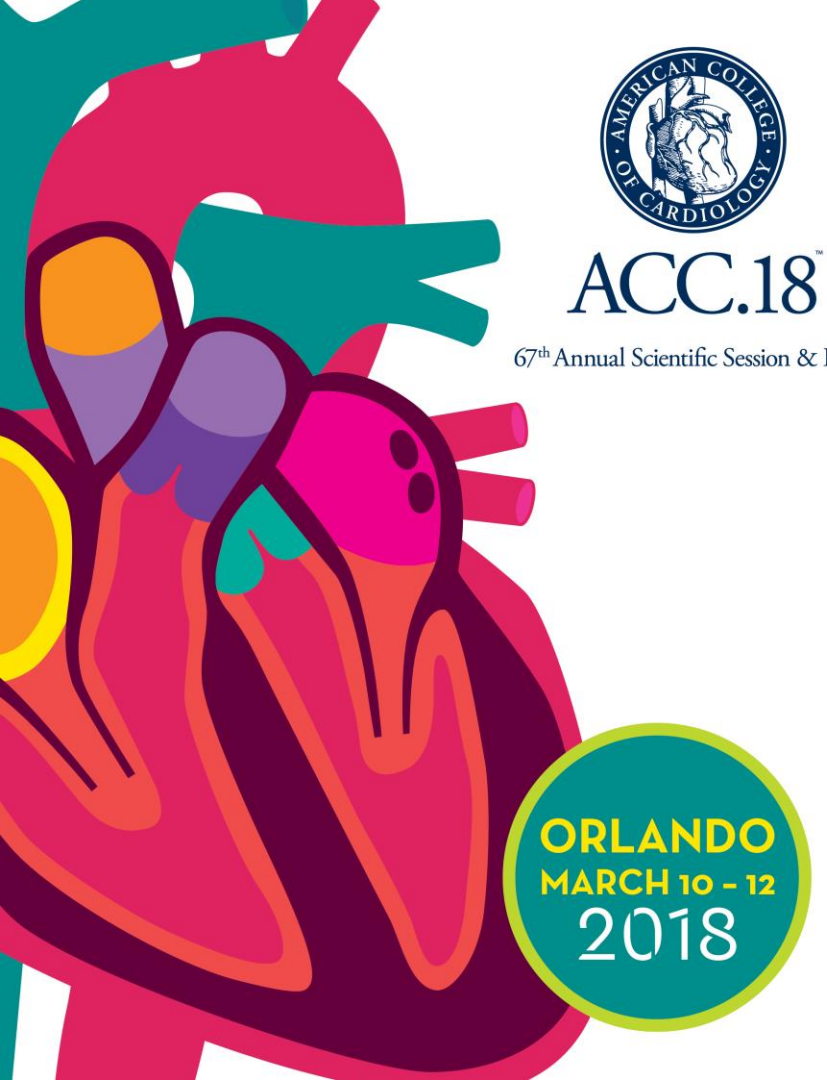


ACC.18

67th Annual Scientific Session & Expo

ORLANDO
MARCH 10 – 12
2018

One-year Clinical Outcomes of the Bio-engineered COMBO stent:

Primary Results from the 3614 All-comer Patients in the COMBO Collaboration

Antonio Colombo, MD, FACC

San Raffaele Hospital, Milan, Italy

On behalf of the COMBO collaborators

Potential conflicts

- Antonio Colombo is the Principal Investigator of the MASCOT Registry dealing with the COMBO stent

Background

- Drug-eluting stents (DES) have improved clinical outcomes in patients after percutaneous coronary interventions (PCI) compared to bare metal stents
- However, risk of *late* in-stent restenosis and *very late* stent thrombosis remains of serious concern with current DES
- A dual-therapy stent has been designed to overcome these adverse clinical outcomes after PCI

Background – The COMBO stent

The COMBO stent (OrbusNeich Medical BV, The Netherlands) consists of a:

- 100µm stainless steel stent strut

Background – The COMBO stent

The COMBO stent (OrbusNeich Medical BV, The Netherlands) consists of a:

- 100µm stainless steel stent strut
- With a biodegradable polymer with:

Background – The COMBO stent

The COMBO stent (OrbusNeich Medical BV, The Netherlands) consists of a:

- 100µm stainless steel stent strut
- With a biodegradable polymer with:
- Sirolimus-elution

Background – The COMBO stent

The COMBO stent (OrbusNeich Medical BV, The Netherlands) consists of a:

