How Can COMBO Benefit AMI Patients?

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Speaker's name : Joshua, LOH, Singapore

☑ I have the following potential conflicts of interest to report:

:

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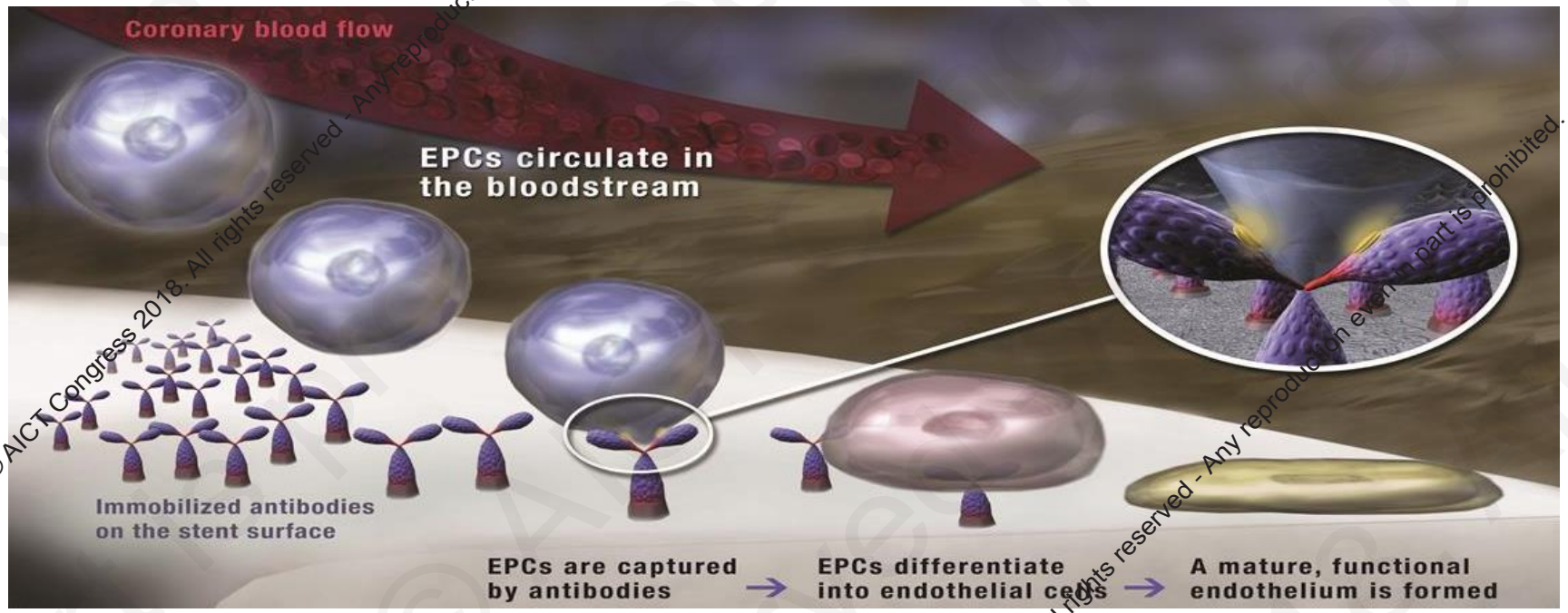
Rationale for using EPC Capture Stent in Primary PCI for STEMI

- Stenting in primary PCI occurs in a highly thrombotic milieu. Risk of delayed endothelial healing with DES. [1] Rapid restoration of functional endothelium may minimize risk of ST.
- EPCs are mobilized in large numbers from bone marrow during STEMI and peak at day 7. [2] Implanting stent with EPC capture will optimally harness the increased levels and improve endothelial healing.
- During primary PCI, it is difficult to fully ascertain patient's suitability for prolonged DAPT (bleeding risk, drug compliance, need for urgent non-cardiac surgery). [3] EPC capture may be safer in early DAPT interruption or short DAPT duration.

1. Nakazawa G. *Circulation* 2008; **118**:1138-1145
2. Shintani S. *Circulation* 2001; 103:2776-2779
3. Latry P. *Eurointervention* 2012; **7**:1413-1419

Rationale for using EPC Capture Stent in Primary PCI for STEMI



- Early restoration of functional endothelium may be beneficial, especially in STEMI

Endothelial progenitor cell capture stent implantation in patients with ST-segment elevation acute myocardial infarction: one-year follow-up

Yian-Ping Lee[1], M… C; Adrian Low[1], MBBS, MRCP; Swe… e-Tiong Yeo[1], MBBS, MRCP; Jim… , MBBS, FACC; Huay Cheem Tan[1]*

1. National University …

20 YEARS OF INNOVATION 1988-2008 TCT 2008 TRANSCATHETER CARDIOVASCULAR THERAPEUTICS

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Antibody-coated Stent Shows Promising Results at One Year

Endothelial progenitor cell-capturing stent could reduce restenosis without the need for prolonged dual-antiplatelet therapy.

ABSTRACT

New stent technology that promotes accelerated endothelial healing has shown promising clinical results, raising hopes that restenosis can be avoided without increasing the risk of stent thrombosis, according to the results of two separate studies presented here.

The studies evaluated the safety and efficacy of endothelial progenitor cell-capturing stents, which are coated with an antibody that helps promote rapid endothelialization by capturing circulating endothelial progenitor cells.

Accelerated endothelialization is thought to reduce restenosis by inhibiting neointimal hyperplasia and smooth muscle cell proliferation. It may also reduce the risk of thrombosis by restoring a functional endo-

turing stents in patients with STEMI who underwent primary percutaneous coronary intervention had a low complication rate and good clinical outcomes. The patients received dual antiplatelet therapy for one month.

Lead investigator **Tan Huay-Cheem, MD,** of National University Hospital, and colleagues enrolled 321 patients with acute STEMI undergoing primary PCI between January 2005 and April 2007. All patients were implanted with the EPC-capturing stent and followed for one year.

The study endpoints were major adverse coronary events defined as death, MI, and target lesion revascularization. Researchers reported that at one year there were three reported cases of stent thrombosis (0.9%), 42 cases of MACE (13.1%), 24 deaths (7.5%), 12 recurrent MIs (3.7%), and 16 target vessel revascu-

tion in patients with STEMI … at one year with comparable rates of target vessel revascularization compared with published series using drug-eluting stents," Lee said. "Yet there is no safety concern, such as late stent thrombosis [found with] drug-eluting stents, with no reported incidence of late stent thrombosis in our largest world registry to date investigating the use of this stent in patients with STEMI."

The researchers are nearing completion of a follow-up study of a cohort of 100 asymptomatic patients who have undergone PCI. This study is expected to determine the late loss and patterns of in-stent restenosis with the EPC-capture stent in STEMI patients.

