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1-Year Results of the REMEDEE Registry

Clinical Outcomes After Deployment of the Abluminal Sirolimus-Coated Bioengineered (Combo) Stent in a Multicenter, Prospective All-Comers Registry

Pier Woudstra, MD,[a] Deborah N. Kalkman, MD,[a] Peter den Heijer, MD, PhD,[b] Ian B.A. Menown, MD,[c] Andrejs Erglis, MD,[d] Harry Suryapranata, MD, PhD,[e] Karin E. Arkenbout, MD, PhD,[f] Andrés Iñiguez, MD, PhD,[g] Arnoud W.J. van't Hof, MD, PhD,[h] Philippe Muller, MD,[i] Jan G.P. Tijssen, PhD,[a] Robbert J. de Winter, MD, PhD[a]

ABSTRACT

OBJECTIVES This registry evaluated the safety and clinical outcomes of the Combo stent in an all-comers population in routine clinical practice. We report 1-year results.

BACKGROUND Limitations of current generation drug-eluting stents (DES) are 3-fold: stent thrombosis, neoatherosclerosis related to impaired healing, and repeat revascularization due to (late-) in-stent restenosis. The Combo stent combines an abluminal biodegradable coating eluting sirolimus and a luminal anti-$CD34^{+}$ antibody layer to attract endothelial progenitor cells in order to promote vessel healing, thus preventing neointima formation and restenosis.

METHODS The REMEDEE (Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt) post-market registry was an international, multicenter, prospective trial that evaluated clinical outcomes after deployment of the Combo stent, in an all-comers population of patients treated with a Combo stent in the setting of routine clinical care. Clinical endpoints were target lesion failure (TLF), defined as a composite of cardiac death, nonfatal myocardial infarction (MI), or target lesion revascularization (TLR).

RESULTS Between June 2013 and March 2014, a total of 1,000 patients were included in the registry, 49.9% of whom presented with acute coronary syndrome. Mean age was 65 ± 11 years old (range: 34 to 94 years of age), and 74% of patients were male; 58.9% of 1,255 lesions were American Heart Association type B2 or C lesions. The primary endpoints were 5.7% TLF, 1.7% cardiac death, 0.7% target vessel MI, and 4.4% TLR. Definite stent thrombosis occurred in 0.5% of subjects; no thrombosis occurred after 9 days post-stenting.

CONCLUSIONS This registry showed excellent 1-year results of novel Combo bioengineered stent technology in an all-comers patient population. (Prospective Registry to Asses the Long-term Safety and Performance of the Combo Stent [REMEDEE]; NCT01874002) (J Am Coll Cardiol Intv 2016;■:■-■) © 2016 by 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, Amphia Hospital Breda, Breda, the Netherlands; [c]Department of Cardiology, Craigavon Cardiac Centre, Craigavon, United Kingdom; [d]Department of Cardiology, Pauls Stradins Clinical University Hospital, Riga, Latvia; [e]Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands; [f]Department of Cardiology, Tergooi Ziekenhuis, Blaricum, the Netherlands; [g]Department of Cardiology, Hospital Álvaro Cunqueiro-Complejo Hospitalario Universitario, Vigo, Spain; [h]Department of Cardiology, Isala Klinieken, Zwolle, the Netherlands; and the [i]Department of Cardiology, Institut National de Cardiochirurgie et de Cardiologie Interventionnelle, Luxembourg, Luxembourg. OrbusNeich supported this study through an unrestricted grant to Academic Medical Center, University of Amsterdam, but had no part in site monitoring, collection, storage, or analysis of data or decision to submit the manuscript for publication. Dr. den Heijer is a consultant for Medtronic CoreValve and Direct Flow Medical. Dr. Menown has received grant support from Boston Scientific and Biosensors. Dr. van 't Hof has received grant support from The Medicines Company and Abbott Laboratories. Dr. de Winter has received grant support from OrbusNeich, Abbott Laboratories, AstraZeneca, Stentys, and Tryton; and consults for OrbusNeich. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Woudstra and Kalkman contributed equally to this work.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

