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ORIGINAL STUDIES

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Clinical outcomes after permanent polymer or polymer-free stent implantation in patients with diabetes mellitus: The ReCre8 diabetes substudy

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Abstract

Objectives: The purpose of this analysis was to compare target-lesion failure (TLF) of a permanent polymer zotarolimus-eluting stent (PP-ZES) versus a polymer-free amphilimus-eluting stent (PF-AES) in diabetics.

Background: The improvement of outcomes with new-generation drug-eluting stent as seen in the general population is less pronounced among diabetics. The PF-AES introduces an elution-technology with potential enhanced performance in diabetics.

Methods: In this subanalysis of the ReCre8 trial, patients were randomized to either a PP-ZES or PF-AES after stratification for diabetes and troponin status. The primary device-oriented endpoint was TLF, a composite of cardiac death, target-vessel myocardial infarction and target-lesion revascularization.

Results: In the ReCre8 trial, 304 (20%) patients were diabetic and 96 (6%) had insulin-dependent diabetes mellitus. There was no statistically significant difference between the two study arms regarding the primary endpoint (PP-ZES 7.2% vs. PF-AES 4.0%; $p = .21$), although the composite of net adverse clinical events was higher in the PP-ZES arm (15.7 vs. 8.0%; $p = .035$). Stent thrombosis was low in both groups with no cases in the PP-ZES arm and 1 case in the PF-AES arm ($p = .32$). Regarding insulin-treated diabetics, TLF was higher in the PP-ZES arm (14.9 vs. 2.1%; $p = .022$).

Conclusions: Diabetics could potentially benefit from a dedicated stent, releasing sirolimus with a lipophilic carrier (amphilimus-formulation). Future trials should confirm the potential benefit of a PF-AES in this population.

Abbreviations: DAPT, dual antiplatelet therapy; DES, drug-eluting stent; IDDM, insulin-dependent diabetes mellitus; NACE, net adverse clinical events; PCI, percutaneous coronary intervention; PF-AES, polymer-free amphilimus-eluting stent; PP-ZES, permanent polymer zotarolimus-eluting stent; TLF, target-lesion failure.

KEYWORDS
percutaneous coronary intervention, drug-eluting stents, diabetes mellitus

1 | INTRODUCTION

Patients with diabetes mellitus are more susceptible to vascular disease, including coronary artery disease, due to endothelial dysfunction, inflammation and thrombosis.[1,2] As the global prevalence of diabetes mellitus is expected to grow with over 200 million people between 2015 and 2040,[3] this subgroup of coronary artery disease patients becomes more important and requires a special focus in contemporary stent studies. Moreover, it is well-documented that diabetic patients have a higher risk of adverse outcomes following percutaneous coronary intervention (PCI) especially with regard to reinterventions.[4,5] Despite improved outcomes since the development of new-generation drug-eluting stents (DES),[6,7] patients with diabetes mellitus remain at high risk of adverse events following PCI.[8]

Among the diabetic population, insulin-dependent diabetes mellitus (IDDM) patients represent a subgroup of patients with the highest chance of adverse outcomes after PCI.[9,10] Previous studies have shown a two- to four-fold increase in event rates (such as target-lesion failure [TLF], cardiac death and revascularization) in IDDM patients as compared to non-diabetics.[5,11]

The polymer-free amphilimus-eluting stent (PF-AES) was designed with abluminal reservoirs releasing amphilimus – a combination of sirolimus and long-chain fatty acids. This provides a potential benefit for patients with diabetes mellitus as diabetic cells overexpress membrane fatty acid transporters, increasing fatty acid uptake[12] and therefore the uptake of the effectual drug. This may improve outcomes in diabetic patients as diabetic cells are relatively resistant to the antirestenotic drugs used in contemporary stents (e.g., sirolimus).[13]

The RESERVOIR trial[14] compared efficacy of the PF-AES and an everolimus-eluting stent in patients with a history of diabetes. Regarding the primary endpoint of neointimal volume obstruction, noninferior efficacy of the PF-AES was demonstrated with 12 versus 16% obstruction in the everolimus-eluting arm. Similarly, in-stent late loss was lower in the PF-AES arm and a larger minimal lumen diameter was seen at follow-up, suggesting a beneficial effect of the PF-AES in this diabetic subgroup.

