



# Do statins play a role in the early management of the acute coronary syndrome?

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## KEYWORDS

Acute coronary syndrome;  
Myocardial infarction;  
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Acute coronary syndrome (ACS) is associated with a poor prognosis and, despite the availability of a number of treatment strategies, the incidence of subsequent serious complications following an acute event remains high. Although large, long-term clinical trials have established the benefits of statin therapy in the prevention of cardiovascular events and mortality, patients with recent ACS were excluded from these studies. Data from observational studies and a randomized controlled trial support the routine use of statins in ACS and highlight the association between early initiation and reductions in recurrent coronary events and mortality. Preclinical and clinical evidence also indicates that, in addition to their lipid-lowering effects, statins may reduce inflammation, improve endothelial function and increase plaque stability. Ongoing clinical trials with highly efficacious statins are expected to provide valuable information about the most appropriate agent and dose to improve the treatment of patients with ACS.

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## Introduction

Acute coronary syndrome (ACS), including unstable angina and acute myocardial infarction (MI), constitutes a major preoccupation in clinical cardiology. Following the onset of ACS, patients have a higher incidence of recurrent coronary events compared with those with stable coronary disease, and the rate of recurrence is particularly high in the 30 days after an acute presentation.<sup>1</sup> Although treatment strategies, such as antithrombotic therapy and angiotensin-converting enzyme inhibitors, can be used to prevent early events following ACS, the incidence of serious complications remains high.

Statin therapy has been proven to be highly effective in preventing cardiovascular morbidity and mortality in patients with coronary heart disease in large secondary prevention trials.<sup>2–4</sup> However, patients who had experi-

enced an acute coronary event were only enrolled after several months of event-free survival. For example, the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial found that treatment with pravastatin decreased mortality and coronary events in patients who had experienced an episode of unstable angina 6–36 months before study entry.<sup>4</sup> In these trials, benefit was not observed until 1–1.5 years after treatment was initiated.<sup>2–4</sup> More recently, there has been increasing interest as to whether the use of statins early in the course of ACS may improve clinical outcomes. This review will summarize the current evidence supporting the early initiation of statin therapy following ACS and will highlight the mechanisms that may be responsible for these beneficial effects of statins.

## Evidence for the initiation of statin therapy in acute coronary syndrome

The early data supporting initiation of statin therapy in patients with ACS were derived from retrospective

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observational studies. A post hoc analysis of pooled data from the Global Use of Streptokinase or t-PA for Occluded Coronary Arteries (GUSTO) IIb and Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) studies assessed the effect of initiating lipid-modifying therapy at the time of hospital discharge in 3653 patients following an ACS event.<sup>5</sup> After 6 months' treatment, a significant reduction in mortality was observed in those patients who received lipid-modifying therapy compared with those who did not (hazard ratio, 0.48; 95% confidence interval (CI), 0.37–0.63;  $P < 0.0001$ ). Similarly, in the Swedish Registry Study of nearly 20,000 patients with ACS, 1-year mortality was lower in patients who received statin therapy at discharge compared with those who did not receive statin therapy (relative risk [RR]=0.75; 95% CI, 0.63–0.89;  $P = 0.001$ ).<sup>6</sup> In contrast to these findings, there was no relationship between initiation of statin therapy and improved outcomes in the SYMPHONY (Sibrafiban versus aspirin to Yield Maximum Protection from ischaemic Heart events post-acute coronary syndrome) and 2nd SYMPHONY studies following adjustment for statin propensity and covariates (adjusted hazards ratio=0.99; 95% CI, 0.73–1.33).<sup>7</sup> However, outcomes were more favourable in patients with low-density lipoprotein cholesterol (LDL-C) >130 mg/dl (3.4 mmol/l) compared with patients with LDL-C below this level.<sup>7</sup>

