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The REMEDEE-OCT Study

An Evaluation of the Bioengineered COMBO Dual-Therapy CD34 Antibody–Covered Sirolimus-Eluting Coronary Stent Compared With a Cobalt-Chromium Everolimus-Eluting Stent in Patients With Acute Coronary Syndromes: Insights From Optical Coherence Tomography Imaging Analysis

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ABSTRACT

OBJECTIVES The aim of the present study was to evaluate vascular healing of the bioengineered COMBO Dual Therapy Stent compared with a cobalt-chromium (CoCr) everolimus-eluting stent (EES) as assessed by optical coherence tomography in patients with acute coronary syndromes.

BACKGROUND CD34+ cells promote endothelial repair after vascular injury. The bioengineered COMBO Dual Therapy Stent combines CD34+ cell–capturing technology with abluminal sirolimus release, but more data from clinical studies evaluating the vascular response are needed.

METHODS In a prospective randomized multicenter clinical trial, 60 patients with acute coronary syndromes were randomized 1:1 to COMBO or CoCr EES implantation. The primary endpoint was the percentage of uncovered stent struts per stent. Stent assessment by optical coherence tomography was performed at baseline and at 60 days, followed by independent core laboratory analysis.

RESULTS The percentage of uncovered struts per stent was higher with the COMBO than the CoCr EES at 60 days (median 14.7% vs. 7.7%; $p = 0.04$). However, no significant difference in uncovered stent struts was observed in the strut level–based analysis at 60 days, which also accounted for clustering (COMBO vs. CoCr EES; 13.6% vs. 6.9%; $p = 0.09$; generalized linear mixed models–adjusted analysis). Neointimal thickness at 60 days was lower with the COMBO compared with the CoCr EES (median 30.17 vs. 50.26 μm; $p = 0.02$; stent-level analysis). There were no significant differences in the frequency of major adverse cardiac events and each component of major adverse cardiac events within the study population between the 2 groups at 30, 60, 180, 360, and 540 days post-procedure. No target vessel stent thrombosis has been documented within 540 days.

CONCLUSIONS The present multicenter, prospective clinical study for the first time compared the vascular response of the bioengineered COMBO Dual Therapy Stent with a CoCr EES in patients early after acute coronary syndrome by using intracoronary optical coherence tomographic analysis. The percentage of uncovered stent struts per stent was somewhat higher after COMBO versus CoCr EES implantation as detected by optical coherence tomography, associated with reduced neointimal thickness. (J Am Coll Cardiol Intv 2017;10:489–99) © 2017 by the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CoCr = cobalt-chromium

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

GLMM = generalized linear mixed models

OCT = optical coherence tomographic

Drug-eluting stents (DES) significantly mitigate the risk for restenosis and represent an important advance in the catheter-based treatment of coronary artery disease (1). However, a limitation of DES is that the desirable endothelial cell regrowth above stent struts is to some extent inhibited by limus-family analogs that reduce neointimal hyperplasia (1,2). Therefore, despite improved efficacy in the prevention of restenosis and target vessel failure with the introduction of new-generation DES, further optimization with respect to the prevention of late in-stent thrombosis and neoatherosclerosis is warranted (3–9). In particular, acute coronary syndromes (ACS) have been identified as a risk factor for late in-stent thrombosis after DES implantation (6). Late in-stent thrombosis has been related to impaired endothelial repair response after DES implantation, and this delay in arterial healing is more pronounced in the setting of ACS (6,10). In keeping with this, it seems intuitive that novel strategies to promote arterial healing are likely to result in further improved patient outcome not only at short-term but also at long-term follow-up, considering that impaired endothelial function and integrity has been suggested to play a key role in progression of CAD.

We and others have observed that CD34+ cells promote endothelial cell growth and endothelial repair responses after injury (11–15). The COMBO Dual Therapy Stent (OrbusNeich Medical, Fort Lauderdale, Florida) was designed to combine abluminal release of sirolimus from a bioresorbable polymer matrix with a CD34+ cell-capturing mechanism to obtain adequate suppression of neointimal proliferation and restenosis, while promoting endothelial repair. Indeed, preclinical investigations have suggested that stent endothelialization is enhanced with COMBO compared with the Cypher stent (16,17), but more clinical data comparing COMBO with new-generation DES are required. In this respect, the everolimus-eluting Xience stent has been reported to have a particularly rapid endothelial repair response among current-generation DES and was therefore selected as a comparator in the present studies (18).

Optical coherence tomographic (OCT) imaging is increasingly used as a high-resolution intracoronary imaging modality to examine vascular response after coronary stent implantation, but the appropriate interpretation of OCT findings is an ongoing field of clinical and translational research (19–23).

Herein we present a prospective, multicenter randomized study to compare the vascular response after COMBO stent versus new-generation cobalt-chromium (CoCr) everolimus-eluting stent (EES) implantation, as assessed by OCT imaging in patients with ACS.

METHODS

STUDY PROTOCOL. REMEDEE-OCT (Study of Vascular Healing With the Combo Stent Versus the Everolimus Eluting Stent in ACS Patients by Means of OCT) was a prospective multicenter trial (NCT01405287) in which 60 patients presenting with ACS were randomized 1:1 to treatment with the COMBO bioengineered sirolimus-eluting stent (n = 29) versus a new-generation CoCr EES (Xience V, Abbott Vascular, Santa Clara, California) (n = 31) to compare vascular healing using intracoronary OCT imaging. The first procedure was in October 2011, and the last clinical follow-up visit was in January 2014. Group assignment was blinded to the statistician and members of the independent clinical events committee, steering committee, and core laboratory.

