Very Long-Term (15 to 20 Years) Clinical and Angiographic Outcome After Coronary Bare Metal Stent Implantation

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Background—We previously reported that the long-term luminal response after coronary bare metal stenting is triphasic, with an early restenosis phase spanning the 6 months after the index procedure, an intermediate-term regression phase from 6 months to 3 years, and a late renarrowing phase beyond 4 years. However, the clinical significance of late luminal renarrowing remains unknown.

Methods and Results—Angiographic and clinical follow-up of the same cohort of 405 patients with successful Palmaz-Schatz stent placement was extended beyond 15 years. Clinical follow-up was completed in 98% of patients at 5 years and in 81% at 15 years. The incidence of death and cardiac death at 15 years was 45.4% and 20.6%, respectively. Paired long-term (4 to 10 years) and very long-term (>10 years) angiographic studies without intercurrent target lesion revascularization were performed in 55 lesions, and minimal luminal diameter further decreased from 1.88±0.50 mm to 1.60±0.73 mm (P=0.002). Late target lesion revascularization after initial stabilization of the stented segments occurred rarely within 4 years. Beyond 4 years, however, the incidence of late target lesion revascularization increased steadily from 3.3% at 4 years to 24.7% at 15 years. The incidence of definite very late stent thrombosis was low (1.5% at 15 years).

Conclusions—Luminal renarrowing of the stented segment beyond 4 years was a progressive process extending beyond 10 years. The angiographic observation of late in-stent restenosis was clinically relevant because a corresponding progressive increase in the incidence of late target lesion revascularization was observed beyond 4 years and up to 15 to 20 years after bare metal stent implantation. (Circ Cardiovasc Interv. 2010;3:468-475.)

Key Words: stents • restenosis • thrombosis • coronary artery disease • prognosis

Bare-metal stents (BMS) continue to be used in percutaneous coronary intervention (PCI), even after the introduction of drug-eluting stents (DES); however, very long-term outcomes, for example, beyond 10 years, after their implantation has not been clarified.1–4 We previously reported 7 to 11 years’ outcome of 405 patients with successful Palmaz-Schatz stent placement. The long-term luminal response after coronary BMS implantation was demonstrated to be triphasic; 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.1 Although there were sporadic episodes of late target lesion revascularization (TLR) for late in-stent restenosis (ISR), the real clinical significance of late luminal renarrowing has remained unclear.

Clinical Perspective on p 475

The current analysis was designed to extend the follow-up interval of the same cohort of patients beyond 15 years in an attempt to investigate whether the observed late renarrowing beyond 4 years is a progressive process and to investigate the clinical relevance of late ISR.

Study Population

The study population and in-hospital outcomes were previously described.1 Briefly, the current study population included 405 patients (424 lesions) who were discharged alive after successful Palmaz-Schatz stent placement in the Kokura Memorial Hospital from June 1990 through December 1993. All patients gave informed consent.
Clinical Follow-Up
Clinical information was obtained either from a review of the hospital record or by telephone contacts with the patients, the family members, or the primary care physician. Death was regarded as cardiac in origin unless obvious noncardiac causes could be identified. Vascular death was defined as that related to cerebral, aortic or peripheral vascular disease, or renal disease. Myocardial infarction (MI) was defined as an increase in serum creatine kinase activity to more than twice the normal value, in association with new pathological Q waves. Target vessel MI was defined as MI not clearly attributable to a nontarget vessel. Stent thrombosis (ST) was defined according to the Academic Research Consortium definitions and definite ST was evaluated on a patient-level basis in the current analysis.6 TLR was defined as either PCI or coronary artery bypass grafting surgery for restenosis or thrombosis of the original stented lesions that included the proximal and distal edge segments as well as the ostium of the side branches. The device-oriented composite outcomes included cardiac death, target vessel MI, or TLR. The patient-oriented composite outcomes included all-cause death, any MI, or any coronary revascularization.8 Data on angina status according to the Canadian Cardiovascular Society classification were collected at the time of follow-up angiography.6

