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ORIGINAL RESEARCH

Safety of 3-Month Dual Antiplatelet Therapy After Implantation of Ultrathin Sirolimus-Eluting Stents With Biodegradable Polymer (Orsiro): Results From the SMART-CHOICE Trial

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BACKGROUND: This study sought to investigate the safety of 3-month dual antiplatelet therapy (DAPT) in patients receiving ultrathin sirolimus-eluting stents with biodegradable polymer (Orsiro).

METHODS AND RESULTS: The SMART-CHOICE (Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Anti- platelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents) randomized trial compared 3-month DAPT followed by P2Y12 inhibitor monotherapy with 12-month DAPT in 2993 patients undergoing percutaneous coronary intervention. The present analysis was a prespecified subgroup analysis for patients receiving Orsiro stents. As a post hoc analysis, comparisons between Orsiro and everolimus-eluting stents were also done among patients receiving 3-month DAPT. Of 972 patients receiving Orsiro stents, 481 patients were randomly assigned to 3-month DAPT and 491 to 12-month DAPT. At 12 months, the target vessel failure, defined as a composite of cardiac death, target vessel–related myocardial infarction, or target vessel revascularization, occurred in 8 patients (1.7%) in the 3-month DAPT group and in 14 patients (2.9%) in the 12-month DAPT group (hazard ratio [HR], 0.58; 95% CI, 0.24–1.39; *P*=0.22). In whole population who were randomly assigned to receive 3-month DAPT (n=1495), there was no significant difference in the target vessel failure between the Orsiro group and the everolimus-eluting stent group (n=1014) (1.7% versus 1.8%; HR, 0.96; 95% CI, 0.41–2.22; *P*=0.92).

CONCLUSIONS: In patients receiving Orsiro stents, clinical outcomes at 1 year were similar between the 3-month DAPT followed by P2Y12 inhibitor monotherapy and 12-month DAPT strategies. With 3-month DAPT, there was no significant difference in target vessel failure between Orsiro and everolimus-eluting stents.

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Key Words: antiplatelet therapy ■ coronary artery disease ■ percutaneous coronary intervention

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CLINICAL PERSPECTIVE

What Is New?

- Orsiro stents are effective and safe for 3-month dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy.

What Are the Clinical Implications?

- Among patients at high bleeding risk requiring percutaneous coronary intervention, Orsiro stents may be considered in conjunction with a short-term dual antiplatelet therapy.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
DES	drug-eluting stent
EES	everolimus-eluting stent

Polymer is the key component of drug-eluting stents (DESs) for facilitation of drug loading and control of drug release.[1] However, durable polymer of the first-generation DESs has been considered to induce inflammation and to be associated with fatal complications such as late stent thrombosis.[2] To overcome this shortcoming, biodegradable polymer has been applied to the DES system. Early biodegradable polymer DES with thick (120 μm) stainless steel struts demonstrated a reduced risk of very late stent thrombosis compared with the durable polymer sirolimus-eluting Cypher stent (Cordis/Johnson & Johnson, Warren, NJ)[3,4] and comparable efficacy and safety compared with cobalt-chromium everolimus-eluting stents.[5,6] However, in network meta-analyses, early biodegradable polymer DESs were associated with a higher risk of definite stent thrombosis than cobalt-chromium everolimus-eluting stents,[7,8] which might be attributable to thick struts.

The Orsiro stent (Biotronik, Bülach, Switzerland) is a cobalt-chromium biodegradable polymer sirolimus-eluting stent. Its thinness may promote strut coverage and passive coating may prevent detrimental interaction between the metal stent and the surrounding tissue. In several head-to-head comparisons, Orsiro stents demonstrated comparable[9] or superior[10,11] outcomes compared with durable polymer everolimus-eluting stents (EESs). However, data are limited regarding the safety of short duration of dual antiplatelet therapy (DAPT) after implantation of Orsiro stents. Therefore, this study sought to investigate the safety of 3-month DAPT followed by P2Y12 inhibitor monotherapy in patients receiving the Orsiro stents. As a prespecified analysis of the SMART-CHOICE (Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Anti- platelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents) randomized trial,[12] 3-month DAPT was compared with 12-month DAPT among patients receiving Orsiro stents. In addition, the outcomes of Orsiro stent were compared with those of EES among whole patients receiving 3-month DAPT in the SMART-CHOICE trial.

METHODS

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

Study Population

The SMART-CHOICE trial is briefly described in Data S1. Patients were randomly assigned to 3-month DAPT followed by P2Y12 inhibitor monotherapy (aspirin plus P2Y12 inhibitor for 3 months and thereafter P2Y12 inhibitor alone) or 12-month DAPT (aspirin plus P2Y12 inhibitor for at least 12 months). Randomization was performed with a web-based response system in blocks of 4 and was stratified by clinical presentation (stable ischemic heart disease or acute coronary syndrome), enrolling center, type of P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor), and type of stent used. To minimize the bias from different stent devices, the stents used are limited to cobalt-chromium everolimus-eluting Xience stents (Abbott Vascular, Santa Clara, CA, USA), platinum-chromium everolimus eluting Promus/Synergy stents (Boston Scientific, Marlborough, MA), and sirolimus-eluting Orsiro stents with biodegradable polymer. For each patient, all lesions had to be treated with the identical type of stent. The SMART-CHOICE trial was approved by the institutional review board of each participating institution, and written consent was obtained from all patients.

Procedures

Percutaneous coronary intervention (PCI) was conducted according to standard techniques. Detailed procedures are provided in Data S1. After the index procedure, patients received DAPT with aspirin 100 mg once daily plus clopidogrel 75 mg once daily or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily for 3 months in both groups. The administration of aspirin was stopped at 3 months after the index procedure in the 3-month DAPT group but was continued in the 12-month DAPT group. A P2Y12 inhibitor was prescribed continuously in both groups.

