The Effect of Early, Intensive Statin Therapy on Acute Coronary Syndrome

A Meta-analysis of Randomized Controlled Trials

Eddie Hulten, MD, MPH; Jeffrey L. Jackson, MD, MPH; Kevin Douglas, MD, MPH; Susan George, MD; Todd C. Villines, MD

Background: In addition to well-established secondary prevention benefits for atherosclerotic coronary artery disease, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are hypothesized to have short-term benefit in acute coronary syndrome (ACS), yet the data are inconsistent, with some trials underpowered to demonstrate therapeutic benefit. Our objective was to determine the effects of early, intensive statin therapy for ACS.


Study Selection: Randomized controlled trials of statins begun within 14 days of hospitalization for ACS were included.

Data Extraction: Two investigators independently abstracted study quality, characteristics, and outcomes.

Data Synthesis: Thirteen randomized controlled trials published before May 2006 were available, involving 17,963 adults (median number of patients, 135; median follow-up, 6 months). Early, intensive statin therapy for ACS decreased the rate of death and cardiovascular events over 2 years of follow-up (hazard ratio, 0.81 [95% confidence interval, 0.77-0.87]) (Q=58.54; P<.001; I²=95%). Survival curves revealed that this benefit begins to occur between 4 and 12 months, achieving statistical significance by 12 months. There was no evidence of publication bias, and sensitivity analyses did not identify a dominating study or study characteristic.

Conclusions: Early, intensive statin therapy reduces death and cardiovascular events after 4 months of treatment. The validity of this finding would be strengthened by an analysis of individual patient data.

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Author Affiliations: Departments of Internal Medicine (Drs Hulten and George), General Internal Medicine (Drs Jackson and Douglas), and Cardiology (Dr Villines), Walter Reed Army Medical Center, Washington, DC; and Uniformed Services University of the Health Sciences, Bethesda, Md.
pravastatin, cerivastatin, fluvastatin, rosvastatin, pitavastatin, mevastatin, lovastatin, acute coronary syndrome, and myocardial infarction. Search results were limited to randomized controlled trials in adults (age > 18 years). References of reviewed articles were also searched for relevant titles.

STUDY SELECTION

Two reviewers independently conducted the literature search and extraction of relevant articles. The title and abstract of potentially relevant studies and review articles were screened for appropriateness before retrieval of the full articles. We included randomized controlled trials in adults involving comparison of early, intensive statin therapy with some control arm within 14 days of hospitalization for ACS. We defined early statin therapy as being initiated within 14 days of hospitalization for ACS. We defined intensive therapy as a medication regimen begun at a higher than usual dose than recommended by routine treatment following National Cholesterol Education Panel (NCEP) guidelines.9

VALIDITY ASSESSMENT

Two reviewers independently rated study quality using the Jadad instrument for the assessment of the quality of trial reports.10 The Jadad instrument is a point scale ranging from 0 to 8, with points derived from the description of randomization, blinding, inclusion and exclusion criteria, withdrawals, and method of assessing adverse events.

DATA ABSTRACTION

We abstracted characteristics of the study (author, year, country, design, duration, statin name and dosage, comparator drug or placebo, time to initiation of statin therapy, duration of follow-up, and sample size); and patients (age, sex, and baseline and follow-up LDL-C levels). Outcomes abstracted included the combined primary end point from each trial in addition to the individual outcomes of death, myocardial infarction (MI), and hospitalization for recurrent ischemia. Two reviewers independently abstracted data, and disagreements were resolved by consensus.

