Early and Late Benefits of High-Dose Atorvastatin in Patients With Acute Coronary Syndromes

Results From the PROVE IT-TIMI 22 Trial

Kausik K. Ray, MRCP, MD*, Christopher P. Cannon, MD, FACC,* Carolyn H. McCabe, BS,* Richard Cairns, BSc;† Andrew M. Tonkin, MD;‡ Frank M. Sacks, MD,§ Graham Jackson, MD, FRCP,‖ Eugene Braunwald, MD, MACC,* for the PROVE IT-TIMI 22 Investigators

Boston, Massachusetts; Nottingham and London, United Kingdom; and Melbourne, Australia

OBJECTIVES

Our objective was to determine the timing of benefit with intensive statin therapy after an acute coronary syndrome (ACS) in two time windows: an early window soon after an ACS and a late window in more stable patients.

BACKGROUND

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) trial showed that the use of intensive statin therapy improved clinical outcomes over two years in ACS patients versus standard therapy. The relative contributions of early or late effects to the overall clinical efficacy of intensive therapy are presently unclear.

METHODS

A total of 4,162 patients with ACS were recruited in the PROVE IT-TIMI 22 trial. Patients were randomized to intensive statin therapy (atorvastatin, 80 mg) or standard therapy (pravastatin, 40 mg). The composite triple end point of death, MI, or rehospitalization for recurrent ACS was determined in each group at 30 days. The composite triple and primary end points were assessed in stable patients from six months to the end of study, after censoring for clinical events before six months.

RESULTS

The composite end point at 30 days occurred in 3.0% of patients receiving atorvastatin 80 mg versus 4.2% of patients receiving pravastatin 40 mg (hazard ratio [HR] = 0.72; 95% confidence interval [CI], 0.52 to 0.99; p = 0.046). In stable patients, atorvastatin 80 mg was associated with a composite event rate of 9.6% versus 13.1% in the pravastatin 40 mg group (HR = 0.72; 95% CI, 0.58 to 0.89; p = 0.003).

CONCLUSIONS

Intensive statin therapy early after ACS leads to a reduction in clinical events at 30 days, consistent with greater early pleiotropic effects. In stable patients, intensive statin therapy provides long-term reduction in clinical events when compared with standard therapy. Thus, ACS patients should be started in-hospital and continued long-term on intensive statin therapy.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) trial (1) showed the clinical benefits of intensive statin therapy over standard therapy. We sought to evaluate the timing of this benefit by examining the very early clinical as well as the late effects of intensive statin therapy.

METHODS

Patient population and protocol. The design of the PROVE IT-TIMI 22 protocol has been previously described (1) (see the Appendix). Briefly, 4,162 patients who had a total cholesterol level of ñ240 mg/dl and who had been hospitalized for an acute coronary syndrome (ACS) within the previous 10 days were randomly assigned in a 1:1 ratio to pravastatin 40 mg or atorvastatin 80 mg daily, and gatifloxacin versus placebo, in a double-blind fashion. Patients were followed up for 18 to 36 months, with an average follow-up of 24 months.

End points. The primary end point was all-cause mortality, myocardial infarction (MI), unstable angina requiring rehospitalization, revascularization (if performed at least 30 days after randomization), and stroke. We also evaluated a triple composite end point (death, MI, or rehospitalization for recurrent ACS), which is the end point commonly used in ACS trials for evaluation of early outcomes (2). Recurrent ACS was defined as the following: readmission with ischemic pain associated with electrocardiograph changes, an increase in cardiac markers below the threshold for diagnosis of MI, a recurrence of cardiac pain in the hospital distinct from the initial episode or ischemic pain that led to cardiac catheterization and/or revascularization. Patients readmit-
Abbreviations and Acronyms

ACSM = acute coronary syndrome
CI = confidence interval
CRP = C-reactive protein
HR = hazard ratio
LDL-C = low-density lipoprotein cholesterol
MI = myocardial infarction
PROVE IT-TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22
TNT = Treating to New Targets study

