Final 5-Year Results of the TAXUS II Trial

A Randomized Study to Assess the Effectiveness of Slow- and Moderate-Release Polymer-Based Paclitaxel-Eluting Stents for De Novo Coronary Artery Lesions

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Background—The TAXUS II trial was designed to evaluate the safety and efficacy of the commercialized slow-release (SR) and an investigation-only moderate-release (MR) polymer-based TAXUS paclitaxel-eluting stent compared with a bare-metal stent for the treatment of de novo coronary lesions.

Methods and Results—This prospective, randomized, double-blind, controlled trial enrolled 536 patients in 2 consecutive cohorts to compare TAXUS SR (n=131) and TAXUS MR (n=135) with an identical but uncoated bare-metal stent control (n=270). The present analysis reports final 5-year clinical outcomes of TAXUS II. At 5 years, both TAXUS SR and MR showed superior outcomes compared with control. The 5-year rates of major adverse cardiac events were 27.6%, 20.4%, and 15.1% ($P=0.01$); rates of target-vessel revascularization were 22.5%, 16.6%, and 9.0% ($P=0.004$); and rates of target-lesion revascularization were 18.4%, 10.3%, and 4.5% ($P<0.001$) for the control, TAXUS SR, and TAXUS MR groups, respectively. The rates of all-cause death and myocardial infarction were low and similar between groups, with 2 stent thromboses with bare-metal stents compared with no event beyond 2 years with either of the TAXUS stents.

Conclusions—TAXUS II is the first large TAXUS trial to have reached 5-year follow-up. Both the SR and MR stents lowered the rates of target-vessel and target-lesion revascularization, which indicates their sustained efficacy. Furthermore, the low overall rates of all death, myocardial infarction, and stent thrombosis support the long-term safety of the TAXUS stent system. **(*Circulation*. 2009;120:1498-1504.)**

Key Words: coronary disease ■ drugs ■ stents ■ restenosis

Bare-metal stents (BMS) have significantly improved the long-term success of balloon angioplasty by reducing restenosis and the need for subsequent revascularization[1,2]; however, their 20% to 40% restenosis rate hampered their effectiveness as a long-term treatment option for patients with coronary artery disease and created the difficult-to-treat condition of in-stent restenosis.[3] Because the underlying pathophysiological mechanism of in-stent restenosis is neointimal hyperplasia, stents that released antiproliferative agents were tested and have consistently shown significant benefit in further reducing restenosis compared with BMS.[4]

Clinical Perspective on p 1504

For the TAXUS paclitaxel-eluting stent, the series of pivotal trials began with the first-in-humans TAXUS I trial of the slow-release (SR) formulation of the polymer-based TAXUS paclitaxel-eluting stent, which showed a significant reduction in 6-month angiographic restenosis in patients with single de novo coronary lesions.[5] The TAXUS II trial described herein was designed to confirm the long-term safety and efficacy of both the SR and an investigational moderate-release (MR) TAXUS stent in a comparable patient population. As previously reported, the primary end point of 6-month percent in-stent net volume obstruction was significantly lower for the TAXUS stents than for control.[6] Additional follow-up quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) evaluations have established the safety profile of the TAXUS stent system[7–10] and documented its sustained efficacy for restenosis inhibition for up to 2 years.[11,12] This was associated with improved clinical outcomes, as evidenced by the lower rates of major adverse cardiac events (MACE), target-vessel revascularization

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(TVR), and target-lesion revascularization (TLR) at those earlier time points. The present report describes the safety and efficacy outcomes of TAXUS II at the final 5-year follow-up, as predefined in the original study protocol.

Methods

Patient Selection

TAXUS II was a prospective, randomized, double-blind, controlled trial conducted at 38 centers in 15 countries. The study design and methods have been described in detail previously.[6] Briefly, 536 patients with single de novo coronary lesions were randomly assigned (1:1) in 2 consecutive and independent cohorts. Patients in cohort I received the TAXUS SR paclitaxel-eluting stent or an uncoated control BMS of identical design, and those in cohort II received the TAXUS MR paclitaxel-eluting stent or the BMS. The study protocol was reviewed and approved by the ethics review committee of each participating center, and all patients provided written informed consent before enrollment. All patients agreed to not participate in any other trial for 5 years after enrollment to increase accountability and the purity of the data.

