In-Hospital Initiation of Statin Therapy in Acute Coronary Syndromes*

Maximizing the Early and Long-term Benefits

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Patients with acute coronary syndrome (ACS) are at high risk for recurrent coronary events, sudden death, and all-cause mortality. Conventional revascularization therapies reduce the risk of further ischemia but do not affect the underlying atherosclerotic disease. Statins have a proven record in the secondary prevention of coronary heart disease. Furthermore, statins have been shown to exert varying degrees of pleiotropic effects, which may stabilize vulnerable atherosclerotic plaques. A compelling body of evidence from randomized controlled trials demonstrates that high-dose, potent statin therapy initiated immediately after an acute coronary event can significantly reduce early as well as longer-term morbidity and mortality. Furthermore, high-dose, potent statin therapy displays a reasonable safety profile. National guidelines now recommend that in patients with ACS, statin therapy should be initiated in hospital prior to discharge, irrespective of baseline low-density lipoprotein cholesterol levels, to improve clinical outcomes. Every effort should be made to ensure all eligible patients with ACS are initiated and maintained on statin therapy.

Key words: acute coronary syndrome; atherothrombosis; high-sensitivity C-reactive protein; low-density lipoprotein cholesterol; statin

Abbreviations: ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; A to Z = Aggrastat to Zocor; CAD = coronary artery disease; CHAMP = Cardiac Hospitalization Atherosclerosis Management Program; CI = confidence interval; CK = creatine kinase; HPS = Heart Protection Study; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiac event; MI = myocardial infarction; MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; NCEP-ATP III = National Cholesterol Education Program Adult Treatment Panel III; PROVE IT-TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22; UA = unstable angina

Acute coronary syndrome (ACS), which is associated with high rates of morbidity and mortality, refers to the spectrum of acute myocardial ischemia, including unstable angina (UA), ST-segment elevation myocardial ischemia, and acute myocardial ischemia without ST-segment elevation.1-3 The risk of recurrent ischemic events is greatest in the weeks and months immediately following ACS. Despite the widespread use of conventional therapies aimed at modifying platelet function and the coagulation cascade to reduce the risk of further ischemia, patients who have experienced an ACS continue to be at high cardiac risk. Nearly 25% of men and 38% of women die within 1 year of having a first myocardial infarction (MI).4 These statistics highlight the need for improved strategies that target the pathophysiologic mechanisms operating in ACS and treat the underlying atherosclerotic disease.

Evidence from numerous large, randomized, controlled trials5,6 unequivocally demonstrates the ability of statins to reduce coronary morbidity and mortality. However, while the benefits of statin therapy in patients with stable coronary artery disease (CAD) are clearly recognized, it is only recently that the positive impact of initiating statin treatment immediately following the occurrence of ACS has emerged.7,8 This review will present evidence supporting early initiation of statin therapy in ACS, including results from hospital-based initiatives that guide physicians to prescribe statins prior to patient discharge in order to improve treatment rates, patient adherence, and clinical outcomes.

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Manuscript received March 23, 2005; revision accepted May 2, 2005.

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Understanding ACS and Therapeutic Strategies in ACS

Atherothrombosis is the major cause of ACS. It has now become clear that coronary atherosclerosis is not simply an inevitable consequence of aging but rather a chronic inflammatory process that can be converted into an acute clinical event by plaque rupture and arterial thrombosis. Contemporary models suggest that atherosclerotic plaques are not merely passive structures but dynamic inflammatory lesions. Fatty streaks, which can be detected in the arterial intima as early as adolescence, progress into more complicated raised lesions composed of inflammatory cellular material, along with cholesterol ester. Lesions develop into mature atheroma and are vulnerable to rupture. Although the exact inciting factors of the vulnerable plaque rupture are not fully understood, inflammation is accepted to be a pivotal event. The rupture of an unstable atherosclerotic plaque results in the lipid core coming into contact with circulating blood, which triggers platelet activation and coagulation, leading to thrombosis.

