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FASTTRACK CLINICAL RESEARCH
Interventional cardiology

Amphilimus- vs. zotarolimus-eluting stents in patients with diabetes mellitus and coronary artery disease: the SUGAR trial

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Aim Patients with diabetes mellitus are at high risk of adverse events after percutaneous revascularization, with no differences in outcomes between most contemporary drug-eluting stents. The Cre8 EVO stent releases a formulation of sirolimus with an amphiphilic carrier from laser-dug wells, and has shown clinical benefits in diabetes. We aimed to compare Cre8 EVO stents to Resolute Onyx stents (a contemporary polymer-based zotarolimus-eluting stent) in patients with diabetes.

Methods and results We did an investigator-initiated, randomized, controlled, assessor-blinded trial at 23 sites in Spain. Eligible patients had diabetes and required percutaneous coronary intervention. A total of 1175 patients were randomly assigned (1:1) to receive Cre8 EVO or Resolute Onyx stents. The primary endpoint was target-lesion failure, defined as a composite of cardiac death, target-vessel myocardial infarction, and clinically indicated target-lesion revascularization at 1-year follow-up. The trial had a non-inferiority design with a 4% margin for the primary endpoint. A

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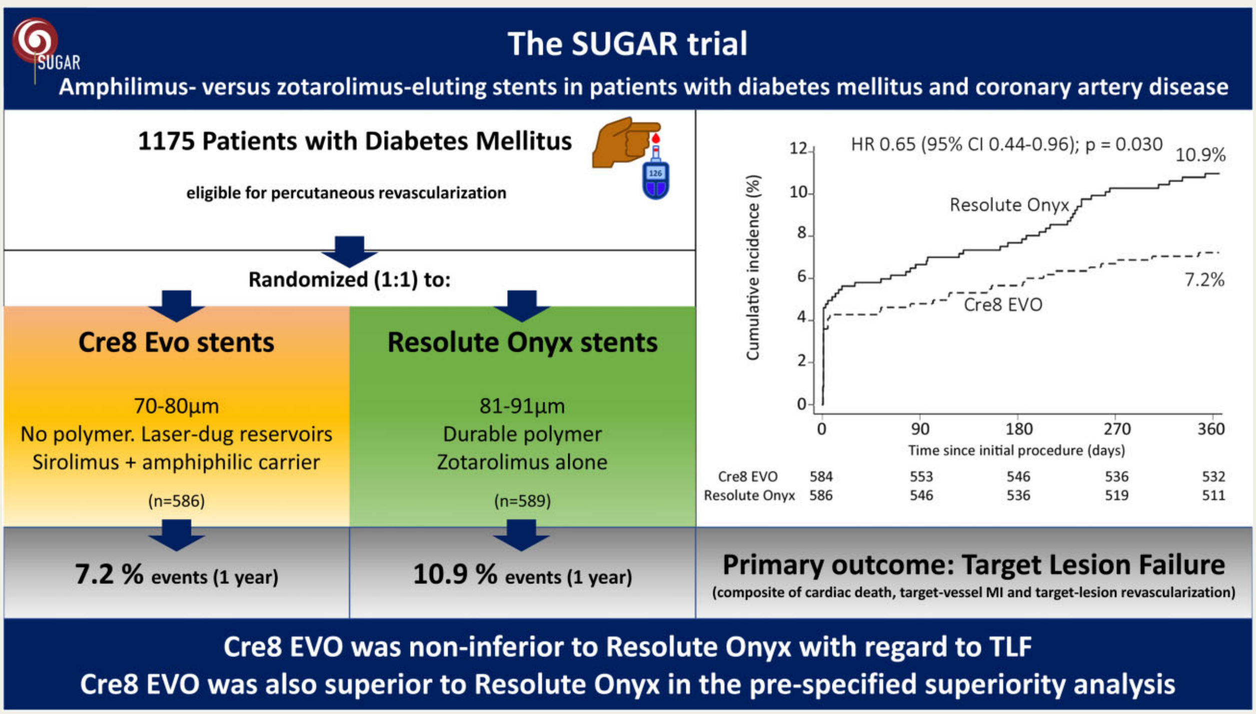
superiority analysis was planned if non-inferiority was confirmed. There were 106 primary events, 42 (7.2%) in the Cre8 EVO group and 64 (10.9%) in the Resolute Onyx group [hazard ratio (HR): 0.65, 95% confidence interval (CI): 0.44–0.96; $P_{non\text{-}inferiority} < 0.001$; $P_{superiority} = 0.030$]. Among the secondary endpoints, Cre8 EVO stents had significantly lower rate than Resolute Onyx stents of target-vessel failure (7.5% vs. 11.1%, HR: 0.67, 95% CI: 0.46–0.99; $P = 0.042$). Probable or definite stent thrombosis and all-cause death were not significantly different between groups.

Conclusion In patients with diabetes, Cre8 EVO stents were non-inferior to Resolute Onyx stents with regard to target-lesion failure composite outcome. An exploratory analysis for superiority at 1 year suggests that the Cre8 EVO stents might be superior to Resolute Onyx stents with regard to the same outcome.

Clinical trial registration ClinicalTrials.gov: NCT03321032.

Graphical Abstract



In the SUGAR trial, 1175 patients with diabetes mellitus and coronary artery disease were randomly assigned to receive Cre8 EVO or Resolute Onyx stents. Patients allocated to Cre8 EVO stents had a reduced risk of target lesion failure at 1-year follow-up.

Keywords Percutaneous coronary intervention • Drug-eluting stents • Diabetes mellitus • Randomized trial

Introduction

Diabetes mellitus is a major health issue that affects more than 463 million human beings worldwide.[1] These patients often have symptomatic coronary artery disease and, as a consequence, percutaneous revascularization of patients with diabetes using drug-eluting stents is commonly performed worldwide. Only in the USA, 240 000 patients with diabetes undergo percutaneous revascularization yearly.[2] However, results of percutaneous coronary intervention with contemporary drug-eluting stents are far from good.[3] Although the second-generation outperformed the first-generation drug-eluting stents,[4] there has been no further outcome improvements in stent technology for patients with diabetes for the past 10 years, and the little evidence available suggests no substantial differences in outcomes between most contemporary drug-eluting stents in diabetes.[5]

Cre8 EVO stents are thin-strut stents devoid of polymer that release a medium dose of sirolimus formulated with an amphiphilic carrier from laser-dug reservoirs located at the stent's abluminal surface.[6] The combination of the drug with a carrier aims to improve drug delivery to the tissue in patients with diabetes who have dose-dependent drug resistance,[7,8] and the thin-device thickness (30% thinner than everolimus- or zotarolimus-eluting stents) allows low thrombogenicity and fast reendothelialization.[9] This technology has shown clinical benefits in patients with diabetes in several small randomized or non-randomized studies.[10–15] Thus, in the SUGAR trial, we sought to compare the Cre8 EVO stent to the Resolute Onyx stent (a contemporary polymer-based drug-eluting stent) in patients with diabetes mellitus and coronary artery disease.

