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Differences in optical coherence tomography findings between an endothelial progenitor cell-capture sirolimus-eluting stent and a paclitaxel-eluting stent: insights from the OCT substudy of the REMEDEE first-in-man trial

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KEYWORDS

- endothelial progenitor cell
- neoatherosclerosis
- neointima
- optical coherence tomography
- sirolimus
- vascular healing

Abstract

Aims: First-generation DES are associated with delayed endothelial coverage and poor stent healing, increasing the risk of late stent thrombosis, late catch-up and neoatherosclerosis. This observational REMEDEE substudy aimed to examine differences in vascular healing by OCT between the EPC-capture sirolimus-eluting COMBO stent and a paclitaxel-eluting stent (TAXUS).

Methods and results: A subset of 33 patients (COMBO=23, TAXUS=10) with *de novo* coronary artery lesions in the REMEDEE study had OCT examination at the nine-month angiographic follow-up. Between-stent differences of OCT strut coverage, apposition, and neointimal morphology were compared by a core laboratory. Four thousand eight hundred and seventy-five COMBO and 2,697 TAXUS stent struts were analysed. More COMBO (98.5%) than TAXUS (97.6%) struts were well apposed and covered (p=0.3998); when overlying the ostium of a side branch, more TAXUS (0.7%) than COMBO (0.2%) struts were uncovered (p=0.0135). The COMBO stent was associated with a more homogeneous neointimal pattern (79.2% vs. 40.0% for TAXUS, p=0.04) and less layering (0.0% vs. 20.0% with TAXUS, p=0.08).

Conclusions: OCT showed nearly complete (98.5%) coverage of the COMBO stent by nine months and significantly more homogeneous neointimal tissue than with the TAXUS. These observations suggest better healing with the COMBO stent in comparison with the TAXUS stent at nine months.

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Abbreviations

BMS bare metal stent(s)
DES drug-eluting stent(s)
DAPT dual antiplatelet therapy
EPC endothelial progenitor cell(s)
IQR interquartile range
OCT optical coherence tomography
REMEDEE Randomised study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt

Introduction

By reducing the rates of restenosis and target vessel revascularisation, drug-eluting stents (DES) have improved the outcome of patients with coronary artery disease[1-3]. However, because DES are associated with delayed endothelial healing[4,5], the development of neoatherosclerosis and the associated risk of (very) late stent thrombosis remains an important safety concern[6,7].

Endothelial progenitor cells (EPC) are circulating bone marrow-derived cells that will be immobilised by vessel injury and differentiate into mature endothelial cells promoting re-endothelialisation and healing[8-10]. In animal models, as well as in human *ex vivo* arteriovenous shunts, stents coated with anti-CD34 antibodies capturing circulating EPC have been shown to accelerate re-endothelialisation and reduce thrombogenicity[11-14].

The aim of the present substudy was to compare the midterm (nine months) vascular healing of a "dual-therapy" EPC-capture stent with abluminal sirolimus-eluting coating (COMBO™ stent; OrbusNeich Medical, Fort Lauderdale, FL, USA) with the TAXUS® Liberté™ paclitaxel-eluting stent (Boston Scientific, Marlborough, MA, USA) in a subset of patients enrolled in the REMEDEE (Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt) multicentre, randomised, controlled trial using frequency-domain optical coherence tomography (OCT).

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Methods

STUDY DESIGN

The COMBO stent combines sirolimus elution from an abluminal biodegradable polymer matrix together with a covalently bound anti-CD34 antibody layer in a "dual-therapy" approach targeting anti-neointimal proliferation as a DES while maintaining the EPC-capturing benefit promoting vessel healing with accelerated stent endothelialisation. REMEDEE is a first-in-man randomised controlled trial[15], with a non-inferiority design to demonstrate the efficacy and safety of the COMBO stent in the treatment of single *de novo* lesions in native coronary arteries (NCT00967902). One hundred and eighty-three patients were randomly assigned (2:1) to receive treatment with the COMBO or TAXUS. The COMBO stent met the study primary endpoint and was found to be non-inferior to TAXUS in nine-month angiographic in-stent late lumen loss of 0.39±0.45 mm, versus 0.44±0.56 mm with TAXUS, $p_{(non\text{-}inferiority)}$=0.0012 [15]. Additionally, IVUS was performed in a subgroup of 66 patients at six sites (45 COMBO and 21 TAXUS). The IVUS follow-up at nine months consisted of 35 patients from the COMBO group and 17 from the TAXUS group. A VH-IVUS comparison of the COMBO with the TAXUS found a significantly less necrotic core area at the maximum site of neointimal hyperplasia of 0.25 mm^2 versus 0.46 mm^2 (p=0.04) and a less confluent necrotic core of 10% versus 80% (p=0.02).

