ORIGINAL RESEARCH

One-Month Dual Antiplatelet Therapy After Bioresorbable Polymer Everolimus-Eluting Stents in High Bleeding Risk Patients

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BACKGROUND: It is unknown whether contemporary drug-eluting stents have a similar safety profile in high bleeding risk patients treated with 1-month dual antiplatelet therapy following percutaneous coronary interventions.

METHODS AND RESULTS: We performed an interventional, prospective, multicenter, single-arm trial, powered for noninferiority with respect to an objective performance criterion to evaluate the safety of percutaneous coronary interventions with Synergy bioresorbable-polymer everolimus-eluting stent followed by 1-month dual antiplatelet therapy in patients with high bleeding risk. In case of need for an oral anticoagulant, patients received an oral anticoagulant in addition to a $P2Y_{12}$ inhibitor for 1 month, followed by an oral anticoagulant only. The primary end point was the composite of cardiac death, myocardial infarction, or definite or probable stent thrombosis at 1-year follow-up. The study was prematurely interrupted because of slow recruitment. From April 2017 to October 2019, 443 patients (age, 74.8±9.2 years; women, 29.1%) at 10 Italian centers were included. The 1-year primary outcome occurred in 4.82% (95% CI, 3.17%–7.31%) of patients, meeting the noninferiority compared with the predefined objective performance criterion of 9.4% and the noninferiority margin of 3.85% ($P_{noninferiority}$<0.001) notwithstanding the lower-than-expected sample size. The rates of cardiac death, myocardial infarction, and definite or probable stent thrombosis were 1.88% (95% CI, 0.36%–2.50%), 3.42% (95% CI, 2.08%–5.62%), and 0.94% (95% CI, 0.35%–2.49%), respectively.

CONCLUSIONS: Among high bleeding risk patients undergoing percutaneous coronary interventions with the Synergy bioresorbable-polymer everolimus-eluting stent, a 1-month dual antiplatelet therapy regimen is safe, with low rates of ischemic and bleeding events.

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Key Words: bioresorbable polymer stent ■ coronary artery disease ■ high bleeding risk ■ percutaneous coronary intervention ■ short DAPT ■ Synergy stent

Dual antiplatelet therapy (DAPT) after stent placement reduces the risk of thrombotic events at the cost of an increase in bleedings.[1–3] Patients at high bleeding risk (HBR) constitute up to 40% of subjects undergoing percutaneous coronary intervention (PCI).[4] As bleeding events following PCI have substantial prognostic implications,[5,6] strategies to avoid them are pivotal to improve patient outcomes. Recent trials on

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CLINICAL PERSPECTIVE

What Is New?

- Among patients with high bleeding risk who are undergoing percutaneous coronary intervention with the Synergy bioresorbable-polymer everolimus-eluting stent, a 1-month dual antiplatelet therapy regimen is safe and associated with low rates of ischemic and bleeding events.

What Are the Clinical Implications?

- Patients with high bleeding risk can be safely and effectively treated with a 1-month dual antiplatelet therapy regimen after percutaneous coronary intervention with the Synergy bioresorbable-polymer everolimus-eluting stent.
- Future studies will need to provide precise tools to further optimize the dual antiplatelet therapy regimen after percutaneous coronary intervention based on individual patients' risks of bleeding and ischemic events.

Nonstandard Abbreviations and Acronyms

ARC	Academic Research Consortium
DAPT	dual antiplatelet therapy
EES	everolimus-eluting stent
HBR	high bleeding risk
OPC	objective performance criteria
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

contemporary drug-eluting stents have shown an acceptable safety profile with a short course of DAPT.[7–13] In patients with HBR receiving 1-month DAPT, the polymer-free biolimus-eluting BioFreedom stent outperformed bare metal stents, and the durable-polymer zotarolimus-eluting Resolute Onyx stent proved to be noninferior to the former.[7,10] Based on this evidence, current guidelines recommend to consider short DAPT duration after drug-eluting stents implantation in patients at HBR.[14] Recently, in a pragmatic trial randomizing 4579 patients with HBR to either 1 or 6 months of DAPT following the implantation of the bioresorbable-polymer sirolimus-eluting Ultimaster stent, the abbreviated regimen reduced the occurrence of major or clinically relevant nonmajor bleedings without increasing ischemic events.[12,13] However, an abbreviated

DAPT regimen may not be applicable to other polymer-coated drug-eluting stents platforms. The Synergy bioresorbable-polymer everolimus-eluting stent (EES; Boston Scientific Corporation, Marlborough, MA) is a thin-strut (74–81 μm) platinum-chromium metal alloy platform coated abluminally with an ultrathin (4 μm) bioresorbable poly(DL-lactide-co-glycolide) polymer.[15] These features were associated with a favorable vascular healing and low thrombogenicity, allowing for a shorter DAPT duration.[16,17] Indeed, the SENIOR (Efficacy and Safety of New Generation Drug Eluting Stents Associated With an Ultra Short Duration of Dual Antiplatelet Therapy. Design of the Short Duration of Dual antiplatElet Therapy With SyNergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization) trial proved the superiority of the Synergy bioresorbable-polymer EES as compared with bare metal stent in elderly patients that received a short course (from 1 to 6 months) of DAPT,[9] and favorable ischemic outcomes were observed among selected HBR patients treated with 3-month DAPT after Synergy stent implantation in the EVOLVE Short DAPT (Prospective, Multicenter, Single-arm Study Designed to Assess the Safety of 3-month Dual Antiplatelet Therapy in Subjects at High Risk for Bleeding Undergoing Percutaneous Coronary Intervention With the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System) trial.[18]

We performed a prospective study to evaluate the safety of the Synergy bioresorbable-polymer EES followed by 1-month DAPT in patients with HBR.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

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) trial was an interventional, prospective, single-arm, multicenter study, powered for noninferiority with respect to an objective performance criterion (OPC). Patients were enrolled at 10 Italian centers.

The trial (EudraCT Number 2016-004510-99, clinicaltrials.gov NCT03112707) was an investigator-initiated study, supported by an unrestricted research grant from Boston Scientific. Local ethics review boards approved the protocol at each site, all the patients provided written informed consent, and the trial adhered to the principles of the Declaration of Helsinki.

Assurance of the accuracy and reliability of data was verified by periodic monitoring visits at each study site.