Methods

Study design

The SUGAR trial was an investigator-initiated, prospective, randomized (1:1), controlled, parallel group, assessor-blinded study that included patients with diabetes undergoing percutaneous coronary intervention in 23 hospitals in Spain (see Supplementary material online, *Appendix*). The study design and statistical plan has been described previously in detail.[16] The study complied with the provisions of the Declaration of Helsinki and the CONSORT 2010 Statement. The institutional review board approved the study protocol at each participating centre.

Patients

Patients were eligible if they were aged 18 years or older, had diabetes according to the American Diabetes Association diagnostic criteria,[17] and had symptomatic coronary artery disease or silent ischemia with at least one coronary lesion with stenosis >50% suitable for percutaneous coronary intervention. The study had an all-comers design with few exclusion criteria: life expectancy < 2 years, cardiogenic shock at presentation, pregnancy, inability to consent (including shock or mechanical ventilation), or conditions that preclude at least one month of dual antiplatelet therapy. No restriction was placed on the clinical presentation (chronic or acute coronary syndromes, including myocardial infarction with or without ST-segment elevation), complexity of lesions, the number of treated vessels or the number of stents implanted. In cases of left main trunk lesion or multivessel disease, each centre was required to present the case in the local Heart Team. All patients provided written informed consent.

Randomization and masking

Patients who met the enrolment criteria were randomized 1:1 to receive either Cre8 EVO or Resolute Onyx stents. There was no stratification by centre or clinical factors. Randomization was performed after successfully crossing the target lesion with a coronary wire, using web-based software with a block size of four. Allocation of stents was at patient-level, meaning that patients should receive exclusively the allocated stent in all lesions after randomization. The adjudication committee was blinded to treatment allocation, but patients and treating clinicians were not.

Procedures

The Cre8 EVO (CID S.p.A, Saluggia, Italy) is a balloon-expandable stent manufactured from cobalt chromium L605 alloy with 70 µm strut thickness for the 2.0–2.25 mm stents and 80 µm for the larger stents. Struts are covered with an ultra-thin (0.3 µm) passive carbon coating. The Cre8 EVO does not have polymer and, therefore, the total-device thickness is 70–80 µm. The antiproliferative drug (sirolimus, 90 µg/cm^2) is loaded into reservoirs, which are dug on the stent's abluminal surface. The sirolimus is formulated with an amphiphilic carrier that enhances drug diffusion to the cell. Seventy per cent of the drug is released within the first 30 days and the remainder is completely eluted by 90 days.

The Resolute Onyx (Medtronic, Minneapolis, MN, USA) is a balloon-expandable stent formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself (rather than classical rings and links design). It is manufactured from a composite metal material, consisting of a cobalt-based alloy shell conforming to ASTM F562 and a platinum–iridium alloy core conforming to ASTM B684, with 81 µm strut thickness for the 2.0–3.5 mm stents and 91 µm for the 4.5–5.0 mm stents. The entire stent is coated (conformal configuration) with a thin (5.6 µm), non-erodible, and biocompatible Biolynx polymer (which is a blend of two different polymers and polyvinyl pyrrolidone). The polymer is designed to release the drug (zotarolimus, 160 µg/cm^2) by 180 days. The total-device thickness is therefore 92–102 µm.

Percutaneous coronary intervention was performed according to the current standard of care.[18] There was no restriction to treat complex lesions such as left main, bifurcations, chronic total occlusions, or those with severe calcification requiring rotational atherectomy or other modification devices, following a pragmatic, all-comers design. Staged procedures were allowed provided that the allocated treatment stent was used in all lesions (patient-level randomization). The revascularization extent was free to local protocols and investigator's decision, although complete revascularization was strongly encouraged whenever feasible. After the procedure, all patients received dual antiplatelet therapy for a minimum of 1 month, although it was recommended 3–6 months for chronic coronary syndromes and 12 months for acute coronary syndromes. Novel P2Y12 inhibitors (ticagrelor 90 mg b.i.d. or prasugrel 10 mg o.d.) were encouraged over clopidogrel (75 mg o.d.) if clinically indicated. If an indication for oral anticoagulation was present, the antithrombotic therapy was free to investigator's decision according to local protocols and current guidelines.[19] Lifestyle changes and use of new glucose-lowering drugs with proven cardiovascular safety, such as sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide 1 receptor agonists,[20] were encouraged. Optimal medical treatment following current European Society of Cardiology guidelines with a particular focus on secondary prevention was recommended after revascularization.[20,21] Routine surveillance angiography was discouraged unless it was clinically indicated.

Cardiac troponin was measured before intervention and at 6–12 h after the study procedure, and subsequent serial measurements in case of suspected ischaemia. In patients with acute coronary syndromes, cardiac biomarkers were measured prior to catheterization. To assess adverse events and clinical status, patients were followed up by telephone or hospital visit at 1 and 6 months, and by hospital visit at 1 year. However, following the coronavirus disease 2019 (COVID-19) pandemic, the steering committee and the ethics committee issued an urgent safety warrant on 12 March 2020 allowing telephone visits at 1-year follow-up for periods when community transmission was uncontrolled and healthcare systems were overwhelmed.[22]

Patient data were captured into secure electronic case report forms. A contract research organization monitored the completeness and accuracy of data (Adknoma Health Research, Barcelona, Spain). Clinical event adjudication was performed by an independent committee in coordination with a central core-laboratory (Barcicore-lab, Barcelona, Spain) (see Supplementary material online, *Appendix*).

