Dual-therapy stent technology for patients with coronary artery disease

A great catch?

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Chapter 10

Current evidence for the safety and efficacy of the bio-engineered dual-therapy COMBO stent

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ABSTRACT

The novel dual-therapy COMBO stent aims to promote vessel healing after percutaneous coronary intervention (PCI) in patients with coronary artery disease. The pro-healing technique consists of an anti-CD34+ antibody layer that attracts circulating endothelial progenitor cells (EPCs), which bind to the stent surface and allow rapid endothelialization by differentiation of the EPCs into normal endothelial cells. The COMBO stent combines this pro-healing technique with an abluminal drug elution of sirolimus. The promise of this dual-therapy stent is that it may safely allow a shortened duration of dual-antiplatelet therapy (DAPT) after stent placement. Moreover, with a mature endothelial layer, lower rates of in-stent restenosis may be expected. Clinical outcomes after COMBO stent implantation have been recently evaluated in both randomized trials and large, prospective, multicenter registries, showing low clinical event rates of in-stent restenosis and stent thrombosis. Randomized clinical trials (HARMONEE and RECOVERY) have demonstrated the non-inferiority of COMBO versus “first in class” second generation and newer generation drug-eluting stents. Safety and efficacy of 3 months of DAPT after COMBO stent placement in patients presenting with acute coronary syndrome has been evaluated in the large REDUCE randomized controlled trial, showing non-inferiority to standard duration of 12 months DAPT. In this review we provide an overview of the current pre-clinical and clinical evidence for the performance of the COMBO stent.
INTRODUCTION

New stent technologies have been developed to overcome the complications after second generation drug-eluting stent (DES) placement, mainly targeting lower in-stent restenosis and stent thrombosis (ST).\textsuperscript{1.2.3.4} Although significant advances have been made compared to bare metal stents (BMS), further reductions in event rates are desirable, primarily to reduce late target lesion revascularization and to facilitate shorter durations of dual-antiplatelet therapy (DAPT) after stent implantation. While the ideal duration of DAPT is debated, at least six months of DAPT after percutaneous coronary intervention (PCI) with DES is recommended by both the European Society of Cardiology and the American College of Cardiology/ American Heart Association (Table \textbf{1}).\textsuperscript{5,6,7} However, DAPT cessation after PCI is not infrequently seen, either due to temporary interruption for elective procedures or disruption due to bleeding or non-compliance.\textsuperscript{8,9} Patients undergoing PCI may require elective surgery, or have a high bleeding risk profile, in whom a DES and shortest possible DAPT duration may offer optimal net benefit. Furthermore, ACS patients of a high bleeding risk predisposition may be at the greatest risk for future bleeding events on DAPT.

The COMBO stent (OrbusNeich Medical, Fort Lauderdale, Florida) is a novel coronary device with a dual-therapy stent (DTS) technology.\textsuperscript{10} This DTS technology consists of an abluminal sirolimus-eluting layer combined with a luminal bio-engineered layer, designed to promote vessel healing by stimulating rapid endothelialization and providing a layer of mature, normal endothelium on the inner surface of the stent.\textsuperscript{11} This novel stent might safely allow shortened duration of DAPT. In this review article we will discuss the design and mechanism of the COMBO stent, pre-clinical study data and the current updates to clinical trial evidence.

DESIGN OF THE COMBO STENT

The COMBO device is a 316L stainless-steel stent in a helical sinusoidal design with a strut thickness of 100µm. Sirolimus is delivered in an abluminal biodegradable polymer in a dosage of 5µg/mm. The circumferential layer consists of murine, monoclonal, anti-human CD34 antibody. This bio-engineered coating was first applied to the Genous Bio-engineered R stent\textsuperscript{TM} stent (OrbusNeich Medical, Fort Lauderdale, Florida, USA).\textsuperscript{12,11} Circulating endothelial progenitor cells (EPCs), derived from the bone marrow, are captured by the immobilized antibodies on the luminal stent surface. Here the EPCs differentiate into mature, functional endothelium (\textbf{Figure 1}). The hypothesis of this novel technology is that not only is rapid endothelialization facilitated, but also by promoting healthy normal endothelium a lower rate of neo-atherosclerosis may be observed, resulting in a lower rate of stent thrombosis and in-stent restenosis.\textsuperscript{13}
Table 1. Recommended duration of P2Y12 inhibitors and aspirin (DAPT) after DES placement according to the European Society of Cardiology and American College of Cardiology/ American Heart Association guidelines after percutaneous coronary intervention.

