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Stent Thrombosis in Drug-Eluting or Bare-Metal Stents in Patients Receiving Dual Antiplatelet Therapy

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CME Objective for This Article: At the completion of this article, the learner should be able to: 1) appraise the current perceptions of stent thrombosis and major adverse cardiovascular and cerebrovascular events in patients undergoing percutaneous coronary intervention with bare metal stents versus drug eluting stents; 2) compare the rates of stent thrombosis 0 to 33 months after stent deployment in DAPT study patients undergoing percutaneous coronary intervention with bare metal stents versus drug eluting stents; and 3) compare the rates of major adverse cardiovascular and cerebrovascular events 0 to 33 months after stent deployment in DAPT study patients undergoing percutaneous coronary intervention with bare metal stents versus drug eluting stents.

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Stent Thrombosis in Drug-Eluting or Bare-Metal Stents in Patients Receiving Dual Antiplatelet Therapy

ABSTRACT

OBJECTIVES This study sought to compare rates of stent thrombosis and major adverse cardiac and cerebrovascular events (MACCE) (composite of death, myocardial infarction, or stroke) after coronary stenting with drug-eluting stents (DES) versus bare-metal stents (BMS) in patients who participated in the DAPT (Dual Antiplatelet Therapy) study, an international multicenter randomized trial comparing 30 versus 12 months of dual antiplatelet therapy in subjects undergoing coronary stenting with either DES or BMS.

BACKGROUND Despite antirestenotic efficacy of coronary DES compared with BMS, the relative risk of stent thrombosis and adverse cardiovascular events is unclear. Many clinicians perceive BMS to be associated with fewer adverse ischemic events and to require shorter-duration dual antiplatelet therapy than DES.

METHODS Prospective propensity-matched analysis of subjects enrolled into a randomized trial of dual antiplatelet therapy duration was performed. DES- and BMS-treated subjects were propensity-score matched in a many-to-one fashion. The study design was observational for all subjects 0 to 12 months following stenting. A subset of eligible subjects without major ischemic or bleeding events were randomized at 12 months to continued thienopyridine versus placebo; all subjects were followed through 33 months.

RESULTS Among 10,026 propensity-matched subjects, DES-treated subjects (n = 8,308) had a lower rate of stent thrombosis through 33 months compared with BMS-treated subjects (n = 1,718, 1.7% vs. 2.6%; weighted risk difference −1.1%, p = 0.01) and a noninferior rate of MACCE (11.4% vs. 13.2%, respectively, weighted risk difference −1.8%, p = 0.053, noninferiority p < 0.001).

CONCLUSIONS DES-treated subjects have long-term rates of stent thrombosis that are lower than BMS-treated subjects. (The Dual Antiplatelet Therapy Study [DAPT study]; NCT00977938) (J Am Coll Cardiol Intv 2015;8:1552–62)

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndromes

BMS = bare-metal stent(s)

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

MACCE = major adverse cardiovascular and cerebrovascular events

PCI = percutaneous coronary intervention

PES = paclitaxel-eluting stent(s)

RD = risk difference

STEMI = ST-segment elevation myocardial infarction

Although drug-eluting stents (DES) have reduced restenosis when compared with bare-metal stents (BMS) for percutaneous coronary intervention (PCI), the relative hazard for stent thrombosis, a potentially catastrophic event, is uncertain. Previous randomized data indicated a higher risk of stent thrombosis after 1 year with DES (1,2), yet more recent studies suggest a lower risk when compared with BMS (3–5). Whether these findings are applicable to a broader range of clinical indications is unknown.

Although current clinical practice guidelines recommend a minimum of only 1 month of dual antiplatelet therapy after BMS placement following elective PCI (compared with 6 to 12 months for DES) (6,7), patients with acute coronary syndromes (ACS) benefit from 12 months of therapy whether or not PCI with stenting is performed (8). A recent randomized trial (DAPT [Dual Antiplatelet Therapy]) demonstrated a reduction in stent thrombosis and non-stent-related myocardial infarction with thienopyridine therapy beyond 12 months following DES placement (9), and consistent findings among a smaller cohort of BMS-treated subjects, which included an increase in bleeding (10). Because BMS remain a commonly used alternative treatment strategy to DES, particularly for patients who present with ACS or in whom dual antiplatelet therapy has a perceived increased bleeding risk (11,12), we aimed to determine whether the risks of stent thrombosis and non-stent-related adverse cardiovascular events differ for BMS and DES in a powered, prospective, comparative analysis.

METHODS

STUDY DESIGN. The DAPT study design has previously been described (13). This double-blind, international randomized controlled trial (NCT00977938) compared the risks and benefits of continued thienopyridine (clopidogrel or prasugrel) versus placebo, when given in addition to aspirin for the prevention of stent thrombosis or major adverse cardiovascular and cerebrovascular events (MACCE) following coronary stenting with either DES or BMS. The results comparing continued thienopyridine versus placebo (randomized treatment) in each of the DES- and BMS-treated cohorts have been reported separately (9,10). Choice of stent type (DES or BMS) was not randomly assigned, although study inclusion/exclusion criteria (including lack of contraindication to DAPT therapy) were similar for both stent types. A prospective secondary analysis was designed to compare rates of stent thrombosis and MACCE between DES- and BMS-treated subjects who were both eligible to receive DAPT for at least 1 year after the index procedure.

