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Two-Year Outcomes After First- or Second-Generation Drug-Eluting or Bare-Metal Stent Implantation in All-Comer Patients Undergoing Percutaneous Coronary Intervention

A Pre-Specified Analysis From the PRODIGY Study (PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia studY)

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Objectives This study sought to assess device-specific outcomes after implantation of bare-metal stents (BMS), zotarolimus-eluting Endeavor Sprint stents (ZES-S), paclitaxel-eluting stents (PES), or everolimus-eluting stents (EES) (Medtronic Cardiovascular, Santa Rosa, California) in all-comer patients undergoing percutaneous coronary intervention.

Background Few studies have directly compared second-generation drug-eluting stents with each other or with BMS.

Methods We randomized 2,013 patients to BMS, ZES-S, PES, or EES implantation. At 30 days, each stent group received up to 6 or 24 months of clopidogrel therapy. The key efficacy endpoint was the 2-year major adverse cardiac event (MACE) including any death, myocardial infarction, or target vessel revascularization, whereas the cumulative rate of definite or probable stent thrombosis (ST) was the key safety endpoint.

Results Clinical follow-up at 2 years was complete for 99.7% of patients. The MACE rate was lowest in EES (19.2%; 95% confidence interval [CI]: 16.0 to 22.8), highest in BMS (32.1%; 95% CI: 28.1 to 36.3), and intermediate in PES (26.2%; 95% CI: 22.5 to 30.2) and ZES-S (27.8%; 95% CI: 24.1 to 31.9) groups (chi-square test = 18.9, p = 0.00029). The 2-year incidence of ST in the EES group (1%; 95% CI: 0.4 to 2.2) was similar to that in the ZES-S group (1.4%; 95% CI: 0.7 to 2.8), whereas it was lower compared with the PES (4.6%, 95% CI: 3.1 to 6.8) and BMS (3.6%; 95% CI: 2.4 to 5.6) groups (chi-square = 16.9; p = 0.0001).

Conclusions Our study shows that cumulative MACE rate, encompassing both safety and efficacy endpoints, was lowest for EES, highest for BMS, and intermediate for PES and ZES-S groups. EES outperformed BMS also with respect to the safety endpoints with regard to definite or probable and definite, probable, or possible ST. (PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY [PRODIGY]; NCT00611286) (J Am Coll Cardiol Intv 2014;7:20–8) © 2014 by the American College of Cardiology Foundation

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Randomized, controlled trials (1,2), meta-analyses (3), and observational studies (4) have consistently shown reduced rates of angiographic restenosis and ischemia-driven target vessel revascularization (TVR) with drug-eluting stents (DES) compared with bare-metal stents (BMS). As a result, most percutaneous coronary interventions worldwide are done with DES rather than BMS. However, the higher rates of very late stent thrombosis (ST) and the concern for a higher risk of late ST after early discontinuation of dual antiplatelet agents with first-generation DES have raised safety concerns (5,6). To address these issues, new DES have been developed with novel materials, designs, and delivery systems, with improved biocompatible polymers, and new antiproliferative agents compared with their predecessors. However, most of these second-generation stents were approved in non-inferiority trials compared with first-generation DES (7–10). Therefore, few studies have directly compared second-generation DES with each other or with BMS.

The purpose of this pre-specified analysis of the PRODIGY (PROlonging Dual Antiplatelet Treatment After Grading stent-induced intimal hyperplasia studY) (11) was to assess device-specific outcomes in an all-comer patient population receiving a balanced proportion of first- or second-generation DES or BMS at the time of intervention.

Methods

Study design and population. PRODIGY is a 4 × 2 randomized, multicenter, open-label clinical trial designed to evaluate the efficacy and safety of prolonging the duration of clopidogrel therapy for up to 24 months in all-comer patients receiving a balanced mixture of stents with varying anti-intimal hyperplasia potency and belonging to both first- and second-generation DES (11,12).

Patients undergoing elective, urgent, or emergent coronary angioplasty with intended stent implantation at 3 referral Italian sites were randomly assigned in a 1:1:1:1 fashion to 1 of 4 stent types, including everolimus-eluting stents (EES), paclitaxel-eluting stents (PES), zotarolimus-eluting Endeavor Sprint stents (ZES-S), or third-generation thin-strut BMS (Medtronic Cardiovascular, Santa Rosa, California). At 30 days, patients in each stent group were randomized in a balanced fashion to either 6 or 24 months of dual antiplatelet treatment. In the 6-month dual antiplatelet therapy group, clopidogrel discontinuation at any time after 30 days was allowed in patients who were randomized to BMS if coronary intervention was indicated by the presence of stable coronary artery disease (12).

Individuals eligible for enrollment were patients 18 years of age or older with chronic stable coronary artery disease or acute coronary syndromes, including non–ST-segment elevation myocardial infarction (MI) and ST-segment elevation MI. They were eligible if they had at least 1 lesion with a stenosis diameter of ≥50% that was suitable for coronary stent implantation in a vessel with a reference vessel diameter of at least 2.25 mm. Selection criteria were broad, reflecting routine clinical practice. We set no limit for the number of treated lesions, vessels, or lesion length and excluded no patients on the basis of comorbid disorders or age, apart from the following pre-specified criteria: known allergy to acetylsalicylic acid or clopidogrel; planned surgery within 24 months of percutaneous coronary intervention unless the dual antiplatelet therapy could be maintained throughout the perisurgical period; history of bleeding diathesis; major surgery within 15 days; active bleeding or previous stroke in the past 6 months; concomitant or foreseeable need for oral anticoagulation therapy; pregnancy; life expectancy <24 months; participation in another trial; and inability to provide informed consent.

