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Late Clinical Events After Drug-Eluting Stents

The Interplay Between Stent-Related and Natural History-Driven Events

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Objectives We evaluated the relative contributions of drug-eluting stent-specific and background natural history-driven causes for adverse clinical events between 1 and 5 years, in the paclitaxel-eluting stent (PES) and bare-metal stent (BMS) cohorts of the TAXUS randomized clinical trial program.

Background Prior studies have demonstrated that clinical events in the first year after BMS are predominantly stent-related but thereafter tend to be driven more by atherosclerotic activity outside the stented segment. It is not known whether the same is true for PES.

Methods Annualized hazard rates (HRs) were calculated for major adverse events in 1,400 TAXUS and 1,397 BMS patients from the randomized and blinded TAXUS I, II, IV, and V trials (median 4.8-year follow-up).

Results Although target vessel revascularization (TVR) during the first year was driven by target lesion revascularization (TLR), TVR after 1 year involved similar numbers of TLR and non-TLR events. Moreover, the annualized HR for non-target lesion TVR and other major adverse events (including death, myocardial infarction, and stent thrombosis) were relatively constant beyond 1 year and not significantly different between PES and BMS.

Conclusions The low and similar late HR for many of the observed late events after BMS and PES suggests that many of the late events after PES reflect background disease activity outside the stented segment rather than stent-related events per se. Analyses of long-term drug-eluting stent outcomes should recognize and attempt to correct for this background event rate by using suitable BMS control subjects. (J Am Coll Cardiol Intv 2009;2:504–12) © 2009 by the American College of Cardiology Foundation

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Current reports on drug-eluting stents (DES) have focused on their ability to reduce restenosis at the target lesion without increasing short- or long-term adverse safety events such as death or myocardial infarction (MI) (1–10). Coronary atherosclerosis, however, is a diffuse and progressive disease, making it unlikely that focal treatment of any single coronary artery segment would prevent the continued occurrence of adverse events caused by disease progression at other (nonstented) sites. The ongoing rates of adverse cardiac events after DES implantation thus reflect the sum of events triggered within the stented segment (typically defined to include 5-mm margins on either end of the stent) and those triggered by atherosclerotic disease activity (stenosis progression or plaque rupture) outside the stented segment. In a seminal analysis of bare-metal stent (BMS) data, Cutlip et al. (11) showed that, although stent-related events predominated during the first year of follow-up, they became less common during years 2 through 5, as natural history-driven events outside the stented segment continued to contribute importantly to late adverse events. Approximately one-half of all target vessel revascularizations (TVRs) that occurred in years 2 to 5 were thus due to progression of disease at nonstented sites (non-target lesion target vessel revascularizations [TL TVRs]) rather than failure of the stent and its margins.

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As longer-term follow-up has become available for DES trials, increasing attention has been paid to late clinical events. However, it is important not to attribute all late adverse events solely to the stents themselves without more clearly understanding which late events are related to the stent itself rather than to ongoing activity of the underlying coronary artery disease outside the stented segment. Moreover, late catch-up in restenosis or effects on the adjacent vessel by DES might alter the relative proportion of stent-related to nonstent-related adverse events in comparison with that previously reported for BMS. This study thus compared the ongoing late event rates in the stented segment and nonstented segments for paclitaxel-eluting stents (PES) and BMS, on the basis of a pooled analysis from the TAXUS double-blinded randomized controlled studies.

Methods

Patient population and study design. We conducted a pooled analysis comparing the performance of the TAXUS Express paclitaxel-eluting slow-release stent (Boston Scientific Corp., Natick, Massachusetts) with BMS in patients with de novo coronary lesions treated in the TAXUS I, II, IV, and V studies (1–4). The TAXUS I, II, and IV trials enrolled patients with relatively simple de novo lesions, whereas the TAXUS V trial allowed enrollment of patients with more complex lesions (e.g., long lesions, smaller vessels). Follow-up is available for TAXUS I (n = 61), II (n = 266), and IV (n = 1,314) through 5 years and for TAXUS V (n = 1,156) through 4 years. Consistent definitions of clinical end points (TVR, target lesion revascularization [TLR], non-TL TLR, MI, and all-cause mortality) were used by the independent Clinical Events Committees across the TAXUS trials (1–4). Stent thrombosis (ST) was retrospectively adjudicated for all studies according to the Academic Research Council (ARC) definitions (12). The Q-wave myocardial infarctions (QWMIs) were classified by the Clinical Events Committee as to their involvement of the target vessel in TAXUS IV and V but was made by the authors blinded to stent identity (BMS or PES) in the TAXUS I (0 QWMI) and TAXUS II (7 QWMI) trials.

