Optimal Duration of Current and Future DES and BVS

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TCTAP 2016
Seoul, Korea

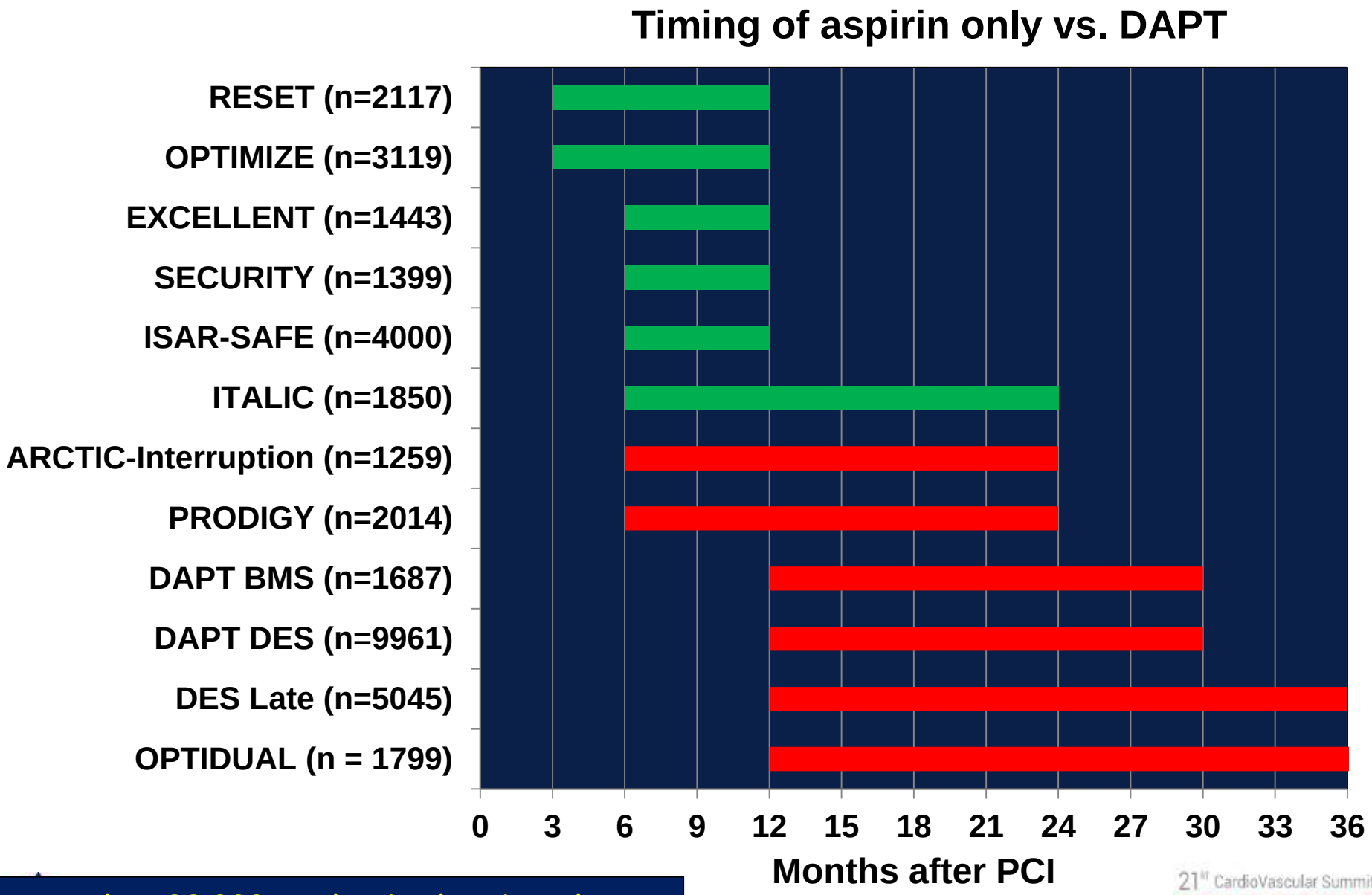
Mount Sinai Heart

21st CardioVascular Summit TCTAP 2016

Duration of DAPT: considerations after DES

1. **Safety and efficacy of prolonged DAPT**
2. **Trade-off between thrombotic and bleeding events**
3. **Use of new-generation DES in current practice**
4. **One size does not fit all – prolonged duration cannot be applied to everyone!**

Trials of DAPT Duration after Stenting: a review of the evidence



More than 30,000 randomized patients!

DAPT STUDY

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 4, 2014 VOL. 371 NO. 23

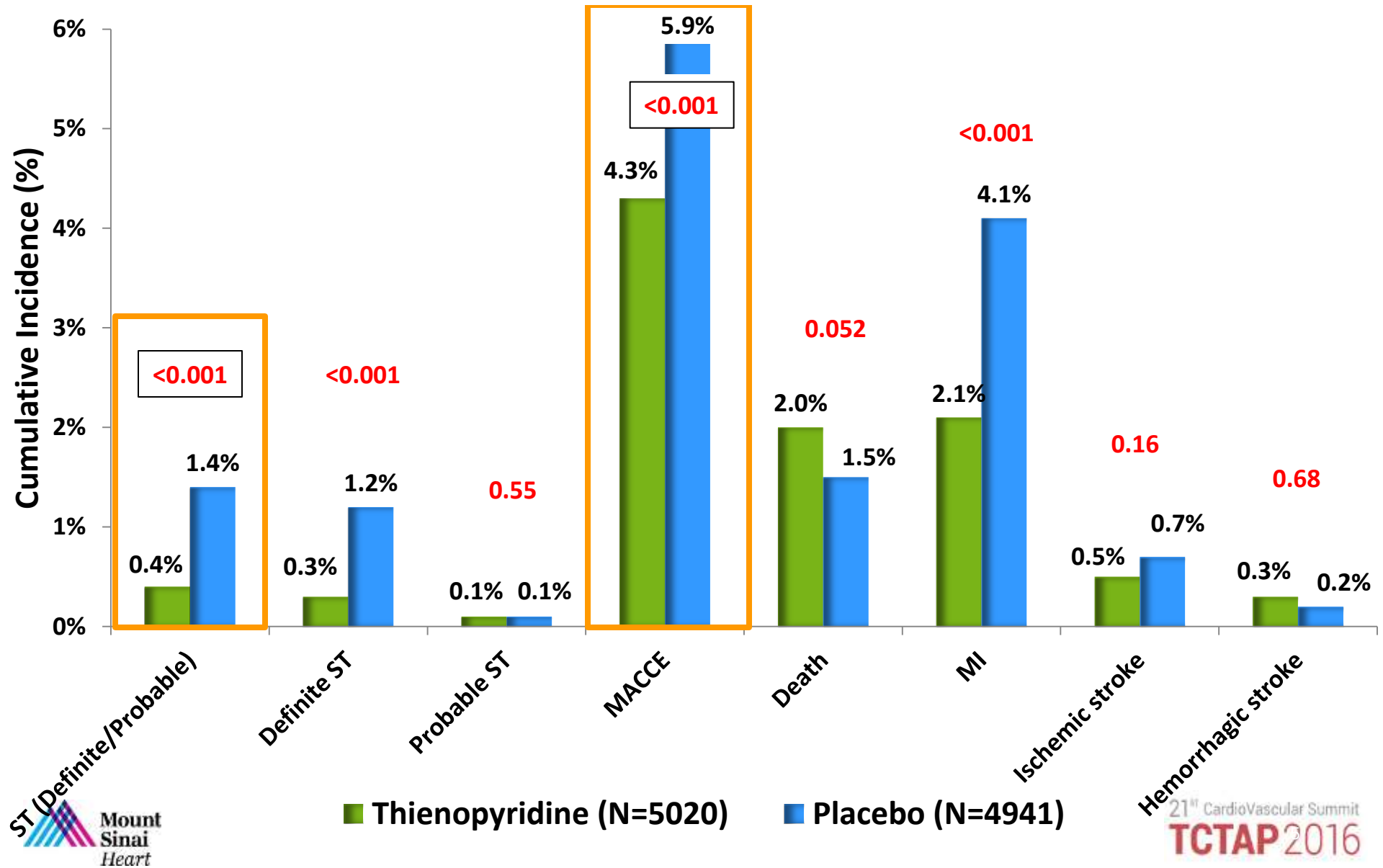
Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereiakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Ph.D., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M.D., Mitchell W. Krucoff, M.D., James Hermiller, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, M.D., David E. Kandzari, M.D., Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver Lee, M.D., Michael J. Rinaldi, M.D., and Joseph M. Massaro, Ph.D., for the DAPT Study Investigators*

Is there a benefit in extending DAPT beyond one year?