The aim of this subanalysis of the ReCre8 trial[15] was to evaluate 12 months post-discharge clinical outcomes after implantation of either a permanent polymer zotarolimus-eluting stent (PP-ZES) or PF-AES in diabetic patients according to enrollment stratification.

2 | MATERIALS AND METHODS

2.1 | Study design and population

The ReCre8 trial[15] was a physician-initiated, prospective, randomized, multicenter trial that compared a PP-ZES (Resolute Integrity, Medtronic Vascular, Santa Rosa, CA) to a PF-AES (Cre8, Alvimedica, Istanbul, Turkey) in an all-comers population requiring PCI. Patients were included across three European PCI centers; University Medical Center Utrecht and Zuyderland Medical Center Heerlen, the Netherlands and the National Institute of Cardiac Surgery and Interventional Cardiology Luxembourg, Luxembourg. The ReCre8 trial was approved by the Medical Research Ethics Committee Utrecht as well as the institutional review boards of each participating center. Written informed consent was obtained from all study participants. The ReCre8 trial was registered at clinicaltrials.gov (NCT02328898).

The study design has been previously reported.[16] In brief, patients were stratified for diabetes mellitus and troponin status after which block-randomization assigned patients in a 1:1 ratio to receive either a PP-ZES or PF-AES. Allocation toward the diabetic stratum occurred by a review of current drug use and medical history at randomization. Patients were treated with either one month (troponin negative patients) or 12 months (troponin positive patients) of dual antiplatelet therapy (DAPT). The ReCre8 trial had an all-comers design with few criteria restricting inclusion. Patients were eligible for inclusion if they were over 18 years of age and there were clinical symptoms of ischemia present requiring patients to undergo PCI with implantation of a DES in a lesion with a reference vessel diameter of 2.5–4.5 mm. This substudy of the ReCre8 trial reports results from a subgroup of patients with a history of diabetes after 12 months follow-up.

2.2 | Study endpoints

The device-oriented primary endpoint of TLF was composed of cardiac death, target-vessel myocardial infarction, and target-lesion revascularization. The patient-oriented secondary endpoint of net adverse clinical events (NACE) was a composite of all-cause death, any myocardial infarction, any unplanned revascularization, stroke, and major bleeding. Additionally, all components of the composite endpoints were analyzed separately. The endpoints that were analyzed in this subanalysis were similar to the endpoints in the main publication. Clinical endpoints were defined according to the Academic Research Consortium.[17] Endpoint definitions were previously described.[15]

2.3 | Statistical analysis

Distributions of dichotomous variables are reported as counts and percentages and were compared between groups using Chi-square or Fisher exact test. Continuous variables are described as mean ± standard deviation and compared using the Independent group Student's *t* test or Wilcoxon Rank Sum test. Kaplan Meier time-to-event estimates for the primary endpoint, secondary endpoint, and

