JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 11, NO. 19, 2018

CORONARY

1-Year Clinical Outcomes of All-Comer Patients Treated With the Dual-Therapy COMBO Stent

Primary Results of the COMBO Collaboration

Robbert J. de Winter, MD, PhD,[a] Jaya Chandrasekhar, MBBS, MS,[b] Deborah N. Kalkman, MD, PhD,[a,b] Melissa B. Aquino, MS,[b] Pier Woudstra, MD,[a] Marcel A. Beijk, MD, PhD,[a] Samantha Sartori, PhD,[b] Usman Baber, MD, MS,[b] Jan G. Tijssen, PhD,[a] Karel T. Koch, MD, PhD,[a] George D. Dangas, MD, PhD,[b] Antonio Colombo, MD,[c] Roxana Mehran, MD,[b] on behalf of the MASCOT, REMEDEE Registry Investigators

ABSTRACT

OBJECTIVES The aim of this study was to evaluate 1-year clinical safety and efficacy of the dual-therapy COMBO stent in a large, all-comers patient-level pooled cohort.

BACKGROUND The COMBO stent (OrbusNeich Medical, Fort Lauderdale, Florida) is a novel stent with abluminal sirolimus elution from a biodegradable polymer and a luminal pro-healing anti-CD34+ antibody layer, which attracts circulating endothelial progenitor cells. These endothelial progenitor cells can quickly mature into normal endothelium, providing rapid endothelialization.

METHODS The MASCOT (Multinational Abluminal Sirolimus Coated biO-engineered stenT) (N = 2,614, 61 global sites) and REMEDEE (Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt Post Market Registry) (N = 1,000, 9 European sites) registries are 2 prospective, multicenter studies evaluating clinical outcomes after attempted COMBO stent placement in all-comer patients undergoing percutaneous coronary intervention. In this patient-level pooled analysis we analyzed 1-year target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization. Furthermore, we determined predictors of 1-year TLF.

RESULTS A total of 3,614 patients (63.5 ± 11.2 years of age; 23.8% women) were included in this analysis. The prevalence of diabetes mellitus was 29.3%, and 54.3% patients presented with acute coronary syndrome. The primary endpoint of 1-year TLF occurred in 140 (3.9%) patients, with incidence of cardiac death in 1.6%, target vessel myocardial infarction in 1.2%, clinically driven target lesion revascularization in 2.2%, and definite stent thrombosis in 0.5% patients. Insulin-treated diabetes mellitus, chronic renal failure, and American College of Cardiology/American Heart Association lesion type B2/C were independent predictors of 1-year TLF.

CONCLUSIONS In this large patient-level pooled analysis of patients treated with the dual-therapy COMBO stent excellent results at 1-year were observed. (MASCOT - Post Marketing Registry [MASCOT]; NCT02183454; Prospective Registry to Assess the Long-term Safety and Performance of the COMBO Stent [REMEDEE Reg]; NCT01874002) (J Am Coll Cardiol Intv 2018;11:1969–78) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.

From the [a]Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [b]Department of Cardiology, Icahn School of Medicine at Mount Sinai Hospital, New York, New York; and the [c]Department of Cardiology, San Raffaele Hospital, Milan, Italy. The Academic Medical Center received an unrestricted research grant from OrbusNeich Medical BV (Hoevelaken, the Netherlands). OrbusNeich Medical (Fort Lauderdale, Florida) is the sponsor of the

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2018.04.038

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CKD = chronic kidney disease

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

DM = diabetes mellitus

PCI = percutaneous coronary intervention

ST = stent thrombosis

TLF = target lesion failure

TLR = target lesion revascularization

TV-MI = target vessel myocardial infarction

Second-generation drug-eluting stents (DES) have improved clinical outcomes after percutaneous coronary intervention (PCI) with the use of thinner stent struts, biodegradable polymers, and novel antiproliferative medication compared with first-generation DES (1,2). Although the rates of target vessel myocardial infarction (TV-MI) and stent thrombosis (ST) have significantly decreased in contemporary PCI, similar decreases in the rates of in-stent restenosis have not been observed (3). Therefore, newer stent technologies have focused on mitigating this adverse outcome (4).

SEE PAGE 1979

The COMBO stent (OrbusNeich Medical, Fort Lauderdale, Florida) was designed to promote rapid and healthy strut coverage using anti-CD34+ antibodies. The stent combines 2 different treatment strategies, an antirestenotic and an antithrombotic strategy, and is therefore referred to as the dual-therapy stent (5). This novel stent is the investigational device of 2 large, prospective registries: REMEDEE (Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt Post Market Registry) and MASCOT (Multinational Abluminal Sirolimus Coated biO-engineered stenT) (6). In the current report from the COMBO collaboration, we conducted a pooled patient-level analysis from the REMEDEE and MASCOT registries, to evaluate the 1-year clinical outcomes after dual-therapy stent treatment in all-comer patients. Furthermore, we sought to identify the predictors of 1-year target lesion failure (TLF) after COMBO stent placement.

METHODS

COMBO STENT. This dual-therapy stent is a stainless steel stent with 100-μm struts and 2 therapeutic layers. The anti-restenotic abluminal layer consists of a biodegradable polymer eluting sirolimus (5 μg/mm) and the pro-healing luminal layer consists of an anti-CD34+ antibody layer. This unique bioengineered antibody layer attracts circulating endothelial progenitor cells that bind to the stent surface. These endothelial progenitor cells, shortly after capture, start to develop into normal endothelial cells, allowing for rapid endothelialization of the stent (**Figure 1**) (7,8). With rapid endothelialization, the dual antiplatelet therapy (DAPT) duration that is recommended for a minimum of 6 months after PCI with DES in current guidelines, might safely be shortened (9,10). Second, with healthy endothelial coverage of the stent lower rates of in-stent restenosis could be expected.