Clinical follow-up was performed at 3, 6, and 12 months after index PCI. At follow-up, data about patients' clinical status, all interventions received, outcome events, and adverse events were recorded. In particular, information on the use of aspirin or a P2Y12 inhibitor was carefully assessed at each follow-up.

End Points

The primary end point was the target vessel failure, defined as a composite of cardiac death, target vessel–related myocardial infarction, or target vessel revascularization at 12 months after the index PCI. Secondary end points included the individual component of the primary end point, all-cause death, any myocardial infarction, repeated revascularization, stent thrombosis, stroke, Bleeding Academic Research Consortium types 2 to 5, and combinations of these end points at 12 months after the index PCI. Major adverse cardiac and cerebrovascular event was defined as a composite of all-cause death, myocardial infarction, or stroke; net adverse clinical event, a composite of all-cause death, any myocardial infarction, stroke, or major bleeding. The definition of each end point is provided in Data S1

Statistical Analysis

The formal power calculation was not done for the present subgroup analyses of the SMART-CHOICE trial. The primary and secondary end points were primarily analyzed by an intention-to-treat principle that included all randomized patients receiving Orsiro stents according to the allocation. Patients who were lost to follow-up were censored at the time of the last known contact. Cumulative event rates were estimated with the Kaplan–Meier method, and Cox regression analysis was performed to compare clinical outcomes between the 3-month and 12-month DAPT groups. In addition, post hoc analyses were performed to compare clinical events between Orsiro stents and EESs (Xience and Promus/Synergy) among patients randomly allocated to the 3-month DAPT. Because stents were not randomized but were chosen by operators, baseline characteristics were adjusted using propensity-score matching and inverse-probability weighted analyses. Details regarding statistical analysis are provided in Data S1. All tests were 2-sided, and a $P<0.05$ was considered statistically significant. Statistical analysis was performed using SAS 9.2 (SAS Institute, Cary, NC) or STATA 16.0 (StataCorp LLC, College Station, TX).

RESULTS

From March 18, 2014, to July 7, 2017, a total of 2993 patients were enrolled. Of these, 972 patients received Orsiro stents; 481 patients were randomly assigned to 3-month DAPT and 491 to 12-month DAPT. Figure 1 demonstrates participants' flow in the present study. Table 1 represents baseline clinical, angiographic, and procedural characteristics according

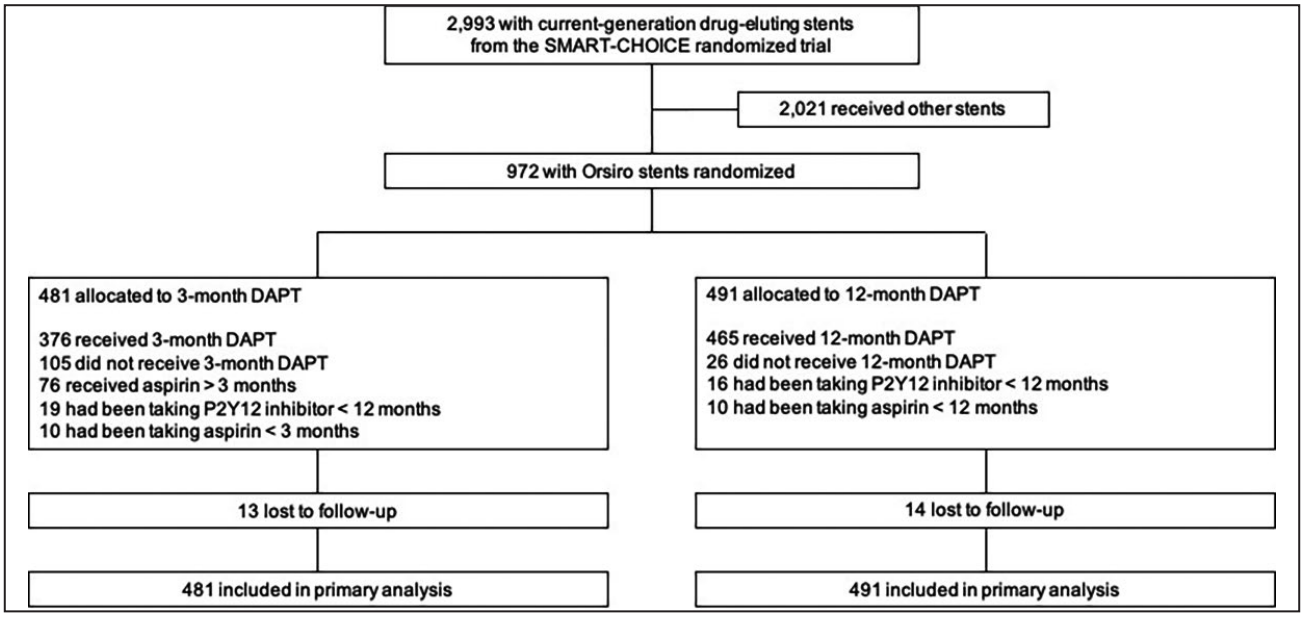

Figure 1. Participants' flow.
DAPT indicates dual antiplatelet therapy.

