

# Lipid-Lowering Therapy For Acute Coronary Syndromes

There is a large amount of evidence that supports the early use of statins in the treatment of acute coronary syndromes. The anti-inflammatory, anti-thrombotic and anti-oxidant properties of this class of medications all promise great potential in reducing the short- and long-term sequelae of acute coronary events by the pacification of coronary plaques and improvement of vasomotor function.



By Graham C. Wong, MD; and Christian Constance, MD

## *Introduction*

The benefits of aggressive lipid-lowering therapy in reducing long-term cardiovascular morbidity and mortality have been firmly established, both in patients with established stable coronary artery disease (CAD) and in high-risk patients without clinically apparent CAD. Although lipid-lowering

agents, in particular the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins), have been shown to be of benefit in both primary and secondary prevention, their greatest effect has been shown in secondary prevention (*e.g.*, in patients who already have established CAD, with a reduction in subsequent cardiovascular events and mortality of approximately 25% to 30% [Figure 1]). Cholesterol-lowering therapy,

### About the author...



Dr. Wong is a cardiology fellow at McGill University and at the Montreal General Hospital, Quebec.

### About the author...



Dr. Constance is an assistant professor and interventional cardiologist at McGill University and a cardiologist at the Montreal General Hospital, Quebec.



	High Cholesterol	Average Cholesterol
1° PREV	WOSCOPS	AFCAPS/TexCAPS
2° PREV	4S LIPID	CARE

WOSCOPS: West of Scotland Coronary Prevention Study  
 AFCAPS/TexCAPS: Air Force/Texas Cholesterol Project  
 4S LIPID: Long-Term Intervention with Pravastatin in Ischemic Disease  
 CARE: Cholesterol and Recurrent Events trial

Figure 1

therefore, should be a mainstay for any patient with established CAD manifested either as a previous history of an acute coronary syndrome (ACS) or a history of a mechanical revascularization procedure, such as percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) surgery.

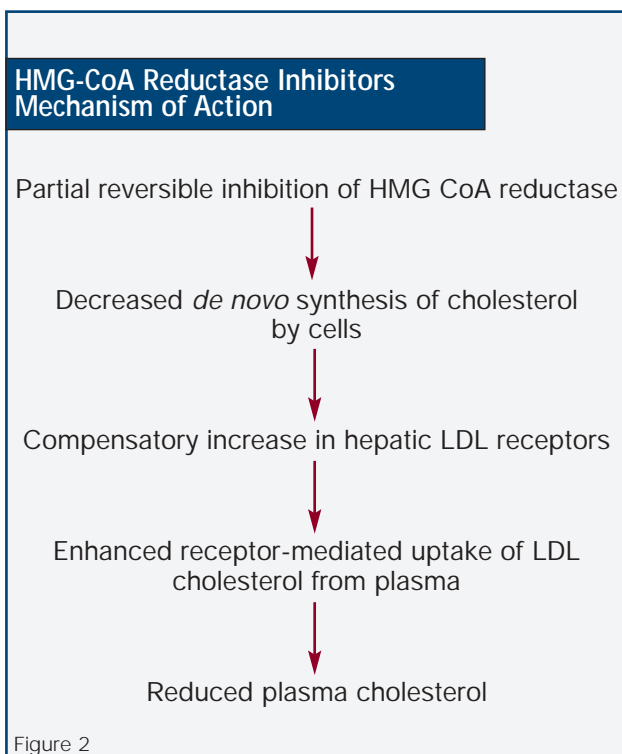
There is considerably less agreement, however, on the benefit of initiating lipid-lowering therapy early in the course of an acute coronary event. The large primary prevention<sup>1,2</sup> and secondary prevention<sup>3-5</sup> statin trials excluded patients who had an acute coronary event within three to six months of randomization. It is unclear from these trials, therefore, if earlier treatment with statins can reduce subsequent coronary events, such as repeat myocardial infarction (MI), death, or the need for revascularization procedures.

Nonetheless, there remain several theoretical advantages to starting lipid-lowering medications early in patients who have suffered an acute coronary event. In addition to lowering levels of both total and low density lipoprotein (LDL) cholesterol, the statin class of lipid-lowering medications have numerous other pleiotropic effects, including effects on vascular endothelial function, plaque stabilization and numerous anti-thrombotic, anti-inflammatory, anti-proliferative and anti-oxi-

dant properties. Early use of these medications in the treatment of ACSs may, therefore, help blunt some of the deleterious hematological and vascular responses to acute coronary artery occlusion, thereby improving clinical outcomes.