EPC-capturing stent in patients with complex lesions

In a separate study, researchers from Amsterdam found that patients implanted with the Genous EPC-capturing stent (OrbusNeich, Hong Kong) showed excellent clinical outcomes at 1 year and did not …long-term

died (0.8% from coronary causes), 2.5% suffered an MI, and 9.7% had target vessel revascularization; definite stent thrombosis was reported in 1.2% of cases. The cumulative rate of major adverse coronary events was 11.4% at one year.

"Our one-year follow-up single-center registry of patients treated with the EPC-capturing stent shows surprisingly good results," **Marco Klomp, MD,** one of the researchers from the Academic Medical Center Amsterdam, said in an interview. "We were therefore … content with the excellent findings in this challenging subset of patients with complex lesions, [including] bifurcational lesions, multivessel disease, and lesions located in the left main coronary artery.

The EPC-capturing stent technology could reduce the need for patients to be on long-term dual-antiplatelet therapy, which has been associated with increased risk of bleeding, following implantation with a drug-eluting stent, Klomp said.

"This is a small study, but results are promising. The eHEALING (Healthy EndotheliAl Lining Inhibits Neointimal Growth) worldwide registry is currently being conducted and the one-year preliminary results of approximately 3,000 pa-

roIntervent 2010

Use of endothelial progenitor cell capture stent (Genous Bio-Engineered R Stent) during primary percutaneous coronary intervention in acute myocardial infarction: Intermediate- to long-term clinical follow-up

Melissa Co, MD,[a] Edgar Tay, MBBS, MRCP,[a] Chi Hang Lee, MBBS, MRCP,[a] Kian Keong Poh, MBBChir, MRCP,[a] Adrian Low, MBBS, MRCP,[a] Jimmy Lim, MBBS, MRCP,[b] Ing Han Lim, MBBS, MRCP,[b] Yean Teng Lim, MBBS, FRCP,[a] and Huay Cheem Tan, MBBS, FRCP[a] *Singapore, Singapore*

Am Heart J 2008

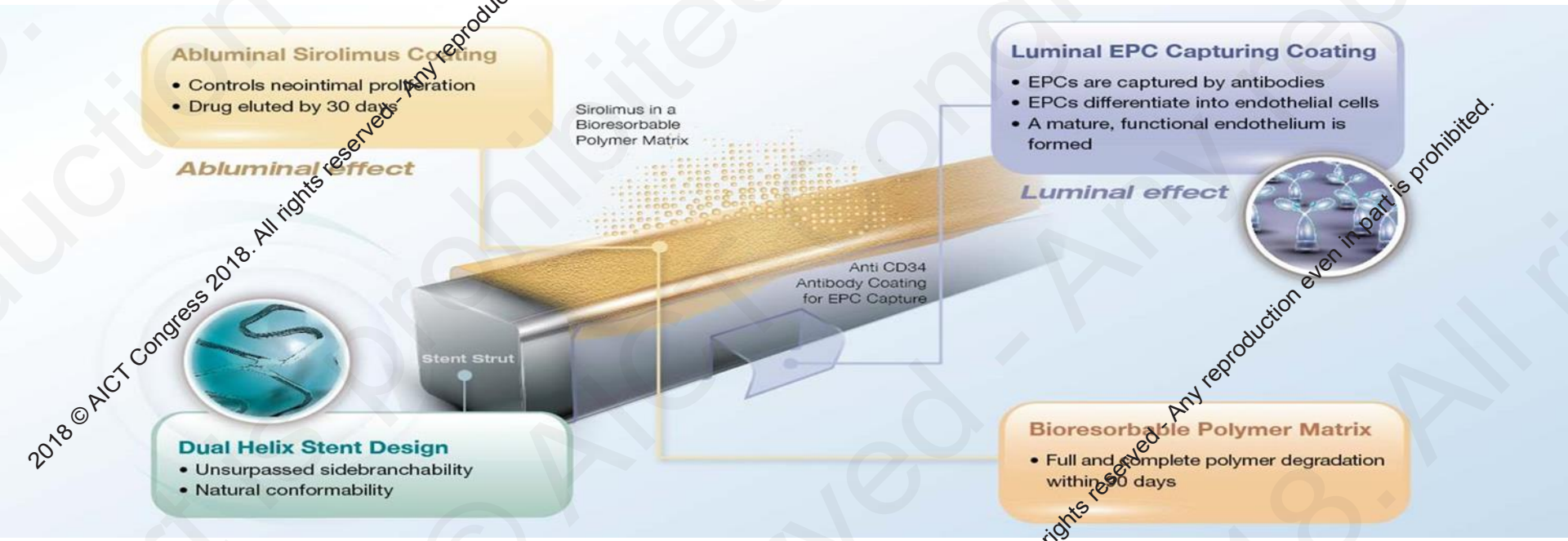
Three-Year FU of Patients with STEMI who Received EPC Capture Stent while undergoing PPCI

- 384 pts who received 465 EPC capture stents (1.2 stents/pt)
- 33.1% had diabetes; mean stent length was 21.04±5.6mm and
- Mean stent diameter was 3.0±0.3mm.
- Dual antiplatelet therapy for 1 mth

	1 Yr	2 Yr	3Yr
Death	25 (6.5%)	26 (6.8%)	27 (7.1%)
MI	14 (3.6%)	16 (4.2%)	18 (4.6%)
TVR	28 (7.2%)	35 (9.1%)	39 (10.2%)
Stent thrombosis	5 (1.3%)	5 (1.3%)	5 (1.3%)
MACE	61(15.9%)	70 (18.2%)	77 (20.1%)