QUANTITATIVE DATA SYNTHESIS

Hazard ratios (HRs) were abstracted and pooled using the methods of Parmar et al.11 In brief, the number of subjects at risk who had the event of interest or who were censored for other reasons for each arm in each trial was abstracted at the nonoverlapping time points: 1 month, 4 months, 1 year, and 2 years. These time points were selected to maximize the amount of data that was directly reported, minimizing the need to calculate data from survival curves. From these data, for each trial, an overall HR was calculated by pooling the natural log of the HR using the inverse of the variance as weights. Variance was calculated based on the number of events and patients at risk in each arm, separately for each time interval, as suggested by Parmar et al.11 The overall HR for each study was then pooled using the random effects model of DerSimonian and Laird.12 Survival curves were created by calculating the event rate, for both arms, based on the number of patients still eligible to have the outcome during that period and the number of events. Variance of these proportions was based on exact binomial methods. These proportions were pooled, at each time point, using the random effects model of DerSimonian and Laird.12 Pooled survival curves were compared using log-rank methods. Assessment for publication bias was done using the modified method of Macaskill et al.13 based on linear regression using the natural log of the HR as the dependent variable and the inverse of the total sample size as the independent variable, as suggested by Peters et al.15

Heterogeneity was assessed by using the I² statistic.16 The I² statistic provides an estimate of the amount of variance due to heterogeneity rather than chance and is based on the traditional measure of variance, the Cochrane Q statistic. We conducted a stratified analysis to assess for potential confounders’ contribution to heterogeneity, including study duration (greater than or less than or equal to the median duration); change in LDL-C level (greater than or less than or equal to the median change in LDL-C level); time to initiation of statin therapy; and study quality. Meta-regression analysis was performed using the same independent variables.16 Meta-regression (restricted maximum likelihood method) was used to calculate the estimated between-study variance (τ² statistic) as a measure of the residual heterogeneity, having adjusted for the covariates. The sensitivity analysis of the effect of quality was based on a component’s analysis in which each quality domain in the Jadad scale was serially tested to see if it had an effect on our study’s reported HRs. To exclude the possibility that any one study was exerting excessive influence on the results, we conducted a sensitivity analysis by systematically excluding each study at a time and then rerunning the analysis to assess the change in effect size. All analyses were performed with Stata version 9.2 (StataCorp, College Station, Tex). All P values were 2 sided with an α level of .05. We followed the QUORUM (the Quality of Reporting Meta-analyses) guidelines for reporting and discussing these meta-analytic results.17

RESULTS

LITERATURE SEARCH

This meta-analysis included 17,963 subjects from 13 trials (Figure 1).18-30 Trials that measured inflammatory markers or angiogram data without clinical outcomes were excluded because they did not meet our a priori search criteria. For example, the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial was excluded because it did not evaluate clinical end points but instead measured atherosclerotic plaque volumes.31 The Prevention of Ischemic Events by Early Treatment with Cerivastatin (PRINCESS) trial was terminated early; we excluded it because it has only been published in abstract form.32 The IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid lowering) trial was excluded because patients were not enrolled within 14 days of hospitalization for ACS (average of 22 months after MI).33
Eligible studies compared treatment with a statin with placebo (9 trials),18,22-26,28-30 placebo for 4 months followed by a lower dose of statin (1 trial),21 a lower dose of statin (1 trial),19 or usual care per the discretion of the patient’s physician (2 trials).20,27 Four studies were international, multicenter trials; 1 was a multicentered trial in the Netherlands, and the remaining were single-center trials in Australia, Germany, Belgium, Canada, Italy, Japan, Turkey, and the Netherlands. The median number of participants in each study was 135 (range, 60-4497). Statins studied included atorvastatin, 80 mg (3 studies);19,20,28 atorvastatin, 20 mg (1 study);27 pravastatin, 40 mg (6 studies);9,18,22-25,30 fluvastatin, 80 mg (2 studies);26,29, and simvastatin, 80 mg (1 study).21 Time to initiation of statin therapy ranged from 1 to 14 days, with a median duration of 4 days. All studies measured death, recurrent MI, and hospital readmission for ACS as an a priori primary outcome. The median duration of follow-up was 6 months (range, 1-48). The mean age of participants was 60 years, and 76% of the participants were male. Agreement for study selection was good (Cohen’s κ = 0.84; P < .001). The median Jadad score was 6 (range, 3-8). We achieved high agreement for Jadad score (quadratic κ = 0.75; P = .02). All differences in agreement were resolved by consensus. Table 1 gives detailed information from individual studies.