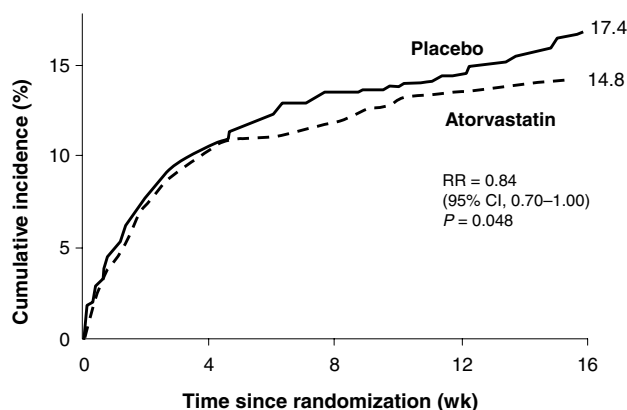
A subgroup analysis of the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study compared the rate of death and non-fatal MI in patients with ACS who received statin therapy on hospital admission, patients who were not treated with statin therapy and patients who had statin therapy withdrawn on admission.<sup>8</sup> The rate of death and non-fatal MI was halved at 30-day follow-up in patients who received statin therapy compared with those who did not (3.7% vs 7.5%;  $P = 0.004$ ). Interestingly, if statin therapy was withdrawn on admission, the incidence of death and non-fatal MI was significantly higher than in the other patient populations (14%;  $P = 0.004$ ).

Although observational data support the clinical benefit of statins for patients with ACS, prospective, randomized controlled trials are required to guide clinical decisions. One prospective study, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, examined the effect of treatment with atorvastatin 80 mg/day compared with placebo initiated 24–96 h after an ACS event (non-Q-wave MI or unstable angina) in over 3000 patients.<sup>9</sup> After 16 weeks' follow-up, atorvastatin treatment significantly reduced the risk of the combined end point of death, non-fatal MI, cardiac arrest or recurrent ischaemia requiring repeated hospitalization compared with placebo (14.8% vs 17.4%; RR=0.84; 95% CI, 0.70–1.00;  $P = 0.048$ ) (Fig. 1).

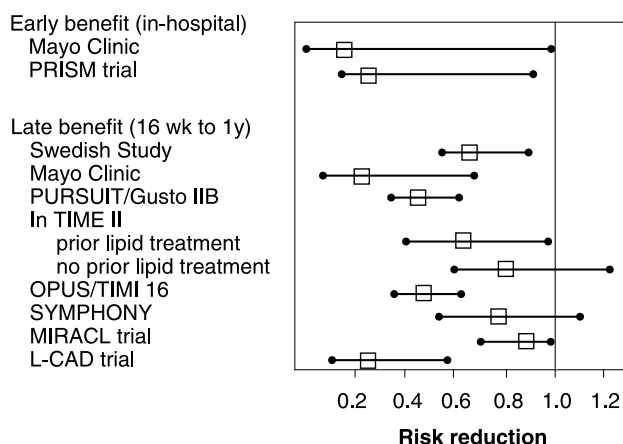
The MIRACL study was, however, subject to a number of limitations.<sup>10</sup> The decrease in incidence of the combined primary end point was primarily due to a reduction in recurrent symptomatic ischaemia requiring hospitalization, and atorvastatin did not appear to prevent the more serious cardiovascular events, including death, and MI. In addition, atorvastatin treatment did not affect the high rate of coronary events during the first 5 weeks after the initial event, and the reduction in events overall was not related to the extent of LDL-C reduction.