Mauri et al. NEJM 2014
DOI: 10.1056/NEJMoa1409312

Co-Primary Effectiveness End Points & Components: 12-30 Months



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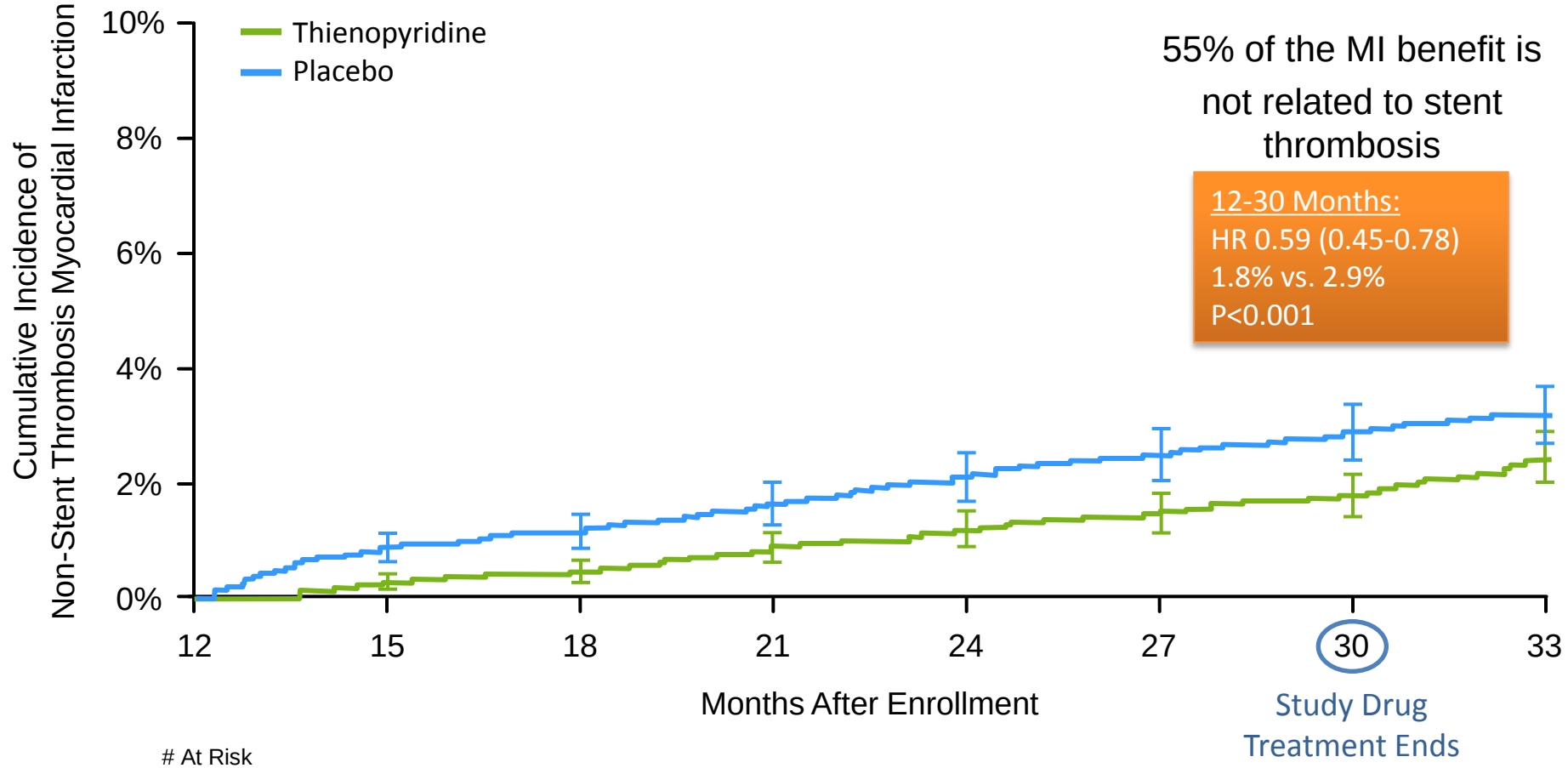
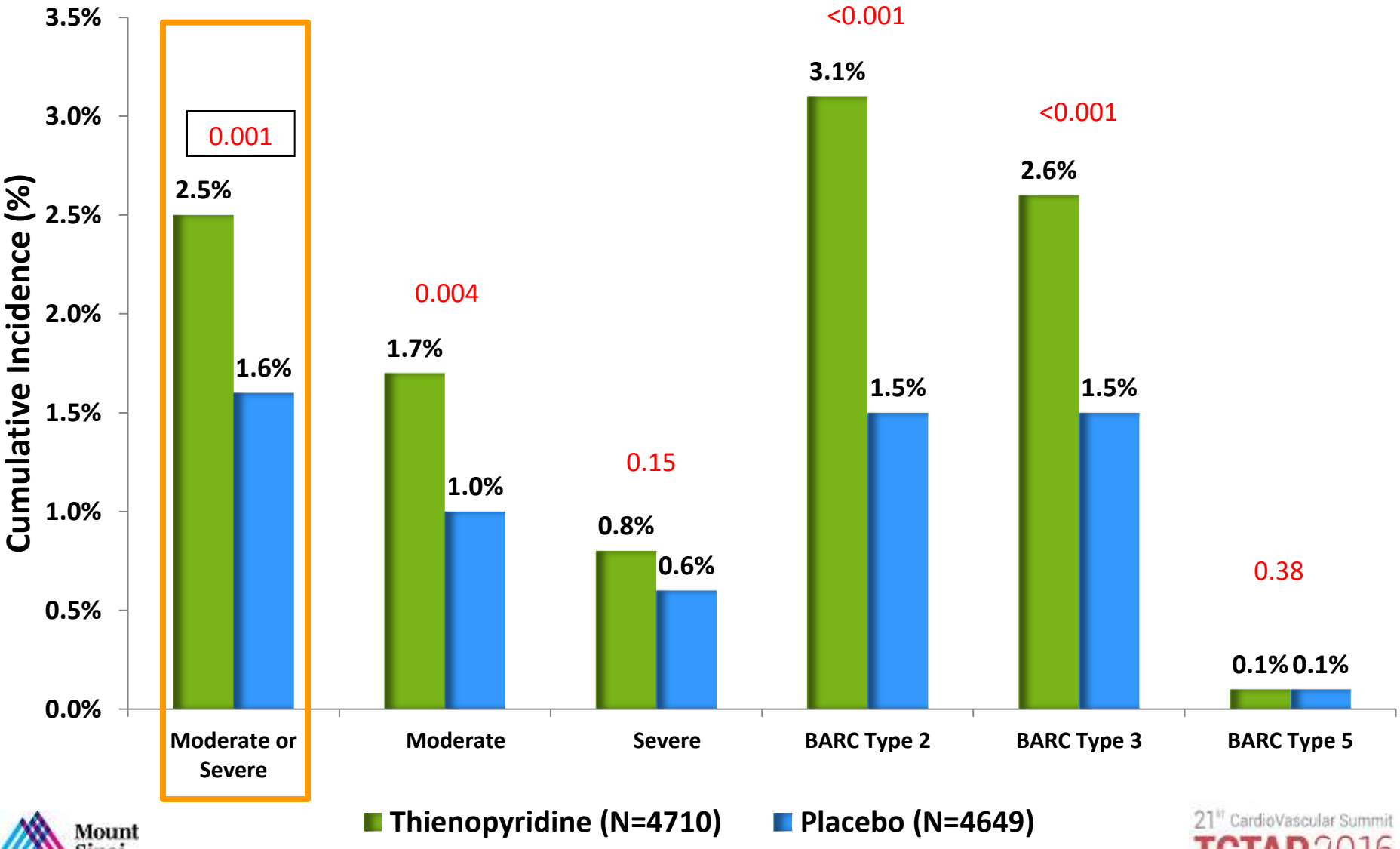
Non-Stent Thrombosis Myocardial Infarction



# At Risk								
Thienopyridine	5020	4920	4851	4792	4721	4641	4588	3066
Placebo	4941	4820	4751	4686	4607	4547	4491	3052

Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months



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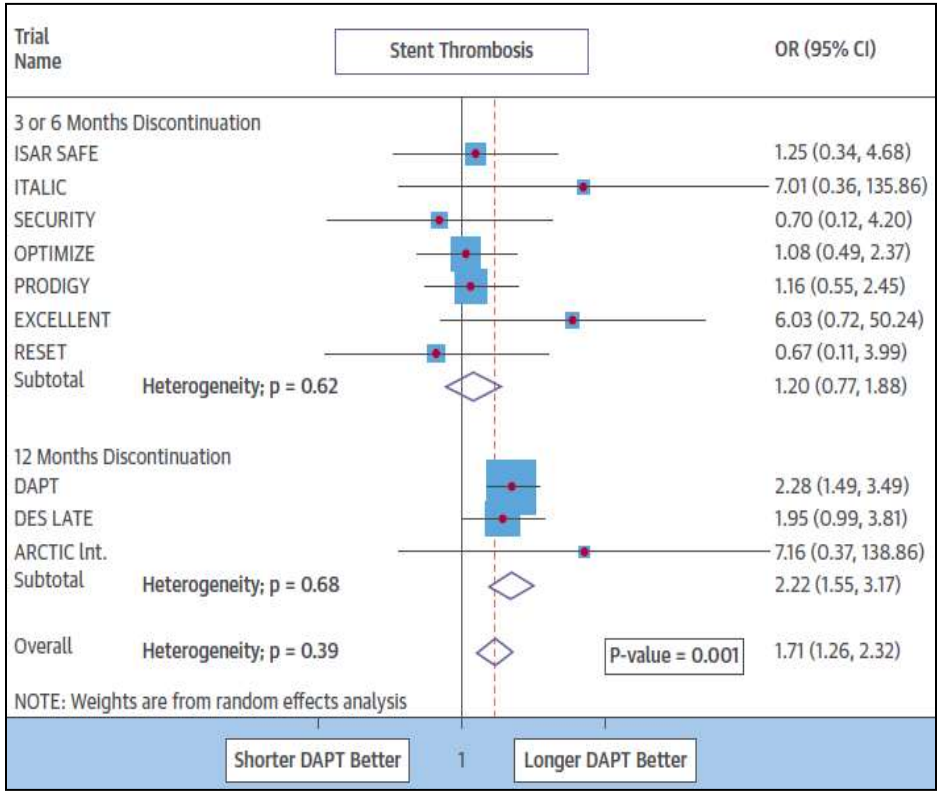
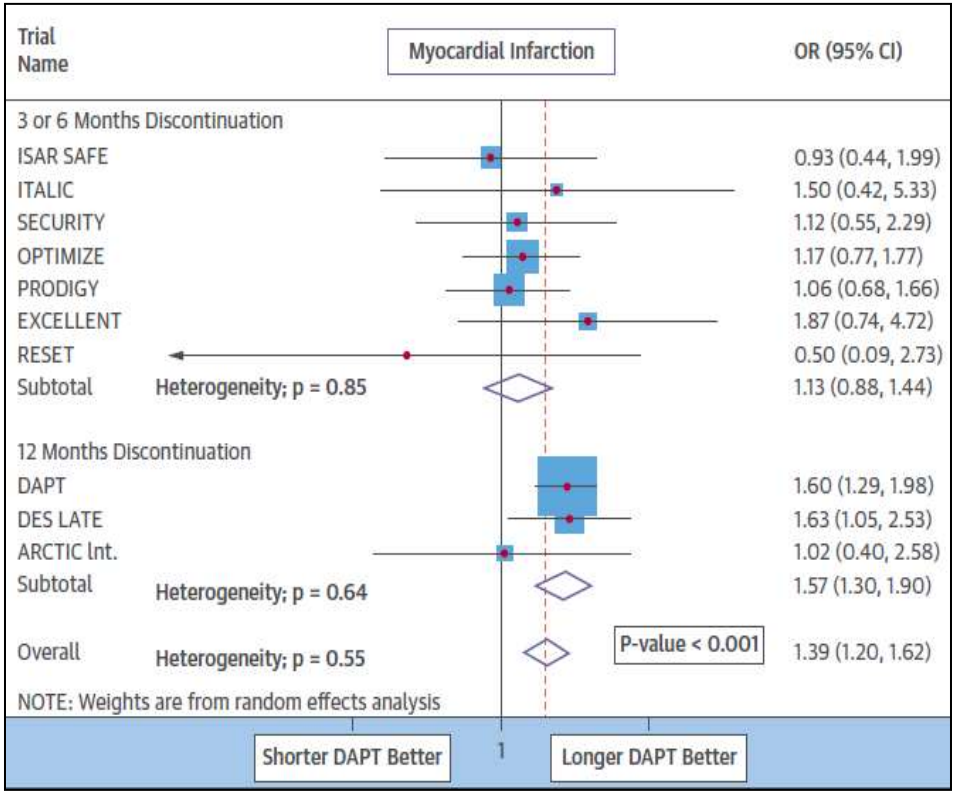
Longer DAPT is associated with lower risk of Stent Thrombosis and Myocardial Infarction