Outcomes

The primary endpoint was target lesion failure, which included cardiac death, target-vessel myocardial infarction, or clinically indicated target-lesion revascularization. Secondary endpoints included the individual components of the primary endpoint, all-cause death, target-vessel revascularization, any revascularization, all myocardial infarctions, target-vessel

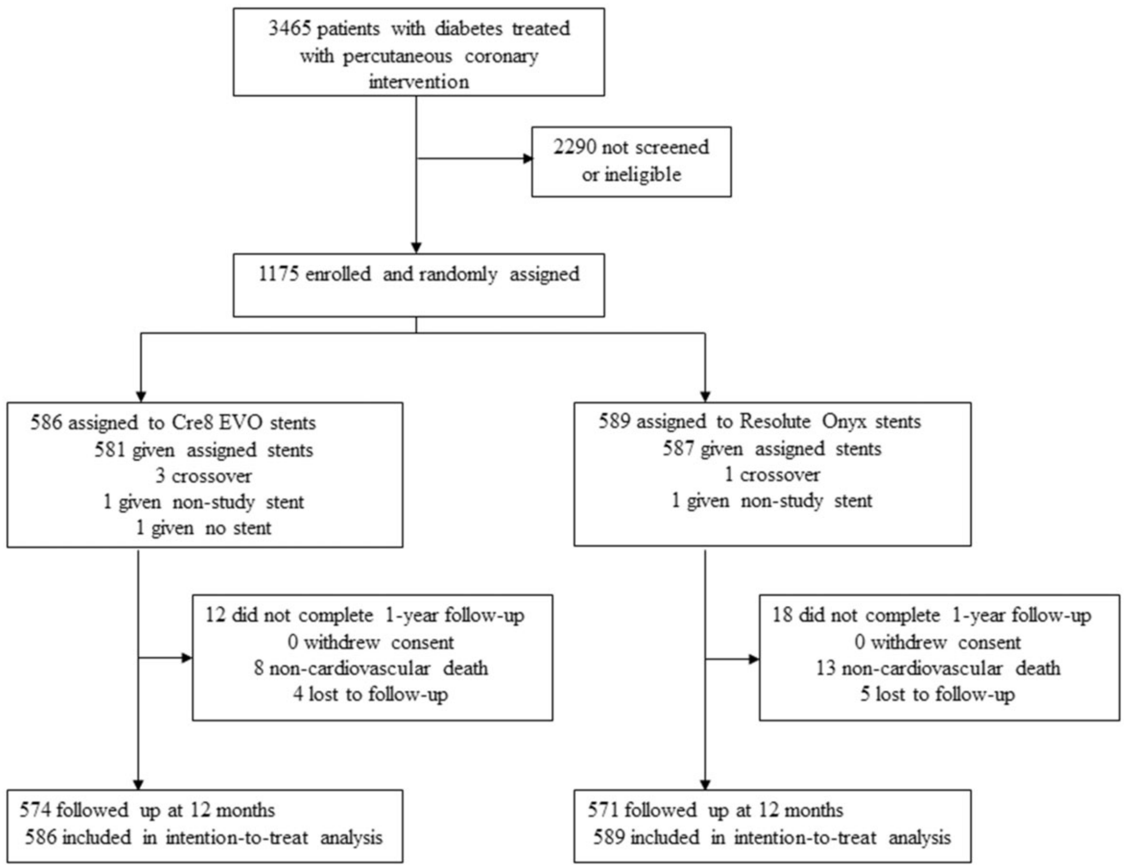


Figure 1 Trial flowchart.

failure, probable or definite stent thrombosis, and major adverse cardiac events.

Myocardial infarction was assessed using the third universal definition[23] as defined in the original study protocol, although due to the changing criteria of myocardial infarction during the conductance of the study, both the third universal definition and the novel Academic Research Consortium (ARC)-2 criteria[24] were obtained. Comprehensive endpoint definitions are listed in the Supplementary material online, *Appendix*.

Statistical analysis

Statistical analyses were performed as previously outlined in the study design publication.[16] All analyses were conducted by independent statisticians of the Clinical Trials Coordination Unit at Centro Nacional de Investigaciones Cardiovasculares Carlos III.

The present study was powered to assess non-inferiority at 1-year of the Cre8 EVO stent compared with the Resolute Onyx stent. The study was also powered to look for superiority at 2 years. If non-inferiority was met at 1 year, a superiority analysis was pre-specified. We expected 8.0% and 11.2% of primary events in the Resolute Onyx group at 1- and 2-year follow-up, respectively,[25] and 5% of events for the Cre8 EVO group at 1-year and 6.5% at 2-year follow-up.[12] The non-inferiority margin at 1 year was set at 4% absolute difference (1.5 relative risk of the 8% expected event rate of control group). Based on the expected event rate and an anticipated 2% of patients lost to follow-up, we calculated that 1164 patients would provide at least 90% power with a one-sided $\alpha = 0.025$ to test for non-inferiority, and 80% power to test superiority with a two-sided $\alpha = 0.05$.

Analysis was conducted on an intention-to-treat basis, although additional analyses were also conducted according to the treatment actually received. Categorical variables are reported as frequencies and percentages, whereas continuous variables are presented as means (standard deviation) or median (interquartile range) where appropriate. Composite endpoints were evaluated as time-to-first event, whichever individual component occurred first. The primary outcome analysis was performed using a Cox proportional-hazards model, although relative risks are also reported at the Supplementary material online, *Appendix*. At 1 year, a hazard ratio (HR) and its two-sided 95% confidence interval (CI) was estimated. For all comparisons, differences were considered statistically significant when $P < 0.05$. STATA software version 15.1 (Stata Corp, College Station, TX, USA) was used to perform the analyses. This trial is registered with ClinicalTrials.gov, number NCT03321032.

Results

Between 19 December 2017, and 28 January 2020, we randomly allocated 1175 patients with 1548 diseased vessels to receive either Cre8 EVO stents (586 patients with 879 lesions) or Resolute Onyx stents (589 patients with 950 lesions) (*Figure 1*). Among the 586 patients randomized to Cre8 EVO, 581 actually received the