MI = myocardial infarction

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

PCI = percutaneous coronary intervention

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

TLF = target lesion failure

TLR = target lesion revascularization

Drug-eluting stents (DES) have been shown to be superior to bare metal stents in reducing the rate of repeat revascularization in various patient populations and lesion complexities (1-5). Vascular smooth muscle cell proliferation and neointimal hyperplasia are efficiently inhibited by current generation DES, although there is concern regarding late and very late in-stent-restenosis (6-10). In addition, a major concern in using these cytostatic or cytotoxic drugs is the healing process that is impeded in response to delayed functional endothelialization of the treated segment (11,12). Late "catch-up restenosis" resulting in the need for late repeat revascularization may be associated with an ongoing inflammatory response due to the use of durable polymers. Delayed vascular healing is associated with vasomotor dysfunction and an increased incidence in stent thrombosis (13-17).

The Combo stent (OrbusNeich Medical BV, the Netherlands) consists of a thin (100-μm) stainless steel strut platform and a biodegradable abluminal coating containing antiproliferative sirolimus (5 μg/mm). In addition, the luminal stent surface is covered with anti-CD34$^+$ antibody that captures endothelial progenitor cells, resulting in rapid re-endothelialization of the treated segment. This anti-CD34$^+$ antibody technology has been shown in pre-clinical and clinical work to prevent thrombus formation and enhance vessel healing (18-20), thus combining the benefits from previous endothelial progenitor cell-capturing stents and modern DES technologies. In the REMEDEE (Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt) first-in-man trial, the Combo stent showed rates of angiographic in-stent-restenosis similar to those of the Taxus Liberté paclitaxel-eluting stent (Boston Scientific, Marlborough, Massachusetts) in a patient population with single de novo lesions and no definite or probable stent thrombosis (21).

The aim of this registry was to evaluate the clinical performance of the Combo stent in a real-world, multicenter, multinational, all-comers patient population in routine clinical practice.

METHODS

STUDY OVERSIGHT. This REMEDEE Registry was a multicenter, prospective, clinical outcomes post-market registry of the Combo abluminal sirolimus-coated bioengineered stent. The study was investigator-initiated and coordinated by the Academic Medical Center, University of Amsterdam.

PATIENT POPULATION. A total of 1,000 patients, in whom treatment with a Combo stent in the setting of routine clinical care was attempted, were enrolled in the registry. Treatment with the Combo stent was part of clinical routine. Informed consent for participation in the registry (= upload of data into the REMEDEE Registry) was obtained either before the procedure or immediately after. Exclusion criteria were a high probability of nonadherence to the follow-up requirements (for social, psychological, or medical reasons), current participation in another investigational drug or device study with a planned routine angiographic follow-up, a life expectancy of <1 year, or explicit refusal of participation in the registry. All patients provided written informed consent for uploading of clinical data into the registry. Patients presenting with acute coronary syndrome (ST-segment elevation myocardial infarction [STEMI], non-STEMI [NSTEMI], and unstable angina)

TABLE 1 Baseline Demographics and Clinical Characteristics (N = 1,000)

Patients	
Age, yrs	65 ± 11
Males	739 (73.9)
History of diabetes	184 (18.4)
Requiring oral medication	103 (10.3)
Requiring insulin	64 (6.4)
History of hypertension	580 (58.0)
History of hyperlipidemia	562 (56.2)
Family history of CAD	455 (45.5)
Current smoker	241 (24.1)
Prior myocardial infarction	253 (25.3)
Prior percutaneous intervention	301 (30.1)
Prior CABG	68 (6.8)
Indication for PCI	
Urgent PCI for ACS	303 (30.4)
STEMI	178 (17.8)
NSTE-ACS	83 (8.3)
Unstable angina	42 (4.2)
Elective PCI	695 (69.6)
Stabilized STEMI	21 (2.1)
Stabilized NSTE-ACS	107 (10.7)
Stabilized unstable angina	67 (6.7)
Stable angina and/or documented ischemia	304 (30.4)
Angiographically driven	162 (16.2)
Other	35 (3.5)
Statin therapy	719 (71.9)

