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Clinical outcomes of complex real-world diabetic patients treated with amphilimus sirolimus-eluting stents or zotarolimus-eluting stents: A single-center registry☆

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ABSTRACT

Objective: To assess clinical outcomes of Amphilimus Sirolimus-Eluting Stents (A-SES) as compared to Zotarolimus-Eluting Stents (ZES) in complex real-world diabetic patients.
Background: Patients with diabetes mellitus represent one of the most challenging scenarios with high rates of restenosis and stent thrombosis in the current era of drug-eluting stents. Hence, we assessed the safety of A-SES versus ZES in complex diabetic patients.
Methods: In this observational study, we analyzed all consecutive patients with diabetes mellitus referred to our center from November 2012 to November 2014. The primary outcome was target-lesion failure at 1-year follow-up.
Results: A total of 165 consecutive diabetic patients underwent percutaneous coronary intervention with A-SES or ZES for stable coronary artery disease in our tertiary center. Using the Kaplan Meier method the cumulative incidence of target-lesion failure was 6.7% (5.9% A-SES versus 7.5% ZES, $p = 0.19$) at 1-year follow-up. Event-free survival at 1 year follow-up was similar (89.4% A-SES vs. 83.3% ZES, $p = 0.29$). Interestingly, we did not find any cases of definite-, and only one case of probable stent thrombosis in this high risk cohort.
Conclusion: In this real-world registry, A-SES and ZES seems to be associated with promising 1-year clinical safety outcomes following PCI in a contemporary cohort of high-risk diabetic patients. Our results should be considered hypothesis generating, as the clinical safety of A-SES has to be confirmed in a large trial.

1. Introduction

Patients with diabetes mellitus are at risk for adverse clinical events and account for 20–30% of patients undergoing percutaneous coronary intervention (PCI) worldwide [1]. In general, these patients have smaller vessel calibers, more diffuse coronary artery disease, a more rapid progression of atherosclerosis, and are prone to drug resistance and hypersensitivity reactions to polymers [2]. This drives both restenosis and stent thrombosis, subsequently leading to high event rates in diabetic patients [3]. Therefore, optimal drug-eluting stent (DES)-type remains a matter of debate.

In this registry, we investigate two different DES-platforms. The prior device is a novel Amphilimus Sirolimus-Eluting Stent (A-SES, Cre8 coronary stent system, Alvimedica, Istanbul, Turkey), with a thin (80 μm) cobalt chromium alloy covered with a passive coating to accelerate endothelialization [4,5]. Furthermore, this device is polymer-free DES and uses abluminal reservoirs (Fig. 1) that provide targeted drug-release in which sirolimus is released directly into the vessel wall. Moreover, A-SES is associated with promising clinical outcomes [6–8], especially in diabetic patients. The second device is a durable polymer Zotarolimus-Eluting Stent (ZES, Resolute Integrity, Medtronic Vascular, Santa Rosa, USA) with an established safety profile in diabetics [9].

Current guidelines [10,11] recommend a standard duration of dual antiplatelet therapy (DAPT) of 6 months following DES, or

Abbreviations: A-SES, Amphilimus Sirolimus-Eluting Stent; ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; BMS, Bare-Metal Stent; CI, Confidence Interval; DAPT, Dual AntiPlatelet Therapy; DES, Drug-Eluting Stent; EES, Everolimus-Eluting Stent; HR, Hazard Ratio; MI, Myocardial Infarction; Non-STEMI, Non-ST-segment Elevation Myocardial Infarction; OR, Odds Ratio; PCI, Percutaneous Coronary Intervention; ST, Stent Thrombosis; URL, Upper Reference Limit; ZES, Zotarolimus-Eluting Stent.

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3 months in case of an increased bleeding risk (Class II indication, level of evidence B).

Hence, we investigate the clinical safety of A-SES versus ZES in the complex setting of real-world diabetic patients with stable coronary artery disease.

2. Methods

This single-center retrospective analysis was conducted in patients with diabetes mellitus who underwent PCI for stable coronary artery disease in our center from November 2012 to November 2014. During this period, no other coronary stents were used in diabetic patients, according to institutional preference. Diabetes mellitus was defined as the use of oral antidiabetic medication or insulin during hospitalization. Patients were pre-treated with aspirin and clopidogrel. PCI was performed according to standard techniques with radial access as our default strategy. During coronary angiography, lesions were classified according to the modified ACC/AHA-classification system and bifurcation lesions were defined by the Medina classification, with a provisional approach as a default strategy unless there was clear evidence of a long lesion, or a particularly important side branch. Post-PCI, patients were instructed to use aspirin and clopidogrel for either 3 or 6 months as decided by the operator. Stent choice and the use of glycoprotein IIb/IIIa inhibitors or bivalirudin was at the operator's discretion. All patients gave informed consent for the procedure and local ethics committee approval was waived due to the retrospective nature of this registry.

2.1. Patient follow-up

Data was obtained by our routine PCI-complication registration and entered in a dedicated database. Patients were evaluated during regular hospital visits, by a medical questionnaire, and by telephone assessment at 1-year follow-up. During follow-up, information was obtained concerning the clinical condition of the patient, adverse clinical events, any hospitalizations, and compliance of medication. Data collection was regularly monitored, with complete verification of the source data by an independent researcher. Patients in this registry did not undergo routine angiographic follow-up.

