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Zotarolimus-Eluting Versus Bare-Metal Stents in Uncertain Drug-Eluting Stent Candidates

Marco Valgimigli, MD, PhD,* Athanasios Patialiakas, MD,†‡ Attila Thury, MD, PhD,§ Eugene McFadden, MD,‖ Salvatore Colangelo, MD,¶ Gianluca Campo, MD,† Matteo Tebaldi, MD,† Imre Ungi, MD, PhD,§ Stefano Tondi, MD,# Marco Roffi, MD,** Alberto Menozzi, MD, PhD,†† Nicoletta de Cesare, MD,‡‡ Roberto Garbo, MD,¶ Emanuele Meliga, MD,§§ Luca Testa, MD, PhD,‖‖ Henrique Mesquita Gabriel, MD,¶¶ Flavio Airoldi, MD,## Marco Ferlini, MD,*** Francesco Liistro, MD,††† Antonio Dellavalle, MD,‡‡‡ Pascal Vranckx, MD, PhD,§§§ Carlo Briguori, MD, PhD,‖‖‖ for the ZEUS Investigators

ABSTRACT

BACKGROUND The use of drug-eluting stents (DES) in patients at high risk of bleeding or thrombosis has not been prospectively studied; limited data are available in patients who have a low restenosis risk.

OBJECTIVES This study sought to compare a hydrophilic polymer-based, second-generation zotarolimus-eluting stent (ZES) with a unique drug fast-release profile versus bare-metal stents (BMS) under similar durations of dual-antiplatelet therapy (DAPT).

METHODS We randomly assigned 1,606 patients with stable or unstable symptoms, and who on the basis of thrombotic bleeding or restenosis risk criteria, qualified as uncertain candidates for DES, to receive ZES or BMS. DAPT duration was on the basis of patient characteristics, rather than stent characteristics, and allowed for a personalized 1-month dual antiplatelet regimen. The primary endpoint was the risk of 1-year major adverse cardiovascular events (MACE), which included death, myocardial infarction (MI), or target vessel revascularization (TVR).

RESULTS Median DAPT duration was 32 days (interquartile range [IQR]: 30 to 180 days) and did not differ between the groups. In the ZES group, 140 patients (17.5%) reached the primary endpoint, compared with 178 patients (22.1%) in the BMS group (hazard ratio: 0.76; 95% confidence interval: 0.61 to 0.95; $p = 0.011$) as a result of lower MI (2.9% vs. 8.1%; $p < 0.001$) and TVR rates (5.9% vs.10.7%; $p = 0.001$) in the ZES group. Definite or probable stent thrombosis was also significantly reduced in ZES recipients (2.0% vs. 4.1%; $p = 0.019$).

CONCLUSIONS Compared with BMS, DES implantation using a stent with a biocompatible polymer and fast drug-eluting characteristics, combined with an abbreviated, tailored DAPT regimen, resulted in a lower risk of 1-year MACE in uncertain candidates for DES implantation. (Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates [ZEUS] Study; NCT01385319) (J Am Coll Cardiol 2015;65:805–15) © 2015 by the American College of Cardiology Foundation.

From the *Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; †Interventional Cardiology Unit, Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy; ‡Cardiology Department, Crete Naval Hospital, Crete, Greece; §Cardiology Center and University of Szeged, Szeged, Hungary; ‖Division of Cardiology, Cork University Hospital, Cork, Ireland; ¶Interventional Cardiology, San Giovanni Bosco Hospital, Torino, Italy; #Azienda Unità Sanitaria Locale di Modena-Ospedale, Baggiovara, Italy; **Division of Cardiology, University Hospital, Geneva, Switzerland; ††Interventional Cardiology Unit, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; ‡‡Policlinico S. Marco Zingonia, Bergamo, Italy; §§Azienda Ospedaliera Ordine Mauriziano, Torino, Italy; ‖‖Interventional Cardiology, Ist. Clinico S. Ambrogio, IRCCS San Donato, Milan, Italy; ¶¶Hospital de Santa Cruz, Carnaxide, Lisbon, Portugal; ##IRCCS Multimedica Sesto San Giovanni, Milan, Italy; ***Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; †††Cardiovascular Departments of San Donato Hospital, Arezzo, Italy; ‡‡‡Ospedali Riuniti, Savigliano, Italy; §§§Virga Jesse Ziekenhuis, Hasselt, Belgium; and the ‖‖‖Clinica Mediterranea, Napoli, Italy. The study is an investigator-driven clinical trial, which received funding from Medtronic through an unrestricted grant to the Consorzio Ferrara Ricerche, which employed dedicated personnel for data monitoring, data management, event adjudication, and independent statistical analysis. Dr. Valgimigli has received honoraria for lectures/advisory board and research grants from Merck, Iroko, Eli Lilly,

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

IQR = interquartile range

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

TVR = target vessel revascularization

ZES = zotarolimus-eluting stent(s)

Compared with bare metal stents (BMS), drug-eluting stents (DES) have consistently been shown to reduce restenosis rates, and consequently, the risk of target vessel failure (1–4). However, due to a higher incidence of very late stent thrombosis, first-generation DES raised safety concerns (5–7). Therefore, to restore safety to a level comparable to that after BMS implantation, a prolonged course of dual-antiplatelet therapy (DAPT) has been recommended after DES implantation (8,9).

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Consequently, the use of DES instead of BMS remains controversial in selected patient and/or lesion subsets, including patients at high thrombosis risk, who may have a higher risk for coronary events after DES implantation, and those at high bleeding risk, in whom long-term DAPT poses safety concerns (9,10). Similarly, patients at a low perceived risk for in-stent restenosis may not qualify as good DES candidates, because the need for prolonged DAPT and the long-term risk for adverse events after DES implantation may outweigh the acknowledged benefit of lower reintervention rates.