- **Mean weighted exposure time to DAPT within the S-DAPT and L-DAPT groups was 8.5 months and 23.2 months respectively.**

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Giustino, Dangas et al; JACC 2015

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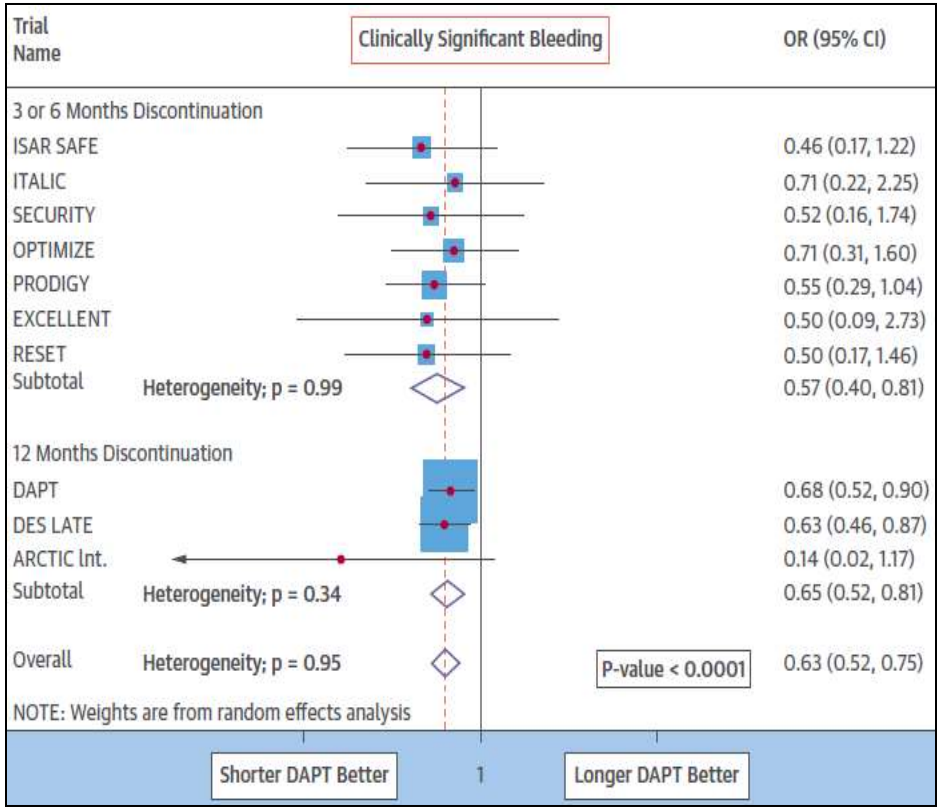
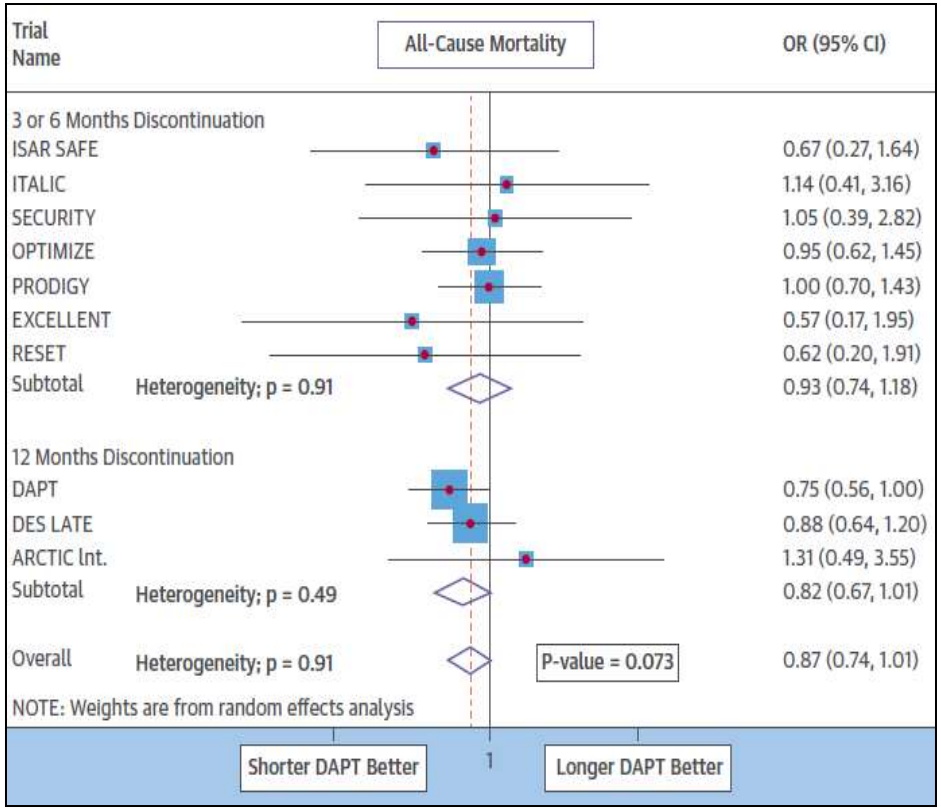
Shorter DAPT is associated with lower risk of Clinically Significant Bleeding and All-Cause Mortality





***CSB defined as a BARC 3 or 5, TIMI major or minor, GUSTO moderate or severe or STEEPLE major**

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Giustino, Dangas et al; JACC 2015

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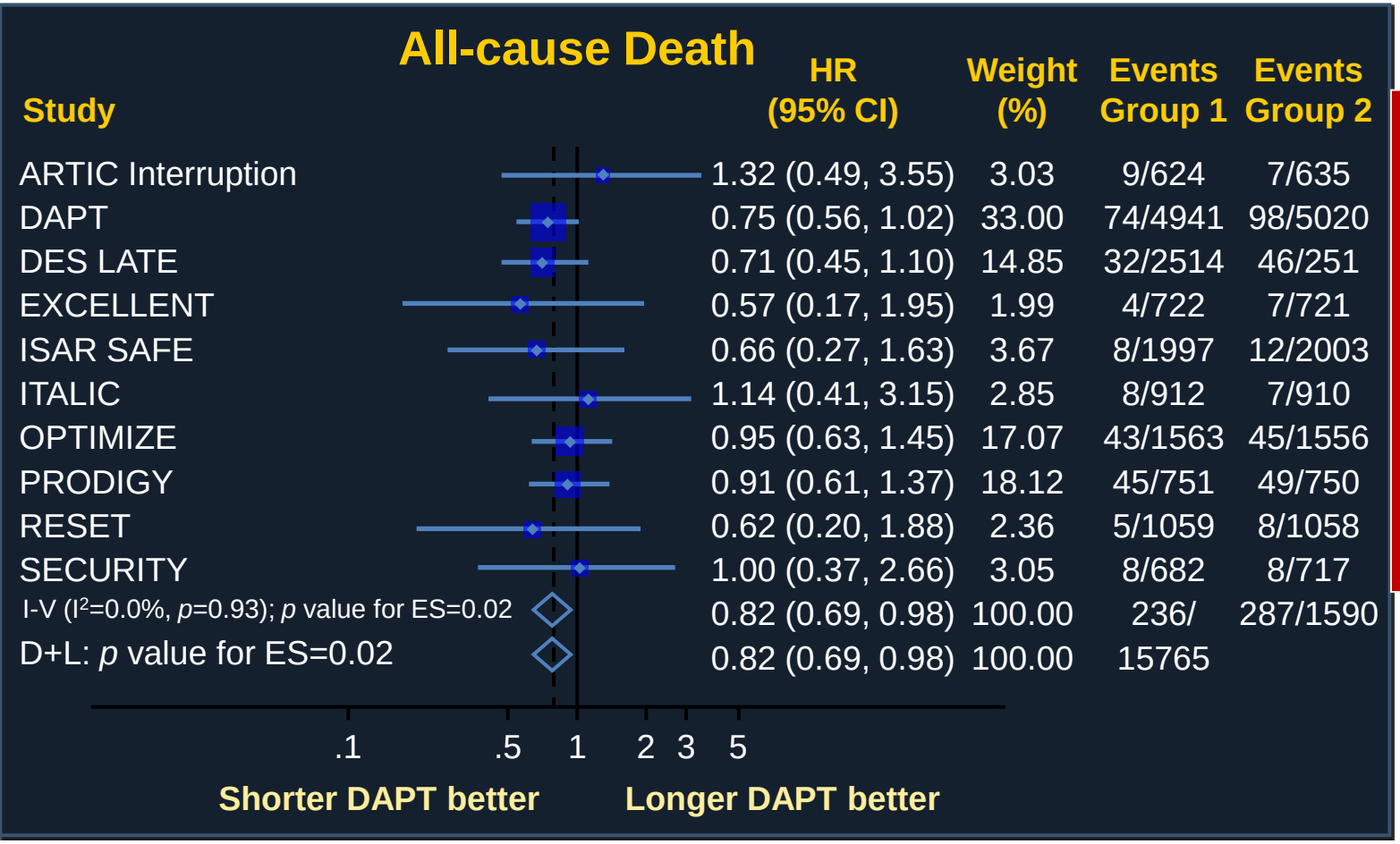
Mortality with Extended Duration DAPT After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts



22% ↑ mortality with prolonged DAPT (p=0.02)

