Long-Term Clinical and Angiographic Follow-Up After Coronary Stent Placement in Native Coronary Arteries

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Background—Although coronary stents have been proved effective in reducing clinical cardiac events for up to 3 to 5 years, longer term clinical and angiographic outcomes have not yet been fully clarified.

Methods and Results—To evaluate longer term (7 to 11 years) outcome, clinical and angiographic follow-up information was analyzed in 405 patients with successful stenting in native coronary arteries. Primary or secondary stabilization, which was defined as freedom from death, coronary artery bypass grafting, and target lesion–percutaneous coronary intervention (TL-PCI) during the 14 months after the initial procedure or after the last TL-PCI, was achieved in 373 patients (92%) overall. Only 7 patients (1.7%) underwent TL-PCI more than twice. After the initial 14-month period, freedom from TL-PCI reached a plateau at 84.9% to 80.7% over 1 to 8 years. However, quantitative angiographic analysis in 179 lesions revealed a triphasic luminal response characterized by an early restenosis phase until 6 months, an intermediate-term regression phase from 6 months to 3 years, and a late renarrowing phase beyond 4 years. Minimal luminal diameter in 131 patients with complete serial data were 2.62 ± 0.4 mm immediately after stenting, 2.0 ± 0.49 mm at 6 months, 2.19 ± 0.49 mm at 3 years, and 1.85 ± 0.56 mm beyond 4 years (P < 0.0001).

Conclusions—The efficacy and safety of coronary stenting seemed to be clinically sustained at 7 to 11 years of follow-up. However, late luminal renarrowing beyond 4 years was common, which demonstrates the need for further follow-up.

Key Words: stents ■ restenosis ■ angioplasty

Coronary stenting has been shown to reduce clinical and angiographic restenosis after balloon coronary angioplasty in 2 randomized trials.1,2 Adjunctive use of potent antiplatelet agents such as ticlopidine or clopidogrel markedly decreased the incidence of stent thrombosis and bleeding complications3 and thereby promoted the widespread use of coronary stents. Despite these favorable observations, there remained concerns about the long-term outcome after the permanent placement of metallic prosthetic devices inside the coronary artery. Medium-term follow-up studies at 3 to 5 years revealed a paucity of late clinical stent-related problems4–8 and even angiographic regression of the stented lesions.8,9 Recently, Choussat et al10 reported clinical stability of the stented target site at 8 to 10 years after coronary stenting. However, there is still no long-term angiographic data supporting sustained patency of the stented target site and absence of local complications specific for permanent implantation of metallic prosthesis. Furthermore, although diffuse in-stent restenosis has been known to be refractory to repeated percutaneous coronary intervention (PCI),11 long-term outcome of those patients undergoing repeated PCI has not yet been fully clarified. To address these issues, we analyzed clinical and angiographic outcome at 7 to 11 years after Palmaz-Schatz stent placement in native coronary arteries.

Methods

Study Patients

From June 1990 through December 1993, 422 consecutive patients (443 lesions) underwent placement of the Palmaz-Schatz stent in native coronary arteries. This study population included all the 143 patients whose 3-year follow-up result was reported previously.8 All stents were placed with a commercially available stent delivery system (Johnson & Johnson) by standard techniques.12 In 411 patients (97%), stents were successfully deployed to the target sites. In-hospital major complications included death in 6 patients (1.4%), stent thrombosis in 9 patients (2.1%), Q-wave myocardial infarction (MI) in 9 patients (2.1%), and urgent coronary artery bypass grafting (CABG) in 3 patients (0.7%). Antiocoagulant therapy after stent placement included aspirin, dipyridamole, dextran, heparin, and warfarin and has been described in detail elsewhere.13 A total of 405 patients (424 lesions) undergoing successful stent placement who were discharged alive constituted the study population for long-term

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follow-up. All the patients gave informed consent for the procedure and the follow-up treatment, which was approved by the institutional review board.

Clinical Follow-Up
Clinical follow-up data were obtained by either a review of the hospital records or telephone contacts with the patients or their referring physicians. When a patient reported a clinical event, it was confirmed by contacts with the referring physician whenever possible. The referring physicians were requested to send all the follow-up angiograms.