Polymer-Based Paclitaxel-Eluting Stent

The TAXUS stent was the NIRx Conformer (Boston Scientific Corp, Natick, Mass, and Medinol Ltd, Jerusalem, Israel), coated with a total loaded dose of paclitaxel 1.0 $\mu g/mm^2$ (loaded drug/stent surface area), incorporated into SR (8.8% drug-to-polymer ratio) or MR (25% drug-to-polymer ratio) formulations. Because of the greater surface density of paclitaxel, the MR formulation delivered a 3-fold greater amount of paclitaxel than the SR formulation.[6] The control stent was an identical but uncoated NIR stent (Boston Scientific Corp and Medinol Ltd). Study stents were 3.0 or 3.5 mm in diameter, 15 mm in length, and premounted on 20 mm balloon-delivery catheters.

Study Procedures

Stents were implanted after balloon predilation as described previously.[6] Per the study protocol, all patients received a 300 mg loading dose of clopidogrel before the procedure, followed by clopidogrel 75 mg/d (or ticlopidine 250 mg twice daily) for at least 6 months. Acetylsalicylic acid ≥75 mg was mandated for at least 12 months after the procedure and recommended indefinitely.

Follow-Up

Clinical follow-up was scheduled per protocol at 1, 6, and 12 months and yearly thereafter for 5 years. Angiographic and IVUS evaluations were scheduled at 6 months for the primary end point. A protocol amendment added an additional QCA and IVUS evaluation substudy at 2-year follow-up.[11] The objective was to establish the vascular responses to both the SR and MR TAXUS stents compared with BMS and, more specifically, to monitor the long-term safety of the TAXUS stents with regard to vascular remodeling, including incomplete apposition and coronary aneurysm.

QCA and IVUS

QCA and IVUS analyses were performed by an independent core laboratory (Cardialysis, BV, Rotterdam, Netherlands) as described previously.[6] Incomplete stent apposition was identified by IVUS and defined as separation of 1 or more stent struts from the vessel wall with evidence of blood flow behind the strut. Incomplete apposition at 2 years was considered "late acquired" if it was not present at the completion of the procedure and at 6-month follow-up.

Study End Points

The primary end point was a significant mean percent reduction of in-stent net volume obstruction at an 80% power (TAXUS stents versus BMS) determined by IVUS at 6 months.[6] Secondary end points were the rates of MACE, defined as cardiac death, myocardial infarction (MI), TVR, or stent thrombosis. Stent thrombosis was defined per protocol as angiographic evidence of a complete occlusion (Thrombolysis In Myocardial Infarction [TIMI] flow 0 or 1) or flow-limiting thrombus (TIMI flow 1 or 2) of the treated artery, or death within the first 30 days after the index procedure without other obvious cause. An event was defined as acute when it occurred ≤24 hours after the index procedure, subacute when it occurred >24 hours to ≤30 days after the index procedure, late when it occurred >30 to ≤365 days after the index procedure, and very late when it occurred >365 days after the index procedure. All potential MACE and stent thromboses were reviewed and adjudicated by a clinical events committee. Stent thrombosis was adjudicated according to the protocol definitions. Subsequently, stent thrombosis in the control and TAXUS SR groups was adjudicated according to the Academic Research Consortium definitions. Safety data were reviewed periodically by an independent data monitoring committee.

Statistical Analyses

The control patients in the 2 cohorts were combined because baseline and 6-month follow-up data showed no significant differences between the 2 control arms of both cohorts.[6] Therefore, 3 groups are reported in the present study: TAXUS SR, TAXUS MR, and the combined control groups. All analyses in the present report were based on the intent-to-treat principle. Comparisons between pairs of treatment groups were performed with a log-rank test for time-to-event variables and χ^2 or Fisher exact test for discrete measures. A P value <0.05 was considered statistically significant. All analyses were performed with SAS System software, version 8.2 (SAS Institute, Cary, NC).

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.