Early and Late Benefits of High-Dose Atorvastatin

Overall efficacy outcome. The composite triple end point of death, MI, or rehospitalization with recurrent ACS was first evaluated over the duration of the trial (mean, two years). The composite end point occurred in 15.7% of patients assigned atorvastatin 80 mg and in 20.0% of patients assigned pravastatin 40 mg, reflecting a hazard risk reduction of 24% (HR = 0.76; 95% CI, 0.66 to 0.88; p = 0.0002) (Fig. 1). Using this triple composite end point, the benefits of intensive statin therapy with atorvastatin 80 mg were seen in a large number of different subgroups (Table 1). Early effects. To evaluate the time to benefit in the acute phase, we first used the primary end point (Fig. 2A). At 15 days, there was a trend to an apparent early benefit with intensive therapy, associated with a 15% risk reduction in the primary end point (HR = 0.85; 95% CI, 0.52 to 1.37). At four months, the primary end point had occurred in 8.2% of patients receiving intensive therapy versus 10.2% of patients on standard therapy, and this had achieved statistical significance (HR = 0.81; 95% CI, 0.65 to 0.98; p = 0.03).

Using the composite triple end point, this early benefit again appeared as early as 15 days after randomization, became significant at 30 days, and remained stable from 30 days onward with progressive narrowing of the confidence intervals (Fig. 2B). The composite end point occurred in 3.0% of the intensive therapy group and in 4.2% of the standard therapy group, representing a 28% risk reduction at 30 days (HR = 0.72; 95% CI, 0.52 to 0.99; p = 0.046) with atorvastatin 80 mg (Fig. 3). The composite triple end point was also reduced by intensive therapy in a wide range of subgroups even at this early 30-day time point (Table 1). Intensive therapy lowered low-density lipoprotein cholesterol (LDL-C) and C-reactive protein (CRP) more than did standard therapy at 30 days and at four months (Table 2).

Late effects. From six months after ACS to the end of the study, the primary end point occurred in 15.1% of patients receiving intensive therapy versus 17.7% of patients randomized to standard therapy, resulting in an 18% reduction in events (HR = 0.82; 95% CI, 0.69 to 0.99; p = 0.037). Even using a conditional hazard analysis beginning at one year after ACS to the end of follow-up, there was a benefit with intensive therapy with an absolute event rate of 5.6% with intensive therapy versus 8.0% with standard therapy (HR = 0.72; CI, 0.54 to 0.95; p = 0.02) (Fig. 4A).
Similarly the composite triple end point, from six months after ACS to the end of study, occurred in 9.6% of the intensive therapy group and 13.1% of the standard therapy group, representing a 28% risk reduction (HR = 0.72; 95% CI, 0.58 to 0.89; p < 0.003) in favor of high-dose atorvastatin 80 mg (Fig. 5). These benefits were seen across a range of subgroups including those with a low baseline LDL-C (Table 1). Evaluation of effects more than one year after ACS showed that intensive therapy was also associated with a reduction in the composite end point (HR = 0.66; 95% CI, 0.58–0.89; p = 0.02) (Fig. 4B).

**Table 1. Risk of Death, Myocardial Infarction, or Rehospitalization With Acute Coronary Syndrome in Different Subgroups by Statin Regimen for the Entire Study, at 30 Days, and Between 6 Months and End of Study**