While the underlying molecular processes of atherogenesis are complex, they are amenable to therapeutic intervention. After an ACS, the primary goal of therapy is to reduce the risk of further ischemic complications. Antiplatelet therapy is the foundation of immediate ACS management. Therapies to decrease platelet aggregation include aspirin, the thienopyridine agent clopidogrel, and platelet glycoprotein IIb/IIIa antagonists. In addition, a fundamental aspect of treatment involves the use of anticoagulant agents such as unfractionated heparin and newer low-molecular-weight heparins. Anti-ischemic treatments include the use of nitrates and β-blockers. Neurohumoral agents such as angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and aldosterone antagonists are utilized for early and long-term cardioprotection.

A critical aspect of preventing future coronary events is stabilizing vulnerable lesions. Although significant therapeutic advances in the treatment of ACS have been made with antiplatelet and anti-thrombotic therapy during the past decade, these therapies alone do not appear to completely stabilize unstable plaques. Results from several clinical trials suggest that early administration of high-dose, potent statin therapy following an ACS may stabilize vulnerable plaques decreasing adverse outcomes in both the short-term and long-term. The likely mechanisms of benefit are not solely attributed to the lipid-lowering effects of statins but, at least in part, to the variety of antiinflammatory and antiproliferative effects, commonly described as pleiotropic effects, exerted by statins. Pleiotropic effects commonly ascribed to statins include improvements in endothelial function and vasomotion, reductions in platelet aggregability and thrombus formation, fibrinolytic and antioxidant activity, as well as decreases in matrix degradation due to reductions in macrophage metalloproteinase production and increases in collagen content. Furthermore, statins are proposed to reduce inflammation within plaques. The most widely examined inflammatory biomarker is high-sensitivity C-reactive protein (hsCRP). Elevated levels of hsCRP have been correlated with increased cardiovascular risk and mortality. C-reactive protein binds to oxidized low-density lipoprotein cholesterol (LDL-C) and apoptotic cells but not to native LDL-C or healthy cells, signifying an association with atherosclerotic plaques. Reductions in hsCRP levels achieved with intensive statin therapy appear to correlate with increased clinical benefit in patients who have experienced an ACS.

Evidence From Clinical Studies

Observational Studies

Results from a number of observational studies have suggested that initiating statin therapy immediately after an acute coronary event is associated with significant reductions in recurrent coronary events and death. The Swedish Register of Information and Knowledge about Swedish Care Units examined the relationship between 1-year mortality and statin therapy initiated during hospitalization or at discharge in patients with first registry-recorded acute MI. The 58-hospital database included patients admitted to Swedish hospitals between 1995 and 1998. Of these patients, 5,528 (mean age, 62 years; 72% male) received statin therapy compared with 14,071 (mean age, 67 years; 70% male) who did not. The unadjusted mortality rate after 1 year was 4.0% (219 deaths) for statin-treated patients and 9.3% (1,307 deaths) for those who did not receive statin treatment. Following adjustment with regression analysis for confounding factors and propensity score for statin use, early statin treatment was associated with a 1.3% absolute risk reduction in 1-year mortality for hospital survivors of acute MI (relative risk, 0.75; 95% confidence interval [CI], 0.63 to 0.89; p = 0.001).

An observational study that pooled data from two large, international, randomized, controlled trials, Global Use of Streptokinase or t-PA for Occluded Coronary Arteries (GUSTO IIb) and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Sup-
expression Using Integrilin Therapy (PURSUIT) also examined the effect of in-hospital lipid-lowering therapy on short-term mortality immediately after an acute ACS. All-cause mortality in 3,653 patients (median age, 62 years; 66% male) that were prescribed lipid-lowering therapy was compared with 17,156 (median age, 65 years; 68% male) who were not. Lipid-lowering therapy was associated with a smaller proportion of deaths at 30 days (17 deaths [0.5%] vs 179 deaths [1.0%]; hazard ratio 0.44; 95% CI, 0.27 to 0.73; p = 0.001) and at 6 months (63 deaths [1.7%] vs 605 deaths [3.5%]; hazard ratio, 0.48; 95% CI, 0.37 to 0.63; p < 0.0001). Even after a propensity analysis was performed to adjust for presumed selection bias in the prescription of a lipid-lowering agent and other potential confounders, prescription of a lipid-lowering agent at hospital discharge remained associated with a significantly reduced risk of death at 6 months (hazard ratio, 0.67; 95% CI, 0.48 to 0.95; p = 0.023).

