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1-Year Clinical Outcomes of All Comers Treated With 2 Bioresorbable Polymer-Coated Sirolimus-Eluting Stents

Propensity Score–Matched Comparison of the COMBO and Ultrathin-Strut Orsiro Stents

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ABSTRACT

OBJECTIVES The aim of this study was to determine 1-year safety and efficacy after treatment with the COMBO and Orsiro stents.

BACKGROUND The COMBO stainless-steel stent has an anti-CD34^{+} antibody coating to capture endothelial progenitor cells, thereby promoting faster endothelialization. The Orsiro is an ultrathin-strut cobalt-chromium stent, covered by an extremely thin layer of amorphous silicon carbide to minimize ion leakage. Both devices elute sirolimus from biodegradable polymers.

METHODS For this analysis we included European patients from the COMBO collaboration, a patient-level pooling of 2 prospective all-comers registries of COMBO stent implantation (n = 2,775), and all patients randomized to the Orsiro stent (n = 1,169) from the Dutch BIO-RESORT (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population) randomized trial. The main outcome of interest was 1-year target lesion failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularization evaluated using propensity score-matched analysis.

RESULTS At baseline, COMBO patients were older and had more insulin-treated diabetes, renal insufficiency, and other comorbidities. However, Orsiro patients included more current smokers and more acute coronary syndrome presentations. Orsiro patients also received longer stents and had more complex target lesions. After propensity score-matched analysis (n = 862/arm), 1-year target lesion failure occurred in 4.1% of COMBO-treated and 2.7% of Orsiro-treated patients (hazard ratio: 1.55; 95% confidence interval: 0.92 to 2.62; p = 0.10). Definite stent thrombosis occurred in 0.5% of COMBO-treated and 0.5% of Orsiro-treated patients (p = 0.99).

CONCLUSIONS A propensity score–matched comparison of all comers treated with the COMBO or Orsiro stent showed no statistically significant differences. Stent thrombosis risk was low and similar between the stents. (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population [BIO-RESORT], NCT01674803; MASCOT-Post Marketing Registry [MASCOT], NCT02183454; Prospective Registry to Assess the Long-term Safety and Performance of the Combo Stent [REMEDEE Reg], NCT01874002)
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Evolutions in stent design for the treatment of coronary artery disease have resulted in increased safety and efficacy after percutaneous coronary intervention (PCI). Contemporary stent designs show several variations in metal alloy, strut size, durable and bioabsorbable polymer coatings, type of drug and drug elution profile, and additional features such as drug reservoirs, silicon carbide layers, and antibody coatings (1–4). Although thicker stent struts are believed to increase the rate of target lesion revascularization (TLR) (5,6), very thin struts may be associated with more longitudinal compression, less radial force, and more elastic stent recoil (7,8). Head-to-head randomized controlled trials comparing modern drug-eluting stents (DES) may aid clinical decision making, but with current low event rates associated with the newer DES, increasingly larger sample sizes are required to demonstrate small differences. Although newer-generation durable-polymer (DP) DES are associated with low rates of stent thrombosis (ST) (9–11), new biodegradable-polymer (BDP) stent technologies have also demonstrated safety and efficacy evidence for low rates of ST and TLR (12,13).

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In this paper, we compare 2 recent stent technologies that combine sirolimus drug elution with a BDP coating: the COMBO stainless-steel stent (OrbusNeich Medical, Fort Lauderdale, Florida) and the ultrathin-strut Orsiro cobalt-chromium stent (Biotronik, Bülach, Switzerland). The COMBO stent additionally includes a luminal prohealing anti-CD4 coating that binds with circulating endothelial progenitor cells to allow rapid healing via strut coverage and endothelialization (14–16). The Orsiro stent includes an extremely thin amorphous silicon carbide layer to minimize ion leakage from the metal (3). Recent observational data have shown safety and efficacy of the COMBO stent up to 3 years in all comers (17–20). The HARMONEE (Japan-USA Harmonized Assessment by Randomized, Multi-Center Study of OrbusNeich's Combo Stent) randomized trial demonstrated noninferiority of the COMBO compared with DP everolimus-eluting stents (21). Similarly, efficacy and safety of the Orsiro stent have been demonstrated in both observational and randomized clinical studies (3,6,22–25). The Orsiro and COMBO platforms have been shown to be noninferior to second-generation DP DES (3,21,22), and the Orsiro stent has been shown to be noninferior to another BDP DES (13). However, the COMBO and Orsiro stents have never been compared. A large randomized comparison between COMBO and Orsiro is under way (SORT OUT X [Combo Stent Versus ORSIRO Stent], NCT03216733; N = 3,140) and currently recruiting patients.

In the present analysis, we pooled patient-level data from 3 clinical studies and used propensity matching to compare the 1-year clinical outcomes of all comers treated with the COMBO (data from the pooled COMBO collaboration) (4) and Orsiro (data from the BIO-RESORT [Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population] trial) stents (3).