Results

A total of 536 patients were randomized to treatment with an uncoated control BMS (n=270), a TAXUS SR stent (n=131), or a TAXUS MR stent (n=135; Figure 1). The control and TAXUS groups were well matched for baseline demographics and clinical characteristics.[6] Follow-up at 5 years was available for 97.4%, 93.1%, and 91.9% of patients in the control, TAXUS SR, and TAXUS MR groups, respectively.

Safety Outcomes

The 5-year cumulative MACE rates and their components are presented in Table 1. The overall MACE rate was reduced significantly by 26% in the TAXUS SR group and by 45% in the TAXUS MR group compared with the control group. This beneficial effect was primarily attributable to a 26% reduction in the TVR rate by TAXUS SR and a 60% reduction by TAXUS MR. Twenty-eight patients died during follow-up (12 in the control group, 9 in TAXUS SR, and 7 in TAXUS MR), and 9 of these deaths were deemed by the clinical events committee to be cardiac in origin (4 in the control group, 3 in TAXUS SR, and 2 in TAXUS MR). Rates of MI were similar between groups (7.1% in the control group, 4.7% in TAXUS SR, and 5.3% in TAXUS MR), with the majority being non–Q-wave MI in the control and TAXUS SR groups. The 5-year cumulative rates for death or MI were similar between groups (Figure 2).

By the protocol definition, 8 cases of stent thrombosis were reported in 7 patients during the 5-year follow-up (2 in the control group, 3 in TAXUS SR, and 3 in TAXUS MR; Table 2), which resulted in Kaplan–Meier cumulative rates of 0.8%, 2.3%, and 1.5%, respectively (P=NS; Figure 3). The corre-

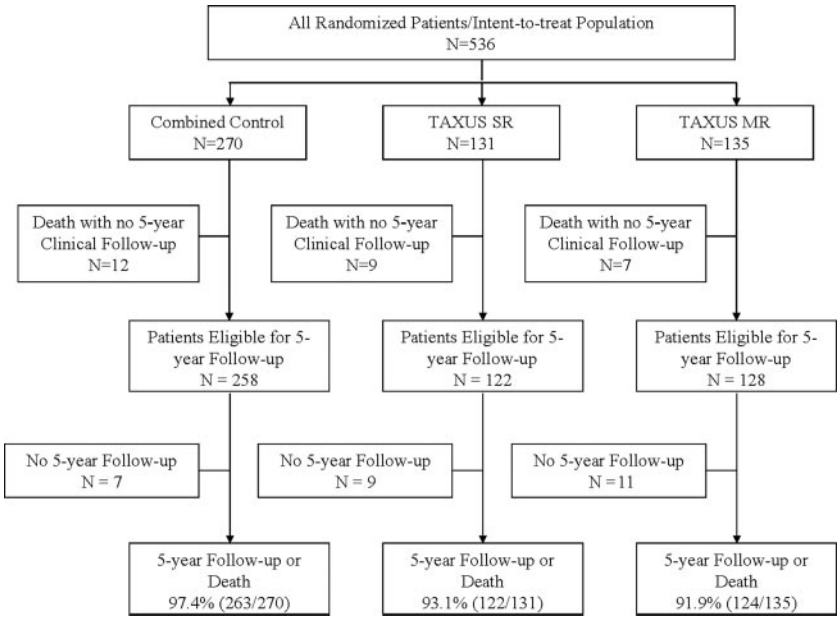

Figure 1. Flow of patients with regard to inclusion and follow-up rates.

sponding overall rates with the Academic Research Consortium definitions of definite or probable thrombosis were similar between the control (0.8%) and SR (2.3%; P=NS) groups. One stent thrombosis was acute (TAXUS SR), 2 stent thromboses were late (1 in TAXUS SR and 1 in TAXUS MR), and 5 were very late (2 in the control group, 1 in TAXUS SR, and 2 in TAXUS MR). One patient with a TAXUS MR stent had 2 stent thromboses at 317 and 558 days after the index procedure, respectively. Seven of 8 stent thromboses resulted in MI on the same day, but no deaths were observed for the duration of the study. Of note, no stent thrombosis occurred beyond 2 years with the TAXUS stents in contrast to 2 very late stent thromboses that occurred at 988 and 1756 days, respectively, in the control group (Table 3). Thienopyridine use was similar between groups at all time points (>97% at 1 month, >85% at 6 months, and 11% to 15% beyond 1 year), whereas more than 88% of patients were taking aspirin at 5-year follow-up. Except for the patient whose stent thrombosis occurred at 1756 days in the control group (whose antiplatelet therapy status was unknown), all patients were taking aspirin at the time of the event (Table 3).

