Polymer-free DES in Elderly Patients

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DISCLOSURE

1. Nothing to disclose regarding the slides

✓ Elderly Patients undergoing PCI

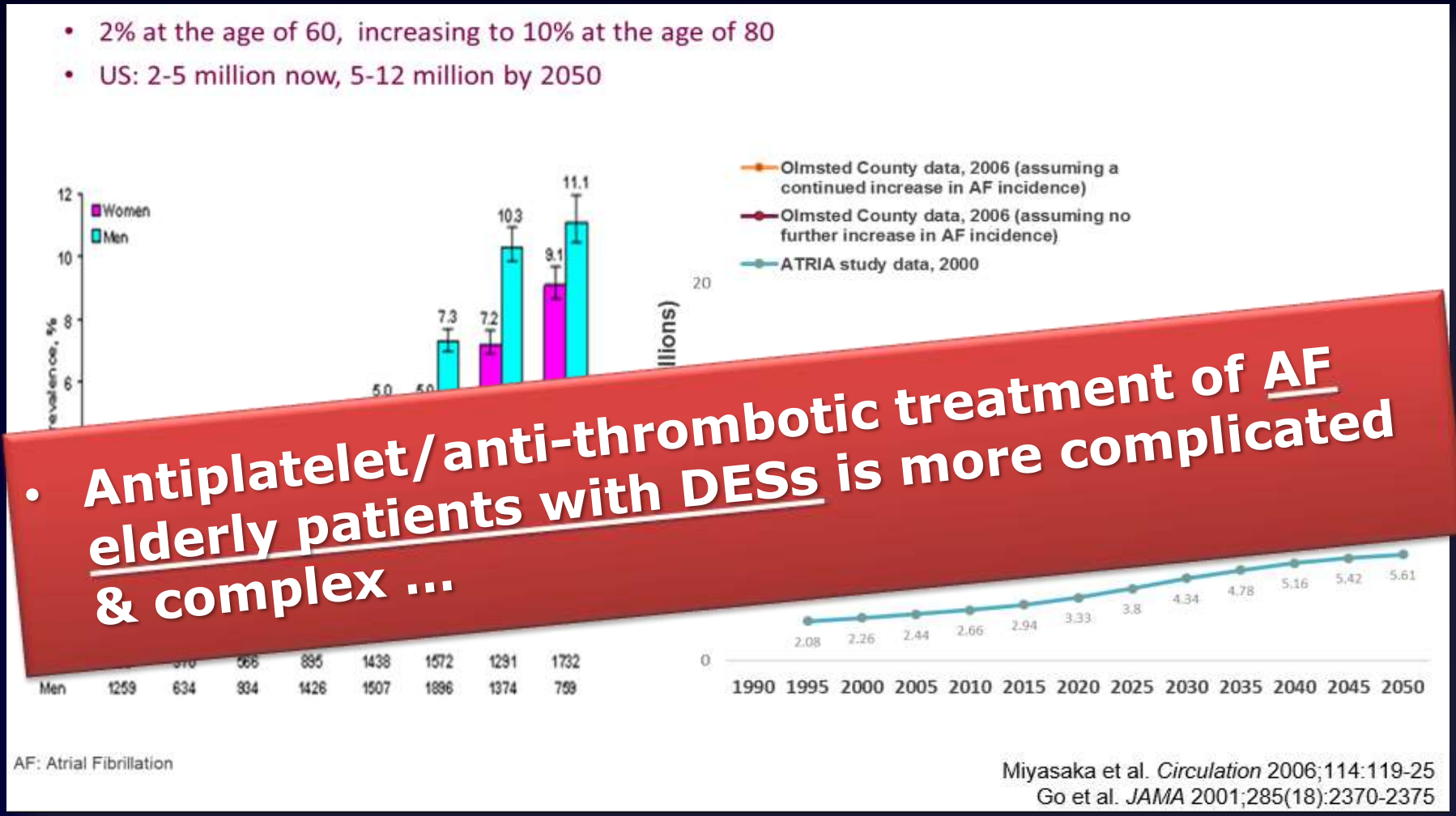
→ Because the population is aging …
Elderly patients are prominent group !!!

- CAD lesions in elderly patients are complex, severe, and diffuse
- Non-cardiac surgery could be more frequently performed
- Incidence of atrial fibrillation is higher
  - Poorly represented in prior studies on DES and DAPT duration
  - No clear recommendation for PCI and DAPT strategies

Often treated with BMS and short DAPT, as a strategy to reduce bleeding complications.

1. Atrial Fibrillation in elderly patients

- Epidemiology of AF (US), Disease of elderly patients



- **Antiplatelet/anti-thrombotic treatment of AF elderly patients with DESs is more complicated & complex …**

2. SENIOR-PLATELET study

Rate of high platelet reactivity (PRU>235) in patients treated with an MD of 75 mg of clopidogrel

- **Elderly patients have both high ischemic & bleeding risks**

[illegible] patients present an impaired response to clopidogrel with a **high rate of HPR**

Silvain et al, Eur Heart J 2012

3. Non-cardiac surgery in elderly patients?

- Discontinuation of antiplatelet therapy was commonly associated with non-cardiac surgery in DES-treated patients.
  - ✓ Surgeons usually requested to discontinue antiplatelet therapy for bleeding control.
  - ✓ However, current guideline still recommended that the elective non-cardiac surgery should be postponed at least 3 or 6 to 12 months after DES implantation and to keep antiplatelet therapy.
- As the patients is getting old, non-cardiac surgery is more frequently performed.

However, **impact of age on the incidence and timing of non-cardiac surgery after coronary stent implantation was not sufficiently evaluated.**

Objective & Methods

- … evaluated the incidence and timing of non-cardiac surgery after DES implantation according to the age.

A total of 37,915 consecutive patients treated by DES implantation between 2000 and 2014 were included in this retrospective study.

Methods (1)

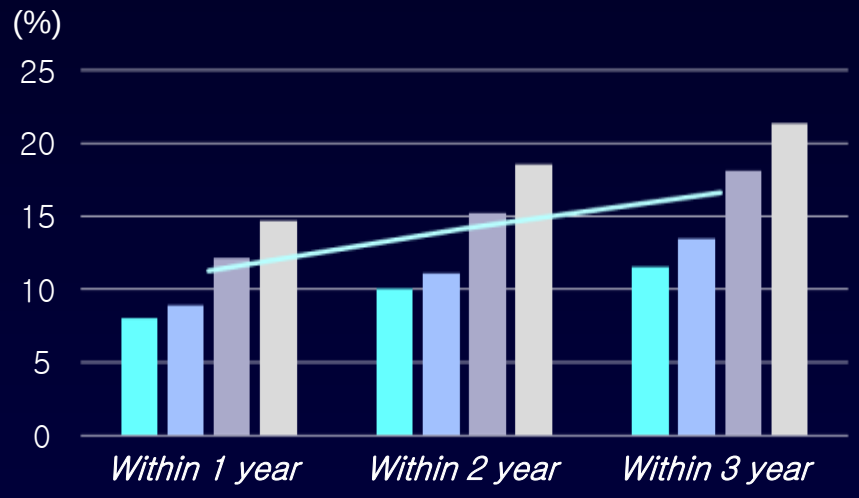
- **4 groups according to the patients' age:**
  1. **under 50 years (n=5,785)**
  2. **between the ages of 50 and 59 (n=9,639)**
  3. **between the ages of 60 and 69 (n=13,566)**
  4. **between the ages of 70 and 79 (n=8,925)**

- **No of patients who underwent non-cardiac surgery:**
  1. **4,263 (11.2%) within one year,**
  2. **5,357 (14.1%) within two years,**
  3. **6,311 (16.6%) within three years after DES implantation.**

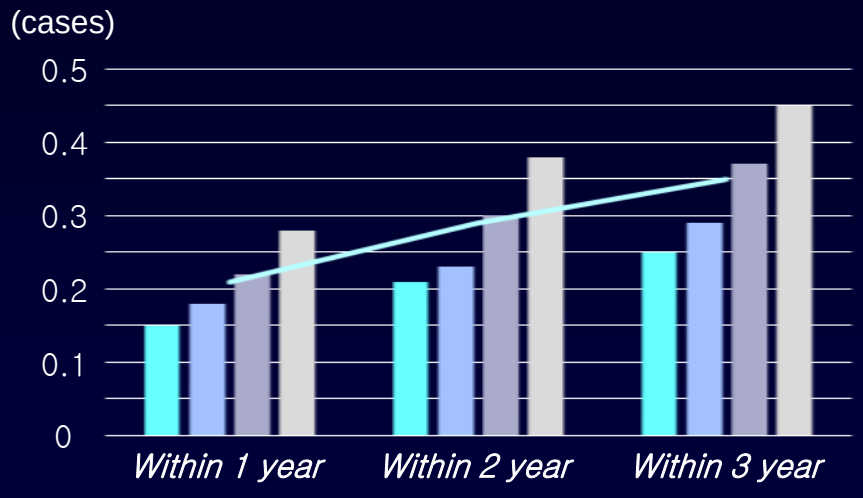
2018 Manuscript submitted

Incidence of non-cardiac surgery after DES implantation according to the age

%Patients underwent surgery

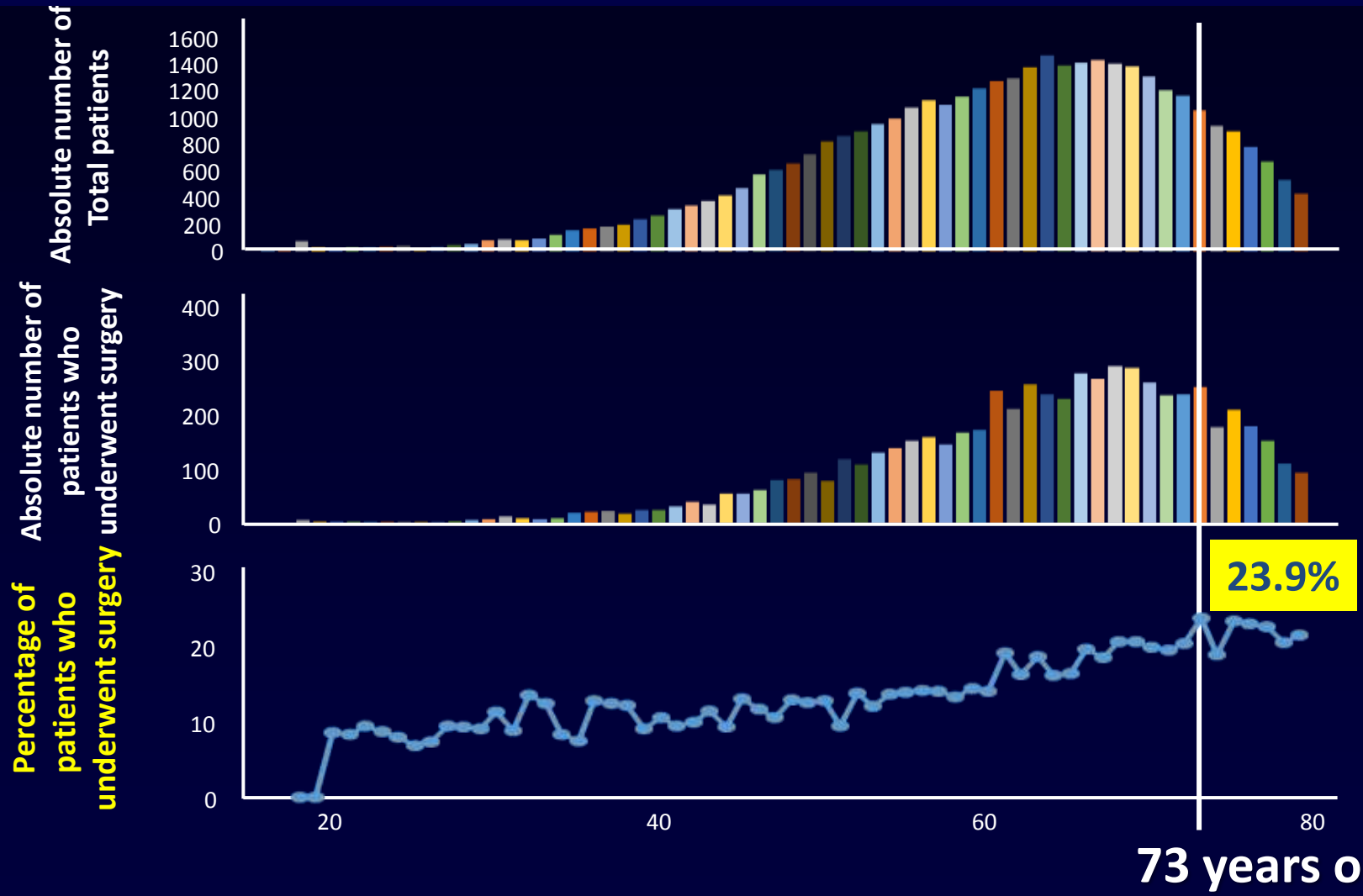


Mean number of surgery



< 50 years old
Between the ages of 50 and 59
Between the ages of 60 and 69
Between the ages of 70 and 79
Total population

