

# Lipid-lowering therapy after myocardial infarction: Is it worth it?

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## Résumé

DANS CE NUMÉRO (page 991), le Dr Marc Rivière et ses collègues utilisent des données tirées de l'étude scandinave sur la survie grâce à la simvastatine pour évaluer les répercussions qu'a sur les coûts une thérapie de longue durée à la simvastatine chez les personnes qui ont survécu à un infarctus du myocarde (IM). Ils présentent des données convaincantes sur les coûts et l'utilisation des ressources pour appuyer leur conclusion selon laquelle la thérapie à la simvastatine est rentable dans un contexte canadien. L'étude scandinave portait toutefois sur des patients dont les taux de cholestérol étaient plus élevés que ceux de la majorité des personnes qui ont survécu à un IM en Amérique du Nord. Il est donc rassurant de constater que d'autres recherches canadiennes ont démontré les avantages d'une thérapie aux statines chez les patients dont les taux de cholestérol de base sont inférieurs à ceux des sujets de la cohorte scandinave. La possibilité de transposer les répercussions sur les coûts directement dans la population nord-américaine est moins claire.

For too many survivors of myocardial infarction (MI), the story has just begun. Even the most optimistic Canadian data confirm that 1 year after hospital discharge survivors under age 75 have a 6.1% chance of reinfarction and a 5.3% chance of death.<sup>1</sup> The struggle to develop secondary prevention strategies to lower these risks continues. The benefits of acetylsalicylic acid (ASA) and  $\beta$ -blocker therapy have been demonstrated,<sup>2</sup> but the suppression of asymptomatic ventricular arrhythmias with antiarrhythmic agents has been proven ineffective.<sup>3</sup> Although elevated levels of serum cholesterol have for some time been associated with increased risk of infarction and reinfarction, cholesterol-lowering therapy was not shown to reduce mortality until very recently; indeed, there was concern that it could lead to an unacceptable increase in the risk of death from noncardiovascular causes.

The degree of lipid lowering achieved with dietary modification and the earlier lipid-lowering agents (such as the resins and niacin) was generally modest at best. Moreover, the effectiveness of these strategies was compromised by compliance problems and drug intolerance. The introduction of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors — the "statins" — gave clinicians and investigators a powerful new tool. These well-tolerated drugs can produce sustained reductions of 25% to 35% in total and low-density lipoprotein (LDL) cholesterol levels, and an increasingly convincing case developed their use in both primary and secondary prevention. Clinical trials demonstrated that secondary prevention with lipid-lowering therapy can stop and even reverse the progression of atherosclerotic lesions.<sup>4,5</sup> Interestingly, the small improvements noted in vascular lesions did not appear to explain the much greater reductions in ischemic events.

More recently, the landmark Scandinavian Simvastatin Survival Study (4S) provided definitive evidence of the benefit of lowering LDL-cholesterol levels in patients with elevated lipid levels and established coronary artery disease (CAD).<sup>6</sup> Simvastatin therapy given over a median period of 5.4 years lowered LDL cholesterol levels by 35% from baseline. Over the study period the relative risk of death from CAD was 42% lower in the simvastatin group; the relative risk of



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death from all causes in the treatment group (the primary end point of the trial) was 30% lower. The cholesterol-lowering hypothesis was finally proven correct.

A number of important questions remain. Does the degree of benefit achieved by lipid-lowering therapy vary with patients' lipid levels, or do all patients with proven CAD benefit equally, since "their lipid levels [are] clearly too high for them"?<sup>7</sup> Is lipid-lowering therapy cost-effective? Does its cost-effectiveness vary with the degree of risk?

Several researchers have examined the cost-effectiveness of lipid-lowering therapy on the basis of the 4S results. Extrapolated to the US and Sweden, the trial data suggest that hospitalization costs could be decreased by more than 30% over 5 years.<sup>8,9</sup> Other researchers have estimated that only 13 patients with established CAD would have to be treated for 5 years to prevent a second cardiovascular event.<sup>10</sup>

In this issue (page 991) Dr. Marc Rivière and colleagues evaluate the cost implications of long-term simvastatin therapy in Canadian patients with CAD, using the 4S results as a basis for projecting the anticipated benefits of simvastatin therapy over 15 years. A secondary (and perhaps the most valuable) objective was to determine the structure of costs associated with major coronary and cerebrovascular events in Canada. Such analysis is critical to any assessment of the cost-effectiveness of lipid-lowering agents. Not surprisingly, hospitalization was the main determinant of costs for acute events, averaging 86% of the total. The highest projected costs (for a 3-month treatment period) per acute cardiovascular event were \$27 526 for stroke and \$21 073 for coronary artery bypass grafting; the cost of usual care for MI was much less, at \$9790. Unfortunately, as in most cost-effectiveness analyses only "hard" costs are identified. The true cost of recurrent ischemic events in patients with established CAD should take into account the effect of the disease and its treatment on quality of life. Surely the efficacy of therapy must be assessed more broadly than in simple terms of lives saved or death delayed.