Quantitative comparative analysis and OCT imaging were performed at baseline and 60-day follow-up, and results were analyzed by an independent core laboratory. Clinical follow-up was scheduled at 30,

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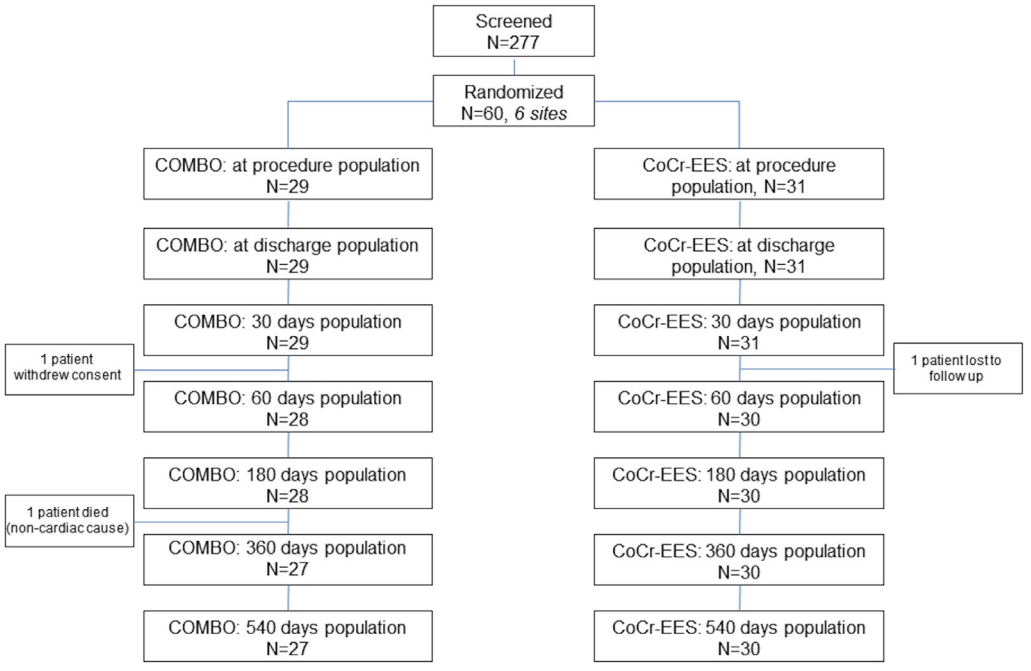
FIGURE 1 Study Flowchart: Patient Enrollment, Randomization, and Follow-Up



CoCr = cobalt-chromium; EES = everolimus-eluting stent(s).

60, 180, 360, and 540 days. A study flowchart is presented in Figure 1.

INCLUSION AND EXCLUSION CRITERIA. The eligibility criteria for study enrollment were as follows: ACS (i.e., ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction); single de novo or nonstented lesion of >50% and <100% diameter stenosis, located in a native coronary artery ≥2.5 mm and ≤3.5 mm in diameter; and lesion length ≤20 mm amenable to percutaneous treatment with DES. Patients with chronic total occlusions were excluded from the study, although 100% occlusion by fresh thrombus was allowed. Subjects who met all of the eligibility criteria and provided written informed consent approved by the appropriate medical ethics committee, Institutional Review Board, or human research ethics committee were successfully enrolled and randomly assigned to receive a COMBO stent or a CoCr EES. A complete list of exclusion criteria is presented in the Online Appendix.

OCT IMAGING ACQUISITION AND ANALYSES. Images were acquired using the C7-XR OCT Intravascular Imaging System (St. Jude Medical, St. Paul, Minnesota) after intracoronary administration of 200 μg of nitroglycerin through conventional guiding catheters. A 0.014-inch guidewire was positioned distally, and the OCT catheter (C7 Dragonfly, St. Jude Medical) was advanced to the distal end of the stent. The entire length of the region of interest was scanned using the integrated automated pull-back device at 20 mm/s. During image acquisition, coronary blood flow was replaced by contrast dye infusion. All images were digitally stored and submitted to core laboratory off-line evaluation (Imaging Core Laboratory, Harrington Heart and Vascular Institute, University Hospitals Case Medical Center, Cleveland, Ohio) and subsequent analysis using proprietary software (St. Jude Medical). All cross-sectional images (frames) were initially screened for quality assessment and excluded from analysis if any portion of the image was out of the screen or the image had poor quality caused by residual blood or sew-up artifact (24). Frames with side branches occupying >45° of the cross section were excluded from analysis. Frame-based analysis was performed considering every 3 frames (0.6-mm interval) along the entire target segment. Lumen, stent, and neointimal hyperplasia areas and volumes were calculated as previously described (25,26). The center of the luminal surface of the strut blooming was determined for each strut, and

its distance to the lumen contour was calculated automatically to determine strut-level intimal thickness. Strut malapposition was determined when the negative value of strut-level intimal thickness was greater than the strut thickness, according to the stent manufacturer's specifications, with the addition of a compensation factor of 20 μm to correct for strut blooming. The blooming compensation factor was determined on the basis of the analysis of 2,250 struts. Highly reproducible measurements for strut apposition and coverage using the described methods have been reported (27). Qualitative imaging assessment was performed in every frame for the presence of abnormal intrastent tissue, which was defined as any mass protruding beyond the stent struts into the lumen, with irregular surface and a sharp intensity gap between mass and neointimal tissue (28,29). Neointimal heterogeneity index was defined as the ratio between maximal neointimal thickness and average neointimal thickness in each frame using 360° chord data (26). Tissue properties were assessed as follows: after a region of interest was manually drawn on the tissue covering the stent struts, tissue attenuation, backscatter, intensity, and half width (i.e., the distance from peak intensity to its half intensity) were automatically obtained using a dedicated tool provided by the proprietary software (28). The definition of dissections was previously reported (30).

ENDPOINTS. Besides OCT assessment of the percentage of uncovered stent struts per stent at 60 days (the primary endpoint), several secondary OCT endpoints were analyzed and are listed in the Online Appendix. Clinical secondary endpoints included major adverse cardiac events, defined as a composite of cardiac death, myocardial infarction (Q-wave or non-Q-wave), emergent coronary artery bypass surgery, and clinically justified target lesion revascularization by repeat percutaneous coronary intervention or coronary artery bypass graft surgery at hospital discharge and 30, 60, 180, 360, and 540 days post-procedure and target vessel stent thrombosis at 30, 60, 180, 360, and 540 days post-procedure per Academic Research Consortium definition (Online Appendix). The independent clinical events committee reviewed and adjudicated all clinical endpoint events according to the study protocol. In case of an intervention or event, the clinical events committee determined whether it was clinically indicated and whether the cause of the event was cardiac related.