The COMBO stent received the Conformité Européene mark in 2013 and has been available on the European market since then. China Food and Drug Administration and Japanese Pharmaceuticals and Medical Devices Agency approval are currently pending.

MASCOT AND REMEDEE REGISTRIES. The REMEDEE registry (NCT01874002) is a European, prospective, multicenter, investigator-initiated registry evaluating outcomes in patients undergoing PCI with attempted COMBO stent placement. Primary results have been published previously (6,11). The registry included 9 European sites in 5 different countries (the Netherlands, Latvia, Northern Ireland, Spain, and Luxembourg). A thousand patients were enrolled between June 2013 and March 2014. This registry involves the collection of baseline demographic, clinical, and angiographic data, as well as follow-up data in consecutive patients who had the COMBO stent to treat (a) coronary lesion(s) in the setting of routine clinical care. Follow-up was conducted by either outpatient visit or telephone call with the patient at 30 days, 6 months, 12 months, and yearly, with this ongoing to 5 years post-COMBO stent placement. Full baseline and event monitoring was done on site with collection of all documentation of events. All events were adjudicated by an independent clinical event committee.

The MASCOT study (NCT02183454) is a post-marketing registry. This multicenter, multinational, prospective registry population consists of all-comer

MASCOT registry. Dr. de Winter has received institutional research grant support from OrbusNeich. Dr. Mehran has received institutional research grant support from AstraZeneca, Bayer, Beth Israel Deaconess, Bristol-Myers Squibb/Sanofi, CSL Behring, Eli Lilly, Daiichi Sankyo, Medtronic, Novartis, and OrbusNeich; has received medical monitor funding from Claret Medical; has served as a consultant for Abbott Vascular, Boston Scientific, CardioKinetix, Cardiovascular Systems Inc., Medscape, Shanghai BraccoSine Pharmaceutical, Spectranetics; has received executive committee or advisory board funding from Janssen Pharmaceuticals, Osprey Medical, Bristol-Myers Squibb; has served on the Data Safety Monitoring Board for Watermark Research Partners; and has a spouse that has served as a consultant to The Medicines Company and Abiomed. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 26, 2018; revised manuscript received March 21, 2018, accepted April 21, 2018.

patients undergoing PCI with attempted placement of at least 1 COMBO stent as part of routine clinical care. A total of 2,614 patients were enrolled from 61 global centers (Europe, Asia, Middle East, and South America) between June 2014 and March 2016. Patients were contacted at 30 ± 7 days, 6 months ± 14 days, and 12 months ± 28 days of follow-up. Independent monitoring was performed for data quality. All events were adjudicated by an independent clinical event committee. The primary endpoint was TLF at 1-year follow-up.

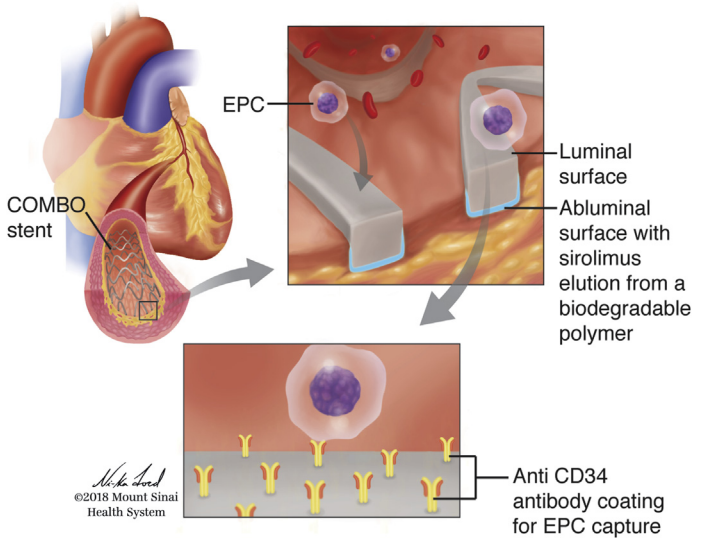
There were limited exclusion criteria for both registries: high probability of nonadherence to the follow-up requirements (due to social, psychological, or medical reasons), currently participating in another investigational drug or device study in which routine angiographic follow-up is planned, a life expectancy of <1 year, or explicit refusal of participation in the registry. The MASCOT registry additionally excluded patients undergoing PCI for treatment of ST, however, treatment of in-stent restenosis with COMBO was allowed in both registries. In both studies, DAPT was prescribed per local recommendations and in keeping with guidelines.

All patients provided written informed consent for enrollment in the registries. Conduct of the studies was in keeping with the Declaration of Helsinki and Good Clinical Practice. The study investigators are shown in the Online Appendix.

This study is a pre-specified pooled patient-level analysis of the MASCOT and REMEDEE registries. **Figure 2** presents the consort diagram. The REMEDEE registry was initiated and conducted by the Academic Medical Center-University of Amsterdam. The Academic Medical Center-University of Amsterdam received an unrestricted research grant from OrbusNeich Medical for the conduct of the registry. OrbusNeich Medical was the sponsor of the MASCOT registry (management of sites with respect to regulatory and contractual aspects). OrbusNeich Medical had no part in the COMBO collaboration, and they were not involved in the analysis of the data, presentation, or handling of results.