All institutions received approval from their institutional review boards, and each subject provided written informed consent for study participation.

STUDY OBJECTIVES AND HYPOTHESIS. We hypothesized that DES-treated subjects would have stent thrombosis and MACCE (composite of death, myocardial infarction, or stroke) rates that were noninferior to those of BMS-treated subjects through 33 months following the index stent procedure.

STUDY POPULATION AND PROCEDURES. In brief, subjects who were candidates for dual antiplatelet

CSL-Behring, Daiichi-Sankyo-Lilly, GlaxoSmithKline, Janssen, Medtronic, Merck-Sharpe Dohme, Novartis, Pfizer, Regeneron, Sanofi, Servier, and The Medicines Company; and is a stockholder in Aterovax. Dr. Gershlick has received lecture fees and travel bursaries from Medtronic, The Medicines Company, AstraZeneca, and Abbott Vascular. Dr. Meredith is an international proctor for the Lotus Valve for Boston Scientific; and is on the Scientific Advisory Boards of Boston Scientific and Medtronic. Dr. Ormiston is on the advisory board of and receives minor honoraria from Boston Scientific. Dr. Tanguay has received consultant's fees/honoraria and research funding from Abbott Vascular, AstraZeneca, and Eli Lily and Company. Dr. Windecker has received research funding (to his institution) from Abbott, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, The Medicines Company, and St. Jude Medical; and has received speaker's fees from AstraZeneca, Eli Lilly and Company, Abbott, Biotronik, Boston Scientific, Medtronic, and Bayer. Dr. Garratt is a consultant for Boston Scientific, Daiichi-Sankyo/Lilly, The Medicines Company, AstraZeneca, Abbott Vascular; and receives research support from Abbott Vascular, CeloNova; and has equity in Infarct Reduction Technologies, Guided Delivery Systems, and Arstasis. Dr. Kandzari has received research/grant support from Medtronic, Boston Scientific, and Biotronik; and has received consulting honoraria from Medtronic and Boston Scientific. Dr. Lee is a consultant to and receives research funding from Boston Scientific. Dr. Simon is on the Advisory Board of Medtronic. Dr. Mauri has received grants (to her institution) from Abbott, Boston Scientific, Cordis, Medtronic, Eli Lilly and Company, Daiichi Sankyo, Sanofi, Bristol-Myers Squibb, and Biotronik; and is a consultant for Medtronic, Eli Lilly and Company, Boehringer Ingelheim, AstraZeneca, and Biotronik. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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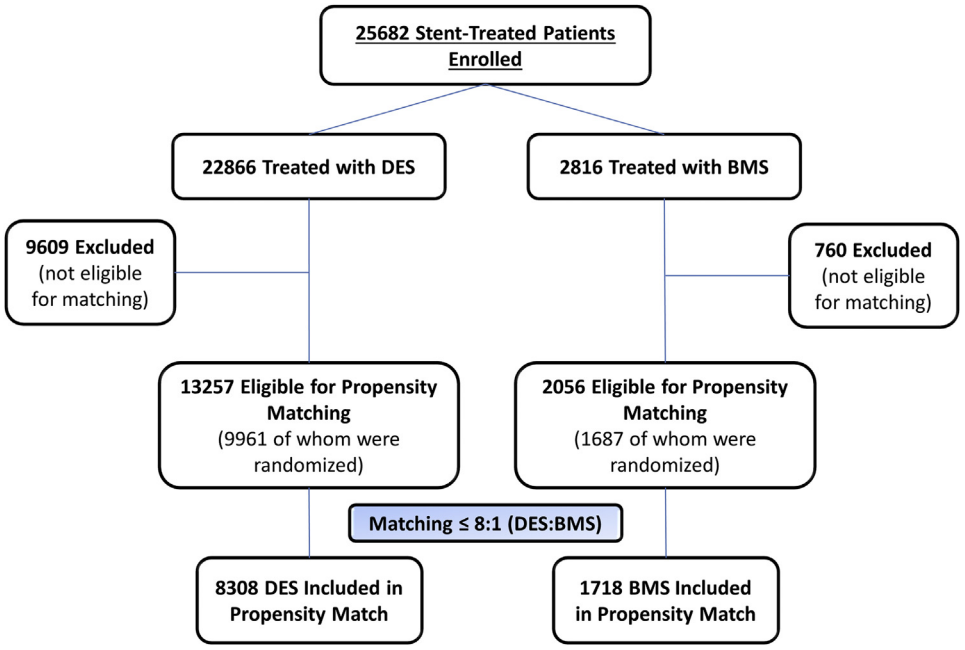
FIGURE 1 Subject Flow Diagram