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft; CAD = coronary artery disease; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Lesion and Stent Characteristics (N = 1,255)

TIMI flow pre-procedure	
0	14.5
1	4.4
2	9.8
3	71.2
Thrombus present	15.0
Thrombus aspiration	10.8
AHA/ACC lesion type	
A	16.4
B1	24.7
B2	36.9
C	22.0
Lesion length, mm	15.0 (12-20)
Reference vessel diameter, mm	3.0 (3.0-3.5)
Percentage stenosis by visual estimate	90 (80-99)
Pre-dilatation performed	69.9
Total stent length, mm	21.4 ± 10.5
Total stent diameter, mm	3.2 ± 0.5
Pressure, atm	13.6 ± 2.8
Multiple vessel PCI	10.5
Device success	98.7
Procedural success	97.9

Values are valid %, mean ± SD, or median (interquartile range).
Abbreviations as in Table 1.

and patients with elective percutaneous coronary intervention (PCI) were eligible for enrollment.

DEVICE. The Combo bioengineered sirolimus-eluting stent consists of a 100-μm-thick strut of type 316L stainless steel alloy abluminally coated with a biocompatible, biodegradable polymer containing sirolimus. Covalently attached to this matrix is a layer of murine, monoclonal, anti-human $CD34^+$ antibody.

TABLE 3 Primary Endpoint and Clinical Outcomes at 1-Year Follow-Up (N = 1,000)

Primary endpoint: TLF	57 (5.7)
Cardiac death	17 (1.7)
Target vessel MI	7 (0.7)
TLR	43 (4.4)
PCI	34 (3.4)
CABG	10 (1.0)
Stent thrombosis	
Definite ST	5 (0.5)
Probable ST	1 (0.1)
Other events	
Overall death	19 (1.9)
Non-cardiac death	2 (0.2)
Any repeat PCI	116 (11.7)
Target vessel PCI	48 (4.9)
Any CABG	13 (1.3)

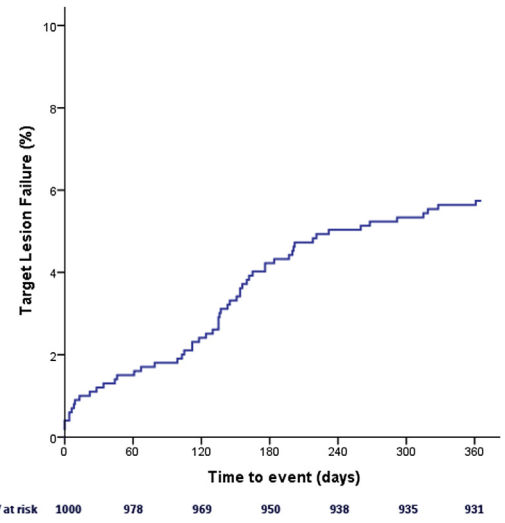
Values are number of events (Kaplan-Meier estimates).
TLF = target lesion failure, a composite of cardiac death, myocardial infarction (unless documented to arise from the nontreated coronary artery), and target lesion revascularization (TLR); other abbreviations as in Table 1.

The Combo stent is Conformité Européenne (CE)-marked and available on the European market.

CLINICAL FOLLOW-UP. Patients were contacted at 30 and 180 days and at 1 year by telephone call or during a scheduled outpatient clinic visit. Follow-up data will be collected up to 5 years post-procedure. If patients cannot be reached, referring cardiologists and general practitioners are contacted for additional information. Patients were monitored for major adverse cardiac events including (cardiac) death, MI, hospitalization for angina, and revascularization by PCI or coronary artery bypass graft (CABG). Hospital records were obtained and reviewed to complete event source information. All data were handled according to good clinical practice guidelines. The recommendation for dual antiplatelet therapy (DAPT) was according to the European Society of Cardiology (ESC) guidelines, 6 months for elective cases and 12 months for acute coronary syndrome (ACS) patients.

