COMBO Plus EPC Capture DES: Proven concept to hard clinical evidence

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
Consulting Fees/Honoraria	Abbott Vascular, American College of Cardiology, AstraZeneca, Medscape, Shanghai BraccoSine, Spectranetics Abiomed, The Medicines Company (spouse)
DSMB membership paid to the Institution	Watermark Research Partners
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Speakers fees	LifeSciences Conferences

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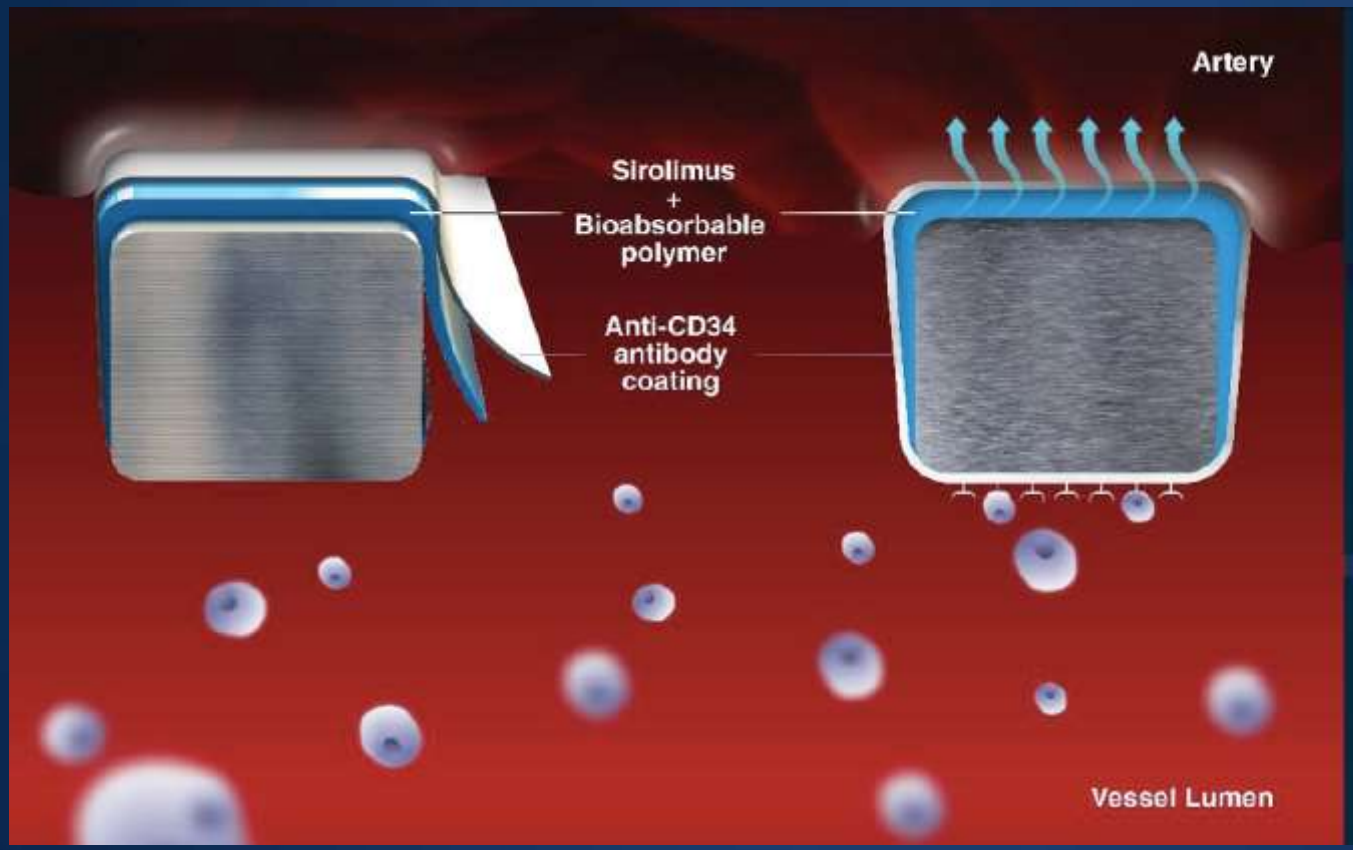
The Combo Plus Dual-Therapy Stent:
Traditional DES with biological therapy



CD34 *Antibodies*
Enable active capture of EPC for fast endothelial coverage

Sirolimus & Polymer Matrix
Drug and bioabsorbable polymer matrix for control proliferation

Stent & Delivery System
Highly conformable stent with excellent radial strength

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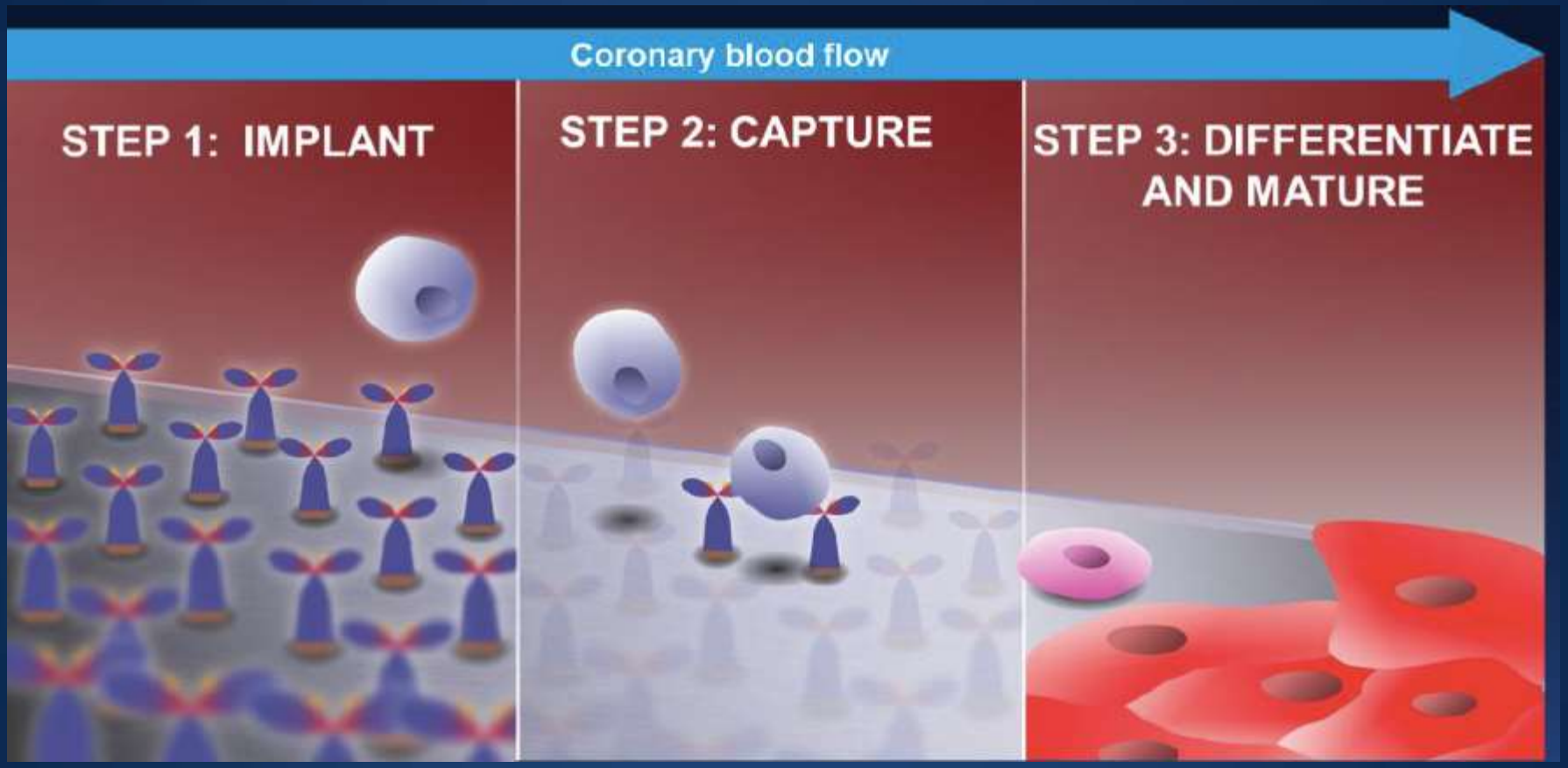
CD34 antibodies capture circulating EPCs



