Dual-therapy stent technology for patients with coronary artery disease

A great catch?

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Chapter 5

1-Year Clinical Outcomes of All-comer Patients Treated with Dual-Therapy COMBO Stent: Primary Results of the COMBO Collaboration

On behalf of the MASCOT and REMEDEE Registry investigators.

Submitted.
ABSTRACT

**Background** The COMBO stent 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 (EPCs). These EPCs can quickly mature into normal endothelium, providing rapid endothelialization.

**Objectives** The aim of this study is to evaluate 1-year clinical safety and efficacy of the dual-therapy COMBO stent (OrbusNeich Medical, USA) in a large, all-comers patient-level pooled cohort.

**Methods** The MASCOT (N=2614, 61 global sites) and REMEDEE (N=1000, 9 European sites) registries are two prospective, multicenter registries evaluating clinical outcomes after attempted COMBO stent placement in all-comer patients undergoing percutaneous coronary intervention (PCI). In this patient-level pooled analysis we analyze 1-year target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction or clinically driven target lesion revascularization. Furthermore, we determine predictors of 1-year TLF.

**Results** A total of 3614 patients (age 64±11; 24% female) are included in this analysis. The prevalence of diabetes mellitus (DM) was 29.3%, prior PCI was 26.7% and 54.3% patients presented with acute coronary syndrome (ACS). The primary endpoint TLF occurred in 140 patients (3.9%). Insulin-treated DM, chronic renal failure and ACC/AHA 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 real world performance at 1-year after the bio-engineered stent is observed. (Clinicaltrial.gov identifier numbers: NCT02183454 and NCT01874002)
CONDENSED ABSTRACT

The bio-engineered COMBO stent (OrbusNeich Medical, USA) is a dual-therapy stent, designed to promote early endothelialization. More than 3600 all-comers patients have received this novel device in clinical, prospective, all-comers, single-arm trials in the global MASCOT and European REMEDEE registries. We report the clinical adjudicated outcomes at 1-year follow-up after treatment with this dual-therapy stent from the largest patient-level pooled analysis. The COMBO stent presents a good clinical efficacy and excellent safety profile. Predictors of 1-year TLF after COMBO treatment are insulin-treated diabetes mellitus, chronic renal failure and complex lesions.
INTRODUCTION

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 to first generation DES.\textsuperscript{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.\textsuperscript{3} Therefore newer stent technologies have focused on mitigating this adverse outcome after coronary stenting.\textsuperscript{4}

The COMBO stent (OrbusNeich Medical, USA) was designed to promote rapid and healthy strut coverage using anti-CD34+ antibodies. The stent combines two different treatment strategies, an anti-restenotic and an anti-thrombotic strategy, and is therefore referred to as the dual-therapy stent (DTS).\textsuperscript{5} This novel stent is the investigational device of two large, prospective registries; the REMEDEE Registry (The Multicenter, Prospective, Clinical Outcomes after Deployment of the Abluminal Sirolimus Coated Bio-Engineered Stent Post Market Registry) and MASCOT registry (The Multinational Abluminal Sirolimus Coated Bio-engineered stentT).\textsuperscript{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 one-year clinical outcomes after dual-therapy stent treatment in the largest cohort of all-comers patients with attempted treatment with COMBO stent. Furthermore, we sought to identify predictors of 1-year target lesion failure (TLF).

METHODS

COMBO stent

This DTS is a stainless steel stent with 100 µm struts and two therapeutic layers (Central Illustration). The anti-restenotic layer consists of a biodegradable polymer eluting sirolimus (5µg/mm) and the pro-healing layer consists of an anti-CD34+ antibody layer. This unique bio-engineered antibody layer attracts circulating endothelial progenitor cells (EPCs) that bind to the stent surface. These EPCs will shortly after capture start to develop into normal endothelial cell, allowing for rapid endothelialization of the stent (Figure 1).\textsuperscript{7,8} With rapid endothelialization, the dual-antiplatelet therapy (DAPT) duration that is recommended for a minimum of 6 months after PCI in current guidelines, might safely be shortened after DTS placement.\textsuperscript{9,10} Secondly, with healthy endothelial coverage of the stent lower rates of in-stent restenosis could be expected.
**Figure 1/Central illustration. The COMBO stent.** The dual-therapy stent technology of the COMBO stent. The dual-therapy treatment mechanism consists of the anti-restenotic sirolimus layer on the abluminal side, and a circumferential anti-CD34+ antibody layer (the endothelial progenitor cell capturing mechanism) for rapid endothelialization.