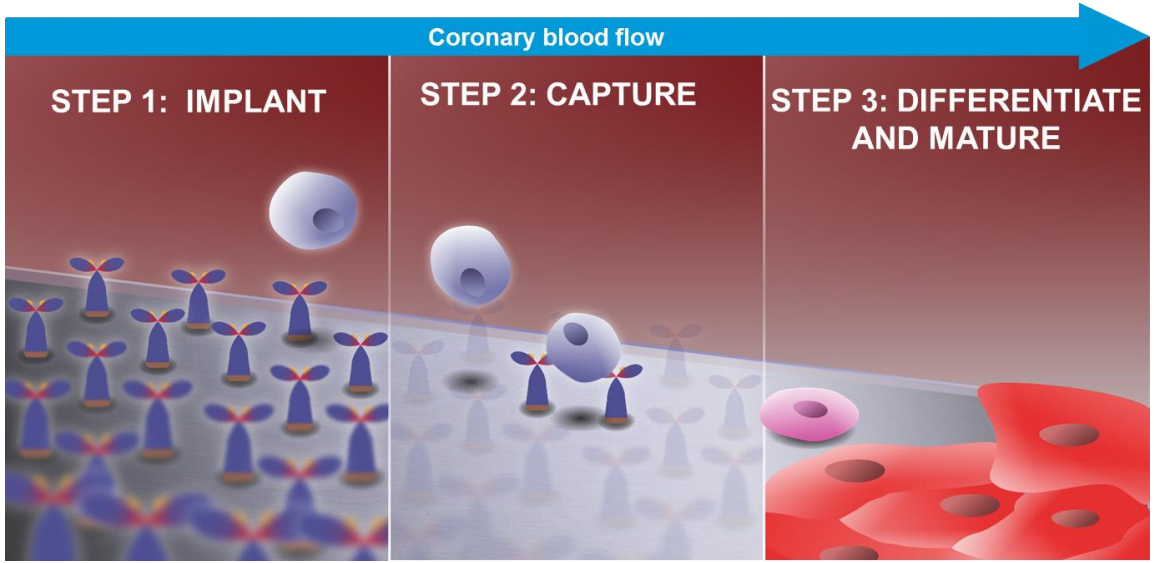
- 100µm stainless steel stent strut
- With a biodegradable polymer with:
- Sirolimus-elution

And a unique layer consisting of:

- Immobilized anti-CD34 antibodies for EPC capture

Pro-healing layer with anti-CD34 antibodies

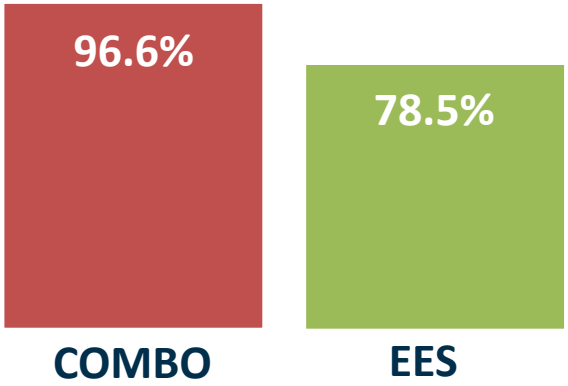
A bio-engineered layer attracts circulating endothelial progenitor cells (EPCs) that can rapidly differentiate into normal endothelium