Table 1. Baseline Characteristics

	Dual Antiplatelet Therapy		*P* Value
	3 mo (n=481)	12 mo (n=491)	
Age, y	65.1±10.7	65.3±10.3	0.71
Male	347 (72.1)	360 (73.3)	0.68
Diabetes mellitus	194 (40.3)	190 (38.7)	0.60
Hypertension	294 (61.1)	314 (64.0)	0.36
Dyslipidemia	211 (43.9)	218 (44.4)	0.87
Current smoking	121 (25.2)	116 (23.6)	0.58
Previous myocardial infarction	26 (5.4)	25 (5.1)	0.83
Previous coronary artery bypass graft surgery	6 (1.3)	5 (1.0)	0.74
Previous revascularization	58 (12.1)	67 (13.7)	0.46
Chronic renal failure	15 (3.1)	16 (3.3)	0.90
Left ventricular ejection fraction (%)	60.0±10.6	59.8±11.1	0.80
Clinical presentation			0.38
Stable angina	227 (47.2)	229 (46.6)	
Unstable angina	126 (26.2)	150 (30.6)	
Non–ST-segment elevation myocardial infarction	86 (17.9)	76 (15.5)	
ST-segment elevation myocardial infarction	42 (8.7)	36 (7.3)	
Multiple-vessel disease	233 (48.4)	233 (47.5)	0.76
Location of lesion treated			
Left main	5 (1.0)	8 (1.6)	0.42
Left anterior descending artery	295 (61.3)	295 (60.1)	0.69
Left circumflex	128 (26.6)	129 (26.3)	0.90
Right coronary artery	176 (36.6)	171 (34.8)	0.57
Lesion complexity			
Calcified lesion	89 (18.5)	90 (18.3)	0.94
Bifurcation lesion	60 (12.5)	61 (12.4)	0.98
Thrombotic lesion	34 (7.1)	33 (6.7)	0.83
Use of intravascular ultrasound	91 (18.9)	110 (22.4)	0.18
Treated lesions per patient	1.4±0.7	1.3±0.6	0.14
Multilesion intervention	150 (31.2)	143 (29.1)	0.48
Multivessel intervention	114 (23.7)	111 (22.6)	0.69
Number of stents per patient	1.5±0.8	1.4±0.7	0.12
Mean stent diameter per patient, mm	3.0±0.4	3.0±0.4	0.91
Total stent length per patient, mm	38.5±22.8	35.9±21.1	0.07

Data are n (%) or means±SD.

to the intention-to-treat analysis in patients receiving Orsiro stents. Although there was no significant difference between the 3-month and 12-month DAPT groups, the mean stent length tended to be longer in the 3-month DAPT group than in the 12-month DAPT group (38.5±22.8 mm versus 35.9±21.1 mm; *P*=0.07). The median duration of aspirin was 96 days (interquartile range, 87–121 days) in the 3-month DAPT group and 365 days (interquartile range, 363–365 days) in the 12-month DAPT group. The proportion of patients receiving aspirin beyond 3 months in the 3-month DAPT group was 15.8% (76/481) at 6 months and 10.8% (52/481) at 12 months. Clopidogrel was used as the P2Y12 inhibitor in 82.5% (802/972) in the entire patients: 82.1% (395/481) in the 3-month DAPT group and 82.9% (407/491) in the 12-month DAPT group. Prasugrel or ticagrelor, potent P2Y12 inhibitors, were used in 17.5% (170/972) in the entire patients: 17.9% (86/481) in the 3-month DAPT group and 17.1% (84/491) in the 12-month DAPT group.

Follow-up for the primary end point was complete for 945 patients (97.2%) in patients receiving Orsiro stents. Table 2 demonstrates clinical outcomes at 12 months. In the intention-to-treat analysis, the primary end point occurred in 8 patients in the 3-month DAPT group and 14 in the 12-month DAPT group.

Table 2. Clinical Outcomes at 12 months

	Dual Antiplatelet Therapy		Hazard Ratio (95% CI)	*P* Value
	3 mo (n=481)	12 mo (n=491)		
Target vessel failure	8 (1.7)	14 (2.9)	0.58 (0.24–1.39)	0.22
Cardiac death	2 (0.4)	5 (1.1)	0.41 (0.08–2.10)	0.28
Target vessel–related myocardial infarction	1 (0.2)	4 (0.8)	0.26 (0.03–2.28)	0.22
Target vessel revascularization	6 (1.4)	8 (1.8)	0.76 (0.26–2.19)	0.61
All-cause death	5 (1.1)	6 (1.3)	0.85 (0.26–2.78)	0.79
Any myocardial infarction	2 (0.4)	8 (1.7)	0.25 (0.05–1.20)	0.08
Repeated revascularization	11 (2.4)	12 (2.6)	0.93 (0.41–2.11)	0.86
Stent thrombosis	0	0	…	…
Stroke	6 (1.3)	3 (0.4)	2.05 (0.51–8.18)	0.31
Bleeding BARC types 2–5	13 (2.8)	19 (4.0)	0.69 (0.34–1.40)	0.30
Major bleeding	7 (1.5)	5 (1.0)	1.43 (0.46–4.51)	0.54
Major adverse cardiac and cerebrovascular events	13 (2.8)	14 (2.9)	0.95 (0.45–2.02)	0.89
Net adverse clinical events	16 (3.4)	16 (3.3)	1.02 (0.51–2.04)	0.95

Data are n or n (%). The percentages are Kaplan–Meier estimates. BARC indicates Bleeding Academic Research Consortium.

The cumulative rates of primary end point were 1.7% in the 3-month DAPT group and 2.9% in the 12-month DAPT group (hazard ratio [HR], 0.58; 95% CI, 0.24–1.39; *P*=0.22) (Figure 2A). Also, the cumulative rates of the net adverse clinical event did not differ between the 3- and 12-month DAPT groups (3.4% versus 3.3%; HR, 1.02; 95% CI, 0.51–2.04; *P*=0.95) (Figure 2B). Stent thrombosis did not occur in both groups. The landmark analyses showed that the risks of primary end point (HR, 0.59; 95% CI, 0.23–1.51; *P*=0.27) and net adverse clinical event (HR, 1.11; 95% CI, 0.51–2.43; *P*=0.80) were not significantly different between the 3- and 12-month DAPT groups (Figure S1). In per-protocol analysis, results were consistent with those from the intention-to-treat analysis (Tables S1 and S2). The treatment effects of 3-month DAPT compared with 12-month DAPT were consistent across various subgroups for the primary end point (Figure S2).

