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ORIGINAL ARTICLE

One-Month Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention With Zotarolimus-Eluting Stents in High-Bleeding-Risk Patients

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BACKGROUND: Despite treatment guidance endorsing shortened dual antiplatelet therapy (DAPT) duration in high bleeding risk (HBR) patients after drug-eluting stents, limited evidence exists to support these recommendations. The present study was designed to examine the safety and effectiveness of 1-month DAPT duration following percutaneous coronary intervention with zotarolimus-eluting stents in HBR patients.

METHODS: Onyx ONE Clear was a prospective, multicenter, nonrandomized study evaluating the safety and effectiveness of 1-month DAPT followed by single antiplatelet therapy in HBR patients undergoing percutaneous coronary intervention with Resolute Onyx drug-eluting stents. The primary analysis of cardiac death or myocardial infarction between 1 month and 1 year was performed in the prespecified one-month clear population of patients pooled from the Onyx ONE US/Japan study and Onyx ONE randomized controlled trial. One-month clear was defined as DAPT adherence and without major adverse events during the first month following percutaneous coronary intervention.

RESULTS: Among patients enrolled in Onyx ONE US/Japan (n=752) and Onyx ONE randomized controlled trial (n=1018), 1506 patients fulfilled one-month clear criteria. Mean HBR characteristics per patient was 1.6 with 44.7% having multiple risks. By 2 months and 1 year, respectively, 96.9% and 89.3% of patients were taking single antiplatelet therapy. Between 1 month and 1 year, the rate of the primary end point was 7.0%. The 1-sided upper 97.5% CI was 8.4%, less than the performance goal of 9.7% (P<0.001).

CONCLUSIONS: Among HBR patients who were event free before DAPT discontinuation at 1 month, favorable safety and effectiveness through 1 year support treatment with Resolute Onyx drug-eluting stents as part of an individualized strategy for shortened DAPT duration following percutaneous coronary intervention.

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Key Words: drug-eluting stents ■ goals ■ hemorrhage ■ Japan ■ stents

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Drs Kandzari and Kirtane served as co-principal investigators for the Onyx ONE Clear study.

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For Sources of Funding and Disclosures, see page 231.

WHAT IS KNOWN

- Patients with high bleeding risk represent nearly one-third of those encountered in clinical practice yet until recently have been systematically excluded from drug-eluting stent trials.
- Despite treatment guidance endorsing shortened dual antiplatelet therapy duration in high bleeding risk patients, limited evidence exists to support recommendations—especially with contemporary generation drug-eluting stents—underscoring the need for additional study for this indication.

WHAT THE STUDY ADDS

- Among high bleeding risk patients undergoing percutaneous coronary intervention with Resolute Onyx zotarolimus-eluting stents who were event free before dual antiplatelet therapy discontinuation at 1 month, favorable safety and effectiveness between 1 month and 1 year were demonstrated among patients treated in the United States and Japan, thereby extending the results of the recent Onyx ONE randomized controlled trial.
- Further, as a prespecified analysis of the Onyx ONE US/Japan study and Onyx ONE randomized controlled trial patient cohorts fulfilling one-month clear criteria, the primary end point of cardiac death or myocardial infarction between 1 month and 1 year was met compared with a performance goal derived from prior studies of abbreviated dual antiplatelet therapy duration.

Nonstandard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
CD	cardiac death
DAPT	dual antiplatelet therapy
DCS	drug-coated stent
DES	drug-eluting stent
HBR	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
MI	myocardial infarction
OAC	oral anticoagulant
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
SAPT	single antiplatelet therapy
ST	stent thrombosis
TLR	target lesion revascularization

For patients with high bleeding risk (HBR) undergoing percutaneous coronary intervention (PCI), treatment with drug-eluting stents (DESs) necessitates balancing ischemic and bleeding risks with an appropriate course of dual antiplatelet therapy (DAPT). Current societal guidelines recommend DAPT duration of 3 to ≤6 months for patients with HBR.[1,2] Recent studies have reported the safety of shortened DAPT duration in HBR patients,[3,4] including 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 that demonstrated superiority of a polymer-free drug-coated stent (DCS) compared with a similar bare-metal stent in HBR patients treated with 1-month DAPT.[5] Furthermore, the Onyx ONE randomized controlled trial (RCT) demonstrated similar 1-year rates of ischemic events with the Resolute Onyx zotarolimus-eluting stent (Medtronic, Santa Rosa, CA) and the Biolimus A9 DCS in HBR patients receiving 1-month of DAPT.[6]

Despite treatment guidance endorsing shortened DAPT duration in HBR patients, limited evidence exists to support recommendations—especially with contemporary generation DES—underscoring the need for additional study for this indication. The Onyx ONE US/Japan study was an extension of the Onyx ONE RCT examining clinical outcomes following abbreviated DAPT duration among HBR patients undergoing PCI in the United States and Japan. Both the Onyx ONE RCT and Onyx ONE US/Japan studies share similar inclusion/exclusion criteria, data collection, and end point definitions; in addition, both trials utilized the same angiographic core laboratory, clinical events committee and adjudication process, and Data and Safety Monitoring Board. As a registration trial with Food and Drug Administration oversight, patients treated with Resolute Onyx DES from both studies were pooled in a prespecified analysis to permit a larger sample size with appropriate statistical power, termed the Onyx ONE Clear study. The purpose of the Onyx ONE Clear study was to evaluate the safety and effectiveness of DAPT limited to 1 month following PCI with the Resolute Onyx DES among HBR patients or those considered medically unsuitable for >1-month treatment with DAPT.