Table 1 Baseline characteristics

	Cre8 EVO group (*n* = 586)	Resolute Onyx group (*n* = 589)
General characteristics		
Age at randomization (years)	68.6 (9.8)	67.2 (10.6)
Male sex	449 (76.6%)	439 (74.5%)
Medical history		
Hypertension	493 (84.1%)	488 (82.9%)
Dyslipidaemia	485 (82.8%)	471 (80.0%)
Current smoker	111 (18.9%)	144 (24.4%)
Prior myocardial infarction	105 (17.9%)	95 (16.1%)
Prior CABG	21 (3.6%)	15 (2.5%)
Prior PCI	136 (23.2%)	122 (20.7%)
Peripheral artery disease	82 (14.0%)	91 (15.4%)
Cerebrovascular disease	65 (11.1%)	37 (6.3%)
LVEF	56.6 (11.3)	56.7 (10.8)
Indication for index procedure		
Chronic coronary syndromes	243 (41.5%)	229 (38.9%)
NSTE-ACS	277 (47.3%)	280 (47.5%)
STEMI	66 (11.3%)	80 (13.6%)
Diabetes and metabolic characteristics		
Diabetes Type 2	565 (96.4%)	557 (94.6%)
Years with known diabetes	10.6 (8.7)	11.4 (9.2)
Insulin-treated diabetes at randomization	183 (31.2%)	194 (32.9%)
Body mass index	29.4 (5.0)	29.0 (4.5)
Waist circumference (cm)	103.1 (13.5)	102.5 (12.4)
LDL cholesterol (mg/dL)	78.8 (44.7)	80.9 (45.5)
HDL cholesterol (mg/dL)	37.2 (15.9)	38.2 (15.5)
HbA1c (%)	7.4 (1.5)	7.5 (1.5)
Creatinine clearance (mL/min)	70.0 (25.4)	73.1 (24.0)
Haemoglobin (g/L)	13.5 (0.3)	13.8 (0.3)

CABG, coronary artery bypass graft; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

allocated stent, whereas there were three crossovers, one patient received only a non-study stent and one patient was treated with drug-coated balloon angioplasty alone. Two patients in this group received a graft stent in addition to the study stent as a bailout treatment of a coronary perforation. Among the 589 patients randomized to Resolute Onyx, there was one crossover and one patient received only a non-study stent. No patient withdrew consent, 21 died of non-cardiovascular causes and there were 9 patients lost to follow-up. Therefore 574 patients in the Cre8 EVO group and 571 patients in the Resolute Onyx group completed the 12-month follow-up; 586 patients from the Cre8 EVO group and 589 patients from the Resolute Onyx group were included in the intention-to-treat population.

Baseline clinical and procedural characteristics are outlined in *Tables 1 and 2*. Most patients included in the study had Type 2 diabetes (95.5%), 32% were treated with insulin and 12% were randomized in the setting of a ST-segment elevation myocardial infarction. Multivessel disease was present in 50.9% of patients and percutaneous coronary intervention of the left main trunk was

Table 2 Procedural characteristics

	Cre8 EVO group (patients = 586) (lesions = 879)	Resolute Onyx group (patients = 589) (lesions = 950)
Radial	536 (91.5%)	542 (92.0%)
Preload with P2Y12 inhibitor	396 (67.6%)	404 (68.6%)
IIb/IIIa inhibitor	12 (2.0%)	15 (2.5%)
Contrast volume (mL)	190 (80)	193 (77)
Syntax score at randomization[a]	13.0 (9.7)	13.0 (8.7)
Number of diseased vessel		
1	295 (50.3%)	282 (47.9%)
2	189 (32.3%)	200 (34.0%)
3	102 (17.4%)	107 (18.2%)
Intracoronary imaging use per vessel	41 (5.4%)	41 (5.2%)
Number of treated lesions per patient	1.50 (0.83)	1.61 (0.88)
Number of stents per patient	1.63 (1.02)	1.75 (1.07)
Complete revascularization	397 (67.7%)	389 (66.0%)
Staged procedures	21 (3.6%)	30 (5.1%)
Target vessel at randomization		
Left main	28 (3.7%)	25 (3.2%)
Left anterior descending artery	320 (41.8%)	319 (40.7%)
Left circumflex artery	188 (24.6%)	204 (26.1%)
Right coronary artery	229 (29.9%)	235 (30.0%)
TIMI flow 0–1	126 (16.5%)	141 (18%)
Chronic total occlusion	16 (2.1%)	19 (2.4%)
Bifurcation with two stents	43 (5.6%)	38 (4.9%)
Aorto-ostial lesion	13 (1.7%)	12 (1.5%)
AHA/ACC complexity		
A	72 (9.4%)	67 (8.6%)
B1	250 (32.7%)	224 (28.6%)
B2	287 (37.5%)	289 (36.9%)
C	156 (20.4%)	203 (25.9%)
Diameter stenosis (%)	83.3 (17.1)	84.7 (15.1)
Reference vessel diameter by visual estimation	2.98 (0.51)	2.96 (0.50)
Minimum stent diameter	2.91 (0.49)	2.87 (0.49)
Total stented length (mm)	26.5 (13.7)	27.4 (14.9)
Post-dilation	286 (37.4%)	226 (28.9%)
Rotational atherectomy	22 (2.9%)	11 (1.4%)
Procedural complications		
No-reflow	4 (0.5%)	5 (0.6%)
Dissection	22 (2.9%)	24 (3.1%)
Vessel occlusion	4 (0.5%)	1 (0.1%)
Coronary perforation	2 (0.3%)	2 (0.3%)

[a]Syntax score is self-reported.
ACC, American College of Cardiology; AHA, American Heart Association; TIMI, thrombolysis in myocardial infarction.

Table 3 **Medications and metabolic characteristics at discharge and at follow-up**

	Cre8 EVO group (*n* = 586)	Resolute Onyx group (*n* = 589)	*P*-Value
Medication at discharge			
Acetylsalicylic acid	560 (95.6%)	567 (96.3%)	0.54
P2Y12 inhibitors			0.98
Clopidogrel	282 (48.1%)	278 (47.2%)	
Prasugrel	47 (8%)	47 (8%)	
Ticagrelor	241 (41.1%)	249 (42.3%)	
Oral anticoagulation			0.41
Vitamin K antagonists	25 (4.3%)	17 (2.9%)	
Non-vitamin K oral anticoagulant	33 (5.6%)	37 (6.3%)	
Statins	513 (87.5%)	517 (87.8%)	0.90
Glucose-lowering drugs			
Insulin	200 (34.1%)	219 (37.2%)	0.28
Biguanides	392 (66.9%)	408 (69.3%)	0.38
Sulfonylureas	53 (9%)	67 (11.4%)	0.19
Meglitinides	25 (4.3%)	30 (5.1%)	0.50
Thiazolidinediones	1 (0.2%)	0	0.50
Dipeptidyl peptidase-4 inhibitors	157 (26.8%)	149 (25.3%)	0.56
SGLT2 inhibitors	119 (20.3%)	107 (18.2%)	0.35
GLP-1 RA	18 (3.1%)	14 (2.4%)	0.46
Dual antiplatelet therapy			
At 1 month	552 (94.2%)	554 (94.1%)	0.919
At 6 months	504 (86%)	504 (85.6%)	0.830
At 12 months	314 (53.6%)	349 (59.3%)	0.050
Medications at 1 year			
Oral anticoagulation			0.49
Vitamin K antagonists	22 (3.8%)	15 (2.5%)	
Non-vitamin K oral anticoagulant	37 (6.3%)	36 (6.1%)	
Glucose-lowering drugs			
SGLT2 inhibitors	130 (22.2%)	121 (20.5%)	0.49
GLP-1 RA	7 (1.2%)	12 (2.0%)	0.25
Metabolic characteristics at 1-year			
LDL cholesterol (mg/dL)	65.8 (29.1)	65.6 (28.1)	0.88
HDL cholesterol (mg/dL)	42.9 (11.8)	44.0 (12.3)	0.17
HbA1c (%)	7.2 (1.4)	7.4 (1.4)	0.050
Weight	79.9 (15.0)	80.4 (13.8)	0.61
Δ from baseline	–1.1 (5.6)	–0.6 (6.0)	0.20

GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGLT2, sodium-glucose cotransporter 2.

performed in 4.5% of the patients. Syntax score was in the lower tertile in most cases. Baseline and procedural characteristics were broadly similar in the two study groups with minor differences: patients in the Cre8 EVO stent group were on average 1.4 years older, more frequently had cerebrovascular disease and diabetic nephropathy with 3.1 mL/min less mean creatinine clearance, had fewer lesions per patient, and more frequently underwent rotational atherectomy and post-dilation. Medications at discharge and during the study follow-up are detailed in *Table 3*, and were broadly similar in the two study groups, except for a lower frequency of dual antiplatelet therapy in the Cre8 EVO group at 1-year follow-up.

At 1 year, the primary endpoint occurred in 106 patients, 42 (7.2%) in the Cre8 EVO group and 64 (10.9%) in the Resolute Onyx group [difference –3.73% (95% CI: –7.01 to –0.45), one-sided $P < 0.001$ for non-inferiority; HR: 0.65, 95% CI: 0.44–0.96, two-sided $P = 0.030$ for superiority; *Table 4*; *Figure 2*]. Relative risk estimates were consistent with HRs (see Supplementary material online, *Appendix*).

With regard to the secondary endpoints, patients randomized to Cre8 EVO stents had significantly lower rates of target-vessel failure than patients randomized to Resolute Onyx stents [7.5% vs. 11.1%, HR: 0.67 (95% CI: 0.46–0.99), $P = 0.042$]. There was a trend towards statistical significance in terms of a lower rate of clinically indicated target-lesion revascularization (2.4% vs. 3.9%, $P = 0.058$) and major adverse cardiac events (11.7% vs. 15.7%, $P = 0.067$) in the Cre8 EVO group compared with Resolute Onyx. With respect to the other

Table 4 Event rates and hazard ratios (95% confidence interval) of primary and secondary endpoints at 1-year follow-up

	Cre8 EVO group (*n* = 586)	Resolute Onyx group (*n* = 589)	HR (95% CI)	*P*-Value
Primary endpoint target lesion failure	42 (7.2%)	64 (10.9%)	0.65 (0.44–0.96)	0.030
Individual components of the primary endpoint				
Cardiac death	12 (2.1%)	16 (2.7%)	0.75 (0.36–1.59)	0.452
Target-vessel MI	29 (5.3%)	40 (7.2%)	0.74 (0.44–1.23)	0.240
Target-lesion revascularization[a]	14 (2.4%)	23 (3.9%)	0.60 (0.31–1.18)	0.058
Other secondary				
All-cause mortality	20 (3.4%)	29 (5.0%)	0.69 (0.39–1.22)	0.201
Any MI	34 (6.2%)	43 (7.7%)	0.78 (0.50–1.23)	0.289
Any revascularizations	29 (5.0%)	37 (6.3%)	0.78 (0.48–1.27)	0.314
Target-vessel revascularization	18 (3.1%)	24 (4.1%)	0.75 (0.40–1.37)	0.346
Definite stent thrombosis	6 (1.0%)	5 (0.9%)	1.20 (0.37–3.94)	0.760
Probable or definite stent thrombosis	8 (1.4%)	8 (1.4%)	1.00 (0.38–2.67)	0.994
Acute	3 (0.5%)	2 (0.3%)	–	
Subacute	4 (0.7%)	4 (0.7%)	–	
Late	1 (0.2%)	2 (0.3%)	–	
Target-vessel failure	44 (7.5%)	65 (11.1%)	0.67 (0.46–0.99)	0.042
Major adverse cardiac events	64 (11.7%)	88 (15.7%)	0.74 (0.53–1.02)	0.067

MI, myocardial infarction.
[a]All target-lesion revascularizations were clinically indicated.

secondary outcomes, there were no significant differences between groups (*Table 4*). The rate of target-vessel myocardial infarction was not significantly different regardless of the definition used (per protocol or ARC-2) (see Supplementary material online, *Appendix*). There were two COVID-19-related deaths, one in each group.

In the subgroup analyses, we evaluated treatment effect heterogeneity across pre-specified subgroups (*Figure 3*). Treatment effect was consistent across all subsets of patients since no significant interactions were observed.

In the as-treated analyses, 1172 patients were included: 582 patients finally received Cre8 EVO stents and 590 patients received Resolute Onyx stents. Their findings were largely similar to those obtained in the intention-to-treat approach: Cre8 EVO stents significantly reduced the rate of primary endpoint target lesion failure compared with Resolute Onyx stents (6.9% vs. 10.9%, HR: 0.62, 95% CI: 0.42–0.93, $P = 0.019$) (see Supplementary material online, *Appendix*).

Discussion

In this trial, we compared Cre8 EVO stents (a stent that releases a formulation of antiproliferative drug with a carrier from reservoirs) vs. Resolute Onyx stents (a contemporary polymer-based drug-eluting stent) in patients with diabetes undergoing percutaneous coronary revascularization. We found that patients who received Cre8 EVO stents had significantly lower rates of the primary composite endpoint target lesion failure at 1-year follow-up (*Graphical Abstract*). The results were consistent across all the pre-specified subgroups and also in the as-treated analyses.

Patients with diabetes represent up to 38% of patients undergoing percutaneous revascularization,[2] and they are at the highest risk of events after percutaneous revascularization with the new-generation drug-eluting stents. For example, patients with insulin-treated diabetes mellitus who received the former generation of zotarolimus-eluting stents had twice the risk of cardiac death or myocardial infarction at 2 years than patients without diabetes,[25] and percutaneous revascularization of patients with diabetes and multivessel disease is associated with an increased mortality at 5 years compared with surgical revascularization.[3] Thus, diabetes should be a priority line of research in the ischaemic cardiomyopathy field.

