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CLINICAL RESEARCH
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Japan-United States of America Harmonized Assessment by Randomized Multicentre Study of OrbusNEich's Combo StEnt (Japan-USA HARMONEE) study: primary results of the pivotal registration study of combined endothelial progenitor cell capture and drug-eluting stent in patients with ischaemic coronary disease and non-ST-elevation acute coronary syndrome

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Aims Harmonized Assessment by Randomized Multicentre Study of OrbusNEich's Combo StEnt (HARMONEE) (NCT02073565) was a randomized pivotal registration trial of the Combo stent, which combined sirolimus and an abluminal bioabsorbable polymer with a novel endoluminal anti-CD34+ antibody coating designed to capture endothelial progenitor cells (EPC) and promote percutaneous coronary intervention (PCI) site healing.

Methods and results Clinically stabilized PCI subjects were randomized 1:1 to receive Combo or everolimus-eluting stents (EES). Between February 2014 and June 2016, 572 subjects with 675 coronary lesions underwent 1-year angiography and fractional flow reserve, with optical coherence tomography (OCT) in the first 140 patients. The primary clinical endpoint was non-inferior 1-year target vessel failure (TVF). The primary mechanistic endpoint of EPC capture activity was superior strut coverage by OCT. Target vessel failure occurred in 7.0% Combo (20/287) vs. 4.2% EES

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(12/285), a 2.8% [95% confidence interval (95% CI) -1.0%, 6.5%] difference, meeting the non-inferiority hypothesis ($P = 0.02$). There were no cardiac deaths, with one stent thrombosis observed in the EES group. Quantitative coronary angiography late loss with Combo was equivalent to EES. Optical coherence tomography strut coverage at 1 year was superior with Combo vs. EES [91.3% (95% CI 88.7%, 93.8%) vs. 74.8% (95% CI 70.0%, 79.6%), $P < 0.001$], with homogeneous tissue in 81.2% vs. 68.8%, respectively.

Conclusion Combo stent demonstrated non-inferior 1-year TVF and late loss in a randomized comparison to EES, with superior strut-based tissue coverage by OCT as a surrogate of EPC capture technology activity.

Keywords Drug-eluting stents • Randomized controlled trial • Percutaneous coronary intervention • Endothelial progenitor cells • Japan

Introduction

The safety and effectiveness of drug-eluting stents (DES) have been successfully improved by design advances in the three key DES components (struts, polymer, and drug),[1,2] yet safety concerns remain related to both early implantation trauma and long-term healing.[2–4] The Combo stent (OrbusNeich Medical, Inc., Fort Lauderdale, FL, USA) was the first four-component coronary stent, adding an immobilized layer of murine monoclonal anti-CD34+ antibody to the classic three-component design (316L-stainless-steel alloy struts, SynBiosys™ abluminal bioabsorbable urethane-linked copolymer, and sirolimus). This novel component constituted a biological endothelial progenitor cell (EPC) capture technology, designed to actively attract circulating pluripotent cells, which differentiate into functional endothelial cells, contributing to vascular repair while mitigating inflammatory and pro-thrombotic signals.[5,6] First-in-human experience has shown angiographic effectiveness in 183 subjects randomized vs. paclitaxel-eluting stents[7] and encouraging clinical outcomes in 1000 'all comers' subjects receiving Combo stents.[8] These pre-clinical and early human observations motivated further study of this platform.

We report the primary results of the Japan-United States of America (USA) Harmonized Assessment by Randomized, Multicentre Study of OrbusNeich's Combo Stent (HARMONEE; ClinicalTrials.gov #: NCT02073565), a randomized registration trial of the Combo stent compared to an everolimus-eluting stent (EES). This investigation was conducted at multiple centres in Japan and the USA, conducting a study design developed through a collaboration between the Pharmaceuticals and Medical Devices Agency (PMDA) Japan and the United States (U.S.) Food and Drug Administration (FDA), as a 'proof of concept' program through the Harmonization by Doing initiative.[9]

Methods

HARMONEE was a prospective, multicentre, single-blind, randomized, active-controlled clinical trial in percutaneous coronary intervention (PCI) subjects undergoing procedures for ischaemic coronary disease and non-ST-elevation acute coronary syndromes (ACS). Details of the study design and methods have been previously described.[10] Briefly, the three principal objectives of HARMONEE tested whether at 1 year the Combo stent showed: (i) non-inferior target vessel failure (TVF) vs. EES (Xience, Abbott Vascular, Santa Clara, CA, USA); (ii) mechanistic evidence of the biological activity of the EPC capture technology measured as superior 'healthy tissue' strut-level coverage[10] by optical coherence tomography (OCT); and (iii) biological safety in serial serological testing for development of human anti-murine antibodies (HAMA), which was assessed at the index procedure, 30 days, and 1 year in Cohort B subjects.