Among 1495 patients allocated to the 3-month DAPT in the SAMRT-CHOICE trial, 1014 patients were treated with EESs (457 Promus/32 Synergy and 525 Xience). Baseline characteristics between Orsiro stents and EESs in patients with 3-month DAPT are presented in Table S3. The intravascular ultrasound during PCI was less frequently used in Orsiro stent

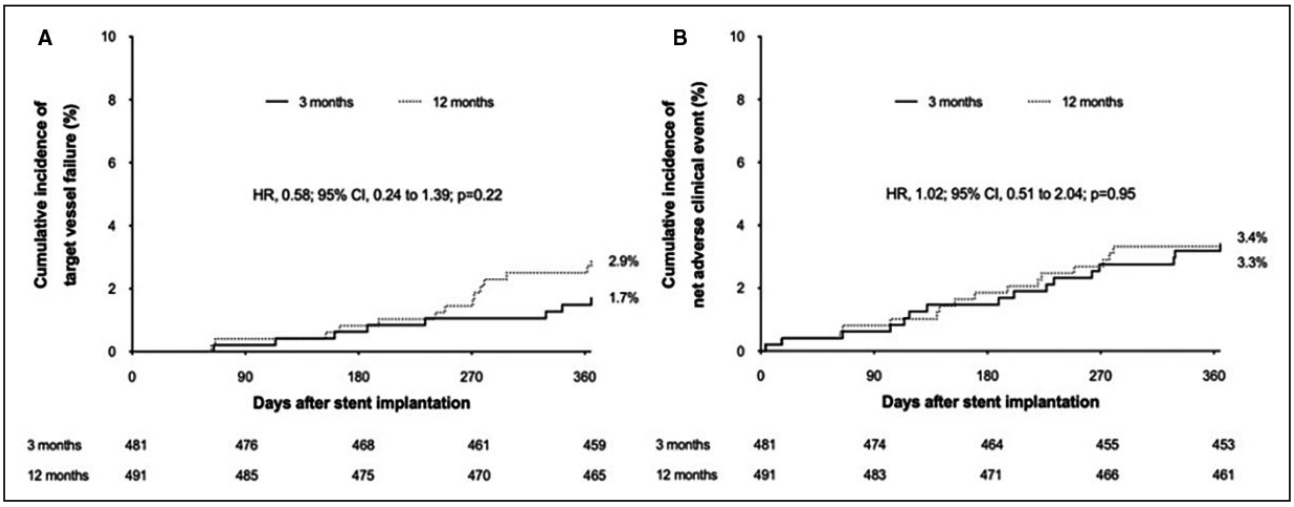

Figure 2. Time-to-event curves for target vessel failure (A) and net adverse clinical event (B) between 3-month (line) and 12-month (dotted line) dual antiplatelet therapy.
HR indicates hazard ratio.

Table 3. Clinical Outcomes at 12 Months in Patients Assigned to 3-Month Dual Antiplatelet Therapy, Grouped by Stent Types

	Stent Types		Unadjusted		Propensity-Score Matching		Inverse-Probability Weighted	
	Orsiro (n=481)	EES (n=1014)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Target vessel failure	8 (1.7)	17 (1.8)	0.96 (0.41–2.22)	0.92	0.80 (0.31–2.04)	0.64	0.92 (0.40–2.15)	0.85
Cardiac death	2 (0.4)	9 (0.9)	0.46 (0.10–2.13)	0.32	0.40 (0.08–2.06)	0.27	0.36 (0.08–1.66)	0.19
Target vessel–related myocardial infarction	1 (0.2)	3 (0.3)	0.69 (0.07–6.66)	0.75	0.33 (0.03–3.20)	0.34	0.67 (0.07–6.39)	0.73
Target vessel revascularization	6 (1.4)	6 (0.6)	2.08 (0.67–6.43)	0.21	2.01 (0.50–8.09)	0.33	2.10 (0.67–6.58)	0.20
All-cause death	5 (1.1)	16 (1.6)	0.65 (0.24–1.78)	0.40	0.62 (0.20–1.91)	0.41	0.52 (0.19–1.40)	0.19
Any myocardial infarction	2 (0.4)	9 (0.9)	0.46 (0.10–2.13)	0.32	0.25 (0.05–1.17)	0.08	0.54 (0.12–2.54)	0.44
Repeated revascularization	11 (2.4)	13 (1.4)	1.76 (0.79–3.93)	0.17	1.58 (0.61–4.12)	0.35	1.71 (0.77–3.82)	0.19
Stent thrombosis	0	3 (0.3)	…	…	…	…	…	…

Data are n or n (%). The percentages are Kaplan–Meier estimates. EES indicates everolimus-eluting stent; and HR, hazard ratio.

than in EES (18.9% versus 27.7%; *P*=0.0002). The median duration of aspirin was 97 days (interquartile range, 88–117 days) in the EES group and clopidogrel as the P2Y12 inhibitor was used in 74.4% (754/1014) of patients with EESs. Table 3 shows clinical outcomes at 12 months between stent types. The cumulative rates of primary end point were 1.7% in Orsiro stent and 1.8% in EES (unadjusted HR, 0.96; 95% CI, 0.41–2.22; *P*=0.92) (Figure 3A). Differences in baseline characteristics were balanced after propensity-score matching (Table S4), and standardized mean differences after adjustments with propensity-score matching and inverse-probability weight were within 0.1 across all matched covariates (Table S5). The comparable effects of Orsiro stent compared with EES were consistent after these adjustments (Table 3).

DISCUSSION

In this analysis from the SMART-CHOICE randomized trial, the 1-year clinical outcomes in patients undergoing Orsiro stent implantation were similar between the 3-month DAPT followed by P2Y12 inhibitor monotherapy and the 12-month DAPT strategies. The results of landmark and per-protocol analyses were similar to those from the intention-to-treat analysis. The treatment effects of 3-month DAPT followed by P2Y12 inhibitor monotherapy for the target vessel failure were consistent among various subgroups. Among whole patients receiving 3-month DAPT, the incidences of adverse cardiac events were not different between Orsiro stents and EESs for 1-year follow-up.