The ethics committees of the 3 participating centers independently approved the protocol, and all participants gave written informed consent.

Treatment protocol and follow-up procedures. All patients received aspirin (160 to 325 mg orally or 500 mg intravenously as a loading dose and then 80 to 160 mg orally indefinitely) and clopidogrel (300 or 600 mg orally as a loading dose) and then 75 mg/day for the treatment duration according to the randomization scheme as follows: for either 6 months in the 6-month dual antiplatelet therapy group in patients randomized to BMS and presenting with stable coronary artery disease, a shorter (but not <30 day) duration of dual antiplatelet therapy was allowed to comply with available evidence or 24 months in the 24-month dual antiplatelet therapy arm irrespective of the previously implanted stent type or indication for the coronary procedure.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
CK-MB = creatine kinase myocardial band
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
ST = stent thrombosis
TLR = target lesion revascularization
TVR = target vessel revascularization
ZES-S = zotarolimus-eluting Endeavor Sprint stent(s)

Anticoagulation during coronary intervention was accomplished through administration of either unfractionated heparin or bivalirudin. All interventions were performed according to current standard guidelines and the final interventional strategy, including administration of glycoprotein IIb/IIIa antagonists, pre- or post-dilation, or the use of intravascular imaging techniques, was left entirely to the discretion of the operator, except for the stent use. Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction flow grade 3.

Follow-up. All randomized patients who were not lost to follow-up, irrespective of their compliance with the assigned

treatment schedule, returned for study visits at 30 days and then every 6 months up to 2 years. During follow-up visits, patients were examined, assessed for adverse events, and underwent 12-lead electrocardiography. Patients lost to follow-up were censored at the time of the last contact.

Study endpoints. The primary aim of this analysis was to compare the 2-year outcomes after first- or second-generation DES or BMS with respect to the occurrence of major adverse cardiac events (MACE), including death of any cause, nonfatal MI, or TVR. This was a pre-specified secondary endpoint of the study, and as no formal sample size assessment was performed. Other secondary objectives included each component of the primary endpoint, cardiovascular death, incidence of stent thrombosis defined on the basis of the Academic Research Consortium criteria (13), and the incidence of target lesion revascularization (TLR) for the entire duration of follow-up or from 1 year onward. Study endpoint definitions were previously reported (11). Periprocedural MI in patients without ongoing ischemia was defined as any increase of >3 times the upper limit of normal in at least 1 blood sample for creatine kinase-myocardial band (CK-MB) fraction in patients with CK-MB values before the procedure within the normal range or at least 50% CK-MB elevation after percutaneous coronary intervention in patients with CK-MB values higher than the upper limit of normal before the procedure. Spontaneous MI was based on the detection of increase and/or decrease in cardiac biomarkers (preferably troponin) with at least 1 value above the upper limit of normal together with evidence of myocardial ischemia with at least 1 of the following: symptoms of ischemia; electrocardiographic changes indicative of new ischemia (new ST-T changes or new left bundle branch block); development of pathological Q waves on the electrocardiogram.

All study endpoints were confirmed on the basis of documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of the patients' treatment-group assignments.

Statistical analysis. Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as mean ± SD. Baseline continuous variables were compared between randomized groups using analysis of

