopt a cardioprotective dietary pattern e.g. ▪ Consider adding plant sterol or stanol-fortified spreads ▪ Eat oily fish regularly ▪ Choose foods which are low in saturated fats and dietary cholesterol ▪ Choose fruits and/or vegetables at every meal and for most snacks ▪ Select whole grains, whole grain breads, or high fibre breakfast cereals in place of white bread and low fibre varieties Consider referral to a dietitian for a personalised eating plan
Physical activity "Look for ways to build physical activity into your day"	Complete a minimum of 30 minutes of moderate intensity physical activity e.g. brisk walking on most days of the week. This may be carried out all at once or accumulated in ten minute bouts during the day. People who are already doing this should increase the amount and intensity of their exercise if possible. Consider issuing a green prescription or referring to a local sports trust such as Push Play (**http://pushplay.sparc.org.nz**)



The recommended dose of ezetimibe is 10 mg per day and there is no additional benefit in using higher doses.[12]

Bottom line: Ezetimibe may be considered in combination with a low dose statin in patients who are not able to tolerate high doses of statins.[18] It may also be considered as an option for monotherapy for people who are intolerant to statins.

Fibrates

Fibrates are a class of medicines that are primarily used for the treatment of specific lipid abnormalities, such as hypertriglyceridaemia.[19] Fibrates currently available in New Zealand are bezofibrate and gemfibrozil (not subsidised). Fenofibrate is often used in clinical trials but is currently not registered in New Zealand.

Fibrates are known to reduce coronary risk, especially in people with type 2 diabetes or with features such as high triglycerides, low HDL-cholesterol and excessive weight. This benefit may relate in part to the HDL-cholesterol raising effects of these medicines. However, while fibrates increase the level of HDL-cholesterol in most patients, they are much less effective than statins in lowering LDL-cholesterol and may need to be given in combination with a statin. This combination is effective but has been associated with an increased risk of myopathy.[22]

Combination treatment with a statin and a fibrate should usually be initiated under specialist advice.[10]

Bottom line: A fibrate e.g. bezafibrate, may be considered in combination with a statin in people with high triglyceride levels or low HDL-cholesterol levels, that have not responded to statin treatment alone, bearing in mind the increased risk of myopathy with combination treatment.

Caution over the use of red yeast rice supplements

Red yeast rice, also known as chinese red rice, is a herbal medicine supplement which is promoted for use as a lipid-lowering agent. The active ingredients occur as a fermentation by-product of cooked rice on which red yeast has been grown. Supplements contain a naturally occurring form of the statin, lovastatin (mevinolin) along with several other mevinic acids and compounds such as sterols, isoflavones and monounsaturated fatty acids.[23]

The lovastatin compound, mevinolin, is likely to make the greatest contribution to the cholesterol lowering effect of this supplement, however the other ingredients may contribute to an additive effect on cholesterol lowering. Supplements may contain from 0 to 5 mg of “statin-like” substances in each capsule or tablet.[23]

Because red yeast rice supplements may contain significant amounts of statin-like substances, they can potentially cause the same adverse effects as statins e.g. myopathy and raised liver enzymes. Red yeast rice is also likely to be subject to the same interactions as statins e.g. grapefruit juice and prescription medicines such as amiodarone, verapamil, diltiazem and warfarin. Red yeast rice supplements may act additively with prescription statins and other lipid lowering medicines.[23]

In the USA, the Food and Drug Administration (FDA) considers red yeast rice supplements that contain statins to be unapproved drugs. The general consensus is that the use of red yeast rice supplements should be avoided.

Red yeast rice supplements do not presently appear to be commonly available in New Zealand, however the product is readily accessible via the internet.

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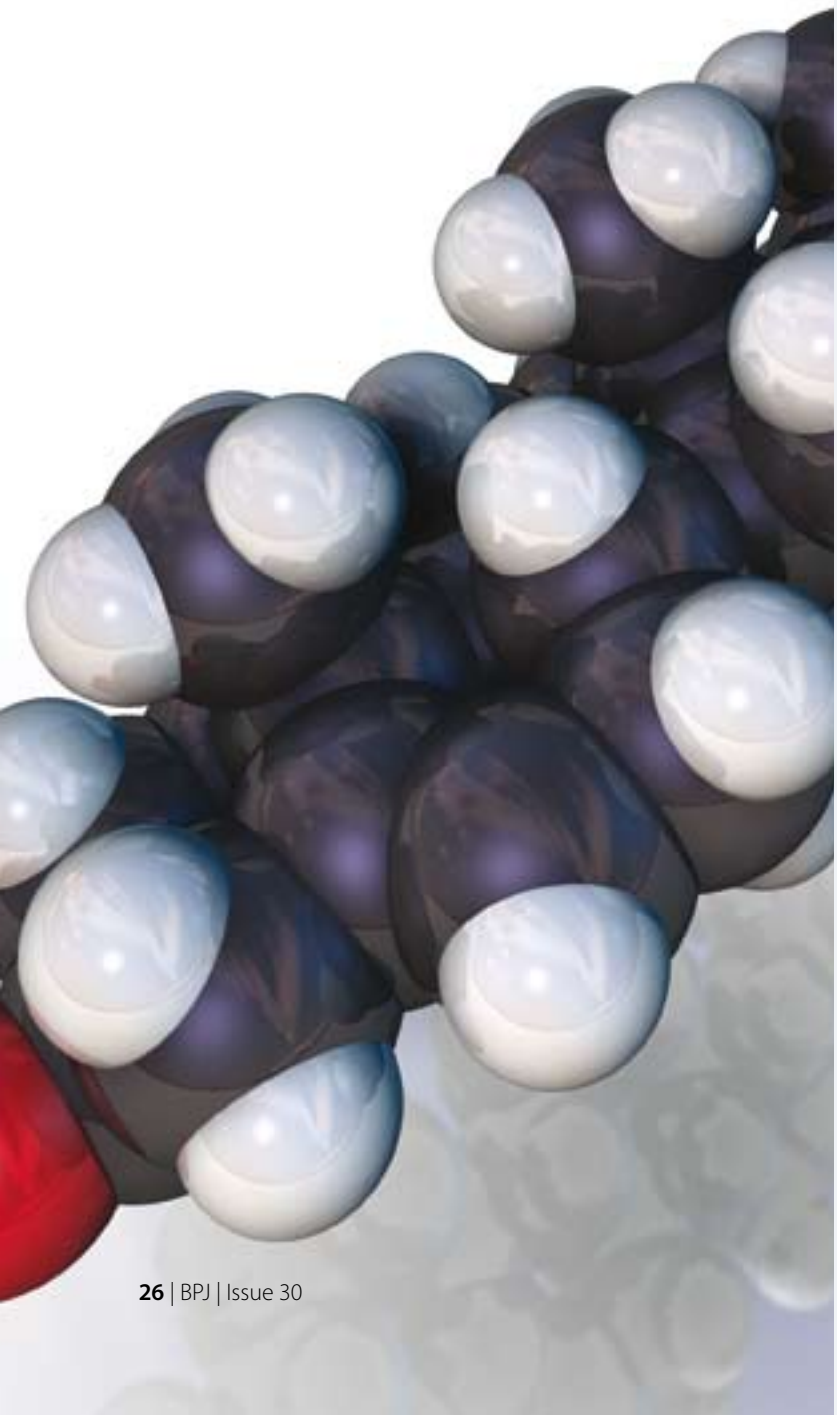

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