### QUANTITATIVE DATA SYNTHESIS

The combined primary end point for all trials included death, recurrent ischemia, and recurrent MI. Six studies included revascularization by percutaneous coronary intervention or...
coronary artery bypass graft within the primary end point. 18,19,26-29 3 studies defined revascularization as a secondary end point,21,22,30 and 4 studies did not evaluate revascularization outcomes.20,23-25

There was no reduction in overall cardiovascular events during the first 4 months of treatment (Figure 2). By the sixth month, there was a significant reduction in overall cardiovascular events (HR, 0.76; 95% CI, 0.70-0.84; Q6=79.4; I6=92.4%) (Table 2), a benefit that persisted through 24 months (HR, 0.81; 95% CI, 0.77-0.87; Q6=58.5; I6=94.9%) (Figure 2). The overall pooled HR for the entire 24 months was 0.84 (95% CI, 0.76-0.94) (Table 2; Figure 3).

In a subgroup analysis (Table 3), over the 24 months of follow-up, there was a reduction in cardiovascular deaths (HR, 0.76; 95% CI, 0.66-0.87; Q4=0.55; I4=0.0%) and ischemia (HR, 0.68; 95% CI, 0.50-0.92; Q4=22.8; I4=82.5%) but not in MIs (HR, 0.89; 95% CI, 0.60-1.33; Q4=15.92; I4=74.9%). For both cardiovascular deaths and ischemia, the benefit began to accrue after 4 months of treatment, with relatively stable HRs thereafter (Figure 3).

The groups treated with early, intensive statin therapy (mean reduction in LDL-C level of 34±9 mg/dL [0.88±0.23 mmol/L]) experienced significantly greater reduction in LDL-C level compared with controls (6±12 mg/dL [0.16±0.31 mmol/L]; P<.001).

While there was evidence of heterogeneity, our analyses using both stratified and meta-regression methods were unable to explain the source of heterogeneity. Variables explored included percentage of LDL-C level reduction, time to initiation of statin therapy, specific statin used, and study duration. In addition, we found no evidence of any effect of study quality on outcomes, in particular whether the studies included allocation concealment and had adequate blinding.

There was no evidence of publication bias either visually or statistically (Peter’s χ2 test, P=.22). Exclusion of any single study did not significantly alter our results.

SAFETY

Safety data showed comparable tolerability for intensive statins and the control arm. Among the 17 963 pa-

Table 2. Pooled Hazard Ratios (HRs) for Any Cardiovascular Event Over 24 Months

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>HR (95% CI)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.02 (0.95-1.09)</td>
<td>Q6=64.8; I6=86.1%</td>
</tr>
<tr>
<td>4</td>
<td>0.84 (0.72-1.02)</td>
<td>Q6=581.6; I6=98.5%</td>
</tr>
<tr>
<td>6</td>
<td>0.76 (0.70-0.84)</td>
<td>Q6=79.4; I6=92.4%</td>
</tr>
<tr>
<td>12</td>
<td>0.80 (0.76-0.84)</td>
<td>Q6=78.7; I6=95.6%</td>
</tr>
<tr>
<td>24</td>
<td>0.81 (0.77-0.87)</td>
<td>Q6=58.5; I6=94.9%</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.84 (0.76-0.94)</td>
<td>Q6=39.5; I6=89.9%</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

Figure 2. Forest plot of any cardiovascular event by duration of treatment. HR indicates hazard ratio; CI, confidence interval.
patients, only 3 cases of rhabdomyolysis were noted (all patients on high-dose simvastatin). There were slightly higher rates of hepatitis in the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial (3.3% intensive group vs 1.1% control) and MIRACL (Myocardial Ischemia Reduction with Aggresive Cholesterol Lowering) study (2.5% vs 0.6%) but no difference in the FLORIDA (Fluvastatin on Risk Diminishment After Acute Myocardial Infarction) trial and PACT (Pravastatin in Acute Coronary Treatment) or PAIS (Pravastatin in Acute Ischaemic Syndromes) trials. Table 4 gives the rates of adverse effects from all 13 trials.