OCT PATIENT COHORT

During the nine-month angiographic follow-up, two of the enrolling REMEDEE centres undertook OCT imaging in a subset of 23 COMBO and 10 TAXUS patients as an integral part of their daily clinical practice. This was not pre-specified in the REMEDEE study protocol. OCT examination was not yet available during the baseline stent implantation procedure. The differences in strut coverage (i.e., healing response) and neointima characteristics between the two stents were examined with OCT imaging. The objective of this comparative substudy was observational and it was not powered for clinical endpoints.

OCT IMAGING PROCEDURE

OCT images were obtained using the frequency-domain C7XR™ OCT system and the Dragonfly™ OCT catheter (both St. Jude Medical, St. Paul, MN, USA) at a pullback speed of 20 mm/sec (5 frames per mm) and a pullback distance of 54 mm, with two sequential pullbacks being used for longer distances.

OCT QUANTITATIVE AND QUALITATIVE ANALYSES

OCT image analyses were performed by observers blinded to the stent type from an independent OCT core laboratory (Cardiovascular Research Foundation, New York, NY, USA) using offline software (OCT System Software B.0.1; LightLab Imaging [now St. Jude Medical]). Analyses included strut coverage and apposition, and all neointimal metrics. Quantitative analysis was performed at 1 mm intervals (1/5 frames) along the length of the stent[16,17]. In case of the presence of blood artefacts, the closest artefact-free frame was used.

Each strut was classified into one of the following categories: (i) well apposed covered, (ii) well apposed uncovered, (iii) malapposed covered, (iv) malapposed uncovered, (v) orifice branch site covered and (vi) orifice branch site uncovered **(Figure 1)**. If the strut was covered with neointima, the neointimal thickness was measured from the endoluminal surface of the tissue to the centre of the strut blooming artefact. An uncovered strut was defined as having no visible tissue on the luminal surface of the strut. To assess malapposition, the distance from the centre of the stent blooming artefact to the nearby endoluminal surface of the intima was measured while the assessor was blinded to the stent type. Malapposition was decided afterwards and defined as being present if the measured distance was greater than the sum of the thickness of the stent strut metal and that of the polymer: 104 µm (100+4 µm) for the COMBO and 113 µm (97+16 µm) for the TAXUS. Stent and luminal cross-sectional areas (CSA)

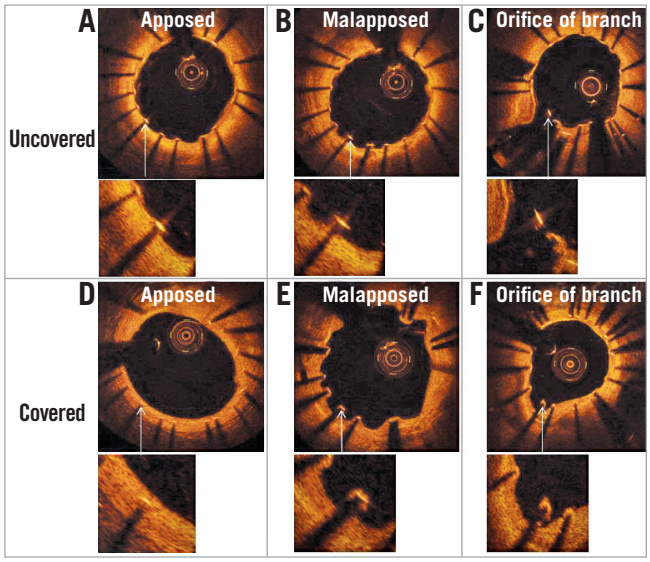

Figure 1. *Classification of stent strut coverage. A) Well apposed struts without tissue coverage. B) Malapposed struts without tissue coverage. C) Uncovered struts overlying the ostium of a side branch. D) Well apposed struts with tissue coverage. E) Malapposed struts with tissue coverage. F) Covered struts overlying the ostium of a side branch.*