### Optimizing lipid therapy in acute coronary syndrome

Aside from these limitations, evidence from MIRACL and the observational studies suggest that statin treatment during ACS has beneficial effects on risk reduction in both the short term (during hospitalization) and long term (up to 1 year) (Fig. 2).<sup>11</sup> Indeed, published guidelines for the prevention of cardiovascular disease endorse the early administration of lipid-lowering therapy in patients presenting with ACS. The National Cholesterol Education Program Adult Treatment Panel III recommends that patients with ACS should receive lipid-lowering therapy on admission or within 24 h.<sup>17</sup> The American College of Cardiology and American Heart Association guidelines for



**Fig. 1** Effect of atorvastatin treatment on time to first ischaemic event (defined as all-cause death, non-fatal myocardial infarction, resuscitated cardiac arrest, recurrent symptomatic myocardial ischaemia with objective evidence requiring emergency rehospitalization) in the MIRACL study. RR, relative risk. (Reproduced with permission from Schwartz et al.<sup>9</sup>)



**Fig. 2** Risk reduction in patients with an acute coronary syndrome treated with lipid-lowering therapy. Mayo Clinic Studies<sup>12,13</sup>; PRISM, The Platelet Receptor Inhibition in Ischemic Syndrome Management<sup>8</sup>; Swedish study;<sup>6</sup> PURSUIT/GUSTO IIB, Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Intelligrin Therapy/Global Use of Streptokinase or t-PA for Occluded Coronary Arteries IIB<sup>5</sup>; InTIME II, Intravenous nPA for Treatment of Infarcting Myocardium Early<sup>14</sup>; OPUS/TIMI 16, Orbofiban in Patients with Unstable Coronary Syndromes/Thrombolysis in Myocardial Infarction Grade 16<sup>15</sup>; SYMPHONY, Sildenafil versus aspirin to Yield Maximum Protection from ischaemic Heart events post-acute coronary syndrome<sup>7</sup>; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering<sup>9</sup>; L-CAD, Lipid-Coronary Artery Disease.<sup>16</sup> (Reproduced with permission from Wright et al.<sup>11</sup>)

non-ST-segment elevation ACS provide more information about the exact timing of statin administration, and recommend starting therapy (along with dietary intervention) 24–96 h after hospital admission and continuing treatment at discharge.<sup>18</sup> In these guidelines, statin treatment is recommended if patients have LDL-C levels >2.6 mmol/l (100 mg/dl).<sup>17,18</sup> However, since a lipid profile assessed during an ACS may not be representative, lipid measurements taken during the past year should be used.<sup>10</sup> After 3 months, lipid levels will have stabilized and statin therapy may be fine-tuned according to each patient's lipid profile.

An important clinical issue relates to the specific lipid treatment which patients admitted with ACS should receive. Further understanding is needed of statin dose and degree of efficacy in the treatment of ACS. A number of studies have shown that statins vary in their ability to lower LDL-C. For example, a recent comparative trial reported LDL-C reductions of 20–30% for pravastatin (10–40 mg/day), 28–46% for simvastatin (10–80 mg/day), 37–51% for atorvastatin (10–80 mg/day) and 46–55% for rosuvastatin (10–40 mg/day).<sup>19</sup> Although there are no clinical trials comparing the ability of statins to mediate pleiotropic effects, those that are more efficacious at inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase may be more effective at reducing the formation of mevalonate and isoprenoid intermediates and therefore have increased pleiotropic actions.

Clinical studies are ongoing to assess the optimum statin treatment regimen for patients with ACS. The Pravastatin Or atorvastatin Evaluation and Infection Therapy (PROVE IT) trial has randomized approximately 4000 patients with an ACS event within the previous 10 days to receive either pravastatin 40 mg/day or atorvastatin 80 mg/day for approximately 2 years.<sup>20</sup> The

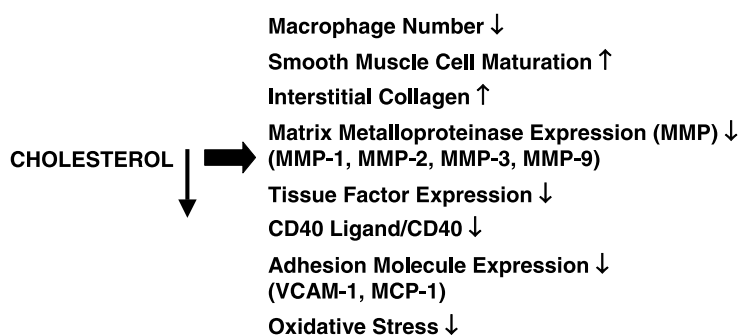
primary end point in this study is the time from randomization until the first occurrence of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization or stroke. Another study, the Limiting Undertreatment of lipids in ACS with Rosuvastatin (LUNAR) study, is currently ongoing and will randomize 1800 patients to receive rosuvastatin 20 mg, rosuvastatin 40 mg or atorvastatin 80 mg within 72 h of hospital admission. Effects on the lipid profile and pleiotropic factors will be assessed over a 12-week period.