Our study is the first powered trial to compare second-generation drug-eluting stents in patients with diabetes, and the first to show a meaningful reduction of events after drug-eluting stent implantation in diabetes since the TUXEDO trial,[4] which showed significant reduction of events with everolimus-eluting stents compared with first-generation drug-eluting stents. Thereafter, there has been few dedicated trials, and the successive subgroup analyses of randomized trials have shown no significant differences in outcomes between most polymer-based drug-eluting stents.[26,27] Importantly, SUGAR is the first trial that has included a broad population of patients with diabetes (all-comers design), and therefore may be considered more representative of the real population with diabetes than previous trials. On the contrary, previous studies comparing stents had very restrictive exclusion criteria,[4] and they systematically excluded complex lesions, left main lesions, chronic total occlusions, or renal dysfunction. The inclusion of complex lesions and complex patients but also for the use of new antiplatelet drugs, new glucose-lowering drugs, functional assessment of intermediate lesions, and systematic radial approach is a strength of our study.

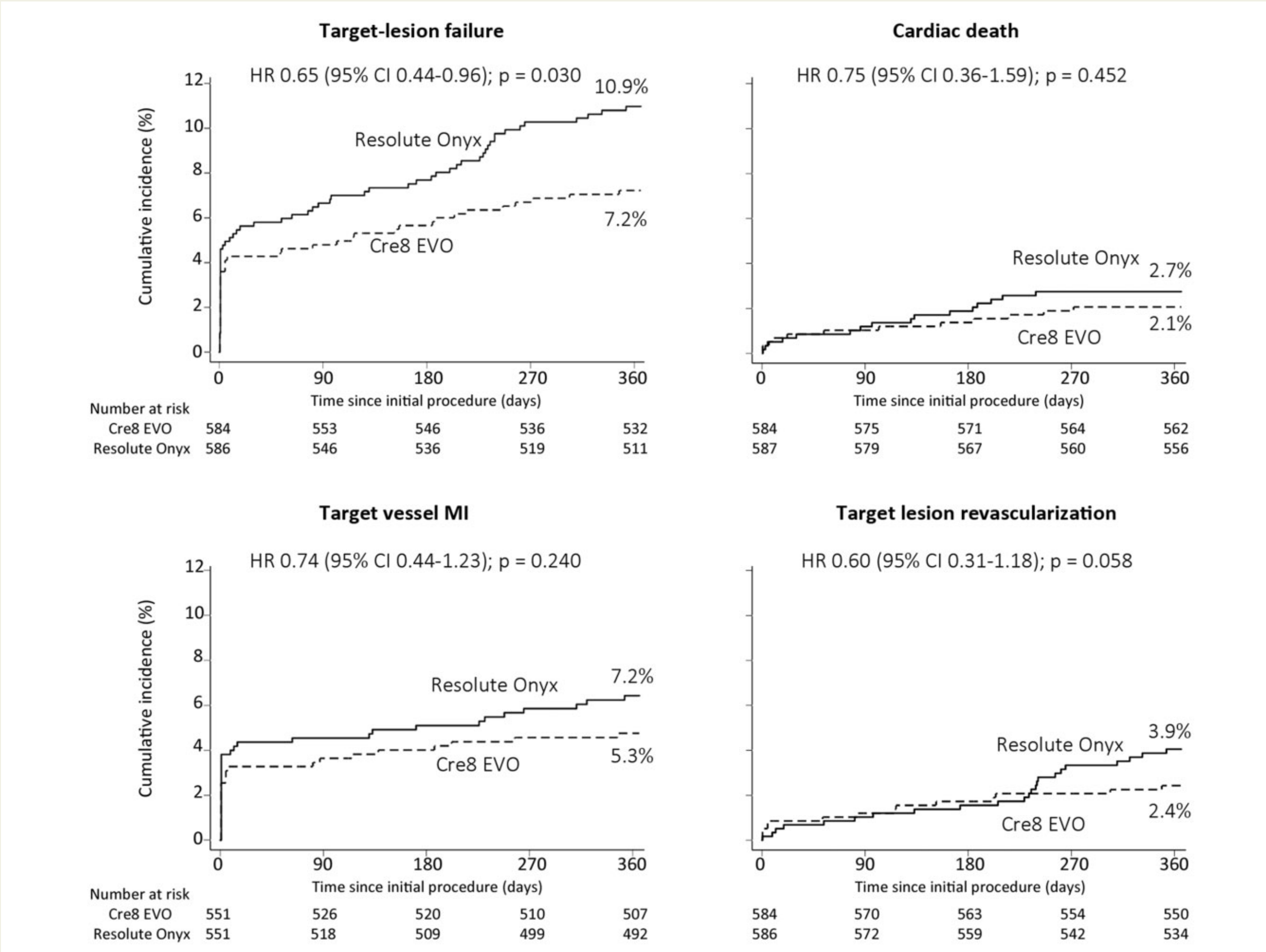


Figure 2 Primary endpoint and its components. Time-to-event curves are shown for patients in the intention-to-treat population who were randomly assigned to receive Cre8 EVO stents or Resolute Onyx stents. CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

Our findings were consistent with previous studies. In the RESERVOIR trial, we showed in a mechanistic way that Cre8 stents effectively reduced neointimal hyperplasia in a selected group of patients with diabetes,[12] and several non-randomized studies and subgroup analyses[10,13–15] have shown a reduction of 40–60% of events with Cre8 stents compared with other drug-eluting stents in diabetes. Indeed, the risk reduction in our study is comparable to the reduction observed in the TUXEDO trial with second-generation vs. first-generation drug-eluting stents.

In our study, the treatment effect seemed to be relatively constant over time. Despite our study was not designed to look for differences in the individual components of the primary endpoint, trends towards lower rates of clinically indicated target-lesion revascularization and ARC-2 target vessel myocardial infarction were observed. Importantly, the curves of target lesion revascularization began to diverge at 8-month follow-up, the time-point when restenosis usually begins to become clinically evident. Considering the complexity of diabetic patients, a significant number of events may be expected after the first year of follow-up.