Clinical Outcomes

Compared with the control group, the TLR rate was reduced by 44% in the TAXUS SR group (log-rank P=0.03) and by 76% in the TAXUS MR group (log-rank P<0.001). Of the 68 patients undergoing TLR, 59 underwent a repeat percutaneous coronary intervention, and 11 underwent a coronary artery bypass graft. The 5-year cumulative rates for TLR are presented in Figure 4.

Table 1. Cumulative Rates of MACE at 5-Year Follow-Up

	Control Group (n=270), % (n)	TAXUS SR (n=131), % (n)	TAXUS MR (n=135), % (n)	*P* (Log-Rank Test)			
				Overall	SR vs Control	MR vs Control	MR vs SR
MACE, overall	27.6 (74)	20.4 (26)	15.1 (20)	0.01	0.07	0.005	0.33
Cardiac death or MI	8.6 (23)	7.1 (9)	6.9 (9)	0.76	0.57	0.54	0.98
Cardiac death	1.5 (4)	2.4 (3)	1.6 (2)	0.82	0.55	0.98	0.64
MI	7.1 (19)	4.7 (6)	5.3 (7)	0.58	0.35	0.49	0.80
Q-wave MI	2.3 (6)	1.6 (2)	3.1 (4)	0.72	0.65	0.63	0.42
Non–Q-wave MI	4.9 (13)	3.9 (5)	2.2 (3)	0.46	0.66	0.21	0.45
TVR, overall	22.5 (60)	16.6 (21)	9.0 (12)	0.004	0.12	0.001	0.09
PCI	20.6 (55)	12.7 (16)	6.8 (9)	<0.001	0.04	<0.001	0.14
CABG	3.4 (9)	3.9 (5)	2.3 (3)	0.75	0.79	0.56	0.46
TLR, overall	18.4 (49)	10.3 (13)	4.5 (6)	<0.001	0.03	<0.001	0.09
PCI	16.5 (44)	7.9 (10)	3.7 (5)	<0.001	0.02	<0.001	0.18
CABG	2.6 (7)	2.3 (3)	0.7 (1)	0.47	0.87	0.22	0.30

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass graft.
Values are estimates of event rates from Kaplan–Meier analysis (No. of patients with event).

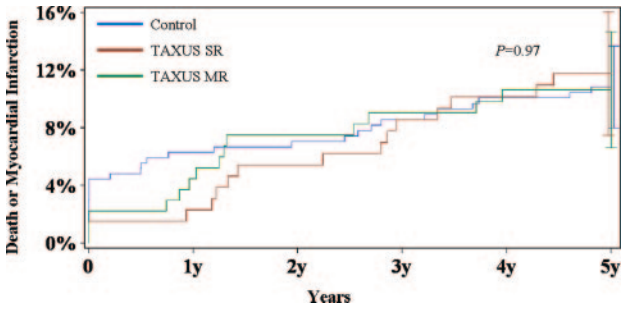

Figure 2. Kaplan–Meier estimates of 5-year cumulative rates of death or MI.

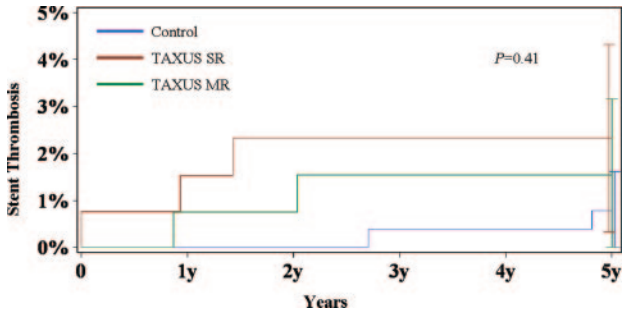

Figure 3. Kaplan–Meier estimates of 5-year cumulative rates of stent thrombosis.

