Choice of Stent Platforms in HBR Patients Insights from the ONYX ONE trial

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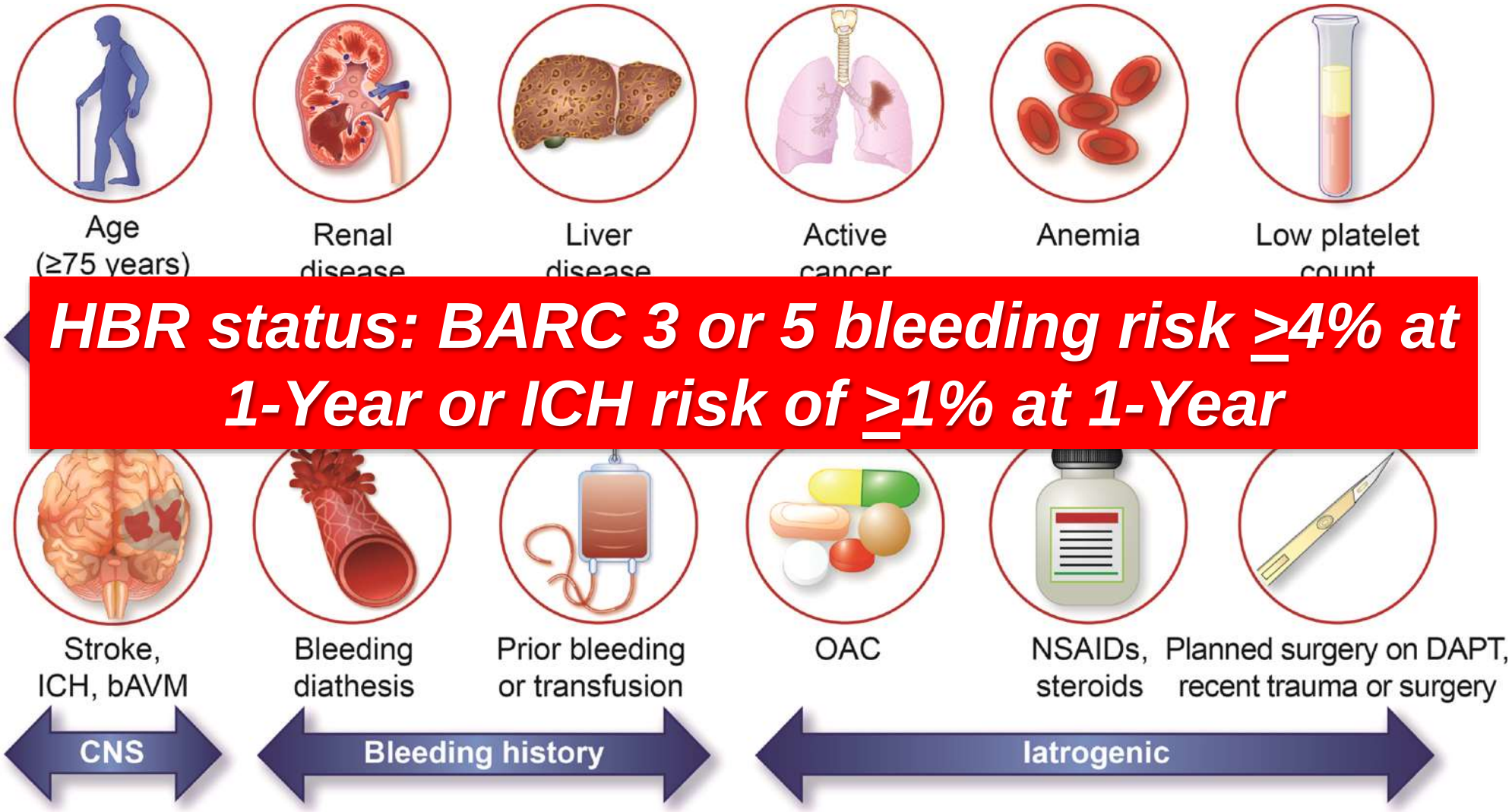
Disclosure Statement of Financial Interest

I, Stephan Windecker, declare the following:

- Research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson&Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, Sinomed
- Unpaid member of the steering/excecutive group of trials funded by Abbott, Abiomed, Amgen, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Polares, Sinomed, V-Wave and Xeltis, but no personal payments by pharmaceutical companied or device manufacturers.

FACTORS ASSOCIATED WITH BLEEDING AFTER PCI

Urban P et al. *Eur Heart J* 2019;40:2632-53

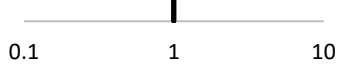


Mortality Risk of MI vs Bleeding After PCI

Valgimigli M. et al. *Eur Heart J*. 2017;38:804-810

- 12944 NSTEACS patients from the TRACER trial
- Impact of MI and bleeding occuring >30 days after PCI on all-cause mortality at 1 year

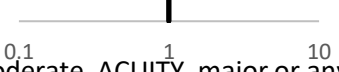
	HR (95%CI)
MI	**5.36** (4.26-6.74)
BARC 1 bleeding	0.89 (0.61-1.34)
BARC 2 bleeding	1.70 (1.23-2.36)
BARC 3 bleeding	**5.73** (4.32-7.59)



Généreux P. et al. *J Am Coll Cardiol*. 2015;66:1036-1045

- 8582 all-comer patients from the ADAPT-DES trial
- Impact of post-discharge MI and bleeding >30 days after PCI on All-cause mortality at 2 years

	HR (95%CI)
Post-discharge MI	**1.92** (1.18-3.12)
Post-discharge bleeding*	**5.03** (3.29-7.66)
With transfusion	4.71 (2.76-8.03)
Without transfusion	5.27 (3.32-8.35)

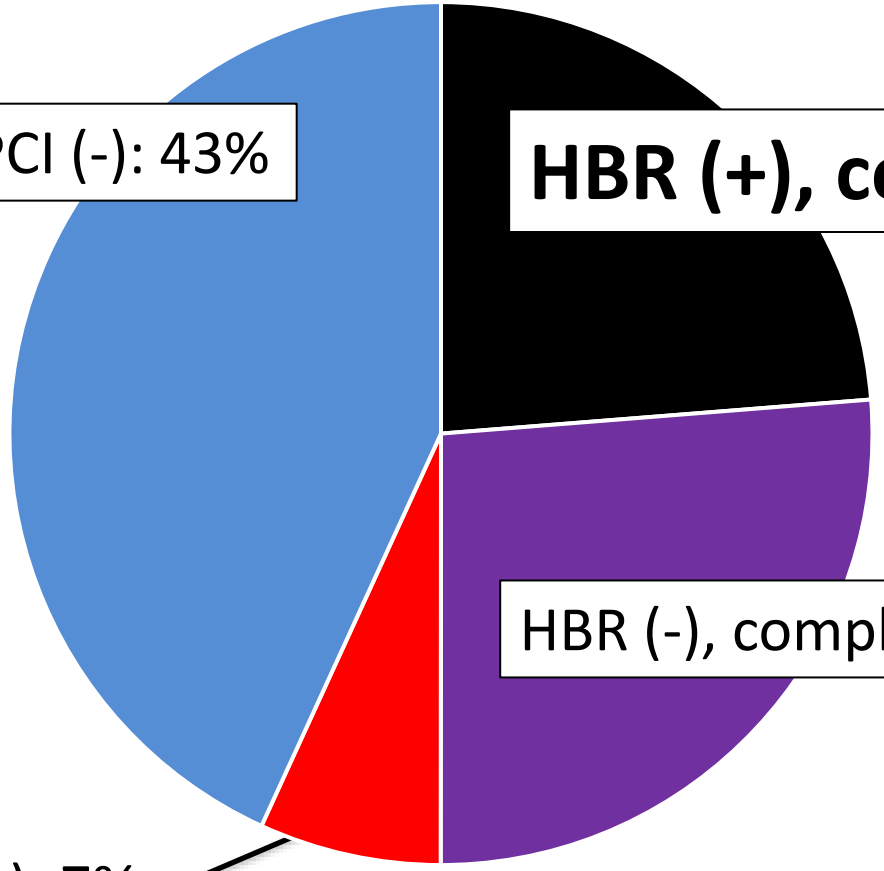


*TIMI major/minor, GUSTO severe/moderate, ACUITY major or any bleeding requires medical attention

Bleeding Risk and Complex PCI frequently Co-exist

Ueki et al. *JACC Cardiovasc Interv.* 2019;12:820-830

Bern PCI Registry 2009-2015 (n=8344)



HBR (-), complex PCI (-): 43%

HBR (+), complex PCI (+): 24%

HBR (-), complex PCI (+): 26%

HBR (+), complex PCI (-): 7%

HBR = PRECISE-DAPT score ≥25

PCI complexity (ESC 2017 DAPT update)
At least 1 of the followings:

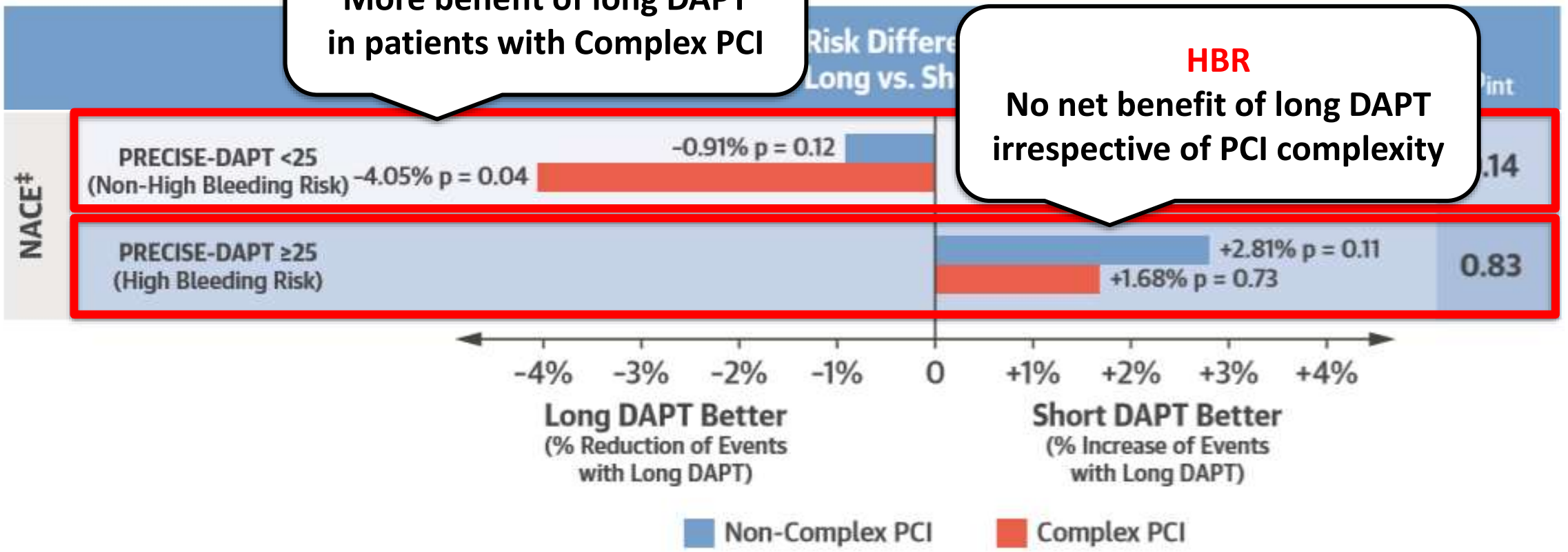
- At least 3 stents implanted
- At least 3 lesions treated
- Total stent length >60mm
- Bifurcation with 2 stents
- Diffuse multivessel disease with DM
- CKD

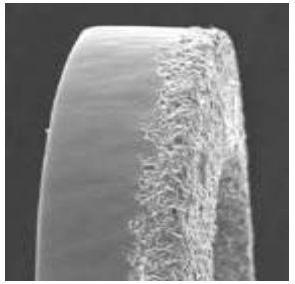
Bleeding or Ischemic Risk, Which Should be Prioritized?

Costa F et al. *J Am Call Cardiol* 2019;73:741-754

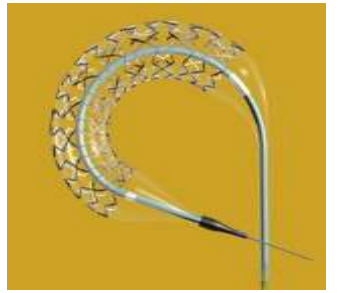
No HBR
More benefit of long DAPT in patients with Complex PCI

HBR
No net benefit of long DAPT irrespective of PCI complexity





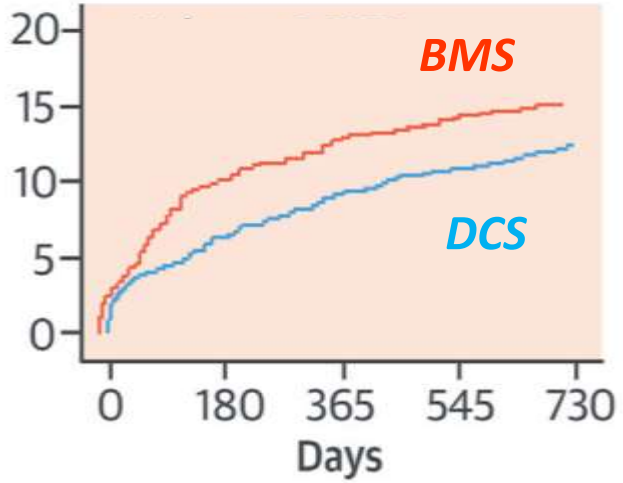
POLYMER-FREE DES VS. BMS IN PATIENTS AT HIGH RISK OF BLEEDING: LEADERS FREE TRIAL



Garot P. et al. *J Am Coll Cardiol.* 2017;69:162-71

2,466 Pts – 2Yr FU. HBR status: Age≥75 Yrs (64%), OAC (36%), Hb<11 g/L or recent transfusion (15%), CrCl <40 ml/min (18%), Planned surgery (16%)

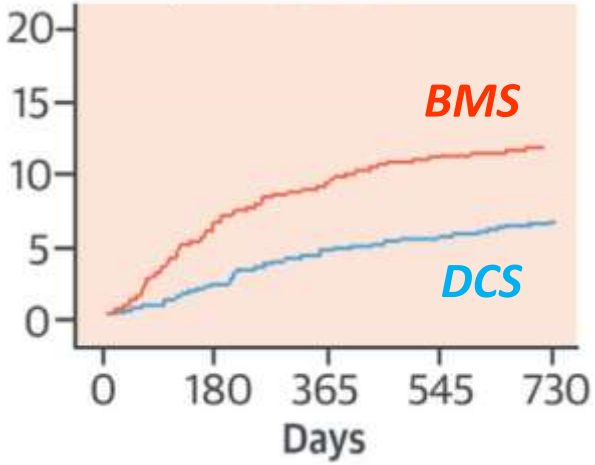
Cdeath, MI or ST



P=0.039

12.6% vs. 15.3%

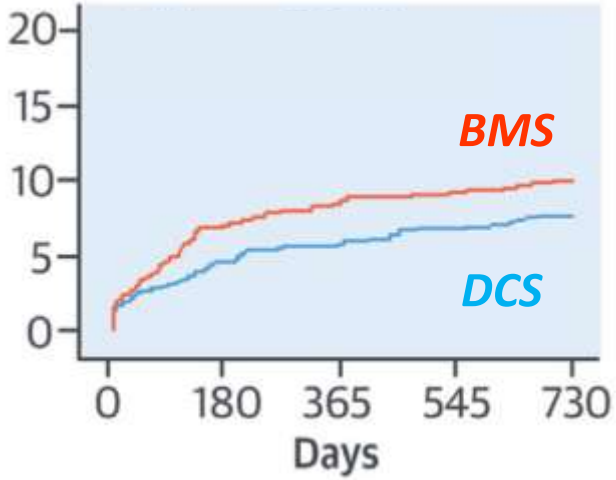
Target-lesion Revasc



P<0.001

6.8% vs. 12%

Any MI



P=0.04

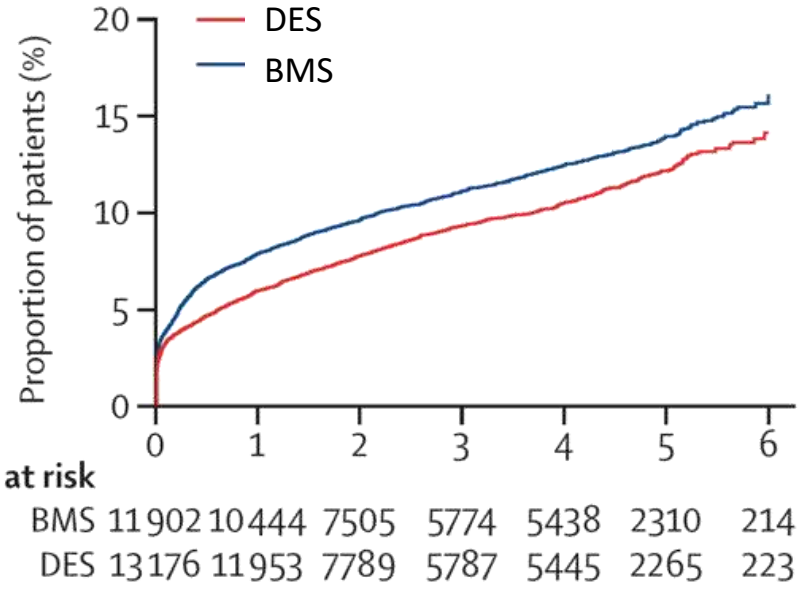
7.4% vs. 10.1%

DES Vs. BMS For PCI: Coronary Stent Trialists' (CST) Collaboration

Piccolo R et al. *Lancet* 2019;393:2503-2510

IPD Meta-analysis of 20 RCTs (N=26,616) - Mean FU 3.2 Yrs – ZEUS, LEADERS FREE & SENIOR included

Cardiac Death or MI



Number at risk

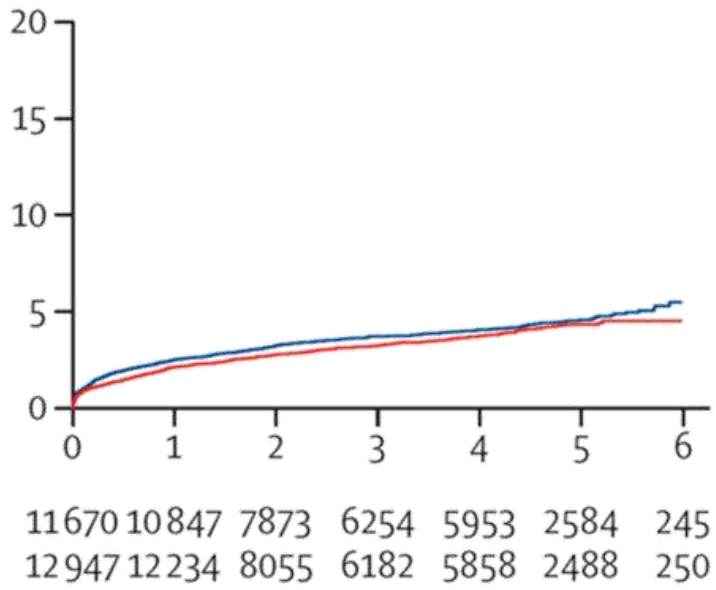
BMS	11902	10444	7505	5774	5438	2310	214
DES	13176	11953	7789	5787	5445	2265	223

