Offsetting Impact of Thrombosis and Restenosis on the Occurrence of Death and Myocardial Infarction After Paclitaxel-Eluting and Bare Metal Stent Implantation

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Background—Drug-eluting stents compared with bare metal stents (BMS) may increase late stent thrombosis (ST), although an accompanying increase in the rates of death and myocardial infarction (MI) has not been observed. We hypothesized that the prevention of restenosis-related adverse events by drug-eluting stents might offset some or all of the excess risk from ST.

Methods and Results—we analyzed a pooled patient-level database from 4 prospective, double-blind trials in which 3445 patients were randomized to paclitaxel-eluting stents or BMS. The occurrence of death or MI within 7 days of ST or target lesion revascularization was assessed. With a median follow-up of 3.2 years, ST occurred in 34 patients (1.0%), 31 (91.1%) of whom sustained death or MI within 7 days. Target lesion revascularization was performed in 425 patients (12.3%), 15 (3.5%) of whom died or had MI within 7 days. ST occurred in 14 BMS and 20 paclitaxel-eluting stent patients, resulting in 12 and 19 deaths or MIs within 7 days, respectively. Target lesion revascularization was performed in 290 BMS and 135 paclitaxel-eluting stent patients, resulting in 11 and 4 deaths or MI events within 7 days, respectively. In total, 23 patients in both the BMS and paclitaxel-eluting stents groups died or had an MI event within 7 days of either ST or target lesion revascularization.

Conclusions—ST, although infrequent, results in a high incident rate of death and MI, whereas the more frequent occurrence of target lesion revascularization is associated with a finite but lower rate of death and MI. The marked reduction in restenosis with drug-eluting stents compared with BMS may counterbalance the potential excess risk from late ST with drug-eluting stents. (Circulation. 2007;115:2842-2847.)

Key Words: mortality • myocardial infarction • restenosis • stent • thrombosis
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Methods

Study Description
To directly test the impact of ST and restenosis on major adverse cardiovascular events after stent implantation, we pooled the databases from the prospective, multicenter, double-blind, placebo-controlled TAXUS-II, TAXUS-IV, TAXUS-V, and TAXUS-VI trials, in which 3445 total patients were randomized to PES (n = 1718) or otherwise identical BMS (n = 1728) for retrospective analysis.1-4 The enrollment criteria and demographic and lesion characteristics of the patients enrolled in these trials have recently been summarized.15 In brief, patients presenting with stable ischemic syndromes eligible for stent implantation in a single de novo noncomplex lesion in a native coronary artery were eligible for enrollment. Each protocol mandated clopidogrel use for at least 6 months and aspirin indefinitely. Before performing any analyses, we specified the following study parameters. First, the occurrence of death and MI events would be measured within 7 days of a first ST episode and target lesion revascularization (TLR) resulting from ischemia. The 7-day window was chosen to maximize the likelihood that death or MI was directly related to the ST or TLR episode rather than a later unrelated cause such as plaque rupture remote from the target lesion site or a primary arrhythmia. Second, for the purposes of this analysis, revascularizations occurring within 30 days of the index procedure (thus likely not a result of restenosis), solely the result of protocol-mandated routine angiographic follow-up absent the presence of ischemia or symptoms (ie, as the result of an “oculostenotic reflex” on the part of the operator), or those performed to treat ST were not counted as TLR events. Third, the latest clinical follow-up available from each trial would be used (currently 34 months and aspirin indefinitely). Before performing any analyses, we specified the following study parameters. First, the occurrence of death and MI events within 7 days of a first ST episode and target lesion revascularization (TLR) resulting from ischemia. The 7-day window was chosen to maximize the likelihood that death or MI was directly related to the ST or TLR episode rather than a later unrelated cause such as plaque rupture remote from the target lesion site or a primary arrhythmia. Second, for the purposes of this analysis, revascularizations occurring within 30 days of the index procedure (thus likely not a result of restenosis), solely the result of protocol-mandated routine angiographic follow-up absent the presence of ischemia or symptoms (ie, as the result of an “oculostenotic reflex” on the part of the operator), or those performed to treat ST were not counted as TLR events. Third, the latest clinical follow-up available from each trial would be used (currently 4 years for TAXUS-II and TAXUS-IV, 3 years for TAXUS-VI, and 2 years for TAXUS-V; median duration of follow-up, 3.2 years for all studies, with all patients and study personnel still blinded). Fourth, analyses would be performed on a per-patient level; if multiple ST or TLR events occurred in a single patient, only the first event of each type would be counted to avoid double counting.

