Bare Metal Stent Thrombosis and In-Stent Neoatherosclerosis

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Background—Very late stent thrombosis (VLST) was reported to occur even in patients with bare metal stent (BMS) implantation, although the annual incidence of VLST after BMS was much lower than that after drug-eluting stent implantation. Pathophysiologic mechanisms of VLST after BMS implantation remain largely unknown.

Methods and Results—From September 2002 to February 2010, we identified 102 patients with definite stent thrombosis (ST) of BMS and 42 control patients with acute coronary syndrome (ACS) unrelated to ST who underwent thrombus aspiration with histopathologic evaluation. There were 40 patients with early ST (EST, within 30 days), 20 patients with late ST (LST, between 31–365 days), and 42 patients with VLST (>1 year). Evidence for fragments of atherosclerotic plaques, such as foamy macrophages, cholesterol crystals, and thin fibrous cap, was more commonly seen in patients with EST (23%) and VLST (31%), whereas these findings were rarely observed in patients with LST (10%). Atherosclerotic fragments were predominantly seen in patients who had EST within 7 days or VLST beyond 3 years. The aspirated thrombi harvested from patients with ST and those with ACS were histologically indistinguishable from each other. Eosinophils were very rarely observed. Plasma level of total cholesterol and triglyceride were significantly higher in VLST cases with atherosclerotic fragments as compared with those without.

Conclusions—Fragments of atherosclerotic plaque were highly prevalent in patients with VLST beyond 3 years. Disruption of in-stent neoatherosclerosis could play an important role in the pathogenesis of VLST of BMS occurring beyond 3 years after implantation. (Circ Cardiovasc Interv. 2012;5:47-54.)

Key Words: stents ■ stent thrombosis ■ coronary artery disease ■ coronary atherosclerosis

Long-term follow-up studies revealed that very late stent thrombosis (VLST) could occur at a rate of 0.1% per year even in patients with bare metal stent (BMS) implantation, although the annual incidence of VLST of BMS was much lower than that after drug-eluting stent (DES) implantation.1–5 Pathological studies of human postmortem specimens in patients with VLST of DES demonstrated extensive inflammatory reactions at the site of DES implantation.6,7 Furthermore, Cook et al8 evaluated 10 patients with VLST by histological examination of aspirated thrombi, demonstrating that VLST was associated with histopathologic signs of inflammation. However, histopathologic studies in patients with VLST of BMS were currently very limited.9 Therefore, in an attempt to understand the pathophysiologic mechanisms of VLST of BMS, we undertook systematic histopathologic evaluation of aspirated thrombi in a large number of patients with stent thrombosis of BMS from a single center.

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WHAT IS KNOWN

- Very late stent thrombosis occurs in patients with bare metal stent implantation, although the annual incidence is much lower than that after drug-eluting stent implantation.
- In-stent neoatherosclerosis with ruptured plaques and thin-cap fibroatheromas has been observed in bare metal stents.

WHAT THE STUDY ADDS

- Atherosclerotic plaques harvested from patients with very late stent thrombosis and those with acute coronary syndrome unrelated to stent thrombosis were histologically indistinguishable from each other; showing foamy macrophages, cholesterol crystals, and thin fibrous cap.
- Disruption of neoatherosclerosis inside the stents could be an important underlying mechanism of very late stent thrombosis beyond 3 years after bare metal stent implantation.

1829 days (IQR, 1152–2711), respectively. From September 2002 to February 2010, 1453 patients with acute coronary syndrome (ACS) underwent thrombus aspiration and histopathologic evaluation of the aspirated thrombi. Among them, we identified 42 patients with ACS unrelated to ST as a control group matched with 42 patients with VLST of BMS regarding age, sex, hypertension, diabetes mellitus, use of insulin, use of oral hypoglycemic drugs, current smoking, chronic renal failure, hemodialysis, left ventricular ejection fraction <40%, and lesion location. Of those 42 patients, 33 (78.6%) were patients with ST-segment elevation myocardial infarction; 3 (7.1%) were those with non–ST-segment elevation myocardial infarction; and 6 (14.3%) were those with unstable angina. The histopathologic findings of aspirated thrombi harvested from patients with VLST of BMS were compared with those with ACS. The study protocol was approved by the institutional review board of Kokura Memorial Hospital. Because of retrospective enrollment, written informed consent from the patients was waived.