Using 3 possible scenarios for the outcome of treatment, Rivière and colleagues present convincing data to support their conclusion that simvastatin therapy for secondary prevention in Canadian patients after MI is cost-effective. But should the 4S data really be used to predict events and project cost-effectiveness in Canada? The benefits of cholesterol reduction are clearly greatest in patients at highest risk. Is the benefit the same for patients with lower baseline cholesterol levels? The 4S trial reported on patients with an average cholesterol level of 6.7 mmol/L (range 5.5–8.0 mmol/L).<sup>6</sup> Surveys of North American patients have shown that the average cholesterol level in MI survivors is 5.4 mmol/L, only slightly higher than the population average.<sup>11,12</sup> Indeed, more than

75% of North American men have cholesterol levels below the lower limit selected for the 4S trial. There can be little doubt that simvastatin therapy for secondary prevention in selected high-risk patients after MI is cost effective. It is not at all clear, however, that this conclusion can be directly extrapolated to the North American population, most of which is in a lower risk group.

Several other factors complicate the extrapolation of the 4S data to North America. Despite the fact that all of the patients in the study had proven CAD, only 37% were taking ASA regularly, as compared with 86% in a Canadian study population of MI survivors.<sup>1</sup> In addition, only 8% of the 4S participants had undergone revascularization in the time between their index event and enrolment in the trial. This is a considerably lower rate than the 54% reported in a recent North American trial.<sup>13</sup> Given the more aggressive use of postinfarction therapies in North America, Canadian and American patients may be at lower risk of recurrent events for reasons other than lower lipid levels. This makes it difficult to extrapolate costs and benefits from the 4S trial.

The Cholesterol and Recurrent Events (CARE) trial addressed many of these concerns by selecting MI survivors with lipid levels comparable to the North American average and who received postinfarction therapies consistent with standard North American practice.<sup>13</sup> In this trial 4159 survivors of MI with serum cholesterol levels lower than 6.2 mmol/L and LDL cholesterol levels between 3.0 and 4.5 mmol/L were treated with pravastatin (40 mg/d) or placebo for 5 years. The treatment group had a 24% reduction in the risk of the primary end points: fatal coronary event or nonfatal MI ( $p = 0.003$ ). There were also significant reductions in the need for coronary revascularization and in the incidence of stroke. Despite earlier concerns about the effect of lipid lowering in women with CAD, pravastatin was found to be more successful in reducing the rate of coronary events among women than among men.

In comparing the CARE trial with the 4S trial, it is important to note that the treatment group in the former was at lower risk than the treatment group in the latter, and that the placebo group had only a 13% event rate in the CARE trial, as compared with 28% in the 4S trial.

In the CARE trial the risk of recurrent events and the benefits of therapy were clearly related to baseline LDL cholesterol levels. For those participants who would have met the selection criteria for the 4S trial, the benefit of lipid lowering was equal or slightly greater than that seen in the 4S trial. On the other hand, for those patients with baseline LDL cholesterol levels lower than 3.2 mmol/L, the pravastatin therapy was not beneficial. This suggests that there may be a threshold below which initiating cholesterol-lowering therapy is not effective. Above this ap-



parent threshold, the benefit of lipid lowering was more closely related to the percentage reduction of cholesterol rather than to baseline cholesterol. The maximum benefit and risk reduction were seen in patients who achieved a reduction of more than 10% in LDL cholesterol levels, regardless of their baseline levels. Similarly, in the 4S trial the benefit of therapy was more closely related to the percentage reduction in cholesterol levels than to the lowest limit of cholesterol level achieved.

The CARE trial also demonstrated that patients over 60 years of age benefited as much as younger patients. It provides valuable information about the potential benefits of lipid lowering therapy for North American MI survivors whose lipid levels are within the average range and who have had the benefit of revascularization therapy. The suggestion of a lower threshold for benefit from lipid-lowering therapy is important and requires confirmation by other trials. The fact that maximum benefit seemed to be achieved simply by a greater than 10% reduction in LDL cholesterol levels also has important therapeutic implications and raises the possibility that therapy with the statins has beneficial effects in addition to lipid lowering. There may, however, be a group of patients for whom lipid-lowering therapy is not beneficial. For this group, a more detailed search for risk factors such as other lipid abnormalities or elevated levels of homocysteine or serum fibrinogen may be important.

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