METHODS

Study Design and Patient Population

The data, analytic methods, and study materials are owned by the sponsor and will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Onyx ONE Clear was a prospective, multicenter, nonrandomized study designed to evaluate the clinical safety and effectiveness of 1-month DAPT in HBR PCI patients after implantation of Resolute Onyx zotarolimus-eluting stents. Patients were entered into Onyx ONE Clear from 2 sequential

investigations, the Onyx ONE US/Japan study, and the Onyx ONE RCT. In the prospective Onyx ONE US/Japan study, patients were enrolled at 42 centers in the United States and 5 centers in Japan (Table I in the Data Supplement). Patients with similar enrollment criteria treated with the Resolute Onyx DES were included from the Onyx ONE RCT, the design, enrollment criteria, and methods of which have been described previously.[6,7] The study was approved by the institutional review board or ethics committee at each enrolling site, and the study adhered to the principles established in the Declaration of Helsinki. Eligible patients signed written informed consent before the interventional procedure. An independent clinical events committee adjudicated all primary and secondary end points following review of original source documents, and study safety oversight was performed by an independent Data and Safety Monitoring Board.

Patients with ischemic heart disease for whom PCI was planned and with HBR characteristics and inability to take DAPT beyond 1 month (eg, planned noncardiac surgery) were considered for enrollment in the study. HBR criteria are listed in Table 1. Patients were excluded if they required a planned PCI >1 month after the index procedure, a planned surgery or procedure necessitating discontinuation of DAPT within 1 month after the index procedure, or were not expected to comply with long-term single antiplatelet therapy (SAPT). There were no restrictions on lesion complexity. Complete inclusion/exclusion criteria are detailed in Table II in the Data Supplement.

Study Procedures

Before the PCI procedure, all patients received a loading dose of aspirin (250–500 mg), and $P2Y_{12}$ inhibitor pretreatment was administered according to institutional standard practice. DAPT use was mandatory for 1-month post-index procedure or following a staged procedure (performed within 1 month of the initial procedure), if indicated. Requirements for DAPT included 75 to 100 mg aspirin daily and the standard daily dose of a $P2Y_{12}$ inhibitor according to individual product labeling, with 75 mg clopidogrel as the preferred agent. Patients discontinued either aspirin or the $P2Y_{12}$ inhibitor at 1 month and thereafter were continued on SAPT. Whether to discontinue aspirin or the $P2Y_{12}$ inhibitor was according to investigator discretion. Patients treated with oral anticoagulants (OACs) were permitted to receive SAPT plus OAC from the date of the index procedure onward.

Patients were followed post-procedure at 1 month by clinic visit and then at 2 and 6 months and 1 year by telephone/clinic visit with planned follow-up through 2 years.

Study End Points

The primary end point was the composite of cardiac death (CD) or myocardial infarction (MI) between 1 month and 1 year among patients in the one-month clear population. To be considered one-month clear, patients were required to be free of any events in the first month after PCI that would preclude early cessation of DAPT, including MI (but excluding periprocedural MI), repeat coronary revascularization, stroke, definite/probable stent thrombosis (ST), or death. Further, patients were required to be adherent to DAPT for the entire 1-month period, defined as no interruption of aspirin or $P2Y_{12}$ inhibitor for >3 cumulative days during the first month after the index PCI. For the one-month clear analysis, the criteria were extended to 1 month beyond a planned staged procedure when performed. All patients included in the primary analysis received treatment with at least 1 Resolute Onyx DES; patients receiving an alternative, nonstudy stent were not included as part of the primary analysis.

Table 1. HBR Criteria for One-Month Clear Patients

HBR inclusion criteria	Onyx ONE Clear (n=1506)	Onyx ONE US/Japan* (n=601)	Onyx ONE RCT* (n=905)	Difference 95% CI†	*P* value†
Age ≥75 y	59.0% (889/1506)	57.7% (347/601)	59.9% (542/905)	−2.2% (−7.2% to 2.9%)	0.422
Oral anticoagulation to continue after PCI	41.0% (617/1506)	43.3% (260/601)	39.4% (357/905)	3.8% (−1.3% to 8.9%)	0.149
Hgb <11 g/dL (or transfusion within 4 wk before procedure)	14.4% (217/1506)	14.1% (85/601)	14.6% (132/905)	−0.4% (−4.1% to 3.2%)	0.823
Creatinine clearance <40 mL/min	12.5% (188/1506)	11.0% (66/601)	13.5% (122/905)	−2.5% (−5.8% to 0.8%)	0.153
Nonskin cancer diagnosed or treated within 3 y	7.4% (112/1506)	5.7% (34/601)	8.6% (78/905)	−3.0% (−5.6% to −0.4%)	0.035
Planned surgery in next 12 mo requiring interruption of DAPT	6.6% (100/1506)	8.2% (49/601)	5.6% (51/905)	2.5% (−0.1% to 5.2%)	0.058
At least 6 mo noncompliance DAPT	4.2% (64/1506)	3.7% (22/601)	4.6% (42/905)	−1.0% (−3.0% to 1.1%)	0.434
NSAID (other than aspirin) or steroids for ≤30 d after PCI	3.1% (47/1506)	4.8% (29/601)	2.0% (18/905)	2.8% (0.9% to 4.8%)	0.002
Hospital admission for major bleeding in prior 12 mo	2.8% (42/1506)	2.7% (16/601)	2.9% (26/905)	−0.2% (−1.9% to 1.5%)	0.874
Stroke in previous 12 mo	2.6% (39/1506)	2.2% (13/601)	2.9% (26/905)	−0.7% (−2.3% to 0.9%)	0.508
Thrombocytopenia (platelets <100 000/mm^3)	1.7% (26/1506)	2.5% (15/601)	1.2% (11/905)	1.3% (−0.2% to 2.7%)	0.070
Prior intracerebral bleed	1.7% (26/1506)	1.7% (10/601)	1.8% (16/905)	−0.1% (−1.4% to 1.2%)	1.000
Severe chronic liver disease	0.9% (14/1506)	1.2% (7/601)	0.8% (7/905)	0.4% (−0.6% to 1.4%)	0.585

Data represented as percentage (n). DAPT indicates dual antiplatelet therapy; DES, drug-eluting stent; HBR, high bleeding risk; Hgb, hemoglobin; NSAID, nonsteroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; and RCT, randomized controlled trial.

