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CLINICAL RESEARCH

CORONARY

Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?

A Pre-Specified Analysis From the ZEUS Trial

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ABSTRACT

OBJECTIVES This study sought to investigate the ischemic and bleeding outcomes of patients fulfilling high bleeding risk (HBR) criteria who were randomized to zotarolimus-eluting Endeavor Sprint stent (E-ZES) or bare-metal stent (BMS) implantation followed by an abbreviated dual antiplatelet therapy (DAPT) duration for stable or unstable coronary artery disease.

BACKGROUND DES instead of BMS use remains controversial in HBR patients, in whom long-term DAPT poses safety concerns.

METHODS The ZEUS (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates) is a multinational, randomized single-blinded trial that randomized among others, in a stratified manner, 828 patients fulfilling pre-defined clinical or biochemical HBR criteria—including advanced age, indication to oral anticoagulants or other pro-hemorrhagic medications, history of bleeding and known anemia—to receive E-ZES or BMS followed by a protocol-mandated 30-day DAPT regimen. The primary endpoint of the study was the 12-month major adverse cardiovascular event rate, consisting of death, myocardial infarction, or target vessel revascularization.

RESULTS Compared with patients without, those with 1 or more HBR criteria had worse outcomes, owing to higher ischemic and bleeding risks. Among HBR patients, major adverse cardiovascular events occurred in 22.6% of the E-ZES and 29% of the BMS patients (hazard ratio: 0.75; 95% confidence interval: 0.57 to 0.98; $p = 0.033$), driven by lower myocardial infarction (3.5% vs. 10.4%; $p < 0.001$) and target vessel revascularization (5.9% vs. 11.4%; $p = 0.005$) rates in the E-ZES arm. The composite of definite or probable stent thrombosis was significantly reduced in E-ZES recipients, whereas bleeding events did not differ between stent groups.

CONCLUSIONS Among HBR patients with stable or unstable coronary artery disease, E-ZES implantation provides superior efficacy and safety as compared with conventional BMS. (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates [ZEUS]; NCT01385319) (J Am Coll Cardiol Intv 2016;9:426–36) © 2016 by the American College of Cardiology Foundation.

Drug-eluting stents (DES) reduce the restenosis rates as compared to bare-metal stents (BMS) (1-3). However, an excessive inhibition of neointimal formation with incomplete endothelialization, observed in the first-generation devices, has been associated with an increased risk of very-late stent thrombosis (ST) after dual antiplatelet therapy (DAPT) discontinuation (4,5). Second-generation DES have been developed to overcome safety concerns and maintain the efficacy similar to first-generation DES. Yet, a minimum course of 3- or 12-month DAPT duration is currently mandated after implantation of newer-generation DES according to current European or American guidelines, respectively (6,7). As a consequence, the use of DES instead of BMS remains controversial in high bleeding risk (HBR) patients, in whom long-term DAPT poses safety concerns.

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The zotarolimus-eluting Endeavor Sprint stent (E-ZES) is a hydrophilic polymer-based second-generation device with a unique drug fast-release profile (8), resulting in less powerful inhibition of intimal hyperplasia, but also in a rapid and/or complete stent strut coverage. This characteristic raises the possibility that it might be feasible to shorten DAPT duration while maintaining superior efficacy compared with BMS (9). The ZEUS (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates) study, which mandated a tailored DAPT duration based on patients' characteristics, showed a lower incidence of major adverse cardiovascular events (MACE) after E-ZES as compared with BMS in uncertain DES recipients. More than 50% of the patients fulfilled at least 1 HBR criterion in this study, and they were to be treated with a 30-day course of DAPT only.

We sought to investigate: 1) the ischemic and bleeding outcomes in relation to the presence or absence of at least 1 HBR criterion within the study population; and 2) assess the efficacy and safety of E-ZES or BMS implantation in HBR patients.

METHODS

STUDY POPULATION. The design and main study findings, including consistency of study results across inclusion criteria, of the ZEUS trial were previously reported (10,11).

Briefly, it was a multinational, randomized single-blinded trial including patients with at least 1 qualifying criterion among the pre-specified uncertain DES recipients undergoing elective, urgent, or emergent percutaneous coronary intervention with intended stent implantation. They were randomly allocated 1:1 to receive E-ZES or a thin-strut (thickness <100 μm) BMS followed by a DAPT regimen independent of stent type, but clinical-profile-driven. Randomization was stratified based upon the presence or absence of HBR status. Patients were deemed at HBR provided they fulfil at least 1 of the pre-specified criteria, including: age older than 80 years; clinical indication for treatment with oral anticoagulant agents; recent bleeding episode(s) that required medical attention or hospitalization if the bleeding diathesis has not been completely resolved; systemic conditions associated with increased bleeding risk (e.g., hematological disorders or any known coagulopathy determining bleeding-diathesis, including prior or current thrombocytopenia, which was defined as platelet count <100,000/mm^3); known anemia, defined as repeatedly documented hemoglobin <10 g/dl; and need for long-term treatment with steroids or nonsteroidal anti-inflammatory drugs.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium
BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
DAPT = dual antiplatelet therapy
E-ZES = zotarolimus-eluting Endeavor Sprint stent(s)
HBR = high bleeding risk
HR = hazard ratio
IQR = interquartile range
MACE = major adverse cardiovascular event(s)
MI = myocardial infarction
ST = stent thrombosis
TIMI = Thrombolysis In Myocardial Infarction
TVR = target vessel revascularization

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

DEVICES AND THERAPY. The Endeavor stent (Medtronic Vascular, Minneapolis, Minnesota) is constituted by a cobalt-based alloy platform (91-μm strut thickness) and a phosphorylcholine-polymer (4.8-μm) loaded with zotarolimus at the dose concentration of 10-μg/mm stent length. The drug is eluted within 15 days of implantation, and concentration within surrounding vascular tissue is not detected already at 30 days after stent deployment (8,9).