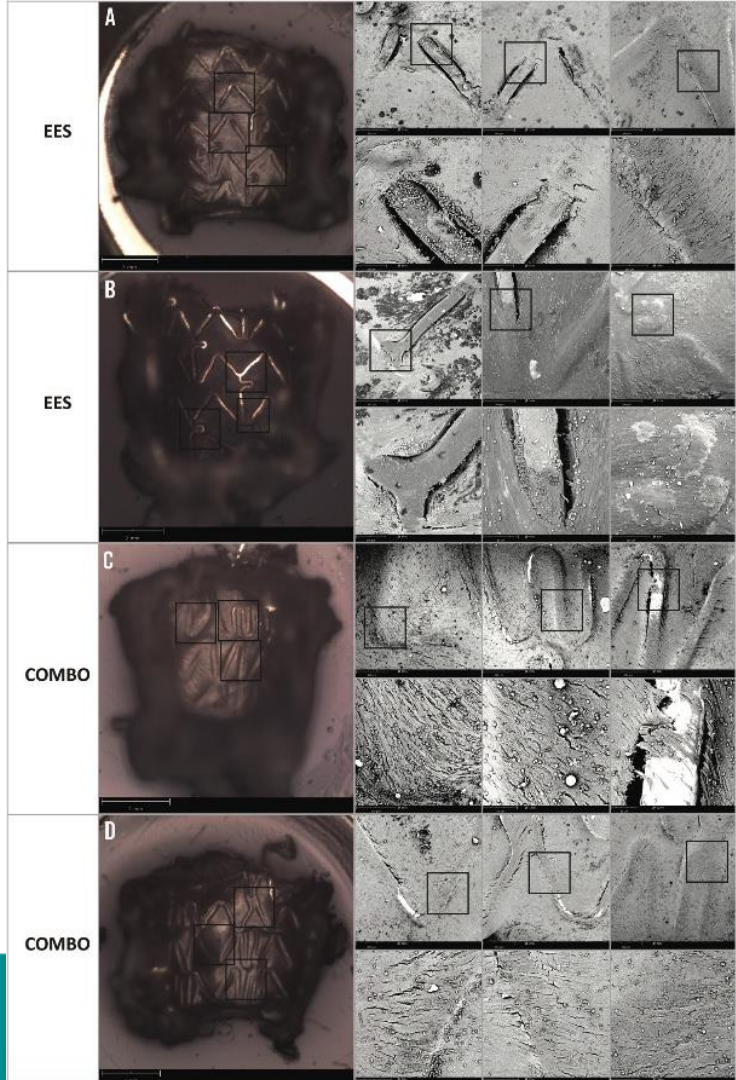
Pro-healing layer- Pre-clinical

Pre-clinical studies confirmed rapid coverage of COMBO

p < 0.038



Stent strut coverage (by SEM) showed a significantly improved endothelialization of the COMBO stent (96.6±3.5%) compared to the EES (78.5±16.8%; p=0.038) at 28 days

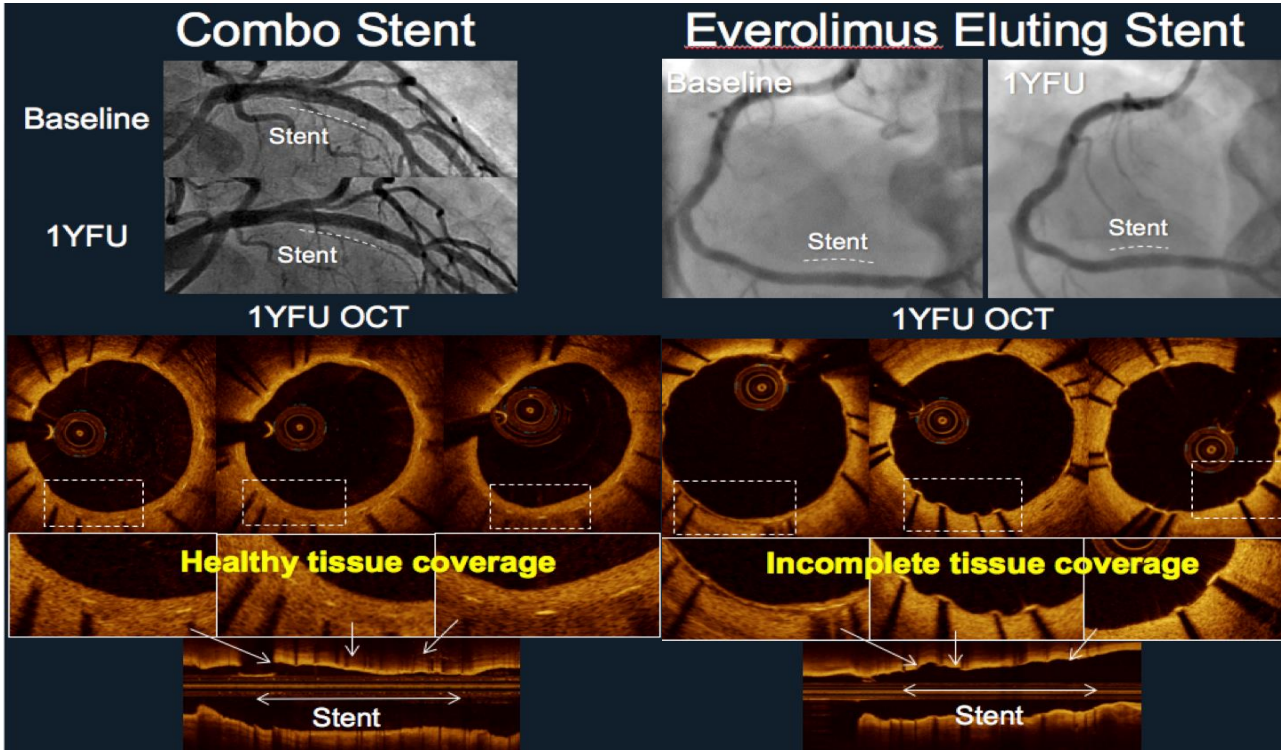


Ellenbroek, G.H., et al., AsiaIntervention, 2016. 2(2): p. 132-140.

