Cholesterol Reduction Rapidly Improves Endothelial Function After Acute Coronary Syndromes

The RECIFE (Reduction of Cholesterol in Ischemia and Function of the Endothelium) Trial

Jocelyn Dupuis, MD, PhD; Jean-Claude Tardif, MD; Peter Cernacek, MD; Pierre Thérioux, MD

Background—Cholesterol lowering reduces coronary events. One mechanism could be improvement of endothelial function. In line with this hypothesis, this study investigates whether cholesterol reduction can result in rapid improvement of endothelial function after acute coronary syndromes.

Methods and Results—Patients with acute myocardial infarction or unstable angina and total cholesterol levels at admission ≥5.2 mmol/L or LDL ≥3.4 mmol/L were randomized to placebo (n = 30) or pravastatin 40 mg daily (n = 30) for 6 weeks. Brachial ultrasound was used to measure endothelium-dependent flow-mediated dilatation (FMD) and response to endothelium-independent nitroglycerin. Changes in the levels of markers of platelet activation, coagulation factors, and plasma endothelin levels were also assessed. Total and LDL cholesterol levels were similar at admission and before randomization in both groups. With pravastatin, but not with placebo, they decreased by 23% (P < 0.05) and 33% (P < 0.01), respectively. FMD was unchanged with placebo, 5.43 ± 0.74% (mean ± SEM) to 5.84 ± 0.81%, but increased with pravastatin, 4.93 ± 0.81% to 7.0 ± 0.79% (P = 0.02), representing a 42% relative increase. Responses to nitroglycerin were similar during the time course of the study in the 2 groups. Markers of platelet activity, coagulation factors, and endothelin levels were not affected by pravastatin.

Conclusions—Cholesterol reduction with pravastatin initiated early after acute coronary syndromes rapidly improves endothelial function after 6 weeks of therapy. (Circulation. 1999;99:3227-3233.)

Key Words: coronary disease ■ cholesterol ■ endothelium ■ risk factors
Endothelial Function After Ischemia

Materials and Methods

Study Objectives

The primary objective was to evaluate the effect of therapy on noninvasively measured endothelial function as assessed by brachial artery flow-mediated dilatation using high-resolution ultrasonography. Secondary objectives included evaluation of the variations of hemostatic factors, platelet activity, and plasma immunoreactive endothelin-1 (ET-1) concentrations. Because this study is based on the use of admission cholesterol as an entry criterion, a tertiary objective was to confirm the reliability of the admission lipid profile and compare the effects of dietary and combined dietary plus pharmacological cholesterol reductions on plasma lipids after only 6 weeks of therapy.

Study Population

Subjects were randomized in a double-blind fashion to placebo (n = 30) or pravastatin (40 mg daily at bedtime; n = 30) for a duration of 6 weeks. Patients admitted to the coronary care unit of the Montreal Heart Institute with a diagnosis of acute myocardial infarction or unstable angina were eligible if they had admission total serum cholesterol ≥5.2 mmol/L or LDL cholesterol ≥3.4 mmol/L and serum triglycerides ≥4.5 mmol/L. Exclusion criteria were the presence of heart failure with an ejection fraction of <40%, administration of lipid lowering agents in the preceding 8 weeks, renal failure with serum creatinine level >200 mmol/L, and patients requiring coronary artery bypass surgery. Premenopausal women were also excluded as well as postmenopausal women on hormone replacement therapy. All patients received and were taught American Heart Association step 2 diet. Vitamin supplements were not permitted. All medications were held constant throughout the entire study. None of the smokers quit during the duration of the study. Coronary angiography was performed for 21 patients in the placebo group and 18 patients in the pravastatin group (P = NS), with angioplasty in 16 patients from each group.

Randomization in the study was done at the end of the in-hospital investigation (time 0) and was continued for a period of 6 weeks. Noninvasive evaluation of endothelial function as well as lipid profiles, hemostatic factors, and ET-1 levels were obtained in the fasting state at time 0 and after 6 weeks of therapy. The study protocol has been approved by the Research and Ethics committees of the Montreal Heart Institute and written informed consent was obtained before inclusion in the study.