The superiority of the Cre8 EVO stent may be related to two stent characteristics. First, patients with diabetes had diffuse coronary artery disease and more extensive coronary calcification,[28] which may result in a heterogeneous drug diffusion. Moreover, patients with diabetes have dose-dependent resistance to antiproliferative mTOR inhibitors.[8] Achieving high therapeutic drug concentrations along the entire arterial tissue is therefore of special importance in patients with diabetes. For these reasons, the formulation of the drug with an amphiphilic carrier, which has shown to enhance drug-diffusion in several tissues, may represent an advantage for patients with diabetes that require enhanced drug diffusion.

The second distinctive characteristic is the device thickness. Several studies have shown that thinner struts are associated with higher shear stress, resulting in lower rates of stent restenosis and thrombosis.[9,29] Moreover, a recent meta-analysis has shown that ultra-thin stents significantly reduce adverse events compared with thicker stents.[30] In our study, since the polymer of Resolute Onyx is non-erodible, the total thickness of the device creating turbulent flow at least during the study follow-up is 92–102 μm, which indeed is 16–33% thicker than the Cre8 EVO stent (70–80 μm).

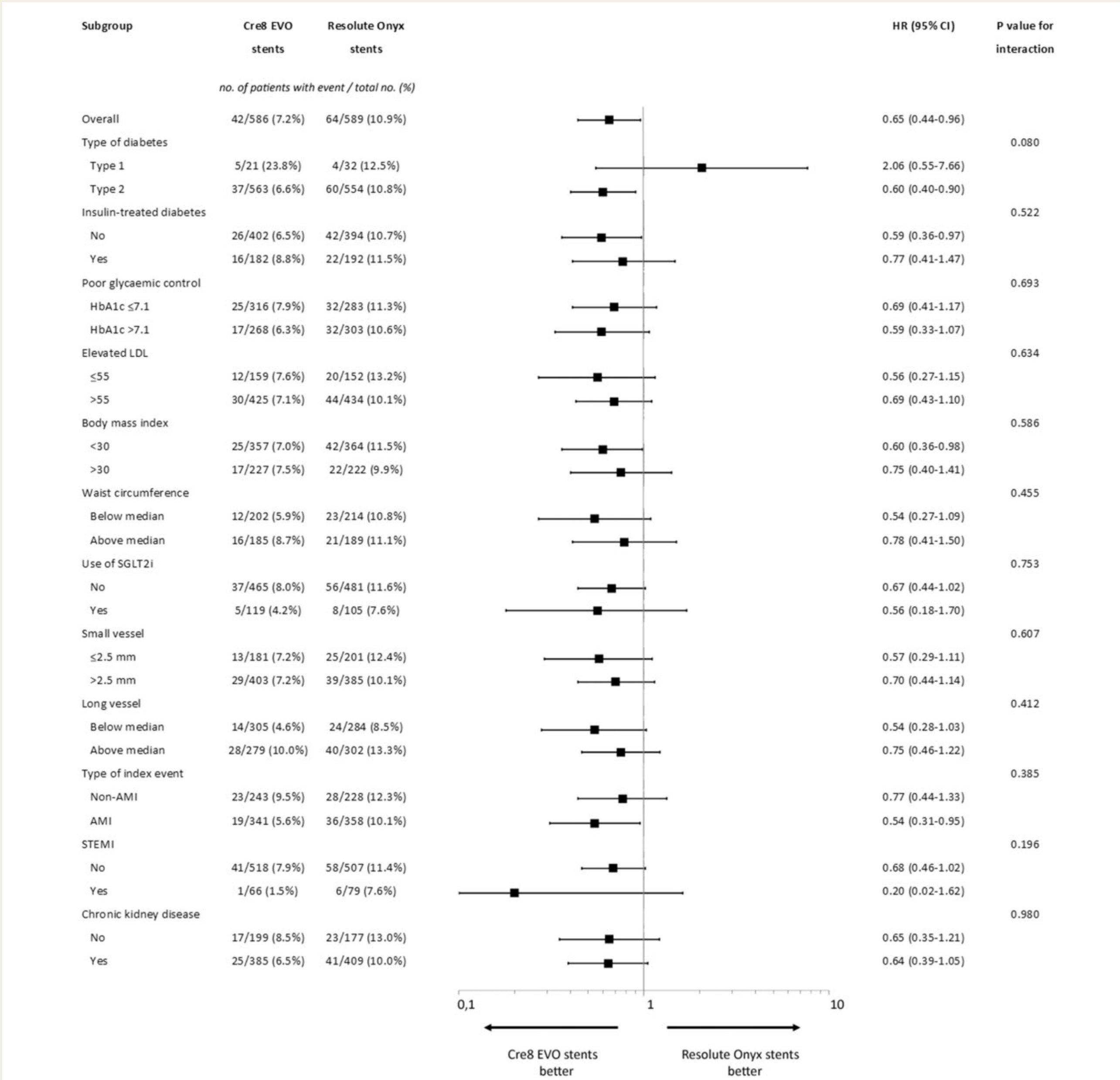


Figure 3 Prespecified subgroup analyses of the primary endpoint. AMI, acute myocardial infarction; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein cholesterol; SGLT2i, sodium-glucose cotransporter 2 inhibitors; STEMI, ST-elevation myocardial infarction.

In our study, patients received dual antiplatelet therapy and oral anticoagulation similarly in both groups up to 6-month follow-up. However, at 1 year, the proportion of patients treated with dual antiplatelet therapy was lower in the Cre8 EVO group. It is likely that, because patients in the Resolute Onyx group had more ischaemic events such as recurrent revascularizations, dual antiplatelet therapy had to be prolonged more frequently, although other factors cannot be ruled out. According to this finding, efficacy would be of remarkable interest especially for patients with high bleeding risk.

Study limitations

In our study, the operators were unavoidably unblinded to the randomization since both devices have evident differences to the naked eye, so patients may have been treated differently on the basis of the allocated device. However, trial outcomes were independently adjudicated by a committee, who were blinded to treatment allocation, and the data of complete revascularization, interventional techniques, or medical treatment suggest no group differences in the appropriateness of the treatment received. Finally, despite the all-comers study design, around 50% of patients included in the present study had one-vessel disease and the mean Syntax score was in the lowest Syntax tertile, likely indicating the compliance of the study operators with current revascularization guidelines. Consequently, it is uncertain if the Cre8 EVO would present similar favourable results in patients with more complex coronary anatomies.