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
BDP = biodegradable-polymer
DAPT = dual-antiplatelet therapy
DES = drug-eluting stent(s)
DP = durable-polymer
MI = myocardial infarction
PCI = percutaneous coronary intervention
ST = stent thrombosis
STEMI = ST-segment elevation myocardial infarction
TLF = target lesion failure
TLR = target lesion revascularization

METHODS

STUDY DEVICES. COMBO stent. The COMBO stent is a stainless-steel stent with 100-μm struts. Abluminally, it is coated with sirolimus (dose 5 μg/mm, 0.75 μg/mm^2) in a BDP, which is eluted within 30 days. The polymer is completely resorbed within 3 months. Luminally, the stent platform is coated with anti-CD34$^+$ antibodies that capture circulating endothelial progenitor cells on the stent surface to facilitate rapid strut coverage and endothelialization (4). This technology, through rapid endothelialization and polymer resorption at 3 months, could allow a shorter duration of dual-antiplatelet therapy (DAPT).

Orsiro stent. The Orsiro stent is an ultrathin-strut cobalt-chromium stent with struts that are nearly one-half as thick as those used in early-generation BDP stents. For stents ≤3.0 mm in nominal diameter, strut thickness is 60 μm, and for stents >3.0 mm,

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strut thickness is 80 μm. The stent is covered with an amorphous silicon carbide layer (PROBIO) and releases sirolimus from a biodegradable poly-L-lactic acid polymer matrix. PROBIO acts as a diffusion barrier, sealing interaction between the bare-metal stent surface and the circulation, reducing ion leakage. The polymer is loaded with sirolimus (dose 1.4 μg/mm^2 stent surface) that is eluted over a period of 12 to 14 weeks. The polymer coating is circumferential and asymmetrical, slightly thicker on the abluminal side than the luminal side (7.4 μm vs. 3.5 μm) and is resorbed after <24 months (3).

Both stents have received the Conformité Européene (CE) mark (COMBO in 2013, Orsiro in 2012) and have been clinically available on the European market since then.

INCLUDED CLINICAL STUDIES. COMBO collaboration. The COMBO collaboration (N = 3,614) is a patient-level pooled database of patients from the all-comers REMEDEE (Prospective Registry to Assess the Long-Term Safety and Performance of the Combo Stent) and MASCOT (Multinational Abluminal Sirolimus Coated BiO-Engineered StenT) registries (4,17,20). The REMEDEE registry (NCT01874002) is a prospective, multicenter, investigator-initiated registry across 9 European sites, evaluating outcomes in patients undergoing PCI with attempted COMBO stent placement. A total of 1,000 patients were enrolled between June 2013 and March 2014. The primary endpoint was target lesion failure (TLF) at 1-year follow-up. Results have been published up to 3-year follow-up (17–19). The MASCOT study (NCT02183454) is a prospective, multicenter, global post-marketing registry of all comers undergoing PCI with attempted placement of at least 1 COMBO stent as part of routine clinical care (20). A total of 2,614 patients were enrolled from 60 global centers (Europe, Asia, the Middle East, and South America) between June 2014 and March 2016, of whom 2,775 were enrolled at European sites. The primary endpoint was TLF at 1-year follow-up.

BIO-RESORT TRIAL. The BIO-RESORT trial (NCT01674803) is an investigator-initiated, randomized clinical trial in all comers, comparing both the Orsiro BDP sirolimus-eluting stent and the Synergy BDP everolimus-eluting stent with a zotarolimus-eluting DP DES (3). Between 2012 and 2015, a total of 3,514 patients were enrolled at 4 Dutch PCI centers; 1,169 patients were randomized to treatment with Orsiro. Implantation procedures were performed per standard techniques. Web-based randomization was performed after guidewire passage or lesion predilation, and it was stratified for diabetes. The primary endpoint was 1-year target vessel failure, and the main results have been reported elsewhere (3).

The investigators from the MASCOT and REMEDEE registries and the BIO-RESORT trial are listed in the Supplemental Appendix.

PATIENT SETTING. Inclusion criteria for the BIO-RESORT trial (3) and COMBO collaboration (4) have been previously published and highlight the all-comers nature of the study protocols. Patients undergoing PCI with attempted COMBO or Orsiro placement according to clinical guidelines and on the basis of operators' judgment were included. The MASCOT registry excluded patients undergoing PCI for treatment of ST. In the BIO-RESORT trial, exclusion criteria were also planned surgery necessitating interruption of DAPT within the first 6 months, known intolerance to components of the investigational product or medication required (e.g., intolerance to concomitant anticoagulation or antiplatelet therapy), and known pregnancy.