R Sethi, HC Tan et al ESC 2011

EPC Capture with Sirolimus Drug Elution – Dual Therapy Stent



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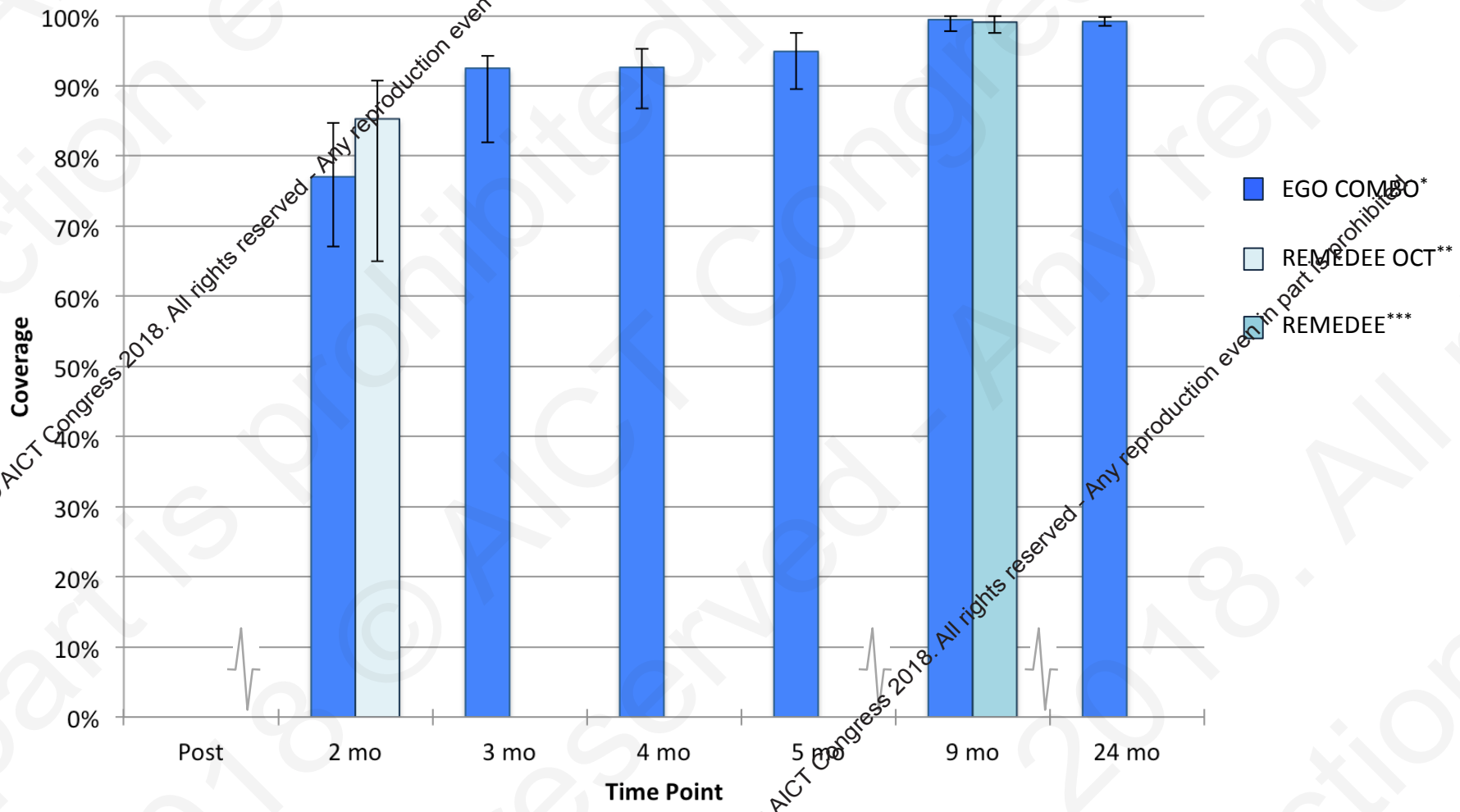
Combo Strut Coverage % (OCT)

Median & IQR (per patient)

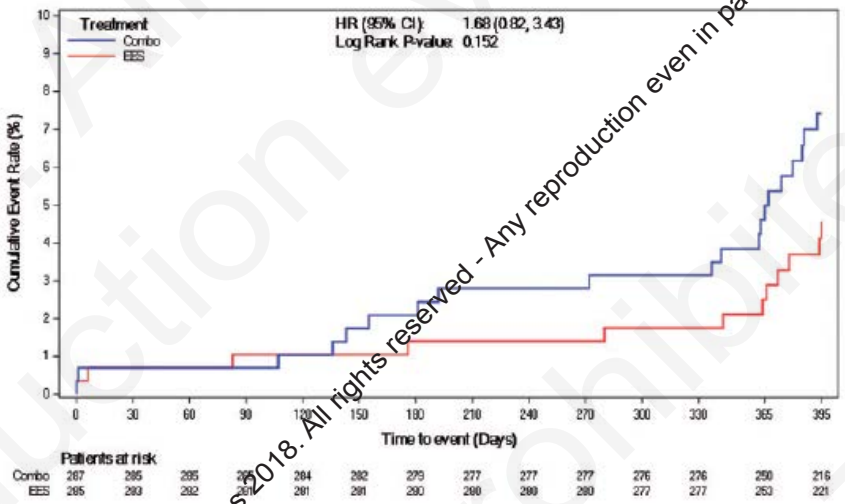


* S. Lee, TCTAP 2014,Lee S, Maehara A et al. *Circ Cardiovasc Interv*. 2016;9:e003469

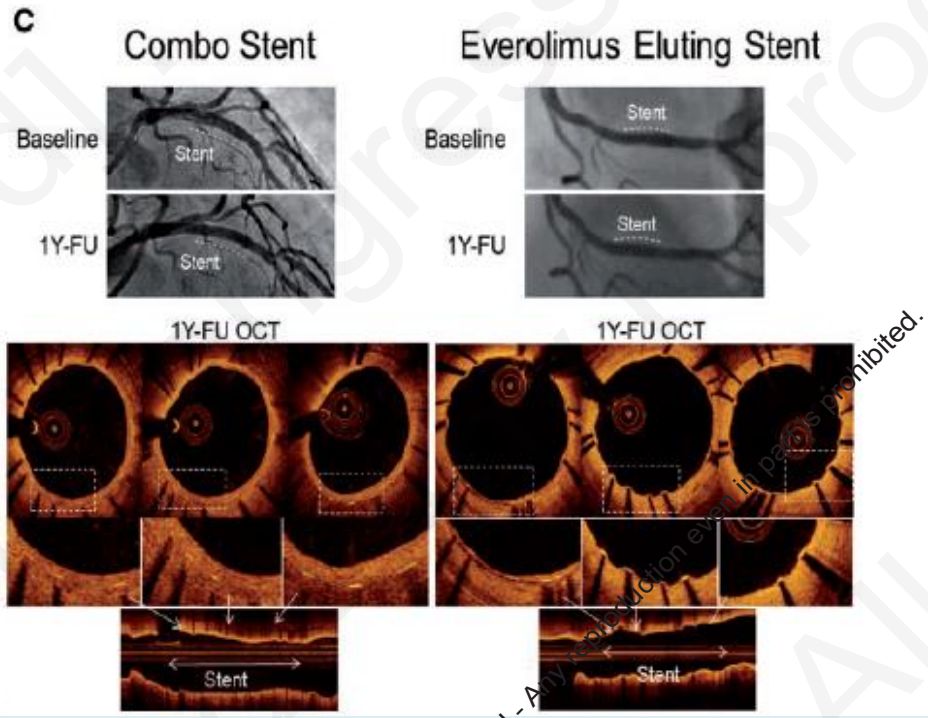
** U. Landmesser, TCT 2012

*** M. Haude, EuroPCR 2012

HARMONEE study: OCT endpoints



Combo demonstrated non-inferior TVF at 1 year compared to **EES**



Combo demonstrated superior healthy tissue strut coverage at 1 year compared to **EES**

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)	

Saito S. *Eur Heart J 2018*; 39:2460-68

The COMBO dual therapy stent in patients presenting with acute ST-elevation myocardial infarction: a one-year follow-up study