Study Population

HBR patients with coronary artery disease were eligible if undergoing PCI with implantation of a Synergy bioresorbable-polymer EES. The bleeding risk was defined according to the presence of at least 1 of the following HBR criteria: age ≥75 years; oral anticoagulation planned to continue after PCI; anemia, defined by a hemoglobin level <11 g/L; transfusion within 4 weeks before inclusion; thrombocytopenia, defined by a platelet count <100 000/mL; hospital admission for bleeding within previous 12 months; stroke within previous 12 months; history of intracerebral hemorrhage; severe chronic liver disease; chronic kidney disease, defined by a creatinine clearance <40 mL/min; cancer within the previous 3 years; planned major, noncardiac surgery in the next 12 months; glucocorticoids or nonsteroidal anti-inflammatory drugs planned for >30 days after PCI; expected nonadherence to >30 days of DAPT. No exclusion was applied on the basis of clinical presentation (except for cardiogenic shock), comorbidities, or procedural characteristics.

Study Procedure

Patients were treated with the implantation of bioresorbable-polymer Synergy EES. At discharge, DAPT with aspirin and a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor, depending on clinical indication) was recommended for a duration of 1 month, followed by a single antiplatelet therapy with aspirin thereafter. In case of need for oral anticoagulation, patients received an oral anticoagulant (vitamin K antagonists or direct oral anticoagulants, depending on clinical indication) in addition to a $P2Y_{12}$ inhibitor (clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily, depending on clinical indication) without aspirin for 30 days, followed by single antithrombotic therapy with anticoagulant thereafter. Vascular access, periprocedural antithrombotic regimen, and lesion preparation were left to the operator's preference.

A summary of the study design is provided in Figure 1.

Study End Points

The primary end point was the composite of cardiac death, myocardial infarction, or definite or probable stent thrombosis at 12 months. Secondary end points included all-cause death, cardiac death, myocardial infarction, stent thrombosis, target-vessel revascularization, target-lesion revascularization, major bleeding according to Bleeding Academic Research Consortium (BARC) criteria, cerebrovascular events, target-lesion failure (composite of cardiac death, target-vessel myocardial infarction, or target-lesion revascularization), and a patient oriented composite endpoint (composite of all-cause death, any myocardial infarction, or any revascularization). Myocardial infarction was defined according to the third Universal Definition of Myocardial Infarction,[19] stent thrombosis according to the Academic Research Consortium (ARC) definitions,[20] and bleeding according to the BARC definitions.[21] Clinical follow-up was performed by visit/telephone contact at 30 days (±5 days) and 1 year (±30 days) after the inclusion. An independent Clinical Event Committee reviewed and adjudicated all primary and secondary end points.

Statistical Analysis

The trial was designed to be powered for noninferiority compared with an OPC, derived by the reported 1-year rate of primary end point of 9.4% in HBR patients treated with the polymer-free biolimus-eluting BioFreedom stent.[7] With a noninferiority margin of 3.85% on an absolute risk scale and accounting for a 4% attrition rate, the inclusion of 1023 patients would have provided >90% power to detect noninferiority.

All patients enrolled in the study were included in the primary analysis of clinical outcomes according to the intention-to-treat principle. Categorical data are reported as percentages (counts divided by the number of patients who could be evaluated). Continuous variables are reported as mean±SD or median (interquartile range). Survival curves for the primary end point as well as secondary end points were constructed for time-to-event variables using Kaplan-Meier estimates. Statistical analyses were performed using Stata version 14 (Stata Corp., College Station, TX).

RESULTS

Patients and Procedural Characteristics

The study was prematurely interrupted because of slow enrollment after the inclusion of 443 patients from April 2017 to October 2019 (Figure 1). Baseline clinical characteristics are reported in Table 1. Patients had a mean±SD age of 74.8±9.2 years, and 29.1% were women and had a high cardiovascular risk profile, as indicated by the prevalence of diabetes (38.1%), hypertension (88.1%), and dyslipidemia (68.5%). Chronic coronary syndromes were the most common indication to PCI, with 39.3% and 19.2% of patients presenting with stable angina and silent ischemia, respectively.

HBR inclusion criteria are summarized in Figure 2. The mean number of HBR criteria per patient was 1.7, and most of the participants (51.7%) met >1 HBR criterion. Age ≥75 years was the most frequent HBR criterion (59.1% overall, 19.6% as the exclusive inclusion
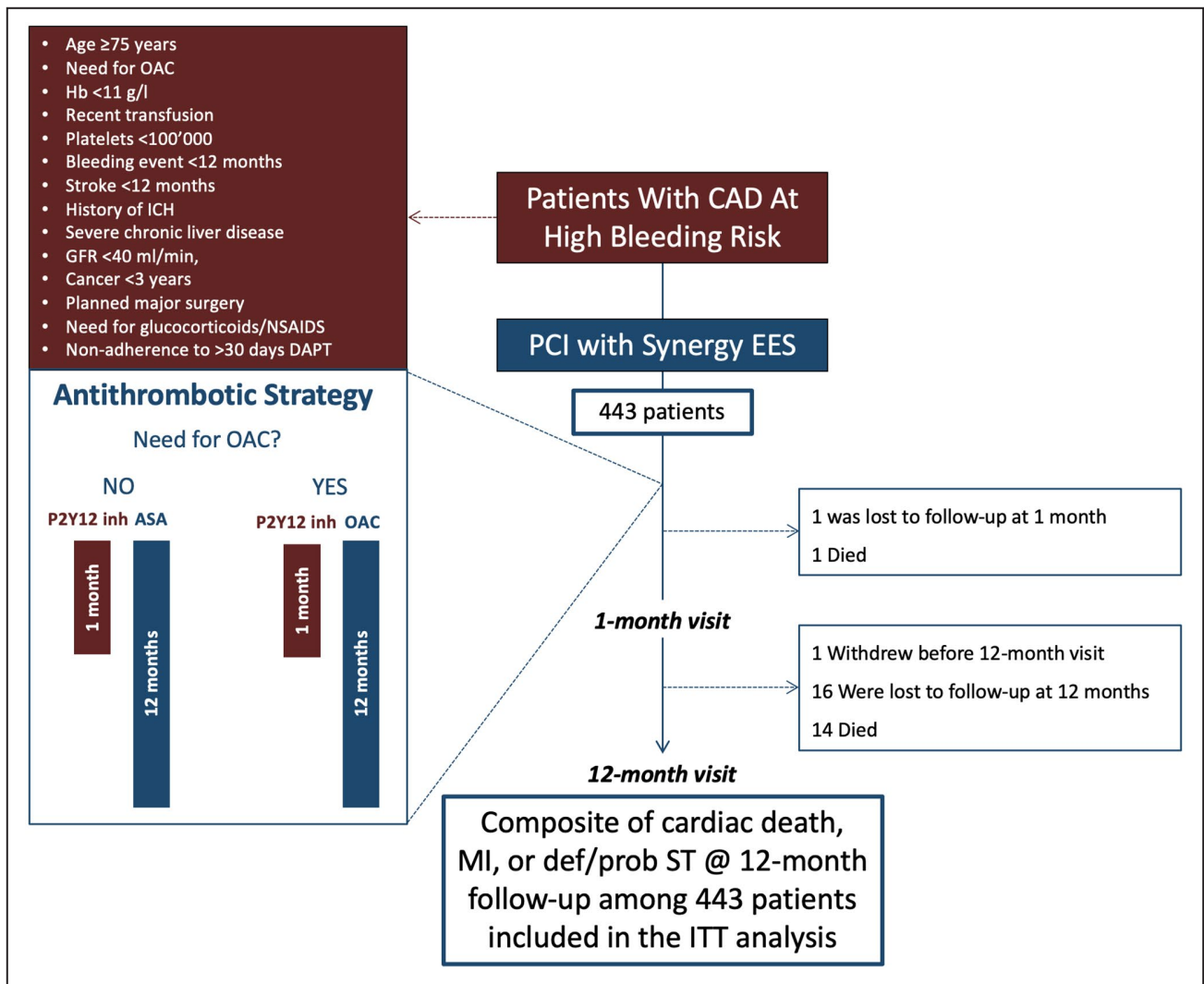
Figure 1. Study design and flowchart.
ASA indicates acetylsalicylic acid; CAD, coronary artery disease; def/prob ST, definite/probable stent thrombosis; EES, everolimus-eluting stent; GFR, glomerular filtration rate; ICH, intracerebral hemorrhage; ITT, intention-to-treat; MI, myocardial infarction, NSAIDs, nonsteroidal anti-inflammatory drugs; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; and ST, stent thrombosis.

