CHAPTER 6

Long-term outcome of second-generation everolimus-eluting stents and Endeavor zotarolimus-eluting stents in a prospective registry of ST-elevation myocardial infarction patients

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M.A. Velders,
H. Boden,
B.L. van der Hoeven,
S.S. Liem,
J.Z. Atary,
E.E. van der Wall,
J.W. Jukema,
M.J. Schalij.

Abstract

Aims: The optimal drug-eluting stent (DES) in ST-elevation myocardial infarction (STEMI) patients remains unclear. We sought to compare the long term performance of everolimus-eluting stents (EES) and Endeavor zotarolimus-eluting stents (E-ZES) in STEMI.

Methods and results: The current analysis of a prospective registry included consecutive patients treated with EES or E-ZES for STEMI. Adjustment for measured confounders was done using Cox regression. In total, 931 patients met the inclusion criteria (412 EES and 519 E-ZES). Baseline characteristics were balanced, apart from a lower rate of renal insufficiency in EES. Median follow-up duration was 2.4 years (IQR 1.6-3.1). Mortality outcomes were similar. Up to three year follow-up, the composite endpoint of cardiac death, target vessel-related myocardial infarction and target lesion revascularization (TLR) was lower in EES; 9.7% vs. 13.7% in E-ZES (HR 0.64, 95% CI 0.42-0.99), primarily driven by reduced TLR rates; 3.4% in EES vs. 7.3% in E-ZES (HR 0.46, 95% CI 0.23-0.92). Definite stent thrombosis rates were low and similar between groups (1.1% in EES vs. 1.9% in E-ZES, p=0.190).

Conclusion: Use of EES led to lower rates of the composite endpoint, driven by reduced TLR. This suggests that EES are more efficacious than Endeavor ZES in STEMI. Definite ST rates were low and the strategy of second generation DES implantation and upfront GPIIb/IIIa inhibitors administration appears to be safe in STEMI.

Introduction

Second generation everolimus-eluting stents (EES) have shown superior results in stable coronary lesions and all-comer patients compared to both bare-metal and first generation paclitaxel-eluting stents (PES).[1-5] Comparison of Endeavor zotarolimus-eluting stents (E-ZES) with bare-metal and PES showed improved outcome after E-ZES implantation in stable coronary lesions.[6-9] Results of these trials have led to widespread use of second generation stents in current clinical practice. Use of drug-eluting stents (DES) in setting of ST-elevation myocardial infarction (STEMI) is however still under investigation. Trials comparing DES in STEMI mainly focused on comparison of bare-metal and first generation DES.[10] Therefore, limited data exist with regard to the performance of different types of second generation DES in patients presenting with STEMI. The current study sought to investigate the long term performance of the second generation EES and Endeavor ZES in an unselected STEMI population.

Methods

Design and patients

The prospective MISSION! registry included all patients treated with primary percutaneous coronary intervention (PCI) for STEMI in a high-volume tertiary center.[11] For the current retrospective analysis, consecutive patients treated between the 1st of January 2007 and the 1st of October 2010 were eligible for inclusion. Patient selection was done according to procedural stent type. All patients treated with either EES (Promus, Boston Scientific, Natick, Massachusetts) or E-ZES (Endeavor, Medtronic Vascular, Santa Rosa, California) were included in the current analysis. E-ZES were implanted in the Leiden University Medical Center from early 2006 and EES were implanted from the beginning of 2007, therefore both stent types were used during the entire inclusion period. Stent choice was left to the discretion of the operator. Patients treated with both stents simultaneously as well as patients treated with other types of drug-eluting or bare-metal stents (BMS) were excluded. Patients were treated and followed according to the institutional STEMI protocol (MISSION!), implemented at Leiden University Medical Center since February 2004.[11] Patients follow a standardized pre-hospital, in-hospital and outpatient clinical framework for decision making and treatment. The pre-hospital protocol included field triage by 12-lead electrocardiogram (ECG) faxed to the operator on call and in-ambulance treatment with loading dose of clopidogrel, aspirin, heparin and intravenous glycoprotein IIb/IIIa inhibitors. Upon arrival at the hospital, patients were transferred directly to the catheterization laboratory or coronary care unit to wait for arrival of the intervention team. Procedures were performed according to current clinical guidelines. If tolerated, patients received beta-blockers, ACE-inhibitors and statins within 24 hours. Additionally, patients were prescribed dual

antiplatelet therapy, consisting of aspirin 100 mg daily for life and clopidogrel 75 mg daily for 12 months. Patients with an indication for a coumadin were subscribed warfarin instead of aspirin.