*Patients treated with Resolute Onyx DES who meet one-month clear criteria.

†Differences and 95% CIs provided for comparison of Onyx ONE US/Japan and Onyx ONE RCT cohorts.

Secondary end points were assessed at all follow-up visits and included rates of all-cause death, CD, major adverse cardiac events (defined as death, MI, or clinically driven repeat target lesion revascularization [TLR]), target vessel failure (defined as CD, target vessel MI, or clinically driven repeat target vessel revascularization), target lesion failure (defined as CD, target vessel MI, or TLR), any coronary revascularization procedure, definite/probable ST, stroke, and bleeding. To be consistent with the LEADERS FREE trial,[5] MI was defined according to the Third Universal Definition of Myocardial Infarction.[8] ST and bleeding events were defined according to the Academic Research Consortium and Bleeding Academic Research Consortium (BARC) criteria, respectively.[9,10] Acute device, lesion, and procedural success were also assessed. Lesion success was defined as achievement of <30% residual stenosis and TIMI 3 flow. Device success was defined as lesion success with the assigned study device. Procedure success was defined as lesion success and absence of in-hospital major adverse cardiac events.

Statistical Analysis

The primary analyses were conducted in the prespecified one-month clear population of patients pooled from the Onyx ONE US/Japan study and Onyx ONE RCT who were treated with Resolute Onyx DES. For the primary end point, a performance goal was established based on a clinically acceptable margin added to an observed composite event rate of CD or MI at 12 months derived from previous studies of abbreviated DAPT duration in HBR patients.[3–5] Following adjustment for exclusion of events from these studies within the first month, the expected CD or MI rate between 1 month and 1 year was estimated to be 6.8%. Addition of a clinically acceptable margin of 2.9% resulted in a performance goal of 9.7%. Assuming a 1-sided α-level of 0.025 and a true event rate of 6.8%, an effective sample size of 1360 patients provided >97% power. Assuming a 20% attrition rate, a total sample size of 1700 patients was required.

Categorical data are reported as percentages (counts/number of evaluable patients) and were compared between United States/Japan and RCT cohorts with the use of Fisher exact test. Continuous data are reported as means±SDs and were tested between groups using 2-sample *t* test. Cumulative incidence curves with Kaplan-Meier rate estimates were generated. To assess the potential impact of missing data, sensitivity analyses were conducted to assess outcomes in best- and worst-case scenarios. Analyses for poolability of the primary end point by region and study were also performed. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC).

RESULTS

From October 2018 to April 2019, a total of 752 patients were enrolled at 47 centers in the United States and Japan, and 751 were included in the 1-year Onyx ONE US/Japan analysis population due to protocol-defined analysis specifications (Figure 1). In the Onyx ONE RCT, 1018 patients were treated with Resolute Onyx DES and consented to be included in the analysis. Of these 1769 patients, 1506 (85.1%) fulfilled the one-month clear criteria with 99% evaluable for the primary end point analysis at 1 year. Differences in baseline and HBR characteristics between patients who did and did not meet one-month clear criteria are shown in Table III in the Data Supplement.

In the Onyx ONE Clear study population, the mean age was 74.0±9.5 years, and nearly one-third (32.3%) of patients were women (Table 2). Overall, the prevalence of diabetes was 39.4%; 26.3% had prior MI, and 35.6% had a history of atrial fibrillation. Approximately one-half of patients (48.6%) presented with an acute

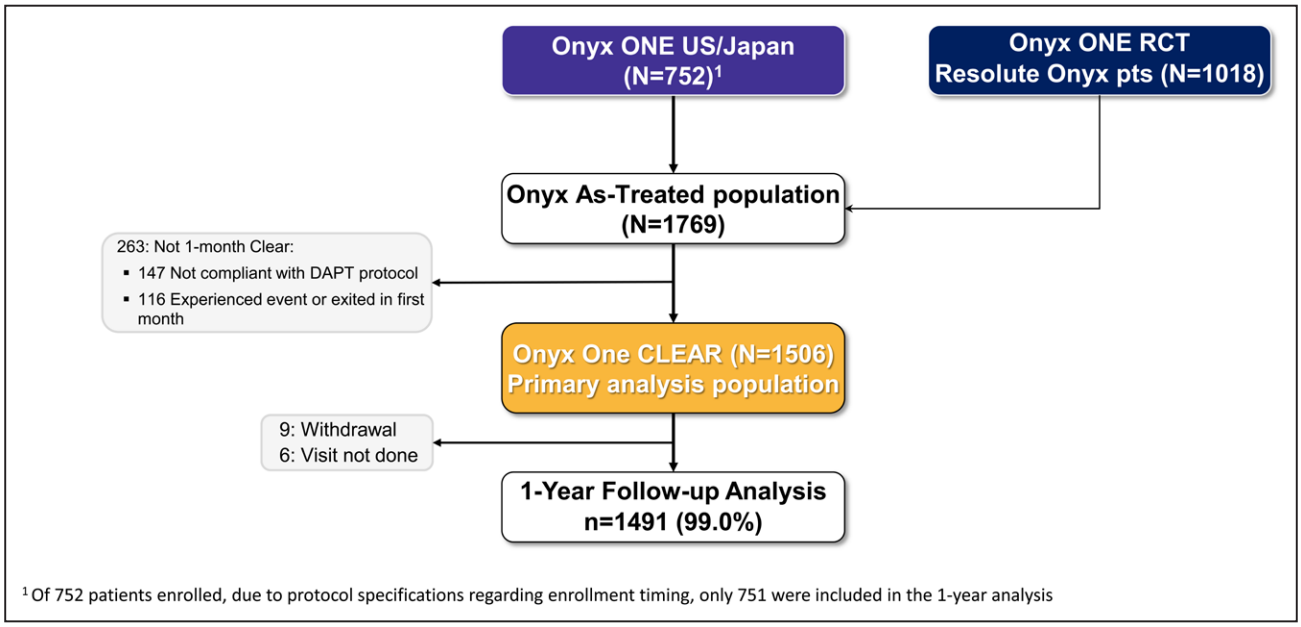

Figure 1. Patient flowchart.
DAPT indicates dual antiplatelet therapy; pts, patients; and RCT, randomized clinical trial.