criterion), followed by oral anticoagulation use (35.7%), anemia (19.0%), and chronic kidney disease (16.5%).

Baseline procedural characteristics are reported in Table 2. The most frequent vascular access was the radial artery. Among a total of 602 target lesions, half (49.2%) were classified as American College of Cardiology/American Heart Association type B2/C, and the left anterior descending artery was the most frequent target vessel. The mean number of stents per patient was 1.7±1.1. Notably, the 1.1% and 9.6% of the indication to PCI was stent thrombosis or in-stent restenosis.

Peri- and intraprocedural pharmacological therapy is summarized in Table S1. DAPT and single antiplatelet therapy with oral anticoagulant had been prescribed in 83.2% and 15.0% of the patients at

discharge (Table S2). Of the patients with an indication to anticoagulation, most of them received direct oral anticoagulant, with rivaroxaban and apixaban being the prevalent (31.2% and 32.0%, respectively); 11.4% of patients were still on DAPT after the first month, and 6.4% of them were still on DAPT at 1 year (Figure S1).

Outcomes

One-year follow-up was completed in 96% of patients with a median follow-up of 366 (interquartile range, 365–377) days. Clinical outcomes at 30 days and at 1 year are reported in Table 3. At 1 year, the primary outcome had occurred in 4.82% (95% CI, 3.17%–7.31%) of patients demonstrating noninferiority compared with the predefined OPC (1-sided 97.5% upper confidence

Table 1. Baseline Clinical Characteristics

	Total (N=443)
Demographics	
Age, y	74.8±9.2
Female sex	129 (29.1)
Race	
White	434 (98.4)
Asian	3 (0.7)
Black	4 (0.9)
Weight, kg	75 (68–85)
BMI, kg/m^2	26.6±4.0
Comorbidities and cardiac history	
Diabetes	166 (38.1)
Diabetes on insulin therapy	62 (14.0)
Hypertension	386 (88.1)
Dyslipidemia	296 (68.5)
Smoking	175 (39.5)
Current	60 (34.3)
Former	115 (65.7)
Family history of CAD	102 (28.9)
Chronic kidney disease*	73 (16.5)
Prior PCI	142 (32.8)
Prior CABG	38 (8.7)
LVEF <50%	142 (40.5)
LVEF	52.5 (43–55)
Atrial fibrillation	158 (36.2)
Permanent	90 (57.3)
Paroxysmal	67 (42.7)
Prior stroke	24 (5.5)
Peripheral artery disease	61 (14.4)
COPD	42 (9.9)
HAS-BLED Score	2 (2–3)
PARIS bleeding score	6 (4–7)
Clinical presentation	
Stable angina	174 (39.3)
Unstable angina	67 (15.1)
NSTEMI	81 (18.3)
STEMI	32 (7.2)
Silent ischemia	85 (19.2)
Other	4 (0.9)
CCS Angina Class	
Class I	134 (50.6)
Class II	76 (28.7)
Class III	48 (18.1)
Class IV	7 (2.6)
NYHA Class	
Class I	148 (53.0)
Class II	93 (33.3)
Class III	34 (12.2)

(Continued)

Table 1. Continued

	Total (N=443)
Class IV	4 (1.4)
Laboratory tests	
WBC Count, ^10/mm^3	7.2 (5.9–8.5)
Hemoglobin, g/dL	13.0 (11.6–14.1)
Platelet count, ^10/mm^3	202.5 (165.5–249.5)
Creatinine, mg/dL	1.1 (0.8–1.4)
Creatinine clearance, mL/min	62 (45–81)
Glycated hemoglobin, %	5.8 (5.5–6.7)
Glucose, mg/dL	107 (97–136)
Total cholesterol, mg/dL	153 (128–188)
LDL, mg/dL	86 (70–113)
HDL, mg/dL	44 (36–54)
Triglycerides, mg/dL	105 (77–135)

Values are mean±SD, median (interquartile range) or n (%). BMI indicates body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment–elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction; and WBC, white blood cell.

*Chronic kidney disease was defined as creatinine clearance <40 mL/min.

limit of the risk difference, −2.09 percentage points, $P_{noninferiority}$<0.001, Figure 3). The 1-year rate of the individual components of the primary end point was 1.88% (95% CI, 0.36%–2.50%) for cardiac death, 3.42% (95% CI, 2.08%–5.62%) for myocardial infarction, and 0.94% (95% CI, 0.35%–2.49%) for definite or probable stent thrombosis. Of 4 cases of stent thrombosis, 1 occurred at day 14 during DAPT with aspirin and clopidogrel therapy, 2 at days 210 and 219 during single antiplatelet therapy with aspirin, and 1 at day 263 during single antithrombotic therapy with direct oral anticoagulant.

At 1 year, the patient-oriented composite end point and target-lesion failure occurred in 10.18% (95% CI, 7.68%–13.44%) and 5.31% (95% CI, 3.56%–7.88%) of the patients, respectively. Of the 9 cases (2.12%; 95% CI, 1.11%–4.04%) of BARC type 3-5 bleeding, 4 occurred during DAPT and 5 during single antithrombotic therapy, 3 with aspirin, 1 with clopidogrel, and 1 with direct oral anticoagulant.

The per-protocol analysis is reported in Table S3.

