Dual-therapy stent technology for patients with coronary artery disease

A great catch?

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Chapter 7

Three year clinical outcomes of patients treated with the COMBO stent: Insights from the REMEDEE Registry


Submitted.
ABSTRACT

**Background** The bio-engineered COMBO stent (OrbusNeich Medical BV, The Netherlands) is a dual-therapy stent. This device combines a sirolimus-eluting layer with an anti-CD34+ antibody layer. The circumferential antibody-coating captures circulating endothelial progenitor cells that can differentiate into normal endothelium. This novel technology may allow a shorter duration of dual antiplatelet therapy after stenting. We present the first 3 year clinical outcomes of patients treated with COMBO stent.

**Methods and results** The prospective, multicenter, investigator-initiated, all-comers REMEDEE Registry evaluates clinical outcomes after COMBO stent treatment. A 1000 patients were enrolled between population June 2013 and March 2014. Patients had a mean of 65yrs ±11, 26% females and 18% diabetics. More than 50% of patients presented with acute coronary syndrome, 60% of treated lesions were AHA/ACC lesion type B2 or C. Target lesion failure at 3 year follow-up occurred in 10.7% of patients (N=105). The separate components cardiac death, target vessel myocardial infarction and target lesion revascularization occurred in 4.1%, 2.0% and 7.1%, respectively of patients. Definite stent thrombosis was observed in 0.7% of all patients.

**Conclusions** At 3-year follow-up patients treated with COMBO stent from a large prospective all-comers cohort, continue to show good clinical outcomes.

*Clinicaltrials.gov identifier: NCT01874002.*
CONDENSED ABSTRACT

The COMBO stent is a sirolimus-eluting stent with a luminal anti-CD34-antibody layer, that attracts endothelial progenitor cells. These cells can differentiate to endothelial cells and stimulate early endothelialisation of the stent. The REMEDEE Registry is the first large, multicenter, prospective, cohort study evaluating the clinical outcomes of 1000 all-comers patients treated with COMBO stent. Target lesion failure at 3 year follow-up is 10.7% and the rate of definite stent thrombosis was 0.7%.

ABBREVIATIONS

- ACS: acute coronary syndrome
- DES: drug eluting stent
- DTS: dual-therapy stent
- EPC: endothelial progenitor cell
- MI: myocardial infarction
- PCI: percutaneous coronary intervention
- ST: stent thrombosis
- TLF: target lesion failure
- TLR: target lesion revascularisation
- TVF: target vessel failure
- Tv-MI: target vessel-myocardial infarction
- TVR: target vessel revascularisation
INTRODUCTION

To better understand safety and efficacy of new coronary stent devices a long-term follow-up is required. Drug-eluting stents (DES) lowered mid-term complication, such as in-stent restenosis, due to chemotoxic drug elution.\textsuperscript{1,2} However, long-term complications, such as late in-stent restenosis and very late stent thrombosis raised questions on safety of the polymer layer, in which the drug is embedded.\textsuperscript{3,4} Bioabsorbable polymers and polymer-free stents are designed to overcome these safety concerns and lowering the rate of late in-stent restenosis.\textsuperscript{5,6,7}

The COMBO stent (OrbusNeich Medical BV, The Netherlands) has a dual-therapy treatment strategy.\textsuperscript{8,9} The stent combines treatment of a sirolimus-elution on the abluminal stent surface with a circumferential anti-CD 34+ antibody layer (\textbf{Figure 1}). The latter layer stimulates endothelialization of the stent by attaching circulating endothelial progenitor cells (EPC's) to the antibodies. The EPC's will mature into endothelial cells.\textsuperscript{10} This technique could facilitate a more rapid formation of a healthy endothelial layer, which might also improve long-term outcomes. This novel device has been evaluated in the all-comers REMEDEE Registry. Our aim is to evaluate three year clinical outcomes after COMBO stent implantation in the large all-comers REMEDEE Registry to address the long-term performance of the COMBO stent. This is the first report on 3 year follow-up after dual-therapy COMBO stent treatment.

\textbf{Figure 1.} Target lesion failure at 3 year follow-up by Kaplan-Meier method.
METHODS

COMBO stent and the REMEDEE Registry
The 100μm stainless steel COMBO stent has a sirolimus layer and an anti-CD34+ antibody layer. The stent received Conformité Européenne (CE) mark in 2013 and FDA approval is currently being awaited.

The study design of the REMEDEE Registry (NCT01874004) has been previously reported. In brief, the REMEDEE is an investigator-initiated, multicenter, prospective all-comers European registry evaluating the COMBO stent. A total of thousand all-comers patients treated with COMBO stent were enrolled between June 2013 and March 2014. Clinical follow-up was conducted by trained research staff through phone contact or clinic visit at 30 days, 6 months, 1, 2 and 3 year follow-up and will be continued up to 5 years. Specific duration of dual antiplatelet therapy (DAPT) regimen was not mandated by the protocol, DAPT was prescribed per local recommendations. The COMBO stent showed good clinical outcomes at one and two years follow-up with target lesion failure rates of 5.7% and 8.5%, respectively.

