Very Late Stent Thrombosis After Primary Percutaneous Coronary Intervention With Bare-Metal and Drug-Eluting Stents for ST-Segment Elevation Myocardial Infarction

A 15-Year Single-Center Experience

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Objectives The purpose of this study was to assess the frequency of very late stent thrombosis (VLST) after stenting with bare-metal stents (BMS) and drug-eluting stents (DES) for ST-segment elevation myocardial infarction (STEMI).

Background Stent thrombosis occurs more frequently after stenting for STEMI than after elective stenting, but there are little data regarding VLST.

Methods Consecutive patients (n = 1,463) who underwent stenting for STEMI were prospectively enrolled in our database. BMS were implanted exclusively from 1995 to 2002, and DES and BMS were implanted from 2003 to 2009. Follow-up was obtained at 1 to 15 years.

Results BMS patients (n = 1,095) were older and had more shock, whereas DES patients (n = 368) had more diabetes and smaller vessels. Stent thrombosis occurred in 107 patients, of which 42 were VLST (>1 year). Stent thrombosis continued to increase to at least 11 years with BMS and to at least 4.5 years with DES. Stent thrombosis rates with BMS versus DES were similar at 1 year (5.1% and 4.0%, respectively) but increased more with DES after the first year (1.9%/year vs. 0.6%/year, respectively). Landmark analysis (>1 year) found DES had a higher frequency of VLST (p < 0.001) and reinfarction (p = 0.003). DES was the only significant independent predictor of VLST (hazard ratio: 3.79, 95% confidence interval: 1.64 to 8.79, p = 0.002).

Conclusions VLST after primary PCI for STEMI occurs with relatively high frequency to at least 11 years with BMS and to at least 4.5 years with DES. Very late stent thrombosis and reinfarction (>1 year) were more frequent with DES. New strategies are needed to manage this problem.

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The use of coronary stents has become the preferred therapy with primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) (1,2). Unfortunately, stent thrombosis (ST) has been a more frequent complication after stenting for STEMI than after elective stenting with both drug-eluting stents (DES) and bare-metal stents (BMS) (3–5). There is concern that very late stent thrombosis (VLST) (>1 year) might be more frequent with DES than with BMS, because of increased frequency of late stent malapposition and poor healing of DES after primary PCI (6–8).

Methods

Study population. The study population consists of 1,463 consecutive patients with STEMI treated with primary PCI at our institution from 1995 through 2009 who received a stent and who did not have STEMI due to ST. Patients were included in our registry if they had electrocardiographic ST-segment elevation ≥1 mm in ≥2 contiguous leads or new left bundle branch block, symptoms of <12-h duration (>12 h for persistent ischemic symptoms or hemodynamic compromise), and were treated with primary PCI. Patients were divided into 2 groups depending on whether they received BMS (n = 1,095) or DES (n = 368).

Treatment protocol. Patients were treated with contemporary standards of care for primary PCI. In the early years this included aspirin, unfractionated heparin, and glycoprotein IIb/IIIa platelet inhibitors, and in very recent years aspirin and bivalirudin were used, usually without glycoprotein IIb/IIIa platelet inhibitors. Ticlopidine (in the early years) or clopidogrel were given immediately before or at the time of PCI. BMS were used exclusively from 1995 to 2002, and DES or BMS were used from 2003 to 2009 at the operator’s discretion. In 368 patients who received DES, 326 received first-generation DES (sirolimus- or paclitaxel-eluting stents), and 42 received second-generation stents (everolimus- and zotarolimus-eluting stents).

Data collection and clinical follow-up. Patients were enrolled prospectively into the database from 1995 through 2009. Procedural data were assessed and entered by the interventional cardiologist at the time of the PCI. Medical records for each patient were reviewed to identify all readmissions for acute coronary syndromes and all readmissions resulting in mortality. Stent thrombosis and myocardial infarction were identified according to the definitions outlined in the following text. Deaths were also sought through the social security death index, in which case the cause of death was determined by death certificates. All deaths, cardiac versus noncardiac deaths, reinfarctions, and all stent thromboses were adjudicated by at least 1 of 3 investigators (B.B., T.S., and M.C.).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
PCI = percutaneous coronary intervention
ST = stent thrombosis
STEMI = ST-segment elevation myocardial infarction
VLST = very late stent thrombosis