Table 2. Baseline Clinical Characteristics

Patient characteristics	Onyx ONE Clear (n=1506)	Onyx ONE US/ Japan* (n=601)	Onyx ONE RCT* (n=905)	Difference 95% CI†	*P* value†
Age, y	74.0±9.5	74.2±9.5	73.8±9.6	0.4 (−0.6 to 1.4)	0.407
Women	32.3% (487/1506)	32.6% (196/601)	32.2% (291/905)	0.5% (−4.4% to 5.3%)	0.866
Body mass index, kg/m²	28.2±5.7	29.7±6.5	27.1±4.9	2.6 (2.0 to 3.2)	<0.001
Race and ethnicity					
White	NA‡	82.4% (495)	NA‡	…	…
Black/African American	NA‡	7.8% (47)	NA‡	…	…
Asian	NA‡	7.3% (44)	NA‡	…	…
Hispanic or Latino	NA‡	3.5% (21)	NA‡	…	…
Other/unknown	NA‡	2.5% (15)	NA‡	…	…
Diabetes	39.4% (593/1506)	42.6% (256/601)	37.2% (337/905)	5.4% (0.3% to 10.4%)	0.041
Insulin treated	13.7% (206/1506)	17.6% (106/601)	11.0% (100/905)	6.6% (2.9% to 10.3%)	<0.001
Hypertension	84.0% (1265/1506)	90.0% (541/601)	80.0% (724/905)	10.0% (6.5% to 13.6%)	<0.001
Hyperlipidemia	72.4% (1091/1506)	84.5% (508/601)	64.4% (583/905)	20.1% (15.9% to 24.4%)	<0.001
Current smoker	9.4% (141/1498)	9.3% (56/601)	9.5% (85/897)	−0.2% (−3.2% to 2.9%)	1.000
Previous MI	26.3% (396/1506)	26.8% (161/601)	26.0% (235/905)	0.8% (−3.7% to 5.4%)	0.720
Previous coronary revascularization	36.2% (545/1506)	49.1% (295/601)	27.6% (250/905)	21.5% (16.5% to 26.4%)	<0.001
Previous stroke or transient ischemic attack	14.1% (212/1506)	16.1% (97/601)	12.7% (115/905)	3.4% (−0.2% to 7.1%)	0.069
Peripheral vascular disease	10.6% (160/1506)	11.0% (66/601)	10.4% (94/905)	0.6% (−2.6% to 3.8%)	0.733
Atrial fibrillation	35.6% (536/1506)	38.9% (234/601)	33.4% (302/905)	5.6% (0.6% to 10.5%)	0.028
Left ventricular ejection fraction ≤35%	12.8% (144/1123)	14.5% (68/468)	11.6% (76/655)	2.9% (−1.1% to 7.0%)	0.149
Silent ischemia	10.8% (156/1441)	12.8% (73/571)	9.5% (83/870)	3.2% (−0.1% to 6.6%)	0.057
Chronic coronary syndrome	40.5% (584/1441)	42.7% (244/571)	39.1% (340/870)	3.7% (−1.5% to 8.8%)	0.171
Acute coronary syndrome	48.6% (701/1441)	44.5% (254/571)	51.4% (447/870)	−6.9% (−12.2% to −1.6%)	0.011
Unstable angina	22.8% (328/1441)	27.5% (157/571)	19.7% (171/870)	7.8% (3.3% to 12.4%)	<0.001
NSTEMI	21.7% (313/1441)	15.2% (87/571)	26.0% (226/870)	−10.7% (−14.9% to −6.6%)	<0.001
STEMI	4.2% (60/1441)	1.8% (10/571)	5.7% (50/870)	−4.0% (−5.9% to −2.1%)	<0.001

Data represented as percentage (n) or mean±SD. DES indicates drug-eluting stent; MI, myocardial infarction; NA, not available; NSTEMI, non–ST-segment–elevation myocardial infarction; RCT, randomized controlled trial; and STEMI, ST-segment–elevation myocardial infarction.

*Patients treated with Resolute Onyx DES who meet one-month clear criteria.

†Differences and 95% CIs provided for comparison of Onyx ONE US/Japan and Onyx ONE RCT cohorts.

‡Race was not collected in Onyx ONE RCT.

coronary syndrome with one-quarter of all patients presenting with MI.

The most common HBR feature fulfilling enrollment criteria was age ≥75 years (59.0%); 44.7% of the study population had multiple bleeding risk characteristics (Table 1). Forty-one percent of patients were prescribed OAC following the procedure, 14.4% had anemia or transfusion before procedure, and 12.5% had a creatinine clearance <40 mL/min. The frequency and distribution of HBR criteria were the same between the Onyx ONE US/Japan and Onyx ONE RCT cohorts (mean HBR characteristics/patient, 1.6 in each study; Table 1).

Overall, the mean (±SD) number of lesions treated per patient was 1.3±0.6, and ≈20% of patients underwent multivessel revascularization. The mean number of stents per patient was 1.7±1.0, and average stent length per patient was 36.9±26.3 mm. By angiographic core laboratory analysis, 78.6% of lesions were identified as class B2/C with 50.0% having moderate/severe calcification (Table IV in the Data Supplement). The prevalence of radial artery access was 65.8% overall, despite observed differences between the Onyx ONE US/Japan and RCT cohorts (51.7% versus 75.3%, respectively; *P*<0.001). The rates of lesion success, device success, and procedural success were 94.6%, 93.3%, and 88.5%, respectively.

