Outcomes of Stent Thrombosis and Restenosis During Extended Follow-Up of Patients Treated With Bare-Metal Coronary Stents

Brendan Doyle, MB, BCh; Charanjit S. Rihal, MD, MBA; Crochan J. O’Sullivan, MB, BCh; Ryan J. Lennon, MS; Heather J. Wiste, BA; Malcolm Bell, MB, BS, FRACP; John Bresnahan, MD; David R. Holmes Jr, MD

Background—Concern regarding risk of late thrombosis after “off-label” treatment with drug-eluting stents has prompted increased use of bare-metal stents (BMS) in current practice. The sequelae of late BMS failures, however, have been poorly characterized.

Methods and Results—We performed a retrospective study of 4503 consecutive patients treated with at least 1 BMS and dual antiplatelet therapy between 1994 and 2000. The cumulative incidence of stent thrombosis was 0.5% at 30 days (95% CI, 0.3% to 0.7%), 0.8% at 1 year (95% CI, 0.6% to 1.1%), and 2.0% at 10 years (95% CI, 1.5% to 2.5%). Risk of late (30 days to 1 year) and very late (>1 year) BMS thrombosis was increased among patients considered off label (P=0.024). When saphenous vein graft interventions were excluded, however, risk after off-label use was not significantly increased (P=0.23). Other correlates included vein graft intervention, prior myocardial infarction (MI), peripheral vascular disease, and ulcerated lesion (P<0.001). Mortality was markedly increased after late and very late BMS thrombosis, particularly during the first 30 days (hazard ratios, 22 [95% CI, 3.1 to 159] and 40 [95% CI, 15 to 107], respectively). The 10-year incidence of clinical restenosis was 18.1% (95% CI, 16.5% to 19.7%), presenting with MI in 2.1% (95% CI, 1.6% to 2.6%). Restenosis presenting with MI was associated with increased mortality compared with no restenosis (hazard ratio, 2.37; P<0.001) and with restenosis with a non-MI presentation (hazard ratio, 2.42; P<0.001).

Conclusions—The incidence of BMS thrombosis and of MI caused by restenosis during extended follow-up is significant. Both complications are associated with mortality. (Circulation. 2007;116:2391-2398.)

Key Words: myocardial infarction • restenosis • stents • thrombosis

Reports of late thrombosis of drug-eluting stents (DES) have drawn intense scrutiny to these implantable medical devices. Evidence of incomplete reendothelialization, aneurysmal vessel wall remodeling, and local hypersensitivity reactions in DES-treated vessels suggests that impaired postintervention healing of the vessel wall may provide a substrate for late (30 days to 1 year) and very late (>1 year) thrombotic events.1–5 Bare-metal stents (BMS) do not possess an antiproliferative coating, and although the risk of restenosis is higher with BMS, this has been perceived as a relatively benign complication.6–8

BMS thrombosis has been studied extensively,9–12 the incidence and outcome of BMS thrombosis among unselected patients in routine clinical practice during very long-term follow-up (>1 year) have been poorly characterized.13 The long-term risk associated with BMS use among patients who would be considered off-label DES recipients is also unknown. In addition, pathological studies have identified restenosis as a mechanism that may underlie fatal late coronary stent occlusion.14 To address the hypothesis that percutaneous coronary intervention (PCI) with BMS is associated with a risk of late thrombosis and that BMS restenosis has a clinically meaningful impact on morbidity and mortality, we performed an analysis of a large cohort of patients treated with BMS and dual antiplatelet therapy between 1994 and 2000.

Methods

A resurgence in BMS use in contemporary practice appears likely, prompted by emerging data linking “off-label” intervention with DES with increased risk of late stent thrombosis.9 The risk associated with BMS failure during extended follow-up is unclear, however. Although early (<30 days)
Inclusion and Exclusion Criteria

All patients were included in this analysis if they had undergone successful deployment of at least 1 coronary stent without the occurrence of a major in-laboratory complication (death, Q-wave myocardial infarction [MI], emergency cardiac surgery, cerebrovascular accident, coronary perforation, or development of cardiogenic shock). Patients were excluded if there was intent not to administer aspirin or a thienopyridine, if they were in cardiogenic shock before the procedure, if brachytherapy was administered, if an investigational drug-coated or eluting stent was used, or if the patient refused permission for his or her records to be used for research (as required by State of Minnesota statute). Angiographic, procedural, and clinical outcomes were prospectively recorded by experienced interventional radiology data techni-
cians. The database supervisor performs routine audits of 10% of all records for quality control purposes. All patients are contacted at 6 and 12 months and annually thereafter. Medical records related to all hospitalizations and cardiac events are obtained. To identify cases of late stent thrombosis and cases of restenosis, the complete medical records (both Mayo and non-Mayo) were evaluated in detail for deaths, major adverse cardiac events, coronary angiograms, PCI, and coronary artery bypass graft (CABG) during the follow-up period.