Definitions

Clinical information was obtained from the medical records. Diabetes mellitus was diagnosed when a patient was treated with insulin or oral hypoglycemic drugs or when casual levels of plasma glucose were >200 mg/dL, fasting levels of plasma glucose were >126 mg/dL, or HbA1c was >6.5% in patients without need for treatment with insulin or oral hypoglycemic drugs. Chronic renal failure was defined as estimated glomerular filtration rates <30 mL/min per 1.73 m². Current smoking included current smokers and ever-smokers who quit smoking within 1 month. According to the Academic Research Consortium definition, definite ST was defined as angiographic evidence of thrombus in association with the symptoms and signs of ACS.10 Angiographic analysis was conducted by the principal investigator (Dr Yamaji). All the study patients were confirmed to fulfill the definition of definite ST.

Thrombus Aspiration

Patients with definite ST underwent thrombus aspiration, using manual aspiration catheters. In brief, all patients received 200 mg of...
Histopathologic Findings of Aspirated Thrombi

The aspirated thrombi were fixed in 10% buffered formalin and embedded in paraffin. Paraffin blocks of the thrombi were sectioned with the use of a rotary microtome and stained with hematoxylin and eosin. Luna and Movat pentachrome stains were used for evaluating eosinophilic infiltrates and the organization of the aspirated thrombi, respectively. An experienced pathologist (Dr Inoue) performed the histopathologic analysis in a blinded manner regarding the timing of ST onset. Evidence for fragments of atherosclerotic plaques was regarded as present when at least 1 of the following pathological findings such as thin fibrous cap, foamy macrophages, or cholesterol crystals was identified. Age of aspirated thrombi was classified into 3 groups, as previously described: (1) fresh thrombus (<1 day); (2) lytic thrombus (1–5 days); and (3) organized thrombus (>5 days). The size of aspirated thrombi was graded on the basis of ordinal classification from 1–4 by visual estimates using a low-power field.

Statistical Analysis

Categorical variables are expressed as number and percentages. Frequency analysis was performed with χ² test, except for ordinal data. Ordinal data such as Thrombolysis In Myocardial Infarction (TIMI) flow grade was analyzed with the Wilcoxon rank sum test or Kruskal-Wallis test. Continuous variables are expressed as mean±SD or median values with IQR, depending on their distributions, and the differences were assessed by unpaired t test. When comparing more than 2 groups, variables were assessed by using 1-way ANOVA. All statistical analyses were performed with JMP 9 (SAS Institute, Cary, NC). All reported probability values were 2-sided, and probability values <0.05 were regarded as statistically significant.

Results

Patients and Lesion Characteristics

Mean age at time of ST onset was 68±10 years, and 88 (87%) patients were male. Prevalence of risk factors included hypertension in 66 patients (65%), hyperlipidemia in 46 patients (46%), diabetes mellitus in 38 patients (38), and current smoking in 39 patients (39%). Medical history before the index BMS implantation procedure included previous myocardial infarction (MI) in 24 patients (24%), previous PCI in 34 patients (33%), and previous coronary artery bypass graft in 4 patients (3.9%). Patient characteristics at the time of ST were not different regardless of the timing of ST onset except for the prevalence of the use of thienopyridines, target lesion revascularization before ST, chronic renal failure, plasma level of total cholesterol, and low-density lipoprotein (Table 1). The characteristics of stented lesions included culprit lesion of ST-segment elevation MI in 44 lesions (43%), bifurcation in 37 lesions (36%), chronic total occlusion in 7 lesions (6.9%), calcified lesion in 7 lesions (6.9%), ostial lesion in 18 lesions (18%), and multiple stents used in 33 lesions (32%) (Table 2). Patient characteristics were well matched between patients with VLST and those with ACS unrelated to ST (Table 3).