ES=effect size

Palmerini, Stone, et al - Lancet 2015

Duration of DAPT: considerations after DES

1. **Safety and efficacy of prolonged DAPT**
2. **Trade-off between thrombotic and bleeding events**
3. **Use of new-generation DES in current practice**
4. **One size does not fit all – prolonged duration cannot be applied to everyone!**

Trade-Off Between Stent Thrombosis and Bleeding Over Time

Incidence rates and standardized incidence risk difference for Stent Thrombosis and Clinically Significant Bleeding per 100 person/year between S-DAPT and L-DAPT

	Stent Thrombosis						Clinically Significant Bleeding					
	S-DAPT		L-DAPT				S-DAPT		L-DAPT			
Study (Ref. #)	No. of Events	IR*	No. of Events	IR*	IRD*	95% CI*	No. of Events	IR*	No. of Events	IR*	IRD*	95% CI*
ARCTIC-Interruption (21)	3	0.33	0	0	0.33	-0.04 to 0.72	1	0.11	7	0.78	-0.67	-1.29 to -0.04
DAPT (7)	69	0.80	31	0.35	0.44	0.22 to 0.67	84	0.98	124	1.42	-0.44	-0.77 to -0.12
DES-LATE (22)	25	0.29	13	0.15	0.13	0.00 to 0.27	63	0.73	99	1.14	-0.41	-0.70 to -0.13
EXCELLENT (19)	6	0.83	1	0.14	0.69	-0.02 to 1.41	2	0.28	4	0.56	-0.27	-0.94 to 0.38
ISAR-SAFE (16)	5	0.50	4	0.40	0.10	-0.48 to 0.69	6	0.60	13	1.30	-0.70	-1.56 to 0.16
ITALIC (17)	3	0.66	0	0	0.66	-0.08 to 1.40	5	1.10	7	1.54	-0.44	-1.94 to 1.05
OPTIMIZE (15)	13	0.84	12	0.77	0.06	-0.56 to 0.69	10	0.64	14	0.90	-0.26	-0.88 to 0.35
PRODIGY (23)	15	0.80	13	0.69	0.11	-0.44 to 0.66	15	0.80	27	1.44	-0.64	-1.32 to 0.03
RESET (14)	2	0.19	3	0.28	-0.09	-0.50 to 0.31	5	0.47	10	0.95	-0.48	-1.20 to 0.24
SECURITY (18)	2	0.29	3	0.42	-0.12	-0.75 to 0.49	4	0.59	8	1.12	-0.53	-1.50 to 0.43
Combined	–	–	–	–	0.21	0.11 to 0.31	–	–	–	–	-0.45	-0.62 to -0.28

For every ST event averted with L-DAPT, approximately 2.1 extra CSB events are estimated to occur (- 0.45 ST / 0.21 CSB per 100 person / year).

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Giustino, Dangas et al; JACC 2015

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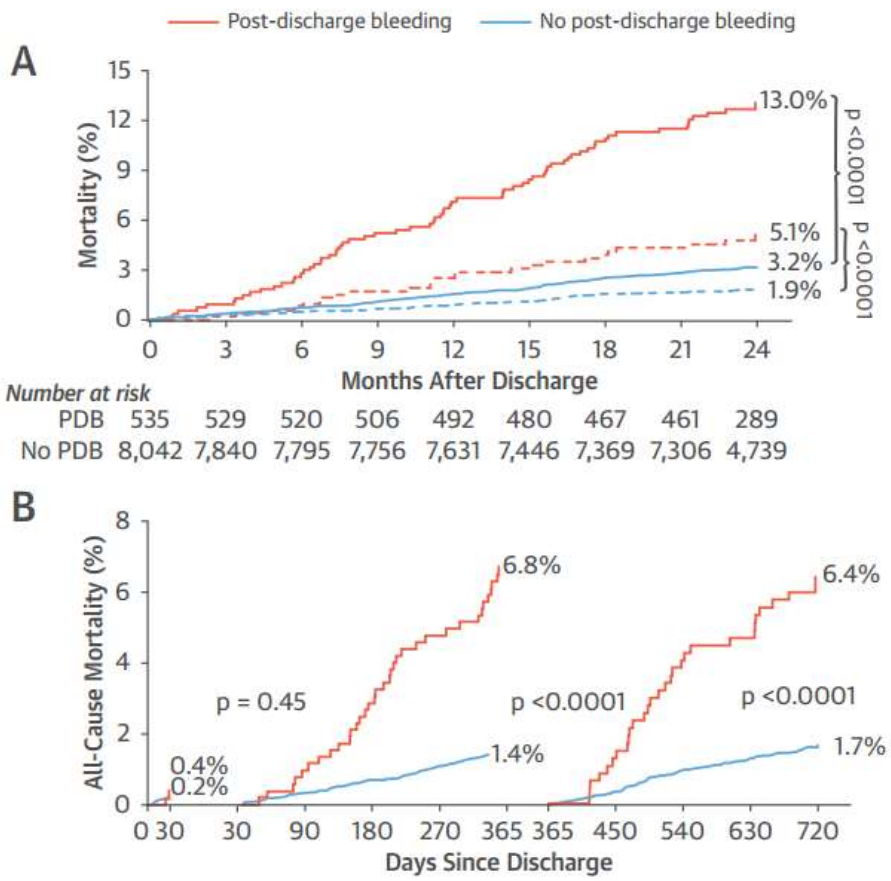
Incidence, Predictors, and Impact of Post-Discharge (PD) Bleeding After Percutaneous Coronary Intervention: Analysis on 8,582 patients from the ADAPT-DES Study

Impact of PD bleeding on 2-year Mortality



PD bleeding Vs. PD MI

Variable*	Adjusted HR (95% CI)	p Value
PDB†	5.03 (3.29-7.66)	<0.0001
With transfusion	4.71 (2.76-8.03)	<0.0001
Without transfusion	5.27 (3.32-8.35)	<0.0001
Post-discharge MI†	1.92 (1.18-3.12)	0.009

Predictors of PD bleeding

Variable*	HR (95% CI)	p Value
Age (per yr increase)	1.02 (1.01-1.03)	<0.0001
Warfarin, at discharge	2.31 (1.78-2.99)	<0.0001
Peripheral artery disease	1.57 (1.25-1.98)	0.0001
Calcified lesion	1.25 (1.05-1.50)	0.01
Bifurcation lesion	1.32 (1.06-1.64)	0.01
Platelet reactivity units (per 10-unit decrease)	1.01 (1.01-1.02)	0.002
Baseline hemoglobin (per g/dl decrease)	1.28 (1.22-1.37)	<0.0001

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Genereux, Giustino et al. - *JACC* 2015

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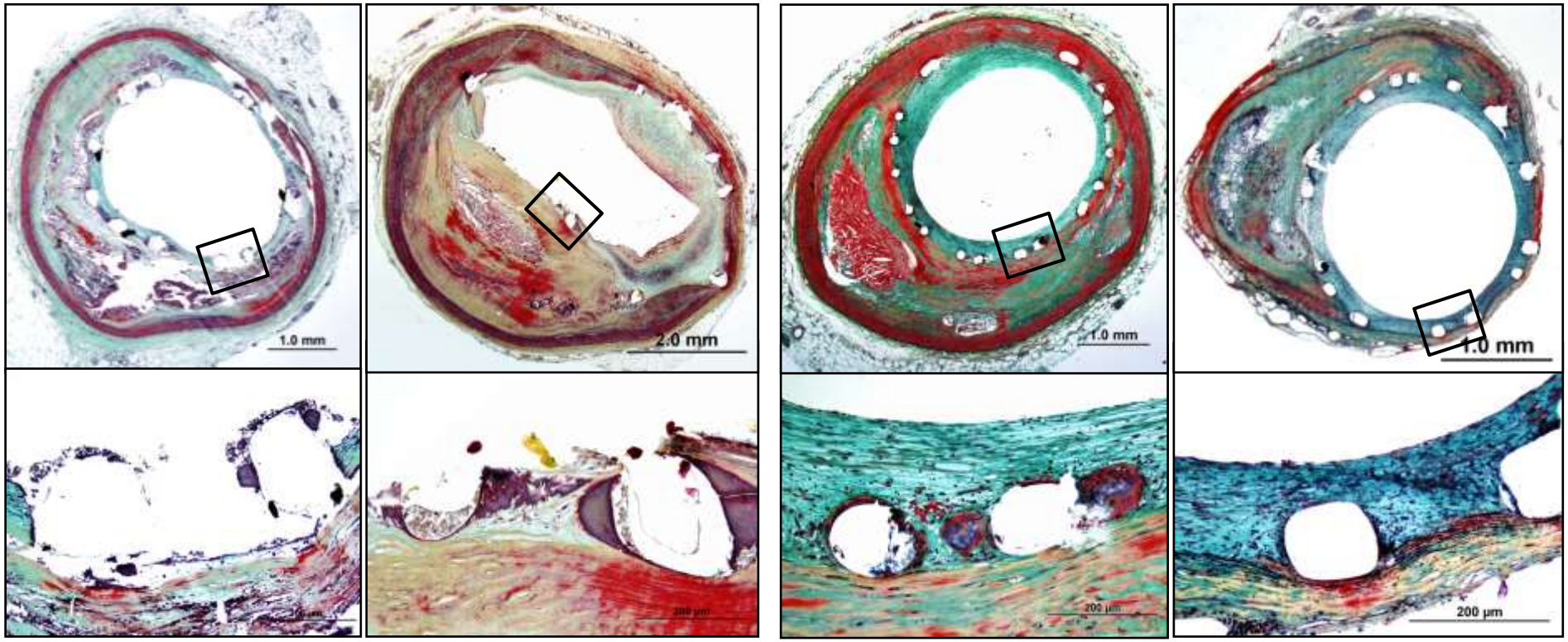
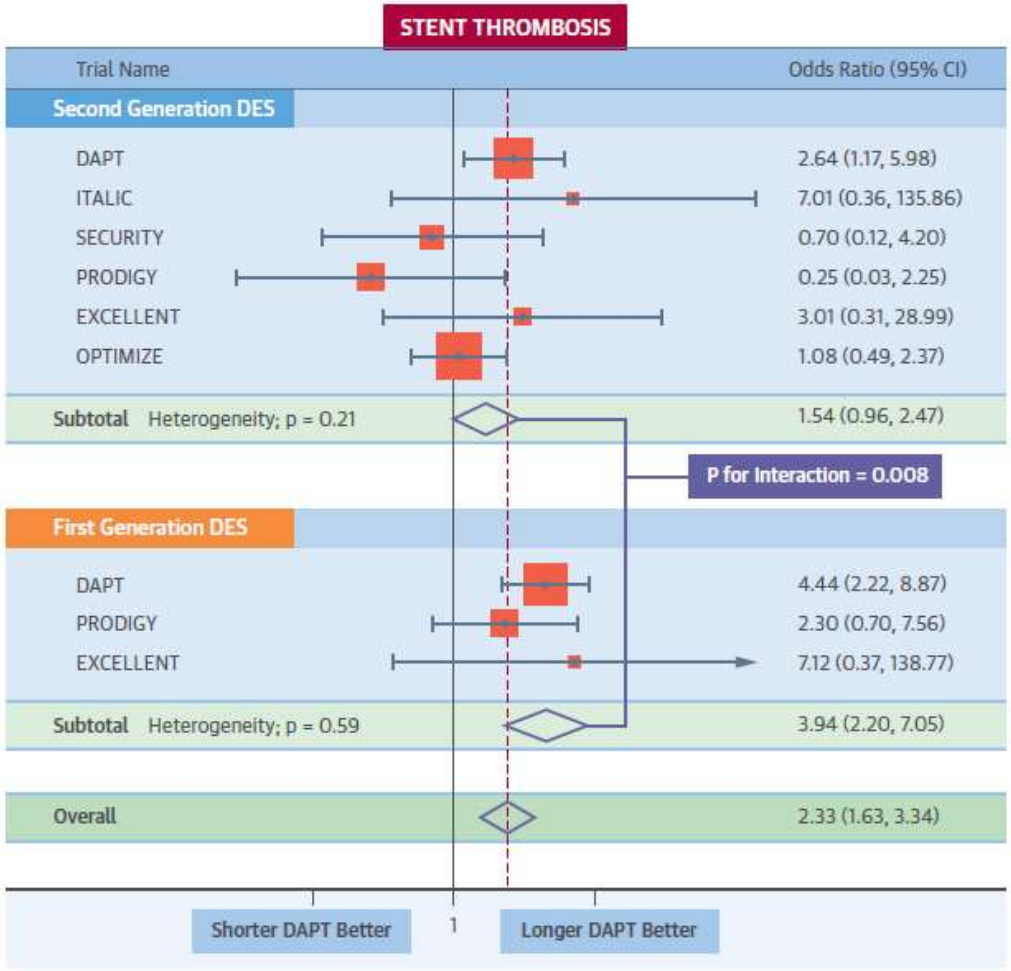
First- Versus Second-Generation DES and risk for Stent Thrombosis.. Where is the difference?