Study Design and Procedure

Standard percutaneous techniques were employed as previously described.12 All patients received dual antiplatelet therapy with aspirin indefinitely and a thienopyridine for 2 to 4 weeks after PCI. Unfractionated heparin was administered on a weight-
adjusted basis immediately before the procedure, aiming for an activated clotting time of 300 seconds when a glycoprotein IIb/IIIa inhibitor was not used and \( \approx 250 \) seconds when a glycoprotein IIb/IIIa inhibitor was given. The activated clotting time was remeasured every 30 to 60 minutes during the proce-
dure, and additional boluses of heparin were given to maintain the activated clotting time in the target range. The decision to use a glycoprotein IIb/IIIa inhibitor was at the discretion of the cardi-
ologist performing the procedure. Stent delivery balloons were inflated to nominal pressure. Throughout the study period, stent delivery was routinely followed by high-pressure (>14 atm) balloon inflations with the use of noncompliant or minimally compliant balloons at sizes equivalent to or slightly larger than nominal stent size to achieve residual diameter stenosis <20%. Intravascular ultrasound was used at the discretion of the operator.

Definitions

Stent thrombosis was defined in accordance with criteria developed in 2006 by an academic research consortium of investigators, regulators, and industry representatives.13 These definitions were proposed as an industry standard to enable comparison of event rates across different trials and studies. This analysis was restricted to cases of definite and probable stent thrombosis. Definite stent thrombosis was defined as in-stent thrombus, with or without vessel occlusion, confirmed by angiography or by pathological examination in a patient with an acute coronary syndrome. Probable stent thrombosis was defined as any unexplained death within 30 days or, regardless of the time after the index procedure, a MI in the distribution of the treated vessel where stent thrombosis is not angiographically confirmed and in the absence of any other obvious cause. Early stent thrombosis included all events occurring within 30 days of PCI, late stent thrombosis included those occurring between 30 days and 1 year after PCI, and very late stent thrombosis included all events occurring after 1 year. Stent thrombosis may be further classified as primary (no target lesion revascularization between the index PCI and the occurrence of stent thrombosis) or secondary (at least 1 target lesion revascular-
ization between the index PCI and the occurrence of stent thrombosis). Clinical restenosis was defined as the presence of symptoms or abnormal functional testing attributed to a stenotic lesion documented at coronary angiography within the treated segment (encompassing the stent and the vessel 5 mm proximal and distal to the stent). Routine follow-up angiography in the absence of a clinical indication was not performed for this cohort. MI restenosis was defined as clinical restenosis presenting with MI. Unstable angina was defined as new-onset chest pain, new onset at rest, or significant unexplained change in pattern of stable angina within the preceding 2 months, including increased fre-
quency, intensity, or duration or decreased responsiveness to nitrates, but without elevation of biomarkers of myocardial injury. The diagnosis of MI was made in accordance with standard criteria.14 Severe renal impairment was defined as creatinine >3.0 mg/dL on dialysis, or previous renal transplant. Peripheral vascular disease was defined as a history of claudication or peripheral vascular surgery (including amputation for ischemia) or angioplasty. “On-label” use was defined as a single stent for a de novo lesion in a native artery; the off-label category included all other patients.

Statistical Analysis

Continuous variables are summarized as mean±SD. Discrete vari-
ables are presented as frequency and percentage. Hazard ratios from Cox proportional hazard models are used to assess unadjusted associations with stent thrombosis >30 days (including >1 year) and with MI presentation restenosis. Ninety-five percent CIs for survival estimates were based on the log transformation. Time-dependent covariate methods were used when estimating the effect of stent thrombosis and restenosis on mortality. For example, all patients had an early stent thrombosis covariate set to 0 immediately after PCI; it was set to 1 on the day stent thrombosis was observed within the first 30 days after PCI. No other variables were treated as time-dependent covariates. Survival curves and plots of scaled Schoenfeld residuals indicated that the increased risk of death from stent thrombosis was highest immediately after stent thrombosis. Thus, separate hazard ratios were calculated for the first 30 days after stent thrombosis and for >30 days after stent thrombosis. In this case, there are 2 time-dependent stent thrombosis variables in the model. One is 0 except for the first 30 days after a stent thrombosis occurs. The other is 0 until 30 days have passed after stent thrombosis occurs; then it remains at 1. The estimated restenosis effect from the Cox model reflects the risk increase for each restenosis; subsequent restenoses were assumed to have the same effect as the first. Thus, the time-dependent restenosis variable was the number of restenoses incurred during follow-up.