Following implantation, the immobilized CD34 antibodies are exposed to the circulating blood

Circulating endothelial progenitor cells (EPC) are captured by the antibodies

EPCs attach and differentiate into mature endothelial cells; an important step in re-establishing healthy neointima

COMBO Technology
Proven healing concept

- Evidence:
  - A-V human shunt
    - Attachment of cells with endothelial signature within hours
  - Porcine study
    - Better coverage at 14 days
  - Rabbit model study
    - Better endothelialization vs. EES at 28 days
  - EGO COMBO
    - Progression of coverage
    - regression of neointima 9 => 24 months
  - HARMONEE OCT sub-study
    - Superior coverage with healthy neointima at 12 months
    - More homogeneous neointima vs. EES

TCT2017

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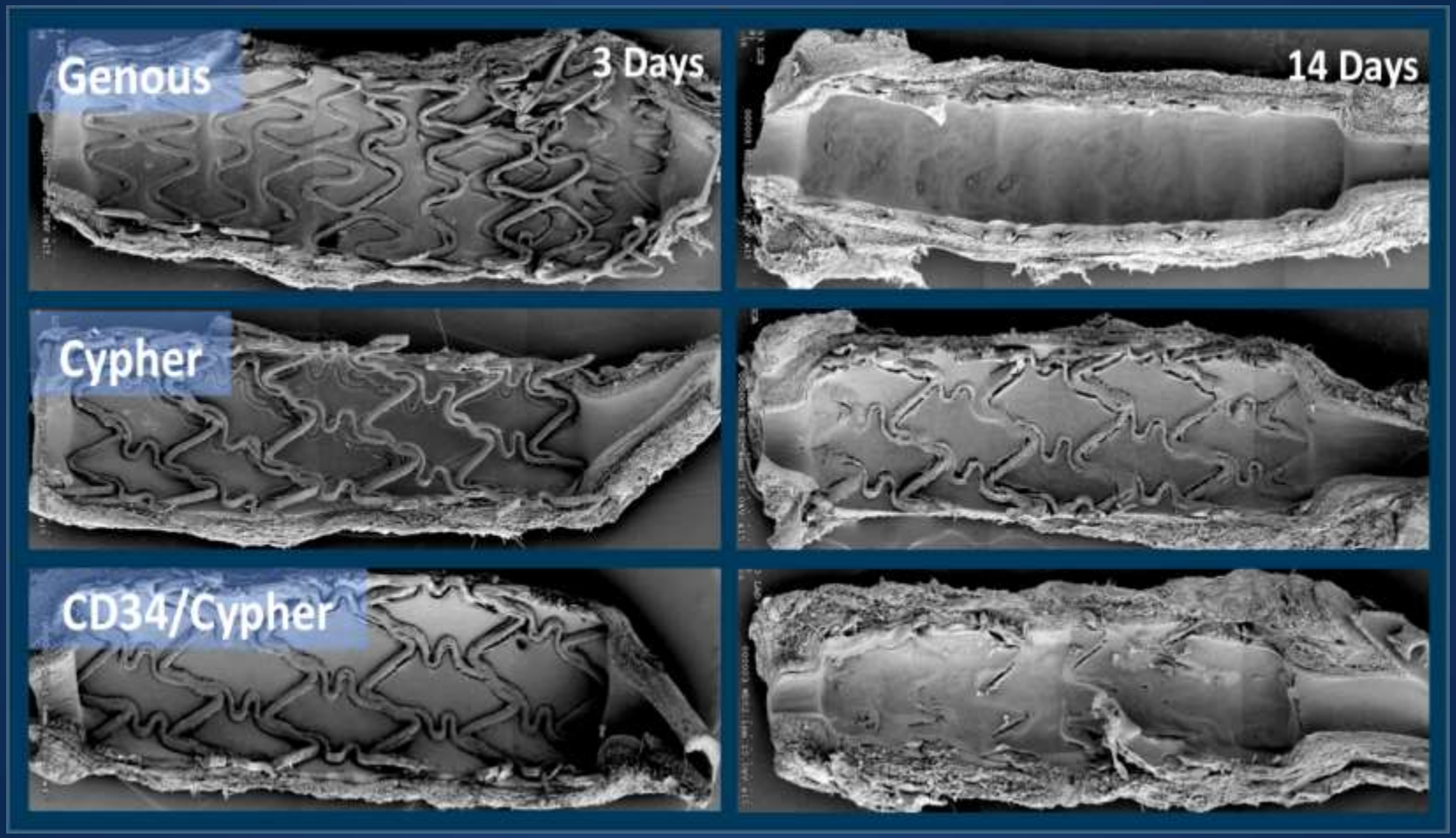
Porcine Model at 14 days



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Nakazawa G, et al. JACC: Cardiovasc Intervent 2010; 3(1): 68-75.

Clinical trials with COMBO

HARMONEE

- **12mo TVF in COMBO vs EES (n=572)**

RECOVERY

- **9mo IS LLL in Combo vs NanoPolymer Free stent (n=432)**

MASCOT

- **12mo TLF registry (n=2614)**

REDUCE

- **3mo vs 12mo DAPT in ACS (n=1500)**

All results have been presented at TCT 2017

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HARMONEE First Report: Randomized Registration Study for COMBO

HBD Proof of Concept Global Trial Program

Japan PMDA & U.S. FDA

Advance Publication by-J-STAGE

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Global Cardiovascular Device Innovation: Japan-USA Synergies

– Harmonization by Doing (HBD) Program, a Consortium of Regulatory Agencies, Medical Device Industry, and Academic Institutions –

Takahiro Uchida, MD; Fumiaki Ikeno, MD; Koji Ikeda, PhD; Yuka Suzuki, PhD; Koji Todaka, MD; Hiroyoshi Yokoi, MD; Gary Thompson, BSc; Mitchel Krucoff, MD; Shigeru Saito, MD
on behalf of the Harmonization by Doing Program Working Group

Background: Global medical devices have become more popular, but investment money for medical device development is not easily available in the market. Worldwide health-care budget constraints mean that efficient medical device development has become essential. To achieve efficient development, globalization is a key to success. Spending large amounts of money in different regions for medical device development is no longer feasible.

Methods and Results: In order to streamline processes of global medical device development, an academic, governmental, and industrial consortium, called the Harmonization by Doing program, has been set up. The program has been operating between Japan and the USA since 2003. The program has 4 working groups: (1) Global Cardiovascular Device Trials; (2) Study on Post-Market Registry; (3) Clinical Trials; and (4) Infrastructure and Methodology Regulatory Convergence and Communication. Each working group has as its goals the achievement of speedy and efficient medical device development in Japan and the USA. The program has held multiple international meetings to deal with obstacles against efficient medical device development.