The zotarolimus-eluting stent (ZES) is a hydrophilic polymer-based, second-generation device with a uniquely fast drug-release profile (11). The phosphorylcholine coating has been shown to reduce thrombus formation on the coated stent struts compared with BMS (12). Although the rapid-release profile may result in less powerful inhibition of intimal hyperplasia, it may also lead to a more rapid and/or complete stent strut coverage compared with other DES (4,13,14), raising the possibility that it might be feasible to shorten DAPT duration while maintaining superior efficacy compared with BMS (15). This could be evaluated further in dedicated studies.

The purpose of this trial was to assess if ZES implantation, followed by a shorter than the currently recommended course of DAPT, on the basis of the patient's clinical profile (tailored DAPT) and independent of stent type, would decrease the incidence of 12-month major adverse cardiovascular events (MACE) in uncertain DES recipients, including those with high bleeding or thrombotic risk and those with low restenosis risk, compared with BMS.

METHODS

STUDY DESIGN AND POPULATION. The ZEUS (Zotarolimus-eluting Endeavor sprint stent in Uncertain DES candidates) trial is a multinational, randomized, single-blinded trial, conducted at 20 sites in 4 European countries (Italy, Switzerland, Portugal, and Hungary). It was designed to evaluate the combined efficacy and safety of ZES compared with BMS, in uncertain DES candidates (16). Detailed inclusion and exclusion criteria have been previously described (16) and are detailed in the Online Appendix. In brief, patients who underwent elective, urgent, or emergent percutaneous coronary intervention with intended stent implantation were randomly assigned in a 1:1 fashion to ZES or a thin-strut (thickness <100 μm) BMS, if they were ages 18 years or older and had at least 1 qualifying criterion among the pre-specified uncertain DES recipients. High-bleeding risk status was defined as the following: a clinical indication for treatment with oral anticoagulant agents; recent bleeding episode(s) that required medical attention; previous bleeding episode(s) that required hospitalization if the bleeding diathesis has not been completely resolved (that is, surgical removal of the bleeding source); age older than 80 years; systemic conditions associated with increased bleeding risk (e.g., hematological disorders or any known coagulopathy-determining bleeding diathesis, including history of or current thrombocytopenia, which was defined as platelet count <100,000/mm^3 [<100 × 10^9/l]; known anemia, defined as repeatedly documented hemoglobin <10 g/dl; and need for long-term treatment with steroids or nonsteroidal anti-inflammatory drugs. High-risk thrombotic criteria were defined as the following: allergy and/or intolerance to aspirin; allergy and/or intolerance to available P2Y$_{12}$ inhibitors; planned surgery (other than

and Medtronic; honoraria for advisory board and lectures from The Medicines Company, Eli Lilly Co., Daiichi Sankyo, Inc., St. Jude, and Abbott Vascular; and fees for lectures from Cordis, CID, and Terumo. Dr. Patialiakas has received grants from the Hellenic Cardiological Society and the Hellenic Institution of Cardiology. Dr. McFadden has received fees from Abbott Vascular and Medtronic for Clinical Event Committee adjudications. Dr. Colangelo is a consultant for Abbott. Dr. Roffi has received institutional research grants from Abbott Vascular, Medtronic, Boston Scientific, Biotronik, and Biosensor. Dr. Ferlini has received consulting honoraria from Abbott Vascular and Eli Lilly. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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skin) within 12 months of percutaneous coronary intervention; patient with cancer (other than skin) and life expectancy >1 year; and patients with systemic conditions associated with thrombosis diathesis (e.g., hematological disorders and any known systemic conditions determining a prothrombotic state, including immunological disorders). Finally, low restenosis risk was fulfilled if no planned stent <3.0-mm diameter was intended to be implanted, regardless of lesion length, apart from left main coronary artery or saphenous graft intervention (17).

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

DEVICES. The Endeavor stent (Medtronic Vascular, Minneapolis, Minnesota) is a cobalt-based alloy stent (91-μm strut thickness) with a phosphorylcholine polymer (4.8 μm) loaded with zotarolimus at a dose concentration of 10 μg/mm stent length. Approximately 95% of the zotarolimus is eluted from the stent within 15 days of implantation, although drug concentrations within surrounding vascular tissue may be detected as late as 30 days after stent deployment.

Although all commercially available thin-strut BMS (strut thickness <100 μm) were allowed to be used in the study, the Tsunami, (Terumo, Leuven, Belgium), Skylor (Medtronic, Minneapolis, Minneapolis), Integrity (Medtronic), Vision (Abbott, Santa Clara, California), and Avant-Garde (CID Vascular, Saluggia, Italy) were the 5 most commonly utilized devices in this stent group.

TREATMENT PROTOCOL AND FOLLOW-UP PROCEDURES. All eligible patients received aspirin (160 to 325 mg orally or 500 mg intravenously as a loading dose and then 80 to 160 mg orally per day) and clopidogrel (300 or 600 mg orally as a loading dose followed by 75 mg/day), or prasugrel (60 mg loading dose followed by 10 or 5 mg/day) or ticagrelor (180 mg loading dose followed by 90 mg twice daily). Patients who were not eligible for DAPT were treated with either aspirin or clopidogrel (or prasugrel or ticagrelor) monotherapy.

Duration of antiplatelet therapy was pre-specified on the basis of the inclusion criteria. Patients at high risk of bleeding had a pre-specified 30-day DAPT regimen. Patients at high risk of thrombosis had a pre-specified tailored duration of therapy on the basis of the specific condition conferring the high risk of thrombosis (Online Appendix). This included a single antiplatelet regimen for patients intolerant of aspirin or available $P2Y_{12}$ inhibitors, and a 30-day regimen in stable patients, or 6 to 12 months in unstable patients, in the group at low risk of restenosis.

Unfractionated heparin or bivalirudin was used for anticoagulation during coronary intervention on the basis of guideline-recommended regimens (8,9). Staging was allowed by protocol; in patients allocated to a 30-day course of DAPT who underwent staged intervention(s), therapy had to be prolonged or restarted for 30 additional days.