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

**MASCOT and REMEDEE Registry**

The REMEDEE Registry (clinicaltrials.gov identifier: NCT01874002) is a European, prospective, multicenter, cohort, post market registry that evaluates outcomes in patients undergoing PCI with attempted Combo stent placement. Primary results have been published previously. The registry is conducted in 9 European sites in 5 different countries (The Netherlands, Latvia, Northern-Ireland, Spain and Luxembourg).
This registry involves the collection of baseline demographic, clinical, and angiographic data, as well as follow-up data in consecutive patients in whom the Combo stent is used to treat (a) coronary lesion(s) in the setting of routine clinical care. All events were adjudicated by an independent clinical event committee. Follow-up is ongoing to 5 years post COMBO stent placement.

The MASCOT study (clinicaltrials.gov identifier: NCT02183454) is a post marketing registry. This multicenter, multinational, prospective registry population consists of all-comers patients undergoing PCI with attempted placement of at least one Combo Stent as part of routine clinical care. A total of 2614 patients were enrolled from 61 global centers (Europe, Asia, Middle East and South America). Patients were contacted at 30 ±7 days, 6 months ±14 days and 12 months ±28 days months of follow-up. The primary endpoint was target lesion failure at one year follow-up. All events were adjudicated by an independent clinical event committee.

There were only limited exclusion criteria in both registries: high probability of non-adherence to the follow-up requirements (due to social, psychological or medical reasons), currently participating in another investigational drug or device study in which a 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 stent thrombosis. In both trials 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 done according to the Declaration of Helsinki and Good Clinical Practice.

**Clinical endpoints**

The primary outcome of interest for the present analysis is TLF at one year follow-up. This composite endpoint consists of cardiac death, TV-MI, and clinically driven target lesion revascularization (TLR) by either PCI of the target lesion or a coronary artery bypass graft (CABG) of the target vessel. Myocardial infarction was adjudicated according to the third universal definition. Secondary endpoint stent thrombosis (definite or probable) were defined according to the academic research consortium (ARC) criteria.

At each contact (30 days, 6 months and 12 months) medication use was registered, including DAPT discontinuation. In MASCOT all DAPT cessation events were also adjudicated by an independent CEC and classified into the following modes: interruption, discontinuation or disruption. 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 $\leq 20\%$ by visual estimation and final TIMI flow 3 by visual assessment. Procedural success was considered in patients with device successful without any peri-procedural complications.

**Data analysis**

The COMBO Collaboration is a pooled patient level analysis. Endpoints were harmonized between both registries; REMEDEE registry considered all TLR, while MASCOT only included clinically driven TLR in the 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, statistics for continuous variables included mean, median, standard deviation, interquartile ranges. Binary variables are described with frequencies, percentages. For time-to-event data, Kaplan-Meier estimates at the indicated time points are displayed along with 95% confidence intervals. In addition, survival curves are constructed for all time to event secondary endpoints using Kaplan-Meier methods. The effect of different baseline variables on clinical outcome was assessed. Univariate and multivariate predictors of TLF were assessed including all risk factor from the Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) thrombotic risk score.\textsuperscript{15} Diabetes mellitus (DM, none, non-insulin treated and insulin treated), acute coronary syndrome (ACS) at admission (no, $T_n$-negative, $T_n$-positive), 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 ($\geq$65 years), hypertension, peripheral vascular disease (PVD), prior myocardial infarction (MI), total stent length $>$30mm and at least one B2/C lesion. Univariate analysis was done for each risk factor with Kaplan-Meier estimates and log-rank tests. Backward multiple regression analysis was done with Cox regression analysis. P values $<0.05$ were considered clinically significant. All descriptive statistical analyses are performed using SPSS statistical software (version 24, SPSS Inc. Chicago, IL, USA).

