Statins are among the most frequently prescribed medicines in New Zealand. It is important they are appropriately prescribed to ensure patient safety. Of note, some interactions with simvastatin have been recently reclassified as contraindications, and fatalities from statin use are still being reported. The Centre of Adverse Reaction Monitoring (CARM) has received 15 reports in New Zealand where simvastatin has been assessed as related to, or may have contributed to a fatal outcome; one as recent as 2013.

**PRESCRIBE APPROPRIATELY**

Statins are effective for the secondary prevention of cardiovascular events caused by atherosclerosis such as stroke and myocardial infarction, but they do not appear to be quite as useful for primary prevention. Prior to treatment, the patient should be adhering to a cholesterol-lowering diet and exercise regimen; encourage them to continue with this during treatment. Other causes of dyslipidaemia such as hypothyroidism, diabetes, liver disease and corticosteroid treatment should also be considered and managed as appropriate.

The overall goal is to reduce cardiovascular risk and the risk of developing diabetes. The intensity of treatment should be dependent on the risk of cardiovascular disease (CVD). The New Zealand Primary Care Handbook recommends:

<table>
<thead>
<tr>
<th>5 year combined CVD risk status</th>
<th>Therapy recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD risk less than 10%</td>
<td>Lifestyle measures; lipid lowering medication is not necessary for most patients</td>
</tr>
<tr>
<td>CVD risk 10-20%</td>
<td>Lifestyle measures and consider lipid lowering medication</td>
</tr>
<tr>
<td>Known CVD or CVD risk over 20%</td>
<td>Lifestyle measures and lipid lowering medication</td>
</tr>
</tbody>
</table>

If lipid lowering medication has been prescribed, recalculate the CVD risk after 6-12 months and assess treatment options. The aim is to achieve a moderate reduction in LDL cholesterol.

Monitor lipid profile every 3-6 months after starting treatment until lipid levels are stable, and annually thereafter. If total cholesterol (TC) > 8mmol/L or TC:HDL cholesterol ratio > 8 then lipid lowering treatment is recommended irrespective of the combined CVD risk.

**Note:** Statins do not need to be dosed at night; choose a regimen that best suits the patient to encourage compliance. Some studies have confirmed that taking simvastatin in the evening is not superior to morning dosing, and is associated with reduced compliance.

**REVIEW HIGH DOSES**

Doses over 40mg should only be considered for patients at high risk of cardiovascular complications who have not achieved their treatment goals with lower doses. Data sheets for simvastatin have recently been updated to caution the use of high doses (80mg daily). High doses are more likely to cause myopathy, but may not offer significant clinical benefits because the dose-response is not linear (ie the 80mg dose only reduces LDL cholesterol by an additional 6% over the 40mg dose). If treatment goals are not being achieved, or if adverse effects are unacceptable, other statins such as atorvastatin or rosuvastatin could be considered.

**Note:** Unless patients are at risk of acute kidney injury, monitoring of kidney function to detect statin-induced renal impairment is not necessary.
INFORM PATIENTS ABOUT MYOPATHY

All patients starting therapy with simvastatin should be asked to report any symptoms of unusual muscle pain, tenderness or weakness. Symptoms typically start within 6 months of initiating the statin. The use of simvastatin is now contraindicated if patients have ever experienced myopathy with any lipid lowering medicines. The risk of myopathy increases in older adults (>65 years), in females, and those with uncontrolled hypothyroidism, diabetes or renal impairment. Pre-existing muscle or liver disease, high dose treatment, concomitant interacting medicines and frailty also contribute to the risk.

Check serum creatine kinase (CK) if there is unexplained muscle pain and discontinue simvastatin if myopathy is suspected. CK greater than 10 times the Upper Limit of Normal (ULN) indicates myopathy.

New Zealand Primary Care Handbook Recommendations

- Muscle pain with no elevated CK – dose reduction or discontinuation may be required
- Muscle pain with CK 3-10 times ULN – dose reduction with weekly monitoring of symptoms and CK or discontinuation
- Muscle pain with CK more than 10 times ULN - discontinue statin immediately

REVIEW USE IN OLDER ADULTS

The benefit of statins in the very old (over 85 years) is less clear than in younger adults. Generally the potential for interactions and side effects is greater and the value of long-term risk reduction is not as clear.

Patients treated with simvastatin 80mg daily who are over 65 years are at greater risk of myopathy compared to those under 65 years. Consider dose reductions particularly for patients in this age group.

Note: Despite observational studies that suggested statins lower the risk of dementia, this has been disproven in randomised trials.

CHECK INTERACTIONS AND CONTRAINDICATIONS

Some medicines in combination with simvastatin can cause high serum simvastatin concentrations, which increases the risk of rhabdomyolysis and potential renal failure. Check the datasheet for a comprehensive list.

Simvastatin is now contraindicated in combination with itraconazole, ketoconazole, erythromycin, clarithromycin, cyclosporin and gemfibrozil. If therapy with these medicines is unavoidable, simvastatin should be suspended during treatment. Be cautious using simvastatin with diltiazem, verapamil, amiodipine and amiodarone; if these medicines are needed, use a lower dose (no more than 20mg per day) or an alternative statin, such as rosuvastatin.

Dose reductions are also advised for patients taking fibrates, terbinafine or colchicine with simvastatin.

Simvastatin should be used with caution if patients consume large amounts of alcohol or if they have a history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to simvastatin use.

Statin-induced hepatotoxicity is rare. Unless there is a reason to suspect liver dysfunction, a baseline alanine transaminase (ALT) test may not be necessary; routine monitoring during treatment is only necessary if there are symptoms of hepatotoxicity.

A recent study suggests there may be an increased risk of diabetes associated with statins. Increased vigilance about testing for diabetes in patients who are taking statins is recommended. Ask patients if they notice increased thirst, urination or blurred vision. All patients taking statins should have their HbA1c tested each time a CVD risk assessment is performed.

Note: Grapefruit juice increases the plasma level of simvastatin, but the effect of typical consumption (250mL daily) is minimal, and is considered of no clinical relevance. Large quantities (over 1L daily) significantly increase plasma levels and should be avoided.
ACKNOWLEDGEMENTS

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REFERENCES