FOLLOW-UP. Protocol-mandated visits at 30 days, 6 months, and 12 months specifically assessed potential intercurrent adverse events and compliance with medications; a 12-lead electrocardiogram was recorded.

STUDY ENDPOINTS. The purpose of this trial was to assess whether ZES implantation followed by a shorter than the currently recommended course of DAPT, tailored to the patient's clinical profile (tailored DAPT) and independent of stent type, would decrease the incidence of 12-month MACE, including all-cause death, nonfatal myocardial infarction (MI), or any target vessel revascularization (TVR), in uncertain candidates for DES transplantation, including those at high bleeding or high thrombotic risk and those at low restenosis risk (16) compared with BMS.

Secondary endpoints included each component of the primary endpoint: cardiac death; Academic Research Consortium-defined stent thrombosis (18); all-cause or ischemic stroke; target lesion revascularization; and bleeding. All potential event triggers were assessed using source documents obtained from the site and centrally adjudicated by the clinical events committee, whose members were unaware of treatment assignment. Detailed definitions of all study endpoints are provided in the Online Appendix.

STATISTICAL ANALYSIS. Assuming an event rate of 15.0% at 1 year for the primary endpoint in patients assigned to BMS (16), we estimated that at least 1,556 patients would need to be enrolled to detect a 33% reduction in the relative risk of the primary endpoint in the ZES group compared with the BMS group, with a statistical power of 85% at a 2-sided significance level of 0.05. The final sample size was increased to 1,600 patients (16).

Categorical variables were expressed as frequencies (percents), whereas continuous variables were expressed as medians (interquartile ranges [IQRs]). Continuous variables were compared between randomized groups using the Wilcoxon rank-sum test, whereas the Fisher exact test was used for binary variables. Further details of statistical analysis are provided in the Online Appendix. A 2-sided p value <0.05 was considered significant. All analyses were performed on an intention-to-treat basis

TABLE 1 Baseline Characteristics of Patients*

	BMS Group (n = 804)	ZES Group (n = 802)
Age, yrs	71.8 ± 12	71.8 ± 11
Median	73.6	73.9
Interquartile range	64.0-81.0	63.8-81.0
Range	31.3-100.2	31.6-94.8
Female	232 (28.9)	241 (30.0)
Body mass index, kg/m^2		
Median	26.5	26.7
Interquartile range	24.2-29.3	24.2-29.4
Diabetes	205 (25.5)	215 (26.8)
Hypertension	605 (75.2)	612 (76.3)
Hyperlipidemia	399 (49.6)	381 (47.5)
Current cigarette use	169 (21.0)	167 (20.8)
Creatinine clearance, ml/min†		
Median	66.0	66.0
Interquartile range	47.9-88.6	46.1-90.8
Patients with creatinine clearance <60 ml/min†	327 (41.7)	317 (41.2)
Patients with creatinine clearance <30 ml/min†	66 (8.4)	64 (8.3)
Patients on dialysis	12 (1.5)	21 (2.6)
Previous MI	190 (23.6)	194 (24.2)
Previous percutaneous coronary intervention	149 (18.5)	155 (19.3)
Previous coronary bypass surgery	59 (7.3)	54 (6.7)
Previous stroke or transient ischemic attack	53 (6.6)	51 (6.4)
Chronic obstructive pulmonary disease	65 (8.1)	55 (6.9)
Peripheral arterial disease	141 (17.5)	117 (14.6)
Left ventricular ejection fraction‡		
Median	50.0	50.0
Interquartile range	40-55	40-56
Clinical presentation		
Stable angina pectoris	295 (36.7)	295 (36.8)
Acute coronary syndrome	509 (63.3)	507 (63.2)
Unstable angina	131 (16.3)	139 (17.3)
Non-ST-segment elevation MI	226 (28.1)	215 (26.8)
ST-segment elevation MI	152 (18.9)	153 (19.1)
Angiographic features		
Single-vessel disease	313 (38.9)	332 (41.4)
Double-vessel disease	285 (35.4)	266 (33.2)
Triple-vessel disease	206 (25.6)	204 (25.4)
Inclusion criteria		
High bleeding risk	404 (50.2)	424 (52.9)
High thrombosis risk	145 (18.0)	140 (17.5)
Low restenosis risk		
Stable coronary artery disease presentation	167 (20.8)	170 (21.2)
Unstable coronary artery disease presentation	301 (37.4)	303 (37.8)

Values are mean ± SD or n (%), unless otherwise indicated. *There were no significant between-group differences. †Available in 784 patients (97.5%) in the BMS group and 769 patients (95.9%) in the ZES group. ‡Available in 748 patients (93%) in the BMS group and 742 patients (93%) in the ZES group.
BMS = bare-metal stent(s); MI = myocardial infarction; ZES = zotarolimus-eluting stent(s).

using STATA version 11.1 (Stata Corp., College Station, Texas).

RESULTS

From June 2011 to September 2012, 5,288 patients were screened and 1,606 were finally randomized (Online Figure 1). The groups were well balanced with regard to baseline clinical and angiographic characteristics (Tables 1 and 2).

The median age was 74 years; approximately one-quarter of the patient population had a history of diabetes or previous MI, and >40% of patients had impaired kidney function. Nearly two-thirds of patients presented with acute coronary syndromes (acute ST-segment elevation MI in 20%), and more than one-half had multivessel disease. One-third of patients received treatment for >1 lesion, and approximately 1 patient in every 4 underwent multivessel intervention. At least 1 complex lesion was treated in approximately 75% of the patients (Table 2).

