Early and Sustained Survival Benefit Associated With Statin Therapy at the Time of Percutaneous Coronary Intervention

Albert W. Chan, MD, MS; Deepak L. Bhatt, MD; Derek P. Chew, MBBS; Martin J. Quinn, MD, PhD; David J. Moliterno, MD; Eric J. Topol, MD; Stephen G. Ellis, MD

Background—Long-term administration of statin therapy has been shown to reduce major coronary events and cardiac mortality within randomized clinical trials. In addition to lowering lipids, statins favorably affect platelet adhesion, thrombosis, endothelial function, inflammation, and plaque stability, which may potentially improve outcome after percutaneous coronary intervention (PCI). Therefore, we hypothesized that statin therapy has an early beneficial effect among patients undergoing PCI.

Methods and Results—Each year from 1993 to 1999, we prospectively collected data among the first 1000 patients undergoing PCI. Patients who presented with acute or recent myocardial infarction or cardiogenic shock were excluded from the analysis. Baseline, procedural, and 6-month data of statin-treated and non–statin-treated patients were compared. Propensity score and multivariate survival analysis were used to adjust for heterogeneity between the two groups. Of 5052 patients who completed follow-up, 26.5% were treated with statin at the time of the procedure. Statin therapy was associated with a mortality reduction at 30 days (0.8% versus 1.5%; hazard ratio, 0.53; \( P = 0.048 \)) and at 6 months (2.4% versus 3.6%; hazard ratio, 0.67; \( P = 0.046 \)). After adjusting for the propensity to receive statin therapy before the procedure and other confounders, statin therapy remained an independent predictor for survival at 6 months after coronary intervention (hazard ratio, 0.65; 95% CI, 0.42 to 0.99; \( P = 0.045 \)).

Conclusions—In this large study cohort, statin therapy among PCI patients seems to be associated with a significant mortality advantage at early and intermediate-term follow-up. (Circulation. 2002;105:691-696.)

Key Words: angioplasty • coronary disease • mortality • stents • statins

Secondary prevention trials of HMG-CoA reductase inhibitors (or statins) have shown a 25% to 30% reduction in ischemic cardiovascular events at long-term follow-up.1–3 Recent studies suggest that the incidence of early deaths and recurrent ischemic events (30 days to 6 months) are also reduced by statin therapy among acute coronary syndrome (ACS) patients.4–6 However, little data are available regarding the effect of these drugs on patients undergoing percutaneous coronary intervention (PCI).

Beyond lowering lipids, statins have favorable effects on platelet adhesion,7 thrombosis,8,9 endothelial function,10 plaque stability, and inflammation.11–15 Like ACS, the vascular injury from coronary angioplasty and stent placement induces platelet activation, thrombosis, and inflammation within the vessel wall and the distal microvasculature. Therefore, in addition to a long-term benefit associated with lipid lowering, we postulated that statin therapy may play a beneficial role early after PCI. To assess this, we compared the outcomes of PCI patients who were pretreated with those who were not.

Methods

Patient Selection

Each year from January 1993 to June 1999, we prospectively followed the first 1000 consecutive residents of the United States who underwent PCI at The Cleveland Clinic Foundation. The demographic and procedural data, including medication use, hemodynamic status, equipment use, and final results of each case, were recorded in an interventional database. Clinical event data during the index hospitalization, at 30 days, and at 6 months were collected by cardiology nurses and research coordinators through patient interview, chart review, and serial telephone contacts. Mortality data were confirmed with the United States Social Security Administration Death Master File. Patients were divided into 2 groups according to whether statin therapy was administered before PCI procedures. Patients who presented with acute myocardial infarction (MI), recent MI (within 7 days of procedure), or cardiogenic shock were excluded from the analysis.

Statistical Analysis

Continuous variables were expressed as mean±SD, and they were compared by Student’s \( t \) test or Mann-Whitney rank sum test. Categorical data were displayed as frequencies and percentages. \( \chi^2 \) test was used for bivariate analysis for categorical data. Kaplan-
Meier estimation and Cox proportional hazards modeling were used for unadjusted and adjusted survival analysis, respectively.