CLINICAL ENDPOINTS. The primary outcome of interest for the present analysis is TLF at 1-year follow-up. This composite endpoint consists of cardiac death, TV-MI, or target lesion revascularization (TLR) by either PCI or coronary artery bypass graft (CABG). Myocardial infarction (MI) was adjudicated according to the third universal definition (12). However, periprocedural cardiac biomarkers were not collected routinely as this was not mandated by both protocols (registry design). Secondary endpoint of ST (definite or probable) was defined according to the Academic Research Consortium criteria (13). Lesion and procedural characteristics are reported by visual estimation, and core lab-adjudicated quantitative coronary angiography was not conducted in both studies.

FIGURE 1 The COMBO Stent

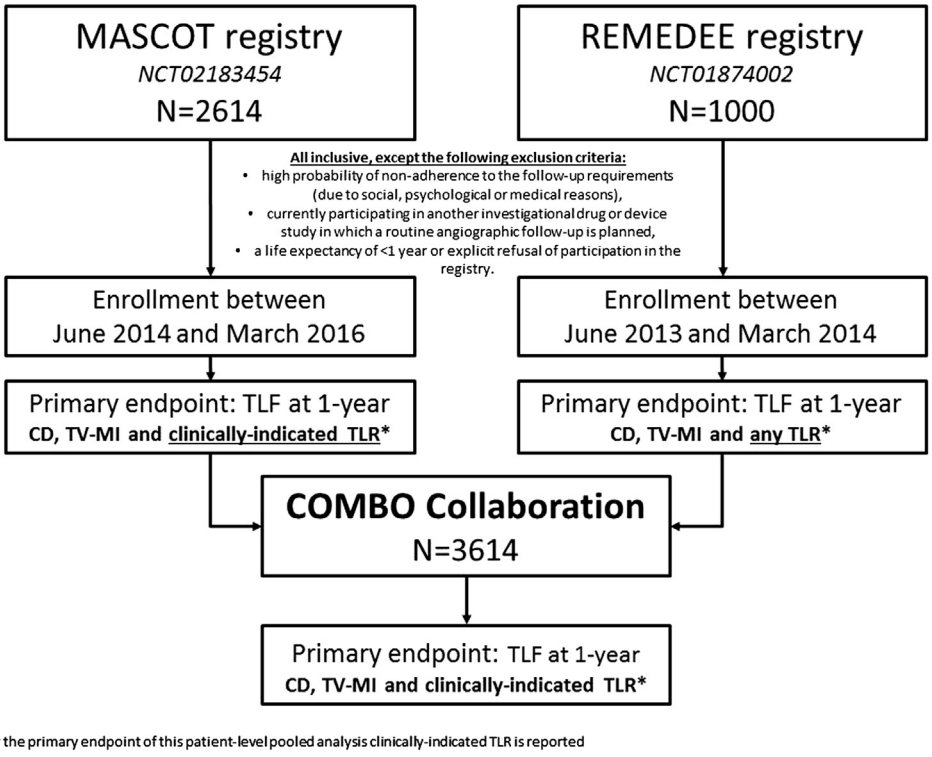


The dual-therapy stent technology of the COMBO stent. The dual-therapy treatment mechanism consists of the antirestenotic sirolimus layer on the abluminal side, and a circumferential (both luminal and abluminal) anti-CD34+ antibody layer (the endothelial progenitor cell [EPC] capturing mechanism) for rapid endothelialization.

At each contact (30 days, 6 months, and 12 months) medication use was registered, including DAPT discontinuation. In the MASCOT registry all DAPT cessation events were also adjudicated by an independent clinical events committee and classified into the following modes: interruption, discontinuation, or disruption (14). Device success was defined as the percentage of patients with successful delivery and deployment of the COMBO stent to the target lesion, final diameter stenosis ≤20% by visual estimation, and final Thrombolysis In Myocardial Infarction flow grade 3 by visual assessment. Procedural success was considered in patients with device success without any periprocedural complications.

DATA ANALYSIS. The COMBO collaboration is a pooled patient level analysis. Endpoints were harmonized between both registries; the REMEDEE registry considered all TLR, whereas the MASCOT registry only included clinically driven TLR in the

FIGURE 2 Overview Table of the Study Design of the COMBO Collaboration



CD = cardiac death; MASCOT = Multinational Abluminal Sirolimus Coated biO-engineered stenT; REMEDEE = Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt Post Market Registry; TLF = target lesion failure; TLR = target lesion revascularization; TV-MI = target vessel myocardial infarction.

primary endpoint. For the present analysis only clinically driven TLR was considered. Variables were controlled to ascertain correct pooling of all variables where possible. Patients were censored at 1 year or at the time of death, whichever came first. In general, summary statistics for continuous variables included mean ± SD or median (interquartile range). Binary variables are described as numbers and frequencies. For time-to-event data, Kaplan-Meier estimates at the indicated time points are displayed along with 95% confidence intervals (CIs). In addition, survival curves are constructed for all time to event secondary endpoints using Kaplan-Meier methods. The effect of different baseline variables on 1-year TLF was assessed. Univariate and multivariate predictors of TLF were assessed including all components of the PARIS (Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients) thrombotic risk score (15). Diabetes mellitus (DM) (none, non-insulin treated, and insulin-treated), acute coronary syndrome (ACS) at admission (non-ACS, troponin negative, troponin positive ACS), current smoking, prior PCI, prior CABG, and chronic kidney disease (CKD) were evaluated. Additionally, associations between other risk factors and TLF were assessed: female sex, older age (≥65 years), hypertension, peripheral vascular disease, prior MI, total stent length >30 mm, and at least 1 B2/C lesion. Univariate analysis was performed for each risk factor with Kaplan-Meier estimates and log-rank tests. Backward multiple regression analysis was performed using Cox regression methods. All p values <0.05 were considered clinically significant. All descriptive statistical analyses were performed using SPSS statistical software version 24 (IBM Corporation, Armonk, New York).