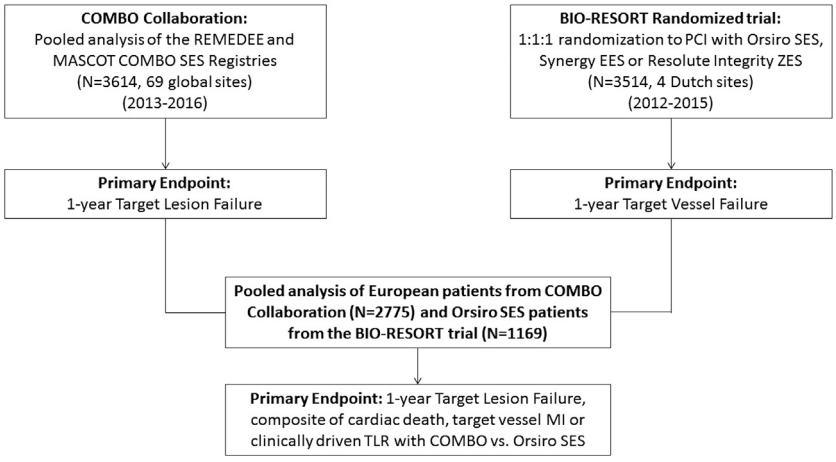
The studies were conducted according to the Declaration of Helsinki and Good Clinical Practice. In both studies, DAPT was prescribed per local recommendations and in keeping with guidelines. All patients provided written informed consent. Follow-up was conducted via telephone or clinic visit by trained research staff members at each participating site at the follow-up time points (3,4). All events were adjudicated by independent clinical event committees.

CLINICAL ENDPOINTS AND DEFINITIONS. The primary outcome of interest was 1-year TLF, a composite of cardiac death, target vessel myocardial infarction (MI), and clinically driven TLR. MI was adjudicated according to the third universal definition in the COMBO collaboration (26). However, no systematic biomarker testing was conducted after PCI in COMBO-treated patients. The BIO-RESORT trial conducted routine post-PCI biomarker testing and included creatine kinase increase as periprocedural MI regardless of symptoms. For this analysis, we considered all patients with clinical symptoms and/or new electrocardiographic or imaging changes with biomarker increase post-PCI as clinically relevant target vessel MI. Secondary endpoints included the individual components of the primary outcome and ST, defined according to the standardized Academic Research Consortium criteria (27).

All procedural data were site reported on the basis of visual assessment of the treating interventional cardiologists in the COMBO collaboration, whereas independent core laboratory assessment was available for all treated lesions in the BIO-RESORT trial.

STATISTICAL ANALYSIS. Patient-level pooled cohort. Patients randomized to treatment with the Orsiro stent (n = 1,169) from the BIO-RESORT trial

FIGURE 1 Study Design



BIO-RESORT = Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population; DES = drug-eluting stent; EES = everolimus-eluting stent; MI = myocardial infarction; PCI = percutaneous coronary intervention; REMEDEE = Prospective Registry to Assess the Long-term Safety and Performance of the Combo Stent; SES = sirolimus-eluting stent; TLR = target lesion revascularization; ZES = zotarolimus-eluting stent.

were compared with COMBO stent-treated patients in the COMBO collaboration for this analysis. We included only European patients to minimize regional factors and ensure comparability of trial performance and reporting. Endpoints were harmonized between both studies; only clinically driven TLR and clinically relevant target vessel MI were included in the primary endpoint. Patients were censored at last follow-up contact date, 1 year, or time of death, whichever came first. Continuous variables are presented as mean ± SD or median (interquartile range) and were compared using Student's *t*-test or the Wilcoxon rank sum test. Categorical variables are presented as frequencies and percentages and were compared using the chi-square test. Clinical outcomes are presented in a time-to-event manner using Kaplan-Meier methods and compared using the log-rank test. We also used multivariate Cox regression methods to evaluate for associations between baseline factors including stent type (reference: Orsiro) and risk for 1-year TLF. Model variables for baseline systemic risk factors were chosen on the basis of known or expected associations with adverse outcomes after PCI.

Propensity-matched analysis. Propensity scores were calculated using all the baseline variables for which imbalance was present (standardized mean difference >0.2). The propensity model was generated in an iterative fashion as described by Rosenbaum and Rubin (28). Patients were greedy matched 1 to 1 using the nearest neighbor method. The caliper was set at 0.1. Subgroup analysis was performed in the propensity-matched cohort for 1-year TLF in patients presenting with ST-segment elevation MI (STEMI) or non-STEMI presentation.

Two-sided p values < 0.05 were considered to indicate statistical significance. All descriptive statistical analyses were performed using SPSS version 24 (SPSS, Chicago, Illinois). Propensity-matched analyses were conducted in R Studio and R version 3.2.2 and the package MatchIt 17 and 18 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 3,944 patients were included in the pooled cohort analysis, 29.6% (n = 1,169) were treated with the Orsiro stent and 70.4% (n = 2,775) with the COMBO stent. **Figure 1** presents the Consolidated Standards of Reporting Trials diagram. **Table 1** shows the baseline and procedural characteristics of the study patients. COMBO patients were older, with higher prevalence of insulin-treated diabetes mellitus, hypertension, renal insufficiency, prior MI, and prior PCI. However, Orsiro patients had a higher prevalence of acute coronary syndrome (ACS) presentation and were more often current smokers. Procedurally, Orsiro patients received on average longer stents and underwent more multilesion PCI, although both stent groups had similar frequencies of multivessel PCI. Orsiro patients more often underwent PCI to the left anterior descending or right coronary artery and had a higher prevalence of complex