Rajiv Ananthakrishna, MD, DM; William Kristanto, MBBS; Li Liu, MD; Yoay Huan Loh, MB, BCh; Edgar L. Tay, MBBS; Koo Hui Chan, BM, MD; Mark Y. Chan, MBBS, MHS; Chi-Hang Lee, MBBS, MD; Adrian F. Low, MBBS; Huay Cheem Tan, MBBS; Joshua P. Loh*, MBBS

Department of Cardiology, National University Heart Centre, Singapore, Singapore

- Prospective registry (Nov 2013)
- Inclusion: All-comer unrestricted STEMI patients undergoing primary PCI
- Device: COMBO stent implanted during index Primary PCI
- Primary endpoint: TLF (Cardiac death, TVMI, clinically driven TLR) at 1 year

AsiaIntervention 2017;3:21-27

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Results

Device delivery success: 100%

Procedural success (Final TIMI 2/3 flow): 100%

Table 3. Clinical outcomes at 30 days, 6 months, and 12 months.

	1 month (n=117)	6 months (n=117)	12 months (n=117)
Death	4 (3.4%)	4 (3.4%)	6 (5.1%)
Cardiac death	4 (3.4%)	4 (3.4%)	5 (4.3%)
MI	2 (1.7%)	3 (2.6%)	4 (3.4%)
TVMI	2 (1.7%)	3 (2.6%)	3 (2.6%)
Definite ST	2 (1.7%)	3 (2.6%)	3 (2.6%)
Definite/probable ST	4 (3.4%)	5 (4.3%)	5 (4.3%)
TLR	2 (1.7%)	4 (3.4%)	4 (3.4%)
TVR	2 (1.7%)	4 (3.4%)	4 (3.4%)
TLF	6 (5.1%)	8 (6.8%)	9 (7.7%)
MACE	6 (5.1%)	8 (6.8%)	11 (9.4%)

Values are n (%). MACE: major adverse cardiac events; MI: myocardial infarction; TLF: target lesion failure; TLR: target lesion revascularisation; TVMI: target vessel myocardial infarction; TVR: target vessel revascularisation; ST: stent thrombosis.

NUHCS Combo AMI Extended Cohort

- Prospective registry
- Recruited from 1 Nov 2013 – 31 Dec 2016 (37 months)
- Inclusion: All-comer unrestricted STEMI patients undergoing primary PCI
- Device: COMBO stent implanted during index Primary PCI
- Primary endpoint : TLF (Cardiac death, TVMI, clinically driven TLR)
- Time points: in-hospital, 1 month, 1 year and longer term
- Median follow up : 704 days (IQR : 388-1043) [=23.4 months]

Sim HW, Tan HC, Loh JP et al. In review.

Results

Baseline demographics

Variables	Patients (n = 260)
Age (years)	56.1 +/- 11.2
Male	231 (88.8)
Hypertension	107 (41.2)
Diabetes mellitus	82 (31.5)
Dyslipidaemia	172 (66.2)
Smoker	139 (53.5)
CVA	11 (4.2)
PVD	8 (3.1)
COPD	2 (0.8)
CKD	10 (3.8)
Prior AMI	39 (15.0)
Prior PCI	17 (6.5)
Prior CABG	8 (3.1)

Sim HW, Tan HC, Loh JP et al. In review.

Results

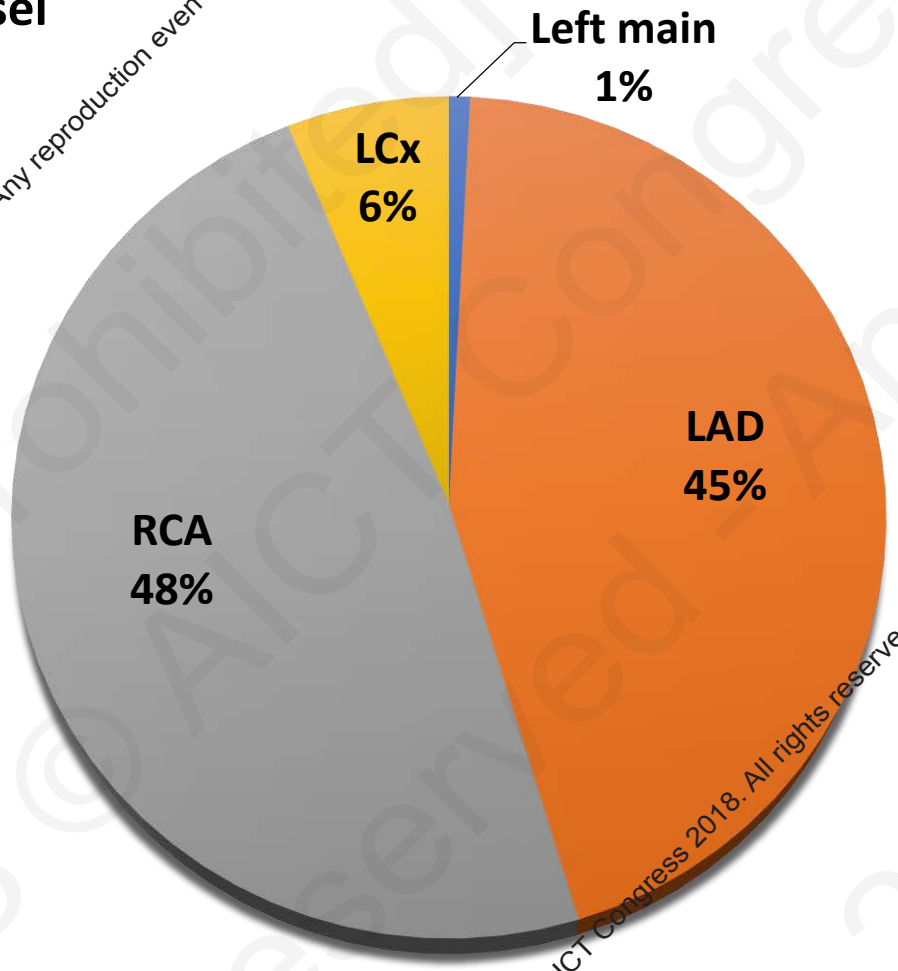
Clinical presentation

Variables	Patients (n = 260)
Cardiogenic shock	28 (10.9)
Ventilated	19 (7.3)
Anterior STEMI	116 (44.6)
Systolic Bp (mmHg)	125.3 ± 27.9
Diastolic Bp (mmHg)	77.8 ± 16.4
Heamoglobin (g/dL)	15.2 ± 5.7
Creatinine (mmol/L)	88.0 ± 41.3
Antiplatelet	
Clopidogrel	42 (16.2)
Ticagrelor	40 (15.4)
Prasugrel	178 (68.5)

Sim HW, Tan HC, Loh JP et al. In review.