RESULTS

BASELINE CHARACTERISTICS. A total of 3,614 patients were included in the analysis. In Table 1 the baseline characteristics of the overall cohort

TABLE 1 Baseline Characteristics of All Patients Included in the REMEDEE and MASCOT Registries (N = 3,614)

Age, yrs	63.5 ± 11.2
Female	861 (23.8)
DM	1,050 (29.3)
Insulin treatment for DM	272 (7.5)
Hypertension	2,422 (67.0)
Hypercholesterolemia	2,101 (58.1)
Family history of CAD	1,107 (30.6)
Congestive heart failure	224 (6.2)
Chronic renal failure	231 (6.4)
Peripheral vascular disease	212 (5.9)
Previous stroke	173 (4.8)
Prior myocardial infarction	858 (23.7)
Previous PCI	966 (26.7)
Previous CABG	206 (5.7)
Current smoker	1,009 (27.9)
Indication for PCI	
Asymptomatic	295 (8.2)
Stable angina	1,346 (37.2)
STEMI	789 (21.8)
NSTEMI	600 (16.6)
Unstable angina	576 (15.9)
Other	6 (0.2)

Values are mean ± SD or n (%).

CABG = coronary artery bypass grafting; CAD = coronary artery disease; DM = diabetes mellitus; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Lesion and Procedural Characteristics (N = 4,445)

Pre-procedure reference vessel diameter, mm	3.1 ± 1.5
Lesion length, mm	19.4 ± 11.2
Diameter stenosis pre-procedure, %	86.7 ± 17.7
Thrombus present	624 (14.0)
If yes, was thrombus aspirated?	334 (53.5)
TIMI flow grade pre-procedure	
0	629 (14.2)
1	350 (7.9)
2	649 (14.7)
3	2,787 (63.1)
Pre-dilatation	2,993 (67.4)
Number of treated lesions per patient	1.2 ± 0.5
Location of lesion	
RCA	1,354 (30.5)
LAD	1,682 (37.9)
LCX	1,305 (29.3)
LMCA	79 (1.8)
Graft	24 (0.5)
ACC/AHA lesion classification	
A	479 (11.0)
B1	1,393 (32.0)
B2	1,672 (38.4)
C	811 (18.6)
Number of COMBO stents per lesion	1.1 ± 0.4
Post-dilatation	2,350 (53.0)
Total stent length, mm	22.7 ± 11.3
Final diameter stenosis, %	2.8 ± 12.5
TIMI flow grade 3 post-procedure	4,343 (98.9)
Procedural medication	
Unfractionated heparin	2,793 (77.3)
GP IIb/IIIa inhibitors	406 (11.2)
$P2Y_{12}$ at discharge	
Clopidogrel	2,470 (68.9)
Ticagrelor	983 (27.4)
Prasugrel	131 (3.7)

Values are mean ± SD or n (%).

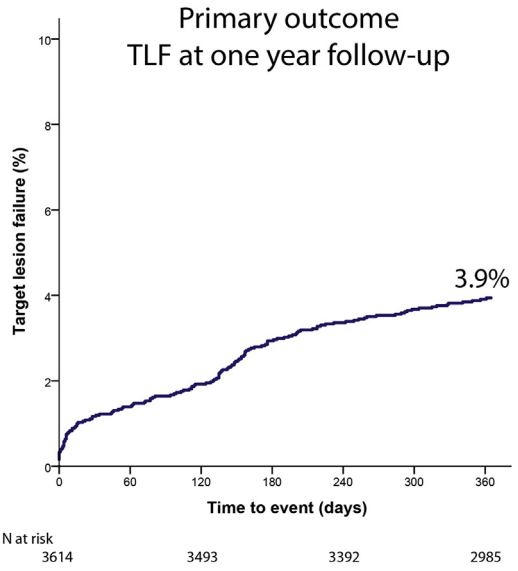
ACC =American College of Cardiology; AHA = American Heart Association; GP = glycoprotein; LAD = left anterior descending artery; LCx = left circumflex artery; LMCA = left main coronary artery; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

are presented. Patients had a mean age of 63.5 ± 11.2 years, 23.8% were women (n = 861), 29.3% of patients had DM, including 272 patients with insulin-treated DM (7.5% of all patients). A history of prior PCI was observed in 26.7% of patients, and 23.7% had a prior MI. Current smokers accounted for 27.9% of all patents. Indication for PCI was ACS in more than one-half of patients (n = 1,965, 54.3%), with 21.8% presenting with ST-segment elevation MI, 16.6% with non-ST segment elevation MI, and 15.9% with unstable angina.

Lesion characteristics are shown in Table 2. A total of 4,445 lesions were treated in 3,614 patients. The most frequently treated vessel was the left anterior descending artery, in 37.0% of cases. American College of Cardiology/American Heart Association lesion type B2/C was observed in 2,483 lesions (57.0%), and treatment of in-stent restenosis accounted for 2.7% of lesions (n = 119). The mean pre-procedural reference vessel diameter was 3.1 ± 1.5 mm, with a lesion length of 19.4 ± 11.2 mm and mean pre-procedural diameter stenosis of 86.7 ± 17.7%. In 14.0% of cases intracoronary thrombus was present, and aspiration was performed in 53.5% of these. Pre-procedural TIMI flow grade 3 was observed in 2,787 lesions (63.1%). TIMI flow grade 3 post-procedure was seen in 4,343 patients (98.9%). In 8 patients no COMBO stent could be implanted. The rate of device success was 96.3% and rate of procedural success was 94.5%.