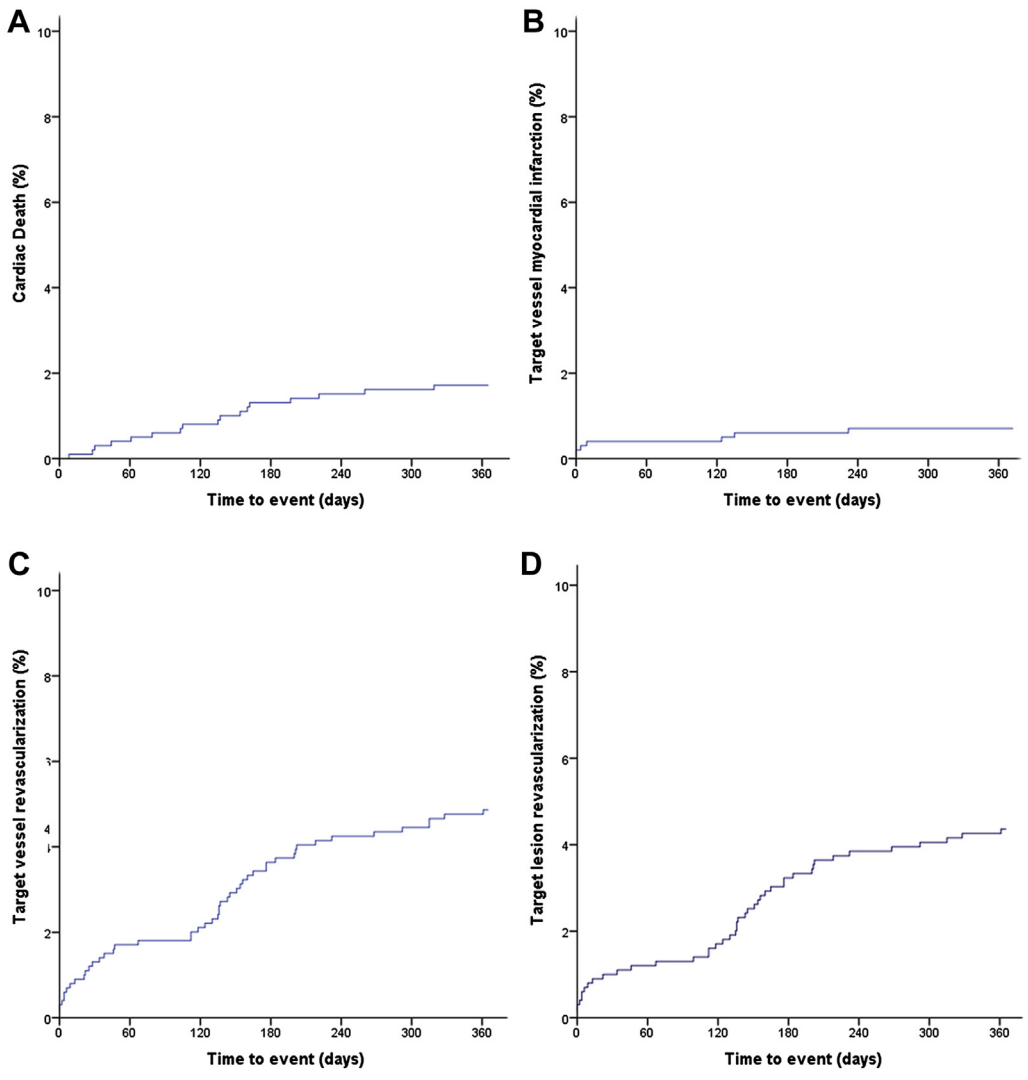
OUTCOMES. The primary outcome was target lesion failure (TLF) at 1-year follow-up, defined as the composite of cardiac death, target vessel-related nonfatal MI or target lesion revascularization (TLR). MI was always considered a target vessel, unless there was documented proof that the infarction arose from the nontreated coronary artery. MI was defined according to the third universal definition of MI (22). Because of the registry design of the study, it was not mandatory to determine cardiac enzymes periprocedurally. TLR was defined as any repeat revascularization by PCI of the treated lesion or CABG of the