Results

Four thousand eight hundred fifty-five patients underwent implantation of at least 1 BMS between July 1, 1994, and April 30, 2000. Of these, 261 patients suffered a major in-laboratory complication and therefore were not included in the analysis. Ninety-one patients denied permission for their medical records to be used for research, leaving a total of 4503 patients for this study. In the PCI registry, follow-up is continued until death, and 93% of patients had follow-up within 2 years of data generation for this study or were deceased. Median follow-up was 7.9 years (interquartile range, 6.7 to 9.1 years) or a cumulative total of 30,249 patient-years.

Baseline clinical characteristics of this patient cohort are summarized in Table 1. Mean age was 65.4 (±11.7) years,
Mean stent diameter was 3.40.6 mm. Patients treated with stents were included a saphenous vein graft in 8%. Two stents were used in 23%. Multivessel stenting was performed in 17% of patients. Lesions treated were American Heart Association type A/B1 in 18%, type B2 in 37%, and type C in 45%. Characteristics of lesions included thrombus in 31% and bifurcation disease in 13%. Glycoprotein IIb/IIIa inhibitors were used in 40% of patients.

Clinical Outcomes
The incidence of death or MI during long-term follow-up was as follows: 5.4% at 30 days (95% CI, 4.7% to 6.0%), 10.4% at 1 year (95% CI, 9.5% to 11.3%), 23.2% at 5 years (95% CI, 21.9% to 24.6%), and 39.9% at 10 years (95% CI, 37.3% to 62.0%).

Stent Thrombosis
There were 74 cases of stent thrombosis. The cumulative incidence of stent thrombosis at 30 days was 0.5% (95% CI, 0.3% to 0.7%), at 1 year was 0.8% (95% CI, 0.6% to 1.1%), at 5 years was 1.3% (95% CI, 1.0% to 1.7%), and at 10 years was 2.0% (95% CI, 1.5% to 2.5%) (Table 3). The diagnosis of stent thrombosis was “definite” in 1.3% (95% CI, 0.8% to 1.6%) and “probable” in 0.7% (95% CI, 0.4% to 0.9%) at 10 years. The timing of stent thrombosis during long-term follow-up is presented in the Figure with annual event rates per 1000 patient-years. Most events occurred in the first year after PCI, but BMS thrombosis was observed as late as the ninth year after the index procedure. Of 52 patients with late or very late stent thrombosis, 45 were primary (no prior restenosis) and 7 were secondary (1 of whom had received brachytherapy). Late or very late stent thrombosis presented with ST-segment elevation MI in 44% of patients (n=23: 18 definite, 5 probable) and non–ST-segment elevation MI in 56% (n=29: 11 definite, 18 probable). Stent thrombosis occurred >5 years after the index procedure in 17 patients (10 definite, 7 probable). Four of these cases involved a stent placed in a saphenous vein graft, and 3 cases were secondary stent thrombosis.

For patients treated with a single stent in a native artery for a de novo lesion (on label), the cumulative incidence of stent thrombosis at 30 days was 0.2% (95% CI, 0.0% to 0.4%), at 1 year was 0.6% (95% CI, 0.2% to 0.9%), at 5 years was 1.0% (95% CI, 0.5% to 1.2%), and at 10 years was 1.4% (95% CI, 0.9% to 2.0%) (Table 3). For all other patients (off label; n=2295), the cumulative incidence of stent thrombosis at 30 days was 0.7% (95% CI, 0.4% to 1.1%), at 1 year was 1.1% (95% CI, 0.7% to 1.5%), at 5 years was 1.7% (95% CI, 1.2% to 2.2%), and at 10 years was 2.5% (95% CI, 1.7% to 3.3%).
3.3%) (Table 3). Indications for off-label treatment included use of 1st stent in 1835 patients (80%), treatment of a restenotic lesion in 456 patients (19.9%), and treatment of a vein graft in 420 patients (18.3%). Increased risk of late and very late stent thrombosis among patients receiving BMS for an off-label indication was statistically significant compared with patients treated for an on-label indication (P = 0.024).

Analysis of clinical correlates of stent thrombosis >30 days (including >1 year) is presented in Table 1, and procedural correlates are presented in Table 2 (the correlates of early stent thrombosis have been described previously for this cohort(12)). Patients with stent thrombosis >30 days were more likely to have a history of MI (72% versus 50%; hazard ratio, 2.8; P = 0.001), acute MI within 24 hours of the index procedure (18% versus 9%; hazard ratio, 2.09; P = 0.046), and prior CABG (38% versus 19%; hazard ratio, 2.93; P < 0.001).