In contrast, in the Sibrafiban vs Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-Acute Coronary Syndromes study, there was no relationship observed between early initiation of statin therapy in ACS and improved clinical outcomes after extensive propensity matching. Data were derived from a combined database of two randomized clinical trials comparing the effects of aspirin to sibrafiban (oral platelet glycoprotein IIb/IIIa inhibitor) in 12,365 ACS patients who were not receiving statin therapy prior to the acute coronary event. A total of 8,413 patients (median age, 61 years; 72% male) who had never received a statin were compared with 3,952 patients (median age, 56 years; 75% male) who were prescribed early treatment with a statin (median, 2.0 days; interquartile range, 1.0 to 3.1 days for initiation of drug therapy). Both 90-day and 1-year mortality rates were dramatically lower for the statin-treated patients in an unadjusted analysis; however, there was no difference in the mortality rate after extensive multivariate statistical adjustments for propensity to prescribe and covariate factors.

It is important to note that in the observational studies assessing the effect of statin therapy in patients with ACS, there were significant differences in the baseline characteristics and in other therapies provided to ACS patients treated and not treated with statins. Despite multivariate and propensity adjustments, there may be a number of residual confounders accounting for the lower mortality rates observed. Despite this limitation, the extent and concordance of the observational data supporting a positive influence of statin therapy in patients with ACS merits consideration. Moreover, these observational studies corroborate the lack of adverse effects of statins when administered following an acute coronary event, and support their overall safety within a complex milieu of drug therapies commonly prescribed during the acute phase. Randomized clinical trials, including the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial and the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, have now provided definitive evidence of the early and long-term efficacy of statins in the treatment of ACS. Therefore, these data suggest that statin therapy should form part of the standard treatment regimen for patients with ACS.

Randomized Controlled Trials

Clinical trials have unequivocally demonstrated that statin treatment reduces cardiovascular morbidity and mortality in patients at high risk of coronary heart disease, as well as in patients with established but stable heart disease. However, prior to the MIRACL and PROVE IT-TIMI 22 trials, no large-scale, randomized, placebo- or active-controlled trial had investigated the effects of statins in patients who had recently had an ACS (Fig 2).

MIRACL

The MIRACL trial was specifically designed to address the gap in knowledge regarding the effects of statin therapy in patients with ACS. A total of 3,086 adults ≥ 18 years old with UA or non-Q-wave acute MI were randomized within 24 to 96 h of hospital admission to receive treatment with atorva-
The primary end point of the trial—death, cardiac arrest, MI, or worsening UA requiring emergency hospitalization at 16 weeks—occurred in 17.4% (269 patients) of the placebo group and 14.8% (228 patients) of the atorvastatin group (relative risk reduction, 16%; 95% CI, 0 to 30; p = 0.048) [Fig 3]. This benefit was due mainly to a significant reduction in recurrent symptomatic ischemia requiring emergency rehospitalization. The atorvastatin group also had a lower risk of symptomatic ischemia with objective evidence and requiring emergency rehospitalization (6.2% vs 8.4%; relative risk, 0.74; 95% CI, 0.57 to 0.95; p = 0.02). In addition, the reduction in risk for the primary end point with atorvastatin appeared to be independent of baseline LDL-C levels.

The MIRACL trial demonstrated that atorvastatin, 80 mg, was effective in reducing the composite of clinical events within the first 16 weeks of an ACS. Furthermore, the MIRACL trial demonstrated that atorvastatin treatment is safe and well tolerated when administered after an acute coronary event. The frequency of serious adverse events for atorvastatin, 80 mg/d, was comparable to placebo (<1%), with no reported cases of myositis. Abnormal liver transaminases (more than three times the upper limit of normal) were low but more common in the atorvastatin group than the placebo group (2.5% vs 0.6%, p < 0.001).

While the results of the MIRACL trial were encouraging, many questions remained. As only the 80-mg dose of atorvastatin was tested, it was unclear whether other less-potent statins and/or lower doses of atorvastatin could yield similar effects. Patients for whom coronary revascularization surgery was planned within 24 to 96 h of the onset of an ACS were excluded from the MIRACL trial. Omission of this large subpopulation of patients was cited as a weakness in the study design, leading some to question whether similar benefits would be seen in an ACS patient population being treated with the invasive management strategy.