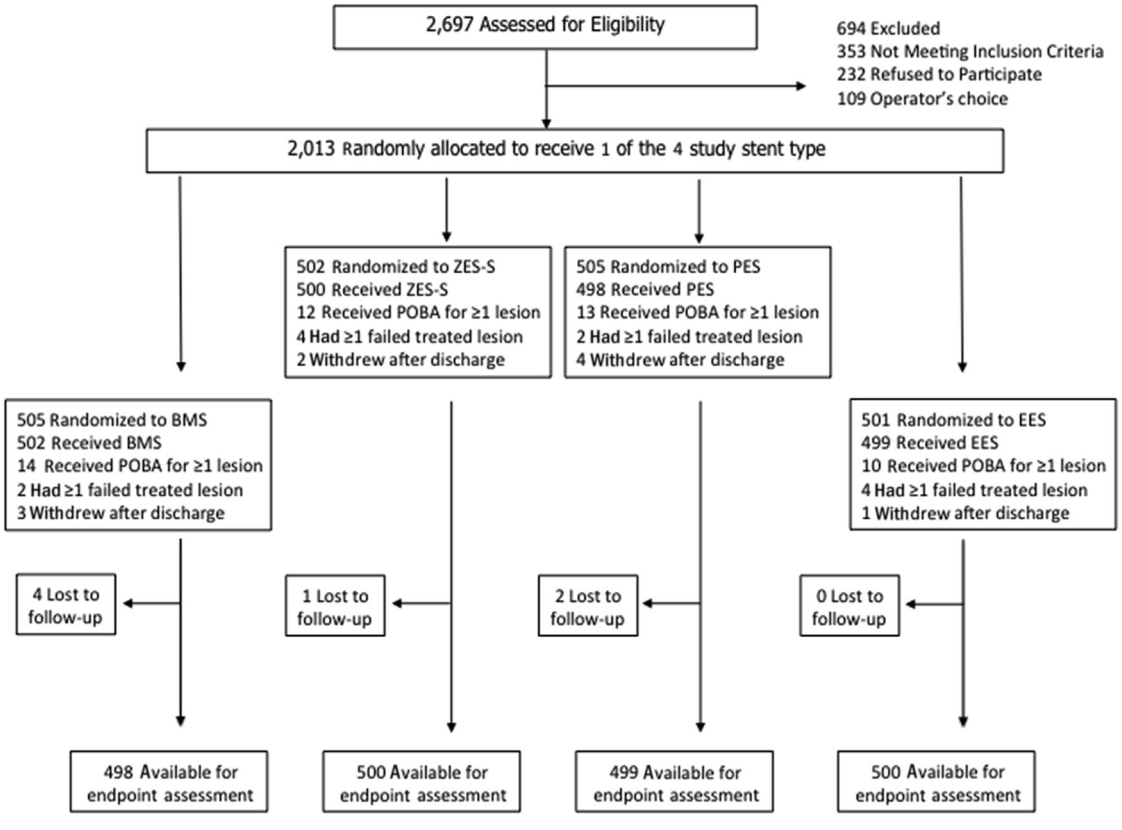

Figure 1. Study Profile

2,013 patients were randomized, 10 withdrew consent, 7 were lost to follow-up so that overall 1,997 patients had complete 2-year follow-up information. BMS = bare-metal stent(s); EES = everolimus-eluting stent(s); POBA = plain balloon angioplasty; PES = paclitaxel-eluting stent(s); ZES-S = zotarolimus-eluting Endeavor Sprint stent(s) (Medtronic Cardiovascular, Santa Rosa, California).

Table 1. Baseline Characteristics of the Patients

Characteristic	BMS (N = 502)	ZES-S (N = 500)	PES (N = 500)	EES (N = 501)	p Value
Age, yrs	69 ± 11	68 ± 11	68 ± 11	68 ± 11	0.47
Male	369 (74)	391 (78)	395 (78)	383 (76)	0.18
Body mass index, kg/m^2	27 ± 4	27 ± 4	27 ± 4	27 ± 4	0.97
Diabetes	118 (24)	118 (24)	140 (28)	120 (24)	0.21
Insulin-dependent	23 (5)	37 (7)	31 (6)	26 (5)	0.64
Hypertension	376 (75)	342 (69)	365 (73)	355 (71)	0.17
Hyperlipidemia	254 (51)	263 (53)	281 (56)	296 (59)	0.09
Current smoking	126 (25)	128 (26)	111 (22)	112 (22)	0.56
Creatinine clearance, ml/min	76 ± 30	79 ± 33	79 ± 32	80 ± 33	0.46
Previous MI	114 (23)	121 (24)	156 (31)	143 (29)	0.12
Previous CABG	45 (9)	57 (11)	54 (11)	61 (12)	0.29
LVEF	50 ± 11	51 ± 11	50 ± 11	51 ± 10	0.63
Clinical presentation					
Stable angina pectoris	122 (24)	137 (27)	154 (31)	125 (25)	0.12
ACS	380 (76)	363 (73)	346 (69)	376 (75)	0.68
Non–ST-segment elevation ACS	209 (42)	191 (38)	197 (39)	214 (43)	0.66
Unstable angina	93 (19)	92 (18)	83 (17)	99 (20)	0.55
NSTEMI	116 (23)	99 (20)	120 (24)	115 (23)	0.38
STEMI	171 (34)	172 (34)	143 (29)	162 (32)	0.56
Angiographic features					0.21
Single-vessel disease	170 (34)	139 (28)	148 (30)	144 (29)	
Multivessel disease	332 (66)	361 (72)	352 (70)	357 (71)	

Values are mean ± SD or n (%).

ACS = acute coronary syndrome; BMS = bare-metal stent(s); CABG = coronary artery bypass graft; EES = everolimus-eluting stent(s); LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PES = paclitaxel-eluting stent(s); STEMI = ST-segment elevation myocardial infarction; ZES-S = zotarolimus-eluting Endeavor Sprint stent(s).

variance, whereas for baseline binary variables, the likelihood ratio, chi-square test, or Fisher exact test was used. Post-hoc comparisons were performed by the Tukey honest significance difference test.

Estimation of the cumulative MACE rate was done with the Kaplan-Meier method, and events were compared by the log-rank test. To investigate the effect of time on outcome, the landmark method was also applied, in which the time to treatment was divided into landmark time intervals (0 to 1 and 1 to 2 years). A 2-sided p value <0.05 was considered significant. All analyses, carried out on the basis of the intention-to-treat principle, were performed using STATA, version 11.1 (StataCorp, College Station, Texas).