CLINICAL OUTCOMES. One-year follow-up was obtained in 3,489 patients (96.5%). Median follow-up duration was 365 days (interquartile range: 365 to 365 days). The primary outcome of TLF occurred in 140 patients (3.9%) at 1-year follow-up. The Kaplan-Meier plot of TLF is illustrated in Figure 3. Cardiac death occurred in 55 patients (1.6%), TV-MI in 43 patients

FIGURE 3 TLF at 1-Year Follow-Up



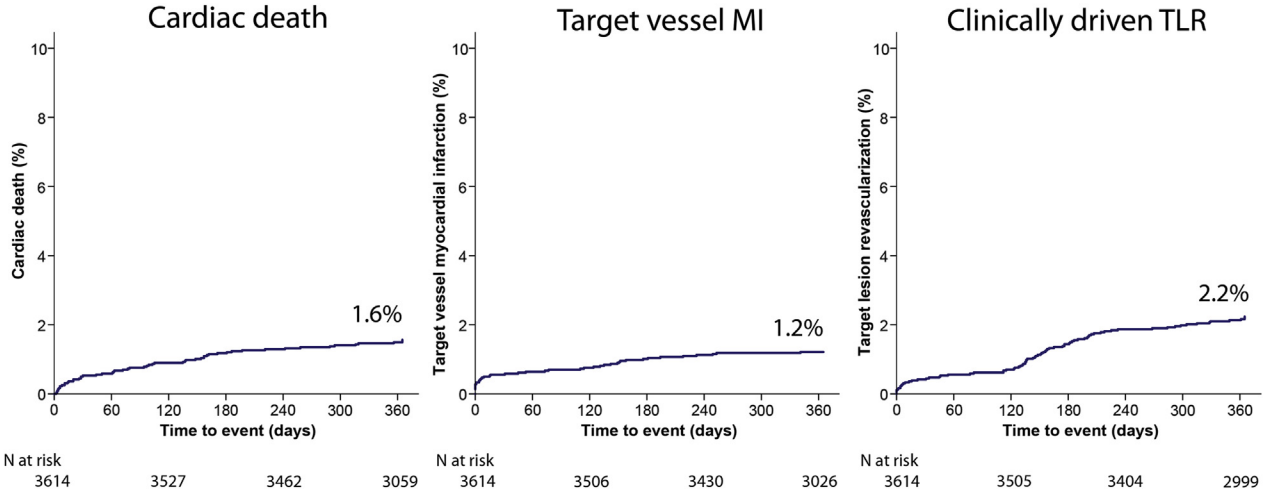
Target lesion failure (TLF) at 1-year follow-up in all-comer patients treated with COMBO stent. Kaplan-Meier estimates of all patients with 1-year TLF from the COMBO collaboration.

(1.2%), and clinically driven TLR in 78 patients (2.2%) (Figure 4). In 17 patients (0.5%) definite ST was observed (Figure 5), of which 5 cases were acute, 6 were subacute, and 6 were late ST. Definite or probable ST was seen in 0.8% of patients (n = 30). Table 3 shows clinical outcomes at 30-day, 6-month, and 1-year follow-up.

Early DAPT cessation was observed at 30 days after index PCI in 86 patients (2.4%). DAPT discontinuation at 6-month follow-up was observed in 174 patients (7.6%).

PREDICTORS OF TLF. Univariate analysis was conducted for associations between 1-year TLF and the 6 baseline variables from the PARIS thrombotic risk score model and 7 additional baseline variables described under the Methods section. Univariate analyses of ACS versus non-ACS, DM versus non-DM, current smoking, and prior PCI showed no statistically significant differences. Insulin-treated DM was associated with higher 1-year TLF with a hazard ratio (HR) of 2.08 (95% CI: 1.30 to 3.34; $p < 0.01$). Troponin-positive ACS (consisting of all ST-segment elevation MI and non-ST segment elevation MI patients; HR: 1.40; 95% CI: 1.01 to 1.96; $p = 0.05$), prior CABG (HR: 1.84; 95% CI: 1.06 to 3.19; $p = 0.03$), CKD (HR: 2.19; 95% CI: 1.34 to 3.59; $p < 0.01$), peripheral vascular disease (HR: 1.97; 95% CI: 1.15 to 2.27; $p = 0.01$), presence of at least 1 B2/C lesion (HR: 1.96; 95% CI: 1.34 to 2.86; $p < 0.01$), and advanced age (HR: 1.41; 95% CI: 1.01 to 1.97; $p = 0.04$) were also associated with higher risk of 1-year TLF on univariate analysis. In multivariate analysis insulin-treated DM, CKD, and presence of at least 1 B2/C lesion were predictors of 1-year TLF, as presented in Table 4.

FIGURE 4 Cardiac Death, Target Vessel MI, and TLR



Kaplan-Meier estimates of all patients with 1-year clinical events from the COMBO collaboration. MI = myocardial infarction; TLR = target lesion revascularization.