HR 0.84

95%CI 0.78-0.90

P<0.001

Cardiac Death



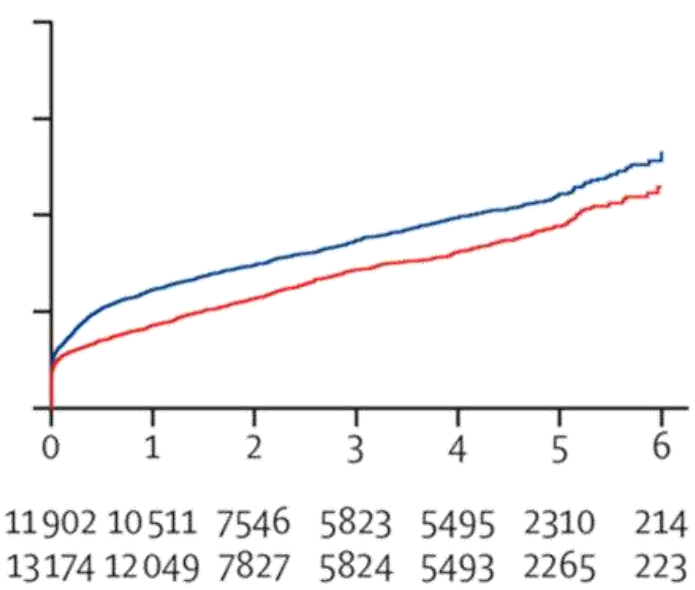
	11670	10847	7873	6254	5953	2584	245
	12947	12234	8055	6182	5858	2488	250

HR 0.89

95%CI 0.78-1.01

P=0.075

Myocardial Infarction



	11902	10511	7546	5823	5495	2310	214
	13174	12049	7827	5824	5493	2265	223

HR 0.79

95%CI 0.71-0.88

P<0.001

2018 Myocardial Revascularization Guidelines: Role of New DES

Neumann F-J et al. *Eur Heart J* 2019;40:87-165

Recommendations	Class	Level
DES are recommended over BMS for any PCI irrespective of: • clinical presentation, • lesion type, • planned non-cardiac surgery, • anticipated duration of DAPT, • concomitant anticoagulant therapy.	I	A

HBR Trials with New-generation DES

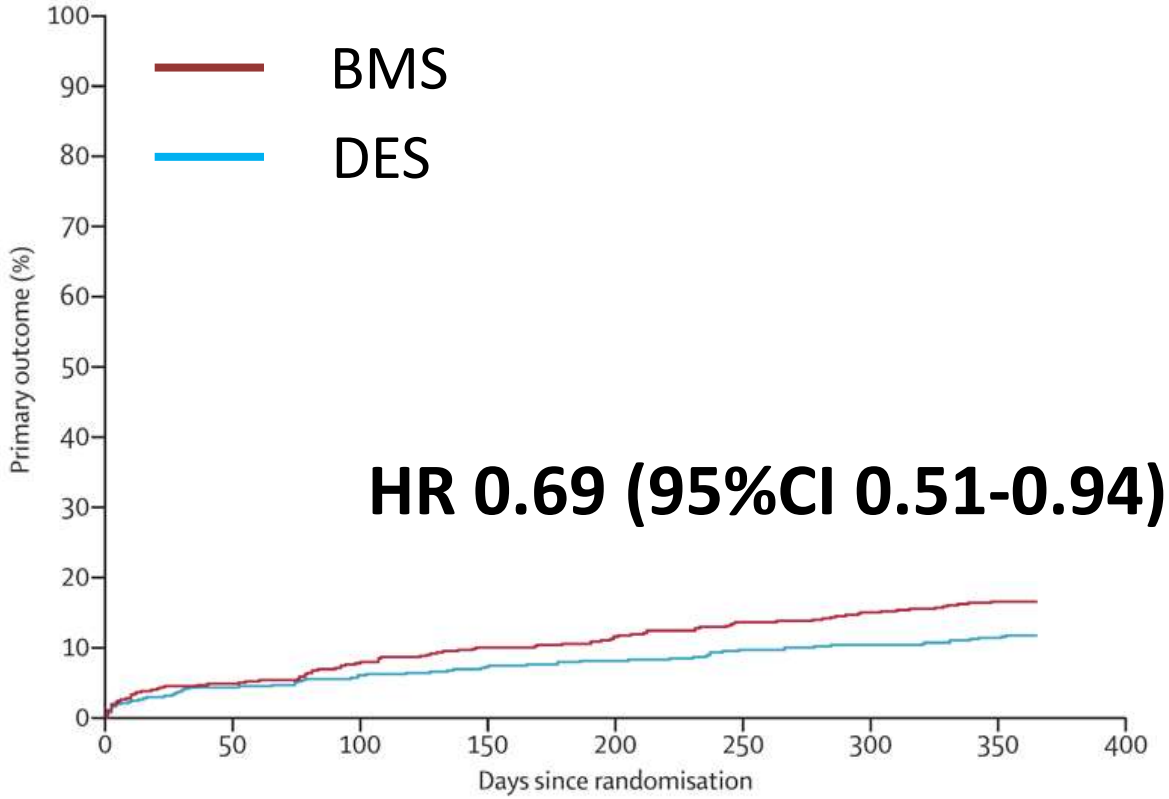
Study	NCT	Device	DAPT Duration	Study Design	Patients
Onyx ONE	NCT03344653	Resolute vs. BioFreedom	1 month	RCT (vs. DCS)	2,000
SENIOR	NCT02099617	Synergy vs. BMS	1 month (CCS) or 6 months (ACS)	RCT (vs. BMS)	1,200
EVOLVE Short DAPT	NCT02605447	Synergy	3 months	Single-arm study	2,009
MASTER-DAPT	NCT03023020	Ultimaster	1 vs. 12 months	RCT (DAPT)	4,300
POEM	NCT03112707	Synergy	1 month	Single-arm study	1,023
XIENCE 90 SHORT DAPT	NCT03218787	Xience	3 months	Single-arm study	2,000
XIENCE 28 GLOBAL	NCT03355742	Xience	28 days	Single-arm study	800
TARGET SAFE	NCT03287167	Firehawk	1 vs. 6 months	RCT (DAPT)	1,720
COBRA REDUCE	NCT02594501	Cobra PzF vs. new-DES	2 weeks vs. 3-6 months	RCT (2x2)	996

BP-EES vs. BMS in Elderly Patients: SENIOR

Varenne O et al. *Lancet* 2018;391:41–50

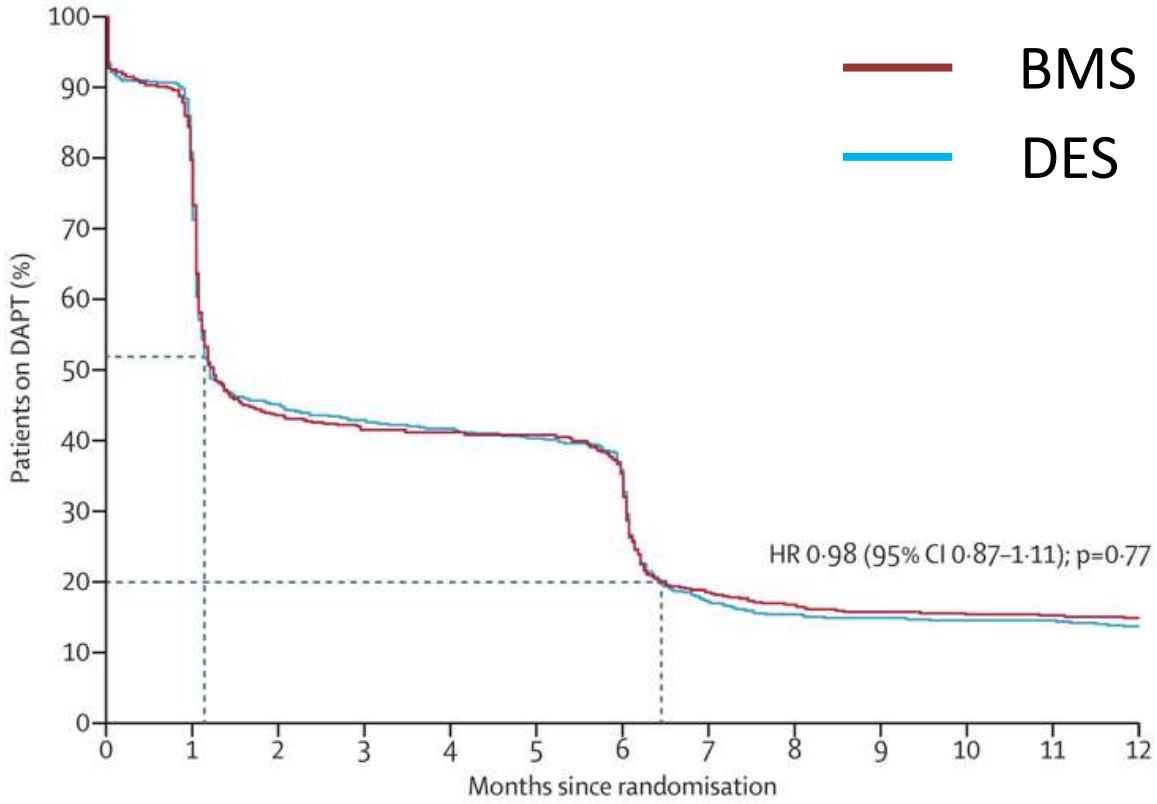
1,200 Patients ≥75 Yrs randomized to SYNERGY EES (N=596) or BMS (N=604)
DAPT for 1 month in CCS and 6-month for ACS

All cause Death, MI, Stroke, ID-TLR



HR 0.69 (95%CI 0.51-0.94)