Primary stabilization was defined as survival without TLR at 14 months after the initial stent implantation procedure. Secondary stabilization was defined as survival without further TLR at 14 months after the last target lesion PCI (TL-PCI). Late TLR was defined as that performed after achievement of primary or secondary stabilization.1

Angiographic Follow-Up
The angiographic studies at 6 months, 1 year, and 3 years were dictated by the study protocol. The early study was defined as either the 6-month study in patients with primary stabilization or the study at 6 months after the last TL-PCI in patients with secondary stabilization. The intermediate-term study was defined as that performed between 27 and 48 months. Angiographic studies beyond 4 years were conducted according to clinical indications. The long-term study was defined as that performed between 4 years and 10 years; the very long-term study was defined as that performed beyond 10 years. Angiographic analyses in the latter long-term and very long-term follow-up studies were performed in patients without previous late TLR events. Quantitative coronary 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.7

Statistical Analysis
Categorical variables are expressed as number and percentages. Continuous variables are expressed as mean±SD or median (range and/or interquartile range [IQR]), depending on their distribution. Numeric data obtained by serial angiography were assessed by longitudinal analysis methods with PROC MIXED commands on SAS. Pairwise comparisons were carried out by ESTIMATE procedure, and Bonferroni adjustment was used for probability values of these pairwise comparisons. Cumulative incidences were calculated by the Kaplan-Meier method. All statistical analyses were performed by 2 physicians (K. Yamaji and T. Kimura T.) and a statistician (T. Morimoto) with SPSS version 15.0 (SPSS Inc, Chicago, Ill), and SAS version 9.2 (SAS Institute Inc, Cary, NC). All reported probability values were 2-sided, and probability values <0.05 were regarded as statistically significant except for pairwise comparisons.

Results
Clinical Follow-Up Outcome
Baseline clinical and angiographic characteristics were previously described (Table 1). Although the study population included patients with high-risk clinical features such as multivessel disease, left ventricular dysfunction, diabetes, prior MI, and chronic renal failure, the majority of lesions represented the classic indication for coronary stenting in terms of vessel size and lesion length. During the early phase of follow-up, 374 patients (92%) achieved either primary or secondary stabilization, constituting the study population for evaluating the incidence of late TLR (Figure 1). Late clinical follow-up information was obtained in 398 patients (98%) at 5 years, 340 patients (84%) at 10 years, and 327 patients (81%) at 15 years.

The cumulative incidence of death, cardiac death, and sudden death at 15 years after stent implantation was 45.4%,
20.6% and 7.1%, respectively (Table 2 and Figure 2A). Among 177 patients who died, the causes of death were cardiac in 72 patients (40.7%), vascular in 30 patients (16.9%) and noncardiovascular in 75 patients (42.4%) (Table 3). The median follow-up interval of the 228 survivors was 15.9 years (range, 1.2 to 19.5 and IQR, 9.6 to 17.4).

The cumulative incidence of any MI and target vessel MI at 15 years was 14.8% and 8.4%, respectively. Very late ST beyond 1 year (Academic Research Consortium definite) occurred in 5 patients at 4, 5, 6, 15 and 17 years after BMS implantation. The cumulative incidence of very late ST was 1.5% at 15 years (Table 2).

Because of the high incidences of death and coronary revascularization, only 16.2% of patients were free from death, MI, or any coronary revascularization at 15 years (Figure 2A). Regarding the device-oriented composite outcomes, however, 74.5% and 49.4% of patients were free from cardiac death or target vessel MI and from cardiac death, target vessel MI, or TLR at 15 years, respectively (Figure 2B).

The cumulative incidence curve of TLR as a first event reached a plateau at 14 months (16.1%) up to 4 years (18.5%). In this time interval, non-TLR was predominant and its cumulative incidence at 14 months and at 4 years was 42.6% and 58.4%, respectively (Table 3). Of note, 240 patients (77 lesions) underwent very late angiographic follow-up beyond 10 years.