Following hospital discharge, patients were intensively monitored and managed in the outpatient clinic for one year, after which they were referred back to the general practitioner or referred to a regular, generally regional, cardiological outpatient clinic. Vital status was gathered through municipality records. Follow-up data were adjudicated and prospectively collected in the electronic patient file (EPD Vision version 8.7.0.1.) by independent clinicians; data from patients participating in the out-patient program were gathered by out-patient chart review and follow-up data of patients not participating in the out-patient program were gathered by telephone interviews.

Definitions

STEMI was defined as symptoms of angina lasting longer than 30 minutes along with electrocardiogram demonstrating STEMI (ST-segment elevation ≥0.2 mV in ≥2 contiguous leads in V1 through V3 or ≥0.1 mV in other leads or presumed new left bundle branch block). Recurrent myocardial infarction was defined as symptoms of angina lasting longer than 30 minutes in addition to troponin levels above the ULN (upper limit of normal) or a 25% re-rise of troponin levels in case of re-infarction after index procedure. Peri-procedural infarction was defined as an elevation of troponins 3 times above ULN for PCI and 5 times above ULN for coronary artery bypass grafting (CABG). Target vessel revascularization (TVR) was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. Target lesion revascularization (TLR) was defined as any repeat PCI or bypass surgery of the target lesion including the 5 mm proximal or distal region of the stented area. Stent thrombosis (ST) was defined according to Academic Research Consortium (ARC) definitions.[12] Furthermore, ARC suggested composite endpoints were defined. The device-oriented endpoint was a composite of cardiac death, MI not clearly related to a non-target vessel and target lesion revascularization (TLR). The patient-oriented endpoint consisted of all-cause mortality, any myocardial infarction and any repeat revascularization procedure.

Statistical analyses

Continuous variables are presented as means with standard deviations (SD) and were compared using Student's t-test. Categorical variables are expressed as counts and percentages and were compared by means of Pearson's χ^2 test. Time to endpoint was analyzed using Kaplan-Meier plots and the log-rank test was applied to compare the cumulative incidences of the endpoints between groups. All statistical tests were 2-tailed and a p-value ≤0.05 was considered statistically significant. Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) were calculated using cox proportional hazard regression models.

Univariable predictors of outcome were entered into multivariable models using a cut-off p-value <0.10. In case of limited number of events, selection of variables was based on effect size.

Results

During the inclusion period a total of 1199 patients were treated with primary PCI. Of these patients 931 met the inclusion criteria of this study: 412 patients received at least one EES and 519 patients at least one E-ZES (figure 1). Median follow-up duration was 2.3 years (IQR 1.6-3.0) for EES patients and 2.4 years (IQR 1.6-3.2) for E-ZES patients. Baseline characteristics (table 1) showed that patients treated with E-ZES more frequently had a history of renal insufficiency. Furthermore, patients treated with EES were more frequently discharged with beta-blockers compared to E-ZES patients (table 2). Other baseline and procedural characteristics were balanced.

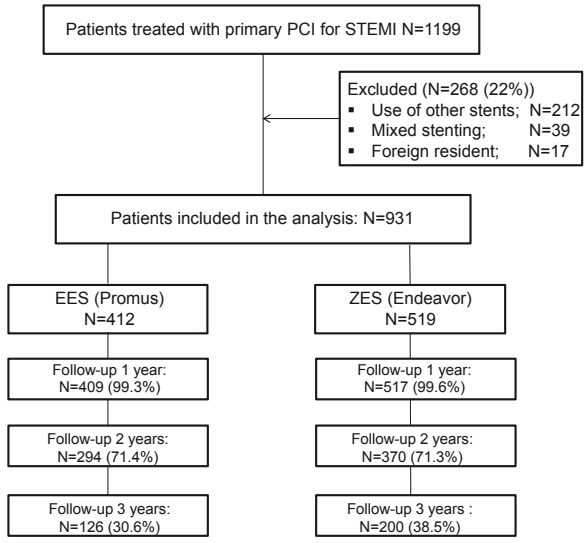

Figure 1. Inclusion and follow-up chart.