CHARACTERIZATION OF THE INCLUDED PATIENT POPULATION. Figure 1A shows the distribution of the inclusion criteria in the recruited patient population. Approximately one-half of the patients (n = 828) entered the study due to high bleeding risk criteria, dictated by age 80 years or older in 425 (26.5%) patients and/or need for oral anticoagulation in 311 (19.4%) patients. Other high bleeding risk criteria included the following: ongoing, recent (within 12 months), or previous bleeding events requiring medical attention or hospitalization in 116 (7.2%) patients; presence of comorbidities determining an increased bleeding risk in 54 (3.4%) patients; known anemia in 68 (4.2%) patients; and need for prolonged treatment with steroids or nonsteroidal anti-inflammatory drugs in 25 (1.6%) patients. A high thrombotic risk was detected in 285 (17.7%) patients on the basis of the following: planned cardiac or noncardiac surgery in 117 (7.3%) patients; intolerance to aspirin (n = 73) or any $P2Y_{12}$ inhibitor (n = 1) in 74 (4.6%) patients; and cancer in 84 (5.2%) patients.

DUAL ANTIPLATELET THERAPY. DAPT was used in 1,532 (95.4%) patients, aspirin and clopidogrel in 1,481 patients (96.7%), and aspirin and prasugrel (n = 49) or ticagrelor (n = 2) in the remaining 51 (3.3%) patients. Figure 1B shows the cumulative frequency of DAPT duration from randomization to the first planned permanent discontinuation in the 2 study groups. The median duration of DAPT, 32 days (IQR: 30 to 180 days), did not differ between groups (33 days [IQR: 30 to 180 days] for BMS vs. 31 days [IQR: 30 to 180 days] for ZES groups; p = 0.69). Overall, 1,077 (67%) patients (533 [66.3%] in the BMS group and 544 [67.8%] in the ZES group) qualified for a 1-month DAPT regimen or a single antiplatelet regimen on the basis of inclusion criteria; the median duration of DAPT in these patients was 31 days (IQR: 30 to 81 days) in the BMS group versus 30 days (IQR: 30 to 48 days) (p = 0.89) in the ZES group. Reasons for prolonging

TABLE 2 Procedural Results and Use of Medications During the Trial*

	BMS (n = 804)	ZES (n = 802)
No. of treated lesions	1,153	1,172
Mean ± SD	1.43 ± 0.72	1.46 ± 0.75
Median	1	1
Interquartile range	1–2	1–2
Range	1–6	1–6
≥2 treated lesions	272 (33.8)	276 (34.4)
Multivessel intervention	229 (25.6)	246 (27.8)
LAD treated	411 (51.1)	421 (52.5)
CFX treated	278 (34.6)	263 (32.8)
RCA treated	317 (39.4)	335 (41.8)
LMCA treated	36 (4.5)	39 (4.9)
SVG treated	12 (1.5)	9 (1.1)
At least 1 complex (type B2 or C) lesion†	590 (73.4)	585 (72.9)
Total ACC/AHA score†‡		
Mean ± SD	6.82 ± 4.2	6.67 ± 4.2
Median	6	6
Interquartile range	4–10	3–9
Number of stents implanted		
Mean ± SD	1.69 ± 1.10	1.70 ± 1.11
Median	1	2
Interquartile range	1–2	1–2
Range	0–9	0–7
Length of stent, mm		
Median	26	30
Interquartile range	18–45	18–47
Range	0–176	0–144
Mean stent diameter, mm		
Median	3	3
Interquartile range	2.80–3.50	2.83–3.50
Patients receiving ≥2 stents	199 (24.8)	201 (25.1)
Patients receiving ≥3 stents	71 (8.8)	93 (11.6)
Patients with overlapping stents	187 (23.3)	193 (24.1)
Quantitative coronary analysis		
Lesion length, mm	16.30 ± 10.48	16.58 ± 10.74
Reference vessel diameter, before, mm	2.85 ± 0.88	2.86 ± 0.76
Minimal lumen diameter, before, mm	1.07 ± 0.56	1.08 ± 0.54
Stenosis, before, %	67 ± 16	68 ± 16
Reference vessel diameter, after, mm	2.90 ± 0.50	2.95 ± 0.51
Minimal lumen diameter, after, mm	2.70 ± 0.50	2.73 ± 0.52
Stenosis, after, %	6.9 ± 7.3	7.01 ± 7.39
Drug therapy at discharge		
Aspirin	745 (92.7)	743 (92.6)
$P2Y_{12}$ inhibitor	781 (97.1)	784 (97.8)
ACE inhibitors	517 (64.3)	514 (64.1)
Beta-blockers	604 (75.1)	588 (73.3)
Statins	695 (86.4)	684 (85.3)
Oral anticoagulant agent	101 (12.6)	107 (13.3)
Proton pump inhibitors	522 (65.1)	520 (65.1)
Drug therapy at 30 days		
Aspirin	739 (91.9)	732 (91.3)
$P2Y_{12}$ inhibitor	753 (93.7)	753 (93.9)
ACE inhibitors	489 (60.8)	506 (63.1)
Beta-blockers	587 (73.0)	590 (73.6)
Statins	670 (83.3)	663 (83.9)
Oral anticoagulant agent	108 (13.4)	105 (13.1)
Proton pump inhibitors	506 (62.9)	506 (63.1)

Continued in the next column

Values are mean ± SD or n (%), unless otherwise indicated. *There were no significant between-group differences. †Calculated in 802 patients in the BMS arm and in 800 patients in the ZES arm; ACC/AHA scores were missing in 6 patients. ‡As described in Ellis et al. (30), type A stenoses were coded 1 point; type B1 stenoses, 2 points; type B2 stenoses, 3 points; and type C stenoses, 4 points.