Results

Culprit vessel



Sim HW, Tan HC, Loh JP et al. In review.

Results

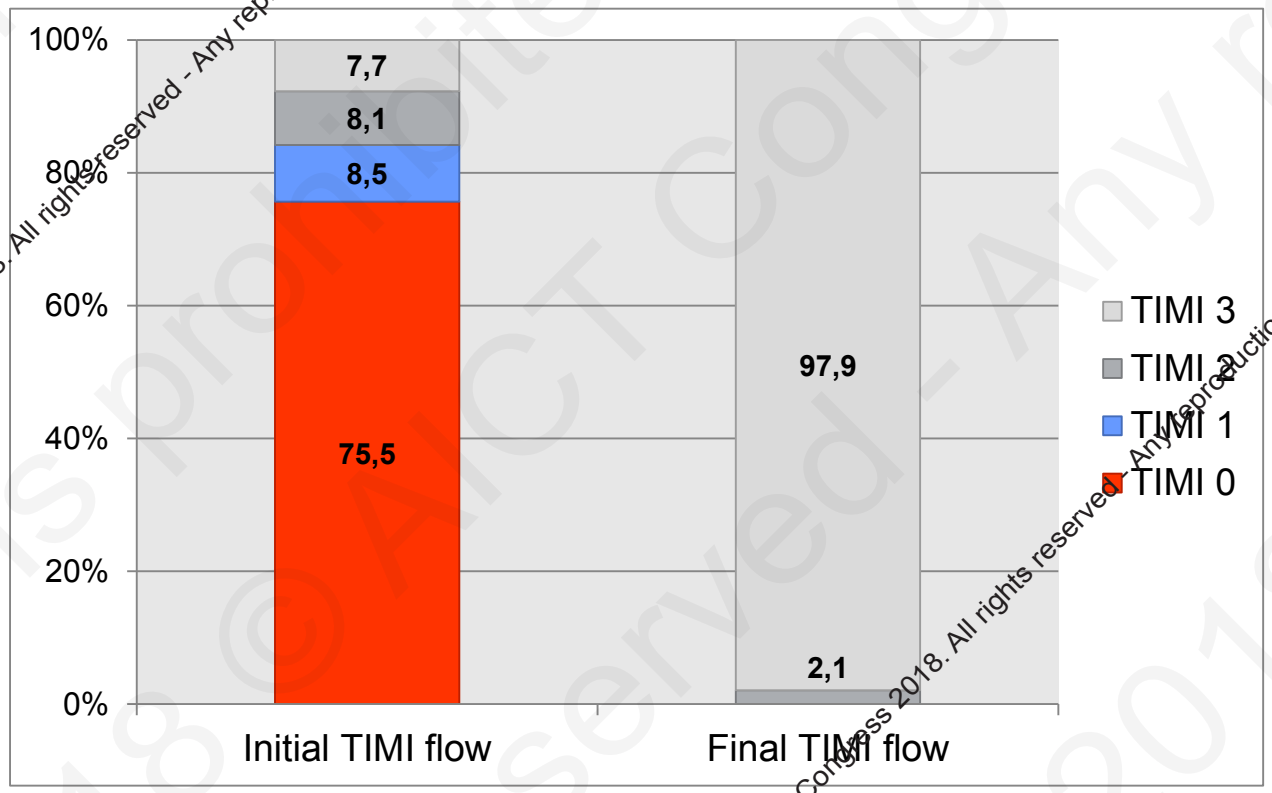
Procedural Characteristics

Variables	Patients (n =260) Lesions (n=284)
Radial Puncture	136 (52.3)
IABP usage	20 (7.7)
Thrombectomy	206 (79.2)
GP IIb/IIIa usage	38 (14.6)
Contrast amount (ml)	99.4 ± 34.4
Direct stenting	164 (63.1)
Overlapping stents	34 (13.1)
Mean no stents/patient	1.2 ± 0.4
Mean no stents/lesion	1.1 ± 0.3
Lesion length (mm)	21.8 ± 10.0
Average stent length (mm)	21.8 ± 6.5
Average stent diameter (mm)	3.01 ± 0.36

Sim HW, Tan HC, Loh JP et al. In review.