To adjust for the bias inherent to the decision about statin therapy before PCI, propensity analysis was performed. Propensity analysis aims to identify patients with similar probability of receiving statin therapy on the basis of observed clinical characteristics. Using a multivariable logistic regression model that includes the baseline characteristics as the independent variables, the probability of being assigned to statin therapy was determined. The variables that were included in the propensity score model were age, sex, body mass index, presentation of unstable angina (angina at rest ≥ 20 minutes, new onset angina < 2 months, angina severity greater than Canadian Cardiovascular Society Classification Class III, or acceleration of angina ≥ 1 class within 2 months), diabetes, hypertension, hypercholesterolemia, present cigarette smoking, renal insufficiency (serum creatinine ≥ 2 mg/dL), peripheral vascular disease (PVD), history of MI, stroke, history of coronary bypass surgery, restenotic lesions, premature coronary artery disease (CAD), use of aspirin, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, calcium-channel receptor blockers, diuretics, or antiarrhythmics, left ventricular ejection fraction, number of diseased coronary arteries, and years of intervention (1993 to 1995, 1996 to 1997, or 1998 to 1999).

The population was then divided into deciles according to the propensity score. Within each decile, the mean propensity scores of the statin and nonstatin groups were compared, as well as their clinical and procedural characteristics. To adjust for the heterogeneity between the 2 groups, the propensity score was then entered as a continuous variable in the Cox proportional hazards model along with 32 potential covariates. These covariates included the baseline variables entered in the propensity score model and other procedural variables that might correlate with outcome, namely lesion morphology (type A or B 1 versus B 2 or C), left anterior descending or LAD intervention, number of diseased coronary arteries, prior MI, previous coronary bypass surgery, restenotic lesion, calcium-channel receptor blockers, diuretics, or antiarrhythmics, left ventricular ejection fraction, number of diseased coronary arteries, and years of intervention (1993 to 1995, 1996 to 1997, or 1998 to 1999).

Results

Baseline Characteristics
During the study period, a total of 6921 patients were scheduled for follow-up within the interventional registry. Data for 274 patients (25.5%) who were taking statin were incomplete in the follow-up and were excluded from the analysis. Of the remaining 6647 patients (96%) who had complete follow-up data, 1595 were excluded from the analysis because of presentation of acute MI, recent MI, or cardiogenic shock. Hence, a total of 5052 patients were included in the final analysis. Of these, 1337 patients (26.5%) were taking statin before the procedure. Table 1 shows the baseline characteristics according to statin treatment. Important differences existed between the 2 groups. Patients who were on statin therapy before coronary intervention were younger, heavier, and more likely to have diabetes mellitus, hypertension, hypercholesterolemia, triple-vessel CAD, prior MI, previous coronary bypass surgery, and PVD and be taking concomitant ACE inhibitors and β-blockers. During the procedure, statin recipients were more likely to have interventions to vein grafts or restenotic lesions and were more likely to receive stents, glycoprotein IIb/IIIa inhibitors, and nonionic contrast. The rates of procedural success, presentation of unstable angina, and left ventricular ejection fraction were similar between the 2 groups.

Unadjusted 30-Day and 6-Month All-Cause Mortality
As depicted on the Kaplan-Meier curve (Figure 1), receiving a statin at the time of procedure was associated with an early (30-day) mortality benefit (0.8% versus 1.5%; hazard ratio, 0.53; log-rank P=0.048), which was sustained at 6 months.
The mortality benefit among subgroups is shown in Figure 2. Comparing the 2 groups with respect to other cardiac events, there was no significant difference in the incidence of nonfatal MI (defined as >3× upper limit of normal of creatine kinase-MB) (1.3% versus 1.1%, P=0.51) or repeat revascularization (13.7% versus 11.8%, P=0.079). The composite endpoint of death, MI, and revascularization was 16.1% for the statin group and 15.5% for the nonstatin group (P=0.66). Repeat revascularization was not associated with increased mortality rate (mortality rate was 0.85% for repeat revascularization compared with 3.5% for patients without repeat revascularization, P=0.001).

**Propensity Analysis**

Within the propensity score analysis, variables that predicted the prescription of statin before PCI were (in descending order) hypercholesterolemia, procedures in recent years (1998 to 1999), concomitant prescription of β-blockers, ACE inhibitors, calcium-channel blockers, or diuretics, triple-vessel coronary disease, restenotic lesion, age <75 years, and male sex. The goodness of fit of the propensity score was given by c statistic (or area under the receiver operating characteristic curve) being 0.83, indicating the propensity model discriminated well between patients who were prescribed statins before PCI and patients who were not. Within each decile of the study population, the propensity scores and baseline characteristics were similar among the statin-treated and non–statin-treated groups.