TABLE 1 Baseline characteristics

	Overall (*n* = 304)	PP-ZES (*n* = 153)	PF-AES (*n* = 151)	*p*-value
Clinical characteristics				
Age (years)	66.5 ± 9.7	67.1 ± 9.6	65.9 ± 9.9	.28
Male sex	224 (73.7)	113 (73.9)	111 (73.5)	.95
Body mass index (kg/m^2)	29.1 ± 4.7	29.0 ± 4.6	29.2 ± 4.8	.75
Hypertension	217 (71.4)	111 (72.5)	106 (70.2)	.53
Hypercholesterolemia	182 (59.9)	89 (58.2)	93 (61.6)	.66
Insulin-treated diabetes mellitus	96 (31.6)	47 (30.7)	49 (32.5)	.75
Current smoker	65 (21.4)	28 (18.3)	37 (24.5)	.22
Family history of cardiovascular disease	104 (34.2)	51 (33.3)	53 (35.1)	.95
Renal insufficiency, eGFR<60[a]	55 (18.1)	31 (20.3)	24 (15.9)	.35
Relevant medical history				
Previous MI	82 (27.0)	42 (27.5)	40 (26.5)	.98
Previous PCI	86 (28.3)	50 (32.7)	36 (23.8)	.087
Previous CABG	39 (12.8)	23 (15.0)	16 (10.6)	.25
Clinical presentation				
Stable angina	140 (46.1)	71 (46.4)	69 (45.7)	.90
Acute coronary syndrome	128 (42.1)	67 (43.8)	61 (40.4)	.55
Coronary anatomy				
Left main	7 (2.3)	4 (2.6)	3 (2.0)	1.00
Left anterior descending artery	154 (50.7)	73 (47.7)	81 (53.6)	.30
Left circumflex artery	123 (40.5)	64 (41.8)	59 (39.1)	.62
Right coronary artery	158 (52.0)	80 (52.3)	78 (51.7)	.91
Arterial bypass graft	6 (2.0)	4 (2.6)	2 (1.3)	.68
Venous bypass graft	11 (3.6)	7 (4.6)	4 (2.6)	.54
Lesion characteristics				
≥1 complex lesion[b]	177 (58.2)	90 (58.8)	87 (57.6)	.83
1 bifurcation lesion	66 (21.7)	31 (20.3)	35 (23.2)	.54
≥1 chronic total occlusion	27 (8.9)	12 (7.8)	15 (9.9)	.52
≥1 small vessel (RVD < 2.75 mm)	110 (36.2)	54 (35.3)	56 (37.1)	.74
Procedural characteristics				
Radial approach	269 (88.5)	135 (88.2)	134 (88.7)	.71
Number of diseased coronary vessels				
1	160 (52.6)	83 (54.2)	77 (51.0)	.92
2	95 (31.3)	45 (29.4)	50 (33.1)	
≥3	49 (16.1)	25 (16.3)	24 (15.9)	

Note: Data are *n* (%) or means ± SD.
Abbreviations: CABG, coronary artery bypass grafting; eGFR, estimated Glomerular filtration rate; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PF-AES, polymer-free amphilimus-eluting stents; PP-ZES, permanent polymer zotarolimus-eluting stents; RVD, reference vessel diameter; STEMI, ST-segment elevation myocardial infarction.
[a]Renal insufficiency was defined as an estimated glomerular filtration rate of less than 60 ml per min per 1 × 73 m^2.
[b]Complex lesions were defined as lesion classification type B2 or C according to the American College of Cardiology/American Heart Association.

individual events were compared using log-rank test. Time-to–first-event was defined as the number of days between primary PCI and occurrence of any component of the primary or secondary endpoint. All analyses were performed on post-discharge events. Follow-up was censored at 12 months. Differences were considered statistically significant at a 2-tailed *p*-value of .05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Figures were generated using GraphPad Prism version 8.3 (GraphPad, Inc., San Diego, CA).

3 | RESULTS

3.1 | Baseline and procedural characteristics

From the total of 1,491 patients included in the ReCre8 trial, 304 patients with diabetes mellitus were included in this analysis. Baseline characteristics were similar between the PP-ZES and PF-AES arm (Table 1). Based on the American College of Cardiology/

