Objectives
The goal of this analysis was to determine whether intensive statin therapy, compared with moderate-dose statin therapy, leads to a reduction in major adverse cardiovascular events (MACE) among patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS).

Background
When compared with moderate-dose statins, intensive statin therapy reduces MACE among patients with ACS. The role of intensive statin therapy specifically among patients who undergo PCI for ACS is unknown.

Methods
Outcomes were compared in 2,868 patients who underwent PCI for ACS just prior to enrollment in the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial, which randomized patients to either atorvastatin 80 mg or pravastatin 40 mg daily. The incidence of the primary composite end point of all-cause mortality, myocardial infarction, unstable angina leading to hospitalization, and revascularization after 30 days and stroke was evaluated, as was the incidence of target vessel revascularization (TVR) and non-TVR during follow-up.

Results
Treatment with 80 mg atorvastatin reduced the incidence of the composite end point (21.5% vs. 26.5%, hazard ratio: 0.78, 95% confidence interval: 0.67 to 0.91, p = 0.002) and lowered the incidence of both TVR (11.4% vs. 15.4%, p = 0.001) and non-TVR (8.0% vs. 10.5%, p = 0.017) compared with 40 mg pravastatin. After adjusting for on-treatment serum low-density lipoprotein cholesterol and C-reactive protein concentrations, the odds of TVR with high-dose statin therapy remained significant (odds ratio: 0.74, p = 0.015) while the odds of non-TVR did not (odds ratio: 0.92, p = 0.55).

Conclusions
Among patients with ACS who undergo PCI, intensive statin therapy reduces MACE compared with moderate-dose statin therapy. The reduction in the incidence of TVR was independent of low-density lipoprotein cholesterol and C-reactive protein lowering and may therefore be due, at least in part, to a pleiotropic effect of high-dose statin therapy. (PROVE IT–TIMI 22; NCT00382460) (J Am Coll Cardiol 2009;54:2290–5) © 2009 by the American College of Cardiology Foundation
larization (TVR) and non-TVR have not been previously reported.

The PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) study enrolled 4,162 ACS patients and randomized them to either intensive therapy with 80 mg atorvastatin daily or moderate therapy with 40 mg of pravastatin daily (1). The goals of this analysis were: 1) to determine whether patients who underwent PCI for their index event derived benefit from intensive statin therapy; and 2) to evaluate whether reductions in TVR and non-TVR remained significant after adjusting for on-treatment levels of LDL-C and C-reactive protein (CRP).

**Methods**

**Patient population.** The design and main results of the PROVE IT–TIMI 22 study have been described (1,8). Briefly, patients at least 18 years old were eligible for inclusion if they had been hospitalized for ACS, either acute MI (with or without electrocardiographic evidence of ST-segment elevation) or high-risk unstable angina, in the preceding 10 days. Patients had to be in stable condition and were to be enrolled after angiography and PCI, if deemed warranted by the treating physician. Finally, patients had to have a total cholesterol level of 240 mg/dl (6.21 mmol/l) or less, measured at the local hospital within the first 24 h after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 h. Patients who were receiving long-term lipid-lowering therapy at the time of their index ACS had to have a total cholesterol level of 200 mg/dl (5.18 mmol/l) or less at the time of screening in the local hospital. Patients were enrolled up to 10 days after the index event.

**Protocol.** Patients were treated with standard medical and interventional therapy for ACS, including aspirin, clopidogrel, or warfarin when indicated. Patients were not permitted to be treated with any lipid-modifying agent other than the study drug. Eligible patients were randomly assigned in a 1:1 ratio to receive 40 mg of pravastatin or 80 mg of atorvastatin daily in a double-blind fashion.

Patients were seen for follow-up visits and received dietary counseling at 30 days, 4 months, and every 4 months thereafter until their final visit. Blood samples for core laboratory assessment were obtained at randomization, 30 days, 4, 8, 12, and 16 months, and at the final visit for the measurement of lipids and other components that were part of the safety assessment. LDL-C levels were monitored, and the protocol specified that the dose of pravastatin was to increase to 80 mg in a blinded fashion if the LDL-C level exceeded 125 mg/dl (3.23 mmol/l) on 2 consecutive visits and the patient had been taking study medication.