<table>
<thead>
<tr>
<th></th>
<th>Stable CAD DES</th>
<th>HBR</th>
<th>ACS DES</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HBR</td>
<td></td>
<td></td>
<td>No HBR</td>
</tr>
<tr>
<td>ACC/AHA guidelines*</td>
<td>In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended</td>
<td>Class I B-NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At least 6 m (clopidogrel)</td>
<td>Discontinuation after 3 mo may be reasonable (clopidogrel)</td>
<td>At least 12m (clopidogrel, prasugrel, ticagrelor)</td>
</tr>
<tr>
<td></td>
<td>Class I</td>
<td>Class IIb</td>
<td>Class I</td>
</tr>
<tr>
<td></td>
<td>&gt;6 m may be reasonable</td>
<td>&gt;12m may be reasonable</td>
<td>&gt;12m may be reasonable</td>
</tr>
<tr>
<td></td>
<td>Class IIb</td>
<td>Class IIb</td>
<td>Class IIb</td>
</tr>
<tr>
<td>ESC guidelines*</td>
<td>6m DAPT</td>
<td>1m DAPT</td>
<td>12m DAPT</td>
</tr>
<tr>
<td></td>
<td>Class IA</td>
<td>Class IIb C</td>
<td>Class IA</td>
</tr>
<tr>
<td></td>
<td>6m DAPT</td>
<td>3m</td>
<td>6m DAPT</td>
</tr>
<tr>
<td></td>
<td>Class IIa B</td>
<td>Class IIa B</td>
<td>Class IIa B</td>
</tr>
<tr>
<td>DAPT &gt;6m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IIb A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. 2017 focused update on dual antiplatelet therapy, ESC clinical practice guidelines.

SIHD= stable ischemic heart disease, CAD= coronary artery disease, ACS = Acute coronary syndrome, DES= drug-eluting stent, BMS= bare metal stent, DCB= drug coated balloon, HBR= high bleeding risk, DAPT= dual antiplatelet therapy.
PRE-CLINICAL DATA

An overview of the preclinical work with the dual-therapy stent is given in Table 2.

Larsen et al performed pre-clinical experiments with the bio-engineered bare-metal Genous\textsuperscript{TM} Bio-engineered R\textsuperscript{TM} stent to evaluate the function of the bio-engineered layer. In 15 patients undergoing coronary angiography an extracorporeal femoral arteriovenous shunt was used, containing a (BMS) and the Genous\textsuperscript{TM} stent. In this shunt model macroscopic thrombi were found on the BMS surface, but none with Genous\textsuperscript{TM}. With scanning electron microscopy (SEM) the Genous\textsuperscript{TM} stent showed better strut coverage (32.5\% enhanced deposition on the struts was observed with Genous\textsuperscript{TM} compared with BMS, p = 0.006). Quantitative polymerase chain reaction (qPCR) revealed increased expression of endothelial markers (KDR/VEGFR2 and E-selectin) with the Genous\textsuperscript{TM} stent, and an increase in pro-thrombogenic markers (tissue factor pathway inhibitor and plasminogen activator inhibitor-1) in BMS.\textsuperscript{14} Additionally 20 rabbits were implanted with Genous\textsuperscript{TM} and BMS in the aorta and iliac arteries for 7 days. SEM and qPCR showed a trend towards increased strut coverage and increased expression of endothelial markers for Genous\textsuperscript{TM} compared with BMS.\textsuperscript{14}
Table 2. Pre-clinical research program with EPC capturing stent technology stents.