A total of 572 subjects were enrolled at 50 sites in Japan and the USA. As previously described,[10] stabilized subjects undergoing elective or urgent PCI were eligible if they satisfied clinical and angiographic criteria. Inclusion required the ability to provide informed consent, age > 19 years, and anatomy suitable for PCI. Target lesions were required to be *de novo* with a visually estimated stenosis ≥50% and <100% in a native coronary artery with a visually estimated diameter of 2.5–3.5 mm and length <29 mm. Up to three lesions could be treated, with a maximum of two lesions per epicardial vessel and a maximum of two target vessels per patient. Patients were excluded with ST-elevation myocardial infarction (STEMI), unstable arrhythmias, shock, ejection fraction <30%, malignancy, known renal insufficiency with creatinine >2.5 mg/dL or dialysis, or pregnancy. Angiographic exclusions included unprotected left main disease, total coronary occlusions, angiographically visible thrombus, and bifurcation lesions with a side branch ≥2 mm in diameter.

Eligible subjects were randomized in a ratio of 1:1 to receive either the Combo stent or EES control. Randomization within each country was stratified for non-STEMI (NSTEMI) vs. elective presentation, and for single- vs. multi-vessel disease. HARMONEE consecutively enrolled subjects into three cohorts (A, B, and C; *Figure 1*). All patients underwent 1-year follow-up angiography. Fractional flow reserve (FFR) during a 2-minute infusion of adenosine or adenosine triphosphate was included with all angiography to support objective ischaemia-driven target vessel revascularization (TVR) without oculostenotic bias in the context of protocol-driven angiographic follow-up. Cohorts A and B underwent additional imaging, including 1-year OCT.

At their own discretion, investigators identified an oral antiplatelet regimen and duration of antiplatelet therapy for each subject before randomization. Post-procedure, subjects received aspirin indefinitely and a $P2Y_{12}$ inhibitor for a minimum of 6 months (1 year for an ACS diagnosis). Scheduled follow-up was 30 days, 6 months, and 1 year. At 1 year, a clinical evaluation was completed prior to protocol cardiac catheterization.

The study was overseen by an independent data and safety monitoring board. An independent, blinded clinical events committee adjudicated primary clinical endpoint events. All invasive mechanistic observations [quantitative coronary angiography (QCA), FFR, and OCT] were analysed by independent blinded core laboratories.[10]

This study was conducted in accordance with current Ministerial Ordinance on Good Clinical Practice for Medical Devices, Ordinance of the Ministry of Health and Welfare No. 36 (Japan) guidelines, U.S. FDA stipulations as an investigational device exemption protocol, International Council for Harmonisation guidelines on Good Clinical Practice,[11,12] the