All commercially available thin-strut BMS were allowed by the protocol. All patients received aspirin and clopidogrel (300 to 600 mg orally as loading dose followed by 75 mg/day), or prasugrel (60 mg as loading dose followed by 10 or 5 mg/day) or ticagrelor (180 mg as loading dose followed by 90 mg twice a day). All HBR patients were treated with DAPT for a pre-specified 30-day period after stent implantation. In case of a staged procedure, DAPT had to be prolonged or restarted for 30 additional days. Patients who were not eligible for DAPT were treated with aspirin or $P2Y_{12}$ inhibitor monotherapy. Unfractionated heparin or bivalirudin was used during percutaneous coronary procedure according to guideline-recommended regimens.

STUDY ENDPOINTS AND FOLLOW-UP. The primary endpoint of the ZEUS trial was MACE at 12 months, defined as a composite of all-cause death, nonfatal MI, and any target vessel revascularization (TVR).

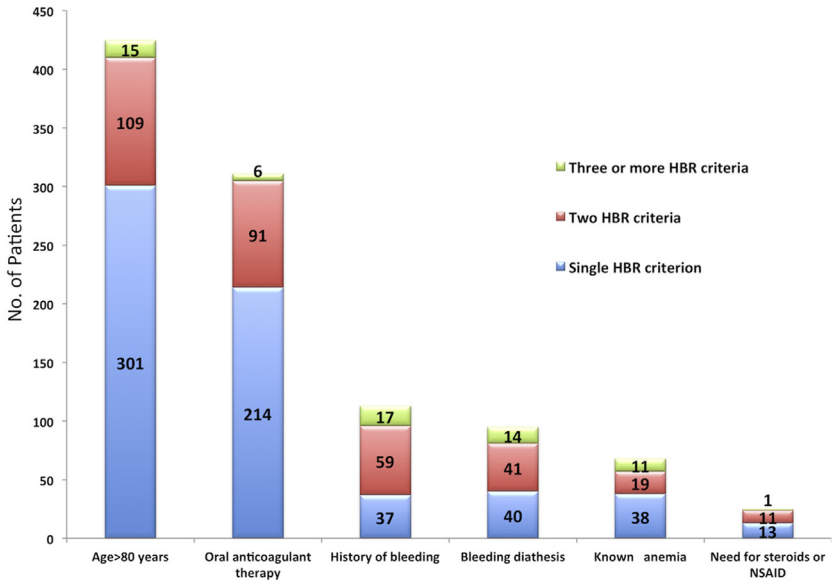
Secondary efficacy endpoints were the composite of death and MI; the composite of cardiovascular death and MI; each component of the primary endpoint; target lesion revascularization, ischemic stroke; definite, probable, possible ST and the composite of definite and probable ST. Secondary safety endpoints comprised bleeding events according to both Bleeding Academic Research Consortium (BARC) and Thrombolysis In Myocardial Infarction (TIMI) classifications. All study endpoint definitions were previously reported (11).

Thirty-day and 6- and 12-month follow-up visits were performed according to study protocol in order to assess potential adverse events and compliance with medications and to record a 12-lead electrocardiogram.

All endpoints were confirmed on the basis of the documentation collected at each site and were centrally adjudicated by the clinical events committee, whose members were unaware of treatment assignment.

STATISTICAL ANALYSIS. In this pre-specified analysis of the ZEUS trial, categorical variables were

FIGURE 1 HBR Criteria in the Study Population



The number of patients fulfilling each high bleeding risk (HBR) criterion is shown in decreasing order. There was a considerable overlap among HBR criteria, with 643 patients (78%) fulfilling 1, 330 (40%) 2, and 65 (8%) ≥3 HBR qualifying features. NSAID = nonsteroidal anti-inflammatory drugs.

expressed as frequency and percentage, and compared using the Fisher exact test, whereas continuous variables were expressed as median and interquartile range, and compared with the Wilcoxon rank sum test.

Estimation of the cumulative incidence of events was performed by the Kaplan-Meier method, and hazard ratios (HRs) with 95% confidence intervals (CIs) and p values were calculated using the stratified Cox regression model. The proportionality assumptions were checked by visual estimation after plotting the log cumulative hazard versus (log) time at follow-up after index procedure and by applying a test for nonproportional hazards using the Schoenfeld residuals, which failed to reject the null hypothesis that event rate was affected by time ($p = 0.48$). Sensitivity analyses were performed testing the consistency of study results in patients with only 1 or at least 2 HBR criteria, as well as investigating the effect of allocated stent type on outcomes according to each HBR criterion when separately appraised.

A 2-sided p value <0.05 was considered significant. All analyses were performed on the basis of the intention-to-treat principle using SPSS version 21.0 (SPSS, Chicago, Illinois).

RESULTS

STUDY POPULATION. From June 2011 to September 2012, a total of 5,288 patients were screened and 1,606 were finally randomized. A total of 828 patients fulfilled 1 or more HBR criteria, of whom 425 (51.3%) age >80 years, 311 (37.6%) had clinical indication to oral anticoagulant (Online Table 1), 113 (13.6%) reported previous or recent bleeding requiring hospitalization or medical attention, 95 (11.5%) presented bleeding diathesis, 68 (8.2%) had known anemia, and 25 (3.0%) were in need of long-term treatment with steroids or nonsteroidal anti-inflammatory drugs. There was a considerable overlap among HBR criteria, with 643 patients (78%) fulfilling 1, 330 (40%) 2. and 65 (8%) ≥3 HBR qualifying features (**Figure 1**).