At 2-month follow-up (as confirmation of DAPT discontinuation at 1 month), 96.9% of patients were adherent with SAPT alone or with OAC (Figure 2). Approximately three-quarters of patients receiving OAC were treated with 1-month DAPT. At 1 year, 89.3% of patients were adherent to SAPT with ≈60% of patients taking aspirin monotherapy and the remainder taking a $P2Y_{12}$ antagonist. Treatment with SAPT and OAC at 1 year was 34.5%, and only 6.5% of patients were prescribed DAPT.

The primary end point of CD or MI from 1 month to 1 year was met with a rate of 7.0% compared with the

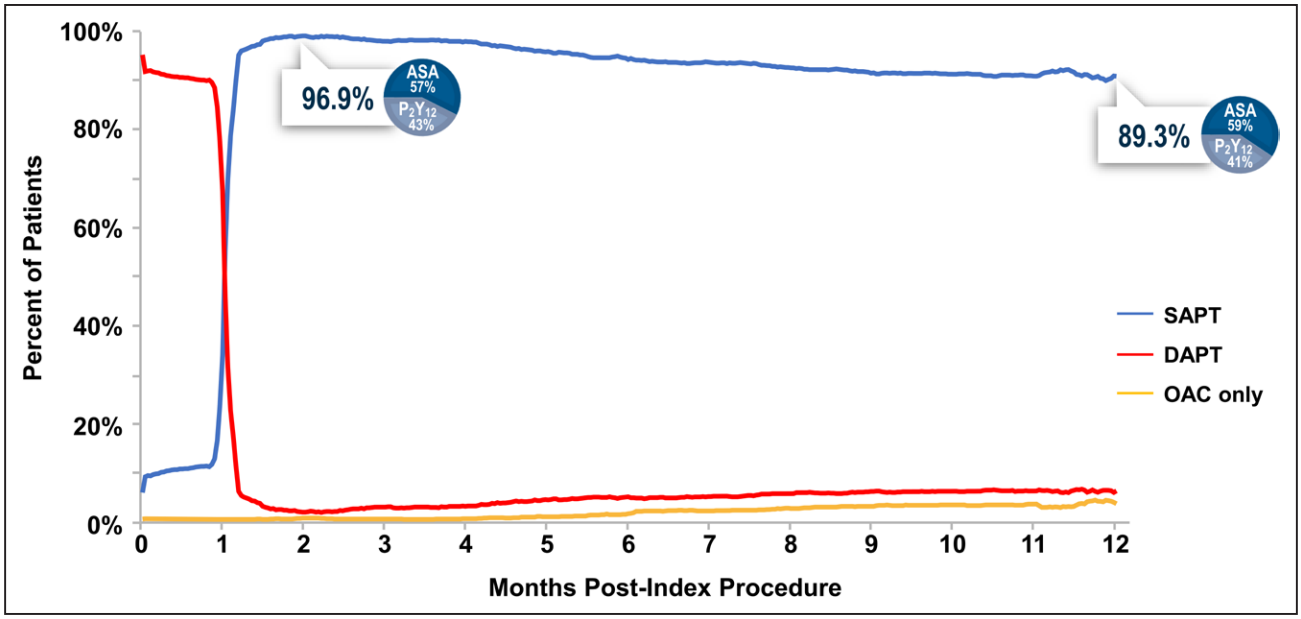

Figure 2. Antithrombotic therapy.
DAPT indicates dual antiplatelet therapy; OAC, oral anticoagulation therapy; and SAPT, single antiplatelet therapy.

performance goal of 9.7% ([1-sided upper 97.5% CI, 8.4%] $P<0.001$; Table 3). Kaplan-Meier analyses demonstrated similar rates of CD or MI for the overall Onyx ONE Clear, Onyx ONE US/Japan, and Onyx ONE RCT cohorts (Figure 3). Sensitivity analyses for patients with missing data provided consistent results. Between 1 to 6 months, the rate of CD or MI was 3.7% in the overall population, and through 1 year, it occurred in 6.9% and 7.1% of patients in the Onyx ONE RCT and the ONE US/Japan study, respectively ($P=0.92$). Regarding component end points, CD was significantly higher in the Onyx ONE RCT than in Onyx ONE US/Japan (3.5% versus 1.3%; $P=0.012$), but rates of MI did not statistically differ (4.0% versus 6.1%, respectively; $P=0.084$). However, analyses of the poolability by study and by region demonstrated consistency between studies (Table V in the Data Supplement) and between regions (Table VI in the Data Supplement) despite some differences in the baseline characteristics.

Secondary end points measured from 1 month to 1 year included TLR (3.4%), death (6.0%), target lesion failure (8.1%), and Academic Research Consortium definite/probable ST (0.7%; Table 3). Clinically driven target vessel revascularization, but not TLR, was significantly higher in Onyx ONE US/Japan patients compared with Onyx ONE RCT patients. Rates of bleeding were 13.1% for BARC 1 to 5, 11.7% for BARC 2 to 5, and 4.0% for BARC 3 to 5. The rates of bleeding according to BARC criteria types 3 through 5 were higher in Onyx ONE US/Japan patients compared with Onyx ONE RCT patients (6.6% versus 2.3%; $P<0.001$).

Prespecified subgroup comparisons revealed differences in rates of CD or MI at 1 year among several baseline and procedural characteristics (Figure 4). For example, higher rates of the primary composite end point were observed in patients presenting with acute coronary syndromes and in those with comorbidities (eg, diabetes and renal failure) or greater lesion complexity/stent length.

DISCUSSION

Among HBR patients undergoing PCI with Resolute Onyx zotarolimus-eluting stents who were event free before DAPT discontinuation at 1 month, favorable safety and effectiveness through 1 year were demonstrated among patients treated in the United States and Japan, thereby extending the results of the recent Onyx ONE RCT. Further, as a prespecified analysis of the Onyx ONE US/Japan study and Onyx ONE RCT patient cohorts fulfilling one-month clear criteria, the composite rate of CD or MI between 1 month and 1 year was less than a prespecified performance goal derived from prior studies of abbreviated DAPT duration, meeting the primary end point of the study. Based on the evidence from the pooled Onyx ONE Clear analysis, treatment with Resolute Onyx DES may be considered a safe and effective strategy as part of an individualized approach to shortened DAPT duration in select patients undergoing PCI.