Table 3 presents clinical outcomes up to three years. During the first year, the patient-oriented endpoint was balanced between the groups. The device-oriented composite endpoint occurred in 4.7% of EES patients and in 8.7% of E-ZES patients (HR 0.56 in multivariable analysis, 95% CI 0.32-0.97). This was driven by both lower rates of target vessel-related MI (HR 0.27, 95% CI 0.08-0.93) and TLR (HR 0.21, 95% CI 0.06-0.72). In addition, the individual rate of TVR was lower in patients treated with EES compared to E-ZES patients (HR 0.53, 95% CI 0.29-0.98) and definite ST showed a trend toward a lower rate in EES patients (HR 0.16, 95% CI 0.02-1.28).

The rate of the device-oriented endpoint remained significantly lower up to three years follow-up (figure 2A), with 9.7% of EES patients versus 13.7% of E-ZES patients reaching the endpoint (HR 0.64, 95% CI 0.42-0.99). This was mainly driven by TLR (figure 2B), which showed rates of 3.4% in EES patients versus 7.3% in E-ZES patients (HR 0.46, 95% CI 0.23-0.92).

Table 1. Baseline characteristics

	EES (N=412)	**E-ZES** (N=519)	p-Value
Age, years	61.0 ± 12.4	61.9 ± 12.4	0.292
Male	309 (75.0)	378 (72.8)	0.455
Insulin dependent diabetes mellitus	18 (4.4)	18 (3.5)	0.484
Non-insulin dependent diabetes mellitus	35 (8.5)	49 (9.5)	0.607
Hypertension	164 (40.3)	198 (38.6)	0.600
Hypercholesterolemia	86 (21.2)	104 (20.4)	0.758
Family history of cardiovascular disease	169 (41.8)	214 (42.1)	0.929
Current smoker	185 (45.7)	230 (45.0)	0.840
Previous MI	42 (10.2)	50 (9.7)	0.791
Previous PCI	34 (8.3)	42 (8.1)	0.928
Previous CABG	14 (3.4)	14 (2.7)	0.538
History of peripheral vascular disease	17 (4.1)	25 (4.8)	0.605
History of cerebrovascular disease	16 (3.9)	24 (4.7)	0.567
History of malignancy	21 (5.1)	40 (7.7)	0.107
History of renal insufficiency*	7 (1.7)	24 (4.6)	0.013
Symptom to balloon inflation			0.348
0-6 hours	246 (86.0)	328 (85.6)	
6-12 hours	28 (9.8)	44 (11.5)	
12-24 hours	8 (2.8)	10 (2.6)	
>24 hours	4 (1.4)	1 (0.3)	
Diagnosis to balloon inflation, minutes (IQR)	78 (66-98)	80 (67-98)	0.660
Door to balloon inflation, minutes (IQR)	41 (30-63)	40 (32-56)	0.601
Out-of-hospital cardiac arrest	19 (4.6)	34 (6.6)	0.205
Cardiogenic shock	13 (3.2)	21 (4.0)	0.472

* Defined as eGFR<60 ml/min/1.73m^2. Data are expressed as mean ± standard deviation, n (%) or median (interquartile range [IQR]).