**Multivariate Analysis of 6-Month Mortality**

Using Cox proportional hazards model to adjust for all potential variables, statin therapy at the time of PCI remained an independent predictor for survival at 6 months (hazard ratio, 0.65; 95% CI, 0.42 to 0.99; P=0.045). When the propensity score was included in the model with all the covariates, the estimation of statin pretreatment effect did not change significantly (Table 2). Other predictors for mortality are listed in Table 3. Advanced age, renal insufficiency, low body weight, poor left ventricular function, and history of PVD were all independent predictors for mortality. β-blocker use at the time of procedure and successful revascularization were associated with survival benefit.

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**Figure 1.** Kaplan-Meier estimates of survival according statin therapy before PCI.

(2.4% versus 3.6%; hazard ratio, 0.67; log-rank P=0.046).

**Figure 2.** Six-month mortality comparison between treatments stratified by subgroups. GP indicates glycoprotein.

**TABLE 2. Six-Month Mortality of Patients Pretreated With Statins Versus Those not Pretreated With Statins at Time of PCI**

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>95% CI of Hazard Ratio</th>
<th>Statin groups</th>
<th>Non-statin groups</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 yrs</td>
<td>6/438 (4.5)</td>
<td>26/196 (2.2)</td>
<td>47/860 (5.7)</td>
<td>0.76</td>
</tr>
<tr>
<td>Age &lt; 75 yrs</td>
<td>23/863 (2.3)</td>
<td>10/643 (0.8)</td>
<td>89/2899 (3.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Male</td>
<td>25/697 (3.6)</td>
<td>54/845 (6.3)</td>
<td>69/333 (3.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Female</td>
<td>75/697 (10.7)</td>
<td>48/697 (7.1)</td>
<td>47/845 (5.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Current smoker</td>
<td>52/207 (2.4)</td>
<td>27/113 (2.4)</td>
<td>74/387 (4.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>13/665 (2.0)</td>
<td>36/665 (5.4)</td>
<td>54/277 (4.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>Prior MI</td>
<td>3/665 (0.5)</td>
<td>30/665 (4.1)</td>
<td>25/665 (3.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>No MI</td>
<td>5/665 (0.8)</td>
<td>27/665 (4.0)</td>
<td>107/665 (16.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Normal renal function</td>
<td>5/665 (0.8)</td>
<td>27/665 (4.0)</td>
<td>107/665 (16.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>5/665 (0.8)</td>
<td>27/665 (4.0)</td>
<td>107/665 (16.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hx of stroke</td>
<td>5/665 (0.8)</td>
<td>27/665 (4.0)</td>
<td>107/665 (16.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>No hx of stroke</td>
<td>5/665 (0.8)</td>
<td>27/665 (4.0)</td>
<td>107/665 (16.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hx of PVD</td>
<td>16/665 (2.4)</td>
<td>16/665 (2.4)</td>
<td>42/379 (5.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>No hx of PVD</td>
<td>4/665 (0.6)</td>
<td>27/665 (4.0)</td>
<td>94/277 (2.5)</td>
<td>0.016</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>5/631 (0.8)</td>
<td>27/631 (4.2)</td>
<td>39/631 (6.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>No ACE inhibitor</td>
<td>12/631 (1.9)</td>
<td>20/631 (3.2)</td>
<td>113/631 (17.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor</td>
<td>16/631 (2.5)</td>
<td>16/631 (2.5)</td>
<td>42/379 (5.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>No GP IIb/IIIa inhibitor</td>
<td>4/631 (0.6)</td>
<td>16/631 (2.5)</td>
<td>94/277 (3.4)</td>
<td>0.016</td>
</tr>
<tr>
<td>Restrictive lesion</td>
<td>7/631 (1.1)</td>
<td>20/631 (3.2)</td>
<td>113/631 (17.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>De-novo lesion</td>
<td>18/631 (2.9)</td>
<td>18/631 (2.9)</td>
<td>42/379 (5.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Stent</td>
<td>14/631 (2.2)</td>
<td>14/631 (2.2)</td>
<td>42/379 (5.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>No stent</td>
<td>12/631 (1.9)</td>
<td>12/631 (1.9)</td>
<td>113/631 (17.6)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Hazard Ratio 95% CI P