The Onyx ONE Clear study was designed in parallel with the Onyx ONE RCT[6] to broaden the study population to both the United States and Japan and amplify the number of HBR patients treated with 1-month DAPT following PCI with durable polymer Resolute Onyx zotarolimus-eluting stents by combining patients in the US/Japan cohort with Onyx patients from Onyx ONE

Table 3. Clinical Outcomes Between 1 mo and 1 y in One-Month Clear Patients

	Onyx ONE Clear (n=1506)	Onyx ONE US/Japan* (n=601)	Onyx ONE RCT* (n=905)	Difference, 95% CI†	*P* value†
Primary end point: CD or MI	7.0% (104/1491)	7.1% (42/595)	6.9% (62/896)	0.1% (−2.5% to 2.8%)	0.918
CD, MI, or definite/probable ST	7.0% (104/1491)	7.1% (42/595)	6.9% (62/896)	0.1% (−2.5% to 2.8%)	0.918
CD or TV MI	6.5% (97/1491)	6.6% (39/595)	6.5% (58/896)	0.1% (−2.5% to 2.6%)	1.000
Death or TV MI	9.7% (144/1491)	9.6% (57/595)	9.7% (87/896)	−0.1% (−3.2% to 2.9%)	1.000
Death	6.0% (89/1491)	4.5% (27/595)	6.9% (62/896)	−2.4% (−4.7% to −0.0%)	0.059
CD	2.6% (39/1491)	1.3% (8/595)	3.5% (31/896)	−2.1% (−3.6% to −0.6%)	0.012
Non-CD	3.4% (50/1491)	3.2% (19/595)	3.5% (31/896)	−0.3% (−2.1% to 1.6%)	0.883
Target lesion failure	8.1% (121/1491)	8.7% (52/595)	7.7% (69/896)	1.0% (−1.8% to 3.9%)	0.498
Target vessel failure	8.8% (131/1491)	9.9% (59/595)	8.0% (72/896)	1.9% (−1.1% to 4.9%)	0.225
MACE	11.7% (174/1491)	12.3% (73/595)	11.3% (101/896)	1.0% (−2.4% to 4.3%)	0.565
MI	4.8% (72/1491)	6.1% (36/595)	4.0% (36/896)	2.0% (−0.3% to 4.3%)	0.084
TV MI	4.4% (65/1491)	5.5% (33/595)	3.6% (32/896)	2.0% (−0.2% to 4.2%)	0.071
Clinically driven TLR	3.4% (50/1491)	4.2% (25/595)	2.8% (25/896)	1.4% (−0.5% to 3.4%)	0.144
Clinically driven TVR	4.3% (64/1491)	5.7% (34/595)	3.3% (30/896)	2.4% (0.2% to 4.6%)	0.036
ST, ARC definite/probable	0.7% (10/1491)	0.8% (5/595)	0.6% (5/896)	0.3% (−0.6% to 1.2%)	0.532
Definite ST	0.7% (10/1491)	0.8% (5/595)	0.6% (5/896)	0.3% (−0.6% to 1.2%)	0.532
Probable ST	0.0% (0/1491)	0.0% (0/595)	0.0% (0/896)	NA	NA
Stroke	1.5% (22/1491)	1.3% (8/595)	1.6% (14/896)	−0.2% (−1.4% to 1.0%)	0.829
Bleeding					
BARC 1–5	13.1% (195/1491)	18.7% (111/595)	9.4% (84/896)	9.3% (5.6% to 12.9%)	<0.001
BARC 2–5	11.7% (175/1491)	16.8% (100/595)	8.4% (75/896)	4.2% (2.0% to 6.4%)	<0.001
BARC 3–5	4.0% (60/1491)	6.6% (39/595)	2.3% (21/896)	8.4% (4.9% to 11.9%)	<0.001

Data represented as percentage (n) or mean±SD. ARC indicates Academic Research Consortium; BARC, Bleeding Academic Research Consortium; CD, cardiac death; DES, drug-eluting stent; MACE, major adverse clinical event; MI, myocardial infarction; NA, not available; RCT, randomized controlled trial; ST, stent thrombosis; TLR, target lesion revascularization; TV MI, target vessel-related myocardial infarction; and TVR, target vessel revascularization.

*Patients treated with Resolute Onyx DES who meet one-month clear criteria.

†Differences and 95% CIs provided for comparison of Onyx ONE US/Japan and Onyx ONE RCT cohorts.

RCT. The study was designed as a single-arm trial given the infrequent use of bare-metal stents and absence of a comparator DES with approval of a 1-month DAPT indication in both geographies. Nevertheless, both Onyx ONE RCT and Onyx ONE US/Japan shared similar enrollment criteria and end point definitions, in addition to methods of data assessment, adjudication, and oversight. As two related but independent studies, differences in both the study populations and clinical events were expected. However, the intent was not to compare studies but to instead establish a population of >1500 patients with similar HBR criteria that would provide adequate power to evaluate the clinical safety and effectiveness of this specific DES with a 1-month DAPT regimen. Analyses of the primary end point demonstrated consistency across studies and regions, supporting the poolability of the study cohorts and in turn the broad applicability of our findings across the enrolled geographies and patient populations.

Patients with HBR are estimated to represent nearly one-third of those encountered in clinical practice[11,12]; yet until recently, they have been systematically excluded from DES trials. A commonly overlooked reality is that conditions increasing bleeding risk rarely exist in isolation, often coexisting with comorbidities and angiographic complexity denoting high ischemic risk. A strength of the present study is that patients were representative of those treated in a real-world setting with nearly half having multiple bleeding risk criteria along with significant coexisting cardiovascular risk (≈40% diabetes) and undergoing PCI for both high-risk clinical indications (≈50% presenting with acute coronary syndromes) and complex lesion anatomy. Nevertheless, despite the high-risk profile of the study population, transition to SAPT occurred in 97% of patients event free at 1 month and was maintained in ≈90% of individuals at 1 year.