Time to DAPT Interruption

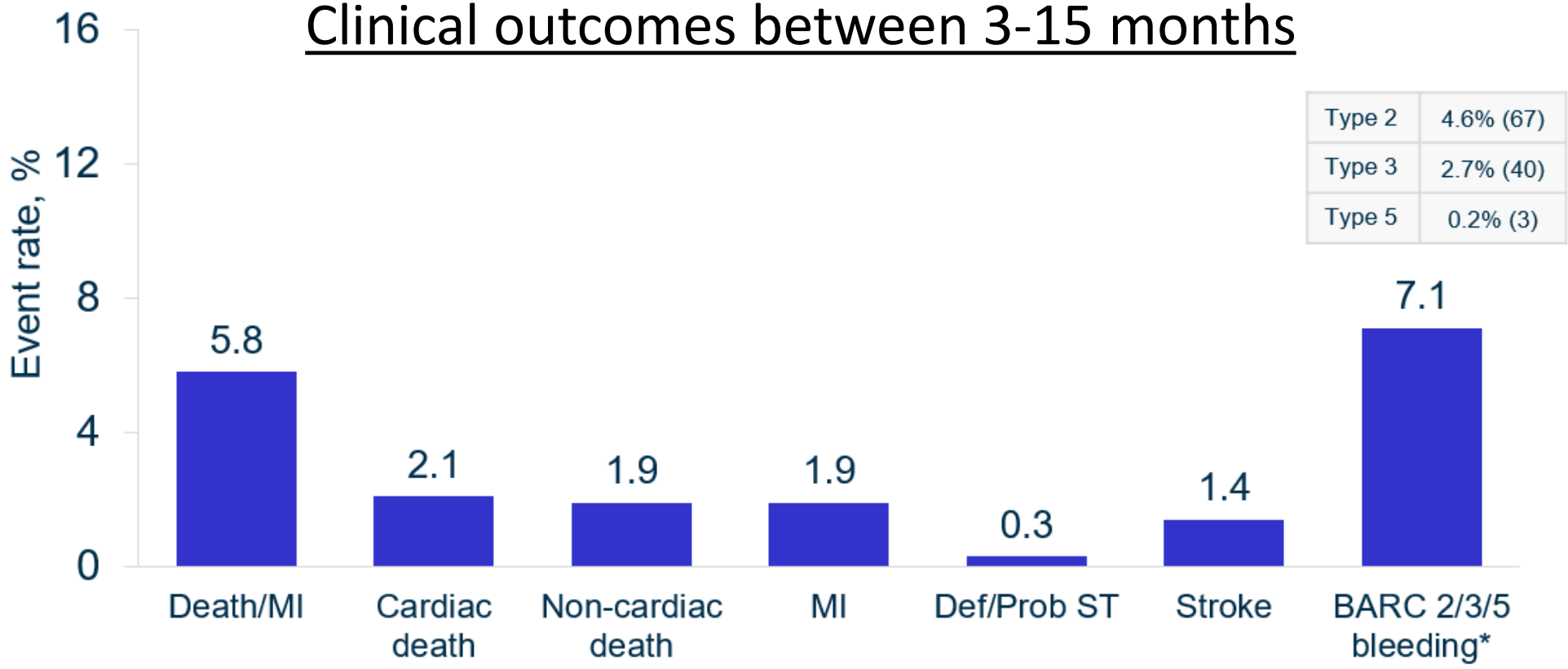


EVOLVE SHORT DAPT: 3-MONTH DAPT IN HBR PATIENTS TREATED WITH SYNERGY

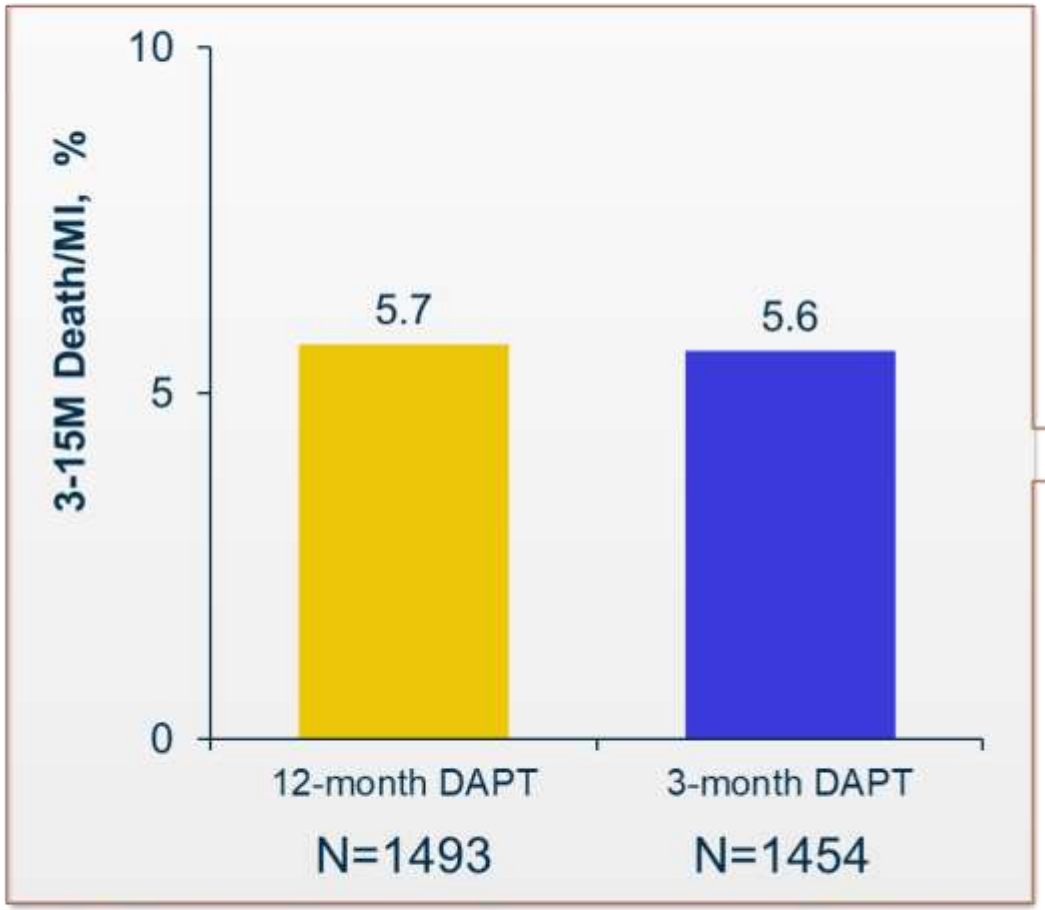
Kirtane A et al Presented at TCT 2019

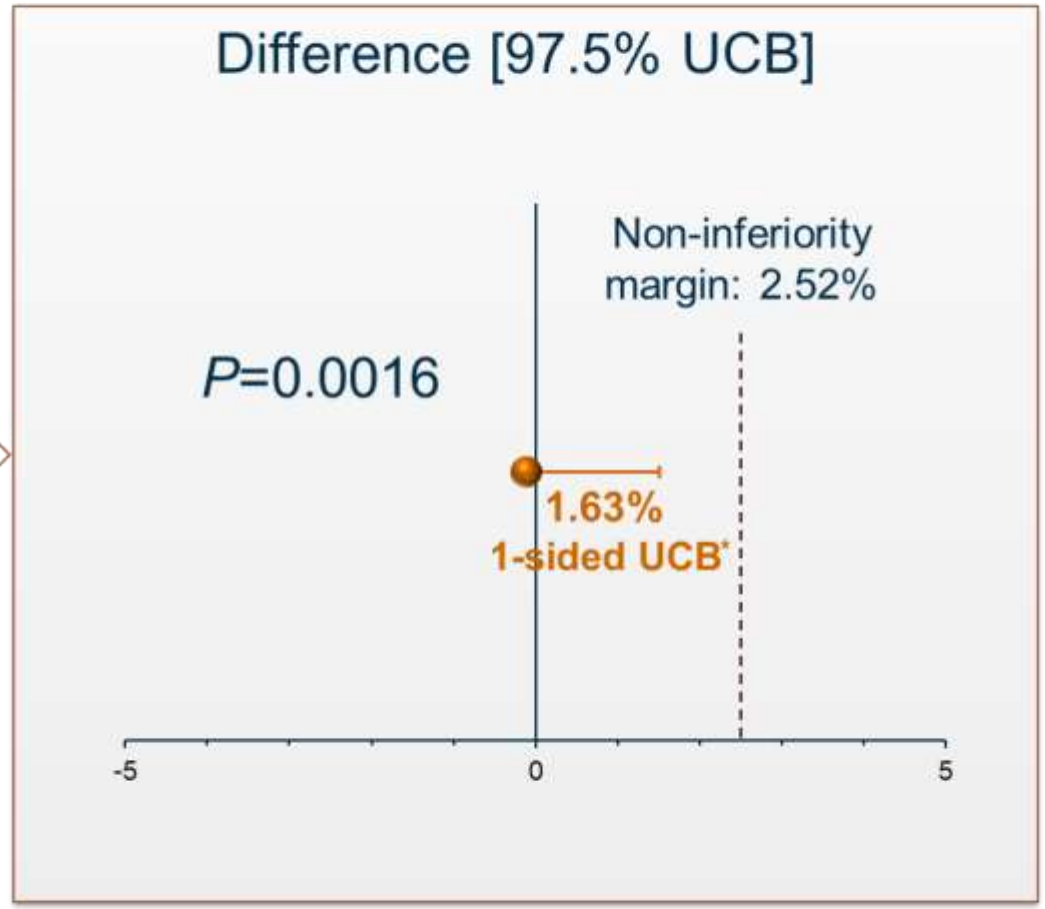
- Multicenter, single-arm study
- Analysis population: 1487 event-free HBR patients treated with Synergy and 3-month DAPT followed by aspirin alone
- Age 76 yo, male 66%, DM 10%, mean 1.3 HBR criteria/pt, mean stent length 28mm

Clinical outcomes between 3-15 months



Co-Primary Endpoint: Adjusted Death/MI between 3-15 months with 3-Month DAPT Compared to Historical Control





Patients with respective event or sufficient follow-up included in the denominator

*One-sided 97.5% Upper Confidence Bound (Lower); Worst-case scenario analysis: all reported MI in control group between 6-15m assumed within 3-6m & not CEC adjudicated

DURABLE-POLYMER DES VS. POLYMER-FREE DCS IN HBR PATIENTS TREATED WITH 1-MONTH DAPT: ONYX ONE

Windecker S et al. *N Engl J Med* 2020;26:1208-1218

Prospective, Multicenter, Single-blind Randomized Trial

High Bleeding Risk patients undergoing PCI
(no lesion, vessel limitations)

Resolute Onyx™ ZES
with 1 Month DAPT
(N=1000)

1:1 randomization
84 global sites
Enrollment Nov 2017 – Sep 2018

BioFreedom™ DCS
with 1 Month DAPT
(N=1000)