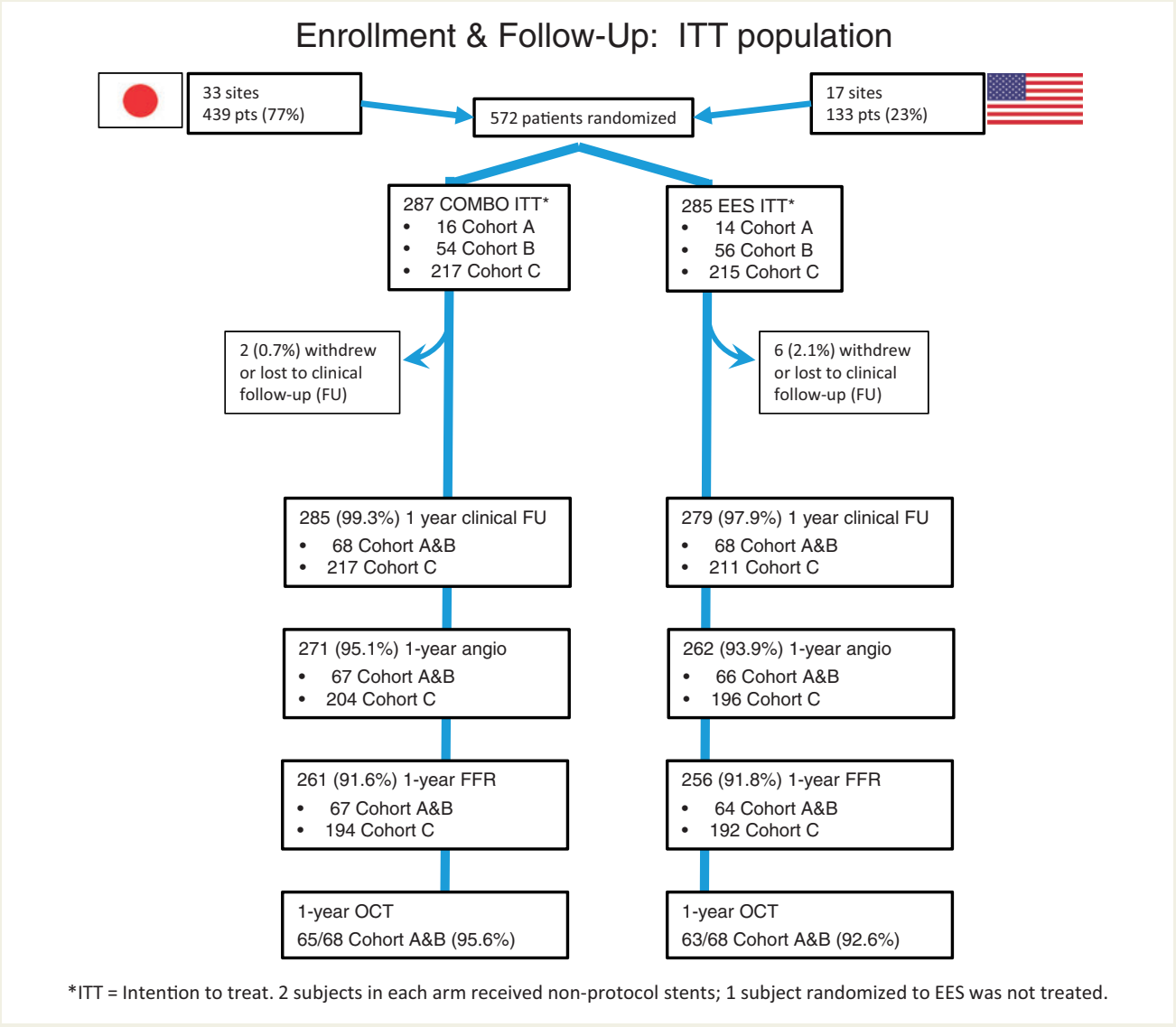


Figure 1 Diagram of patient and procedural follow-up for Cohorts A, B, and C. Cohort A: 6-month OCT and 12-month OCT, FFR, and angiographic assessments. Cohort B: 12-month OCT, FFR, and angiographic assessments. Cohort C: 12-month FFR and angiographic assessments. EES, everolimus-eluting stent; FFR, fractional flow reserve; FU, follow-up; ITT, intention-to-treat; OCT, optical coherence tomography.

Declaration of Helsinki, and all other applicable national and local laws and regulations. The research protocol was approved by the Duke University Health System Institutional Review Board, as well as the locally appointed ethics committee at each of the participating sites.

Primary clinical endpoint analysis

Non-inferiority to EES on 1-year TVF [defined as composite of adjudicated cardiac death, target vessel myocardial infarction (MI), or ischaemia-driven TVR by percutaneous or surgical methods in the intention-to-treat (ITT) population] was implemented using the Farrington–Manning score test, assuming a two-sided Type I error of 0.05. Assuming a mix of simple and complex patients, as allowed by the protocol's inclusion criteria (including non-STEMI ACS clinical presentations and multivessel anatomy), the 1-year TVF rate of 9% for 1980 non-STEMI real-world EES patients in the Bern-Rotterdam Registry was used to power this study.[13] Based on this assumption, 81% power to detect non-inferiority with an absolute margin of 7% required at least 542 evaluable subjects (271 per arm).

Assay sensitivity for the study's non-inferiority design using imputed bare metal stent 1 year TVF and late loss as previously described[14] were conducted per protocol and are presented in the Supplementary material online, *Table S1* and *Figure S1*. A time-to-event analysis was conducted using the Kaplan–Meier rates [95% confidence interval (95% CI)] for TVF at 1 year. A log-rank test assessed the statistical significance of observed differences in the time-to-event distributions between study device groups. A Cox proportional hazards model estimated the hazard ratio (HR, 95% CI) for the Combo to EES device.

Mechanistic (optical coherence tomography) endpoint analysis

'Healthy tissue' 1-year strut coverage per lesion evaluated by an independent, blinded OCT core laboratory was defined as strut-level

Table 1 Baseline clinical characteristics

Characteristics	Combo (*n* = 287)	EES (*n* = 285)	*P*-value[a]
Age (years)			0.437
Mean (SD)	67.6 (9.6)	66.5 (10.4)	
Non-STEMI presentation	14 (4.9%)	12 (4.2%)	0.841
MV CAD	33 (11.5%)	31 (10.9%)	0.895
Female	76 (26.5%)	73 (25.6%)	0.849
Race			0.339
Asian (non-Japanese)	1 (0.3%)	1 (0.4%)	
Japanese	219 (76.3%)	219 (76.8%)	
Black or African American	10 (3.5%)	4 (1.4%)	
White/Caucasian	57 (19.9%)	59 (20.7%)	
Other	0	2 (0.7%)	
Previous MI	45 (15.7%)	45 (15.8%)	1.000
Previous PCI	72 (25.1%)	83 (29.1%)	0.301
Previous CABG	4 (1.4%)	5 (1.8%)	0.751
Hypertension	218 (76.0%)	220 (77.2%)	0.767
Congestive heart failure	11 (3.8%)	24 (8.5%)	0.024
Diabetes			0.046
Insulin dependent	24 (8.4%)	18 (6.3%)	
Non-insulin dependent	93 (32.4%)	75 (26.3%)	
Cigarette smoking (current/former)	191 (67.7%)	175 (62.5%)	0.215
Chronic renal insufficiency	11 (3.8%)	5 (1.8%)	0.204
Hypercholesterolemia	225 (78.4%)	227 (79.6%)	0.758
DAPT			0.203
6 months	5 (2.0%)	11 (4.3%)	
1 year	247 (98.0%)	243 (95.7%)	
Statins at 1 year	233 (83.5%)	228 (85.4%)	0.557
Beta-blockers at 1 year	103 (36.9%)	100 (37.5%)	0.930

CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; EES, everolimus-eluting stent; MI, myocardial infarction; MV CAD, multivessel coronary artery disease; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.
[a]*P*-values were generated using the Wilcoxon rank-sum and the Fisher's exact tests for continuous and categorical variables, respectively.

neointimal thickness (NIT) boundary condition pre-specifying both: (i) >40 μm NIT and (ii) normal FFR > 0.80 from the 140 ITT Cohorts A and B subjects.[10] All visible struts at 0.6 mm intervals along the entire stented segment(s) were measured. To test the difference in mean struts NIT between the Combo and Xience stents at the subject-level, the 140-patient A and B cohort yielded >99% power to detect the difference in NIT, assuming an NIT difference of 0.050 mm, a common standard deviation of 0.050 mm, and a two-sided Type I error of 0.05. For the strut-level data analysis of repeated strut measurements on the same subject (i.e., correlated continuous data within a patient), we utilized a mixed-effects model analysis (PROC MIXED in SAS©, version 9.4, SAS Institute, Inc., Cary, NC, USA), which allows for specifying a working correlation structure among measurements on the same subject to account for correlation. For this analysis, a combined symmetry working correlation structure was specified in the model to obtain the reported results and the *P*-values. Blinded assessment of tissue covering stents as homogeneous or heterogeneous was also performed as a qualitative indication of healthy tissue structure. The further secondary endpoint of neoatherosclerosis was defined by OCT as lipid (a signal-poor region with strong attenuation and diffuse border), calcification (a signal-poor or heterogeneous region with well-delineated border), or neointimal rupture (a break in the fibrous cap connecting to the lumen with the underlying lipidic neointimal tissue) within the stented segment.

Secondary analyses

In the Cohorts A and B patients, QCA late loss evaluated by an independent and treatment-blinded core laboratory was compared directly between Combo and EES.[10] Ischaemia-driven TVR at 1 year, including use of target vessel FFR, were also analysed as secondary endpoints.

Human anti-murine antibodies

All Cohort B subjects submitted blood samples to a core laboratory at baseline, 30 days, and 12 months for measurement of HAMA levels. A minimum sample size of 40 Combo patients provided 86.5% power to exclude an anti-antibody response upper bound of 8.0%, assuming a two-sided Type I error of 0.05 and an underlying seroconversion rate of 5 per thousand.

Results

Patient characteristics

Between February 2014 and June 2016, a total of 572 patients [439 (77%) from 33 sites in Japan and 133 (23%) from 17 sites in the USA] were enrolled and randomized (287 Combo, 285 EES). One-year follow-up was obtained in more than 98% (*Figure 1*). Baseline characteristics were well balanced between arms, with the exception of diabetes and congestive heart failure (*Table 1*). Mean age was 67 years, 26% were women, 76.6% had hypertension, and 36.7% were diabetic. At 1 year, 96.9% were on dual antiplatelet therapy and there was no difference between the treatment arms. Multivessel coronary artery disease was seen in 11.2%, and 4.5% presented with NSTEMI. Lesion and stent characteristics are shown in Supplementary material online, *Table S2*. A total of 674 lesions were treated. Device success was seen in 100% of patients, and procedure success in 99.1%. There were no significant differences between control and treatment arms.

Clinical outcomes: 1-year target vessel failure

Table 2 shows the primary outcome and components for Combo vs. EES. Target vessel failure at 1-year was observed in 20 subjects in the Combo arm (7.0%) compared to 12 subjects in the EES arm (4.2%). The observed 1-year TVF difference of 2.8% (95% CI -1.0%, 6.5%) was statistically significant for non-inferiority hypothesis ($P = 0.02$). There were no cardiac deaths. Target vessel MI rates were very low (1.7% Combo, 1.1% EES). The ischaemia-driven TVR component contributed most of the TVF events (6.3% Combo, 3.9% EES). There was no stent thrombosis out to 1 year with Combo. A single definite stent thrombosis occurred in the EES group on dual antiplatelet therapy within 14 days of PCI. Pre-specified subgroup analyses for the primary endpoint of 1-year TVF are summarized as HRs (95% CIs), as well as interaction *P*-values in a forest plot (Supplementary material online, *Figure S2*). No subgroup, including nation of origin, showed significant interaction with the TVF endpoint.

