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A Randomized Comparison of Reservoir-Based Polymer-Free Amphilimus-Eluting Stents Versus Everolimus-Eluting Stents With Durable Polymer in Patients With Diabetes Mellitus

The RESERVOIR Clinical Trial

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ABSTRACT

OBJECTIVES The aim of this study was to compare the efficacy of amphilimus-eluting stents (AES) with that of everolimus-eluting stents (EES) in patients with diabetes mellitus (DM).

BACKGROUND The AES is a polymer-free drug-eluting stent that elutes sirolimus formulated with an amphiphilic carrier from laser-dug wells. This technology could be associated with a high efficacy in patients with DM.

METHODS This was a multicenter, randomized, noninferiority trial. Patients with DM medically treated with oral glucose-lowering agents or insulin and de novo coronary lesions were randomized in a 1:1 fashion to AES or EES. The primary endpoint was the neointimal (NI) volume obstruction assessed by optical coherence tomography at 9-month follow-up.

RESULTS A total of 116 lesions in 112 patients were randomized. Overall, 40% were insulin-treated patients, with a median HbA_{1c} of 7.3% (interquartile range: 6.7% to 8.0%). The primary endpoint, NI volume obstruction, was 11.97 ± 5.94% for AES versus 16.11 ± 18.18% for EES, meeting the noninferiority criteria ($p = 0.0003$). Pre-specified subgroup analyses showed a significant interaction between stent type and glycemic control ($p = 0.02$), with a significant reduction in NI hyperplasia in the AES group in patients with the higher HbA_{1c} ($p = 0.03$). By quantitative coronary angiography, in-stent late loss was 0.14 ± 0.24 for AES versus 0.24 ± 0.57 mm for EES ($p = 0.27$), with a larger minimal lumen diameter at follow-up for AES ($p = 0.02$), mainly driven by 2 cases of occlusive restenosis in the EES group.

CONCLUSIONS AES are noninferior to EES for the coronary revascularization of patients with DM. These results suggest a high efficacy of the AES and may support the potential benefit of this stent in patients with DM. (A Randomized Comparison of Reservoir-Based Polymer-Free Amphilimus-Eluting Stents Versus Everolimus-Eluting Stents With Durable Polymer in Patients With Diabetes Mellitus [RESERVOIR]; NCT01710748) (J Am Coll Cardiol Intv 2016;9:42–50)

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Patients with diabetes mellitus (DM) remain at high risk of in-stent restenosis and adverse cardiovascular events despite the use of drug-eluting stents (DES) (1,2). Second-generation DES provide superior safety and efficacy results compared with first-generation DES (3,4). However, stent thrombosis and restenosis rates remain an issue of continued concern (5).

The amphilimus-eluting stent (AES) is a third-generation DES devoid of polymer that elutes sirolimus formulated with an amphiphilic carrier (so-called amphilimus) from laser-dug wells on the stent's abluminal surface (6). This technology might be associated with a high efficacy in patients with DM (7). The aim of this trial was to assess the efficacy of the AES in patients with DM compared with the cobalt chromium everolimus-eluting stent with nonerodible polymer (EES).

ABBREVIATIONS AND ACRONYMS

AES = amphilimus-eluting stent(s)

DES = drug-eluting stent(s)

DM = diabetes mellitus

EES = cobalt chromium everolimus-eluting stent

NI = neointimal

OCT = optical coherence tomography

TLR = target lesion revascularization

METHODS

STUDY DESIGN AND PATIENT SELECTION. A full description of the trial was previously reported (8). Briefly, the RESERVOIR (A Randomized Comparison of Reservoir-Based Polymer-Free Amphilimus-Eluting Stents Versus Everolimus-Eluting Stents With Durable Polymer in Patients With Diabetes Mellitus) trial was a multicenter, prospective, open-label, assessor-blinded, active treatment-controlled, randomized clinical trial aimed to compare the results of AES and EES in patients with DM. This study was an investigator-driven initiative and was promoted by the Spanish Society of Cardiology and the Spanish Heart Foundation.

The target population consisted of diabetic patients with documented silent ischemia, stable angina, unstable angina, or non-ST-segment elevation myocardial infarction. Patients were eligible if they had a single de novo lesion per coronary artery (in a maximum of 2 major coronary arteries), with a length ranging from 12 to 25 mm and a reference diameter of 2.5 to 3.5 mm by visual estimation. The target lesion had to be treated with a single stent, although additional stents were allowed in case of suboptimal results. Major exclusion criteria included ST-segment elevation myocardial infarction occurring at less than 48 h, left main or ostial left descending artery stenosis, bifurcations with a side branch >2.5 mm in diameter, stent restenosis, chronic renal failure with a glomerular filtration rate <30 ml/min, or a left ventricular ejection fraction <30%. Patients with DM treated only with diet and lifestyle changes were also excluded.

