



## High Dose Statin Therapy for All Patients with Coronary Artery Disease?

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Statins are the most efficacious drugs for reducing both low density lipoprotein-cholesterol levels and cardiovascular events. They therefore have a key role in the management of atherosclerotic vascular diseases. Recent trials have demonstrated that statin treatment in high doses (80 mg daily) reduced cardiovascular events in patients with coronary artery disease. Nevertheless, there are still some questions regarding high dose statin treatment in CAD patients that are still unresolved, namely: Is this treatment justified in CAD patients regardless of their LDL-C levels? Should we treat all CAD patients by the most aggressive approach or should we pre-specify among them a high risk group in which lower target levels of LDL-C are recommended? Is high dose statin monotherapy the only therapeutic option? Is high dose statin treatment that safe? How cost-effective is this approach?

In a review article in this issue of *IMAJ*, Shechter and colleagues [1] call for intensive statin therapy (defined as "any statin therapy >40 mg/daily") in patients with CAD. They base their recommendation on eight trials in which statin treatment (80 mg daily) was compared to placebo or treatment with lower doses of statins – all showing greater beneficial effect with the high dose regimen and a relatively safe adverse-event profile.

The growing evidence on the effectiveness of statin treatment in CAD patients – resulting in reduction of coronary events, stroke, death from cardiovascular causes and the need for coronary revascularization – has led to a consensus that statins have a central role in the management of atherosclerotic vascular diseases. The data summarized by Shechter et al. are impressive, but the questions mentioned above still remain.

Recent guidelines recommend an LDL-C level of less than 100 mg/dl in CAD patients unless they belong to the "very high risk group." This group includes patients with acute coronary syndrome, diabetes, severe and poorly controlled risk factors such as smoking, and the metabolic syndrome [2]. In these patients, reducing LDL to less than 70 mg/dl is considered a "therapeutic option." However, there is a growing tendency among some physicians to recommend aggressive lipid lowering

in all CAD patients, regardless of LDL-C levels. This approach is based on the belief that the beneficial effect of aggressive statin treatment is due to non-lipid-related pleiotropic effects, such as anti-inflammatory and antithrombotic effects, improvement of endothelial function and enhanced nitric oxide production [3]. The mega statin trials provide conflicting data regarding the question how much of the reduction in CAD events is due to the LDL-lowering effect. For example, in the Heart Protection Study that compared 40 mg/day simvastatin to placebo, statin therapy led to similar 24% reductions in relative risk of major vascular events in patients with baseline LDL-C  $\leq$ 135 mg/dl as with LDL <100 mg/dl (corresponding to the more commonly used method of calculated LDL-C of  $\sim$ 115 mg/dl) [4]. However, in the Pravastatin or Atorvastatin Evaluation and Infection Thrombolysis in Myocardial Infarction 22 (PROVE IT) trial, conducted in patients with acute coronary syndrome, stratification by baseline LDL-C levels showed that the benefit of 80 mg atorvastatin compared to 40 mg pravastatin was greater among the patients with a baseline LDL-C level  $\geq$ 125 mg/dl, a 34% hazard ratio reduction, compared with only 7% reduction among patients with baseline LDL-C <125 mg/dl [5]. Moreover, 73% of the patients in this trial had a baseline LDL-C <125 mg/dl, and in this large subgroup the modest trend toward benefit of 80 mg daily of atorvastatin over 40 mg pravastatin was not statistically significant [5]. Therefore, current guidelines, including the recent joint recommendations of Israeli medical societies for prevention of coronary heart disease and atherosclerosis still base their recommendations on LDL-C target levels, implying that the type and dosage of statin prescribed to the individual patient depend on his or her LDL-C goals. Further analysis of the PROVE-IT trial showed that combining LDL-C and the inflammatory marker C-reactive protein had a better predictive value for coronary events than looking at LDL-C data only [6], implying that determining CRP levels may be helpful in some cases for risk stratification and setting therapeutic goals.

Most of the trials that evaluated the effect of aggressive statin therapy on coronary events in patients with established

CAD = coronary artery disease

LDL-C = low density lipoprotein-cholesterol

CRP = C-reactive protein

CAD included patients with acute coronary syndromes. The first large study aimed at assessing the effect of aggressive statin therapy on cardiovascular events only in patients with stable CAD was the Treating New Targets (TNT) trial, published recently [6]. In this study, 10,001 patients were randomly assigned to 10 or 80 mg daily doses of atorvastatin and followed for 4.9 years. Treatment by higher statin dosage led to a 22% reduction in major cardiovascular events, with an absolute risk reduction of 2.2%. Comparing the high dose with the low dose group, there was no difference in overall mortality with a statistically non-significant decrease in mortality from cardiovascular causes but a statistically non-significant increase in mortality from non-cardiovascular causes [7]. Those results led to a dispute regarding whether aggressive statin therapy is indicated in stable CAD [8,9]. Several authors have expressed concern about the long-term safety of aggressive statin therapy and that some patients achieving target LDL-C with lower statin levels may not have needed maximal doses. In an editorial, Pitt [8] concludes: "We need further reassurance as to the safety of this approach before we can advocate a major shift in our current goals for LDL cholesterol levels in patients with stable CHD."