Disposition of subjects in the study. A BMS-treated subject was matched to a variable number of DES-treated subjects without replacement, up to a maximum of 8. BMS = bare-metal stent(s); DES = drug-eluting stent(s).

therapy and who received treatment with either DES or BMS were recruited. Stent treatment was performed according to site standards of care using only Food and Drug Administration–approved DES and BMS devices. DES types included Cypher sirolimus-eluting stent (Cordis, Warren, New Jersey), Endeavor zotarolimus-eluting stent (Medtronic, Santa Rosa, California), TAXUS paclitaxel-eluting stent (Boston Scientific, Marlborough, Massachusetts), and Xience/Promus everolimus-eluting stents (Abbott Vascular, Santa Clara, California, or Boston Scientific). DES-treated subjects were those who received DES at the index procedure, regardless of any other type of stent received at or after the index procedure. BMS-treated subjects were those treated with BMS only, during the index procedure or the following 6 weeks. All subjects signed the consent and were enrolled into the trial within 3 days of the index procedure, and all received open-label aspirin plus thienopyridine (either clopidogrel or prasugrel) for the first 12 months. At 12 months, subjects who were alive and free from myocardial infarction, stroke, repeat coronary revascularization, stent thrombosis, and moderate or severe bleeding and who demonstrated compliance with thienopyridine treatment (defined as having taken 80% to 120% of the drug without an interruption of longer than 14 days) were then eligible for randomization to continued thienopyridine or placebo, and all continued aspirin.

PROPENSITY ANALYSIS COHORT. Because DES use was more prevalent than BMS use during the time of enrollment, we employed a propensity-matched study design for DES-BMS comparisons rather than randomization to stent type, but required the same inclusion criteria for DES- and BMS-treated subjects (13). The propensity analysis cohort included enrolled subjects (randomized or not). The DAPT study utilized uniform enrollment and randomization criteria, and central endpoint adjudication, yet allowed enrollment via 5 contributing studies (13). Although all randomized subjects were to be followed for 33 months regardless of the study source, in 2 contributing studies subjects who were not randomized were not followed beyond 12 months (Xience V USA DAPT [XIENCE V USA Dual Antiplatelet Therapy (DAPT) Cohort], NCT01106534; EDUCATE [EDUCATE: The MEDTRONIC Endeavor Drug Eluting Stenting: Understanding Care, Antiplatelet Agents and Thrombotic Events], NCT01069003), and in 3 of the contributing studies, subjects were consented for follow-up through 33 months regardless of randomization status (TAXUS Libertē Post Approval Study,

TABLE 1 Propensity Analysis Cohort Baseline Characteristics

Measure*	Before Match		After Match (Weighted for match ratio)		
	DES (n = 13,257)	BMS (n = 2,056)	DES (n = 8,308)	BMS (n = 1,718)	Standardized Difference
Clinical characteristics					
Age, yrs, mean	61.9	59.8	60.6	60.3	0.035
Female	27.0	25.6	26.4	26.4	0.000
Race, non-white†	10.0	8.1	9.0	8.6	0.014
Hispanic or Latino ethnic group	3.7	5.1	4.8	4.7	0.005
Weight, kg, mean	91.0	88.2	89.5	88.7	0.054
BMI, kg/m^2, mean	30.4	29.6	29.8	29.8	−0.004
Diabetes mellitus	32.0	23.8	25.8	25.6	0.005
Hypertension	76.3	67.0	69.7	69.6	0.002
Cigarette smoker	25.0	42.2	36.5	38.7	−0.045
Stroke/TIA	3.4	4.9	4.4	5.0	−0.028
Congestive heart failure	5.6	4.8	5.2	5.0	0.009
Peripheral arterial disease	6.6	6.0	6.5	6.4	0.004
Prior PCI	33.4	20.2	23.2	22.7	0.012
Prior CABG	13.1	7.5	8.3	8.3	0.000
Previous MI	22.6	20.5	21.0	21.6	−0.015
Positive stress test	40.3	20.7	28.6	24.2	0.100
Indication for PCI					
STEMI	10.5	36.1	27.6	27.6	0.000
NSTEMI	15.1	20.8	20.6	21.9	−0.032
Stable angina	37.5	23.5	28.1	27.8	0.007
Unstable angina‡	18.0	9.8	11.3	11.4	−0.003
Other	18.9	9.8	12.4	11.3	0.034
Procedure characteristics					
Number of treated lesions per subject, mean	1.3	1.2	1.2	1.2	0.047
Number of treated vessels per subject, mean	1.1	1.1	1.1	1.1	0.028
Treated vessel(s)					
Native coronary	96.4	96.5	96.4	96.3	0.005
Left main	1.0	0.3	0.8	0.3	0.057
LAD	40.6	30.4	33.2	31.8	0.030
RCA	31.7	45.3	39.2	42.9	−0.075
Circumflex	23.1	20.6	23.3	21.3	0.048
Venous graft	2.9	3.5	3.1	3.7	−0.033
Arterial graft	0.7	0.0	0.6	0.1	0.100
Modified ACC/AHA lesion class B2 or C	47.0	50.6	48.7	48.7	0.000
Number of stents per subject, mean	1.5	1.3	1.4	1.3	0.051
Minimum stent diameter, mm, per subject					
<3	48.9	25.5	30.3	28.9	0.031
3	30.1	32.2	32.0	32.7	−0.015
>3	21.0	42.3	37.7	38.5	−0.016
Total stent length, mm, per subject, mean	28.5	23.9	24.6	24.2	0.038
Prasugrel at discharge	38.7	12.8	16.6	15.0	0.044
Clopidogrel at discharge	61.3	87.2	83.4	85.0	−0.044