All studies were conducted according to Good Clinical Practice and were approved by their respective institutional review committees, with all patients having provided informed written consent.

Statistical analysis. All statistical analyses were performed by the Biostatistics Section of Clinical Sciences at Boston Scientific Corporation with SAS version 9.0 (Cary, North Carolina). Annualized hazard rates (HRs) were calculated for TVR, TLR, non-TL TVR, MI (including QWMI in target and nontarget vessels), all-cause mortality, and ARC definite or probable ST, with the person-time method, expressed as the event rate/100 patient-years (equivalent to the percent event rate/patient/year). Annualized HRs were calculated for the time periods 0 to 1 year and 2 to 5 years. Patients with multiple events occurring in different time periods were considered to have the event in each time period (e.g., a patient with MIs at 180 days and 1,000 days would be counted as having an MI in both the 0- to 1-year period and the 2- to 5-year period).

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
HR = hazard rate
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
QWMI = Q-wave myocardial infarction
ST = stent thrombosis
TL TVR = target lesion target vessel revascularization
TLR = target lesion revascularization
TVR = target vessel revascularization
VLST = very late stent thrombosis

The approximate Poisson method was used to calculate the 95% confidence intervals around the annualized HR. Hazard rate differences between groups were calculated with the log-rank test with significance set at $p < 0.05$. Similar calculations were performed for high-risk subgroups, including patients with medically treated diabetes, long lesions (>28 mm), small vessels (≤2.5 mm), and multiple stents compared with patients who did not have any of the previous characteristics (low-risk subgroup). Predictors for

clinical outcomes were assessed with backward step-wise Cox proportional hazards regression with significance set at $p < 0.05$. A value of $p < 0.1$ was required for the variable to be entered into the model, with the exception of treatment with PES, which was forced into the model.

Results

HRs for clinical end points during 5 years of follow-up. The annualized HR of death and MI were low and similar for PES and BMS during both the first year and subsequent