Results

From December 2006 to December 2008, a total of 2,789 patients underwent screening and 2,013 were finally recruited into the study and randomized to receive 1 of the 4 stent types. Ten patients (0.5%) withdrew consent after intervention, resulting in a final patient population of 2,003 patients (Fig. 1).

The 4 stent groups were well balanced with regard to baseline and angiographic characteristics (Tables 1 and 2), with the only exception of the circumflex artery being more frequently treated in the PES and EES groups compared with the other stent groups.

Adherence to aspirin therapy during the course of the study was high and did not differ across stent groups, whereas BMS-treated patients received a shorter duration of clopidogrel therapy. Secondary prevention medications, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, and statins did not differ among the 4 stent groups during follow-up (Table 3).

Follow-up and clinical outcomes. Clinical follow-up at 2 years was complete for 99.7% of patients with overall 5 and 2 patients being lost to follow-up after 6 and 12 months, respectively.

The 2-year cumulative risk of death of any cause, nonfatal MI or TVR was not homogeneously distributed across the 4 stent types (chi-square = 18.9, p = 0.00029), with BMS- and EES-treated patients showing the highest (32.1%) and the lowest (19.2%) event rates, respectively (Fig. 2). Patients receiving ZES-S (27.8%) or PES (26.2%) demonstrated intermediate cumulative outcomes. The 12-month landmark analysis failed to show significant heterogeneity across stent types (p = 0.11). Yet, the event rate remained numerically lower in the EES-treated patients compared with other stent platforms (Fig. 2).

No clear signal of heterogeneity was noted for the composite of death or nonfatal MI (Fig. 3) or death alone across stent groups. The cumulative rate of nonfatal MI rate also did not differ at 24 months. Yet, the incidence of nonfatal MI from 12 months onward was higher in the PES group compared with other stent platforms, even if with borderline significance (p = 0.045).

The cumulative incidence of TVR or TLR alone differed across stent types and was consistent with the known potency of each stent to suppress intimal hyperplasia (Fig. 4). In particular, both TVR and TLR rates were lowest in the EES group (6.2% and 5.2%, respectively), roughly 3-fold higher in BMS patients (18.3% and 17.1%, respectively), and intermediate in patients who received PES (7.8% and 6.8%, respectively) or ZES-S (12.2% and 11.6%, respectively) (Fig. 4).

The cumulative rate of definite ST did not significantly differ among the 4 stent groups. On the other hand, the incidence of definite or probable ST varied significantly across stent types (chi-square = 16.9, p = 0.0001), being lowest in EES- (1.0%) and ZES-S– (1.4%) treated patients compared with the BMS (3.6%) and PES (4.6%) groups (Fig. 5). The difference in cumulative ST rates across stent groups was driven by higher risks of late ST in the BMS and by very late ST in the PES groups compared with EES- or ZES-S patients.

Table 2. Procedural Results

Characteristic	BMS (N = 502)	ZES-S (N = 500)	PES (N = 500)	EES (N = 501)	p Value
No. of treated lesions	1.47 ± 0.8	1.57 ± 1.0	1.58 ± 1.0	1.55 ± 0.9	0.22
≥2	170 (34)	192 (38)	190 (38)	194 (39)	0.34
≥3	46 (9)	59 (12)	65 (13)	58 (12)	0.28
≥4	15 (3)	27 (5)	25 (5)	18 (4)	0.18
Artery treated					
LAD	290 (58)	295 (59)	285 (57)	287 (57)	0.76
CFX	147 (29)	149 (30)	163 (33)	186 (37)	0.03
RCA	190 (38)	179 (36)	176 (35)	177 (35)	0.80
SVG treated	9 (2)	13 (3)	12 (2)	13 (3)	0.73
At least 1 complex (type B2 or C) lesion*	318 (63)	343 (69)	339 (68)	315 (63)	0.17
Total ACC/AHA score*†	3.8 ± 2.1	3.9 ± 2.2	3.9 ± 2.3	3.9 ± 2.2	0.38
No. of stents implanted	1.82 ± 1.2	1.91 ± 1.3	1.81 ± 1.3	1.77 ± 1.1	0.34
Length of stent, mm	39 ± 35	41 ± 32	39 ± 29	37 ± 24	0.13
Quantitative coronary analysis					
Lesion length, mm	13.07 ± 8.45	13.18 ± 8.32	14.09 ± 9.51	13.13 ± 8.35	0.49
RVD, before, mm	2.64 ± 0.54	2.64 ± 0.51	2.69 ± 0.53	2.63 ± 0.56	0.31
MLD, before, mm	0.60 ± 0.39	0.61 ± 0.38	0.58 ± 0.41	0.59 ± 0.41	0.66
% Stenosis, before	78 ± 14	77 ± 13	79 ± 14	78 ± 16	0.55
RVD, after, mm	2.76 ± 0.50	2.74 ± 0.42	2.86 ± 0.47	2.76 ± 0.50	0.47
MLD, after, mm	2.42 ± 0.56	2.46 ± 0.46	2.53 ± 0.46	2.45 ± 0.49	0.27
% Stenosis, after	10.57 ± 8.25	9.68 ± 8.74	10.01 ± 7.48	11.04 ± 8.67	0.32

Values are mean ± SD or n (%). *Calculated in 1,928 patients who presented at least 1 de novo lesion; ACC/AHA score was missing in 3 patients. †As previously described (28), type A stenoses were coded 1 point, type B1 stenoses 2 points, type B2 stenoses 3 points, and type C stenoses 4 points. $p < 0.05$ versus BMS group on post-hoc analysis.