were measured, and the percentage neointimal CSA was calculated (stent area-lumen area)/(stent area×100).

For neointimal morphological qualitative analysis, every individual frame was examined. The cross-sectional OCT morphological appearance of the neointimal tissue was labelled as: (i) homogeneous, (ii) heterogeneous, or (iii) layered, as reported by Gonzalo[18]. Features suggestive of neoatherosclerosis (lipidic plaque and/or calcification within the neointima), together with the presence of microvessels, macrophages, thin-cap fibroatheroma, intraluminal material with mass protruding into the lumen ≥250 μm), and neointimal rupture, were also evaluated[19,20].

STATISTICAL ANALYSIS

Continuous variables are expressed as median and interquartile range (IQR). Generalised estimating equation (GEE) relative risk statistics were used to assess differences in the median strut coverage. Categorical variables are expressed as percentages. Comparisons between stents were performed with the Pearson's chi-square test for categorical variables and Student's t-test or analysis of variance for continuous variables. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS software, Version 16.0.1 (SPSS Inc., Chicago, IL, USA).

Results

Thirty-three patients (COMBO 23 and TAXUS 10) underwent OCT evaluation at nine-month angiographic follow-up. Baseline demographics, clinical and lesion characteristics were similar[15]. Four thousand eight hundred and seventy-five COMBO struts and 2,697 TAXUS struts were analysed. Planar and volumetric analysis of the stents is presented in **Table 1** and **Table 2**.

Table 1. OCT planar analysis.

	COMBO (n=23) Median [IQR]	TAXUS (n=10) Median [IQR]	*p*-value
Minimum lumen area site			
Lumen CSA (mm²)	4.24 [3.30, 6.56]	4.93 [2.84, 5.78]	0.4567
Stent CSA (mm²)	6.11 [4.60, 9.04]	6.47 [6.05, 7.12]	0.9064
Neointima CSA (%)	27.1 [15.4, 38.3]	22.0 [14.3, 48.3]	0.9376
Minimum stent area site			
Stent CSA (mm²)	6.03 [4.23, 8.46]	5.96 [5.72, 6.46]	0.9844
Proximal most normal-looking site			
Lumen CSA (mm²)	7.06 [3.72, 8.92]	8.45 [5.72, 8.95]	0.4278
Distal most normal-looking site			
Lumen CSA (mm²)	6.08 [4.49, 9.79]	6.27 [5.13, 6.87]	0.8408

CSA: cross-sectional area

Table 2. OCT volumetric analysis.

Stent segment	COMBO (n=23) Median [IQR]	TAXUS (n=10) Median [IQR]	*p*-value
Stent length (mm)	18.4 [17.3, 23.4]	24.3 [20.4, 26.2]	0.0312
Neointimal volume (%)	15.3 [12.0, 22.4]	16.1 [7.4, 27.4]	0.9376
Normalised* lumen CSA (mm²)	5.91 [3.85, 8.35]	6.03 [4.49, 7.16]	0.9688
Normalised stent CSA (mm²)	7.14 [4.83, 9.60]	7.15 [6.19, 7.73]	0.8447
Normalised neointima CSA (mm²)	1.25 [0.91, 1.52]	1.18 [0.58, 1.70]	0.8142

*total volume/length. CSA: cross-sectional area

At the strut level **(Table 3)**, more COMBO struts (98.5%) were well apposed and fully covered as compared with TAXUS (97.6%) (p=0.3998). Over the ostia of side branches, more TAXUS struts lacked tissue coverage (0.7%) compared with the COMBO (0.2%),

Table 3. OCT strut coverage and malapposition (strut level, by generalised estimating equations [GEE]).