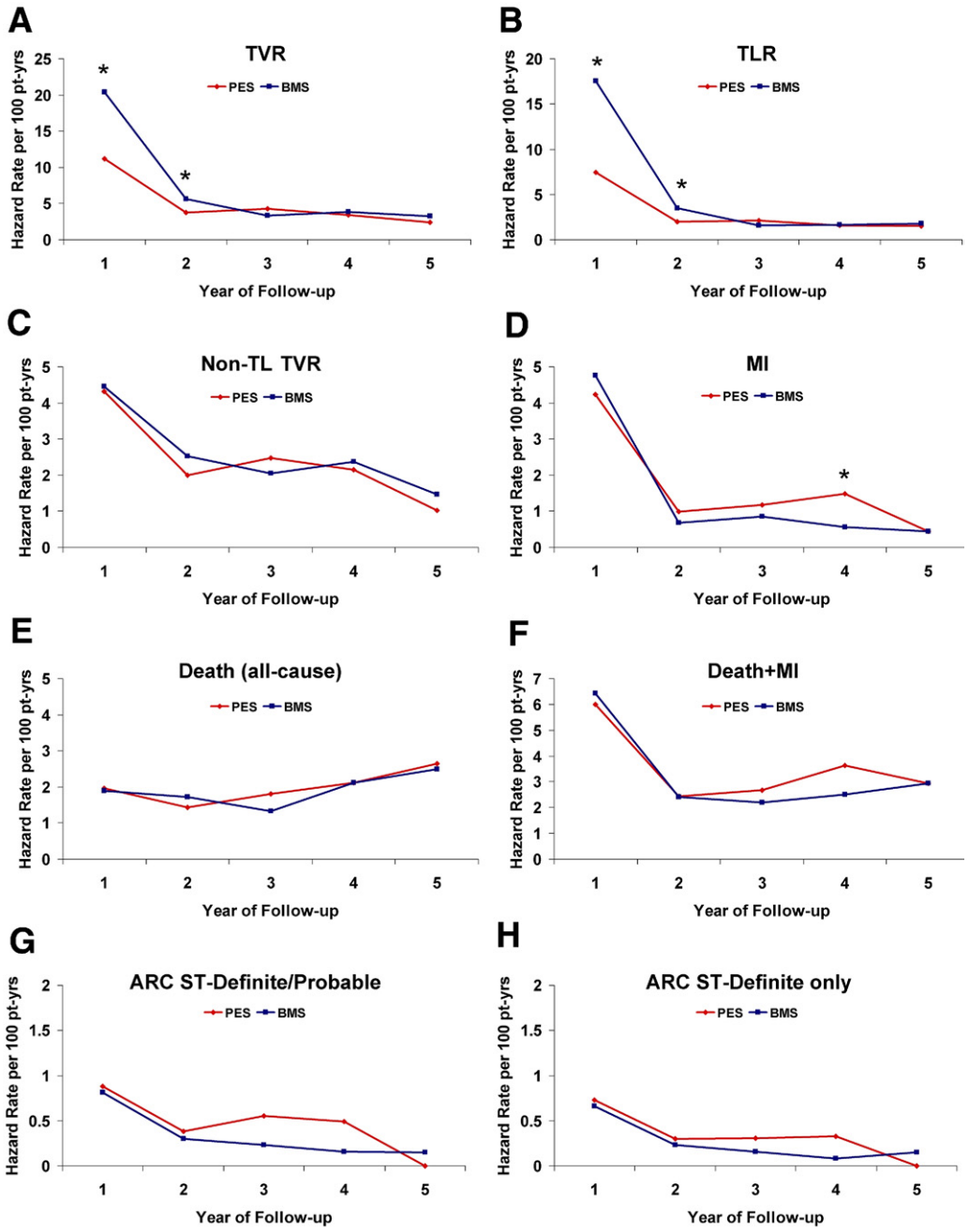

Figure 1. Hazard Rates for Clinical Outcomes by Year and Treatment Group for the Pooled TAXUS Trials

(A) Target vessel revascularization (TVR); **(B)** target lesion revascularization (TLR); **(C)** non-target lesion target vessel revascularization (TL TVR); **(D)** myocardial infarction (MI); **(E)** all-cause mortality; **(F)** all death+MI; **(G)** Academic Research Council (ARC) stent thrombosis (ST) definite+probable; **(H)** ARC ST definite only. BMS = bare-metal stent(s); PES = paclitaxel-eluting stent(s).

years 2 to 5, with the exception of an isolated slight increase in the HR for MI in PES in year 4. Overall, these data are consistent with the observation that PES do not increase the long-term risk of either death or MI (Figs. 1D to 1F, Table 1).

Hazard rates for ST, both ARC-definite and ARC-definite+probable, were also low and relatively constant. Although the annual HR was numerically greater in the PES compared with the BMS cohort (0.40% vs. 0.22%, p = 0.12) in years 2 to 5, there was no significant difference between BMS and PES throughout the follow-up period (Figs. 1G and 1H). The rates of clopidogrel use were similar between groups at hospital discharge and at years 1, 2, 3, 4, and 5 (Fig. 2).

Repeat revascularization. As previously described, PES treatment significantly reduced the HR of TVR versus BMS in year 1 and to a lesser extent during year 2 (1–4). Thereafter, the annualized HR for TVR remained low, relatively constant, and similar over time between PES and BMS (Fig. 1A, Table 1). The early difference in TVR was driven by the difference in TLR, which thereafter decreased for both stent types (Fig. 1B, Table 1). In contrast, the rate of TVR outside the stented segment and its margins (non-TL TVR) was relatively constant at approximately 2%/year in years 2 to 5, not differing significantly between PES and BMS and thus more consistent with the natural disease progression rather than a stent-specific effect (Figs. 1C and 1D, Table 1). Figure 3 demonstrates that these non-TL TVR events contributed equally with TLR to the low ongoing rate of TVR that occurs beyond year 1 in both the combined BMS and PES arms. Similar results were seen when BMS and PES were analyzed separately (data not shown).

QWMI rates in target and nontarget vessels. The annualized rates of overall QWMI, target vessel QWMI, and nontarget vessel QWMI were low and did not differ significantly between PES and BMS in either the first year or years 2 to 5 (Table 1). Of note, the annualized rate of QWMI in the non-target vessel (without either a DES or BMS) was similar to that of QWMI in the PES or BMS stented target vessel.