The Kaplan–Meier curves for TVF (*Figure 2*) and TVR (Supplementary material online, *Figure S3*) show clear late-loaded

events in both EES and Combo arms around the time of the 1-year follow-up catheterization. Concomitant FFR was acquired in 90% of patients. Rates of normal and abnormal FFR were similar in both groups. Target lesion revascularization (TLR) rates were higher in patients with abnormal FFR than with normal FFR, as shown in *Table 3*.

Quantitative coronary angiography: angiographic late lumen loss

At 1 year, 131/140 (94%) Cohorts A and B patients had angiographic core laboratory QCA of 153 lesions. In-stent and in-segment late loss, as well as binary restenosis, were quite low and comparable, as shown in *Table 4*.

Table 2 Clinical outcomes at 1 year

	Combo ($n = 287$)	EES ($n = 285$)	*P*-value
Target vessel failure[b]	20 (7.0%)	12 (4.2%)	0.202
Difference (95% CI)	2.8% (-1.0%, 6.5%)		0.02[a]
Cardiac death	0	0	NA
Target vessel MI	5 (1.7%)	3 (1.1%)	0.725
TVR (ischaemia-driven)	18 (6.3%)	11 (3.9%)	0.253
TLR (ischaemia-driven)	12 (4.2%)	8 (2.8%)	0.496
TLF[c]	19 (6.6%)	12 (4.2%)	0.268
All-cause death	2 (0.7%)	0	0.499
Non-fatal MI	8 (2.8%)	5 (1.8%)	0.577

CI, confidence interval; EES, everolimus-eluting stent; MI, myocardial infarction; NA, not applicable; TLF, target lesion failure; TLR, target lesion revascularization; TVF, target vessel failure; TVR, target vessel revascularization.
[a]Non-inferiority *P*-value for TVF; other *P*-values were generated using the Wilcoxon rank-sum and the Fisher's exact tests for continuous and categorical variables, respectively.
[b]Adjudicated composite of cardiac death, target vessel MI, or ischaemia-driven TVR by percutaneous or surgical methods.
[c]Adjudicated composite of death, non-fatal MI, or ischaemia-driven target lesion revascularization.

Optical coherence tomography

At 1 year, 128/140 (91.4%) Cohorts A and B patients (65 Combo, 63 EES) had OCT studies of 133 lesions. A mean of 46 cross-sections and 361 struts were analysable per lesion, for a total of 25 292 Combo, and 22 726 EES analyses (*Table 5*). Healthy tissue strut coverage was seen in 91.3% (95% CI 88.7%, 93.8%) with Combo and 74.8% (95% CI 70.0%, 79.6%) with EES, significant for superiority ($P < 0.001$, *Table 5*). Qualitative characterization of the tissue covering struts showed homogeneous tissue in 81.2% of analysed Combo lesions vs. 68.8% of EES (*Table 6*). There was no evidence of stent deformation in either group.

Human anti-murine antibodies

Human anti-murine antibody samples were collected from 110 subjects (56 Combo and 54 EES) in Cohort B. All subjects were HAMA negative at baseline, and all subjects remained HAMA negative through 1 year.

Discussion

Percutaneous coronary intervention outcomes are largely driven by the pathophysiology of healing at the implantation site. Localized dilatation barotrauma, tissue, and blood element responses to foreign body implantation into small mobile coronary vessels and cellular interactions with polymer and mTor inhibitor drugs all influence endothelial recovery. The Academic Research Consortium definition of stent thrombosis as early, late, and very late is based on the sequential role of these factors over time.[15] Advances in-stent metallurgy, matrix polymers, and anti-proliferative drugs have improved both the effectiveness and safety of DES platforms.[2] Nevertheless,