Bleeding after PCI was significantly associated with mortality during follow-up. Moreover, of patients undergoing PCI, the proportion of patients with high bleeding risk is increasing. Therefore, shortening of DAPT duration or avoidance of unnecessary prolonged DAPT is of paramount importance. 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 first revealed that polymer-free umirolimus-coated stents followed by 1-month DAPT reduced major adverse cardiac events compared with bare-metal stents.[13] Although Orsiro stents showed excellent outcomes in several randomized trials with conventional duration of DAPT,[9–11] it was also reported to be associated with increased risk of stent thrombosis and all-cause mortality compared with the current-generation DESs in recent studies.[14,15] Therefore, we compared 3-month DAPT followed by P2Y12 inhibitor monotherapy with 12-month DAPT among patients receiving Orsiro stents.

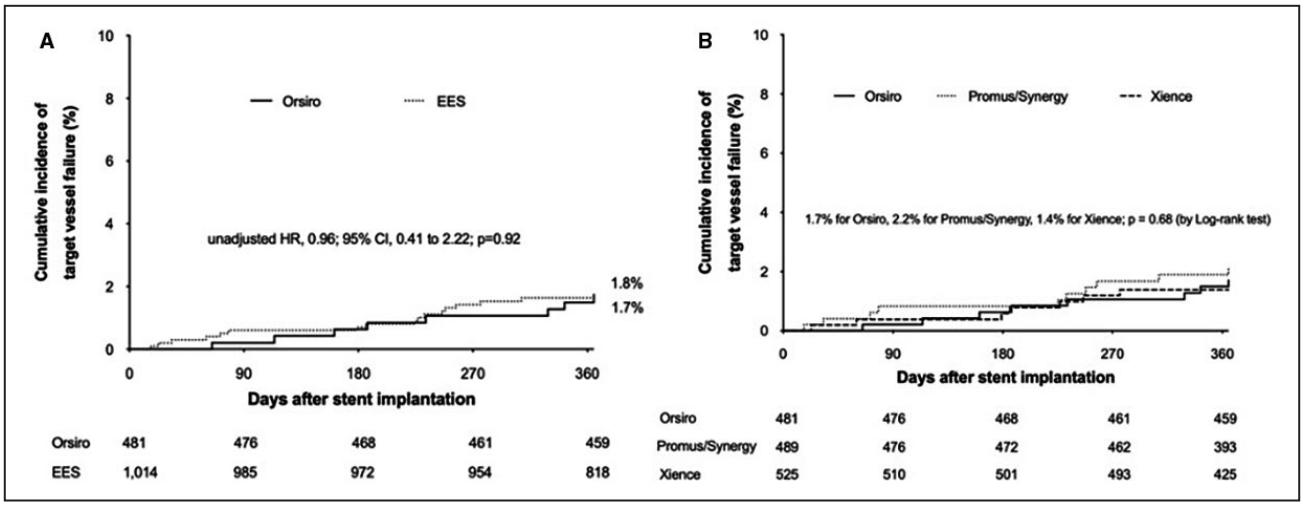

Figure 3. Time-to-event curves for target vessel failure between Orsiro stents (line) and everolimus-eluting stents (EES; dotted lines).
HR indicates hazard ratio. (**A**) Orsiro versus EES; (**B**) Orsiro versus Promus/Synergy versus Xience.

The STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent) trial enrolling 3045 patients who underwent everolimus-eluting Xience stent implantation demonstrated that 1 month of DAPT followed by clopidogrel monotherapy, compared with the 12-month DAPT, resulted in a significantly lower rate of cardiovascular and bleeding events at 1-year follow-up.[16] Recently, the Onyx ONE (Resolute Onyx in One Month Dual Antiplatelet Therapy for High-Bleeding Risk Patients) trial showed that Resolute Onyx DES implantation was noninferior to BioFreedom drug-coated stent, both with 1-month DAPT among patients undergoing PCI and with high bleeding risk.[17] Given that the performances of current-generation DESs are excellent and comparable to each other, extrapolation of the results of these trials to other DESs may be possible. However, we believe that it is desirable and prudent to demonstrate the safety of short-duration DAPT in each stent. The results of the present study support that the short duration of DAPT may be feasible and safe in patients receiving Orsiro stents like other current-generation DESs.

In the present analysis, the safety of short-term DAPT in patients receiving Orsiro stents is obviously based on remarkable advances of technology. The Orsiro stent had hybrid coating that consists of the combination of active (BIOlute) and passive coatings (PROBIO).[18] The BIOlute active coating consists of a biodegradable poly-L-lactic acid polymer that elutes sirolimus in which 50% of the drug is released within 30 days and 80% within 3 months (complete degradation of coating within 1–2 years).[19] The PROBIO passive coating encapsulates the metal stent and minimizes interaction between metal and surrounding tissue at sites of contact.[18] The configuration of the coating is asymmetrical and thicker on the abluminal side than on the luminal side (7.4 versus 3.5 μm, respectively), which results in a higher drug dose on the abluminal side of the DES.[20] The Orsiro stent is based on the cobalt-chromium stent platform with a strut thickness of 60 μm in stents with a nominal diameter ≤3.0 mm and 80 μm in stents with a nominal diameter >3.0 mm.[18] Notably, covered struts per lesion assessed by optical coherence tomography were 90% at 3 months after Orsiro stent implantation.[21] Although the strut coverage identified by optical coherence tomography does not exactly represent the reendothelization of coronary stent, nearly covered stent struts potentially enable the 3-month DAPT in patients receiving Orsiro stents.

The present study has several limitations. First, the sample size is inadequate for definite conclusion. Second, the included patients were generally at a low risk of ischemia and bleeding. Specifically, mean age was about 65 years old, and the sample of patients with acute coronary syndrome was low. Thus, the present results may not be generalized into elderly patients or patients with acute coronary syndrome and should be interpreted cautiously. Third, there is a possibility of biases caused by low adherence and treatment crossover, especially in the 3-month DAPT group. However, intention-to-treat and per-protocol analyses showed similar results, suggesting that these potential biases are likely small. Fourth, aspirin is usually recommended as mono antiplatelet therapy following DAPT.[22] However, the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial recently demonstrated that the P2Y12 inhibitor monotherapy after 3 months of DAPT among high-risk patients undergoing PCI was effective and safe.[23] Fifth, type of stents used was not randomized but was determined

by operators in the SMART-CHOICE trial. Unmeasured confounders might affect the clinical outcomes according to stent types, although multiple sensitivity analyses, including propensity-score matching and inverse-probability weighting, were performed to adjust baseline differences. Finally, despite the interactions between P2Y12 inhibitors and gastrointestinal medications, especially proton pump inhibitors, related data were not available.