FIGURE 1 Target Lesion Failure Cumulative Event Rate of Primary Endpoint



Target lesion failure by Kaplan-Meier method.

FIGURE 2 Cardiac Death, Target Vessel MI, Target Vessel Revascularization, Target Lesion Revascularization by Kaplan-Meier Method



(A) Cumulative event rate of the individual endpoint cardiac death by Kaplan-Meier method. **(B)** Cumulative event rate of the individual endpoint target vessel related myocardial infarction by Kaplan-Meier method. **(C)** Cumulative event rate of the individual endpoint target vessel revascularization by Kaplan-Meier method. **(D)** Cumulative event rate of the individual endpoint target lesion revascularization by Kaplan-Meier method.

target vessel. Stent thrombosis was defined according to Academic Research Consortium criteria (23). Device success was defined as successful Combo stent placement with thrombolysis in MI (TIMI) flow grade 3 post-stenting and less than 20% residual stenosis. Procedural success was defined as device success together with the absence of any in-hospital adverse events, all major adverse cardiac events, and any event that prolonged hospital stay.

All clinical events were adjudicated by an independent clinical event committee, which consisted of 2 interventional cardiologists from St. Antonius Hospital, Nieuwegein, the Netherlands.

STATISTICAL ANALYSIS. All descriptive statistical analyses were performed using SPSS version 22 software (SPSS Inc., Chicago, Illinois). Data are mean ± SD for continuous variables or percentages for dichotomous variables, unless otherwise mentioned. Baseline and procedural characteristics were reported by investigators. Lesion characteristics and lesion dimensions were visually estimated by the operator.

For time-to-event data, Kaplan-Meier estimates at the indicated time points are displayed along with 95% confidence intervals. In addition, survival curves were constructed for all time-to-event secondary endpoints, using Kaplan-Meier methods. For missing data in the time-to-event analyses, subjects were censored at their last known follow-up.