### Table 2. Cumulative Incidences of Clinical Events

<table>
<thead>
<tr>
<th>Event</th>
<th>14 Months</th>
<th>4 Years</th>
<th>10 Years</th>
<th>15 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>19 (4.7)</td>
<td>42 (10.4)</td>
<td>122 (31.7)</td>
<td>164 (45.4)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>13 (3.2)</td>
<td>21 (5.3)</td>
<td>51 (14.5)</td>
<td>65 (20.6)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>7 (1.8)</td>
<td>9 (2.3)</td>
<td>20 (6.1)</td>
<td>22 (7.1)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>5 (1.3)</td>
<td>10 (2.6)</td>
<td>25 (7.3)</td>
<td>30 (9.8)</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>1 (0.3)</td>
<td>11 (2.9)</td>
<td>46 (13.8)</td>
<td>69 (23.8)</td>
</tr>
<tr>
<td>MI</td>
<td>2 (0.5)</td>
<td>9 (2.4)</td>
<td>36 (10.9)</td>
<td>43 (14.8)</td>
</tr>
<tr>
<td>Target vessel MI</td>
<td>1 (0.3)</td>
<td>6 (1.6)</td>
<td>21 (6.2)</td>
<td>25 (8.4)</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>9 (2.2)</td>
<td>10 (2.5)</td>
<td>12 (3.1)</td>
<td>13 (3.7)</td>
</tr>
<tr>
<td>Definite very late stent thrombosis</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td>3 (0.9)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Any coronary revascularization</td>
<td>140 (35.2)</td>
<td>175 (44.7)</td>
<td>228 (61.6)</td>
<td>248 (71.8)</td>
</tr>
<tr>
<td>TLR</td>
<td>64 (16.1)</td>
<td>73 (18.5)</td>
<td>98 (27.0)</td>
<td>115 (36.0)</td>
</tr>
<tr>
<td>Non-TLR</td>
<td>85 (21.3)</td>
<td>122 (31.4)</td>
<td>185 (51.4)</td>
<td>203 (61.0)</td>
</tr>
<tr>
<td>Any CABG</td>
<td>8 (2.0)</td>
<td>22 (5.8)</td>
<td>35 (10.0)</td>
<td>46 (15.8)</td>
</tr>
<tr>
<td>TL-CABG</td>
<td>3 (0.8)</td>
<td>13 (3.5)</td>
<td>18 (5.2)</td>
<td>21 (6.8)</td>
</tr>
<tr>
<td>Any PCI</td>
<td>135 (34.0)</td>
<td>167 (42.6)</td>
<td>216 (58.4)</td>
<td>233 (67.3)</td>
</tr>
<tr>
<td>TL-PCI</td>
<td>61 (15.4)</td>
<td>66 (16.7)</td>
<td>87 (24.0)</td>
<td>102 (32.0)</td>
</tr>
</tbody>
</table>

Incidence rates were estimated by the Kaplan-Meier survival method. CABG indicates coronary artery bypass grafting.
21.3% and 31.4%, respectively (Figure 2C). Beyond 4 years, however, progressive increase in the incidence of TLR was observed from 18.5% at 4 years to 36.0% at 15 years. The cumulative incidence of non-TLR increased from 31.4% at 4 years to 61.0% at 15 years (Figure 2C).

Late TLR occurred rarely within 4 years after BMS implantation. Beyond 4 years, however, the cumulative incidence of late TLR increased steadily from 3.3% at 4 years to 24.7% at 15 years (Figure 2D). The cumulative incidences of late TLR at 15 years were 24.0% in patients with primary stabilization and 27.6% in patients with secondary stabilization, respectively. Symptomatic status at the time of late TLR included asymptomatic in 24 patients (36%), class 1 or 2 angina in 18 patients (27%), class 3 or 4 angina in 20 patients (30%), and acute MI in 5 patients (8%). In 24 asymptomatic patients, 11 patients had myocardial ischemia detected by exercise ECG, thallium perfusion scintigraphy, or echocardiography; 2 patients underwent coronary artery bypass grafting for restenosis at the target lesion during cardiovascular surgery for severe mitral regurgitation or complication of the non-TLR procedure; 2 patients underwent late TLR after 1-year follow-up angiographic studies dictated by the protocol, which had been postponed beyond 14 months after the initial stent implantation procedure. Information on the indications of late TLR were not available for the remaining 9 asymptomatic patients.