Pro-healing layer – OCT confirmed

1-year OCT healthy tissue strut level coverage

Number of lesions/ patients	COMBO (69/61)	EES (64/60)	P-value
Mean (%) [95% CI]	91.56 [88.98, 94.13]	74.82 [70.02, 79.62]	<0.001



HARMONEE trial results, presented by dr. Krucoff at TCT 2017. ClinicalTrials.gov Identifier: NCT02073565

Aim

To evaluate the safety and efficacy of the novel COMBO stent in a real-world, multicenter, global, all-comers patient population in routine clinical practice.

Methods

Pooled patient-level analysis consisting of consecutive all-comers patients with attempted COMBO stent placement from:

- **MASCOT registry:** Enrollment between 2014-2016, N=2614, 61 global sites
- **REMEDEE registry:** Enrollment between 2013-2014, N=1000, 9 European sites

Patients were contacted at 30 days, 6 months and 12 months FUP by outpatient visit or telephone call for clinical follow-up. Independent monitoring+ adjudication of events were performed for data quality.

Methods

Both studies all inclusive except:

Exclusion criteria:

- high probability of non-adherence to the follow-up requirements (due to social, psychological or medical reasons),
- currently participating in another investigational drug or device study in which a routine angiographic follow-up is planned,
- a life expectancy of <1 year or explicit refusal of participation in the registry.

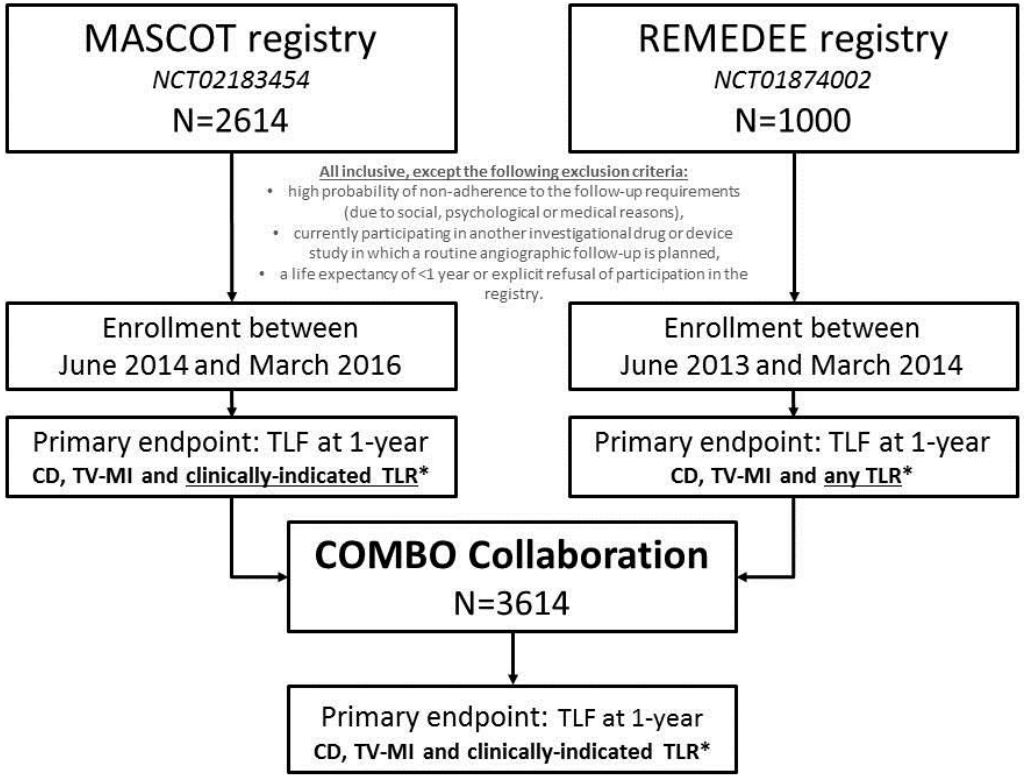
Methods

Role of manufacturer:

- The Academic Medical Center received an unrestricted research grant from OrbusNeich Medical BV for the conduct of the REMEDEE registry
- OrbusNeich Medical was the sponsor of the MASCOT registry

COMBO Collaboration:

OrbusNeich Medical BV had no part in the analysis of the data or presentation of results.



* MASCOT used clinically driven TLR and the REMEDEE registry used any TLR in TLF. Clinically driven TLR is evaluated in this analysis.

Methods

Primary endpoint: Target lesion failure (TLF),
a composite of cardiac death, TV-MI, and clinically-driven TLR

All events were adjudicated by an independent clinical event committee.

In both trials DAPT was prescribed per local recommendations and in keeping with guidelines.