TABLE 1 Baseline Characteristics of Pooled and Propensity-Matched Patients in the European COMBO Collaboration and Orsiro Arm of the BIO-RESORT Trial

	COMBO	Orsiro	p Value
Pooled sample	(n = 2,775)	(n = 1,169)	
Demographic characteristics			
Age, yrs	65.08 ± 10.84	64.18 ± 10.73	0.02
Female	703 (25.3)	315 (26.9)	0.31
Diabetes mellitus	704 (25.5)	211 (18.0)	<0.001
Insulin-treated diabetes mellitus	205 (7.4)	70 (6.0)	<0.001
Current smoking	738 (26.6)	341 (29.8)	<0.001
Hypertension	1,895 (68.9)	550 (47.0)	<0.001
Previous CABG	189 (6.8)	80 (6.8)	1.00
Previous PCI	788 (28.5)	214 (18.3)	<0.001
Previous MI	684 (24.9)	209 (17.9)	<0.001
Renal insufficiency	192 (7.0)	46 (3.9)	<0.001
Peripheral arterial disease	208 (7.8)	92 (7.9)	1.00
Previous stroke	149 (5.4)	73 (6.2)	0.33
Acute coronary syndrome	1,520 (54.8)	818 (70.0)	<0.001
Procedural characteristics			
Treated vessel			
Left anterior descending coronary artery	1,349 (48.6)	614 (52.5)	0.03
Left circumflex coronary artery	687 (24.8)	320 (27.4)	0.10
Left main coronary artery	60 (2.2)	23 (2.0)	0.79
Right coronary artery	895 (32.3)	423 (36.2)	0.02
Bypass graft	58 (2.1)	22 (1.9)	0.76
Number of lesions treated			<0.001
1	2,319 (83.6)	853 (73.0)	
2	385 (13.9)	255 (21.8)	
3	64 (2.3)	56 (4.8)	
4	5 (0.2)	5 (0.4)	
5	1 (0.04)	0 (0.00)	
Worst lesion complexity (ACC/AHA lesion type)			<0.001
A	292 (10.6)	32 (2.7)	
B1	804 (29.3)	190 (16.3)	
B2	1,112 (40.5)	488 (41.7)	
C	506 (18.4)	454 (38.8)	
Total stent length, mm	23.62 ± 14.21	39.20 ± 28.32	<0.001

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target lesions (i.e., American College of Cardiology/American Heart Association lesion type C) compared with patients treated with COMBO stents.

CLINICAL OUTCOMES OF THE POOLED COHORT. One-year follow-up was complete in 99.0% of Orsiro patients and 96.5% of COMBO patients. The median duration of follow-up was 365 days (interquartile range: 365 to 365 days). Table 2 shows the 1-year Kaplan-Meier estimates of all clinical outcomes between the 2 stent groups from the pooled cohort. The primary outcome of 1-year TLF occurred in 4.1% of COMBO patients and 3.1% of Orsiro patients (p = 0.13). There were no statistically significant differences in secondary endpoints between the 2 stent groups. Definite ST occurred in 0.5% of COMBO patients and in 0.3% of Orsiro patients (p = 0.48).

In a multivariate Cox regression model, we analyzed for baseline risk factors associated with TLF, shown in Table 3. Hypertension and renal insufficiency were associated with significantly increased risk for 1-year TLF, whereas insulin-treated diabetes and older age were associated with a trend toward greater risk. ACS and stent type were not associated with higher risk for 1-year TLF.

PROPENSITY-MATCHED ANALYSIS. After propensity score matching, 862 well-balanced patient pairs were derived. Table 1 shows the baseline and procedural characteristics of the matched cohort. Table 2 presents the Kaplan-Meier estimates of the primary and secondary endpoints in the matched cohort. The incidence of 1-year TLF was 4.1% in COMBO patients and 2.7% in Orsiro patients (hazard ratio: 1.55; 95% confidence interval: 0.92 to 2.62; p = 0.10; reference: Orsiro) (Central Illustration). There were no statistically significant differences between the groups in the rates of cardiac death, target vessel MI, or clinically driven TLR (Figure 2). Definite ST occurred with a similar incidence in COMBO and Orsiro patients (0.5% each; p = 0.99).

In a subgroup analysis that assessed patients from the matched cohort who (at the index PCI procedure) were treated for STEMI or non-STEMI, 1-year TLF occurred in 4.8% of COMBO patients (n = 17) and in 2.3% of Orsiro patients (n = 10) (p = 0.06).

DISCUSSION

The present patient-level pooled, propensity score-matched analysis is the first to compare 1-year clinical outcomes in 862 matched pairs of patients treated with these 2 novel BDP sirolimus-eluting stent platforms. The main findings are as follows. First, patients undergoing PCI with COMBO stents were older, with more comorbidities, but patients treated with Orsiro stents had a higher prevalence of current smoking and ACS presentation at index PCI. Orsiro patients were more likely to undergo multilesion PCI and treatment of complex coronary lesions than COMBO patients. Second, in a well-balanced patient cohort obtained by propensity score matching, the incidence of 1-year TLF with COMBO and Orsiro stents differed nonsignificantly (4.1% and 2.7%, respectively), and the rates of definite ST were similar (0.5% with both stents). Third, in a subgroup analysis of patients with MI from the propensity score-matched cohort, there was a nonsignificantly higher TLF rate in COMBO patients (4.8% and 2.3%, respectively). A randomized comparison between these novel coronary stent technologies with long-term follow-up is needed to definitively assess potential differences in clinical outcomes at 1-year follow-up and beyond.