Table 2. Procedural characteristics

	EES (N=412)	**E-ZES** (N=519)	p Value
Culprit vessel			0.899
Left main stem	4 (1.0)	7 (1.3)	
Left anterior descending	179 (43.4)	229 (44.1)	
Left circumflex	70 (17.0)	78 (15.0)	
Right coronary artery	154 (37.4)	200 (38.5)	
Bypass graft	5 (1.2)	5 (1.0)	
Pre-dilation	363 (88.1)	470 (90.6)	0.226
Post-dilatation	154 (37.5)	180 (34.7)	0.379
Glycoprotein IIb/IIIa inhibitors	397 (97.3)	501 (96.5)	0.503
Number of vessel disease*			0.944
1	163 (39.6)	211 (40.7)	
2	151 (36.7)	187 (36.0)	
3	98 (23.8)	121 (23.3)	
Pre-procedure TIMI (grade)			0.881
0	251 (61.1)	309 (59.5)	
1	72 (17.5)	88 (17.0)	
2	53 (12.9)	76 (14.6)	
3	35 (8.5)	46 (8.9)	
Post-procedure TIMI 2 or more	406 (98.8)	511 (98.6)	0.857
Stent length culprit vessel, mean ± SD	28 ± 13	29 ± 14	0.792
Stent diameter culprit vessel, mean ± SD	3.3 ± 0.4	3.2 ± 0.4	0.136
Number of stents in culprit, mean ± SD	1.6 ± 0.8	1.6 ± 0.9	0.552
Discharge medication			
Aspirin	397 (99.0)	502 (99.2)	0.741
Clopidogrel	399 (99.5)	505 (99.8)	0.433
ACE-inhibitor	393 (98.0)	492 (97.2)	0.453
Statin	396 (98.8)	499 (98.6)	0.858
Beta-blocker	387 (96.5)	470 (92.9)	0.018

Data are expressed as mean ± standard deviation or n (%). * >50% visual stenosis. TIMI = thrombolysis in myocardial infarction; other abbreviations as in Table 1.

Table 3. Clinical outcomes

	EES (N=412)	**E-ZES** (N=519)	Crude Hazard Ratio (95% CI)	p-Value	Multivariable Hazard Ratio (95% CI)	p-Value
1 year outcomes						
All-cause mortality	17 (4.1)	27 (5.2)	0.84 (0.46-1.53)	0.567	-	
Cardiac mortality	14 (3.6)	26 (5.0)	0.73 (0.39-1.37)	0.325	-	
Myocardial infarction, any	6 (1.5)	17 (3.4)	0.44 (0.17-1.12)	0.084	0.44 (0.17-1.10)	0.080
Target vessel-related MI	3 (0.8)	12 (2.4)	0.27 (0.08-0.93)	0.038	0.27 (0.08-0.93)	0.037
Revascularization, any	44 (11.1)	74 (14.8)	0.73 (0.51-1.07)	0.105	-	
Target vessel revascularization	15 (3.8)	37 (7.4)	0.50 (0.27-0.91)	0.022	0.53 (0.29-0.98)	0.041
Target lesion revascularization	3 (0.8)	17 (3.4)	0.22 (0.06-0.75)	0.015	0.21 (0.06-0.72)	0.013
Definite stent thrombosis	1 (0.3)	8 (1.6)	0.16 (0.02-1.25)	0.080	0.16 (0.02-1.28)	0.084
All-cause mortality, any MI, any revascularization	60 (14.7)	98 (19.0)	0.77 (0.56-1.06)	0.108	-	
Cardiac death, target vessel related MI, TLR	19 (4.7)	45 (8.7)	0.55 (0.33-0.94)	0.028	0.56 (0.32-0.97)	0.037
Up to 3 years						
All-cause mortality	28 (7.6)	39 (8.7)	0.85 (0.52-1.39)	0.512	-	
Cardiac mortality	20 (5.6)	29 (5.7)	0.92 (0.52-1.61)	0.761	-	
Myocardial infarction, any	20 (7.0)	29 (6.7)	0.86 (0.49-1.52)	0.605	-	
Target vessel-related MI	8 (2.7)	19 (4.3)	0.52 (0.23-1.20)	0.124	-	
Revascularization, any	74 (21.5)	108 24.5)	0.84 (0.63-1.13)	0.247	-	
Target vessel revascularization	32 (9.9)	56 (12.9)	0.70 (0.45-1.08)	0.108	-	
Target lesion revascularization	11 (3.4)	31 (7.3)	0.44 (0.22-0.87)	0.019	0.46 (0.23-0.92)	0.027
Definite stent thrombosis	3 (1.1)	9 (1.9)	0.42 (0.11-1.54)	0.190	-	
All-cause mortality, any MI, any revascularization	99 (27.3)	144 (31.4)	0.84 (0.65-1.09)	0.193	-	
Cardiac death, target vessel-related MI, TLR	34 (9.7)	64 (13.7)	0.66 (0.44-0.99)	0.049	0.64 (0.42-0.99)	0.046

Data are n (%). Percentages are cumulative incidences of events from Kaplan Meier analysis. Hazard ratios were calculated using cox proportional hazard models.