Methods

Statistical analysis: Endpoints were harmonized between both registries. Variables were controlled to ascertain correct pooling of all variables where possible. Kaplan-Meier estimates at the indicated time points are displayed.

Additionally, predictors of TLF were assessed.

Results – Baseline characteristics

	N=3614
Age (yrs)	63.5± 11.2
Female	861 (23.8)
Diabetes Mellitus	1050 (29.3)
Insulin treatment	272 (7.5)
Hypertension	2422 (67.0)
Hypercholesterolemia	2101 (58.1)
Family history of CAD	1107 (30.6)
Congestive heart failure	224 (6.2)
Chronic renal failure	231 (6.4)
Peripheral Vascular disease	212 (5.9)
Previous stroke	173 (4.8)
Prior myocardial infarction	858 (23.7)
Previous PCI	966 (26.7)
Previous CABG	206 (5.7)
Current smoker	1009 (27.9)
Indication for PCI	
asymptomatic	295 (8.2)
stable angina	1346 (37.2)
STEMI	789 (21.8)
NSTEMI	600 (16.6)
unstable angina	576 (15.9)
other	6 (0.2)

CAD: coronary artery disease. PCI: percutaneous coronary intervention. CABG: coronary artery bypass graft. STEMI: ST-segment elevated myocardial infarction. NSTEMI: non-ST-segment elevated myocardial infarction.

Results – Baseline characteristics

	N=3614
Age (yrs)	63.5± 11.2
Female	861 (23.8)
Diabetes Mellitus	1050 (29.3)
Insulin treatment	272 (7.5)
Hypertension	2422 (67.0)
Hypercholesterolemia	2101 (58.1)
Family history of CAD	1107 (30.6)
Congestive heart failure	224 (6.2)
Chronic renal failure	231 (6.4)
Peripheral Vascular disease	212 (5.9)
Previous stroke	173 (4.8)
Prior myocardial infarction	858 (23.7)
Previous PCI	966 (26.7)
Previous CABG	206 (5.7)
Current smoker	1009 (27.9)
Indication for PCI	
asymptomatic	295 (8.2)
stable angina	1346 (37.2)
STEMI	789 (21.8)
NSTEMI	600 (16.6)
unstable angina	576 (15.9)
other	6 (0.2)

> 50% ACS

CAD: coronary artery disease. PCI: percutaneous coronary intervention. CABG: coronary artery bypass graft. STEMI: ST-segment elevated myocardial infarction. NSTEMI: non-ST-segment elevated myocardial infarction.

Results – Lesion characteristics

	n= 4445
Pre-procedure reference vessel diameter, mm	3.1±1.5
Lesion length, mm	19.4±11.2
Diameter stenosis pre-procedure	86.7±17.7
Thrombus present	624 (14.0)
If yes, was thrombus aspirated?	334 (53.5)
TIMI flow pre procedure	
TIMI 0	629 (14.2)
TIMI I	350 (7.9)
TIMI II	649 (14.7)
TIMI III	2787 (63.1)
Predilatation	2993 (67.4)

Location of lesion: RCA	1354 (30.5)
LAD	1682 (37.9)
LCX	1305 (29.3)
LMCA	79 (1.8)
Graft	24 (0.5)
AHA/ACC lesion classification: A	479 (11.0)
B1	1393 (32.0)
B2	1672 (38.4)
C	811 (18.6)
Total stent length	22.7±11.3
Final diameter stenosis	2.8±12.5
TIMI flow III post procedure	4343 (98.9)

Values are N (valid %) and mean ±SD. RCA: right coronary artery, LAD: left anterior descending artery, LCx: left circumflex artery, LMCA: left main coronary artery.

Results – Lesion characteristics

	n= 4445
Pre-procedure reference vessel diameter, mm	3.1±1.5
Lesion length, mm	19.4±11.2
Diameter stenosis pre-procedure	86.7±17.7
Thrombus present	624 (14.0)
If yes, was thrombus aspirated?	334 (53.5)
TIMI flow pre procedure	
TIMI 0	629 (14.2)
TIMI I	350 (7.9)
TIMI II	649 (14.7)
TIMI III	2787 (63.1)
Predilatation	2993 (67.4)

Location of lesion: RCA	1354 (30.5)
LAD	1682 (37.9)
LCX	1305 (29.3)
LMCA	79 (1.8)
Graft	24 (0.5)
AHA/ACC lesion classification: A	479 (11.0)
B1	1393 (32.0)
B2	1672 (38.4)
C	811 (18.6)
Total stent length	22.7±11.3
Final diameter stenosis	2.8±12.5
TIMI flow III post procedure	4343 (98.9)