Definitions
All end points were adjudicated by an independent clinical events committee without knowledge of the assigned stent type. Death was defined as due to any cause. MI was defined as either the development of new pathological Q waves >0.04 seconds in duration in ≥2 contiguous leads with an elevated creatine phosphokinase-MB fraction level or, in the absence of Q-waves, an elevation of creatine phosphokinase level to >2.0 times normal with positive creatine kinase-MB (creatine phosphokinase >5.0 times elevated after bypass graft surgery). ST was defined as in the original clinical trials as either an acute coronary syndrome with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel or, in the absence of angiographic confirmation, either acute Q-wave or non-Q-wave MI in the distribution of the treated vessel or death (cardiac or otherwise unexplained) within 30 days. TLR was defined as repeat revascularization (by either percutaneous coronary intervention or coronary artery bypass graft surgery) for ischemia with angiographic restenosis (diameter stenosis >50% anywhere within the stent or the 5-mm proximal or distal stent borders) with either ECG changes at rest or a positive functional study in the distribution of the target vessel or a >70% diameter stenosis with recurrent symptoms only.

Results

Patients
Selected baseline demographic and angiographic features of the DES and BMS groups were well matched, with no significant differences between groups (the Table). The mean age was 62.2 years; 72.3% of the patients were male, and 23.6% had diabetes. Reflecting the complexity of the patients enrolled in TAXUS-V and TAXUS VI, the lesions were moderately long (mean length, 15.2 mm), and 18.8% of patients received multiple stents.

Statistical Analysis
Categorical variables were compared by χ2 or Fisher exact test. Continuous variables are described as mean±SD and were compared by unpaired t tests. All analyses are by intention to treat, including all patients randomized to each stent. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Baseline Clinical and Angiographic Features

<table>
<thead>
<tr>
<th>Baseline Clinical and Angiographic Features</th>
<th>PES (n = 1718)</th>
<th>BMS (n = 1727)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.3±10.9</td>
<td>62.1±10.6</td>
</tr>
<tr>
<td>Male</td>
<td>1238 (72.1)</td>
<td>1252 (72.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>399 (23.2)</td>
<td>415 (24.0)</td>
</tr>
<tr>
<td>Insulin requiring</td>
<td>120 (7.0)</td>
<td>136 (7.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1193 (69.4)</td>
<td>1174 (68.0)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1202/1711 (70.3)</td>
<td>1215/1722 (70.6)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>382/1708 (22.5)</td>
<td>370/1718 (21.5)</td>
</tr>
<tr>
<td>Angina class*</td>
<td>0/1</td>
<td>882 (51.3)</td>
</tr>
<tr>
<td>2</td>
<td>445 (25.9)</td>
<td>452 (26.2)</td>
</tr>
<tr>
<td>3</td>
<td>311 (18.1)</td>
<td>294 (17.0)</td>
</tr>
<tr>
<td>4</td>
<td>80 (4.7)</td>
<td>91 (5.3)</td>
</tr>
<tr>
<td>Target coronary artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>715/1707 (41.9)</td>
<td>7231/1721 (41.9)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>440/1707 (25.8)</td>
<td>419/1721 (24.3)</td>
</tr>
<tr>
<td>Right coronary</td>
<td>552/1707 (32.3)</td>
<td>581/1721 (33.8)</td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>2.74±0.51</td>
<td>2.73±0.51</td>
</tr>
<tr>
<td>Minimal luminal diameter, mm</td>
<td>0.90±0.35</td>
<td>0.91±0.36</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>67.1±10.8</td>
<td>66.9±11.4</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>15.2±7.9</td>
<td>15.1±8.0</td>
</tr>
<tr>
<td>Stents, n</td>
<td>1.21±0.48</td>
<td>1.19±0.46</td>
</tr>
<tr>
<td>Total stent length, mm</td>
<td>24.6±11.3</td>
<td>24.3±11.2</td>
</tr>
<tr>
<td>≥1 Stent implanted</td>
<td>331/1709 (19.3)</td>
<td>314/1721 (18.2)</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n (%) as appropriate.
*Canadian Cardiovascular System classification. There were no significant differences between groups.