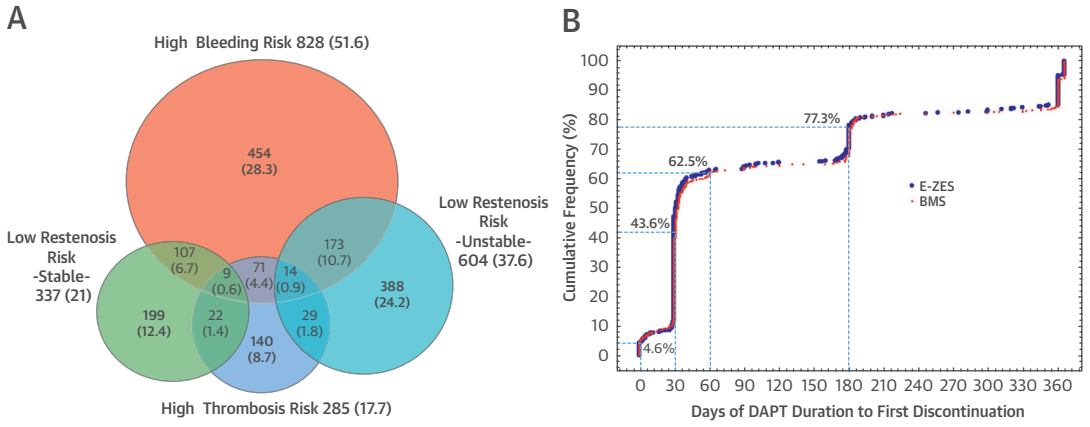
ACC/AHA = American College of Cardiology/American Heart Association; ACE = angiotensin-converting enzyme; CFX = circumflex artery; LAD = left anterior descending artery; LMCA = left main coronary artery; RCA = right coronary artery; SVG = saphenous vein graft; other abbreviations as in Table 1.

DAPT beyond 30 days in this patient population included planned staged procedures or new coronary lesions that required intervention.

There were 74 (4.6%) patients with aspirin or $P2Y_{12}$ inhibitor intolerance who did not receive DAPT; 499 (62.1%) patients in the BMS group and 505 (63.0%) patients in the ZES group received DAPT for <2 months (p = 0.72). DAPT was restarted during follow-up in 42 (5.2%) patients in the BMS group and in 27 (3.4%, p = 0.084) patients in the ZES group, mostly due to new coronary events and/or new unplanned coronary intervention. As a result, the cumulative DAPT duration trended slightly longer in the BMS group (median [IQR]: 34 days [30 to 184 days] vs. 33 days [30 to 180 days] in the ZES group, p = 0.063) (Online Figure 2).

CLINICAL OUTCOMES. During follow-up, 140 patients (17.5%) in the ZES group and 178 patients (22.1%) in the BMS arm reached the primary endpoint (hazard ratio [HR]: 0.76; 95% confidence interval [CI]: 0.61 to 0.95; p = 0.011), supporting the primary hypothesis of superior efficacy (**Central Illustration A**, **Table 3**). The difference between groups reflected a significant reduction in MI (2.9% in the ZES group vs. 8.1% in the BMS group; HR: 0.35; 95% CI: 0.22 to 0.56; p < 0.001) (**Central Illustration B**) and a significant decrease in TVR in the ZES group (5.9% in the ZES group vs. 10.7% in the BMS group; HR: 0.53; 95% CI: 0.37 to 0.75; p = 0.001) (**Central Illustration C**, **Table 3**). Although all-cause and cardiovascular mortality did not differ significantly in the ZES cohort (11.1% and 7.6%, respectively) and the BMS cohort (11.4%; HR: 0.97; 95% CI: 0.72 to 1.29; p = 0.83 and 8.3%; HR: 0.91; 95% CI: 0.64 to 1.29; p = 0.65, respectively) (**Table 3**), the composite of any death or nonfatal MI, as well as of cardiovascular death or

FIGURE 1 Characterization of the Study Population and Duration of Dual Antiplatelet Therapy



(A) Venn diagram: the **numbers reported outside each circle** indicate the cumulative frequency of each recruiting condition, including high bleeding risk (n = 828 [51.6%]), high thrombotic risk (n = 285 [17.7%]), low restenosis risk with unstable presentation (n = 604 [37.6%]), and low restenosis risk with stable presentation (n = 337 [21%]), whereas the **numbers reported in each circle** of the Venn diagram indicate the frequency of each recruiting condition as a standalone feature, and the **numbers in the overlap regions** reflect the frequency with which each recruiting condition overlap with others. **(B)** The cumulative frequency curve for the duration of DAPT in each stent group during follow-up. Duration of DAPT was quantified in days of therapy from randomization to first planned permanent discontinuation (when either of the drugs was stopped on the basis of protocol recommendations or by the treating physician, with no intention to restart treatment at a later date). BMS = bare-metal stent(s); DAPT = dual antiplatelet therapy; ZES = zotarolimus-eluting stent(s).

nonfatal MI were both significantly reduced in the ZES group (13.1% vs. 17.4%; HR: 0.73; 95% CI: 0.57 to 0.94; p = 0.018 and 9.7% vs. 14.6%; HR: 0.65; 95% CI: 0.49 to 0.87; p = 0.004, respectively).

The rate of definite stent thrombosis trended lower in the ZES group (1.0% in the ZES group vs. 2.2% in the BMS group; HR: 0.44; 95% CI: 0.19 to 1.02; p = 0.054), whereas the composite of definite or probable thrombosis (2.0% vs. 4.1%; HR: 0.48; 95% CI: 0.27 to 0.88; p = 0.019) (**Central Illustration, D**) and definite, probable, or possible stent thrombosis (4.7% vs. 7.2%; HR: 0.65; 95% CI: 0.43 to 0.97; p = 0.045) were both significantly reduced in the ZES group. Bleeding endpoints, reported in **Table 3**, did not differ between groups.

SUBGROUP ANALYSIS. As shown in **Figure 2**, when outcomes in terms of the primary endpoint of death from any cause, MI, or TVR, as well as for the secondary endpoint of death from any cause or MI were separately appraised across patients at high risk of bleeding or thrombosis or at low risk of restenosis, there was no signal of heterogeneity.