No. and percentage of patients who underwent non-cardiac surgery within 3 years

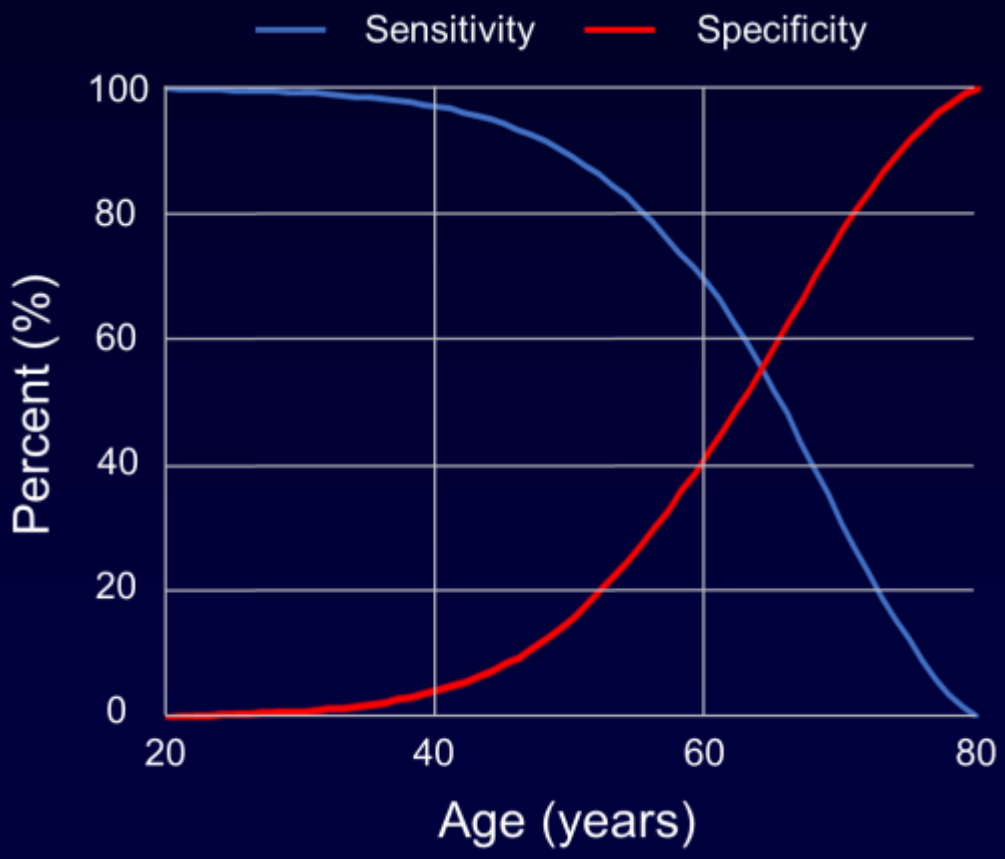


The percentage of non-cardiac surgery within 3 years after DES reached the peak in the patients' age of 73 years

Incidences of non-cardiac surgery within one year after DES implantation

1. under 50; 8.0% (461/5,785),
2. 50-59; 8.9% (855/9,639),
3. 60-69; 12.1% (1,636/13,566),
4. 70-79; 14.7% (1,311/8,925)

(p-value for trend <0.01).



Cut-off age

Best predicted to increase No. of non-cardiac surgery within one year after DES implantation

: 62 years old

-Sensitivity 60.7%
-Specificity 51.9%

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CORONARY

Short-Term Versus Long-Term Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Elderly Patients

A Meta-Analysis of Individual Participant Data From 6 Randomized Trials

Seung-Yul Lee, MD,[a] Myeong-Ki Hong, MD, PhD,[b,c,d] Tullio Palmerini, MD,[e] Hyo-Soo Kim, MD,[f] Marco Valgimigli, MD,[g] Fausto Feres, MD,[h] Antonio Colombo, MD,[i] Martine Gilard, MD,[j] Dong-Ho Shin, MD,[b,c] Jung-Sun Kim, MD,[b,c] Byeong-Keuk Kim, MD,[b,c] Young-Guk Ko, MD,[b,c] Donghoon Choi, MD,[b,c] Yangsoo Jang, MD,[b,c,d] Gregg W. Stone, MD[b]

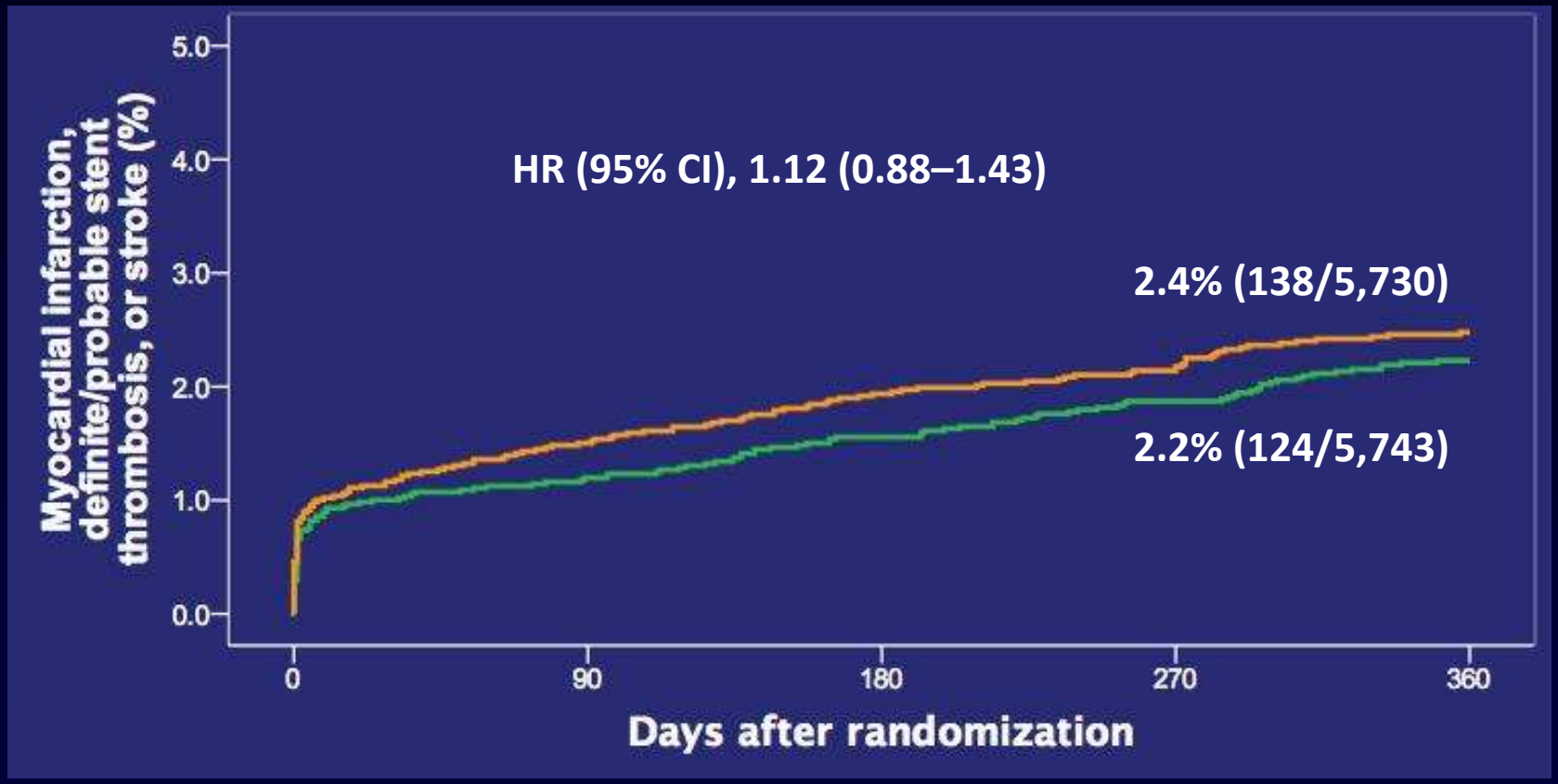
- **6 randomized trials comparing short-term DAPT (3 or 6 months) with long-term DAPT (12 or 24 months) were included [N = 11,473].**

Primary study outcome 12-month risk of a composite of MI, definite or probable ST, or stroke.

DAPT random trials using new-generation DES

- RESET (REal Safety and Efficacy of a 3-month dual antiplatelet Therapy following E-ZES implantation)
- EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting)
- PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study)
- OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice)
- SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy)
- ITALIC (Is There A LIfe for DES After Discontinuation of Clopidogrel)

Cardiac and Cerebrovascular Events: All Patients

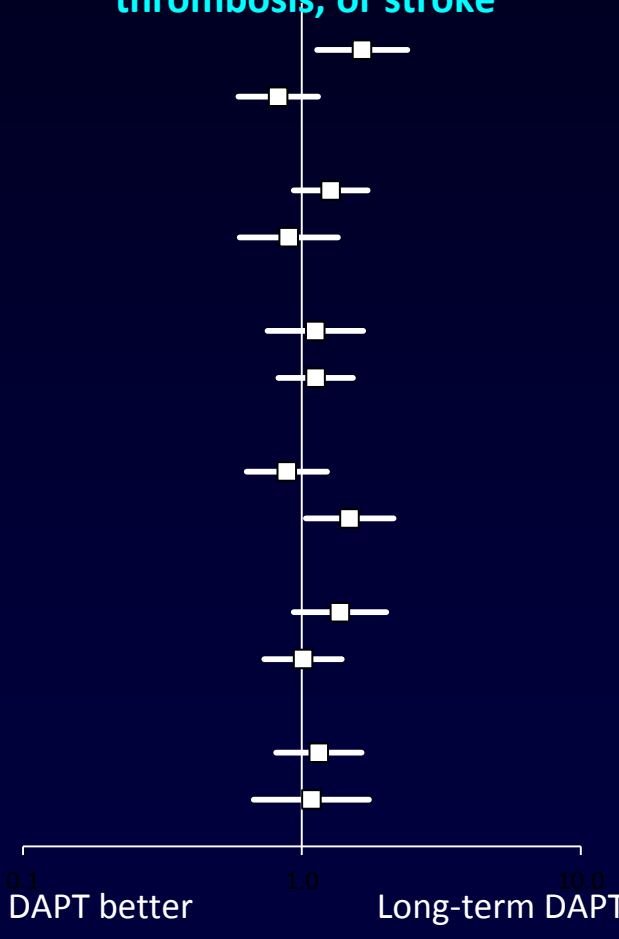


The risk of primary outcome was **not significantly different between short-term and long-term DAPT** in overall patients