Clinical Follow-up

1mo | 2mo | 6mo | 1yr | 2yr

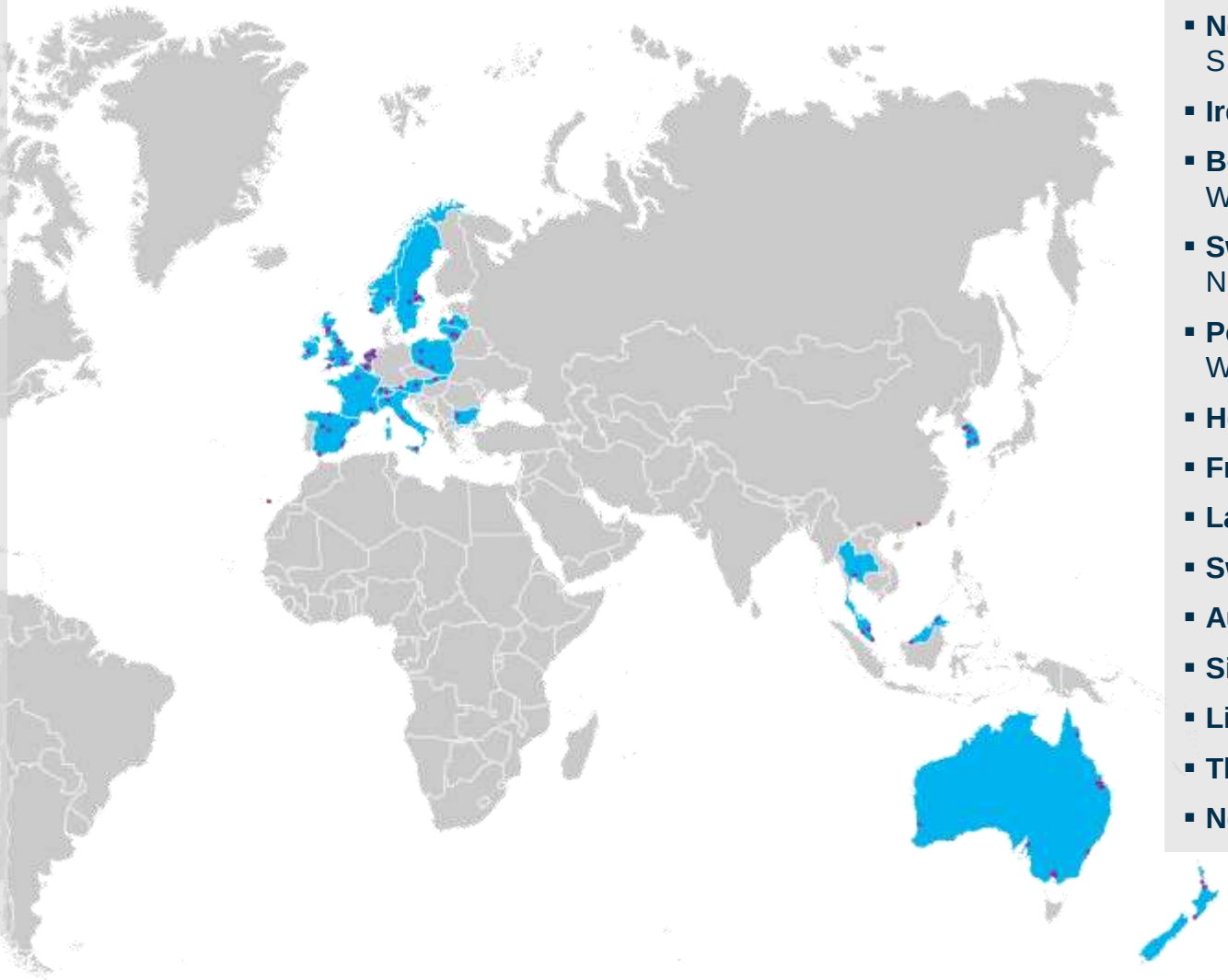
Primary safety endpoint: Cardiac death, MI or stent thrombosis (def/prob) at 1 year

2° Efficacy endpoint (powered): Target Lesion Failure (TLF: cardiac death, TV-MI or cd-TLR) at 1 year

Other secondary endpoints: Lesion, device and procedure success rates, BARC bleeding, individual components of primary endpoints

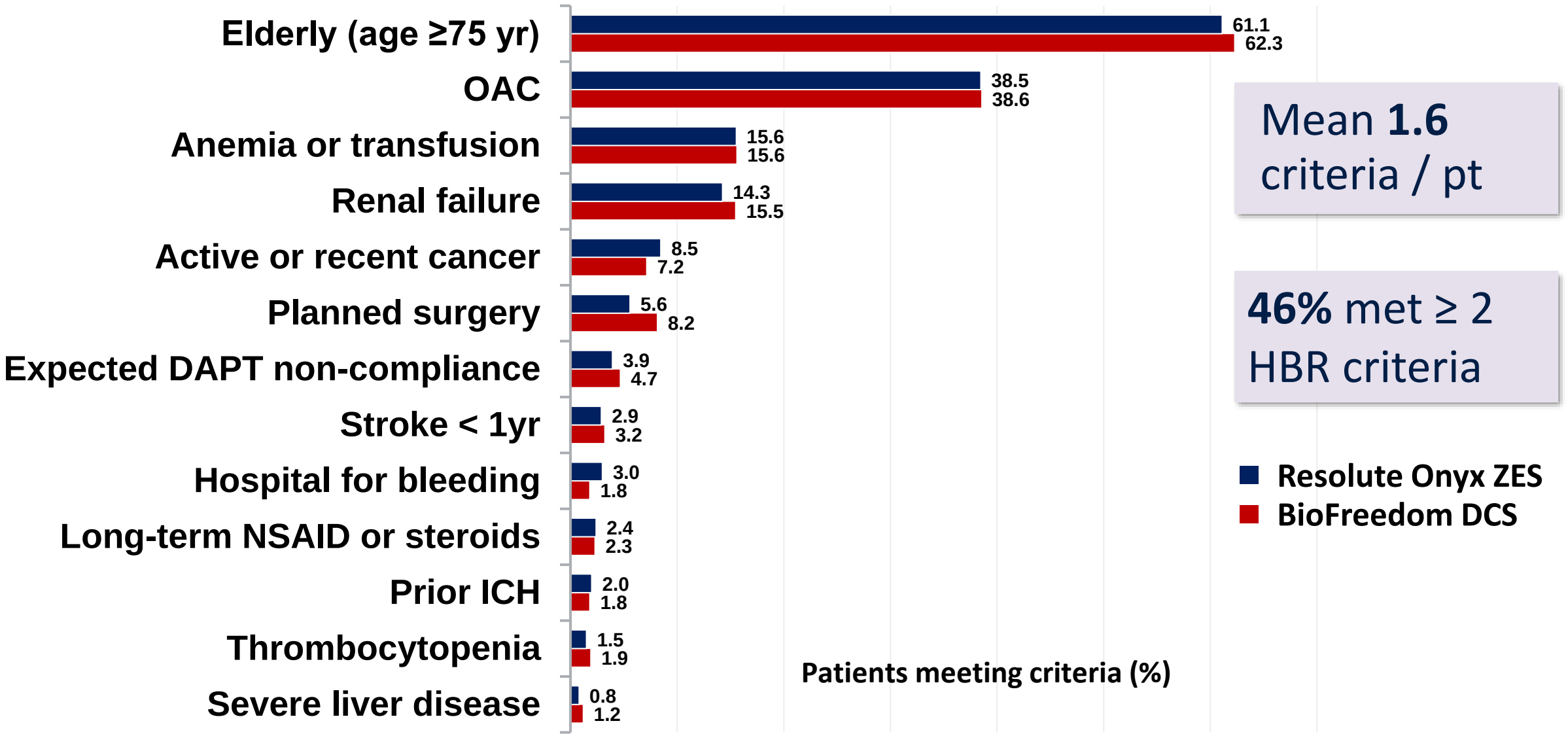
84 Participating Centers

- **Republic of Korea:** H-S Kim, S-H Hur, Y Jang, IH Chae, MH Jeong, J Yoon, H-C Gwon, K Chang, S-J Park
- **Spain:** E Pinar, R Moreno, F Bosa, B Vaquerizo, J De la Torre, A Cequier, V Mainar, I Cruz
- **Slovakia:** M Hudec
- **Malaysia:** AKA Ghapar, TK Ong, HB Liew, AA Nuruddin
- **Australia:** C Tie, A Conradie, A Walton, C Hammett, P Garrahy, C Raffel, G Starmer, A Sinhal, S Shetty, R Bhindi, R Whitbourn
- **Italy:** F Fabbiocchi, A Latib, G Sardella, C Tamburino
- **Netherlands:** E Kedhi, A Van 't Hof, R Troquay, P Agostoni, S Somi, P van der Harst
- **Bulgaria:** I Petrov
- **United Kingdom:** D Muir, K Oldroyd, A Sharp, R Anderson, N Uren, A Zaman, S Kalra, P Strike



- **New Zealand:** S Pasupati, S Harding, M Webster
- **Ireland:** D Mylotte
- **Belgium:** A Aminian, P Lancelotti, W Desmet
- **Sweden:** E Diderholm, R Kastberg, N Witt, O Frobert, L Henareh
- **Poland:** A Wlodarczak, M Lesiak, W Wojakowski
- **Hong Kong:** F Tam, MKY Lee
- **France:** B Chevalier, M Silvestri
- **Latvia:** A Grave, A Kalnins
- **Switzerland:** T Moccetti, S Windecker
- **Austria:** G Toth, G Friedrich
- **Singapore:** P Ong, KH Chan
- **Lithuania:** A Baranauskas, R Unikas
- **Thailand:** D Tresukosol
- **Norway:** A Opdahl, AI Larsen