Uchida T et al, Circulation Journal 2013

HARMONEE trial study design

Study Objective

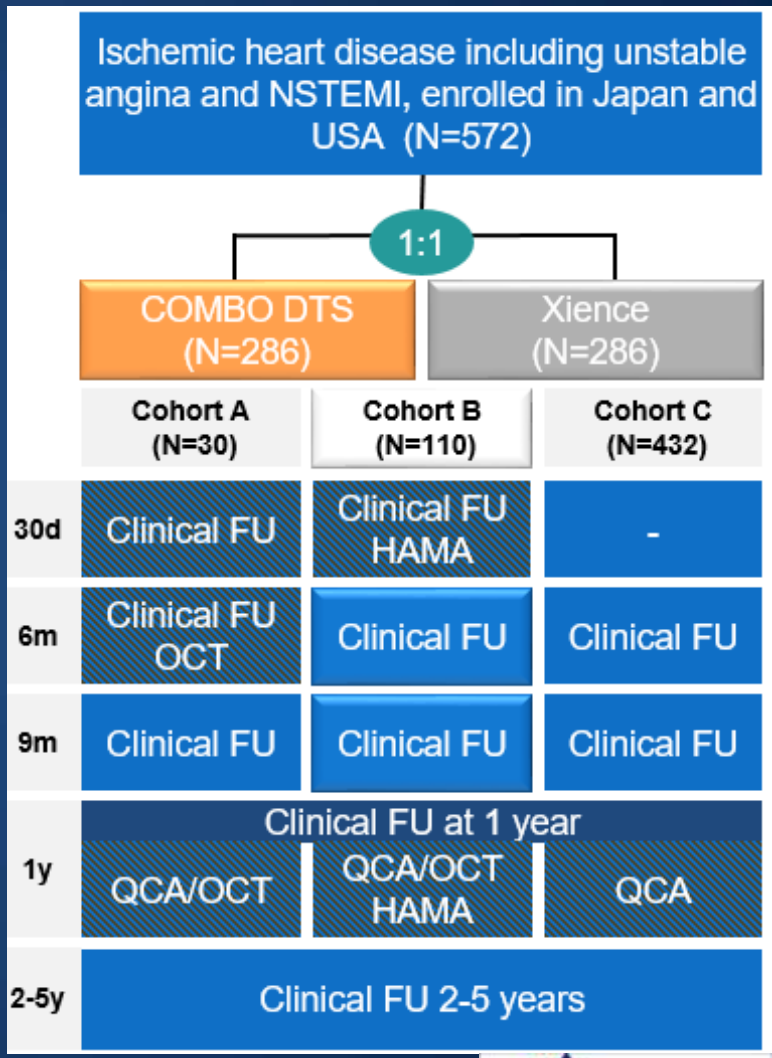
To demonstrate the effectiveness of COMBO vs. Xience in the treatment of significant ischemic heart disease, including UA and NSTEMI patients

Primary Endpoint

Ischemia & FFR driven TVF at 1 year, TVF defined as cardiac death, tv-MI, or ischemia-driven TVR

Principal Investigators

Mitch Krucoff, MD, Duke UMC
Durham, NC, USA
Shigeru Saito, ShonanKamakura General Hospital, Kamakura, Japan



ClinicalTrials.gov identifier: NCT02073565

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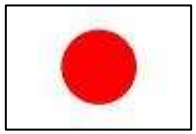
Enrollment & Follow-Up: ITT population



33 sites
439 pts (77%)

572 patients randomized

17 sites
133 pts (23%)

287 COMBO

285 EES

3 (1.0%) non-protocol stent

2 (0.7%) withdrew or lost to FU

2 (0.7%) non-protocol stent

6 (2.1%) withdrew or lost to FU

285 (99.3%) 1 year clinical FU

279 (97.9%) 1 year clinical FU

271 (95.1%) 1 year angio FU

261 (91.6%) 1 year FFR

262 (93.9%) 1 year angio FU

256 (91.8%) 1 year FFR

Cohort A&B 1 year OCT FU (n=70)

65 (92.9%)

Cohort A&B 1 year OCT FU (n=70)

63 (90.0%)

HARMONEE

Harmonized Assessment by Randomized, Multi-center Study of OrbusNEich's COMBO StEnt

Primary Clinical Endpoint: 1 year TVF non-inferiority

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HARMONEE

Harmonized Assessment by Randomized, Multi-center Study of OrbusNEich's COMBO StEnt

1 Year Target Vessel Failure (TVF)* Combo vs. EES Non-inferiority** (ITT Population)

	Combo (N=287)	EES (N=285)	Difference (95%CI)	Non-inferiority p-value
TVF	20 (7.0%)	12 (4.2%)	0.028 (-0.010, 0.065)	0.020

*Composite of cardiac death, target-vessel MI, or ischemia-driven target-vessel revascularization (TVR) by percutaneous or surgical methods.
** Non-inferiority margin 0.07

- SAP assumption: 9.0%
- TVF assay sensitivity not met (underpowered)

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1 Year Composite Outcomes (ITT Population)

HARMONEE
Harmonized Assessment by Randomized, Multi-center Study of OrbusNEich's COMBO StEnt

	Combo (N=287)	EES (N=285)
Target vessel failure (TVF)[1]	20 (7.0%)	12 (4.2%)
Cardiac death	0	0
Target-vessel MI	5 (1.7%)	3 (1.1%)
TVR (ischemia-driven)	18 (6.3%)	11 (3.9%)
Target lesion failure (TLF)[2]	19 (6.6%)	12 (4.2%)
All-cause death	2 (0.7%)	0
Nonfatal MI	11 (3.8%)	8 (2.8%)
TLR (ischemia-driven)	16 (5.6%)	9 (3.2%)
ARC ST (poss/prob/def)	0	1 (0.35%)

[1]Composite of cardiac death, target-vessel MI, or ischemia-driven target-vessel revascularization (TVR) by percutaneous or surgical methods.
[2]Composite of death, MI or ischemia-driven target lesion revascularization.

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1 Year QCA Core Laboratory Late Loss [mean (SD)]* (Cohorts A and B: N=140)

	Combo	EES
N (lesions/patients)	77/65	76/66
In-stent late loss (mm)	0.293 (0.435)	0.219 (0.352)
In-segment late loss (mm)	0.229 (0.398)	0.220 (0.359)
Restenosis		
In-stent	1 (1.3%)	2 (2.6%)
In-segment	2 (2.5%)	3 (3.9%)

* All comparisons p=NS

HARMONEE

Harmonized Assessment by Randomized, Multi-center Study of OrbusNEich's COMBO StEnt

EPC Technology
Primary Mechanistic Endpoint
1 year "healthy tissue"-- superiority
(OCT core laboratory)