Lee & Hong et al. 2018 JACC interv

Cardiac and Cerebrovascular Events: All Patients

Subgroup	Unadjusted HR (95% CI)	Unadjusted HR (95% CI)	p for interaction
		Myocardial infarction, definite/probable stent thrombosis, or stroke	
Age < 65 years old (n=6,152)	**1.65 (1.13–2.39)**		**0.0384**
Age ≥ 65 years old (n=5,319)	**0.82 (0.59–1.15)**		
Male (n=8,019)	1.27 (0.94–1.72)		0.7002
Female (n=3,454)	0.90 (0.60–1.35)		
Diabetes (n=3,593)	1.12 (0.75–1.66)		1.0000
No diabetes (n=7,796)	1.12 (0.83–1.53)		
Stable IHD (n=6,714)	0.88 (0.64–1.23)		0.2064
ACS (n=4,758)	1.48 (1.03–2.13)		
Multi-vessel disease (n=4,507)	1.37 (0.94–2.01)		0.7946
Single vessel disease (n=6,457)	1.01 (0.73–1.39)		
LAD (n=4,802)	1.15 (0.81–1.64)		1.0000
No LAD (n=2,822)	1.08 (0.67–1.74)		



✓ **A significant interaction between age and DAPT duration was identified.**

Events of MI, ST, or Stroke at 12 Months Stratified Based on Short- and Long-Term DAPT, and Grouped by Patient Age (Either <65 or ≥65 Years of Age)

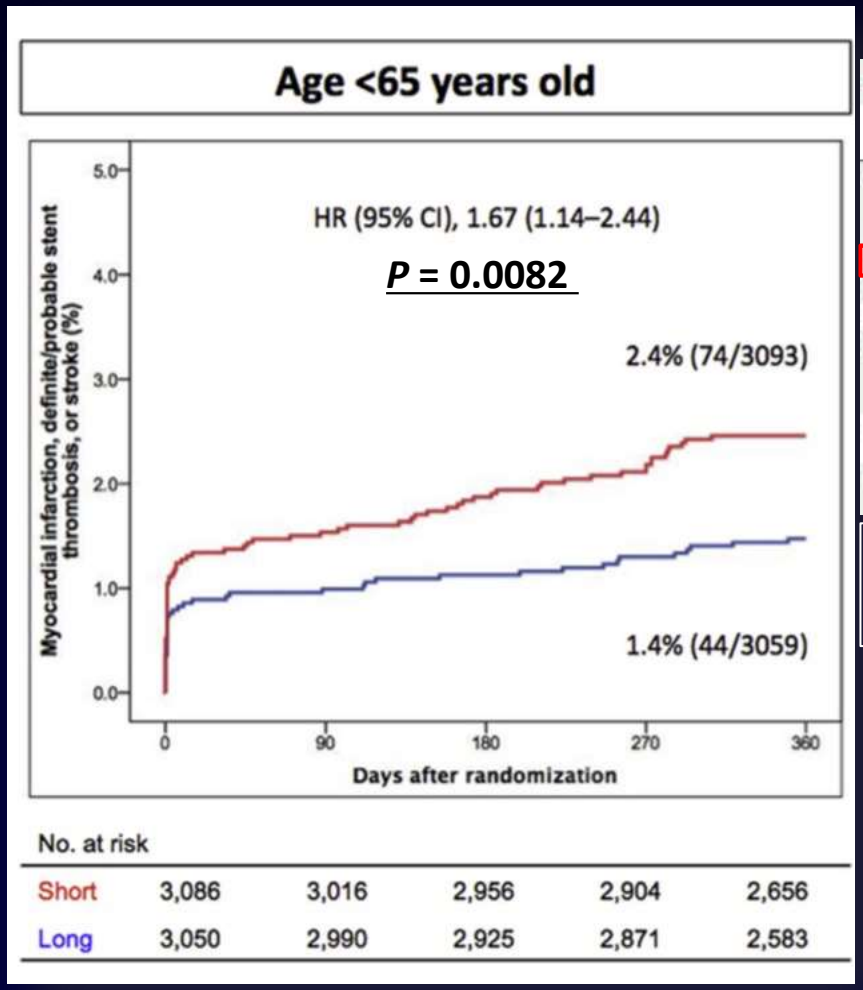


TABLE 2 Clinical Outcomes at 12 Months According to Duration of DAPT in Patients' Age <65 Years of Age

	≤6-Month DAPT (n = 3,093)	12-Month DAPT (n = 3,059)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
All-cause death	21 (0.7)	41 (1.3)	0.50 (0.30-0.85)	0.0097	0.51 (0.30-0.88)	0.0154
Cardiac	13 (0.4)	25 (0.8)	0.51 (0.26-1.00)	0.0500	–	–
Noncardiac	8 (0.3)	16 (0.5)	0.49 (0.21-1.14)	0.0989	–	–
Myocardial infarction	60 (1.9)	37 (1.2)	1.59 (1.05-2.39)	0.0275	1.56 (1.03-2.36)	0.0355
Definite or probable stent thrombosis	14 (0.5)	10 (0.3)	1.37 (0.61-3.09)	0.4447	–	–
Stroke*	9 (0.3)	6 (0.2)	–	–	–	–
Bleeding	29 (0.9)	37 (1.2)	0.76 (0.47-1.24)	0.2724	0.74 (0.45-1.22)	0.2437
Major	9 (0.3)	15 (0.5)	0.59 (0.26-1.34)	0.2073	–	–
Minor	21 (0.7)	22 (0.7)	0.93 (0.51-1.69)	0.8029	–	–
Myocardial infarction or definite/probable stent thrombosis	65 (2.1)	40 (1.3)	1.59 (1.07-2.35)	0.0214	1.57 (1.06-2.33)	0.0262
Myocardial infarction, definite/probable stent thrombosis, or stroke	74 (2.4)	44 (1.4)	1.65 (1.13-2.39)	0.0089	1.67 (1.14-2.44)	0.0082

- The difference was driven by a higher risk of MI in patients with short-term DAPT.

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Events of MI, ST, or Stroke at 12 Months Stratified Based on Short- and Long-Term DAPT, and Grouped by Patient Age (Either <65 or ≥65 Years of Age)

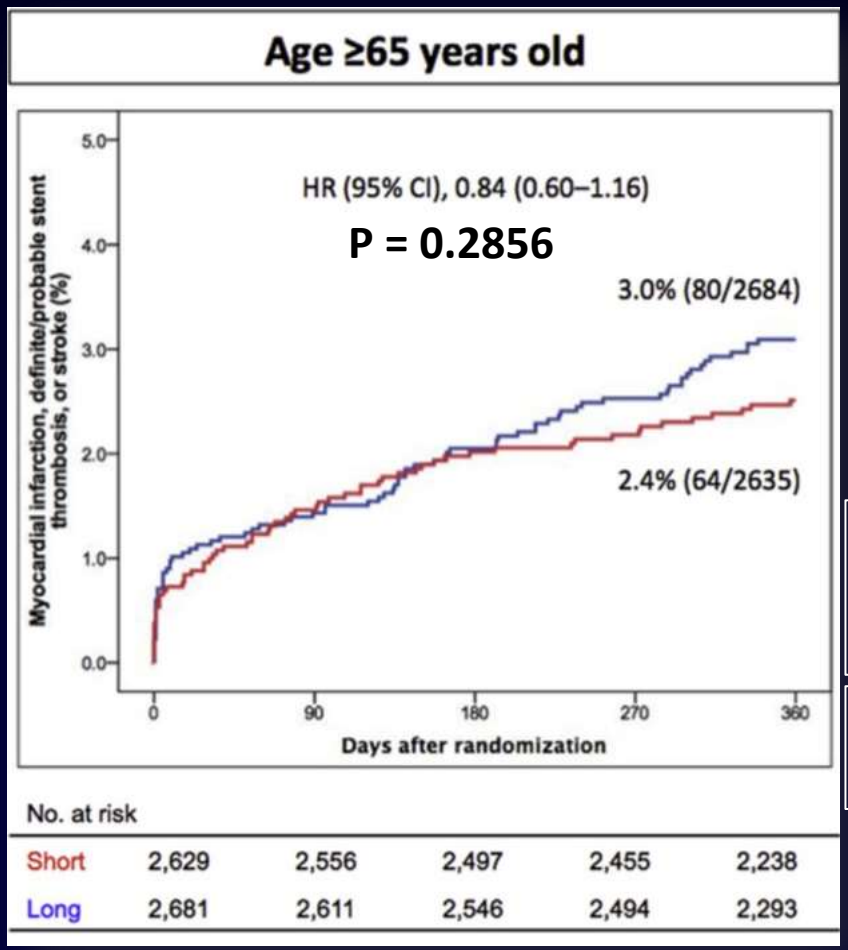


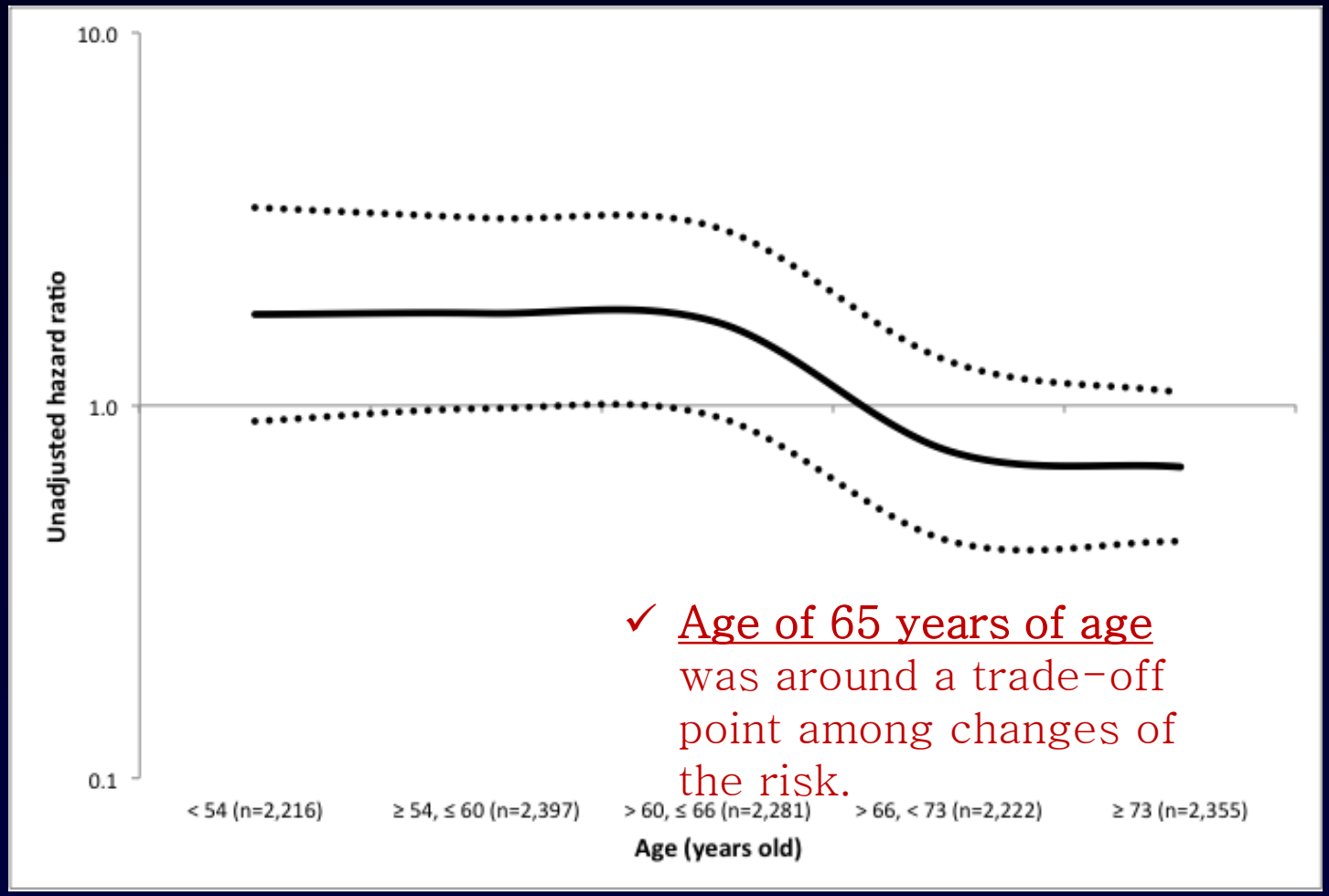
TABLE 3 Clinical Outcomes at 12 Months According to Duration of DAPT in Patients ≥65 Years of Age