STATISTICAL ANALYSIS. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina) JMP version 9.0 (SAS Institute), and SPSS Advanced Statistics version 22 (IBM, Armonk, New York). Continuous variables were first checked for normal distribution using the Shapiro-Wilk test and then separated into variables with normal and nonparametric distributions. Mean values with SDs were derived from normally distributed parameters, and nonparametric data are described as medians with interquartile ranges. In the event of normal distribution, variables were compared using the Student *t* test. The Wilcoxon rank sum test was used when nonparametric data were compared. A p value ≤ 0.05 was considered to indicate statistical significance. Categorical variables are expressed as counts and percentages and were compared using the Fisher exact test. The standardized difference was calculated as mean or proportion difference divided by the SD of the difference.

The sample size was calculated on the basis of the primary endpoint at 60-day follow-up. An arcsin ($\sqrt{p}$) transformation was applied to the coverage proportion (p) to normalize the distribution of the variable. Subsequently, the standard sample size calculation for the 2-sample *t* test was performed for the transformed variable. The following assumptions were taken into consideration: at 60 days after stent implantation, the median coverage percentage is 80% with the EES and 95% with COMBO, and individual coverage percentages are dispersed in 95% intervals (0.35 to 1.0) and (0.75 to 1.00), respectively. These assumptions were based on previous studies evaluating endothelial healing in preclinical large-animal models. A sample size of 30 patients in each group (i.e., 60 in total) was needed to reject the null hypothesis with power of 90% ($\beta = 0.90$) and a 2-sided α value of 0.05. The total sample size accounts for 25% loss to follow-up. For strut-level analysis of clinical OCT parameters, nested generalized linear mixed models (GLMM) with Dunnett's correction for multiple testing were used to investigate group differences in consideration of multiple measurements per patient (31). Within these models, stent type was considered as a fixed effect within each patient, while the experimental factor frame number and strut angle were considered as nested random effects. Considering a binary data structure, a binomial distribution was assumed. Data assessed by GLMM analysis at strut level were expressed as estimated mean values with 95% confidence intervals. The statistical tests were 2-tailed, and a p value <0.05 was considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS. Sixty patients with an ACS were included in the present study. Patient characteristics are shown in Table 1. No differences were documented regarding to baseline demographics. Except for a greater prevalence of smoking in the CoCr EES group, patients were similar in terms of cardiovascular risk factors. The location of lesions and pre-procedural TIMI (Thrombolysis In Myocardial Infarction) flow was also similar in both populations. There was no significant difference regarding device and procedural characteristics, outlined in Table 2.

TABLE 1 Baseline Characteristics Comparing COMBO Stent and Cobalt-Chromium Everolimus-Eluting Stent in the Clinical Setting (N = 60)

	COMBO Stent (n = 29)	CoCr EES (n = 31)	Standardized Difference	p Value
Patients with 100% compliance with eligibility criteria	27 (93.1)	30 (96.8)		
Age, yrs	62.8 ± 10.7	59.4 ± 11.3	0.217	0.240
Male	24 (82.8)	21 (67.7)	1.373	0.180
BMI, kg/m^2	27.3 (25.2–31.0)	28.1 (25.6–33.0)	NA*	0.230
Cardiovascular risk factors				
Hypertension	18 (62.1)	17 (54.8)	0.570	0.570
Hyperlipidemia	18 (62.1)	17 (54.8)	0.570	0.570
Diabetes mellitus	4 (13.7)	4 (12.9)	0.101	1.000
Smoking, current	6 (20.7)	12 (38.7)	−1.562	0.010
Family history of CVD	12 (41.4)	13 (41.9)	−0.044	0.970
Comorbidities				
Prior MI	2 (6.9)	0 (0.0)	1.466	0.230
Prior stroke/TIA	2 (6.9)	0 (0.0)	1.466	0.230
Chronic renal failure	0 (0.0)	2 (6.5)	−1.468	0.490
Hemodynamic data				
Systolic BP, mm Hg	131.3 ± 21.5	139.3 ± 19.3	−0.277	0.130
Diastolic BP, mm Hg	76.8 ± 11.4	81.0 ± 11.8	−0.256	0.170
LVEF, %	56.0 (52.5–62.5)	55.0 (45.0–64.3)	NA*	0.680
Clinical presentation				
STEMI	13 (44.8)	9 (29.0)	1.282	0.210
NSTEMI	16 (55.2)	22 (71.0)	−1.282	
Target lesion				
LAD	15 (51.7)	16 (51.6)	0.009	0.970
LCx	9 (31.0)	9 (29.0)	0.169	
RCA	5 (17.2)	6 (19.4)	−0.212	
Pre-procedure TIMI flow grade				
0	6 (20.7)	10 (32.3)	−1.026	0.790
1	2 (6.9)	2 (6.5)	0.069	
2	4 (13.7)	4 (12.9)	0.101	
3	17 (58.6)	15 (48.4)	0.799	

Values are n (%), mean ± SD, or median (interquartile range). *Because the Wilcoxon rank sum test was used when nonparametric data were compared, and this test compares the median instead of the mean, the standardized difference is not presented.

BMI = body mass index; BP = blood pressure; CoCr = cobalt-chromium; CVD = cardiovascular disease; EES = everolimus-eluting stent; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NA = not applicable; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; TIMI = Thrombolysis in Myocardial Infarction.