1st-generation DES ***2nd-generation DES***



Representative Images of 2nd- vs. 1st-generation DES in Human Coronary Arteries

Extended Duration DAPT After DES: Second vs. First Generation DES



Significant attenuation of the risk for ST with shorter DAPT in patients with 2nd-generation DES

Giustino, G. et al. J Am Coll Cardiol. 2015; 65(13):1298–310.

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Giustino G et al. *JACC* 2015;65:1298–310

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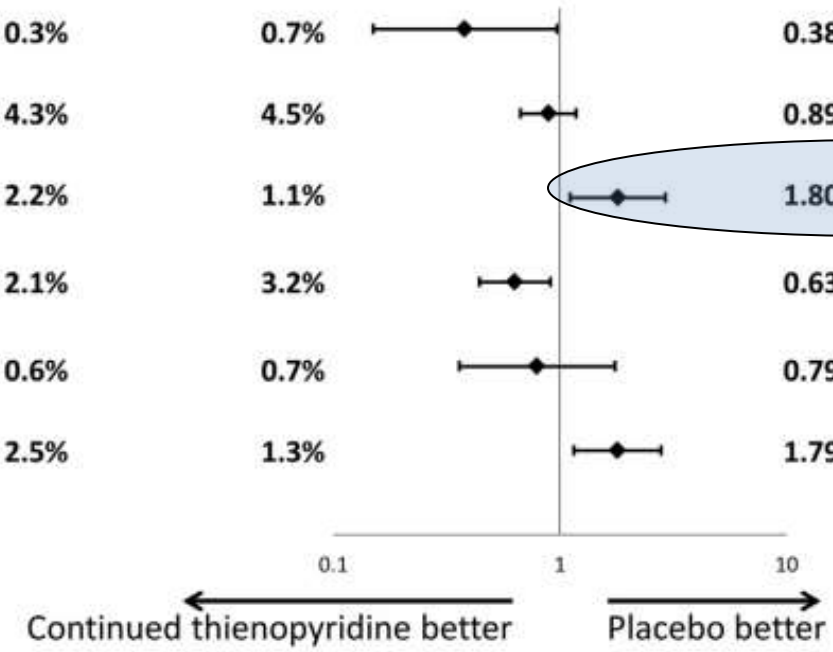
30 versus 12 months DAPT in patients treated with EES (N=4,703) in the DAPT trial

FIGURE 3 Outcomes (12 to 30 Months) in Randomized Patients According to Treatment Arm

A

Outcome	Continued Thienopyridine N=2345	Placebo N=2358	HR (95% CI)	P Value
Stent Thrombosis	0.3%	0.7%	0.38 (0.15, 0.97)	0.04
MACCE	4.3%	4.5%	0.89 (0.67, 1.18)	0.42
Death	2.2%	1.1%	1.80 (1.11, 2.92)	0.02
Myocardial Infarction	2.1%	3.2%	0.63 (0.44, 0.91)	0.01
Stroke	0.6%	0.7%	0.79 (0.36, 1.75)	0.56
Bleeding	2.5%	1.3%	1.79 (1.15, 2.80)	0.01



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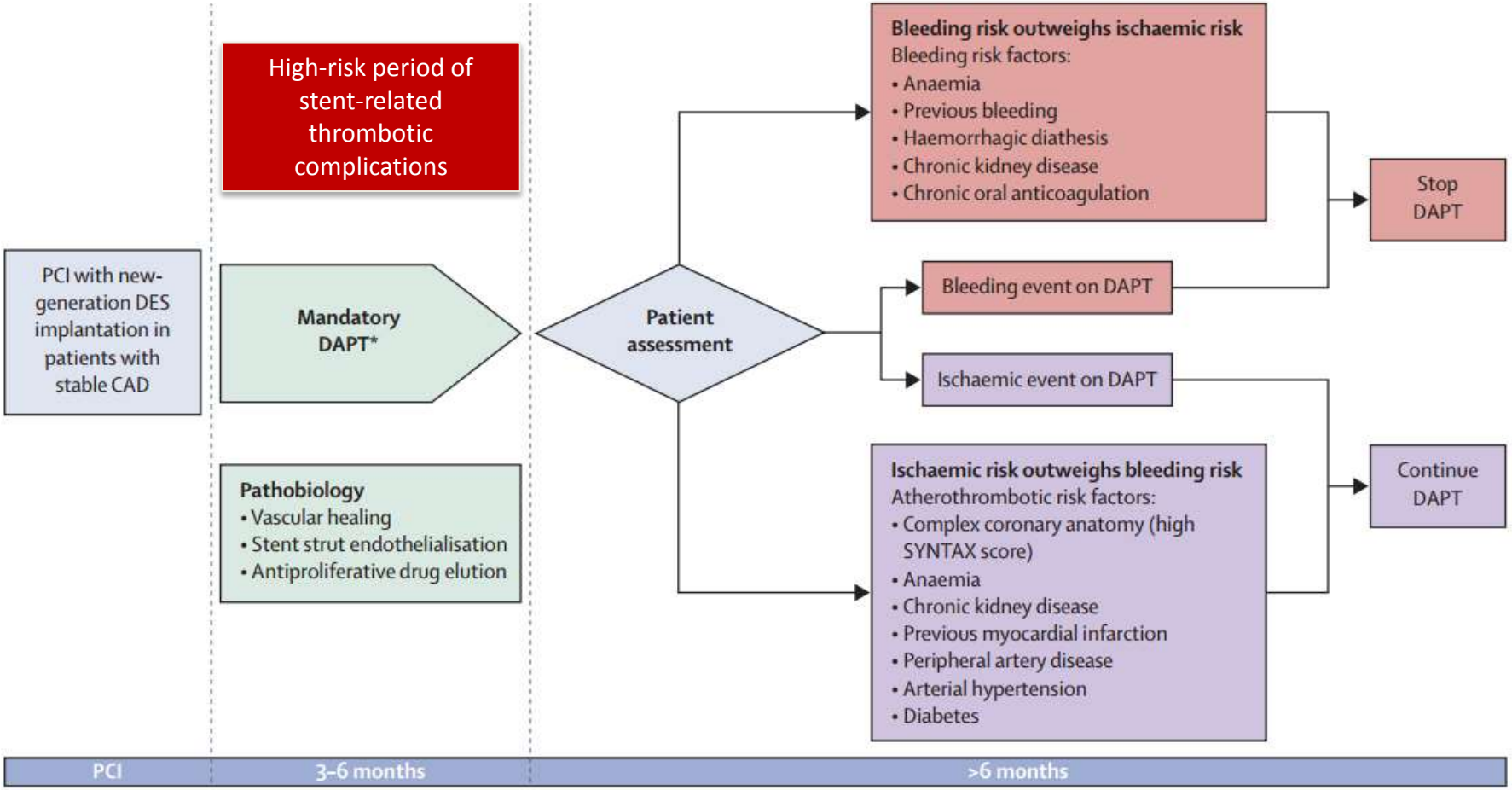
Algorithm for the management of dual antiplatelet therapy after new-generation drug-eluting stent implantation in patients with stable coronary artery disease



Piccolo R, Giustino G, Mehran R, Windecker S – The Lancet 2015

DAPT Score: How to individualize therapy?

