Combining Statins and Fibrate

1. Is there a rule if you have to combine statins and fibrate?

Question submitted by: Dr. Jean Proulx, Quebec, Quebec

When fibrates must be added to statin therapy for dyslipidemia, there is a reported increased risk of muscle toxicity, as high as 1% to 5% with most of the statins when gemfibrozil is used. Only pravastatin and fluvastatin appear to have little muscle toxicity when used in combination with gemfibrozil, despite the observation that gemfibrozil doubles plasma concentrations of pravastatin.

Toxicity can also be minimized by using other statins in relatively low doses. It is recommended that pravastatin or perhaps fluvastatin (at 80 mg q.d.) is the statin of choice in patients treated with gemfibrozil (or other fibric acid derivatives). However, it should be used cautiously and only if the benefit is likely to outweigh the low risk of muscle toxicity.

Glucuronidation, which is an important pathway for renal excretion of lipophilic statins, appears to be significantly inhibited by gemfibrozil but not fenofibrate. In clinical studies, serum levels of statins increase 1.9- to 5.7-fold in gemfibrozil-treated subjects but are unchanged in fenofibrate-treated subjects.

Fenofibrate appears to be safer. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial of fenofibrate in almost 10,000 patients with Type 2 diabetes, there was a low incidence of myopathy (< 1%) that was not different from placebo, whether or not patients were also taking a statin. Fenofibrate then is the preferred fibrate in patients who require combined therapy with a statin and fibrate.

Despite the increased risk of myopathy associated with statin therapy, routine monitoring of serum creatine kinase (CK) levels is not recommended. However, it is useful to obtain a baseline serum CK before initiation of statin therapy for reference in case symptoms develop.

Patients treated with statins should be alerted to report the new onset of myalgias or weakness.

Coenzyme Q10 (CoQ10) supplementation is frequently discussed. However, there is little published evidence of the benefit of CoQ10 for the treatment of myopathy.

Consequently there is inadequate evidence to recommend CoQ10 supplementation for prevention of statin-induced muscle toxicity. Although there is very limited evidence for benefit, if a patient requires a statin and experiences muscle pain while on pravastatin or fluvastatin (the two statins felt to have the lowest risk of myopathy), some experts have suggested a trial of supplementation with CoQ10 at a dose of 150 mg to 200 mg q.d. prior to rechallenge and during the course of statin therapy.

Answered by:
Dr. Wayne Warnica

Indefinite Usage of Clopidogrel

2. Can clopidogrel be used indefinitely?

Question submitted by: Dr. E.J Franczak

The quick answer is yes. However, the question does deserve some further discussion. To my knowledge, there are no long-term side-effects that would make it a risk for prolonged therapy. For those in whom antiplatelet therapy is prescribed for the long-term and who have a clear ASA allergy, clopidogrel is recommended in the guidelines as the preferred alternate therapy. Ticlopidine is an alternate choice, but because of the greater potential for side-effects, it is not used as frequently. As with any other drug, the potential for allergies is always present.

Probably the major side-effect is the economic one. Clopidogrel is not cheap and many provincial formularies are reluctant to fund it for the long-term except for those with a clear indication and an inability to tolerate ASA.

Answered by:
Dr. Wayne Warnica

Elevated Triglycerides

3. How serious are elevated triglycerides (Over 180) in an otherwise healthy adult?

Question submitted by: Dr.

The normal level of triglycerides is < 1.7 mmol/L (< 150 mg/dl). Hypertriglyceridemia is associated with an increased risk for CV disease. Large cohort studies established an odds ratio between 1.5 to 1.7,[1] the predictive value is higher in young individuals and those with central obesity.

When triglycerides are borderline high (1.7 mmol/L to 2.2 mmol/L), emphasis should be placed upon weight reduction and increased physical activity.

When triglycerides are very high (≥ 5.6 mmol/L), the goal is to prevent pancreatitis by lowering triglycerides with the combination of lifestyle measures and a triglyceride-lowering drug such as a fibrate or nicotinic acid.

Reference
1. Sarwar N, Danesh J, Eiriksdottir G, et al: Triglycerides and The Risk of Coronary Heart Disease: 10,158 Incident Cases Among 262,525 Participants in 29 Western Prospective Studies. Circulation 2007; 115(4):450-8.

Answered by:
Dr. J. G. Fodor

Dosing in Long-Term Anticoagulation

4. How much "fine tuning" do you suggest for anticoagulant doses in long-term anticoagulation?

Question submitted by: Dr.

Long-term anticoagulation with warfarin is challenging owing to the narrow therapeutic range of warfarin, the significant risks associated with under-anticoagulation and over-anticoagulation, the effect of comorbidities such as liver disease and the multitude of prescription and OTC medications or herbal remedies which interact with warfarin.

Multiple studies have confirmed that failure to maintain the INR within the therapeutic range is associated with increased thromboembolic and bleeding complications. At the same time, these studies show that despite our best efforts, our patients run INR's outside of the therapeutic range a significant proportion of the time, up to 35% in some studies; anticoagulation clinics have been shown to be highly effective at improving this number. Patient education regarding medication adherence and interactions is a key component of these clinics. The Canadian Medical Protective Association recognizes anticoagulation issues as a major cause of litigation in Canada.

Owing to the fact that the peak INR effect of a dose of warfarin occurs between one and three days after the dose, a roller-coaster effect may occur if the dose is not adjusted ahead of the anticipated effect.

In my practice, I usually start with an initial dose of 5 mg for two days, with an INR check on the morning of the third day. Depending on the INR curve, I usually check the INR two to three times a week initially, with a decreasing frequency thereafter. Many chronic, stable patients can be safely managed with an INR check every three to four weeks.

I have found home INR monitoring with self-adjustment to be useful in highly selected patients.

Answered by:
Dr. Brett Heilbron