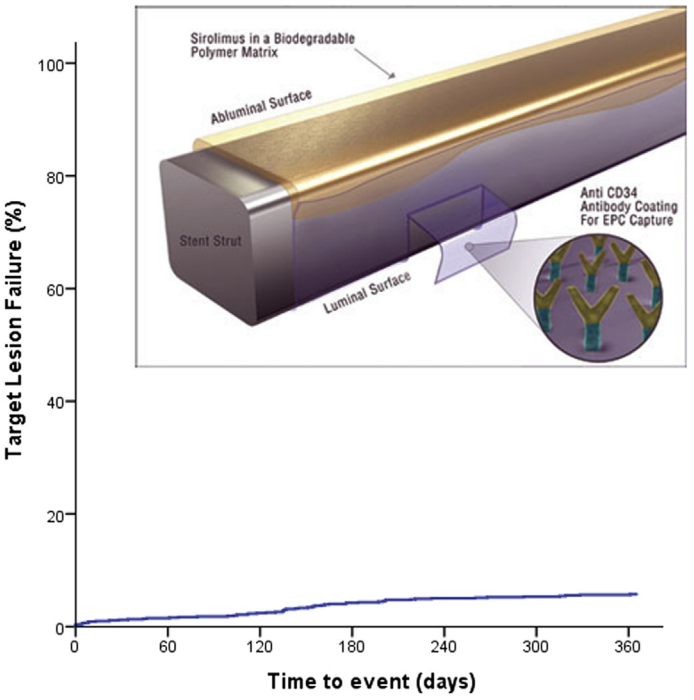
RESULTS

PATIENT CHARACTERISTICS. Between June 2013 and March 2014, a total of 1,000 patients from 9 European sites were included (Academic Medical Center, Amphia Hospital, Radboud University Medical Center, Isala Klinieken, and Tergooi Hospital in the Netherlands; Craigavon Cardiac Centre in the United Kingdom; Pauls Stradins Clinical University Hospital in Latvia; Hospital Álvaro Cunqueiro-Complejo Hospitalario Universitario de Vigo in Spain; and Institut National de Cardiochirurgie et de Cardiologie Interventionnelle in Luxembourg).

Baseline characteristics are shown in Table 1. Mean age was 65 ± 11 years (range: 34 to 94 years of age), representative of an all-comers patient population. An 18.4% subset of patients were diabetics; 6.4% of all patients required insulin treatment. Hypertension was present in 58.0% of patients, and dyslipidemia was present in 56.2%. Medical history of patients reported prior MI in 25.3% and prior PCI in 30.1%, and 6.8% had previously undergone CABG. The indication for the PCI procedure showed 30.4% for urgent PCI for ACS, whereas elective patients (69.6%) consisted of 3.0% stabilized STEMI, 15.4% stabilized NSTE-ACS, 9.6% stabilized unstable angina, 43.6% stable angina and/or documented ischemia, 23.2% angiographically driven, and 5.2% other indications.

ANGIOGRAPHIC CHARACTERISTICS. Lesion and stent characteristics are shown in Table 2. A total of 1,255 lesions were treated, again representative of an all-comers population, consisting of 1.3% left main artery, 50.6% left anterior descending artery, 20.2% left circumflex artery, 26.1% right coronary artery, and 1.8% bypass graft. Multivessel PCI was undertaken in 10.5% of patients. Median lesion length was 15.0 mm, and interquartile range (IQR) was 12 to 10 mm, with a median reference vessel diameter of 3.0 mm and an IQR of 3 to 3.5 mm. Median diameter stenosis pre-procedure was 90% (IQR: 80 to 99%). Thrombus was present in 15.0% of patients, and thrombus aspiration was performed in 10.8% of patients. American Heart Association/American College of Cardiology lesions were as follows: 16.4% had type A; 24.7% had type B1; 36.9% had type B2; and 22% had type C.

CENTRAL ILLUSTRATION Combo Stent Design and TLF at 12 Months After Stent Implantation



Woudstra, P. et al. J Am Coll Cardiol. 2016;■(■):■–■.

The novel bioengineered Combo stent combines an abluminal sirolimus eluting coating with a luminal anti-CD34+ antibody layer to promote vessel healing. In the true all-comers REMEDEE Registry the primary endpoint of target lesion failure (TLF) at 1-year follow-up was 5.7%.

FIGURE 3 Stent Thrombosis Definite Stent Thrombosis by Kaplan-Meier Method

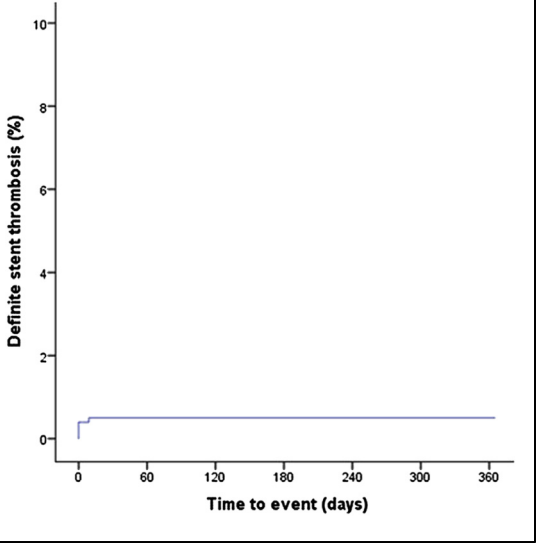


TABLE 4 Comparison of Clinical Outcomes in Second- and Third-Generation DES After 12 Months Follow-Up