Conclusions

In patients with diabetes undergoing percutaneous revascularization, Cre8 EVO stents were non-inferior to Resolute Onyx stents with regard to target-lesion failure composite outcome. An exploratory analysis for superiority at 1 year suggests that the Cre8 EVO stents might be superior to the Resolute Onyx stents with regard to the same outcome.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Saeedi P, Petersohn I, Salpea P *et al.*; IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract* 2019;**157**:107843.
2. Inohara T, Kohsaka S, Spertus JA *et al.* Comparative trends in percutaneous coronary intervention in Japan and the United States, 2013 to 2017. *J Am Coll Cardiol* 2020;**76**:1328–1340.
3. Farkouh ME, Domanski M, Sleeper LA *et al.*; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;**367**:2375–2384.
4. Kaul U, Bangalore S, Seth A *et al.*; TUXEDO-India Investigators. Paclitaxel-eluting versus everolimus-eluting coronary stents in diabetes. *N Engl J Med* 2015;**373**: 1709–1719.
5. Bavishi C, Chugh Y, Kimura T *et al.* Biodegradable polymer drug-eluting stent vs. contemporary durable polymer drug-eluting stents in patients with diabetes: a meta-analysis of randomized controlled trials. *Eur Heart J Qual Care Clin Outcomes* 2020;**6**:81–88.
6. Romaguera R, Brugaletta S, Gomez-Lara J *et al.* Rationale and study design of the RESERVOIR trial: a randomized trial comparing reservoir-based polymer-free amphilimus-eluting stents versus everolimus-eluting stents with durable polymer in patients with diabetes mellitus. *Catheter Cardiovasc Interv* 2015;**85**:E116–E122.
7. Woods TC. Dysregulation of the mammalian target of rapamycin and p27Kip1 promotes intimal hyperplasia in diabetes mellitus. *Pharmaceuticals (Basel)* 2013;**6**: 716–727.
8. Lightell DJ Jr, Woods TC. Relative resistance to mammalian target of rapamycin inhibition in vascular smooth muscle cells of diabetic donors. *Ochsner J* 2013;**13**: 56–60.
9. Koskinas KC, Chatzizisis YS, Antoniadis AP, Giannoglou GD. Role of endothelial shear stress in stent restenosis and thrombosis: pathophysiologic mechanisms and implications for clinical translation. *J Am Coll Cardiol* 2012;**59**:1337–1349.
10. Carrié D, Berland J, Verheye S *et al.* Five-year clinical outcome of multicenter randomized trial comparing amphilimus – with paclitaxel-eluting stents in de novo native coronary artery lesions. *Int J Cardiol* 2020;**301**:50–55.
11. Pivato CA, Leone PP, Petriello G *et al.* The Cre8 amphilimus-eluting stent for the treatment of coronary artery disease: safety and efficacy profile. *Expert Rev Med Devices* 2020;**17**:267–275.
12. Romaguera R, Gómez-Hospital JA, Gomez-Lara J *et al.* 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. *JACC Cardiovasc Interv* 2016;**9**:42–50.
13. Hemert ND, Rozemeijer R, Voskuil M *et al.*; ReCre8 Study Investigators. Clinical outcomes after permanent polymer or polymer-free stent implantation in patients with diabetes mellitus: the ReCre8 diabetes substudy. *Catheter Cardiovasc Interv*; doi:10.1002/ccd.29685. Publshed online ahead of print 3 April 2021.
14. Godino C, Pivato CA, Chiarito M *et al.*; Italian Nobori Stent ProspectIve REgistry-1 (INSPIRE-1) and AmphilimuS iTalian mUlticenTre rEgistry (ASTUTE) investigators. Polymer-free amphilimus-eluting stent versus biodegradable polymer biolimus-eluting stent in patients with and without diabetes mellitus. *Int J Cardiol* 2017;**245**:69–76.
15. Sardella G, Stella P, Chiarito M *et al.* Clinical outcomes with reservoir-based polymer-free amphilimus-eluting stents in real-world patients according to diabetes mellitus and complexity: the INVESTIG8 registry. *Catheter Cardiovasc Interv* 2018;**91**:884–891.
16. Romaguera R, Salinas P, Brugaletta S *et al.* Second-generation drug-eluting stents in diabetes (SUGAR) trial: rationale and study design. *Am Heart J* 2020;**222**: 174–182.
17. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. *Diabetes Care* 2018;**41**: S13–S27.
18. Neumann FJ, Sousa-Uva M, Ahlsson A *et al.*; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019; **40**:87–165.
19. Hindricks G, Potpara T, Dagres N *et al.*; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498.
20. Cosentino F, Grant PJ, Aboyans V *et al.*; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;**41**:255–323.

21. Visseren FLJ, Mach F, Smulders YM *et al.*; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–3337.
22. Romaguera R, Ojeda S, Cruz-Gonzalez I, Moreno R. Spanish Cardiac Catheterization and Coronary Intervention Registry. 30th official report of the Interventional Cardiology Association of the Spanish Society of Cardiology (1990–2020) in the year of the COVID-19 pandemic. *Rev Esp Cardiol (Engl Ed) 2021;S1885-5857(21)00317-0*. doi:10.1016/j.recesp.2021.07.018.
23. Thygesen K, Alpert JS, Jaffe AS *et al.*; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Circulation* 2012;**126**:2020–2035.
24. Garcia-Garcia HM, McFadden EP, Farb A *et al.*; Academic Research Consortium. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. *Circulation* 2018;**137**:2635–2650.
25. Silber S, Serruys PW, Leon MB *et al.* Clinical outcome of patients with and without diabetes mellitus after percutaneous coronary intervention with the resolute zotarolimus-eluting stent: 2-year results from the prospectively pooled analysis of the international global RESOLUTE program. *JACC Cardiovasc Interv* 2013;**6**:357–368.
26. Iglesias JF, Heg D, Roffi M *et al.* Five-year outcomes in patients with diabetes mellitus treated with biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents. *J Am Heart Assoc* 2019;**8**:e013607.
27. Olesen KKW, Pareek M, Madsen M *et al.* Ten-year outcomes of sirolimus-eluting versus zotarolimus-eluting coronary stents in patients with versus without diabetes mellitus (SORT OUT III). *Am J Cardiol* 2020;**125**:349–353.
28. Heath JM, Sun Y, Yuan K *et al.* Activation of AKT by O-linked N-acetylglucosamine induces vascular calcification in diabetes mellitus. *Circ Res* 2014;**114**:1094–1102.
29. Kolandaivelu K, Swaminathan R, Gibson WJ *et al.* Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation* 2011;**123**:1400–1409.
30. Madhavan MV, Howard JP, Naqvi A *et al.* Long-term follow-up after ultrathin vs. conventional 2nd-generation drug-eluting stents: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J* 2021;**42**:2643–2654.