TABLE 2 Lesion and procedural characteristics

	Diabetic population			
	Overall (*n* = 447)	PP-ZES (*n* = 225)	PF-AES (*n* = 222)	*p*-value
Procedural characteristics				
No. of stents per lesion	1.30 ± 0.6	1.31 ± 0.7	1.29 ± 0.6	.81
No. of stents per patient	1.91 ± 1.3	1.92 ± 1.2	1.90 ± 1.3	.88
Total stent length, mm	51.1 ± 21.8	50.7 ± 19.7	51.5 ± 24.3	.98
Stent diameter, mm	2.96 ± 0.4	2.96 ± 0.4	2.96 ± 0.4	.86
Multi overlapping stents	87 (19.5)	43 (19.1)	44 (19.8)	.87
Lesion complexity				
ACC/AHA class A	55 (12.3)	27 (12.0)	28 (12.6)	.87
ACC/AHA class B1	148 (33.1)	78 (34.7)	70 (31.5)	
ACC/AHA class B2	105 (23.5)	53 (23.6)	52 (23.4)	
ACC/AHA class C	138 (30.9)	66 (29.3)	72 (32.4)	
GP IIb/IIIa antagonist use	33 (7.4)	13 (5.8)	20 (9.0)	.21
Procedural success	440 (98.4)	221 (98.2)	219 (98.6)	.68

Note: Data are *n* (%) or means ± SD.
Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; GP IIb/IIIA, glycoprotein IIb/IIIa; PF-AES, polymer-free amphilimus-eluting stents; PP-ZES, permanent polymer zotarolimus-eluting stents.

American Heart Association criteria,[18] 58% presented with at least one complex lesion. Over half of the diabetic population was treated with only one month of DAPT as they presented with troponin negative disease. Compliance with the prescribed use of DAPT and aspirin was high and did not differ between the study arms (Table S1).

Procedural characteristics were comparable between the PP-ZES and PF-AES arm (Table 2). On average, 1.30 stents per lesion and 1.91 stents per patient were implanted. Procedural success was similar at 98.2 and 98.6%.

3.2 | Clinical outcomes in PP-ZES versus PF-AES

Post-discharge clinical outcomes after 12 months are shown in Table 3. The primary endpoint of TLF did not statistically differ between the two study arms (PP-ZES 7.2% vs. PF-AES 4.0%; $p = .21$), as shown in Figure 1. The secondary endpoint of NACE occurred more frequently in the PP-ZES group (15.7 vs. 8.0%; $p = .035$), mostly driven by a higher (cardiac) death rate. There were no significant differences among the separate components of the endpoints.

A total of nine cardiac deaths occurred in the first year following stent implantation. In the PP-ZES arm, there were two cases of end-stage heart failure, two unsuccessful resuscitations without a known cause, one unsuccessful resuscitation with major bleeding while on DAPT, and two unknown causes of death. The two cases of cardiac death in the PF-AES arm were one case of sudden, unwitnessed death and a patient with cardiac decompensation and subsequent asystole.

One case of stent thrombosis (0.7%) occurred in the PF-AES arm with no cases in the PP-ZES arm. This case of stent thrombosis occurred in a troponin negative patient 290 days after stent implantation.

Results for the subgroup of IDDM patients are shown in Table 3. Among IDDM patients, TLF was more frequent in patients treated with the PP-ZES as compared to the PF-AES (14.9 vs. 2.1%; $p = .022$). Similarly, there was a higher incidence of NACE among patients in the PP-ZES arm (29.8 vs. 8.3%; $p = .009$). The event rate for the individual endpoint of all-cause death was higher in the PP-ZES arm (14.9 vs. 2.1%; $p = .024$).

4 | DISCUSSION

The main findings of this pre-specified subanalysis of the ReCre8 trial are (a) there was no statistically significant difference in TLF between the PP-ZES arm and the PF-AES arm; (b) patients treated with the PF-AES had a lower NACE rate in the diabetic population and the insulin-dependent diabetic population; and (c) a lower rate of TLF and all-cause death was observed in patients treated with PF-AES in a population of insulin-dependent diabetics.

Patients in this trial reflect a real-world population of patients undergoing PCI due to its all-comers design without exclusion criteria for clinical presentation and only one restrictive angiographic criterion.