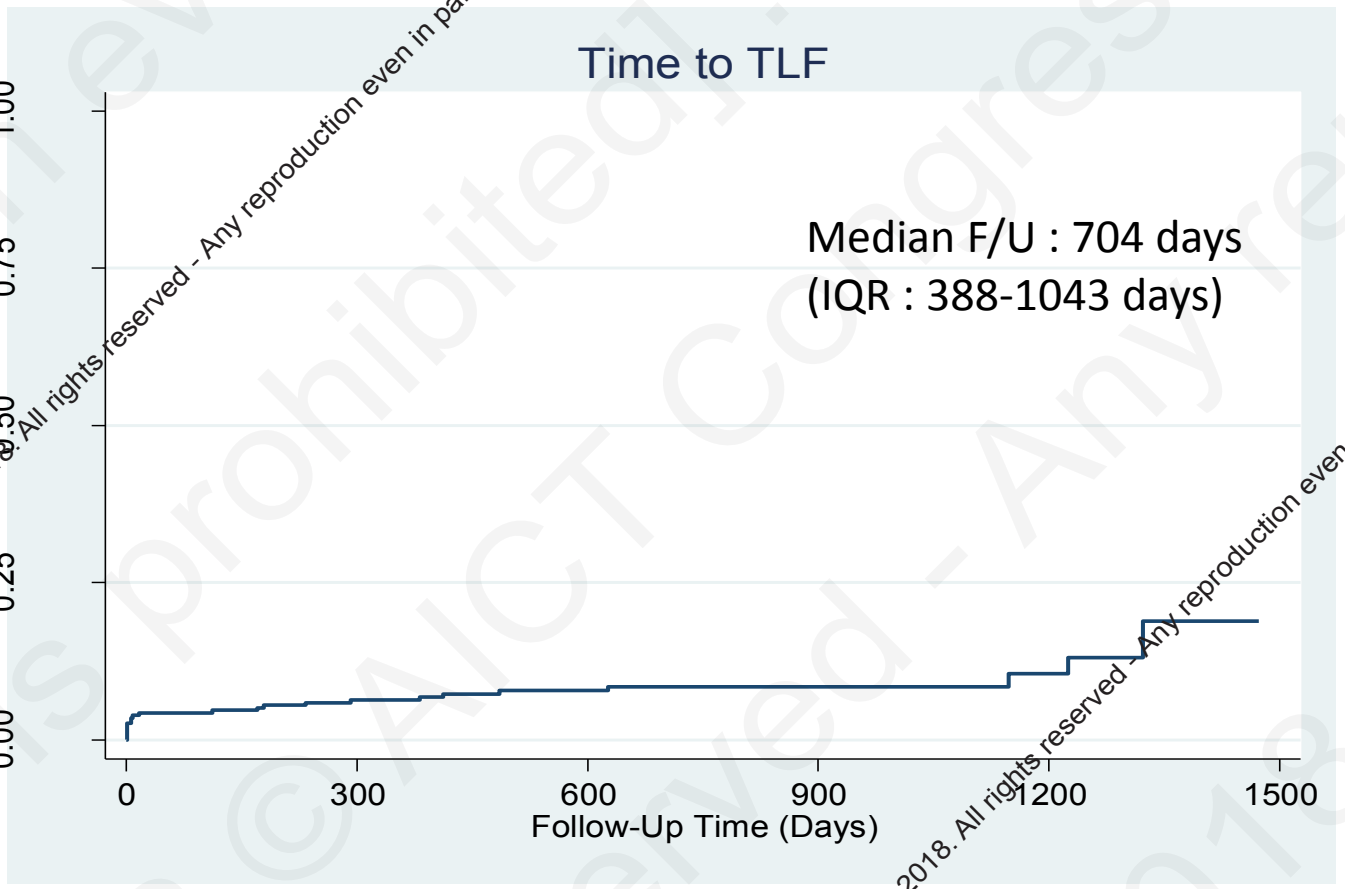
Results

- Device delivery success: 100%
- Procedural success (Final TIMI 2/3 flow): 100%



Sim HW, Tan HC, Loh JP et al. In review.

Results



	In-hospital	1 month	1 year	Longer term (median 23.4 months)
TLF	**9 (3.5%)**	**10 (3.8%)**	**17 (6.5%)**	**23 (8.8%)**

Sim HW, Tan HC, Loh JP et al. In review.

Results

Clinical Outcomes – Whole cohort

	In-hospital (n = 260)	1 month (n = 260)	1 year (n = 260)	Longer term 23.4 mths (n=260)
Death	7 (2.7)	7 (2.7)	11 (4.2)	13 (5.0)
Cardiac death	7 (2.7)	7 (2.7)	10 (3.8)	11 (4.2)
MI	3 (1.2)	4 (1.5)	8 (3.1)	12 (4.6)
TV-MI	3 (1.2)	3 (1.2)	6 (2.3)	9 (3.4)
Definite / Probable ST	3 (1.2)	5 (1.9)	6 (2.3)	7 (2.7)
Definite ST	3 (1.2)	3 (1.2)	4 (1.5)	5 (1.9)
TLR	3 (1.2)	3 (1.2)	6 (2.3)	10 (3.8)
TVR	3 (1.2)	3 (1.2)	7 (2.7)	12 (4.6)
TLF	9 (3.5)	10 (3.8)	17 (6.5)	23 (8.8)
MACE	9 (3.5)	11 (4.2)	20 (7.7)	28 (10.8)

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Results

Multivariate Cox regression model for TLF

Variables	Adjusted HR	95% CI	p-value
Cardiogenic shock	4.881	1.877-12.694	0.001
Anterior MI	0.822	0.306-2.212	0.698
Age	1.044	0.995-1.096	0.081
Diabetes	0.900	0.314-2.580	0.844
Clopidogrel use	0.385	0.082-1.793	0.224
Lesion length	0.991	0.944-1.041	0.732
Post reference vessel diameter	0.731	0.226-2.362	0.731

HR = hazard ratio; CI = confidence interval; MI = myocardial infarction

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Results

Excluding cardiogenic shock

	In-hospital (n = 232)	1 month (n = 232)	1 year (n = 232)	Longer term 23.4 mths (n = 232)
Death	0 (0)	2 (0.8)	4 (1.7)	5 (2.2)
Cardiac death	0 (0)	2 (0.8)	3 (1.3)	4 (1.7)
MI	1 (0.4)	3 (1.3)	7 (3.0)	11 (4.7)
TV-MI	1 (0.4)	2 (0.8)	5 (2.2)	8 (3.4)
Definite / Probable ST	2 (0.8)	4 (1.7)	5 (2.2)	6 (2.6)
Definite ST	2 (0.8)	2 (0.8)	3 (1.3)	4 (1.7)
TLR	1 (0.4)	2 (0.8)	5 (2.2)	9 (3.9)
TVR	1 (0.4)	2 (0.8)	6 (2.6)	11 (4.7)
TLF	1 (0.4)	4 (1.7)	9 (3.9)	15 (6.5)
MACE	1 (0.4)	5 (2.2)	13 (5.6)	19 (8.2)

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Stent thrombosis

	Demo-graphics	Treated lesions	Timing of ST	Predisposing factors	Angiographic findings	Treatment
1	58 M LVEF 55%	pRCA 3.5 x 33mm	Definite ST Acute <1 hour	Non-absorption of antiplatelet due to vomiting and hypotension	Thrombus at stented segments	Thrombus aspiration, POBA, GPIIb/IIIa
2	61 M LVEF 60%	dRCA 2.5 x 13mm	Definite ST Acute <1 hour		OCT : thrombus at stented segment with stent underexpansion	Thrombus aspiration and further post dilatation to stent
3	70 M LVEF 35%	pLAD 3.0 x 18mm	Definite ST Acute 2 hour	Heart failure, incomplete inhibition of platelet activation, probable clopidogrel resistance	IVUS : well expanded stent, no edge dissection of malapposition. MLA 5.2mm^2	Thrombus aspiration, GPIIb/IIIa, change to ticagrelor
4	48 M LVEF 50%	dRCA 3 x 33mm	Definite ST Late 6 months	Drug non compliance DM	Focal ISR with superimposed thrombus	DEB
5	55 M LVEF 60%	m-dRCA 2.5 x 18mm + 3.5 x 18mm	Definite ST Very late 3 years	Still smoking	Thrombus segment proximal to stent with severe ISR of stent	Stented with 3.5 X 16mm Synergy II DES
6	58 M LVEF 25%	pLAD 2.5 x 23mm	Probable ST (death) Subacute 15 days	Low LVEF DM, small vessel disease	NA	NA
7	62 M LVED 35%	pLAD 3.5 x 33mm	Probable ST (death) Subacute 7 days	Low LVEF	NA	NA

Results

- Expanded cohort (n=260) with longer-term follow-up
- TLF occurred in 6.5% at 1-year, and 8.8% longer-term (23.4 months)
- TLR on our cohort was 2.3% at 1-year, and 3.8% longer-term (23.4 months)
- Definite ST of 1.5% at 1-year, and 1.9% longer-term (23.4 months)
- 100% device success rate