DISCUSSION

POEM is the first study evaluating the safety of 1-month DAPT after PCI with the Synergy bioresorbable-polymer EES in an unrestricted cohort of HBR patients. The study findings can be summarized as follows:

1. The population enrolled had a high prevalence of comorbidities, and the complexity of the lesion was comparable to an all-comers population.
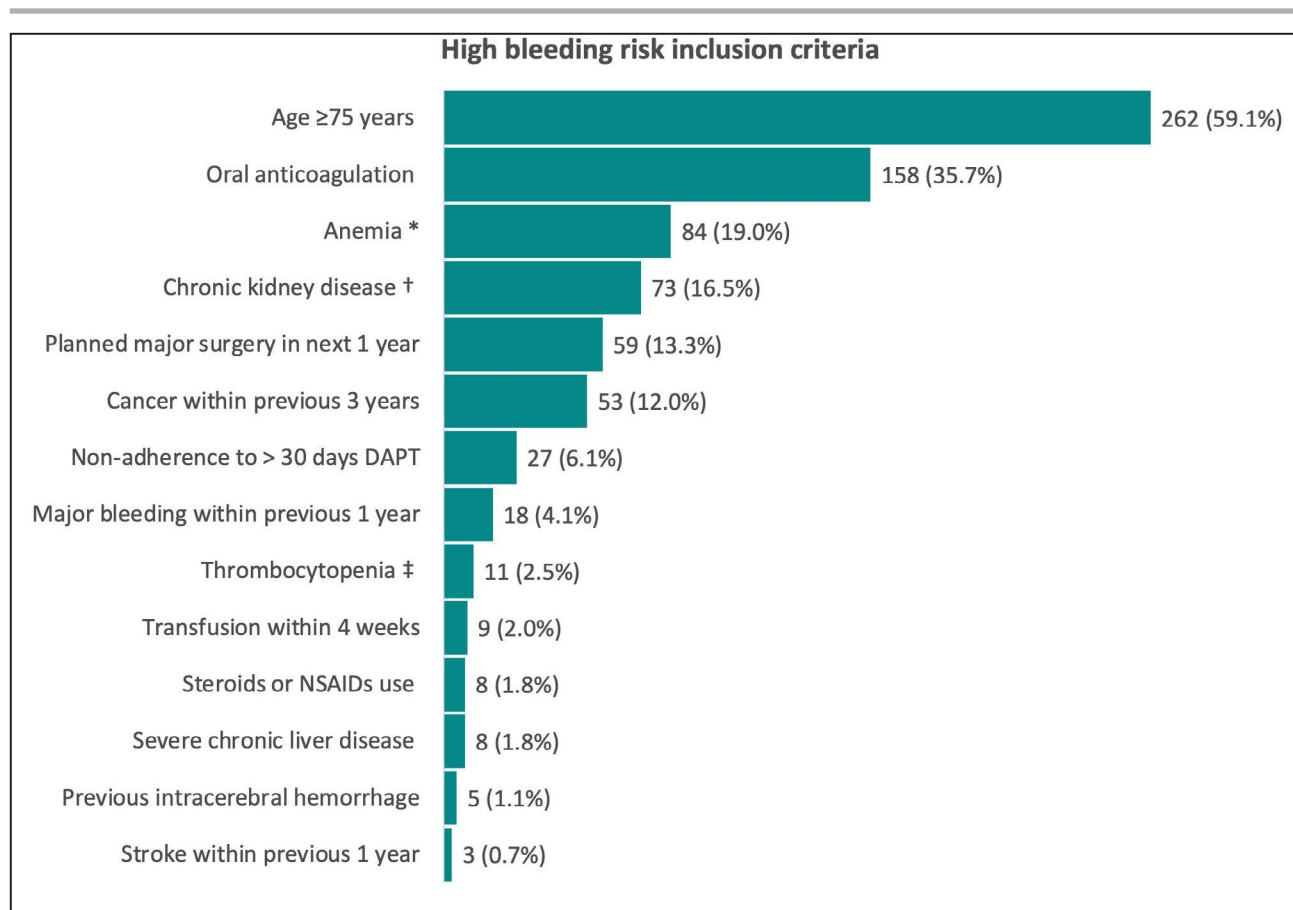
High bleeding risk inclusion criteria

Criterion	Value
Age ≥75 years	262 (59.1%)
Oral anticoagulation	158 (35.7%)
Anemia *	84 (19.0%)
Chronic kidney disease †	73 (16.5%)
Planned major surgery in next 1 year	59 (13.3%)
Cancer within previous 3 years	53 (12.0%)
Non-adherence to > 30 days DAPT	27 (6.1%)
Major bleeding within previous 1 year	18 (4.1%)
Thrombocytopenia ‡	11 (2.5%)
Transfusion within 4 weeks	9 (2.0%)
Steroids or NSAIDs use	8 (1.8%)
Severe chronic liver disease	8 (1.8%)
Previous intracerebral hemorrhage	5 (1.1%)
Stroke within previous 1 year	3 (0.7%)

Figure 2. High bleeding risk inclusion criteria.
DAPT indicates dual antiplatelet therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; and PCI, percutaneous coronary intervention. *Anemia was defined as hemoglobin level <11 g/dL. †Chronic kidney disease was defined as creatinine clearance <40 mL/min. ‡Thrombocytopenia was defined as platelet count <100.000/mm³.

2. The bleeding risk profile of the study population was somewhat high in view of the presence of >1 HBR criterion in the majority of patients.
3. The overall rates of ischemic and bleeding events were low, and the study met the noninferiority hypothesis in terms of ischemic outcomes as compared with the prespecified OPC.

One-Month DAPT After Synergy Bioresorbable-Polymer EES

The present trial evaluated the feasibility of a 1-month DAPT regimen after the implantation of the Synergy bioresorbable-polymer EES in HBR patients undergoing PCI. We chose a DAPT of 1 month's duration because the greater ischemic benefit is usually observed within the initial 30 days following PCI, while the hazard for hemorrhagic events becomes more significant thereafter.[2,3,22,23] The primary end point, which was a composite of ischemic outcomes, was met despite the inclusion of a smaller-than-anticipated number of patients because of slow enrollment. Moreover, the short

DAPT regimen was associated with low rates of bleeding events, although the trial population qualified for HBR. It is noteworthy that all the ischemic outcomes had favorable rates despite the baseline characteristics of the population, which were in line with other all-comers registries.[24,25] Indeed, no exclusion was applied on the basis of clinical presentation (except for cardiogenic shock), comorbidities, or other procedural characteristics.