In the main publication,[15] no significant differences were observed between the two study stents in the overall group of patients undergoing PCI. In the current analysis of a subgroup of diabetic patients, evaluation of differences between the two stent types favored PF-AES in the diabetic population regarding the endpoint of NACE. Among IDDM patients, evaluation of outcomes favored PF-AES regarding TLF, NACE, and all-cause death. The sole case of stent thrombosis in our trial after 290 days was observed in the PF-AES arm. As this patient presented with troponin negative disease, DAPT

TABLE 3 Post-discharge clinical outcomes at 12 months

	Diabetic patients				Insulin-dependent diabetic patients			
	Overall (*n* = 303)	PP-ZES (*n* = 153)	PF-AES (*n* = 150)	*p*-value	Overall (*n* = 95)	PP-ZES (*n* = 47)	PF-AES (*n* = 48)	*p*-value
TLF[a]	17 (5.6)	11 (7.2)	6 (4.0)	.21	8 (8.4)	7 (14.9)	1 (2.1)	.022
NACE[b]	36 (11.9)	24 (15.7)	12 (8.0)	.035	18 (18.9)	14 (29.8)	4 (8.3)	.009
All-cause death	13 (4.3)	9 (5.9)	4 (2.7)	.16	8 (8.4)	7 (14.9)	1 (2.1)	.024
Cardiac death	9 (3.0)	7 (4.6)	2 (1.3)	.094	6 (6.3)	5 (10.6)	1 (2.1)	.080
Any MI	3 (1.0)	0 (0.0)	3 (2.0)	.084	2 (2.1)	0 (0.0)	2 (4.2)	.17
TV-MI	1 (0.3)	0 (0.0)	1 (0.7)	.32	0 (0.0)	0 (0.0)	0 (0.0)	-
Stent thrombosis[c]	1 (0.3)	0 (0.0)	1 (0.7)	.32	0 (0.0)	0 (0.0)	0 (0.0)	-
Late (31d to 12 m)	1 (0.3)	0 (0.0)	1 (0.7)		0 (0.0)	0 (0.0)	0 (0.0)	-
Any unplanned revascularisation	16 (5.3)	10 (6.5)	6 (4.0)	.29	5 (5.3)	4 (8.5)	1 (2.1)	.14
TLR	7 (2.3)	4 (2.6)	3 (2.0)	.69	2 (2.1)	2 (4.3)	0 (0.0)	.14
Stroke	3 (1.0)	3 (2.0)	0 (0.0)	.080	3 (3.2)	3 (6.4)	0 (0.0)	.063
Major bleeding	6 (2.0)	5 (3.3)	1 (0.7)	.10	3 (3.2)	2 (4.3)	1 (2.1)	.55

Note: Data are *n* (%).

Abbreviations: MI, myocardial infarction; NACE, net adverse clinical events; PF-AES, polymer-free amphilimus-eluting stents; PP-ZES, permanent polymer zotarolimus-eluting stents; TLF, target-lesion failure; TLR, target-lesion revascularisation; TV-MI, target-vessel myocardial infarction.

[a]TLF was defined as a composite of cardiac death, target-vessel myocardial infarction and target-lesion revascularisation.

[b]NACE was defined as all-cause death, any myocardial infarction, any unplanned revascularisation, stroke and major bleeding.

[c]Definite or probable stent thrombosis.

duration was one month. Considering this event occurred over eight months after DAPT was discontinued, it does not appear to be linked to early DAPT cessation.

With TLF rates of 7.2% in the PP-ZES arm and 4.0% in the PF-AES arm at 12 months follow-up, our findings were comparable to rates reported in other trials. The ASTUTE registry[19] found a TLF rate of 4.9% 12 months after PF-AES implantation in a diabetic population. When compared to our results, the Investig8 registry[20] found higher event rates for TLF, target-lesion revascularization, myocardial infarction, and cardiovascular death in their diabetic population following PF-AES implantation. These results were assessed at a longer follow-up duration of 18 months which may explain higher event rates. However, time-to-event curves show no new target-lesion revascularization events after 360 days and only few TLFs in the last six months of follow-up.