Frequency and Implications of ST
A total of 38 ST events occurred in 34 patients (1.0%), including 14 patients assigned to BMS and 20 patients assigned to PES. Before 30 days, ST occurred in 8 PES patients versus 10 BMS patients. Between 30 days and 1 year, ST occurred in 4 PES patients versus 2 BMS patients. Thus, before 1 year, ST occurred in 12 patients in each of the PES and BMS groups (P=0.99). After 1 year, a first ST occurred in 8 PES patients and in 2 BMS
patients ($P=0.06$) (Figure 1). Of the 34 patients with ST events, death or nonfatal MI within 7 days developed in 31 (91.1%). Death within 7 days of ST occurred in 3 of 14 BMS patients and in 3 of 20 PES patients (21.4% versus 15.0%; $P=0.67$). Nonfatal MI within 7 days of ST occurred in 9 BMS patients and in 16 PES patients (64.3% versus 80.0%; $P=0.56$), representing an excess of 7 ST-related death or nonfatal MI events due to treatment with PES rather than BMS (Figure 1).

**Frequency and Implications of TLR**

TLR was performed during the follow-up period in 498 patients; 425 qualified as TLR resulting from ischemia as defined in the present study (Figure 2). Ischemia-driven clinical TLR was performed in 290 BMS patients and 135 PES patients (16.8% versus 7.9%, respectively; $P=0.0001$). Of the 425 patients with ischemia-driven clinical TLR events, 15 (3.5%) developed death or nonfatal MI within 7 days. Of these 15 events, 7 (all clinical presentation with nonfatal MI) occurred before and 8 (7 nonfatal MI and 1 death) developed after the TLR procedure. Death within 7 days of TLR occurred in 1 of 290 BMS patients and in 0 of 135 PES patients (0.3% versus 0%; $P=0.99$). Nonfatal MI within 7 days of TLR occurred in 10 BMS patients and in 4 PES patients (3.5% versus 3.0% of all TLR; $P=0.99$). Thus, death or nonfatal MI as a result of TLR developed in 11 BMS patients and 4 PES patients (3.8% versus 3.0%; $P=0.78$), representing 7 fewer TLR-related death or nonfatal MI events after treatment with PES rather than BMS (Figure 2).

**Summed Effect of Stent Thrombosis and TLR**

As shown in Figure 3, among patients assigned to BMS, the 14 ST events combined with the 290 TLR events resulted in 23 patients sustaining death or nonfatal MI. Among patients assigned to PES, the 20 ST events combined with the 135 TLR events resulted in 8 patients sustaining death or nonfatal MI. The rate of first ST was similar between PES and BMS before 1 year but tended to be greater with PES after 1 year. This resulted in an excess of 7 patients with death or nonfatal MI in the group assigned to PES because of 7 additional nonfatal MIs (with the same number of deaths in both groups).
TLP events also resulted in 23 patients sustaining death or nonfatal MI. The timing of these events, however, varied by stent type. As shown in Figure 4, within 1 year of implantation, 12 ST events and 247 TLP events occurred among BMS patients, resulting in 20 patients with death or nonfatal MI, whereas 12 ST events and 99 TLP events occurred among PES patients, resulting in 13 patients with death or nonfatal MI (P = 0.23 for comparison of death or MI before 1 year). In contrast, between 1 year and the latest follow-up, 2 ST events and 43 TLP events resulted in 3 patients with death or nonfatal MI among BMS patients, whereas 8 ST events and 36 TLP events among PES patients resulted in 10 patients with death or nonfatal MI (P = 0.05 for comparison of death or MI after 1 year).