With regard to the follow-up events, only the out-of-hospital events were analyzed on per-patient basis. The major clinical events studied were death, MI, CABG, and PCI ≤ 50% at follow-up for stented target lesions (TLs) and non-TLs. Death was regarded as cardiac except for those of proven noncardiac origin. MI was defined as an increase in serum creatinine kinase activity to more than twice the normal value, in association with new pathological Q waves. TL-PCI was defined as that involving not only inside the stent but also the stent edges within the injured segment of the initial procedure. Discrimination of TL-PCI from non-TL-PCI was assessed by a consensus of 2 experienced angiographers, who analyzed the initial and follow-up angiograms side by side. Primary stabilization of the stented lesion was defined as survival without TL-PCI or CABG at 14 months after the initial procedure. When patients underwent early TL-PCI, secondary stabilization was defined as survival without further TL-PCI or CABG at 14 months after the last TL-PCI. The specific time point of 14 months was chosen because many patients in this study underwent the angiographic study at 1 year, which tended to be a driving force of TL-PCI. Late TL-PCI was defined as that performed after achievement of primary or secondary stabilization.

Angiographic Follow-Up
In the initial series of patients of this study population, follow-up angiography was to be performed 6 months, 1 year, and 3 years after the procedure according to the study protocol. In the later series of patients, only the follow-up angiography at 6 months was dictated by the protocol. The 6-month follow-up studies were defined as those performed between 4 and 14 months after the procedure. When the patients underwent TL-PCI, follow-up angiography at 6 months after the TL-PCI was recommended. The early follow-up studies were defined as either 6-month studies in patients with primary stabilization or those studies at 6 months after the last TL-PCI in patients with secondary stabilization. The 3-year follow-up studies were defined as those performed between 27 and 48 months. The late follow-up studies beyond 4 years were not dictated by the protocol but were performed according to the decision of the attending physicians. If a patient underwent multiple angiographic studies beyond 4 years, the late follow-up study was defined as either the latest one in patients without late TL-PCI or that at the time of late TL-PCI.

Quantitative angiographic analysis was performed with the Cardiovascular Angiography Analysis System II. Detailed methods and reproducibility of quantitative angiographic analysis in our laboratory were described previously. Restenosis was defined as stenosis ≥ 50% at follow-up.

Statistical Analysis
Values were expressed as mean ± SD except for rates of event-free survival, which were expressed as mean ± SEE. Paired numerical data obtained by serial angiography were compared by the paired t test, and other continuous variables were compared with the unpaired t test. Categorical variables were compared with the χ² test. Rates of event-free survival were studied with Kaplan-Meier analysis and displayed as survival curves. Comparison between curves was performed by the log-rank method. Multivariate predictors of late death were analyzed by Cox proportional hazards regression. Adjusted hazard ratios, 95% confidence intervals, and probability values were reported. Probability values < 0.05 were considered statistically significant.

Results
Patient, Lesion, and Procedural Characteristics
The patient, lesion, and procedural characteristics of the 405 study patients are shown in Table 1. Focal lesions in large arteries were preferentially selected for stent placement, as evidenced by the large reference diameter with a short lesion length. Multiple overlapping stents were used very infrequently. Therefore, the study population reflected classic characteristics of coronary stenting.
Outcome of Clinical Follow-Up
Clinical follow-up information was obtained in 400 patients (99%) at 3 years and 396 patients (98%) at 7 years. The follow-up interval of the 298 survivors was 8.4 ± 1.4 years (range, 1–11 years).

Primary stabilization was achieved in 317 patients (78%); 19 patients who died and 8 and 61 patients who required CABG and TL-PCI within 14 months, respectively, were excluded. Among the 61 patients undergoing TL-PCI, 3 patients died, 1 patient received CABG, and 1 patient was lost to follow-up within 14 months. Therefore, secondary stabilization was achieved in 56 patients (92%). Primary or secondary stabilization was achieved in 373 patients (92%) overall. The number of TL-PCI procedures to achieve secondary stabilization was only 1 in 41 patients (73%), 2 in 8 patients (14%), 3 in 5 patients (8.9%), 5 in 1 patient (1.8%), and 6 in 1 patient (1.8%). Therefore, only 7 (1.7%) of 405 study patients underwent TL-PCI more than twice.