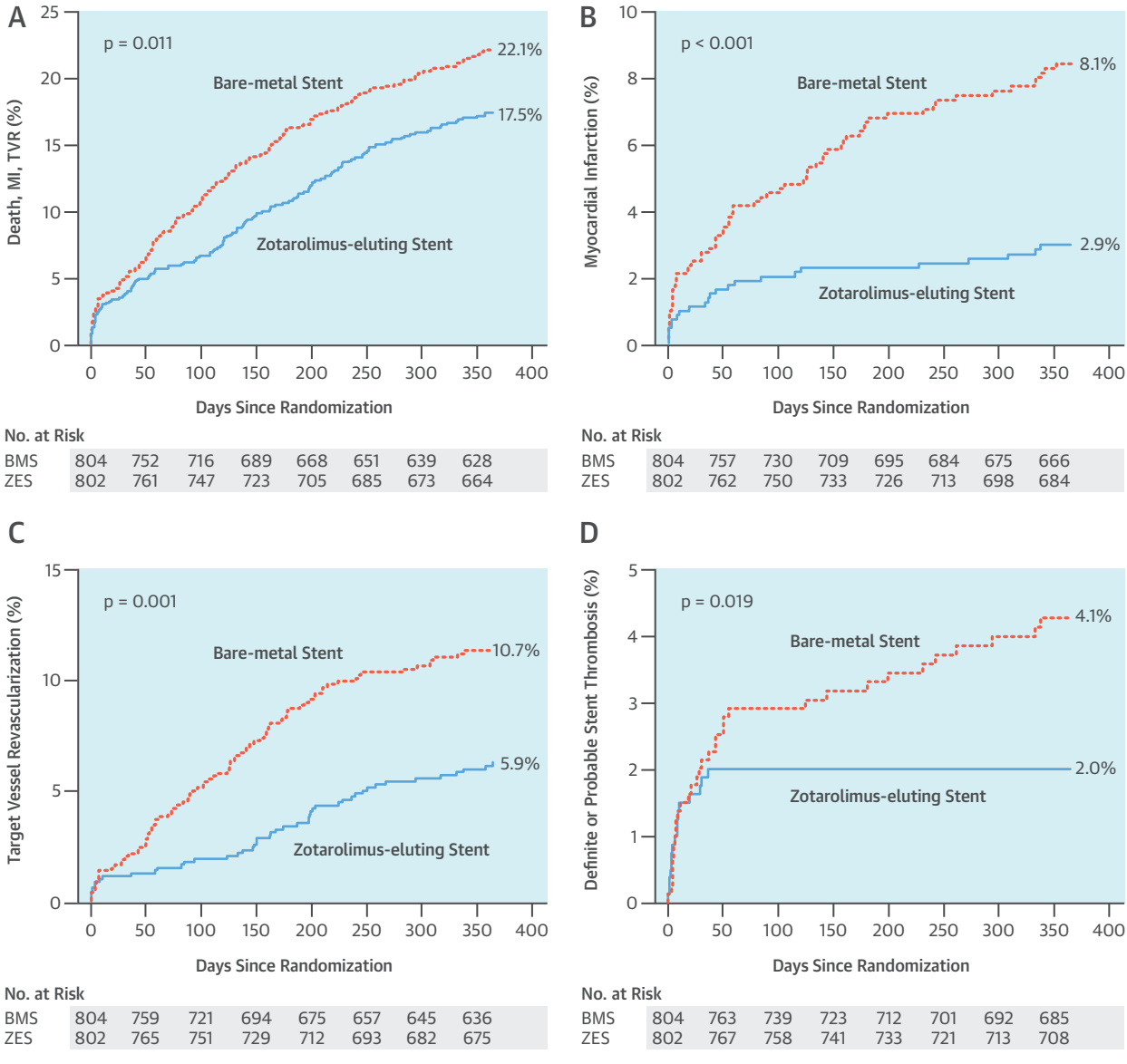
DISCUSSION

The ZEUS study focused on a unique patient population that was largely excluded from the pivotal DES trials that led to regulatory approval. We studied patients with high bleeding risk, high thrombotic risk, or low restenosis risk. Furthermore, the duration of antiplatelet therapy specified in the protocol was based not on the type of stent implanted (DES vs. BMS), but on the patient's perceived risk profile.

The advent of DES led to the recommendation that a more prolonged course of DAPT be mandated, compared with the shorter duration recommended for BMS (1,19). Hence, the effect of DES implantation has never been disentangled from that offered by a prolonged DAPT regimen.

The principal research question posed was whether the use of ZES compared with BMS, both with similar short courses of DAPT, would translate into a reduction of MACE at 1 year (**Central Illustration**). The primary hypothesis of superior efficacy of the ZES was confirmed and driven by a lower TVR rate and a lower rate of MI in the ZES group compared with the BMS group. Our study results confirmed the previously demonstrated benefit of lower TVR rates in more selected populations by showing an almost 50% relative and 5% absolute reduction of this endpoint in the ZES group compared with the BMS group. We also observed an unexpected reduction in the overall rates of MI and stent thrombosis that favored the use of

CENTRAL ILLUSTRATION **Zotarolimus-Eluting Stent in Uncertain Drug-Eluting Stent Candidates: Kaplan-Meier Curves of Study Outcomes**



Valgimigli, M. et al. J Am Coll Cardiol. 2015; 65(8):805–15.

(A) Rates of events for the primary composite outcome (death, MI, or TVR) and the principal secondary outcomes, including **(B)** MI, **(C)** TVR, and **(D)** definite or probable stent thrombosis at 1 year are shown. BMS = bare-metal stent(s); MI = myocardial infarction; TVR = target vessel revascularization; ZES = zotarolimus-eluting stent(s).