Endpoints definitions
Target lesion failure (TLF) is the primary focus of this 3-year outcome analysis. Target lesion failure is a composite endpoint defined as cardiac death, target vessel myocardial infarction (tv-MI) or target lesion revascularization (TLR). TLR consisted of all target lesion percutaneous coronary intervention (PCI) and all target vessel coronary artery bypass grafting (CABG). Not only clinically-driven TLR, but all TLR are taken into account for analysis. T-MI was defined according to the third universal definition, with the limitation that we did not collect peri-procedural markers for myocardial ischemia (troponin T or I, CK-MB), therefore we report spontaneous MI only. Stent thrombosis was classified according to the definition of the Academic Research Consortium. All events were adjudicated by an independent clinical event committee.

Subgroup analyses
Subgroup analyses for three year clinical outcomes will be performed for the following subgroups: patients with and without diabetes mellitus (DM), patients presenting with acute coronary syndrome (ACS) and patients stratified according to gender.

Statistical analysis
Categorical data are shown with counts and percentages, continuous variables are shown in mean ± standard deviation, unless otherwise mentioned. For time-to-event data, Kaplan-Meier estimates were used for all endpoint analyses. Follow-up was
censored at the last known date of follow-up, or at 36 months, whichever came first. All endpoints were evaluated in the unselected patient population, which consisted of all patients who were enrolled after signing an informed consent and in whom placement of a COMBO stent was attempted. Statistical analyses were performed using SPSS version 24.0 (Chicago, IL, USA). Subgroup analyses are done with univariate analysis using Kaplan-Meier estimates and log-rank tests.

RESULTS

Patient cohort
Baseline, procedural and lesion characteristics have been described previously (Table 1).11,12 Patients were of a mean age of 65±11 years, 26.1% of patients were female, 18.4% had DM and 6.4% of patients were on insulin treatment. Hypertension was observed in 58.0% of patients, hypercholesterolemia in 56.2% and chronic renal failure in 6.1% of patients. A positive family history for coronary artery disease (CAD) was noted in 45.5%. In 30.4% of patient urgent PCI was indicated, ACS was the presentation in 49.9% of patients. A total of 1255 lesions were treated. Thrombus was present in 15.0% of lesions, and thrombus aspiration was performed in 10.8%. AHA/ACC lesion type B2/C was in 58.9% of cases. Mean total stent length was 21.4±10.5mm, mean stent diameter as 3.2±0.5mm.

Clinical outcomes
Three year follow-up was obtained in 980 patients (98.0%). TLF occurred in 105 patients (10.7%) at 3-years follow-up (Figure 1 and Table 2). This consists of 40 patients (4.1%) with cardiac death, 19 TV-MI (2.0%) and 69 patients with TLR (7.1%) (Figure 2).

One additional definite stent thrombosis (ST) case has occurred between two and three years follow-up. This ST occurred at 1037 days post COMBO stent implantation. The patient presented with a ST-segment elevated myocardial infarction (STEMI). There was a thrombus in COMBO stent and 95% stenosis of the distal stent. Thrombus aspiration was performed. Throughout 3 years of follow-up the ST rate is 0.7%.

Sub analysis according to sex showed a numerically higher TLF rate in male patients compared with female patients (11.6% vs. 8.1%, respectively; p=0.13). A significant higher TLF rate was observed in diabetic patients compared with nondiabetic patients (22.3% vs. 7.3%; p<0.001). TLF was observed in 11.7% of ACS patients compared to 9.7% in non-ACS patients; p=0.29. Kaplan-Meier plots of these subgroups are illustrated in Figure 3.
Table 1. Baseline, procedural and lesion characteristics.

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<tr>
<th>Patient (N = 1000)</th>
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<td>Age, yrs</td>
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<td>±11</td>
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<tr>
<td>Female</td>
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<td>History of Diabetes</td>
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<td>Requiring insulin</td>
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<td>History of Hypertension</td>
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<td>History of Hyperlipidemia</td>
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<tr>
<td>Family history of CAD</td>
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<td>Current smoker</td>
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<tr>
<td>Chronic renal failure</td>
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<tr>
<td>Prior myocardial infarction</td>
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<tr>
<td>Prior CABG</td>
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<td>Presenting with ACS</td>
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<td>Radial access site</td>
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<td>Catheter size, 6 French</td>
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<tr>
<td>Imaging used (OCT/IVUS)</td>
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<tr>
<td>Total contrast used, mL</td>
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<td>117</td>
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<th>Lesions (N = 1255)</th>
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<td>TIMI flow 0 pre-procedure</td>
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<td>Thrombus present and thrombus aspiration</td>
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<tr>
<td>AHA/ACC lesion type B2/C</td>
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<tr>
<td>Lesion length, mm</td>
<td>15.0</td>
<td>12-20</td>
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<tr>
<td>Reference vessel diameter, mm</td>
<td>3.0</td>
<td>3.0-3.5</td>
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<tr>
<td>Percentage stenosis by visual estimate</td>
<td>90</td>
<td>80-99</td>
</tr>
<tr>
<td>Total stent length, mm</td>
<td>21.4</td>
<td>±10.5</td>
</tr>
<tr>
<td>Total stent diameter, mm</td>
<td>3.2</td>
<td>±0.5</td>
</tr>
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Figure 2. Cardiac death, tv-MI and TLR at 3 year follow-up by Kaplan-Meier method.
Figure 3. Subgroup analysis according to diabetes status, sex, and acute coronary syndrome presentation.
**DISCUSSION AND LIMITATIONS**