COMBO AND ORSIRO STENTS. Interestingly, in the present analysis we noted significant patient differences between the groups. This may be a function of different study designs; whereas BIO-RESORT was a randomized trial from 4 Dutch centers, the COMBO collaboration was an observational study enrolling patients from more than 40 centers across Europe. Although randomized trials are typically challenged in the recruitment of high-risk patients, nonconsecutive patient selection in observational registries can also bias the final patient cohort and, ultimately, clinical comparisons. We noted that the COMBO patients had more baseline comorbidities, while Orsiro patients were more often current smokers and were more often treated for troponin-positive ACS. A previous COMBO report from the REMEDEE registry noted that patients with ACS carry higher risk for TLR compared with their counterparts (29), plausibly because of systemic risk factors, late malapposition in the setting of STEMI, and other factors related to patient compliance and secondary prevention. Similarly, in the COMBO collaboration, biomarker-positive ACS was noted to be an independent predictor of composite TLF events (4).

Procedurally, in the present analysis we noted that Orsiro patients tended to receive longer stents and more often underwent multilesion PCI and stenting in complex target lesions. Moreover, as reported in the principal publications, fractional flow reserve-guided PCI was performed more frequently during the index procedure in the Orsiro patients (12%) than in the COMBO patients (2.3%), which may have had an impact on decisions for treating more than 1 lesion and overall outcomes (3,4). The reported rate of post-dilation also varied: 53% in the COMBO collaboration and 81% in BIO-RESORT (3,4).

Because of the baseline and procedural differences between the stent groups, we performed propensity score matching to analyze a well-balanced patient cohort that showed that the 1-year rates of TLF with COMBO and Orsiro stents differed nonsignificantly (4.1% vs. 2.7%). Moreover, there were no significant differences in the rates of the secondary endpoints of target vessel MI, cardiac death, and TLR, and the rates of ST up to 1 year were similar and low. In a multivariate Cox model, adjusted for baseline risk factors, stent type was not a statistically significant risk factor for 1-year TLF ($p = 0.10$); however, patient factors, including renal failure and hypertension, resulted in an elevated risk (4,30). Moreover, as shown previously, older patients and those with insulin-treated diabetes showed a trend toward more TLF events (4).

TABLE 1 Continued

	COMBO	Orsiro	p Value
Propensity-matched sample	(n = 862)	(n = 862)	
Demographic characteristics			
Age, yrs	64.08 ± 11.28	63.89 ± 10.70	0.71
Female	229 (26.6)	227 (26.3)	0.96
Diabetes mellitus	171 (19.8)	159 (18.4)	0.50
Insulin-treated diabetes mellitus	58 (6.7)	54 (6.3)	0.76
Current smoking	254 (29.5)	255 (29.6)	1.00
Hypertension	472 (54.8)	440 (51.0)	0.14
Previous CABG	57 (6.6)	57 (6.6)	1.00
Previous PCI	176 (20.4)	170 (19.7)	0.76
Previous MI	168 (19.5)	158 (18.3)	0.58
Renal insufficiency	50 (5.8)	34 (3.9)	0.09
Peripheral arterial disease	52 (6.0)	68 (7.9)	0.16
Previous stroke	40 (4.6)	53 (6.1)	0.20
Acute coronary syndrome	585 (67.9)	592 (68.7)	0.76
Procedural characteristics			
Treated vessel			
Left anterior descending coronary artery	417 (48.4)	454 (52.7)	0.08
Left circumflex coronary artery	204 (23.7)	224 (26.0)	0.29
Left main coronary artery	17 (2.0)	14 (1.6)	0.72
Right coronary artery	300 (34.8)	260 (30.2)	0.05
Bypass graft	13 (1.5)	18 (2.1)	0.47
Number of lesions treated			0.91
1	700 (81.2)	691 (80.2)	
2	141 (16.4)	146 (16.9)	
3	19 (2.2)	23 (2.7)	
4	2 (0.2)	2 (0.2)	
Worst lesion complexity (ACC/AHA lesion type)			0.43
0	8 (0.9)	5 (0.6)	
A	45 (5.2)	31 (3.6)	
B1	185 (21.5)	179 (20.8)	
B2	387 (44.9)	399 (46.3)	
C	237 (27.5)	248 (28.8)	
Total stent length, mm	29.41 ± 19.05	30.27 ± 17.30	0.33

Values are mean ± SD or n (%).