<table>
<thead>
<tr>
<th>Subgroup*</th>
<th>Overall HR (95% CI)†</th>
<th>p</th>
<th>Randomization to 30 Days HR (95% CI) †</th>
<th>p</th>
<th>6 Months to End of Study HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥58 yrs</td>
<td>0.91 (0.74–1.1)</td>
<td>0.3</td>
<td>0.98 (0.61–1.58)</td>
<td>0.9</td>
<td>0.86 (0.64–1.14)</td>
<td>0.3</td>
</tr>
<tr>
<td>Age &lt;58 yrs</td>
<td>0.62 (0.5–0.77)</td>
<td>&lt;0.0001</td>
<td>0.53 (0.34–0.84)</td>
<td>0.007</td>
<td>0.58 (0.41–0.82)</td>
<td>0.002</td>
</tr>
<tr>
<td>Male</td>
<td>0.78 (0.66–0.91)</td>
<td>0.003</td>
<td>0.68 (0.47–1)</td>
<td>0.05</td>
<td>0.7 (0.53–0.91)</td>
<td>0.006</td>
</tr>
<tr>
<td>Female</td>
<td>0.7 (0.52–0.95)</td>
<td>0.02</td>
<td>0.82 (0.44–1.54)</td>
<td>0.5</td>
<td>0.76 (0.48–1.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetics</td>
<td>0.68 (0.51–0.9)</td>
<td>0.007</td>
<td>0.51 (0.25–1.03)</td>
<td>0.06</td>
<td>0.72 (0.47–1.11)</td>
<td>0.1</td>
</tr>
<tr>
<td>Non-diabetics</td>
<td>0.77 (0.65–0.92)</td>
<td>0.003</td>
<td>0.79 (0.55–1.14)</td>
<td>0.2</td>
<td>0.7 (0.54–0.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Smokers</td>
<td>0.78 (0.66–0.92)</td>
<td>0.003</td>
<td>0.59 (0.4–0.88)</td>
<td>0.01</td>
<td>0.74 (0.58–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>0.69 (0.52–0.94)</td>
<td>0.02</td>
<td>1.06 (0.6–1.88)</td>
<td>0.8</td>
<td>0.64 (0.41–1.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.81 (0.67–0.98)</td>
<td>0.03</td>
<td>0.82 (0.52–1.25)</td>
<td>0.4</td>
<td>0.77 (0.58–1.02)</td>
<td>0.07</td>
</tr>
<tr>
<td>No hypertension</td>
<td>0.65 (0.54–0.85)</td>
<td>0.0009</td>
<td>0.59 (0.35–0.98)</td>
<td>0.04</td>
<td>0.64 (0.45–0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>UA</td>
<td>0.72 (0.56–0.91)</td>
<td>0.007</td>
<td>0.58 (0.31–1.06)</td>
<td>0.08</td>
<td>0.66 (0.47–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>0.78 (0.6–1.01)</td>
<td>0.06</td>
<td>0.68 (0.38–1.19)</td>
<td>0.2</td>
<td>0.91 (0.6–1.36)</td>
<td>0.6</td>
</tr>
<tr>
<td>STEMI</td>
<td>0.78 (0.61–1.01)</td>
<td>0.06</td>
<td>0.89 (0.52–1.5)</td>
<td>0.7</td>
<td>0.65 (0.43–0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL ≥125 mg/dl</td>
<td>0.6 (0.45–0.81)</td>
<td>0.0008</td>
<td>0.31 (0.15–0.64)</td>
<td>0.002</td>
<td>0.66 (0.42–1.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>LDL &lt;125 mg/dl</td>
<td>0.83 (0.7–0.99)</td>
<td>0.04</td>
<td>0.92 (0.63–1.36)</td>
<td>0.7</td>
<td>0.76 (0.59–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>HDL ≥40 mg/dl</td>
<td>0.72 (0.58–0.9)</td>
<td>0.005</td>
<td>0.59 (0.35–0.99)</td>
<td>0.05</td>
<td>0.73 (0.51–1.02)</td>
<td>0.07</td>
</tr>
<tr>
<td>HDL &lt;40 mg/dl</td>
<td>0.8 (0.66–0.98)</td>
<td>0.03</td>
<td>0.81 (0.52–1.24)</td>
<td>0.3</td>
<td>0.75 (0.58–0.96)</td>
<td>0.05</td>
</tr>
<tr>
<td>Prior statin</td>
<td>0.78 (0.6–1.01)</td>
<td>0.06</td>
<td>0.8 (0.34–1.5)</td>
<td>0.5</td>
<td>0.72 (0.59–1.03)</td>
<td>0.07</td>
</tr>
<tr>
<td>No prior statin</td>
<td>0.75 (0.62–0.89)</td>
<td>0.0013</td>
<td>0.69 (0.46–1.01)</td>
<td>0.06</td>
<td>0.71 (0.54–0.94)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Median age = 58 years, Smoking is defined as current or prior history. †Atorvastatin versus pravastatin, determined by a Cox proportional hazards model (with the treatment as the only covariate, stratified by gatifloxacin or placebo).

CI = confidence interval; HDL = high-density lipoprotein; HR = hazard ratio; LDL = low-density lipoprotein; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

**DISCUSSION**

Acute coronary syndrome is increasingly recognized as a diffuse process involving the entire coronary vasculature (3), and although therapeutic revascularization by percutaneous coronary intervention may address the culprit lesion, recurrent events may reflect disease progression or instability elsewhere in the vascular tree. Although anti-thrombotic and anti-platelet agents “passivate” the thrombotic components of ACS, their effects on plaque stabilization or atherosclerosis disease progression are less clear. Therefore,
stabilization of vulnerable plaques has emerged as an important target for systemic therapy. The biological effects of statins on inflammation, endothelial function, and coagulation (the so-called pleiotropic effects) are consistent with actions that would lead to plaque stabilization (3). The results of this analysis from the PROVE IT-TIMI 22 trial show that intensive statin therapy with atorvastatin 80 mg, when compared with standard therapy with pravastatin 40 mg, is associated with a significant reduction in the composite clinical end point of death, MI, or rehospitalization for recurrent ACS as early as 30 days after randomization after ACS. Indeed a trend in favor of intensive therapy was already noted at 15 days after randomization (Fig. 2). In addition, in patients stable for 6 or even 12 months, continued intensive statin therapy resulted in a further significant reduction in both the primary end point and the triple composite end point through follow-up (mean of 24 months). A similar finding has now been seen in stable revascularized patients with coronary artery disease in the Treating to New Targets (TNT) trial (4).