Table 1. Baseline Variables by Stent Type

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>BMS (n = 1,095)</th>
<th>DES (n = 368)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;70 yrs</td>
<td>269 (24.6%)</td>
<td>70 (19.0%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Female</td>
<td>351 (32.1%)</td>
<td>104 (28.3%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Diabetes</td>
<td>150 (13.7%)</td>
<td>75 (20.4%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Prior infarction</td>
<td>129 (11.8%)</td>
<td>39 (10.6%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Prior bypass surgery</td>
<td>58 (5.3%)</td>
<td>11 (3.0%)</td>
<td>0.071</td>
</tr>
<tr>
<td>Current smoker</td>
<td>569 (52.0%)</td>
<td>192 (52.2%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>372 (34.0%)</td>
<td>151 (41.0%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>89 (8.1%)</td>
<td>13 (3.5%)</td>
<td>0.003</td>
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<table>
<thead>
<tr>
<th>Angiographic and procedural variables</th>
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<tbody>
<tr>
<td>Infarct artery</td>
</tr>
<tr>
<td>Left main/left anterior descending</td>
</tr>
<tr>
<td>Circumflex artery</td>
</tr>
<tr>
<td>Right coronary artery</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
</tr>
<tr>
<td>3-vessel coronary disease</td>
</tr>
<tr>
<td>Ejection fraction &lt;40%</td>
</tr>
<tr>
<td>TIMI flow grade 2–3 pre-PCI</td>
</tr>
<tr>
<td>TIMI flow grade 3 post-PCI</td>
</tr>
<tr>
<td>GP IIb/IIIa platelet inhibitor</td>
</tr>
<tr>
<td>Balloon size (stent size) ≥2.75 mm</td>
</tr>
<tr>
<td>Multiple stents</td>
</tr>
</tbody>
</table>

BMS = bare-metal stent(s); DES = drug-eluting stent(s); GP = glycoprotein; TIMI = Thrombolysis In Myocardial Infarction.
Probable ST occurred when there was an infarct in the territory of the stented vessel without angiographic confirmation or when there was unexplained sudden death within 30 days. In-hospital reinfarction was defined as occurring when there were recurrent ischemic symptoms associated with re-elevation of the cardiac markers or documented occlusion of the infarct artery. Post-hospital reinfarction was defined as occurring when there was a repeat hospital admission for ischemic symptoms associated with elevation of the cardiac markers. All deaths were categorized as cardiac or noncardiac.

Statistical analyses. Statistical comparisons of categorical variables were performed with the chi-square or Fisher exact test, as appropriate. Two-sided Student t tests were used for comparing continuous variables. Late clinical outcomes were assessed by Kaplan-Meier estimates and compared with log-rank statistics. Multivariable analyses of predictors of late cardiac outcomes were performed with Cox proportional hazards regression models. All clinical and angiographic and procedural variables in Table 1 were entered into the Cox regression models, and backward elimination at alpha = 0.05 was used to select significant predictors. Type of stent (DES vs. BMS) was retained in all the models. To avoid excluding patients from the analyses who had missing evaluations of ejection fraction, an indicator of ejection fraction missing/not missing was also included. To allow comparisons between DES and BMS, which had different durations of follow-up, Kaplan-Meier curves were compared out to 4.5 years.

Because stent type (DES or BMS) was not randomly assigned, propensity analyses by covariate adjustment were employed (15). Logistic regression was used to calculate a propensity score for each patient, and balance of the stent type predictors was assessed within each quintile of the score. Because all stents were BMS before 2003, the propensity score was set equal to 0 (i.e., 0 probability of DES) for all procedures performed before 2003. The propensity score and any of its predictors that were not balanced between BMS and DES within every score quintile were included in Cox regression models, along with the variables selected by backward elimination described in the preceding text. Analyses were conducted on the entire set of data (1995 to 2009) and on the subset during which both BMS and DES were being used (2003 to 2009). All analyses were performed with SPSS (SPSS, Inc., Chicago, Illinois) and SAS 9.2 (SAS Institute, Cary, North Carolina) software.

