Statin Therapy:
Friend or Foe?

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The statins are a class of cholesterol lowering agents that work by inhibiting the HMG-CoA-reductase enzyme. Statins have been shown to be effective in reducing:

- all cause mortality,
- coronary heart disease (CHD) mortality,
- MI,
- revascularization and
- stroke rates.

Furthermore, the benefit derived from statins appears to be proportional to the degree of LDL-C reduction.[1] As such, guidelines for lipid reduction have become more aggressive with 2006 Canadian guidelines recommending high-risk patients be treated to a target LDL-C of < 2.0 mmol/L (Table 1).[2]

Although registry data suggest that primary care physicians are knowledgeable about current lipid targets, one-half of their patients are not meeting recommended lipid targets.[3] Furthermore, the majority of patients not reaching targets are high risk.[4] Explanations provided for the use of relatively low doses of statins include:

- fear of side-effects at higher doses on the part of either the patient or the physician and
- compliance issues.[4]

Therefore, we will review the evidence behind the risks associated with statin therapy in this paper.

Fred's case

Fred is a 55-year-old man with a past medical history of MI and dyslipidemia. His LDL-C has been within target on 10 mg of rosuvastatin for the last year.

He presents to his FP's office with a 2-day history of generalized muscle aches. Lab work done reveals a slightly elevated creatine kinase (CK) at 400 U/L. Fred is informed that rosuvastatin is the most likely cause of his muscle symptoms and is instructed to stop it immediately.

Further history from Fred reveals that he helped his friend move into a new house a few days ago. He reports no recent illness and has not started any new medications.

Turn to page 67 for more on Fred.

Effects of statins on the liver

A small proportion of patients (1%)[5] will experience elevations in alanine and aspartate transaminases. These increases are usually seen in the first six months of treatment, are asymptomatic and reversible by dose reduction or discontinuation of the drug. Liver enzymes may also return to normal with watchful waiting alone.

Although the elevation in liver function tests (LFTs) appears to be dose related, large randomized controlled trials (RCTs) suggest that the risk with high dose statin therapy is still small (0.9% to 3.3%).[6]

Table 1
2006 Canadian Lipid Guidelines

Risk	FRS	LDL target (mmol/L)
Low	< 10%	< 5.0
Medium	10-19%	< 3.5
High	≥ 20%	< 2.0

FRS: Framingham Risk Score

Table 2
Drugs metabolized by cytochrome P450 system

- Fibrates (*e.g.*, gemfibrozil, fenofibrate)
- Macrolide antibiotics (*e.g.,*.erythromycin, clarithromycin)
- Azol anti-fungals (*e.g.,* itraconazole, ketoconazole, miconazole)
- Anti-arrhythmics (*e.g.,*verapamil, amiodarone)
- Protease inhibitors (*e.g.,*atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir)
- Cyclosporine

The clinical significance of these elevations in LFTs remains unclear. It has been suggested that the effects on transaminases may be a marker of hepatic reaction to lower lipid levels rather than actual hepatotoxicity.[6]

Management of elevated LFTs

Prior to initiating statin therapy, it is recommended that baseline LFTs be measured and active liver disease be excluded in those with baseline abnormalities. If baseline abnormalities remain stable and active liver disease has been ruled out, it may be reasonable to start statin therapy while monitoring transaminases every three months. Treatment can be continued if transaminases remain stable.[6]

In patients with normal LFTs at baseline, but who develop asymptomatic increases in aminotransferase (ALT)/alanin aminotransferase (AST) three times over the upper limit of normal (ULN), the enzymes should be checked within a week and treatment stopped temporarily if enzymes are not improving. In patients with asymptomatic elevations in AST/ALT two to three times ULN, monitoring may be sufficient as these may resolve while on treatment.

It should be noted that liver enzyme changes associated with statin therapy are usually limited to AST and ALT elevations. Increases in γ-glutamyl transpeptidase (GGT), bilirubin, or alkaline phosphatase should prompt investigations into other causes.

Effects of statins on muscle

There is a spectrum of muscle-related adverse events described with statin use including:

- myalgias (muscle pain without creatine kinase [CK] elevations),
- myopathy (muscle pain with CK elevations) and
- rhabdomyolysis (severe myopathy involving myoglobin release and risk of renal failure; CK > 10 times ULN is commonly used as a cutoff).[7]

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Myalgias

Despite popular belief, there is no clear evidence that statins cause myalgias. For example, in the Heart Protection Study (HPS), patients in the placebo treated group reported unexplained weakness or muscle pain with the same frequency as simvastatin treated patients.[8] Unusual physical activity, trauma, infections and thyroid disease should be considered as possible explanations when statin treated patients complain of myalgias.

Myopathy and rhabdomyolysis

A systematic review involving > 74,000 patients enrolled in 35 RCTs found no evidence of increased rates of CK elevations or rhabdomyolysis in statin vs. placebo treated patients.[7] Although there may be a small increase in risk with high-dose statin therapy, the real risk is associated with drug interactions, particularly with other drugs metabolized by the cytochrome P450 system (Table 2). Prior to initiating statin therapy, a thorough review of patient medication lists should be undertaken.

Detecting and managing

Routine measurement of CK is not considered useful for detecting myopathy and American College of Cardiology/American Heart Association guidelines now recommend screening only if symptoms are reported by patients.[7]

If moderate elevations in CK are detected (three to 10 times ULN), the patient's symptoms and CK levels should be monitored weekly. If rhabdomyolysis is detected (CK > 10 times ULN), statin treatment should be discontinued and attempts made to identify possible causes, such as drug interactions or comorbid conditions that increase risk of myopathy (*i.e.*, renal impairment, thyroid disease, older age). The patient may be rechallenged with a smaller dose or a different statin at a later time.

Fred's case cont'd...

Fred's muscle symptoms are more likely due to his recent physical activity rather than due to statin therapy. The correct management strategy in this case would be to follow Fred's symptoms and repeat a CK in one week's time to ensure resolution.

Take-home message

- Statin therapy reduces morbidity and mortality associated with CAD
- Half of patients in whom statin therapy is indicated are not meeting recommended lipid targets, often due to conservative prescribing practices amongst physicians
- Elevations in transaminases and muscle toxicity are infrequent and reversible side-effects of statin therapy. The fear of these potential side-effects should not preclude the prescription of high-dose statin therapy when appropriate

References
1. Cholesterol Treatment Trialists (CTT) Collaborators. Efficacy and Safety of Cholesterol-Lowering Treatment: Prospective Meta-Analysis of Data from 90,056 Participants in 14 Randomised Trials of Statins. Lancet 2005: 366(9493):1267-78.
2. McPherson R, Frohlich J, Fodor G, et al: Canadian Cardiovascular Society Position Statement—Recommendations for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease. Can J Cardiol 2006; 22(11):914-27.
3. Yan AT, Yan RT, Tan M, et al: Contemporary Management of Dyslipidemia in High-Risk Patients: Targets Still Not Met. Am J Med 2006: 119(8):676-83.
4. Bourgault C, Davignon J, Fodor G, et al: Statin Therapy in Canadian Patients with Hypercholesterolemia: The Canadian Lipid Study—Observational (CALIPSO). Can J Cardiol 2005: 21(13): 1187-93.

For more references, please contact **diagnosis@sta.ca**.