Randomization occurred after successful pre-dilation and was performed on a 1:1 basis through an interactive Web response system (computer-generated sequence allocation), which was facilitated by an independent contract research organization (Adknoma Health Research, Barcelona, Spain). There was no stratification. The members of the clinical events committee and angiographic and optical coherence tomography (OCT) core laboratory personnel were blinded to treatment allocation.

The study was performed according to the provisions of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of each participating center. Written informed consent was obtained from all patients.

STUDY DEVICES. The AES (Cre8 coronary stent system, Alvimedica, Istanbul, Turkey) is a balloon-expandable stent manufactured from a cobalt chromium L605 alloy with an 80-μm strut thickness and has an ultrathin (0.3 μm) passive carbon coating. The AES does not have polymer, and the antiproliferative drug (sirolimus, 90 μg/cm^2) is loaded into reservoirs, which are dug on the stent's abluminal surface (6). The sirolimus is formulated with a mixture of long-chain fatty acids (so-called amphilimus) to act as a carrier and to control the drug release. Thus, 65% to 70% of the drug is released within the first 30 days, and the remainder is completely eluted by 90 days (9).

The EES (Xience Prime or Xience Expedition coronary stent system, Abbott Vascular, Abbott Park, Illinois) is a balloon-expandable cobalt chromium L605 stent, with an 81-μm strut thickness. The whole stent is coated (conformal configuration) with a thin (7.8 μm), nonerodible and biocompatible fluorinated copolymer. The polymer is designed to release 80% of the drug (everolimus, 100 μg/cm^2) by 30 days and the remainder by 120 days (10).

STUDY PROCEDURES. Procedures were performed according to standard techniques. Successful pre-dilation was mandatory before randomization. Post-dilation was encouraged by protocol, although it

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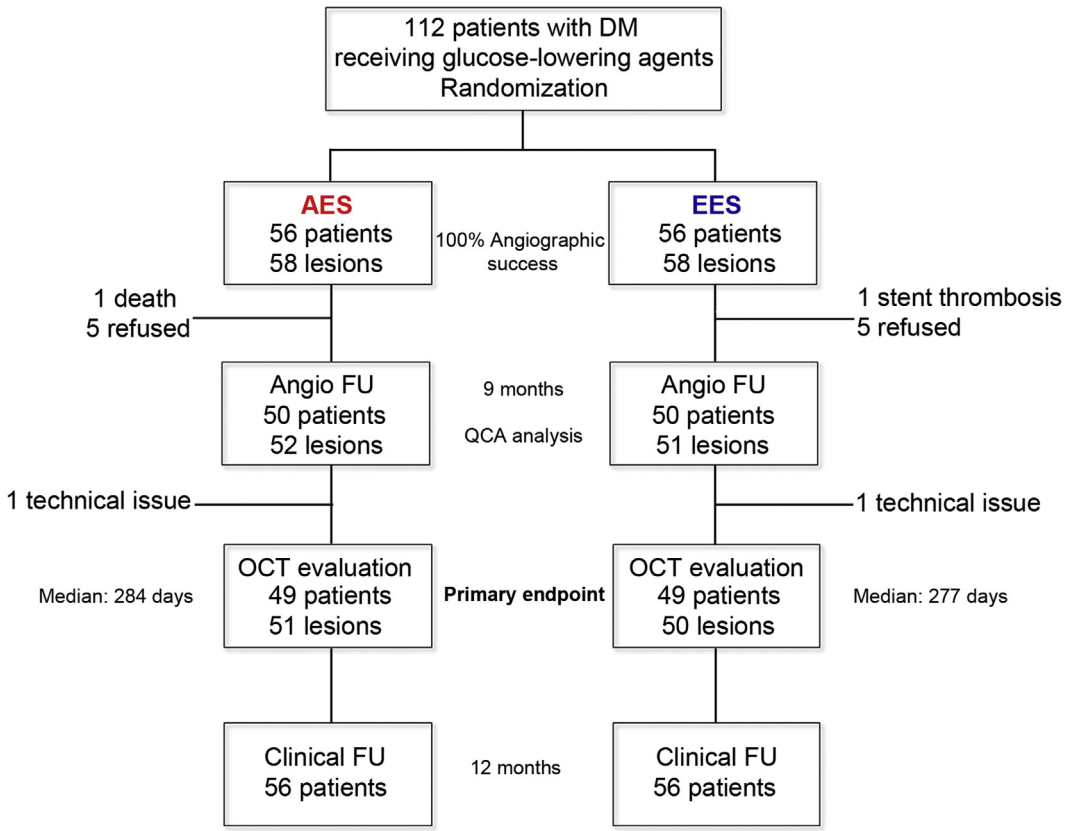
was not mandatory. The use of nonstudy stents in staged procedures at different epicardial vessels was allowed and was left to the operator's discretion.

