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Impact of angiographic coronary artery disease complexity on ischemic and bleeding risks and on the comparative effectiveness of zotarolimus-eluting vs. bare-metal stents in uncertain drug-eluting stent candidates☆

Giuseppe Gargiulo [a,b], Athanasios Patialiakas [c], Raffaele Piccolo [b], Attila Thury [d], Salvatore Colangelo [e], Gianluca Campo [f,g], Matteo Tebaldi [f], Imre Ungi [d], Stefano Tondi [h], Marco Roffi [i], Alberto Menozzi [j], Nicoletta de Cesare [k], Roberto Garbo [e], Emanuele Meliga [l], Luca Testa [m], Henrique Mesquita Gabriel [n], Marco Ferlini [o], Francesco Liistro [p], Antonio Dellavalle [q], Pascal Vranckx [r], Carlo Briguori [s], Stephan Windecker [a], Marco Valgimigli [a,*], For the Zotarolimus-eluting Endeavor sprint stent in Uncertain DES candidates (ZEUS) Investigators

[a] Department of Cardiology, Bern University Hospital, Bern, Switzerland
[b] Department of Advanced Biomedical Sciences, University Federico II of Naples, Italy
[c] Cardiology Department, Crete Naval Hospital, Crete, Greece
[d] Department of Cardiology, University of Szeged, Hungary
[e] Interventional cardiology, San Giovanni Bosco Hospital, Torino, Italy
[f] Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Ferrara, Italy
[g] Maria Cecilia Hospital, GVM Care and Research, Cotignola, RA, Italy
[h] Azienda Ospedaliero-Universitaria di Modena, Ospedale Civile di Baggiovara, Italy
[i] Division of Cardiology, University Hospital, Geneva, Switzerland
[j] Interventional Cardiology Unit, Azienda Ospedaliero-Universitaria di Parma, Italy
[k] Policlinico S. Marco, IOB, Zingonia-Osio Sotto (BG), Italy
[l] Azienda Ospedaliera Ordine Mauriziano Torino, Italy
[m] Department of Cardiology, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy
[n] Hospital de Santa Cruz, Carnaxide, Lisbon, Portugal
[o] Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[p] Cardiovascular Departments of San Donato Hospital, Arezzo, Italy
[q] Ospedale SS. Annunziata – Savigliano, Italy
[r] Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Faculty of Medicine and Life Sciences University of Hasselt, Hasselt, Belgium
[s] Clinica Mediterranea, Napoli, Italy

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ABSTRACT

Background: The impact of coronary artery disease (CAD) extension/complexity on outcomes and on the comparative benefits/risks of zotarolimus-eluting stent (ZES) versus bare-metal stents (BMS) remains unclear in patients at high risk of bleeding or thrombosis or at low restenosis risk.
Methods: We performed a post-hoc analysis of the ZEUS trial. The impact of coronary anatomic complexity measured by the SYNTAX score on the differences in outcomes following ZES and BMS was assessed at 1 year.
Results: The mean SYNTAX score was 16.3 ± 13.1 with a median of 12 (IQR: 7 to 22). We stratified patients according to SYNTAX tertiles (0–8: $n = 563$; >8–19 $n = 532$; >19: $n = 511$), and observed that the higher the score, the correspondingly higher was the rate of the primary endpoint of major adverse cardiovascular events (MACE) and other ischemic events, but not bleeding after adjustment. The superior efficacy of ZES versus BMS for MACE was consistent across SYNTAX tertiles (tertile 1: HR 0.71, 95% CI 0.44–1.13; tertile 2: HR 0.71, 95% CI 0.46–1.09; tertile 3: HR 0.83, 95% CI 0.61–1.10) without significant heterogeneity (p for trend = 0.55). This between-groups difference mainly reflected a reduction in MI and TVR without effect on mortality. There was no significant interaction between the SYNTAX score and allocated stent type with respect to ischemic and bleeding endpoints.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Department of Cardiology, Bern University Hospital, CH-3010 Bern, Switzerland.
E-mail address: marco.valgimigli@insel.ch (M. Valgimigli).