The cumulative survival rates were 76.1 ± 2.2% at 8 years (Figure 1a). Among 107 patients who died during follow-up, the causes of death were cardiac in 41%, noncardiac but vascular in 20%, and noncardiovascular in 39% (Table 2). By multivariate analysis of various factors that may have affected late mortality, age, chronic renal failure as defined by serum creatinine level ≥ 1.3 mg/dL, left ventricular dysfunction as defined by ejection fraction < 0.4, and diabetes mellitus were found to be independent predictors of late death (Table 3).

At 8 years, 90.5 ± 1.6% of patients were free from Q-wave MI. Among 35 documented episodes of Q-wave MI, only 3 (8.6%) were related to problems at the stented lesions. Major event-free survival rates (death/MI/CABG and death/MI/CABG/TL-PCI) were 67.2 ± 2.4% and 57.2 ± 2.5% at 8 years, respectively (Figure 1b). After the initial 14-month period, freedom from TL-PCI reached a plateau at 84.9 ± 1.8% to 80.7 ± 2.0% over 1 to 8 years (Figure 1c). Although sporadic episodes of late TL-PCI did occur beyond 5 years, late revascularization procedures were predominantly targeted to progressive disease at nontarget sites (Figures 1c and 1d). Because of the frequent need for PCI for new lesions, only 36.7 ± 2.4% of patients were completely free from any events at 8 years (Figure 1b).

Outcome of Angiographic Follow-Up
The 6-month follow-up studies were performed in 394 patients (95%; 412 lesions) at 193 ± 54 days after the procedure. Angiographic restenosis was found in 82 lesions (20%). Among 56 patients with secondary stabilization, the minimal luminal diameter (MLD) immediately after the final TL-PCI was significantly smaller than that after initial stent placement (2.13 ± 0.49 mm versus 2.47 ± 0.44 mm; P = 0.004). Angiography at 6 months after the final TL-PCI was performed in 51 patients at 13.6 ± 7.2 months after the initial procedure. MLD at the early study was significantly smaller in patients with secondary stabilization compared with those with primary stabilization (1.63 ± 0.42 mm versus 2.04 ± 0.5 mm; P = 0.0001). Ten patients (20%) fulfilled the criteria of angiographic restenosis but did not undergo further revascularization procedures.

Table 2. Causes of Death

<table>
<thead>
<tr>
<th>Death Category</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>44 (41)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>21</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8</td>
</tr>
<tr>
<td>Acute MI</td>
<td>5</td>
</tr>
<tr>
<td>Postoperative death (CABG)</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
</tr>
<tr>
<td>Noncardiac vascular death</td>
<td>21 (20)</td>
</tr>
<tr>
<td>Stroke</td>
<td>8</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>6</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>1</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>42 (39)</td>
</tr>
</tbody>
</table>

Figure 1. Kaplan-Meier curves showing rates of (a) survival, (b) event-free survival, (c) freedom from repeated PCI for either TLs or new lesions (NL), and (d) freedom from late TL-PCI.
The late follow-up studies beyond 4 years were performed in 182 patients (51%) out of 355 survivors at 4 years, with a mean interval of 6.6 ± 1.6 years. Symptomatic status at the time of the late studies included acute MI in 15 patients (9%), congestive heart failure in 5 patients (3%), class 3 or 4 angina in 35 patients (19%), and class 1 or 2 angina in 49 patients (27%). Seventy-eight patients (43%) were asymptomatic but underwent the late angiographic studies according to the decision of the attending physicians. Compared with the patients without late studies, patients with late studies were younger (62.8 ± 8.6 versus 64.8 ± 9.4 years; \( P \leq 0.0001 \)) and were followed longer (8.4 ± 1.1 versus 8.0 ± 1.4 years; \( P = 0.001 \)). Other baseline characteristics and outcome at the early angiographic studies were not different between the 2 groups (data not shown). Cine films were available for quantitative analysis in 173 patients (179 lesions). MLD decreased significantly from 1.98 ± 0.51 mm at the early study to 1.83 ± 0.58 mm at the late study (\( P < 0.0001 \); Figure 2a). This late decrease in MLD was similarly seen in both groups of patients with primary and secondary stabilization (Figures 2b and 2c). In 131 lesions with the 3-year study, MLD increased significantly from 2.0 ± 0.49 mm at the early study to 2.19 ± 0.49 mm at the 3-year study (\( P < 0.0001 \)), but it decreased significantly to 1.85 ± 0.56 mm at the late study (\( P < 0.0001 \); Figure 2d). Among the 78 asymptomatic patients at the time of the late follow-up study, complete sequential angiographic study was performed in 54 patients (57 lesions). The triphasic luminal response was also seen in these patients.