> 50% B2/C

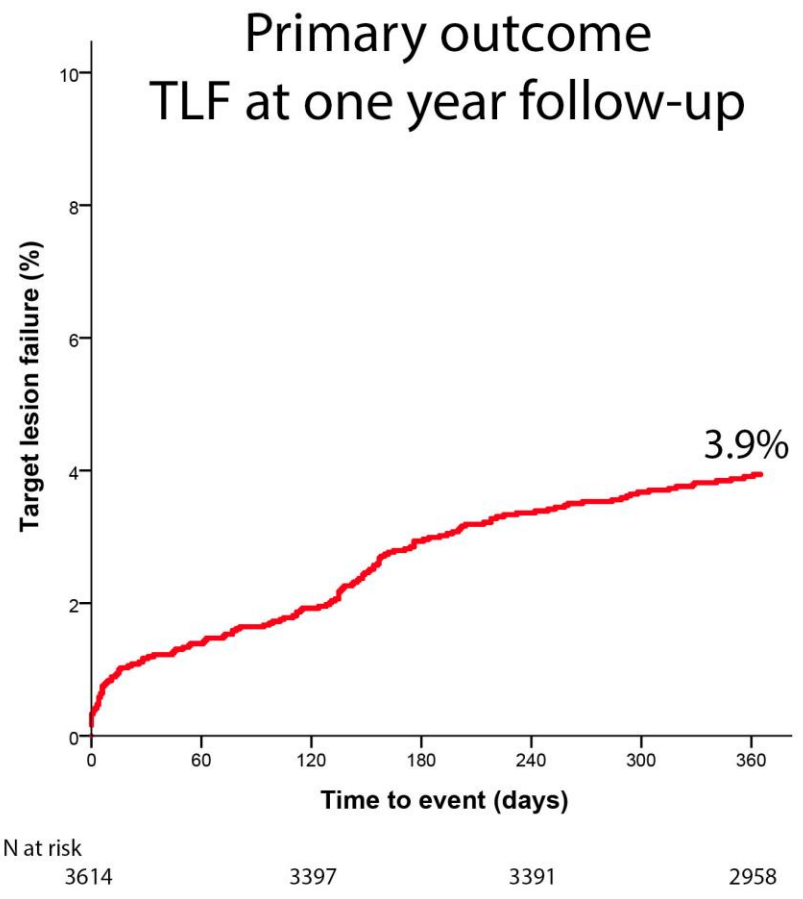
Values are N (valid %) and mean ±SD. RCA: right coronary artery, LAD: left anterior descending artery, LCx: left circumflex artery, LMCA: left main coronary artery.

Results – Primary endpoint

TLF at 1-year follow-up was observed in 140 patients (3.9%)

TLF defined as:

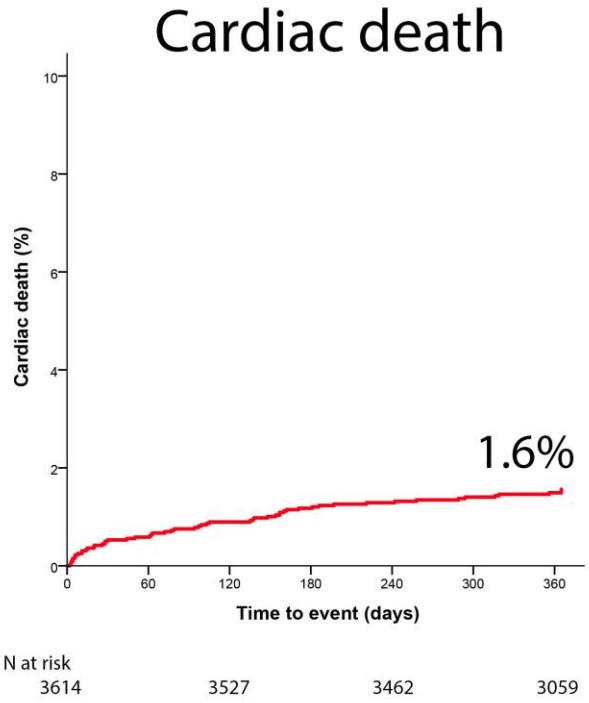
Cardiac death, TV-MI* and clinically driven TLR