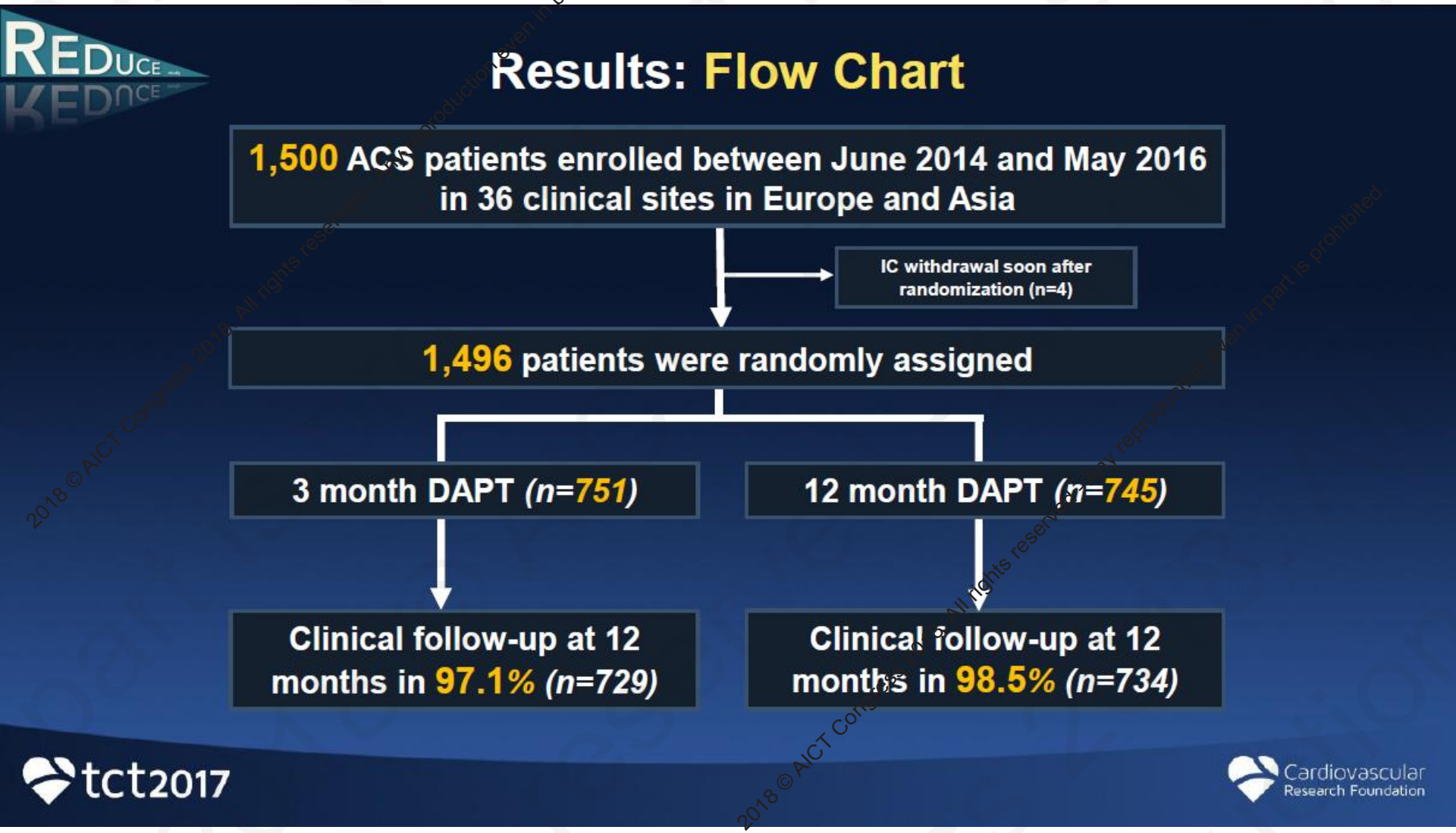
Sim HW, Tan HC, Loh JP et al. In review.

Comparison of 1-year clinical outcomes with current generation DES in STEMI

	NUHCS registry	Sudhir et al [1]	Tomai et al [2]
Stent	Combo Stent	Xience V	Bio-Matrix
N	260	125	311
TLF(%)	6.5	9.1	NR
TLR(%)	2.3	3.3	NR
MACE(%)	7.7	NR	3.2
Cardiac death(%)	3.8	3.3	2.3
Cardiogenic shock(%)	10.9	NR	3.8
ST (Definite / probable	2.3	0.85	0.96

1. *Catheter Cardiovasc Interv* 2013;82:E385-94 2. *Catheter Cardiovasc Interv* 2015;85:352-8

REDUCE (1500 ACS patients)



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REDUCE (1500 ACS patients)

Results: Baseline

Baseline Characteristics

	3 month DAPT n = 751	12 month DAPT n = 734	P
Age (Mean ± SD)	61.2 ± 11.6	60.5 ± 12.0	NS
Female Gender (%)	17.4	22.7	0.01
STEMI diagnosis	49.3	45.2	NS
Diabetes Mellitus (%)	21.6	19.5	NS
Smoking (%)	42.1	42.7	NS
Hypercholesterolemia (%)	46.3	44.9	NS
Hypertension (%)	50.7	50.7	NS
Family history of CAD (%)	35.0	36.0	NS
Previous ACS (%)	12.5	11.8	NS
Previous PCI (%)	11.7	9.8	NS

Angiographic Characteristics

	3 month DAPT n = 751	12 month DAPT n = 734	P
Radial access (%)	76.1	76.9	NS
Multivessel disease (%)	36.1	33.8	NS
Target vessel (%): - LAD	48.0	44.2	NS
- RCA	31.2	33.0	NS
- RCX	19.5	22.0	NS
Initial TIMI flow 3 (%)	46.6	49.0	NS
Thrombosuction (%)	12.5	13.6	NS
Total stent length (mm, mean ± SD)	25.5 ± 12.8	25.2 ± 12.7	NS
Procedural success (%)	99.3	99.7	NS
PCI additional segments (%)	20.3	21.9	NS

