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ORIGINAL RESEARCH

Percutaneous Coronary Interventions Using a Ridaforolimus-Eluting Stent in Patients at High Bleeding Risk

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BACKGROUND: Patients treated with percutaneous coronary intervention are often considered to be at a high bleeding risk (HBR). Drug-eluting stents have been shown to be superior to bare-metal stents in patients with HBR, even when patients were given abbreviated periods of dual antiplatelet therapy (DAPT). Short DAPT has not been evaluated with the EluNIR ridaforolimus-eluting stent. The aim of this study was to evaluate the safety and efficacy of a shortened period of DAPT following implantation of the ridaforolimus-eluting stent in patients with HBR.

METHODS AND RESULTS: This was a prospective, multicenter, binational, single-arm, open-label trial. Patients were defined as HBR according to the LEADERS-FREE (Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk) trial criteria. After percutaneous coronary intervention, DAPT was given for 1 month to patients presenting with stable angina. In patients presenting with an acute coronary syndrome, DAPT was given for 1 to 3 months, at the investigator's discretion. The primary end point was a composite of cardiac death, myocardial infarction, or stent thrombosis up to 1 year (Academic Research Consortium definite and probable). Three hundred fifteen patients undergoing percutaneous coronary intervention were enrolled, and 56.4% presented with acute coronary syndrome; 33.7% were receiving oral anticoagulation. At 1 year, the primary end point occurred in 15 patients (4.9%), meeting the prespecified performance goal of 14.1% (P<0.0001). Stent thrombosis (Academic Research Consortium definite and probable) occurred in 2 patients (0.6%). Bleeding Academic Research Consortium type 3 and 5 bleeding occurred in 6 patients (1.9%).

CONCLUSIONS: We observed favorable results in patients with HBR who underwent percutaneous coronary intervention with a ridaforolimus-eluting stent and received shortened DAPT, including a low rate of ischemic events and low rate of stent thrombosis.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03877848.

Key Words: antithrombotic therapy ■ coronary artery disease ■ high bleeding risk ■ percutaneous coronary intervention

Drug-eluting stents (DESs) have replaced bare-metal stents for the treatment of both stable and acute coronary syndromes.[1–3] The incidence of patients treated with percutaneous coronary intervention (PCI) who are considered to be at a high bleeding risk (HBR) is high, ranging from 10% to 30% in different studies.[4,5] DESs have been shown to be superior to bare-metal stents in patients with HBR.[6–8]

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CLINICAL PERSPECTIVE

What Is New?

- Percutaneous coronary intervention using the EluNIR ridaforolimus-eluting stent, followed by an abbreviated dual antiplatelet therapy regimen, is associated with low rates of ischemic events at 1 year follow-up.

What Are the Clinical Implications?

- These results expand the available options of evidence-based drug-eluting stent platforms for use with an abbreviated dual antiplatelet therapy regimen in patients with high bleeding risk undergoing percutaneous coronary intervention.

Nonstandard Abbreviations and Acronyms

DES	drug-eluting stent
RES	ridaforolimus-eluting stent

Until recently, prolonged dual antiplatelet therapy (DAPT) was the norm following DES implantation. DAPT duration is directly correlated with the risk of bleeding after PCI, which in turn is associated with increased mortality.[9,10] Thus, attempts to shorten the duration of treatment with DAPT to as short as 1 month have been tested with encouraging results and low rates of stent thrombosis.[11] Recently, several contemporary DESs have been studied in patients with HBR with abbreviated DAPT durations. Both randomized trials[12] as well as observational studies[13–15] have shown promising results. Although similar in many respects, important differences exist among DESs including drug, dose, polymer, and stent design, which necessitate testing of this treatment approach on a stent-by-stent basis.

The EluNIRstent (Medinol, Tel-Aviv, Israel) is a new thin-strut DES that elutes ridaforolimus and is coated with an elastic copolymer. It was designed to enable rapid and controlled vessel healing. In the BIONICS (BioNIR Ridaforolimus-Eluting Coronary Stent System in Coronary Stenosis) trial, the ridaforolimus-eluting stent (RES) was noninferior to the zotarolimus-eluting stent for the primary end point of target lesion failure at 12 months and had low rates of stent thrombosis in a broad population of patients.[16] The RES has also been shown to be safe and effective in multiple high-risk patient subgroups.[17–19]

The aim of this trial was to evaluate the safety and efficacy of a shortened period of DAPT following implantation of a RES in patients with HBR.

METHODS

Trial and Study Population

We conducted a prospective, multicenter, binational (Israel and United Kingdom), single-arm, open-label clinical trial (ClinicalTrials.gov number, NCT03877848). Patients fulfilling at least 1 clinical criterion for HBR, as defined in the LEADERS-FREE (Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk) trial,[6] were enrolled before undergoing PCI and were followed thereafter. These criteria were chosen to enable a comparison with the landmark LEADERS-FREE trial.

The trial population consisted of patients undergoing PCI for chronic coronary syndrome, unstable angina pectoris, silent ischemia, and non–ST-segment–elevation myocardial infarction. Patients with recent (<24 hours) ST-segment–elevation myocardial infarction, left ventricular ejection fraction <30%, a history of stent thrombosis, PCI during the previous 12 months with a nonstudy stent, and those with active bleeding were excluded. Only patients who were implanted with the study stent were included. Patients who received a nonstudy stent were deregistered and not included in the analysis.