Baseline patient characteristics stratified according to the presence or absence of HBR status are shown in Online Tables 2 and 3.

Among HBR patients, of whom 424 (51.2%) were randomized to receive E-ZES, and 404 (48.8%) to BMS, baseline clinical and angiographic features were well-matched between stent groups (**Tables 1 and 2**). The median age was 80 years; diabetes was observed in roughly one-third of the population, hypertension in more than 80%, impaired kidney function in approximately 60% of the patients, and 65% of patients had acute coronary syndrome at presentation (**Table 1**). One third of the patients underwent multivessel intervention, and at least 1 complex lesion was treated in approximately three-fourths of the patients (**Table 2**).

TABLE 1 Baseline Characteristics of Patients at HBR

	Bare-Metal Stent (n = 404)	Endeavor Stent (n = 424)	p Value
Age, yrs			
Median	80.5	80.4	0.83
Interquartile range	72.3–84.4	72.8–84.9	
Female	145 (35.9)	150 (35.4)	0.89
Body mass index, kg/m^2			
Median	26	26	0.96
Interquartile range	24–29	24–29	
Diabetes	117 (29.0)	137 (32.3)	0.33
Hypertension	336 (83.2)	344 (81.1)	0.47
Hyperlipidemia	193 (47.8)	191 (45.0)	0.44
Current cigarettes use	45 (11.1)	44 (10.4)	0.36
Creatinine clearance, ml/min*			
Median	54.3	54.8	0.90
Interquartile range	39.1–69.9	38.7–69.9	
Patients with GFR <60 ml/min*	242 (61.3)	241 (59.5)	0.61
Patients with GFR <30 ml/min*	51 (12.9)	52 (12.8)	>0.99
Patients on dialysis	6 (1.5)	14 (3.3)	0.11
Prior MI	114 (28.2)	117 (27.6)	0.88
Prior PCI	83 (20.5)	90 (21.2)	0.86
Prior CABG	38 (9.4)	39 (9.2)	>0.99
Prior stroke or TIA	34 (8.4)	32 (7.5)	0.70
COPD	43 (10.6)	32 (7.5)	0.15
PAD	94 (23.3)	76 (17.9)	0.06
Left ventricular ejection fraction†			
Median	49	48	0.59
Interquartile range	40–55	40–55	
Clinical presentation			
Stable angina pectoris	140 (34.7)	147 (34.7)	>0.99
Acute coronary syndrome			
Unstable angina	69 (17.1)	72 (17.0)	>0.99
Non-ST-segment elevation MI	133 (32.9)	140 (33.0)	>0.99
ST-segment elevation MI	62 (15.3)	65 (15.3)	>0.99
Angiographic features			
Single-vessel disease	125 (30.9)	138 (32.5)	0.716
Double-vessel disease	144 (35.6)	146 (34.4)	
Triple-vessel disease	132 (32.7)	139 (32.8)	

Values are n (%), unless indicated otherwise. *Calculated in 395 patients in the BMS arm and in 405 patients in the E-ZES arm. †Calculated in 380 patients in the BMS arm and in 397 patients in the E-ZES arm.

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtrate rate; HBR = high bleeding risk; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

DUAL ANTIPLATELET THERAPY. The duration of DAPT—which largely consisted of aspirin and clopidogrel—was almost 5-fold shorter in patients with HBR criteria (median [interquartile range]: 30 [20 to 30] days) as compared with those without HBR criteria (median [interquartile range]: 174 [30 to 190] days; $p < 0.0001$).

TABLE 2 Procedural Results and Use of Medications During the Trial in Patients at HBR

	Bare-Metal Stent (n = 404)	Endeavor Stent (n = 424)	p Value
Treated lesions, n			
Median	1	1	0.82
Interquartile range	1–2	1–2	
≥2 Treated lesions*	154 (38.1)	151 (35.7)	0.47
Multivessel intervention	130 (32.2)	141 (33.3)	0.77
LAD treated	196 (48.5)	234 (55.2)	0.06
CFX treated	155 (38.4)	141 (33.3)	0.13
RCA treated	161 (39.9)	162 (38.2)	0.67
LMCA treated	27 (6.7)	26 (6.1)	0.78
SVG treated	6 (1.5)	8 (1.9)	0.79
At least 1 complex (type B2 or C) lesion	310 (76.7)	321 (75.7)	0.75
Total ACC/AHA score†			
Median	7	7	0.94
Interquartile range	4–11	4–11	
Stents implanted, n			
Median	1	1	>0.99
Interquartile range	1–2	1–2	
Length of stent, mm			
Median	28	30	0.96
Interquartile range	18–46	18–44	
Mean stent diameter, mm‡			
Median	3	3	0.14
Interquartile range	2.75–3.50	2.75–3.25	
Patients receiving ≥2 stents	182 (45.0)	191 (45.0)	>0.99
Patients receiving ≥3 stents	73 (18.1)	77 (18.2)	>0.99
Patients with overlapping stents	103 (25.5)	106 (25.0)	0.87
Quantitative coronary analysis			
Lesion length, mm§	16.88 ± 10.44	16.44 ± 10.64	0.28
Reference vessel diameter, before, mm§	2.65 ± 0.59	2.67 ± 0.61	0.90
Minimal lumen diameter, before, mm§	0.89 ± 0.48	0.88 ± 0.51	0.28
Stenosis, before, %§	66 ± 15	68 ± 16	0.23
Reference vessel diameter, after, mm‡	2.86 ± 0.50	2.86 ± 0.51	0.89
Minimal lumen diameter, after, mm§	2.65 ± 0.52	2.64 ± 0.55	0.81
Stenosis, after, %§	7.4 ± 8.6	7.5 ± 11.4	0.47
Drug therapy at discharge			
Aspirin	377 (93.3)	386 (91.0)	0.25
$P2Y_{12}$ inhibitor	387 (95.8)	410 (96.7)	0.58
ACE inhibitor	234 (57.9)	240 (56.6)	0.73
Beta-blocker	307 (76.0)	299 (70.5)	0.08
Statin	321 (79.5)	347 (81.8)	0.43
Oral anticoagulation	96 (23.8)	100 (23.6)	>0.99
Proton pump inhibitor‖	290 (71.8)	293 (69.4)	0.49
Drug therapy at 30 days			
Aspirin	373 (92.3)	383 (90.3)	0.33
$P2Y_{12}$ inhibitor	364 (90.1)	389 (91.7)	0.47
ACE inhibitor¶	213 (52.7)	242 (57.1)	0.40
Beta-blocker¶	297 (73.5)	297 (70.0)	0.54
Statin¶	303 (75.0)	336 (79.2)	0.25
Oral anticoagulation	100 (24.8)	97 (22.9)	0.81
Proton pump inhibitor#	267 (69.0)	270 (66.5)	0.49