	COMBO (n=4,875) % (n) or Median [IQR]	TAXUS (n=2,697) % (n) or Median [IQR]	*p*-value
Well apposed covered	98.5 (4,801)	97.6 (2,633)	0.3998
Well apposed uncovered	1.2 (60)	1.6 (44)	0.5311
Malapposed covered	0.2 (8)	0.6 (15)	0.1646
Malapposed uncovered	0.1 (4)	0.2 (5)	0.4035
Orifice branch site covered	0.5 (24)	0.8 (22)	0.2518
Orifice branch site uncovered	0.2 (8)	0.7 (19)	0.0135
Total covered struts	98.6 (4,809)	98.2 (2,648)	0.4855
Total uncovered struts	1.3 (64)	1.8 (49)	0.4469
Neointimal thickness (mm)	0.16 [0.13, 0.19]	0.16 [0.11, 0.20]	0.8953

resulting in a significant GEE relative risk (p=0.0135). Analysed at the stent level, 99.1% and 98.4% of the COMBO and TAXUS stents were considered well apposed and covered (p=0.2705).

Based on qualitative analysis (**Table 4**, **Figure 2**, **Figure 3**), the COMBO stents had a more uniform and homogeneous neointimal response (79.2%), while the TAXUS was more variable and heterogeneous (p=0.04) (**Figure 2**-**Figure 4**). No case of thin-cap fibroatheroma, neointimal rupture or calcification was observed with either stent. All other qualitative parameters were similar between stents.

Table 4. OCT qualitative analysis.

	COMBO (n=24*) % (n)	TAXUS (n=10) % (n)	*p*-value
Neointimal tissue appearance			
Homogeneous	79.2 (19)	40.0 (4)	0.04
Heterogeneous	20.8 (5)	40.0 (4)	0.40
Layered	0.0 (0)	20.0 (2)	0.08
Peri-strut low-intensity area	33.3 (8)	70.0 (7)	0.07
Microvessel	8.3 (2)	30.0 (3)	0.14
Macrophage-like appearance	4.2 (1)	10.0 (1)	0.51
TCFA-like neointima	0.0 (0)	0.0 (0)	N/A
Neointimal rupture	0.0 (0)	0.0 (0)	N/A
Neointimal calcification	0.0 (0)	0.0 (0)	N/A
Total lesions with single abnormal intraluminal tissue	4.2 (1)	10.0 (1)	0.51

*sample with partial image was included in the qualitative data, but excluded from the quantitative data. N/A: not available; TCFA: thin-cap fibroatheroma

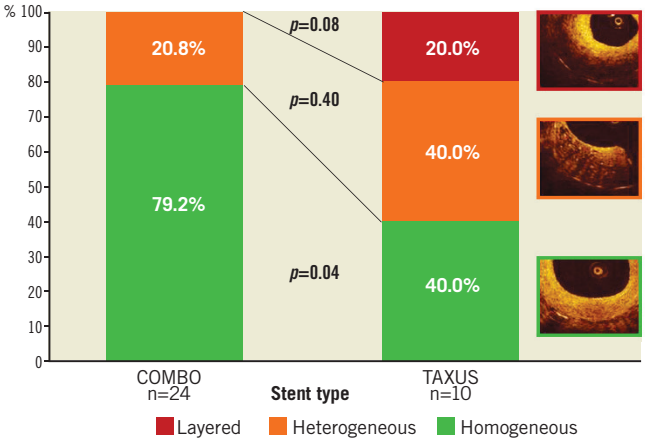

Figure 2. *Neointimal tissue characterisation (OCT). COMBO (n=24); TAXUS (n=10).*