The patient-oriented composite endpoint (figure 2C) and cardiac mortality (figure 2D) did not differ during long term follow-up. Moreover, definite ST (figure 3) showed comparable rates. ST occurred sub-acutely (24 hours to 30 days after PCI) in 6 cases, of which 1 in EES and 5 times in E-ZES. Late ST (30 days to 1 year after PCI) occurred in 2 E-ZES patients and very late ST (later than 1 year) occurred in 2 EES patients and 1 E-ZES patient. Dual antiplatelet therapy compliance was similar between the groups, showing a 99% rate for aspirin/coumadin adherence and 98% for clopidogrel adherence at one year. Of the patients suffering from late ST, 2 were using aspirin and one was using both aspirin and clopidogrel at time of ST.

Discussion

The major finding of this observational investigation, comparing long term outcomes of EES and Endeavor ZES in an unselected STEMI population up to three year follow-up, was that EES implantation was independently associated with lower rates of the device-related endpoint of cardiac mortality, target vessel-related MI and TLR compared to E-ZES. This was driven by lower rates of TLR in EES patients. Furthermore, definite ST rates were low and the strategy of second generation DES implantation and upfront GPIIb/IIIa inhibitors administration appears to be safe in STEMI.

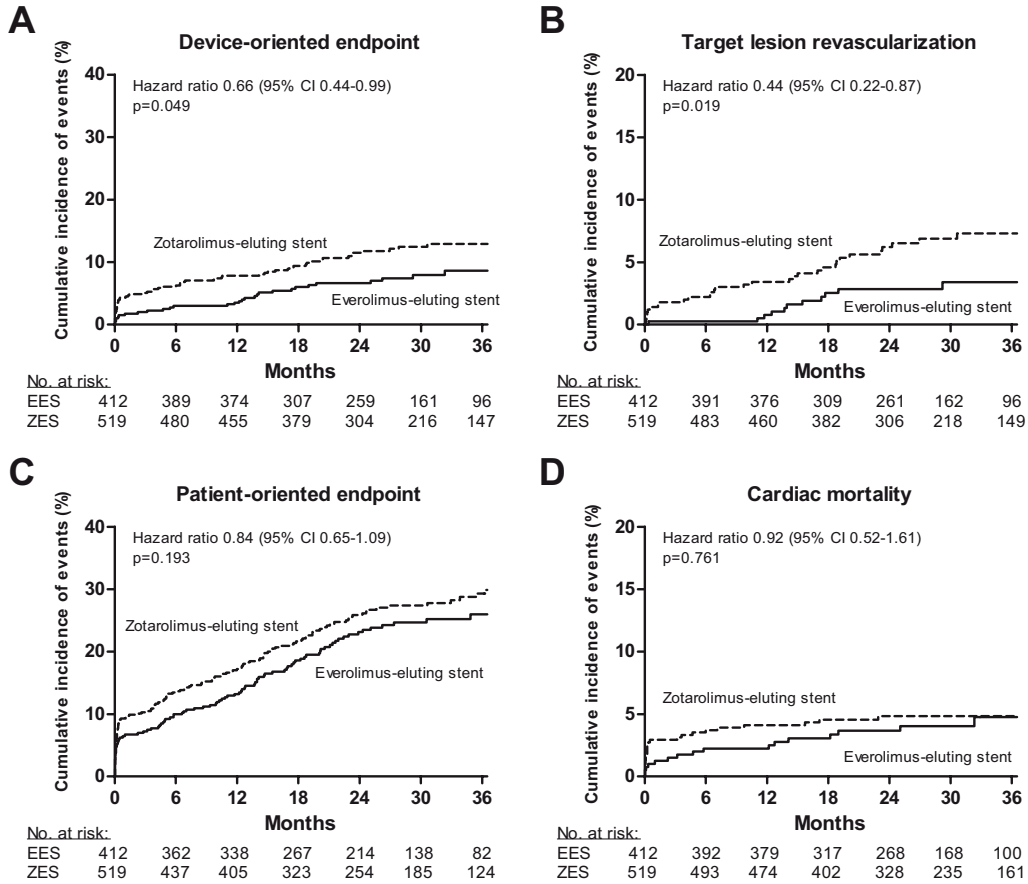

Figure 2: (A) Device-oriented endpoint (composite of cardiac death, target vessel-related MI and target lesion revascularization) up to three year follow-up. **(B)** Target lesion revascularization up to three year follow-up. **(C)** Patient-oriented endpoint (composite of all-cause mortality, any myocardial infarction and any revascularization procedure) up to three year follow-up. **(D)** Cardiac mortality up to three year follow-up. Hazard ratios are calculated using crude cox proportional hazards analyses with E-ZES as reference group.