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Among HBR patients, 14 (3%) patients in each stent group received treatment with a single antiplatelet agent after stent implantation; among those who received DAPT, treatment was stopped within the first 15, 30, and 60 days in 5 (1.2%), 151 (37.4%), and 291 (72.0%) patients in the BMS and 10 (2.4%), 245 (57.8%), and 323 (76.2%) in the E-ZES group, respectively ($p < 0.001$). Reasons for prolonging DAPT beyond 30 days included planned or unplanned procedures in de novo lesions, which were evenly distributed between stent groups, or need for reintervention in previously instrumented coronary segments, which explained the longer DAPT duration in the BMS group.

BLEEDING RISK CRITERIA AND OUTCOMES. Any actionable BARC bleeding was almost 2-fold higher in patients with (7.7%) as compared with those without (3.9%; HR: 2.32; 95% CI: 1.49 to 3.62; $p < 0.001$) at least 1 HBR criterion whereas major BARC (4.2% vs. 1.5%; HR: 2.93; 95% CI: 1.51 to 5.70; $p = 0.001$) and major or minor TIMI bleeding (2.8% vs. 1.0%; HR: 2.87; 95% CI: 1.28 to 6.41; $p = 0.011$) were almost three-fold greater in the former group. There was evidence of an additive effect on bleeding outcomes with respect to the presence of only 1 or more than 1 HBR features (Figure 2).

The cumulative risk of death, MI or TVR was doubled in HBR (25.7% vs. 13.5%; $p < 0.001$) as compared with other patients, driven by higher rates of death (16.5% vs. 5.7%; $p < 0.001$) or MI (6.9% vs. 4.0%; $p = 0.012$). Definite or probable ST was also increased in HBR patients (4.3% vs. 1.7%; $p = 0.002$).

When adjustment was implemented for baseline imbalances, residual bleeding (BARC type 2, 3, or 5 HR: 1.33, 95% CI: 0.75 to 2.36, $p = 0.332$; BARC type 3 or 5 HR: 2.05, 95% CI: 0.84 to 4.98, $p = 0.114$; TIMI major or minor HR: 2.15, 95% CI: 0.73 to 6.29, $p = 0.163$) and mortality (adjusted HR: 1.46; 95% CI: 0.95 to 2.25; $p = 0.083$) risks no longer differed.

STENT TYPES AND OUTCOMES IN HBR PATIENTS. At 12 months, the primary endpoint occurred in 96 (22.6%) patients in the E-ZES and in 117 (29%) patients in the BMS group (HR: 0.75; 95% CI: 0.57 to 0.98; $p = 0.033$), owing to lower MI (3.5% vs. 10.4%; HR: 0.33; 95% CI: 0.18 to 0.60; $p < 0.001$) and TVR (5.9% vs. 11.4%; HR: 0.50; 95% CI: 0.30 to 0.80; $p = 0.005$) rates in the E-ZES compared with BMS cohort (Figure 3, Table 3). The composite of death and MI (18.4% vs. 24.8%; HR: 0.72; 95% CI: 0.53 to 0.96; $p = 0.027$) as well as cardiovascular death or MI (14.6% vs. 20.3%; HR: 0.70; 95% CI: 0.50 to 0.97; $p = 0.032$) were lower in the E-ZES group, whereas mortality did not differ (Table 3). Definite or probable ST (2.6% vs. 6.2%; HR: 0.42; 95% CI: 0.21 to 0.85; $p = 0.016$) and definite, probable or possible ST (6.6% vs. 10.6%; HR: 0.61; 95% CI: 0.38 to 0.98; $p = 0.042$) were respectively more than halved or reduced by almost 40% in E-ZES-treated patients (Table 3).

Interestingly, the occurrence of ST appeared evenly distributed in the BMS group when considering the on versus off-DAPT follow-up duration, whereas only 1 of 11 ST cases in patients allocated to E-ZES occurred while patients were off DAPT.

A trend towards a lower bleeding risk was noted in the E-ZES cohort with respect to BARC 2, 3, or 5 events (6.1% vs. 9.4%; HR: 0.65; 95% CI: 0.39 to 1.07; p = 0.089), whereas major BARC or TIMI major or minor events did not differ between stent groups (Table 3).