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Models</th>
<th>Stent type</th>
<th>Study duration</th>
<th>Results</th>
</tr>
</thead>
</table>
| Larsen et al.     | 1     | Extracorporeal AV shunt in 15 patients undergoing CAG                 | BMS and GS | 120 minutes    | Macroscopic: substantial presence of mural thrombi in the BMS, none in GS  
SEM: Increase in stent-strut cell coverage in GS  
qPCR: expression of some endothelial markers higher in GS |
|                   | 2     | Extracorporeal AV shunt in a baboon                                    | BMS and GS | 120 minutes    | BMS occluded in <65 min, GS patent for >2 hours  
SEM: more CD34+ cells to adhere to the GS-strut, no difference in monocyte adherence |
|                   | 3     | Silicon tube with rotation of human monocytes and human CD34+ cells   | BMS and GS | 120 minutes    | Confocal microscopy: more CD34+ cells to adhere to the GS-strut, no difference in monocyte adherence |
|                   | 4     | 20 rabbits, aorta and iliac arteries                                   | BMS and GS | 7 days         | SEM: increased strut coverage in GS  
qPCR: increased levels of endothelial markers in GS |
| Nakazawa et al.   | 1     | 7 pigs, 21 coronary arteries                                           | 9 single (3 GS, 3 SES, 3 BMS) and 12 overlapping stents (4 GS+GS, 4 GS+SES, 4 SES+SES) | 14 days | SEM: Single stents: More strut coverage in BMS and GS compared with SES. Overlapping stents: from highest to lowest coverage: GS+GS, GS+SES, SES+SES  
Microscopy: slightly increased expression of CD31/PECAM-1 GS+GS and GS+SES compared with SES+SES  
Confocal microscopy: most expression of CD31/PECAM-1 on GS  
SEM: SES group has the least endothelial coverage, GS the most |
|                   | 2     | 13 pigs, 22 coronary arteries                                         | GS, SES and SES-anti-CD34+ | 3 and 14 days | Confocal microscopy: more CD31/PECAM-1 on GS  
SEM: SES group has the least endothelial coverage, GS the most |
| Granada et al.    | 1     | 12 pigs, 36 coronary arteries                                          | COMBO abluminal and COMBO circumferential | 3, 14 and 28 days | Microscopy: similar neointimal thickness seen in abluminal and circumferential drug-elution.  
SEM: no significant difference between abluminal or circumferential drug-elution. |
|                   | 2     | 21 pigs, 96 coronary and mammary vessels                              | LD COMBO, COMBO, Cypher | 6 hours and at 1, 3, 7, 14, 28, and 35 days | Intra-arterial sirolimus concentrations: Rapidly decline LD COMBO after 24h, similar seen in COMBO and Cypher |
|                   | 3     | 18 pigs 50 coronary vessels                                           | LD COMBO, COMBO, Cypher, Xience, GS | 14 or 28 days | OCT: highest protruding struts with Cypher, smallest NIT in COMBO, highest NIT Xience  
Microscopy: consistent with OCT findings |

AV: arteriovenous, BMS: bare metal stent, CAG, coronary artery bypass grafting; GS: Genous stent.  
SEM: scanning electron microscopy, qPCR: quantitative polymerase chain reaction, LD COMBO: 2.5 μg sirolimus/mm SES-anti-CD34+ stent, COMBO: 2.5 μg sirolimus/mm SES-anti-CD34+ stent, OCT: optical coherence tomography, NIT: neointimal thickness.
Another pre-clinical study was conducted by Nakazawa et al. to assess the differences in stent endothelialization between BMS, SES and Genous™ for single stenting and overlapping stents. They showed that the greatest percentage of endothelialization was found with single stent technique with Genous™ and BMS, compared to SES (99% vs. 55%, p=0.048). In overlapping stents endothelialization was significantly greater in Genous™+Genous™ (95±6%) when compared with Genous™+SES (79±5%) and SES +SES (36±14%). Moreover, they were the first to investigate endothelialization of the newly developed SES-anti-CD34. They compared the SES-anti-CD34 with single therapy SES, showing increased endothelialization for dual-therapy SES at 3 and 14 days after stenting (Figure 2).