Unadjusted 0.67 0.46–0.99 0.046
Adjusted for propensity score 0.64 0.42–0.97 0.034
Adjusted for covariates 0.65 0.42–0.99 0.045
Adjusted for covariates and propensity score 0.65 0.42–0.99 0.045
TABLE 3. Independent Predictors for Mortality at 6 Months

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>0.65</td>
<td>0.42–0.99</td>
<td>0.045</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>3.45</td>
<td>2.17–5.50</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index ≤21 kg/m²</td>
<td>2.66</td>
<td>1.56–4.53</td>
<td>0.0003</td>
</tr>
<tr>
<td>LVEF ≤0.35</td>
<td>2.29</td>
<td>1.55–3.39</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diuretic</td>
<td>1.87</td>
<td>1.29–2.71</td>
<td>0.0010</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.82</td>
<td>1.19–2.80</td>
<td>0.0059</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>1.69</td>
<td>1.17–2.44</td>
<td>0.0053</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa blockers</td>
<td>1.65</td>
<td>1.15–2.38</td>
<td>0.0070</td>
</tr>
<tr>
<td>β-blockers</td>
<td>0.71</td>
<td>0.50–0.99</td>
<td>0.047</td>
</tr>
<tr>
<td>Procedural success</td>
<td>0.64</td>
<td>0.41–1.00</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Discussion

On the basis of our 7-year registry data, HMG-CoA reductase inhibitor therapy before PCI seems to be associated with an early and sustained mortality reduction. The survival benefit emerged as early as 1 month after the index procedure and persisted thereafter. After adjustment for factors that might be associated with early and intermediate mortality after PCI, statin therapy remained an independent predictor for survival benefit at 6 months. Furthermore, considering the continued evolution of interventional practice, this mortality benefit remained evident after adjusting for the years in which the index procedure was performed. This extent of mortality reduction is comparable to reductions previously reported in statin-treated patients presenting with acute MI and acute coronary syndromes.4–6

Our findings contrast somewhat to the secondary prevention trials with statin therapy (Scandinavian Simvastatin Survival Study, Cholesterol and Recurrent Events trial, and Long-Term Intervention with Pravastatin in Ischaemic Disease trial),1–3 which reported reductions in several ischemic endpoints, including recurrent infarction and revascularization. However, these trials did not examine the effect of early statin therapy in the context of unstable coronary syndromes or vascular damage. These trials initiated therapy late in the recuperative phase of patients’ index presentation and observed a benefit after ≥2 years of statin therapy. Within our study, patients were receiving statin therapy at the time of vascular injury, and the mortality benefit was seen within weeks to months. These data corroborate the findings of Aronow et al.6 who observed an early mortality benefit (hazard ratio for 6-month mortality with lipid-lowering therapy, 0.67; 95% CI, 0.48 to 0.95; P = 0.023) among ACS patients on statin treatment at the time of discharge. Similar findings have also been observed in the post-MI patients (hazard ratio for 1-year mortality with statin therapy, 0.75; 95% CI, 0.63 to 0.89; P = 0.001).3

In the MIRACL study,7 that randomized 3086 ACS patients to either early atorvastatin therapy or placebo, the primary composite endpoints of death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia were significantly lowered with atorvastatin therapy at 16 weeks (14.8% versus 17.4%; relative risk, 0.84; 95% CI, 0.70 to 1.00; P = 0.048). The mortality reduction in MIRACL was not significant (4.2% for atorvastatin versus 4.4% for placebo, P = 0.94), although this study was not of adequate size to show a mortality difference. Nevertheless, these observations raise the possibility that the mechanism of mortality reduction with statins might be independent of its serologic lipid-lowering effect.18

Within the context of PCI, 3 trials have previously focused on the effect of these agents on angiographic restenosis. Both the Prevention of Restenosis by Elior After Transluminal Coronary Angioplasty (PREDICT) trial19 and the Lovastatin Restenosis Trial20 failed to demonstrate a reduction of angiographic restenosis at 6 months with statins. In the PREDICT trial, mortality occurred in 1.5% of patients within the statin group and 0.5% within the nonstatin group at 6 months (P = 0.62). Similarly, mortality difference was not demonstrated in the Lovastatin Restenosis Trial, possibly because of the small number of patients (statin versus nonstatin, 1.0% versus 0.3%, P = 0.62). The more recent Fluvastatin Angiographic Restenosis (FLARE)18 trial observed a lower composite of death or MI with fluvastatin (1.4% versus 4.0%, P = 0.025), although this analysis was not prespecified. One of the differences between FLARE and the other 2 trials was that patients in the FLARE trial were pretreated with fluvastatin for 2 to 4 weeks before PCI, compared with those in PREDICT who were not pretreated and those in the Lovastatin Restenosis Trial who received 7 to 10 days pretreatment. Consistent with the findings of the FLARE trial, our study suggests that there is an early mortality reduction associated with statin therapy after PCI.