In conclusion, the 3-month DAPT followed by P2Y12 inhibitor monotherapy was as safe as the 12-month DAPT after Orsiro stent implantation for target vessel failure at 1 year.

APPENDIX

The SMART-CHOICE Investigators

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Supplemental Material

Data S1.

Supplement Methods

Study population

The SMART-CHOICE trial was an investigator-initiated, multicenter, open-label, noninferiority, randomized study performed at 33 sites in Korea (12). The trial compared P2Y12 inhibitor monotherapy after 3 months of dual antiplatelet therapy (DAPT) with 12 months of DAPT in patients receiving current-generation drug-eluting stents. Eligible patients were aged 20 years or older and had 1 or more coronary artery stenoses of 50% or greater in a native coronary artery with visually estimated diameter of 2.25 mm or greater and 4.25 mm or smaller amenable to stent implantation and underwent percutaneous coronary intervention. Exclusion criteria included hemodynamic instability/cardiogenic shock, active pathologic bleeding or drug-eluting stent implantation within 12 months before the index procedure. Notably, patients on anticoagulation or other medications potentially related to bleeding were included in the SMART-CHOICE trial if there was no bleeding at the time of study participation.

Procedures

The diameter and length of the stent were determined according to the operators' discretion. Intravascular imaging or fractional flow reserve was done if clinically indicated. All patients received 300 mg of aspirin and a 300 mg or 600 mg clopidogrel loading dose orally before percutaneous coronary intervention, unless they had previously received these antiplatelet medications. For patients with acute coronary syndrome, a loading dose of 60 mg prasugrel or 180 mg ticagrelor was used.

End points

All deaths were considered cardiac unless a definite non-cardiac cause could be established. Myocardial infarction was defined as elevated cardiac enzyme levels (cardiac troponin or myocardial band fraction of creatine kinase) above the upper reference limit with ischemic symptoms or electrocardiographic findings indicative of ischemia. However, periprocedural enzyme-level elevation within 48 hours after the index

procedure without concomitant ischemic symptoms or electrocardiographic findings indicative of ischemia was excluded in the assessment of study end points (24). Stroke was defined as any non-convulsive focal or global neurologic deficit of abrupt onset lasting for more than 24 hours or leading to death, which was caused by ischemia or hemorrhage within the brain. Stent thrombosis was defined as definite or probable stent thrombosis according to the Academic Research Consortium classification (24). Bleeding was defined as Bleeding Academic Research Consortium type 2 to 5 bleeding; major bleeding, Bleeding Academic Research Consortium type 3 to 5 bleeding (25).

Statistical analysis

For per-protocol analysis, patients who did not receive the assigned treatment were excluded based on the regular assessments of study participants every 3 months. A landmark analysis was performed with a landmark of aspirin discontinuation at 3 months. Prespecified subgroup analysis of the primary end point was performed to evaluate the consistency of treatment effects of 3-month DAPT compared with 12-month DAPT, using Cox regression model with tests for interaction. For propensity-score matching and inverse-probability weighted analyses, propensity scores were calculated using a logistic regression model for Orsiro stents and everolimus-eluting stents. The following variables were considered for the propensity score: age more than 65 years old, male, diabetes mellitus, current smoking, previous myocardial infarction, clinical presentation of acute myocardial infarction, complex lesion, use of intravascular ultrasound, and multi-lesion intervention. The propensity-score mating was performed using nearest neighbor method without calipers. Covariate balances were assessed with absolute standardized mean differences. Categorical variables are presented as numbers (percentages) and compared with the $\chi 2$ test or Fisher exact test. Continuous variables are presented as mean ± SD and compared with the *t* test.

Table S1. Baseline characteristics, according to the per-protocol analysis.

	Dual antiplatelet therapy		P
	3 months (n=376)	12 months (n=465)	
Age (years)	64.9 ± 10.6	65.0 ± 10.2	0.87
Male	271 (72.1)	342 (73.6)	0.63
Diabetes mellitus	153 (40.7)	179 (38.5)	0.52
Hypertension	230 (61.2)	298 (64.1)	0.38
Dyslipidemia	162 (43.1)	209 (45.0)	0.59
Current smoking	95 (25.3)	108 (23.2)	0.49
Previous MI	21 (5.6)	23 (5.0)	0.68
Previous revascularization	42 (11.2)	64 (13.8)	0.26
Chronic renal failure	10 (2.7)	14 (3.0)	0.76
Left ventricular ejection fraction (%)	59.8 ± 10.4	60.1 ± 11.0	0.70
Clinical presentation			0.20
Stable angina	174 (46.3)	219 (47.1)	
Unstable angina	97 (25.8)	143 (30.7)	
Non- ST-segment elevation MI	71 (18.9)	71 (15.3)	
ST-segment elevation MI	34 (9.0)	32 (6.9)	
Multiple vessels disease	182 (48.4)	219 (47.1)	0.71
Location of lesion treated			
Left main	3 (0.8)	8 (1.7)	0.36
Left anterior descending artery	232 (61.7)	279 (60.0)	0.62
Left circumflex	99 (26.3)	120 (25.8)	0.86
Right coronary artery	142 (37.8)	166 (35.7)	0.54
Calcified lesion	64 (17.0)	84 (18.1)	0.69
Bifurcation lesion	42 (11.2)	55 (11.8)	0.77
Thrombotic lesion	30 (8.0)	30 (6.5)	0.39
Use of intravascular ultrasound	66 (17.6)	101 (21.7)	0.13
Treated lesions per patient	1.4 ± 0.7	1.3 ± 0.6	0.16
Multi-lesion intervention	122 (32.5)	137 (29.5)	0.35
Multi-vessel intervention	93 (24.7)	107 (23.0)	0.56
Number of stents per patient	1.5 ± 0.7	1.4 ± 0.7	0.13
Stent length per patient, mm	38.6 ± 22.5	36.4 ± 21.3	0.14

Data are n (%) or means ± SD. MI denotes myocardial infarction.