Regarding the PP-ZES, the BIONICS randomized trial[8] reported higher rates of TLF, myocardial infarction, and target-lesion revascularization as compared to event rates in our study. Remarkably, none of the patients treated with the PP-ZES in our diabetic population had a post-discharge myocardial infarction within 12 months following PCI. In the PF-AES arm, three cases of post-discharge myocardial infarction occurred (2.0%). Of the three cases, one (0.7%) was a target-vessel myocardial infarction indicating TLF. As this difference was not statistically significant, and the ReCre8 trial was not powered for evaluation of subgroups or events occurring at low rates, this is not indicative of any difference between the two study stents.

Similar to the BIONICS trial, patients in the SORT-OUT III substudy[21] that were implanted with the PP-ZES had a myocardial infarction rate of 4.7% after 18 months. However, with the exception of cardiac death all evaluated endpoints were notably higher when compared to our event rates, a finding that is unlikely to be due to extended follow-up duration alone. As compared to the SORT-OUT III substudy, the higher rate of cardiac death among our patients may in part be attributable to the great difference in clinical presentation with a ST-segment elevation myocardial infarction among the diabetic population of the SORT-OUT III (3–7%) and the ReCre8 trial (17%).

A notable finding in our clinical outcomes is the large proportion of revascularizations in a non-target lesion. From all revascularizations at 12 months follow-up, 56% in the diabetic population and 60% in the insulin-dependent diabetic population was not caused by restenosis of the culprit lesion. This is in line with previous studies regarding the impact of disease progression in diabetic patients following PCI. A single-center study including diabetic patients undergoing multivessel PCI[22] reported that from 21 repeat revascularizations, 12 (57%) were – at least in part – caused by disease progression. Similarly, a study including patients with diabetes after implantation of at least one DES[23] reported that disease progression contributed to 53% of repeat revascularizations. This shows that we need to attend to secondary prevention measures, specifically in this high-risk population.

In our analyses, the difference in event rates between the diabetic and IDDM population was greater among patients treated with the PP-ZES. At 12 months follow-up, the rates of both TLF (7.2 vs. 14.9%) and NACE (15.7 vs. 29.8%) were twice as high in the IDDM population as compared to the entire group of diabetics. Interestingly, this finding was not seen in the population treated with the PF-AES: NACE was similar at 8% and TLF was even lower in the IDDM population (4.0 vs. 2.1%). This might suggest that the absence of a polymer