ACC = American College of Cardiology; AHA = American Heart Association; BIO-RESORT = Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population; CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Despite the high prevalence of ACS in Orsiro patients, the rate of 1-year MI was extremely low with Orsiro, as shown in the present study and other meta-analytic data (31). Indeed, subgroup data from the propensity-matched cohort in the present study suggest that patients with MI undergoing PCI with Orsiro stents may tend to have a lower 1-year TLF risk than patients with MI treated with COMBO stents, but this finding should be seen in the context of a higher frequency of potent $P2Y_{12}$ inhibitor use among the Orsiro-treated patients. Interestingly, a recently published subgroup analysis from a randomized trial that compared Orsiro stents with everolimus-eluting stents showed that Orsiro stents resulted in lower 1-year rates of TLF in patients with ACS, driven by lower rates of MI and a

TABLE 2 1-Year Clinical Outcomes

	COMBO	Orsiro	p Value
Pooled cohort	(n = 2,775)	(n = 1,169)	
TLF	113 (4.1)	36 (3.1)	0.13
Cardiac death	36 (1.3)	10 (0.9)	0.23
TV MI	33 (1.2)	14 (1.2)	0.99
TLR	68 (2.5)	18 (1.6)	0.07
Definite/probable stent thrombosis	21 (0.8)	5 (0.4)	0.20
Definite stent thrombosis	14 (0.5)	4 (0.3)	0.48
Propensity-matched cohort	(n = 862)	(n = 862)	
TLF	35 (4.1)	23 (2.7)	0.10
Cardiac death	11 (1.3)	3 (0.3)	0.07
TV MI	11 (1.3)	10 (1.2)	0.81
TLR	21 (2.5)	13 (1.5)	0.15
Definite/probable stent thrombosis	8 (0.9)	4 (0.5)	0.24
Definite stent thrombosis	4 (0.5)	4 (0.5)	0.99

Values are n (Kaplan-Meier %).

MI = myocardial infarction; TLF = target lesion failure; TLR = target lesion revascularization; TV = target vessel.

similar incidence of clinically driven TLR (32). Supportive of these data are findings from a small optical coherence tomographic analysis by Secco et al. (33) in Orsiro-treated patients with STEMI, which showed low rates of incomplete strut coverage (1.8%) at 3 months from PCI. In the recent BIONYX (Bioresorbable Polymer Orsiro Versus Durable Polymer Resolute Onyx Stents) trial, the Orsiro stent was shown to have a target vessel failure rate similar to that of the Resolute Onyx zotarolimus-eluting stent in all comers (25).

TABLE 3 Multivariate Cox Regression Model for Baseline Factors Associated With 1-Year TLF

		95% CI		
	HR	Lower Limit	Upper Limit	p Value
Stent type (COMBO vs. Orsiro)	1.416	0.939	2.135	0.10
Sex	0.839	0.557	1.263	0.40
Age	1.016	0.998	1.034	0.08
Previous heart failure	1.270	0.685	2.357	0.45
Hypercholesterolemia	1.107	0.758	1.616	0.60
Peripheral arterial disease	1.435	0.843	2.443	0.18
Medically treated diabetes mellitus	0.601	0.224	1.618	0.31
Insulin-dependent diabetes mellitus	0.568	0.302	1.071	0.08
Renal insufficiency	1.777	1.031	3.061	0.04
Hypertension	0.625	0.423	0.924	0.02
Previous CABG	1.410	0.801	2.481	0.23
Previous PCI	0.968	0.622	1.508	0.89
Previous myocardial infarction	1.292	0.828	2.016	0.26
Acute coronary syndrome	1.175	0.817	1.691	0.39
Current smoking	1.098	0.754	1.599	0.63

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

Nevertheless, our findings are hypothesis generating, and evidence from a randomized trial comparing COMBO with Orsiro is needed. Despite statistical adjustments with propensity score matching, enrollment bias remains a relevant issue. Compared with the BIO-RESORT randomized trial, the COMBO collaboration comprised all comers participating in observational registries, with no exclusions with respect to anticipated short DAPT duration.