**RESULTS**

**Baseline characteristics**

A total of 3,614 patients were included in the analysis. In Table 1 the baseline characteristics are presented of the total cohort of patients in the COMBO collaboration. Patients had a mean age of $63.5 \pm 11.2$, 23.8% were female, 29.3% of patients had DM, 7.5% of patients with insulin treatment. 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 patients.
Indication for PCI was ACS in more than half of patients (n=1965, 54.3%), with 21.8% presenting with ST-segment elevated MI (STEMI), 16.6% with non-ST segment elevated MI (NSTEMI) and 15.9% with unstable angina.

**Table 1.** Baseline characteristics of all patients included in the REMEDEE and MASCOT registries.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=3614</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63.5± 11.2</td>
</tr>
<tr>
<td>Female</td>
<td>861 (23.8)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1050 (29.3)</td>
</tr>
<tr>
<td>Insulin treatment</td>
<td>272 (7.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2422 (67.0)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2101 (58.1)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>1107 (30.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>224 (6.2)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>231 (6.4)</td>
</tr>
<tr>
<td>Peripheral Vascular disease</td>
<td>212 (5.9)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>173 (4.8)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>858 (23.7)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>966 (26.7)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>206 (5.7)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1009 (27.9)</td>
</tr>
<tr>
<td>Indication for PCI</td>
<td></td>
</tr>
<tr>
<td>asymptomatic</td>
<td>295 (8.2)</td>
</tr>
<tr>
<td>stable angina</td>
<td>1346 (37.2)</td>
</tr>
<tr>
<td>STEMI</td>
<td>789 (21.8)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>600 (16.6)</td>
</tr>
<tr>
<td>unstable angina</td>
<td>576 (15.9)</td>
</tr>
<tr>
<td>other</td>
<td>6 (0.2)</td>
</tr>
</tbody>
</table>


Lesion characteristics are shown in **Table 2.** A total of 4445 lesions were treated in 3614 patients. The most frequent treated vessel was the left anterior descending, in 37.0% of cases. American Heart/American College of Cardiology lesion type B2/C was observed in 2483 lesions (57.0%). The mean pre-procedural reference vessel diameter was 3.1±1.5mm, with a lesion length of 19.4±11.2mm and mean pre-procedural diameter stenosis of 86.7±17.7%. In 14.0% of cases intracoronary thrombus was present, of which
53.5% was aspirated. Pre-procedural Thrombolysis In Myocardial Infarction (TIMI) flow III was observed in 2787 lesions (63.1%). TIMI III flow post-procedure was seen in 4343 patients (98.9%). Device success was 96.3% and procedural success was 94.5%.

**Table 2.** Lesion characteristics

<table>
<thead>
<tr>
<th>Lesion characteristic</th>
<th>n= 4445</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-procedure reference vessel diameter, mm</td>
<td>3.1±1.5</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>19.4±11.2</td>
</tr>
<tr>
<td>Diameter stenosis pre-procedure</td>
<td>86.7±17.7</td>
</tr>
<tr>
<td>Thrombus present</td>
<td>624 (14.0)</td>
</tr>
<tr>
<td>If yes, was thrombus aspirated?</td>
<td>334 (33.5)</td>
</tr>
<tr>
<td>TIMI flow pre procedure</td>
<td></td>
</tr>
<tr>
<td>TIMI 0</td>
<td>629 (14.2)</td>
</tr>
<tr>
<td>TIMI I</td>
<td>350 (7.9)</td>
</tr>
<tr>
<td>TIMI II</td>
<td>649 (14.7)</td>
</tr>
<tr>
<td>TIMI III</td>
<td>2787 (63.1)</td>
</tr>
<tr>
<td>Predilatation</td>
<td>2993 (67.4)</td>
</tr>
<tr>
<td>Location of lesion</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>1354 (30.5)</td>
</tr>
<tr>
<td>LAD</td>
<td>1682 (37.9)</td>
</tr>
<tr>
<td>LCX</td>
<td>1305 (29.3)</td>
</tr>
<tr>
<td>LMCA</td>
<td>79 (1.8)</td>
</tr>
<tr>
<td>Graft</td>
<td>24 (0.5)</td>
</tr>
<tr>
<td>AHA/ACC lesion classification</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>479 (11.0)</td>
</tr>
<tr>
<td>B1</td>
<td>1393 (32.0)</td>
</tr>
<tr>
<td>B2</td>
<td>1672 (38.4)</td>
</tr>
<tr>
<td>C</td>
<td>811 (18.6)</td>
</tr>
<tr>
<td>Postdilatation</td>
<td>2350 (53.0)</td>
</tr>
<tr>
<td>Total stent length</td>
<td>22.7±11.3</td>
</tr>
<tr>
<td>Final diameter stenosis</td>
<td>2.8±12.5</td>
</tr>
<tr>
<td>TIMI flow III post procedure</td>
<td>4343 (98.9)</td>
</tr>
</tbody>
</table>