The present study is important when considered in context with the results from prior investigations suggesting that bleeding risk, more than ischemic risk, often determines clinical decision-making regarding DAPT duration.[13,14] Notably, despite limiting DAPT use to 1 month following PCI, bleeding events were still relatively common between 1 month and 1 year, demonstrating both the appropriateness of the inclusion criteria and study population regarding hemorrhagic risk. Alternatively, the results of the present study challenge prior

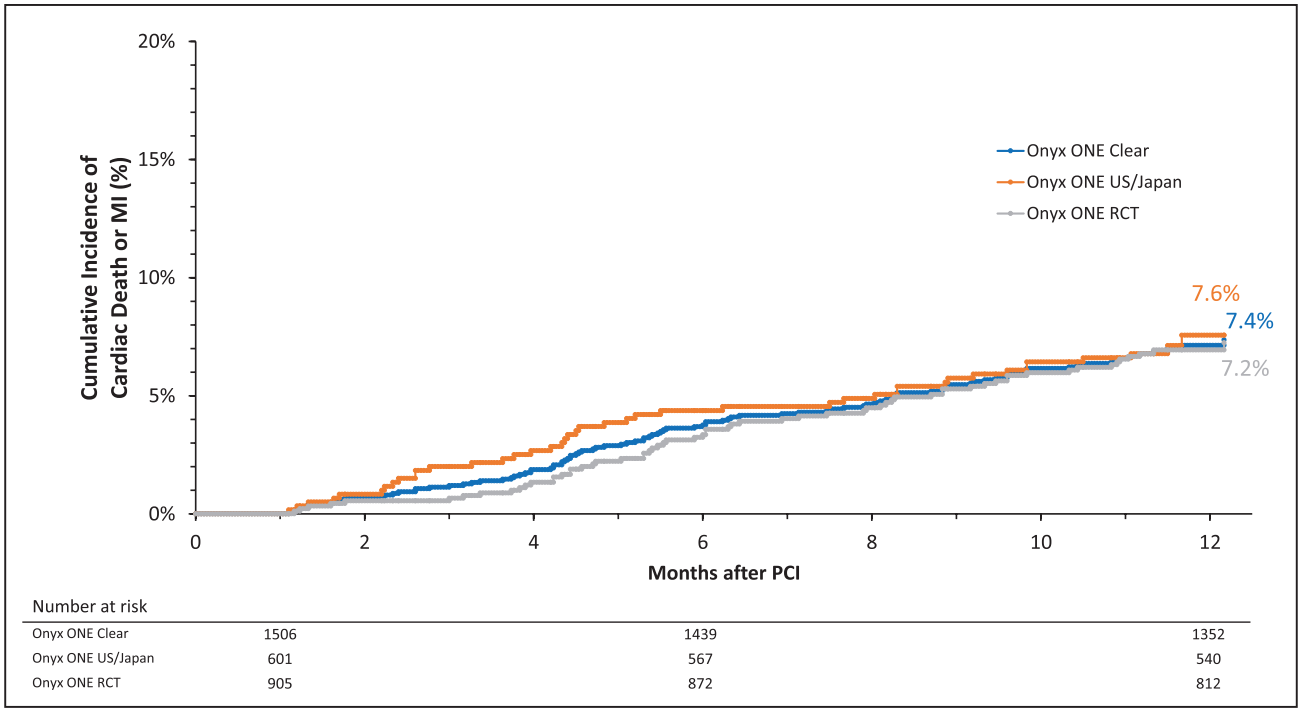

Figure 3. Kaplan-Meier rates of cardiac death or myocardial infarction (MI) for patients in Onyx ONE Clear, Onyx ONE US/Japan, and Onyx ONE randomized controlled trial (RCT) study populations.
The Onyx ONE Clear population is comprised of the one-month clear populations from Onyx ONE RCT and Onyx ONE US/Japan. PCI indicates percutaneous coronary intervention.

observations that bleeding and ischemic risk parallel one another.[3,15] Specifically, among prior studies including HBR patients, not only were actionable bleeding events more common but occurrence of ischemic events was also of similar higher relative risk. In the present study among HBR patients without ischemic events in the first month following PCI, however, the 1-year rate of late ST occurred in <1% of patients, not substantially different than seen in other contemporary DES studies inclusive of broad, less selective patient populations.[16] In total, the rate of MI was <5%, and clustering of ischemic events within the early period following transition to SAPT at 1 month was not apparent. Further, the 1-year rate of CD or MI in the US/Japan study is similar to that observed in landmarked analyses over the same time interval for both the Resolute Onyx DES and polymer-free BioFreedom DCS in the Onyx ONE RCT,[6] and the late ST rate is comparable to that observed with DCS in the LEADERS FREE II study.[17] The favorably low rate of clinically driven TLR (3.4% at 1 year) is also relevant given that in the prior randomized comparison of DCS and BMS in an HBR population, the benefit of DCS was principally driven by a significant reduction in TLR and a lower rate of MI, adjudicated equally as both spontaneous and restenosis related.[5]

Recognizing that societal guidelines are reduced to providing treatment options for this unique but commonly encountered patient population based on both opinion and limited evidence, the Onyx ONE Clear study provides important data to inform treatment decisions for patients commonly encountered in clinical practice yet underrepresented by evidence-based medicine. Applying a practical assessment of bleeding risk, the study introduces a method by which practitioners might tailor both antithrombotic and stent therapy based on individual assessment of risk and benefit. Notably, the HBR criteria in the present study were more inclusive than in prior studies examining 1-month DAPT duration following DES revascularization.[4,18] Also, unlike prior studies that inform antiplatelet therapy prescription (but not stent selection) and are inclusive of patients free of ischemic and bleeding events for durations >1 month,[19,20] the Onyx ONE Clear study addressed the other, less predictable end of the spectrum related to stent and DAPT decision-making at the time of revascularization. Notably in regard to DES selection, although European guidelines address 1-month DAPT following DES for selected patients with HBR, this recommendation (IIb level C) is based on 2 studies with DES that are either no longer manufactured or have limited commercial availability.[2]