Intraprocedural anticoagulation at the index procedure was administered according to the current practice guidelines. The use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. After the index procedure, dual antiplatelet therapy was recommended for 12 months. The use of ticagrelor (90 mg bid) or prasugrel (10 mg/day) was recommended for acute coronary syndromes if no contraindication (11).

Clinical follow-up was performed at discharge, 8 months, and 1 year after the index procedure. The angiographic and OCT follow-up was scheduled at 9 months. OCT pullbacks were obtained with the C7 Dragonfly system (St. Jude Medical, St. Paul, Minnesota) using a nonocclusive technique. A complete metabolic profile including body mass index, creatinine, HbA_{1c}, and high-density and low-density lipoprotein cholesterol was assessed in all patients at baseline and at the angiographic follow-up.

STUDY ENDPOINTS. The primary endpoint was the neointimal (NI) volume obstruction at 9 months, assessed by OCT, which is defined as the NI volume (mm^3) divided by the stent volume (mm^3) multiplied by 100. The secondary endpoints included the relative frequency of uncovered struts, the relative frequency of malapposed struts, the NI thickness, the maximal NI area obstruction assessed by OCT (12), and the angiographic in-stent late loss. Although this study was not powered to compare clinical events, the following clinical endpoints were also evaluated: ischemia-driven target lesion revascularization (TLR), target vessel revascularization, cardiac death, and probable or definite stent thrombosis. A full description of all study endpoints was previously reported (8).

FIGURE 1 Study Flowchart



AES = amphilimus-eluting stent(s); DM = diabetes mellitus; EES = everolimus-eluting stent(s); FU = follow-up; OCT = optical coherence tomography; QCA = quantitative coronary angiography.

TABLE 1 Baseline Characteristics and Metabolic Profile

	AES (n = 56)	EES (n = 56)	p Value
Age, yrs	66.7 ± 9.8	67.2 ± 8.8	0.75
Female	11 (19.6)	17 (30.4)	0.19
Risk factors			
Hypertension	46 (82.1)	49 (87.5)	0.43
Hyperlipidemia	45 (80.4)	47 (83.9)	0.62
Ever smoked	30 (53.6)	35 (62.5)	0.33
Metabolic profile			
Body mass index	29.6 ± 4.3	29.1 ± 3.4	0.47
HbA_{1c}	7.5 ± 1.2	7.5 ± 1.2	0.80
LDL cholesterol	82.8 ± 39.2	80.7 ± 32.5	0.76
HDL cholesterol	34.4 ± 11.8	36.2 ± 9.2	0.36
Creatinine	0.99 ± 0.26	0.95 ± 0.23	0.34
Vascular complications			
Diabetic retinopathy	6 (10.7)	8 (14.3)	0.57
Diabetic nephropathy	9 (16.1)	13 (23.2)	0.34
Previous MI	13 (23.2)	17 (30.4)	0.39
Previous PCI	22 (39.3)	19 (33.9)	0.56
Previous CABG	1 (1.8)	1 (1.8)	1.0
Previous stroke	6 (10.7)	8 (14.3)	0.57
Peripheral artery disease	8 (14.3)	13 (23.2)	0.23
Diabetes treatment			
Insulin	21 (37.5)	24 (42.9)	0.56
Biguanides	48 (53.9)	41 (74.5)	0.14
Sulfonylurea	15 (26.8)	14 (25)	0.83
Meglitinides	4 (7.1)	4 (7.1)	1.0
Thiazolidinediones	0	0	
α-Glucosidase inhibitors	0	0	
Dipeptidyl peptidase inhibitors	14 (25)	7 (12.5)	0.09
Statins (any)	55 (98.2)	53 (94.6)	0.31
ACE inhibitors	45 (80.4)	39 (69.6)	0.19

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; AES = amphilimus-eluting stent(s); CABG = coronary artery bypass graft; EES = everolimus-eluting stent(s); HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 2 Clinical and Procedural Characteristics