**End points.** The outcome measure in the current analysis was the time from randomization until the first occurrence of a component of the primary end point from the PROVE IT–TIMI 22 trial: death from any cause, MI, documented unstable angina requiring rehospitalization and revascularization (PCI or coronary artery bypass grafting [CABG]) at least 30 days after randomization, and stroke. An additional outcome measure was the rate of TVR and non-TVR procedures performed at least 30 days after randomization over the period of follow-up (mean 24 months). TVR was defined as revascularization (either PCI or CABG) of a vessel previously treated by PCI during the index hospitalization. Non-TVR was defined as revascularization of a vessel that had not been treated by PCI during the index hospitalization.

**Statistical analysis.** Continuous variable values are reported as the median and interquartile range, and categorical data are reported as percentages. In the comparison of baseline characteristics, differences in continuous variables were analyzed using the Wilcoxon rank sum test, and differences in categorical variables were analyzed using the chi-square test. Event rates were calculated using the Kaplan-Meier cumulative failure function. Cox proportional hazard models were used for the analysis of clinical end points and statin randomization treatment.

Univariate analyses were performed to explore the associations between the intensity of statin therapy and rates of TVR and non-TVR. Multivariate logistic regression analysis was performed to assess the independent association between the intensity of statin therapy and rates of TVR and non-TVR, adjusting for the 30-day on-treatment LDL-C and CRP concentrations. A separate model adjusting for the on-treatment improvement (change) in LDL-C and non-TVR, adjusting for the 30-day on-treatment LDL-C and CRP concentrations. A separate model adjusting for the on-treatment improvement (change) in LDL-C and CRP was additionally constructed. All analyses were performed using Stata version 9.0 (Stata Corp., College Station, Texas).

**Results**

**Baseline characteristics.** Of the 4,162 patients enrolled in the trial, 2,868 (68.9%) underwent PCI for the index ACS prior to randomization. The baseline characteristics are displayed in Table 1. Patients who underwent PCI for the treatment of the index event were significantly younger, were less likely to have diabetes mellitus, hypertension, or peripheral arterial disease or to have had a prior MI or CABG; and were more likely to have been taking a statin at the time of the index event. Patients who underwent PCI had a higher median baseline CRP and were more likely current smokers. Despite these differences, the baseline characteristics of the 80 mg atorvastatin versus 40 mg pravastatin comparison in
At the time of randomization, the median serum LDL-C concentration at 30 days was 106 mg/dl in both groups. The CRP concentration at 30 days were 87 mg/dl in the 40 mg pravastatin/no PCI group, and 9.4 mg/l in the 80 mg atorvastatin/no PCI group (p < 0.001).

Clinical outcomes. Among patients who underwent PCI for the index event, the 2-year Kaplan-Meier estimated event rate for the primary composite end point (death from any cause, MI, documented unstable angina requiring rehospitalization and revascularization [PCI or CABG] at least 30 days after randomization, and stroke) was 21.5% among patients receiving 80 mg atorvastatin and 26.5% among those receiving 40 mg pravastatin, representing a 22% relative risk reduction in the hazard ratio (HR) favoring atorvastatin (HR: 0.78, 95% confidence interval [CI]: 0.70 to 0.87, p = 0.001) (Fig. 1A, Table 3). The composite of cardiovascular death, nonfatal MI, recurrent ischemia, and rehospitalization for unstable angina was reached by 15.4% of patients randomized to 80 mg atorvastatin and 20.1% of those randomized to 40 mg pravastatin (HR: 0.73, 95% CI: 0.61 to 0.87, p = 0.001) (Fig. 1B).