Values are N (valid %) and mean ±SD. RCA: right coronary artery, LAD: left anterior descending artery, LCx: left circumflex artery, LMCA: left main coronary artery.
Clinical outcomes

One-year follow-up was obtained in 3489 patients (96.5%). In 8 patients no COMBO stent could be implanted. The primary outcome TLF occurred in 140 patients (3.9%) at one year follow-up. The Kaplan-Meier plot of TLF is illustrated in Figure 2. Cardiac death occurred in 55 patients (1.6%), TV-MI in 43 patients (1.2%) and clinically driven TLR in 78 patients (2.2%) (Figure 3).

In 17 patients (0.5%) definite stent thrombosis was observed (Figure 4), definite or probable stent was seen thrombosis in 0.8% of patients (n=30).

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

Figure 2. TLF at one year follow-up. Target lesion failure at one-year follow-up in all-comers patients treated with COMBO stent. Kaplan-Meier estimates of all patients from the COMBO collaboration.
Figure 3. Cardiac death, target vessel myocardial infarction and target lesion revascularization. Kaplan-Meier estimates of all patients from the COMBO collaboration.
Predictors of TLF

Univariate analysis was done with the 6 baseline variables from the PARIS thrombotic risk score model and 7 additional baseline variables as indicated in the methods. Univariate analyses of ACS versus non-ACS, DM versus non-DM, current smoking, prior PCI showed no statistical significant differences. Insulin treated (IT)DM was associated with 1-year TLF with a HR of 2.08 (95% CI: 1.30-3.34), p<0.01. Troponin positive ACS patients (consisting of all STEMI and NSTEMI patients, HR= 1.40, 95% CI: 1.01-1.96, p=0.05), prior CABG (HR=1.84, 95% CI: 1.06-3.19, p=0.03), CKD (HR=2.19, 95% CI: 1.34-3.59, p<0.01), peripheral vascular disease (PVD) (HR= 1.97, 95% CI: 1.15-2.27, p=0.01), at least 1B2/C lesion (HR=1.96, 95% CI: 1.34-2.86, p<0.01) and advanced age (HR= 1.41, 95% CI: 1.01-1.97, p=0.04) were also associated with higher TLF with univariate analysis. In the multivariate analysis ITDM, CKD and at least one B2/C lesion were predictors of 1-year TLF, as presented in Table 3.
### Table 3. Predictors of TLF at one-year after COMBO stent placement.