### Table 3. Univariate and Multivariate Predictors of Late Death

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate Analysis</th>
<th></th>
<th></th>
<th></th>
<th>Multivariate Analysis</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>( P )</td>
<td>Hazard Ratio (95% CI)</td>
<td>( P )</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.07 (1.04–1.1)</td>
<td>&lt;0.0001</td>
<td>1.06 (1.04–1.09)</td>
<td>&lt;0.0001</td>
<td></td>
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</tr>
<tr>
<td>Female sex</td>
<td>0.8 (0.47–1.34)</td>
<td>0.389</td>
<td>0.02 (0.92–1.1)</td>
<td>0.365</td>
<td></td>
<td></td>
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<tr>
<td>History of CABG</td>
<td>0.65 (0.25–1.66)</td>
<td>0.365</td>
<td>0.12 (0.49–1.18)</td>
<td>0.217</td>
<td></td>
<td></td>
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<tr>
<td>Multivessel disease</td>
<td>0.8 (0.51–1.25)</td>
<td>0.327</td>
<td>0.76 (0.49–1.18)</td>
<td>0.217</td>
<td></td>
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<tr>
<td>History of MI</td>
<td>1.02 (0.64–1.62)</td>
<td>0.948</td>
<td>0.76 (0.49–1.18)</td>
<td>0.217</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1.9 (1.24–2.9)</td>
<td>0.003</td>
<td>1.65 (1.1–2.46)</td>
<td>0.015</td>
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<tr>
<td>Chronic renal failure</td>
<td>2.29 (1.44–3.64)</td>
<td>0.0005</td>
<td>2.26 (1.45–3.54)</td>
<td>0.0003</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>0.97 (0.65–1.46)</td>
<td>0.893</td>
<td>0.97 (0.65–1.46)</td>
<td>0.893</td>
<td></td>
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<tr>
<td>Hypercholesterolemia</td>
<td>1.07 (0.6–1.92)</td>
<td>0.823</td>
<td>1.07 (0.6–1.92)</td>
<td>0.823</td>
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<tr>
<td>Left ventricular dysfunction</td>
<td>2.67 (1.55–4.59)</td>
<td>0.0004</td>
<td>2.17 (1.37–3.45)</td>
<td>0.001</td>
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<tr>
<td>Class 3 or 4 angina</td>
<td>0.9 (0.6–1.36)</td>
<td>0.617</td>
<td>0.9 (0.6–1.36)</td>
<td>0.617</td>
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</tr>
<tr>
<td>Use of ACE inhibitors</td>
<td>1.08 (0.55–2.13)</td>
<td>0.819</td>
<td>0.52 (0.23–1.14)</td>
<td>0.101</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of statins</td>
<td>0.52 (0.23–1.14)</td>
<td>0.101</td>
<td>0.52 (0.23–1.14)</td>
<td>0.101</td>
<td></td>
<td></td>
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</tbody>
</table>

ACE indicates angiotensin-converting enzyme; CI, confidence interval.

### Figure 2. Serial changes in MLD and reference diameter (RD) at the stented sites for (a) all lesions (n=179), (b) lesions with primary stabilization (n=153), (c) lesions with secondary stabilization (n=26), and (d) lesions studied at 3 years (n=131).
who were asymptomatic at the time of the late follow-up study (1.95±0.5 mm at the early study, 2.14±0.42 mm at the 3-year study, and 1.87±0.49 mm at the late study; P<0.0001). Angiographic restenosis was observed in 50 lesions (28%) at the late study. However, late TL-PCI was performed only in 20 lesions because many of the lesions with angiographic restenosis were in the range of 50% to 60% diameter stenosis. (Figure 3). Treatment strategies after the late angiographic studies were PCI for new lesions in 73 patients (41%), PCI for late in-stent restenosis in 14 patients (8%), PCI for both late in-stent restenosis and new lesions in 6 patients (3%), CABG in 9 patients (4%), and medical management in 80 patients (44%).

In the previous report of 3-year follow-up after coronary stenting,8 we described a patient with formation of aneurysm at the stent site. The patient died from a cerebral infarction unrelated to the aneurysm 5 years after the initial procedure. No other potentially deleterious vascular effects were noted on late angiographic follow-up.