Scaling of event rates with markers of diffuse or aggressive disease. Hazard rates for TVR, TLR, and non-TL TVR during years 2 to 5 are generally increased in complex subgroups as compared with lower-risk patients without these risk factors (Figs. 4A to 4C), although these differences reached statistical significance only for diabetes (TVR) and for small vessels (TVR and non-TL TVR). The annual HRs for all-cause death after 1 year were generally low (approximately 1.9%/year) but were significantly increased in patients with diabetes (HR: 2.6, 95% confidence interval: 1.9 to 3.3, p = 0.01) (Fig. 4D). The annual HRs for MI also trended upward in the high-risk subgroups of both the PES and BMS groups, although it did not reach statistical significance (Fig. 4E). The incidence of ARC ST (definite+probable) in the years 2 to 5 of follow-up were too low to allow an accurate comparison of HRs across subgroups (Fig. 4F).

Taken together, the observation that the annual HR for non-TL TVR increases progressively (with parallel trends in MI) in the presence of these markers of diffuse or aggressive atherosclerosis and does so equally for both PES and BMS during years 2 to 5 supports these events being driven in common by background disease activity rather than by a stent-related etiology.

Table 1. Annualized HRs and Hazard Ratios With 95% CIs for PES and BMS in the Pooled TAXUS Clinical Trials

	Year 1				Years 2–5			
	Annualized HR, % (95% CI)				Annualized HR, % (95% CI)			
	BMS (n = 1,397)	PES (n = 1,400)	Hazard Ratio (95% CI)	p Value	BMS (n = 1,349)	PES (n = 1,345)	Hazard Ratio (95% CI)	p Value
TVR	20.4 (17.9–22.9)	11.2 (9.4–13.0)	0.55 (0.45–0.67)	<0.0001	3.8 (3.2–4.4)	3.3 (2.7–3.8)	0.87 (0.69–1.09)	0.21
TLR	17.6 (15.3–19.9)	7.5 (6.0–8.9)	0.42 (0.33–0.53)	<0.0001	2.0 (1.6–2.4)	1.6 (1.3–2.0)	0.81 (0.59–1.11)	0.19
Non-TL TVR	4.5 (3.3–5.6)	4.3 (3.2–5.4)	0.97 (0.68–1.39)	0.87	2.1 (1.7–2.5)	1.8 (1.4–2.2)	0.88 (0.65–1.19)	0.41
MI	4.8 (3.6–5.9)	4.2 (3.1–5.4)	0.89 (0.62–1.27)	0.52	0.6 (0.4–0.9)	1.0 (0.7–1.3)	1.59 (0.99–2.55)	0.054
QWMI	0.4 (0.1–0.7)	0.7 (0.2–1.1)	1.80 (0.60–5.38)	0.28	0.2 (0.1–0.3)	0.3 (0.1–0.4)	1.34 (0.57–3.19)	0.50
Target vessel	0.3 (0–0.6)	0.4 (0–0.8)	1.50 (0.42–5.32)	0.53	0.1 (0–0.2)	0.2 (0.1–0.3)	2.02 (0.61–6.70)	0.24
Nontarget vessel	0.1 (-0.1–0.2)	0.2 (0–0.5)	3.00 (0.31–28.87)	0.32	0.1 (0–0.2)	0.1 (0–0.2)	0.80 (0.22–2.99)	0.74
NQWMI	4.4 (3.2–5.5)	3.5 (2.5–4.6)	0.81 (0.55–1.19)	0.28	0.5 (0.3–0.7)	0.7 (0.5–1.0)	1.59 (0.92–2.74)	0.10
Death	1.9 (1.2–2.6)	2.0 (1.2–2.7)	1.04 (0.61–1.78)	0.89	1.8 (1.4–2.2)	1.9 (1.5–2.3)	1.04 (0.77–1.41)	0.79
Death or MI	6.4 (5.1–7.8)	6.0 (4.7–7.3)	0.93 (0.68–1.26)	0.64	2.4 (2.0–2.9)	2.8 (2.3–3.3)	1.15 (0.89–1.49)	0.29
ARC ST-definite/probable	0.8 (0.3–1.3)	0.9 (0.4–1.4)	1.09 (0.48–2.47)	0.83	0.2 (0.1–0.4)	0.4 (0.2–0.6)	1.82 (0.84–3.93)	0.12
ARC ST-definite	0.7 (0.2–1.1)	0.7 (0.3–1.2)	1.11 (0.45–2.74)	0.82	0.2 (0–0.3)	0.3 (0.1–0.4)	1.73 (0.68–4.38)	0.25

ARC = Academic Research Consortium; BMS = bare-metal stent(s); CI = confidence interval; HR = hazard rate; MI = myocardial infarction; NQWMI = non–Q-wave myocardial infarction; PES = paclitaxel-eluting stent(s); ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization.