ZES. The risk of MI was reduced in the ZES group by >60% on a relative basis and by 5% on an absolute basis. At post hoc analysis, rate of type I (spontaneous) and type IVb (stent thrombosis-related) MI were significantly reduced in the ZES arm, whereas other types of MI, including peri-procedural events, did not differ between the 2 groups. The composite of definite or probable stent thrombosis was reduced by >50% in the ZES group, with an absolute difference in event rates of 2.1%. At sensitivity analysis, the benefit in terms of the study primary endpoint appeared consistent throughout the subgroups, including in those who (as per protocol) received an abbreviated 30-day DAPT regimen or a single

TABLE 3 Outcome Rates at 12 Months According to Treatment Group

	BMS (n = 804)	ZES (n = 802)	Hazard Ratio (95%CI)	p Value
Primary efficacy endpoint				
Death from any cause, myocardial infarction or target vessel revascularization	178 (22.1)	140 (17.5)	0.76 (0.61–0.95)	0.011
Secondary efficacy endpoints				
Death from any cause or myocardial infarction	140 (17.4)	105 (13.1)	0.73 (0.57–0.94)	0.018
Death from cardiovascular cause or myocardial infarction	117 (14.6)	78 (9.7)	0.65 (0.49–0.87)	0.004
Death from any cause	92 (11.4)	89 (11.1)	0.97 (0.72–1.29)	0.83
Death from cardiovascular cause	67 (8.3)	61 (7.6)	0.91 (0.64–1.29)	0.65
Myocardial infarction	65 (8.1)	23 (2.9)	0.35 (0.22–0.56)	<0.001
Target vessel revascularization	86 (10.7)	47 (5.9)	0.53 (0.37–0.75)	0.001
Target lesion revascularization	84 (10.4)	42 (5.2)	0.48 (0.33–0.70)	<0.001
Ischemic stroke	12 (1.5)	9 (1.1)	0.75 (1.32–1.77)	0.71
Definite stent thrombosis*	18 (2.2)	8 (1.0)	0.44 (0.19–1.02)	0.054
Probable stent thrombosis*	15 (1.9)	8 (1.0)	0.53 (0.23–1.25)	0.21
Possible stent thrombosis*	25 (3.1)	22 (2.7)	0.86 (0.49–1.53)	0.60
Definite or probable stent thrombosis*	33 (4.1)	16 (2.0)	0.48 (0.27–0.88)	0.019
Definite, probable, or possible stent thrombosis*	58 (7.2)	38 (4.7)	0.65 (0.43–0.97)	0.045
Safety endpoints				
TIMI classification	17 (2.1)	14 (1.7)		0.72
Major or minor				
Major	13 (1.6)	7 (0.9)		0.26
Minor	4 (0.5)	7 (0.9)		0.39
Requiring medical attention	35 (4.4)	28 (3.5)		0.44
BARC classification†				
Type 5 or 3	25 (3.1)	22 (2.7)		0.77
Type 5, 3 or 2	53 (6.6)	41 (5.1)		0.24
Type 5	7 (0.9)	4 (0.5)		0.55
Type 5A	4 (0.5)	3 (0.4)		>0.99
Type 5B	3 (0.4)	1 (0.1)		0.63
Type 4	0	0		…
Type 3	18 (2.2)	18 (2.2)		>0.99
Type 3A	6 (0.7)	5 (0.6)		>0.99
Type 3B	10 (1.2)	12 (1.5)		0.68
Type 3C	2 (0.2)	1 (0.1)		>0.99
Type 2	28 (3.5)	19 (2.4)		0.24

Values are n (%), unless indicated otherwise. *Stent thrombosis was defined according to Academic Research Consortium criteria. †Type 5 refers to fatal bleeding; Type 4 are coronary artery bypass-related bleedings; Type 3 bleedings are divided into: 3A, overt bleeding plus hemoglobin drop of 3 to <5 g/dL or any transfusion with overt bleeding; 3B, overt bleeding plus hemoglobin drop ≥5 g/dl or cardiac tamponade or bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) or bleeding requiring intravenous inotropes; and 3C, intracranial hemorrhage or intraocular bleed compromising vision. Type 2 bleedings are any overt, actionable sign of hemorrhage that does not fit the criteria for Types 3, 4, or 5, but does meet at least 1 of the following criteria: 1) requiring nonsurgical medical intervention by a health care professional; 2) leading to hospitalization or increased level of care; or 3) prompting evaluation.

BARC = Bleeding Academic Research Consortium; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

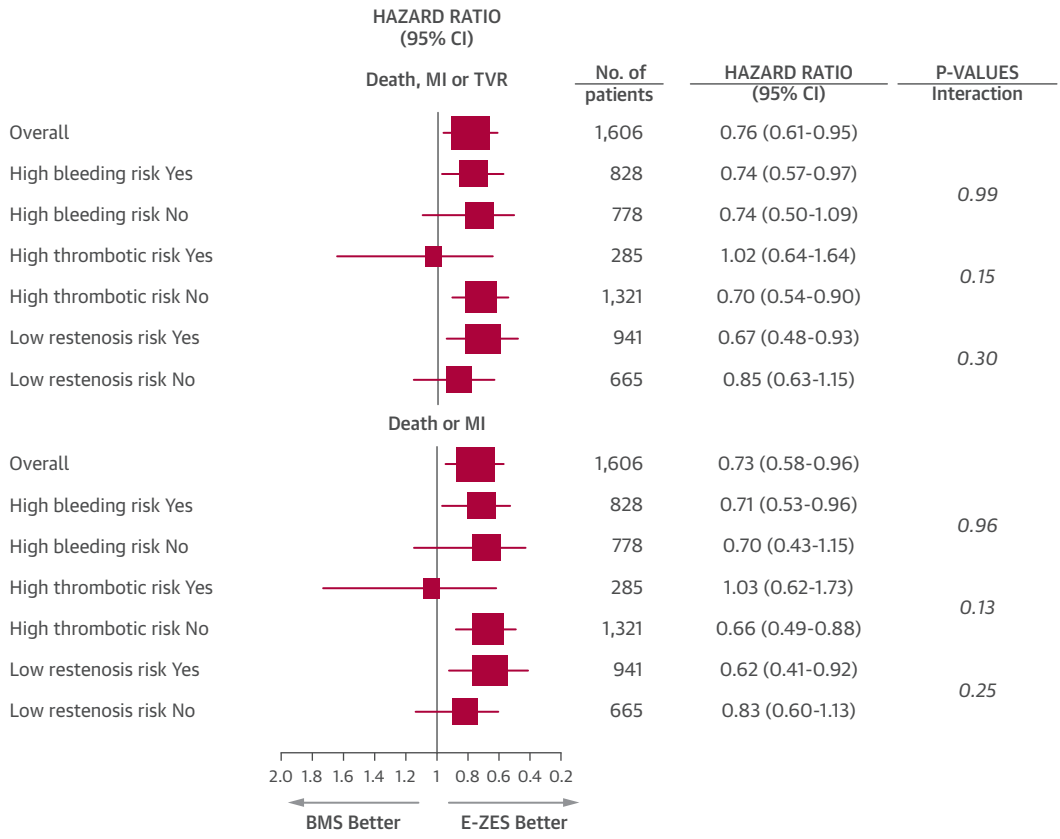
antiplatelet agent. Hence, our results suggest, for the first time, that ZES implantation followed by a personalized duration of DAPT, including a 30-day course of DAPT, is a novel and attractive strategy to reduce rates of MACE without increasing the risk of bleeding. The cumulative duration of DAPT trended longer in the BMS group, driven by the higher number of patients in this group who experienced a new MI and/or reintervention in the target vessel during follow-up. Although bleeding events did not differ between the 2 study groups at 1 year, further follow-up is needed to ascertain the long-term clinical implications of these findings, specifically the effect on cumulative bleeding endpoints of long-term DAPT duration in the BMS group and in the subgroup of patients (numerically almost 2-fold more than in the ZES group) who required reintervention for in-stent restenosis.