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Conclusions: The SYNTAX score was predictor of major adverse cardiovascular events but not bleeding and ZES provided superior efficacy and safety than BMS across the whole spectrum of CAD complexity. SYNTAX score may be routinely used for the assessment of the ischemic risk (but not bleeding) after PCI and should not guide the decision-making for DES versus BMS in patients undergoing PCI.

1. Introduction

The Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score is an angiographic scoring system that was developed to quantify the complexity and extension of coronary artery disease (CAD) in patients undergoing coronary revascularization. It has become an important tool to assist in deciding the optimal revascularization strategy in patients with complex CAD [1–4]. The score has been found to predict ischemic event recurrences and mortality during long-term follow-up percutaneous coronary intervention (PCI) in various patient populations, including all-comers, those with multivessel/complex disease, for whom the score was originally developed, or with ST-segment elevation myocardial infarction (STEMI) [2,5–8].

The ZEUS trial included patients at high bleeding risk, high thrombotic risk or low restenosis risk to assess the efficacy and safety of drug-eluting stent (DES) implantation using a stent with a biocompatible polymer and fast drug-eluting characteristics, instead of a bare-metal stent (BMS), followed, in all patients, by an abbreviated, tailored dual antiplatelet therapy (DAPT) [9]. In this context of selected patients, it remains unclear if CAD extension and/or complexity impacts on outcomes in terms of ischemic and bleeding risks and how it may affect the comparative safety and effectiveness of the two allocated stent types.

2. Methods

2.1. Study population

The design and main study findings of the ZEUS trial (NCT01385319) were previously reported [9–11]. Briefly, it was a multinational, randomized single-blinded trial which was conducted at 20 sites in 4 European countries (Italy, Switzerland, Portugal, and Hungary) and included patients with at least 1 qualifying criterion among the pre-specified uncertain DES recipients (high bleeding risk, high thrombosis risk or low restenosis risk) undergoing elective, urgent, or emergent PCI with intended stent implantation. Patients were randomly allocated 1:1 to receive Endeavor Sprint zotarolimus-eluting stent (*E*-ZES) or a thin-strut (thickness < 100 mm) BMS followed by a DAPT regimen independent of stent type, but clinical-profile–driven.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics committees of all participating centers independently approved the protocol, and all participants gave written informed consent.

2.2. Devices and therapy

The E-ZES (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. All commercially available thin-strut BMS were allowed by the protocol.

All 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 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).

Duration of antiplatelet therapy was pre-specified on the basis of the inclusion criteria. Patients at high bleeding risk had a pre-specified 30-day DAPT regimen. Patients at high thrombosis risk had a pre-specified tailored duration of therapy on the basis of the specific condition conferring the high risk of thrombosis. This included a single antiplatelet regimen for patients intolerant of aspirin or available P2Y12 inhibitors, and a 30-day regimen in stable patients, or 6 to 12 months in unstable patients, in low restenosis risk patients.

As anticoagulation during PCI, unfractionated heparin or bivalirudin were used according to guidelines.

Staged procedures were 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.

2.3. Study endpoints and follow-up

The aim of the ZEUS 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 major adverse cardiovascular events (MACE), including all-cause death, non-fatal myocardial infarction (MI), or any target vessel revascularization (TVR), compared with BMS [9].

Secondary efficacy endpoints included each component of the primary endpoint, cardiovascular death, the composite of death and MI, the composite of cardiovascular death and MI; target lesion revascularization (TLR), ischemic stroke, and Academic Research Consortium–defined stent thrombosis (ST). Type of MI was also adjudicated according to the third universal definition of MI. Secondary safety endpoints comprised bleeding events according to both Bleeding Academic Research Consortium (BARC) and Thrombolysis In Myocardial Infarction (TIMI) classifications. Study endpoint definitions were previously reported [9]. 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.

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

2.4. SYNTAX score

A single senior interventional cardiologist (AP), blinded to clinical data, clinical presentation, and outcomes calculated the SYNTAX score at baseline for each patient by scoring all coronary lesions with a diameter stenosis ≥50%, in vessels ≥1.5 mm, using the SYNTAX score algorithm available online (http://www.syntaxscore.com).