	≤6-Month DAPT (n = 2,635)	12-Month DAPT (n = 2,684)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
All-cause death	76 (2.9)	66 (2.5)	1.18 (0.85-1.64)	0.3231	1.15 (0.83-1.60)	0.4110
Cardiac	45 (1.7)	42 (1.6)	1.11 (0.73-1.68)	0.6417	–	–
Noncardiac	31 (1.2)	24 (0.9)	1.31 (0.77-2.24)	0.3147	–	–
Myocardial infarction	41 (1.6)	55 (2.1)	0.77 (0.52-1.16)	0.2085	0.80 (0.53-1.20)	0.2751
Definite or probable stent thrombosis	14 (0.5)	14 (0.5)	1.04 (0.49-2.17)	0.9271	–	–
Stroke	17 (0.7)	22 (0.8)	0.79 (0.42-1.48)	0.4607	–	–
Bleeding	39 (1.5)	63 (2.4)	0.63 (0.42-0.94)	0.0248	0.64 (0.43-0.95)	0.0276
Major	13 (0.5)	29 (1.1)	0.46 (0.24-0.88)	0.0196	–	–
Minor	27 (1.0)	35 (1.3)	0.79 (0.48-1.31)	0.3585	–	–
Myocardial infarction or definite/probable stent thrombosis	47 (1.8)	58 (2.2)	0.84 (0.57-1.23)	0.3703	0.86 (0.58-1.27)	0.4430
Myocardial infarction, definite/probable stent thrombosis, or stroke	64 (2.4)	80 (3.0)	0.82 (0.59-1.15)	0.2487	0.84 (0.60-1.16)	0.2856

- **Short-term DAPT was associated with increased risk of ischemic events in younger patients, but not in elderly patients.**
- **Major bleeding risks significantly increased in long-term DAPT in elderly patients**

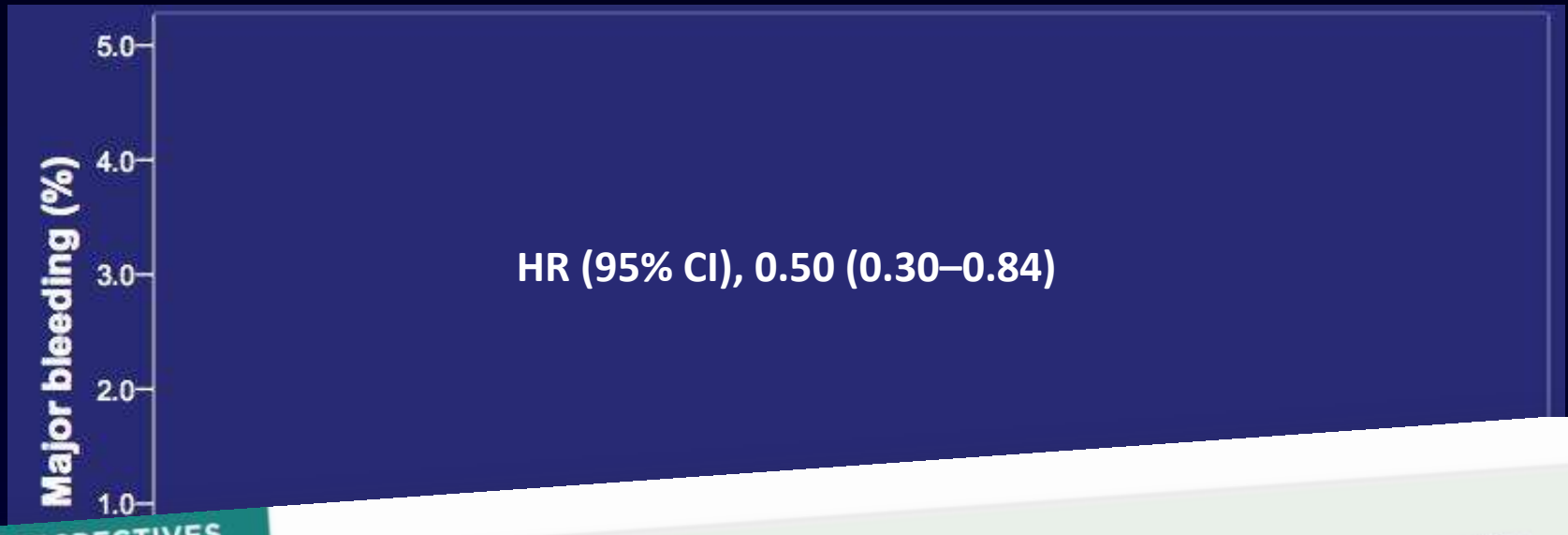
Lee & Hong et al. 2018 JACC interv

Risk of primary outcomes with short-term DAPT (vs. long-term) decreased according to the quintile of age !



Unadjusted hazard ratio and 95% CI were represented as line and dotted line, respectively.

Major Bleeding Events: All Patients



PERSPECTIVES

WHAT IS KNOWN? Qualified studies (i.e., patient-level meta-analyses from randomized trials with larger number of patients) to evaluate the optimal duration of DAPT in DES-treated elderly patients have been very limited. Consequently, the optimal duration of DAPT among elderly patients remains controversial.

WHAT IS NEW? Short-term DAPT after next-generation DES implantation, compared with long-term DAPT, may be more beneficial in elderly patients than in younger patients.

WHAT IS NEXT? Further randomized studies to evaluate optimal duration of DAPT in elderly patients receiving new-generation DES are required.

(HR=0.50; 95% CI=0.30 to 0.84; p= 0.0081) in the overall group, and particularly in elderly patients **(HR=0.46; 95% CI=0.24-0.88; p= 0.0196)**.

Lee & Hong et al. 2018 JACC interv

Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial

Olivier Varenne, Stéphane Cook, Georgios Sideris, Sasko Kedev, Thomas Cuisset, Didier Carrié, Thomas Hovasse, Philippe Garot, Rami El Mahmoud, Christian Spaulding, Gérard Helft, José F Diaz Fernandez, Salvatore Brugaletta, Eduardo Pinar-Bermudez, Josepa Mauri Ferre, Philippe Commeau, Emmanuel Teiger, Kris Bogaerts, Manel Sabate, Marie-Claude Morice, Peter R Sinnaeve, for the SENIOR investigators

Summary

Background Elderly patients regularly receive bare-metal stents (BMS) instead of drug-eluting stents (DES) to shorten the duration of double antiplatelet therapy (DAPT). The aim of this study was to compare outcomes between these two types of stents with a short duration of DAPT in such patients.

Lancet 2018; 391: 41-50
Published Online
November 1, 2017

Randomized (1:1); 1,200 patients aged 75 years and above

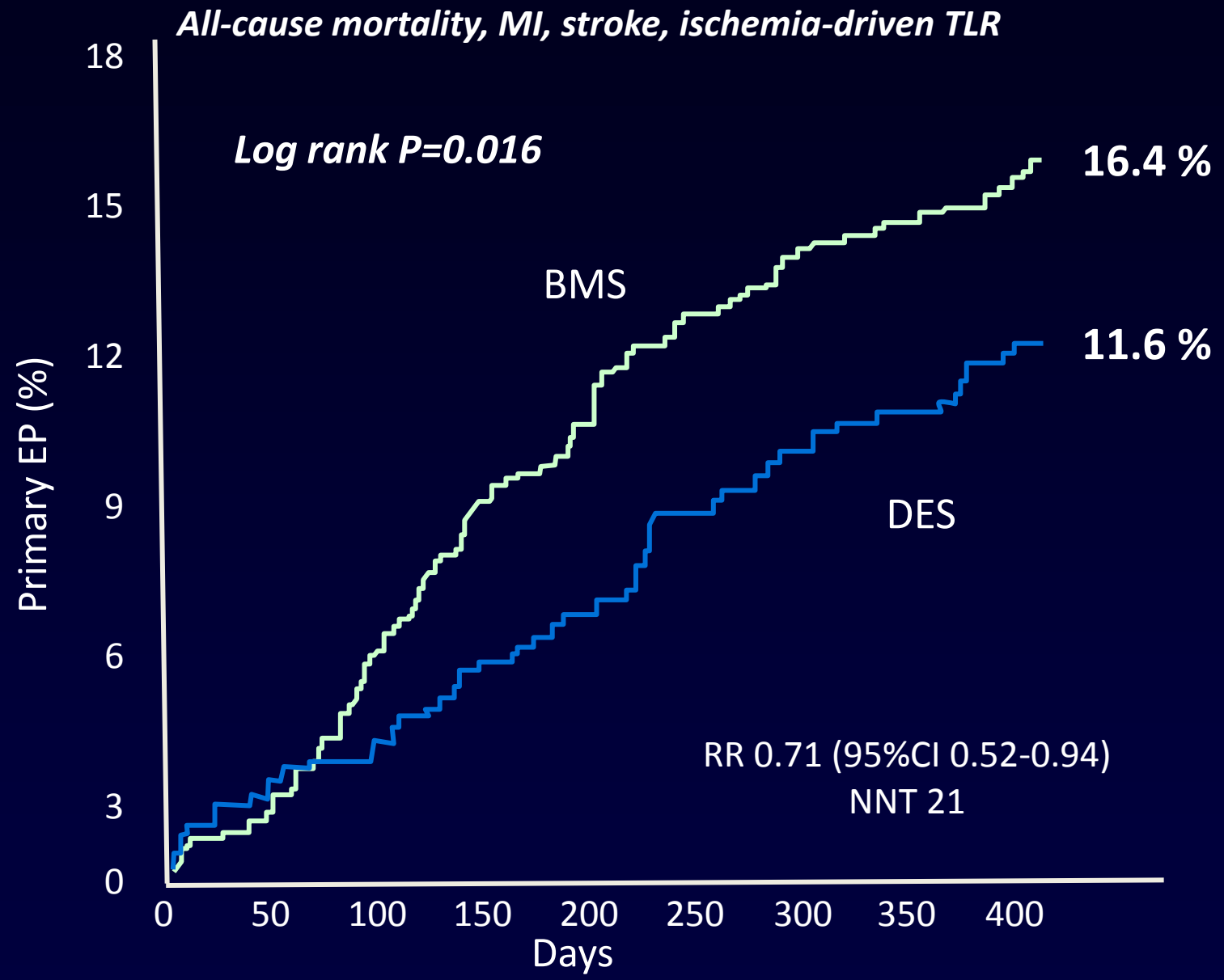
Tailored DAPT: 1 mo in stable and 6 mo in ACS pts
Prespecified by the investigator prior to randomization