Myocardial infarction has long been considered an off-label indication for DES. While first generation DES have been shown to reduce revascularization rates in STEMI patients compared to BMS, the benefit is offset by a higher risk of very late ST.[13,14] Stenting in acute coronary syndromes was found to be an independent predictor of ST after DES implantation.[15] Delayed endothelialization, thrombotic burden, stent underexpansion and stent malapposition have been identified as mechanisms for the higher rate of ST after DES implantation in patients with acute coronary syndromes.[16-18] Moreover, evaluation of patient adherence to dual antiplatelet therapy is complicated by the acute setting of myocardial infarction. Second generation stents have been developed to reduce the incidence of ST while attempting to improve the efficacy of DES. In this study, we compared the second generation EES and E-ZES. The EES is a thin strut (81 µm), cobalt-chromium, Multi-Link™ stent with a biocompatible polymer eluting everolimus, a sirolimus-analogue. Eighty percent of the everolimus is eluted in the first 28 days. EES showed faster endothelialization compared to first generation stents in pre-clinical studies.[19] The Endeavor ZES is based on a cobalt-chromium Driver™ platform, consisting of 91 µm struts covered by a biomimetic phosphorylcholine polymer releasing the sirolimus-analogue zotarolimus. The Endeavor stent releases 95% of its inhibitory drug within 28 days, which is the fastest elution of all stents currently in use.

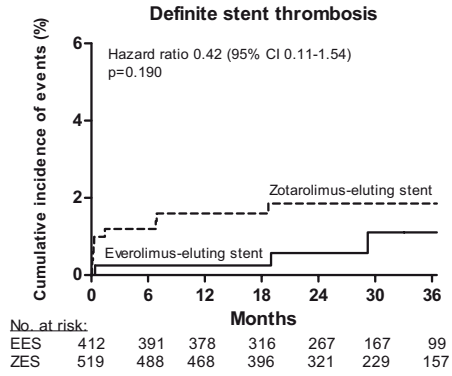

Figure 3. Definite stent thrombosis.

In the current study, patients treated with EES showed lower rates of the composite endpoint of cardiac mortality, target vessel-related MI and TLR compared to E-ZES patients up to three year follow-up. The difference was driven by lower rates of TLR in EES patients. This observation is in line with previous studies demonstrating an association of EES with lower late luminal loss (average 0.14 mm, compared to 0.6mm in E-ZES) which is a strong surrogate endpoint for TLR.[20,21] This indicates that EES have a higher potential for suppressing neointimal growth. It underlines that more aggressive inhibition of intimal hyperplasia is not directly related to a higher risk of ST but that other factors like stent design, polymer properties and release characteristics of the drug also play a role.

Recently, Hannan et al. performed a propensity score matched comparison of EES and E-ZES and found a reduced rate of repeat revascularizations for EES patients during two year follow-up,[22] reflecting the current results. Ten percent of patients included in their registry were treated for MI within 24 hours, however exact diagnosis was not mentioned. Trials or registries focusing on use of EES or E-ZES in STEMI patients specifically are limited. The Evaluation of Xience-V stent in Acute

Myocardial Infarction (EXAMINATION) trial randomized MI patients to EES or BMS and reported lower rates of TVR, TLR and definite ST in the EES group after 1 year.[23] A comparison of EES and SES was made in The XienceV Stent vs. Cypher Stent in Primary PCI for Acute Myocardial Infarction (XAMI) trial, which included 96% STEMI patients, and suggested superior MACE rates in EES compared to SES up to 1 year follow-up, although the trial was not powered for this.[24] Additionally, Kedhi et al.,[25] comparing EES with PES in the indication of STEMI in a post-hoc analysis, observed superior outcomes of EES up to two years of follow-up. Rates of mortality, MI and revascularizations were relatively low compared to the current study. This is most likely due to a higher risk population in the current analysis, since no patients were excluded on account of clinical or angiographic characteristics. In contrast, the HORIZONS-AMI trial reported markedly higher rates of definite ST after PES implantation (4.2% at 3 years) despite inclusion of lower risk patients, indicating that there might be improved safety with use of second generation stents in STEMI.[26]