Endothelial Function

The examinations were performed early in the morning at the noninvasive imaging laboratory of the Montreal Heart Institute in a quiet, dimly lit room. Patients were in a fasting state, did not use tobacco on the morning of the examination, and rested in a supine position for a minimum of 10 minutes before study. All drugs, with the exception of salicylates, were withheld on the morning of the study. High resolution ultrasound examination of the brachial artery was performed with a 7.5-MHz transducer connected to a Hewlett Packard Sonos 1000 echocardiographic machine. Images were recorded on a S-VHS tape. A nontortuous segment of the brachial artery on the arm, above the antecubital fossa, was identified. The distance between the tip of the third finger and the transducer was recorded to serve as an index of transducer position for repeated examinations. Baseline imaging was performed by scanning the brachial artery in a longitudinal fashion. After optimization of depth and gain settings, appropriate. Correlation between the absolute changes in total cholesterol, LDL cholesterol, and apo B values and absolute changes in percent FMD were done by linear regression analysis. All values were expressed as mean±SEM and P < 0.05 was considered significant.

Results

A few more women, smokers, and patients with previous hypertension were present in the placebo group, but the differences were not statistically significant (Table 1). Admission diagnosis was the same: 44% Q wave myocardial infarction in the placebo patients and 39% in the pravastatin patients, and non-Q wave myocardial infarction/unstable angina in 56% and 61%, respectively. Ejection fraction was within the normal range in both groups. Total and LDL cholesterol were similarly elevated in the 2 treatment arms both at admission and before randomization.

Thrombostatic Factors and Endothelin Levels

Immunoreactive ET-1 levels were measured as previously described in detail.13 Commercially available enzyme immunoassay kits were used to determine the concentrations of thrombin-antithrombin III complex (Enzygnost R TAT micro, Behring Diagnostics), plasminogen activator inhibitor 1 (ASSERACHROM R PAI-1, Diagnostica Stago), von Willebrand factor (ASSERACHROM R vWF, Diagnostica Stago), tissue factor (IMUBIND R TF, American Diagnostica) and total tissue factor pathway inhibitor (IMUBIND R TFP, American Diagnostica). These tests were performed on a Dynatech MR 300 microplate reader (Dynatech Laboratories Inc.). Chromogenic assays were used for the quantitative determination of fibrinogen (IL Test TM Fibrinogen-C, Instrumentation Laboratory), factor VIII:C (ACTICHROM R Factor VIII:C, American Diagnostica) and for factor VII activity (Coaset R FVII, Chromogenix). These assays were performed on an ACL TM 3000 PLUS instrument (Instrumentation Laboratory).

Flow cytometry served for the quantitative assessment of the glycoprotein IIb/IIIa complex in its activated state using PAC-1 FITC (Becton Dickinson, San Jose, CA) and nonactivated state with anti-CD41 PE (Serotec, Oxford, England) and for P-selectin expression using anti-CD 62P FITC (Serotec). The samples were analyzed in an EPICS R XL flow cytometer (Coulter Corporation).

Statistical Analysis

Five patients withdrew from the trial and did not come to the second visit. Consequently, 27 patients in the placebo group and 28 in the pravastatin group completed the trial and were included in the analysis. Differences between baseline clinical characteristics of the 2 groups were compared using χ² tests for noncontinuous variables and by 2-tailed independent t tests for continuous variables. Variations in serum lipids measured at admission, at time 0, and after 6 weeks were evaluated by mixed-model ANOVA followed by multiple comparisons with t tests where appropriate. Differences in all other parameters measured at time 0 and after 6 weeks were evaluated by 2-tailed paired t tests (within group comparisons) and independent group t tests (between group comparisons) where appropriate. Correlation between the absolute changes in total cholesterol, LDL cholesterol, and apo B values and absolute changes in percent FMD were done by linear regression analysis. All values are reported as mean±SEM and P < 0.05 was considered significant.