OCT AND QUANTITATIVE COMPARATIVE ANALYSIS MEASUREMENTS. OCT post-procedural analysis was obtained in a total of 56 patients, of whom 27 received COMBO stents and 29 were treated with CoCr EES. At 60 days, a total of 53 patients were analyzed, 24 COMBO patients and 29 CoCr EES patients (Figure 2). In the clinical study, the percentage of uncovered struts per stent was higher with the COMBO stent than the CoCr EES, but no significant difference in uncovered stent struts was observed in the stent strut level-based analysis at 60 days (COMBO vs. CoCr EES; 13.6% [8% to 22.1%] vs. 6.9% [4.1% to 11.4%]; p = 0.09; GLMM-adjusted analysis) (Table 3, Online Figures 1 and 2). The maximal length of segments with uncovered struts was similar in both groups at 60 days (COMBO vs. CoCr EES; 5.4 mm [3.0 to 8.8 mm] vs. 3.2 mm [1.2 to 7.5 mm]; p = 0.19). Similarly, no significant difference was noted in the maximal length of segments with malapposed struts both post-procedure (0.6 mm [0.0 to 1.8 mm] vs. 0.8 mm [0.0 to 2.4 mm]; p = 0.70) and at 60-day follow-up (0.6 mm [0.0 to 1.2 mm] vs. 0.6 mm [0.0 to 1.4 mm]; p = 0.79).

The neointimal thickness of COMBO was reduced compared with the CoCr EES in the stent-level analysis (median; 30.17 vs. 50.26 μm; p = 0.02; stent-level analysis) (Table 3), but no significant differences were observed after 60 days in the strut-level analysis of both groups receiving COMBO or CoCr EES (34.85 μm [11.11 to 58.59 μm] vs. 54.94 μm [32.92 to 76.95 μm]; p = 0.22) (Table 3).

Morphometric parameters at baseline and 60-day follow-up were similar between the 2 stents (Online Table 1), except that the COMBO stent compared with the CoCr EES had significantly lower neointimal area (0.25 mm^2 [0.09 to 0.43 mm^2] vs. 0.42 mm^2 [0.25 to 0.65 mm^2]; p = 0.02) and neointimal volume (4.5 mm^3 [1.43 to 7.51 mm^3] vs. 8.71 mm^3 [4.98 to 11.75 mm^3]; p < 0.01) and lower stent volume (113.3 mm^3 [97.35 to 133.2 mm^3] vs. 138.1 mm^3 [106.74 to 178.16 mm^3]; p = 0.04) at 60 days. There was no significant difference between both groups regarding total malapposition volume, maximal malapposition volume, and maximal malapposition distance (Online Table 1). No acute stent thrombosis was detected in either group.

In quantitative comparative analysis, the percentage diameter stenosis at 60-day follow-up was similar in both stent groups (COMBO vs. CoCr EES; 0.07 [0.02 to 0.11] vs. 0.09 [0.04 to 0.14]; p = 0.19). No difference was noted in terms of follow-up binary restenosis (diameter stenosis >50%) between the COMBO and CoCr EES groups (0% vs. 3.3%; p = 1.00).

TABLE 2 Device and Procedural Characteristics, COMBO Stent vs. Cobalt-Chromium Everolimus-Eluting Stent in Clinical Setting (N = 60)

	COMBO Stent (n = 29)	CoCr EES (n = 31)	Standardized Difference	p Value
Target lesion type				
Single de novo	29 (100)	31 (100)		
Thrombus present	17 (58.6)	17 (54.8)	0.296	0.790
Thrombus aspirated	13/17 (76.5)	12/17 (70.6)	0.39	1.000
RVD, mm	3.0 (2.8-3.5)	3.0 (2.6-3.5)	NA*	0.700
Lesion length, mm	13.6 (10.0-15.0)	13.0 (12.0-15.0)	NA*	0.920
Target lesion treatment				
Lesion pre-dilated	26 (89.7)	27 (87.1)	0.31	1.000
Number of stents per lesion	1.0 (1.0-1.0)	1.0 (1.0-1.0)	NA*	0.330
First stent length, mm	18.0 (18.0-18.0)	18.0 (15.0-18.0)	NA*	0.660
First stent diameter, mm	3.16 ± 0.36	3.24 ± 0.36	−0.172	0.390
QCA measurements				
Baseline pre-PCI				
Pre-procedure RVD, mm	2.56 (2.13-2.83)	2.60 (2.32-2.89)	NA*	0.390
Pre-procedure MLD, mm	0.48 (0.34-0.64)	0.41 (0.27-0.57)	NA*	0.340
Pre-procedure %DS	83.1 (75.3-90.6)	85.5 (77.3-91.7)	NA*	0.550
Baseline post-PCI				
Final stented lesion length, mm	15.0 (13.51-17.96)	15.29 (11.57-17.24)	NA*	0.400
Final RVD, mm	3.01 (2.54-3.33)	3.04 (2.77-3.21)	NA*	0.900
Final MLD, mm	2.68 ± 0.40	2.77 ± 0.38	−0.15	0.410
Final %DS	6.9 ± 6.9	7.1 ± 5.5	−0.031	0.880
Lumen gain, mm	2.14 ± 0.52	2.33 ± 0.45	−0.281	0.140

Values are n (%), n/N (%), median (interquartile range), or mean ± SD. *Because the Wilcoxon rank sum test was used when nonparametric data were compared, and this test compares the median instead of the mean, the standardized difference is not presented.

MLD = minimal luminal diameter; %DS = percent diameter stenosis; QCA = quantitative comparative analysis; RVD = reference vessel diameter; other abbreviations as in Table 1.

CLINICAL OUTCOMES. For both the intention-to-treat and per patient analysis sets, there were no significant differences for the frequency of the overall outcome measure, major adverse cardiac events, and each component of major adverse cardiac events within the study population between the 2 groups at 30, 60, 180, 360, and 540 days post-procedure (Online Table 2). Also, no target vessel stent thrombosis was documented within each scheduled follow-up period.