	REMEDEE Registry	TWENTE		DUTCH PEERS		LEADERS		RESOLUTE International Registry
	Combo, ECS + SES	Resolute, ZES	Xience V, EES	Resolute, ZES	Promus, EES	Biomatrix, BES	Cypher, SES	Resolute, ZES
N	1,000	697	694	906	905	857	850	2,349
TLF	5.7	7.9	6.8	6.0	5.0	6.5	7.4	7.0
TVF	6.2	8.2	8.1	6.0	5.0	10.6	12.0	7.7
TV-MI	0.7	4.6	4.6	2.0	1.0	5.8*	4.6*	3.1
Clinically indicated TVR	4.9	3.3	2.7	3.0	3.0	5.8	7.1	4.2
Clinically indicated TLR	4.4	2.7	1.4	2.0	2.0	5.1	5.8	3.4
Definite ST	0.5	0.6	0.0	0.3	1.0	2.0	2.0	0.7
Acute (0–1 day)	0.4	0.0	0.0	0.2	0.1	1.6	1.6	0.1
Subacute (2–30 days)	0.1	0.1	0.0	0.0	0.3	1.6	1.6	0.4
Late (31–360 days)	0.0	0.4	0.0	0.1	0.2	0.4	0.5	0.1
Probable ST (0–360)	0.1	0.3	1.2	0.2	0.2	0.8	0.2	0.3
Cardiac death	1.7	1.0	1.4	2.0	1.0	2.1	2.7	1.4

Values are n or %. Target lesion failure (TLF) is a composite of cardiac death, myocardial infarction (unless documented to arise from the nontreated coronary artery), and target lesion revascularization (TLR). *TVR and non-TVR myocardial infarction.

BES = biolimus-eluting stent(s); EES = everolimus-eluting stent(s); SES = sirolimus-eluting stent(s); ST = stent thrombosis; TVR = target vessel revascularization; ZES = zotarolimus-eluting stent(s); other abbreviations as in Table 1.

Device success was seen in 98.7% of patients; stenosis of more than 20% was seen in 0.9% of patients after the procedure; 1.3% demonstrated TIMI flow grade <3; and unsuccessful stent delivery occurred in 3 patients (0.3%). In 2 cases, it was not possible to reach the target lesion with successful retrieval of the Combo stent. In 1 case. there was no stent placement because the patient developed severe dyspnea, and the procedure was canceled for safety reasons. Procedural success was 97.9%.

CLINICAL OUTCOMES. We obtained clinical follow-up at 1 year for 980 patients (98.0%). The primary endpoint of this study was adjudicated device-orientated TLF at 1-year follow-up. Table 3 shows the primary endpoint components. Kaplan-Meier curves are presented in Figures 1 and 2A and Central Illustration. The primary endpoint TLF was present in 5.7% of patients. Cardiac death occurred in 1.7% of patients. Target vessel MI was observed in 7 patients (0.7%). These were all spontaneous MIs. Target lesion revascularization (target lesion PCI and target vessel CABG) was performed in 4.4% of patients. Target vessel revascularization, PCI, and CABG were performed in 4.9% of patients.

Definite stent thrombosis was seen in 5 patients (0.5%) and probable stent thrombosis in 1 patient. In 5 of these 6 patients, indication for PCI was acute coronary syndrome, and stent thrombosis occurred acutely or subacutely. No stent thrombosis occurred between 9 days and 12 months follow-up after Combo stent deployment (Figure 3).