Further development of this novel stent technique was undertaken by Granada et al. They investigated abluminal versus circumferential sirolimus elution on the stent surface of the anti-CD34 coated COMBO stent. Abluminal elution of sirolimus showed better endothelialization on histology at 3, 14 and 28 days post stent-placement in a pig model. Proceeding with the abluminal drug-delivery COMBO stent the investigators tested two different drug dosages (low dose 2.5µg sirolimus/mm or 5µg sirolimus/mm) to assess neointimal formation and inflammation, compared to Cypher (Cordis, Miami, United States of America) and Xience V stents (Abbott Vascular, Santa Clara, California). Less neointimal formation and inflammation was observed on optical coherence tomography (OCT) and histological analysis with COMBO (normal and low dose) but maintaining an enhanced endothelialization. COMBO 5µg sirolimus/mm showed less neointimal thickness compared to COMBO 2.5µg sirolimus/mm (Figure 3).

In conclusion, preclinical studies investigating the healing ability of the pro-healing COMBO stent showed promising results, while maintaining the antirestenotic effect of sirolimus-elution.
Figure 2. Endothelialization of the pro-healing technology. A. Strut coverage above struts with scanning electron microscopy (SEM) after Genous™ stent (GS), single therapy SES (SES) and the bio-engineered SES (SES-anti-CD34). B. CD31/PECAM expression. C. SEM images.

Reprinted from JACC: Cardiovascular Interventions, Nakazawa et al, Anti-CD34 Antibodies Immobilized on the Surface of Sirolimus-Eluting Stents Enhance Stent Endothelialization, 68-75 Copyright (2010), with permission from Elsevier.
**CLINICAL EVIDENCE**

**Randomized clinical trials**

All the current randomized clinical trials are summarized in Table 3. The first-in-man Randomized study to Evaluate the safety and effectiveness of an abluminal sirolimus coated bio-Engineered StEnt (REMEDEE) trial compared angiographic in-stent late lumen loss (LLL) at 9 months after stent placement in patients treated with COMBO or paclitaxel-eluting Taxus Liberté stent (PES) (Boston Scientific, Natick, Massachusetts). The COMBO stent was non-inferior to PES for LLL at 9 months follow-up (0.39±0.45 mm versus 0.44±0.56 mm, \( p_{\text{noninferiority}} = 0.0012 \)). Secondary endpoints included adjudicated major adverse cardiac events (MACE), with low event rates in both stent-groups (8.9% in patients treated with COMBO and 10.2% in patients with PES, \( p= 0.80 \)).

Reprinted from Circ Cardiovasc Interv, Granada et al, Development of a novel prohealing stent designed to deliver sirolimus from a biodegradable abluminal matrix, 257-266, Copyright (2010), with permission from Wolters Kluwer Health.
Table 3. Clinical research program with the COMBO stent.

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial number</th>
<th>N=</th>
<th>Patients</th>
<th>Comparator</th>
<th>Primary endpoint</th>
<th>Follow-up period</th>
<th>Primary Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMEDEE</td>
<td>NCT00967902</td>
<td>183</td>
<td>First in man</td>
<td>Taxus Liberté</td>
<td>LLL</td>
<td>9 months</td>
<td>COMBO non-inferior to PES</td>
</tr>
<tr>
<td>REMEDEE-OCT</td>
<td>NCT01405287</td>
<td>60</td>
<td>ACS</td>
<td>Xience V</td>
<td>Strut coverage</td>
<td>60 days</td>
<td>Higher percentage of uncovered struts in COMBO</td>
</tr>
<tr>
<td>HARMONEE</td>
<td>NCT02073565</td>
<td>572</td>
<td>Predominantly stable CAD</td>
<td>Xience V</td>
<td>TVF</td>
<td>1-year</td>
<td>COMBO non-inferior to EES</td>
</tr>
<tr>
<td>REDUCE</td>
<td>NCT02118870</td>
<td>1496</td>
<td>ACS</td>
<td>3 months versus 12 months DAPT</td>
<td>Composite endpoint of all-cause death, MI, ST, stroke, TVR or bleeding (BARC type II, III and V)</td>
<td>1-year</td>
<td>Short duration DAPT non-inferior to standard duration DAPT</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>NCT02542007</td>
<td>432</td>
<td>Predominantly unstable angina</td>
<td>Nano polymer free</td>
<td>TLF</td>
<td>1-year</td>
<td>COMBO non-inferior to Nano polymer free</td>
</tr>
<tr>
<td>SORT OUT X</td>
<td>NCT03216733</td>
<td>3140</td>
<td>All-comers</td>
<td>Orsiro</td>
<td>TLF</td>
<td>1-year</td>
<td>Currently enrolling patients</td>
</tr>
</tbody>
</table>