DISCUSSION

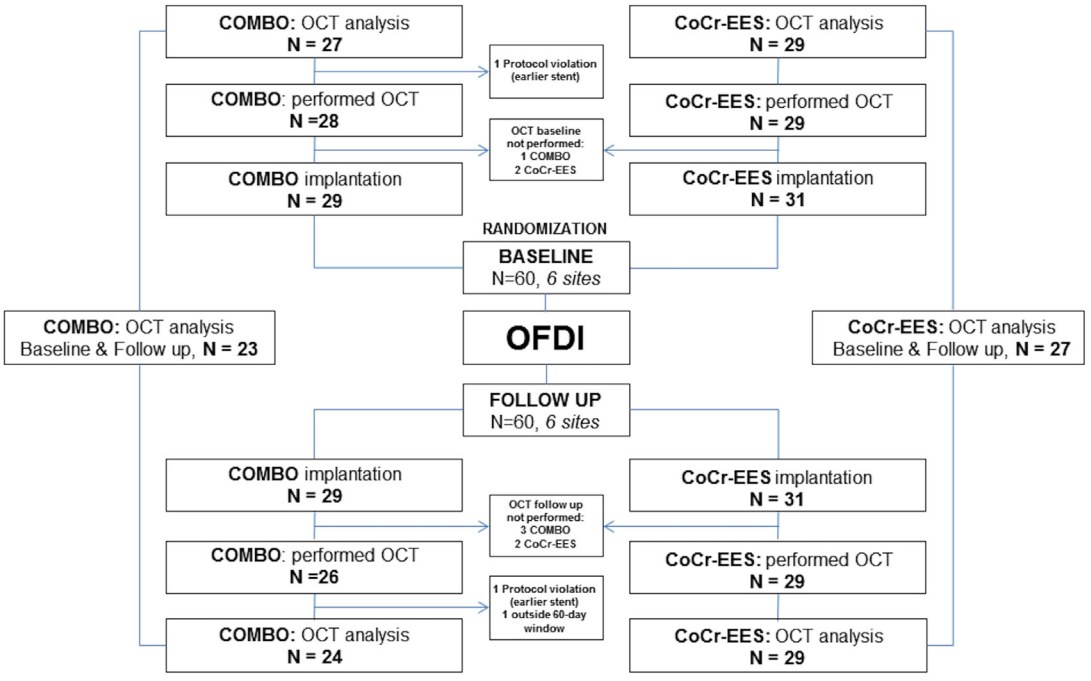
The present prospective randomized multicenter study examined for the first time the vascular response of a novel bioengineered dual-therapy pro-healing abluminal sirolimus-eluting stent designed to actively capture CD34+ cells (COMBO) compared with a contemporary CoCr EES early after coronary implantation in patients with ACS using intracoronary OCT imaging. In the analysis of the protocol-defined primary endpoint, COMBO showed a somewhat higher percentage of uncovered struts in the per stent analysis compared with the CoCr EES on 60-day OCT follow-up in patients with ACS. However, no significant differences of uncovered stent struts were observed in the stent strut level-based analysis at 60 days after GLMM adjustment, an analysis that takes also into account the clustering. The availability of post-procedural OCT examinations in the REMEDEE-OCT study adds to the validity of the present observations, as stent strut embedding was similar between groups immediately after the procedure.

For the secondary OCT endpoints, the COMBO group differed significantly from the CoCr EES group with regard to the following endpoints: neointimal thickness, percentage protruding struts, neointimal volume, neointimal eccentricity index, and rate of uncovered to total strut in the frame by OCT with 10% uncovered struts. These observations suggest slightly thinner neointima formation after COMBO versus CoCr EES implantation at 60-day follow-up in patients with ACS.

RATIONALE FOR A BIOENGINEERED STENT DESIGN. Long-term outcomes after coronary DES implantation depend on the response to the 3 following stent components: the metal alloy and design, the (polymer) coating, and the drug (32). The proliferation of vascular smooth muscle cells in response to vessel dilation is regarded as a major limitation of bare-metal stent implantation because of the high rate of restenosis (33). The substantial reduction of late lumen loss after DES implantation compared with bare-metal stent has been somewhat tempered by the occurrence of late or very late stent thrombosis, late catch-up of restenosis, and the development of neoatherosclerosis (34). New-generation DES have been designed to overcome some of the limitations of first-generation DES (1). Thinner stent struts and biocompatible polymer coatings allow greater deliverability, improved endothelial healing, and reduced restenosis and thrombus generation (1,35). However, increasing target lesion revascularization rates between 1 and 5 years after treatment and late or very late stent thrombosis remain concerns with currently available DES (1,32).

In-stent neoatherosclerosis has been proposed as 1 trigger of late and very late stent thrombosis (6,36). Accelerated neoatherosclerosis after DES implantation is likely promoted by endothelial injury or dysfunction (37). Endothelial dysfunction after injury may persist for >3 months and can be detected by impaired endothelium-dependent vasodilation (38). Moreover, evidence for neointimal rupture

FIGURE 2 Study Flowchart: Optical Coherence Tomographic Analysis



OCT = optical coherence tomographic; OFDI = optical frequency domain imaging; other abbreviations as in Figure 1.

after DES implantation was reported by Kang et al. (39) as assessed by OCT imaging and intravascular ultrasound. Thus, restoration of endothelial continuity and function remains an important aim in order to avoid early and late complications, including stent thrombosis (40,41). Different strategies to promote endothelial repair after vessel wall injury in response to coronary stent implantation have been developed and already investigated both in preclinical and clinical settings. Previously, no benefit with regard to clinical outcomes and restenosis has been documented after catheter-based local intracoronary gene transfer of vascular endothelial growth factor and *VEGF* gene-eluting stents after both angioplasty and stent implantation (42,43). The CD34+ antibody-covered stent rapidly binds CD34+ cells that are known to promote endothelial growth (11–15). Initial safety and efficacy data for the bioengineered CD34+ antibody covered stent have been reported from the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First in Man) trial and HEALING (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth II) trial (22).