2.5. Statistical analysis

Categorical variables were 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.

The population was stratified according to SYNTAX score tertiles and sensitivity analyses were performed using different cutoff values. 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 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. Cox-regression analysis with interaction testing was performed to determine whether the effect of stent type on the primary efficacy endpoint was consistent across SYNTAX subgroups. The interaction between treatment effect and SYNTAX score was also explored modelling the score as a continuous variable and was analyzed with a fractional polynomial interaction [12].

We also evaluated the effect of SYNTAX score on clinical outcomes in the overall population irrespective of stent randomization. We analyzed rates of clinical events according to SYNTAX tertiles, and we also modulated the score as a continuous variable testing the risk of ischemic and bleeding events in the overall population by means of both unadjusted and multivariable-adjusted, restricted cubic splines with three knots of the distribution (10th, 50th, and 90th percentiles). Multivariable adjustment of MACE and BARC type 2 to 5 bleeding was performed by including in the model all variables with a *p* value <0.1 at univariable analysis.

Sensitivity analyses were also performed testing the consistency of study results according to pre-defined 3 major criteria qualifying patients for inclusion (i.e. HBR, HTR, LRR).

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 23.0 (SPSS, Chicago, Illinois) and Stata 13.

3. Results

From June 2011 to September 2012, a total of 5288 patients were screened and 1606 were finally randomized. Approximately one-half

of the patients ($n = 828$) entered the study due to HBR criteria, mainly due to age 80 years or older in 425 (26.5%) patients and/or need for oral anticoagulation in 311 (19.4%) patients. A high thrombotic risk and a low-restenosis risk were detected in 285 (17.7%) and in 941 (58.6%) patients, respectively. The median age was 74, nearly two-thirds of patients presented with acute coronary syndromes (acute STEMI in 20%). In total, the SYNTAX score ranged from 0 to 81, with a mean ± SD of 16.3 ± 13.1 and a median of 12 (interquartile range: 7 to 22) (**Supplementary Fig. 1**). In the main analysis, the overall population was stratified according to SYNTAX tertiles (0 to 8: $n = 563$; >8 to 19 $n = 532$; >19: $n = 511$), and the ZES and BMS groups remained well balanced with regard to baseline clinical and angiographic characteristics (**Supplementary Tables 1 and 2**). Patients in the highest SYNTAX tertile were older, more frequently with diabetes, renal dysfunction, history of MI or CABG, multivessel disease and more frequently received multivessel intervention, had complex lesions, and received multiple stents, reflecting the higher CAD complexity.

3.1. SYNTAX score and clinical outcomes

During follow-up, 71 patients (12.6%) in the first SYNTAX tertile, 87 patients (16.4%) in the second SYNTAX tertile, and 160 patients (31.3%) in the third SYNTAX tertile reached the primary endpoint ($p < 0.0001$; Fig. 1, Table 1). Similarly, all-cause death ($p < 0.0001$), cardiovascular death ($p < 0.0001$), MI ($p < 0.0001$), TVR ($p < 0.0001$), TLR ($p < 0.0001$), and definite ST ($p = 0.001$), as well as BARC bleeding ($p = 0.011$) were significantly higher according to SYNTAX score tertiles (Fig. 1, Table 1). When analyzing SYNTAX score as a continuous variable, or after multivariable adjustment for possible confounders, the SYNTAX score remained an independent predictor of the primary outcome, as well as of all additional secondary ischemic endpoints but stroke, whereas it did not remain associated to bleeding events (Fig. 2, **Supplementary Tables 3 and 4**).