Values are %, except as noted. Characteristics are shown among drug-eluting stent– and bare-metal stent-treated subjects before and after propensity matching. After match, means, proportions, and standardized differences are weighted for the variable match ratio. *For most variables, 0% to 3% of subjects had missing values; 23% of patients were missing stress test information due to the variable not being collected in one contributing study. †Race and ethnic group were self-reported. ‡This category included unstable angina without reported elevation of cardiac enzymes.

ACC = American College of Cardiology; AHA = American Heart Association; BMI = body mass index; BMS = bare-metal stent(s); CABG = coronary artery bypass graft; DES = drug-eluting stent(s); LAD = left anterior descending coronary artery; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

NCT00997503; CYPRESS [CYPHER for Evaluating Sustained Safety], NCT00954707; The Dual Antiplatelet Therapy [DAPT] Study, NCT00977938). Subjects enrolled in the latter 3 studies were therefore considered eligible for propensity-matched analysis and evaluation of 0- to 33-month data. The present analysis is restricted to those subjects who reached at least the 30-month follow-up visit window (30 months ± 30 days), or those who had experienced a stent thrombosis or MACCE event before that time, in order to ensure comparable follow-up duration between analysis groups.

STUDY ENDPOINTS. The effectiveness endpoints were cumulative incidence of definite/probable stent thrombosis (14) and incidence of MACCE at 0 to 33 months in the propensity-matched DES versus BMS comparison. These events were adjudicated by an independent clinical events committee blinded to treatment assignment and administered by Harvard Clinical Research Institute. An unblinded independent central data monitoring committee oversaw the safety of all subjects.

STATISTICAL ANALYSIS. Due to the nonrandomized nature of DES versus BMS comparisons, differences between DES- and BMS-treated subjects with respect to distribution of baseline characteristics were expected (11,12). To account for this, the primary analysis was conducted on a subsample created by matching BMS- to DES-treated subjects exactly on prevalence of ST-segment elevation myocardial infarction (STEMI) and then matching on remaining baseline characteristics via propensity score, using a caliper width of 0.10. A BMS-treated subject was matched to a variable number of DES-treated subjects without replacement, up to a maximum of 8 (15). The 55 variables used in propensity score matching are listed in Online Figure 1. To assess the adequacy of the match, weighted standardized differences in clinical characteristics between groups were calculated, with absolute differences of <10% considered evidence of balance. Additional secondary events not expected to differ between DES after match and BMS were compared to assess for residual confounding. These included moderate or severe bleeding (GUSTO [Global Utilization of Streptokinase and TPA for Occluded Arteries] classification) (16) at 12 to 30 months, stroke, and non-stent thrombosis-related myocardial infarction.

BMS and weighted DES event rates were calculated, where the DES subject weight was the inverse of the number of DES subjects matched to the same BMS subject. Noninferiority was assessed via risk differences (RDs) using the Nam and Kwon (17) method to account for sample size and for

TABLE 2 Propensity Analysis Cohort Baseline Stent Thrombosis Risk Factors

Measure	Before Match		After Match (Weighted for Match Ratio)		
	DES (n = 13,257)	BMS (n = 2,056)	DES (n = 8,308)	BMS (n = 1,718)	Standardized Difference
Any clinical	32.1	62.4	54.8	55.7	−0.018
Enzyme-positive ACS (STEMI or NSTEMI)	25.6	56.9	48.2	49.5	−0.026
Renal insufficiency/failure	4.8	4.0	4.0	3.9	0.005
LVEF <30%*	1.9	4.2	3.5	3.5	0.000
Any lesion-related	33.3	37.9	33.7	33.7	0.000
>2 vessels stented	0.5	0.0	0.1	0.1	0.000
>2 lesions per vessel	2.3	1.2	1.4	1.3	0.009
Lesion length ≥30 mm*	11.1	6.6	7.0	6.7	0.012
Bifurcation lesion side branch ≥2.5 mm	6.0	4.4	4.9	4.7	0.009
In-stent restenosis of a DES	4.5	0.8	1.1	0.9	0.020
Vein bypass graft stented	3.4	3.6	3.4	3.8	−0.021
Unprotected left main stented	0.6	0.1	0.2	0.2	0.000
Thrombus-containing lesion	10.5	25.6	20.1	20.1	0.000
Prior brachytherapy	0.3	0.1	0.1	0.1	0.000
Any risk factor	51.8	69.3	64.0	63.9	0.002