### *Pharmacology of the Statin Class of Lipid-Lowering Agents*

The HMG CoA reductase inhibitors, or statins, inhibit the rate-limiting step in cholesterol synthesis and increase expression of the LDL receptor (Figure 2). The end result is a decrease in the production of very LDL and LDL particles and an increase in cellular uptake of these molecules *via* the LDL receptor. Increased cellular uptake, however, is probably the more important of the two effects, since production of the HMG CoA reductase enzyme is up-regulated soon after initiation of statin therapy. In addition to their effects on total and LDL cholesterol, statins also cause a modest (5% to 10%) reduction in triglycerides and similar increases (5% to 10%) in high density lipoprotein (HDL). Although statins are generally well-tolerated medications, clinicians need to be aware of the uncommon, but clinically important, side effects of myositis and



elevation of liver transaminases.

### ***Anti-Atherosclerotic and Anti-Inflammatory Properties of the Statins***

The original angiographic trials investigating statins showed significant reductions in cardiovascular mortality and morbidity, which were subsequently confirmed with large secondary prevention<sup>3-5</sup> and primary prevention<sup>1,2</sup> trials. Although it was originally hypothesized lipid-lowering would reduce cardiac events through regression of pre-existing, cholesterol-laden plaques, angiographic trials demonstrated minimal, if any, significant change in plaque size after statin treatment.<sup>6</sup> Moreover, the clinical benefit of statin therapy appeared to be independent of starting lipid levels, with equally impressive benefits seen in patients with both elevated and average cholesterol levels at study entry.

This discordance between the reduction in clinical events, absolute cholesterol lowering and lack of plaque regression, prompted a search for other mechanisms to explain the decrease in cardiovascular morbidity and mortality seen with statin therapy. Subsequent *in vitro* and *in vivo* research has since determined statins have numerous other biological effects, in addition to lowering lipid levels. These include:

- Beneficial effects on endothelial function and vasomotor tone;
- Plaque stabilization *via* negative modulation of inflammatory cells;
- Reduced oxidation of LDL; and
- Anti-platelet and anti-thrombotic effects (Table 1).

It is well-known that ACSs, ranging from unstable angina (UA) and non-ST elevation acute myocardial infarction to ST elevation acute MI, are caused by rupture of a vulnerable plaque with the formation of a superimposed fibrin and platelet-rich clot. Moreover, it is also clear that patients who have suffered an ACS are at greater short-term risk for subsequent cardiac events, presumably as a result of continued plaque instability. Given the numerous “non-lipid” effects of the HMG Co A reductase inhibitors, there is much theoretical evidence that would justify the use of this class of medications early in the treatment of ACSs (see Figure 3).

### ***Cholesterol-Lowering and Endothelial Function***

Normal endothelial cells actively secrete nitric oxide (NO). This chemical controls the vasodilation of arterial vessels and also decreases overall thrombogenicity *via* several biochemical mechanisms. Endothelial function and NO release are depressed in

Table 1

## Non-Lipid Effects of HMG CoA Reductase Inhibitors

Clinical Effect	Proposed Mechanism
Improved endothelial function	<ul style="list-style-type: none"> <li>Lowered levels of oxidized LDL improves NO production</li> </ul>
Decreased platelet activation	<ul style="list-style-type: none"> <li>Lowered thromboxane B<sub>2</sub> production</li> <li>Decreases production of platelet-activating factor</li> </ul>
Improved plaque stability	<ul style="list-style-type: none"> <li>Increases plaque collagen content</li> <li>Decreases activity of degradative enzymes and cytokines</li> </ul>
Decreased inflammation	<ul style="list-style-type: none"> <li>Decreased migration and adhesion of inflammatory cells</li> </ul>

patients with hypercholesterolemia and other coronary risk factors. In addition, high levels of oxidized and total LDL cholesterol have both been shown to inhibit NO production and increase its inactivation. Statins have been shown to improve endothelial function within three to six months of treatment, potentially by enhancing NO production as a result of lowered levels of oxidized and total LDL cholesterol.

### *Cholesterol-Lowering and Platelet Function*

Platelet aggregation and reactivity to activating stimuli are both increased in the presence of hypercholesterolemia, potentially by increased production of thromboxane B<sub>2</sub> and platelet activating factor. LDL cholesterol lowering, therefore, potentially may decrease the ability of platelets to react and aggregate in response to a vascular insult, such as

plaque rupture.