The dissociation between the rates of mortality and other ischemic endpoints deserves particular attention. An effect on mortality, independent of other ischemic endpoints, was similarly observed in other clinical trials, such as the oral IIb/IIIa inhibitors.21 These observations suggest pathophysiological mechanisms beyond the traditional paradigm of coronary thrombosis and ischemia and infarction. Similar to the results from the study by Aronow et al.,6 statin administration was associated with a benefit on mortality alone and was independent of a reduction in MI or revascularization. Definitive mechanisms accounting for the mortality reduction of statins after PCI have not been elucidated. As suggested in the experimental and clinical settings, plausible mechanistic explanations include plaque stabilization (eg, decreased secretion of matrix metalloproteinases by macrophages, inhibition of endogenous cholesterol synthesis in macrophages, and reduction of number of inflammatory cells in atherosclerotic plaques),22–24 improvement of endothelial function, increased nitric oxide synthesis,25 and reduction of platelet activation and adhesion.26–28 These effects may be expected to result in reduction in thrombogenesis.29 Although all of these mechanisms would be expected to contribute to the late benefit across all ischemic endpoints observed in the primary and secondary prevention studies, these effects do not necessarily and adequately account for the isolated mortality benefit observed within this and other studies. Therefore, an alternative theory, such as the anti-inflammatory effect of statin, remains intriguing.

As in coronary instability, vascular injury during PCI is associated with a systemically measurable inflammatory re-
response,29–31 and the degree of inflammation has been shown to correlate with cardiovascular risks.15,29–32 Interestingly, the association between systemic inflammation and adverse outcome among ACS patients is primarily expressed as an excess in mortality with a lesser effect on MI.33 The Pravastatin Inflammation C-Reactive Protein Evaluation (PRINCE) study34 confirms the effect of pravastatin on C-reactive protein lowering, a marker of the anti-inflammatory effect. The effect was noted as early as 12 weeks after administration and was independent of the changes in LDL cholesterol levels. The mortality reduction associated with statin therapy explained on the basis of anti-inflammatory effects seems plausible, but with the present evidence, it remains speculative.11–15

Limitations

Our analysis has several limitations. First, the treatment with statin therapy was nonrandomized. Despite careful use of regression models to adjust for potential confounders that may affect major cardiac events, unmeasurable factors may still exist. Physician or patient bias may also affect the rate of revascularization. However, the statin-treated patients in our cohort carried more high-risk comorbidities at the time of PCI. Furthermore, adjustment for glycocalcyprotein IIb/IIIa inhibitor use, which was associated with worse outcome in our multivariate model, might be able to adjust for some nonmeasured variables that were deemed important predictors of adverse outcomes by the operators. Second, the discharge medication as well as the compliance on statin therapy was unknown during follow-up. However, any crossover of the comparison groups would only lead to underestimation of the treatment effect and, hence, may additionally strengthen our conclusion about the beneficial effect of statins before PCI. Likewise, the length of statin pretreatment that would be required to produce the observed mortality reduction remains unknown. However, because previous studies have shown that statin therapy improves endothelial function and lowers serum inflammatory markers as early as 6 to 12 weeks,10,11,13,34 the treatment effect may again be underestimated in our study if the duration of statin pretreatment was shorter than this amount of time.

Third, this population-based data may be limited by the self-reported MI and revascularization rates, which are considered the softer endpoints. Furthermore, the discordance of mortality and nonfatal ischemic event rates may be partly accounted for by the fact that statin is taken by a selected group of patients with elevated cholesterol levels, which in turn is an established risk factor for progression of CAD and prothrombotic events.

Conclusions

Within this large observational study, we have noted an early mortality benefit related to statin therapy before PCI. This benefit was seen within the first month after PCI and was sustained at 6 months. The mechanism may be independent of lipid lowering, and, hence, additional research is warranted to elucidate this process. These data suggest the need to evaluate prospectively the impact of pretreatment with statins within a randomized trial design, in particular targeting patients with elevated inflammatory markers before coronary intervention.

References


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