Characteristic	AES, 56 Patients/ 58 Lesions	EES 56 Patients/ 58 Lesions	p Value
Clinical presentation			0.09
Stable	31 (55.4)	22 (39.3)	
Acute coronary syndrome	25 (44.6)	34 (60.7)	
LV ejection fraction	57.8 ± 9.3	57.7 ± 7.8	0.75
$P2Y_{12}$ inhibitor			0.27
Clopidogrel	43 (76.8)	49 (87.5)	
Prasugrel	11 (19.6)	5 (8.9)	
Ticagrelor	2 (3.6)	2 (3.6)	
Acetylsalicylic acid	56 (100)	56 (100)	1.00
Glycoprotein IIb/IIIa inhibitors	0	2 (3.6)	0.15
Radial access	50 (89.3)	49 (87.5)	0.77
No. of vessels diseased	1.61 ± 0.65	1.61 ± 0.73	1.00
Target vessel			0.16
LAD	19 (32.8)	28 (48.3)	
LCX	19 (32.8)	17 (29.3)	
RCA	20 (34.5)	13 (22.4)	
Type B2/C lesion	27 (46.6)	25 (43.1)	0.71
Total contrast volume, ml	236.3 ± 103.2	224.8 ± 67.4	0.48
Total stent length	21.5 ± 6.9	20.7 ± 7.6	0.53
Stent diameter, mm	3.04 ± 0.35	2.93 ± 0.33	0.07
No. of stents per lesion	1.12 ± 0.33	1.05 ± 0.22	0.19
Maximal balloon pressure	16.41 ± 2.8	16.62 ± 2.3	0.65
Post-dilation	14 (23.7)	7 (12.1)	0.10
Angiographic success	58 (100)	58 (100)	1.00

Values are n (%) or mean ± SD.

LAD = left anterior descending artery; LCX = left circumflex artery; LV = left ventricular; RCA = right coronary artery; other abbreviations as in Table 1.

ANGIOGRAPHY AND OCT ANALYSIS. Quantitative coronary angiography analysis was performed at a central core lab (BARCICORE Lab, Barcelona, Spain) by experienced analysts blinded to the type of stent implanted. The analysis was performed using dedicated coronary angiography analysis software (CAAS version 5.9, Pie Medical BV, Maastricht, the Netherlands).

OCT data were also analyzed at a central core lab (BARCICORE Lab) by experienced analysts blinded to the type of stent implanted and clinical data, using proprietary offline software (LightLab Imaging, St. Jude Medical). Cross-sections at 1-mm intervals within the stent segment and 5 mm proximal and distal to the stent edges were analyzed. Frames with overlapped stents or side-branch take off were not considered for analysis. For totally occluded vessels that were not associated with stent thrombosis, it was estimated that the entire length of the stent was filled with NI hyperplasia (13).

STATISTICAL ANALYSIS. The study sample size was determined based on the primary endpoint of 9-month NI volume obstruction, assuming no difference in mean. On the basis of previously published data on a wide population, we expected a NI volume obstruction of 15.0% for the EES and an SD of 10.7% (14). The noninferiority margin was set at 5.3% (equaling 35% of the expected primary endpoint in the EES group) (8). Given these assumptions, 102 subjects would have provided an 80% power to demonstrate the noninferiority. To account for dropout and to ensure enough OCT data, ~112 patients were eventually required.

For continuous variables, differences between groups were evaluated by Student *t* test, whereas for discrete variables, chi-square or Fisher exact test was used. Normality of angiographic and OCT endpoint

TABLE 3 Paired QCA Results

	AES 50 Patients/ 52 Lesions	EES 49 Patients/ 50 Lesions	p Value
Before index procedure			
RVD, mm	2.69 ± 0.54	2.55 ± 0.49	0.16
MLD, mm	0.92 ± 0.42	0.89 ± 0.34	0.65
Diameter stenosis	66.12 ± 14.88	64.72 ± 12.28	0.61
Curvature, cm^{-1}	0.272 (0.133–0.679)	0.361 (0.156–0.549)	0.71
After index procedure			
RVD, mm	2.70 ± 0.47	2.64 ± 0.48	0.50
MLD, mm			
In-stent	2.51 ± 0.37	2.43 ± 0.36	0.24
In-segment	2.15 ± 0.50	2.06 ± 0.53	0.37
Diameter stenosis			
In-stent	8.53 ± 12.82	7.53 ± 8.60	0.68
In-segment	18.82 ± 7.81	19.79 ± 10.51	0.60
Acute gain, mm			
In-stent	1.59 ± 0.40	1.54 ± 0.43	0.52
In-segment	1.22 ± 0.46	1.17 ± 0.60	0.59
Curvature, cm^{-1}	0.209 (0.107–0.357)	0.197 (0.109–0.400)	0.88
Change in curvature, cm^{-1}	0.070 (−0.014–0.385)	0.089 (0.003–0.207)	0.67
9-month follow-up			
RVD, mm	2.67 ± 0.45	2.52 ± 0.50	0.13
MLD, mm			
In-stent	2.38 ± 0.44	2.19 ± 0.59	0.07
In-segment	2.09 ± 0.45	1.84 ± 0.61	0.02
Late lumen loss, mm			
In-stent	0.14 ± 0.24	0.24 ± 0.57	0.27
In-segment	0.06 ± 0.30	0.21 ± 0.61	0.34
Diameter stenosis			
In-stent	13.01 ± 10.01	14.69 ± 21.55	0.64
In-segment	19.56 ± 10.58	24.66 ± 17.95	0.08
Binary restenosis*			
In-stent	1 (1.9)	2 (4)	0.61
In-segment	2 (3.8)	3 (6)	0.68
Curvature, cm^{-1}	0.187 (0.091–0.355)	0.246 (0.098–0.434)	0.39