Findings in Perspectives

Recently, the MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen) trial showed that 1-month DAPT, compared with 6 months, reduced bleeding events without any ischemic trade-off in patients with HBR undergoing PCI.[12,13] However, the findings from MASTER DAPT need to be interpreted in light of the use of the bioresorbable-polymer sirolimus-eluting Ultimaster stent, and caution should be adopted before

Table 2. Angiographic and Procedural Characteristics

	Total (N=443 patients)* (N=602 lesions)†
Access site*	
Femoral	73 (16.5)
Radial	369 (83.3)
Brachial	1 (0.2)
Target vessel†	
LMT	28 (4.7)
LAD	273 (45.4)
LCX	153 (25.4)
RCA	142 (23.6)
Graft	6 (1.0)
In-stent restenosis†	58 (9.6)
Thrombus†	30 (5.0)
In-stent thrombosis*	5 (1.1)
Bifurcations†	109 (18.1)
1 stent	83 (76.1)
2 stents	26 (23.9)
Medina class†	
A (1 1 1)	29 (27.1)
B (1 1 0)	14 (13.1)
C (1 0 1)	9 (8.4)
D (0 1 1)	9 (8.4)
E (1 0 0)	19 (17.8)
F (0 1 0)	13 (12.1)
G (0 0 1)	14 (13.1)
AHA/ACC B2/C lesions†	296 (49.2)
Before dilatation†	435 (72.3)
After dilatation†	486 (80.7)
Total Synergy stent implanted*	1.7±1.1
Mean Synergy stent diameter†	3.5±4.6
Total Synergy stent length*	40.8±25.9
IVUS†	15 (2.5)
OCT†	7 (1.2)
Rotablation†	31 (5.2)

Values are mean±SD, or n (%). AHA/ACC indicates American Heart Association/American College of Cardiology; CTO, chronic total occlusion; DES, drug-eluting stent; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main trunk artery; OCT, optical coherence tomography; and RCA, right coronary artery.
*Refers to unique patient.
†Refers to unique lesion.

1-month DAPT therapy is recommended in other settings. Based on the POEM findings, we suggest that such strategy may be applied to other bioresorbable-polymer thin-strut device, such as the Synergy stent, and other drug-eluting stents (namely BioFreedom, Resolute Onyx, and Xience stents) evaluated in contemporary trials enrolling and treating HBR patients with an abbreviated DAPT regimen (Figure 4). The wide range of the ischemic outcomes' rates reported in these studies is in part attributable to intrinsic differences between observational single arm registries and randomized trials. Besides differences in events ascertainment and patient population, inclusion of subjects must be performed before the intervention (usually represented by PCI) in randomized trials, while in registries, such as POEM, it may occur afterwards, when procedural results are known. Accordingly, the rates of procedural success ranged from 83% to 94% in the LEADERS FREE (Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug Coated Stent Versus the Gazelle Bare Metal Stent in Patients With High Risk of Bleeding) and the ONYX ONE (Randomized Controlled Trial With Resolute Onyx in One Month Dual Antiplatelet Therapy for High-Bleeding Risk Patients) trials,[7,10] while patients were enrolled in the POEM most likely after a successful PCI, similarly to the patients included in the XIENCE 28 Study.[11] Although this introduces a selection bias, the antithrombotic treatment is an adaptive strategy that should be decided after a careful assessment of the results of the PCI, with patients undergoing unsuccessful PCI maintained on DAPT as long as possible. Therefore, the lower event rates of POEM should be interpreted in view of these differences and may be more representative of what we should expect in the real world. Notably, the outcomes were adjudicated according to the Third Universal Definition of Myocardial Infarction,[19] as prespecified in the original protocol; however, the rates of periprocedural myocardial infarction could have been higher if a more conservative definition had been used.[20,26] Even after excluding periprocedural events, the rates of spontaneous myocardial infarction reported in POEM (1.40%; 95% CI, 0.63%–3.09%) compare favorably with those observed in other HBR trials (ranging from 1.9% to 7.1%).[7,10,18]

The POEM findings add to the body of evidence from the SENIOR and EVOLVE Short DAPT trials evaluating a short DAPT regimen after the Synergy bioresorbable-polymer EES implantation. However, both of these trials included a population at lower bleeding risk and adopted a more conservative DAPT duration as compared with POEM. The SENIOR trial enrolled patients aged ≥75 years, which represents only a minor ARC-HBR criterion, while in POEM only 19.6% of the patients were enrolled because of this criterion only.[9,27] Furthermore, in case of acute coronary syndrome, a 6-month DAPT was mandated in the SENIOR trial.[9] Conversely, the EVOLVE Short DAPT trial evaluated a 3-month DAPT after excluding those patients with myocardial infarction or with complex lesions and including subjects at lower bleeding risk, as reflected by a lower number of HBR criteria per patient.[18] Taken together, all these trials provide consistent results and reassure the safety of a short DAPT regimen following PCI with the implantation of the Synergy bioresorbable-polymer EES.

Table 3. Clinical Outcomes at 30 Days and 1 Year Follow-up

	30 days follow-up (N=443) n (%; 95%CI)	1 year follow-up (N=443) n (%; 95%CI)
Primary end point*	13 (2.94; 1.72–5.01)	21 (4.82; 3.17–7.31)
Patient-oriented composite end point†	15 (3.39; 2.06–5.57)	44 (10.18; 7.68–13.44)
Target lesion failure‡	11 (2.49; 1.38–4.45)	23 (5.31; 3.56–7.88)
Death	1 (0.23; 0.03–1.61)	15 (3.51; 2.13–5.76)
Cardiac death	1 (0.23; 0.03–1.61)	8 (1.88; 0.36–2.50)
Any MI	12 (2.71; 1.55–4.73)	15 (3.42; 2.08–5.62)
Periprocedural MI	9 (2.03; 0.93–3.82)	9 (2.03; 0.93–3.82)
Spontaneous MI	3 (0.69; 0.22–2.11)	6 (1.40; 0.63–3.09)
Target-vessel MI§	9 (2.03; 1.06–3.87)	12 (2.74; 1.57–4.78)
Repeat revascularization	4 (0.91; 0.34–2.40)	21 (4.94; 3.25–7.48)
Target-lesion revascularization	1 (0.23; 0.03–1.64)	8 (1.92; 0.97–3.80)
Target-vessel revascularization	2 (0.46; 0.12–1.84)	10 (2.39;1.29–4.39)
Other-vessel revascularization	1 (0.23; 0.03–1.59)	16 (3.82; 2.36–6.16)
Cerebrovascular events		
Stroke	0	0
Transient ischemic attack	0	0
Intracerebral hemorrhage	1 (0.23; 0.03–1.61)	2 (0.46; 0.12–1.85)
Bleeding events		
BARC type 1-5	8 (1.84;0.92–3.65)	20 (4.70; 3.06–7.19)
BARC type 2-5	6 (1.38; 0.62–3.05)	17 (4.00; 2.50–6.35)
BARC type 3-5	3 (0.69; 0.22–2.12)	9 (2.12; 1.11–4.04)
Stent thrombosis		
Definite or probable	1 (0.23; 0.03–1.61)	4 (0.94; 0.35–2.49)
Definite	0	1 (0.24; 0.03–1.67)
Probable	1 (0.23; 0.03–1.61)	3 (0.41; 0.23–2.17)

Values are n (%). BARC indicates Bleeding Academic Research Consortium; and MI, myocardial infarction. Percentages are Kaplan-Meier that indicate patients who had an event up to 30 and 365 days after the index procedure.