3.2. SYNTAX score and the comparative effectiveness of ZES vs. BMS

The superior efficacy of ZES versus BMS for the primary endpoint was consistent across SYNTAX teriles (tertile 1: HR 0.71, 95% CI 0.44–1.13; tertile 2: HR 0.71, 95% CI 0.46–1.09; tertile 3: HR 0.83, 95% CI 0.61–1.10) with no signal of heterogeneity (p for trend = 0.55). The difference between ZES and BMS groups mainly reflected a reduction in MI (tertile 1: HR 0.23, 95% CI 0.07–0.83; tertile 2: HR 0.20, 95% CI 0.06–0.70; tertile 3: HR 0.45, 95% CI 0.25–0.79; p for trend = 0.21), and TVR (tertile 1: HR 0.29, 95% CI 0.12–0.68; tertile 2: HR 0.66, 95% CI 0.35–1.27; tertile 3: HR 0.60, 95% CI 0.36–0.98; p for trend = 0.21), but not mortality (tertile 1: HR 1.15, 95% CI 0.62–2.15; tertile 2: HR 0.81, 95% CI 0.47–1.42; tertile 3: HR 1.01, 95% CI 0.67–1.52; p for trend = 0.84) (**Supplementary Table 5**). When MI types were further considered, both type 1 and type 4b were significantly higher according to SYNTAX tertiles ($p < 0.0001$ for both) and were reduced in the ZES as compared to BMS arm, consistently across SYNTAX score tertiles (**Supplementary Table 6**). The rate of definite, definite/probable and definite/probable/possible stent thrombosis trended lower in the ZES group in all the SYNTAX tertiles without heterogeneity. No heterogeneity was observed across SYNTAX tertiles for all ischemic and bleeding outcomes (**Supplementary Table 5**), nor for MACE and BARC type 2–5 when SYNTAX score was modelled as a continuous variable (Fig. 3).

3.3. Additional analyses

The consistency of ZES benefits over BMS, irrespective of angiographic CAD complexity, was confirmed when the study population was stratified based on the median SYNTAX score value (i.e. 12), when the first two tertiles were combined and contrasted to the third one or based on the SYNTAX score boundaries which were generated in the context of the SYNTAX trial of 0–22, 23–32, ≥33) (data not shown). Similarly, when population was stratified according to single or multivessel disease (**Supplementary Table 7**).

Finally, there was no signal of heterogeneity for ZES benefits over BMS across SYNTAX tertiles when main outcomes (the primary endpoint of death from any cause, MI, or TVR, as well the secondary endpoint of death from any cause or MI or the individual endpoints of MI and TVR) were separately appraised across patients at high risk of bleeding or thrombosis or at low risk of restenosis (**Supplementary Table 8**).

4. Discussion

The ZEUS study focused on a unique patient population composed of patients with high bleeding risk, high thrombotic risk, or low restenosis risk who were largely excluded from the pivotal DES trials that led to regulatory approval. The main findings of the present analysis can be summarized as follows:

1. Anatomic complexity as assessed by the SYNTAX score independently predicted major adverse cardiovascular events, and death, MI, TVR or ST in the overall population as well as in each of the three patient categories which were included.