There was no limit to the number of vessels treated, the number of lesions per vessel, or individual lesion length; however, the total planned stenting in the coronary tree could not exceed 60 mm. Bifurcation lesions with dual stent implantation and unprotected left main lesions were not allowed (see a list of the full angiographic inclusion and exclusion criteria in Data S1).

The study was approved by the institutional review board or ethics committee at each enrolling site, and eligible patients signed written informed consent before the interventional procedure.

Device Description

The EluNIR RES[16] is an 87-μm strut thickness cobalt-chromium alloy platform with dual-pattern strut width design consisting of narrow and ultranarrow struts (72 μm and 40 μm in width, respectively) providing a low metal-to-artery ratio. A proprietary coating of an elastomer, an elastic copolymer and drug, permits controlled elution of ridaforolimus, while minimizing coating irregularities such as peeling, cracking, and flaking. The stent was designed to enable rapid and controlled stent coverage by endothelial cells.

Trial Procedures

Before PCI, all patients received a loading dose of aspirin (300–325 mg if no prior therapy, 75–325 mg if chronic therapy) and a P2Y12 receptor antagonist. For patients on chronic treatment with clopidogrel, a loading dose of 300 mg was required; for patients

receiving prior ticagrelor or prasugrel, a loading dose was allowed but not mandated. In patients with stable angina, loading of the P2Y12 receptor antagonist was permitted immediately after PCI to accommodate the variability in local practices of the timing of loading between participating centers. The choice of P2Y12 receptor antagonist was at the investigator's discretion, but the use of prasugrel was discouraged to minimize the risk of bleeding in elderly patients with HBR.

Anticoagulation with unfractionated heparin, bivalirudin, or low-molecular-weight heparin, with or without a glycoprotein IIb/IIIa inhibitor, was prescribed according to local practice.

After PCI, DAPT was given for 1 month to patients presenting with chronic coronary syndrome. After 30 days, single antiplatelet therapy (SAPT) was given (either aspirin or a P2Y12 inhibitor).

Patients presenting with an acute coronary syndrome (ACS) received DAPT for 1 to 3 months at the investigator's discretion followed by SAPT (a P2Y12 inhibitor).

Patients receiving long-term oral anticoagulation received either SAPT with clopidogrel, or DAPT (with clopidogrel) for 1 month (triple therapy), followed by SAPT with clopidogrel (75 mg QD) for 6 months in stable patients and 12 months in patients with ACS.

Clinical events were assessed during hospital stay and at 30 days, 3 months (patients with ACS), 6 months, and at 12 months after the index procedure. Events were adjudicated by an independent clinical end points committee.

Study End Points and Definitions

The primary end point was a composite of cardiac death, myocardial infarction (MI), or stent thrombosis at 1 year (Academic Research Consortium [ARC] definite and probable).[20] Key secondary end points included target lesion failure, defined as the composite of cardiac death, target vessel-related MI or ischemia-driven target lesion revascularization, major adverse cardiac events (cardiac death, MI, or ischemia-driven target lesion revascularization), and target vessel failure (all-cause death, target vessel-related MI, or ischemia-driven target vessel revascularization). Bleeding complications were evaluated as individual components and as a composite of Bleeding Academic Research Consortium (BARC) type 3 and 5 bleeding.[21]

Periprocedural MI was defined according to the Society of Coronary Angiography and Interventions criteria.[22] Spontaneous MI was defined according to the Fourth Universal Definition of Myocardial Infarction.[23]

Statistical Analysis

Sample size calculations were based on the outcomes of the LEADERS-FREE study.[6] In LEADERS-FREE, the incidence of the primary safety end point among the Biofreedom drug-coated stent (DCS) group was 9.4% at 1 year. With an upper bound of 1.5-fold (similar to the noninferiority margin chosen by previous similar studies)[13,15] and an α of 0.05, a performance goal of 14.1% was chosen (absolute margin of 4.7%). We calculated that a sample size of ≈300 patients was required to provide 80% power. To account for 5% drop-out, a total of ≈316 patients needed to be enrolled.

Continuous variables are presented as means, standard deviations, medians, first and third quartiles, minimums, maximums, and 95% CIs for the means. Categorical variables, the number within each category, and the percentage out of the total number of available observations are summarized.

The primary end point was summarized descriptively with patient counts, percentages, and 1-sided 95% exact binomial confidence interval. An exact test for a single binomial proportion was performed at 5% significance level. The null hypothesis assumed that the upper bound of the 97.5% confidence interval exceeded the performance goal, and the alternative hypothesis was that the upper bound fell below the performance goal. Analysis of the secondary end points (at 30 days, 6 months, and 1 year) were summarized by Kaplan-Meier estimated event rates and number of events and was performed on the full analysis set population, defined as all subjects who have been enrolled into the trial who have received at least 1 study stent. Analysis of the primary end point was also performed on a modified full analysis set defined as all subjects who had received at least 1 study stent and had no ischemic events while on DAPT (30 days for stable patients, 1–3 months for patients with ACS). Subgroups analysis of the primary end point stratified by presentation, age group, sex, diabetes status, and use of oral anticoagulant (OAC) was prespecified in the study protocol. In addition, a subgroup analysis confined to patients fulfilling the ARC HBR criteria (which was not prespecified because these criteria were not yet published at the time of the design and initiation of enrollment for this study) was performed as well.

All statistical analyses were performed using Statistical Analysis System (version 9.4; SAS Institute, Cary, NC).