This systematic review provides evidence that early, intensive therapy with statins is associated with a reduction of adverse cardiovascular outcomes, particularly cardiovascular death, unstable angina, and revascularization when prescribed within 14 days of hospitalization for ACS. These benefits took more than 4 months to begin to accrue and were sustained for 2 years. During these 2 years, there was slightly less than a 20% reduction in the risk of experiencing an adverse coronary event. There was no significant evidence that reduction in LDL-C level influenced these results.

Our findings are similar to and extend on a recent meta-analysis exploring the effects of statin use in ACS. Similar to our findings, Briel et al found no evidence of benefit through 4 months. This may not be a surprising finding since 1 potential benefit of statins may be plaque stabilization, which may take several months to occur. Moreover, in most studies there were relatively few events in the first few months after the initiation of treatment. Our study extends their analysis by using meta-analytic survival methods to explore the effects of statins over a longer period.

Although there is evidence of statistical heterogeneity, we took measures to mitigate the impact of this heterogeneity on our results. We used a random effects model to pool HRs and conducted both stratified analyses and meta-regression to investigate the heterogeneity, although this sensitivity analysis may be underpowered with only 13 trials. The PROVE IT–TIMI 22 trial used 40-mg pravastatin as the control arm, and the PACT trial used a relatively low dose of statin (20-mg pravastatin, then 40-mg), which may explain in part why these studies did not have as robust a hazard reduction as the other studies, which used a more intensive statin therapy than the PACT trial and a less intense control than the PROVE IT–TIMI 22 trial.

There are limitations to conducting a meta-analysis of these data. First, as described previously, there was evidence of significant statistical heterogeneity. It may not be appropriate to pool results of interventions with different doses or different types of statins (since statins are known to have differing potency and effects). It is notable that 4 trials used usual care or a low to moderate dose of statins for the control arm (because of ethical considerations), which may have reduced their power to detect a benefit for early, intensive statin therapy compared with the other 9 trials that used a placebo.

Second, there are limited trials available. Having fewer trials reduces the power to detect publication bias and conduct stratified analyses, which may affect some of our conclusions with regard to bias but not necessarily the pooled HRs.

Third, our results noted an overall reduction in all cardiovascular outcomes, particularly cardiovascular death, unstable angina, and revascularization. There was no significant evidence that reduction in LDL-C level influenced these results.

Table 3. Pooled Hazard Ratios (HRs) for Subgroups Over 24 Months

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>Myocardial Infarction (HR 95% CI)</th>
<th>Ischemia (HR 95% CI)</th>
<th>Cardiovascular Death (HR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.07 (0.94-1.21)</td>
<td>0.81 (0.69-0.94)</td>
<td>0.83 (0.58-1.18)</td>
</tr>
<tr>
<td>4</td>
<td>0.90 (0.56-1.44)</td>
<td>0.92 (0.49-1.70)</td>
<td>0.82 (0.49-1.36)</td>
</tr>
<tr>
<td>6</td>
<td>0.53 (0.22-1.26)</td>
<td>0.50 (0.44-0.58)</td>
<td>0.69 (0.07-6.80)</td>
</tr>
<tr>
<td>12</td>
<td>1.79 (1.08-2.96)</td>
<td>0.52 (0.12-2.31)</td>
<td>0.64 (0.24-1.72)</td>
</tr>
<tr>
<td>24</td>
<td>0.43 (0.24-0.78)</td>
<td>0.70 (0.51-0.97)</td>
<td>0.74 (0.63-0.86)</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.89 (0.60-1.33)</td>
<td>0.68 (0.50-0.92)</td>
<td>0.76 (0.66-0.87)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
events and recurrent ischemia but not recurrent MI or cardiovascular death. This inconsistency was not anticipated. We would have expected that for statins to have benefits with regard to all-cause mortality, the intervention should likewise have reduced the rate of recurrent MI. Although the trials recorded event rates for death, cardiovascular death, strokes, and numerous other outcomes such as reperfusion and by-pass surgery, it is possible that statins may have had some effect not tested for in this or other studies that benefited mortality. It is also possible that there was no significant reduction in MI due to random error or to the small number of trials available for pooling.