Values are %. *For most variables, 0% to 3% of subjects had missing values; 6% of patients were missing LVEF.
ACS = acute coronary syndrome; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

correlation of subjects within each matched cohort (this RD does not necessarily equal the difference between BMS and weighted DES event rates). Noninferiority margins of 0.97% for stent thrombosis and 2.28% for MACCE were used. After noninferiority was met, we subsequently conducted a 2-sided test for difference at the 0.05 significance level. As a secondary analysis, the crude rates of events between groups and propensity-adjusted noninferiority analysis were performed on all eligible DES- and BMS-treated subjects (Online Table 1, Online Methods Section 2.3).

Also, given recent randomized data indicating lower rates of stent thrombosis with newer (everolimus- and zotarolimus-eluting) compared with older (paclitaxel- and sirolimus-eluting) DES, we examined the consistency of the stent thrombosis comparison to BMS by individual DES type (18,19). Finally, we estimated the effect of a possible unmeasured confounder using a Bayesian probabilistic approach based on Monte Carlo (Markov Chain Monte Carlo) sampling (20), and convergence of the Markov Chain Monte Carlo sampler using the Brooks-Gelman-Rubin method (21) assuming: 1) independence of the possible confounder from all measured covariates; 2) an odds ratio on each outcome that could range from one-third to 3; and 3) with prevalence of 30% versus 70% between the 2 treatment groups. All analyses presented were pre-specified except this sensitivity analysis evaluation of consistency of treatment effect across DES types (vs. BMS), and comparison of 12-month outcomes between DES and BMS.

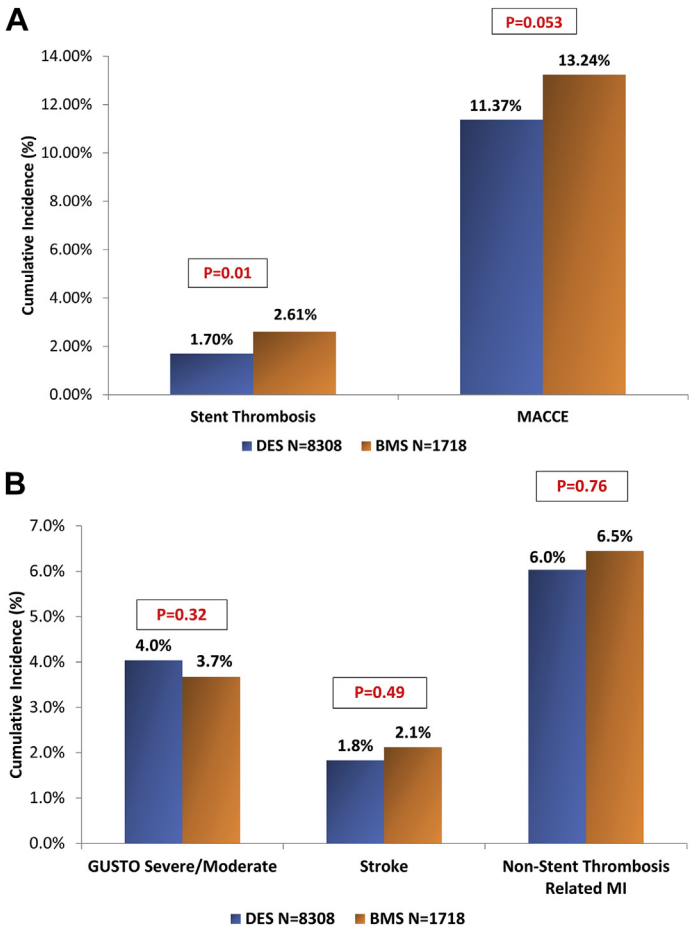
All statistical analyses were conducted at Harvard Clinical Research Institute with SAS software, version 9.2. (SAS Institute, Cary, North Carolina), and for Markov Chain Monte Carlo sampling, JAGS Software version 3.4.0. Noninferiority p values are 1-sided and are considered significant at the 0.025

TABLE 3 Primary Outcomes: Stent Thrombosis and MACCE at 0 to 33 Months Among Propensity-Matched Subjects Treated With DES or BMS

	DES (n = 8,308)	BMS (n = 1,718)	Weighted Risk Difference	1-Sided 97.5% Upper CL	1-Sided p Value Noninferiority	p Value for Difference
Stent thrombosis	1.7	2.6	−1.1	−0.27	<0.001	0.01
Definite	1.4	2.5	−1.1			0.01
Probable	0.3	0.13	0.1			0.56
MACCE (death, MI, stroke)	11.4	13.2	−1.8	0.03	<0.001	0.053
Death	4.2	5.1	−0.8			0.16
Cardiac	2.4	2.9	−0.6			0.19
Vascular	0.3	0.3	0.1			0.64
Noncardiovascular	1.6	2.0	−0.3			0.39
MI	7.2	8.1	−0.8			0.27
Stroke (total)	1.8	2.1	−0.2			0.49
Ischemic	1.5	1.6	−0.1			0.67
Hemorrhagic	0.4	0.4	0.1			0.75
Uncertain type	0.05	0.3	−0.2			0.12

Values are %. Drug-eluting stent outcome rates and risk differences are weighted according to the matched set. The 1-sided tests of noninferiority on the co-primary endpoints of stent thrombosis and MACCE were based on noninferiority margins of 0.97% and 2.28%, respectively.
CL = confidence limit; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; other abbreviations as in Table 1.