**Registries**

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial number</th>
<th>N=</th>
<th>Patients</th>
<th>Comparator</th>
<th>Primary endpoint</th>
<th>Follow-up period</th>
<th>Primary Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGO-COMBO</td>
<td>NCT01756807</td>
<td>61</td>
<td>All-comers</td>
<td>-</td>
<td>Strut coverage</td>
<td>2-5 months</td>
<td>Strut coverage COMBO: 77.1%, 92.5%, 92.7%, 94.9%</td>
</tr>
<tr>
<td>REMEDEE registry</td>
<td>NCT01874002</td>
<td>1000</td>
<td>All-comers</td>
<td>-</td>
<td>TLF *</td>
<td>1-year</td>
<td>TLF rate of 5.7%</td>
</tr>
<tr>
<td>MASCOT</td>
<td>NCT02183454</td>
<td>2614</td>
<td>All-comers</td>
<td>-</td>
<td>TLF</td>
<td>1-year</td>
<td>TLF rate of 3.4%</td>
</tr>
</tbody>
</table>

The prospective multicenter Study of Vascular Healing With the Combo Stent Versus the Everolimus Eluting Stent in ACS Patients by Means of OCT (REMEDEE-OCT study) randomized 60 patients with ACS to treatment with COMBO or everolimus-eluting Xience V stent (EES) (Abbott Vascular). The primary endpoint was the median percentage of uncovered stent struts per stent, measured by (OCT) at 60 days after stent implantation. A higher percentage of uncovered struts were observed in COMBO (14.7% versus 7.7% in EES, p=0.04), even after accounting for clustering (13.6% versus 6.9%, p=0.09). This is a remarkable and somewhat disappointing finding. The authors correctly note that stent strut coverage may not necessarily reflect strut endothelialization. A thin layer of endothelial cells of less than 40 μm may not be visible with OCT. Neointimal thickness at 60 days was lower with COMBO compared with EES (30.17 versus 50.26 µm, p<0.02). MACE in the REMEDEE-OCT, defined as the composite of cardiac death, myocardial infarction (Q-wave or non-Q-wave), emergent coronary artery bypass surgery, or clinically justified target lesion revascularization by repeat PCI or coronary artery bypass graft surgery at hospital discharge was assessed as secondary outcome. No significant differences in MACE between COMBO and EES were observed at 30, 60, 180, 360 and 540 days post-procedure and no ST was observed in both arms.

Another OCT study, the EGO-COMBO study (OCT Evaluation of Healing of Combo Stent), is a prospective single-center OCT study evaluating healing profile from 2 months post COMBO implant to two years follow-up. Sixty-one patients underwent longitudinal OCT analyses at baseline PCI and at the time of early (2-5 months), 9 month and 24 month follow-up. At 3 months follow-up 92.5% of struts were covered. A recent publication suggested a cut-off value of 90% covered struts on OCT as safe for discontinuation of DAPT, when three additional criteria were met: no frame with a ratio of uncovered to total stent struts of >30%, incomplete stent apposition (defined as a separation between strut and vessel wall with a distance greater than the thickness of the strut) area ≤2 mm² and last intraluminal defect (defined as an irregularly shaped structure, free from the vessel wall or attached to the vessel wall or the stent) area <300 µm². Unfortunately, these numbers were not provided in EGO-COMBO, so no statement can be given on safe cessation of DAPT based on OCT findings. However, another interesting finding was observed. Neointimal regression was seen from 9 months to 24 months of follow-up (median neointimal volume decreased from 17.8% to 15.7%). This finding should be further evaluated in other OCT studies comparing COMBO with other new-generation DES with sequential OCT measurements.