Fourth, it would be better to conduct a pooled analysis of the patient data from each of these trials. A meta-analysis based on data abstracted from the literature has much less ability to explore and explain the possible sources of heterogeneity compared with one based on individual patient data. We strongly recommend that one be conducted.

It is worth noting that studies have demonstrated that patients are more likely to continue taking medications after hospital discharge if prescribed during the initial inpatient stay. In one study of medication compliance, 77% of patients who began treatment with statins as inpatients were compliant with their dosage regimens compared with only 40% of those who began treatment with a statin after hospitalization. Furthermore, improved drug compliance is associated with improved cholesterol parameters and reduced mortality among cardiovascular patients. Although there were insufficient data to investigate compliance in this analysis, this is an important consideration for any treatment regimen.

<table>
<thead>
<tr>
<th>Source/Group</th>
<th>No. of Patients</th>
<th>AST/ALT &gt;3 x Normal</th>
<th>Myalgia or Myositis</th>
<th>Rhabdomyolysis</th>
<th>Discontinuation of Therapy</th>
<th>Severe Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al, 2001 (MIRACL)</td>
<td>Treatment 1538</td>
<td>38 (2.5)</td>
<td>0</td>
<td>0</td>
<td>173 (11.3)</td>
<td>3 Treatment group patients hospitalized for hepatitis</td>
</tr>
<tr>
<td>Control 1548</td>
<td>9 (0.6)</td>
<td>0</td>
<td>0</td>
<td>160 (10.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson et al, 2004 (PACT)</td>
<td>Treatment 1710</td>
<td>7 (0.4)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Control 1698</td>
<td>5 (0.3)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannon et al, 2004 (PROVE IT-TIMI22)</td>
<td>Treatment 2099</td>
<td>69 (3.3)</td>
<td>69 (3.3)</td>
<td>0</td>
<td>638 (30.4)</td>
<td>None</td>
</tr>
<tr>
<td>Control 2063</td>
<td>23 (1.1)</td>
<td>56 (2.7)</td>
<td>0</td>
<td>681 (33.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lien et al, 2002 (FLORIDA)</td>
<td>Treatment 265</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>30 (11.3)</td>
<td>None</td>
</tr>
<tr>
<td>Control 275</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>37 (13.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Lemos et al, 2004 (A to Z)</td>
<td>Treatment 2243</td>
<td>19 (0.8)</td>
<td>9 (0.4)</td>
<td>3 (0.1)</td>
<td>41 (1.8)</td>
<td>Rhabdomyolysis in 3 treatment group patients</td>
</tr>
<tr>
<td>Control 2210</td>
<td>8 (0.4)</td>
<td>1 (0.05)</td>
<td>0</td>
<td>34 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Den Hartog et al, 2001 (PAIS)</td>
<td>Treatment 50</td>
<td>0</td>
<td>2 (4)</td>
<td>0</td>
<td>3 (6)</td>
<td>None</td>
</tr>
<tr>
<td>Control 47</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arntz et al, 2000 (L-CAD)</td>
<td>Treatment 70</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>22 (31.4)</td>
<td>None</td>
</tr>
<tr>
<td>Control 56</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kayikcioglu et al, 2002 (PTT)</td>
<td>Treatment 40</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Control 37</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dzakzak et al, 2004 (ESTABLISH)</td>
<td>Treatment 35</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2 (5.7)</td>
<td>None</td>
</tr>
<tr>
<td>Control 35</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1 (2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serruys et al, 2002 (LIPS)</td>
<td>Treatment 844</td>
<td>10 (1.2)</td>
<td>0</td>
<td>0</td>
<td>174 (20.6)</td>
<td>None</td>
</tr>
<tr>
<td>Control 833</td>
<td>3 (0.4)</td>
<td>3 (0.4)</td>
<td>0</td>
<td>196 (23.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kesteloot et al, 1997 (LAMIL)</td>
<td>Treatment 36</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Control 33</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dupuis et al, 2005 (RECIFE)</td>
<td>Treatment 30</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Control 30</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colivicchi et al</td>
<td>Treatment 41</td>
<td>0</td>
<td>1 (2.4)</td>
<td>0</td>
<td>1 (2.4)</td>
<td>None</td>
</tr>
<tr>
<td>Control 40</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST aspartate aminotransferase; NA, not applicable.
Use of intensive statin therapy is often avoided by clinicians owing to fear of increased adverse events due to the higher statin dose or, in patients with only mild elevations in LDL-C level, of driving LDL-C level below a theoretical safe value. Our study showed that intensive statin therapy and controls experienced comparable rates of hepatitis, myositis, and rhabdomyolysis. Serious adverse events were rare (Table 4). A recent analysis of 49 completed trials using atorvastatin demonstrated that 80-mg atorvastatin, when compared with 10 mg, is safe and well tolerated. In addition, in an analysis of the PROVE IT–TIMI 22 trial, there was no adverse effect on safety with lower achieved LDL-C level (<40 mg/dL [1.04 mmol/L]). In fact, patients who achieved LDL-C values of 40 to 60 mg/dL (1.04-1.55 mmol/L) and lower than 40 mg/dL (<1.04 mmol/L) had fewer major cardiac events compared with all other groups. The IDEAL trial studied intensive statin therapy in 8888 outpatients with a history of MI and noted no difference in adverse effect rates for intensive vs low-dose statin therapy. These safety data, combined with recent biological data highlighting reduction in atherosclerotic progression and highly sensitive C-reactive protein level in patients receiving high-dose statins, make intensive statin therapy compelling and reassuring to health care providers caring for patients with ACS.