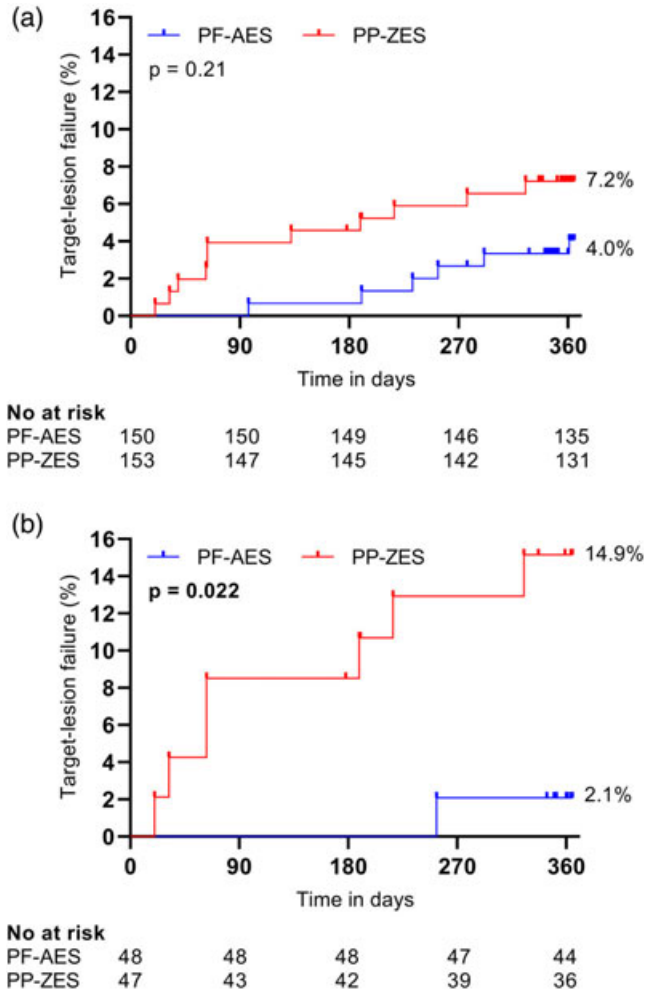

FIGURE 1 Kaplan–Meier time-to-event estimates for TLF compared using log-rank test. (a) TLF for PP-ZES and PF-AES in diabetic patients. (b) TLF for PP-ZES and PF-AES in insulin-dependent diabetic patients. TLF was defined as a composite of cardiac death, target-vessel myocardial infarction and target-lesion revascularization. PF-AES, polymer-free amphilimus-eluting stents; PP-ZES, permanent polymer zotarolimus-eluting stents; TLF, target-lesion failure [Color figure can be viewed at wileyonlinelibrary.com]

and the lipophilic (amphilimus) drug carrier is especially beneficial in IDDM patients.

One of the aspects in which our study differs from most contemporary stent studies is the duration of DAPT. Current guidelines by the European Society of Cardiology and European Association for Cardio-Thoracic Surgery[24] recommend treating patients with six months of DAPT after elective PCI in stable coronary artery disease. With prior studies on the PF-AES[25] in mind, patients in the ReCre8 trial with troponin negative disease were treated with one month of DAPT.[15] In this subanalysis, over half of our diabetic population consisted of patients with troponin negative disease. In addition to the previously described events, stent thrombosis was low at 0.3% and stroke occurred in 1% of diabetic patients. Major bleeding occurred in 2.0% of patients.

A recently published study design for the SUGAR trial[26] may shed an interesting new light on the current analysis. In a diabetic population, this trial compares the use of improved adaptations of the PP-ZES and PF-AES used in this trial. An all-comers diabetic population undergoing PCI will be randomized to either the Resolute Onyx (successor of the PP-ZES) or the Cre8 EVO (successor of the PF-AES). The trial recommends treatment with three to 6 months of DAPT in stable patients and 12 months in patients with an acute coronary syndrome. An estimated 1,164 patients will be followed up to two years and trial completion is expected in the end of 2023.

5 | LIMITATIONS

This study has several limitations. First, as this report was a subanalysis of the ReCre8 trial, this analysis was not powered to detect differences between the different subgroups and therefore outcomes are considered to be hypothesis-generating. As a result, some of the findings may rely on chance. Second, patients were stratified for diabetes based on drug use and medical history at randomization. No additional information was collected for type of diabetes or HbA1c. Therefore, there is a possibility of crossover bias. Lastly, treating physicians and patients were not blinded for the allocated treatment arm. Since the endpoints were defined according to international standards and were rigorously adjudicated by a blinded, independent clinical event committee, we do not expect that the lack of a double-blind design changed our findings.

6 | CONCLUSION

Based on the results of this subanalysis of the ReCre8 trial, diabetic patients could potentially benefit from a dedicated polymer-free stent design releasing sirolimus formulated with a lipophilic carrier (amphilimus formulation). Future randomized controlled trials should confirm the potential benefit of a PF-AES in this specific patient population.

7 | IMPACT ON DAILY PRACTICE

Diabetic patients are at a higher risk of ischemic events, especially reintervention, after PCI. Based on this pre-specified subanalysis of the ReCre8 trial, diabetic patients and particularly IDDM patients could potentially benefit from a dedicated polymer-free stent design with a specific lipophilic (amphilimus) drug carrier.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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