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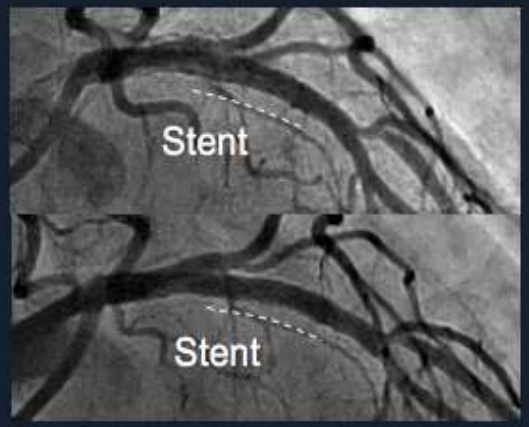
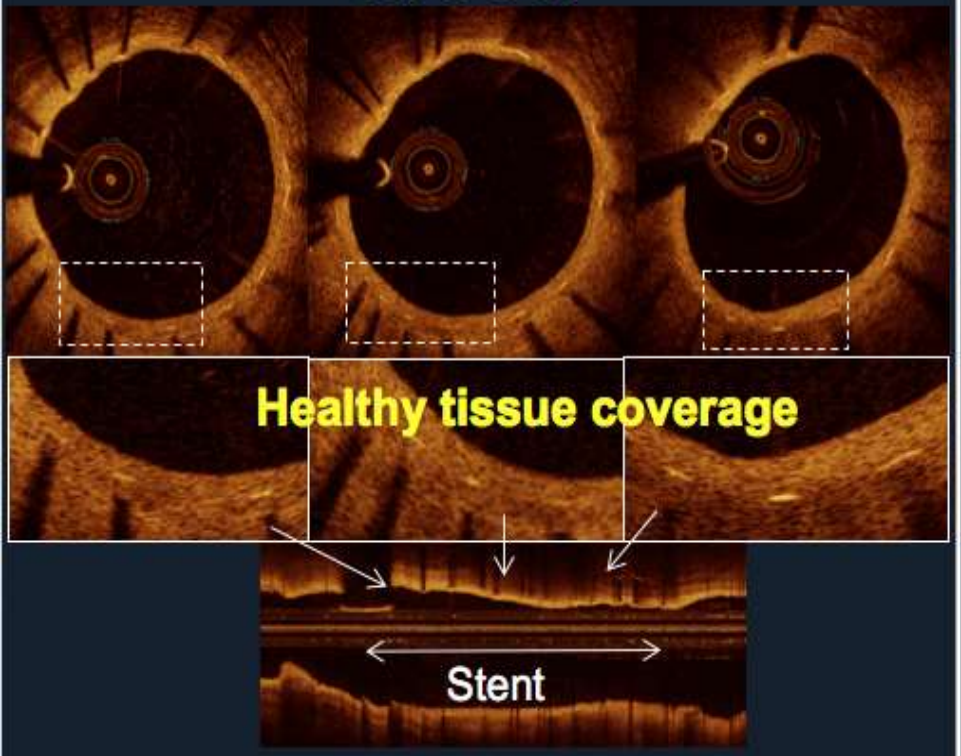
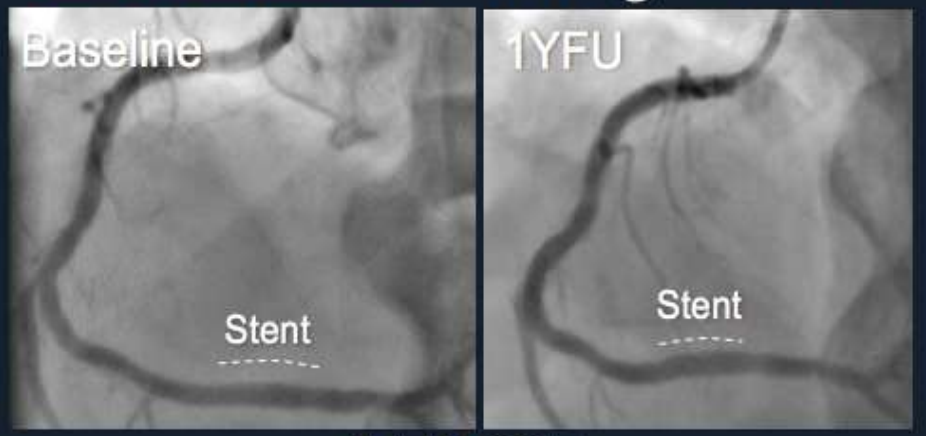
Combo Stent



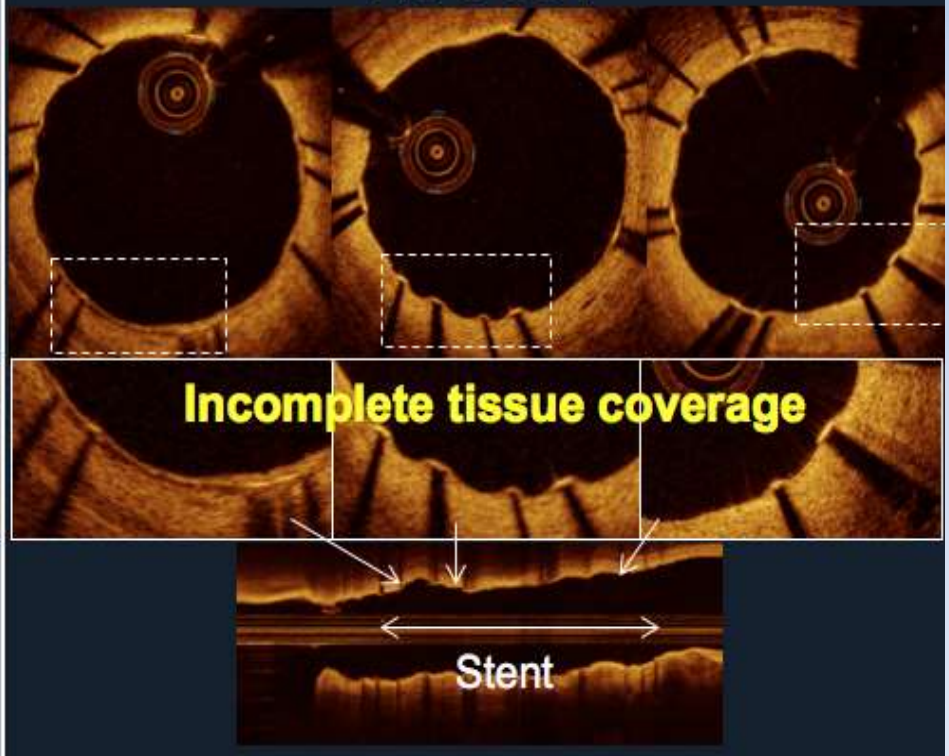
1YFU OCT



Everolimus Eluting Stent



1YFU OCT



Courtesy Dr. Akiko Maehara, CRF OCT Core Laboratory

1 Year OCT Qualitative Homogeneous Neointimal Tissue (Cohorts A and B, N=140)

HARMONEE
Harmonized Assessment by Randomized, Multi-center Study of OrbusNEich's COMBO StEnt

Number of lesion/patients	**Combo (69/61)**	**EES (64/60)**
Homogenous NIT	**81.2%**	**68.8%**

HARMONEE

Harmonized Assessment by Randomized, Multi-center Study of OrbusNEich's COMBO StEnt

Primary 1 year safety:

Zero HAMA conversions

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RECOVERY Study Design

Study Objective

To evaluate safety and efficacy of the COMBO stent compared to the Nano polymer-free stent

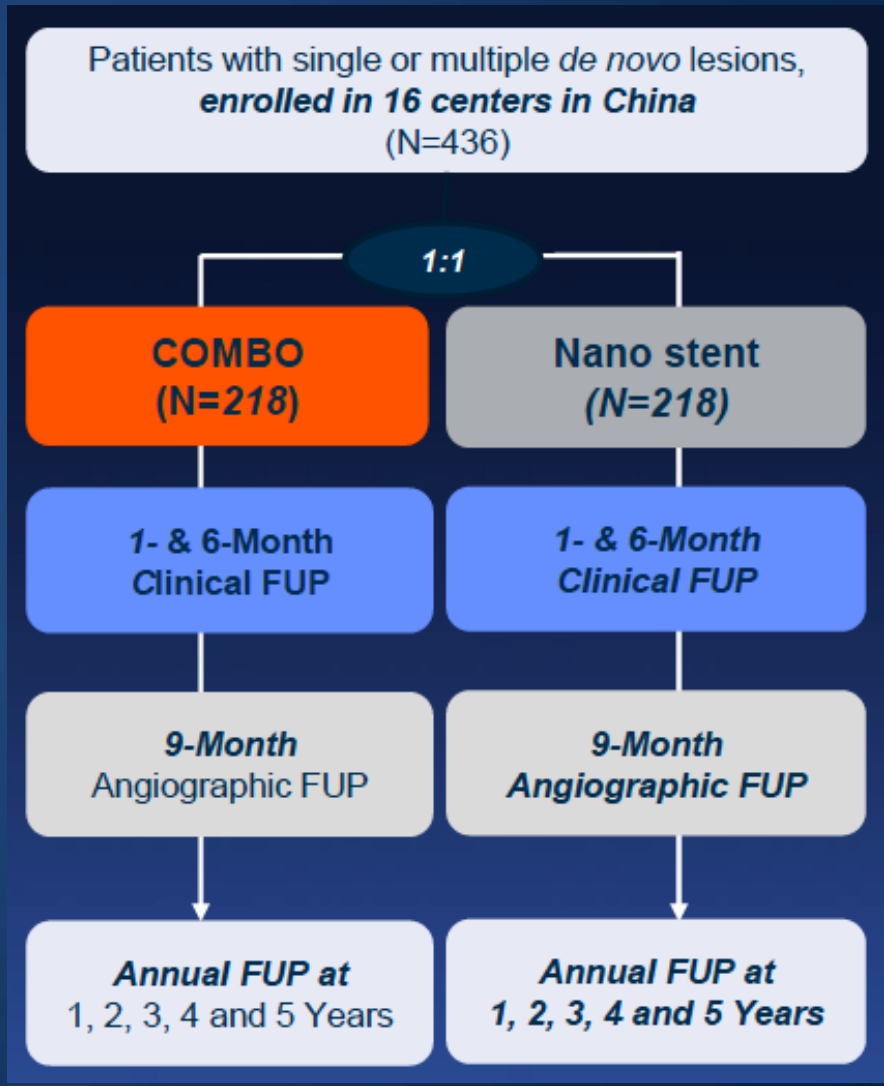
Primary Endpoint

In-Segment LLL at 9 months

Principal Investigators

Tao Ling, First Affiliated Hospital of the Forth Medical University, Xi'an, Shanxi, China