Current American College of Cardiology guidelines recommend the following:

- Class I statins for patients with ACS with an LDL-C level greater than 130 mg/dL (3.37 mmol/L); 
- Class IIa statins for patients with ACS with an LDL-C level greater than 100 mg/dL (2.59 mmol/L).

The guidelines make note of the beneficial outcomes of the MIRACL and L-CAD (Lipid-Coronary Artery Disease) trials and the good evidence for safety but make no universal recommendation for early, intensive statin therapy. Our meta-analysis suggests that there might be a role for early intensive therapy, though the benefit will take several months to begin to accrue. Additional trials are ongoing, including the FACS (Fluvastatin for Acute Coronary Syndrome), LUNAR (Limiting Undertreatment of lipids in ACS with Rosuvastatin), and JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) trials.

In summary, available evidence supports early, intensive statin therapy for patients with ACS. While the benefit may take up to 6 months to begin to accrue, our analysis suggests that there may be a stable, 20% reduction in the rate of cardiovascular events over at least 2 years. There is no significant evidence that reduction in LDL-C level explains these beneficial effects. Our finding of benefits beyond reduction of LDL-C level are also consistent with the findings from the IDEAL trial. The dosing regimen with the most evidence for beneficial effects to date is 80-mg atorvastatin, begun within 14 days of hospitalization for ACS. Our analysis was limited in its ability to explore the sources of heterogeneity in these data. We recommend that a pooled analysis using patient-level data be performed as soon as possible.

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Correspondence: Eddie Hulten, MD, MPH, 6900 Georgia Ave NW, Washington, DC 20307 (edward.hulten@us.army.mil).
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REFERENCES
32. Wright RS. The prevention of ischemic events by early treatment with cerivastatin (PRINCESS) study. Paper presented at: the Annual Congress of the European Society of Cardiology; August 28-September 1, 2004; Munich, Germany.
35. Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet. 1993;341:418-426.