Histopathologic Findings of Aspirated Thrombi

One patient with EST and 4 patients with ACS unrelated to ST were excluded from the histopathologic analysis because of insufficient amount of material. Thrombi were mainly composed of erythrocytes, platelets, neutrophils, and fibrin, without any differences according to the timing of ST onset. Eosinophils were sparsely observed, as shown in Figure 1. Thrombus age was also not markedly different according to the timing of ST onset (Table 4).

Evidence for fragments of atherosclerotic plaques, including thin fibrous cap, foamy macrophages, or cholesterol crystals, was identified in 24 patients (24%). Evidence for fragments of atherosclerotic plaques was more commonly seen in patients with EST (23%) and VLST (31%), whereas these findings were rarely observed in patients with LST (10%) (Table 4). Evidence for fragments of atherosclerotic plaques was predominantly seen in patients who had EST within 7 days (26%) or VLST...
beyond 3 years (39%) after BMS implantation (Figure 2). The histological appearance of fragments of atherosclerotic plaques was similar between the 2 groups of patients with EST and VLST. Either thin fibrous cap, foamy macrophages, or cholesterol crystals was observed in 20 (48%) patients with ACS unrelated to ST. The prevalence of fragments of atherosclerotic plaques in patients with VLST beyond 3 years (39%) appeared to be similar to the prevalence in patients with ACS unrelated to ST (Table 4). The appearance of fragments of atherosclerotic plaques harvested from patients with ST and those with ACS unrelated to ST was histologically indistinguishable from each other. A representative case with fragments of atherosclerotic plaques in aspirated thrombi at the time of VLST (1686 days after BMS implantation) was illustrated in Figure 3.

Patient and lesion characteristics of the VLST cases were generally similar regardless of presence or absence of evidence for fragments of atherosclerotic plaques in the aspirated thrombi (Table 5). However, plasma levels of total cholesterol and triglyceride were significantly higher in VLST cases with fragments of atherosclerotic plaques than those without.

### Table 3. Characteristics in Patients With VLST and Those With ACS Unrelated to ST

<table>
<thead>
<tr>
<th></th>
<th>VLST (n=42)</th>
<th>VLST &gt;3 Years (n=33)</th>
<th>ACS (n=42)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>68±10</td>
<td>68±9</td>
<td>69±9</td>
<td>0.97 0.91</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>38 (90)</td>
<td>31 (94)</td>
<td>38 (90)</td>
<td>1.00 0.58</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>27 (64)</td>
<td>20 (61)</td>
<td>27 (64)</td>
<td>1.00 0.91</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>19 (45)</td>
<td>19 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>10 (24)</td>
<td>8 (24)</td>
<td>10 (24)</td>
<td>1.00 0.97</td>
</tr>
<tr>
<td>Insulin</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>1.00 0.70</td>
</tr>
<tr>
<td>Current smoking</td>
<td>16 (38)</td>
<td>14 (42)</td>
<td>16 (38)</td>
<td>1.00 0.55</td>
</tr>
<tr>
<td><strong>Lipid profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>172±34</td>
<td>175±36</td>
<td>174±40</td>
<td>0.81 0.93</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>116±61</td>
<td>119±67</td>
<td>104±72</td>
<td>0.41 0.36</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>43±10</td>
<td>43±10</td>
<td>45±11</td>
<td>0.61 0.49</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>106±32</td>
<td>109±34</td>
<td>107±37</td>
<td>0.83 0.82</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>4 (10)</td>
<td>4 (11)</td>
<td>4 (10)</td>
<td>1.00 0.72</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>2 (5)</td>
<td>2 (6)</td>
<td>2 (5)</td>
<td>1.00 0.80</td>
</tr>
<tr>
<td><strong>Left ventricular dysfunction, LVEF &lt;40%</strong></td>
<td>6 (14)</td>
<td>4 (12)</td>
<td>6 (14)</td>
<td>1.00 0.78</td>
</tr>
<tr>
<td>Lesion location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>16 (38)</td>
<td>10 (30)</td>
<td>16 (38)</td>
<td>1.00 0.78</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>25 (60)</td>
<td>22 (67)</td>
<td>25 (60)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex coronary artery</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Left main coronary artery</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n (%). VLST indicates very late stent thrombosis; ACS, acute coronary syndrome; ST, stent thrombosis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