Values are mean ± SD, median (25% to 75% percentile), or n (%). *Diameter stenosis ≥50%.
MLD = minimal vessel diameter; QCA = quantitative coronary angiography; RVD = reference vessel diameter; other abbreviations as in Table 1.

distribution was verified by Shapiro-Wilk test, and the Wilcoxon-Mann-Whitney test was used instead of the Student *t* test when appropriate. To account for the nonindependence of struts within lesions in secondary endpoints such as the percentage of struts malapposed or uncovered, generalized estimating equation models and nonparametric analysis of aggregated data were used. To explore whether the results of the primary endpoint were consistent across important pre-specified subgroups (treatment with insulin, higher HbA_{1c}, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, stent size, and target vessel) (8), a post-hoc linear regression analysis with formal interaction testing was performed. The p value for noninferiority was 1 tailed, and all other p values were 2 tailed. Statistical significance was set at the 0.05 level for all comparisons. Statistical analyses were performed using SPSS version 18.0 (SPSS, Chicago, Illinois).

DATA MANAGEMENT. The investigators designed the trial and were responsible for its conduct and analysis. Collected data were entered into an electronic database, with 100% verification against source data by the contract research organization. Clinical events were adjudicated by an independent clinical event committee blinded to the treatment received.

RESULTS

From October 2012 to October 2013, 112 patients (116 lesions) were enrolled in the study: 56 patients (58 lesions) were assigned to AES and 56 patients (58 lesions) were assigned to EES (Figure 1).

Baseline characteristics and metabolic profile were well matched between groups (Table 1). Overall, 40% of patients were treated with insulin. The median HbA_{1c} at baseline was 7.3 (interquartile range: 6.7 to 8.0) and did not change at follow-up (7.3; interquartile range: 6.8 to 8.1), whereas low-density lipoprotein cholesterol was significantly reduced from baseline to follow-up (mean change, −8.9 mg/dl; 95% confidence interval: −1.5 to −16.4, p = 0.02), with no differences between groups. Clinical and procedural characteristics were also well balanced (Table 2). Angiographic success was achieved in all cases.

QUANTITATIVE ANGIOGRAPHIC CHARACTERISTICS. A total of 100 patients (103 lesions) underwent angiographic follow-up surveillance, with paired data analyzable for 99 patients (102 lesions). Angiographic characteristics are shown in Table 3. After stent implantation, reference vessel diameter, minimal lumen diameter, and acute gain were similar in both groups.

At 9-month follow-up, a larger minimal lumen diameter (mean difference, 0.25 mm; 95% confidence interval: 0.04 to 0.46 mm, p = 0.02) and a numerically lower diameter stenosis (p = 0.08) were observed for AES than for EES. In-stent and in-segment late lumen loss were, respectively, 0.14 ± 0.24 for AES versus 0.24 ± 0.57 for EES (p = 0.27) (Figure 2) and 0.06 ± 0.30 for AES versus 0.21 ± 0.61 for EES (p = 0.34). Stent conformability (change in curvature) was also similar in both groups.

OPTICAL COHERENCE TOMOGRAPHY. A total of 101 (51 AES, 50 EES) of 103 lesions with invasive follow-up

at 9 months had analyzable OCT data (1 OCT scan in the EES group could not be performed due to OCT system failure, and 1 OCT scan in the AES group was not analyzable due to poor image quality). Analyzable OCT data were available in all cases of TLR before any intervention was performed.

OCT results are presented in Table 4. The primary endpoint, NI volume obstruction, was 11.97 ± 5.94% for AES and 16.11 ± 18.18% for EES, reaching the noninferiority (upper 1-sided 95% confidence interval: 2.6, p for noninferiority = 0.0003, p for superiority = 0.22) (Figure 3). Post-hoc linear regression analysis with interaction testing demonstrated consistency of the results with no significant interactions between treatment assignment and OCT outcomes across 6 pre-specified groups, with the exception of patients with HbA_{1c} greater than median (Figure 4). In this subgroup, AES showed a significantly lower NI volume obstruction than EES (mean difference, 10.62%; 95% confidence interval: −22.68% to −1.69%, p = 0.025). Stent endothelialization was nearly complete in most cases, with no differences between groups.