Table S2. Clinical outcomes at 12 months, according to the per-protocol analysis.

	Dual antiplatelet therapy		Hazard ratio (95% CI)	P
	3 months (n=376)	12 months (n=465)		
Target vessel failure	7 (1.9)	14 (3.0)	0.62 (0.25 – 1.53)	0.30
Cardiac death	2 (0.5)	5 (1.1)	0.50 (0.10 – 2.56)	0.40
Target vessel-related myocardial infarction	1 (0.3)	4 (0.9)	0.31 (0.04 – 2.78)	0.30
Target vessel revascularization	5 (1.5)	8 (1.8)	0.77 (0.25 – 2.35)	0.64
All-cause death	5 (1.3)	6 (1.3)	1.04 (0.32 – 3.39)	0.96
Any myocardial infarction	2 (0.5)	8 (1.7)	0.31 (0.07 – 1.46)	0.14
Repeated revascularization	9 (2.5)	12 (2.7)	0.93 (0.39 – 2.20)	0.86
Stent thrombosis	0	0	-	-
Stroke	3 (0.8)	3 (0.6)	1.25 (0.25 – 6.17)	0.79
Bleeding BARC type 2-5	7 (1.9)	16 (3.5)	0.54 (0.22 – 1.30)	0.17
Major bleeding	4 (1.1)	5 (1.1)	0.99 (0.27 – 3.70)	0.99
Major adverse cardiac and cerebrovascular events	10 (2.7)	14 (3.0)	0.89 (0.39 – 2.00)	0.77
Net adverse clinical events	11 (2.9)	16 (3.4)	0.85 (0.39 – 1.83)	0.68

Data are n or n (%). The percentages are Kaplan–Meier estimates. BARC denotes Bleeding Academic Research Consortium; CI, confidence interval.

Table S3. Baseline characteristics in patients assigned to 3-month dual antiplatelet therapy from the SMART-CHOICE trial.

	Orsiro stents (n=481)	Everolimus-eluting stents (n=1,014)	P
Age (years)	65.1 ± 10.7	64.4 ± 10.7	0.25
> 65 years old	267 (55.5)	524 (51.7)	0.17
Male	347 (72.1)	740 (73.0)	0.73
Diabetes mellitus	194 (40.3)	376 (37.1)	0.23
Hypertension	294 (61.1)	627 (61.8)	0.79
Dyslipidemia	211 (43.9)	462 (45.6)	0.54
Current smoking	121 (25.2)	303 (29.9)	0.06
Previous myocardial infarction	26 (5.4)	36 (3.6)	0.09
Previous revascularization	58 (12.1)	114 (11.2)	0.64
Chronic renal failure	15 (3.1)	29 (2.9)	0.78
Left ventricular ejection fraction (%)	60.0 ± 10.6	60.0 ± 11.0	0.98
Clinical presentation of acute myocardial infarction	128 (26.6)	275 (27.1)	0.84
Multiple vessels disease	233 (48.4)	516 (50.9)	0.38
Complex lesion	163 (33.9)	323 (31.9)	0.43
Use of intravascular ultrasound	91 (18.9)	281 (27.7)	0.0002
Treated lesions per patient	1.4 ± 0.7	1.3 ± 0.6	0.12
Multi-lesion intervention	150 (31.2)	280 (27.6)	0.15
Multi-vessel intervention	114 (23.7)	223 (22.0)	0.46
Number of stents per patient	1.5 ± 0.8	1.4 ± 0.7	0.21
Stent length per patient, mm	38.5 ± 22.8	37.9 ± 22.4	0.60

Data are n (%) or means ± SD.

Table S4. Baseline characteristics in patients assigned to 3-month dual antiplatelet therapy from propensity-score matched population.

	Orsiro stents (n=481)	Everolimus-eluting stents (n=481)	P
Age (years)	65.1 ± 10.7	65.0 ± 11.2	0.44
> 65 years old	267 (55.5)	261 (54.3)	0.70
Male	347 (72.1)	365 (75.9)	0.19
Diabetes mellitus	194 (40.3)	194 (40.3)	1.00
Hypertension	294 (61.1)	305 (63.4)	0.46
Dyslipidemia	211 (43.9)	188 (39.1)	0.13
Current smoking	121 (25.2)	122 (25.4)	0.94
Previous myocardial infarction	26 (5.4)	26 (5.4)	1.00
Previous revascularization	58 (12.1)	50 (10.4)	0.41
Chronic renal failure	15 (3.1)	10 (2.1)	0.31
Left ventricular ejection fraction (%)	60.0 ± 10.6	59.6 ± 12.4	0.63
Clinical presentation of acute myocardial infarction	128 (26.6)	116 (24.1)	0.37
Multiple vessels disease	233 (48.4)	227 (47.2)	0.70
Complex lesion	163 (33.9)	162 (33.7)	0.95
Use of intravascular ultrasound	91 (18.9)	95 (19.8)	0.74
Treated lesions per patient	1.4 ± 0.7	1.4 ± 0.6	0.69
Multi-lesion intervention	150 (31.2)	152 (31.6)	0.89
Multi-vessel intervention	114 (23.7)	128 (26.6)	0.30
Number of stents per patient	1.5 ± 0.8	1.4 ± 0.7	0.20
Stent length per patient, mm	38.5 ± 22.8	38.5 ± 23.9	0.97

Data are n (%) or means ± SD.

Table S5. Standardized differences of variables used in propensity-score matching and inverse-probability weighted analyses.