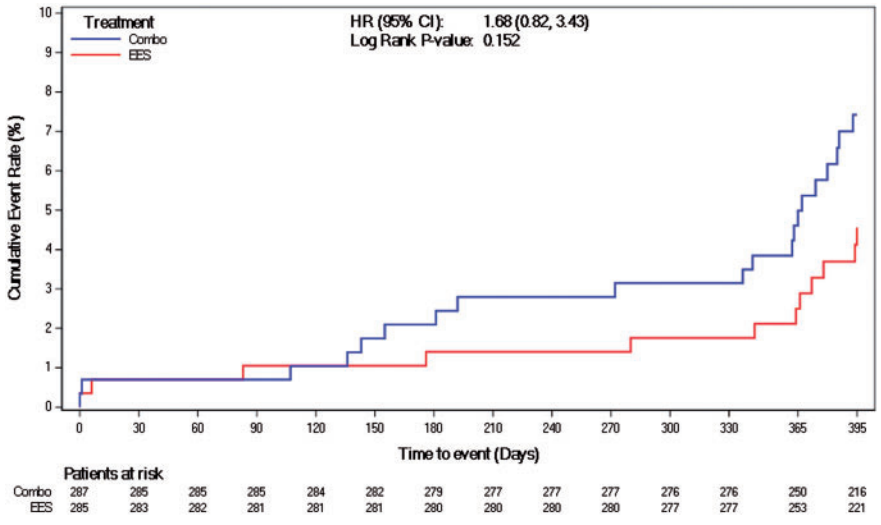
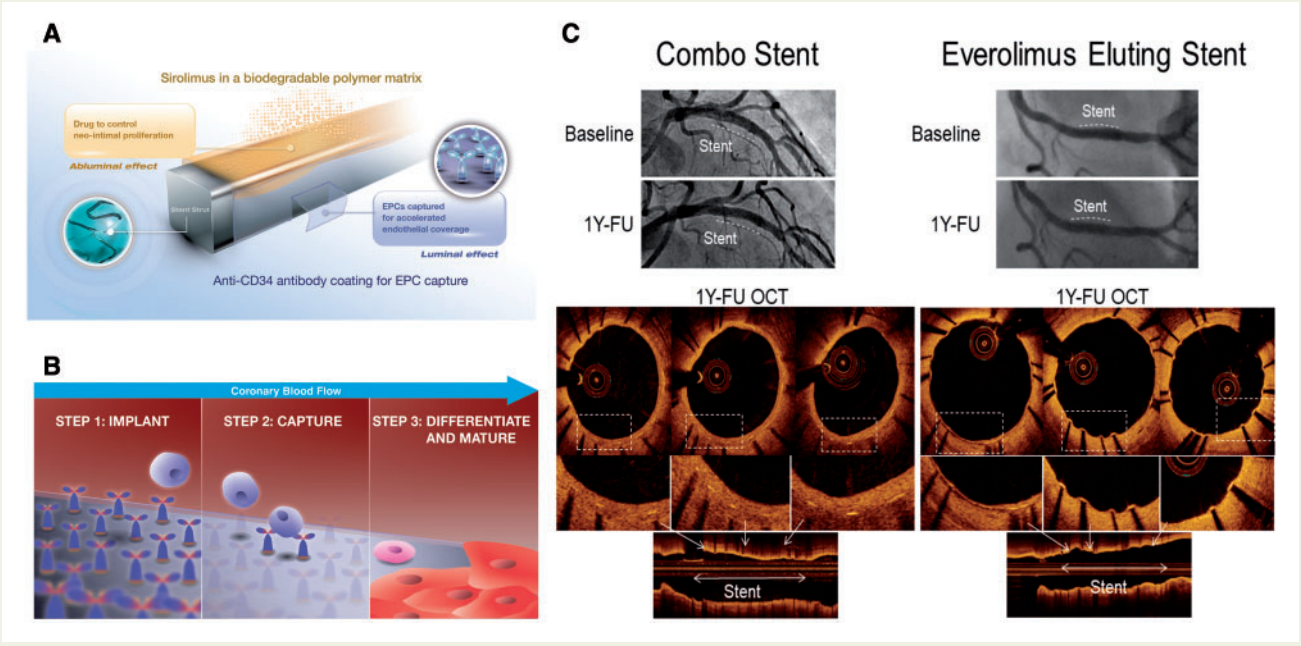


Figure 2 One-year Kaplan–Meier curves for target vessel failure (intention-to-treat population). CI, confidence interval; EES, everolimus-eluting stent; HR, hazard ratio.



Take home figure Combo Stent Technology in HARMONEE. (*A*) Combo stent design: with abluminal bioabsorbable polymer-eluting sirolimus and endoluminal anti-CD34+ antibody. (*B*) Anti-CD34+ antibody mechanism of action: attracting CD34+ endothelial progenitor cells to stent site that mature to functional endothelium. (*C*) HARMONEE mechanistic 'healthy endothelium' surrogate superiority: representative images index procedure (baseline) and 1-year angiographic results with Combo and everolimus-eluting stents that are quantitatively similar, but optical coherence tomography at 1 year shows more complete strut coverage and more homogeneous tissue with Combo than with everolimus-eluting stent. EPC, endothelial progenitor cell; FU, follow-up; OCT, optical coherence tomography.

Table 3 Fractional flow reserve results at 1-year angiography

Variable	Combo ($n = 287$)	EES ($n = 285$)	*P*-value[a]
1-year FFR completed	261 (90.9%)	256 (89.8%)	0.673
1-year FFR value, mean (95% CI)	0.89 (0.88, 0.90)	0.91 (0.90, 0.92)	0.179
Patients with FFR ≤0.80	33 (12.6%)	28 (10.9%)	0.587
1-year TLR in patients with FFR ≤0.80	6 (18.2%)	4 (14.3%)	0.741
1-year TLR in patients with FFR >0.80	2 (0.9%)	3 (1.3%)	1.000
1-year TLR in patients with no 1-year FFR available	4 (15.4%)	1 (3.5%)	0.178