FIGURE 2 Propensity-Matched DES and BMS Subjects, 0 to 33 Months Follow-Up



(A) Stent thrombosis and MACCE. **(B)** Events not related to stent. MACCE = major adverse cardiovascular and cerebrovascular events; MI = myocardial infarction; other abbreviations as in Figure 1.

level; all other p values are 2-sided and considered significant at the 0.05 level.

RESULTS

STUDY POPULATION. Enrollment in the DAPT study was conducted between August 2009 and July 2011. A total of 13,257 DES-treated and 2,056 BMS-treated subjects were eligible for propensity matching, with a median follow-up of 990 and 990 days, respectively (Figure 1). Results comparing only randomized subjects (continued thienopyridine or placebo) have been reported separately (9,10).

Although the same inclusion and exclusion criteria were applied to all enrolled subjects, DES- and BMS-treated subjects differed according to clinical and procedural characteristics (Table 1). DES-treated subjects were more likely to have a history of diabetes mellitus, hypertension, previous PCI, and to have longer lesions, with smaller reference vessel diameter, whereas BMS-treated subjects were more likely to present with STEMI, or non-STEMI, and have evidence of thrombus in the treated lesion.

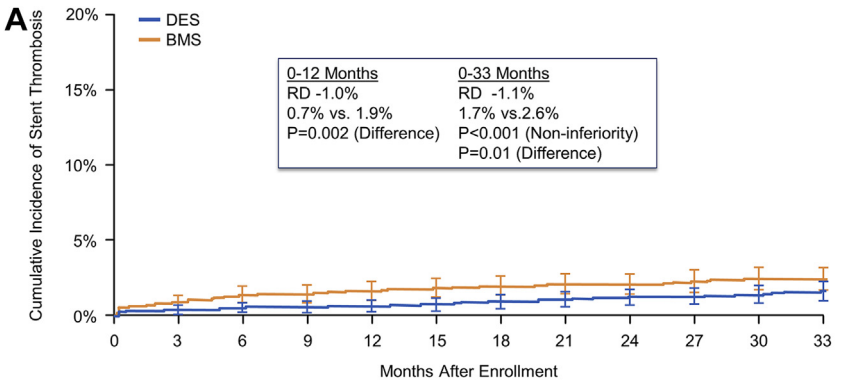
PROPENSITY MATCH DES VERSUS BMS COHORT. Propensity-matched cohorts were similar with respect to clinical- and lesion-related variables, with standardized differences within 10% for all match variables (Table 1, Online Figure 1). Importantly, prespecified risk factors for stent thrombosis were similar between matched DES- and BMS-treated subjects with at least 1 risk factor present in 64.0% and 63.9% respectively (Table 2). Thienopyridine therapy adherence did not differ between matched DES and BMS groups (94.5% vs. 94.4%, $p = 0.86$) at 12 months follow-up. Among subjects in the propensity-matched sample, 61.4% of DES and 76.0% of BMS were also randomized.

After matching, DES-treated subjects had an incidence of stent thrombosis over the 0- to 33-month period that was lower than that of BMS-treated subjects (1.7% vs. 2.6%, weighted RD: −1.1%, 1-sided upper 97.5% confidence limit −0.27%, noninferiority $p < 0.001$, p for difference = 0.01) (Table 3, Figure 2A) In addition, DES-treated subjects had an incidence of MACCE that was noninferior to that of BMS-treated subjects (11.4% vs. 13.2%, weighted RD −1.8%, 1-sided upper 97.5% confidence limit 0.03%, noninferiority $p < 0.001$; p for difference = 0.053). For both stent thrombosis and MACCE, the major portions of this RD were observed within the first 12 months (0 to 12 months, weighted RD: −1.0%, p for difference = 0.002 for stent thrombosis; −1.8% weighted RD, p for difference = 0.011 for MACCE) (Figure 3). A secondary analysis using propensity score adjustment was consistent with the primary analysis (Online Table 1).

Moderate or severe bleeding events were similar for matched DES and BMS (4.0% vs. 3.7% weighted RD: 0.5%, $p = 0.32$) (Figure 2B) as was the incidence of stroke (1.8% vs. 2.1%, weighted RD: −0.2%, p = 0.49) (Table 3, Figure 2B), and myocardial infarction not related to stent thrombosis (6.0% vs. 6.5%, weighted RD: −0.2%; $p = 0.76$) (Figure 2B).