In the PCI cohort, there were significant reductions in several of the individual components of the primary and
secondary end points in favor of 80 mg atorvastatin, including recurrent ischemia (13.0% vs. 17.1%, HR: 0.71, 95% CI: 0.58 to 0.86, p < 0.001), rehospitalization for unstable angina (3.3% vs. 4.7%, HR: 0.65, 95% CI: 0.45 to 0.96, p = 0.029), revascularization ≥30 days after randomization (16.6% vs. 21.0%, HR: 0.76, 95% CI: 0.64 to 0.90, p = 0.002), the composite of death and MI (7.1% vs. 9.9%, HR: 0.71, 95% CI: 0.55 to 0.92, p = 0.009), and strong trends favoring atorvastatin in all-cause mortality alone (1.5% vs. 2.5%, HR: 0.62, 95% CI: 0.37 to 1.02, p = 0.057) and MI alone (5.8% vs. 7.7%, HR: 0.75, 95% CI: 0.56 to 1.00, p = 0.052). There was no significant difference between 80 mg atorvastatin and 40 mg pravastatin in terms of the incidence of stroke among patients treated with PCI during the index hospitalization.

Among patients who were medically managed for the index event, comprising less than one-third of the full trial population, there were no significant differences between patients randomized to 80 mg atorvastatin or 40 mg pravastatin in terms of the primary end point (24.5% vs. 25.2%, HR: 0.97, 95% CI: 0.78 to 1.21, p = 0.779) and secondary end point (16.6% vs. 21.0%, HR: 0.76, 95% CI: 0.64 to 0.90, p = 0.002). However, neither of the interaction p values were significant evaluating the difference between the benefit of intensive- compared with moderate-dose statin therapy as a function of treatment strategy (PCI vs. no PCI) (p = 0.119 for interaction for primary end point). The interaction p value for the secondary end point was 0.124.

Effect of treatment allocation on TVR versus non-TVR.
High-dose statin therapy compared with moderate-dose therapy reduced the incidence of both TVR (11.4% vs. 15.4%, odds ratio [OR]: 0.73, 95% CI: 0.59 to 0.87, p < 0.001) and non-TVR (8.0% vs. 10.5%, OR: 0.75, 95% CI: 0.59 to 0.95, p = 0.017) (Fig. 2). After adjusting for 30-day on-treatment serum LDL-C and CRP concentration, in-