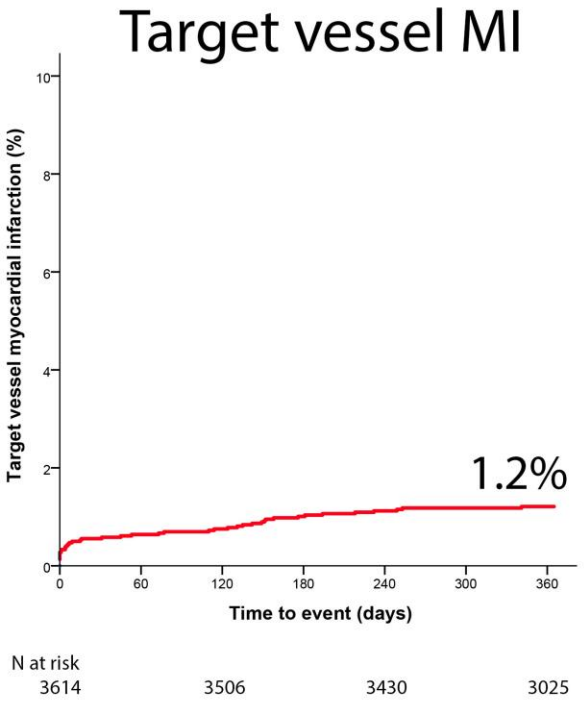


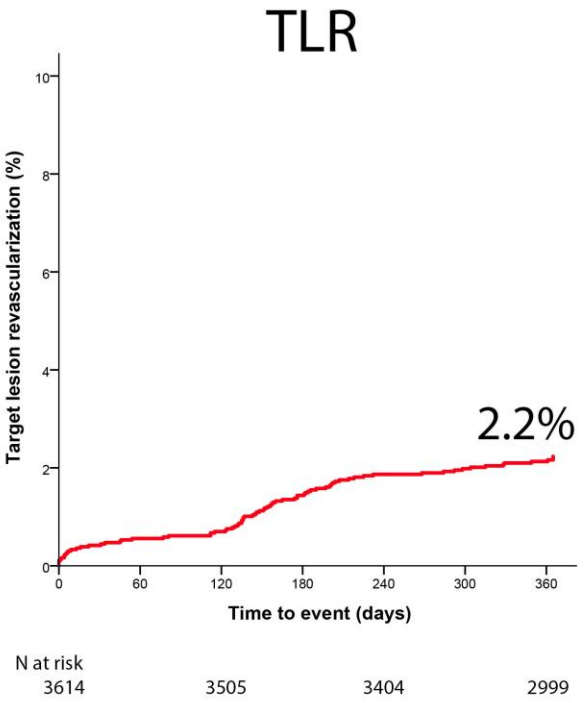
***Third universal definition, including periprocedural MI.**

Thygesen K et al. Third Universal Definition of Myocardial Infarction. *J Am Coll Cardiol*. 2012;60(16):1581-1598. In both registries periprocedural cardiac biomarkers were not routinely obtained.

Results – Secondary endpoints







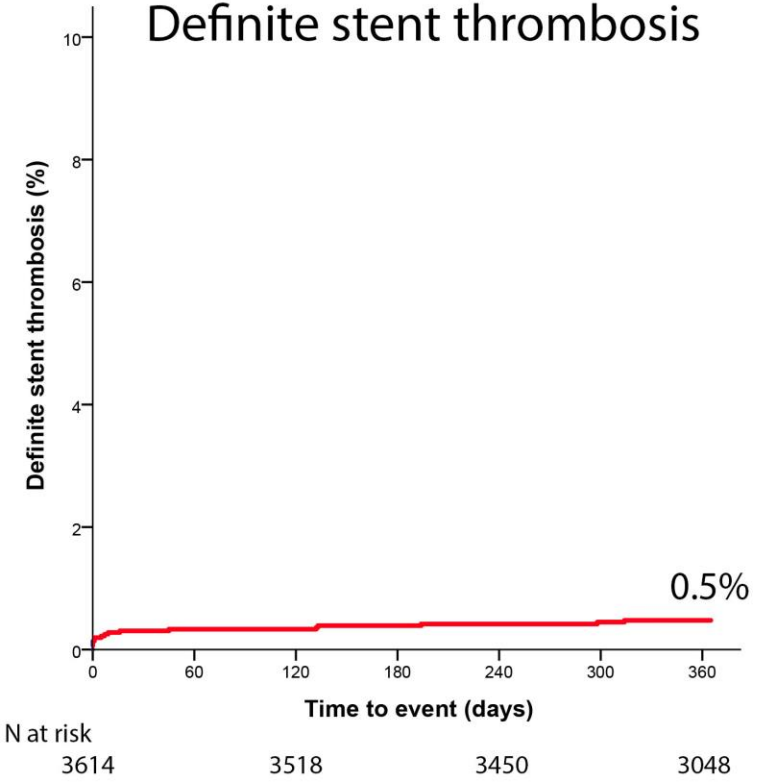
Results – Secondary endpoint

Very low definite ST rate:

0.5% (n=17) at 1 year follow-up

Definite or probable ST rate:

0.8% (n=30) at 1 year follow-up



Results – Predictors of TLF univariate

PARIS thrombotic risk score model*		Univariate	Multivariate
Diabetes mellitus	DM versus non-DM	1.32 (0.93-1.87) p=0.12	
	ITDM vs all others	2.08 (1.30-3.34) p<0.01	1.85 (1.14-3.01) p=0.01
Acute coronary syndrome	ACS vs non-ACS	1.36 (0.97-1.91) p=0.08	
	trop+ ACS vs all others	1.40 (1.01-1.96) p=0.05	ns
Current smoking		1.15 (0.80-1.65) p=0.46	
Prior PCI		1.30 (0.91-1.85) p=0.15	
Prior CABG		1.84 (1.06-3.19) p=0.03	ns
Chronic renal failure		2.19 (1.34-3.59) p<0.01	2.07 (1.25-3.43) p<0.01

Additional risk factors		Univariate	Multivariate
Female sex		0.99 (0.67-1.46) p=0.94	
Advanced age	>65 years vs ≤65 years	1.41 (1.01-1.97) p=0.04	ns
Hypertension		0.76 (0.56-1.11) p=0.17	
Peripheral vascular disease		1.97 (1.15-2.27) p=0.01	ns
Prior MI		1.38 (0.96-1.98) p=0.08	
Total stent length	>30mm vs ≤30 mm	1.09 (0.75-1.60) p=0.64	
At least 1 B2/C lesion*		1.96 (1.34-2.86) p<0.01	1.94 (1.33-2.85) p<0.01

PCI: percutaneous coronary intervention. CABG: coronary bypass graft. MI: myocardial infarction . **American College of Cardiology/American Heart Association lesion classification.

*PARIS risk scores: Baber U, et al. J Am Coll Cardiol. 2016;67(19):2224-2234.

Results – Predictors of TLF multivariate

PARIS thrombotic risk score model*		Univariate	Multivariate
Diabetes mellitus	DM versus non-DM	1.32 (0.93-1.87) p=0.12	
	ITDM vs all others	2.08 (1.30-3.34) p<0.01	1.85 (1.14-3.01) p=0.01
Acute coronary syndrome	ACS vs non-ACS	1.36 (0.97-1.91) p=0.08	
	trop+ ACS vs all others	1.40 (1.01-1.96) p=0.05	ns
Current smoking		1.15 (0.80-1.65) p=0.46	
Prior PCI		1.30 (0.91-1.85) p=0.15	
Prior CABG		1.84 (1.06-3.19) p=0.03	ns
Chronic renal failure		2.19 (1.34-3.59) p<0.01	2.07 (1.25-3.43) p<0.01

Additional risk factors		Univariate	Multivariate
Female sex		0.99 (0.67-1.46) p=0.94	
Advanced age	>65 years vs ≤65 years	1.41 (1.01-1.97) p=0.04	ns
Hypertension		0.76 (0.56-1.11) p=0.17	
Peripheral vascular disease		1.97 (1.15-2.27) p=0.01	ns
Prior MI		1.38 (0.96-1.98) p=0.08	
Total stent length	>30mm vs ≤30 mm	1.09 (0.75-1.60) p=0.64	
At least 1 B2/C lesion**		1.96 (1.34-2.86) p<0.01	1.94 (1.33-2.85) p<0.01

PCI: percutaneous coronary intervention. CABG: coronary bypass graft. MI: myocardial infarction. **American College of Cardiology/American Heart Association lesion classification.

ITDM, CKD and at least 1 B2/C lesion are predictors of 1-year TLF

*PARIS risk scores: Baber U, et al. J Am Coll Cardiol. 2016;67(19):2224-2234.

Conclusions

- In this largest cohort of patients (from two prospective independent registries; n=3614) treated with a novel bioengineered dual therapy stent:
- The COMBO stent was found safe (def/prob ST 0.8%) and effective (TLF 3.9%) at ONE year follow-up
- Future randomized trials should test safety and effectiveness of this novel stent compared to current third generation DES

COMBO Collaborators

Antonio Colombo, MD
Roxana Mehran, MD
Usman Baber, MD
George D. Dangas, MD, PhD
Robbert J. de Winter, MD, PhD
Jan G. Tijssen, PhD
Karel T. Koch, MD, PhD
Pier Woudstra, MD
Marcel A. Beijk, MD, PhD
Melissa B. Aquino, MS
Samantha Sartori, PhD
Jaya Chandrasekhar, MBBS, MS
Deborah N. Kalkman, MD

On behalf of all MASCOT and REMEDEE registry investigators