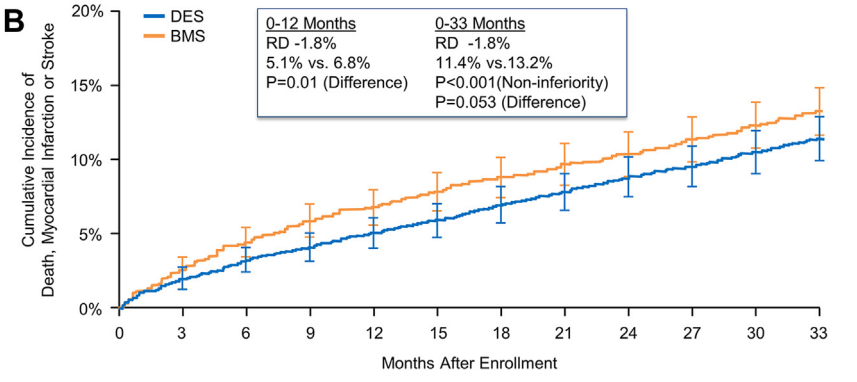
Although the RD favoring DES (vs. BMS) for MACCE was similar for each of the 4 separate DES types, the RD favoring DES (vs. BMS) for stent thrombosis was evident for all DES types except the TAXUS paclitaxel-eluting stent (PES) (Figure 4). In a Bayesian sensitivity analysis examining the impact of a plausible unmeasured confounder, we found that the primary conclusions remained robust.

FIGURE 3 Cumulative Incidence of Primary Outcomes in Propensity-Matched DES- or BMS-Treated Subjects



No. At Risk

DES	8308	8233	8181	8125	8066	8008	7948	7896	7843	7804	7702	5013
BMS	1718	1691	1666	1648	1631	1620	1611	1598	1589	1578	1563	922



No. At Risk

DES	8308	8155	8051	7976	7895	7800	7719	7644	7559	7497	7372	4780
BMS	1718	1670	1639	1613	1597	1579	1562	1547	1535	1518	1500	884

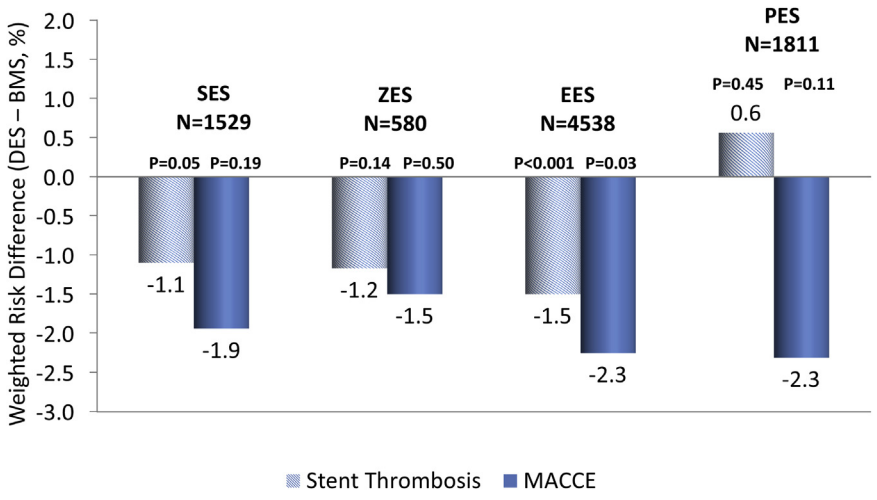
Weighted Kaplan-Meier curves for cumulative incidence of stent thrombosis **(A)** and MACCE **(B)**, according to drug-eluting vs. bare metal stents in propensity-matched subjects. ARC = Academic Research Consortium; RD = risk difference; ST = stent thrombosis; other abbreviations as in Figures 1 and 2.

DISCUSSION

We found that propensity-matched BMS-treated subjects had higher rates of stent thrombosis compared with DES-treated subjects, with the largest portion of RD accrued during the first year after stent treatment. In addition, rates of MACCE were noninferior among DES- versus BMS-treated subjects through 33 months and were significantly lower following DES at 1 year.

Previous randomized trials comparing outcomes following DES or BMS have either utilized older-generation DES (1,2) or, more recently, been limited to subjects with acute myocardial infarction (5). Unfortunately, dual antiplatelet therapy duration and adherence have not been uniform across stent types in many of these studies. Similarly, in retrospective observational studies, important variables related to dual antiplatelet therapy adherence and/or previous bleeding history are often not included and may confound comparisons between stent types. In this regard, the DAPT study was designed to include a prospective propensity-matched comparison of DES- and BMS-treated subjects with uniform inclusion criteria (specifically requiring subjects to be eligible for continued thienopyridine therapy), uniform clinical follow-up, and blinded adjudication of endpoints

FIGURE 4 Primary Outcomes by DES Type



Matched weighted risk differences (versus bare-metal stents) over 0- to 33-month time course. Risk differences for stent thrombosis favor DES except for PES. Risk differences for MACCE favor DES. Abbreviations as in Figures 1 and 2.