Data Management

All data were submitted to a central data coordinating facility (Cardiovascular Research Foundation, New York, NY). An independent clinical events committee (Cardiovascular Research Foundation) adjudicated all primary and secondary clinical end points. An independent data safety monitoring board was responsible for regular review of the clinical safety data. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified

researchers trained in human subject confidentiality protocols may be sent to Medinol Ltd at brendak@medinol.com.

RESULTS

Patients

Between May 2019 and March 2020, 889 patients were screened for the trial, and 5 patients were deregistered (for receiving a nonstudy stent). Ultimately, 315 patients undergoing PCI were enrolled in 17 medical centers in the United Kingdom and Israel. Follow-up through 1 year was completed for 310 out of 315 (98.4%) of the patients; 1 patient was lost to follow-up, and 4 withdrew consent. The mean age was 75.2±9.8 years, diabetes was present in 160 patients (50.8%), and hypertension in 277 patients (88.2%). One hundred thirty-eight patients (43.6%) presented as chronic coronary syndrome, and 177 patients (56.4%) as ACS (25.4% presented with non–ST-segment–elevation MI). By Corelab assessment, moderate or severe calcification was present in 55.4% of lesions (23.0% moderate, 32.4% severe), 81.8% of lesions were classified as B2/C according to the American Heart Association/American College of Cardiology classification, and 24.6% of lesions involved bifurcations (Table 1). Patients had 1.5±0.7 of the LEADERS-FREE HBR criteria on average, and the most common HBR criterion was age ≥75 years. One hundred six patients (33.7%) were receiving oral anticoagulation (see Table 2). ARC-HBR (4) criteria are listed in Table S1. Overall, 267 patients (84.8%) qualified as HBR according to the ARC definitions. One hundred ninety-nine patients (63.2%)

Table 1. Baseline Characteristics

Characteristic	Value (N=315)
Age, y	75.2±9.8
Men	218 (69.2)
Body mass index, kg/height (m)^2	28.2±5.0
Diabetes	160 (50.8)
Hypertension	277 (88.2)
Hyperlipidemia	272 (87.5)
Previous myocardial infarction	167 (53.7)
Previous PCI	146 (46.6)
Previous coronary bypass surgery	45 (14.3)
Current smoker	35 (11.1)
Atrial fibrillation	108 (34.5)
Stroke	39 (12.4)
Transient ischemic attack	32 (10.2)
MI, on admission	80 (25.4)
Chronic coronary syndrome, on admission	138 (43.6)
Acute coronary syndrome, on admission	177 (56.4)
Procedural data	
Femoral approach	36 (11.4)
Radial approach	277 (87.9)
IVUS	6 (1.9)
OCT	1 (0.3)
No. of lesions treated per patient	1.2±0.5
No. of stents used per patient	1.1±0.3
Total stent length, mm	26.4±16.4
Angiographic complexity	
Lesion length, mm	18.2±9.2
Greater than or equal to moderate calcification	207 (55.4)
B2/C lesion classification*	306 (81.8)
Bifurcation lesion	92 (24.6)

Values are n (%) or mean±SD. IVUS indicates intravascular ultrasound; MI, myocardial infarction; OCT, optical coherence tomography; and PCI, percutaneous coronary intervention.

*American Heart Association/American College of Cardiology classification.

Table 2. Distribution of HBR Criteria (LEADERS-FREE Definition[6])

Criterion	Value (N=315) n (%)
Age ≥75 y	209 (66.3)
Oral anticoagulation therapy planned to continue after PCI	106 (33.7)
Surgery planned in next 6–12 mo*	16 (5.1)
Stroke in previous 12 mo	9 (2.9)
Hospital admission for major bleeding in previous 12 mo	3 (1.0)
Previous intracerebral hemorrhage	2 (0.6)
Nonskin cancer within previous 3 y	17 (5.4)
Severe chronic liver disease†	0 (0)
Creatinine clearance <40 mL/min	33 (10.5)
Hemoglobin <11 g/dL or transfusion within 12 wk before procedure	57 (18.1)
Platelets <100 000/mm^3	5 (1.6)
NSAID or glucocorticoid use for ≥30 d after PCI	4 (1.3)
Expected nonadherence to prolonged dual antiplatelet therapy	11 (3.5)
Preprocedural/during medication	
Aspirin	275 (87.3)
Clopidogrel	289 (91.7)
Ticragerol	36 (11.4)
Prasugrel	4 (1.3)
Vitamin K antagonist	14 (4.4)
NOAC	90 (28.6)

HBR indicates high bleeding risk; LEADERS-FREE, Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk; NOAC, new oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; and PCI percutaneous coronary intervention.

*Within 6 mo in stable patients and 12 mo in patients with acute coronary syndrome.

†Defined as patients who have developed any of the following: variceal hemorrhage, ascites, hepatic encephalopathy, or jaundice.

had at least 1 major criterion, and 146 patients (46.3%) at least 2 minor criteria.

Procedural Data

Radial access was used in the vast majority of patients (87.9%). The mean number of stents used per patient was 1.1±0.3, and mean total stented length was 26.4±16.4 mm. Device success was achieved in 376 out of the 381 lesions treated (98.7%).

