



STATIN STATUS

In recent months, SDIS has received several queries regarding possible interactions, updated guidelines and new indications for the use of statins. This newsletter will address the most frequently asked questions and update pharmacists on the latest research on HMG CoA reductase inhibitors.

Antioxidants and Statins

Traditionally, antioxidant supplements have been frequently recommended to patients for protection against cardiovascular disease. However, recent studies have failed to show any benefits of these agents on cardiovascular outcomes.¹⁻³ In fact, a study published in the New England Journal of Medicine suggested antioxidant supplements may actually have detrimental effects in patients with heart disease.⁴ This study compared the combination of simvastatin + niacin with *and* without antioxidant supplements in patients who had coronary artery disease and low HDL (high density lipoprotein).⁴ Compared to the patients not using antioxidant supplements, patients using simvastatin + niacin + antioxidant supplements (vitamin E, C, β -carotene and selenium) experienced smaller benefits on HDL-2 levels, the more cardioprotective component of HDL.^{4,5} Furthermore, coronary artery obstructions appeared to regress in the patients receiving simvastatin and niacin but not in the patients taking antioxidant supplements.⁴

Although more study is required, these findings suggest that antioxidant supplementation may negate the HDL-2 raising effects of lipid modifying therapy.^{4,5} However, there is still good data to suggest *dietary sources of antioxidants (i.e. fruits and vegetables)* still decrease the risk of cardiovascular events.⁵

Grapefruit Juice and Statins

This interaction is well understood by most pharmacists. Since the Health Canada Advisory was issued in June, SDIS has been asked on a number of occasions to clarify the current recommendations with regards to grapefruit juice drug interactions. Firstly, not all statins are susceptible to this interaction. The mechanism of the grapefruit juice interaction with atorvastatin, lovastatin and simvastatin is inhibition of CYP 3A4, thereby increasing the plasma concentration and absorption of the drug in question.⁶ Fluvastatin is not likely to interact as it is metabolized by CYP 2C9.⁶⁻⁸ Pravastatin is not likely to interact because it is only *minimally* metabolized by CYP 3A4.⁶⁻⁹ It is believed that particular constituents of grapefruit juice, specifically the flavonoids naringin and naringenin, as well as furanocoumarins, bergapten and 6,7-dihydroxybergamottin are responsible for this interaction.⁶

The updated recommendations suggest those on a statin (other than pravastatin and fluvastatin) should avoid grapefruit juice altogether.^{6,10} A recent study showed that as little as 250mls (one 8oz glass) of grapefruit juice can interact with statins.⁶ In addition, with daily consumption of grapefruit juice, the effects of the interaction can persist for up to three days after the last

glass.⁶ For this reason, it is in the patient's best interest not to drink grapefruit juice while on HMG CoA reductase inhibitors (or other drugs metabolized by CYP 3A4). Certain references suggest the fruit itself could also be a potential problem.^{6, 10}

The question now posed to pharmacists is what juice or fruit would not interact with statins. Pharmacists can safely suggest orange juice as a good alternative to grapefruit juice.⁶ With respect to fruit, the data is limited and very preliminary. Sweet oranges and tangerines appear to be safer than sour oranges.⁶ Lime juice may potentiate the interaction, however lemons likely do not.⁶

Dementia and Statins

Although further studies are required, epidemiologic data suggests statins may reduce the risk of developing dementia.^{11, 12} The mechanism is believed to involve lipid and vasculature changes in the brain associated with dementia.¹¹⁻¹³ Pravastatin and lovastatin, but not simvastatin were associated with this risk reduction.¹¹⁻¹⁴ However, this information only suggests that statins *may* play a role in reducing the prevalence of cognitive impairment. More studies are required before statins can be recommended for the sole purpose of decreasing or preventing the pathological processes of dementia.

Diabetes and Statins

The results from the Health Protection Study, the largest statin trial to date, have recently been published. There was strong evidence to support aggressive control of cardiovascular risk reduction in patients with type 2 diabetes.¹⁵ The study included 20,536 men and women (aged 40-80) who were at high risk for coronary heart disease, including diabetic patients, with low baseline cholesterol prior to statin treatment.^{15, 16} The findings of this study demonstrated that lowering cholesterol with the addition of simvastatin 40mg daily to other treatment regimens (i.e. aspirin, beta blockers, ACE inhibitors and antihypertensive therapies), reduced the risk of fatal and non-fatal myocardial infarctions and stroke by almost 25% for every 1mmol/l reduction in cholesterol.¹⁵ This is critical information for diabetic patients. Type 2 diabetics have an increased risk for a serious cardiovascular event compared to a non-diabetic patients with the same cholesterol level.¹⁵ Therefore, aggressive lipid modifying therapy is warranted to prevent cardiovascular events in this high risk population.^{15, 16}

And Briefly.....

Simvastatin has been evaluated in children to treat heterozygous familial hypercholesterolemia (heFH).¹⁷ Doses of up to 40mg of simvastatin daily were reported to be safe and effective therapy for the treatment of heFH in children.¹⁸

Pharmacists may also be asked questions pertaining to the use of statins in osteoporosis. Results from an animal study have suggested that statins may increase bone formation.¹⁹ Further research is required to conclusively determine the mechanism and pharmacologic effect of statins on bone formation in humans.

An Austrian study has looked at the possibility of statins playing a role in treating multiple sclerosis (MS).²⁰ This study indicated statins may be as effective as interferon, a drug currently being used for MS.²⁰ In addition, when statins were combined with interferon, an additive effect was observed. Researchers believe statins have an immunological activity that *may* decrease the inflammation of myelin which causes damage in MS.^{20, 21} A study to evaluate simvastatin

specifically in MS has already started and the results of this study should be available by next year.²⁰

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