The primary results of the RECOVERY (Safety and Efficacy of the Combo Bio-engineered Sirolimus-eluting Stent Versus the Nano Polymer-free Sirolimus-eluting Stent in the Treatment of Patients With de Novo Stenotic Lesions), HARMONEE (Japan-USA Harmonized Assessment by Randomized, Multi-Center Study of OrbusNEich’s Combo
StEnt) and REDUCE (Randomized Evaluation of short-term DUal anti platelet therapy in patients with acute coronary syndrome treated with the COMBO dual-therapy stent) trials were presented at the Transcatheter Therapeutics Congress 2017 in Denver, Colorado. RECOVERY showed non-inferiority of COMBO stent to the polymer-free sirolimus-eluting Nano stent (Lepu Medical Technology, Beijing, China) with regards to angiographic in-segment late-loss at 9 months (COMBO 0.29±0.04mm versus Nano 0.31±0.03mm, \( p_{\text{noninferiority}} = 0.0001 \)). No definite and probable ST with both COMBO and Nano stents were observed throughout one year follow up.

The HARMONEE trial conducted in the United States and Japan is the first randomized controlled trial comparing COMBO with the best-in-class everolimus-eluting Xience stent (EES) (Xience V, Xience Prime, Xience Xpedition, Xience Alpine stents; Abbott Vascular). The trial was designed to assess 3 endpoints/hypotheses (see Figure 4): 1) non-inferiority of COMBO for 1-year clinical efficacy and safety compared with second-generation EES, 2) superiority of COMBO compared with EES for LLL at 12 months follow-up assessed with OCT and 3) a superior intimal tissue coverage of stent struts on OCT with COMBO at 12 months, compared to EES. A total of 572 patients were enrolled with mean age 68 years, 26% females, approximately 35% of patients had diabetes mellitus. In this head-to-head comparison event rates were lower than expected in both arms (assumed event rate of 9.0%), with a target vessel failure rate of 7.0% in COMBO and 4.2% in EES. The non-inferiority boundary was met (\( p_{\text{noninferiority}} = 0.02 \)), although the study was clearly underpowered. TLF event rates were numerically higher in patients treated with COMBO, driven by a higher ischemia-driven target-vessel revascularization. The ‘spike’ of target vessel revascularization (TVR) at 1 year, more prominent in the COMBO-arm, is thought to be related to the protocol mandated re-catheterization, despite the use of fractional flow reserve (FFR). The secondary objectives revealed the following findings: LLL (0.293 versus 0.219) and binary in-stent restenosis (1.3% versus 2.6%) were similar between COMBO stent and EES and superior healthy tissue strut coverage (homogenous tissue quality) was observed with COMBO (81.2%) versus EES (68.8%).

The REDUCE trial is an investigator-initiated, prospective multicenter trial that randomized patients with ACS to a DAPT duration of 3 months (short DAPT) or standard 12 months after COMBO stent placement.22 This non-inferiority study included 1496 patients, of mean age 61 years and approximately 20% women, to investigate the composite primary endpoint of ischemic (cardiac death, MI, stroke, ST or TVR) and bleeding endpoints (BARC II, III and V). The non-inferiority margin was met, with an observed 8.2% event rate in the 3 months DAPT-arm and 8.4% event rate in the 12 months DAPT-arm, \( p_{\text{noninferiority}} < 0.001 \). However, numerically higher rates of cardiac
death, MI and ST were observed in patients with short DAPT. Bleeding rates were not significantly different in patients with 3 months compared with 12 months DAPT (2.5% versus 3.0%, p=0.54).