2.2. Study outcome and definitions

The primary outcome is defined as target-lesion failure composed of: cardiac death, target vessel myocardial infarction, and target lesion revascularization, according to the Academic Research Consortium (ARC)-definitions [12]. Target-vessel MI was defined as any MI not clearly attributable to a non-target vessel, and >3 the upper-reference-limit (URL) of troponin within 48 h post-PCI, or >5 the URL of troponin within 72 h following coronary bypass artery grafting, or >1 URL after the periprocedural period. Bleeding complications were defined according to the Bleeding Academic Research Consortium (BARC)-criteria [13]. Angiographic success was defined as TIMI-III flow and a residual diameter stenosis of 20% or less. Major adverse clinical event-free survival was defined as survival with freedom of any MI, unplanned revascularization, or major bleeding (BARC > 3) at 1-year follow-up.

Fig. 1. Macroscopic picture of the abluminal reservoirs on the surface of the Cre8 stent, filled with an amphilimus formulation (obtained with permission of Moretti C. et al. [4]).

2.3. Statistical analysis

Categorical variables were analyzed using the χ^2 test, or Fisher exact test as appropriate and reported as absolute numbers and percentages. Continuous variables are reported as mean ± standard deviation and analyzed using Student's *t*-test, or the Mann-Whitney test in case of non-normal distribution. TLF and event Free survival at 1 year follow-up were assessed using the Kaplan-Meier method with associated log-rank Cox–Mantel test. Data for patients that were lost-to-follow-up were censored at the time of the last contact. *P*-values are two-sided unless otherwise specified and were considered significant at <0.05. All statistical analyses were performed using SPSS version 23 (Inc., Chicago, IL, USA). Kaplan-Meier curves of the cumulative incidence of TLF and event-free survival at 1 year follow-up were generated with GraphPad Prism software version 7 (GraphPad, Inc., San Diego, CA).

3. Results

From November 2012 to November 2014, 165 consecutive diabetic patients were analyzed. Baseline characteristics reveal an extended risk-profile with high prevalence of hypertension, dyslipidemia, obesity, and 3-vessel disease (Table 1). Insulin-dependent diabetes mellitus was common (65 patients, 40.9%). A history of MI was more frequent in patients treated with A-SES as compared to ZES (68.2% vs. 47.3%, $p = 0.008$).

Table 1
Baseline characteristics of diabetic patients eligible for percutaneous coronary intervention.

	Overall (n = 165)	A-SES (n = 85)	ZES (n = 80)	*p*-value
Clinical patient characteristics				
Age, years, n (%)	69.1 (9.6)	69.2 (9.8)	68.8 (9.5)	0.79
Male gender, n (%)	124 (78.0)	63 (74.1)	61 (82.4)	0.21
BMI, Kg/m^2, mean (sd)	29.5 (5.1)	30.1 (5.8)	28.8 (4.0)	0.12
Estimated GFR in ml/min, mean (sd)	67.2 (20.6)	66.0 (20.4)	68.7 (20.9)	0.41
Three vessel disease, n (%)	72 (45.3)	38 (44.7)	34 (45.9)	0.42
Prior myocardial infarction, n (%)	93 (58.5)	58 (68.2)	35 (47.3)	0.008
Prior PCI, n (%)	106 (66.7)	58 (68.2)	48 (64.9)	0.65
Prior CABG, n (%)	30 (18.9)	15 (17.6)	15 (20.3)	0.67
Prior PAD, n (%)	46 (28.9)	20 (23.5)	26 (35.1)	0.11
LVEF, mean (sd)	50.3 (11.1)	50.5 (9.9)	50.1 (12.4)	0.81
Cardiovascular risk factors				
Hypertension, n (%)	150 (94.3)	82 (96.5)	68 (91.9)	0.21
Dyslipidemia, n (%)	145 (91.2)	77 (90.6)	68 (91.9)	0.77
Current smoker, n (%)	50 (30.3)	22 (25.9)	28 (35.0)	0.20
Positive family history, n (%)	67 (42.1)	36 (42.4)	31 (41.9)	0.95
Insulin-dependent diabetes mellitus, n (%)	65 (40.9)	34 (40.0)	31 (41.9)	0.81
Pre-procedural medical therapy				
Aspirin, n (%)	136 (82.4)	70 (82.4)	66 (82.5)	0.98
Beta-blockers, n (%)	128 (77.6)	68 (80.0)	60 (75.0)	0.44
Calcium channel blockers, n (%)	48 (29.1)	22 (25.9)	26 (32.5)	0.35
ACE inhibitors, n (%)	93 (56.4)	53 (62.4)	40 (50.0)	0.11
Angiotensin-II-inhibitors, n (%)	51 (30.9)	28 (32.9)	23 (28.8)	0.56
Statins, n (%)	150 (90.9)	79 (92.9)	71 (88.8)	0.35

ACE = Angiotensin Converting Enzyme, A-SES = Amphilimus Sirolimus-Eluting Stents, BMI = Body Mass Index, CABG = Coronary Artery Bypass Grafting, DM = Diabetes Mellitus, GFR = Glomerular Filtration Rate, LVEF = Left Ventricular Ejection Fraction, PCI = Percutaneous Coronary Intervention, PAD = Peripheral Arterial Disease, ZES = Zotarolimus-Eluting Stents.

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