ADDITIONAL ANALYSES. The consistency of outcomes with respect to the presence of a single or multiple HBR features is shown in Figure 4. The primary endpoint outcomes in relation to each HBR criterion are shown in Online Figure 1. A further sensitivity analysis focusing on patients with atrial fibrillation showed consistent findings (Online Figure 2).

DISCUSSION

Patients at HBR represent a well sizable portion of coronary artery disease population undergoing percutaneous coronary stenting. However, these patients have been largely excluded from major randomized controlled trials evaluating different stent types. Although multiple bleeding risk scores or single individual risk factors for bleeding exist (12–14), HBR status is rarely defined according to objective risk criteria (15–17). The lack of standardized algorithms for the identification of HBR patients hampers comparability across studies and limit their external validity in clinical practice.

TABLE 2 Continued

	Bare-Metal Stent (n = 404)	Endeavor Stent (n = 424)	p Value
Dual antiplatelet therapy duration			
Median	31	30	0.009
Interquartile range	30–177	30–53	
Range	0–365	0–365	

Values are n (%) or mean ± SD, unless indicated otherwise. *Calculated in 404 patients in the BMS arm and in 423 in the E-ZES arm. †Calculated in 402 patients in the BMS arm and in the 422 in the E-ZES arm. ‡Calculated in 395 patients in the BMS arm and in the 416 patients in the E-ZES arm. §Calculated in 396 patients in the BMS arm and in 422 patients in the E-ZES arm. ||Calculated in 404 patients in the BMS arm and in 422 in the E-ZES arm. ¶Calculated in 389 patients in the BMS arm and in 407 patients in the E-ZES arm. #Calculated in 387 patients in the BMS arm and in the 406 patients in the E-ZES arm.

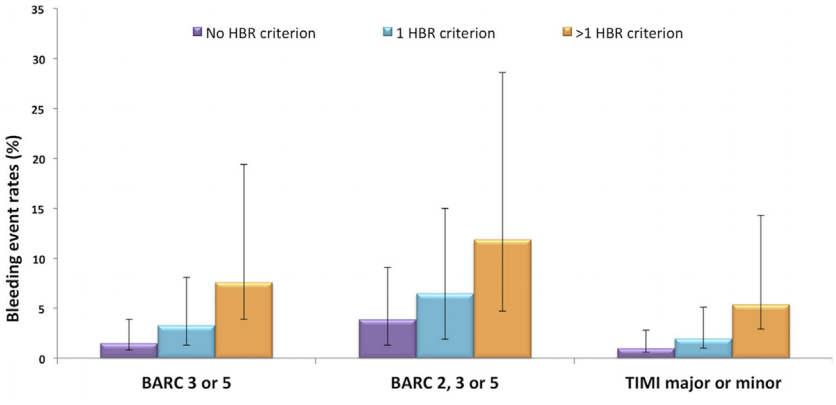
ACC/AHA = American College of Cardiology/American Heart Association; ACE = angiotensin-converting enzyme; HBR = high bleeding risk; LAD = left anterior descending coronary artery, CFX = circumflex coronary artery, RCA = right coronary artery, LMCA = left main coronary artery, SVG = saphenous vein graft.

As a reflection of limited evidence for the use of DES in this population, 6 of 10 (576 of 946) participants preferred BMS whereas only 1 out of 20 (44 of 946) responders vouched for the value of newer-generation DES for HBR patients in a recent European survey (18).

MAIN STUDY FINDINGS. In the ZEUS trial, 828 patients fulfilling at least 1 pre-specified HBR criterion were randomized to receive BMS or E-ZES, which is a hydrophilic polymer-based second-generation device with a unique drug, fast-release profile. In this selected high-risk patient population, the study protocol mandated 30-day DAPT irrespective of the stent type. The results of our study can be summarized as follows:

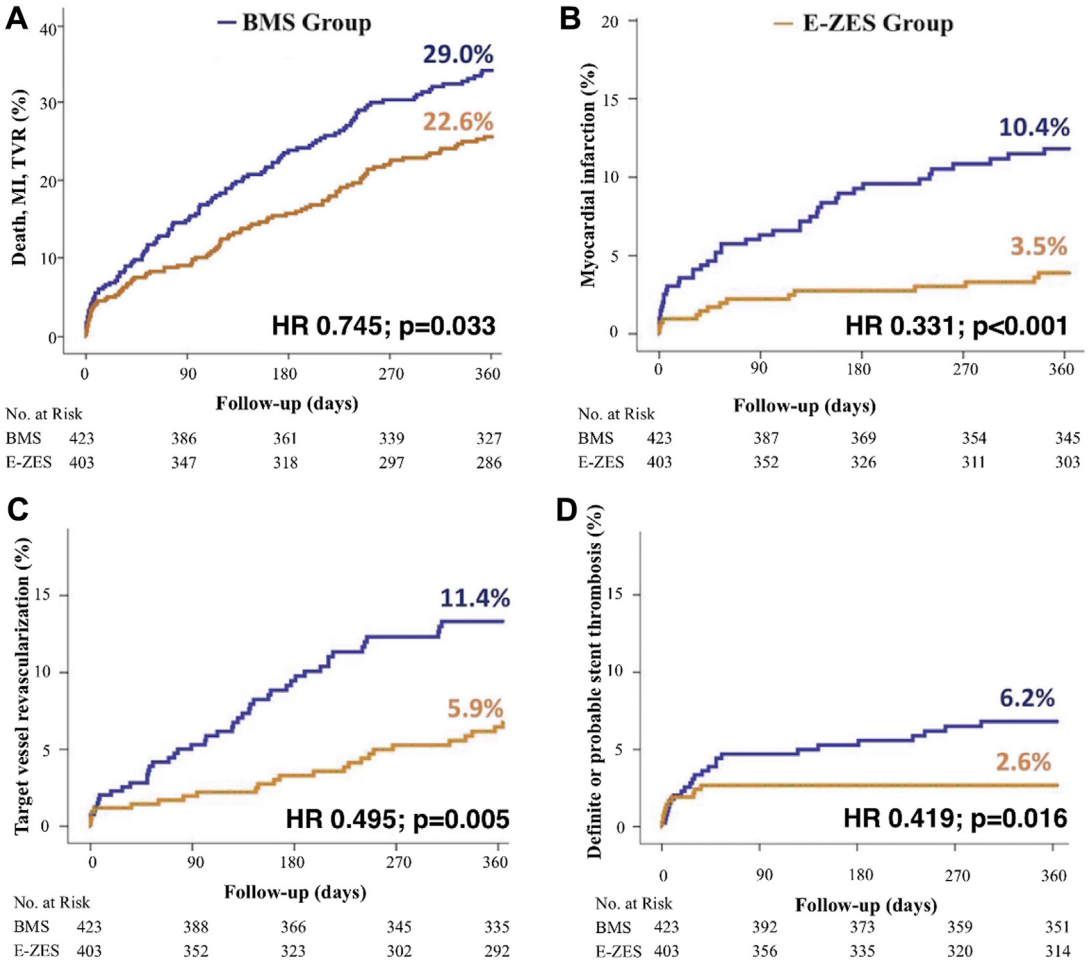
- Patients at HBR, who have been selected according to pre-specified objective criteria, displayed higher

FIGURE 2 Bleeding Event Rates According to The Presence and Number of HBR Criteria



There was evidence of an additive effect on bleeding outcomes with respect to the presence of only 1 or more than 1 high bleeding risk (HBR) features; p value for trend <0.001. **Vertical bars** represent 95% confidence intervals. BARC = Bleeding Academic Research Consortium; TIMI = Thrombolysis In Myocardial infarction.

FIGURE 3 Clinical Outcomes in the HBR Population Treated With Zotarolimus-Eluting Stents Versus BMS



Rate of events for primary composite endpoint of death, myocardial infarction (MI), and target vessel revascularization (TVR) **(A)**, MI **(B)**, TVR **(C)**, or definite or probable stent thrombosis **(D)** at 12 months. BMS = bare-metal stent(s); E-ZES = zotarolimus-eluting Endeavor Sprint stent(s); HBR = high bleeding risk; HR = hazard ratio.

risk of bleeding, consistently across all assessed bleeding scales, which was proportionally greater depending on the number of HBR criteria simultaneously fulfilled as compared with patients without HBR features.

- Patients at HBR were also at higher MACE risk as compared with patients who were not at HBR status, driven by higher death and MI rates. ST was almost 3-fold greater in patients with as compared with those without HBR criteria. This observation reinforces the notion that bleeding predictors largely overlap with risk factors for ischemic complications and highlights the challenge of identifying a safe and effective anti-thrombotic treatment in this patient population in clinical practice.
- HBR patients derived benefits in terms of reductions of MACE, MI, TVR, and ST when treated with E-ZES as compared with BMS, which is consistent with study results observed in the overall population (11). At sensitivity analyses, results remained entirely consistent focusing on patients who displayed 2 or more HBR features, or evaluating each HBR criterion separately. A further analysis restricted to patients with atrial fibrillation, which was the most frequent indication to oral anticoagulation, confirmed overall study findings.
- Despite comparable protocol-mandated DAPT durations in both stent groups, cumulative treatment duration with aspirin and $P2Y_{12}$ inhibitor was significantly longer in BMS as compared with E-ZES

TABLE 3 Outcome Rates at 12 Months According to Treatment Group in Patients at HBR

	Bare-Metal Stent (n = 404)	Endeavor Stent (n = 424)	Hazard Ratio (95% Confidence Interval)	p Value
Primary efficacy endpoint				
Death for any cause, myocardial infarction, or target vessel revascularization	117 (29.0)	96 (22.6)	0.745 (0.568–0.977)	0.033
Secondary efficacy endpoints				
Death for any cause or myocardial infarction	100 (24.8)	78 (18.4)	0.715 (0.531–0.963)	0.027
Death for cardiovascular cause or myocardial infarction	82 (20.3)	62 (14.6)	0.695 (0.499–0.968)	0.032
Death for any cause	70 (17.3)	67 (15.8)	0.913 (0.652–1.278)	0.595
Death for cardiovascular cause	51 (12.6)	50 (11.8)	0.931 (0.629–1.378)	0.720
Myocardial infarction	42 (10.4)	15 (3.5)	0.331 (0.184–0.598)	<0.001
Target vessel revascularization	46 (11.4)	25 (5.9)	0.495 (0.304–0.806)	0.005
Target lesion revascularization	45 (11.1)	22 (5.2)	0.443 (0.266–0.739)	0.002
Ischemic stroke	11 (2.7)	5 (1.2)	0.432 (0.150–1.245)	0.120
Definite stent thrombosis*	10 (2.5)	4 (0.9)	0.381 (0.119–1.217)	0.103
Probable stent thrombosis*	15 (3.7)	7 (1.7)	0.448 (0.182–1.099)	0.079
Possible stent thrombosis*	18 (4.5)	17 (4.0)	0.870 (0.448–1.689)	0.681
Definite or probable stent thrombosis*	25 (6.2)	11 (2.6)	0.419 (0.206–0.853)	0.016
Definite, probable, or possible stent thrombosis*	43 (10.6)	28 (6.6)	0.610 (0.379–0.983)	0.042
Safety endpoints				
TIMI classification				
Major or minor	13 (3.2)	10 (2.4)	0.734 (0.322–1.674)	0.462
Major	10 (2.5)	6 (1.4)		0.318
Minor	3 (0.7)	4 (0.9)		>0.99
Requiring medical attention	25 (6.2)	16 (3.8)		0.148
BARC classification†				
Type 5 or 3	20 (5.0)	15 (3.5)	0.718 (0.368–1.404)	0.333
Type 5, 3, or 2	38 (9.4)	26 (6.1)	0.648 (0.393–1.068)	0.089
Type 5	4 (1.0)	2 (0.5)		0.441
Type 5A	3 (0.7)	1 (0.2)		0.362
Type 5B	1 (0.2)	1 (0.2)		>0.99
Type 4	0	0		–
Type 3	16 (4.0)	13 (3.1)		0.572
Type 3A	5 (1.2)	2 (0.5)		0.276
Type 3B	9 (2.2)	10 (2.4)		>0.99
Type 3C	2 (0.5)	1 (0.2)		0.616
Type 2	18 (4.5)	11 (2.6)		0.185