Observational registry (15,20) data and 3 independent randomized controlled trials (21–24) have provided reassurance on the safety of reducing DAPT duration to 6 months, or even 3 months, after ZES implantation. Moreover, long-term results of the PROTECT (Randomized Study Comparing Endeavor With Cypher Stents) study suggested that adherence to DAPT modifies the outcome of stent thrombosis to a greater extent after sirolimus-eluting stent deployment than after ZES deployment, which is most likely due to differential healing characteristics (25). These findings reinforce the concept that DAPT use should be taken into consideration when interpreting the incidence of stent thrombosis and ischemic outcomes in studies that evaluate different stent platforms (25). The results of the ZEUS study further extend these findings by demonstrating that a very short (30-day) course of therapy in the ZES group did not pose a significant risk, whereas it achieved superior clinical efficacy.

The ZES is a unique second-generation device, in that it is completely hydrophilic polymer-based, and has a specific fast-release drug profile. Although the rapid-release profile (<2 weeks) results in less powerful inhibition of intimal hyperplasia (4), it leads to more rapid and complete stent strut coverage compared with other DES, suggesting that it might be feasible to shorten DAPT duration while maintaining superior efficacy compared with BMS (11,15,26). The thrombogenicity of BMS has long been recognized (27).

The polymer coating in the ZES is hydrophilic and highly biocompatible, and potentially serves as a barrier to diminish the thrombogenic potential of the metal stent struts (11). Multiple studies comparing new-generation DES versus BMS have observed a lower stent thrombosis and/or target vessel-related MI risk after DES (5,28,29). The interplay between the lower thrombogenicity of the device and the ability to reduce late loss-related coronary events has been formulated as a putative explanation for

FIGURE 2 Subgroup Analyses



Subgroup analyses for the 3 major inclusion criteria for which randomization was stratified are shown, with HRs and 95% CIs for the primary endpoint of death from any cause, MI, or TVR, as well as for the secondary endpoint of death for any cause or MI in 1,606 patients randomly assigned to either ZES or BMS. The p value for interaction represents the likelihood of interaction between the variable and the relative treatment effect. CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; TVR = target vessel revascularization; other abbreviations as in Figure 1.

these findings. However, all these studies have systematically mandated a prolonged (and frequently much longer) DAPT regimen for DES patients compared with BMS patients (4,28,29). Hence, these studies (unlike ours) failed to disentangle the effects of the device from those of the concomitant antiplatelet therapy.

STUDY LIMITATIONS. Our study had several limitations. It was not powered to assess the effect of ZES implantation with tailored duration of DAPT on purely stent-driven endpoints, such as definite or probable stent thrombosis. Nevertheless, our observation of a lower risk of stent thrombosis in the ZES arm was reassuring. This study had a single-blind design, and no specific safeguards were adopted to ensure that patients and treating physicians remained unaware of treatment allocation beyond formal recommendations in the protocol. Thus, our study should be regarded as an open-label study with evident limitations.

Because of the unique properties of the ZES, our results should not be extrapolated to newer generation DES coated with the same or other antiproliferative agents and diverse polymers.

Because the ZES has been associated with a lower efficacy in preventing TVR compared with other more potent first- or second-generation DES (4), it remains unclear if other DES may offer similar advantages, especially in patients at high risk of bleeding or thrombosis.

Further research is needed to ascertain if the tailored DAPT regimen tested in our study can be safely implemented in patients who receive other

DES. Longer follow-up is needed to assess the durability of our study results over time.

CONCLUSIONS

The ZEUS study showed that a treatment strategy consisting of ZES implantation followed by a personalized course of DAPT, including a 30-day course of therapy, resulted in a lower risk of MACE compared with BMS in patients at high risk of bleeding or thrombosis or at low risk of restenosis.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Marco Valgimigli, Thoraxcenter, Ba 587, Erasmus Medical Center, Rotterdam, the Netherlands. E-mail: m.valgimigli@erasmusmc.nl.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with contraindications to DES exhibited better outcomes when treated with ZES followed by a relatively short course of DAPT compared with BMS, as assessed in terms of survival and freedom from MI or TVR.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether other types of DES offer similar advantages over BMS when DAPT is adjusted according to individual patient characteristics rather than stent type.

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KEY WORDS drug-eluting stent(s), dual-antiplatelet therapy, high bleeding risk, high thrombotic risk, zotarolimus-eluting stent(s)

APPENDIX For a list of investigators and the patient selection criteria and duration of dual antiplatelet therapy and supplemental figures, please see the online version of this article.