Usefulness of Statin Pretreatment to Prevent Contrast-Induced Nephropathy and to Improve Long-Term Outcome in Patients Undergoing Percutaneous Coronary Intervention

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Contrast-induced nephropathy (CIN) is an important cause of mortality and morbidity in patients undergoing angiography. This study investigated whether statins decrease incidence of CIN in the setting of percutaneous coronary intervention (PCI) and evaluated the influence of such potential benefit on long-term outcome. Four-hundred thirty-four patients undergoing PCI were prospectively enrolled and followed up to 4 years. Patients were stratified according to preprocedural statin therapy (260 statin treated, 174 statin naive). CIN was defined as a postprocedural increase in serum creatinine of $\geq 0.5$ mg/dl or $> 25\%$ from baseline. Follow-up assessment included 4-year occurrence of major adverse cardiac events. Statin-treated patients had a significantly lower incidence of CIN (3\% vs 27\%, $p < 0.0001$; 90\% risk decrease) and had better postprocedural creatinine clearance ($80 \pm 20$ vs $65 \pm 16$ ml/min, $p < 0.0001$). Benefit of statin before treatment was observed in all subgroups, except in patients with a pre-existing creatinine clearance $< 40$ ml/min. During follow-up, CIN was a predictor of poorer outcome; 4-year survival free of major adverse cardiac events was highest in statin-treated patients without CIN (95\%, $p = 0.015$) and lowest in statin-naive patients with CIN (53\%, $p \leq 0.018$). In conclusion, patients receiving statins before PCI have a significant decrease of CIN; this early protective effect translates into better long-term event-free survival. These results may lend further support to utilization of statins as adjuvant pharmacologic therapy before PCI. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101:279–285)

Pretreatment with atorvastatin before percutaneous coronary intervention (PCI) has significantly decreased the occurrence of periprocedural myocardial infarction\textsuperscript{1,2} and decreased postoperative atrial fibrillation after cardiac surgery,\textsuperscript{3} possibly through anti-inflammatory effects.\textsuperscript{4} Inflammatory mechanisms and oxidative stress may be also involved in the pathogenesis of contrast-induced nephropathy (CIN)\textsuperscript{5,6}; hence, the rationale for a prospective evaluation of statin benefit in this setting. A recent review of a large insurance database has shown that statin therapy is associated with a lower occurrence of CIN after PCI,\textsuperscript{7} and similar results were retrospectively observed after cardiac catheterization in patients with chronic renal impairment.\textsuperscript{8} However, no study has addressed the issue of whether prevention of CIN with statins would improve long-term clinical outcome.

Methods

Four-hundred eighty consecutive patients undergoing PCI at Campus Bio-Medico University of Rome from June 1, 2000 to June 1, 2001 were evaluated (Figure 1). Patients had signs and/or symptoms of myocardial ischemia and angiographic evidence of significant coronary disease warranting PCI. To minimize the potential role of hemodynamic instability as a cause of postprocedural renal failure, 46 patients with ST-segment elevation acute myocardial infarction $< 48$ hours, cardiogenic shock, or left ventricular ejection fraction $< 30\%$ were excluded. Thus, 434 patients giving informed consent were enrolled. The study population was prospectively divided into statin-treated patients (n = 260) and statin-naive patients (n = 174) at the time of intervention. PCI was performed with standard technique. A nonionic, low-osmolar (915 mOs/m/kg), iodinated contrast agent (iobitridol, Xenetix, Guerbet, Roissy CdG Cedex, France) was used in all interventions. Patients received aspirin (100 mg/day) and ticlopidine 250 mg 2 times/day from the day before or clopidogrel 300 mg 6 hours before the procedure. All patients continued ticlopidine 250 mg 2 times/day or clopidogrel 75 mg/day for $\geq 1$ month, and they were discharged on long-term statin therapy, unless contraindicated.