**PROVE IT-TIMI 22**

The PROVE IT-TIMI 22 trial has extended the findings of the MIRACL trial, while also demonstrating the greater benefits of intensive lipid-lowering therapy with atorvastatin, 80 mg, compared to conventional lipid-lowering therapy with pravastatin, 40 mg. In total, 4,162 men and women aged > 18 years who had been hospitalized for an ACS within the preceding 10 days (patients had to be in stable condition and were enrolled after a percutaneous revascularization procedure if one was planned) were randomized to either standard therapy (pravastatin, 40 mg/d) or intensive therapy (atorvastatin, 80 mg/d) for a mean follow-up period of 2 years. The combined primary end point was death from any cause, MI, documented UA requiring hospitalization, stroke, and revascularization surgery performed after 30 days from randomization. At 2 years, primary end point event rates were 26.3% in the pravastatin 40 mg/d group and 22.4% in the atorva-
statin 80 mg/d group, representing a 16% relative reduction in favor of atorvastatin (absolute risk reduction, 3.9%; 95% CI, 5 to 26; p = 0.005) [Fig 4]. Among the individual components of the primary end point, there was a consistent pattern of benefit favoring high-dose atorvastatin over standard-dose pravastatin, which included a significant 14% reduction in the need for revascularization (p = 0.04), a 29% reduction in the risk of recurrent UA (p = 0.02), and trends for reductions in the rates of all-cause mortality (28%, p = 0.07) and of death or MI (18%, p = 0.06). This benefit was seen on top of a background of evidence-based ACS management. Three fourths of the patients were treated with an early invasive strategy, and the majority of patients were treated with multiple medications for secondary prevention, including antiplatelet therapy, β-blockers, and ACE inhibitors. The benefits of intensive statin treatment as compared with standard therapy were apparent as early as 30 days and were consistent over time. Analysis also revealed that the benefit of high-dose atorvastatin was consistent across the prespecified subgroups, which included men and women, patients with UA and those with MI, and those with or without diabetes mellitus. Moreover, the higher dose of atorvastatin was associated with a safety profile that was comparable to that observed with the lower dose of pravastatin. The rates of discontinuation of treatment due to an adverse event, patient preference, or for other reasons were 21.4% in the pravastatin group and 22.8% in the atorvastatin group at 1 year (p = 0.30) and 33.0% and 30.4%, respectively, at 2 years (p = 0.11). The percentage of patients who had elevations in creatine kinase (CK) levels more than three times the upper limit of normal was 1.5% in the atorvastatin group and 1.1% in the pravastatin group. Furthermore, discontinuation from myalgia or CK elevations was comparable between groups (2.7% of pravastatin-treated patients vs 3.3% of atorvastatin-treated patients [p = 0.23]).

The results from the PROVE IT-TIMI 22 trial provided compelling evidence that among ACS patients, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen. These findings indicate that patients with ACS derive substantial benefit from early and continued lowering of LDL-C to levels substantially below conventional National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) target levels in addition to other standard ACS treatments.

Other Trials

In addition to the MIRACL and PROVE IT-TIMI 22 trials, clinical trials have also assessed the benefits of other statin regimens following an ACS. The data from these trials do not consistently demonstrate significant clinical event reductions but do provide further evidence of benefit.

The Fluvastatin on Risk Diminishing After Acute Myocardial Infarction Trial

The Fluvastatin on Risk Diminishing After Acute Myocardial Infarction trial studied the effect of early statin therapy on major adverse cardiac events (MACEs) in 540 patients with ACS whose cholesterol values were < 250 mg/dL. Patients were randomized within 14 days of an ACS. The primary end point of the trial was the effect of fluvastatin, 80 mg, on cardiac ischemia measured by ambulatory ECG monitoring at 6 weeks and 12 months after ACS. There was no significant difference in ambulatory ischemia at 6 weeks or 12 months between the groups, and 1-year mortality in the fluvastatin group was 2.6%, vs 4.0% in the placebo group. While the study was not powered to assess the incidence of MACEs, there was a trend toward improvement in cardiac events in patients with severe ischemia at baseline in the fluvastatin group (p = 0.084).