CLINICAL OUTCOMES. Clinical follow-up was obtained for all patients at 12 months (Table 5). No significant differences were observed in any of the pre-specified endpoints between groups, although numerically there were more target vessel revascularizations in the EES group (5.2% vs. 12.1%, p = 0.18). Importantly, aggressive coronary artery disease progression was observed, with 1 in every 10 patients in both groups requiring unscheduled revascularization of a nontarget vessel during the follow-up.

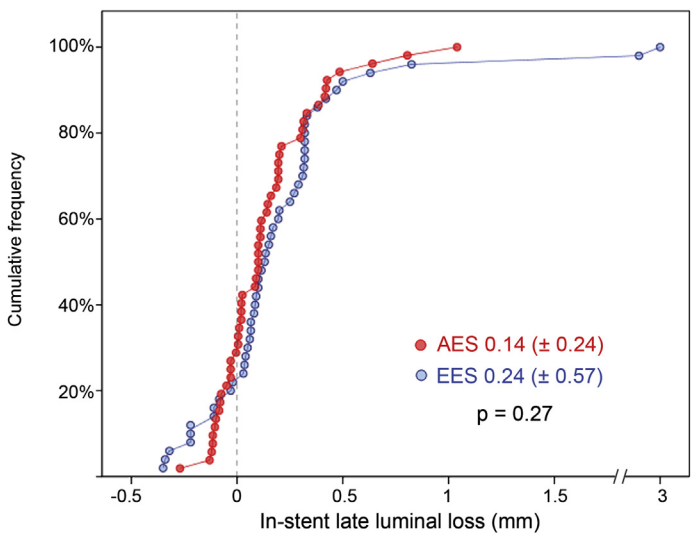
There was 1 case of definite late stent thrombosis (104 days after implantation) in the EES group. This patient was on dual antiplatelet therapy with clopidogrel, and the cause of the stent thrombosis was related to severe restenosis. There was 1 unwitnessed death 13 days after AES implantation that was judged to be a probable stent thrombosis. One patient in the AES group underwent unscheduled coronary angiography due to progressive angina, which showed severe stenosis of a jailed diagonal branch (<2.5 mm) with a patent study stent; the operator decided to perform kissing balloon angioplasty, and therefore, although the study stent was widely patent, it was judged to be a target lesion revascularization.

DISCUSSION

In the RESERVOIR study, we compared the efficacy of a novel elution technology (drug-elution from laser-dug wells and formulation with an amphiphilic carrier) with the classic elution from a durable polymer in patients with DM. Our findings showed that AES were not inferior to EES in patients with DM.

The concept of a polymer-free DES is attractive because the lack of polymer may avoid late events caused by chronic inflammation associated with some durable polymers (15). However, despite the use of microporous surfaces, direct application of the drug

FIGURE 2 Cumulative Frequency of In-stent Late Luminal Loss by Quantitative Coronary Angiography



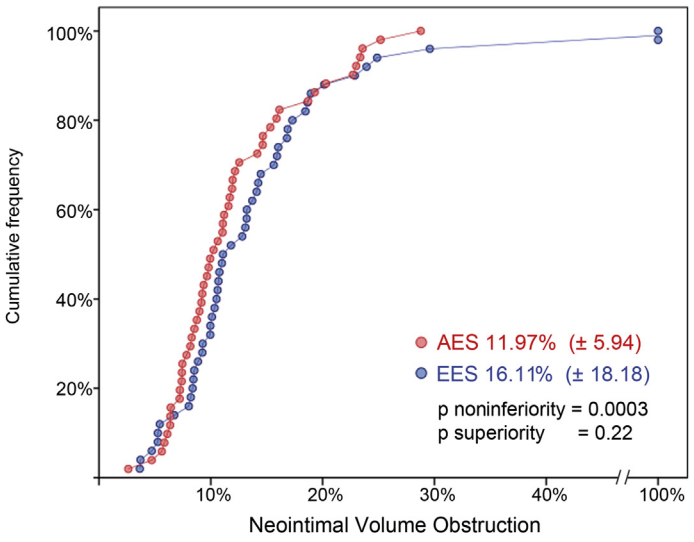
AES are depicted in **red** and EES in **blue**. Abbreviations as in Figure 1.