By study design, blood samples were drawn before and 24 hours after PCI for measurement of serum creatinine; further determinations of creatinine beyond 24 hours were done if clinically indicated; in such cases, the peak postprocedural value was used for the purpose of this study. Creatinine clearance was calculated by applying the Cockcroft-Gault formula: creatinine clearance $= ([140 - \text{age}] \times \text{weight/serum creatinine} \times 72)$ with female gender adjustment (creatinine clearance$_{\text{female}} = \text{creatinine clearance} \times \frac{f}{m}$).
Patients with baseline renal failure (defined as pre-procedural serum creatinine ≥1.5 mg/dl or creatinine clearance <70 ml/min) underwent intravenous hydration with normal saline at 1 ml/hour/kg body weight for ≥12 hours before and 24 hours after angioplasty. CIN was defined as a postprocedural increase in serum creatinine of ≥0.5 mg/dl or >25% from baseline; postprocedural acute renal failure was defined as a rapid decrease in renal glomerular filtration with >2 mg/dl creatinine increase from baseline. Exceeding weight- and creatinine-adjusted maximum contrast doses were also calculated using the formula body weight (kilograms) × 5 ml/serum creatinine.

PCI success was defined as a postprocedural Thrombolysis In Myocardial Infarction grade 3 flow and decrease of stenosis to <30% residual narrowing by quantitative analysis; incidence of major in-hospital complications (death, myocardial infarction, urgent coronary revascularization) was also recorded. Periprocedural myocardial infarction was defined as an increase in creatine kinase-MB >5 times after intervention.

Patients were prospectively followed for 4 years by office visits and/or telephone interviews or contact with a referring physician at 1, 3, 6, and 12 months and yearly thereafter. Follow-up evaluation included occurrence of major adverse cardiac events (MACEs; cardiac death, myocardial infarction, or repeat coronary revascularization) and verification of continued statin therapy. Clinical, procedural, and laboratory data were prospectively entered in a computerized database and retrospectively analyzed. The study was approved by the institutional review board of the university.

Results

In the statin-treated group, 153 patients (59%) were taking atorvastatin, 77 (30%) simvastatin, 19 (7%) rosvuastatin, and 280 (10%) pravastatin. The remaining 280 (10%) patients were taking rosuvastatin. The baseline characteristics of the patients in the statin-treated group were compared with those of the patients in the no-statin group.
treated patients had a significantly lower incidence of CIN (3% vs 27%, p = 0.0001; Figure 2); mean postprocedural serum creatinine was also lower in the statin group (1.2 ± 0.4 vs 1.4 ± 0.4 mg/dl, p <0.0001) and creatinine clearance was significantly better (p <0.0001; Figure 2). Occurrence of postprocedural acute renal failure was rare and similar in the 2 groups (1%, p = 0.99). In patients with CIN, those receiving statins had significantly lower postprocedural creatinine peak levels (1.6 ± 0.5 vs 2.3 ± 1.4 mg/dl, p = 0.007). No patient with CIN required dialysis, and all were discharged when renal function returned to baseline after aggressive hydration. Patients with low-density lipoprotein cholesterol levels below the median (96 mg/dl) had 1 episode of CIN versus 6 patients in the group with levels above the median (p = 0.13). Length of stay after intervention was shorter in statin-treated than in statin-naive patients (2.2 ± 0.6 vs 2.4 ± 0.6, p = 0.01) and longer in patients with CIN (2.7 ± 0.9 vs 2.2 ± 0.6 days, p = 0.001); as expected, length of stay was shortest in statin-treated patients without CIN (2.2 ± 0.4 days, p =0.036).

Multivariable analysis (Figure 3) identified statin pre-
treatment as strong predictor of decreased risk of CIN (OR 0.10, 95% CI 0.02 to 0.18, p = 0.0001); female gender, diabetes mellitus, previous myocardial infarction, increased baseline serum creatinine level, decreased baseline creati-
nine clearance, and amount of contrast load were independent predictors associated with increased risk. In a subgroup analysis (Figure 4) that included age, gender, presence of diabetes mellitus, therapy with angiotensin-converting enzyme inhibitors, left ventricular ejection fraction, clinical presenta-
tion, previous myocardial infarction, baseline renal function, and extension of coronary artery disease, a significant benefit of statins was maintained in all subgroups, except for patients with a baseline creatinine clearance <40 ml/min (OR 0.35, 95% CI 0.10 to 1.7, \(p = 0.18\)).