**Discussion**

The principal findings from the present patient-level pooled meta-analyses of the 4 major randomized trials of PES versus BMS, with a median follow-up of 3.2 years, include the following. First, ST events, although infrequent (~1% of patients) with both PES and BMS, are associated with a high incidence (~90%) of death or nonfatal MI within 7 days. Although the rates of ST were similar with PES and BMS in the first year after stent implantation, a trend toward a small increase in ST with PES beyond 1 year was present, which resulted in a numerical excess of PES-assigned patients dying or experiencing a nonfatal MI between 2 and 4 years of follow-up. Second, TLP events, although much more frequent than ST (~10% to 20% of patients), were associated with a finite but lower incidence (~3.5%) of death or nonfatal MI within 7 days. The marked reduction in TLP with PES compared with BMS within the first year after implantation resulted in fewer TLP-related deaths and nonfatal MI events with PES throughout the entire follow-up period. Third, the counterbalancing effects of ST (more common with PES) and TLP (more common with BMS) offset each other so that the overall rates of composite death or nonfatal MI within 7 days attributable to these adverse events were similar with the 2 stent types during the follow-up period of 3.2 years. Fourth, the offsetting impact of ST and TLP on the occurrence of adverse events varied with the duration after stent implantation; DES compared with BMS use was associated with a lower incidence of death or MI before 1 year of follow-up but a greater occurrence of death or MI after 1 year.

**Impact of ST and TLP**

In the present study, the occurrence of ST was associated with death within 7 days in 17.6% of patients, nonfatal MI in 73.5% of patients, and death or nonfatal MI in 91.1% of patients, consistent with prior reports. The frequency of major adverse cardiovascular events was similar after PES and BMS thrombosis. Also consistent with earlier studies, there were no differences in the rates of ST (or resultant death and MI) between PES and BMS within the first year after implantation. However, after 1 year and through the latest follow-up, ST was slightly more common with PES than BMS, leading to a numerical increase of 7 patients with death or MI events among patients assigned to PES.

Whereas it is widely appreciated that ST results in a high rate of death or nonfatal MI, restenosis has historically been considered a benign process, with most affected patients presenting with recurrent stable angina. Four recent studies have challenged
this assumption, however, by reporting MI rates ranging from 3.5% to 19.4% in patients presenting with symptomatic BMS restenosis.\textsuperscript{19-22} In the largest such study, 9.5% of 1186 patients from the Cleveland Clinic with BMS in-stent restenosis presented with acute MI, and the revascularization procedures required to treat the restenosis resulted in 8 deaths (0.7%).\textsuperscript{19} In the present study, 425 patients developed $\geq 1$ episodes of clinical restenosis severe enough to require TLR, resulting in 14 nonfatal MIs and 1 death (3.5% total rate of death or nonfatal MI). One half of the MI events were Q-wave MIs, which are strongly associated with late death even when occurring after percutaneous coronary intervention.\textsuperscript{26} One half of the death or MI events occurred before the TLR procedure (ie, as the presenting clinical syndrome); the remainder occurred as a complication of the revascularization procedure required to treat the restenotic lesion. Finally, although the per-case incidence of death or nonfatal MI associated with TLR was relatively low, the cumulative effect of the marked reduction in TLR frequency among patients randomized to PES rather than BMS led to 7 fewer deaths or nonfatal MI events in the cohort assigned to PES. As such, the benefits of PES in markedly reducing restenosis compared with BMS exactly offset the adverse effect of the increase in late ST with PES, so similar total numbers of patients developed death or nonfatal MI within 7 days of either ST or TLR after randomization to PES versus BMS.

Timing of Death and MI

When considering the counterbalancing influences of ST and TLR on the net rates of death or nonfatal MI, we should note that within the first year after stent implantation, 7 fewer patients assigned to PES rather than BMS experienced death or MI, reflecting the time course of restenosis (typically occurring within the first year) and the similar rates of ST with PES and BMS in this interval. In contrast, after 1 year, death or MI occurred in 7 more patients assigned to PES rather than BMS, attributable to the increase in late ST with PES during this time period in concert with the low rates of TLR with both stent types. These observations have important implications. If incremental late ST events continue to accrue in the PES arm beyond the median 3.2-year follow-up duration of the present study, more patients with death or nonfatal MI resulting from treatment with PES rather than BMS would accumulate. Conversely, this study also suggests that if the excess risk of late ST with DES can be eliminated by future stent designs or adjunct pharmacology, by reducing restenosis, DES has the potential to actually lower death and MI rates compared with BMS.