HBR Inclusion Criteria



Baseline Characteristics

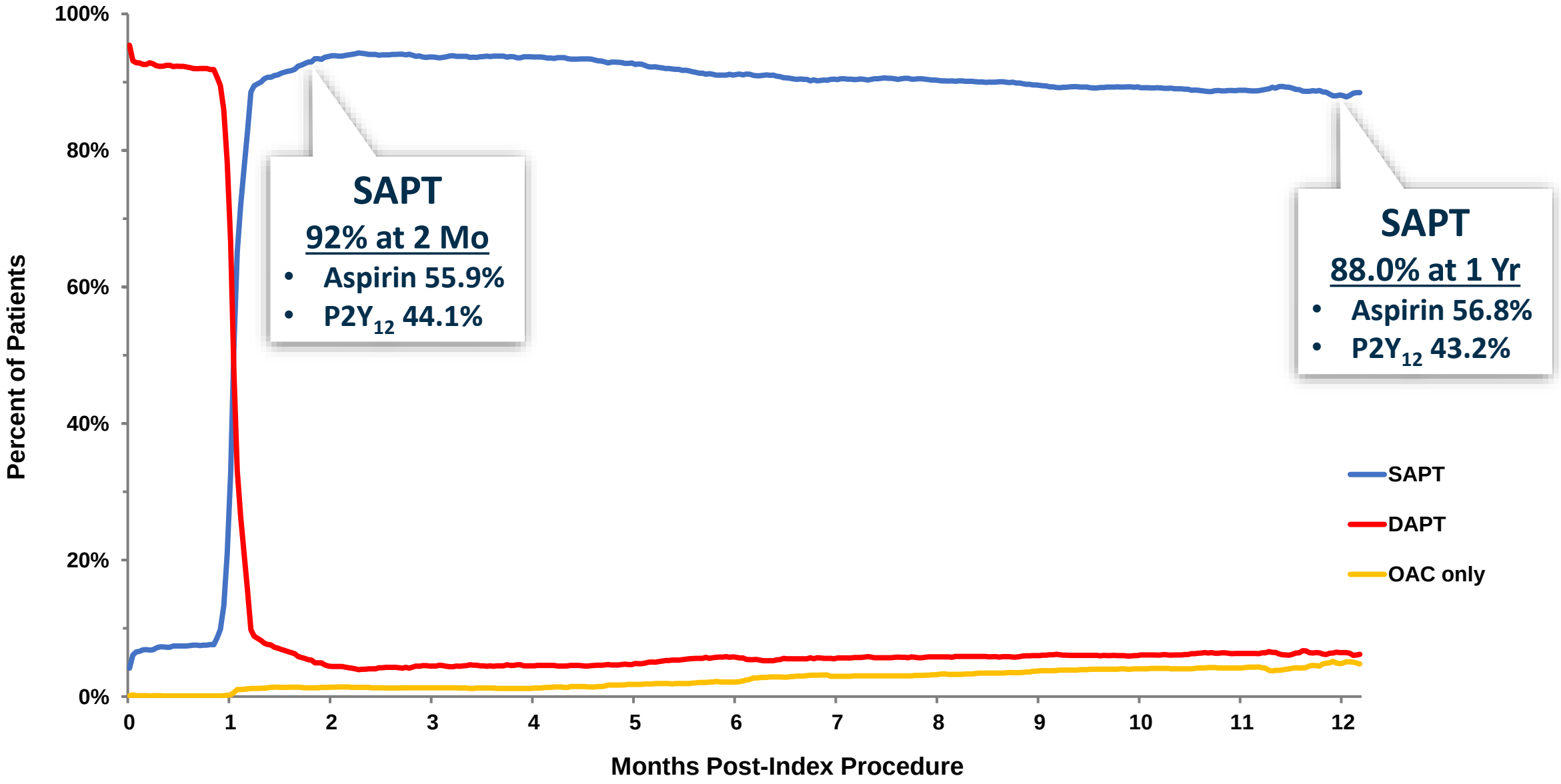
% or mean ± SD	Resolute Onyx (N=1003)	BioFreedom (N=993)
Age (yrs)	74.0 ± 9.5	74.1 ± 9.8
Female	32.5	34.2
Diabetes	38.7	38.5
Hypertension	79.4	81.3
Hyperlipidemia	64.1	62.3
Previous MI	26.3	25.1
Previous revascularization	31.3	29.8
Atrial fibrillation	32.7	31.8
Silent ischemia	9.1	11.0
Chronic coronary syndrome	38.1	38.6
Acute coronary syndrome	52.8	50.4
STEMI	6.2	5.1
Non-STEMI	27.1	27.0
Unstable angina	19.5	18.3

Procedural Characteristics

% or mean ± SD	Resolute Onyx (N=1003)	BioFreedom (N=993)	*P*-value
Cross-over to other study stent	0.2 (2)	4.0 (40)	<0.001
Pre-procedural QCA			
Lesion length (mm)	21.2 ± 12.5	20.8 ± 12.7	0.48
RVD (mm)	2.84 ± 0.46	2.83 ± 0.44	0.74
MLD (mm)	0.89 ± 0.41	0.90 ± 0.41	0.42
% Diameter stenosis	68.6 ± 13.4	68.2 ± 13.2	0.44
Post-procedural QCA			
% Diameter stenosis (in-stent)	9.9 ± 8.7	11.2 ± 9.4	<0.001
% Diameter stenosis (in-segment)	20.2 ± 9.8	21.2 ± 10.3	0.02
Acute gain (mm, in-stent)	1.72 ± 0.49	1.67 ± 0.48	0.004
Acute gain (mm, in-segment)	1.43 ± 0.50	1.39 ± 0.50	0.045
Lesion success[1]	93.8	94.2	0.67
Device success[2]	92.8	89.7	0.007
Procedure success[3]	83.3	86.2	0.09

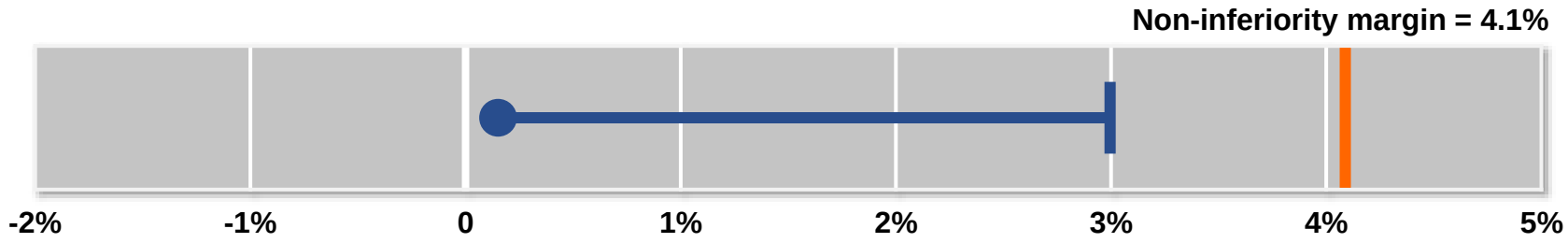
[1] The attainment of <30% residual stenosis by QCA (or <20% by visual assessment) and TIMI flow 3 after the procedure, using any percutaneous method.
[2] The attainment of <30% residual stenosis by QCA (or <20% by visual assessment) and TIMI flow 3 after the procedure, using the assigned device only.
[3] The attainment of <30% residual stenosis by QCA (or <20% by visual assessment) and TIMI flow 3 after the procedure, using any percutaneous method without the occurrence of MACE during the hospital stay.

Antithrombotic Therapy Transition After PCI



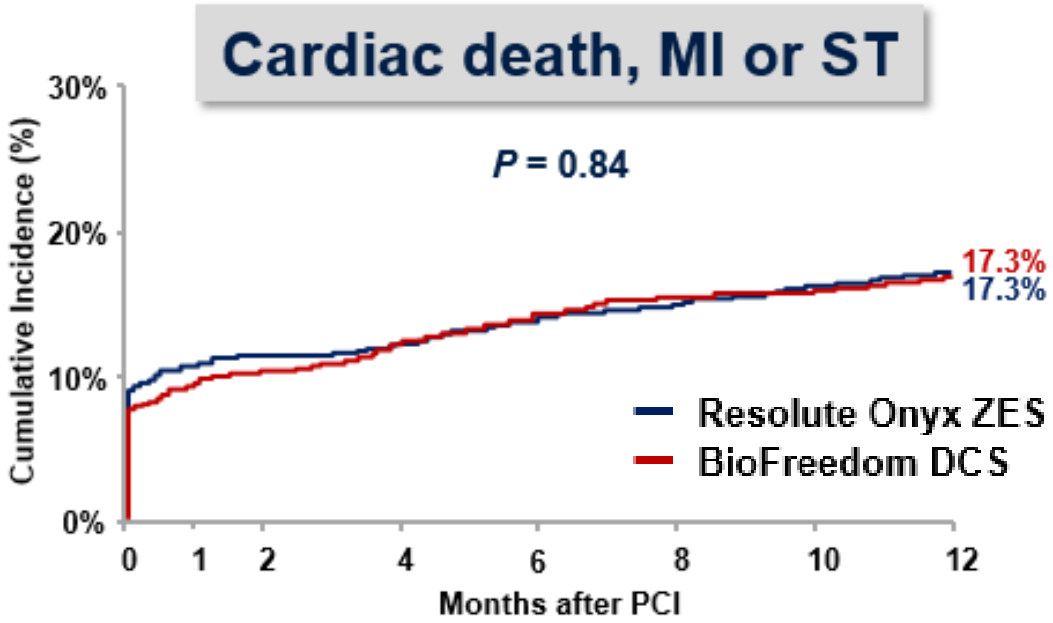
Primary Safety Endpoint: Cardiac Death, MI, ST