### *Cholesterol Lowering and Plaque Stabilization*

The likelihood of a plaque to rupture, thereby exposing the cholesterol-rich pro-inflammatory contents to the bloodstream, depends to a large extent on the stability of the fibrous cap overlying the lipid core. Statins have been shown to increase the structural integrity of this cap by increasing the collagen content of the cap, decreasing the activity of various proteases and cytokines that degrade the matrix of the cap, and reducing the migration and adhesion of various inflammatory cells that release these degradative enzymes. Moreover, by lowering levels of oxidized LDL cholesterol, overall oxidative stress within the plaque is reduced, thereby helping to increase its overall stability.

Unfortunately, in spite of this wealth of the-

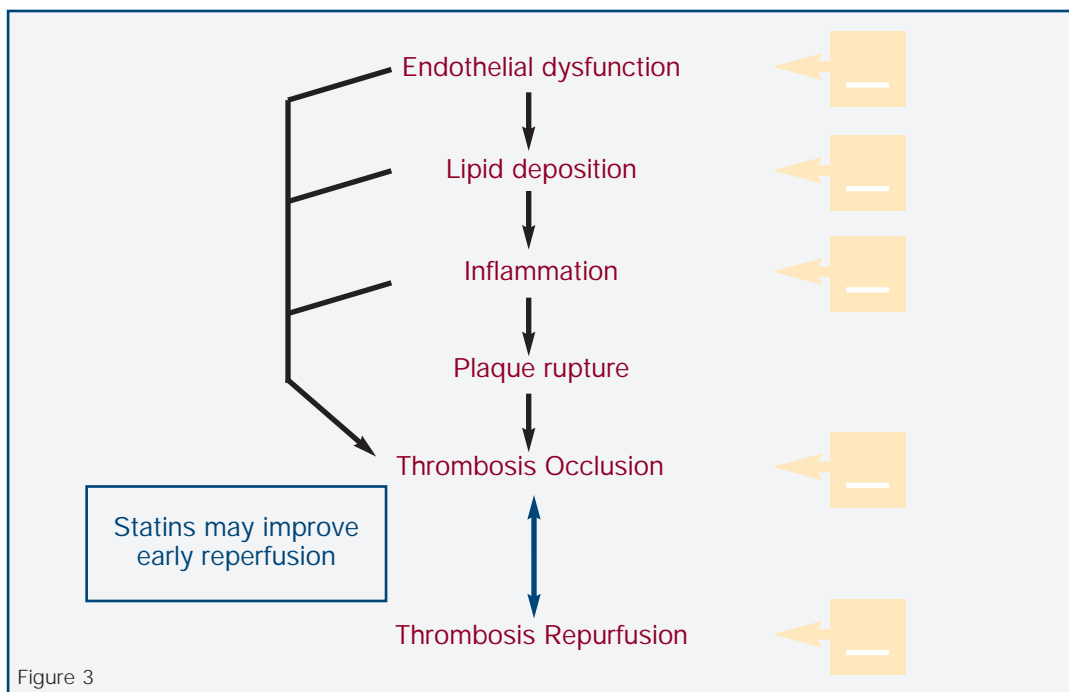


Figure 3

oretical data, there is little prospective data that has demonstrated reductions in clinical events with these medications. Their use, therefore, cannot really be justified. In fact, the most recent American College of Cardiology/ American Heart Association (ACC/AHA) guidelines do not recommend early use of this class of medication after ACSs, and instead recommend initiation of dietary and lifestyle modifications to treat hypercholesterolemia.<sup>7</sup>

### *Retrospective Data*

There are several retrospective trials that support the early use of statins following an ACS. A retrospective Scandinavian study of 19,599 patients under the age of 80, who presented with an acute MI between 1995 and 1998, showed a statistically significant reduction in mortality with early statin treatment.<sup>8</sup> The investigators divided the study cohort into patients who were started on a statin at or before discharge (5,528 patients)

and patients who were not (14,071). The study found early statin treatment was associated with a 25% relative risk reduction in one-year total mortality (95% CI 11% to 37%,  $p = 0.001$ ). Although there appeared to be significant baseline and treatment differences between patients who were prescribed statins at discharge and those who were not, the investigators used a novel statistical tool, called a propensity analysis, using 42 confounding clinical variables to try and match patients by probability of being treated with statins. With this analysis, it was found that the one-year reduction in mortality remained when outcomes of patients treated with statins were matched with those of patients who had a similar likelihood of being prescribed a statin, yet were not. This analysis, therefore, suggested improved survival was, in fact, related to statin treatment, rather than related to any effects of selection bias.