The Pravastatin in Acute Coronary Treatment Trial

The Pravastatin in Acute Coronary Treatment trial assessed the effects of administering pravastatin within 24 h of the onset of symptoms in patients with UA, non-ST-segment elevation MI, or ST-segment elevation MI. A total of 3,408 patients were
randomly assigned to treatment with pravastatin, 20 to 40 mg (n = 1,710), or matching placebo (n = 1,698) for a 4-week period. The primary end point of a composite of death, recurrence of MI, or readmission to hospital for UA within 30 days occurred in 199 patients (11.6%) in the pravastatin group and in 211 patients (12.4%) in the placebo group. A relative risk reduction of 6.4% favored allocation to pravastatin but was not statistically significant (95% CI, −13.2 to 27.6%).43

**The Lescol Intervention Prevention Study**

The Lescol Intervention Prevention Study44 examined the effect of in-hospital initiation of statins in patients undergoing percutaneous coronary intervention with stent. Of these patients, 50% had an ACS. A total of 1,677 patients with total cholesterol levels between 135 mg/dL and 270 mg/dL were randomly assigned to receive fluvastatin, 80 mg/d (n = 844), or matching placebo (n = 833) at hospital discharge following percutaneous coronary intervention. The median follow-up period was 3.9 years. The study end point was a composite of MACEs, defined as cardiac death, nonfatal MI, or a reintervention procedure. At follow-up, MACE-free survival time was significantly longer in the fluvastatin group compared with the placebo group (p = 0.01). While 21.4% of the patients in the fluvastatin group had at least one MACE, one or more MACEs occurred in 26.7% of the patients in the placebo group (p = 0.01). Of interest is the fact that this result was not dependent on baseline total cholesterol levels.

**The Aggrastat to Zocor Trial**

The Aggrastat to Zocor (A to Z) trial,45 a large, randomized, double-blind, controlled trial, compared the early initiation of an intensive statin regimen with delayed initiation of a less-intensive regimen in patients with ACS. The investigators randomized 4,497 patients following an ACS event to receive either simvastatin, 40 mg/d, for 1 month and then 80 mg/d thereafter (n = 2,265) or to a regimen of placebo for 4 months and then simvastatin, 20 mg/d, thereafter (n = 2,232). The intensive regimen failed to show a statistically significant benefit for reducing the primary composite end point of cardiovascular death, MI, readmission for ACS, or stroke compared with the less-intensive regimen (absolute risk reduction, 2.3%; hazard ratio, 0.89; 95% CI, 0.76 to 1.04; p = 0.14).

A number of explanations have been proposed to explain why the clinical benefit observed with intensive statin therapy in the MIRACL and PROVE IT-TIMI 22 trials was not mirrored in the A to Z trial. In an editorial21 accompanying the publication of the A to Z trial results, it was speculated that, taken together, the MIRACL, PROVE IT-TIMI 22, and A to Z trials demonstrated that the beneficial effects of statin therapy in ACS cannot be predicted entirely from the degree of LDL-C reduction. The authors21 attributed the favorable clinical benefits observed with intensive statin therapy in the MIRACL and PROVE IT-TIMI 22 trials to increases in hsCRP levels. In the MIRACL and PROVE IT-TIMI 22 trials, the difference in hsCRP levels between treatment groups was 34% and 38%, respectively, at trial completion. In the A to Z trial, the between-group reduction was much smaller (16.7%; Table 1). The authors21 proposed that the early benefits of statin therapy may be derived largely from the antiinflammatory effects of the drugs, whereas the delayed benefits are more likely to be lipid modulated. This view is also sup-

<table>
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<th>PROVE IT-TIMI 22 Trial</th>
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*Reproduced with permission from Nissen.21 NA = data not available.† SI conversion factor: to convert LDL-C to mmol/L, multiply by 0.0259.‡ Measured 120 days after randomization.¶ Measured 90 days after randomization. †‡ Elevation of CK level higher than 10 times the upper limit of normal.
ported, at least in part, by the A to Z trial investigators,45 who commented that the lack of a concurrent antiinflammatory effect, determined by hsCRP levels, in the A to Z trial may have contributed to the delayed treatment effect observed. The A to Z trial design had patients in the intensive simvastatin study arm not being titrated up to the 80 mg/d dose until after the first month. The investigators45 postulated that intensive therapy may be required immediately after the onset of ACS during the period of greatest clinical instability to achieve greatest clinical benefit.