Four-year clinical follow-up was obtained in 430 of 434 patients (99%). Incidence of late MACEs was significantly lower in patients receiving statins at the time of intervention (6% vs 36%, \(p < 0.0001\)), and this was driven by a decrease in cardiac death and repeat coronary intervention (Table 3). Multivariable analysis (Table 4) demonstrated that statin therapy was independently associated with a lower risk of MACEs during follow-up; CIN, older age, and impaired left ventricular ejection fraction were predictors of poorer outcome. Event-free survival was higher in statin-treated patients at 48 months (94% vs 66%, \(p < 0.0001\)) and in patients without CIN (87% vs 61%, \(p < 0.0001\); Figure 5).

Actuarial life-table analysis (Figure 6) showed that 4-year event-free survival was best in statin-treated patients and no CIN (95%, \(p \leq 0.015\) vs other groups) and worst in statin-naive patients with CIN (53%, \(p \leq 0.018\) vs other groups); survival of statin-treated patients with CIN was similar to that of statin-naive patients who did not develop CIN (72% vs 71%).

**Discussion**

This study indicates that patients receiving statin treatment before PCI have a decreased incidence of postprocedural CIN compared with patients not receiving statins; this benefit is associated with improved long-term clinical outcome, including a significant decrease in cardiac death at 4 years.

Chronic renal failure worsens prognosis in patients with coronary artery disease and in those undergoing coronary angioplasty,\textsuperscript{12,13} and development of CIN after PCI correlates with increased risk of early and late cardiovascular events.\textsuperscript{14,15} Although the pathogenesis of CIN is not completely known, multiple mechanisms may be involved. Af-
After contrast exposure, there is a brief period of vasodilation followed by renal vasoconstriction, and various molecules (i.e., angiotensin, vasopressin, and endothelin) appear to mediate this decrease in renal blood flow.5,6 Because statins induce downregulation of angiotensin receptors and decrease endothelin synthesis,16,17 these drugs may prevent CIN by decreasing the period of renal hypoperfusion and ischemia. Another mechanism responsible for CIN is direct damage to tubular cells mediated by oxygen-free radicals, proinflammatory cytokines, and complement activation, with subsequent cytoplasmic vacuolization, necrosis, interstitial inflammation, and tubular obstruction by protein precipitates.5,6,18 Statins may decrease inflammation and improve endothelial function by inhibiting nuclear factor-κB, a transcription factor that acts on genes encoding for proinflammatory mediators,19 decreasing expression of endothelial adhesion molecules,20,21 increasing nitric oxide bio-

![Figure 4. Subgroup analysis showing benefit of statin therapy in different patient subsets.](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statin Pretreatment</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>Yes (n = 258)</td>
<td>No (n = 172)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (2%)</td>
<td>11 (8%)</td>
</tr>
<tr>
<td>Clinically driven repeat angiography</td>
<td>3 (2%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Restenosis with target lesion revascularization</td>
<td>8 (4%)</td>
<td>30 (22%)</td>
</tr>
<tr>
<td>Repeat PCI*</td>
<td>1 (1%)</td>
<td>11 (8%)</td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>7 (4%)</td>
<td>27 (20%)</td>
</tr>
<tr>
<td>Total MACEs</td>
<td>4 (2%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Total MACEs</td>
<td>12 (6%)</td>
<td>50 (36%)</td>
</tr>
</tbody>
</table>

*p Target plus nontarget vessel revascularization.

Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin therapy</td>
<td>0.17</td>
<td>0.08–0.34</td>
<td>0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>1.4</td>
<td>0.68–3.0</td>
<td>0.34</td>
</tr>
<tr>
<td>Age ≥65 yrs</td>
<td>2.1</td>
<td>1.2–3.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.9</td>
<td>0.95–3.9</td>
<td>0.07</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;40%</td>
<td>2.1</td>
<td>1.3–3.8</td>
<td>0.01</td>
</tr>
<tr>
<td>CIN</td>
<td>2.6</td>
<td>1.2–5.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Balloon angioplasty</td>
<td>5.1</td>
<td>0.68–37</td>
<td>0.11</td>
</tr>
<tr>
<td>Stent length &lt;15 mm</td>
<td>0.62</td>
<td>0.34–1.1</td>
<td>0.12</td>
</tr>
<tr>
<td>Stent diameter &lt;3 mm</td>
<td>1.4</td>
<td>0.83–2.5</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* Target plus nontarget vessel revascularization.
availability,\(^{19,22}\) attenuating production of reactive oxygen species,\(^{23}\) and protecting against complement-mediated injury.\(^{24}\) In addition, experimental data have shown that statins exert nephroprotective effects in a rat model of long-term inhibition of nitric oxide synthesis by amelioration of vascular endothelial growth factor expression and decrease of RhoA activity.\(^{25}\) Thus, by all those actions, statins may provide protection against CIN.

In our study, patients treated with a variety of statins undergoing PCI had a 90% risk decrease of CIN; this was independent of possible confounding factors and probably not related to cholesterol lowering. This beneficial effect was observed despite a higher risk profile (i.e., higher prevalence of unstable syndromes, complex lesions, multivessel coronary disease, and previous coronary revascularization) present in patients receiving statins. Thus, the “sickest” cardiac patients obtain the greatest benefit with statins. Renal protection was observed even in patients more prone to develop postprocedural renal failure, such as older patients or diabetics, and it resulted in a significant decrease in length of stay. When patients developed CIN, their peak creatinine levels after PCI were significantly attenuated if they were taking statins. Patients with severely impaired baseline renal function (creatinine clearance <40 ml/min) had less benefit, probably due to multiple nonreversible pathogenetic mechanisms involved in advanced renal failure.\(^{26}\)

Importantly, prevention of CIN by statin therapy leads to a significant long-term decrease of adverse events; statin-treated patients without CIN had a 90% relative decrease of MACEs at 4 years compared with the worst scenario of statin-naïve patients who developed CIN. CIN was associated with an excess mortality of 5% and an excess event rate of 25% at 4 years; similar results were obtained in a previous observational analysis in 7,586 patients.\(^{14}\) Accordingly, a 24% absolute decrease in the incidence of CIN, as observed in this study, would translate into 3 lives saved and prevention of 15 cardiac events per 1,000 patients treated per year.

Mechanisms underlying improved late outcome are not completely clear. Vulnerability to contrast agents may be a marker of multisystem atherosclerosis responsible for late cardiac complications, as suggested by the correlation between cardiovascular risk (i.e., previous myocardial infarction) and postprocedural renal impairment. Accordingly, the same CIN-protective mechanisms exerted by statins during PCI (i.e., anti-inflammatory effects and improvement of endothelial function) may play a role in the decrease of cardiac events in the long term. In fact, thanks to statin therapy, the event-free survival curve of patients who developed CIN was essentially equal to that of statin-naïve patients without CIN.

The present study presents limitations inherent to all nonrandomized analyses. However, randomized, placebo-controlled trials using statins to prevent contrast-induced renal impairment during cardiovascular procedures would be difficult to design, due to the current widespread use of statins in patients with coronary artery disease. Because a single serum creatinine determination was obtained 24 hours after the procedure by study design, and further mea-
surements were performed only if clinically indicated (i.e., evidence of worsening renal function), some patients with a late increase in serum creatinine could have been missed and the incidence of CIN underestimated; however, most patients developing CIN present a >0.5 mg/dl increase in serum creatinine within 24 hours from contrast exposure,27 and, in our study, the incidence of such complication was similar to other large observational series.7,28 Although in our cohort the mean duration of statin pretreatment was 10 months and atorvastatin was the drug most frequently used, we cannot establish specific correlations between duration of therapy or type of statin and protection against CIN.

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