Aneurysm and Incomplete Stent Apposition

Paired 6-month and 2-year QCA data on aneurysm formation and postprocedure, 6-month, and 2-year IVUS data on incomplete stent apposition were available for 208 patients in the QCA and IVUS substudy. At 2 years, the aneurysm observed in the patient from the control group at 6 months was persistent; however, the 3 aneurysms observed in the TAXUS groups (2 in TAXUS SR and 1 in TAXUS MR) at 6 months resolved by 2 years. The patient with the persistent aneurysm in the control group did not experience any MACE for the duration of the study.

At 2 years, 15 patients were identified with incomplete stent apposition: 9.0% (8/89) in the control group, 8.7% (4/46) in the TAXUS SR group, and 6.4% (3/47) in TAXUS MR group. Of these 15 patients, 3 (2 in the control and 1 in the TAXUS MR group) had shown complete stent apposition after the procedure and at 6-month follow-up, which indicates late-acquired malapposition. All 3 patients were taking aspirin, and none experienced any MACE for the duration of the study.

Discussion

The TAXUS paclitaxel-eluting stent family is supported by a robust series of randomized trials and registries.[13–16] TAXUS II is an important element because it was the first prospective, randomized, double-blind, controlled trial specifically designed to assess the long-term safety and efficacy of the TAXUS paclitaxel-eluting stent in the treatment of de novo coronary lesions. It is also the first trial to compare 2 different formulations of the TAXUS stents (the commercialized SR and an investigation-only higher-dose MR formulation), as well as the first large TAXUS trial to reach 5-year follow-up. The main findings of this final 5-year clinical follow-up are as follows: (1) TAXUS stents improve the rates of MACE, TVR, and TLR; (2) the MR formulation, which delivers a 3-fold greater amount of paclitaxel, was as effective as or more effective than the SR formulation, with equivalent safety events, thereby establishing a clear safety margin; (3) both TAXUS formulations were associated with low rates of death and MI; and (4) although the study was underpowered to detect differences in low-frequency events, there was no suggestion that either TAXUS formulation increased the incidence of stent thrombosis compared with control. No new events were observed beyond 2 years with either TAXUS formulation.

Previous reports of the TAXUS I and II trials have suggested good medium-term (2 years) safety and efficacy of TAXUS stents,[11,12,17] but the long-term safety of drug-eluting stents (DES) was still questioned.[18,19] The present study is therefore important because it provides a longer follow-up that demonstrates that patients treated with TAXUS SR and MR stents had continued efficacy benefits and ongoing safety compared with patients treated with BMS. Other larger trials have supported these observations,[13] and the clear safety margin of the higher-dose TAXUS MR formulation has been supported by a similar reduction in the rate of TVR (relative reduction of 37%) at 2-year follow-up in patients with long and complex coronary lesions. A similar safety margin has also been established in the higher-risk patients enrolled in the TAXUS VI trial.[20]

Among the angiographic and IVUS substudy patients, there was no increase in aneurysm or late-acquired malappo-

Table 2. Rates of Stent Thrombosis During 5-Year Follow-Up*

				P			
	Control (n=270)	TAXUS SR (n=131)	TAXUS MR (n=135)	Overall	SR vs Control	MR vs Control	MR vs SR
Overall	0.8 (2/251)	2.7 (3/113)	1.7 (2/117)	0.32	0.18†	0.59†	0.68†
Acute	0.0 (0/270)	0.8 (1/131)	0.0 (0/135)	0.24	0.33†	Undefined	0.49†
Subacute	0.0 (0/270)	0.0 (0/131)	0.0 (0/135)	Undefined	Undefined	Undefined	Undefined
Late	0.0 (0/269)	0.8 (1/131)	0.7 (1/135)	0.25	0.33†	0.33†	>0.99†
Very late	0.8 (2/265)	0.8 (1/130)	1.5 (2/132)	0.84	>0.99†	0.60†	>0.99†

Values are % (count/sample size) from binary analysis.
P values are from the χ^2 test of homogeneity or Fisher exact test.
*Events were adjudicated according to per protocol definitions.
†Fisher exact test was used.