Limitations

Onyx ONE Clear was a single-arm study investigating a selected patient population free of events that would preclude DAPT discontinuation at 1 month. Whether these results may be extended to the ≈15% of patients

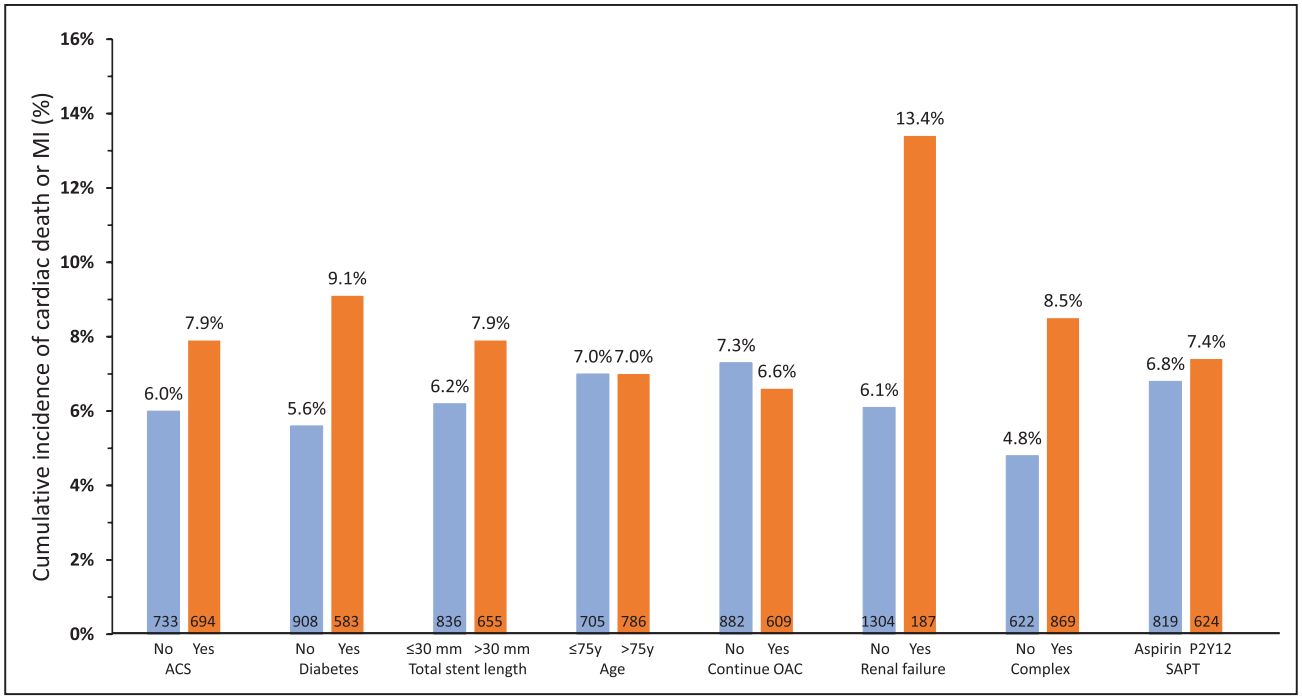

Figure 4. One-year cardiac death or myocardial infarction (MI) according to prespecified subgroups.
ACS indicates acute coronary syndrome; OAC, oral anticoagulation; and SAPT, single antiplatelet therapy.

experiencing an ischemic event or unable to adhere to the DAPT protocol within 1 month of revascularization is unknown. Second, previous limited, nonrandomized data in patients treated with the Resolute Onyx DES suggested a low risk of ischemic events with DAPT interruption following periods as brief as 1 month post-revascularization.[21] The present large-scale study thus confirms the safety and effectiveness of this stent for this application. Whether similar safety and effectiveness in like patients can be extended to other commercially available DES is uncertain. Third, the study was not powered for assessment of low-frequency events, such as ST. Fourth, future studies are warranted to assess the implications of the use of aspirin or $P2Y_{12}$ inhibitor monotherapy after 1 month in this study. Fifth, because ascertainment of patient race and ethnicity was limited to the United States and Japan, additional study regarding the safety and effectiveness of 1-month DAPT across different races and ethnicities is needed. Finally, the consideration of DAPT duration post-PCI relies on an individualized balance between ischemic and bleeding risk, and clinical decision-making should be performed in the context of both these study results and patient-specific characteristics. Whether the balance of ischemic and bleeding outcomes in HBR patients would be improved by DAPT durations >1 month was also not evaluated. The present study results, therefore, do not indicate that all patients with characteristics that forecast bleeding complications or early discontinuation should be limited to 1-month DAPT but instead demonstrate the safety and effectiveness of this strategy when clinically appropriate.

Conclusions

Among patients with HBR characteristics or inability to take extended DAPT following PCI with Resolute Onyx zotarolimus-eluting stents and who were event free before DAPT discontinuation at 1 month, favorable safety and effectiveness between 1 month and 1 year were demonstrated among patients treated in the United States and Japan. These results, combined in a prespecified analysis with patients from Onyx ONE RCT fulfilling one-month clear criteria, demonstrated a 1-year CD or MI rate of 7.0%, thereby meeting the primary end point compared with a performance goal derived from prior studies of abbreviated DAPT duration. Based on the evidence from the pooled Onyx ONE Clear analysis, treatment with Resolute Onyx DES may be considered a safe and effective strategy as part of an individualized approach to shortened DAPT duration following PCI.

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