**Inclusion/Exclusion Criteria and Consent**

N= 572*
Randomized 1:1 COMBO versus EES

**Cohort A (N=30)**
Serial 6M & 12M OCT
12M QCA, FFR
COMBO N=15, EES N=15

**Cohort B (N=110)**
12M QCA, OCT and FFR
HAMA base, 30D and 12M
COMBO N=55, EES N=55

**Cohort C (N=432)**
12M Angio/FFR only
COMBO N=216, EES N=216

**Early and Late OCT**
Observational
N= 30

**Intimal Tissue Coverage**
Superiority
N= 140

**HAMA**
Observational
N= 110

**Primary endpoint**
Ischemia & FFR driven TVF
N= 572*

* Includes an assumed 5% 1 year lost to follow-up
base = at baseline, D = days, M = months

**Figure 4.** The study design of the HARMONEE trial.

Adaptation of the HARMONEE Flowchart Figure from Am Heart J, 187, Kong et al., Rationale and design of the Japan-USA harmonized assessment by randomized, multicenter study of OrbusNEich’s combo StEnt (Japan-USA HARMONEE): Assessment of a novel DES platform for percutaneous coronary revascularization in patients with ischemic coronary disease and non-ST-elevation acute coronary syndrome, 112-121, Copyright Elsevier (2017).
REGISTRY DATA

The Multicenter, Prospective, Clinical Outcomes after Deployment of the Abluminal Sirolimus Coated Bio-Engineered Stent (Combo Bio-Engineered Sirolimus Eluting Stent) Post Market Registry (REMEDEE registry) is a prospective, investigator-initiated, multicenter, European all-comers registry that enrolled 1000 patients between June 2013 and March 2014. This registry was the first to evaluate clinical outcomes after PCI with COMBO stent in all-comers patients. Clinical follow up to 5 years is ongoing. The primary endpoint of the REMEDEE Registry was (TLF) at one year follow-up, a composite of cardiac death, target-vessel myocardial infarction (TV-MI) and any (TLR). All events were adjudicated by an independent clinical event committee (CEC). One year TLF occurred in 5.7% of patients, with a 1.7% rate of cardiac death, 0.7% TV-MI and 4.4% TLR. Definite or probable ST was observed in 0.6% of patients. When these clinical results are compared with outcomes of other DES all-comers trials, they are amongst the lowest rates, driven by low TV-MI and cardiac death rates. TLF at two year follow-up remained low (8.4%) with a TLR rate of 5.9%. Subgroup analyses have been performed on one year clinical outcomes in patients with diabetes mellitus (DM) and patients presenting with ACS. In the ACS sub-analysis, there was a statistical trend towards higher TLF, in patients presenting with ACS compared to patients treated in an elective setting (7.1% versus 4.4%, p=0.07). In the pre-specified DM sub-analysis, patients with insulin-treated DM (ITDM) had a significantly higher TLF rate compared with patients without DM (non-DM) or with non-ITDM: 4.4% in non-DM, 6.8% in nITDM and 20.3% in ITDM (p<0.001). In an exploratory analysis of patients from the REMEDEE registry treated with shorter duration of DAPT than recommended in the guidelines (duration of DAPT < 6 months, n=78) no safety issues were observed, with no ST in patients with early DAPT discontinuation.

Propensity score matched analysis has been performed of REMEDEE registry patients treated with COMBO and patients from the DUTCH PEERS trial, treated with Resolute Integrity zotarolimus eluting stents (Medtronic, Dublin, Ireland) and Promus Element EES (Boston Scientific, Marlborough, USA), showing similar event rates at two year follow-up in all-comers patients (7.9% in COMBO vs 6.4% in PROMUS Element/Resolute Integrity, p=0.26). Longer follow up of the REMEDEE patients up to five years will be collected to assess the incidence of late target lesion revascularization in order to assess the potential clinical effects of intimal hyperplasia regression that was seen in previous studies.