Characteristics	Impact on Combined Treatment Effect	% of Variation Explained	DAPT Score
Age ≥ 75	-1.2%	6.0%	**-2**
Age 65 - < 75	-0.5%	2.2%	**-1**
Age < 65 (reference)	-	-	**0**
Prior PCI or MI	1.1%	14.6%	**1**
Stent Diameter < 3 mm	0.9%	10.1%	**1**
CHF or LVEF < 30%	1.9%	9.9%	**2**
MI at Presentation	1.0%	9.6%	**1**
Paclitaxel-Eluting Stent	1.0%	8.8%	**1**
Cigarette Smoker	0.7%	4.3%	**1**
Diabetes	0.6%	4.3%	**1**

Low DAPT Score (< 2)
NNT to prevent ischemia = 153
NNH to cause bleeding 64

High DAPT Score ≥ 2
NNT to prevent ischemia = 34
NNH to cause bleeding = 272

Yeh, R et al. JAMA 2016

Predicting Risks for Coronary Thrombosis and Major Bleeding After PCI with DES: Risk Scores from PARIS Registry

Integer Risk Score for Major Bleeding

Parameter	Score				
Age, years	< 50	50-59	60-69	70-79	>80
	0	+1	+2	+3	+4
BMI, kg/m^2	<25		25-34.9	> 35	
	+2		0	+2	
Current Smoking	Yes		No		
	+2		0		
Anemia	Present		Absent		
	+3		0		
CKD*	Present		Absent		
	+2		0		
Triple Therapy on discharge	Yes		No		
	+2		0		

*Defined as CrCl < 60 mL/min/1.73 m2

Integer Risk Score for Coronary Thrombosis

Parameter	Score		
Diabetes Mellitus	None	Non-Insulin	Insulin
	0	+1	+3
Acute Coronary Syndrome	No	Yes, Tn (-)	Yes, Tn (+)
	0	+1	+2
Current Smoking	Yes		No
	+1		0
CKD*	Present		Absent
	+2		0
Prior PCI	Yes		No
	+2		0
Prior CABG	Yes		No
	+2		0

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Baber, Mehran, Giustino et al – JACC 2016 in press

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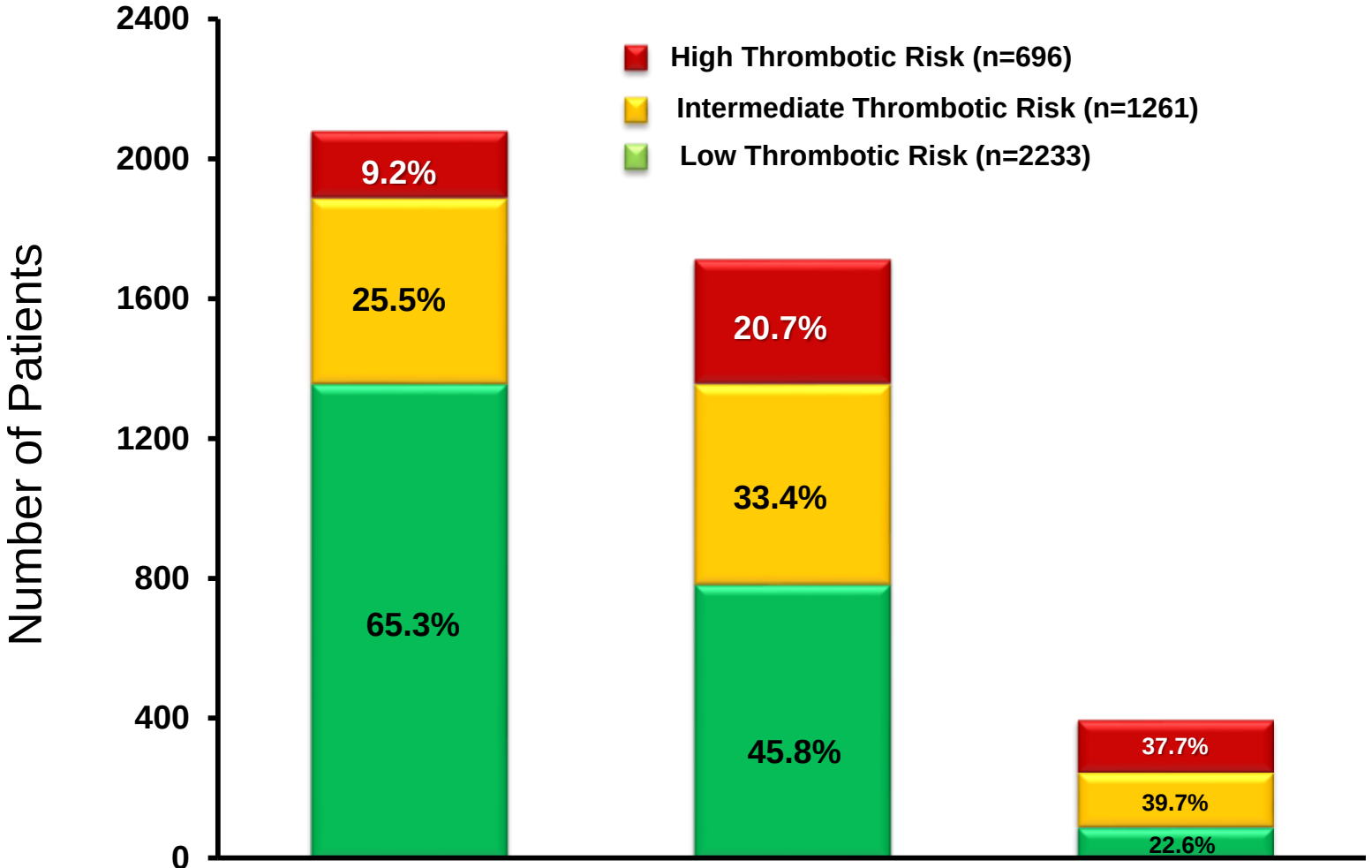
Cross-Classification by Thrombotic and Bleeding PARIS Risk Score Categories



	Low Bleeding Risk	Intermediate Bleeding Risk	High Bleeding Risk	Total
High Thrombotic Risk	191	355	150	696
Int Thrombotic Risk	530	573	158	1261
Low Thrombotic Risk	1358	785	90	2233
Total	2079	1713	398	4190

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Baber, Mehran et al – JACC 2016 in press

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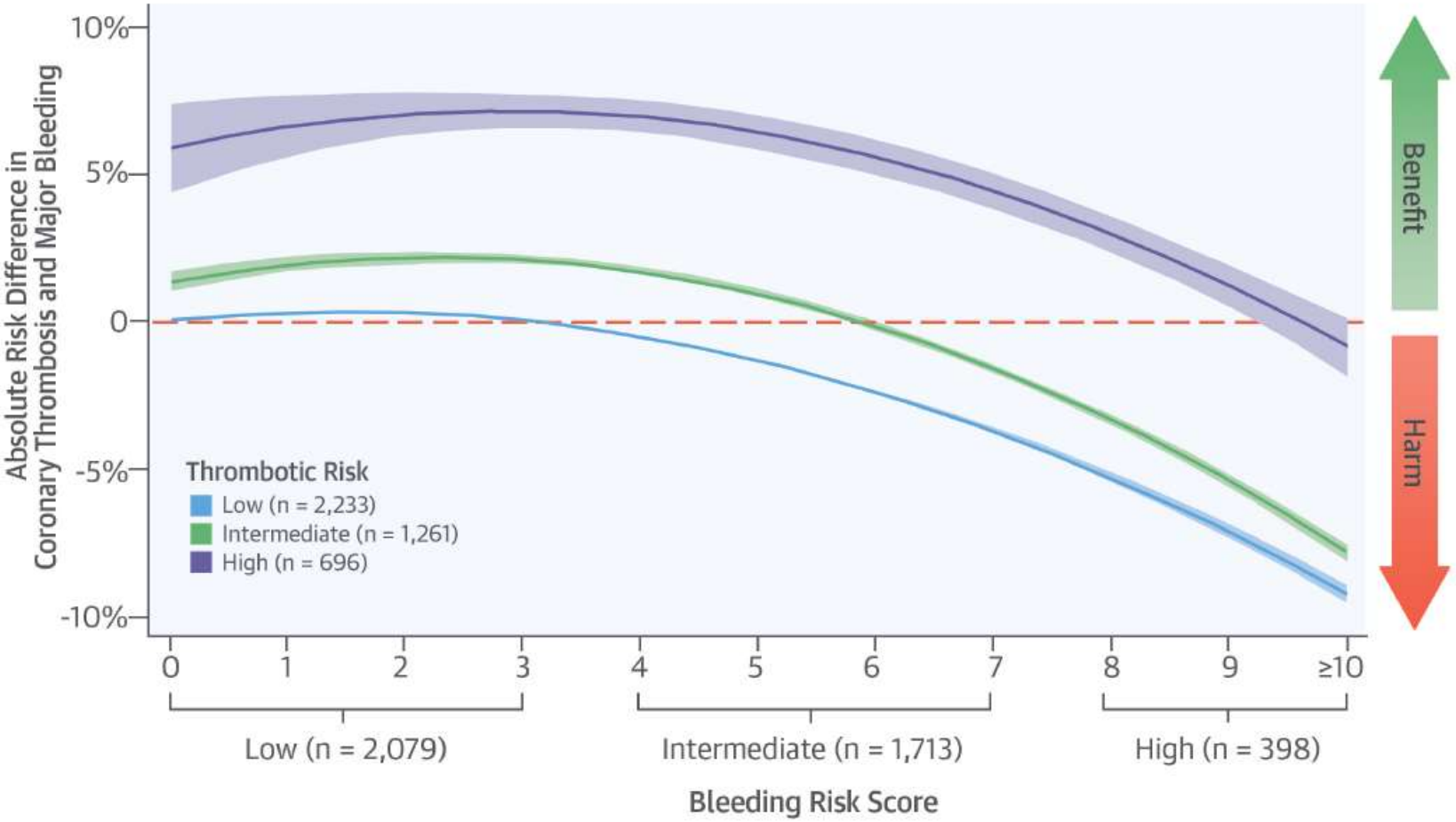
Risk/Benefit Trade-off with Prolonged DAPT as a Function of Thrombotic and Bleeding Risk



Baber, Mehran et al – JACC 2016 in press

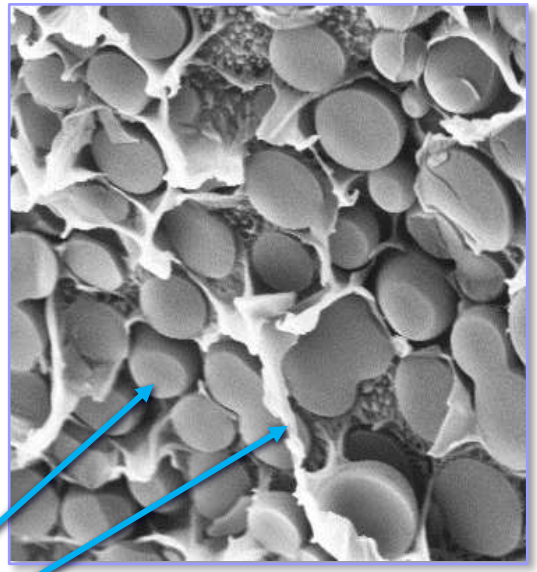
Three Approaches to Improve Early and Late DES Outcomes