A history of congestive heart failure (16% versus 10%; hazard ratio, 2.24; P = 0.037), cerebrovascular accident (18% versus 10%; hazard ratio, 2.26; P = 0.026), and peripheral vascular disease (23% versus 10%; hazard ratio, 3.11;

### Table 2. Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n = 4503)</th>
<th>Patients Without Stent Thrombosis (n = 4429)</th>
<th>Patients With Stent Thrombosis &gt;30 d (n = 52)</th>
<th>Hazard Ratio for Stent Thrombosis &gt;30 d (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention in LAD</td>
<td>1994 (44)</td>
<td>1964 (44)</td>
<td>17 (33)</td>
<td>0.608 (0.340–1.085)</td>
<td>0.092</td>
</tr>
<tr>
<td>Intervention in LCx</td>
<td>1206 (27)</td>
<td>1187 (27)</td>
<td>13 (25)</td>
<td>0.918 (0.490–1.720)</td>
<td>0.79</td>
</tr>
<tr>
<td>Intervention in RCA</td>
<td>1649 (37)</td>
<td>1628 (37)</td>
<td>14 (27)</td>
<td>0.610 (0.331–1.126)</td>
<td>0.11</td>
</tr>
<tr>
<td>Intervention in vein graft</td>
<td>376 (8)</td>
<td>360 (8)</td>
<td>14 (27)</td>
<td>4.646 (2.516–8.581)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent size, mm</td>
<td>3.4±0.6</td>
<td>3.4±0.6</td>
<td>3.6±0.8</td>
<td>1.228 (1.000–1.508)</td>
<td>0.050</td>
</tr>
<tr>
<td>Total stents placed</td>
<td></td>
<td></td>
<td></td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2668 (59)</td>
<td>2630 (59)</td>
<td>31 (60)</td>
<td>1.000 (reference)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1239 (28)</td>
<td>1216 (27)</td>
<td>16 (31)</td>
<td>1.13 (0.62–2.07)</td>
<td>0.69</td>
</tr>
<tr>
<td>≥3</td>
<td>596 (13)</td>
<td>583 (13)</td>
<td>5 (10)</td>
<td>0.75 (0.29–1.93)</td>
<td>0.55</td>
</tr>
<tr>
<td>Multivessel stenting</td>
<td>779 (17)</td>
<td>765 (17)</td>
<td>7 (13)</td>
<td>0.757 (0.341–1.678)</td>
<td>0.49</td>
</tr>
<tr>
<td>Lesion class</td>
<td></td>
<td></td>
<td></td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Type A, B1 lesion</td>
<td>780 (18)</td>
<td>771 (18)</td>
<td>6 (13)</td>
<td>1.000 (reference)</td>
<td></td>
</tr>
<tr>
<td>Type B2 lesion</td>
<td>1583 (37)</td>
<td>1565 (37)</td>
<td>15 (33)</td>
<td>1.227 (0.476–3.162)</td>
<td>0.67</td>
</tr>
<tr>
<td>Type C lesion</td>
<td>1899 (45)</td>
<td>1859 (44)</td>
<td>25 (54)</td>
<td>1.810 (0.743–4.412)</td>
<td>0.19</td>
</tr>
<tr>
<td>Calcium</td>
<td>1756 (41)</td>
<td>1752 (41)</td>
<td>18 (38)</td>
<td>0.890 (0.494–1.602)</td>
<td>0.70</td>
</tr>
<tr>
<td>Ulcer</td>
<td>503 (12)</td>
<td>486 (12)</td>
<td>11 (24)</td>
<td>2.288 (1.162–4.505)</td>
<td>0.017</td>
</tr>
<tr>
<td>Thrombus</td>
<td>1293 (31)</td>
<td>1270 (31)</td>
<td>19 (41)</td>
<td>1.609 (0.894–2.893)</td>
<td>0.11</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>558 (13)</td>
<td>553 (13)</td>
<td>3 (6)</td>
<td>0.447 (0.139–1.439)</td>
<td>0.18</td>
</tr>
<tr>
<td>Ejection fraction &lt;40%</td>
<td>382 (8)</td>
<td>374 (8)</td>
<td>7 (13)</td>
<td>1.929 (0.870–4.280)</td>
<td>0.11</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa use</td>
<td>1815 (40)</td>
<td>1781 (40)</td>
<td>22 (42)</td>
<td>1.159 (0.668–2.011)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Values are expressed as n (%), HR (95% CI), or mean±SD. LAD indicates left anterior descending coronary artery; LCx, left circumflex coronary artery; and RCA, right coronary artery. Patients with stent thrombosis >30 d includes all late and very late stent thrombosis events. Sum of percentages for treated vessels exceeds 100% because some patients underwent multivessel intervention.