A similar study was recently published which retrospectively analyzed the study population enrolled in the Global Utilization of

Streptokinase and t-PA for Occluded coronary arteries (GUSTO) IIb and Platelet IIb/IIIa Underpinning the Receptor for Suppression of Unstable Ischemia Trial (PURSUIT) ACS trials and compared clinical outcomes according to whether or not patients were prescribed statins at discharge.<sup>9</sup>

GUSTO IIb studied the use of the direct thrombin inhibitor hirudin *versus* standard treatment with unfractionated heparin in patients presenting with ischemic electrocardiogram (ECG) changes and typical chest pain within 12 hours of enrollment.

PURSUIT compared the use of the glycoprotein IIb/IIIa inhibitor eptifibatid *versus* placebo in patients with chest pain within 24 hours and either ischemic ECG changes and/or elevations of creatine kinase containing M and B subunits within 12 hours of enrollment. Neither study had a firm policy on the use of lipid-lowering agents, and their use was left up to the discretion of the treating physician.

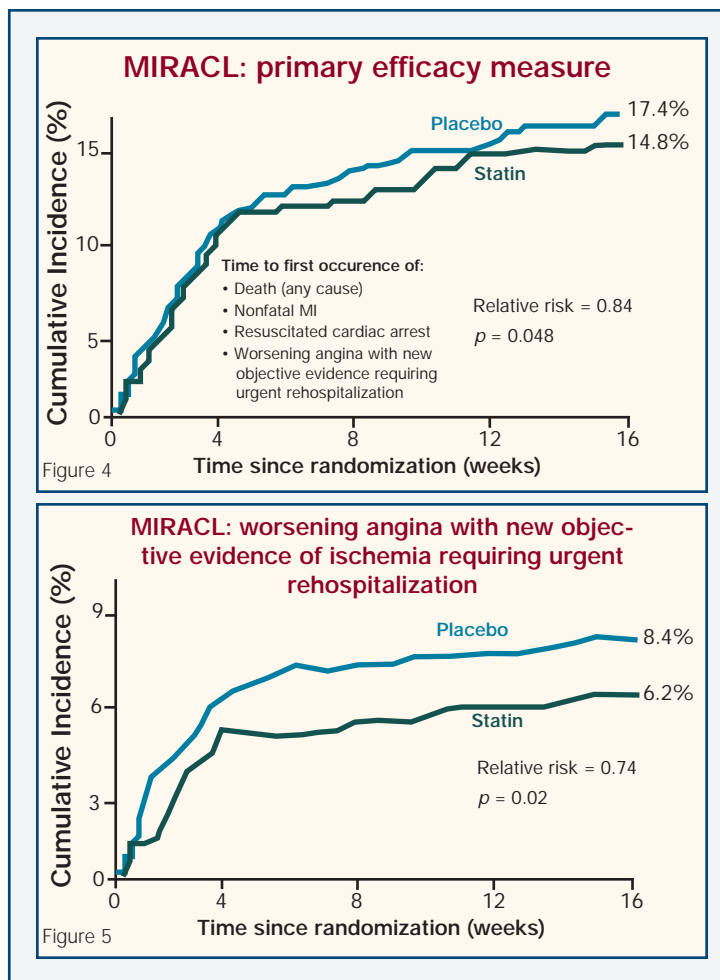
Overall, 3,653 patients in both the GUSTO IIb and PURSUIT cohorts were discharged on a lipid-lowering agent, compared to 17,156 patients who were not. As with the Scandinavian study, a propensity analysis was used to match treated patients with patients who had a similar likelihood to have been prescribed a lipid-lowering agent, yet were not prescribed such an agent. Using this analysis and after controlling for other confounding co-factors, the authors found lipid-lowering therapy at discharge was still associated with a 33% reduction in risk of death at six months (95% CI 5% to 52%,  $p = 0.023$ ). The authors noted, however, that although lipid-lowering therapy was associated with a significant reduction in death, there was no such association between lipid-lowering therapy and a reduced risk of re-infarction — even though such an association was consistently seen in all three HMG CoA reductase secondary prevention trials. The authors postulated this apparent lack of effica-

cy of early statin prescription on re-infarction rates could possibly be explained by the fact that patients on lipid-lowering drugs may be more likely to seek medical attention for ischemic symptoms. This, in turn, increases the number of recorded events, compared to patients in whom lipid-lowering therapy was not prescribed (so-called “ascertainment bias”).