ACC/AHA = American College of Cardiology/American Heart Association; CFX = circumflex artery; LAD = left anterior descending artery; MLD = minimal lumen diameter; RCA = right coronary artery; RVD = reference vessel diameter; SVG = saphenous vein graft; other abbreviations as in Table 1.

These findings remained consistent when definite, probable, or possible ST rates were examined.

Discussion

The main findings of our analysis support the concept that both efficacy and safety differ considerably across the 4 stent types used in the present prospective all-comer patient study. In particular, cumulative MACE rates, encompassing both safety and efficacy endpoints, were lowest for EES-, highest for BMS-, and intermediate for PES- and ZES-S–treated patients.

Although DES are more effective than BMS in reducing restenosis, their safety has continued to be questioned in view of the ongoing propensity of first-generation DES for very late ST and the perceived need for prolonged dual antiplatelet therapy after any DES implantation (5,6). Moreover, it has been hypothesized that DES safety may be inversely related to its efficacy (i.e., the higher the stent potency in late luminal loss inhibition, the more prothrombotic the stent can be) (14). We randomly assigned patients to receive BMS, ZES-S, PES, or EES, providing, respectively, no, mild, moderate, or high potency toward intimal hyperplasia suppression. Moreover, stent platforms were selected for being representative of both first- and second-generation DES technology.

Impact of stent selection on efficacy endpoints. The cumulative rates of TVR or TLR observed at 2-year follow-up significantly differed across the 4 stent types and were consistent with known potency of each stent platform to inhibit intimal hyperplasia. In particular, both TVR and TLR were highest in the BMS and lowest in the EES groups. Interestingly, a similar pattern was observed for both stent types at the 1-year landmark analysis, with the BMS group showing the highest (3.2%), and the EES group the lowest (1.4%) rates of late TVR. On the other hand, ZES-S– and PES-treated patients showed heterogeneous behavior in terms of TVR or TLR throughout follow-up. ZES-S patients had an incidence of TVR within the first year, which was intermediate between that of the BMS and EES groups, whereas the late need for reintervention was low and similar in EES-treated patients. Interestingly, PES patients showed an opposite TVR pattern over time, showing among the lowest and highest TVR rates within or after the first year of follow-up, respectively.

Our findings should be interpreted as confirmatory of previous observations in terms of both cumulative TVR rates and distribution pattern of events over time (7,15–20).

Table 3. Use of Medications During the Trial

Drug Therapy	BMS (N = 502)	ZES-S (N = 500)	PES (N = 500)	EES (N = 501)	p Value
At 30 days					
No. evaluated	492	493	490	495	
Aspirin	492 (100)	493 (100)	490 (100)	495 (100)	>0.99
Clopidogrel	491 (100)	247 (99.6)	245 (100)	248 (100)	0.55
Aspirin and clopidogrel	491 (100)	491 (100)	490 (100)	495 (100)	0.75
ACE inhibitors or angiotensin II receptor antagonist	415 (84)	419 (84)	421 (84)	417 (84)	0.81
Beta-blockers	397 (81)	419 (85)	409 (83)	414 (84)	0.69
Statins	436 (89)	446 (90)	441 (88)	461 (92)	0.22
At 6 months					
No. evaluated	481	485	477	486	
Aspirin	476 (99)	481 (99)	472 (99)	484 (100)	0.44
Clopidogrel	333 (69)	480 (99)*	471 (99)*	481 (99)*	<0.001
Aspirin and clopidogrel	333 (69)	476 (98)*	466 (98)*	480 (99)*	<0.001
ACE inhibitors or angiotensin II receptor antagonist	405 (84)	412 (85)	418 (88)	426 (87)	0.41
Beta-blockers	389 (81)	408 (84)	406 (85)	415 (85)	0.29
Statins	423 (88)	438 (90)	429 (90)	387 (93)	0.12
At 12 months					
No. evaluated	468	478	464	480	
Aspirin	456 (97)	473 (99)	457 (98)	478 (99)	0.22
Clopidogrel	241 (51)	244 (51)	235 (51)	245 (51)	0.89
Aspirin and clopidogrel	238 (51)	243 (51)	229 (49)	245 (51)	0.23
ACE inhibitors or angiotensin II receptor antagonist	404 (86)	414 (87)	411 (88)	411 (86)	0.41
Beta-blockers	381 (81)	396 (83)	384 (83)	399 (83)	0.79
Statins	410 (88)	430 (90)	418 (90)	445 (93)	0.22
At 18 months					
No. evaluated	465	473	455	472	
Aspirin	453 (97)	464 (98)	449 (99)	467 (99)	0.42
Clopidogrel	233 (50)	224 (47)	223 (49)	232 (49)	0.89
Aspirin and clopidogrel	231 (50)	222 (47)	218 (48)	230 (49)	0.47
ACE inhibitors or angiotensin II receptor antagonist	393 (85)	400 (85)	394 (87)	411 (87)	0.71
Beta-blockers	365 (78)	382 (81)	369 (81)	382 (81)	0.59
Statins	405 (87)	415 (88)	410 (90)	409 (87)	0.62
At 24 months					
No. evaluated	457	465	450	468	
Aspirin	444 (97)	454 (98)	440 (98)	463 (99)	0.79
Clopidogrel	226 (49)	214 (46)	217 (48)	228 (49)	0.89
Aspirin and clopidogrel	224 (49)	211 (45)	213 (47)	226 (48)	0.47
ACE inhibitors or angiotensin II receptor antagonist	349 (76)	369 (79)	368 (82)	365 (78)	0.21
Beta-blockers	355 (78)	345 (74)	328 (73)	345 (74)	0.49
Statins	364 (80)	374 (80)	350 (83)	387 (86)	0.12