### Table 3. Incidence of Stent Thrombosis and Restenosis During Extended Follow-Up* of All Patients

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>5 Years</th>
<th>10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events, No. at Risk</td>
<td>% (95% CI)</td>
<td>Events, No. at Risk</td>
</tr>
<tr>
<td>All stent thrombosis</td>
<td>37, 4233</td>
<td>0.8 (0.6–1.1)</td>
<td>57, 3662</td>
</tr>
<tr>
<td>On-label patients</td>
<td>12, 2101</td>
<td>0.6 (0.2–0.9)</td>
<td>20, 1851</td>
</tr>
<tr>
<td>Off-label patients</td>
<td>25, 2132</td>
<td>1.1 (0.7–1.5)</td>
<td>37, 1811</td>
</tr>
<tr>
<td>Restenosis</td>
<td>421, 3854</td>
<td>9.6 (8.8–10.5)</td>
<td>592, 3184</td>
</tr>
<tr>
<td>Stable angina</td>
<td>242, 4018</td>
<td>5.6 (4.9–6.2)</td>
<td>329, 3399</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>151, 4111</td>
<td>3.5 (2.9–4.0)</td>
<td>225, 3498</td>
</tr>
<tr>
<td>MI</td>
<td>45, 4214</td>
<td>1.0 (1.3–0.7)</td>
<td>76, 3635</td>
</tr>
<tr>
<td>Positive stress test</td>
<td>16, 4240</td>
<td>0.4 (0.2–0.5)</td>
<td>27, 3667</td>
</tr>
<tr>
<td>Other unstable presentation</td>
<td>8, 4248</td>
<td>0.2 (0.1–0.3)</td>
<td>12, 3684</td>
</tr>
</tbody>
</table>

*Percentages are the cumulative rates of the event from Kaplan-Meier estimates. There were 667 patients with restenosis and 836 total presentations with restenosis. Therefore, percentages for presentations of restenosis do not total the sum for overall restenosis.

†P = 0.024 compared with on-label risk for stent thrombosis.
P<0.001) was also associated with late stent thrombosis. Procedural correlates of stent thrombosis >30 days (Table 2) included vein graft BMS intervention (27% versus 8%; hazard ratio, 4.65; P<0.001) and ulcerated lesions (24% versus 12%; hazard ratio, 2.29; P=0.017).

Risk of death is markedly increased during the first 30 days after early stent thrombosis (hazard ratio, 140; 95% CI, 70 to 283; P<0.001); late stent thrombosis (hazard ratio, 22; 95% CI, 3.1 to 149); and very late stent thrombosis (hazard ratio, 40; 95% CI, 15 to 107; P<0.001). Even after the initial 30-day period after a stent thrombosis event has passed, hazard ratios for death are increased for both early (hazard ratio, 3.2; 95% CI, 1.3 to 7.8; P=0.009) and very late stent thrombosis (hazard ratio, 4.5; 95% CI, 2.7 to 7.7; P<0.001), although this additional late mortality risk was not statistically significant for late stent thrombosis (hazard ratio, 1.7; 95% CI, 0.6 to 4.4; P=0.31).

**Clinical Restenosis**

There were 836 occurrences of clinical restenosis among 667 patients. The cumulative incidence (95% CI) of at least 1 restenosis was 9.6% (8.8% to 10.5%) at 1 year, 13.9% (12.8% to 14.9%) at 5 years, and 18.1% (16.5% to 19.7%) at 10 years. The 10-year incidence of restenosis by mode of presentation was stable angina 9.0% (95% CI, 8.0% to 10.0%); unstable angina 7.4% (95% CI, 6.3% to 8.6%); MI 2.1% (95% CI, 1.6% to 2.6%); and other unstable presentation such as decompensated heart failure or ventricular arrhythmia 0.4% (95% CI, 0.2% to 0.6%). Restenosis presented as an asymptomatic positive stress test in 1.4% (95% CI, 0.7 to 2.2%) (Table 3). The timing of MI caused by restenosis is illustrated in the Figure with the use of annual event rates per 1000 patient-years. Most events occurred in the first year after the index procedure, with a lower annual rate thereafter. Although infrequent, events were observed several years after the index procedure.

Among 87 patients with an MI presentation of restenosis, peak creatine kinase-MB (normal range, <4.3 ng/mL) was 29.62±39.3 ng/mL (median, 13.9 ng/mL). Presentation was with non-ST-segment elevation MI in 87% (n=76) and with ST-segment elevation MI in 13% (n=11). Patients with MI presentation of restenosis were more likely to have a history of high cholesterol (hazard ratio, 2.31; 95% CI, 1.3 to 4.1; P=0.005), cerebrovascular accident/transient ischemic attack (hazard ratio, 2.84; 95% CI, 1.7 to 4.8; P<0.001), congestive heart failure (hazard ratio, 2.36; 95% CI, 1.3 to 4.1; P=0.003), peripheral vascular disease (hazard ratio, 2.55; 95% CI, 1.5 to 4.4; P<0.001), diabetes (hazard ratio, 1.91; 95% CI, 1.2 to 3.0; P=0.006), and prior CABG (hazard ratio, 2.51; 95% CI, 1.6 to 3.9; P<0.001). Angiographic correlates of MI restenosis were vein graft intervention (hazard ratio, 3.50; 95% CI, 2.1 to 5.8; P<0.001) and intervention in an eccentric lesion (hazard ratio, 3.30; 95% CI, 1.2 to 9.0; P=0.021).