The distribution of antithrombotic treatment throughout the 1-year follow-up is shown in Figure 1 and Table S2. In the chronic coronary syndrome group, 108 out of 136 (79.4%), 122 out of 136 (89.7%), and 127 out of 136 (93.4%) discontinued DAPT and were treated with SAPT (either alone or in combination with OAC) at 1, 3, and 6 months post-PCI, respectively. OAC use in this group remained stable throughout the follow-up period at 56 out of 136 (41.1%), 55 out of 136 (40.4%), and 53 out of 136 (40.5%) at 1, 3, and 6 months post-PCI, respectively. In patients with ACS, the fraction of patients who discontinued DAPT and were treated with SAPT was 85 out of 177 (48.0%), 158 out of 173 (91.3%), and 161out of 171 (94.2%) at 1, 3, and 6 months post-PCI, respectively. OAC use throughout the follow-up period was 58 out of 177 (32.7%), 59 out of 173 (34.1%), and 56 out of 171 (32.7%) at 1, 3, and 6 months post-PCI, respectively.

Clinical Outcomes

Clinical outcomes are presented in Figures 2 and 3 and Table 3. At 1 year, the primary end point, which was a composite of cardiac death, MI, or stent thrombosis, occurred in 15 patients (4.9% [95% CI, 2.3%–7.5%]), meeting the prespecified performance goal (P<0.0001) (see Figure 2). In a prespecified subgroup analysis, all subjects who had no ischemic events while on DAPT (30 days for stable patients, up to 3 months for patients with ACS) were analyzed for the primary end point. In this modified group, the primary end point was 3.4% (Table 3).

For the 84.8% of patients fulfilling the ARC HBR criteria, the event rate for the primary end point at 1 year was 5.5%, similar to the full cohort (Table 3).

Subgroup analysis stratified by presentation, age, sex, diabetes, OAC status, and DAPT duration (1 month for stable patients/1–3 months for patients with ACS) did not show any interaction for the primary end point (Table S3).

At 1 year, mortality was observed in 10 patients (3.7%) and cardiovascular mortality in 3 patients (1.0%). The secondary end points of target vessel failure and major adverse cardiac events occurred in 11 patients (3.5%) and 16 patients (5.2%), respectively. MI occurred in 12 patients (3.9%), and stent thrombosis (ARC definite and probable) occurred in 2 patients (0.6%). The primary bleeding end point, BARC type 3 and 5 bleeding, occurred in 6 patients (1.9%) (see Figure 3 and Table 3).

DISCUSSION

Patients with HBR treated with RES, who received 1 to 3 months of DAPT, demonstrated low rates of the primary end point, a composite of cardiac death, MI, or stent thrombosis, at 1 year (4.9%, with an upper bound of the 95% CI at 7.5%), significantly lower than the predefined performance goal (P<0.0001) and well below the 9.4%-point estimate of the DCS arm in LEADERS-FREE. The risk for BARC 3 to 5 bleeding was 1.9%.

These results support the growing body of evidence showing that using modern DESs enables patients with HBR to be treated safely with abbreviated periods of DAPT. The LEADERS-FREE trial[6] showed that DCS use reduced the risk for the safety end point of ischemic events (a composite of cardiac death, MI, or stent thrombosis) compared with bare-metal stents with only 1 month of DAPT (9.4% versus 12.9%, P<0.005).

The Onyx ONE Clear trial compared a polymer-based zotarolimus-eluting stent with the same polymer-free DCS from the LEADERS-FREE trial in 1996 patients with HBR with 1 month of DAPT. The trial used the same HBR definitions and end points as the LEADERS-FREE trial. At 1 year, the primary outcome (a safety composite of death from cardiac causes, MI, or stent thrombosis at 1 year) was observed in 17.1% in the zotarolimus-eluting stent group and in 16.9% in the DCS group (P=0.01 for noninferiority).[12] Excellent results with abbreviated DAPT for patients with HBR were also reported in real-world observational trials. In the XIENCE short DAPT program, 1392 patients with HBR who underwent PCI with an everolimus-eluting stent and switched to SAPT at 1 month (having been adherent to DAPT and event free since PCI) had a 3.5% risk for death/MI between 1 month and 1 year, which was noninferior to an historical control group of patients with HBR treated with everolimus-eluting stents and receiving 6 months DAPT who had a 4.3% risk for death/MI between 1 month and 1 year.[14] BARC 3 to 5 bleeding occurred in 2.2% in the 1 month DAPT cohort.

In the Onyx ONE Clear registry, the risk for cardiac death/MI between 1 month and 1 year in 1506 patients who underwent PCI with a zotarolimus-eluting stent and were event free and discontinued DAPT at 1 month post-PCI was 7.0%, with a 4.0% risk for BARC 3 to 5 bleeding.[13] The POEM (Performance of Bioresorbable Polymer-Coated Everolimus-Eluting Synergy Stent in Patients at HBR Undergoing Percutaneous Coronary Revascularization Followed by 1-Month Dual Antiplatelet Therapy) registry reported an 4.8% 1-year event rate for cardiac death/MI/definite or probable stent thrombosis at 1 year in 443 patients with HBR who underwent PCI with everolimus-eluting stents and