Values are n (%), unless indicated otherwise. *Stent thrombosis was defined according to the criteria of the Academic Research Consortium. †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 tamponed or bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) or bleeding requiring intravenous inotropes, 3C: intracranial hemorrhage or intraocular bleed compromising vision; Type 2 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; and 3) prompting evaluation.

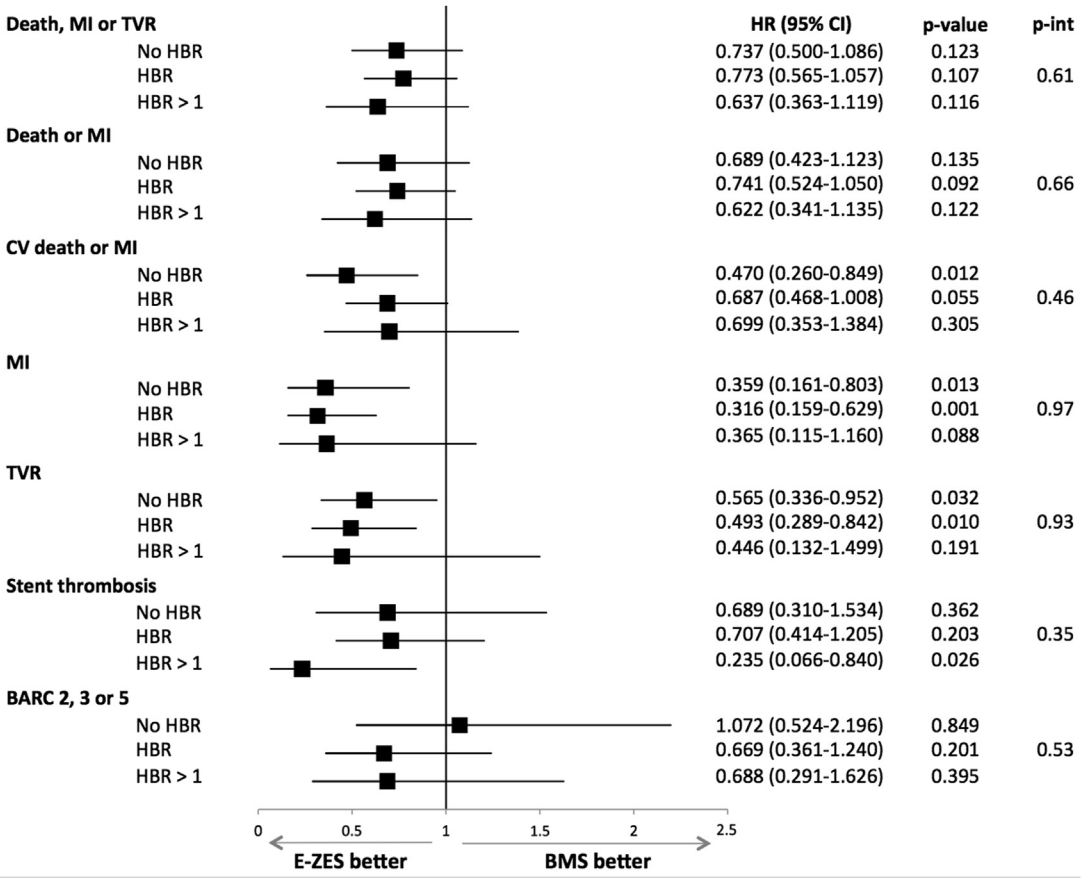
BARC = Bleeding Academic Research Consortium; HBR = high bleeding risk; TIMI = Thrombolysis In Myocardial Infarction.

patients (Table 2), reflecting a higher TVR rate in the former group of patients. Bleeding events trended higher in the BMS compared with the E-ZES groups, reflecting the longer DAPT after BMS implantation.

COMPARISON WITH OTHER STUDIES. Randomized controlled trials, which have so far compared DES versus BMS, have recommended either a longer DAPT regimen in the DES arm or a similarly prolonged course of DAPT in BMS patients so to match the extended course of therapy after DES (19,20). Hence, no study has so far disentangled the effects of DES versus BMS from those offered by long-term DAPT.