DISCUSSION

MAIN RESULTS. This primary report from the COMBO collaboration presents the largest cohort evaluating 1-year clinical outcomes in patients treated with the COMBO dual-therapy stent. The main findings are: 1) The treatment of CAD with the COMBO stent resulted in overall low clinical event rates, with 1-year TLF of 3.9% and 1-year definite or probable ST of 0.8%; 2) 1-year rate of cardiac death was 1.6%, TV-MI was 1.2%, and clinically driven TLR was 2.2%; and 3) insulin-treated DM, chronic kidney disease, and presence of at least 1 B2/C lesion were independent predictors of 1-year TLF after COMBO stent placement, emphasizing the need for improving treatment options in these patient groups.

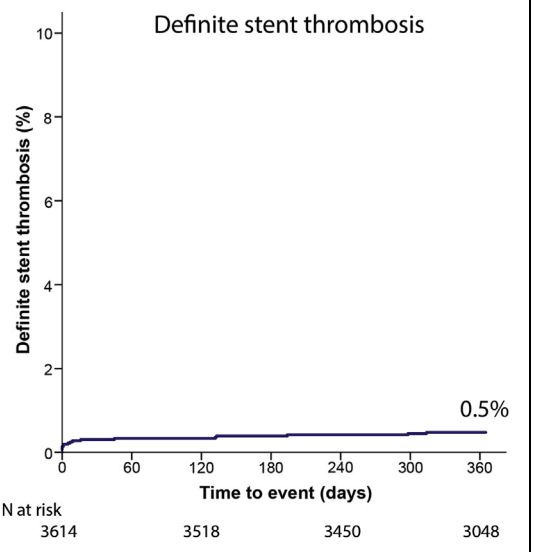
CLINICAL PERFORMANCE OF THE COMBO STENT. The presented low event rates at 1 year after COMBO stent placement are in line with previous publications investigating clinical outcomes with the COMBO stent (16–18). Both in-stent restenosis and stent thrombosis rates are low. Safety profile of the COMBO stent appears excellent when compared with other newer generation DES, especially when compared with results from randomized trials evaluating clinical outcomes of current in use DES and drug-eluting bioresorbable scaffolds (19–24).

PREDICTORS OF TLF. In this all-comers patient cohort of over 3,600 patients treated with COMBO insulin-treated DM, CKD, and at least 1 B2/C lesion were prognostic baseline characteristics that independently predicted 1-year TLF. Insulin-treated DM and CKD were also found to be predictors in the PARIS thrombotic risk score model. This model was developed to predict the occurrence of coronary thrombotic events (defined as ST or myocardial infarction) at 2-year follow-up and was derived from 5,031 patients undergoing PCI in the PARIS registry (14,15). However, the other PARIS thrombotic risk factors; non-insulin-dependent DM, (troponin-positive) ACS, current smoking, prior PCI, and prior CABG were not associated with higher risk of TLF in our dataset in a multivariate regression model. This discordance may be explained by different follow-up periods (1 year vs. 2 years of follow-up) and/or different study endpoints (TLF vs. coronary thrombotic event), or less likely may be attributed to a specific treatment effect of the COMBO stent.

CKD is a well-known risk factor for adverse outcomes in male and female patients (25–27). A recently published study showed that insulin-treated DM patients have a higher risk of death or myocardial infarction at 1-year follow-up irrespective of presence of CKD (28). Similar to our findings, CKD resulted in an overall higher risk of adverse clinical outcomes compared with insulin-treated DM. In patients with insulin-treated DM receiving DES higher rates of in-stent restenosis and other adverse clinical outcomes are reported, compared to other patients (29–31). The American College of Cardiology/American Heart Association lesion classification is an indicator of severity of the lesion and has been shown to be a good predictor of adverse clinical outcomes (32).

FUTURE PERSPECTIVES. The REMEDEE registry will report clinical outcomes up to 5-year follow-up. The SORT OUT X (Randomized Clinical Comparison of a

FIGURE 5 Definite Stent Thrombosis



Kaplan-Meier estimates of all patients with definite stent thrombosis from the COMBO collaboration.

TABLE 3 Clinical Outcomes at 30-Day, 6-Month, and 12-Month Follow-Up

	30-Day Follow-Up	6-Month Follow-Up	12-Month Follow-Up
Target lesion failure	42 (1.2)	105 (3.0)	140 (3.9)
Cardiac death	19 (0.5)	42 (1.2)	55 (1.6)
Target vessel myocardial infarction	20 (0.6)	36 (1.0)	43 (1.2)
Target lesion revascularization, clinically driven	15 (0.4)	51 (1.4)	78 (2.2)
Definite stent thrombosis	11 (0.3)	14 (0.4)	17 (0.5)
Definite or probable stent thrombosis	23 (0.6)	26 (0.7)	30 (0.8)

Values are n (Kaplan-Meier %).