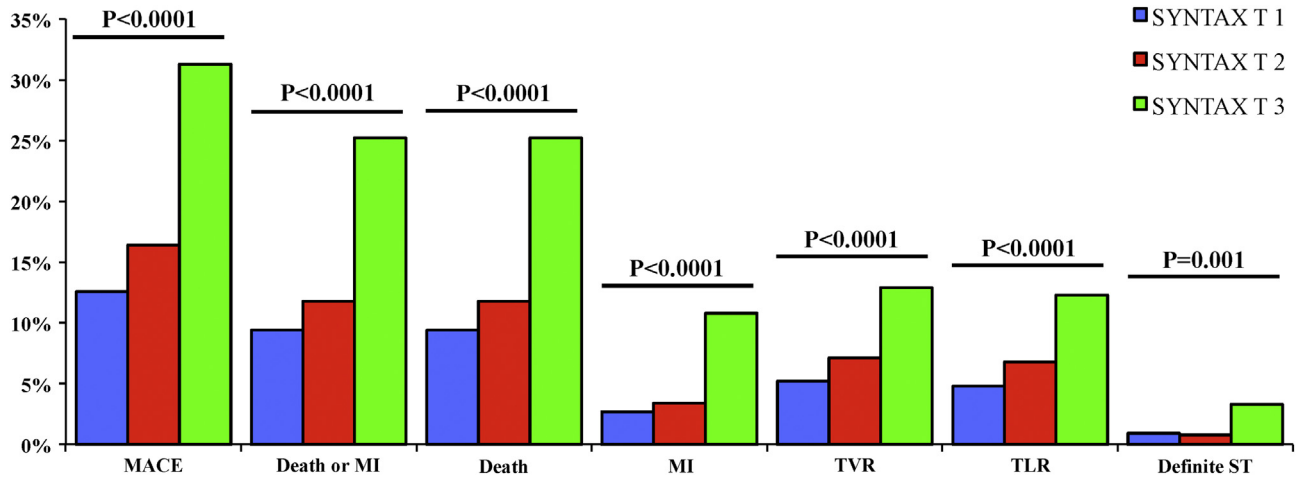

Fig. 1. Ischemic events according to SYNTAX score tertiles.

Table 1
Clinical Outcomes at 12 months according to SYNTAX score tertiles.

	SYNTAX Low Tertile 1 (0–8) (*N* = 563)	SYNTAX Intermediate Tertile 2 (>8–19) (*N* = 532)	SYNTAX High Tertile 3 (>19) (N = 511)	P value
Primary efficacy endpoint				
Death from any cause, MI or TVR	71 (12.6)	87 (16.4)	160 (31.3)	<0.0001
Secondary efficacy endpoints				
Death from any cause or MI	53 (9.4)	63 (11.8)	129 (25.2)	<0.0001
Death from cardiovascular cause or MI	36 (6.4)	46 (8.6)	113 (22.1)	<0.0001
Death from any cause	40 (7.1)	50 (9.4)	91 (17.8)	<0.0001
Death from cardiovascular cause	23 (4.1)	32 (6.0)	73 (14.3)	<0.0001
MI	15 (2.7)	18 (3.4)	55 (10.8)	<0.0001
TVR	29 (5.2)	38 (7.1)	66 (12.9)	<0.0001
TLR	27 (4.8)	36 (6.8)	63 (12.3)	<0.0001
Ischemic stroke	6 (1.1)	6 (1.1)	9 (1.8)	0.55
Definite ST	5 (0.9)	4 (0.8)	17 (3.3)	0.001
Probable ST	4 (0.7)	5 (0.9)	14 (2.7)	0.01
Possible ST	8 (1.4)	12 (2.3)	27 (5.3)	<0.0001
Definite or probable ST	9 (1.6)	9 (1.7)	31 (6.1)	<0.0001
Definite, probable, or possible ST	17 (3.0)	21 (3.9)	58 (11.4)	<0.0001
Safety endpoints				
TIMI classification				
Major or minor	6 (1.1)	11 (2.1)	14 (2.7)	0.13
Major	5 (0.9)	6 (1.1)	9 (1.8)	0.42
Minor	1 (0.2)	5 (0.9)	5 (1.0)	0.19
Requiring medical attention	14 (2.5)	22 (4.1)	27 (5.3)	0.06
BARC classification				
Type 5 or 3	10 (1.8)	14 (2.6)	23 (4.5)	0.027
Type 5, 3 or 2	22 (3.9)	30 (5.6)	42 (8.2)	0.011
Type 5	3 (0.5)	5 (0.9)	3 (0.6)	0.68
Type 5A	1 (0.2)	4 (0.8)	2 (0.4)	0.35
Type 5B	2 (0.4)	1 (0.2)	1 (0.2)	0.82
Type 4	0	0	0	–
Type 3	7 (1.2)	9 (1.7)	20 (3.9)	0.007
Type 3A	3 (0.5)	3 (0.6)	5 (1.0)	0.62
Type 3B	3 (0.5)	5 (0.9)	14 (2.7)	0.005
Type 3C	1 (0.2)	1 (0.2)	1 (0.2)	0.99
Type 2	12 (2.1)	16 (3.0)	19 (3.7)	0.30

Abbreviations: BARC=Bleeding Academic Research Consortium; MI = Myocardial infarction; ST = Stent thrombosis; TIMI = Thrombolysis in myocardial infarction; TLR = Target lesion revascularization; TVR = Target vessel revascularization.