<table>
<thead>
<tr>
<th>PARIS thrombotic risk score model</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td><strong>DM versus non-DM</strong></td>
<td>1.32 (0.93-1.87) p=0.12</td>
</tr>
<tr>
<td></td>
<td><strong>ITDM vs all others</strong></td>
<td>2.08 (1.30-3.34) p&lt;0.01</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td><strong>ACS vs non-ACS</strong></td>
<td>1.36 (0.97-1.91) p=0.08</td>
</tr>
<tr>
<td></td>
<td><strong>trop+ ACS vs all others</strong></td>
<td>1.40 (1.01-1.96) p=0.05</td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior PCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CABG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced age &gt;65 years vs ≤65 years</td>
<td>1.41 (1.01-1.97) p=0.04</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.76 (0.56-1.11) p=0.17</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.97 (1.15-2.27) p=0.01</td>
<td>ns</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1.38 (0.96-1.98) p=0.08</td>
<td></td>
</tr>
<tr>
<td>Total stent length &gt;30mm vs ≤30 mm</td>
<td>1.09 (0.75-1.60) p=0.64</td>
<td></td>
</tr>
<tr>
<td>At least 1 B2/C lesion*</td>
<td><strong>1.96 (1.34-2.86) p&lt;0.01</strong></td>
<td><strong>1.94 (1.33-2.85) p&lt;0.01</strong></td>
</tr>
</tbody>
</table>


### 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 DTS. The main findings of the primary results of the patient-level pooled analysis are: 1) The treatment of CAD with the COMBO stent results in overall low clinical event rates, with 1-year TLF of 3.9% and 1-year def/prob ST of 0.8% 2) At least one AHA/ACC type B2/C lesion, insulin treated DM and chronic kidney disease are predictors of high 1-year TLF after COMBO stent, emphasizing the need for improving treatment options in these patient groups.
Clinical performance of the COMBO stent

The presented low event rates at one year after COMBO stent placement are in line with previous publications. Both in-stent restenosis rates and in-stent thrombosis rates are low. Safety profile of the COMBO stent appears excellent when compared to newer generation DES and especially when compared to the prior available bioresorbable scaffolds.

New coronary stent techniques have focused on thinner stent struts (64-81µm) and novel ways to deliver the drug, using crystalline delivery or biodegradable polymers or even polymer-free technology. The MiStent is a 64µm strut cobalt-chromium stent with a crystalline sirolimus. The DESSOLVE III trial compared one year clinical outcomes in all-comer patients with Xience everolimus-eluting stent (Abbott Vascular, USA). Device-oriented composite endpoint (DOCE) consisting of cardiac death, TV-MI or clinically indicated TLR was observed in 40 patients (5.8%) of the MiStent group and in 45 patients (6.5%) of the Xience group, p=0.0001, at one-year follow-up.

The BIO-RESORT trial evaluated Resolute Integrity zotarolimus-eluting stent (Medtronic, USA), the Synergy everolimus-eluting stent (Boston Scientific, USA) and the Orsiro stent (Biotronik, Switzerland) stent, showing non-inferiority of Synergy and Orsiro sirolimus-eluting stents compared to Resolute Integrity. At one-year clinical follow-up the primary endpoint consisting of cardiac death, TV-MI or target vessel revascularization occurred in 5% of all three groups.

Predictors of TLF

In this all-comer patient cohort of over 3600 patients treated with COMBO ITDM, CKD and at least one B2/C lesion are prognostic baseline characteristics that are predictors of adverse clinical outcome. ITDM and CKD were also found to be predictors in the PARIS thrombotic risk score model. This model is developed to predict the occurrence of the endpoint coronary thrombotic event (CTE, defined as stent thrombosis or myocardial infarction) at 2-year follow-up and is derived from 5031 patients undergoing PCI in the PARIS trial. However the other PARIS 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 difference could be explained by a different time measure (1 year versus 2 years of follow-up) or the analyzed endpoint (TLF versus CTE) or by treatment effect of COMBO stent.