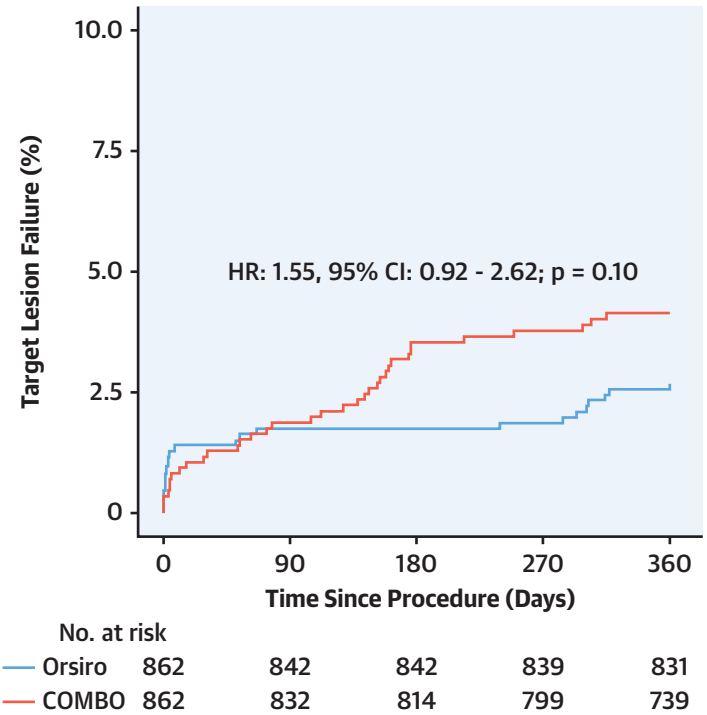
FUTURE IMPLICATIONS. COMBO and Orsiro are 2 relatively new BDP sirolimus-eluting stents with unique advantageous device features. Optical coherence tomographic data have demonstrated neointimal regression between 9 and 24 months in COMBO-treated patients and excellent outcomes without ST events up to 3 years (34). However, randomized long-term data as well translational data are warranted to compare strut coverage and stent healing with these platforms in high-risk subgroups. Long-term follow-up data in all comers will be available from the REMEDEE registry and the BIO-RESORT trial. In addition, the SORT OUT X trial (NCT03216733) will enroll 3,140 all comers to assess the clinical performance (primary endpoint: TLF at 1 year) of COMBO versus Orsiro in a randomized manner. The prespecified event rate of 1-year TLF is estimated at 4.2%.

STUDY LIMITATIONS. The main limitation of this analysis is the nonrandomized comparison between 1 study arm of a randomized clinical trial and a registry database. In general, patients with more comorbidities tend to be excluded from randomized trials. In this pooled cohort, there were imbalances with respect to a higher prevalence of ACS in BIO-RESORT patients, and patients with anticipated short-term DAPT were excluded from this trial. To minimize bias, we performed propensity score-matched analysis, which showed no statistically significant differences in clinical outcomes. Although the analysis of 862 patient pairs in the 2 stent arms resulted in a total of 1,724 well-balanced patients, current randomized clinical trials in all-comers populations typically require larger patient numbers to evaluate potential between-DES differences in the rate of 1-year TLF. We admit that the somewhat limited number of patients in the propensity score-matched analysis limits the power of our present analysis. The adjudication of MI events was influenced by routine cardiac biomarker assessment post-PCI in the BIO-RESORT trial; however, as outlined in the "Methods" section, we considered only biomarker increases in the context of symptoms and/or electrocardiographic or imaging evidence of ischemia. Routine follow-up angiography or follow-up with

CENTRAL ILLUSTRATION **Comparison Between COMBO and Orsiro Stents**

1-Year Target Lesion Failure for COMBO Versus Orsiro Stents

	COMBO stent	ORSIRO stent
Stent platform	Stainlesssteel	Cobalt-chromium
Strut thickness	100 μm	60 μm for stents ≤3.0 mm 80 μm for stents >3.0 mm
Polymer type	Biodegradable	Biodegradable
Polymer resorption	Completely resorbed within 3 months	Resorbed after <24 months
Antiproliferative drug type	Sirolimus 0.75 μg/mm^2	Sirolimus 1.4 μg/mm^2
Drug elution kinetics	Eluted within 30 days	Eluted over a period of 12-14 weeks
Unique feature	Luminal anti-CD34+ antibody covering captures endothelial progenitor cells	Silicon-carbide layer (PROBIO); releases sirolimus from a biodegradable polymer. PROBIO acts as a diffusion barrier between the bare-metal stent surface and the circulation.