TABLE 4 Optical Coherence Tomography Results

	AES 49 Patients/51 Lesions (8,280 Struts)	EES 49 Patients/50 Lesions (8,991 Struts)	p Value
Lumen volume, mm^3	126.1 ± 59.3	109.3 ± 45.4	0.16
Stent volume, mm^3	142.1 ± 63.3	124.4 ± 49.5	0.21
NI volume, mm^3	16.0 ± 9.1	15.1 ± 7.6	0.82
Mean NI area stenosis, %	12.1 ± 5.8	16.3 ± 18.2	0.24
Maximal % of lumen stenosis	23.4 ± 11.5	28.4 ± 20.2	0.49
Mean NI thickness, μm	89.6 ± 48.0	87.2 ± 47.5	0.97
Uncovered struts, %	2.2 ± 3.3	3.4 ± 6.9	0.83
Malapposed struts, %	0.9 ± 1.6	1.1 ± 3.9	0.08
Malapposed and uncovered, %	0.6 ± 1.2	0.9 ± 3.8	0.46
Lesions with ≥5% of uncovered struts	6 (11.8)	8 (17.0)	0.46
Lesions with ≥5% of uncovered and malapposed struts	2 (4.3)	1 (2.0)	0.61

Values are mean ± SD or n (%).
NI = neointimal; other abbreviations as in Table 1.

FIGURE 3 Cumulative Frequency of Neointimal Volume Obstruction (Primary Endpoint)

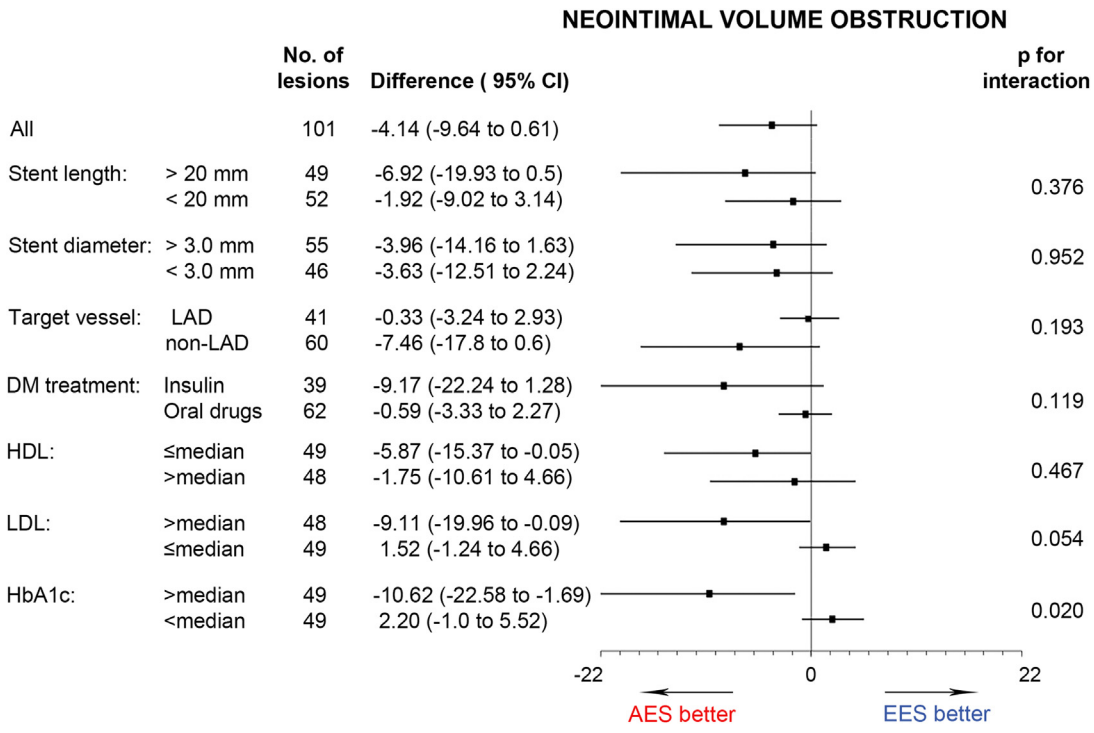


AES are depicted in **red** and EES in **blue**. Abbreviations as in Figure 1.

to the metallic surface of the stent led in most cases to fast elution, which was clinically translated to an impaired antirestenotic efficacy, even with the use of higher doses of drug than polymer-based DES (16,17). By contrast, our study shows that drug-elution can be performed in a timely manner by formulating the drug with an amphiphilic carrier in the absence of a polymer. In addition, elution from reservoirs allows almost all of the drug to be delivered to the vessel wall, as opposed to DES with polymer in a conformal configuration (in which a significant proportion of the drug is released to the blood) (9). To the best of our knowledge, this is the first study to show non-inferiority of a polymer-free DES compared with the cobalt chromium EES, which is the DES with the most robust evidence of safety and efficacy in patients with DM (18,19).