Xu Bo, Secondary Affiliated Hospital of Harbin University, Harbin, Heilongjaing, China



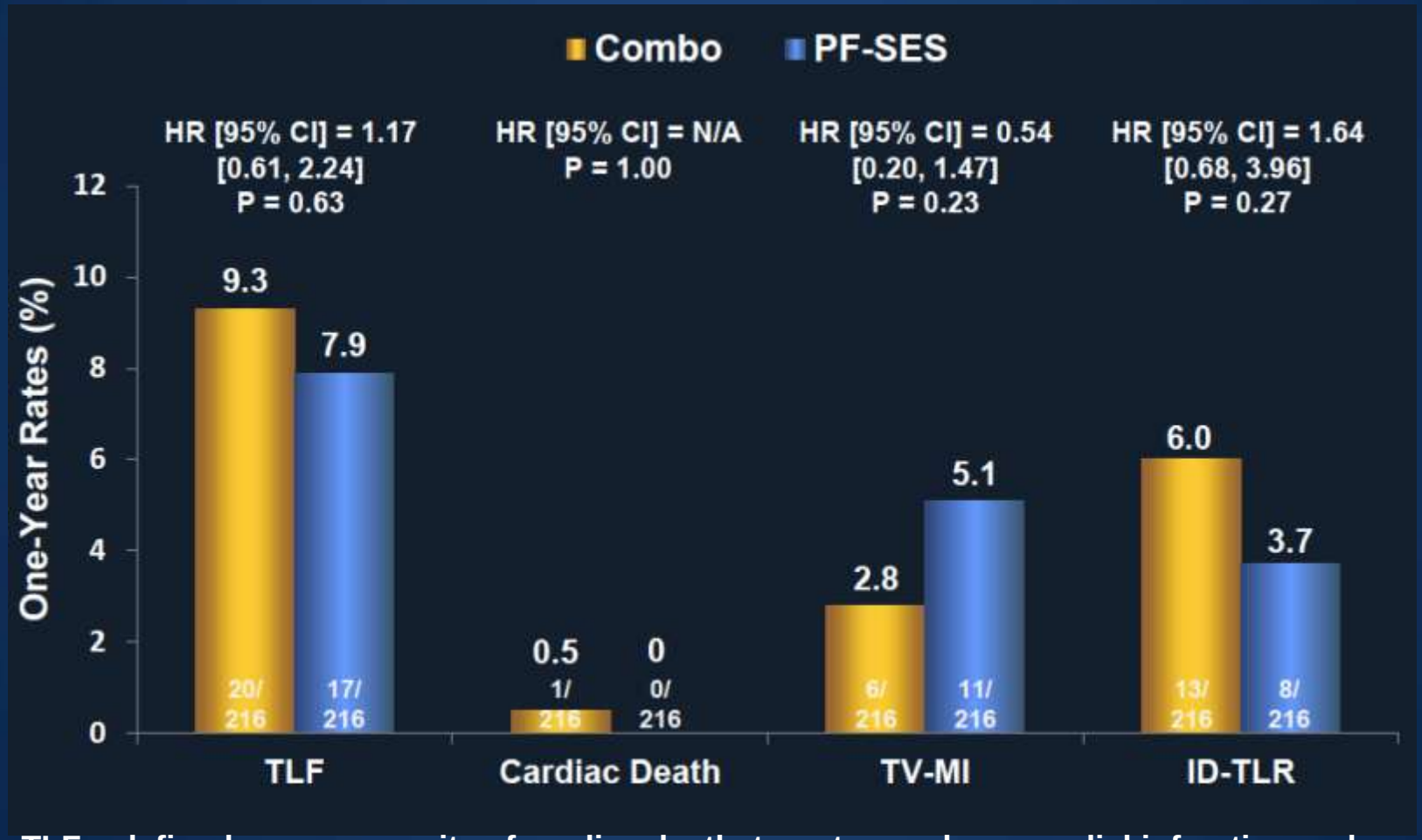
Primary Endpoint: In-Segment Late Loss at 9 Months

Combo (N = 187)	PF-SES (N = 195)	Difference : 0.01mm Upper 2-sided 95% CI: 0.09 mm	Noninferiority P ≤0.0001
0.30 ± 0.47	0.31 ± 0.44		

Primary Non-Inferiority Endpoint Met

Presented at TCT 2017

One year TLF and components



TLF – defined as a composite of cardiac death, target vessel myocardial infarction and ischemia-driven target lesion revascularization

Presented at TCT 2017

MASCOT Study Design

Study Objective

To evaluate long-term safety and performance of the COMBO Dual Therapy Stent in routine clinical practice

Primary Endpoint

TLF at 12 months defined as cardiac death, non-fatal target vessel MI and TLR

Principal Investigator

Antonio Colombo, San Raffaele Hospital, Milan, Italy

Data Coordinating Director

Roxana Mehran, Mount Sinai Medical

1-year Outcomes

	N=2614
Primary endpoint: TLF	**88 (3.4%)**
All cause Death	53 (2.0%)
• Cardiac	36(1.4%)
• Non Cardiac	14 (0.5%)
• Cardiovascular	39 (1.5%)
Non-fatal MI	
• Not clearly attributed to a non-target vessel	36 (1.4%)
• Any	49 (1.9%)
Ischemia driven revascularization	
• TLR	37 (1.4%)
• TVR	12 (0.5%)
• NTVR	37 (1.4%)
• Any	72 (2.8%)
Def/Prob Stent Thrombosis	24 (0.9%)
• Def ST	12 (0.46%)
• Prob ST	12 (0.46%)
MACE	137 (5.2%)
Stroke	11(0.42%)
Bleeding	
• Major	46 (1.8%)
• Minor	63 (2.4%)
• Nuisance	20 (0.8%)
• Any	124 (4.8%)

Associations between DAPT cessation and 1-year outcomes

	Adj* HR	95% CI	P value
TLF			
Discontinuation	1.20	0.47-3.10	0.70
Disruption	2.52	0.61-10.36	0.20
MACE			
Discontinuation	0.70	0.28-1.75	0.44
Disruption	3.18	1.17-8.68	0.024
Major bleeding			
Discontinuation	1.04	0.24-4.64	0.95
Disruption	3.44	0.47-25.5	0.23