![Figure 1](http://circinterventions.ahajournals.org/Downloaded from)
The main findings of the present study are as follows: (1) Evidence for fragments of atherosclerotic plaques, including foamy macrophages, cholesterol crystals, and thin fibrous cap, was commonly seen in the aspirated thrombi retrieved from patients with EST and VLST of BMS; (2) these findings were predominantly observed within 7 days or beyond 3 years after index BMS implantation; (3) the appearance of fragments of atherosclerotic plaques harvested from patients with ST and those with ACS unrelated to ST was histologically indistinguishable from each other; (4) eosinophils were very rarely observed in the aspirated thrombi in patients with VLST of BMS.

Long-term follow-up studies revealed that VLST could occur at a rate of 0.1% per year even in patients with BMS implantation, although the annual incidence of VLST after BMS was much lower than that after DES.1,2,4,12,13 In this single-center study, we identified 45 patients with VLST of BMS in 8 years of study period. Fragments of atherosclerotic plaque were observed in 13 (39%) of 33 VLST cases beyond 3 years. Considering the limited capacity of thrombus aspiration to retrieve constituents of coronary arterial wall, prevalence of fragments of atherosclerotic plaque in the aspirated thrombi seemed to be high in this study. These components of atherosclerotic plaque might represent neoatherosclerosis developing after BMS implantation. It would be reasonable to postulate that disruption of neoatherosclerosis inside the stents was causally related to ST of BMS.

Postmortem human pathological studies demonstrated that neointimal hyperplasia consisting of synthetic-type smooth muscle cells and abundant matrix substances developed within a few months after BMS implantation. In the ensuing several months, transformation of smooth muscle cells from synthetic to contractile type and fibrotic maturation of the matrix substances could lead to formation of more stable neointimal tissue inside the stent struts of BMS.14,15 These pathological observations were consistent with the time course of luminal change in the stented segment and clinical stability within 3–4 years after BMS implantation.16 However, pathological studies of BMS beyond 90 days showed inflammatory infiltrates associated with stents composed

**Figure 2.** Time distribution of patients with ST and with evidence for fragments of atherosclerotic plaques. Each dot indicates a patient with ST and with pathological findings of atherosclerotic plaques (foamy macrophages, cholesterol crystals or thin fibrous cap). Left box ranged from 0–30 days. Middle box ranged from 1–12 months. Right box ranged from 1–13 years. Evidence for fragments of atherosclerotic plaques was predominantly seen in patients with ST either within 7 days or beyond 3 years after index stent implantation.
predominantly by macrophages, with smaller numbers of T cells and rare B cells. These inflammatory responses to chronic injuries from metallic prosthetic device could further promote plaque instability. Inoue et al18 reported that prominent infiltration by foamy macrophages with strong collagen-degrading matrix metalloproteinase immunoreactivity was observed around the struts in lesions evaluated 4 years after BMS implantation. Nakazawa et al19 also reported that in-stent unstable neatherosclerosis, such as ruptured plaques and thin-cap fibroatheroma, was observed in BMS at later time point as compared with DES. Furthermore, angiographic study demonstrated that a white appearance mainly occupied by the neointima at 6- to 12-month follow-up often changed to a partial yellow and red lumen composed of atherosclerotic plaque and thrombus beyond 4 years.20 The time course of these changes in the stented vessel wall was in line with the results of long-term clinical and angiographic studies after BMS implantation.1,21 The finding that evidence for fragments of atherosclerotic plaques in patients with VLST was found almost exclusively beyond 3 years after BMS implantation in the current study was consistent with these clinical, angiographic, and pathological observations. Although there is no postmortem human pathological study in patients with ST of BMS, it seemed to be very plausible that disruption of in-stent neatherosclerosis could lead to stent thrombosis of BMS.