The PROVE IT-TIMI 22 investigators also evaluated relationships between LDL-C and hsCRP levels achieved after treatment and the risk of recurrent MI or death from coronary causes (Fig 5). Patients in whom statin therapy resulted in LDL-C levels $< 70 \text{ mg/dL}$ had lower event rates than those with higher levels ($2.7$ events vs $4.0$ events per 100 person-years, $p = 0.008$). A similar difference was observed between those who had hsCRP levels $< 2 \text{ mg/L}$ after statin therapy and those who had higher levels ($2.8$ events vs $3.9$ events per 100 person-years, $p = 0.006$), an effect present at all levels of LDL-C achieved. For patients with posttreatment LDL-C levels $\geq 70 \text{ mg/dL}$ and a hsCRP level $\geq 2 \text{ mg/L}$, the event rate was $4.6$ per 100 person-years. Patients who had LDL-C levels $< 70 \text{ mg/dL}$ and hsCRP levels $< 2 \text{ mg/L}$ after statin therapy had the lowest rate of recurrent events ($1.9$ events per 100 person-years). In addition, atorvastatin was more likely than pravastatin to result in low levels of LDL-C and hsCRP.

**Figure 5.** The PROVE IT-TIMI 22 trial: the relationship between LDL-C and hsCRP levels achieved after treatment and the risk of recurrent MI or death from coronary causes. LDL = low-density lipoprotein. Reproduced with permission from Ridker et al.50

**Translating Evidence Into Practice**

Despite the compelling scientific evidence that secondary prevention medical therapies reduce mortality in patients with established CAD, these therapies continue to be underutilized in patients receiving conventional care. The timing for initiation of appropriate therapy in ACS patients is critical due to the elevated risk for subsequent coronary events. Although it is well known that there is long-term benefit with lipid-lowering therapy in secondary prevention, prescribing a statin immediately after an acute coronary event is often not considered because of several factors. Firstly, LDL-C levels decline within hours of an acute coronary event, thus measurements taken during the acute phase can be erroneous. Consequently, it may not be evident that the patient requires lipid-lowering therapy, or physicians may simply decide to wait until more accurate values are obtainable. Secondly, there is the question of whether lipid lowering is effective in treating the short-term complications of ACS. For some physicians, the supposition is that the positive impact of lipid-lowering therapy manifests only over a longer time scale; therefore, they may view it as preferable to wait rather than add another medication during this unstable period.

Hospital-based programs such as the Cardiac Hospitalization Atherosclerosis Management Program (CHAMP),46 Guidelines Applied in Practice,47 American Heart Association’s Get With The Guidelines Program, and others48,49 have demonstrated that prescribing cardiovascular protective therapies prior to hospital discharge in ACS patients is associated with long-term patient compliance and improved clinical outcomes. The CHAMP initiative focused on in-hospital initiation of a combination of cardiovascular protective medications (ie, aspirin, statins [irrespective of baseline LDL-C], β-blockers, and ACE inhibitors) in conjunction with diet and exercise counseling before hospital discharge in patients with established CAD. Treatment rates and clinical outcome were compared in patients discharged after ACS in the 2-year period before (1992–1993) and the 2-year period after (1994–1995) CHAMP was implemented. In the pre- and post-CHAMP patient groups, among other significant increases in medication usage, statin use increased from $6\%$ to $58\%$ ($p < 0.01$). In-hospital initiation of therapy resulted in a dramatic improvement in long-term medication adherence rates. There was also a significant increase in patients achieving an LDL-C level $\leq 100 \text{ mg/dL}$ ($6\%$ vs $58\%$, $p < 0.001$). The increased use of evidence-based therapies resulted in a substantial reduction in recurrent MI and a $57\%$ reduction in 1-year mortality.

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These improvements in treatment rates have been sustained over a 10-year period (Fig 6). The proof of concept provided by CHAMP shows that in-hospital initiation of lipid lowering and other evidence-based cardiovascular protective therapy results in improved treatment rates, more patients achieving goal, and improved clinical outcomes. Many other studies have now confirmed these findings.