### Table 3. Causes of Death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>72 (40.7%)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>25</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>18</td>
</tr>
<tr>
<td>Acute MI</td>
<td>11</td>
</tr>
<tr>
<td>Postoperative death (CABG)</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>15</td>
</tr>
<tr>
<td>Vascular death</td>
<td>30 (16.9%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>12</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>10</td>
</tr>
<tr>
<td>Aortic aneurysim</td>
<td>6</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>75 (42.4%)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting.

Late TLR occurred rarely within 4 years after BMS implantation. Beyond 4 years, however, the cumulative incidence of late TLR increased steadily from 3.3% at 4 years to 24.7% at 15 years (Figure 2D). The cumulative incidences of late TLR at 15 years were 24.0% in patients with primary stabilization and 27.6% in patients with secondary stabilization, respectively. Symptomatic status at the time of late TLR included asymptomatic in 24 patients (36%), class 1 or 2 angina in 18 patients (27%), class 3 or 4 angina in 20 patients (30%), and acute MI in 5 patients (8%). In 24 asymptomatic patients, 11 patients had myocardial ischemia detected by exercise ECG, thallium perfusion scintigraphy, or echocardiography; 2 patients underwent coronary artery bypass grafting for restenosis at the target lesion during cardiovascular surgery for severe mitral regurgitation or complication of the non-TLR procedure; 2 patients underwent late TLR after 1-year follow-up angiographic studies dictated by the protocol, which had been postponed beyond 14 months after the initial stent implantation procedure. Information on the indications of late TLR were not available for the remaining 9 asymptomatic patients.

### Angiographic Follow-Up Result

The patient and lesion flow chart for the angiographic analysis is shown in Figure 1. Median intervals from the
The previously reported luminal renarrowing of the stented segment beyond 4 years after BMS implantation was a progressive process extending beyond 10 years; and (2) the angiographic observation of progressive renarrowing was clinically relevant because a corresponding progressive increase in the incidence of late TLR was observed beyond 4 years after BMS implantation.

Regarding the mechanisms of progressive late luminal renarrowing, Inoue et al. reported that in lesions evaluated >4 years after BMS implantation, prominent infiltration by lipid-laden macrophages with strong collagen-degrading matrix metalloproteinase immunoreactivity was observed around the struts and in 2 of these arteries, the surface contacting the stent was focally disrupted and covered by nonocclusive mural thrombi. Furthermore, an imaging study using optical coherence tomography demonstrated that neointima in the BMS-treated segments >5 years after stent implantation were characterized by marked signal attenuation and a diffuse border with intraintimal neovascularization,

Discussion

The main findings of the current analysis were as follows: (1) The previously reported luminal renarrowing of the stented
suggesting the presence of lipid-laden atherosclerotic neointima. These nouveau atherosclerotic changes and inflammation could be one of the underlying mechanisms of late luminal renarrowing. These inflammatory and atherosclerotic responses within the neointima might be related to the immune type responses to the metallic material because serial angiographic studies in those lesions undergoing balloon angioplasty revealed no change in MLD from 6 months to 7 to 12 years. Rupture or erosion of these nouveau atherosclerotic plaques might occasionally lead to thrombosis of the stented segment. Furthermore, healing of clinically silent rupture of these nouveau atherosclerotic plaques could result in increased plaque burden and late luminal renarrowing. It is intriguing that these nouveau atherosclerotic changes and inflammation could be seen much earlier after DES implantation, which might be one of the underlying mechanisms of delayed restenosis and very late stent thrombosis of polymer-based DES.