### *Prospective Trials*

To date, there is only one prospective trial investigating the efficacy of early treatment of ACSs with lipid-lowering agents. The recently reported Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study randomly assigned 3,086 patients presenting with an ACS to treatment with either 80 mg of the HMG CoA reductase inhibitor atorvastatin or placebo, within 24 to 96 hours of presentation to hospital (in addition to standard care).<sup>10</sup> Patients were followed for 16 weeks for the combined primary end point of death, non-fatal acute MI, resuscitated cardiac arrest or recurrent symptomatic angina requiring hospitalization and with objective evidence of ischemia. Figures 4 and 5 summarize the primary end point and the numerous prespecified secondary end points.

The two groups were well-matched in terms of patient characteristics, including baseline lipid parameters. Mean LDL levels were 3.2 mmol/L, mean HDL levels were 1.2 mmol/L and mean triglyceride levels were 2.0 mmol/L. It is interesting to note the mean LDL cholesterol levels of MIRACL patients at study entry were lower than what is commonly seen in patients with coronary disease (3.6 mmol/L to 3.9 mmol/L, on average). The combined primary end point occurred in 228 patients (14.8%) in the atorvastatin group and in 269 patients in the placebo group (17.4%), giving a



relative risk reduction of 16% (95% CI 0% to 30%,  $p = 0.048$ ), which barely met statistical significance. No significant differences were found between treatment and control groups in each of the individual primary end points, except for a statistically significant reduction in symptomatic ischemia requiring re-hospitalization with objective evidence of ischemia (6.2% versus 8.4%,  $p = 0.02$ ).

## Unanswered Questions and Future Studies

The MIRACL study was the first trial to show the benefits lipid-lowering therapy may

potentially extend to the acute setting. Several issues require clarification, however, before this strategy can be universally adopted. It is still unclear as to the optimal timing of when to start lipid-lowering, as there was a 24- to 96-hour window in which to begin atorvastatin therapy in MIRACL. More importantly, it is also unclear as to which is the principal mechanism by which statin medications exerted their effect in MIRACL. Finally, it was noted that patients in the MIRACL trial who had entry LDL levels below the median of 3.2 mmol/L had paradoxically higher event rates. This raises the question of whether or not there exists an LDL level below which treatment with a statin could prove to be harmful.<sup>11</sup> It is well-known that LDL concentrations in patients who present with an ACS are often lower

than baseline (perhaps due to sympathetic over-activity), and may not necessarily reflect their usual values. More work is needed, therefore, to define the subset of patients who will benefit from this class of drugs and also to define the optimal time of commencement of therapy.

There are currently several other ongoing clinical trials investigating the benefits of early initiation of lipid-lowering therapy in ACSs that will, hopefully, answer these and other questions. The Aggrastat to Zocor (A to Z) trial is evaluating the efficacy of simvastatin on reducing recurrent ischemic events following a non-ST elevation acute coronary syndrome. The only ongoing trial comparing two different

## Case Discussion

It was necessary to thrombolyse Mr. Franklin and give him acetylsalicylic acid (180 mg stat) followed by 80 mg once a day as quickly as possible, since there is overwhelming evidence of benefit from these drugs shown in many different trials. The patient was also put on beta blockers.

Mr. Franklin's cholesterol levels were not available when the patient was seen in the emergency room. A statin was prescribed, however, because of the recent prospective data for the MIRACL trial, which showed a 26% reduction in recurrent symptomatic ischemia when given in the acute setting.

statis head to head is the PRavastatin Or Atorvastatin Evaluation And Infection Therapy (PROVE-IT) trial, which, in addition to comparing the efficacy of these two statins, is also investigating the efficacy of antibiotic therapy in the treatment of ACSs.

diac morbidity and mortality associated with unstable coronary syndromes.

## Summary

There is a tremendous body of anecdotal evidence that supports the early use of statins in the treatment of ACSs. The anti-inflammatory, anti-thrombotic and anti-oxidant properties of this class of medications all promise great potential in reducing the short- and long-term sequelae of acute coronary events by the pacification of coronary plaques and improvement of vasomotor function. The results of the MIRACL trial are promising and suggest statins are safe to use and may soon become a valuable and powerful tool in our treatment protocols for ACSs. There are, however, many questions that need to be answered before their routine early use can be recommended, including optimal timing of intervention and proper patient selection. The new trials that are currently under way hopefully will answer these questions and improve our understanding regarding the best use of these medications to reduce car-