DISCUSSION

This study shows low repeat revascularization and low stent thrombosis rates in an all-comers registry of patients treated with 1 or more Combo stents. Device and procedural success were high, and the primary endpoint occurred in 5.7% of patients. Definite stent thrombosis occurred within several hours in 3 patients presenting with STEMI, an event usually related to mechanical issues, edge dissection in a highly thrombotic lesion, geographic miss or plaque protrusion through the stent struts not visible on angiography. Importantly, there was no stent thrombosis between 9 days and 12 months follow-up. Current data support the potential of the Combo stent; the combined technology of the antiproliferative sirolimus release, and the unique endothelial cells capturing pro-healing technology.

Patients were enrolled from unselected clinical practice rather than by randomized study and thus included patients across a large age range and all indications, including left main and venous grafts. A large proportion of patients presented with acute coronary syndrome. Device success and procedural success were high.

We compared our results with 1-year outcomes from other studies with second and third generation DES in an all-comers population, the TWENTE II, DUTCH PEERS, and LEADERS trials and the RESOLUTE international registry (Table 4) (24–27). The TLF, TVR, MI, and stent thrombosis rates in the REMEDEE registry

are among the lowest compared to the other studies. Importantly, these studies used the definition of clinically indicated TVR or TLR whereas we report all TLR or TVR. The low stent thrombosis rates may be related to the $CD34^+$ capturing layer of the Combo stent, which promotes early endothelialization (28).

The REMEDEE registry was part of a larger clinical program that included the HARMONEE USA/Japan randomized study (N = 572), the REDUCE study (comparing 3 months with 12 months of DAPT in ACS patients [N = 1,500]), and the MASCOT registry (N = 2,500). The HARMONEE trial was a multicenter, single-blind, randomized, active-controlled, clinical trial that is currently enrolling patients. An estimated number of 572 patients will be randomized to the Combo stent or an Everolimus Eluting stent (EES), primary endpoint is TVF at 1-year follow-up (NCT02073565). It is currently debated if DAPT duration should be prolonged beyond 1 year after MI (29–31). However, a patient-tailored treatment strategy is always preferable. In patients treated with Combo stent it is hypothesized that DAPT duration could be shortened. The early endothelialization should provide safe discontinuation of DAPT after one month. In this registry no stent thrombosis was seen 9 days to 12 months after Combo stent implantation, and a substantial proportion of our patients were included after acute coronary syndrome. The REDUCE study will show whether 3 months of DAPT is sufficient after Combo stent placement.

STUDY LIMITATIONS. This is the first report of the clinical outcomes of the Combo dual therapy stent in a large all-comers everyday patient population. There was a balanced patient enrollment by the nine participating centers and inclusion was completed in a short period of time, indicating the all-comers nature of the study. All events were fully monitored and adjudicated by an independent clinical event committee.

This study was limited by its observational registry design. No control group was assigned to compare the use of the Combo stent in clinical practice.

CONCLUSIONS

This registry was the first to show excellent clinical 1-year results of novel Combo bioengineered technology. High initial procedural success, low revascularization rates, and low stent thrombosis rates were observed in this true all-comers patient population. Follow-up will be extended up to 5 years, providing data on long-term clinical outcome after Combo stent placement. Data from ongoing randomized trials and registries may confirm the excellent clinical outcomes observed in the current study.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Robbert J. de Winter, Department of Cardiology, room B2-137, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail: r.j.dewinter@amc.uva.nl.

PERSPECTIVES

WHAT IS KNOWN? Complications after current generation drug-eluting stents placement remain stent thrombosis, neoatherosclerosis, and in-stent-restenosis.

WHAT IS NEW? The bioengineered sirolimus-eluting stent Combo stent has a unique luminal endothelial progenitor cell-capturing layer. In this multicenter, multinational, prospective post-market registry excellent clinical outcomes at 1-year follow-up after Combo stent placement are observed, including low stent thrombosis rates and no stent thrombosis beyond 9 days post-procedure.

WHAT IS NEXT? Randomized controlled trials with the novel Combo stent and registries are ongoing and may confirm the outstanding results found in this registry.

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