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

Nicole D. van Hemert MD¹ | Rik Rozemeijer MD, PhD¹
Michiel Voskuil MD, PhD¹ | Mère Stein MD, PhD² | Peter Frambach MD³
Saskia Z. Rittersma MD, PhD¹ | Adriaan O. Kraaijeveld MD, PhD¹
Geert E. H. Leenders MD, PhD¹ | Pim van der Harst MD, PhD¹
Pierfrancesco Agostoni MD, PhD⁴ | Pieter R. Stella MD, PhD¹ | The ReCre8 Study Investigators

¹Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands
²Department of Cardiology, Zuyderland Medical Center, Heerlen, The Netherlands
³Department of Cardiology, National Institute of Cardiac Surgery and Interventional Cardiology, Luxembourg, Luxembourg
⁴Department of Cardiology, Ziekenhuis Netwerk Antwerpen (ZNA) Middelheim, Antwerp, Belgium

Correspondence
Pieter R. Stella, Department of Cardiology, University Medical Center Utrecht, Heidelberglaan 100, room E04.201, 3508 GA, Utrecht, The Netherlands.
Email: p.stella@umcutrecht.nl

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.
Patients with diabetes mellitus are more susceptible to vascular disease, including coronary artery disease, due to endothelial dysfunction, inflammation and thrombosis. As the global prevalence of diabetes mellitus is expected to grow with over 200 million people between 2015 and 2040, this subgroup of coronary artery disease patients becomes more important and requires a special focus in contemporary stent studes. 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. Despite improved outcomes since the development of new-generation drug-eluting stents (DES), patients with diabetes mellitus remain at high risk of adverse events following PCI.

Among the diabetic population, insulin-dependent diabetes mellitus (IDDM) patients represent a subgroup of patients with the highest chance of adverse outcomes after PCI. 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.

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 and therefore the uptake of the effectual drug. This may improve outcomes in diabetic patients as diabetic cells are relatively resistant to the anti-restenotic drugs used in contemporary stents (e.g., sirolimus).

The RESERVOIR trial 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, non-inferior 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 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 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. 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. Endpoint definitions were previously described.

**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
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/American Heart Association.
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 2** Lesion and procedural characteristics

| Lesion complexity       | Overall (\( n = 447 \)) | PP-ZES (\( n = 225 \)) | PF-AES (\( n = 222 \)) | \( p \)-value |
|-------------------------|--------------------------|------------------------|------------------------|--------------|
| 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)              | .87          |
| ACC/AHA class B2        | 105 (23.5)               | 53 (23.6)              | 52 (23.4)              | .87          |
| ACC/AHA class C         | 138 (30.9)               | 66 (29.3)              | 72 (32.4)              | .87          |
| GP IIb/IIla 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/IIla, glycoprotein IIb/IIla; PF-AES, polymer-free amphibilimus-eluting stents; PP-ZES, permanent polymer zotarolimus-eluting stents.
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 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 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 reported higher rates of TLF, myocardial infarction, and target-lesion revascularization 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 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 study, 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 (37%–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 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 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

| 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* | 17 (5.6) | 11 (7.2) | 6 (4.0) | .21 | 8 (8.4) | 7 (14.9) | 1 (2.1) | .022 |
| NACEB | 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<sup>c</sup> | 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) | .32 | 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.

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

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

<sup>c</sup>Definite or probable stent thrombosis.
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 recommend treating patients with six months of DAPT after elective PCI in stable coronary artery disease. With prior studies on the PF-AES in mind, patients in the ReCre8 trial with troponin-negative disease were treated with one month of DAPT. 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 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 six 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 re-intervention, 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.

ACKNOWLEDGEMENTS

The authors thank all contributing research nurses, technicians and personnel who participated in the successful execution of this study. The authors express special thanks to Yvonne Breuer, Manager, Department of Research and Development and Astrid Links, Data Manager, University Medical Center Utrecht, and all physicians involved in the execution of this study.
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.