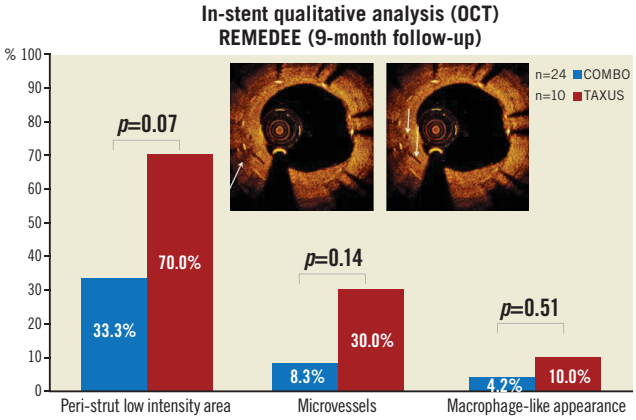

Figure 3. *Qualitative tissue characterisation (OCT, in-stent).*

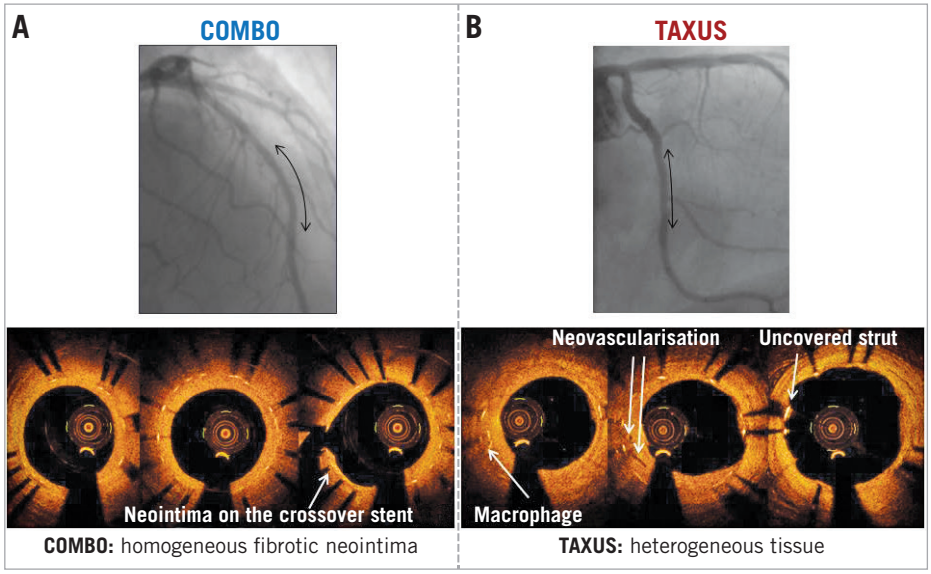

Figure 4. *Case examples of neointimal tissue. A) COMBO: homogeneous fibrotic intima. B) TAXUS: heterogeneous tissue.*

Discussion

The present study is a small-scale observational study comparing the vascular healing response associated with the COMBO and TAXUS stents using OCT. At nine-month follow-up, the major findings are: 1) neointimal volume and thickness were similar between the two stents, but 2) the neointima over the COMBO stents was more uniform and homogeneous whereas it was more variable and heterogeneous with TAXUS, 3) fewer COMBO struts at the orifice branch sites were uncovered. These observations could represent the pro-healing capability of the COMBO stent, as reflected by the better strut coverage indicative of better endothelial healing, while retaining its antiproliferative properties (neointimal suppression) as a DES.

By quantitative analysis, 98.5% of the COMBO struts were well apposed and covered compared with 97.6% of the TAXUS struts (p=0.3998). Even across the ostium of a side branch, which is often associated with impaired healing and the development of late stent thrombosis[21], more COMBO struts were covered than TAXUS. These clinical observations are consistent with animal studies which have demonstrated enhanced re-endothelialisation when EPC are present at the site of vessel wall injury[11-14], and that the combination of anti-CD34 antibodies with sirolimus results in a faster and greater degree of endothelialisation than sirolimus alone[14]. These differences can be related to various factors in the stent design, including: (i) sirolimus vs. paclitaxel, (ii) abluminal vs. conformal drug delivery, and (iii) fully biodegradable vs. permanent drug delivery polymer matrix[4,5].