Values are n (%). *p < 0.05 versus BMS group on post-hoc analysis.
ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

Impact of stent selection on safety endpoints. The composite of death or nonfatal MI did not formally differ across stent types. Consistent findings were noted for cumulative death of any cause and MI rates, separately analyzed.

Yet, MI rates at the 1-year landmark analysis were not homogeneously distributed across the 4 stent types, with a roughly 2-fold increase of events in patients treated with PES (4.8%) compared with EES (2.4%). ST rates were also not homogeneously distributed across stent types, both with respect to the cumulative incidence or distribution of events over time. EES-treated patients showed the lowest cumulative rate of ST at 2 years, which was the result of a consistently low incidence of acute/subacute, late, and very late ST. Similar findings were noted for the ZES-S group. On the other hand, the PES and BMS groups had the highest risk of cumulative ST, which was driven by a high incidence of late ST rates in the BMS and very late (>1 year) ST in the PES groups.

Intimal hyperplasia is known to peak at 11 to 14 weeks after BMS implantation and then it stabilizes or even mildly regresses (the so-called compaction phenomenon) over time (21). Therefore, it remains possible that the high rate of late ST in the BMS group may reflect symptomatic late loss–driven occlusive or subocclusive restenosis. The possible contribution of late luminal loss to late ST was postulated in several previous head-to-head trials or registry data (15,22,23), and it has major clinical implications, as it would question the concept that stent safety inversely relates to stent potency in inhibiting intimal hyperplasia. Alternatively, some DES polymers may increase the biocompatibility of the BMS surface and as such render the stent itself less thrombogenic (24).

The relatively higher risk of very late ST with PES compared with the second-generation DES tested in the current study is not new and is consistent with many previous observations (9,20). This finding reinforces the concept that DES safety is highly heterogeneous across DES types. In particular, we even observed an improved safety profile for EES, with respect to definite or probable ST, compared with BMS. In this regard, the EXAMINATION (Evaluation of the Xience-V stent in Acute Myocardial INfArcTION) trial was the first reasonably sized study of second-generation DES and BMS and reported significantly lower rates of ST with EES than with BMS at 1-year follow-up (25). A recent network meta-analysis involving 49 randomized studies, of which only 2 directly comparing EES with BMS corroborated this possible paradigm shift (26).

Therefore, our data, although preliminary, suggest that stent safety may not be necessarily disconnected from efficacy, which has major clinical and pathophysiological implications.

Study limitations. First, the open-label design may have introduced the potential for bias. We minimized this potential with the requirement that all events were adjudicated by independent committees unaware of the treatment

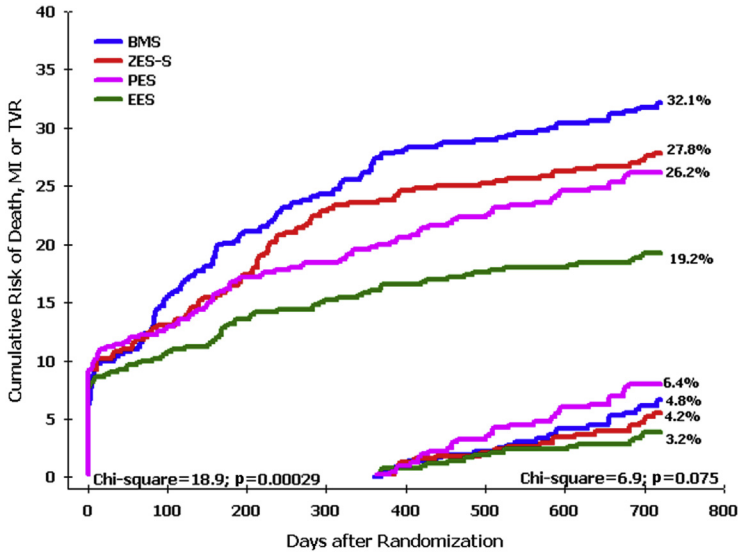

Figure 2. Cumulative Incidence of the Key Efficacy Endpoint According to Stent Group

Cumulative incidence curves are shown for the key efficacy endpoints of death of any cause, myocardial infarction (MI), or target vessel revascularization (TVR) at 2-year follow-up and from 1-year landmark analysis. The p values were calculated using the log-rank test. Other abbreviations as in Figure 1.

assignments. Our study was not powered for the comparison of the 4 stent platforms. As such, our findings are exploratory and hypothesis generating and deserve further confirmation.