1. Metallic DES with bioabsorbable polymers
2. Metallic DES, polymer-free
3. Bioresorbable scaffolds (BRS)

Abluminal Bioabsorbable Polymer
SYNERGY Stent (BSC)

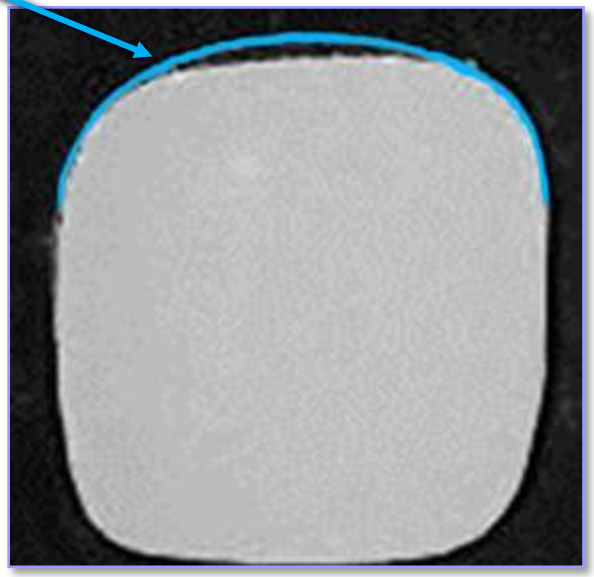
Everolimus Drug
PLGA Polymer

Drug & Polymer Coating



SEM of coating (x5000)

Abluminal (4µm)



Luminal

Platform
Platinum chromium
- 74 µg (0.0029in)

Polymer Coating
PLGA
- Abluminal
- 4 µm thick
- Undetectable in 4 mo

Drug
Everolimus
- 100 µg/cm^2
- Elutes in 3 months

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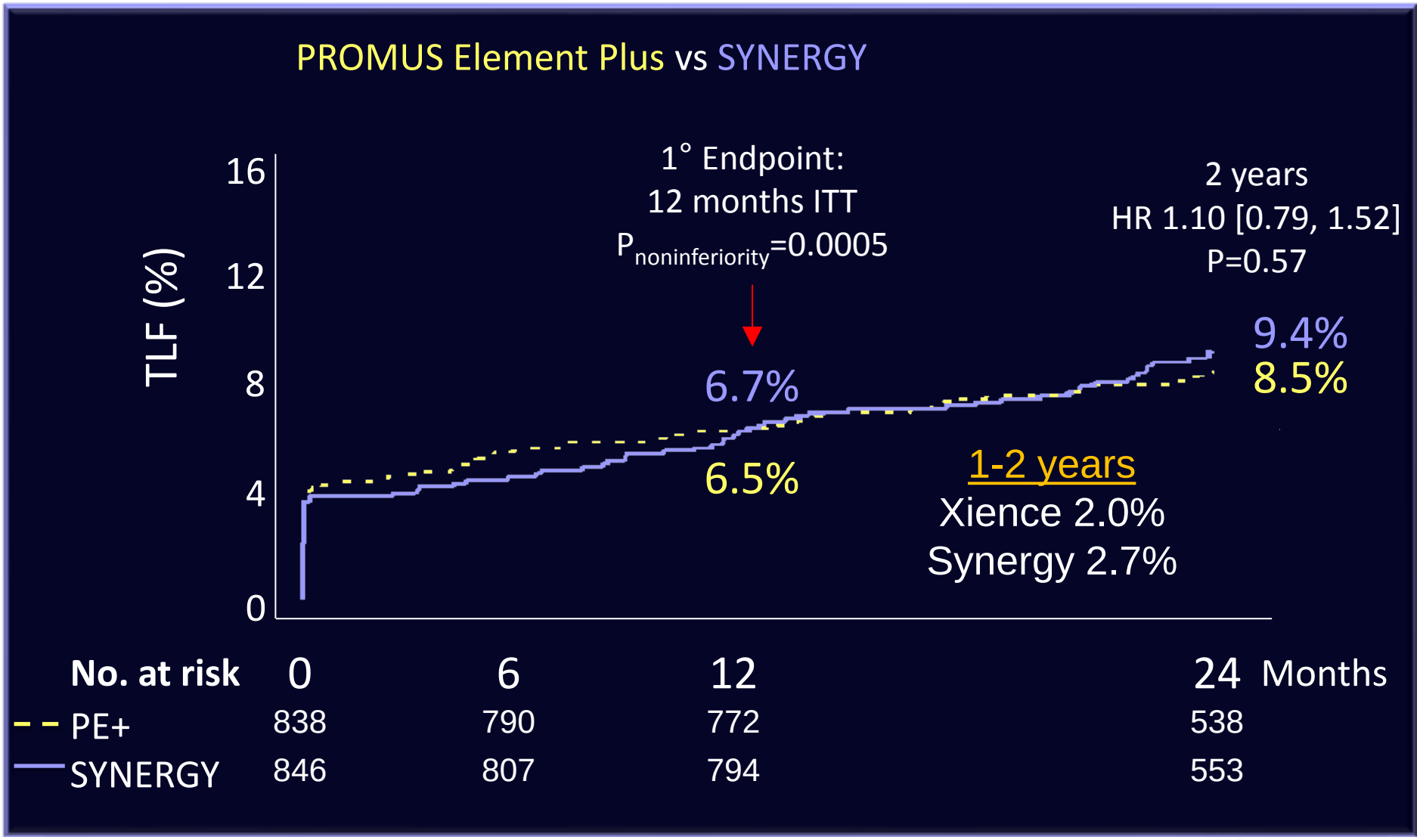
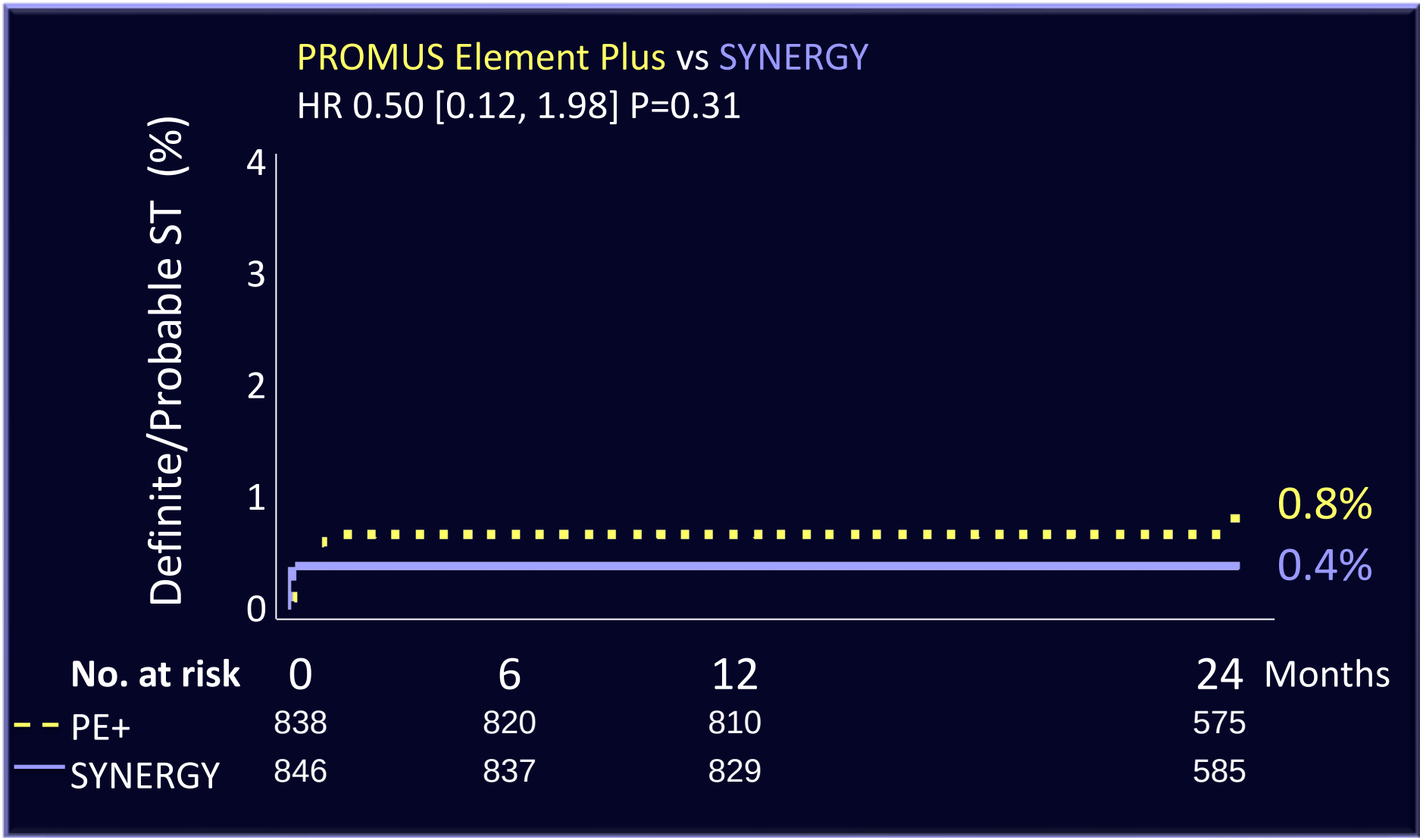
EVOLVE II TLF at 1 and 2 years