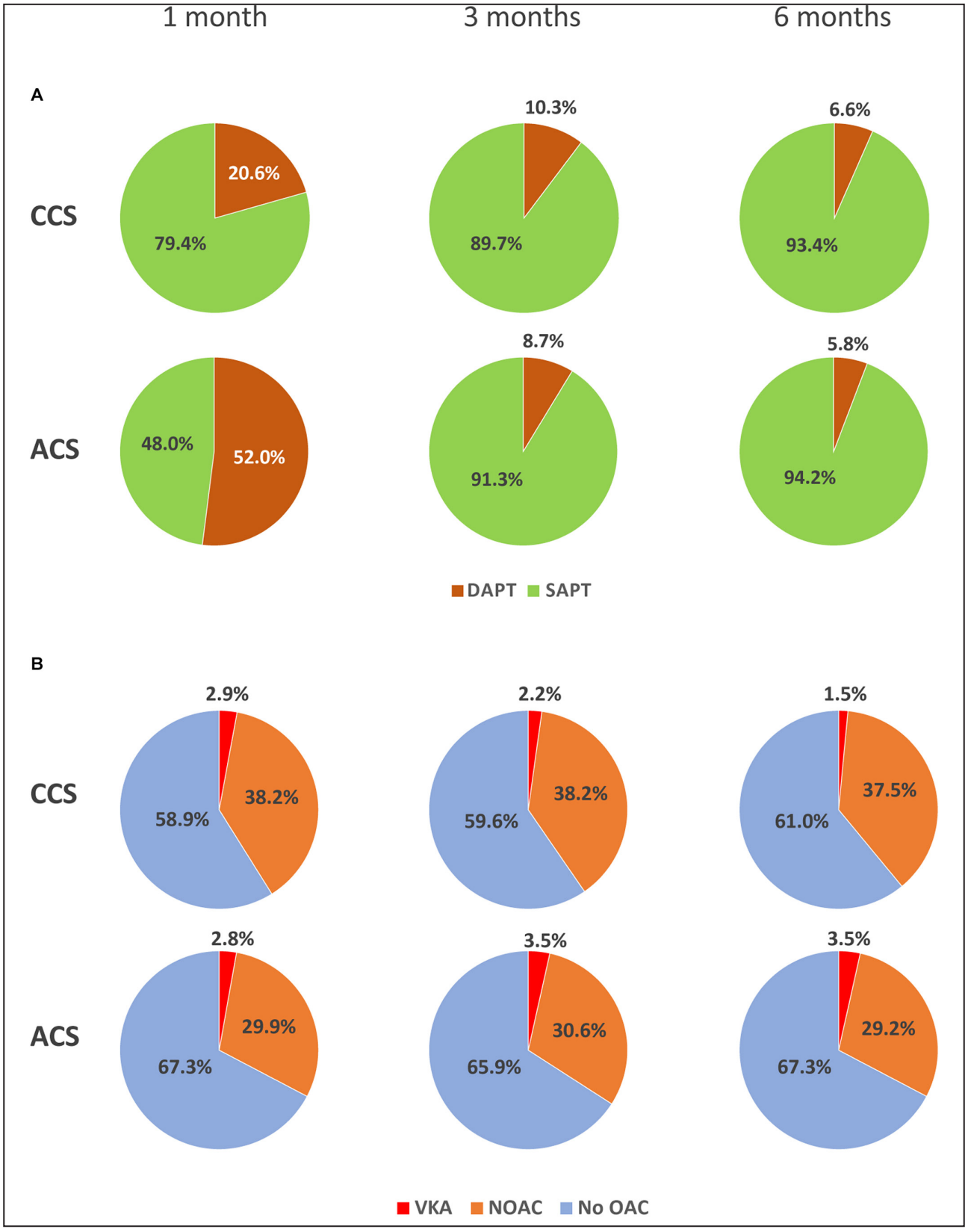

Figure 1. Distribution of antithrombotic regimen throughout the follow-up.
Distribution of antiplatelet (**A**) and anticoagulant (**B**) treatment throughout the follow-up period stratified by clinical presentation. ACS indicates acute coronary syndromes; DAPT, dual antiplatelet therapy; CCS, chronic coronary syndrome; NOAC, novel anticoagulant; OAC, oral anticoagulant; SAPT, single antiplatelet therapy; and VKA, vitamin K antagonist.

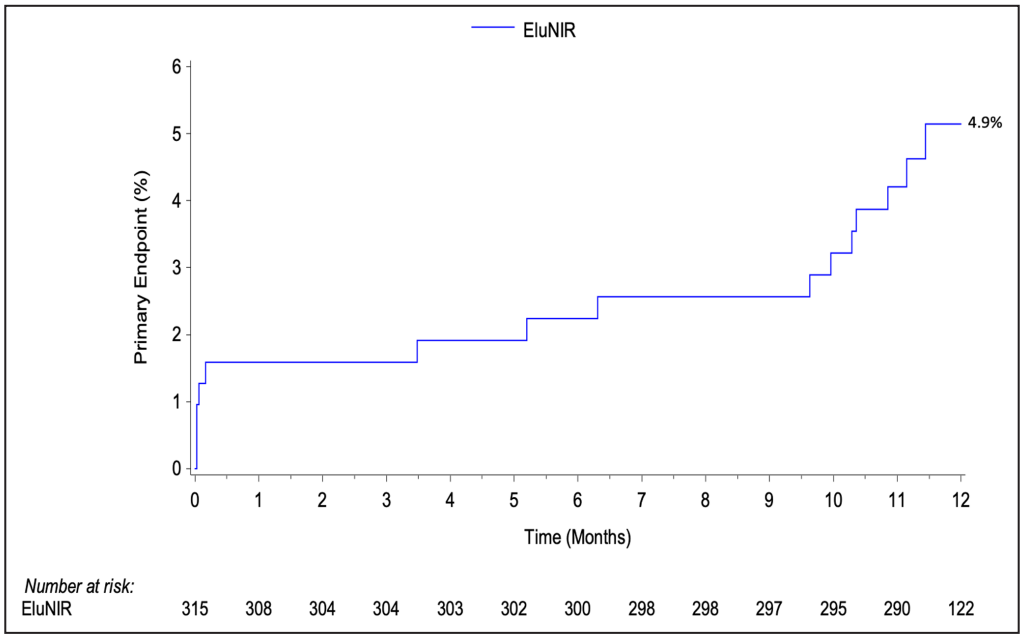

Figure 2. Kaplan-Meier curve for the primary end point.