This is particularly true considering that the analyses of multiple safety and efficacy endpoints at 2 years or from the landmark of 1-year follow-up for the 4 randomized stent groups made possible multiple comparisons, for which a formal level of significance was not corrected.

The focus of the current analysis was to contrast the performance of the 4 different stent types. Hence, we did not specifically investigate the possible stent type by clopidogrel duration interaction because this information was previously reported (27).

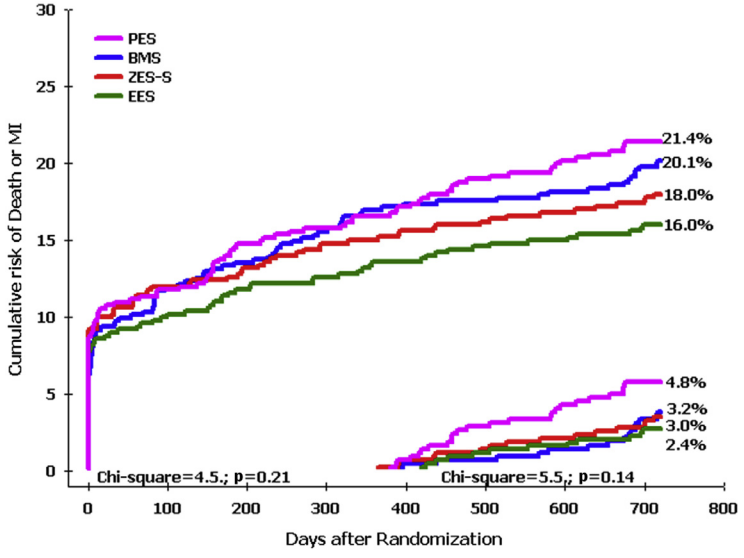

Figure 3. Cumulative Incidence of Death or Nonfatal MI According to Stent Group

Cumulative incidence curves are shown for death of any cause or myocardial infarction (MI) at 2-year follow-up and from 1-year landmark analysis. The p values were calculated using the log-rank test. Abbreviations as in Figure 1.

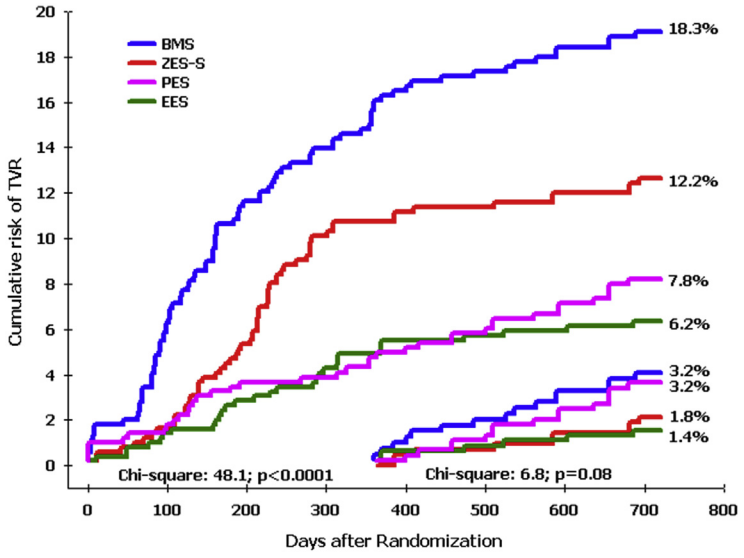

Figure 4. Cumulative Incidence of TVR According to Stent Group

Cumulative incidence curves are shown for the death for TVR at 2-year follow-up and from 1-year landmark analysis. The p values were calculated using the log-rank test. Abbreviations as in Figure 2.

Conclusions

Our study suggests that the unrestricted EES implantation in a broad consecutive patient population is associated with the lowest MACE risk across the 4 randomized stent platforms. The superiority of EES was driven by a better efficacy profile in terms of TVR rates compared with both BMS or ZES-S but importantly also by an improved safety profile with respect to ST rates compared with PES or BMS. Finally, PES and ZES-S were associated with MACE rates, which were intermediate between EES and BMS, as a result of a suboptimal safety and efficacy profile, respectively.

The observation that EES implantation is associated with a lower ST rate compared with BMS is consistent with

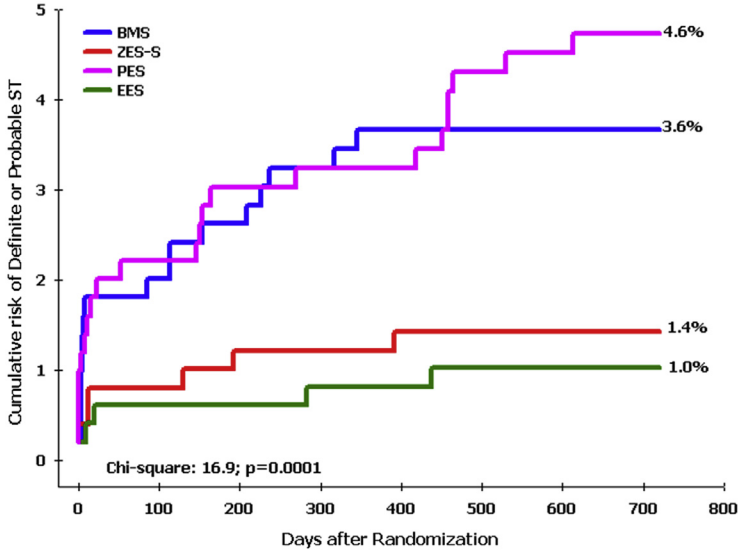

Figure 5. Cumulative Incidence of the Key Safety Endpoint According to Stent Group