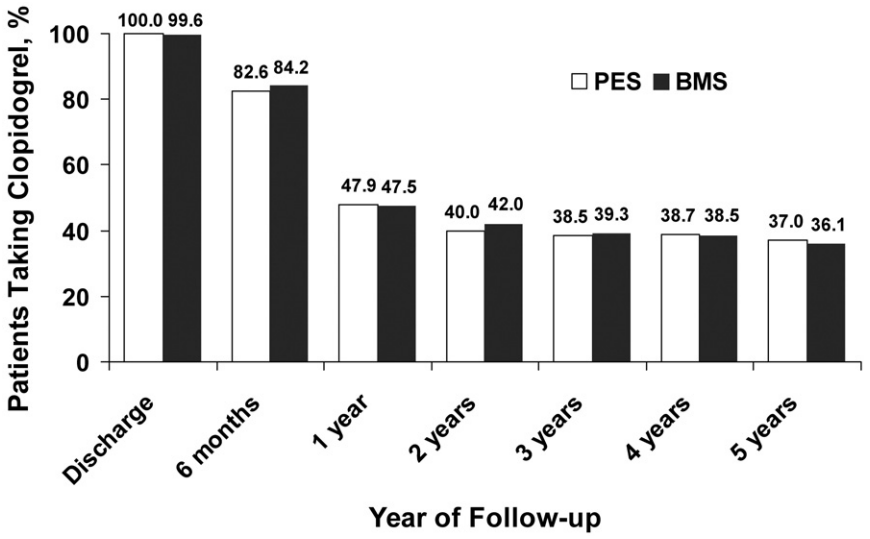

Figure 2. Clopidogrel Use Over Time for Patients Treated With DES or BMS

BMS = bare-metal stent(s); PES = paclitaxel-eluting stent(s).

Predictors of clinical outcomes in years 2 through 5. The PES treatment was forced into the multivariate models and was not an independent predictor of any of the adverse outcomes in years 2 to 5 (Table 2). Significant predictors for TVR, non-TL TVR, MI, and death were generally related to comorbid conditions (including patient risk factors for coronary artery disease) rather than to lesion-related characteristics or stent type (PES vs. BMS). Moreover, the fact that diabetes was a significant predictor of TVR (but not of TLR) further supports the importance of the aggressiveness of background natural history in driving late events.

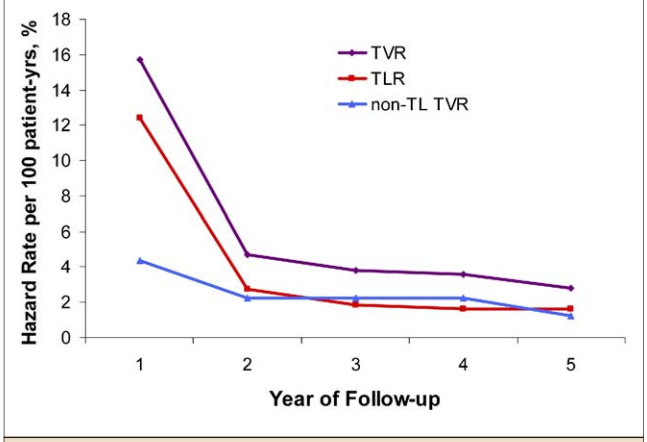

Figure 3. Hazard Rates for TVR and its Components, TLR and Non-TL TVR

Hazard rates for TVR and its components, TLR and non-TL TVR, by year for the combined BMS and DES groups in the pooled TAXUS trials. Abbreviations as in Figure 1.

Discussion

The results presented here for randomized PES and BMS patients parallel the earlier work of Cutlip et al. (11), on the basis of BMS alone, in demonstrating that many late adverse cardiac events occurring 2 to 5 years after coronary stenting are related to disease activity outside the stented segment rather than late failures of the stented segment itself. This is an important finding, because many studies of DES have attributed most or all of the late events to failure of these devices, with some early studies (13,14) suggesting increased late mortality not confirmed by later analyses (15,16).