### Table 2: Effect of Statin Therapy on Lipids and CRP

<table>
<thead>
<tr>
<th>Statin Regimen</th>
<th>Baseline</th>
<th>30 Days</th>
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</thead>
<tbody>
<tr>
<td><strong>Patients with PCI for index event</strong></td>
<td></td>
<td></td>
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<tr>
<td>Total cholesterol, mg/dl (median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin, 40 mg</td>
<td>181</td>
<td>162</td>
</tr>
<tr>
<td>Atorvastatin, 80 mg</td>
<td>181</td>
<td>120</td>
</tr>
<tr>
<td>p value</td>
<td>0.460</td>
<td>&lt;0.001</td>
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<td>LDL-C, mg/dl (median)</td>
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<td></td>
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<tr>
<td>Pravastatin, 40 mg</td>
<td>106</td>
<td>89</td>
</tr>
<tr>
<td>Atorvastatin, 80 mg</td>
<td>107</td>
<td>56.5</td>
</tr>
<tr>
<td>p value</td>
<td>0.700</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C, mg/dl (median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin, 40 mg</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>Atorvastatin, 80 mg</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>p value</td>
<td>0.687</td>
<td>&lt;0.001</td>
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<td>Triglycerides, mg/dl (median)</td>
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<td></td>
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<tr>
<td>Pravastatin, 40 mg</td>
<td>156</td>
<td>143</td>
</tr>
<tr>
<td>Atorvastatin, 80 mg</td>
<td>157</td>
<td>109.5</td>
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<tr>
<td>p value</td>
<td>0.243</td>
<td>&lt;0.001</td>
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<td>CRP, mg/l (median)</td>
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<tr>
<td>Pravastatin, 40 mg</td>
<td>13.0</td>
<td>21.4</td>
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<tr>
<td>Atorvastatin, 80 mg</td>
<td>13.5</td>
<td>1.55</td>
</tr>
<tr>
<td>p value</td>
<td>0.931</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Patients without PCI for index event</strong></td>
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<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dl (median)</td>
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<td></td>
</tr>
<tr>
<td>Pravastatin, 40 mg</td>
<td>178</td>
<td>159</td>
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<tr>
<td>Atorvastatin, 80 mg</td>
<td>180</td>
<td>121</td>
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<tr>
<td>p value</td>
<td>0.213</td>
<td>&lt;0.001</td>
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<tr>
<td>LDL-C, mg/dl (median)</td>
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<td></td>
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<tr>
<td>Pravastatin, 40 mg</td>
<td>105</td>
<td>87</td>
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<tr>
<td>Atorvastatin, 80 mg</td>
<td>105</td>
<td>58</td>
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<tr>
<td>p value</td>
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<td>HDL-C, mg/dl (median)</td>
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<td></td>
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<td>Pravastatin, 40 mg</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>Atorvastatin, 80 mg</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>p value</td>
<td>0.354</td>
<td>&lt;0.001</td>
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<tr>
<td>Triglycerides, mg/dl (median)</td>
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<td></td>
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<tr>
<td>Pravastatin, 40 mg</td>
<td>150</td>
<td>126</td>
</tr>
<tr>
<td>Atorvastatin, 80 mg</td>
<td>159</td>
<td>106.2</td>
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<tr>
<td>p value</td>
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<td>&lt;0.001</td>
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<tr>
<td>CRP, mg/l (median)</td>
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<td></td>
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<tr>
<td>Pravastatin, 40 mg</td>
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<td>26.3</td>
</tr>
<tr>
<td>Atorvastatin, 80 mg</td>
<td>9.37</td>
<td>1.88</td>
</tr>
<tr>
<td>p value</td>
<td>0.364</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Abbreviations as in Table 1.
tensive statin therapy remained associated with a reduction in the rate of TVR (OR: 0.74, 95% CI: 0.59 to 0.95, \( p = 0.015 \)), but was not significantly associated with a reduction in the rate of non-TVR (OR: 0.92, 95% CI: 0.70 to 1.21, \( p = 0.55 \)). Adjustment for the on-treatment improvement in LDL-C and CRP concentrations, there was no significant difference between intensive and moderate therapy in non-TVR, but there remained a significant difference in TVR, suggesting that the reduction in TVR might be mediated, at least in part, by a pleiotropic mechanism of high-dose atorvastatin not accounted for by reductions in LDL-C or markers of systemic inflammation.

**Discussion**

In this post-hoc subgroup analysis of the PROVE IT–TIMI 22 study, patients who underwent PCI for ACS and were randomized to high-dose atorvastatin had a significant reduction in adverse cardiovascular events compared with PCI patients randomized to moderate-dose pravastatin. Additionally, after adjusting for mean on-treatment LDL-C and CRP concentrations, there was no significant difference between intensive and moderate therapy in non-TVR, but there remained a significant difference in TVR, suggesting that the reduction in TVR might be mediated, at least in part, by a pleiotropic mechanism of high-dose atorvastatin not accounted for by reductions in LDL-C or markers of systemic inflammation.

There was no significant interaction between the benefit of intensive- compared with moderate-dose statin therapy as a function of PCI, although, as previously reported (9), in the subgroup of patients who were medically managed (comprising less than one-third of the trial), there was not a statistically significant reduction in adverse cardiovascular events with high-dose atorvastatin.

This is the first report of intensive versus moderate statin therapy in PCI patients. Prior studies have demonstrated the benefit of standard-dose statin therapy over placebo in PCI patients (10), and the results presented here demonstrate an additional 22% relative decrease in major adverse cardiac events associated with intensive therapy over moderate lipid-lowering therapy. These data, coupled with those from studies enrolling patients with stable coronary disease who have undergone PCI (11), strongly suggest that patients who undergo PCI should be treated with intensive statin therapy. Indeed, the most recent PCI guidelines recommend that patients undergoing PCI should be started on a statin before discharge and that it is reasonable to target an LDL-C <70 mg/dl (12).