Results

Of 1,463 patients treated with primary PCI and stenting for STEMI from 1995 to 2009, clinical follow-up was complete or was obtained to at least 4 years in 85.0% of patients. Stent
Figure 2. Landmark Analysis Showing Kaplan-Meier Estimates of VLST and Reinfarction After Primary PCI With DES and BMS for STEMI

(A) Landmark analysis of the cumulative frequency of very late stent thrombosis (VLST) (>1 year) comparing BMS and DES. (B) Landmark analysis of the cumulative frequency of reinfarction (>1 year) comparing BMS and DES. The BMS were implanted exclusively from 1995 to 2002, whereas both stents were implanted from 2003 to 2009. Abbreviations as in Figure 1.
thrombosis occurred in 107 of 1,463 patients (92 definite and 15 probable, including 13 sudden unexplained deaths <30 days) and resulted in 23 acute deaths (21.5%) and 92 (86.0%) reinfarctions. Reinfarction occurred in 171 patients. Of these, 112 (65.5%) occurred in the target vessel, of which 92 (82.1%) were due to ST. Reinfarction occurred in nontarget vessels or unknown location in 59 patients. Of the 92 reinfarctions due to ST, 63 were STEMI, including 42 of 67 (62.7%) with BMS and 21 of 25 (84.0%) with DES.

Of the 107 patients with ST, 38 were early (<30 days), 27 were late (31 days to 1 year), and 42 were very late (>1 year). Eighty percent (80%) of patients with DES and 55% of patients with BMS were taking clopidogrel at the time of VLST. Very late stent thrombosis resulted in reinfarction. Of the 42 reinfarctions due to DES, 27 were STEMI, including 42 of 67 (62.7%) with BMS and 21 of 25 (84.0%) with DES.

Baseline variables comparing DES and BMS. Patients receiving BMS compared with DES were older and had more cardiogenic shock, more 3-vessel coronary disease, and less Thrombolysis In Myocardial Infarction flow grade 2 to 3 on initial angiography. Patients receiving DES had more diabetes, smaller vessel size, and more anterior wall infarction (Table 1).

**Frequency of ST.** Kaplan–Meier estimates of the frequency of ST for DES and BMS are shown in Figure 1. The frequency of ST at 1 year was similar with DES and BMS (4.0% and 5.1%, respectively). The cumulative frequency of ST continued to increase out to at least 4.5 years with DES and out to at least 11 years with BMS but increased more after the first year with DES than BMS (1.9%/year vs. 0.6%/year). Landmark analysis after 1 year with Cox regression showed that DES compared with BMS was the strongest and only significant predictor of VLST (hazard ratio [HR]: 3.79, 95% confidence interval [CI]: 1.64 to 8.79, p = 0.002) (Fig. 2, Table 2).

**Frequency of other cardiac events.** Kaplan–Meier estimates of other cardiac events are shown in Figure 3 and Table 2. Cardiac mortality was higher with BMS than with DES, due to higher hospital and 30-day mortality. Reinfarction and reinfarction of the target vessel occurred more frequently after the first year with DES than BMS. Reinfarction of the nontarget vessel was similar with DES and BMS. Landmark analyses after 1 year showed that DES compared with BMS was a significant predictor of both reinfarction (HR: 2.01, 95% CI: 1.15 to 3.50, p = 0.014) and reinfarction of the target vessel (HR: 3.16, 95% CI: 1.50 to 6.64, p = 0.002) (Fig. 2, Table 2).

**Outcomes in the DES era (2003 to 2009).** We also compared outcomes between DES and BMS in the DES era (2003 to 2009) when both stents were being implanted (Fig. 4, Table 3). The frequency of ST was high with both stent types, and there were no significant differences in ST and other outcomes.
Figure 3. Kaplan-Meier Estimates of Mortality and Reinfarction Rates After Primary PCI With DES and BMS for STEMI

(A) Cumulative cardiac mortality rates after primary PCI for STEMI comparing BMS and DES. (B) Cumulative reinfarction rates after primary PCI for STEMI comparing BMS and DES. BMS were implanted exclusively from 1995 to 2002, whereas both stents were implanted from 2003 to 2009. Abbreviations as in Figure 1.
between DES and BMS. Landmark analyses showed that the frequency of VLST (>1 year), reinfarction (>1 year), and reinfarction of the target vessel (>1 year) were significantly greater with DES compared with BMS before and after adjustments with Cox Regression (Fig. 4, Table 3).