treated with 1 month of DAPT. Risk for BARC 3 to 5 bleeding was 2.1%.[15]

When comparing our cohort to those of the recent registries mentioned above, the HBR profile of our cohort was similar to those of previous trials in terms of overall risk factors (mean 1.5 in our cohort compared with 1.7, 1.5, and 1.6 for POEM, XIENCE 28, and Onyx ONE Clear, respectively) and the frequency of the leading HBR risk factors (age >75 years, need for OAC, hemoglobin <11 g/dL, and creatinine clearance <40 mL/min). Likewise, age (75.2 compared with 74.8, 76, and 74.0 years) and female sex (30.8% compared with 29.1%, 32.5%, and 32.3%) were similar between the 3 studies. Our cohort had a higher prevalence of several comorbidities: diabetes (50.8% compared with 38.3%, 37%, and 39.4%), and dyslipidemia (87.5% compared with 68.5%, 67.5%, and 72.4%), previous PCI (46.6% compared with 32.8%, 28%, and 36.2%), and previous MI (53.7% compared with 16.4% in XIENCE 28 and 26.3% in Onyx ONE Clear). The fraction of patients presenting with MI in our cohort (25.4%) was similar to that in POEM (25.4%) and Onyx ONE Clear (25.9%) and somewhat higher compared with XIENCE 28 (17.6%).

In terms of angiographic characteristics, all studies enrolled primarily patients with single-vessel disease; however, the fraction of B2/C-grade lesions in our cohort (81.8%) was similar to Onyx ONE Clear (78.6%) and considerably higher compared with XIENCE 28 (35.8%) and POEM (49.2%). Total stent length in our cohort (26 mm) was similar to XIENCE 28 (27 mm) and shorter compared with POEM and Onyx ONE Clear (40 mm and 37 mm, respectively). Use of the radial approach in our cohort was 87.9%, similar to POEM (83.3%) and considerably higher compared with XIENCE 28 (70.8%) and Onyx ONE Clear (65.8%). In summary, our cohort included patients with a similar HBR profile and baseline demographics, slightly higher prevalence of several comorbidities, and more challenging lesions compared with similar studies published recently.

The primary outcome (cardiac death/MI/stent thrombosis at 1 year) occurred in 4.9% in our cohort

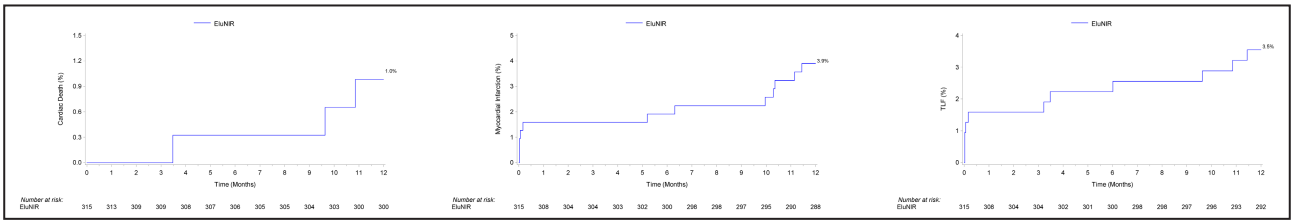

Figure 3. Secondary end points at 1 year.
Left: cardiac death. Center: TLF. Right: myocardial infarction. TLF indicates target lesion failure.

Table 3. Clinical Outcomes at 1 Year

Outcome	N (%)
Primary outcome: cardiac death, myocardial infarction, or stent thrombosis*	15 (4.9), *P*<0.0001
Primary outcome: modified analysis set	10 (3.4)
Primary outcome: patients with ARC HBR†	14 (5.5)
Target lesion failure‡	11 (3.7)
Target vessel failure§	20 (7.1)
Major adverse cardiac event‖	16 (5.5)
All-cause death	10 (3.7)
Cardiac death	3 (1.0)
Any myocardial infarction	12 (4.2)
Periprocedural myocardial infarction#	4 (1.3)
Spontaneous myocardial infarction**	8 (2.9)
Stent thrombosis	
Definite or probable	2 (0.6)
Definite	2 (0.6)
Probable	0 (0.0)
Early (≤30 d)	1 (0.3)
Late (31–365 d)	1 (0.3)
Target lesion myocardial infarction	5 (1.6)
Target vessel myocardial infarction	7 (2.2)
Ischemia-driven target lesion revascularization	3 (1.0)
Ischemia-driven target vessel revascularization	6 (2.1)
Stroke	4 (1.3)
Bleeding event¶	
BARC type 1–5	8 (2.6)
BARC type 2–5	8 (2.6)
BARC type 3–5	6 (1.9)

P value represents the significance of the difference from the performance goal (14.1%). ARC indicates Academic Research Consortium; BARC, Bleeding Academic Research Consortium; and HBR, high bleeding risk.