MI presentation with restenosis was associated with significantly greater mortality risk compared with no restenosis (hazard ratio, 2.37; 95% CI, 1.72 to 3.27; P<0.001) and with a non-MI presentation of restenosis (hazard ratio, 2.42; 95% CI, 1.68 to 3.47; P<0.001). There was no significant difference in long-term survival between patients with no restenosis and patients with non-MI presentation of restenosis (hazard ratio, 0.99; 95% CI, 0.85 to 1.14; P=0.85).

**Stent Thrombosis and Clinical Restenosis in Native Coronary Arteries**

The cumulative incidence of stent thrombosis after off-label native coronary intervention (vein graft interventions excluded) was 1.1% (95% CI, 0.6% to 1.6%) at 1 year, 1.4% (95% CI, 0.8% to 1.9%) at 5 years, and 2.1% (95% CI, 1.3% to 2.9%) at 10 years (Table 4). Risk for late and very late stent thrombosis among patients treated for off-label native coronary indications was not significantly different from that observed among patients treated for an on-label indication (P=0.23).

Risk of death is increased during the first 30 days after native coronary BMS thrombosis: early stent thrombosis (hazard ratio, 142; 95% CI, 68 to 297; P<0.001); late stent thrombosis (hazard ratio, 33; 95% CI, 4.6 to 241); and very late stent thrombosis (hazard ratio, 14; 95% CI, 2.0 to 102; P=0.008). After the initial 30-day period after a stent thrombosis event has passed, hazard ratios for death remained increased for both early (hazard ratio, 4.1; 95% CI, 1.7 to 10; P=0.001) and very late stent thrombosis (hazard ratio, 4.3; 95% CI, 2.2 to 8.2; P<0.001), although this additional late mortality risk was not statistically significant for late stent thrombosis (hazard ratio, 1.8; 95% CI, 0.6 to 5.6; P=0.30).

The incidence of clinical restenosis among patients undergoing PCI for native coronary arteries is presented in Table 4. Among patients with native coronary intervention, MI presentation with restenosis was associated with significantly greater mortality risk compared with no restenosis (hazard ratio, 2.26; 95% CI, 1.49 to 3.42; P<0.001) and with a non-MI presentation of restenosis (hazard ratio, 2.33; 95% CI, 1.46 to 3.70; P<0.001). There was no significant difference in long-term survival between patients with no restenosis and patients with non-MI presentation of restenosis (hazard ratio, 0.95; 95% CI, 0.81 to 1.13; P=0.56).
Late and Very Late BMS Thrombosis

We found that the incidence of BMS thrombosis during long-term follow-up of unselected patients in routine practice is a significant issue. The greatest number of events occurred within the first year after PCI, and the annual event rate thereafter was relatively low. By 10 years, however, the cumulative incidence of stent thrombosis had more than doubled from that observed at 1 year. Even among patients treated with a single stent in a native artery for a de novo lesion (considered an on-label DES indication), a significant number of very late events were observed. These data suggest that very long-term follow-up of patients treated with either DES or BMS may be required before the relative safety of these devices can be assessed definitively.

An alternative explanation is the undisputed fact that atherosclerosis is often a progressive disease. If the index lesion was also correlated with late BMS thrombosis. It is logical to consider the possibility that such preexisting disease or absence of runoff, leading to proximal graft occlusion regardless of prior stent location. Vein grafts accounted for 27% of all late and very late stent thromboses in this cohort.

Although statistical power is limited by a relatively small number of adverse events, the correlates of BMS thrombosis occurring at any time after 30 days (including prior MI or cerebral infarction, peripheral vascular disease, prior CABG, prior cerebrovascular accident, prior congestive heart failure, and peripheral vascular disease). The incidence of MI caused by BMS restenosis was 2.1% (95% CI, 1.6% to 2.6%) at 10 years. (4) Late BMS thrombosis, very late BMS thrombosis, and MI presentation of restenosis are all associated with significantly decreased survival during long-term follow-up (P<0.001).

Clinical Restenosis and MI

In this real-world setting, the risk of MI caused by restenosis was 2.1% at 10 years (95% CI, 1.6% to 2.6%), in agreement with recently published data. This presentation of restenosis was associated with decreased survival during long-term follow-up. These findings question an approach to stent selection in current practice that may favor BMS as the safe option because of the “benign” nature of restenosis. Indeed, it is interesting to note that a possible increased risk of late and very late stent thrombosis occurring within saphenous vein grafts. Total occlusion of an aged graft may develop secondary to diffuse disease or absence of runoff, leading to proximal graft occlusion regardless of prior stent location. Vein grafts accounted for 27% of all late and very late stent thromboses in this cohort.