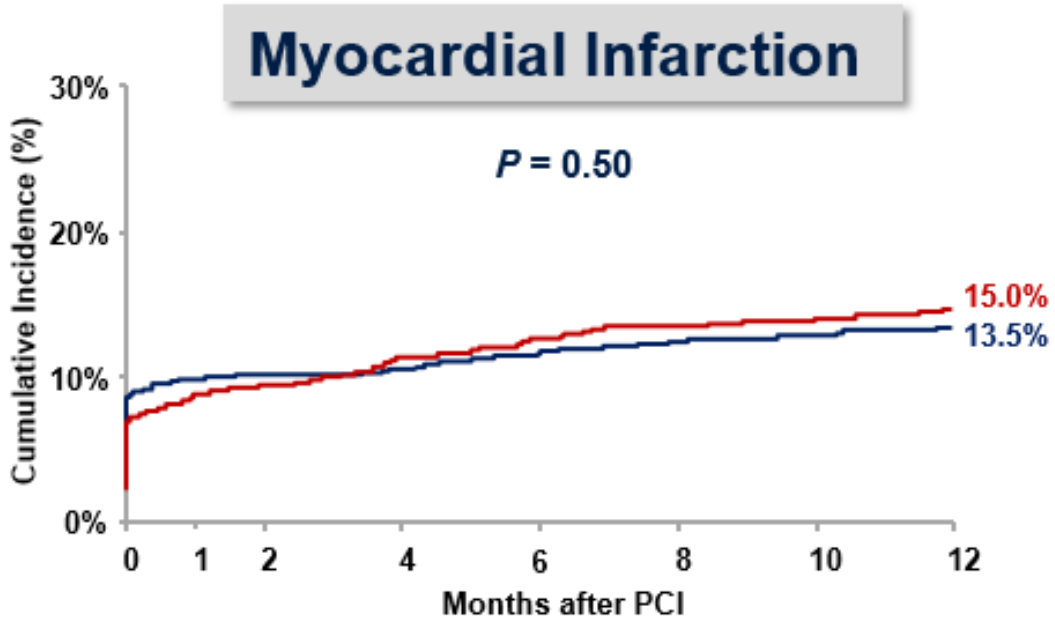
Resolute Onyx (N=1003)	BioFreedom (N=993)	Difference: 0.2% Upper 1-sided 95% CI: 3.0%	*P*-value non-inferiority
17.1%	16.9%		0.011