The annual rates of death observed in this study beyond 1 year are similar to those reported by Cutlip et al. (11) in their pooled BMS analysis and those reported in coronary artery disease patients treated with medical therapy alone (17–23), including studies of primary prevention (24–28). Given the absence of stents in these patient populations and the similar rates in PES and BMS arms of the current study, these data support the observation that neither BMS nor DES alter the low annual event rates seen with medical therapy of stable coronary artery disease and that late death and MI after either type of stenting are primarily driven by the natural history of underlying atherosclerotic disease rather than by the stent itself.

The same observation can be made regarding late revascularization after stenting. The annual rate of repeat TVR in years 2 to 5 remained approximately 3.5% for both PES and BMS in the current study, with fully one-half of all such TVRs beyond 1 year related to disease progression outside

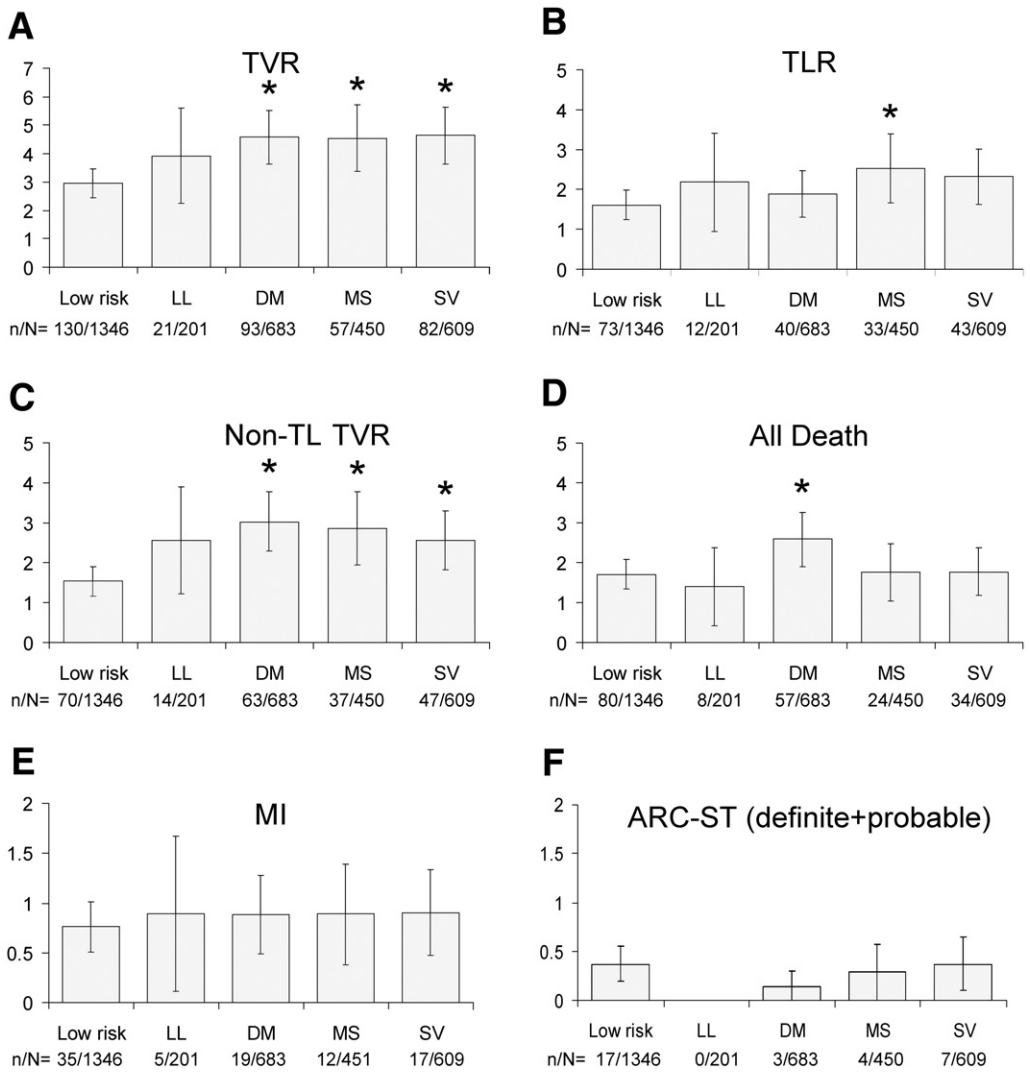

Figure 4. Mean ± SD HRs by Subgroup for Clinical Outcomes in Years 2 to 5 of Follow-Up for the Pooled TAXUS (BMS and DES Combined) Trials