*ARC definitions.

†Analysis included 267 out of 315 (84.8%) of the overall cohort.

‡Target-lesion failure was defined as a composite of cardiac death, target-lesion myocardial infarction, or ischemia-driven target-lesion revascularization.

§Target-vessel failure was defined as a composite of all-cause death, target-vessel myocardial infarction, or ischemia-driven target-vessel revascularization.

‖A major adverse cardiac event was defined as cardiac death, myocardial infarction, or ischemia-driven target-lesion revascularization.

¶Bleeding was defined according to BARC criteria.

#Periprocedural myocardial infarction was defined according to the Society of Coronary Angiography and Interventions criteria.

**Spontaneous myocardial infarction was defined according to the Fourth Universal Definition of Myocardial Infarction.

compared with 9.4% in LEADERS-FREE (DCS arm) and 17.0% in Onyx ONE Clear. The corresponding figures for BARC 3 to 5 bleeding events were 1.9% compared with 7.2% and 4.9%. Perhaps a more relevant comparison is to the real-world registries mentioned above, which are both more contemporary and similar in terms of design to our study. Both Onyx ONE Clear and POEM used the same composite primary end point used in our study (cardiovascular death/MI/stent thrombosis at 1 year), and the outcomes in our cohort are in line, if not somewhat better at 4.9% compared with 10.2% in POEM and 7.0% in Onyx ONE Clear. For the period between 1 and 12 months post-PCI in patients without events in the first 30 days post-PCI, the corresponding rate for these patients in our cohort was 3.4%. The primary end point in XIENCE 28 (a composite of overall death/MI between 1 and 6 months post-PCI) occurred in 3.5% of patients. BARC 3 to 5 bleeding was also similar at 1.9% in our cohort, 2.1% in POEM, 4.0% in Onyx ONE Clear (1–12 months), and 2.2% in XIENCE 28 (1–6 months).

The RES achieved favorable results in the presence of a similar HBR profile and overall patient characteristics; our cohort showed a higher prevalence of several cardiovascular risk factors such as diabetes, dyslipidemia, previous MI, and previous PCI. This may be partly explained by the stent's unique properties: elastic polymer (elastomer) that permits a controlled and sustained release of ridaforolimus, which has been shown to have low toxicity to vascular endothelial cells enabling rapid healing of the artery after PCI.[16] Additionally, the RES's unique cell design allows for a more uniform drug distribution in the vessel wall. Finally, due to its ultranarrow struts the RES has a low metal-to-artery ratio, which may also allow for favorable vascular healing. Of note, patients with ST-segment–elevation MI and unprotected left main PCI were excluded from our cohort, although their prevalence in previous studies was low (4.7% and 5.6% patients with ST-segment–elevation MI and 3.0% and 1.3% left main PCI in LEADERS-FREE and Onyx ONE Clear, respectively), and considering that the overall clinical presentation in terms of chronic coronary syndrome/acute coronary syndrome in our cohort was similar to the previous studies, this is not likely to have played a major role.

The lower rates of BARC 3 and 5 bleeding could be a result of the higher rate and proficiency of radial access. Alternatively, the low rates of ischemic events could be another explanation for the low rates of bleeding, which did not necessitate reloading with antiplatelets and anticoagulants, associated with increased bleeding.

Our study has several limitations. The sample size is modest; the upper limit of the performance goal for the primary end point was set at 50% over the DCS arm of the LEADERS-FREE trial (similar to POEM and Onyx ONE Clear, where the upper limit was set at 41% and 43%, respectively). We do note, however, that the eventual upper limit of the 95% CI for the point estimate of the primary end point was 7.5%, which is below the 9.4%-point estimate of the DCS arm in LEADERS-FREE. We did not collect data on the use of intravascular imaging, HBR criteria were defined according to the LEADERS-FREE trial not the ARC consensus

statement,[4] which is the common standard in current practice, but was not yet available during the design of this trial. However, when applying the ARC definitions, 84.8% of our cohort fulfilled the ARC HBR criteria, and a subgroup analysis confined to these patients showed consistent results with the overall cohort. Most importantly, the lack of an internal comparison group is a limitation of this trial. However, we used the exact HBR definitions as used in previous trials and the same primary end point enabling a comparison with the results of former HBR trials.[6,12–15]

In conclusion, we observed favorable results in patients with HBR who underwent PCI with the EluNIR RES and received a shortened DAPT protocol, including a low rate of ischemic events and low rates of stent thrombosis. These results expand the knowledge about DES use in patients with HBR and support the clinical use of RES in this population using an abbreviated DAPT regimen.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Tables S1–S3