2. The SYNTAX score appeared at univariable analysis to be marginally but significantly associated to bleeding events. However, after adjustment, the SYNTAX score did not remain associated to the bleeding risk across different bleeding scales in the overall population as well as in high bleeding risk, high thrombotic risk, or low restenosis risk patients when separately appraised.
3. The SYNTAX score did not show significant interaction with the randomly allocated treatment suggesting that ZES remains superior to BMS across the whole spectrum of CAD complexity.

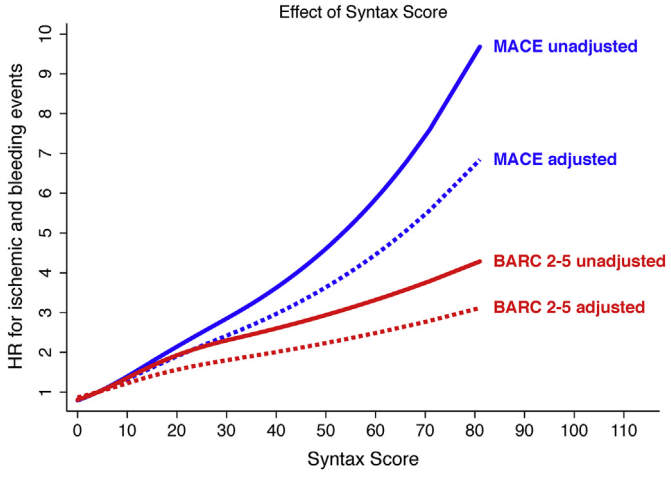

Fig. 2. Spline curves for the HR of the MACE and BARC type 2–5 bleeding vs. SYNTAX score modelled as a continuous variable. Patients with SYNTAX score in the first decile (corresponding to score value ≤4; $n = 211$) represent the referent group with the HR set to 1. The variables used for the adjustments are listed in the Table 4. BARC: Bleeding Academic Research Consortium; HR: hazard ratio; MACE: major adverse cardiovascular events.

Optimal DAPT regimen and stent selection remain topics of great debate [13,14]. The *E*-ZES is a hydrophilic polymer-based second-generation device with a unique drug fast-release profile which results in less powerful inhibition of intimal hyperplasia, but also in a rapid and/or complete stent strut coverage. This property allows shortening DAPT duration while maintaining superior efficacy compared with BMS. The ZEUS study, which mandated a tailored DAPT duration based on patients' characteristics, showed a lower incidence of MACE after E-ZES as compared with BMS in uncertain DES recipients [9]. E-ZES implantation provided superior efficacy and safety as compared with conventional BMS also among high bleeding risk patients (>50% of the patients fulfilled at least 1 criterion) who were to be treated with a 30-day course of DAPT only [11].

The present study is the first to assess the impact of SYNTAX score in uncertain DES candidates undergoing PCI. It confirms the ability of the SYNTAX score to identify patients who are at highest risk of adverse events also in the specific subsets of high bleeding risk, high thrombotic risk and low restenosis risk patients. This provides further evidence supporting the potential utility of the SYNTAX score in the assessment of ischemic risk in patients undergoing PCI.

When comparing DES and BMS performance, angiographic characteristics and complexity of CAD might have an important role,