DES: Synergy, n=596 vs. **BMS, n=604**

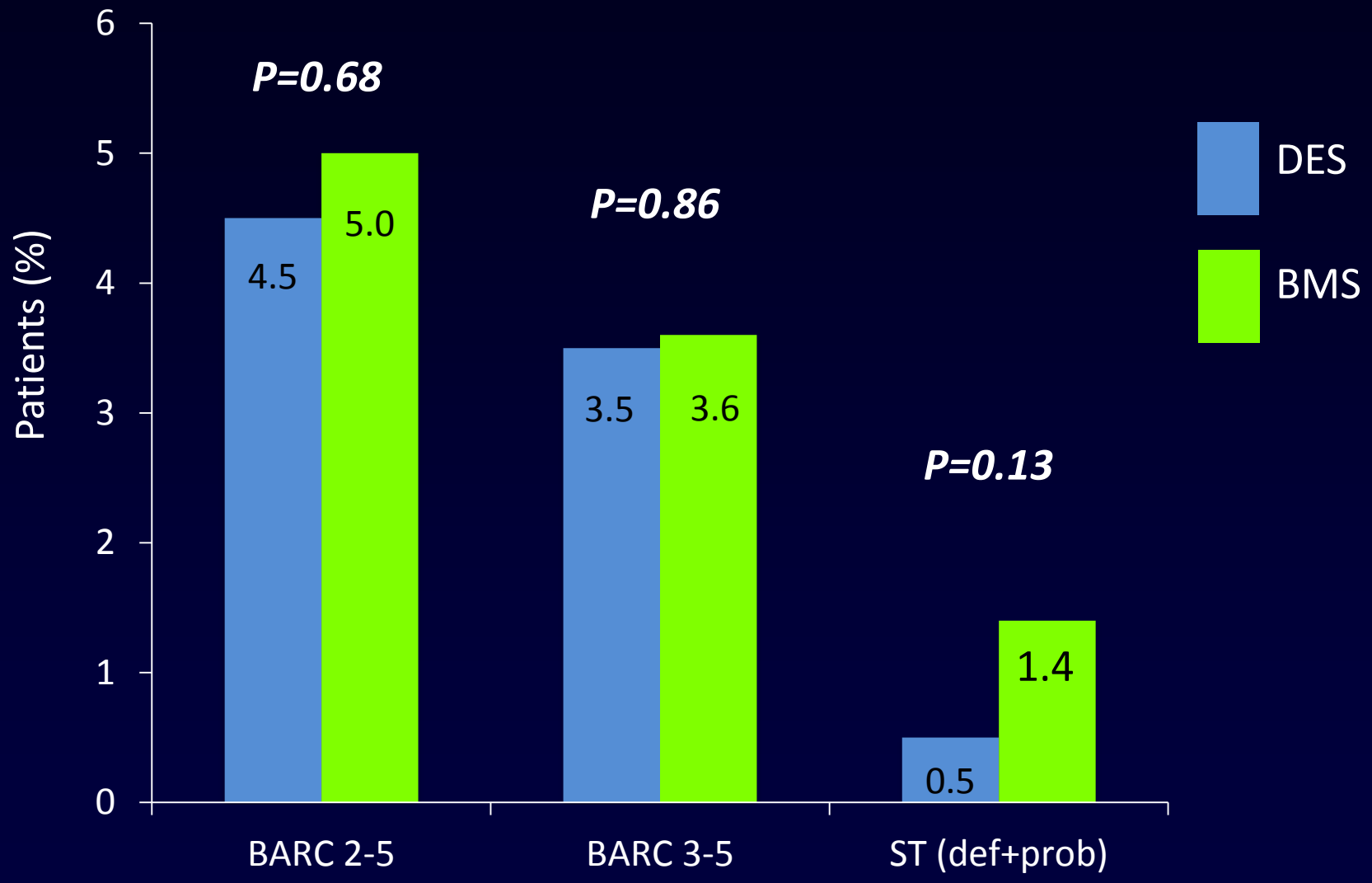
- **Primary End Point 1y:** all-cause mortality, non-fatal MI, stroke, ID-TLR
- **Secondary End Points 1y:** Bleeding BARC 2-5/3-5, stent thrombosis

Varenne O. et al. *Lancet*. 2017

Primary End Point



Safety Endpoints



SENIOR randomized trial

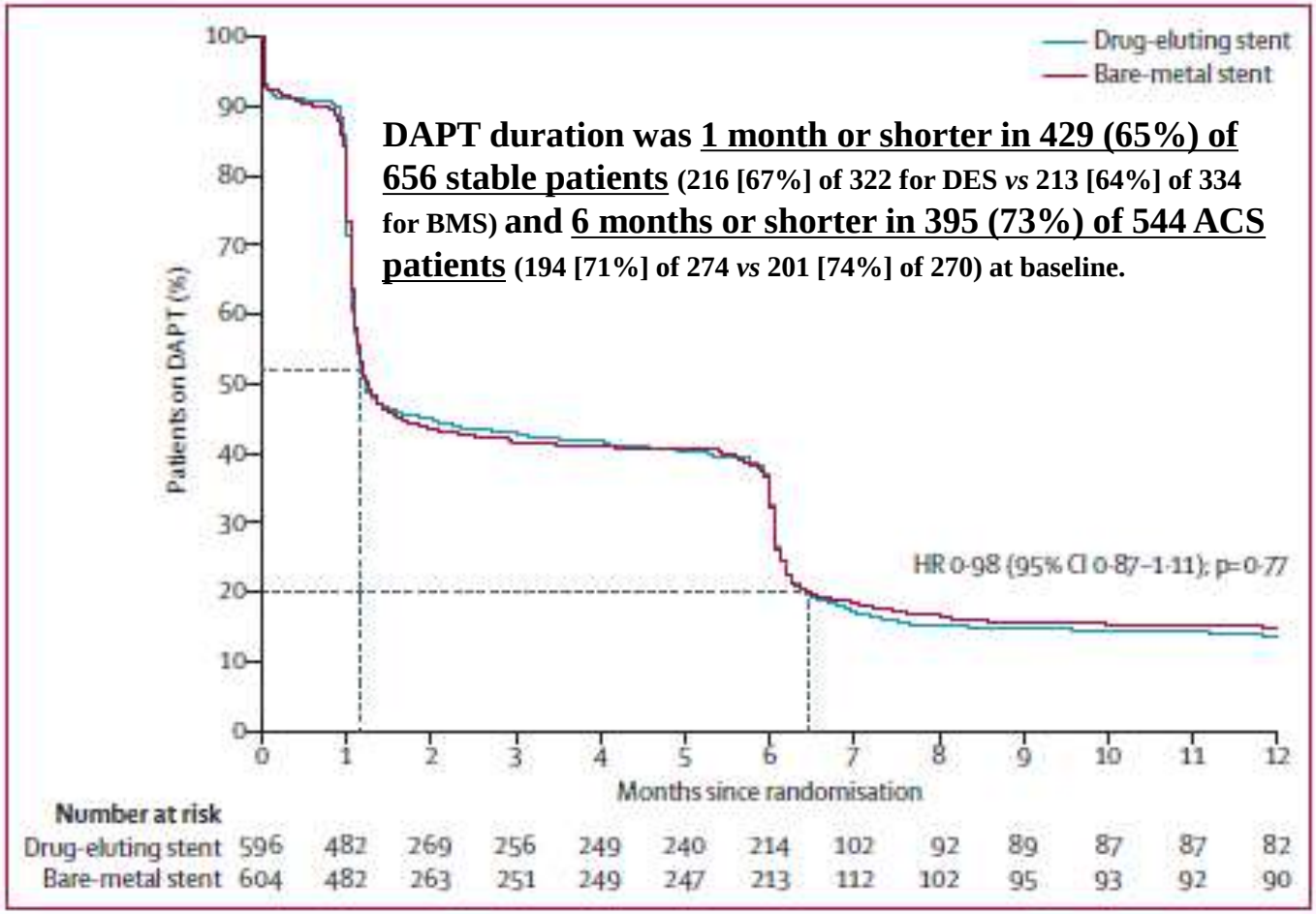


Figure 3: Time to interruption for DAPT treatment
No patients were censored. DAPT=dual antiplatelet therapy.

Evolution of DES Technology

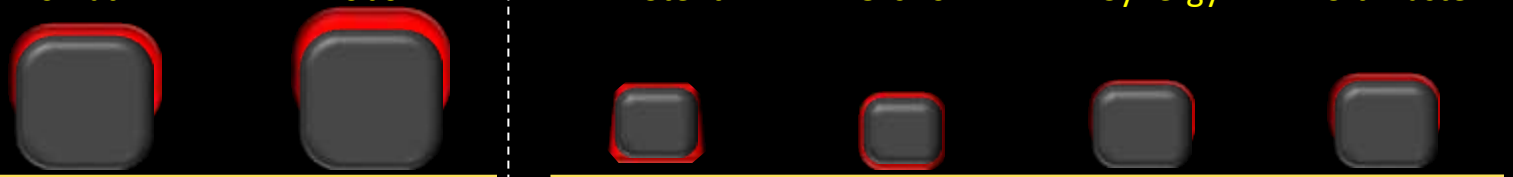
1st Generation

2nd Generation

Durable Polymer Stents

	Cypher	TAXUS Express	TAXUS Liberte	Resolute Integrity	Xience Alpine	Promus PREMIER
Strut Thickness	140 µm	132 µm	96 µm	89 µm	81 µm	81 µm
Coat Thickness	7µm / side	16µm/side	14µm/side	6µm / side	8µm / side	8µm / side

Bioabsorbable Polymer Stents



	Biomatrix	Nobori	MiStent	Orsiro	Synergy	Ultimaster
Strut Thickness	120 µm	125 µm	64µm	60µm	74µm	80µm
Coat Thickness	10 µm	20 µm	5µm luminal 15µm Abluminal	4-7µm / side	4 µm	14 µm

1st Generation Future Technologies

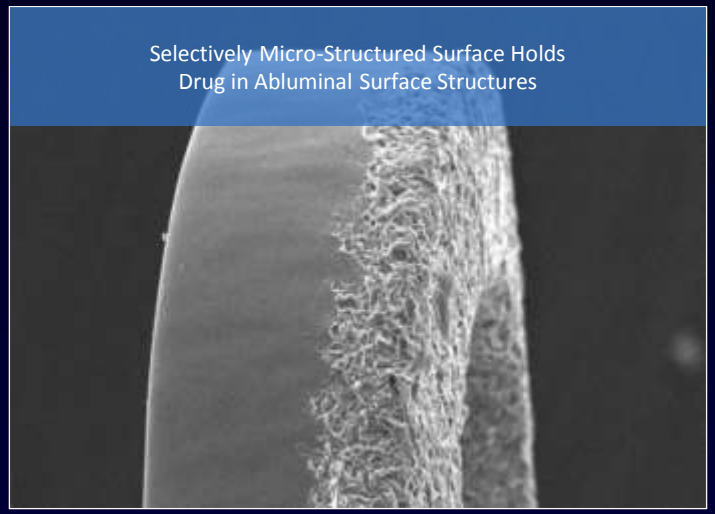
Polymer Free Stents

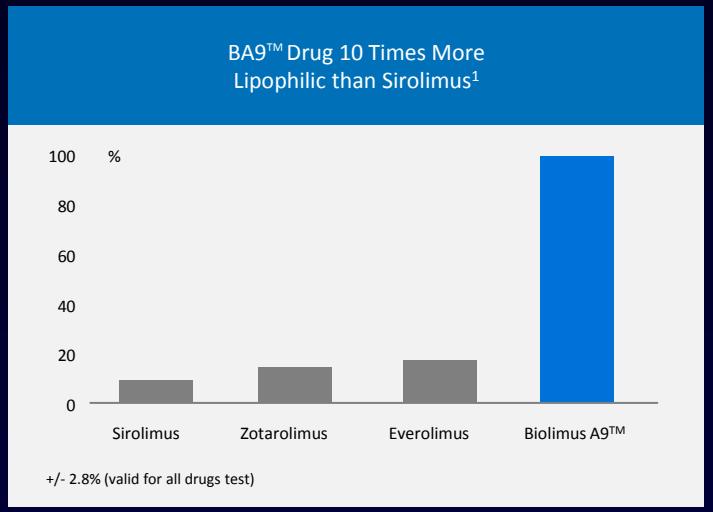
	BIOFREEDOM	Drug Filled Stent
Strut Thickness	112	86
Coat Thickness	NA	NA

Fully Bioresorbable Stents

	BVS	ELIXIR DESolve	DREAMS II
Strut Thickness	150 µm	150 µm	150 µm
Coat Thickness	3 µm / side	<3 µm / side	8 µm / side

BioFreedom™ Drug Coated Stent (DCS)





- Avoid any possible polymer-related adverse effects
- Rapid drug transfer to vessel wall (98% within one month)
- Good fit with short DAPT

LEADERS FREE Trial

Prospective, double-blind randomized (1:1) trial
2466 **High bleeding risk (HBR) PCI patients**

BioFreedom™
DCS, n=1239

vs.