REFERENCES

1. Palmerini T, Biondi-Zoccai G, Della Riva D, Mariani A, Sabaté M, Smits PC, Kaiser C, D'Ascenzo F, Frati G, Mancone M, et al. Clinical outcomes with bioabsorbable polymer- versus durable polymer-based drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol*. 2014;63:299–307. doi: 10.1016/j.jacc.2013.09.061
2. Bangalore S, Kumar S, Fusaro M, Attubato MJ, Feit F, Slater J, Kumar S, Bhatt DL. Short- and long-term outcomes with drug eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation*. 2012;125:2873–2891. doi: 10.1161/CIRCULATIONAHA.112.097014
3. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabatè M, Kim HS, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet*. 2012;379:1393–1402. doi: 10.1016/S0140-6736(12)60324-9
4. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J*. 2019;40:2632–2653. doi: 10.1093/eurheartj/ehz372
5. Frigoli E, Smits P, Vranckx P, Ozaki Y, Tijssen J, Jüni P, Morice MC, Onuma Y, Windecker S, Frenk A, et al. Design and rationale of the management of high bleeding risk patients post bioresorbable polymer coated stent implantation with an abbreviated versus standard DAPT regimen (MASTER DAPT) study. *Am Heart J*. 2019;209:97–105. doi: 10.1016/j.ahj.2018.10.009
6. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, Lipiecki J, Richardt G, Iñiguez A, Brunel P, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med*. 2015;373:2038–2047. doi: 10.1056/NEJMoa1503943
7. Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrié D, Hovasse T, Garot P, El Mahmoud R, Spaulding C, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomized single-blind trial. *Lancet*. 2018;391:41–50. doi: 10.1016/S0140-6736(17)32713-7
8. Valgimigli M, Patialiakas A, Thury A, McFadden E, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, et al. Zotarolimus-eluting versus baremetal stents in uncertain drug-eluting stent candidates. *J Am Coll Cardiol*. 2015;65:805–815. doi: 10.1016/j.jacc.2014.11.053
9. Chhatriwalla A, Amin A, Kennedy K, House JA, Cohen DJ, Rao SV, Messenger JC, Marso SP. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA*. 2013;309:1022–1029. doi: 10.1001/jama.2013.1556
10. Doyle B, Rihal C, Gastineau D, Holmes D. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. *J Am Coll Cardiol*. 2009;53:2019–2027. doi: 10.1016/j.jacc.2008.12.073
11. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321:2414–2427. doi: 10.1001/jama.2019.8145
12. Windecker S, Latib A, Kedhi E, Kirtane AJ, Kandzari DE, Mehran R, Price MJ, Abizaid A, Simon DI, Worthley SG, et al. Polymer-based or polymer-free stents in patients at high bleeding risk. *N Engl J Med*. 2020;382:1208–1218. doi: 10.1056/NEJMoa1910021
13. Kandzari DE, Kirtane AJ, Windecker S, Latib A, Kedhi E, Mehran R, Price MJ, Abizaid A, Simon DI, Worthley SG, et al. One-month dual antiplatelet therapy following percutaneous coronary intervention with zotarolimus-eluting stents in high-bleeding-risk patients. *Circ Cardiovasc Interv*. 2020;13:e009565. doi: 10.1161/CIRCINTERVENTIONS.120.009565
14. Mehran R, Cao D, Angiolillo DJ, Bangalore S, Bhatt DL, Ge J, Hermiller J, Makkar RR, Neumann FJ, Saito S, et al. XIENCE 90 and XIENCE 28 investigators. 3- or 1-month DAPT in patients at high bleeding risk undergoing everolimus-eluting stent implantation. *JACC Cardiovasc Interv*. 2021;14:1870–1883. doi: 10.1016/j.jcin.2021.07.016
15. Pivato CA, Reimers B, Testa L, Pacchioni A, Briguori C, Musto C, Esposito G, Piccolo R, Lucisano L, De Luca L, et al. One-month dual antiplatelet therapy after bioresorbable polymer everolimus-eluting stents in high bleeding risk patients. *J Am Heart Assoc*. 2022;11:e023454. doi: 10.1161/JAHA.121.023454
16. Kandzari DE, Smits PC, Love MP, Ben-Yehuda O, Banai S, Robinson SD, Jonas M, Kornowski R, Bagur R, Iniguez A, et al. Randomized

comparison of ridaforolimus- and zotarolimus-eluting coronary stents in patients with coronary artery disease: primary results from the BIONICS trial (BioNIR Ridaforolimus-Eluting Coronary Stent System in Coronary Stenosis). *Circulation*. 2017;136:1304–1314. doi: 10.1161/CIRCULATIONAHA.117.028885

17. Konigstein M, Kandzari DE, Smits PC, Love MP, Banai S, Golomb M, Perlman GY, Ozan MO, Liu M, Ben-Yehuda O, et al. Outcomes of patients with coronary arterial bifurcation narrowings undergoing provisional 1-stent treatment (from the BIONICS trial). *Am J Cardiol*. 2020;126:8–15. doi: 10.1016/j.amjcard.2020.04.002
18. Danenberg HD, Konigstein M, Golomb M, Kandzari DE, Smits PC, Love MP, Banai S, Ozan MO, Liu M, Perlman GY, et al. Incidence and predictors of target lesion failure in patients with lesions in small vessels undergoing PCI with contemporary drug-eluting stents: insights from the BIONICS study. *Cardiovasc Revasc Med*. 2021;25:1–8. doi: 10.1016/j.carrev.2020.10.018
19. Konigstein M, Ben-Yehuda O, Smits PC, Love MP, Banai S, Perlman GY, Golomb M, Ozan MO, Liu M, Leon MB, et al. Outcomes among diabetic patients undergoing percutaneous coronary intervention with contemporary drug-eluting stents: analysis from the BIONICS randomized trial. *JACC Cardiovasc Interv*. 2018;11:2467–2476. doi: 10.1016/j.jcin.2018.09.033
20. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351. doi: 10.1161/CIRCULATIONAHA.106.685313
21. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449
22. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol*. 2013;62:1563–1570. doi: 10.1016/j.jacc.2013.08.720
23. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138:e618–e651. doi: 10.1161/CIR.0000000000000617