(A) TVR; **(B)** TLR; **(C)** non-TL TVR; **(D)** all-cause mortality; **(E)** MI; **(F)** ARC ST definite/probable. $*p < 0.05$ versus patients with no risk factors. DM = medically treated diabetes mellitus; LL = long lesions; SV = small vessels; MS = multiple stents; other abbreviations as in Figure 1.

of the stented segment (the stent plus 5 mm proximal and distal margins).

Similarly, the overall annual risk of QWMI is low and roughly equal in PES and BMS (0.27%/year and 0.20%/year, respectively, p = 0.50). Approximately one-half of all late QWMIs occurred in nonstented vessels (thus completely unrelated to the stent), and annual HRs of cardiac adverse events (TVR, MI, and death) in years 2 to 5 were more closely associated with markers of diffuse or aggressive coronary artery disease (long lesions or diabetes) than stent type, consistent with disease-related rather than stent-related (or DES-specific) late events.

It is not clear whether this analysis can be extended to late and very late stent thrombosis (VLST) after DES. Wenaweser et al. (29) suggested a constant ongoing approximately 0.5%/year ST HR for DES during years 2 to 4 and assumed that this finding was unique to DES. Some meta-analyses have suggested that the frequency of VLST might be slightly higher for PES than BMS (30,31) or that DES might have increased ST events after withdrawal of thienopyridine treatment (32–34). In contrast, randomized trials in lower-risk patients comparing DES and BMS have shown essentially identical ST rates through 1 year and similarly low rates of late ST during years 2 through 5 (0.25%/year for BMS and 0.35%/year for PES), when the ARC definitions are employed (35). Brar et al. (36) and the TRITON–TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition

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Table 2. Multivariate Predictors of Clinical Outcomes During Years 2 Through 5 in the Pooled TAXUS Trials

Baseline Variable	Coefficient	Hazard Ratio (95% CI)	p Value
TVR			
Age	−0.02	0.98 (0.97–0.99)	0.004
Diabetes requiring medication	0.28	1.32 (1.02–1.69)	0.03
PES treatment*	−0.14	0.87 (0.69–1.10)	0.24
TLR			
Age	−0.03	0.97 (0.96–0.99)	<0.001
Lesion length	0.02	1.02 (1.00–1.04)	0.03
Pre-procedure reference vessel diameter	−0.34	0.71 (0.52–0.97)	0.03
PES treatment*	−0.20	0.82 (0.60–1.12)	0.20
Non-TL TVR			
Diabetes requiring medication	0.46	1.59 (1.15–2.19)	0.005
Hypertension treatment	0.40	1.49 (1.01–2.19)	0.04
PES treatment*	−0.14	0.87 (0.64–1.18)	0.37
MI			
Current smoker	0.74	2.10 (1.30–3.42)	0.003
Prior MI	0.60	1.82 (1.14–2.90)	0.01
PES treatment*	0.42	1.52 (0.95–2.45)	0.08
All-cause mortality			
Age	0.06	1.06 (1.05–1.08)	<0.001
Current smoker	0.74	2.10 (1.43–3.08)	<0.001
Hyperlipidemia treatment	−0.47	0.63 (0.46–0.86)	0.004
Pre-procedure % diameter stenosis	−0.02	0.98 (0.97–1.00)	0.02
Diabetes requiring medication	0.45	1.60 (1.06–2.31)	0.02
PES treatment*	−0.04	0.96 (0.71–1.31)	0.80
ARC ST (definite+probable)			
Age	−0.04	0.96 (0.92–0.99)	0.02
LAD lesion location	−1.0	0.37 (0.15–0.91)	0.03
PES treatment*	0.65	1.91 (0.88–4.14)	0.10

*Indicates variable was forced into the model.
Abbreviations as in Table 1.