Pathological studies of human postmortem specimens in patients with VLST of DES demonstrated extensive inflammatory and hypersensitivity reactions at the site of DES implantation.6,7 Cook et al8 reported the observations of aspirated thrombi in patients with VLST of BMS that were consistent with the current study; they also reported that VLST of DES was associated with histopathological signs of inflammation and that eosinophilic infiltrates were more common in thrombi harvested from patients with VLST as compared with other causes of MI. In the current analysis, eosinophils were rarely observed in the aspirated thrombi in patients with VLST of BMS. Therefore, the mechanisms of VLST might be different between DES and BMS, although neatherosclerosis has been reported to develop much earlier in the DES-treated lesions than in the BMS-treated lesions.

More extensive investigation of thrombectomy specimens would be necessary to understand the role of neatherosclerosis in the pathogenesis of VLST of DES.

Fragments of atherosclerotic plaque were also seen in patients with EST within 7 days after BMS implantation. Because ruptured atherosclerotic plaques underneath the stented lesion in patients with acute coronary syndrome were virtually not covered by neointima within 7 days, fragments of atherosclerotic plaque could be retrieved in the aspirated thrombi in patients with EST within 7 days.22 Furthermore, disruption of stable atherosclerotic plaques by stent implantation procedure could also lead to retrieval of fragments of atherosclerotic plaque in patients with EST within 7 days. Because the histological appearance of the aspirated thrombi was similar between the 2 groups of patients with ST and with ACS unrelated to ST, components of neatherosclerosis might be similar to those in classic atherosclerotic plaque. It is intriguing that the plasma levels of total cholesterol and triglyceride were significantly higher in VLST patients with fragments of atherosclerotic plaque than those without.

**Study Limitations**

The present study has important limitations. First, absence of fragments of atherosclerotic plaque does not necessarily mean absence of neatherosclerosis in the stented segment, due to the limited ability of thrombus aspiration to retrieve the constituents of the arterial wall. Second, we did not make quantitative assessment of the histopathologic specimens. Furthermore, the size of aspirated thrombi was classified subjectively. Third, we did not perform imaging analysis such as intravascular ultrasound and optical coherence tomography. Therefore, we could not assess stent malapposition and neointimal coverage of the stent. Finally, it is not possible to discriminate plaque rupture in the stented segment with that in the adjacent nonstented segment.

**Conclusions**

Pathological features of atherosclerosis such as foamy macrophages, cholesterol crystals, and thin fibrous cap were observed in patients with EST within 7 days and patients with
Table 5. Patient and Lesion Characteristics at Time of Index Stent Implantation Among VLST Patients With or Without Fragments of Atherosclerotic Plaques

<table>
<thead>
<tr>
<th>Characteristics of the index procedure</th>
<th>Value</th>
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<tbody>
<tr>
<td>Lesion location</td>
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<tr>
<td>Left anterior descending coronary artery</td>
<td>0.06</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td></td>
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<tr>
<td>Left circumflex coronary artery</td>
<td></td>
</tr>
<tr>
<td>Left main coronary artery</td>
<td></td>
</tr>
<tr>
<td>Bifurcation</td>
<td>0.76</td>
</tr>
<tr>
<td>Chronic total occlusion</td>
<td>0.55</td>
</tr>
<tr>
<td>Calcification</td>
<td>0.55</td>
</tr>
<tr>
<td>Ostium</td>
<td>0.052</td>
</tr>
<tr>
<td>Indication for the index procedure</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Table 5. Continued

<table>
<thead>
<tr>
<th>Fragments of Atherosclerotic Plaques</th>
<th>Present (n=13)</th>
<th>Absent (n=29)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaques</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n (%).

*ST indicates stent thrombosis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; TLR, target lesion revascularization; CPK, creatine phosphokinase; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

VLST beyond 3 years after BMS implantation. Disruption of neoatherosclerosis inside the stents could be an important underlying mechanism of VLST beyond 3 years after BMS implantation. The appearance of fragments of atherosclerotic plaques harvested from patients with ST and those with ACS unrelated to ST was histologically indistinguishable from each other.

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Disclosures

None.

References


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