**Main findings**

The long-term three year clinical results can be summarized as follows: 1) target lesion failure at 3 year was observed 10.7% in patients treated with COMBO 2) Adverse outcomes at 3 year follow-up remain significantly higher in patients with DM 3) no significant differences are seen between clinical outcomes of females and males or ACS and non-ACS patients 4) very low stent thrombosis rate is observed at 3 year follow-up.

**Three year clinical outcomes after DES**

Although comparison between different studies must be done with caution – inclusion and exclusion criteria might differ and dissimilar patients are included – we try to compare these results with other DES. The SORT OUT IV trial compared an everolimus eluting stent (EES), either Xience V (Abbott Vascular) or PROMUS (Abbott Vascular, USA) with a sirolimus eluting stent (SES) Cypher Select+ (Cordis, USA) in all-comers patients. In the published three year results EES did not significantly differ from SES. TLR occurred in of 3.6% EES and 4.8% SES, p=0.13. Definite ST occurred in 0.2% of EES and 1.4% of SES, p=0.002. Stent-related outcome (cardiac death, tv-MI and ischemia-driven TLR) was observed in 6.7% of EES versus 7.6% in SES. These event rates are lower compared to the TLF rate of the REMEDEE Registry. This could be explained by differences in baseline characteristics (older patients in REMEDEE Registry with higher number comorbidities such as DM patients). Another explanation is the endpoint definition, the REMEDEE registry included all TLR, and SORT OUT IV included ischemia-driven TLR. A recent patient level pooled analysis compared patients treated with biolimus-eluting Nobori stent (biodegradable polymer, BP-BES, Terumo Corp., Tokyo, Japan) versus Xience.
everolimus-eluting stents (durable polymer, DP-EES) from the NEXT\textsuperscript{17,18} and COMPARE II\textsuperscript{19,20} trials using propensity score matching. This analysis showed no significant differences between BP-BES and DP-EES at three year follow-up with regards to device oriented clinical outcomes (DOCE), consisting of cardiac death, MI (not clearly attributed to a non-target vessel) and TLR. DOCE at 3 years was 12.6% in BP-BES and 11.9% in DP-EES, which is similar to the event rate observed in this registry.\textsuperscript{21} In a meta-analysis comparing EES with paclitaxel-eluting stents (PES) from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SPIRIT) clinical trials program outcomes three year results showed a TLF rate of 12.5% in PES and 8.9% in EES.\textsuperscript{22} Yet again, comparison is hampered by inclusion criteria (simple lesions only in SPIRIT I and II).

When we compare our three year results with results from the DUTCH PEERS trial comparing Resolute Integrity (3 year TLF of 9.7%) and Promus Element (3 year TLF of 8.9%) target lesion failure rates are numerically higher in COMBO.\textsuperscript{23} Though a propensity score matched analysis of the two year clinical results from DUTCH PEERS and the REMEDEE registry showed no significant difference in TLF.

**Ongoing COMBO stent trials**

The REDUCE trial compared 3 months of DAPT after ACS in patients treated with COMBO with standard 12 months of DAPT. Primary outcome was a composite endpoint of bleeding and ischemic events (cardiac death, MI, stroke, ST or TVR or BARC II, III and V bleeding). Clinical follow-up will be obtained to 2 year follow-up.\textsuperscript{24} REMEDEE Registry will continue to collect clinical follow-up data up to 5 years. SORT OUT X trial (clinicaltrials.gov number: NCT03216733), a randomized controlled trial comparing COMBO with Orsiro (Biotronik, Germany) stent is currently enrolling patients. The primary endpoint is device-oriented TLF and TLR at 12 months follow-up. Clinical follow-up will be continued through 5 years.

**Limitations**

The main limitation of this single-arm registry is that it has no comparator, which makes comparison between other DES difficult. Comparison of clinical results at three year follow-up is also hampered because there is a lack of long-term follow-up of new stent technologies. For all novel coronary devices, initial good clinical effects could over time change resulting in safety or efficacy issues at longer follow-up. Therefore we conclude that investigation of long-term results of new devices is needed.
CONCLUSION

Three year clinical outcomes after COMBO stent placement are presented in this analysis from a large all-comers post-marketing registry. Low event rates are observed in patients treated with the dual-therapy COMBO stent.

Impact on daily practice
Long-term clinical outcomes after novel drug-eluting stent placement should be evaluated to gain more insight into overall performance. In this analysis 3 year clinical outcomes are evaluated in all-comers patients treated with the dual-therapy COMBO stent. Target lesion failure is observed in 10.7% of patients at 3-year post stent placement. Overall stent thrombosis remains low, with a definite stent thrombosis rate at 3 years of 0.7%.

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Conflict of interest statement
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