with Prasugrel–Thrombolysis In Myocardial Infarction) (37) further demonstrate that more prolonged or more potent thienopyridine therapy can offer similar reduction of death, MI, and ST in both DES- and BMS-treated patients, suggesting a mechanism of benefit more via protection against natural history-driven (rather than stent-specific) events. In fact, 1 study showed a significant increase in death or MI in the 90 days after clopidogrel discontinuation for both BMS and medically treated (non-stented) acute coronary syndrome patients, suggesting that increased cardiac events after clopidogrel withdrawal is not unique to DES (38). The current study shows years 2 to 5 annualized HRs (and 95% confidence intervals) for ARC definite or probable ST of 0.2 (0.1 to 0.4) for BMS and 0.4 (0.2 to 0.6) for PES, with $p = 0.12$ for a difference and $p = 0.10$ for a stent-type effect in multivariate modeling. Absent sufficiently large and adequately-powered trials comparing DES with BMS, we cannot exclude that DES might have a differential need for more prolonged dual antiplatelet therapy to protect against potentially delayed or incomplete healing (39). By the same token, neither can we assume (without suitable BMS control subjects) that all ARC-defined VLST events occurring after DES reflect thrombosis initiated by the stent as opposed to natural history-driven plaque rupture occurring outside of the stented segment.

In that regard, 1 interesting finding of the current study is that the rate of QWMI in nonstented vessels was 0.09% to 0.11%/year and thus of the same magnitude as the rate of QWMI observed in BMS- or PES-treated vessels. Neither the ARC definite or probable ST definitions nor, in many cases, acute angiography can definitively distinguish whether the causative thrombus has been initiated within the stent (perhaps due to incomplete healing, poor apposition, or local inflammation) or by a ruptured plaque in the adjacent vessel outside the stent. The MIs resulting from plaque rupture would thus count as ARC ST (even if no stent were present), and their occurrence might explain some of the VLST events observed in BMS that are presumably well-healed by 1 year after implantation. Studies comparing DES with suitable BMS control subjects will

thus be needed to understand the relative roles of stent-specific DES VLST versus natural history-driven events and the potential benefit of more prolonged dual antiplatelet therapy against each problem (40).

There are several limitations to the current analysis. First, with the exception of the TAXUS V trial (which included vessels as small as 2.25 mm and lesions as long as 38 mm), only patients with relatively uncomplicated lesions were included. The results of this study thus might not be fully applicable to a broader patient population, although patients with more advanced disease would likely have an even greater relative contribution from natural history-driven events. By the same token, these results should not be compared directly with natural history studies that have not included more complex TAXUS V-like lesions. Second, event adjudication for the longer follow-up intervals (after 1 year) was more difficult, because of a limited ability to separate cardiac death from all-cause death, greater difficulty in determining the cause of late MIs, and reliance on the core angiographic laboratory to separate TLR from non-TL TVR. Third, there was not tight control of the use of acetylsalicylic acid or clopidogrel after 1 year to ascertain the potential benefit of sustained dual antiplatelet therapy on late cardiac events. By virtue of the double-blind design of the included studies, however, the dual antiplatelet therapy usage patterns remained comparable for PES and BMS throughout the follow-up period. Fourth, the TAXUS clinical trial program was not specifically designed to evaluate these low rates of late adverse events and would not be powered to detect small differences in these rates. Nonetheless, this is the largest randomized cohort of DES patients with long-term follow-up, and the analysis does provide unique insights into the relationship of late cardiac adverse events with DES versus BMS and the relative roles of stent-specific and natural history-driven late events. Similar data on long-term follow-up with DES versus BMS are only available for the Cypher sirolimus-eluting stent (Cordis, Johnson & Johnson Company, Miami Lakes, Florida) (41) and show analogous findings to the current study.

Conclusions

These data suggest that PES significantly reduce TLR (stent and 5 mm proximal and distal margins) during the first year after procedure but that they do not reduce the late ongoing 2% to 4% annual rate of repeat revascularization of the target vessel due to disease progression outside the stented zone. Late ongoing non-TL TVR, death, MI, and to some extent ARC-defined VLST occur at roughly equal rates in both DES and BMS but are increased in patients with markers of more diffuse or aggressive atherosclerosis. Clinical trials attempting to evaluate long-term DES outcomes must recognize and attempt to correct for these underlying natural history-driven events by using suitable BMS control subjects. At the same time, we should continue our efforts to develop pro-healing, next-generation DES designs that might reduce any DES-specific late events stemming from delayed or incomplete stent strut coverage.

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