CI, confidence interval; EES, everolimus-eluting stent; FFR, fractional flow reserve; TLR, target lesion revascularization.
[a]*P*-values were generated using the Wilcoxon rank-sum and the Fisher's exact tests for continuous and categorical variables, respectively.

safety concerns persist, including early stent thrombosis rates for both BMS and DES platforms,[2,3] as well as long-term needs for prolonged dual antiplatelet therapy with attendant bleeding risk.[3,16–19]

Combo incorporated abluminal bioabsorbable polymer-based sirolimus delivery with a novel endoluminal anti-CD34+ antibody designed to enhance healing by attracting circulating CD34+ EPCs to carpet the PCI site and mature into functional endothelium. The HARMONEE study demonstrated that this platform delivers 1-year clinical and angiographic outcomes that are non-inferior to EES, with OCT-based mechanistic evidence of superior endothelial strut coverage with more homogeneous tissue, suggesting possible *in vivo* evidence of EPC capture technology activity.

These outcomes are reported in the context of no device- or design-related safety concerns, including zero deaths or stent thromboses and zero incidence of HAMA serologic conversion. In a collective experience with 180 active device exposures (124 from previous studies[7] and 56 from present study), the absence of HAMA conversion after Combo implantation yields an upper 95% binomial confidence limit, excluding a sensitization response rate greater than 2.0%, constituting negligible concerns for safety.[20]

As a pivotal registration study of the very first DES platform to integrate a biologically engineered fourth component into the classic three-component device, the HARMONEE study included unique features exploring both patient- and device-related endpoints. Key features of this trial, including the strut-level healthy tissue OCT endpoint, resulted from interactive dialogue across investigators, imaging and histopathological experts, the manufacturer, and regulatory authorities (including both PMDA Japan and U.S. FDA), facilitated through the global Harmonization by Doing program.[9] Inclusion criteria were enriched[21] to encompass both multivessel coronary artery disease and NSTEMI ACS patients. Imaging with angiography and OCT were combined with the application of physiologic assessment

Table 4 Cohorts A and B quantitative coronary angiography core laboratory [mean (SD)]

	Combo	EES	*P*-value[a]
n (lesions)	86	80	
Reference vessel diameter, pre- (mm)	2.73 (0.43)	2.75 (0.46)	0.770
Minimal lumen diameter, pre- (mm)	0.95 (0.348)	0.95 (0.409)	0.611
Lesion length (mm)	16.70 (7.10)	14.67 (6.33)	0.029
% diameter stenosis, pre-	65.49 (10.9)	65.11 (15.5)	0.749
In-stent minimal lumen diameter, post- (mm)	2.64 (0.37)	2.70 (0.43)	0.313
In-segment minimal lumen diameter, post- (mm)	2.36 (0.43)	2.42 (0.50)	0.448
In-stent % diameter stenosis, post-	7.64 (6.2)	7.37 (5.2)	0.941
In-segment % diameter stenosis, post-	14.75 (9.3)	14.87 (9.2)	0.883
In-stent late loss, 1 year (mm)	0.293 (0.435)	0.219 (0.352)	0.220
In-segment late loss, 1 year (mm)	0.229 (0.398)	0.220 (0.359)	1.000
In-stent minimal lumen diameter, 1 year (mm)	2.32 (0.48)	2.50 (0.56)	0.032
In-segment minimal lumen diameter, 1 year (mm)	2.10 (0.45)	2.21 (0.54)	0.213
In-stent % diameter stenosis, 1 year	15.34 (13.6)	12.70 (12.0)	0.117
In-segment % diameter stenosis, 1 year	22.48 (13.09)	21.04 (12.83)	0.350

Cohorts: Cohort A: 6-month OCT and 12-month OCT, FFR, and angiographic assessments. Cohort B: 12-month OCT, FFR, and angiographic assessments. Cohort C: 12-month FFR and angiographic assessments.
EES, everolimus-eluting stent; QCA, quantitative coronary angiography; SD, standard deviation.
[a]*P*-values are from the Wilcoxon rank-sum test.

Table 5 Mechanistic optical coherence tomography endpoints at 1 year (Cohorts A and B)

	Combo	EES	*P*-value
Healthy tissue strut coverage (>40 μm) (%)			<0.001[a]
n (lesions)	62	60	
Mean (95% CI)	91.27 (88.71, 93.84)	74.82 (70.02, 79.62)	
Percentage of covered struts (%)			0.022[a]
n (lesions)	69	64	
Mean (95% CI)	99.16 (98.64, 99.67)	98.76 (98.25, 99.28)	
Mean NIH thickness, mm (lesion level)			<0.001[a]
n (lesions)	69	64	
Mean (95% CI)	0.181 (0.162, 0.200)	0.104 (0.091, 0.116)	
NIH thickness, mm (strut level)			<0.001[b]
n (struts)	25 292	22 726	
Mean (95% CI)	0.180 (0.178, 0.181)	0.107 (0.106, 0.108)	

Cohorts: Cohort A: 6-month OCT and 12-month OCT, FFR, and angiographic assessments. Cohort B: 12-month OCT, FFR, and angiographic assessments. Cohort C: 12-month FFR and angiographic assessments.
CI, confidence interval; EES, everolimus-eluting stent; NIH, neointimal hyperplasia.
[a]*P*-values were generated using the Wilcoxon rank-sum test.
[b]*P*-values were generated using the mixed-effects model.

with FFR to maximize invasive data collection, while hoping to mitigate oculostenotic TLR events.