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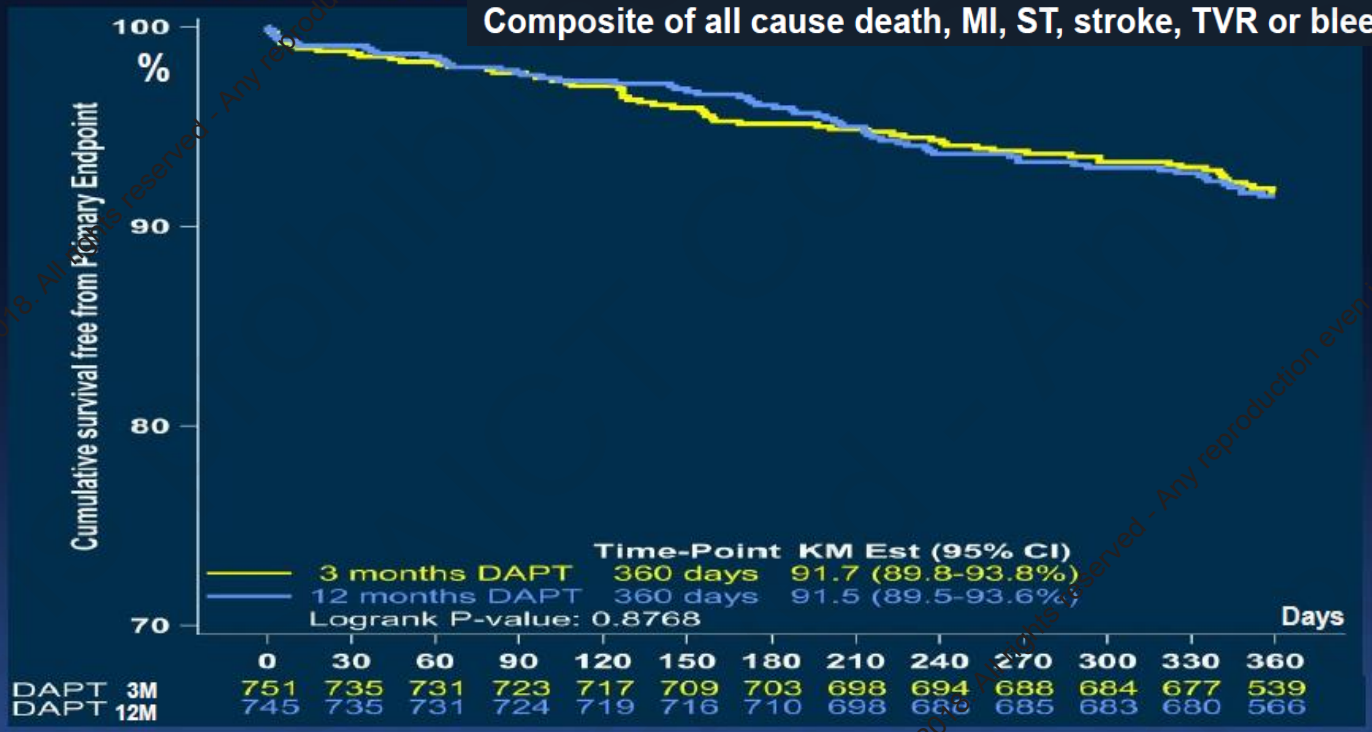
REDUCE (1500 ACS patients)

Results: Primary Study Endpoint

Composite of all cause death, MI, ST, stroke, TVR or bleeding *(BARC II, III, V)*



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

Confirmed by PP and AT analyses, and after adjustment for gender *(adjusted OR (95% CI) = 0.95 (0.66–1.38), p=0.81)*

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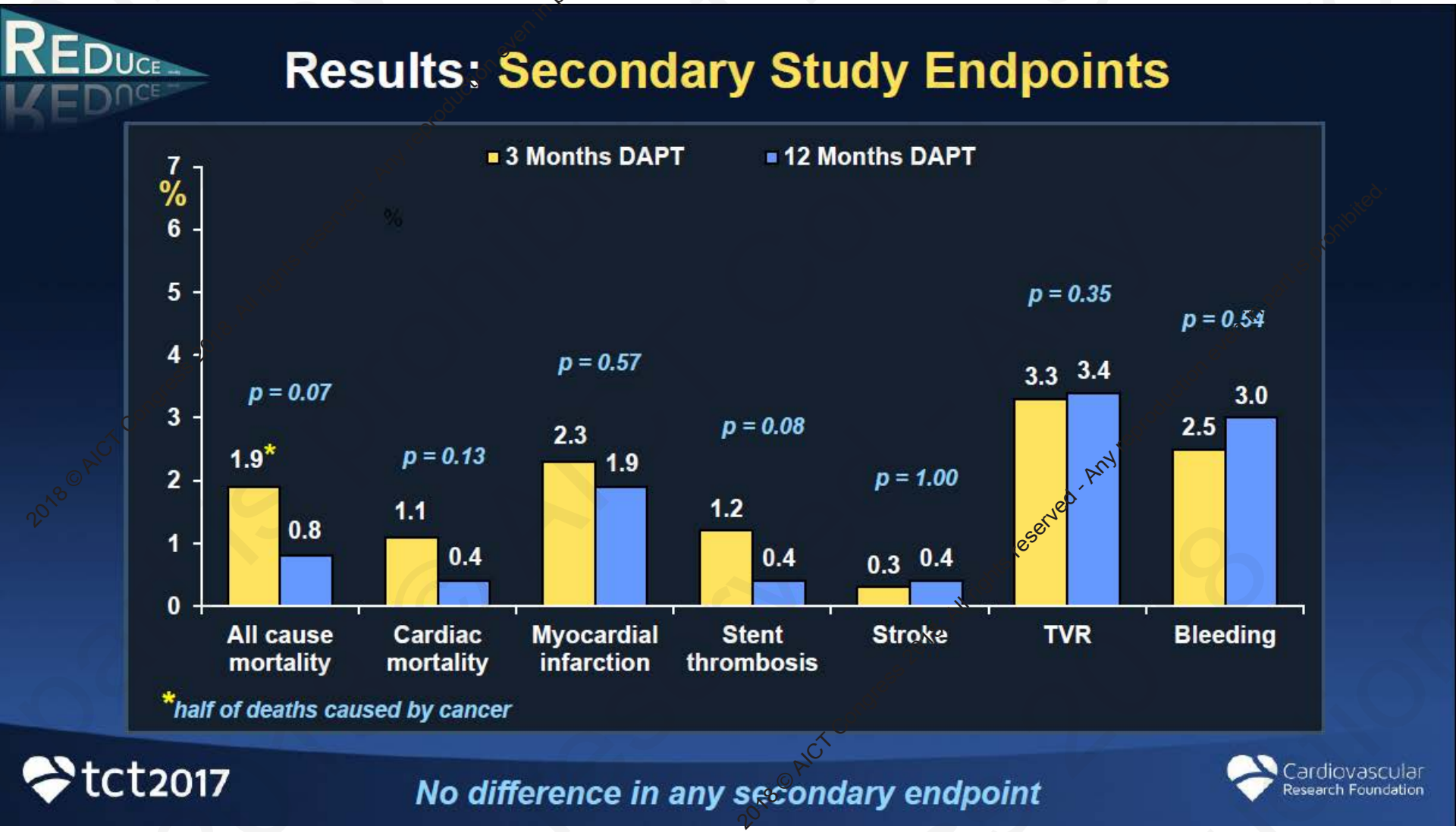
REDUCE (1500 ACS patients)



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Conclusions

- The established prohealing property of the Combo stent potentially provide benefits for use in high thrombotic risk STEMI patient subset
- The NUHCS Combo AMI registry shows favorable outcomes in an all-comers STEMI population, and provide a platform for further evaluation in larger cohorts
- Early comparative studies suggest comparable efficacy and safety with new generation DES
- There is potential for Combo stent use in patients who do not tolerate prolonged DAPT

Thank you

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