*Primary end point was a composite of cardiac death, any MI, or definite or probable stent thrombosis.

†Patient-oriented composite end point was a composite of death, any MI, or any revascularization.

‡Target-lesion failure was a composite of cardiac death, target-vessel MI, or target-lesion revascularization.

§Target-vessel MI includes either periprocedural or spontaneous target-vessel MI.

HBR Patients

A consensus definition of the bleeding risk in patients undergoing PCI has been developed by the ARC-HBR only recently (2019).[27] Still, the inclusion criteria of available HBR trials designed before 2019 and including POEM are largely overlapping, with age being the most common one and with a mean number of HBR criteria met per patient of 1.7 in POEM, 1.6 in the ONYX ONE, 1.7 in the LEADERS FREE, 1.5 in XIENCE 28, and 2.1 in MASTER DAPT.[7,10–12,18] Of note, even if oral anticoagulation represented the second most frequent inclusion criterion in all of them, substantial differences in combination of anticoagulant and antiplatelet therapy should be noted in the study designs. POEM patients requiring oral anticoagulation received an oral anticoagulant in addition to a P2Y$_{12}$ inhibitor without aspirin for 30 days, followed by single antithrombotic therapy with oral anticoagulant thereafter. This strategy has never been tested and expands the body of evidence from prior trials evaluating patients requiring PCI while on oral anticoagulants.[28–30] Despite meeting the primary end point, the sample size of POEM did not allow performance of subgroup analyses and drawing inferential conclusions on the safety of this strategy in this particular subset of patients. Notwithstanding, these encouraging findings are in keeping with guidelines updates from both the United States and Europe recommending the use of a less potent antithrombotic strategy among patients with HBR, in whom aspirin is discontinued at the time of hospital discharge unless an excessive thrombotic risk is perceived.[31,32]

Study Limitations

The present trial should be interpreted in view of several limitations. First, the study was prematurely interrupted after the inclusion of 443 patients because of slow
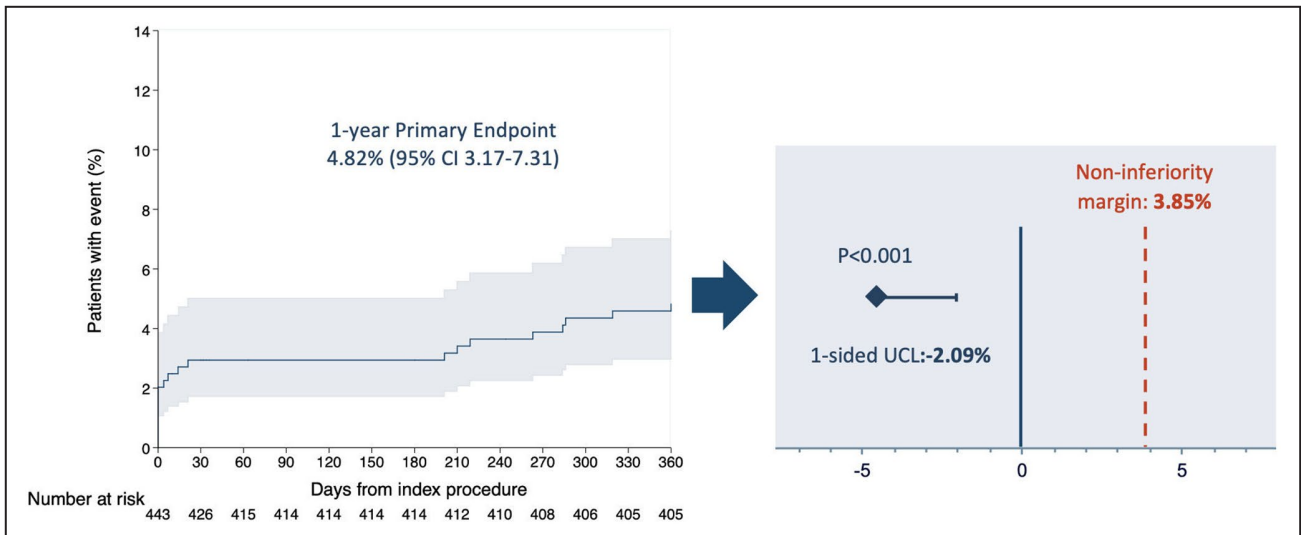
Figure 3. **Primary end point analysis.**
On the left, Kaplan-Meier time to event curve for the primary outcome (composite of cardiac death, any myocardial infarction, or definite or probable stent thrombosis) with 95% CI. On the right, the difference between POEM primary outcome and objective performance criterion is represented by the rhombus with 1-sided 97.5% upper confidence limit (UCL) indicated by the error bar.

recruitment. The second limitation was the absence of a comparator arm (ie, either a different device or a different antithrombotic strategy). However, the study was designed with the aim of testing a noninferiority primary hypothesis against an OPC, a strategy generally accepted for the evaluation of coronary stents.[33]
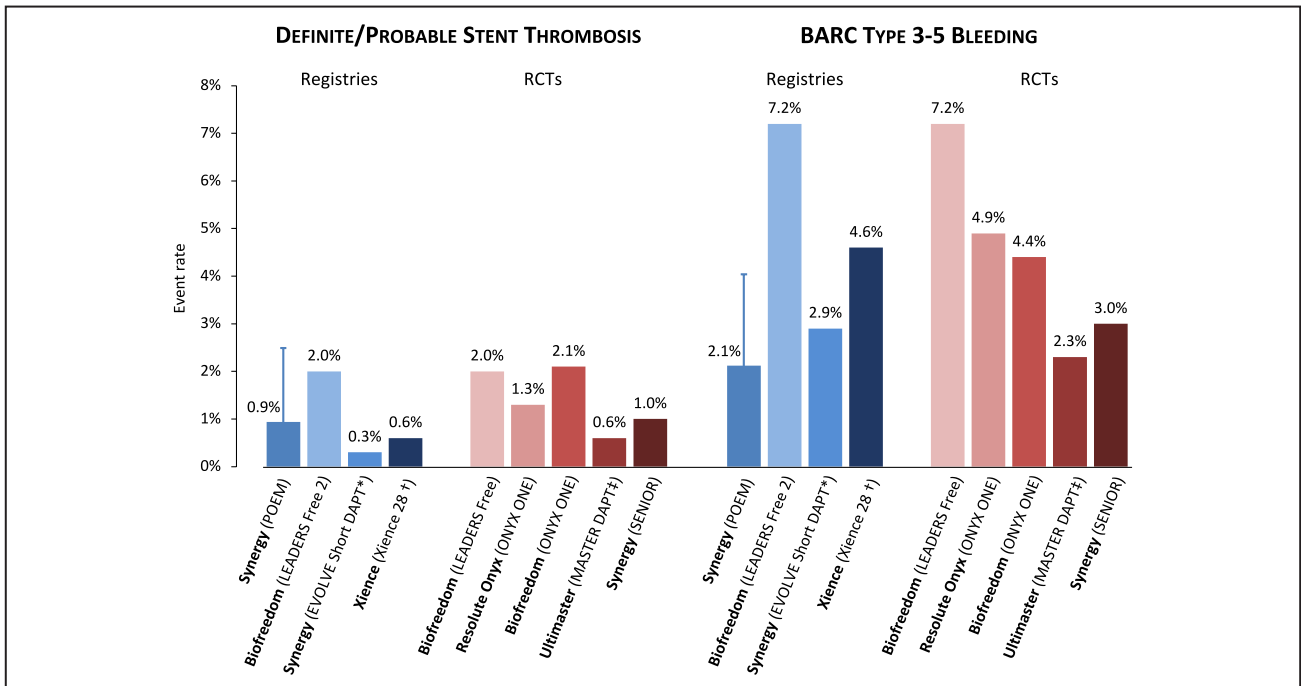