TABLE 4 Predictors of TLF at 1 Year After COMBO Stent Placement

PARIS Thrombotic Risk Score Model		Univariate HR (95% CI), p Value	Multivariate HR (95% CI), p Value
DM	DM vs. non-DM	1.32 (0.93–1.87), p = 0.12	
	ITDM vs. all others	**2.08 (1.30–3.34), p < 0.01**	**1.85 (1.14–3.01), p = 0.01**
ACS	ACS vs. non-ACS	1.36 (0.97–1.91), p = 0.08	
	Trop+ ACS vs. all others	**1.40 (1.01–1.96), p = 0.05**	**ns**
Current smoking		1.15 (0.80–1.65), p = 0.46	
Prior PCI		1.30 (0.91–1.85), p = 0.15	
Prior CABG		**1.84 (1.06–3.19), p = 0.03**	**ns**
Chronic kidney disease		**2.19 (1.34–3.59), p < 0.01**	**2.07 (1.25–3.43), p < 0.01**
Additional risk factors			
Female		0.99 (0.67–1.46), p = 0.94	
Advanced age	**>65 yrs vs. ≤65 yrs**	**1.41 (1.01–1.97), p = 0.04**	**ns**
Hypertension		0.76 (0.56–1.11), p = 0.17	
Peripheral vascular disease		**1.97 (1.15–2.27), p = 0.01**	**ns**
Prior MI		1.38 (0.96–1.98), p = 0.08	
Total stent length	>30 mm vs. ≤30 mm	1.09 (0.75–1.60), p = 0.64	
At least 1 B2/C lesion		**1.96 (1.34–2.86), p < 0.01**	**1.94 (1.33–2.85), p < 0.01**

The **bold rows** indicate the univariate and multivariate predictors of 1-year TLF.

ACS = acute coronary syndrome(s); DM = diabetes mellitus; ITDM = insulin-treated diabetes mellitus; MI = myocardial infarction; PARIS = Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients; trop+ = troponin positive; other abbreviations as in Table 1.

Combined Sirolimus Eluting and Endothelial Progenitor Cell COMBO Stent With a Sirolimus-eluting OSIRO Stent in Patients Treated With Percutaneous Coronary Intervention) trial (NCT03216733) is currently enrolling all-comers patients. Patients are assigned in a 1:1 manner to either the COMBO stent or Orsiro stent (Biotronik, Bülach, Switzerland), a very thin-strut sirolimus-eluting stent (60 μm for nominal stent sizes; ≥3.5 mm: 80 μm) to compare 1-year TLF. The results from this trial may provide better understanding of the added value of the pro-healing layer.

STUDY LIMITATIONS AND STRENGTHS. In this large patient-level pooled analysis of patients treated with the novel COMBO stent the main limitation is the lack of a comparator arm. Moreover, shorter DAPT duration after COMBO stent was not a primary endpoint of this analysis. Due to the registry design, DAPT had to be prescribed according to national and international guidelines. Therefore, the hypothetical benefit of the rapid endothelialization by the pro-healing layer could not be evaluated in this analysis. Further, angiographic data were operator reported and not adjudicated by an independent core laboratory.

However, this is the largest cohort of patients treated with the novel COMBO stent. Patients in this patient-level pooled analysis were enrolled globally and represent a real-world all-comer PCI population. This analysis has allowed not only examination of clinical outcomes after COMBO dual-therapy stent, but also evaluation of predictors of TLF at 1-year follow-up. The COMBO dual-therapy stent is noted to be a safe and effective device, with promising results regarding the short duration of DAPT. Upcoming trials should focus on patients with high risk for anticipated early DAPT cessation, including those at high bleeding risk, to assess the safety and efficacy of novel stents in these patients.

CONCLUSIONS

In the largest cohort of all-comers patients treated with the novel dual-therapy COMBO stent, this platform was observed to be safe and effective. In our study of over 3,500 all-comers patients enrolled globally, TLF at 1-year follow-up was 3.9%. The 1-year definite or probable ST rate was 0.8%. Future randomized trials will test these results against other third-generation devices.

ACKNOWLEDGMENTS The authors thank all patients for their participation in these registries. All interventional cardiologists and catheterization laboratory nurses are acknowledged for their contributing work.

ADDRESS FOR CORRESPONDENCE: Dr. Roxana Mehran, Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1030, New York, New York 10029. E-mail: roxana.mehran@mountsinai.org.

PERSPECTIVES

WHAT IS KNOWN? The novel dual-therapy COMBO stent has shown rapid endothelialization in preclinical work and smaller clinical studies. The COMBO stent has been investigated in 2 large all-comer registries, with over 3,500 patients treated with this stent.

WHAT IS NEW? In this international research collaboration, we present the 1-year clinical event rates of patients treated with the COMBO stent across several global sites. One-year TLF rates remain low after COMBO dual-therapy stenting. Insulin-treated diabetes mellitus, chronic kidney disease, and B2/C type lesions were independent predictors of 1-year TLF.

WHAT IS NEXT? A large randomized clinical trial is currently enrolling patients (the SORT OUT X trial) to compare treatment with either the COMBO or Orsiro stent. Results will objectively demonstrate the value of the added pro-healing layer to DES.

REFERENCES

1. Navarese EP, Kowalewski M, Kandzari D, et al. First-generation versus second-generation drug-eluting stents in current clinical practice: updated evidence from a comprehensive meta-analysis of randomised clinical trials comprising 31 379 patients. Open Heart 2014;1:e000064.

2. Alfonso F, Fernandez C. Second-generation drug-eluting stents moving the field forward. J Am Coll Cardiol 2011;58:26–9.

3. Byrne RA, Stone GW, Ormiston J, Kastrati A. Coronary balloon angioplast, stents, and scaffolds. Lancet 2017;390:781–92.

4. Stefanini GG, Byrne RA, Windecker S. State of the art: coronary artery stents – past, present and future. EuroIntervention 2017;13:706–16.

5. Granada JF, Inami S, Aboodi MS, et al. Development of a novel prohealing stent designed to deliver sirolimus from a biodegradable abluminal matrix. Circ Cardiovasc Interv 2010;3:257–66.

6. Woudtsra P, Kalkman DN, den Heijer P, et al. 1-year results of the REMEDEE registry. J Am Coll Cardiol Intv 2016;9:1127–34.