Currently available single-therapy stents containing either antiproliferative drugs or other therapeutic agents (i.e., CD34 antibodies) still have limitations, and there is therefore significant interest in bioengineered stent concepts that may further improve safety and outcomes after percutaneous coronary intervention. In this context, the COMBO Dual Therapy Stent has been engineered to combine abluminal release of sirolimus from a biodegradable matrix with a CD34 antibody to recruit CD34+ cells that are known to promote endothelial repair responses (16,44). Indeed, preclinical investigations have suggested that stent endothelialization examined by scanning electron microscopic analysis occurs faster with COMBO compared with Cypher stent implantation (16). Furthermore, less neointimal thickness with COMBO versus Cypher and Xience V was documented in preclinical studies (16). In the first-in-human REMEDEE trial with the COMBO Dual Therapy Stent or paclitaxel-eluting stent implantation, angiographic in-stent late lumen loss was noninferior with the COMBO Dual Therapy Stent compared with the paclitaxel-eluting stent at 9 months (45). No Academic

TABLE 3 Optical Coherence Tomographic Analysis, COMBO Stent vs. Cobalt-Chromium Everolimus-Eluting Stent, Clinical Study

	Post-Procedure			Follow-Up (60 Days)			Post-Procedure vs. Follow-Up*	
	COMBO (n = 27)	CoCr EES (n = 29)	p Value	COMBO (n = 24)†	CoCr EES (n = 29)	p Value	COMBO p Value	CoCr EES p Value
Stent-level analysis								
Analyzed frame numbers	27 (24–31)	28 (24–31)	0.74	28 (21–31)	28 (25–31)	0.42	0.11	0.15
Not analyzable frames, %	6.45 (0.00–10.71)	6.67 (3.45–12.00)	0.49	9.23 (0.00–13.08)	9.43 (4.17–12.20)	0.53	0.2	0.03
Analyzed struts per patient, n	249 (218–320)	273 (223–358)	0.4	244.5 (178.5–287.5)	272 (242–371)	0.04	0.1	0.32
Analyzed struts/cross-section, n	9.71 (8.97–10.60)	10.12 (8.79–11.68)	0.48	8.88 (8.16–9.90)	10.37 (8.61–11.61)	<0.01	0.08	0.87
LIT struts per patient, %				0.00 (0.00–1.67)	0.84 (0.00–1.24)	0.29		
Protruding struts per patient, %				5.21 (1.53–8.19)	0.85 (0.40–2.95)	0.04		
Uncovered struts per stent, %				14.70 (9.30–34.97)	7.73 (1.58–22.48)	0.04		
Uncovered nonmalapposed struts, %				13.87 (9.30–34.16)	7.72 (1.28–17.44)	0.03		
Stent strut malapposition	11 (42.3)	15 (50.0)	0.6	14 (58.3)	15 (51.7)	0.78	0.11	0.93
Maximal length of segments (mm) with uncovered struts				5.40 (3.00–8.80)	3.20 (1.20–7.50)	0.19		
Maximal length of segments (mm) with malapposed struts	0.60 (0.00–1.80)	0.80 (0.00–2.40)	0.7	0.60 (0.00–1.20)	0.60 (0.00–1.40)	0.79	0.18	0.04
Neointimal thickness, mm				0.04 (0.03–0.06)	0.06 (0.04–0.08)	0.04		
Neointimal thickness based on 360 chords, μm				30.17 (16.57–51.78)	50.26 (31.43–75.00)	0.02		
NHI‡				5.04 (3.60–10.97)	3.67 (2.90–5.30)	0.02		
Embedded struts post-procedure, %	8.15 (3.13–21.91)	11.46 (6.12–20.48)	0.4					
Stent eccentricity index	0.91 (0.90–0.93)	0.91 (0.88–0.92)	0.48	0.92 (0.90–0.93)	0.92 (0.90–0.93)	0.78	0.48	<0.01
Frames with 30% uncovered struts, %				15.23 (6.27–52.10)	6.67 (0.00–29.03)	0.04		
Dissection post-procedure at stent distal edges	8 (29.6)	4 (14.3)	0.2	0 (0.00)	0 (0.00)	NA	<0.01	0.04
Dissection post-procedure at stent proximal edges	11 (40.7)	7 (24.1)	0.25	0 (0.00)	0 (0.00)	NA	<0.01	<0.01
Dissection post-procedure behind the stent	15 (15.7)	16 (55.2)	1.0	0 (0.00)	0 (0.00)	NA	<0.01	<0.01
Strut-level analysis with GLMM								
% Uncovered struts				13.6 (8–22.1)	6.9 (4.1–11.4)	0.090		
% Uncovered malapposed				0.8 (0.4–1.5)	0.8 (0.4–1.4)	0.970		
Covered LIT				0.5 (0.2–1.0)	0.8 (0.4–1.4)	0.400		
NIT of strut (μm)				34.85 (11.11–58.59)	54.94 (32.92–76.95)	0.220		
Covered protruding				3.4 (2.1–5.5)	1.4 (0.9–2.3)	0.030		

Values are median (interquartile range) or n (%). For continuous outcome, the Mann-Whitney *U* test was used for comparison of COMBO versus CoCr EES, and the Wilcoxon signed rank test was used for comparison of post-procedure versus follow-up. For categorical outcome, the Fisher exact test was used for comparison of COMBO vs. CoCr EES, and the generalized estimating equation model was used for comparison of post-procedure vs. follow-up. *Only cases with OCT pullbacks at both post-procedure and follow-up were used for comparison of post-procedure vs. follow-up; n = 23 for COMBO and n = 27 for CoCr EES. †Combo group for morphometric analysis at follow-up, n = 23, 1 patient (05-011) was excluded because of a catheter problem. ‡Maximal NIH thickness divided by the average value of 360 NIH measurements.

GLMM = generalized linear mixed models; LIT = low intensity tissue; NEI = neointimal eccentricity index; NHI = neointimal heterogeneity index; NIH = neointimal hyperplasia; NIT = neointimal thickness; OCT = optical coherence tomographic; other abbreviations as in Table 1.