Table 3. Antiplatelet Therapy in Patients With Stent Thrombosis*

Stent Type	Age, y/Sex	Treated Artery	Days to ST	Interval to ST	Aspirin at ST	Clopidogrel		Clinical Presentation	Outcome
						At ST	Days Off		
Control									
1	44/M	RCA	988	Very late	Yes	No	958	Q-wave MI	Alive
2	43/M	RCA	1756	Very late	Unknown	Unknown	Unknown	Non–Q-wave MI	Alive
TAXUS SR									
1	50/M	RCA	0	Acute	Yes	Yes	NA	Non–Q-wave MI	Alive
2	72/M	LAD	341	Late	Yes	No	179	Q-wave MI	Alive
3	59/M	RCA	522	Very late	Yes	No	362	Non–Q-wave MI	Alive
TAXUS MR									
1	56/M	LCx	317†	Late	Yes	No	163	Q-wave MI	Alive
2	54/F	RCA	743‡	Very late	Yes	No	582	NA	Alive

ST indicates stent thrombosis; M, male; F, female; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex artery; and NA, not available.

*Events were adjudicated according to per protocol definitions.

†Patient had another ST at 558 days.

‡ST occurred within 2-year follow-up window (60 days, per protocol).

sition compared with BMS. Furthermore, in patients treated with either the SR or MR formulation, there was no correlation between the aneurysms and incomplete stent apposition observed at 6 months or 2 years and the occurrence of MACE during the 5-year follow-up. Although the small numbers in the present study preclude definitive statements, there is no evidence that paclitaxel at the higher dose has an adverse impact on long-term remodeling. Although Boston Scientific Corporation chose the TAXUS SR formulation for commercial use (as the minimum effective formulation for the treatment of de novo lesions based on the 12-month follow-up of the present trial), there was a suggestion in both the present trial and TAXUS VI[20] that the 3-fold higher dose MR formulation may offer slightly greater antirestenotic potency. The fact that patients treated with the TAXUS MR stent were also free of adverse events through 5-year follow-up establishes a clear therapeutic safety margin for the SR formulation, which has been implanted in more than 4 million patients worldwide. The favorable results of the TAXUS paclitaxel-eluting stent family of trials cannot be extrapolated to other paclitaxel-eluting stents, which have used different polymers,[21,22] or polymer-free release, which showed complete loss of effect after 2 years despite initial positive results.[23,24]

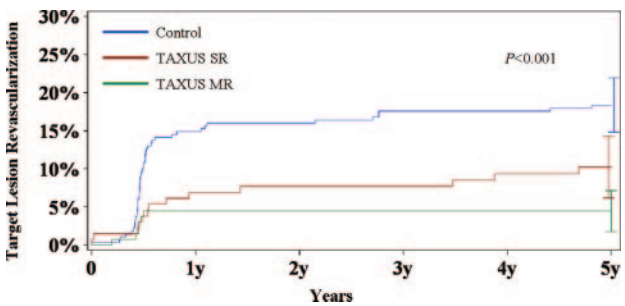

Figure 4. Kaplan–Meier estimates of 5-year cumulative rates of TLR.

Stent thrombosis remains an uncommon but serious complication of percutaneous coronary stenting with both BMS and DES. Because DES might interfere with or delay normal endothelial coverage, there has been concern that they are associated with a higher incidence of stent thrombosis than BMS.[25–27] Stent thrombosis rates of DES and BMS have proven virtually identical up to 1 year, albeit with more prolonged dual-antiplatelet therapy for DES versus BMS (3 to 6 months versus 1 month, respectively). Despite the lack of definitive evidence, the American College of Cardiology and American Heart Association recommend additional thienopyridine treatment, ideally for up to 12 months after DES implantation, in patients at low risk for bleeding.[28] Similarly, although a statistically significant increase in the occurrence of very late stent thrombosis with DES has not yet been demonstrated, many physicians elect to prescribe ongoing dual-antiplatelet therapy to protect against this possibility or atherothrombotic events at other sites.