** Adjusted for age, sex and center*

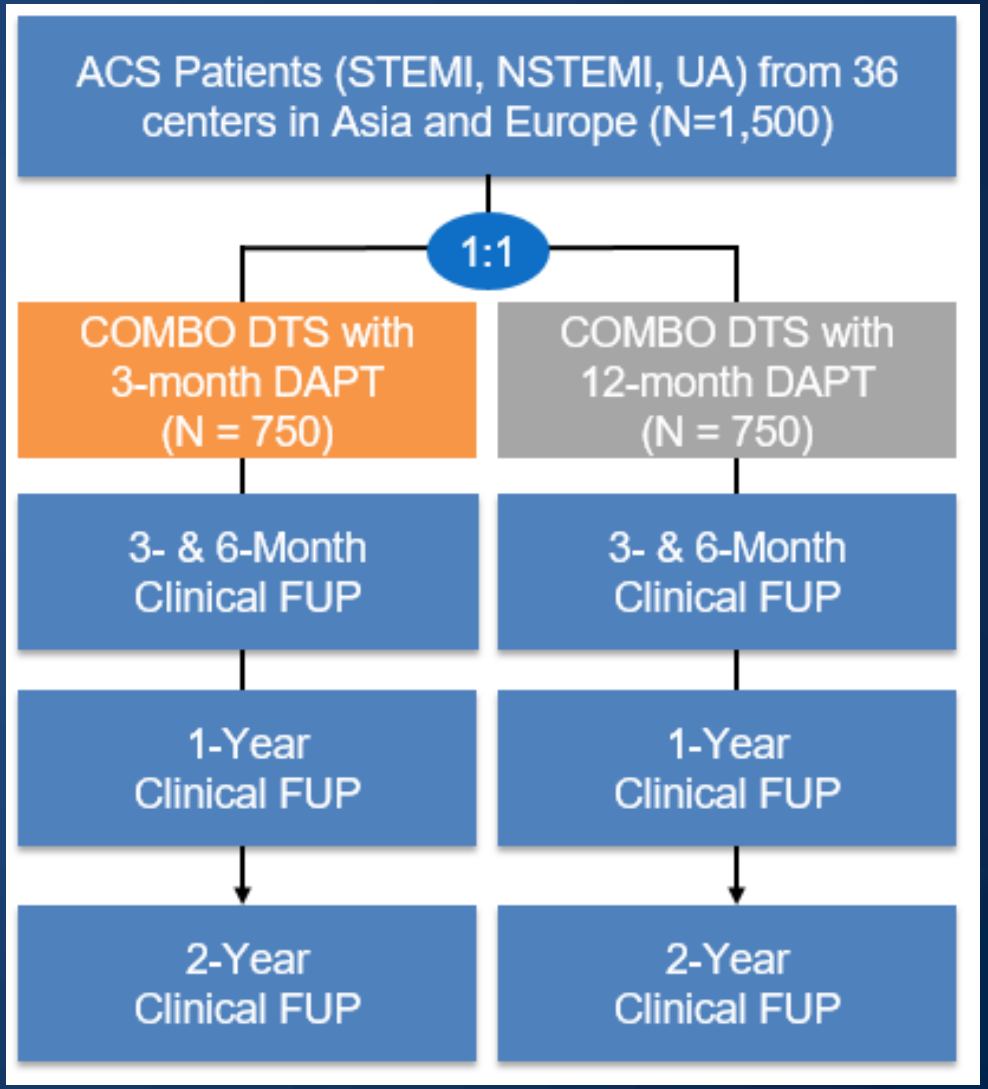
REDUCE study design

Study Objective
Demonstrate a non-inferiority of 90 d vs. 360 d DAPT in ACS patients treated with COMBO

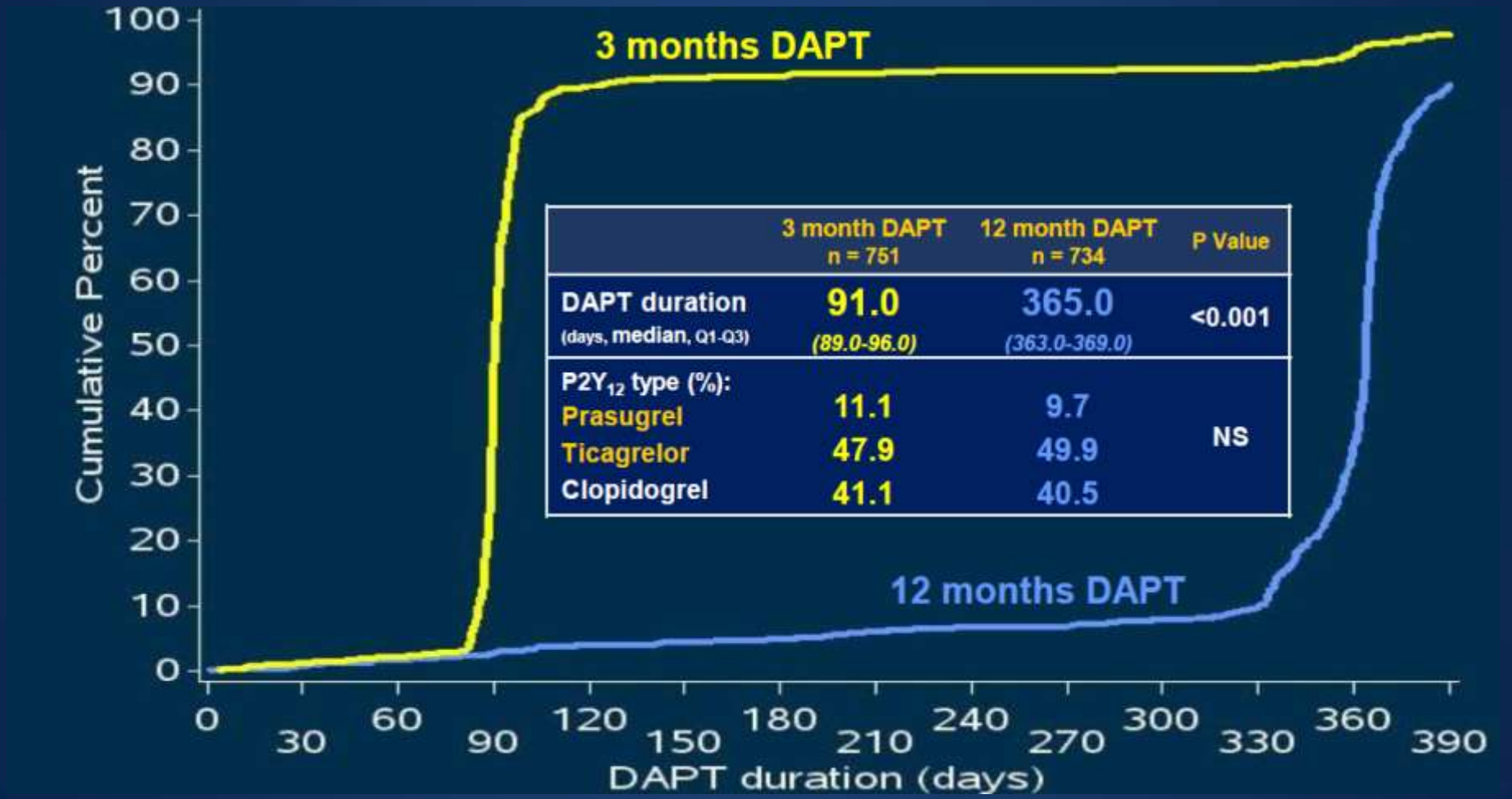
Primary Endpoint
Composite of all cause mortality, MI, Stroke, Major Bleeding (BARC type 2, 3 or 5)

Principal Investigators
Harry Suryapranata, Radboud University Hospital
Nijmegen, The Netherlands