Discussion

The major finding of this study is that the frequency of ST after primary PCI for STEMI is high with both BMS and DES and continues to increase to at least 11 years with BMS and to at least 4.5 years with DES. After the first year, VLST, reinfarction, and reinfarction of the target vessel were significantly higher with DES compared with BMS. Very late stent thrombosis resulted in reinfarction in all cases with both BMS and DES, but STEMI was more common with DES.

Randomized trials comparing DES with BMS with primary PCI for STEMI have shown similar rates of ST at 1 year (9–13). Data on ST rates after 1 year have been limited, but some data are becoming available. Two small trials, the SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction) and TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty) trials, found no differences in the rates of ST between DES and BMS at 3 and 4 years (16,17). Another small trial, the PASSION (Paclitaxel Eluting Stent Versus Conventional Stent in ST-segment Elevation Myocardial Infarction) trial, found higher rates of ST with DES versus BMS at 5 years (3.6% vs. 1.7%, p = 0.20), raising some concern about safety with DES (18). The largest trial, the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, found no differences in rates of ST between DES and BMS at 2 years (4.3% vs. 4.3%, p = 0.98) (19). None of these trials found any differences in mortality or reinfarction between DES and BMS at late follow-up.

Our data showing that the frequency of ST with BMS continues to increase to 11 years after stent implantation are somewhat unexpected. Previous studies after elective implantation of BMS have found that VLST is uncommon (20,21). Serial angiographic studies after BMS implantation have shown that late loss is generally complete by 9 to 12 months, after which there is stabilization and often regression of late loss (22). However, most of the late stent thromboses with BMS in our study had severe restenosis associated with thrombotic occlusion, indicating that restenosis with BMS can occur very late after implant in some patients and can result in VLST. New strategies might be needed to deal with this problem of VLST with BMS.

It is not clear whether the increased frequency of VLST with DES compared with BMS in our study is a true difference or might be related to selection bias. In most observational databases comparing DES and BMS, selection bias has favored DES. Bare-metal stents are generally implanted in
patients who are sicker, are expected to have limited life expectancy, are at risk for bleeding, or who are thought to be less compliant with medical therapies. This bias seems to be true in our study, because mortality was higher in patients treated with BMS compared with DES. These differences are likely due to selection bias, because all the differences in mortality occurred in the first 30 days, when the type of stent would not be expected to affect mortality. It is possible that selection bias involving variables affecting ST might be different from those affecting mortality. DES might be chosen for diabetic patients and patients with small vessels and long lesions, because of the higher risk of restenosis in these patients. This could increase the risk of VLST with DES. We adjusted for these variables in the Cox regression analyses and propensity analyses, but we might not have been able to correct for all the differences. There is also potential bias related to the historical time that these stents were implanted. The BMS were implanted from 1995 to 2009, and DES were implanted from 2003 to 2009. Differences in treatment protocols between these time periods could affect outcomes. However, one might expect that outcomes, including VLST, might be worse in the earlier time period (when most BMS were implanted) when stent deployment techniques and antiplatelet therapy were less optimal. We compared rates of VLST between DES and BMS in the DES era (2003 to 2009) when both types of stent were implanted and found similar outcomes with a higher frequency of VLST with DES. Another possibility for the differences in outcomes is that the “real world” population in our registry might be different from the patient populations enrolled in randomized trials. Differences in the use of dual antiplatelet therapy do not seem to be a likely explanation for differences in VLST rates, because most patients were not taking dual antiplatelet therapy after 1 year and the frequency of dual antiplatelet therapy use was low in both BMS and DES patients at the time of VLST.

There are previous data to support the position that the frequency of VLST is truly higher with DES than BMS, because of differences between the 2 stent types. As stated earlier, when DES are implanted for STEMI, there is an increased incidence of late malapposition and poor healing that could predispose to VLST (6–9). Randomized trials with elective stenting have shown small but significant increased rates of VLST with DES compared with BMS (23,24). The PASSION trial, which evaluated DES versus BMS for STEMI and had follow-up data to 5 years, showed trends for increased rates of VLST with DES (18). The relatively short follow-up in the HORIZONS-AMI trial and the small sample sizes in the other randomized trials comparing DES with BMS with primary PCI might have so far prevented the detection of significant differences in VLST between the 2 types of stents (16,17,19).

Although it is not clear whether the differences in the frequency of VLST between DES and BMS are real or are related to selection bias, it is clear that the frequency of ST and continued late occurrence of ST after stenting for STEMI in this “real world” STEMI population are disturbingly high for both BMS and DES.