The mechanism underlying the difference in benefit between patients who underwent PCI and those who were medically managed is unknown. Patients who underwent PCI had a significant reduction in TVR, a possible surrogate for in-stent restenosis. That patients who were medically managed could not benefit in this regard may account for at least part of the difference in clinical outcomes.

The clinical benefit of statins in secondary prevention is derived, at least in part, from their LDL-C-lowering effect (4). However, there is increasing evidence that the benefits of statin therapy in patients with ACS may also be due to non–LDL-C-lowering effects referred to as pleiotropic mechanisms (5–7,13). Pleiotropic effects have been speculated to include benefits in the reduction of inflammation, plaque stability, and endothelial function, and the magnitude and timing of reductions in cardiovascular events seen in some clinical trials may not be explained solely by LDL-C lowering (1,14).

The modest effects of statins on coronary artery luminal diameter determined angiographically in prior trials (15–19) compared with the dramatic reductions in clinical coronary

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**Table 3** Outcomes by Statin Therapy Among Patients With PCI for Index Event

<table>
<thead>
<tr>
<th>End Point for Patients With PCI for Index Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>2-Yr Event Rates (%)</th>
<th>Log-Rank p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>0.78 (0.67–0.91)</td>
<td>TVR</td>
<td>0.001</td>
</tr>
<tr>
<td>Death/MI/RI/UA with rehospitalization</td>
<td>0.73 (0.61–0.87)</td>
<td>21.5</td>
<td>0.015</td>
</tr>
<tr>
<td>Death</td>
<td>0.62 (0.37–1.02)</td>
<td>26.5</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>0.75 (0.56–1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.24 (0.49–3.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>0.71 (0.58–0.86)</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>UA with rehospitalization</td>
<td>0.65 (0.45–0.96)</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Revascularization after 30 days</td>
<td>0.76 (0.64–0.90)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; RI = recurrent ischemia; other abbreviations as in Table 1.

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**Figure 2** TVR Versus Non-TVR

Incidence of target vessel revascularization (TVR) and non-TVR among patients who underwent percutaneous coronary intervention for the index event stratified by treatment allocation. Multivariate odds ratio (OR) adjusted for on-treatment low-density lipoprotein cholesterol and C-reactive protein concentrations.
events seen in clinical trials suggests a possible role of lipid-lowering agents in plaque stabilization in addition to their role in reversing atherosclerosis. Reductions in circulating LDL-C levels may play a role in altering plaque structure and plaque biology (20). However, some of the effects of statins on plaque stability appear to be independent of LDL-C lowering (21). For instance, statins inhibit geranylgeranylation and farnesylation of the GTP binding proteins Rho and Ras, which clearly play a role in the progression of atherosclerosis (22,23). Whether these pleiotropic effects are clinically relevant remains to be definitively proven, although the results presented here are provocative in that regard.

Study limitations. Strict enrollment criteria are used in clinical trials, and the results observed here may not be applicable to all patients in clinical practice. While we analyzed the association of intensive and standard lipid-lowering therapy with TVR, the association with target lesion revascularization was not evaluated. Detailed angiographic findings were not collected. The present study was conducted in the era of bare-metal stents, and the applicability of these results to patients treated with drug-eluting stents is not known. Patients who achieved similar LDL-C and CRP in the 2 treatment arms may have very different baseline characteristics, and comparing the 2 treatment arms after adjusting for LDL-C and CRP is not a randomized comparison. Though the OR for non-TVР is not significant after adjusting for LDL-C and CRP, the 95% CIs for TVR and non-TVР overlap with that for the reduction in the primary composite outcome.

Conclusions

Among patients treated with PCI in the PROVE IT–TIMI 22 study, high-dose statin therapy reduced TVR and non-TVР as well as the primary composite end point. The benefits in non-TVР, but not TVR, appear to be explained by reductions in on-treatment LDL-C and CRP, suggesting a possible pleiotropic mechanism of high-dose statin therapy.

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