Gazelle™
BMS, n=1227

DAPT mandated for 1 month only, followed by long-term SAPT

- Primary safety endpoint:
  Composite of cardiac death, MI, definite/probable stent thrombosis at 1 year (non-inferiority then superiority)
- Primary efficacy endpoint:
  Clinically-driven TLR at 1 year (superiority)

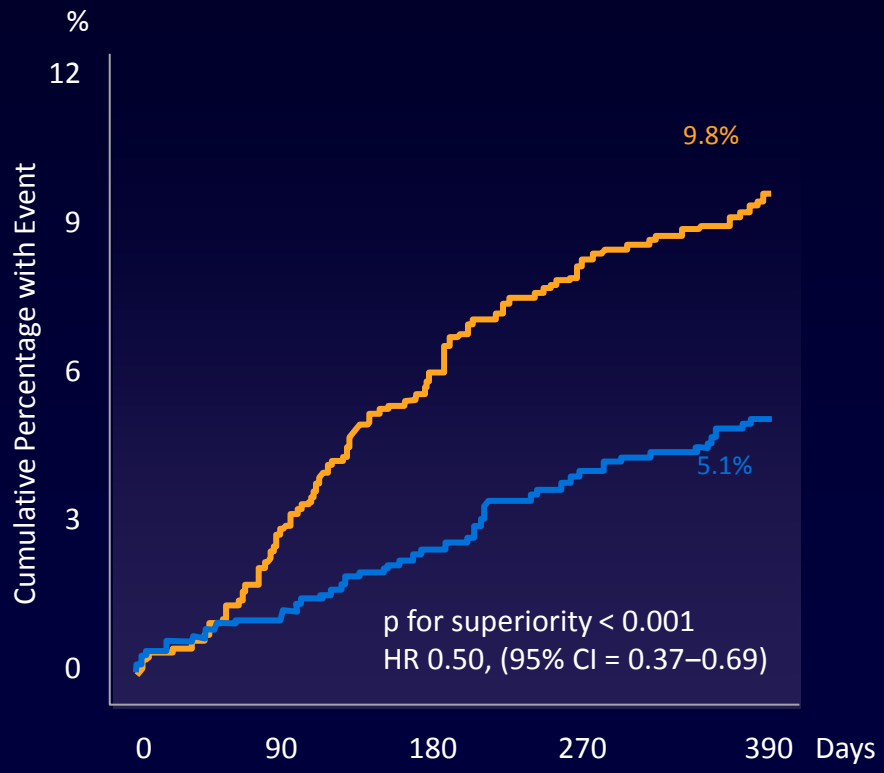
Urban P et al. N Engl J Med 2015;373:2038-47

Primary Endpoints at 1 Year

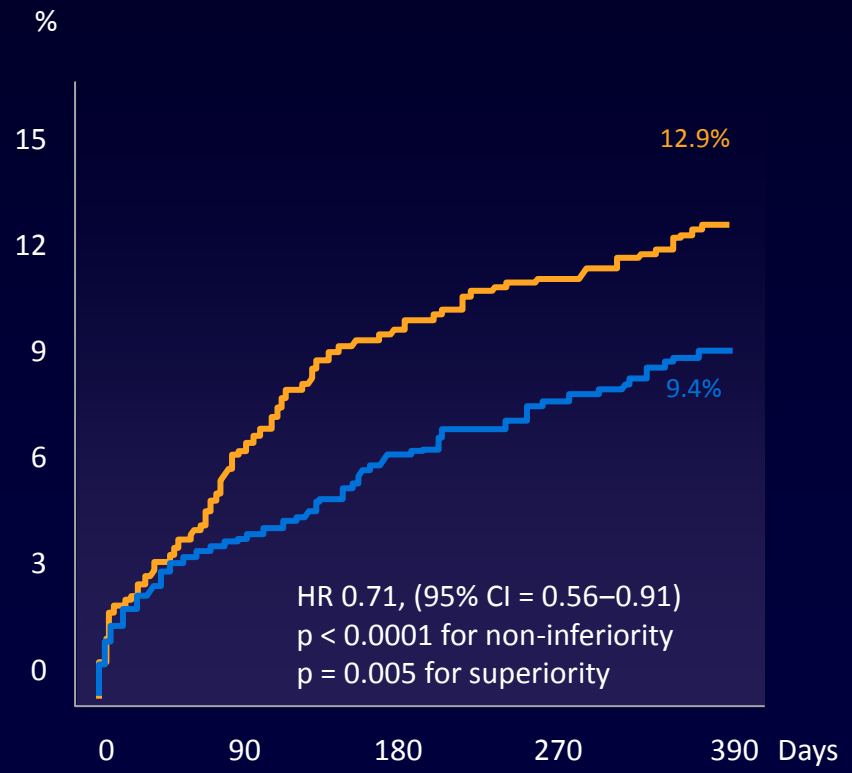
Urban P et al. N Engl J Med 2015;373:2038-47

DCS BMS

Efficacy (cd-TLR)



Safety (cardiac death, MI, ST)



LEADERS FREE Trial

Table 2. Primary and Secondary End Points.*

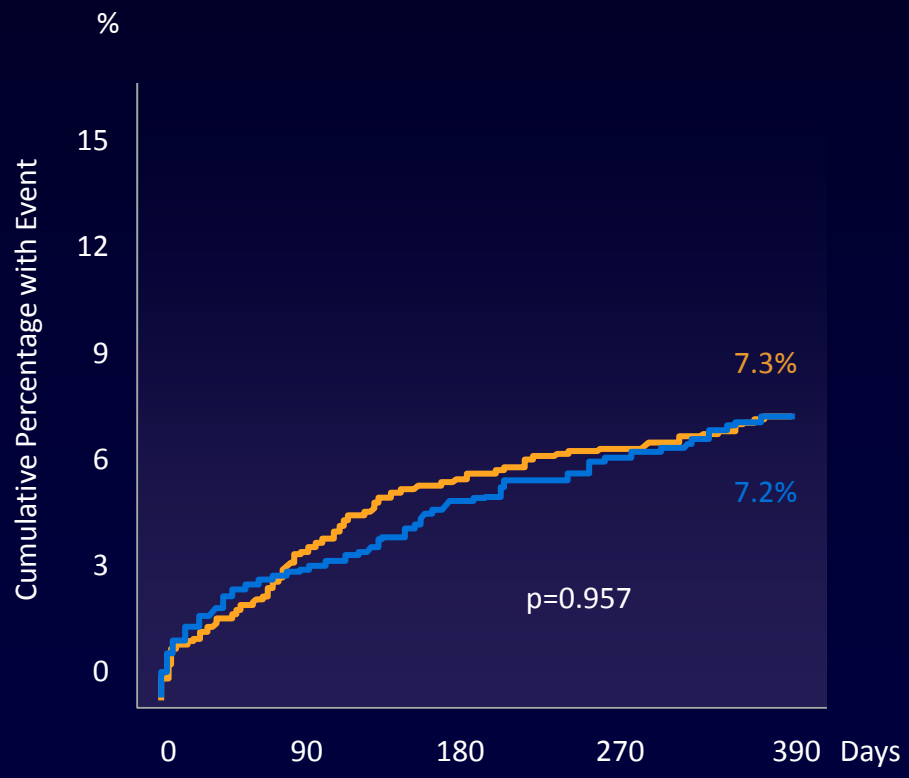
End Point	Drug-Coated Stent (N=1221)	Bare-Metal Stent (N=1211)	Hazard Ratio (95% CI)	P Value
	no. of events (% of patients)			
Primary safety end point: cardiac death, myocardial infarction, or stent thrombosis	112 (9.4)	154 (12.9)	0.71 (0.56–0.91)	0.005†
Primary efficacy end point: clinically driven TLR	59 (5.1)	113 (9.8)	0.50 (0.37–0.69)	<0.001
Death				
From any cause	97 (8.0)	108 (9.0)	0.89 (0.67–1.17)	0.39
From cardiac causes	50 (4.2)	63 (5.3)	0.78 (0.54–1.14)	0.20
Myocardial infarction‡				
Any	72 (6.1)	104 (8.9)	0.68 (0.50–0.91)	0.01
Q-wave infarction	6 (0.5)	7 (0.6)	0.85 (0.29–2.53)	0.77
Non–Q-wave infarction	57 (4.8)	80 (6.9)	0.70 (0.50–0.98)	0.04
Undetermined type	10 (0.8)	25 (2.1)	0.39 (0.19–0.82)	0.01
Stent thrombosis‡				
Definite or probable	24 (2.0)	26 (2.2)	0.91 (0.53–1.59)	0.75
Definite	16 (1.3)	17 (1.4)	0.93 (0.47–1.84)	0.84
Probable	8 (0.7)	9 (0.8)	0.88 (0.34–2.28)	0.80
Possible	25 (2.2)	27 (2.3)	0.91 (0.53–1.57)	0.74
Acute	5 (0.4)	5 (0.4)	0.99 (0.29–3.43)	0.99
Subacute	7 (0.6)	10 (0.8)	0.69 (0.26–1.82)	0.45
Early: acute + subacute	12 (1.0)	15 (1.2)	0.79 (0.37–1.70)	0.55
Late	13 (1.1)	11 (1.0)	1.17 (0.52–2.61)	0.70