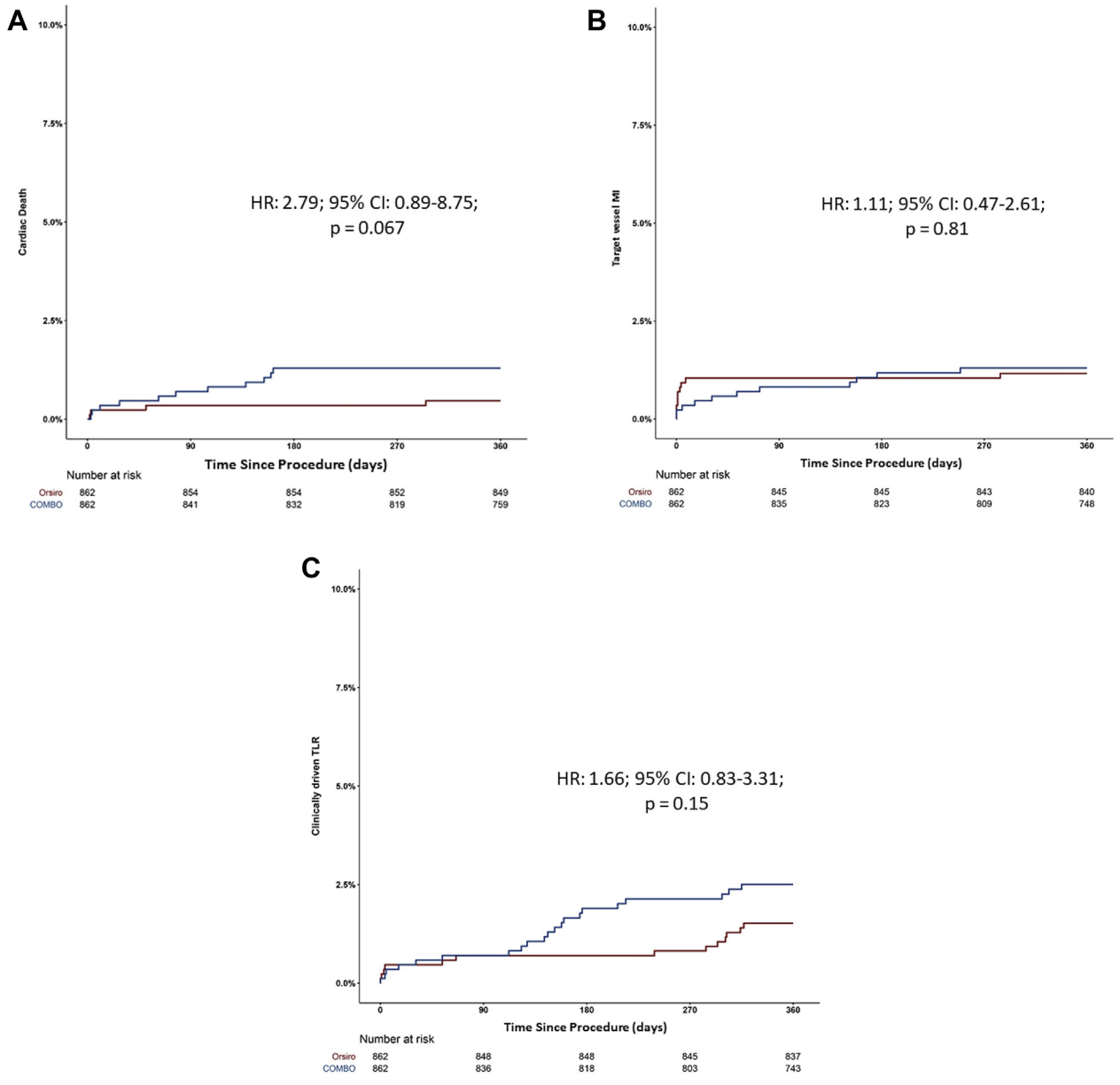


Chandrasekhar, J. et al. J Am Coll Cardiol Intv. 2020;13(7):820-30.

Cumulative incidence of 1-year target lesion failure in all comers treated with the COMBO stent in the COMBO collaboration versus the Orsiro stent in the BIO-RESORT trial: results from the propensity-matched cohort. CI = confidence interval; HR = hazard ratio.

intracoronary imaging (e.g., to obtain data on completeness of strut coverage) was not performed. A special DAPT duration was not mandated; therefore we cannot draw any conclusion regarding the suitability of short-term DAPT with these stents. The present data are unique; although follow-up was limited to 1 year, longer-term data remain of interest.

FIGURE 2 **1-Year Cardiac Death, Target Vessel MI, and TLR in All Comers Treated With the COMBO Stent in the COMBO Collaboration Versus the Orsiro Stent in the BIO-RESORT Trial: Results From the Propensity Score–Matched Cohort**



BIO-RESORT = Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; TLR = target lesion revascularization.

CONCLUSIONS

This patient-level, pooled, propensity score–matched analysis is the first to compare the novel COMBO and ultrathin-strut Orsiro stents in all comers, showing low 1-year TLF rates with both devices. There were no statistically significant differences between the 2 stent types, but randomized clinical trials with long-term follow-up may be warranted to directly compare both new-generation BDP stents.

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PERSPECTIVES

WHAT IS KNOWN? BDP DES may reduce the long-term risk for adverse clinical events and have been shown to be noninferior to contemporary DP DES. The COMBO sirolimus-eluting stent is luminally coated with antibodies to capture circulating endothelial progenitor cells for faster endothelialization, and its polymer is resorbed at 3 months. The Orsiro sirolimus-eluting stent uses an ultrathin-strut platform that is covered by an extremely thin silicon carbide layer to minimize ion leakage, and its polymer is resorbed within 2 years.

WHAT IS NEW? This patient-level pooled analysis of all comers who were treated in 3 studies with COMBO and ultrathin-strut Orsiro stents is the first to compare 1-year clinical outcomes with both devices. The analysis of a well-balanced (propensity score–matched) patient population resulted in 1-year TLF (primary composite endpoint) rates of 4.1% with the COMBO stent and 2.7% with the Orsiro stent, but this difference was not statistically significant. The rates of definite ST were low and similar (0.5% for both stents), which may be interpreted as a safety signal for both devices.

WHAT IS NEXT? Randomized clinical trials with longer term follow-up and imaging studies for mechanistic data are warranted to compare these new-generation DES.

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KEY WORDS anti-CD34$^+$ antibody coating, COMBO dual-therapy stent, endothelial progenitor cell capture, percutaneous coronary intervention, ultrathin-strut Orsiro stent

APPENDIX For a list of investigators, steering committee members, and clinical coordinating center members, please see the online version of this paper.