**Study limitations.** Our study is a single-center observational study and, as discussed in the preceding text, has the potential for selection bias that might affect outcomes. Our study is also limited by historical time differences when DES and BMS were implanted, which could affect outcomes, although our results are similar when we analyzed the DES era when both DES and BMS were being implanted. We have data on dual

### Table 3. Clinical Outcomes With DES Versus BMS in the DES Era (2003 to 2009)

<table>
<thead>
<tr>
<th></th>
<th>DES (n = 263)</th>
<th>BMS (n = 293)</th>
<th>Log-Rank p Value</th>
<th>Cox Multivariable Regression HR (95% CI) p Value</th>
<th>Propensity Analysis HR (95% CI) p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-landmark Kaplan-Meier analysis*</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>6.2%</td>
<td>8.6%</td>
<td>0.09</td>
<td>0.58 (0.40–1.14) 0.14</td>
<td>0.98 (0.58–1.71) 0.98</td>
</tr>
<tr>
<td>Stent thrombosis (ARC definite/probable)</td>
<td>6.8%</td>
<td>5.1%</td>
<td>0.58</td>
<td>1.13 (0.65–1.98) 0.66</td>
<td>1.11 (0.63–1.97) 0.71</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>11.1%</td>
<td>7.2%</td>
<td>0.21</td>
<td>1.29 (0.82–2.04) 0.27</td>
<td>1.28 (0.80–2.04) 0.30</td>
</tr>
<tr>
<td>Reinfarction target vessel</td>
<td>8.4%</td>
<td>5.4%</td>
<td>0.26</td>
<td>1.30 (0.77–2.21) 0.32</td>
<td>1.24 (0.72–2.13) 0.44</td>
</tr>
<tr>
<td>Reinfarction nontarget vessel or unknown</td>
<td>3.0%</td>
<td>2.1%</td>
<td>0.65</td>
<td>1.23 (0.51–2.98) 0.64</td>
<td>1.25 (0.50–3.10) 0.63</td>
</tr>
<tr>
<td>Landmark Kaplan-Meier analysis* (≥ 1 yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis (ARC definite/probable)</td>
<td>4.9%</td>
<td>1.7%</td>
<td>0.045</td>
<td>2.76 (0.98–7.78) 0.055</td>
<td>2.72 (0.95–7.74) 0.061</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>8.5%</td>
<td>3.4%</td>
<td>0.019</td>
<td>2.38 (1.13–5.04) 0.024</td>
<td>2.33 (1.06–4.99) 0.030</td>
</tr>
<tr>
<td>Reinfarction target vessel</td>
<td>5.8%</td>
<td>1.7%</td>
<td>0.017</td>
<td>3.22 (1.17–8.89) 0.024</td>
<td>2.97 (1.06–8.36) 0.039</td>
</tr>
</tbody>
</table>

*Event rates are Kaplan-Meier estimates at 4.5 years. Abbreviations as in Table 2.
antiplatelet therapy in patients who had ST but do not have data on patients without ST to assess the impact of this therapy on outcomes. The great majority of DES implanted were first-generation sirolimus-eluting or paclitaxel-eluting stents, and our results might not apply to second-generation stents.

**Clinical implications.** Our results might have implications regarding the management of patients treated with primary PCI and stenting for STEMI. The high incidence of VLST after stenting for STEMI with both DES and BMS should encourage evaluation of new strategies to prevent VLST, including procedural techniques to optimize stent deployment (such as more frequent use of intravascular ultrasound, post-dilation, and thrombectomy) and longer or more intensive antiplatelet therapies. The development of newer-generation stents, including new polymers and bio-absorbable stents, might also help to reduce this complication. If VLST rates and reinfarction rates are truly higher with DES compared with BMS, the benefit of reduced restenosis with DES might not be worth the increased risk of ST and reinfarction, and BMS might be a more appropriate choice in many patients with STEMI.

**Conclusions**

Stent thrombosis following primary PCI for STEMI is high with both BMS and DES and continues to increase to at least 11 years with BMS and to at least 4.5 years with DES. After the first year, VLST and reinfarction were significantly higher with DES compared with BMS. New strategies are needed to manage this problem.

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**REFERENCES**


**Key Words:** percutaneous coronary intervention ■ stent thrombosis ■ ST-segment elevated myocardial infarction.