Major Bleeding at 1 Year

Urban P et al. N Engl J Med 2015;373:2038-47

DCS BMS

BARC 3-5

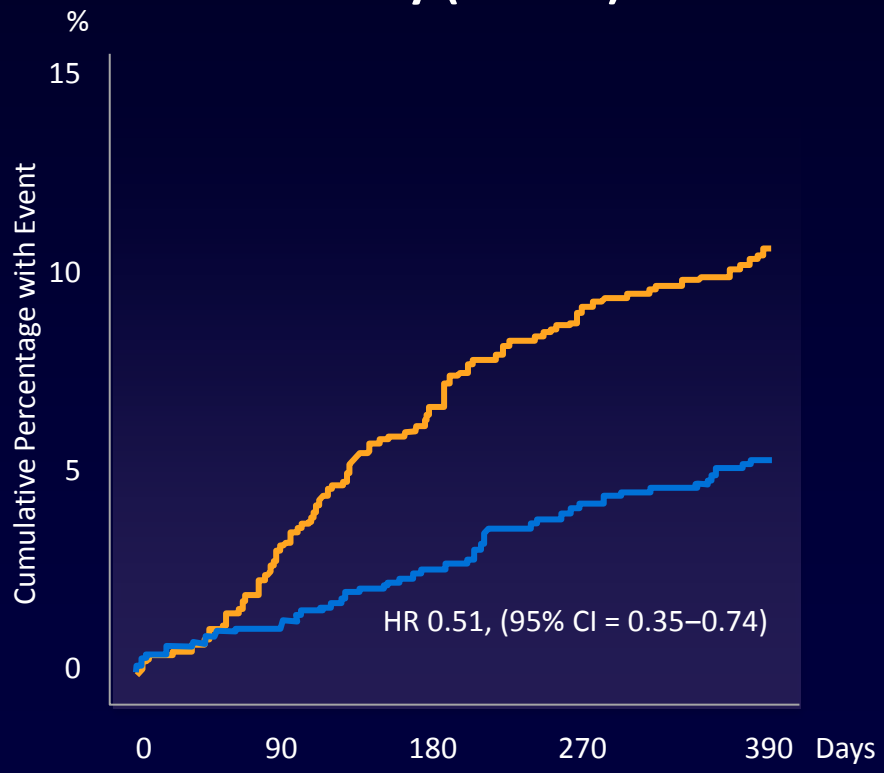


Subgroup Analysis: Elderly Patients

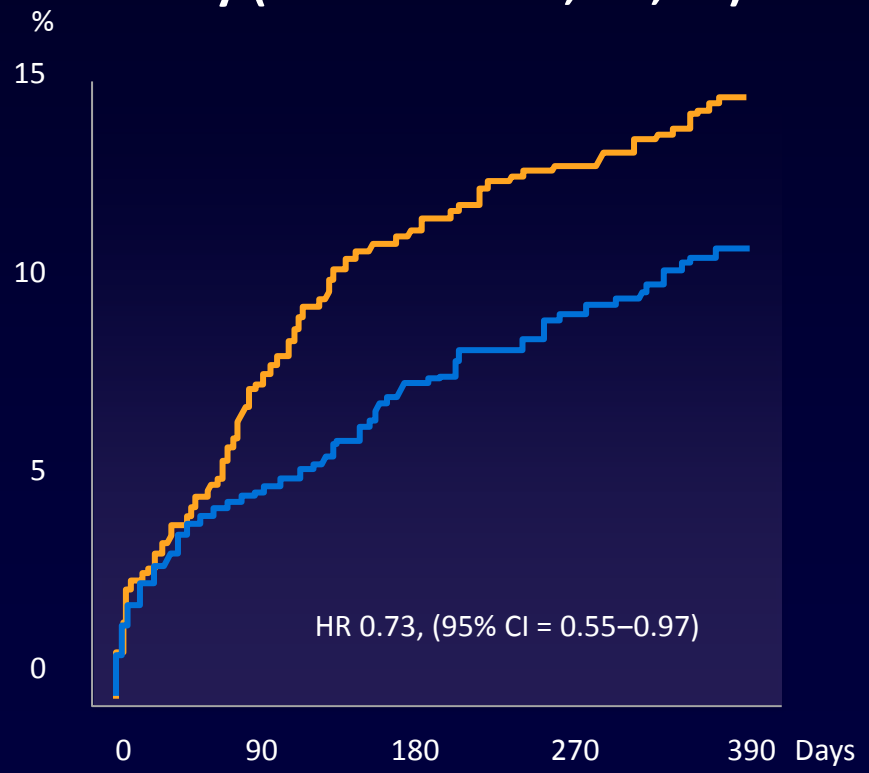
All patients from the LEADERS FREE trial aged 75 or more who completed follow-up were included in this analysis (n=789; 68.4% of the overall trial HBR patients).

DCS BMS

Efficacy (cd-TLR)



Safety (cardiac death, MI, ST)



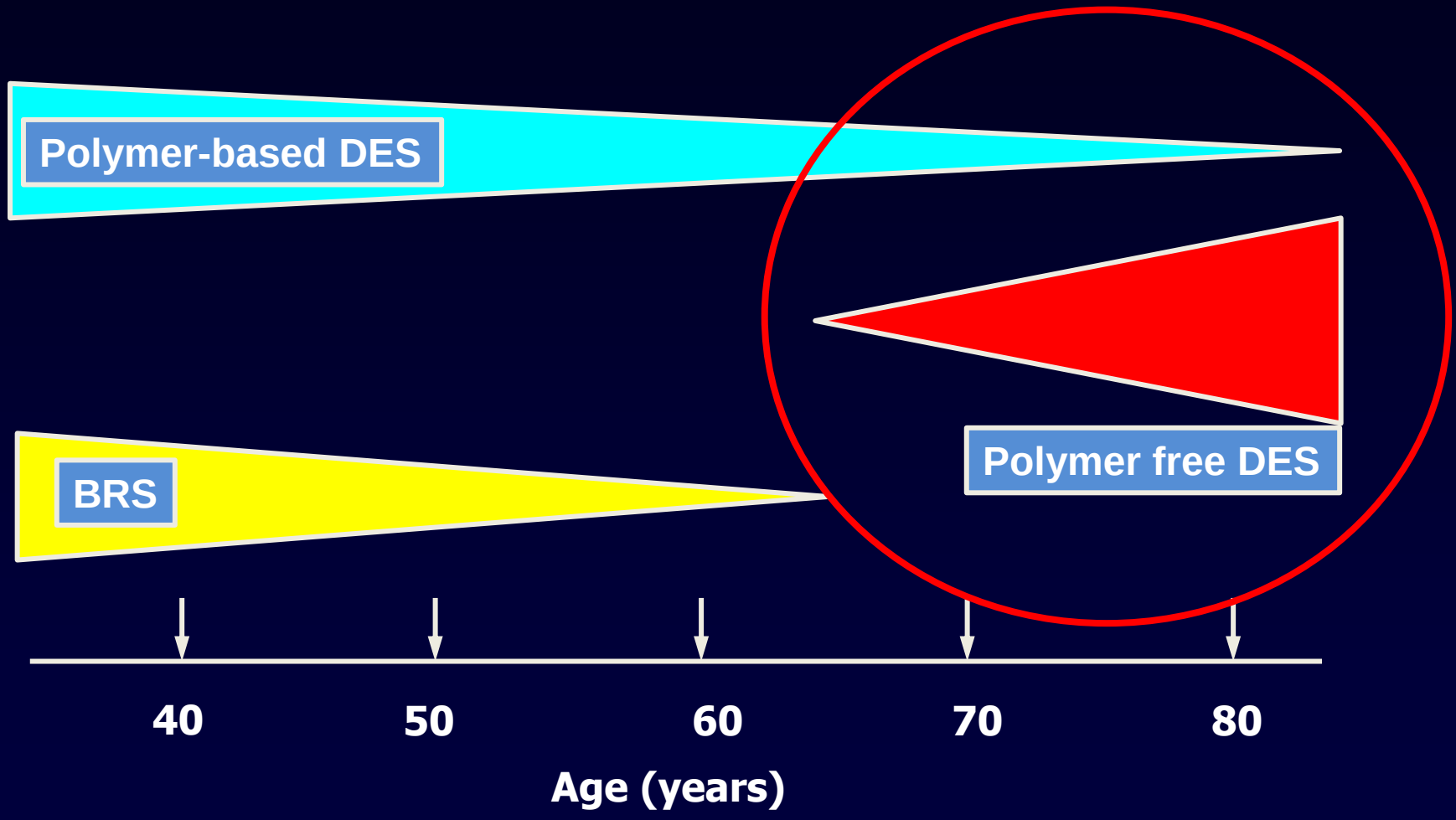
Morice MC. et al. Int J Cardiol. 2017;243:110-115

Short-term DAPT in Elderly Patients

- In elderly patients receiving newer-generation DES, short-term DAPT may reduce major bleeding events without an increase of ischemic events compared to long-term DAPT.

- Polymer-free DES can further could improve the safety of stent therapy in elderly patients.

DES & age; Selection of DES considering age



THE TAKE-HOME MESSAGE

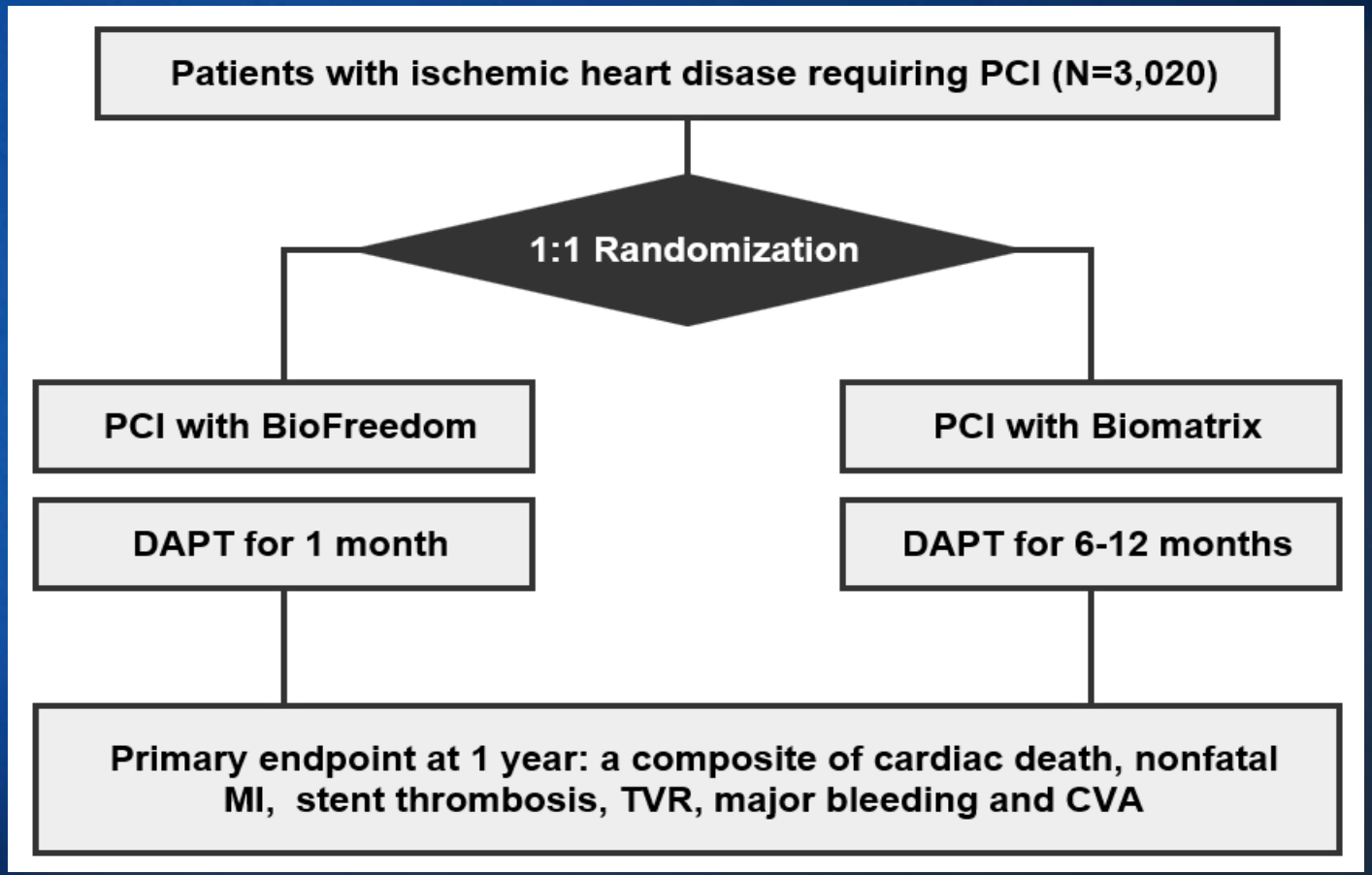
- Elderly patients received more non-cardiac surgery compared to younger patients.

  → Physicians are advised to carefully select DES type in treatment of the patients aged 62 years and older considering the possibility of cessation of DAPT.

- Polymer-free DES implantation with short-term (1 month) DAPT may be a reasonable treatment modality in elderly patients.

Active Ongoing !