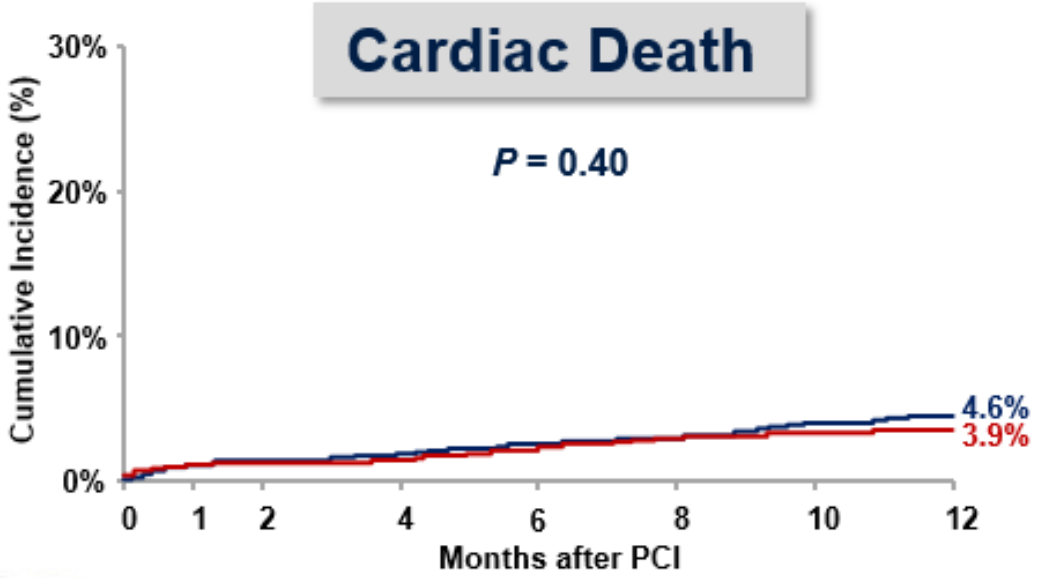


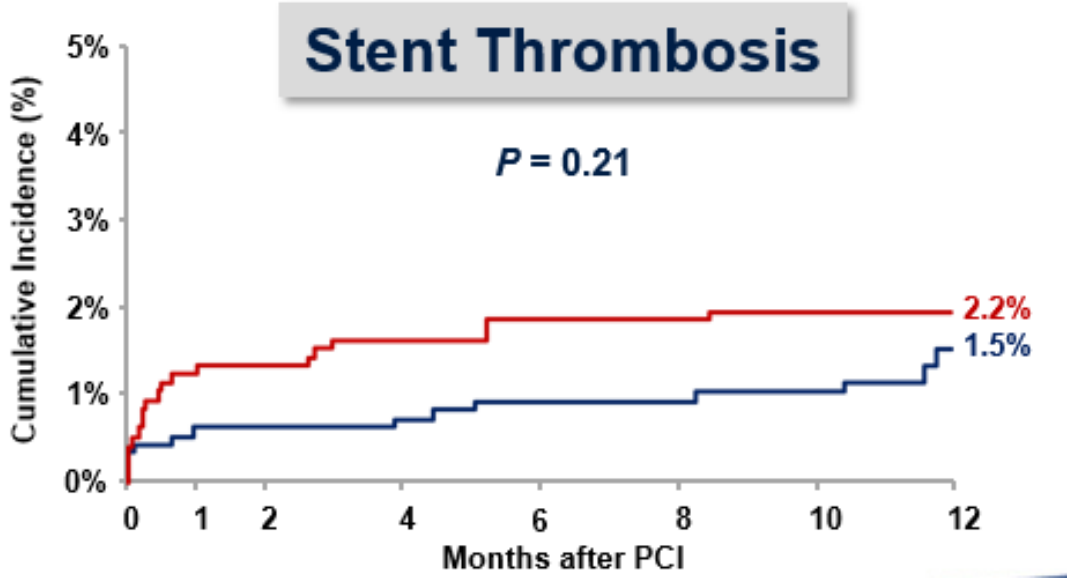
Non-Inferiority Endpoint Met

Primary Safety Endpoint and Components

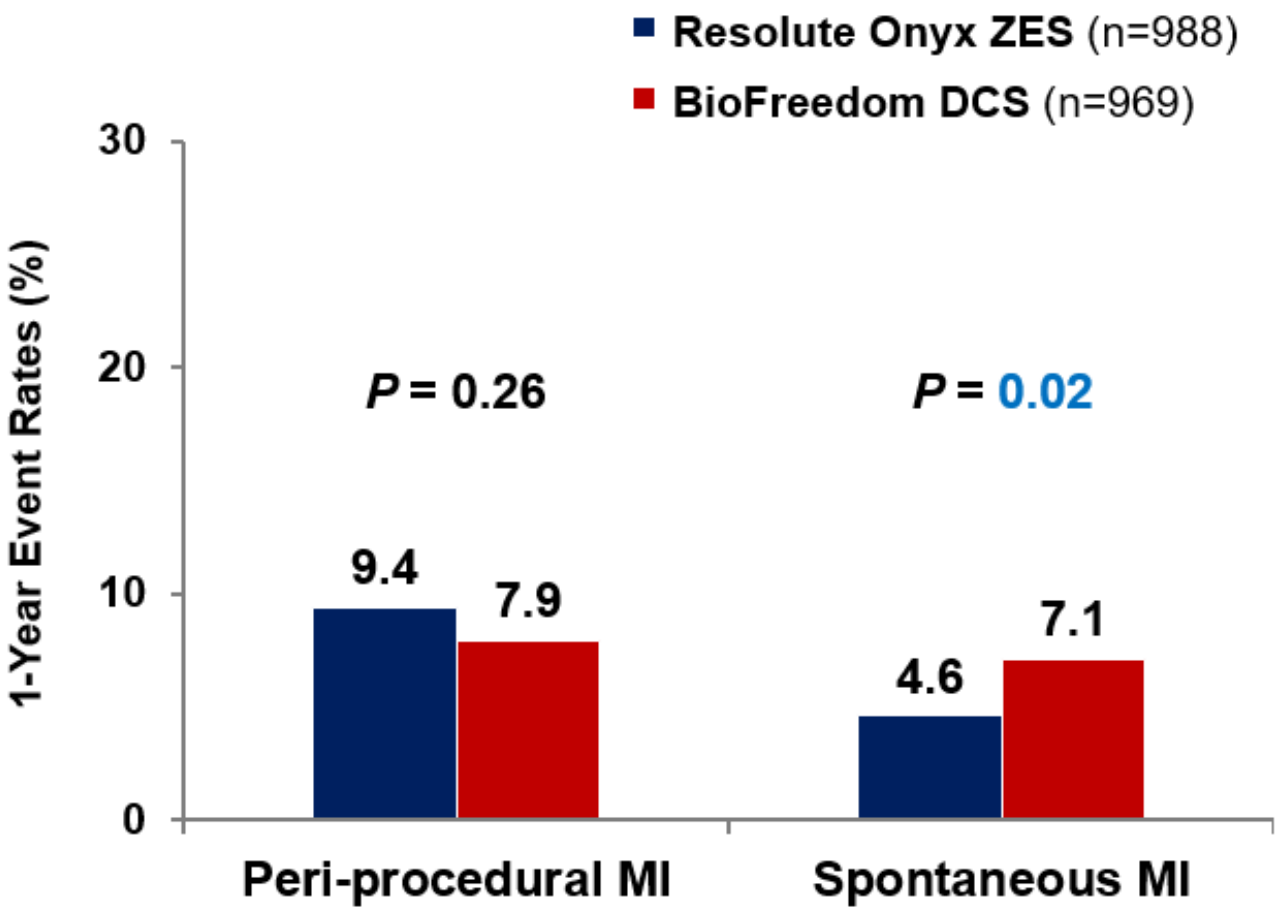




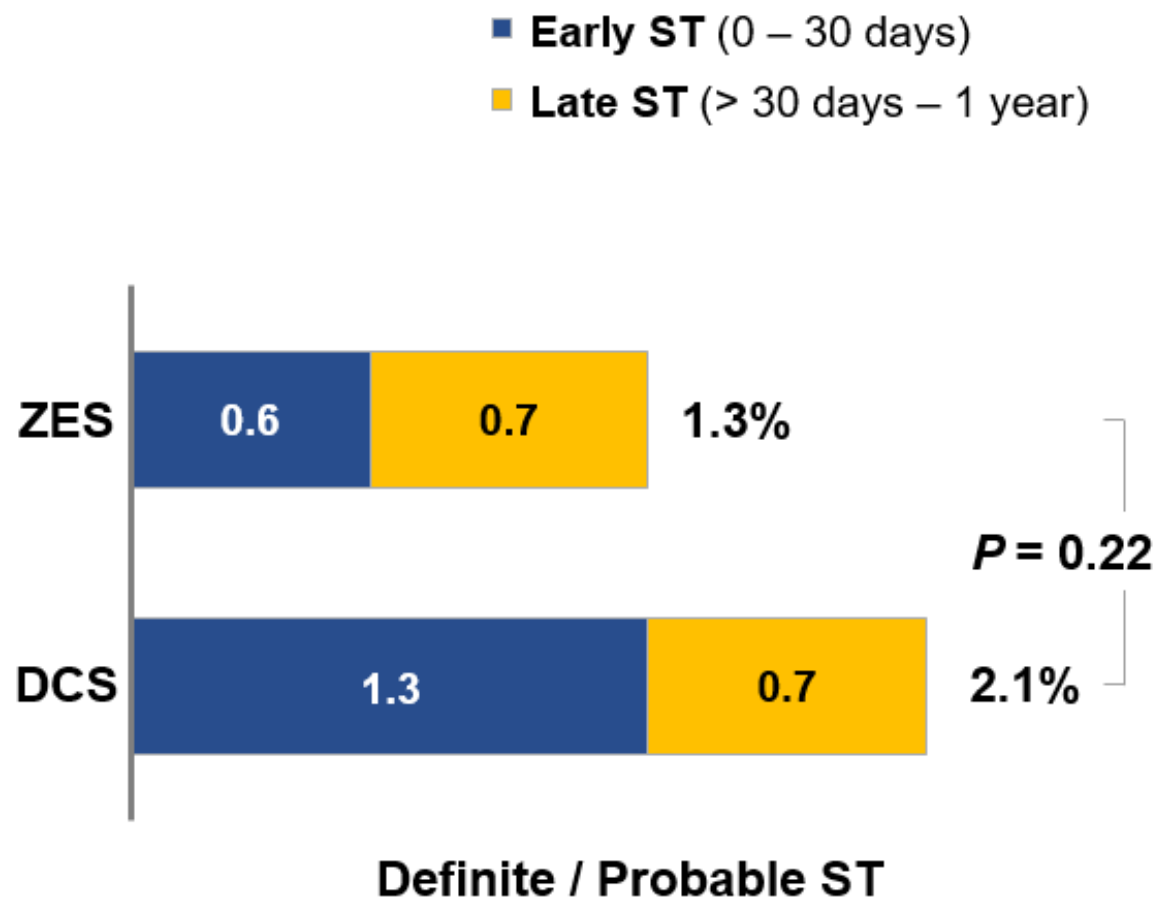




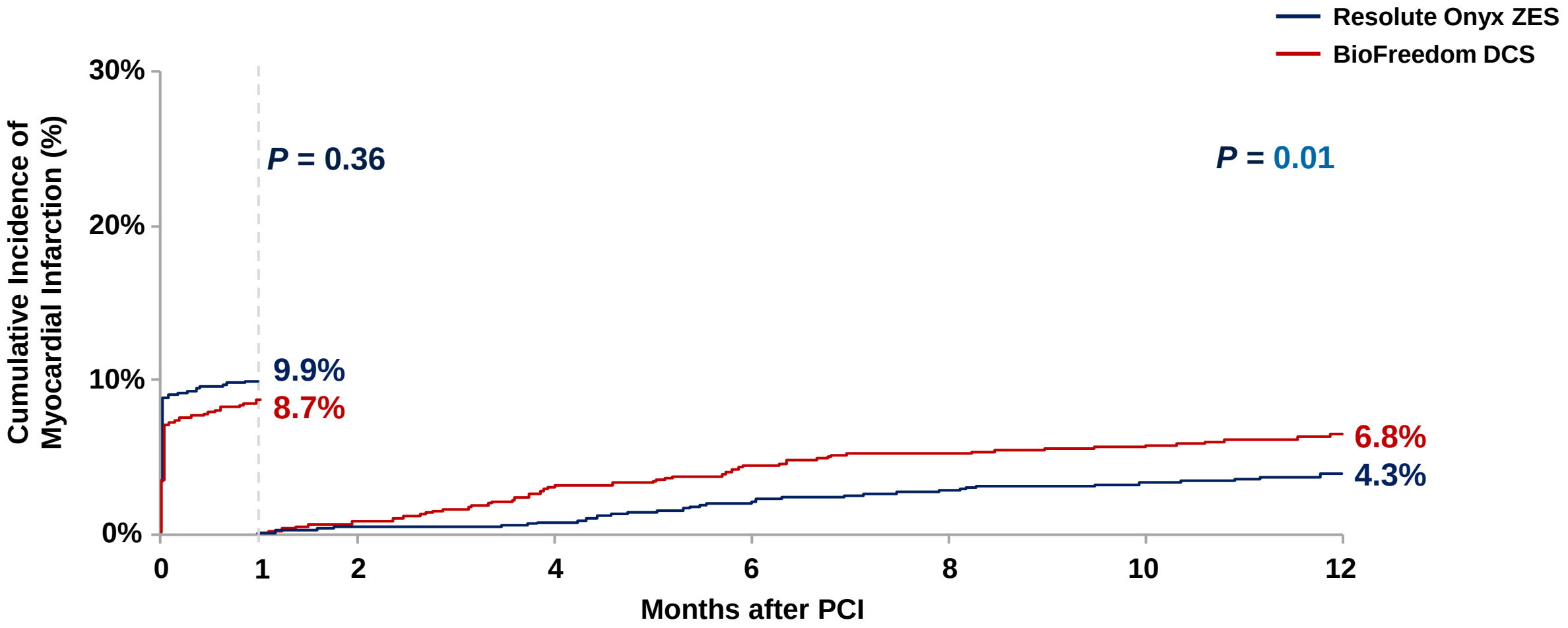
Myocardial Infarction



Stent Thrombosis

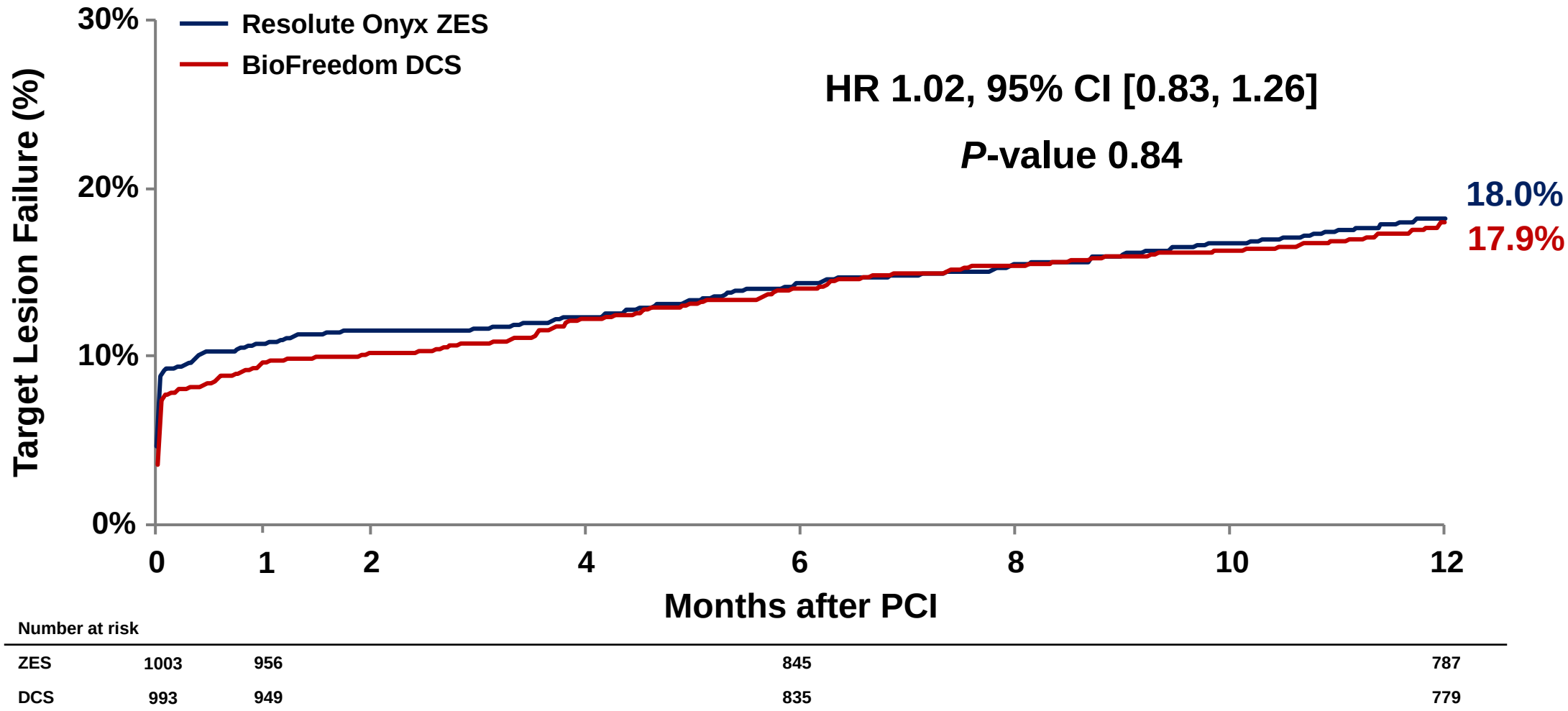


Landmark of Myocardial Infarction



MI assessed by the Third Universal Definition of Myocardial Infarction

Powered Secondary Effectiveness Endpoint: TLF



Summary of ONYX ONE

- ONYX ONE is a contemporary trial:
  - First trial comparing DES versus DCS
  - Investigating 1-month DAPT
  - Very complex HBR patient and lesion population
- Among HBR patients treated with 1-month DAPT after PCI, Resolute Onyx was as safe and effective as BioFreedom
- Resolute Onyx had improved angiographic outcomes and greater device success post-PCI