The OCT morphological findings that the neointimal tissue quality inside the COMBO stents had a more homogeneous pattern while that for the TAXUS was layered or heterogeneous suggest a favourable alteration in the development of neointimal hyperplasia; however, it remains unclear whether these differences originate from the recruitment of circulatory EPC, the nature of the polymer matrix and/or the antiproliferative drug. In the case of the COMBO stent, all of the sirolimus is eluted and the polymer is completely resorbed at the nine-month time point, whereas the permanent polymer of the TAXUS stent may lead to chronic inflammatory effects[4,22].

It has been reported that early neointima formation may represent a homogeneous tissue[23,24], which may indicate normal neointima[20], while heterogeneous patterns may be associated with worse subsequent outcome[25]. Neoatherosclerosis is frequently observed in bare metal stents (BMS) and DES, and is a final common pathway leading to late stent failure[26,27]. There are, however, significant differences in the timing of development and incidence of lesions between different stent types. Indeed, after reviewing the histology findings of autopsy cases, Nakazawa and colleagues found that the accelerated neoatherosclerotic changes could occur just four months after DES implantation, while the same changes occurred beyond two years in BMS and remained a rare finding up to four years[28]. They also found that the incidence of neoatherosclerosis was significantly greater with DES and, if present, the DES would remain patent for a shorter period of time (median of 420 days with DES vs. 2,160 with BMS)[29].

OCT qualitative analysis revealed the presence of significantly more morphologically homogeneous tissue with the COMBO in comparison with the TAXUS. These observed OCT healing patterns with the COMBO are consistent with the VH-IVUS findings at nine-month follow-up of the REMEDEE study[15], revealing a dense composition and morphology of the neointimal tissue, with significantly less confluent necrotic core in the COMBO stent. This could reflect the pro-healing benefits of the immobilised anti-CD34 antibody and the reduced magnitude of inflammation with the rapid disappearance of biodegradable polymer within 90 days. These observational results suggest that the COMBO stent shows improved stent healing compared with the TAXUS stent.

Limitations

This OCT substudy in the REMEDEE trial has the following limitations. First, our results are derived from an observational study at a single time point at nine months in a small number of patients with stable angina and relatively simple coronary lesions. Second, despite the high resolution of OCT, abnormal in-stent tissue including late fibrin accumulation, excessive inflammation or abundant extracellular matrix, may be difficult to discriminate, casting difficulties on interpreting true healthy neointima. Third, further studies with long-term follow-ups are required to evaluate the relationships between early stent re-endothelialisation, vascular healing, and clinical performance.

Conclusions

Treatment of *de novo* coronary artery lesions with the dual-therapy EPC-capturing sirolimus-eluting COMBO stent was safe and effective. OCT confirmed the complete coverage of the COMBO stent and the dense homogeneous nature of the in-stent neointimal tissue at nine months, which is consistent with the previously reported observation with VH-IVUS.

Impact on daily practice

DES are often associated with delayed endothelial coverage and poor stent healing with an increased risk of late stent thrombosis and the development of neoatherosclerosis. The aim of the present substudy was to compare the midterm (nine months) vascular healing profile of a unique "dual-therapy" EPC-capturing stent with abluminal sirolimus-eluting coating (COMBO stent) to that observed with a first-generation monotherapy paclitaxel-eluting stent (TAXUS) using OCT. Both devices were equally effective in controlling neointimal proliferation, yet the healing profile as assessed by OCT demonstrated a marked difference in tissue homogeneity and uniformity in favour of the COMBO stent, which may translate into better long-term clinical outcomes.

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Conflict of interest statement

M. Haude has received support from Abbott, Biotronik, OrbusNeich, Medtronic, and Volcano. A. Maehara has received speaker's fees from St. Jude Medical, research grant support from Boston Scientific, and is a consultant to Boston Scientific and ACIST. R. Mehran is a consultant to and/or receives honoraria from AstraZeneca, Abbott Vascular, Boston Scientific, Covidien, CSL Behring, Janssen (J & J), Merck, Maya Medical, Regado Biosciences and Sanofi, and also receives research/grant support from AstraZeneca, BMS/Sanofi Aventis, DSI/Eli Lilly and The Medicines Company. The other authors have no conflicts of interest to declare.

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