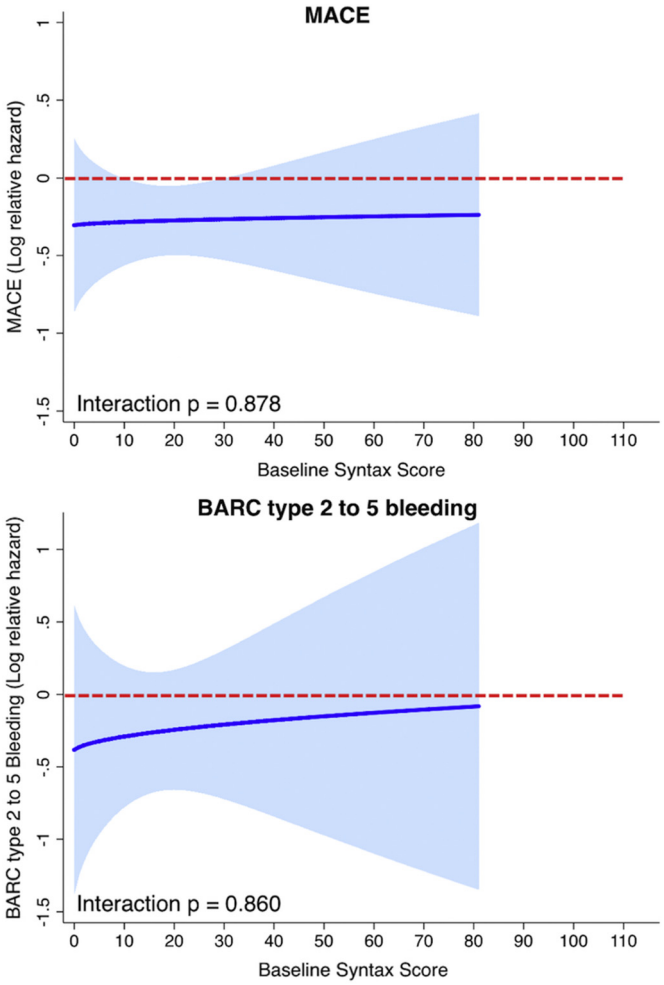

Fig. 3. Fractional polynomial interaction between randomized stent and SYNTAX score for the MACE and BARC type 2–5 bleeding. The treatment-by-SYNTAX interaction is analyzed by considering SYNTAX score as a continuous variable. The red line represents the treatment effect of ZES vs. BMS and the area represents the 95% CI of treatment effect.

particularly when a very short (30-day) course of DAPT is required, therefore we explored whether the benefits of ZES over BMS were consistent across SYNTAX score strata. Although SYNTAX score properly identifies patients at higher risk of events and could be hypothesized to help deciding the stent selection in uncertain DES candidates, we found that ZES was superior to BMS irrespective of CAD extension and complexity. Thus, a very short (30-day) course of DAPT in the ZES group did not pose a significant risk, whereas it achieved superior clinical efficacy even in patients with intermediate-to-high angiographic complexity of CAD as compared to BMS. Interestingly, we noted that higher SYNTAX score seemed also to be associated with increased risk of bleeding. This predictive feature of the score, however, was not attributable to the score per se but was rather influenced by concomitant patients' characteristics; indeed, this effect was not significant after adjustment. This analysis carries new important implications as it confirms the specific ability of this score to predict ischemic but not bleeding recurrences after PCI and provides strong rational for combining in future analyses this score with dedicated algorithms modelled to predict the bleeding risk [15,16].

An additional intriguing observation in our current analysis merits further discussion. A trend towards lower bleeding risk was previously noted in the ZES vs BMS groups with respect to BARC 2, 3, or 5 bleeding in the overall population or in HBR patients [9,11], despite the randomized nature of the comparison and the fact that both patient groups received a similarly short/tailored course of DAPT after index intervention. This was justified by higher TVR rate in the BMS group over the course of follow-up, owing to the need to re-institute a DAPT regimen thereafter. When the SYNTAX score was modelled as a continuous variable, the benefits towards lower BARC 2, 3 or 5 bleeding occurrences were apparently more evident in patients with low SYNTAX score value. However, interaction testing with respect to the bleeding risk and the SYNTAX score, modelled as continuous variable, was negative and when BARC 3 or 5 events were considered across SYNTAX score tertiles, the greatest relative risk reduction for bleeding in favour of the ZES arm was noted in the highest tertile. Hence, there is clear signal that the use of a ZES instead of a BMS in our patient population has potential to mitigate the bleeding risk consistently across angiographic CAD complexity strata.