The Multinational Abluminal Sirolimus Coated BiO-Engineered StenT –The MASCOT Post-Marketing Registry (MASCOT) is the largest prospective, multicenter, international registry that enrolled 2614 patients across 60 sites in less than two years, between June...
2014 to March 2016. The primary endpoint was one-year TLF, a composite of cardiac death, TV-MI or clinically-driven TLR. The primary results have been presented at the Transcatheter Therapeutics Congress 2017 in Denver, Colorado. The primary endpoint was observed in 3.4% (n=88) of patients, with a definite or probable ST rate of 0.9% at one-year follow-up. The MASCOT registry also collected systematic data on adherence to DAPT during follow up and adjudicated DAPT according to the mode of cessation as physician recommended discontinuation, temporary interruption for <14 days or non-recommended disruption due to bleeding or non-compliance as per the PARIS registry definitions. Any DAPT cessation was observed in 24.8% patients at 12 months follow-up (including 21.7% discontinuation, 2.2% disruption and 0.9% interruptions). Interestingly however, 6 month rate of any DAPT cessations were low, suggesting that physicians across these global sites tended to continue DAPT up to 12 months in these patients. The MASCOT registry also adjudicated bleeding endpoints. Major bleeding (Bleeding Academic Research consortium types 3 or 5) was noted in 1.8% (n=46) patients.

EXPERT SUMMARY

The large global research program investigating preclinical and clinical outcomes of the COMBO stent has given much insight into the performance of the bio-engineered COMBO stent. Its safety profile has been assessed in both randomized trials and all comer registries, showing low ST rates and acceptably low rates of in-stent restenosis. RCT’s have demonstrated the non-inferiority of COMBO with Nano SES and Xience EES.

Indeed, the clinical results in patients treated with COMBO stent are excellent, even beyond one year follow-up. Moreover, no special implantation technique is required for COMBO. For instance the pre-dilatation, sizing, and post-dilatation (PSP) technique needed for bioresorbable scaffolds, and issues with stent dislodgements and longitudinal foreshortening seen with some metallic stents have not been observed to be of concern with COMBO.

Nevertheless, despite the anticipated benefits of the COMBO stent allowing shorter DAPT duration, only limited data are available. Short duration of DAPT after the bare metal EPC capturing Genous™ stent has been reported and showed no differences between short DAPT (<15 days) and long DAPT. The results of the REDUCE trial suggest that 3 months of DAPT in ACS-patients treated with COMBO stent may be feasible, however additional studies are warranted.
Future directions

Further prospective clinical data after PCI with the DTS-COMBO is emerging. The highly anticipated SORT OUT X trial is currently recruiting patients. This is an investigator-initiated, randomized clinical trial comparing the sirolimus-eluting DTS COMBO stent with the sirolimus-eluting biodegradable polymer Orsiro stent (Biotronik, Berlin, Germany). This trial will allow evaluation of the added value of the bio-engineered pro-healing technique from the COMBO stent compared to the new generation Orsiro stent. Clinicaltrials.gov identifier: NCT03216733. Furthermore, long-term follow-up from the REMEDEE registry will provide up to 5 year clinical outcomes.

Despite this, a gap exists for relevant clinical research on the safety of DAPT discontinuation in COMBO treated patients. Randomized controlled trials in patients with an indication for short duration of DAPT are needed with this platform. Certainly, a randomized comparison between COMBO and stents that are designed to safely shorten DAPT, such as the polymer- and carrier free BioFreedom stent (Biosensors International, Switzerland), powered for relevant clinical endpoints, would be extremely useful in assessing the safety and efficacy of these stent platforms in patients that might benefit the most from such technologies.

CONCLUSION

The bio-engineered COMBO stent has shown low clinical events rates and a remarkable safety profile with a low incidence of target lesion failure and stent thrombosis. Although limited trial data support the feasibility of short DAPT with this stent, additional, prospective clinical data are needed to confirm the safety of short DAPT after COMBO stent placement. Future trials should focus on patients with greater predisposition for DAPT disruption such as patients at high bleeding risk who may stand to gain maximum benefit from this technology.
REFERENCES