The ST rates found in the E-ZES group of this study were somewhere in between the results of PES and EES. E-ZES have previously been compared with SES in the setting of STEMI by Kim et al.[27] Up to one year follow-up, E-ZES showed a similar incidence of ST (1.0% vs. 1.8%). Additional studies found no differences in outcome between PES, SES and E-ZES in STEMI patients up to 18 months follow-up.[28-31] In these studies, the E-ZES groups showed variable ST rates ranging from zero to 2.9 percent. Longer term data on the performance of E-ZES in STEMI are lacking.

Recent results from the RESOLUTE all-comers trial showed non-inferiority of the Resolute ZES (R-ZES, characterized by a new biocompatible polymer with a more gradual release of zotarolimus) compared to EES. The 2 year definite ST rate was 2.0% in the R-ZES compared to 1.0% in EES.[32] In contrast, the recent TWENTE trial found a trend toward a reduction in definite/probable ST after 1 year in patients treated with R-ZES compared to EES.[33] These results suggest that improved safety and efficacy outcomes of the R-ZES compared to E-ZES are possibly due to improvements in polymer and elution pattern. However this remains speculation without definitive randomized clinical data. In this study a trend between lower 1 year ST rates in EES was seen, due to differences in the incidence of ST in the early period after stent implantation. From previous studies it is known that acute ST is related to procedure related factors like dissection, undersizing of stent, TIMI flow less than 3 after procedure and lack of glycoprotein IIb/IIIa inhibitors.[34] However, no acute ST were observed in our population. Sub-acute ST, which occurred in 6 instances, is related to a variability of factors, among which diabetes mellitus, left ventricular function under 40%, complex lesions and acuteness of PCI.[35] The role of procedure related factors is smaller in sub-acute ST, suggesting that the higher early rate of ST in E-ZES might be due to differences in stent design. However, long term rates of ST were similar in our population, supporting adequate safety of both second generation stents during long term follow-up.

Study limitations

The current observational cohort included the entire range of STEMI patients encountered in daily practice. Optimal care consisted of low diagnosis- and door-to-balloon times, up-front glycoprotein IIb/IIIa inhibitors and an intensive outpatient management program. There are however several limitations to the current study design. Because the Endeavor ZES is no longer clinically in use, the Resolute ZES might have been a better comparator for EES. Furthermore, results must be interpreted with caution due to the non-randomized, observational nature of the study. Although a wide range of baseline and angiographic characteristics were balanced between the groups, bias could have occurred during the selection of the patients. Multivariable Cox proportional hazards analyses were performed to correct for confounders but unmeasured characteristics may have influenced comparison of the groups. Propensity score matching may have provided more adequate correction for confounding but was not possible due to limitations in population size. The study was underpowered to detect differences in rare events like ST. Additionally, the adjudication of repeat MI events was not performed according to the latest trial protocols and this may have led to underestimation of MI events though there is no reason to suspect that this favored any of the stent types. Moreover, this was a single center investigation and there were no predefined endpoints which may have increased chances of type 2 error, therefore results of this analysis should be considered hypothesis-generating. Whether the advantage of EES in setting of STEMI remains when compared to the newer generation R-ZES is yet to be explored. Large randomized trials with long term follow-up and sufficient power are necessary to decide which newer generation stent is most suitable for STEMI patients.

Conclusions

The current retrospective investigation of EES and Endeavor ZES in setting of STEMI found lower rates of the device-oriented endpoint in EES patients compared to E-ZES patients, driven by lower rates of TLR. This suggests that EES is more efficacious than E-ZES in setting of ST-elevation myocardial infarction up to three years follow-up. Furthermore, definite ST rates were low and the strategy of second generation DES implantation and upfront GPIIb/IIIa inhibitors administration appears to be safe in STEMI.

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