Cumulative incidence curves are shown for the key safety endpoint of definite or probable stent thrombosis (ST) at 2-year follow-up. The p values were calculated using the log-rank test. Abbreviations as in Figure 1.

a paradigm shift, which has major potential clinical implications and should be confirmed by appropriately powered clinical investigations.

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REFERENCES

1. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
2. Valgimigli M, Campo G, Percoco G, et al. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. JAMA 2008;299:1788–99.
3. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030–9.
4. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. N Engl J Med 2007;357:1393–402.
5. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007;297:159–68.
6. Valgimigli M, Campo G, Gambetti S, et al. Three-year follow-up of the MULTIcentre evaluation of Single high-dose Bolus TiRofiban versus Abciximab with Sirolimus-eluting STEnt or Bare-Metal Stent in Acute Myocardial Infarction StudY (MULTISTRATEGY). Int J Cardiol 2013;165:134–41.
7. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201–9.
8. Stone GW, Midei M, Newman W, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903–13.
9. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–74.
10. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136–46.
11. Valgimigli M, Campo G, Percoco G, et al. Randomized comparison of 6- versus 24-month clopidogrel therapy after balancing antiintimal hyperplasia stent potency in all-comer patients undergoing percutaneous coronary intervention Design and rationale for the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY). Am Heart J 2010;160:804–11.
12. Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012;125:2015–26.
13. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
14. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation 2007;115:1440–55; discussion 1455.
15. Camenzind E, Wijns W, Mauri L, et al. Stent thrombosis and major clinical events at 3 years after zotarolimus-eluting or sirolimus-eluting coronary stent implantation: a randomised, multicentre, open-label, controlled trial. Lancet 2012;380:1396–405.
16. Kandzari DE, Leon MB, Popma JJ, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. J Am Coll Cardiol 2006;48:2440–7.
17. Leon MB, Kandzari DE, Eisenstein EL, et al. Late safety, efficacy, and cost-effectiveness of a zotarolimus-eluting stent compared with a paclitaxel-eluting stent in patients with de novo coronary lesions: 2-year follow-up from the ENDEAVOR IV trial (Randomized, Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv 2009;2:1208–18.
18. Leon MB, Nikolsky E, Cutlip DE, et al. Improved late clinical safety with zotarolimus-eluting stents compared with paclitaxel-eluting stents in patients with de novo coronary lesions: 3-year follow-up from the ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease) trial. J Am Col Cardiol Intv 2010;3:1043–50.
19. Park DW, Kim YH, Yun SC, et al. Comparison of zotarolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for coronary revascularization: the ZEST (comparison of the efficacy and safety of zotarolimus-eluting stent with sirolimus-eluting and paclitaxel-eluting stent for coronary lesions) randomized trial. J Am Coll Cardiol 2010;56:1187–95.
20. Smits PC, Kedhi E, Royaards KJ, et al. 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: a randomized open label trial). J Am Coll Cardiol 2011;58:11–8.
21. Kimura T, Yokoi H, Nakagawa Y, et al. Three-year follow-up after implantation of metallic coronary-artery stents. N Engl J Med 1996;334:561–6.
22. Kimura T, Morimoto T, Kozuma K, et al. Comparisons of baseline demographics, clinical presentation, and long-term outcome among patients with early, late, and very late stent thrombosis of sirolimus-eluting stents: observations from the Registry of Stent Thrombosis for Review and Reevaluation (RESTART). Circulation 2010;122:52–61.
23. Oikawa Y, Yajima J, Costa MA, et al. Intravascular ultrasound, angioscopic and histopathological characterisation of heterogeneous patterns of restenosis after sirolimus-eluting stent implantation: insights into potential "thromborestenosis" phenomenon. EuroIntervention 2010;6:380–7.
24. Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation 2011;123:1400–9.
25. Sabate M, Cequier A, Iniguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. Lancet 2012;380:1482–90.
26. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393–402.
27. Valgimigli M, Borghesi M, Tebaldi M, Vranckx P, Parrinello G, Ferrari R. Should duration of dual antiplatelet therapy depend on the type and/or potency of implanted stent? A pre-specified analysis from the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY). Eur Heart J 2013;34:909–19.
28. Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group. Circulation 1990;82:1193–202.

Key Words: all-comer randomized clinical trial ■ bare-metal stent(s) ■ everolimus-eluting stent(s) ■ paclitaxel-eluting stent(s) ■ zotarolimus-eluting stent(s).

APPENDIX

For supplemental material, please see the online version of this article.