The recent DAPT trial (21) that compared 30- versus 12-month duration of DAPT after stent implantation in patients with stable or unstable coronary artery disease, showed a significant decrease of very late stent thrombosis and major adverse cardiovascular and cerebrovascular events at 30 months after stent implantation in the long-term DAPT arm. Yet, patients exposed to long-term DAPT also experienced a borderline and significant increase in overall mortality at 30 and 33 months, respectively (21). Patients

FIGURE 4 Clinical Outcomes in Zotarolimus-Eluting Stents Versus BMS According to the Absence or Presence of a Single or Multiple HBR Features



Patients without HBR criteria (No HBR), fulfilling 1 (HBR 1) or more than 1 (HBR>1) HBR criteria are shown, with HR and 95% confidence intervals (CI), for the primary endpoint of all-cause death, MI, and TVR; death or MI; cardiovascular (CV) death or MI; MI; TVR; definite, probable, or possible stent thrombosis and BARC type 2, 3, or 5 bleeding events among patients randomly assigned to either E-ZES or BMS group. P-int = p value for interaction. Abbreviations as in Figures 2 and 3.

who received BMS implantation, at discretion of the treating physician were excluded from primary analysis, whereas only patients who were free from ischemic and bleeding events after 12-month DAPT were included in the study. Hence, patients at HBR were excluded from the DAPT trial, and this study was not designed to answer the question as to which type of stent should be better used at the time of intervention in patients fulfilling 1 or more HBR criteria.

The WOEST (What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing) trial (22) included a total of total of 573 patients receiving oral anticoagulant (~70% due to atrial fibrillation) who were randomly assigned to clopidogrel alone (experimental treatment) or clopidogrel plus aspirin (control treatment) for a period of 1 month after BMS and 12 months after DES implantation. The primary endpoint, consisting of any TIMI bleeding, was significantly lower in the dual therapy group, largely driven by minimal or minor bleeding, without an increase in MI, TVR, stroke or stent thrombosis.

The ISAR-TRIPLE (Intracoronary Stenting and Antithrombotic Regimen-Testing of a Six-Week Versus a six-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting) trial (23) is the largest randomized trial investigating triple therapy after DES implantation in patients with clinical indication to oral anticoagulant (~85% due to atrial fibrillation). A total of 614 patients were randomly

assigned to therapy with clopidogrel for 6 weeks (n = 307) or 6 months (n = 307). The primary endpoint, a composite of death, MI, ST, stroke, or TIMI major bleeding, failed to show the anticipated superiority of short- versus long-term triple therapy duration.

The ZEUS study is therefore the first randomized controlled trial comparing 2 different stent types in HBR patients after mandating a similarly short course of DAPT. An interesting observation was that BMS patients received a longer cumulative DAPT duration as compared with those assigned to E-ZES, reflecting the more frequent need to re-start DAPT after reintervention for in-stent restenosis or ST. Given the observation that long-term DAPT duration may be paramount in patients receiving DES implantation for the treatment of an in-stent restenosis (24), our current findings may further justify the selection of a safe DES over a BMS in this patient population to minimize the risk of in-stent restenosis, which would then require reintervention followed by a prolonged course of DAPT.

The lower risk of MI or ST observed in patients treated with E-ZES as compared to BMS, despite a similarly short DAPT duration in both stent groups, is consistent with the mounting evidence that lower in-stent intimal hyperplasia may carry not only greater efficacy (e.g., lower TVR), but also improved safety (e.g., lower ST or stent-related MIs) (4, 25,26).

STUDY LIMITATIONS. By design, our study does not address the topic of optimal DAPT duration after stenting. On the other hand, the results of our investigation challenge the current wisdom that BMS is per se a safer coronary device as compared with DES under a similarly short DAPT duration. Because of the unique properties of the E-ZES, our results should not be extrapolated to newer-generation DES coated with the same or other antiproliferative agents and diverse or no polymers. As for all substudies, type I and type II errors are not corrected for. Hence, our results should be hypothesis-generating. Further research is needed to ascertain whether the tailored DAPT regimen tested in our study can be safely implemented in patients receiving other DES. The recently reported LEADERS-FREE (A Randomized Clinical Evaluation of the BioFreedom™ Stent) trial (27) largely reproduced our study findings in terms of both better efficacy and safety in an HBR population after the use of a drug-coated stent as compared with the corresponding BMS. Therefore, it remains to be seen whether other permanent or bioresorbable polymer-based DES could be safely employed after a 30-day DAPT regimen.

CONCLUSIONS

Our study provides proof of concept that in HBR patients who undergo stent implantation, E-ZES as compared with conventional BMS followed by 30-day DAPT regimen provides superior efficacy and safety. Future studies are needed to assess the tolerability and safety of more contemporary DES when followed by an abbreviated DAPT duration in this challenging patient population.

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PERSPECTIVES

WHAT IS KNOWN? The use of DES instead of BMS is matter of debate in patients at high bleeding risk, in whom the benefits of DES in terms of ischemic endpoints could be reduced by an increase of bleeding events due to a long-term DAPT.

WHAT IS NEW? Our study demonstrated that the use of a specific drug-eluting stent (zotarolimus-eluting Endeavor Sprint stent), followed by a very short DAPT regimen, in a HBR population with stable or unstable coronary artery disease, provides superior efficacy and safety as compared with available BMS.

WHAT IS NEXT? Further research is needed to ascertain whether an abbreviated DAPT regimen, as tested in our study, can be safely implemented in patients receiving other types of DES.

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

APPENDIX For supplemental figures and tables, please see the online version of this article.