### Potential mechanisms for the role of statins in the treatment of acute coronary syndrome

In addition to modifying the lipid profile, statins have cholesterol-independent pleiotropic effects that may contribute to their beneficial effects in ACS, such as improving endothelial function, reducing inflammation and increasing plaque stability.

Preclinical studies indicate that statins improve endothelial function. By inhibiting HMG-CoA reductase, statins reduce the formation of mevalonate and isoprenoid intermediates, thereby preventing the isoprenylation of small GTPases, and up-regulating the expression of endothelial nitric oxide synthase.<sup>21</sup> The subsequent increase in nitric oxide production has been shown to preserve endothelial function, inhibit platelet aggregation and attenuate leucocyte–endothelium interactions.<sup>22–24</sup> Statins may also repair damaged endothelium by promoting mobilization of endothelial progenitor cells and accelerating re-endothelialization of injured vessels.<sup>25–27</sup>

Preclinical and clinical evidence also suggests that statins have anti-inflammatory properties. Several



**Fig. 3** Beneficial effects of lipid lowering on the biology of plaque stability in hypercholesterolaemic rabbits. MMP, matrix metalloproteinase; VCAM, vascular cell adhesion molecule; MCP, monocyte chemoattractant protein. (Reproduced with permission from Libby and Aikawa.<sup>32</sup>)

studies have confirmed that statin therapy reduces C-reactive protein (CRP) levels, a marker for underlying systemic inflammation that has been shown to predict future cardiovascular events in individuals with ACS.<sup>28–31</sup> In a recent randomized trial, plasma levels of CRP increased significantly from baseline during the first 5 days after an ACS event in patients treated with placebo (188%;  $P = 0.048$ ), but were not significantly different from baseline in patients treated with atorvastatin.<sup>31</sup>

In addition to mediating plaque stability by reducing inflammation, statins may increase plaque stability via a number of other mechanisms (Fig. 3). For example, matrix metalloproteinases (MMPs) degrade collagen and weaken the fibrous cap of atherosclerotic plaque, thereby promoting further events.<sup>32,33</sup> Preclinical evidence indicates that statins reduce the expression of MMPs and this may lead to increased plaque stability.<sup>34</sup>

A number of the mechanisms determined by experimental studies have been confirmed in the clinical setting. In a study of patients with familial hypercholesterolaemia, simvastatin and atorvastatin markedly decreased serum levels of the pro-inflammatory soluble CD40 ligand (CD40L).<sup>35</sup> Interestingly, reductions in CD40L did not correlate with changes in cholesterol levels, suggesting that the effect was independent of lipid lowering.<sup>35</sup> Short-term simvastatin therapy has also been shown to improve cardiac function in a recent study of patients with non-ischaemic cardiomyopathy, and this was accompanied by significant reductions in inflammatory cytokines and improved neurohormonal imbalance.<sup>36</sup>

## Conclusions

The utility of statins in the treatment of ACS is still under investigation. Nevertheless, available data support the routine initiation of lipid-modifying therapy before hospital discharge for reducing recurrent coronary events in the months following an ACS event. Preclinical and clinical studies have also highlighted a number of cholesterol-dependent and -independent mechanisms that

may be responsible for the positive effects of statins. However, further studies are required to ascertain the most appropriate agent and dose to improve outcomes in patients with ACS.

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