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TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=27)</th>
<th>Pravastatin (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>56.2 2.3</td>
<td>55.7 2.1</td>
</tr>
<tr>
<td>Male/Female, n (%)</td>
<td>22/5</td>
<td>26/2</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>17 (62)</td>
<td>14 (50)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>8 (29)</td>
<td>5 (18)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>0 (0)</td>
<td>1 (3.5)</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q wave infarct</td>
<td>12 (44)</td>
<td>11 (39)</td>
</tr>
<tr>
<td>Non-Q wave infarct/unstable angina</td>
<td>15 (56)</td>
<td>17 (61)</td>
</tr>
<tr>
<td>Peak CPK level, U/L</td>
<td>987 213</td>
<td>1126 211</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>59 2.2</td>
<td>56 2.1</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>122 3.6/72 2.5</td>
<td>116 3.4/74 4.3</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67 2.2</td>
<td>70 2.9</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.41 0.14</td>
<td>6.39 0.19</td>
</tr>
<tr>
<td>LDL</td>
<td>4.34 0.18</td>
<td>4.15 0.14</td>
</tr>
<tr>
<td>HDL</td>
<td>1.12 0.08</td>
<td>1.03 0.06</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.19 0.20</td>
<td>2.19 0.18</td>
</tr>
<tr>
<td>**Medication use, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>25 (93)</td>
<td>28 (100)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>23 (85)</td>
<td>25 (89)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>5 (19)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>8 (30)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>6 (22)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

CPK indicates creatine phosphokinase; ACE, angiotensin-converting enzyme.

Lipids

The mean delay between admission and randomization into the study was 10.4 0.69 days. During this period, there was a significant and similar fall in total cholesterol of 12% in the placebo group and 9% in the pravastatin group (Figure 1). After 6 weeks of therapy, total cholesterol increased to return to baseline value in the placebo group, while a further decrease occurred in the pravastatin group for an overall of 23% reduction compared with admission values. LDL cholesterol levels also decreased between admission and the time of randomization by 7% in both groups. After 6 weeks, LDL had increased back to near admission values in the placebo group while there was a further decrease in the pravastatin group, which resulted in a 33% total reduction compared with admission. HDL cholesterol mildly but significantly decreased in both groups during the hospital phase and remained at that level in the placebo group while it significantly increased after 6 weeks with pravastatin therapy. Triglyceride levels were not significantly modified throughout the course of the study.

Endothelial Function

Analyzable brachial artery ultrasound examinations were obtained from all patients in the pravastatin group. In the placebo group, 3 examinations could not be analyzed because of poor image quality. At randomization, the brachial artery diameter was similar in the placebo group, 3.9 0.11 mm, and the pravastatin group, 4.0 0.09 mm; this remained similar at 6 weeks, 3.9 0.12 and 4.1 0.09 mm, respectively. Endothelium-dependent dilatation measured from percent flow-mediated dilatation of the brachial artery was similar in both groups at randomization (Figure 2). In the placebo group, percent FMD did not significantly vary from 5.43 0.74% at randomization to 5.84 0.81% at 6 weeks. It, however, increased in the pravastatin-treated group from 4.93 0.81% to 7.0 0.79% (P=0.02, Figure 2), representing a 42% relative increase. Similar results were obtained when brachial artery diameters or absolute variations in brachial artery diameters were analyzed instead of percent increase. In the pravastatin group, no correlations were detected between the improvement in percent FMD and the fall in total cholesterol (r=0.05, P=0.25) and in LDL cholesterol (r=0.04, P=0.39). Endothelium-independent responses tested by sublingual nitroglycerin were similar in both groups at all time points of the study (Figure 2).

Other Analysis

Variations in other lipid fractions, thrombostatic factors, platelet function tests, and ET-1 concentrations are shown in Table 2. There were no differences and no variations in LP(a) levels. Apo B concentrations significantly decreased by 20% in the pravastatin group, but the change did not correlate with the improvement in percent FMD (r=0.02, P=0.48). Thrombin antithrombin complex, fibrinogen and factor VIII-c levels were mildly elevated at time 0 and similarly decreased after 6 weeks of pravastatin therapy or placebo. At baseline, platelets were clearly hyperresponsive to stimulation with a...
low concentration of adenosine diphosphate, as demonstrated by an important expression of P-selectin at the membrane surface. This hyperresponse was not present at 6 weeks in all patients. Plasminogen activator inhibitor, von Willebrand factor, tissue factor, and factor VII-c levels did not show any consistent changes throughout the study. Tissue factor pathway inhibitor levels were reduced by pravastatin therapy. ET-1 levels were mildly elevated in both groups throughout the duration of the study with no effect of therapy.