Our study showed a significant interaction between the metabolic control assessed by the HbA_{1c} and the stent type effect, with a significant reduction of NI hyperplasia in the AES group in poorly controlled patients. In patients with DM, as glucose uptake and oxidation are impaired, the heart is forced

FIGURE 4 Analysis of the Primary Endpoint in the Pre-Specified Variables



Pre-specified subgroup analyses showed a significant interaction between the stent type effect and the metabolic control assessed by the HbA1c. CI = confidence interval; DM = diabetes mellitus; HDL = high density lipoprotein; LAD = left anterior descending artery; LDL = low-density lipoprotein; other abbreviations as in Figure 1.

to use fatty acids almost exclusively for adenosine triphosphate generation. Fatty acid membrane transporters are overexpressed, resulting in an increased fatty acid cardiac uptake (20). Thus, it is possible that the use of fatty acids as a carrier could enhance drug penetration of insulin-resistant cells, which could increase its efficacy (21).

Our angiographic and clinical results are consistent with those of previous studies. A post-hoc analysis of the NEXT (Multicenter Randomized Trial Comparing Amphilimus- With Paclitaxel-Eluting Stents in De Novo Native Coronary Artery Lesions) trial (7) showed a late loss of the AES in the subgroup of patients with diabetes of 0.12 ± 0.28 mm, as well as a TLR frequency up to 12 month <6%. Likewise, the late loss and need for TLR of the EES are consistent with those described in the ESSENCE DIABETES (Randomized Comparison of Everolimus-Eluting Stent Versus Sirolimus-Eluting Stent Implantation for De Novo Coronary Artery Disease in Patients With Diabetes Mellitus) trial (3) or in a post-hoc analysis of patients with DM of the Comparison of an Everolimus-Eluting Stent and a Paclitaxel-Eluting Stent in Patients With Coronary Artery Disease) (22). Of note, in lesions treated with EES, there was a trend for a smaller reference vessel diameter and a smaller stent size than lesions treated with AES, which may have contributed to the higher late loss.

Importantly, 1 in 10 patients in our trial underwent unscheduled revascularization of nontarget vessels or in nonstented segments of the target vessels due to coronary artery disease progression or plaque destabilization. These findings are in agreement with those of previous studies (1) and highlight the particularly high risk of diabetic patients not only for restenosis but also for disease progression (23). Thus, regardless of improvements in DES technology, patients with DM are likely to remain in the near future at high risk of cardiovascular events after percutaneous coronary revascularization (24).

Patients with DM represent 20% to 30% of cases undergoing percutaneous coronary revascularization at present. Even so, few interventional studies have focused on patients with DM, and the endothelialization pattern after new-generation DES implantation in diabetic patients is not well understood. Indeed, the RESERVOIR study is the first trial to evaluate the endothelialization of AES and EES by OCT in these patients. Our results showed a similar amount of NI hyperplasia than the general population (14), which would be consistent with previous intravascular ultrasound studies performed in the DES era (25). Thus, after DES implantation, patients with DM would exhibit similar NI hyperplasia than nondiabetic patients, and the DES patency at follow-up would be primarily determined by the smaller lumen post-procedure (25).

TABLE 5 Clinical Events at 12 Months

Event	AES 56 Patients/ 58 Lesions	EES 56 Patients/ 58 Lesions	p Value
Cardiac death	1 (1.8)	0	1.0
Myocardial infarction	0	1 (1.8)	1.0
Definite stent thrombosis*	0	1 (1.7)	1.0
Definite or probable stent thrombosis*	1 (1.7)	1 (1.7)	1.0
Ischemia-driven target lesion revascularization*	3 (5.2)	5 (8.6)	0.46
Target vessel revascularization*	3 (5.2)	7 (12.1)	0.18
Unscheduled nontarget vessel revascularization	6 (10.7)	6 (10.7)	0.99

Values are n (%). *Lesion-based analysis.
Abbreviations as in Table 1.

STUDY LIMITATIONS. The present study has limitations that should be acknowledged. This study was unpowered to detect differences in individual clinical endpoints between the 2 groups. Moreover, studies with protocol-mandated late invasive assessment may overestimate the rate of repeat revascularization. Therefore, our findings should be confirmed or refuted by larger, longer term follow-up studies in patients with DM. Finally, all comparisons performed besides the primary endpoint analysis must be considered exploratory.

CONCLUSIONS

The present study is the first to show the noninferiority of a polymer-free AES compared with the EES in patients with DM, and it demonstrates that formulation of the drug with an amphiphilic carrier results in noninferior efficacy compared with the classic elution from SPIRIT III durable polymers. Results suggest a high efficacy of AES in patients with DM, which must be confirmed by a large randomized clinical trial.

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PERSPECTIVES

WHAT IS KNOWN? Patients with DM remain at high risk of cardiovascular events even with the use of second-generation polymer-based DES.

WHAT IS NEW? This is the first study to show the noninferiority of a polymer-free DES compared with the cobalt chromium EES. Formulation of the antiproliferative drug with an amphiphilic carrier is associated with a high efficacy in this high-risk population.

WHAT IS NEXT? Large trials are warranted to find the best stent technology for patients with DM who are not candidates for surgical revascularization.

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