CKD is well known risk factor for adverse outcome in male and female patients. A recently published study showed that ITDM patients have a higher risk of death or myocardial infarction at 1-year follow-up irrespective of presence of CKD. Similar to our findings, CKD resulted in an overall higher risk of adverse clinical outcomes
In patients with ITDM treated with DES higher numbers of in-stent restenosis are reported and overall higher adverse clinical outcomes.\textsuperscript{29,30,31} The ACC/AHA lesion classification in an indicator of severity of the lesion and is a good predictor of adverse clinical outcomes.\textsuperscript{32}

**Early DAPT cessation after COMBO**

In this analysis only few patients had DAPT cessation before the recommended period. The REDUCE study (clinicaltrials.gov identifier: NCT02118870) randomized ACS patients, who were treated with COMBO stent to either standard 12 months of DAPT or 3 months of DAPT. Results were presented at the Transcatheter Therapeutics congress in November 2017. This trial showed non-inferiority of 3 months of DAPT with regards to the primary composite endpoint consisting of all-cause death, MI, ST, stroke TVR or bleeding (BARC II, III and V) with an 8.2\% event rate in the 3 months DAPT-arm and 8.4\% event rate in 12 months DAPT-arm, $p_{\text{non-inferiority}}<0.001$. The BioFreedom stent (Biosensors Europe, Switzerland) is a polymer-free biolimus A9-eluting stent that could also allow for shorter DAPT duration.\textsuperscript{33} In the LEADERS FREE trial, a randomized study comparing BioFreedom with the bare-metal Gazelle stent (Biosensors Interventional Technologies, Singapore) in 2466 patients at high bleeding risk with only one month of DAPT. High bleeding risk was defined as having one or more of baseline characteristics that predispose higher bleeding risk.\textsuperscript{34} Therefore the patient population differs significantly with the study population in the COMBO cohort. At 390 days 112 patients (9.4\%) treated with BioFreedom stent and 154 patients (12.9\%) treated with Gazelle BMS experienced either cardiac death, myocardial infarction or stent thrombosis ($p=0.005$). Efficacy endpoint clinically driven TLR was observed in 59 patients (5.1\%) from the BioFreedom-arm and 113 patients (9.8\%) of BMS-arm ($p<0.001$).\textsuperscript{34} Continued beneficial effects of treatment with BioFreedom compared to BMS are reported at two-year follow-up with regards to safety and efficacy.\textsuperscript{35} No data is currently available comparing patients treated with BioFreedom and COMBO stent.

The SORT OUT X trial (clinicaltrials.gov identifier: NCT03216733) is currently enrolling all-comers patients. Patients are assigned in a 1:1 manner to either COMBO or Orsiro, a very thin strut sirolimus-eluting stent (60 µm, and for nominal stent sizes ≥ 3.5mm: 80µm) to compare 1-year TLF. The results from this trial may provide better understand of the added value of the pro-healing layer.

**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 comparator. 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 guideline recommendations. Also, angiographic data was 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 are enrolled from all over the globe and represent a real-world all-comers PCI population. This analysis has allowed not only examination of clinical outcomes after COMBO dual-therapy stent, but also to evaluate predictors of TLF at one-year follow-up. The COMBO dual therapy stent presents itself as a safe and efficient device, with promising results regarding short duration of DAPT. Upcoming trials should focus on patients with high risk of or indication for DAPT cessation, including high bleeding risk, to assess the safety and efficacy of novel stents in these patients.

CONCLUSION

In the largest cohort of all-comers patients treated with the novel dual-therapy COMBO stent, the COMBO stent was safe and efficient. In our study of over 3500 all-comer patients from all over the world, TLF at one year follow-up was 3.9%. One-year definite and probable stent thrombosis rate was 0.8%. Future randomize trials will test these results against other third generation devices.

Clinical perspectives

Competency in Patient Care
The novel dual-therapy COMBO stent has shown rapid endothelialization in pre-clinical work. The COMBO stent has been investigated in two large all-comers registries, with over 3500 patients treated with this stent.

Translational Outlook 1
In this international research collaboration we present the one-year clinical event rates of patients treated with COMBO from all over the world. Target lesion failure rates remain low after dual-therapy stenting. Insulin treated DM, CKD and B2/C lesions are predictor of higher 1-year TLF.

Translational Outlook 2
A large randomized clinical trial is currently enrolling patients, SORT OUT X. This study randomizes all-comers patient to treatment with either COMBO or Orsiro stent. Results will reveal the value of the added pro-healing layer to drug-eluting stents.
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APPENDIX

Appendix I

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