Giuseppe De Luca, Eastern Piedmont University, Novara, Italy



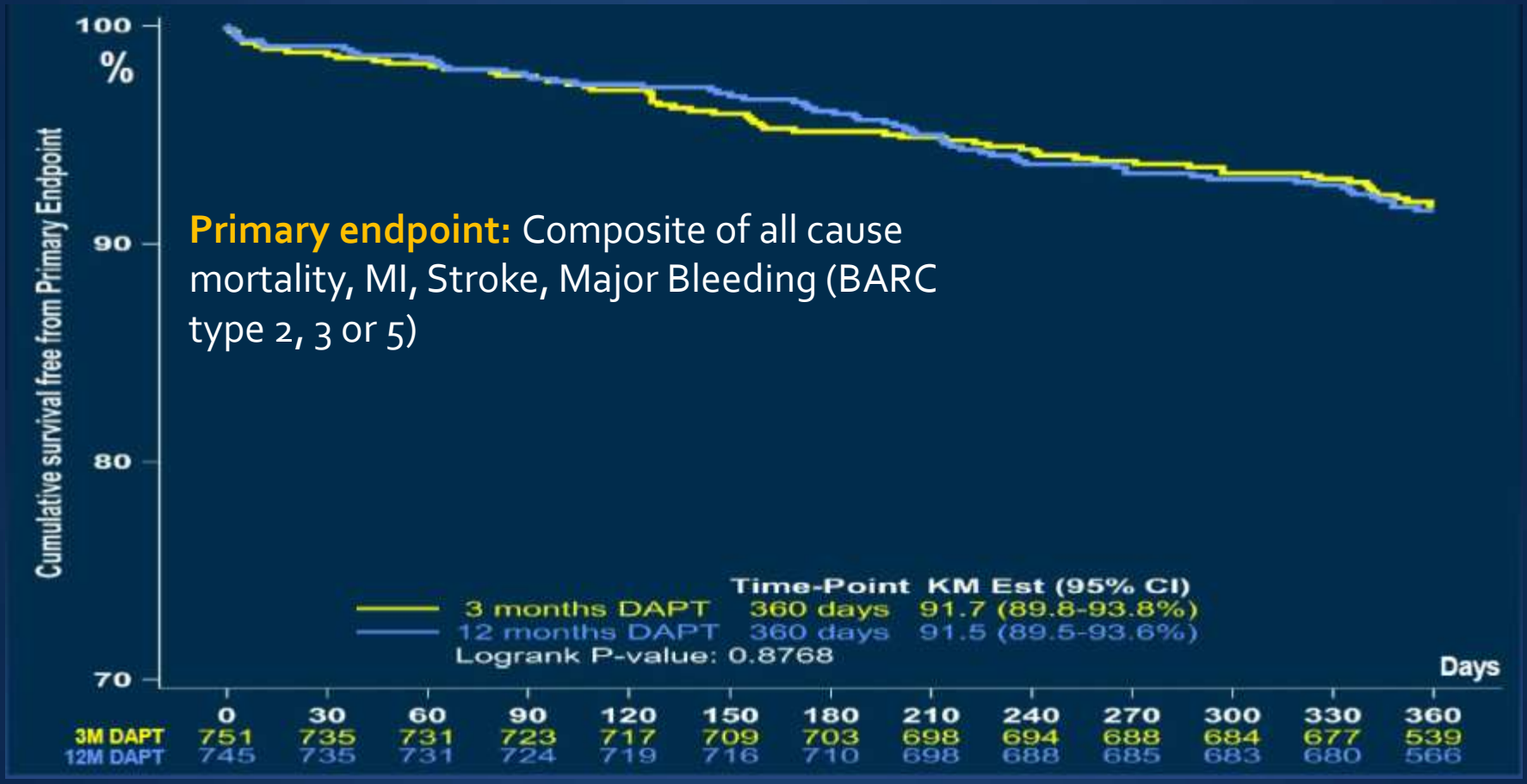
REDUCE study results



	3 month DAPT n = 751	12 month DAPT n = 734	P Value
DAPT duration (days, median, Q1-Q3)	91.0 (89.0-96.0)	365.0 (363.0-369.0)	<0.001
$P2Y_{12}$ type (%):			
Prasugrel	11.1	9.7	NS
Ticagrelor	47.9	49.9	
Clopidogrel	41.1	40.5	

Presented at TCT 2017

REDUCE study results



Analysis set	3 month DAPT n = 729	12 month DAPT n = 734	Risk difference	Upper bound of 1 sided 97.5% CI	OR (95% CI)	P non-inferiority
Intention to treat	8.2	8.4	-0.002	0.027	0.97 (0.67-1.41)	<0.001

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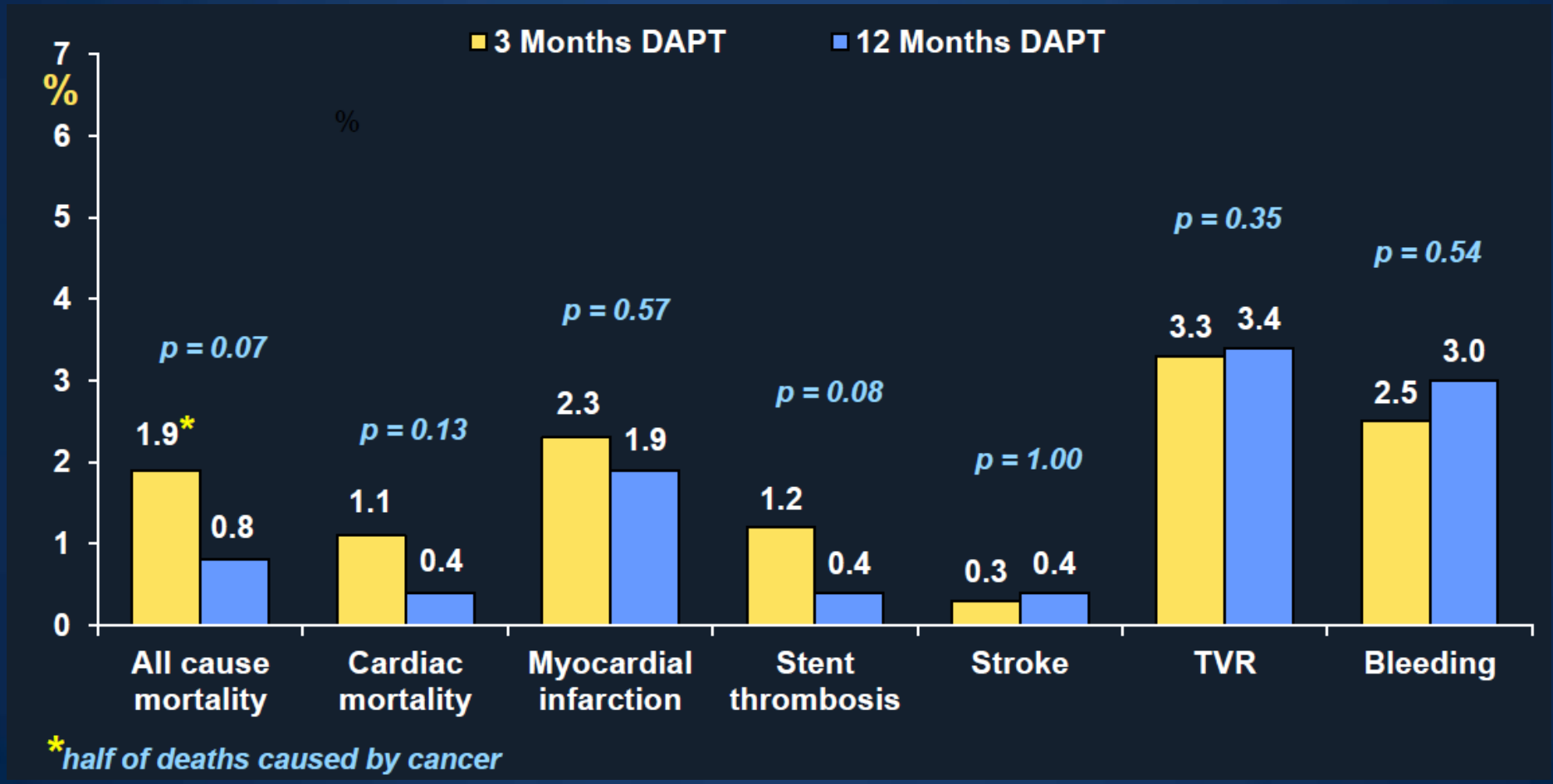
REDUCE study results