Limitations

Several limitations of our results relate to these key study features. First, the enrolled cohort was less complex than expected, with <5% ACS and <12% multivessel patients enrolled, resulting in the actually observed 1-year TVF with EES (4.2%) being much lower than the protocol-assumed control rate (9%) used to power the study. Consequently, further study is needed to provide certainty as to whether or not the non-inferiority of Combo to EES seen in the relatively simple patients that were enrolled in the HARMONEE study applies to patients with a more complex medical history and anatomy.

A second important limitation of the HARMONEE study is the relevance of the primary OCT observations. Statistically, strut-level coverage with healthy tissue met the superiority requirement for this prospective primary mechanistic endpoint, with important support from the qualitative observation of more frequent homogeneous

Table 6 Optical coherence tomography qualitative and safety outcomes at 1 year

	Combo ($n = 69$ lesions)	EES ($n = 64$ lesions)	*P*-value[a]
Mean number of cross-sections	47	46	0.508
Mean number of analysable struts	367	355	0.297
Qualitative OCT assessment			
Neointimal tissue structures			<0.001
Homogenous	56 (81.2%)	44 (68.8%)	
Heterogeneous	4 (5.8%)	19 (29.7%)	
Layered	9 (13.0%)	1 (1.6%)	
Presence of thrombi	1 (1.4%)	1 (1.6%)	1.00
Presence of stent deformation	0	0	NA
Presence of edge dissection	0	0	NA
Presence of neoatherosclerosis	2 (2.9%)	1 (1.6%)	1.000

EES, everolimus-eluting stent; NA, not applicable; OCT, optical coherence tomography.
[a]*P*-values were generated using the Wilcoxon rank-sum and the Fisher's exact tests for continuous and categorical variables, respectively.

tissue substrate. Nevertheless, it is notable that even from an independent blinded core laboratory analysis, OCT observations constitute a surrogate measure, and not a classical histopathological tissue characterization *per se*. Furthermore, the degree to which these observations actually predict better clinical outcomes is unproven and cannot be derived from these 1-year results, since there was only one stent thrombosis in the entire study, and overall clinical outcomes were non-inferior. Furthermore, as an *in vivo* imaging surrogate, it is notable that there is no current histopathological validation of the actual sensitivity/specificity of the boundaries we used to define 'healthy tissue' or its direct relationship to EPC technology activity *per se*. Neointimal thickness by OCT was greater with Combo than with EES, without significant difference in QCA late loss. Therefore, confirming and validating that the primary OCT mechanistic superiority of Combo vs. EES in HARMONEE is driven by EPC capture and has clinical relevance will be an important area for ongoing post-market study.

Finally, the role of physiologic evaluation of 1-year target lesions with FFR based on the results of this study was very unclear. Fractional flow reserve was incorporated into the study design: (i) to mitigate oculostenotic TLRs in a study using protocol-driven angiographic follow-up; (ii) to confirm ischaemic physiology for definition of ischaemia-driven TLR; and (iii) as a component of the OCT healthy tissue definition in order to exclude patients with restenosis from the healthy tissue cohort. Despite the use of FFR in 90% of patients at 1-year angiography, the Kaplan–Meier curves clearly show that not only is the TVF primary endpoint largely driven by TLR events, but these events cluster around 1-year catheterization in a typically oculostenotic pattern. Target lesion revascularization was performed in 1.3% of patients with normal FFR, and in approximately 12% with abnormal FFR, equally across the two treatment groups. Consequently, the role of FFR in this study design, and in future applications, will require additional investigation.

Conclusion

Contemporary DES design advances have improved PCI safety and effectiveness, but unmet needs related to mechanisms of site healing persist. The Combo stent was the first-in-class to execute a novel biological EPC capture technology in addition to the standard three-component DES design. In HARMONEE, clinical outcomes with Combo were non-inferior vs. EES, with mechanistically superior healthy tissue strut coverage likely related to activity from the EPC capture technology, and with no safety concerns. While the HARMONEE protocol allowed for enrolment of more complex real-world NSTEMI patients, those who actually enrolled in the study itself constituted a relatively low-risk population. Looking to the future, studies should develop further insight into the clinical impact of maturing endothelial cells in the setting of PCI (including dependence on adjunctive dual antiplatelet therapy) and in high-risk patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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