7. Larsen K, Cheng C, Tempel D, et al. Capture of circulatory endothelial progenitor cells and accelerated re-endothelialization of a bio-engineered stent in human ex vivo shunt and rabbit denudation model. Eur Heart J 2012;33:120–8.

8. Nakazawa G, Granada JF, Alviar CL, et al. Anti-CD34 antibodies immobilized on the surface of sirolimus-eluting stents enhance stent endothelialization. J Am Coll Cardiol Intv 2010;3:68–75.

9. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the. Eur Heart J 2018;39:213–360.

10. Levine GN, Bates ER, Bittl JA, et al. ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082–115.

11. Kalkman DN, Woudstra P, Menown IBA, et al. Two-year clinical outcomes of patients treated with the dual-therapy stent in a 1000 patient all-comers registry. Open Heart 2017;4:e000634.

12. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.

13. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

14. Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet 2013;382:1714–22.

15. Baber U, Mehran R, Giustino G, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. J Am Coll Cardiol 2016;67:2224–34.

16. Haude M, Lee SWL, Worthley SG, et al. The REMEDEE trial: a randomized comparison of a combination sirolimus-eluting endothelial progenitor cell capture stent with a paclitaxel-eluting stent. J Am Coll Cardiol Intv 2013;6:334–43.

17. Jaguszewski M, Aloysius R, Wang W, et al. The REMEDEE-OCT study: an evaluation of the bioengineered COMBO dual-therapy CD34 antibody–covered sirolimus-eluting coronary stent compared with a cobalt-chromium everolimus-eluting stent in patients with acute coronary syndromes: insights from optical coherence tomography imaging analysis. J Am Coll Cardiol Intv 2017;10:489–99.

18. Lee SWL, Lam SCC, Tam FCC, et al. Evaluation of early healing profile and neointimal transformation over 24 months using longitudinal sequential optical coherence tomography assessments and 3-year clinical results of the new dual-therapy endothelial progenitor cell capturing sirolimus-elu. Circ Cardiovasc Interv 2016;9:e003469.

19. Sorrentino S, Giustino G, Mehran R, et al. Everolimus-eluting bioresorbable scaffolds versus everolimus-eluting metallic stents. J Am Coll Cardiol 2017;69:3055–66.

20. Wykrzykowska JJ, Kraak RP, Hofma SH, et al. Bioresorbable scaffolds versus metallic stents in routine PCI. N Engl J Med 2017;376:2319–28.

21. Xu B, Gao R, Yang Y, et al. Biodegradable polymer-based sirolimus-eluting stents with differing elution and absorption kinetics. J Am Coll Cardiol 2016;67:2249–58.

22. Tijssen RYG, Kraak RP, Lu H, et al. Expert Review of Medical Devices Evaluation of the MiStent sustained sirolimus eluting biodegradable polymer coated stent for the treatment of coronary artery disease : does uniform sustained abluminal drug release result in earlier strut coverage and better safety profile ? Evaluation of the MiStent sustained sirolimus eluting biodegradable polymer coated stent for the treatment of coronary artery disease : does uniform sustained. Expert Rev Med Devices 2017;14:325–34.

23. de Winter RJ, Katagiri Y, Asano T, et al. A sirolimus-eluting bioabsorbable polymer-coated stent (MiStent) versus an everolimus-eluting durable polymer stent (Xience) after percutaneous coronary intervention (DESSOLVE III). Lancet 2018;391:431–40.

24. Birgelen C Von, Kok MM, Heijden LC Van Der, et al. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIORESORT): a three-arm, randomised, non-inferiority trial. Lancet 2016;388:2607–17.

25. Angelantonio E Di, Chowdhury R, Sarwar N. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. BMJ 2010;341:c4986.

26. Baber U, Giustino G, Sartori S, et al. Effect of chronic kidney disease in women undergoing percutaneous coronary intervention with drug-eluting stents. J Am Coll Cardiol 2016;9:28–38.

27. Saltzman AJ, Stone GW, Claessen BE, et al. Long-term impact of chronic kidney disease in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. J Am Coll Cardiol Intv 2011;4:1011–9.

28. Chamaria S, Bhatheja S, Vengrenyuk Y, et al. Prognostic relation between severity of diabetes mellitus (on or off insulin) ± chronic kidney disease with cardiovascular risk after percutaneous coronary intervention. Am J Cardiol 2018;121:168–76.

29. Zhao L, Xu W, Wang L, et al. Influence of insulin resistance on in-stent restenosis in patients undergoing coronary drug-eluting stent implantation after long-term angiographic follow-up. Coron Artery Dis 2015;26:5–10.

30. Cutlip DE, Chhabra AG, Baim DS, et al. Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. Circulation 2004;110:1226–31.

31. Kereiakes DJ, Cutlip DE, Applegate RJ, et al. Outcomes in diabetic and nondiabetic patients treated with everolimus- or paclitaxel-eluting stents results from the SPIRIT IV clinical trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System). J Am Coll Cardiogy 2010;56:2084–9.

32. Theuerle J, Yudi MB, Farouque O, et al. Utility of the ACC/AHA lesion classification as a predictor of procedural, 30-day and 12-month outcomes in the contemporary percutaneous coronary intervention era. Catheter Cardiovasc Interv 2017 Nov 15 [E-pub ahead of print].

KEY WORDS drug-eluting stent(s), endothelial progenitor cell anti-CD34+ antibody, percutaneous coronary intervention, stent healing

APPENDIX For a list of investigators, please see the online version of this paper.