Figure 4. **Findings in perspectives.**
Event rates observed in POEM as compared with those observed in contemporary DES trials that enrolled and treated HBR patients with a short DAPT regimen following PCI. The Synergy bioresorbable-polymer everolimus-eluting stent was used in the POEM, SENIOR and EVOLVE Short DAPT trials. The BioFreedom polymer-free bioliomus-eluting stent was used in LEADERS FREE, LF II, and ONYX ONE trials. The Resolute Onyx durable-polymer zotarolimus-eluting stent was used in the ONYX ONE trial. The Xience durable-polymer was used in the XIENCE 28 trial. The Ultimaster bioresorbable-polymer sirolimus-eluting stent was used in the MASTER DAPT trial. Event rates are through 1 year follow-up except for *the EVOLVE Short DAPT (events observed between 3 and 15 months), for †the XIENCE 28 (events observed at 6 months) and for ‡the MASTER DAPT (events observed between 1 and 12 months) trials. BARC indicates Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; PCI, percutaneous coronary intervention; and ST, stent thrombosis.

Third, since patients were included after PCI, we cannot exclude a selection bias resulting in a lower-than-expected event occurrence and in a slow recruitment rate. Therefore, the correct implication for clinical practice is that a 1-month DAPT strategy after implantation of the Synergy bioresorbable-polymer EES is justifiable only after a careful evaluation of the procedural results. Furthermore, most of the 1-year follow-up was performed by telephone contact because of mobility restrictions related to the COVID-19 pandemic. However, the accuracy and reliability of data was verified by periodic monitoring visits at each study site, limiting the risk of underreporting adverse events. Finally, the inclusion criteria of the POEM trial were based on the LEADERS FREE trial, as the ARC-HBR criteria were published afterwards. Therefore, the POEM patients, as those enrolled in HBR trials published so far, cannot be fully defined HBR according to the ARC-HBR criteria, and dedicated future trials are required.[27]

CONCLUSIONS

Among HBR patients undergoing PCI with the Synergy bioresorbable-polymer EES, a 1-month DAPT regimen resulted in a noninferior ischemic outcome as compared with a prespecified OPC and was associated with low rates of ischemic and bleeding events. Based on these findings, PCI with the Synergy bioresorbable-polymer EES followed by 1-month DAPT seems a safe and effective strategy in patients with HBR.

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Disclosures

Dr Testa has received consulting fees and personal and institutional honoraria, and has served on the advisory board participation from Abbott, Medtronic, Biotronik, Boston Scientific, Terumo Lifesciences, Meril, Cardionovum, and Concept Medical. Dr Piccolo has received speaker fees from Abbott Vascular and Biotronik and has served on the advisory board for Daiichi-Sankyo. Dr De Luca has received speaker fees from AstraZeneca, Daiichi Sankyo, and Sanofi. Dr Stefanini has received speaker fees from Abbott Vascular and Boston Scientific. The remaining authors have no disclosures to report.

Supplemental Material

Figure S1
Tables S1–S3

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SUPPLEMENTAL MATERIAL

PRINCIPAL INVESTIGATORS AND KEY PERSONNEL

Executive Committee: Giulio G. Stefanini (principal investigator), Bernhard Reimers, Gianluigi Condorelli (co-principal investigators). **Steering Committee**: Luca Testa, Gennaro Sardella, Carlo Briguori, Raffaele Piccolo, Giuseppe Ferrante. **Study Coordination**: Carlo Andrea Pivato, Andrea De Marco. **Data Management & Monitoring**: CD Pharma Group Srl (Milan, Italy). **Clinical Events Committee:** Davide Cao, Jorge Sanz Sanchez, Nicolas Amabile (chair).

SUPPLEMENTAL FIGURES

Figure S1. Time course of antithrombotic regimen.