Research Consortium-defined definite or probable stent thrombosis was reported during the observation out to 12 months (45). Interestingly, the current REMEDEE-OCT study did not detect acceleration of stent strut coverage as determined by OCT imaging in the per stent and the GLMM-adjusted analysis, taking into account the clustering effect. It is noteworthy that the REMEDEE-OCT trial was performed in the setting of ACS, in which the healing process is substantially delayed (10,46–49). Significant differences in OCT analysis of both stent systems with regard to percentage protruding stent struts, neointimal volume, neointimal eccentricity index, and rate of uncovered to total strut in the frame by OCT with 10% uncovered struts may be related to less pronounced neointima formation early after COMBO stent versus CoCr EES implantation, which is also in line with the preclinical observations described previously.

The present study was designed, at least in part, on the basis of reports from pathology studies suggesting that the ratio of uncovered stent struts to total stent struts represents a surrogate marker for stent

endothelialization (6). However, several more recent studies have indicated that the OCT stent strut coverage may not necessarily reflect strut endothelialization (21,23,50). Thus, the accuracy of OCT imaging to assess the early vascular response and coverage after stent implantation is likely limited in case of thin neointimal coverage (i.e. <20 to 40 μm). This could be caused by the suboptimal OCT resolution for stent strut evaluation, strut blooming, and/or hyperreflectivity. However, whether stent strut coverage correlates with stent endothelialization may depend on the clinical setting, and this needs to be further evaluated.

Assessment of strut coverage after stent implantation by OCT imaging has historically been "equated" with evaluation of stent endothelialization, which was also based on data from pathologic analyses. However, the clinical interpretation of OCT stent strut coverage needs further validation.

STUDY LIMITATIONS. This multicenter prospective randomized study, REMEDEE-OCT, was not powered for clinical outcomes. Moreover, because the prespecified primary endpoint does not take into account the clustering observed in OCT investigations, GLMM adjustment was used to report the difference in strut coverage (strut-level analysis), which is considered methodologically more appropriate by many investigators today, and did not reveal a significant difference between the groups. OCT detection of stent strut coverage likely does not represent a reliable surrogate for early stent endothelialization in different clinical settings, and very thin neointima formation may not necessarily be detected by OCT for various reasons. A cautionary interpretation of the OCT findings of stent strut coverage is therefore currently advocated.

CONCLUSIONS

The present multicenter, prospective clinical study for the first time compared the vascular response of the bioengineered COMBO Dual Therapy Stent with a CoCr EES early (i.e., 2 months) post-percutaneous coronary intervention in patients after ACS using intracoronary OCT analysis. The study revealed a somewhat higher percentage of uncovered stent struts per stent after COMBO versus CoCr EES implantation as assessed by OCT imaging. However, no significant differences in uncovered stent struts were observed in the strut-level analysis (GLMM adjusted), which also accounted for clustering. There was somewhat thinner neointima formation observed in the per stent analysis, corresponding to preclinical studies that may, at least in part, explain these observations. In the present study, there was a very low rate of clinical events in both groups after COMBO and CoCr EES implantation, and no stent thrombosis was observed at 540-day of follow-up.

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PERSPECTIVES

WHAT IS KNOWN? CD34+ cells can promote endothelial repair responses after vascular injury.

WHAT IS NEW? The present study compared for the first time the vascular response 2 months after bioengineered COMBO Dual Therapy Stent (combining CD34+ cell-capturing technology with abluminal sirolimus release) versus CoCr EES implantation in patients with ACS using intracoronary OCT analysis. The percentage of uncovered stent struts per stent was higher after COMBO versus CoCr EES implantation as detected by OCT after 2 months (median, 14.7% vs. 7.7%; $p = 0.04$), but no significant difference of uncovered stent struts was observed in the strut level–based GLMM-adjusted analysis accounting for clustering.

WHAT IS NEXT? Whether short-term dual-antiplatelet therapy for 90 days is safe in patients with ACS receiving the COMBO stent is currently examined in a larger clinical trial (REDUCE [Short-Term Dual Anti Platelet Therapy in Patients With ACS Treated With the COMBO Dual-Therapy Stent]; NCT02118870).

REFERENCES

1. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013;368:254–65.

2. Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27:1500–10.

3. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med 2006;355:1093–104.

4. Windecker S, Meier B. Late coronary stent thrombosis. Circulation 2007;116:1952–65.

5. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.

6. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41.

7. Luscher TF, Steffel J, Eberli FR, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. Circulation 2007;115:1051–8.

8. Landmesser U, Hornig B, Drexler H. Endothelial function: a critical determinant in atherosclerosis? Circulation 2004;109 21 Suppl 1:II27–33.

9. Grines CL, Bonow RO, Casey DE Jr., et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Circulation 2007;115:813–8.

10. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008;118:1138–45.

11. Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. Science 1997;275:964–7.

12. Yeh ET, Zhang S, Wu HD, Korbling M, Willerson JT, Estrov Z. Transdifferentiation of human peripheral blood CD34+-enriched cell population into cardiomyocytes, endothelial cells, and smooth muscle cells in vivo. Circulation 2003; 108:2070–3.

13. Inoue T, Sata M, Hikichi Y, et al. Mobilization of CD34-positive bone marrow-derived cells after coronary stent implantation: impact on restenosis. Circulation 2007;115:553–61.

14. Shantsila E, Watson T, Tse HF, Lip GY. New insights on endothelial progenitor cell subpopulations and their angiogenic properties. J Am Coll Cardiol 2008;51:669–71.

15. Mocharla P, Briand S, Giannotti G, et al. AngiomiR-126 expression and secretion from circulating CD34(+) and CD14(+) PBMCs: role for proangiogenic effects and alterations in type 2 diabetics. Blood 2013;121:226–36.

16. Granada JF, Inami S, Aboodi MS, et al. Development of a novel prohealing stent designed to deliver sirolimus from a biodegradable abluminal matrix. Circ Cardiovasc Interv 2010;3:257–66.

17. Nakazawa G, Granada JF, Alviar CL, et al. Anti-CD34 antibodies immobilized on the surface of sirolimus-eluting stents enhance stent endothelialization. J Am Coll Cardiol Intv 2010;3:68–75.

18. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333–42.

19. Guagliumi G, Sirbu V. Optical coherence tomography: high resolution intravascular imaging to evaluate vascular healing after coronary stenting. Catheter Cardiovasc Interv 2008;72:237–47.

20. Prati F, Zimarino M, Stabile E, et al. Does optical coherence tomography identify arterial healing after stenting? An in vivo comparison with histology, in a rabbit carotid model. Heart 2008; 94:217–21.

21. Templin C, Meyer M, Muller MF, et al. Coronary optical frequency domain imaging (OFDI) for in vivo evaluation of stent healing: comparison with light and electron microscopy. Eur Heart J 2010;31:1792–801.

22. Aoki J, Serruys PW, van Beusekom H, et al. Endothelial progenitor cell capture by stents coated with antibody against CD34: the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First in Man) Registry. J Am Coll Cardiol 2005;45:1574–9.

23. Tearney GJ, Regar E, Akasaka T, et al., for the International Working Group for Intravascular Optical Coherence Tomography. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol 2012; 59:1058–72.

24. Bezerra HG, Costa MA, Guagliumi G, Rollins AM, Simon DI. Intracoronary optical coherence tomography: a comprehensive review clinical and research applications. J Am Coll Cardiol Intv 2009;2:1035–46.

25. Mehanna EA, Attizzani GF, Kyono H, Hake M, Bezerra HG. Assessment of coronary stent by optical coherence tomography, methodology and definitions. Int J Cardiovasc Imaging 2011;27: 259–69.

26. Attizzani GF, Bezerra HG, Ormiston J, et al. Serial assessment by optical coherence tomography of early and late vascular responses after implantation of an absorbable-coating sirolimus-eluting stent (from the first-in-human DESSOLVE I trial). Am J Cardiol 2013;112:1557–64.

27. Gonzalo N, Garcia-Garcia HM, Serruys PW, et al. Reproducibility of quantitative optical coherence tomography for stent analysis. EuroIntervention 2009;5:224–32.

28. Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary arterial thrombus by optical coherence tomography. Am J Cardiol 2006; 97:1713–7.

29. Kume T, Okura H, Kawamoto T, et al. Images in cardiovascular medicine. Fibrin clot visualized by optical coherence tomography. Circulation 2008; 118:426–7.

30. Chamie D, Bezerra HG, Attizzani GF, et al. Incidence, predictors, morphological characteristics, and clinical outcomes of stent edge dissections detected by optical coherence tomography. J Am Coll Cardiol Intv 2013;6: 800–13.

31. Malle C, Tada T, Steigerwald K, et al. Tissue characterization after drug-eluting stent implantation using optical coherence tomography. Arterioscler Thromb Vasc Biol 2013;33: 1376–83.

32. Garg S, Serruys PW. Coronary stents: looking forward. J Am Coll Cardiol 2010;56 10 Suppl: S43–78.

33. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937–48.

34. Finn AV, Otsuka F. Neoatherosclerosis: a culprit in very late stent thrombosis. Circ Cardiovasc Interv 2012;5:6–9.

35. Niu X, Yang C, Chen D, He S, Yan D, Yao Y. Impact of drug-eluting stents with different coating strategies on stent thrombosis: a meta-analysis of 19 randomized trials. Cardiol J 2014; 21:557–68.

36. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol 2011;57:1314–22.

37. Finn AV, Kolodgie FD, Harnek J, et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. Circulation 2005;112: 270–8.

38. van Beusekom HM, Whelan DM, Hofma SH, et al. Long-term endothelial dysfunction is more pronounced after stenting than after balloon angioplasty in porcine coronary arteries. J Am Coll Cardiol 1998;32:1109–17.

39. Kang SJ, Mintz GS, Akasaka T, et al. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. Circulation 2011;123:2954–63.

40. Kipshidze N, Dangas G, Tsapenko M, et al. Role of the endothelium in modulating neointimal formation: vasculoprotective approaches to attenuate restenosis after percutaneous coronary interventions. J Am Coll Cardiol 2004;44: 733–9.

41. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. Circulation 2003; 108:1701–6.

42. Hedman M, Hartikainen J, Syvanne M, et al. Safety and feasibility of catheter-based local intracoronary vascular endothelial growth factor gene transfer in the prevention of postangioplasty and in-stent restenosis and in the treatment of chronic myocardial ischemia: phase II results of the Kuopio Angiogenesis Trial (KAT). Circulation 2003; 107:2677–83.

43. Walter DH, Cejna M, Diaz-Sandoval L, et al. Local gene transfer of phVEGF-2 plasmid by gene-eluting stents: an alternative strategy for inhibition of restenosis. Circulation 2004;110: 36–45.

44. Costa MA, Simon DI. Molecular basis of restenosis and drug-eluting stents. Circulation 2005;111:2257–73.

45. Haude M, Lee SW, Worthley SG, et al. The REMEDEE trial: a randomized comparison of a combination sirolimus-eluting endothelial progenitor cell capture stent with a paclitaxel-eluting stent. J Am Coll Cardiol Intv 2013;6: 334–43.

46. Nakano M, Yahagi K, Otsuka F, et al. Causes of early stent thrombosis in patients presenting with acute coronary syndrome: an ex vivo human autopsy study. J Am Coll Cardiol 2014;63:2510–20.

47. Ormiston JA, Webster MW. Stent thrombosis: has the firestorm been extinguished? Lancet 2012;379:1368–9.

48. Raber L, Kelbaek H, Ostojic M, et al. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. JAMA 2012;308:777–87.

49. Sabate M, Cequier A, Iniguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION):1 year results of a randomised controlled trial. Lancet 2012;380:1482–90.

50. Prati F, Guagliumi G, Mintz GS, et al. Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. Eur Heart J 2012;33:2513–20.

KEY WORDS COMBO stent, early vascular healing response, neointimal hyperplasia, OCT

APPENDIX For supplemental methods, tables, and figures, please see the online version of this article.