Despite the pivotal role of the TAXUS II trial and its 5-year results, it is clearly underpowered to evaluate rare events, such as very late stent thrombosis. Of note, no patient treated with a TAXUS stent presented with a thrombotic event beyond 2 years, and the 2 stent thromboses in the control group occurred 32 and 58 months after the index procedure, respectively. Although this is not expected with arguably well-covered BMS, very late stent thrombosis with BMS has been reported previously.[29,30] In a TAXUS meta-analysis, the cumulative 1- to 4-year stent thrombosis rate was 0.6% with BMS and 1.3% with paclitaxel-eluting stents ($P=0.24$), which corresponds to an annual rate of stent thrombosis between 1 and 5 years of 0.25% for BMS and 0.35% for TAXUS SR ($P=0.40$).[31] If there is a small potential increase in the occurrence of late stent thrombosis, the lack of any adverse effect on the long-term safety outcomes of TAXUS stents may be due to the offsetting of adverse events such as death or acute MI due to the significant reduction of in-stent restenosis.[13,32]

The main benefit of a DES is a reduction in in-stent restenosis. This was evident in the primary end point of mean percent in-stent net volume obstruction by IVUS at 6 months. The superior IVUS and angiographic performance of both the TAXUS SR and MR stents, including a 64% reduction of neointimal obstruction within the stent,[6] was sustained at 2-year follow-up.[11,12] Although angiographic restenosis was not reevaluated at 5-year follow-up, its clinical correlate (repeat TLR) showed a sustained reduction by 44% (TAXUS SR) and 76% (TAXUS MR) compared with BMS, which suggests the sustained efficacy of TAXUS stents in reducing restenosis. Because the majority of TVRs and TLRs occur within the first 6 months after the index procedure, the sustained benefit at 5-year follow-up is evidence that there is no late catch-up in TLR, which supports the sustained efficacy of TAXUS stents.

The main limitations of the present study were the small sample size and the fact that it was powered to detect differences in the surrogate IVUS end point but not powered for clinical adverse events such as MACE, death, MI, or stent thrombosis. Also, the fact that the patients had relatively low-risk lesions prevents the conclusions of TAXUS II from being extrapolated to other, broader patient populations. Nonetheless, subsequent trials have evaluated TAXUS SR stents in more challenging anatomic and clinical situations.[15,16,33]

In conclusion, both the commercialized SR and the investigation-only higher-dose MR TAXUS stents had low and similar rates of cardiac death, MI, and stent thrombosis that were similar to those for BMS through 5 years of clinical follow-up. This supports the long-term safety profile of the SR formulation, showing a clear safety margin through the results of the 3-fold-higher-dose MR formulation. The initial 6-month and 2-year clinical benefits of TAXUS stents in reducing TLR were sustained, as demonstrated by the continued significantly lower rates of TLR compared with BMS through 5 years. Finally, within the limitations of a small trial, there was no evidence of increased late stent thrombosis with either the SR or MR stent, a finding supported by the patient-level meta-analysis of the TAXUS trials.[13]

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CLINICAL PERSPECTIVE

TAXUS II was the first randomized, double-blind, controlled trial specifically designed to assess the long-term safety and efficacy of the TAXUS paclitaxel-eluting stent for the treatment of de novo coronary artery lesions. It is also the first large TAXUS trial to reach 5-year follow-up and the first trial designed to compare the performance of the slow-release and an investigational moderate-release formulation of the TAXUS stent with an otherwise identical bare-metal stent. Through 5 years, both the slow- and moderate-release stents significantly lowered the rates of target-vessel and target-lesion revascularization without increasing the rates of death, myocardial infarction, or stent thrombosis compared with bare-metal stents. The absence of stent thrombosis beyond 2 years in the slow- and moderate-release stents with 2 events in the bare-metal stent arm provides reassurance that there is no excessive long-term risk of stent thrombosis with paclitaxel-eluting stents compared with bare-metal stents. Furthermore, the sustained reduction in revascularization rates up to 5 years with both the slow- and moderate-release stents provides evidence that there is no late catch-up phenomenon. Finally, the moderate-release formulation, which delivers a 3-fold greater amount of paclitaxel than the slow-release formulation, demonstrated equivalent safety through 5 years, thereby establishing a clear safety margin for the slow-release formulation, which has been implanted in more than 4 million patients worldwide.