Clinical Evolution
The 5 patients who did not complete the study did not present any adverse events. During the 6 weeks of the study, there were 3 adverse events in the placebo group: one non-Q wave myocardial infarction, one unstable angina caused by early restenosis after angioplasty, and one hospitalization for dyspnea attributed to heart failure. In the pravastatin-treated group, there were 2 rehospitalizations for chest pain: one patient did not demonstrate restenosis of the previously dilated artery and the other had no evidence of myocardial ischemia on dipyridamole stress testing. None of the patients presenting those clinical complications stopped study medications.

Discussion
This study documents that pravastatin therapy rapidly initiated after myocardial infarction or unstable angina prevents the increase in cholesterol levels observed in the following weeks and is associated with an early improvement in endothelial function. It also provides new insights into the evolution of acute phase reactants, thrombogenic and endothelial markers, and platelet activation in the weeks following an acute coronary syndrome.

Blood Lipids
As in previous studies,14,15 blood lipid values in the placebo group decreased in the days following the acute phase but subsequently increased to levels observed at admission in the following weeks. This study also showed that early treatment with an HMG-CoA reductase inhibitor not only prevented this increase but also further decreased blood lipids. Thus, in the placebo group, LDL cholesterol decreased by 7% between admission and the time of randomization and subsequently increased to admission levels. With pravastatin, the levels decreased by an additional 26%, resulting in a total 33% reduction compared with admission levels. These findings give support to the recommendation of the ACC/AHA task force on risk reduction16 that cholesterol values measured immediately on hospital admission provide a reasonable estimate of baseline cholesterol and can be used to select potential candidates for cholesterol lowering drugs.

Cholesterol Reduction Rapidly Improves Endothelial Function
Our study further supports the validity of the current recommendations by demonstrating, for the first time, an early improvement in endothelium-dependent dilatation with treatment started soon after the acute phase of coronary syndromes. This extends the previous observations that cholesterol lowering improves endothelium-dependent dilatation in the coronary arteries5,17 as well as in peripheral vessels.6–8 Flow-mediated dilatation of the brachial artery correlates well with coronary response to the endothelium-dependent dilator acetylcholine.18 Such an improvement may be particularly important soon after acute coronary syndromes when the risk of recurrence is high. The RECIFE trial has addressed this issue in a population composed of hypercholesterolemic coronary patients with other risk factors and with standard cardiovascular therapy for their condition. We have thus demonstrated, for the first time, that cholesterol reduction can also rapidly improve endothelium-dependent vasodilation in a high-risk group of patients with proven active coronary lesions and that brachial artery ultrasonography is a useful noninvasive method for evaluating endothelial function after acute coronary syndromes. It becomes particularly relevant to evaluate the rapidity of onset of action of cholesterol lowering drugs in a population that may profit from rapid stabilization of their active lesions.

Improved endothelial function has been postulated as one of the mechanisms by which cholesterol lowering induces plaque stabilization and reduces myocardial infarctions as well as coronary deaths.19 In patients with obstructive coronary artery disease, lipid lowering reduces myocardial ischemia detected by ambulatory ECG monitoring done 4 to 6 months after initiating therapy.20 The present mechanistic study was not designed to evaluate the incidence of recurrent
ischemic episodes but raises the hypothesis that early improvement in endothelial function could translate into earlier plaque stabilization and, perhaps, earlier and greater events reduction in these higher risk patients. Larger scale trials will be necessary to confirm this hypothesis.