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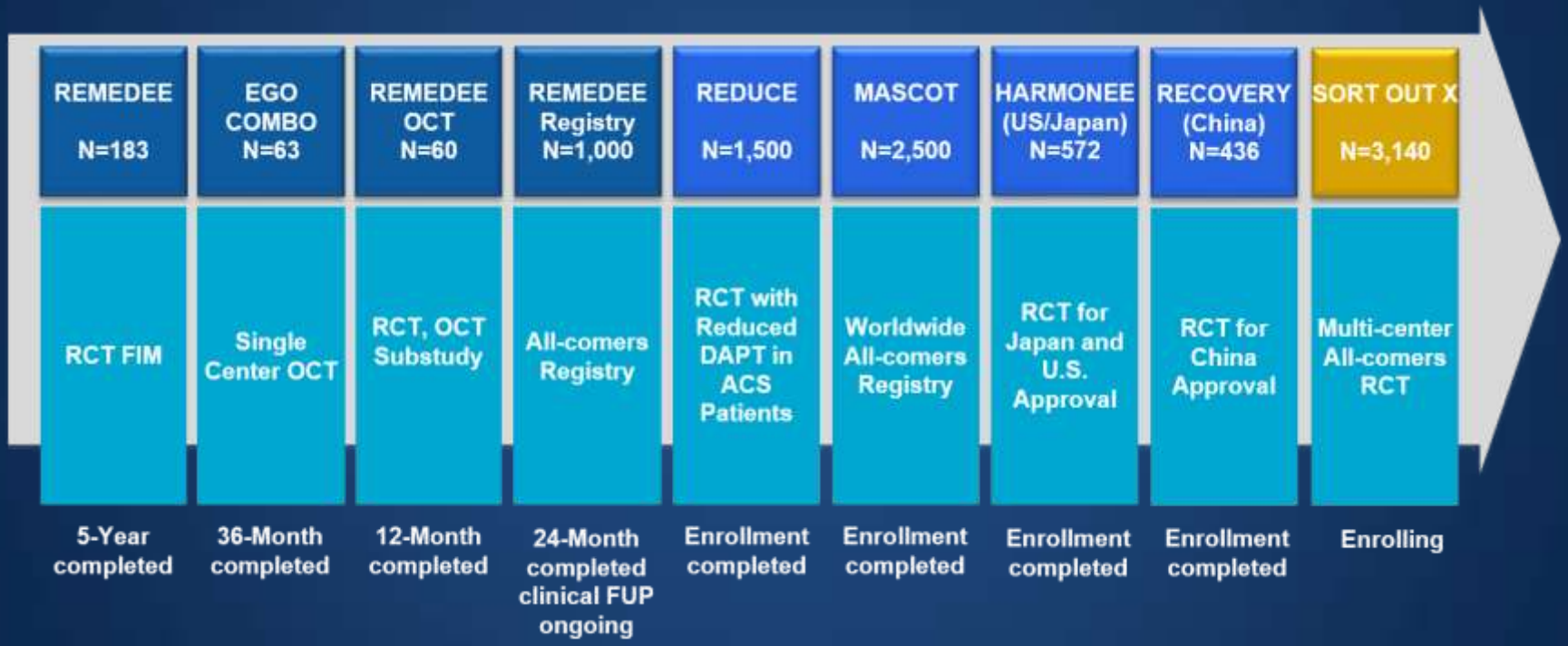
Combo Clinical Trial Program



7,000+ Patients
(Patients receiving COMBO Stent: 6,168
Enrollment ongoing)

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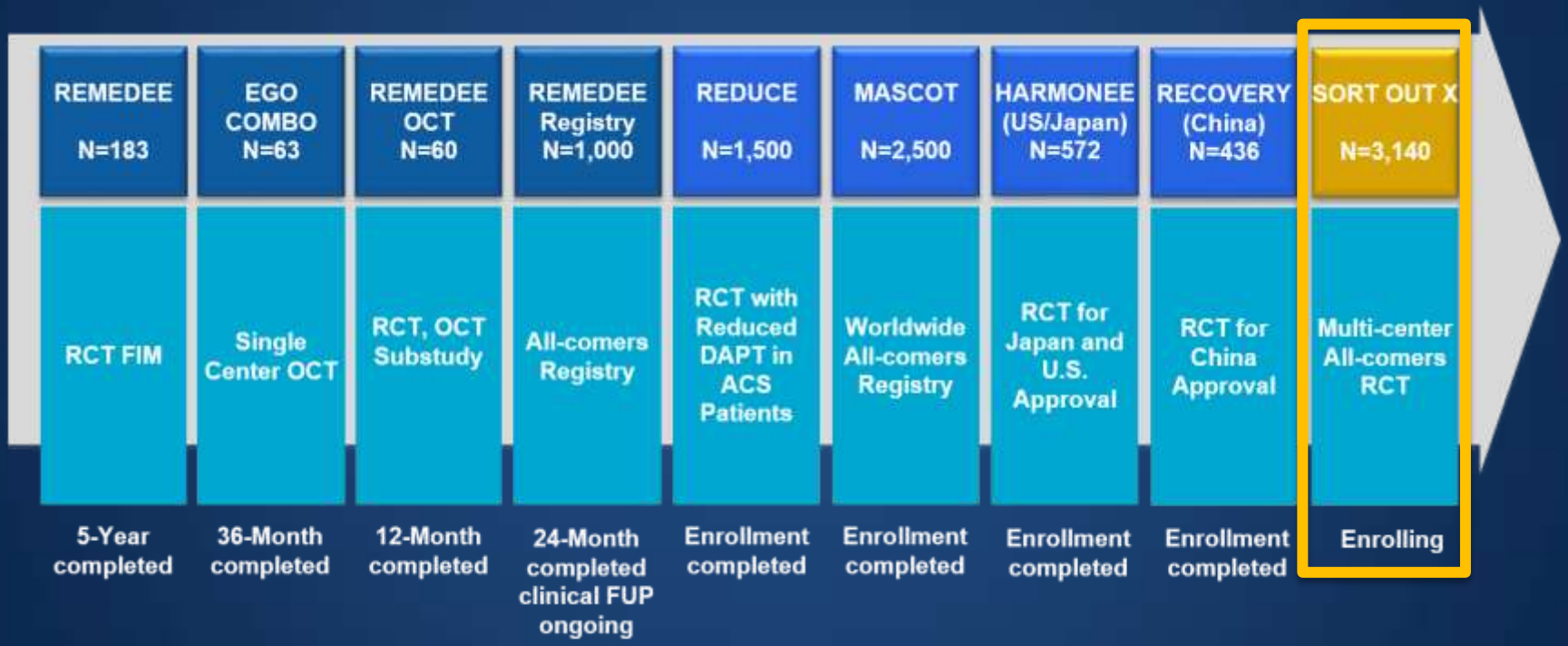
Combo Clinical Trial Program



7,000+ Patients
(Patients receiving COMBO Stent: 6,168
Enrollment ongoing)

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SORT OUT X

PI: Dr. Jakobsen, Aarhus University Hospital Skejby

ClinicalTrials.gov Identifier: NCT03216733

Randomized controlled trial

- COMBO versus Orsiro stent (1:1 randomization)
- N= 3140 all-comer patients

Primary endpoint

Target Lesion Failure (TLF): cardiac death, target-vessel myocardial infarction (MI), or ischemia-driven target-lesion revascularization at 12 months

→ Currently enrolling patients

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Conclusions

- **COMBO is an active multifaceted stent with an CD34 antibody coating that recruits circulating endothelial progenitor cells-promoting healing**
- **COMBO has been shown in clinical trials to be safe and effective, as compared to other DES and in 'all comers' registries and randomized clinical trials**
- **Among ACS patients treated with COMBO stent, 3-months DAPT is not inferior to 12-months DAPT**
- **SORT OUT X will reveal the value of the added pro-healing layer to drug-eluting stents.**

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