The early benefits of intensive statin therapy observed in the PROVE IT-TIMI 22 trial are in sharp contrast with the stabilization of vulnerable plaques has emerged as an important target for systemic therapy. The biological effects of statins on inflammation, endothelial function, and coagulation (the so-called pleiotropic effects) are consistent with actions that would lead to plaque stabilization (3). The results of this analysis from the PROVE IT-TIMI 22 trial show that intensive statin therapy with atorvastatin 80 mg, when compared with standard therapy with pravastatin 40 mg, is associated with a significant reduction in the composite clinical end point of death, MI, or rehospitalization for recurrent ACS as early as 30 days after randomization after ACS. Indeed a trend in favor of intensive therapy was already noted at 15 days after randomization (Fig. 2). In addition, in patients stable for 6 or even 12 months, continued intensive statin therapy resulted in a further significant reduction in both the primary end point and the triple composite end point through follow-up (mean of 24 months). A similar finding has now been seen in stable revascularized patients with coronary artery disease in the Treating to New Targets (TNT) trial (4).

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The early benefits of intensive statin therapy observed in the PROVE IT-TIMI 22 trial are in sharp contrast with the
Program on the Surgical Control of Hyperlipidemias (POSCH) trial (5), in which ileal bypass was associated with a dramatic early reduction in LDL-C but no early reduction in clinical events. Also, in patients with stable coronary artery disease, the apparent benefit from statin therapy is frequently delayed beyond one year (6). Our findings suggest that the clinical benefits observed in ACS patients occur before the greater reductions in LDL-C with intensive statin therapy are likely to have had any significant effect on disease progression. In the PROVE IT-TIMI 22 trial, the median CRP level at 30 days was 1.6 mg/l in the atorvastatin 80 mg group compared with 2.3 mg/l in the pravastatin 40 mg arm (p \( < 0.001 \)), supporting greater early anti-inflammatory pleiotropic effects with intensive statin therapy (7).

In the PROVE IT-TIMI 22 trial, stable patients who were free of clinical events at six months showed a similar benefit in favor of intensive statin therapy (atorvastatin, 80 mg) compared with standard-dose statin therapy (pravastatin, 40 mg) for both the primary and the composite triple end points. This suggests that there is continuing benefit from the use of intensive statin therapy beyond the acute period. The long-term clinical benefits of statin therapy versus placebo are thought to be related to the greater reduction in LDL-C, which may retard progression of atherosclerotic disease (8). Recent trials using clinical (1,7) and ultrasound end points (8) have shown that intensive therapy achieves a greater reduction in LDL-C and CRP levels compared with standard statin therapy, and that these are associated with a reduction in clinical events and in the rate of progression of atherosclerosis. After ACS, potential benefits from other pleiotropic effects such as improved endothelial function could also play an important role in improving outcome more than six months after ACS. The present analysis does not differentiate between the relative contributions of the lipid lowering from the pleiotropic effects of statins in reducing long-term events in stable patients, and both processes are likely to be important. This is supported by the observations in the PROVE IT-TIMI 22 trial that lowering the CRP level was of equal importance as lowering the LDL-C level in reducing adverse outcomes (7).

**Study limitations.** The conditional analysis of the late benefits (censoring at six months) should be considered observational and not as part of a randomized analysis.

**CONCLUSIONS**

The PROVE IT-TIMI 22 trial shows that intensive versus standard statin therapy leads to a reduction in clinical events within 30 days after an ACS, within a time window consistent with the early pleiotropic effects seen with statins. In stable patients, intensive statin therapy is also associated with a long-term reduction in clinical events during follow-up. Thus, intensive statin therapy provides two windows of cardioprotection in patients with ACS. Treatment of patients with ACS should begin in-hospital with high-dose intensive statin therapy to achieve these early clinical benefits and should be continued long-term.

**REFERENCES**


APPENDIX

For the full study protocol, please see the online version of this article.