Discussion

The major findings of this study were as follows: (1) The incidence of BMS thrombosis was 0.5% at 30 days (95% CI, 0.3% to 0.7%) and 2.0% at 10 years (95% CI, 1.5% to 2.5%). Risk of stent thrombosis during long-term follow-up was increased in the setting of off-label treatment (P=0.024), although when vein graft interventions were excluded, no significant difference in risk was observed after on-label versus off-label treatment. (2) Correlates of BMS thrombosis >30 days (including >1 year) include ulcerated lesion, vein graft intervention, prior MI, prior CABG, prior cerebrovascular accident, prior congestive heart failure, and peripheral vascular disease. (3) The incidence of MI caused by BMS restenosis was 2.1% (95% CI, 1.6% to 2.6%) at 10 years. (4) Late BMS thrombosis, very late BMS thrombosis, and MI presentation of restenosis are all associated with significantly decreased survival during long-term follow-up (P<0.001).

Table 4. Incidence of Stent Thrombosis and Restenosis During Extended Follow-Up* of Patients With Native Coronary Interventions Only (Vein Graft Interventions Excluded)

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>5 Years</th>
<th>10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events, No.</td>
<td>% (95% CI)</td>
<td>Events, No.</td>
</tr>
<tr>
<td>All stent thrombosis</td>
<td>32,385</td>
<td>0.8 (0.5–1.1)</td>
<td>45,383</td>
</tr>
<tr>
<td>On-label patients</td>
<td>12,210</td>
<td>0.6 (0.2–0.9)</td>
<td>20,185</td>
</tr>
<tr>
<td>Off-label patients</td>
<td>20,1750</td>
<td>1.1 (0.6–1.6)</td>
<td>25,1532</td>
</tr>
<tr>
<td>Restenosis</td>
<td>387,3710</td>
<td>9.5 (8.6–10.4)</td>
<td>510,2965</td>
</tr>
<tr>
<td>Stable angina</td>
<td>220,3654</td>
<td>5.6 (4.8–6.3)</td>
<td>291,3144</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>136,3740</td>
<td>3.4 (2.9–4.0)</td>
<td>193,3241</td>
</tr>
<tr>
<td>Ml</td>
<td>35,3839</td>
<td>0.9 (0.6–1.2)</td>
<td>57,3363</td>
</tr>
<tr>
<td>Positive stress test</td>
<td>15,3856</td>
<td>0.4 (0.2–0.6)</td>
<td>25,3384</td>
</tr>
<tr>
<td>Other unstable presentation</td>
<td>7,3864</td>
<td>0.2 (0.0–0.3)</td>
<td>11,3400</td>
</tr>
</tbody>
</table>

*Percentages are the cumulative rates of the event from Kaplan-Meier estimates. There were 580 patients with restenosis and 720 total presentations with restenosis. Therefore, percentages for presentations of restenosis do not total the sum for overall restenosis.

†P<0.03 compared with on-label risk for stent thrombosis.

Discussion

The incidence of BMS thrombosis during long-term follow-up was 0.5% at 30 days (95% CI, 0.3% to 0.7%) and 2.0% at 10 years (95% CI, 1.5% to 2.5%). Risk of stent thrombosis during long-term follow-up was increased in the setting of off-label treatment (P=0.024), although when vein graft interventions were excluded, no significant difference in risk was observed after on-label versus off-label treatment. (2) Correlates of BMS thrombosis >30 days (including >1 year) include ulcerated lesion, vein graft intervention, prior MI, prior CABG, prior cerebrovascular accident, prior congestive heart failure, and peripheral vascular disease. (3) The incidence of MI caused by BMS restenosis was 2.1% (95% CI, 1.6% to 2.6%) at 10 years. (4) Late BMS thrombosis, very late BMS thrombosis, and MI presentation of restenosis are all associated with significantly decreased survival during long-term follow-up (P<0.001).

Late and Very Late BMS Thrombosis

We found that the incidence of BMS thrombosis during long-term follow-up of unselected patients in routine practice is a significant issue. The greatest number of events occurred within the first year after PCI, and the annual event rate thereafter was relatively low. By 10 years, however, the cumulative incidence of stent thrombosis had more than doubled from that observed at 1 year. Even among patients treated with a single stent in a native artery for a de novo lesion (considered an on-label DES indication), a significant number of very late events were observed. These data suggest that very long-term follow-up of patients treated with either DES or BMS may be required before the relative safety of these devices can be assessed definitively.