This study evaluated only one aspect of endothelial function: endothelium-dependant dilation mediated by NO. Although cholesterol and oxidized LDL in particular are clearly associated with endothelial cell dysfunction\(^2\) and reduced bioavailability of NO, pravastatin therapy may improve endothelial function through other mechanisms, some of which could be independent of its cholesterol lowering effects.\(^2\)\(^3\)\(^4\) The improvement in endothelial reactivity found in the RECIFE trial did not correlate with the reductions in various lipid fractions. Possible explanations for this finding include an insufficient sample size and the presence of associated risk factors for endothelial dysfunction in our population that could limit the magnitude of the isolated impact of lipid reduction found in previous trials. We consequently cannot convincingly conclude that cholesterol-independent effects of pravastatin may have contributed to our findings.

**Hemostatic Factors, Platelets Activity, and Endothelin Levels**

It was previously suggested that pravastatin therapy could reduce platelet thrombus formation by studies in ex vivo chambers superfused with blood from stable hypercholesterolemic coronary patients\(^\text{10}\) and improve hemostatic parameters in hypercholesterolemic patients.\(^\text{9}\) In our study, thrombin-antithrombin, fibrinogen, and factor VIII-c were elevated at the time of randomization, probably as part of the acute phase reaction response. Platelets were also hyperresponsive, suggesting a thrombogenic state. These abnormalities were almost completely reversed after 6 weeks with no specific effect of pravastatin. A benefit of therapy on these parameters cannot, however, be excluded because the analyses were performed relatively late past the acute phase. Thus, we cannot exclude that serial determinations could have shown a more rapid improvement with treatment.

Endothelin levels were only mildly elevated at randomization, with no effect of treatment. Previous studies have shown an elevation that resolved early within days after the acute phase.\(^\text{25}\) Although activation of the endothelin system may contribute to the abnormal vascular reactivity brought on by hypercholesterolemia, our results do not support a role for this endothelial function in the short-term improvement found in endothelial reactivity with pravastatin therapy.

Total tissue factor pathway inhibitor (TFPI) levels were decreased by pravastatin therapy. This natural anticoagulant is mostly bound to LDL cholesterol.\(^\text{26}\) For the 2 groups combined, changes in TFPI were directly correlated with changes in LDL cholesterol ($r=0.46$, $P<0.01$); there was a tendency for the pravastatin group alone ($r=0.38$, $P=0.11$) but no correlation for the placebo group alone ($r=0.06$, $P=0.84$). It is unlikely that the reduction in TFPI would represent an adverse effect of therapy because

### TABLE 2. Hemostatic Factors, Endothelin-1, and Lipids Measured at Time 0 and After 6 Weeks of Pravastatin Therapy

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Pravastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 0</td>
<td>Time 0</td>
</tr>
<tr>
<td>LP(a), g/L</td>
<td>0.42±0.10</td>
<td>0.36±0.07</td>
</tr>
<tr>
<td>Apo B, g/L</td>
<td>1.24±0.03</td>
<td>1.34±0.04</td>
</tr>
<tr>
<td>TAT, ng/mL</td>
<td>10.9±3.4</td>
<td>3.0±0.4†</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>4.6±0.3</td>
<td>3.2±0.2†</td>
</tr>
<tr>
<td>PAI-1, ng/mL</td>
<td>39.6±6.9</td>
<td>37.4±6.0</td>
</tr>
<tr>
<td>von Willebrand factor, %</td>
<td>168±57</td>
<td>167±13</td>
</tr>
<tr>
<td>Tissue factor, pg/mL</td>
<td>65±9</td>
<td>78±12</td>
</tr>
<tr>
<td>Factor VIII-c, % standard</td>
<td>153±10</td>
<td>127±9.2†</td>
</tr>
<tr>
<td>Factor VII-c, % standard</td>
<td>103±8</td>
<td>108±6</td>
</tr>
<tr>
<td>TFPI, ng/mL</td>
<td>72±3</td>
<td>76±2</td>
</tr>
<tr>
<td>Platelet, P-selectin, %</td>
<td>1.53±0.20</td>
<td>1.59±0.21</td>
</tr>
<tr>
<td>Basal</td>
<td>28.89±5.22</td>
<td>2.70±0.75‡</td>
</tr>
<tr>
<td>ADP</td>
<td>88.0±4.5</td>
<td>85.4±4.4</td>
</tr>
<tr>
<td>Total GP IIb/IIa, %</td>
<td>4.12±3.3</td>
<td>1.23±0.70</td>
</tr>
<tr>
<td>Basal</td>
<td>81.1±5.2</td>
<td>77.4±5.4</td>
</tr>
<tr>
<td>ADP</td>
<td>1.48±0.8</td>
<td>1.46±0.7</td>
</tr>
</tbody>
</table>