by a central independent clinical events committee (13). Furthermore, among both DES and BMS propensity-matched subjects who were randomized, study medication adherence was identical. Indeed, the similarities in bleeding events, stroke rates, and rates of myocardial infarction not related to stent thrombosis (DES vs. BMS) in the propensity-matched analysis suggest lack of residual confounding. Lastly, the analysis of individual DES types with their matched BMS-treated cohorts provides unique insights into a differential risk of stent thrombosis. Although DES are often aggregated for purpose of analysis, a differential risk for stent thrombosis (lack of RD favoring DES) was evident only for the PES. All other DES included in analysis had lower rates of stent thrombosis compared with BMS. Of note, a higher rate of stent thrombosis has been observed following PES in pooled patient-level data from randomized comparative trials with BMS and appears consistent with the present observation (22). Additionally, the present observation is supported by the facts that: 1) stent thrombosis rates for the sirolimus- and PES and BMS included in propensity match analysis are similar to those reported for similar stent types in previous randomized trials (1,2); and 2) the current results are consistent with recent randomized trial data comparing DES with BMS in subjects with acute myocardial infarction that demonstrate a reduction in stent thrombosis risk for newer DES (5). The observation that all 4 DES types (including PES) have a lower risk for MACCE than their matched BMS cohorts suggests that stent thrombosis is not the sole or main driver of MACCE and that restenosis benefit, common to all 4 DES types (vs. BMS), may be operative. Indeed, BMS-treated subjects accrue both target lesion (stent) related events in ≥2%/year (23) and non-target lesion/vessel events in ≥5% per year following stent deployment (24,25). Atherothrombotic events following BMS may be due to lack of healing/uncovered stent struts, neoatherosclerosis (26), restenosis (27), or disease progression outside the stent, in other regions or vessels. The fact that the major portion of RD between DES and BMS is accrued early, within 12 months, would be consistent both with the known differential occurrence of restenosis between DES and BMS in this time frame as well as the premise that restenosis may not be benign (27).

Although MACCE is influenced by events outside of stent thrombosis, the rates of stent thrombosis and MACCE were both directionally consistent in favor of DES. Comparison of DES with BMS did conclude noninferiority on MACCE as primarily designed, yet did not reach statistical significant difference favoring DES. Nonetheless, the absolute reduction in rates of MACCE associated with DES compared with BMS (1.8 percentage point reduction) was similar or greater in magnitude to that of stent thrombosis (1.1 percentage point reduction). The lack of statistical significance on the MACCE is, therefore, a reflection that only 20% of the MACCE were stent related.

Other, more common MACCE did not differ (and would not be expected to differ) between stent types (e.g., myocardial infarction not related to stent thrombosis).

STUDY LIMITATIONS. There are several limitations of this propensity-matched analysis. First, although propensity score matching was used to overcome confounding related to measured factors, the potential presence of unrecognized confounders remains a limitation of this nonrandomized analysis. However, the lack of differences in bleeding (not expected to differ between stent types), stroke, and myocardial infarction not related to stent thrombosis provide reassurance that residual confounding is limited. Second, although propensity matching is a preferred method to reduce selection bias, inference is limited to the population selected for the match. Although the majority of enrolled BMS-treated subjects were used for the match (84%), a lesser proportion of DES-treated subjects (63%) were selected, and these appear to represent a group with lower lesion complexity and diabetes prevalence, but higher frequency of STEMI indication for revascularization than the overall DAPT study DES-treated population. Third, although we performed a sensitivity analysis to determine the consistency of the DES versus BMS comparison, we did not compare different types of DES to one another, as such comparisons were not randomized, pre-specified, or powered.

CONCLUSIONS

DES were associated with a lower long-term rate of stent thrombosis and a noninferior rate of MACCE compared with BMS, among subjects eligible for treatment with continued thienopyridine and aspirin for at least 1 year.

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PERSPECTIVES

WHAT IS KNOWN? BMS are a commonly used alternative treatment strategy to DES, particularly for patients who present with acute coronary syndrome or in whom dual antiplatelet therapy has increased bleeding risk. BMS are perceived to be associated with fewer adverse ischemic events and to require shorter-duration dual antiplatelet therapy than DES.

WHAT IS NEW? A prospective, powered, propensity-match analysis comparing BMS and DES treated patients enrolled into the DAPT study demonstrated BMS to have increased risk for stent thrombosis during 0 to 33 months following stent deployment with the major portion of risk difference (vs. DES) being present in the first 12 months.

WHAT IS NEXT? This study contributes to the growing body of evidence regarding comparative rates of stent thrombosis and other adverse ischemic events (BMS vs. DES), which may inform future guidelines for both stent use as well as duration of dual antiplatelet therapy.

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KEY WORDS bare-metal stents, drug-eluting stents, dual antiplatelet therapy, stent thrombosis

APPENDIX For an expanded Methods section and a supplemental figure and table, please see the online version of this paper.

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