A Randomized Controlled Comparison Between One vs. More Than Six Months of DAPT After Biolimus A9-eluting Stent Implantation ; ONE-Freedom trial



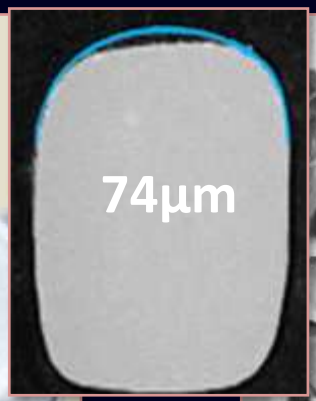
- This study provide the more clear answer regarding Biofreedom with 1-month DAPT comparing DES with conventional DAPT, including the effect of age on outcomes

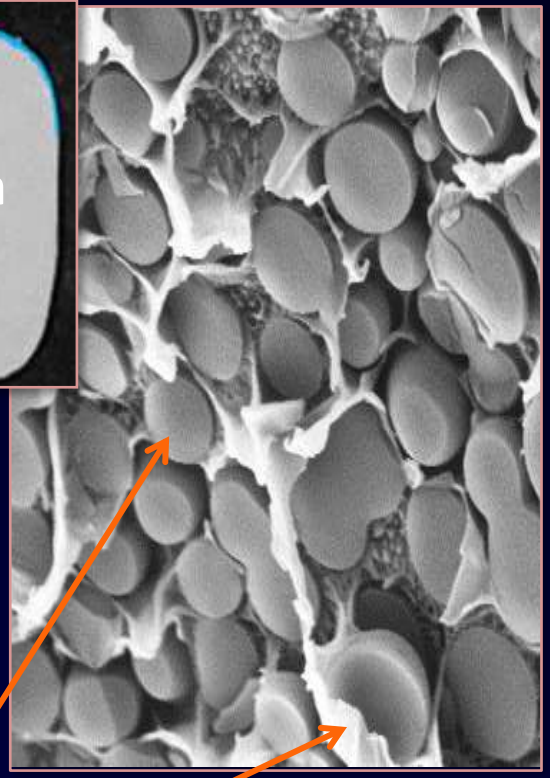
ClinicalTrials.gov Identifier: NCT02513810

P.I. Prof Myeongi-Ki Hong


Thank you for your attention
SEVERANCE CARDIOVASCULAR HOSPITAL
YONSEI UNIVERSITY COLLEGE OF MEDICINE

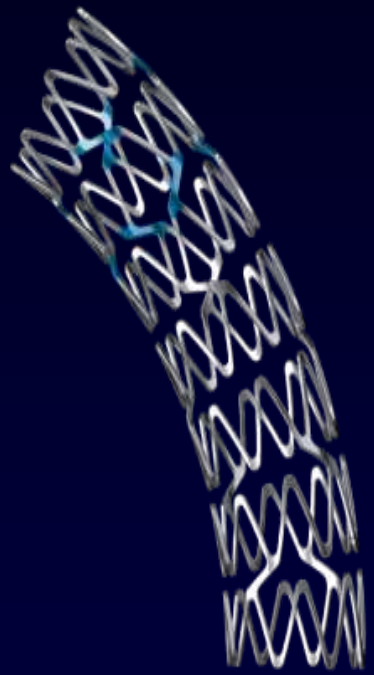
Synergy™ DES used in SENIOR





Everolimus
PLGA Polymer

SEM of coating (x5000)



BMS

Meredith I. et al. *EuroInterv* 2017

SENIOR Randomized Trial

- Objective: To evaluate outcomes with a thin-strut, bioabsorbable polymer DES vs. BMS in elderly patients (≥ 75 years old) treated with short DAPT

- Hypothesis is that DES have:
  - a lower rate of MACCE at 1 year vs. BMS (efficacy)
  - a similar risk of bleeding at 1 year vs. BMS (safety)
  - a similar risk of stent thrombosis at 1 year vs. BMS (safety)

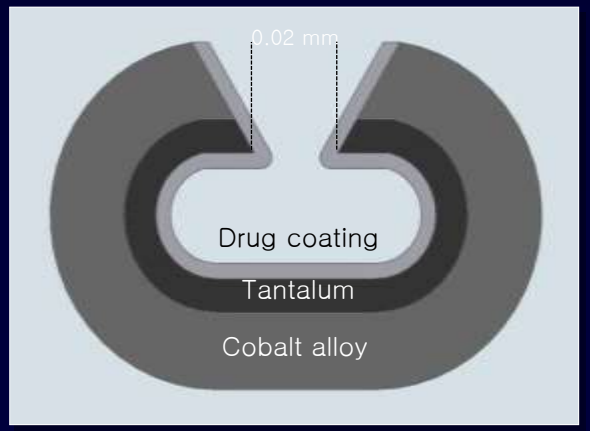
Varenne et al, Lancet 2017

Drug-Filled Stent

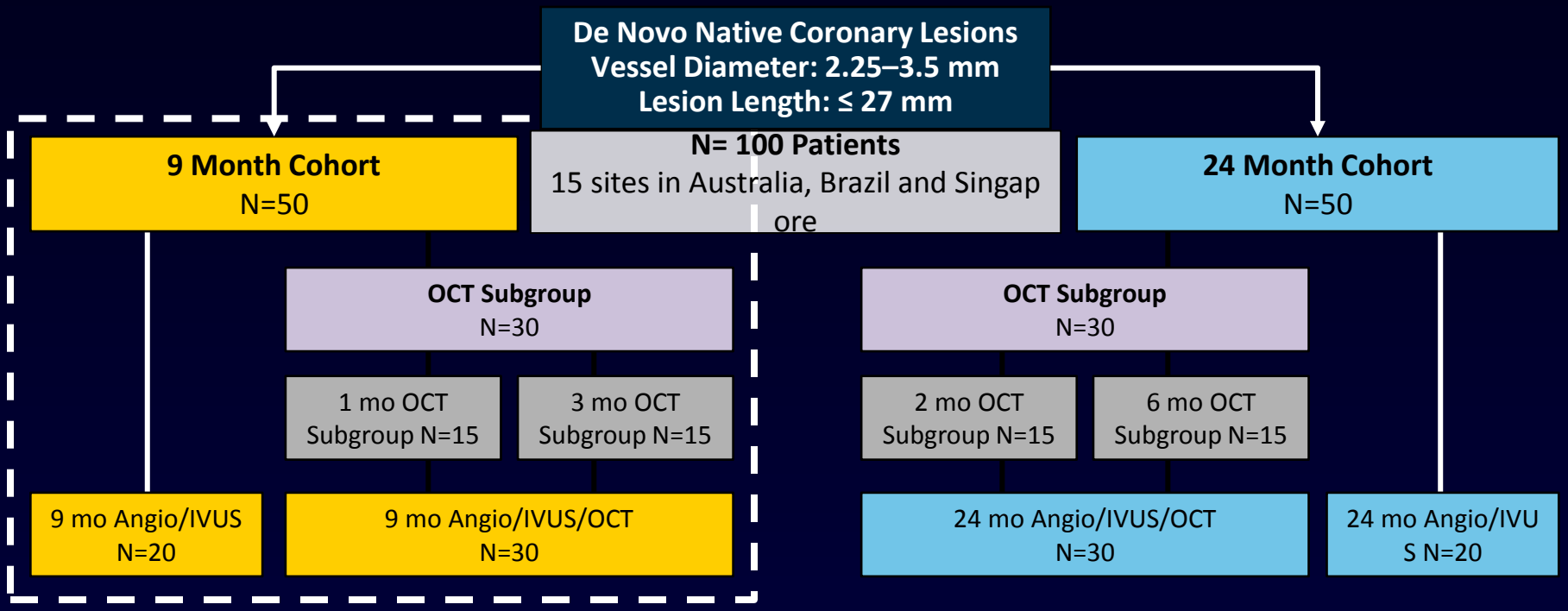
DFS is a novel polymer-free drug-eluting stent (81μm struts)

DFS is made from a tri-layer wire:

- Outer cobalt alloy layer for strength
- Middle tantalum layer for radiopacity
- Core material is removed and becomes an inner lumen that is continuously coated with drug



RevElution Trial



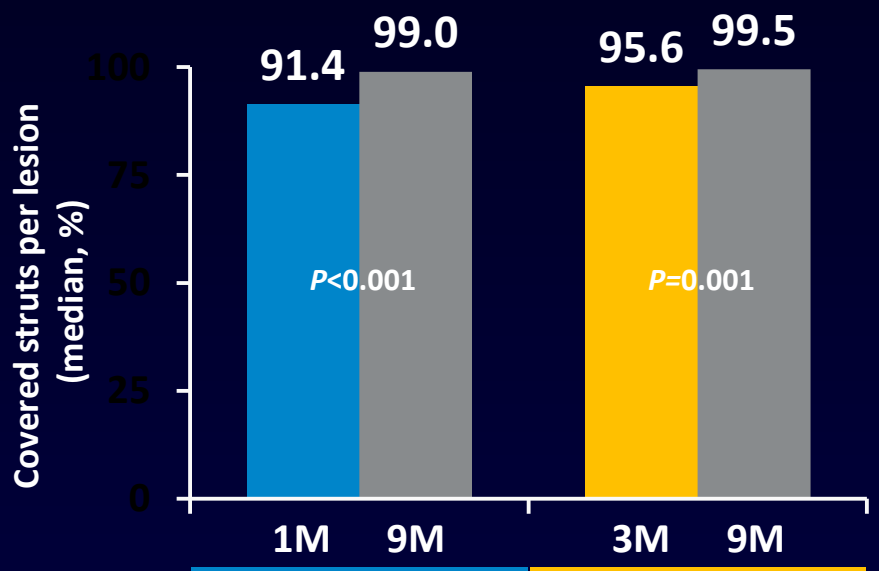
PRIMARY ENDPOINT:	**In-stent late lumen loss at 9 months in 9M cohort (50 pts)**
Key 2˚ Endpoints:	**Major Adverse Cardiac Events (MACE), Target Lesion Failure (TLF) and components**
QCA / IVUS Endpoints:	**% diameter stenosis, in-segment late lumen loss, NIH volume and % volume obstruction**
Key OCT Endpoints:	**Stent strut tissue coverage, neointimal tissue thickness, stent (mal)apposition, % volume obstruction and NIH tissue characterization**
Pharmacokinetic Analysis:	**12 PK timepoints up to 30 days will be assessed**
DAPT Regimen:	**ASA indefinitely and clopidogrel ≥ 6 months (12 m in pts not at high risk of bleeding)**

NCT02480348

RevElution Trial

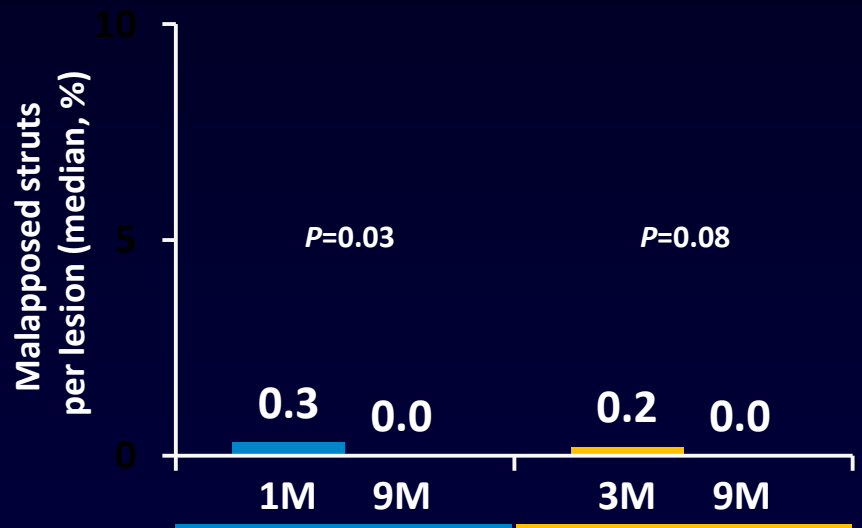
OCT Results at 1, 3 and 9 Months

Covered Struts



	1M OCT Cohort		3M OCT Cohort	
IQR	84.8 to 93.2	97.9 to 99.8	90.3 to 97.2	98.3 to 100
Mean	89.3 ± 6.3	98.1 ± 2.7	92.9 ± 6.0	98.8 ± 2.0

Malapposed Struts



	1M OCT Cohort		3M OCT Cohort	
IQR	0 to 2.3	0 to 0	0 to 7.0	0 to 0
Mean	1.5 ± 2.3	0.1 ± 0.4	1.1 ± 2.2	0.3 ± 0.8

Worthley S, et al. JACC Interv. 2017;10(2):147-156.