From Clinical Trials to Guideline Recommendations

The results of the MIRACL and CHAMP studies, among other studies, prompted the National Cholesterol Education Program to revise the approach taken to initiating lipid-lowering medications. The NCEP-ATP III guidelines recommended in-hospital initiation of lipid-lowering medications in conjunction with diet and exercise counseling as the standard of care. The PROVE IT-TIMI 22 trial has now greatly strengthened the case for intensive LDL-C lowering immediately following an ACS. A revision to the NCEP-ATP III guidelines states that statin therapy should be considered for all patients who have experienced an acute coronary event, irrespective of baseline LDL-C. The American College of Cardiology/American Heart Association now recommend with a class I indication that statin therapy be initiated soon after an ACS if LDL-C levels are > 100 mg/dL and that statin therapy be considered (class IIA indication) in patients with ACS if LDL-C levels are < 100 mg/dL or unknown.53

National guidelines thus indicate that statin therapy, in the absence of contraindications or intolerance, should be initiated in the hospital prior to discharge. Furthermore, as an ACS event may affect LDL-C levels, lipid values measured prior to manifestation of ACS symptoms may be used for treatment decision making. When previous lipid values are unavailable, the default action should be to prescribe a statin. This conclusion is supported by results from major clinical outcome trials that indicate statins produce a clear benefit in reducing coronary morbidity and mortality regardless of baseline cholesterol values. In the Heart Protection Study (HPS), reducing LDL-C from < 3 mmol/L to < 2 mmol/L (ie, from < 116 mg/dL to < 77 mg/dL) was found to produce a similar reduction in risk (approximately 25%) to lowering LDL-C by 1 mmol/L from higher LDL-C concentrations. Furthermore, the PROVE IT-TIMI 22 trial data indicate that patients recently hospitalized for an ACS benefit from early and continued lowering of LDL-C to levels substantially below current guideline recommendations (< 100 mg/dL).

Hospital systems, critical pathways, and tool kits have emerged as a more effective means of overcoming physician, patient, and health-system barriers to implementing evidence-based therapies. Such programs can be used to address early and long-term ACS management and secondary prevention as part of hospital treatment and pre-hospital discharge planning. There is now compelling evidence that intensive statin therapy should be integrated into the ACS critical pathway. Improved use of statin treatment in ACS is an advance that will significantly improve patient care.
**Pharmacoeconomic Data**

In conjunction with clinical trial data supporting the efficacy of administering a statin immediately after a patient has had an ACS, economic data also suggest that this is a cost-effective option.\textsuperscript{56} For example, an economic analysis was conducted using clinical outcomes in the MIRACL trial. The direct cost of atorvastatin was largely offset by the associated decrease in the cost of managing cardiovascular events. This is especially valuable because the coronary event rate in ACS is several times greater than in patients with stable CAD. The net incremental cost of atorvastatin treatment was $157 per patient with a cost-effectiveness ratio of 4,086 dollars per event avoided.

**Conclusions**

Randomized clinical trials demonstrate the early and long-term benefits of in-hospital initiation of intensive statin therapy immediately following an ACS. The collective results from these studies indicate that statin therapy initiated soon after an acute coronary event is both effective and safe.\textsuperscript{30,32,57,58} Evidence suggests that, in addition to their lipid-lowering properties, statins mediate robust pleiotropic actions that contribute to plaque stabilization and improved endothelial function.\textsuperscript{39–62} The putative effects of statins that are independent of lipid-lowering include antithrombotic, antioxidant, and antiinflammatory actions. Inflammation is a primary factor in the rupture of culprit lesions in ACS. Clinical data indicate that intensive statin therapy can modify the inflammatory process by substantially reducing levels of hsCRP.\textsuperscript{29}

It is imperative that physicians practice evidence-based medicine in order to treat ACS patients effectively.\textsuperscript{16} Waiting to initiate statin therapy is ineffective, as this delay in treatment is associated with a greater incidence of death and risk of further complications. Statin treatment should be initiated in patients, regardless of their cholesterol levels, within 24 to 96 h following an ACS, prior to hospital discharge, therefore allowing the patient to accrue maximal clinical benefit. Results from randomized, controlled trials, in particular the MIRACL and PROVE IT-TIMI 22 trials, support this strategy. Hospital-based programs, such as CHAMP, demonstrate that initiating treatment prior to hospital discharge is associated with improved clinical outcomes, increased patient compliance, and greater achievement of lipid goals. Recent treatment guidelines reflect this clinical trial evidence and recommend early initiation of statin therapy in patients with ACS as the national standard of care.

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