	Standardized differences		
	Unadjusted	**Propensity-score matching**	**Inverse-probability weighted**
Age > 65 years old	0.077	0.025	0.007
Male	-0.017	-0.066	-0.004
Diabetes mellitus	0.067	0.013	0.000
Current smoking	-0.106	0.010	-0.008
Previous myocardial infarction	0.090	0.000	0.009
Clinical presentation of acute myocardial infarction	-0.011	0.052	-0.003
Complex lesion	0.043	0.004	0.002
Use of intravascular ultrasound	-0.209	-0.005	-0.004
Multi-lesion intervention	0.078	-0.013	0.006

Figure S1. Landmark analyses at 3 months for target vessel failure (A) and net adverse clinical event (B) between 3-month (line) and 12-month (dotted line) dual antiplatelet therapy.

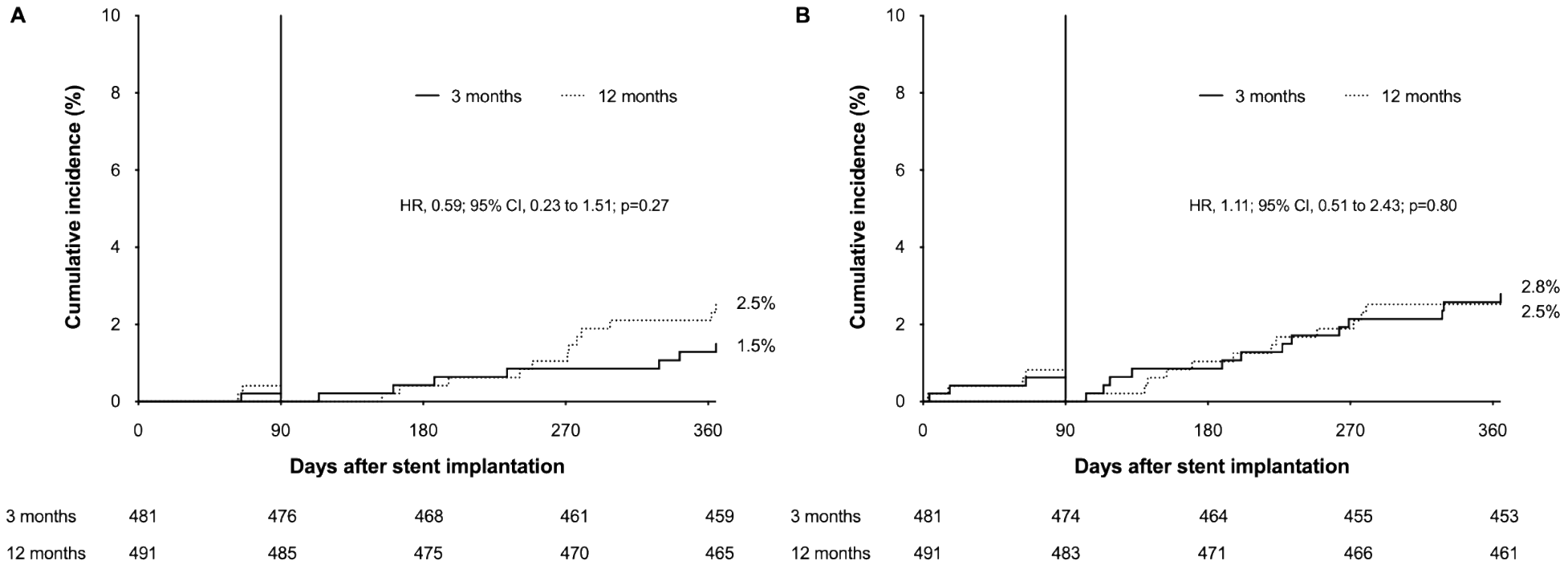
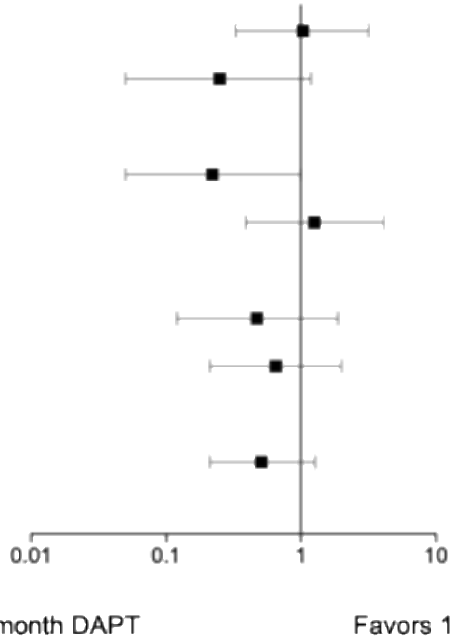


Figure S2. Subgroup analyses for primary end point.

Subgroup	Patients	Target vessel failure		Hazard ratio (95% CI)	p for interaction
		3-month DAPT	12-month DAPT		
Acute coronary syndrome					0.15
Yes	516	6/254 (2.4%)	6/262 (2.3%)	1.03 (0.33 – 3.19)	
No	456	2/227 (0.9%)	8/229 (3.5%)	0.25 (0.05 – 1.18)	
Diabetes mellitus					0.07
Yes	384	2/194 (1.0%)	9/190 (4.7%)	0.22 (0.05 – 1.00)	
No	588	6/287 (2.1%)	5/301 (1.7%)	1.26 (0.39 – 4.13)	
Multivessel intervention					0.72
Yes	225	3/114 (2.6%)	6/111 (5.4%)	0.47 (0.12 – 1.88)	
No	747	5/367 (1.4%)	8/380 (2.1%)	0.65 (0.21 – 1.99)	
P2Y12 inhibitor					0.99
Clopidogrel	802	7/395 (1.8%)	14/407 (3.4%)	0.51 (0.21 – 1.27)	
Prasugrel or ticagrelor	170	1/86 (1.2%)	0/84 (0%)	-	



CI denotes confidence interval; DAPT, dual antiplatelet therapy.