DAPT: dual antiplatelet therapy; OAC: oral anticoagulant; SAPT: single antiplatelet therapy. DAPT includes subjects on DAPT only or DAPT + OAC.
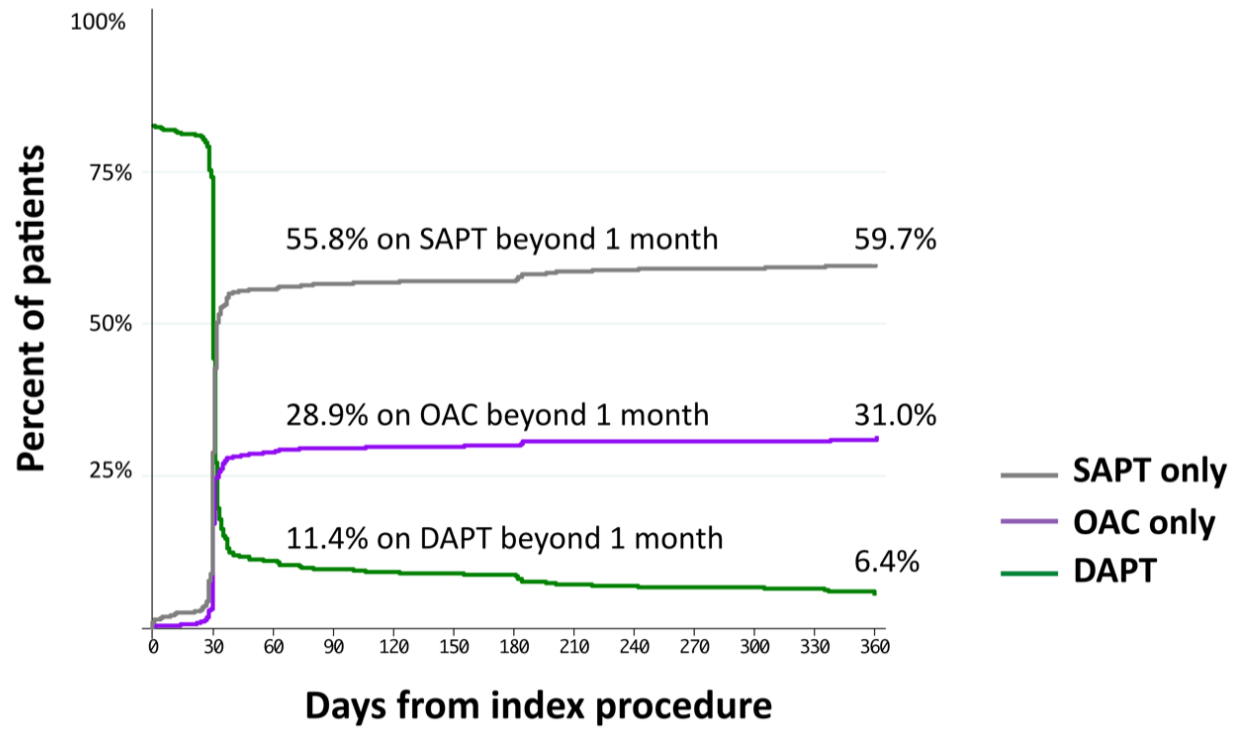
TABLES

Table S1. Peri- and intra-procedural antithrombotic therapy.

	Total *(N= 443)*
Aspirin loading	51 (11.5)
Clopidogrel loading	163 (36.8)
Ticagrelor loading	14 (3.2)
Prasugrel loading	3 (0.7)
Glycoprotein IIb/IIIa inhibitor	6 (1.3)
Bivalirudin	2 (0.4)
Unfractionated heparin	421 (95)

Values are number (%).

Table S2. Antithrombotic medication at discharge.

	Total (N= 443)
Regimen	
DAPT (with or without OAC)	365 (83.2)
DAPT without OAC	276 (62.9)
DAPT with OAC	89 (20.3)
DAPT with Vitamin K antagonist	21 (4.7)
DAPT with Rivaroxaban	19 (4.3)
DAPT with Apixaban	21 (4.7)
DAPT with Dabigatran	19 (4.3)
DAPT with Edoxaban	7 (1.6)
SAPT (with or without OAC)	71 (16.1)
SAPT without OAC	5 (1.1)
SAPT with OAC	66 (15.0)
SAPT with Vitamin K antagonist	14 (3.2)
SAPT with Rivaroxaban	18 (3.2)
SAPT with Apixaban	17 (3.8)
SAPT with Dabigatran	7 (1.6)
SAPT with Edoxaban	10 (2.3)
OAC only	3 (0.7)
Rivaroxaban	1 (0.2)
Apixaban	1 (0.2)
Dabigatran	1 (0.2)

Drugs	
Aspirin	369 (84.0)
Clopidogrel	387 (88.1)
Ticagrelor	44 (10.2)
Prasugrel	1 (0.2)
Vitamin K antagonist	35 (8.0)
DOAC	123 (28.0)
Rivaroxaban	38 (31.2)
Apixaban	39 (32.0)
Dabigatran	27 (22.1)
Edoxaban	17 (14.0)

Values are number (%).

DAPT: dual anti-platelet therapy, DOAC: direct oral anticoagulation therapy, OAC: oral anticoagulation therapy; SAPT: single anti-platelet therapy.

Table S3. Intention-to-treat and Per-protocol analyses evaluating outcomes at 1 year follow-up.

Outcomes	Intention-to-treat (N=443) Number (percent; 95% CI)	Per-protocol (N=367) Number (percent; 95% CI)
Primary endpoint*	21 (4.82; 3.17-7.31)	21 (5.81; 3.82-8.77)
Patient oriented composite endpoint†	44 (10.18; 7.68-13.44)	38 (10.55; 7.79-14.21)
Target lesion failure ‡	23 (5.31; 3.56-7.88)	22 (6.10; 4.06-9.12)
Death	15 (3.51; 2.13-5.76)	15 (4.20; 2.26-6.90)
Cardiac death	8 (1.88; 0.36-2.50)	8 (2.25; 1.13-4.45)
Any MI	15 (3.42; 2.08-5.62)	15 (4.13; 2.51-6.76)
Periprocedural MI	9 (2.03; 0.93-3.82)	9 (2.03; 0.93-3.82)
Spontaneous MI	6 (1.40; 0.63-3.09)	6 (1.69; 0.76-3.72)
Target vessel-MI §	12 (2.74; 1.57-4.78)	12 (3.30; 1.89-5.74)
Repeat revascularization	21 (4.94; 3.25-7.48)	15 (4.25; 2.58-6.95)
Target lesion revascularization	8 (1.92; 0.97-3.80)	7 (2.02; 0.97-4.20)
Target vessel revascularization	10 (2.39;1.29-4.39)	9 (2.59; 1.35-4.91)
Other-vessel revascularization	16 (3.82; 2.36-6.16)	10 (2.89; 1.56-5.30)
Cerebrovascular events		
Stroke	0	0
Transient ischemic attack	0	0
Intracerebral hemorrhage	2 (0.46; 0.12-1.85)	2 (0.56; 0.14-2.22)
Bleeding events		

BARC type 1-5	20 (4.70; 3.06-7.19)	14 (3.97; 2.37-6.61)
BARC type 2-5	17 (4.00; 2.50-6.35)	11 (3.12; 1.74-5.57)
BARC type 3-5	9 (2.12; 1.11-4.04)	7 (1.99; 0.95-4.13)
Stent thrombosis		
Definite or probable	4 (0.94; 0.35-2.49)	4 (1.13; 0.43-2.99)
Definite	1 (0.24; 0.03-1.67)	1 (0.28; 0.08-2.01)
Probable	3 (0.41; 0.23-2.17)	3 (0.85; 0.27-2.61)

Values are number (%).

BARC: Bleeding Academic Research Consortium; MI: myocardial infarction.

Percentages are Kaplan–Meier that indicate patients who had an event up to 30 and 365 days after the index procedure.

* Primary endpoint was a composite of cardiac death, any MI, or definite or probable stent thrombosis.

† Patient oriented composite endpoint was a composite of death, any MI, or any revascularization.

‡ Target lesion failure was a composite of cardiac death, target vessel-MI, or target lesion revascularization.

§ Target vessel-MI includes either periprocedural either spontaneous TV-MI**.**