Another important issue is whether there are other therapeutic options besides statin monotherapy. Aggressive statin therapy can halt the progression of coronary atherosclerosis, as shown in the intravascular ultrasound-based trial REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) [10]. In this study 80 mg daily of atorvastatin resulted in no progression of coronary lesions. However, despite these impressive results it must be remembered that 18 months of aggressive statin treatment did not lead to regression of atherosclerosis. Moreover, in all the trials that evaluated the effect of high dose statins on cardiovascular events, summarized elegantly by Shechter and co-workers in the present journal [1], there was still a substantial number of patients receiving this treatment who developed events, suggesting that aggressive statin monotherapy is not the final word in the management of atherosclerotic vascular diseases. Several other therapeutic options should be mentioned. Although diet and physical exercise have a limited role in LDL-C reduction, their role in preventing the development of type 2 diabetes – a known risk factor for CAD – should not be dismissed [11]. Combining ezetimibe with lower doses of statins is an effective approach to reduce LDL-C levels [12], although data from clinical studies demonstrating reduction in clinical events are still lacking. Previous studies have shown the beneficial effect of reducing coronary events by fibrates, especially in patients with low high density lipoprotein-cholesterol, high triglycerides and metabolic syndrome [13,14]. Ample epidemiologic evidence suggests that HDL-C has a protective role in atherosclerosis; and a study that evaluated combination therapy of simvastatin and 2 g niacin compared with placebo demonstrated a marked reduction in cardiovascular events (1 vs. 12,  $P = 0.003$ ), with a small but significant regression of coronary stenosis [15,16].

HDL-C = high density lipoprotein-cholesterol

Six weeks of intravenous administration of HDL-Milano led to significant regression of atheromatous plaques. New therapies aimed at increasing HDL levels are currently being evaluated; such as cholesteryl ester transfer protein inhibitors and HDL-mimetics [16].

Is high dose statin therapy really that safe and well tolerated? Some of the concerns raised in the past were proven to have little clinical significance, mainly the issue of hepatic toxicity since statins rarely if ever lead to liver failure. However, the ability of statins to produce myopathy cannot be ignored [17]. While rhabdomyolysis is very rare, there are several common complaints seen in daily practice in patients receiving statins; for example, muscle pains, cramps and muscle weakness, often not accompanied by significantly elevated creatine phosphokinase. The temporal association with statin therapy is often strong; indeed, in one study the patients, all with normal CPK levels, had histopathologic findings of myopathy [18]. Yet, these adverse events are not recognized by many of the high dose statin trials. How can we reconcile this discrepancy? Patients included in these trials are highly motivated and thus differ from many of the patients seen in daily practice. In addition, exclusion criteria include other co-morbidities and usage of drugs (including fibrates, macrolide antibiotics, antifungal drugs) or grapefruit juice known to interact with cytochrome P-450, leading to increased incidence of drug interaction and myopathy. Polyneuropathy is another potential adverse event appearing mainly in patients with long exposure to statins [19]. The slight increase in non-cardiovascular mortality in the TNT trial, although not statistically significant, is also a matter of some concern [7]. This increase could be due to chance alone as it was not seen in other trials of 80 mg/day atorvastatin; however, the possibility that high dose statin treatment for a long period (the TNT had the longest observation period among the high dose statin trials: 4.9 years) should not be entirely ruled out until we have data from other long-term studies. None of these adverse effects or considerations is strong enough to justify withholding statin therapy in high risk patients. However, when the absolute risk reduction – added by further increasing statin dosage – is small or questionable, physicians have to carefully weigh the benefits against potential adverse effects.

Cost-effectiveness is another important issue to be considered. Data from the United States show that statin treatment accounts for the largest prescription drug expenditure. Aggressive treatment in all CAD patients will increase the costs tremendously, and as health budgets are restricted worldwide the economic impact of such an approach cannot be taken lightly.

In conclusion, the time has come for a more aggressive approach to lipid-lowering treatment in CAD patients in order to reach target LDL levels without unnecessary delays due to suboptimal doses or unbased fears. Lowering LDL-C levels is still the primary target and statins are the most efficacious drugs proven to reduce both LDL-C levels and cardiovascular

CPK = creatine phosphokinase

events. However, increasing HDL-C levels or decreasing triglyceride levels have also to be considered, and there is a role for drug combinations. Prescribing aggressive statin therapy (80 mg statin daily) to all CAD patients, regardless of their baseline LDL levels, further risk stratification and coexistent medical conditions, is not justified based on current knowledge.

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