An alternative explanation is the undisputed fact that atherosclerosis is often a progressive disease. If the index procedure involves the most severely diseased vessel, then disease progression in this vessel may occur during long-term follow-up, leading to thrombosis of the vessel. This may be attributed to stent thrombosis but may also be due to disease progression. This concept is particularly relevant to stent thrombosis occurring within saphenous vein grafts. Total occlusion of an aged graft may develop secondary to diffuse disease or absence of runoff, leading to proximal graft occlusion regardless of prior stent location. Vein grafts accounted for 27% of all late and very late stent thromboses in this cohort.

Although statistical power is limited by a relatively small number of adverse events, the correlates of BMS thrombosis occurring at any time after 30 days (including prior MI or cerebral infarction, peripheral vascular disease, prior CABG, prior congestive heart failure) point to increased risk among patients with a greater burden of systemic vascular disease. Whether this relates to impaired reendothelialization, rupture of neoatherosclerotic plaque within stented segments, or other mechanism(s) is unclear. Ulceration of the target lesion was also correlated with late BMS thrombosis. It is logical to consider the possibility that such preexisting disruption of coronary endothelium may be a marker of impaired vascular healing and may be associated with higher risk of delayed (or failed) reendothelialization after PCI. Data regarding compliance with antiplatelet therapy (recently highlighted as a predictor of late DES thrombosis) were not available for this cohort. Further studies will be required to elucidate the mechanism(s) of late and very late BMS thrombosis and to determine whether prolonged dual antiplatelet therapy might improve prognosis for patients treated with BMS.
basis after off-label use of DES may also apply to patients treated with BMS.

The finding of increased mortality associated with MI presentation of restenosis also provides insight into recent data demonstrating lower rates of stent thrombosis among BMS-treated patients but overall rates of death and MI that were the same compared with DES treated patients.22,23 A higher incidence of MI caused by restenosis among the BMS group could explain such a discrepancy (target-lesion revascularization was much lower in the DES group22). The risk of death associated with clinical restenosis appears to relate predominantly to the mode of presentation and not to potential adverse events during repeat interventional or surgical procedures; survival among patients with non-MI presentation of restenosis did not differ from that of patients without restenosis.

Limitations

This was a retrospective, observational study, and it is possible that we did not capture all adverse events, thereby resulting in an underestimation of events associated with BMS failure during follow-up. Referral and selection biases are likely operative; however, we achieved high rates of follow-up, and all stent thrombosis events were adjudicated according to a standardized set of criteria for this complication. Several associations between risk factors and late stent thrombosis were estimated, although only 52 such events were observed. Thus, some observed associations may be spurious. In addition, the small number of events results in low statistical power for detecting clinically relevant associations. Finally, the study design does not permit any conclusions to be drawn regarding the impact of these late complications on overall risks and benefits of percutaneous intervention versus medical therapy for patients presenting with ischemic heart disease.

Conclusions

The risk of BMS thrombosis during long-term follow-up is significant and is increased among patients treated for an off-label DES indication. The incidence of MI caused by BMS restenosis (2.1% at 10 years) is similar to the combined incidence of early, late, and very late stent thrombosis (2.0% at 10 years). These data suggest that the current tendency to increase use of BMS in place of DES may not solve the safety issues that have arisen during long-term follow-up of DES-treated patients. Clinical decision making should weigh relative risks of restenosis and thrombosis on the basis of lesion- and patient-specific variables.

Disclosures

None.

References


CLINICAL PERSPECTIVE

Concern regarding late thrombosis of drug-eluting stents has led to a resurgence of bare-metal stent (BMS) use in contemporary practice. This suggests that some clinicians may regard BMS as a safer long-term option for certain patients undergoing percutaneous intervention, despite an increased risk of restenosis compared with drug-eluting stents. However, the incidence and outcomes associated with late BMS thrombosis (and restenosis) are not well described. In this analysis of 4503 patients treated with BMS between 1994 and 2000 at the Mayo Clinic, we found that the cumulative incidence of late BMS thrombosis was significant: 0.5% at 30 days, 0.8% at 1 year, and 2.0% at 10 years. The incidence of restenosis was 18.1% at 10 years, and a significant proportion (>10%) of these patients presented with myocardial infarction. Both late BMS thrombosis and myocardial infarction caused by restenosis were independently associated with decreased survival during long-term follow-up. These data suggest that an assumption of superior long-term safety of BMS (because of the absence of a drug-polymer coating) may not be valid. Stent selection in contemporary practice should weigh relative risks of restenosis and thrombosis on the basis of lesion- and patient-specific variables.
Outcomes of Stent Thrombosis and Restenosis During Extended Follow-Up of Patients Treated With Bare-Metal Coronary Stents
Brendan Doyle, Charanjit S. Rihal, Crochan J. O'Sullivan, Ryan J. Lennon, Heather J. Wiste, Malcolm Bell, John Bresnahan and David R. Holmes, Jr

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