ORCID
Nicole D. van Hemert https://orcid.org/0000-0002-2886-7656
Rik Rozemeijer https://orcid.org/0000-0002-8185-7959
Pierfrancesco Agostoni https://orcid.org/0000-0002-1505-9369

REFERENCES
1. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA. 2002;287:2570-2581.
2. Richard G, Maillard L, Nazzaro MS, et al. Polymer-free drug-coated coronary stents in diabetic patients at high bleeding risk: a pre-specified sub-study of the LEADERS FREE trial. Clin Res Cardiol. 2019;108:31-38.
3. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40-50.
4. Lee TT, Feinberg L, Baim DS, et al. Effect of diabetes mellitus on five-year clinical outcomes after single- vessel coronary stenting (a pooled analysis of coronary stent clinical trials). Am J Cardiol. 2006;98:718-721.
5. Kalkman DN, Woudstra P, den Heijer P, et al. One year clinical outcomes in patients with insulin-treated diabetes mellitus and non-insulin-treated diabetes mellitus compared to non-diabetics after deployment of the bio-engineered COMBO stent. Int J Cardiol. 2017;226:60-64.
6. Stefanini GG, Holmes DRJ. Drug-eluting coronary-artery stents. N Engl J Med. 2013;368:254-265.
7. Dangas GD, Serruys PW, Kereiakes DJ, et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (clinical evaluation of the Xience V Everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). JACC Cardiovasc Interv. 2013;6:914-922.
8. Königstein M, Ben-Yehuda O, Smits PC, et al. Outcomes among diabetic patients undergoing percutaneous coronary intervention with contemporary drug-eluting stents: analysis from the BIONICS randomized trial. JACC Cardiovasc Interv. 2013;6:914-922.
9. Dangas GD, Farkouh ME, Sleeper LA, et al. Long-term outcome of PCI versus CABG in insulin and non-insulin-treated diabetic patients: results from the FREEDOM trial. J Am Coll Cardiol. 2014;64:1189-1197.
10. Pepe M, Sardella G, Stefanini GG, et al. Impact of insulin-treated and non-insulin-treated diabetes mellitus in all-comer patients undergoing percutaneous coronary interventions with polymer-free Biolimus-eluting stent (from the RUDI-FREE registry). Am J Cardiol. 2019;124:1518-1527.
11. PI-S-H, Rhee T-M, Lee JM, et al. Outcomes in patients with diabetes mellitus according to insulin treatment after percutaneous coronary intervention in the second-generation drug-eluting stent era. Am J Cardiol. 2018;121:1505-1511.
12. Glatz JFC, Luiken JFP, Bonen A. Membrane fatty acid transporters as regulators of lipid metabolism: implications for metabolic disease. Physiol Rev. 2010;90:367-417.
13. Woods TC. Dysregulation of the mammalian target of rapamycin and PI3K/PI3K promotes intimal hyperplasia in diabetes mellitus. Pharmaceutica. 2013;6:716-727.
14. 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.
15. Rozemeijer R, Stein M, Voskuil M, et al. Randomized all-comers evaluation of a permanent polymer Zotarolimus-eluting stent versus a polymer-free Amphilimus-eluting stent. Circulation. 2019;139:67-77.
16. Rozemeijer R, Stein M, Frambah P, et al. Rationale and design of amphilimus sirolimus-eluting stents versus zotarolimus-eluting stents in all-comers requiring percutaneous coronary intervention (ReCre8): a multicenter randomized clinical trial. Catheter Cardiovasc Interv. 2018;91:410-416.
17. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115:2344-2351.
18. Ellis SG, Vandomael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease: implications for patient selection. Circulation. 1990;82:1193-1202.
19. Colombo A, Godino C, Donahue M, et al. One-year clinical outcome of amphilimus polymer-free drug-eluting stent in diabetes mellitus patients insight from the ASTUTE registry (Amphilimus Italian multi cenTre registry). Int J Cardiol. 2016;214:113-120.
20. Sardella G, Stella P, Chiariotto 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.
21. Maeng M, Jensen LO, Tilsted HH, et al. Outcome of sirolimus-eluting versus zotarolimus-eluting coronary stent implantation in patients with and without diabetes mellitus (a SORT OUT III substudy). Am J Cardiol. 2011;108:1232-1237.
22. Toutou P, Pavli A, Oreglia J, et al. Impact of atherosclerotic disease progression on mid-term clinical outcome in diabetic patients in the drug-eluting stent era. EuroIntervention. 2009;4:588-592.
23. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur J Cardio-Thoracic Surg. 2018;53:34-78.
24. Prati F, Romagnoli E, Valgimigli M, et al. Randomized comparison between 3-month Cre8 des vs. 1-month vision/Multilink8 BMS neointimal coverage assessed by OCT evaluation: the DEMONSTRATE study. Int J Cardiol. 2014;176:904-909.
25. 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.

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

How to cite this article: van Hemert ND, Rozemeijer R, Voskuil M, et al. Clinical outcomes after permanent polymer or polymer-free stent implantation in patients with diabetes mellitus: The ReCre8 diabetes substudy. Catheter Cardiovasc Interv. 2022;99:366–372. https://doi.org/10.1002/ccd.29685