**Discussion**

Early in-stent restenosis remains a major limitation of coronary stenting. Diffuse in-stent restenosis has been known to be refractory to repeated PCI.11 However, the extent of refractoriness could only be assessed by long-term follow-up study. In the present study, primary or secondary stabilization was achieved in >90% of patients. Furthermore, only 1.7% of all study patients underwent early TL-PCI more than twice. Therefore, although in-stent restenosis is still a vexing problem of coronary stenting, it was truly refractory in a minority of patients in this study. Diffuse in-stent restenosis was reported to be associated with a smaller reference artery diameter, longer lesion length, female sex, longer stent length, and use of coil stents.13 Favorable outcome in terms of infrequent refractory restenosis in our study may be related to our selection of short lesions in big arteries.

Long-term outcome of clinical follow-up in the present study confirmed the observation of Choussat et al.10 who reported the rate of revascularization of stented sites was <10% beyond 1 year for up to 10 years, and late revascularization was performed predominantly to treat progressive disease at nontarget sites. Therefore, the clinical benefits of coronary stenting in terms of reduction in the rate of TL revascularization seemed to be sustained at 7 to 11 years of follow-up. The paucity of clinical events related to the treated sites was similar to the event rates reported after balloon coronary angioplasty. It was also reassuring that long-term angiographic follow-up of a large patient series did not disclose any deleterious vascular effects other than formation of an aneurysm in a patient.

Despite the favorable long-term clinical outcome, a significant decrease in MLD was observed from 6 months to late follow-up by quantitative coronary angiography. In the previous studies, MLD was shown to improve from 6 months to 3 to 4 years after coronary stenting or balloon coronary angioplasty,8,9,17 which was confirmed in this study. Fibrotic scar formation associated with maturation of smooth muscle cells and reduction in matrix proteoglycans was suggested as one of the possible mechanisms of late angiographic regression, protecting the TLs from atherosclerotic progression or plaque rupture after both balloon coronary angioplasty and coronary stenting.18 However, the long-term luminal response after coronary stenting was clearly demonstrated to be triphasic in this study. The early restenosis phase (until 6 months) and the intermediate-term regression phase (from 6 months to 3 years) were followed by a late renarrowing phase beyond 4 years. It is not clear whether the late renarrowing phase is specific for coronary stenting. However, complete sequential angiographic follow-up of 48 lesions undergoing balloon coronary angioplasty revealed no change in MLD from 6 months (2.13±0.6 mm) to 10 years (2.18±0.61 mm).16 Pathological analysis of the stented human coronary arteries demonstrated heavy infiltration of lipid-laden macrophages around the struts beyond 5 years after coronary stenting, which indicated chronic inflammatory reactions. In contrast, it was not until >7 years after balloon coronary angioplasty that a slight infiltration of lipid-laden macrophages was observed in the subendothelial spaces.19 This chronic inflammation might induce late atherosclerotic progression of the treated lesions. These pathological findings are consistent with our angiographic observation of late luminal renarrowing beyond 4 years.

A potential problem with this study is the fact that late angiographic follow-up studies were not dictated by the protocol but were driven by clinical indications. Analysis of the late luminal response might be biased by the predominance of symptomatic patients in the angiographic follow-up group. However, nearly half of those patients with late angiographic studies were asymptomatic. The triphasic luminal response was also seen in these asymptomatic patients. Furthermore, treatment strategies after late angiographic studies were more often PCI for new lesions, which were regarded as the culprit lesions for symptom, rather than PCI for late in-stent restenosis. Therefore, it seems unlikely that the indication of late angiographic follow-up studies heavily biased the observed serial changes in luminal diameter.

It should be noted that there was some discrepancy between the late angiographic restenosis rate and the frequency of TL-PCI. Because many of the lesions with late angiographic restenosis were in the range of 50% to 60%
diameter stenosis, attending physicians tended to decide not to perform PCI. Also, the lesions with late in-stent restenosis were rarely associated with acute MI. If late in-stent restenosis is a self-limited process, late luminal renarrowing of this degree would be clinically acceptable. Therefore, the real clinical impact of late in-stent restenosis could only be clarified by follow-up for a more extended period of time. Progressive luminal renarrowing late after coronary stent placement, as shown in the present study, warrants the need for further follow-up.

Acknowledgments
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References
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