TAT indicates thrombin-antithrombin complex; PAI-1, plasminogen activator inhibitor; TFPI, tissue factor pathway inhibitor; ADP, adenosine diphosphate; and GP, glycoprotein.

* $P<0.05$; † $P<0.01$ vs time 0; ‡ $P<0.05$; § $P<0.01$ vs placebo.
others have shown that neither the carrier-free TFPI nor the magnitude of the vascular pool of TFPI, nor its anticoagulant potency, were affected by therapeutic lowering of LDL by lovastatin therapy.\(^{26}\)

**Study Limitations**

Patients in the RECIFE trial presented other conditions known to cause endothelial dysfunction, such as smoking, high blood pressure, and diabetes. Some baseline clinical characteristics were differently distributed and although nonstatistically significant, these differences and their combination could have influenced the results. Also, many other factors not measured in this study could have influenced the results: for example, plasma homocysteine concentrations, also known to affect endothelial function, were not measured. However, because there were no differences in percent FMD at randomization and none of the patients took vitamins or folate supplements, it is unlikely that variations in homocysteine levels or the effect of nonstudy medications could explain our findings. Antioxidant vitamins such as vitamins E and C were also prohibited during the study to eliminate potential effects on endothelial reactivity. Therapy with the tissue specific angiotensin-converting enzyme inhibitor quinapril improves coronary vasodilation to acetylcholine after 6 months of therapy.\(^{27}\) In the present study, the tendency for a greater use of angiotensin-converting enzyme inhibitors in the placebo group, however, was not associated with significant modifications of percent FMD after 6 weeks.

**Conclusion and Clinical Implications**

Despite the highly publicized efficacy of lipid lowering therapy in secondary prevention, hypercholesterolemia is still underdetected and undertreated after acute coronary syndromes.\(^{13}\) Why some physicians are still poorly compliant with The National Cholesterol Education Program guidelines is unclear but may result from concern with the validity of in-hospital cholesterol values and the lack of demonstrated short-term benefit of therapy.

In the present study, we have shown that cholesterol reduction with pravastatin initiated early after acute coronary syndromes rapidly improves endothelial function after 6 weeks of therapy. We confirm that the admission cholesterol levels adequately reflect homeostasis and should be used to avoid delays in initiating therapy. Larger scale trials are required to determine whether the rapid improvement of endothelial function in the acute and early recovery phase is associated with a reduction in cardiovascular events. Such a trial is presently underway: the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial evaluates the effect of Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering on early recurrent ischemic events. Such a trial is presently underway: the recovery phase is associated with a reduction in cardiovascular events. Such a trial is presently underway: the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial evaluates the effect of Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering on early recurrent ischemic events.

**Pharmacologic lowering of cholesterol**


**Conclusion and Clinical Implications**

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RECIFE is a French acronym that translates in English as reef. The vascular endothelium, not unlike a reef, is a delicate structure whose equilibrium is essential to the maintenance of surrounding life. Any disruption of this equilibrium may carry immediate and longer term consequences; we believe that, conversely, any signs of improvement must be considered seriously for their potential immediate and long-term impacts.

**Acknowledgments**

Dr Dupuis and Dr Tardif are scholars from the Fonds de la Recherche en Santé du Québec. This work was supported in part by an unrestricted grant from Bristol-Myers Squibb, Canada. The authors would like to thank Suzanne Bujold, Johanne Marquis, Marie Gagnon, Ginette Grenier, Johanne Vincent, Marta Ghitescu, Jacynta Rivard, Charles Dupont, and Micheline De Belder.

**References**


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