There is evidence suggesting that the use of DES, instead of BMS, leads not only to TVR but also MI, ST and cardiac mortality benefits [9,11,17,18]. Indeed, an intriguing finding of the ZEUS trial is that ZES compared with BMS significantly reduced TVR as expected, but also provided a significant reduction of MI, owing to a significant reduction of both type I (spontaneous) and type 4b (ST-related) MI, and here we confirmed that this effect was consistent in all SYNTAX score tertiles. The reduction of ST antagonizes previous concerns about DES-related ST and further confirms large evidence accumulated in last years that new-generation DES are associated with lower ST than BMS. Lower rates of spontaneous MI might be interpreted in light of the fact that DES reduces restenosis, which has historically been considered a benign process presenting in most cases with recurrent stable angina, while today is well known to be also related to MI occurrence. Conversely, in the Norwegian coronary stent trial (NORSTENT), which recruited 9013 patients with stable or unstable CAD and assigned them to PCI with the implantation of either contemporary DES (96% received either everolimus- or zotarolimus-eluting stents) or BMS [19], the composite outcome of death from any cause and nonfatal spontaneous MI, or quality of life, did not differ in-between groups. It was therefore suggested that, based on the excellent results achieved with BMS in NORSTENT, contemporary BMS still should be considered a viable alternative for some setting of patients, such as those who need anticoagulation, those who cannot complete the longer DAPT period because of a need for noncardiac surgery or other medical conditions with increased bleeding risk, those who have cancer and those with low restenosis rates [14]. On this scenario, our study adds to the current knowledge and could contribute to this debate by showing that DES is superior to BMS in specific clinical settings (still considered from someone "uncertain" candidates to DES) and irrespective of the angiographic complexity of the coronary disease. This finding further supports the most recent European guidelines recommending the use of new-generation DES over BMS in all patients undergoing PCI [4].

4.1. Study limitations

The present study has some limitations. First, the ZEUS study was not powered to explore SYNTAX subgroups, thus, it should be considered hypothesis-generating only. Yet, our results may not apply to patients with very high SYNTAX score who were only marginally represented in our study population; however, the absence of heterogeneity across SYNTAX subgroups was consistently observed even when different cutoffs were used or when the score was modelled as continuous. Second, it 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, therefore it should be considered as an open-label study with evident limitations. Third, the findings apply to the studied ZES (Endeavor Sprint, which is no longer on the market) and cannot be expended to other new-generation DES. Fourth, longer follow-up is required to confirm durability of these findings. However, given the proven superior efficacy of other DES to inhibit intimal hyperplasia as

compared to the Endeavor-ZES, it remains likely that other DES would have resulted in even greater efficacy as compared to BMS in preventing the need for re-intervention in the previously instrumented vessel(s). Fifth, the present findings should be interpreted considering that the majority of patients received a clopidogrel-based DAPT (prasugrel or ticagrelor at discharge were in <1%). Finally, we did not test intra/inter-observer variability in the SYNTAX score calculation, however, the single observer performing the blinded angiographic analysis was an experienced interventionalist and was well trained for SYNTAX score calculation.

5. Conclusion

Among patients with high bleeding risk, high thrombotic risk, or low restenosis risk undergoing PCI, anatomic complexity as assessed by the SYNTAX score predicted major adverse cardiovascular but no bleeding events. The SYNTAX score did not show significant interaction with treatment effect suggesting that in these patient categories ZES remains superior to BMS, both with similar short courses of DAPT, across the whole spectrum of CAD complexity.

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Conflict of interest

Dr. Gargiulo reports research grant support from Cardiopath PhD program. Dr. Roffi reports institutional research grants from Medtronic, Biotronik, Boston Scientific, Terumo, Abbott Vascular, outside the submitted work. Dr. Ferlini reports individual payment as consultant or for advisory board or as a speaker from Eli Lilly, Astra Zeneca, Biosensors, Chiesi, The Medicines Company, Daiichi Sankyo, MSD, outside the submitted work. Dr. Liistro reports personal fees from Medtronic, outside the submitted work. Dr. Vranckx reports personal fees from Bayer Health Care and Daicchi Sankyo, outside the submitted work. Dr. Windecker reports research contract to the institution from Amgen, Abbott, Biotronik, Boston Scientific, St Jude, outside the submitted work. Dr. Valgimigli reports grants from The Medicines Company and Terumo, during the study, grants from Astra Zeneca, personal fees from Abbott, Amgen, and Bayer, outside the submitted work. Other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.120.

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