Study Strengths and Limitations

The present study is the first to attempt to directly examine whether the salutary benefits of DES in reducing restenosis might reduce major adverse cardiovascular events such as death and nonfatal MI, thereby offsetting potential DES risks such as late ST. Derived from a large patient-level meta-analysis of prospective, placebo-controlled trials (which are still blinded at the time of analysis), with 100% on-site monitoring for adverse events, these data may be considered particularly robust. Nonetheless, several limitations should be mentioned. First, despite randomization of 3445 patients, the ST, death, and MI rates are still low, adding some uncertainty as to whether the reduction of TLR with PES compared with BMS offsets some of, all of, or more than the excess ST risk. Second, the protocol definition of ST did not attribute unexplained death or MI after 30 days to thrombotic occlusion; thus, the present study might have underestimated the true rate and impact of late ST. However, restenosis may present as coronary occlusion in as many as 10% of patients,\textsuperscript{19} and patients dying or developing MI from restenosis in whom TLR was not performed were likewise not included in the present analysis. Furthermore, several deaths or MI events occurring before 30 days in patients without angiographic follow-up that were attributed to ST may have been inappropriately assigned. In addition, the results of the present analysis might vary if, rather than the prespecified protocol definitions of ST, alternative post hoc ST definitions were applied, such as those recently described by the Academic Research Consortium.\textsuperscript{27} However, these definitions expand the number of ST events by counting additional unexplained deaths and MIs as surrogates for possible ST, which would introduce a tautological bias to the present analysis. Moreover, when we examined the impact of applying different Academic Research Consortium definitions to the present analysis, the conclusions were not materially changed. Third, the prespecified 7-day window used to identify death and MI events as a consequence of ST and TLR likely excluded some later related major adverse cardiovascular events but was considered necessary to avoid confounding with other causes of death and MI not directly related to the incident event. Fourth, the current retrospective analysis was performed post hoc and thus must be considered hypothesis generating. Fifth, the severity and prognostic implications of MI may vary with origin (whether associated with ST or TLR). In the present analysis, the combined ST and TLR events occurring during the 4-year follow-up period resulted in 11 Q-wave and 11 non–Q-wave MIs in patients assigned to PES (with 1 early death attributed to MI), whereas 8 Q-wave and 13 non–Q-wave MIs occurred in patients assigned to BMS (with 1 MI-attributed early death). The present study was underpowered to determine whether the prognostically more important Q-wave MIs\textsuperscript{26} occur with greater frequency with one versus the other stent type and was not designed to measure infarct size between the 2 groups. Finally, it is unknown whether the relative rates and implications of ST and TLR would be the same for patients and lesions not meeting the enrollment criteria of these 4 trials. Similarly, these specific results apply only to the comparison of PES with the control BMS stents tested in the TAXUS trials; the absolute and relative safety and efficacy profiles of these and other DES (and BMS) platforms may differ when stents are used in higher-risk patients and more complex lesions (as recently reported),\textsuperscript{28,29} although the same general principles would be expected to apply.

Conclusions and Clinical Implications

The present study demonstrates, as expected, that among patients with stable ischemic syndromes undergoing stent implantation in a single de novo, noncomplex native coronary artery lesion, a small increase in the risk of late ST with DES compared with BMS may result in an excess rate of death and nonfatal MI. However, by markedly reducing the high rates of restenosis that would have occurred after BMS implantation, DES may directly reduce the subsequent occurrence of
death and nonfatal MI, offsetting the incremental ST risk. These data emphasize the multifactorial causes of major adverse cardiovascular events after stent implantation and the complex interplay between the risks and benefits of new technologies such as DES on overall patient outcomes.

Source of Funding
The present study was funded in part by Boston Scientific Corp., Natick, Mass.

Disclosures
Dr Stone is a consultant to and has received lecture fees from Boston Scientific, Abbott Vascular, and Xtent; owns equity in Devax and Xtent; and is on the board of directors of Devax. Dr Ellis is a consultant to Boston Scientific. Dr Dawkins has received lecture fees and an unrestricted research grant from Boston Scientific. Drs Friedman, Baim, and Koglin are full-time employees of Boston Scientific. The other authors report no disclosures.

References
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*Circulation.* 2007;115:2842-2847; originally published online May 21, 2007; doi: 10.1161/CIRCULATIONAHA.106.687186

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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