In our previous report suggesting the presence of late luminal renarrowing beyond 4 years after BMS implantation, we stated that the real clinical impact of late ISR could only be clarified by follow-up for a more extended period of time. In the current analysis, progressive increase in the incidence of late TLR corresponded to the angiographic observation of progressive renarrowing beyond 4 years after BMS implantation. Furthermore, these late ISR requiring late TLR are not always benign; 38% of the late TLR procedures were driven by severe angina or acute MI. Therefore, late ISR of BMS appears to be a clinically relevant entity. Considering the fact that the stented segments in the current cohort of patients constituted the relatively small portion of the entire coronary artery segments, the rough estimate of 1.6% per year for TLR as opposed to that of 2.7% per year for non-TLR beyond 4 years might suggest more aggressive atherosclerotic progression in the stented segments than in the nonstented native coronary artery segments. However, the incidence of very late ST (0.1% per year) after BMS implantation was consistent with the incidences reported previously and appeared to be lower than the incidences after DES implantation (0.3 to 0.6% per year). These observations might suggest a more vulnerable nature of DES-associated inflammation and nouveau atherosclerotic changes as compared with responses of the vessel wall late after BMS implantation. Furthermore, information on outcomes of DES beyond 5 years after implantation is currently very limited. Because vascular responses appear to be augmented beyond 4 years after BMS implantation, careful monitoring on longer-term outcomes of DES beyond 5 years should be mandatory.

Despite progressive increase in the incidence of late TLR, the incidences of serious cardiac events such as death, sudden death, or MI beyond 4 years appeared not to be disproportionate to the incidences within 4 years. Therefore, the present study could provide reassurance regarding very long-term safety of coronary stenting with BMS.

Our present study has several important limitations. First, 36% of patients were asymptomatic at the time of late TLR, although nearly half of these patients had myocardial ischemia documented by noninvasive functional tests. The clinical
significance of late TLR in asymptomatic patients remains unclear. Furthermore, even in symptomatic patients, we could not identify the revascularization procedure for the culprit lesion in cases in which non-TLR and TLR were performed in the same session. TLR could be an innocent bystander revascularization at least in some cases. Therefore, the high rate of late TLR observed in this study could not be directly translated into the high rate of clinically driven late TLR. Second, introduction of the unusual definition of late TLR after primary or secondary stabilization might be confusing. However, it would be important to recognize that late TLR could also occur in patients with secondary stabilization. Cumulative incidence curves for first TLR and late TLR were quite consistent (Figure 2C and 2D). Third, the number of patients with paired long-term and very long-term angiographic studies was relatively small. It is possible that the observed significant very late luminal narrowing reflected type 1 error. Furthermore, the angiographic outcomes might be significantly biased by ascertainment bias given that the majority of patients who were restudied in the very late time period were those with clinical issues. Predominance of symptomatic patients in the angiographic subgroup might exaggerate the angiographic observation of progressive luminal narrowing beyond 4 years. Even in asymptomatic patients at late angiographic studies, most patients underwent angiography according to the clinical indications including positive stress test results and therefore, the angiographic measurement was biased because of selection. However, the cumulative distribution function curve of late loss between long-term and very long-term studies showed ongoing late loss of at least 0.5 mm in a substantial proportion of lesions and a distribution that is similar to late loss between early and long-term studies. Even given the possible ascertainment bias, this could suggest that long-term and very long-term luminal narrowing represented a real phenomenon and not a finding caused by outliers. Fourth, timings of angiographic studies were not blinded to the quantitative coronary angiography operators. Fifth, the current study population did not have adequate statistical power to estimate the incidence of a rare event such as ST. Sixth, factors affecting disease progression such as medication compliance and changes in smoking status were not ascertained. Also, adjuvant pharmacology evolved with time, and this also may have influenced observations. These issues are relevant to comparisons for absolute rates of events seen among different time periods. Finally, the present study had no control group. However, the results from this very long-term follow-up study after BMS implantation would be an important benchmark for the long-term outcome of current and future generation of DES including totally bioabsorbable stents. Late ISR of BMS necessitating late TLR in almost one fourth of patients appears to be a clinically important issue that should be addressed with future development of improved coronary stent.

Conclusion
The previously reported late luminal narrowing of the stented segment beyond 4 years after BMS implantation was confirmed to be a progressive process extending beyond 10 years. The angiographic observation of late ISR was clinically relevant because a corresponding progressive increase in the incidence of late TLR was observed beyond 4 years and up to 15 to 20 years after coronary BMS implantation.

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Disclosures
None.

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