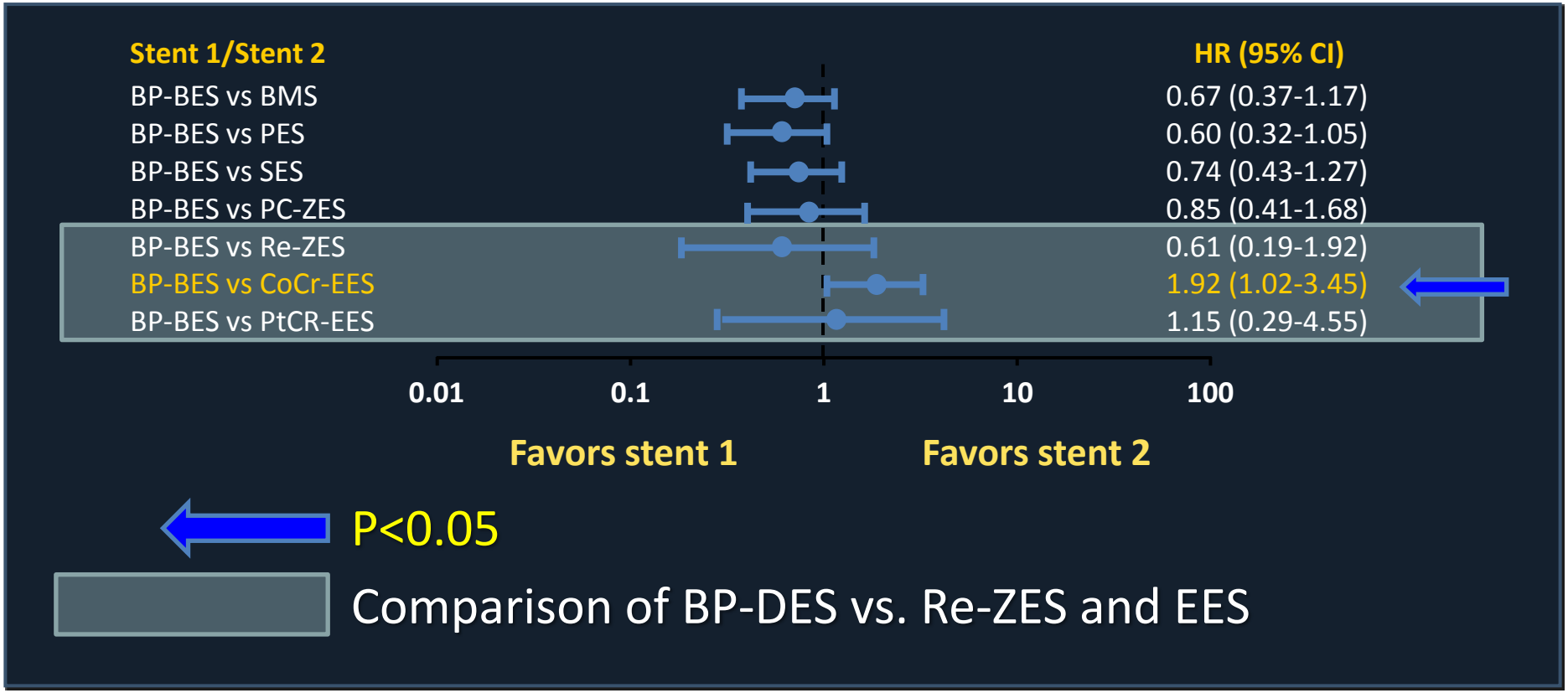
Stent Thrombosis at 2 years



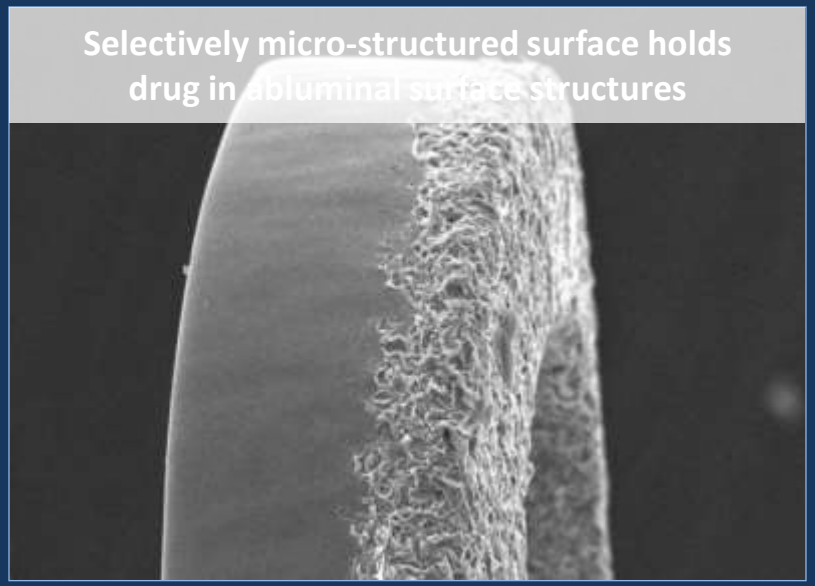
Bioabsorbable Polymer-based vs. Durable Polymer-based DES and BMS

Evidence network: 89 RCTs, 85,490 pts

Long-term Definite Stent Thrombosis

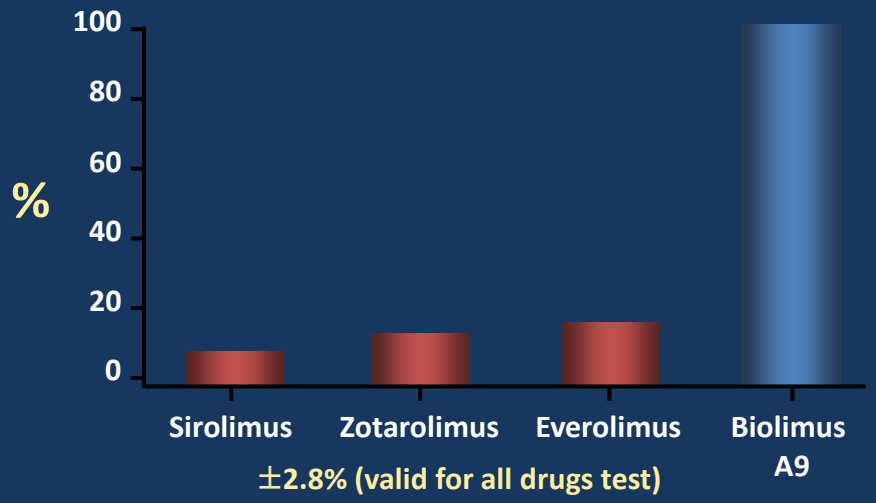


BioFreedom Drug Coated Stent (DCS)



12 mo in-stent LL ~0.17 mm (n=31)

Biolimus A9 is 10x more lipophilic than sirolimus[1]



Potential Advantages:

- Rapid drug transfer to vessel wall (98% within one month[2])
- Avoid possible polymer-related adverse effects
- Safe to shorten DAPT?

LEADERS FREE Trial Design

Objective: To determine in patients at high bleeding risk, using one month DAPT, whether the BioFreedom DCS is as safe and more effective than a Gazelle BMS

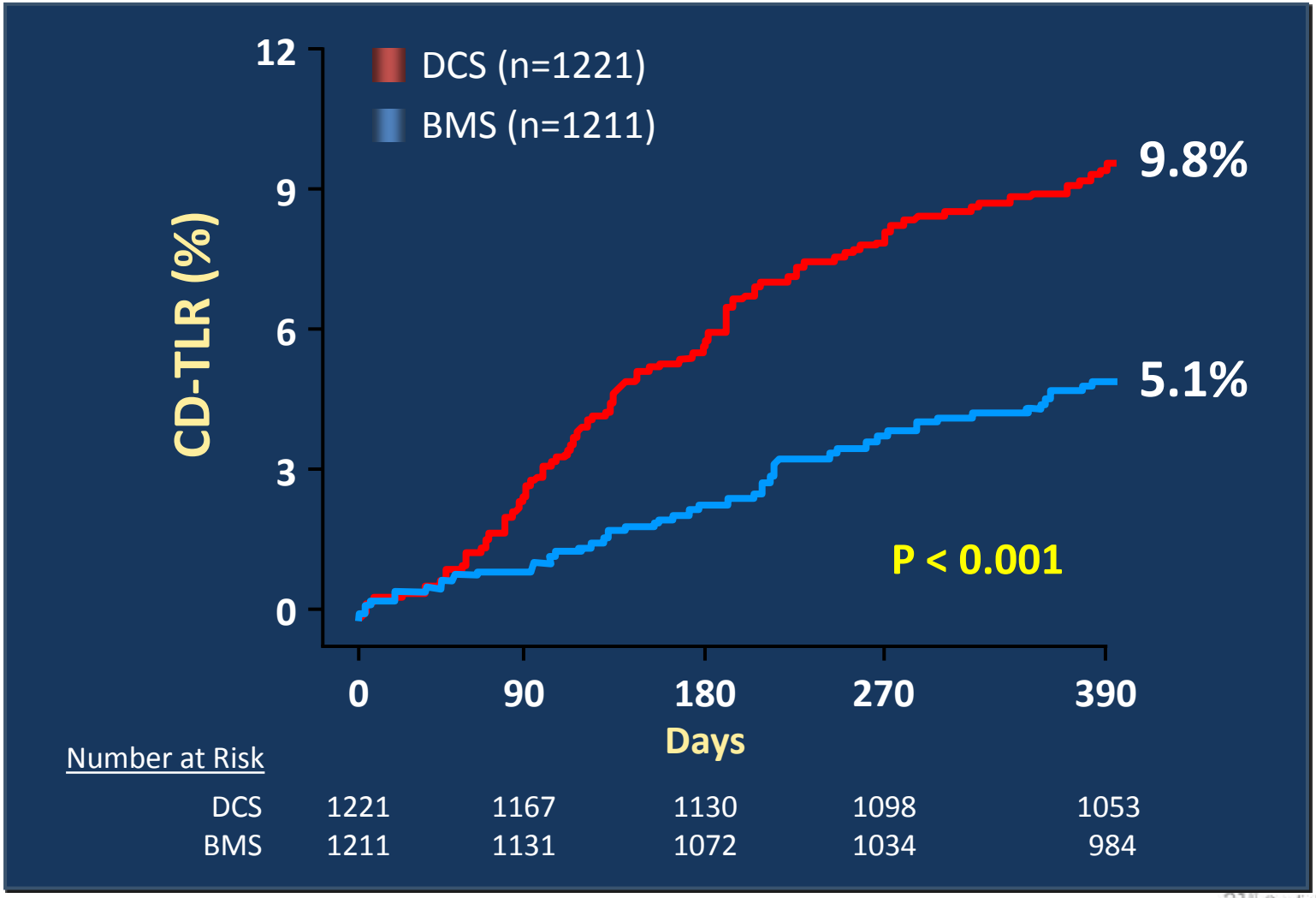
Prospective, double-blind randomized (1:1) trial
In 2466 high bleeding risk (HBR) PCI patients

BioFreedom™ DCS **VS.** **Gazelle™ BMS**

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

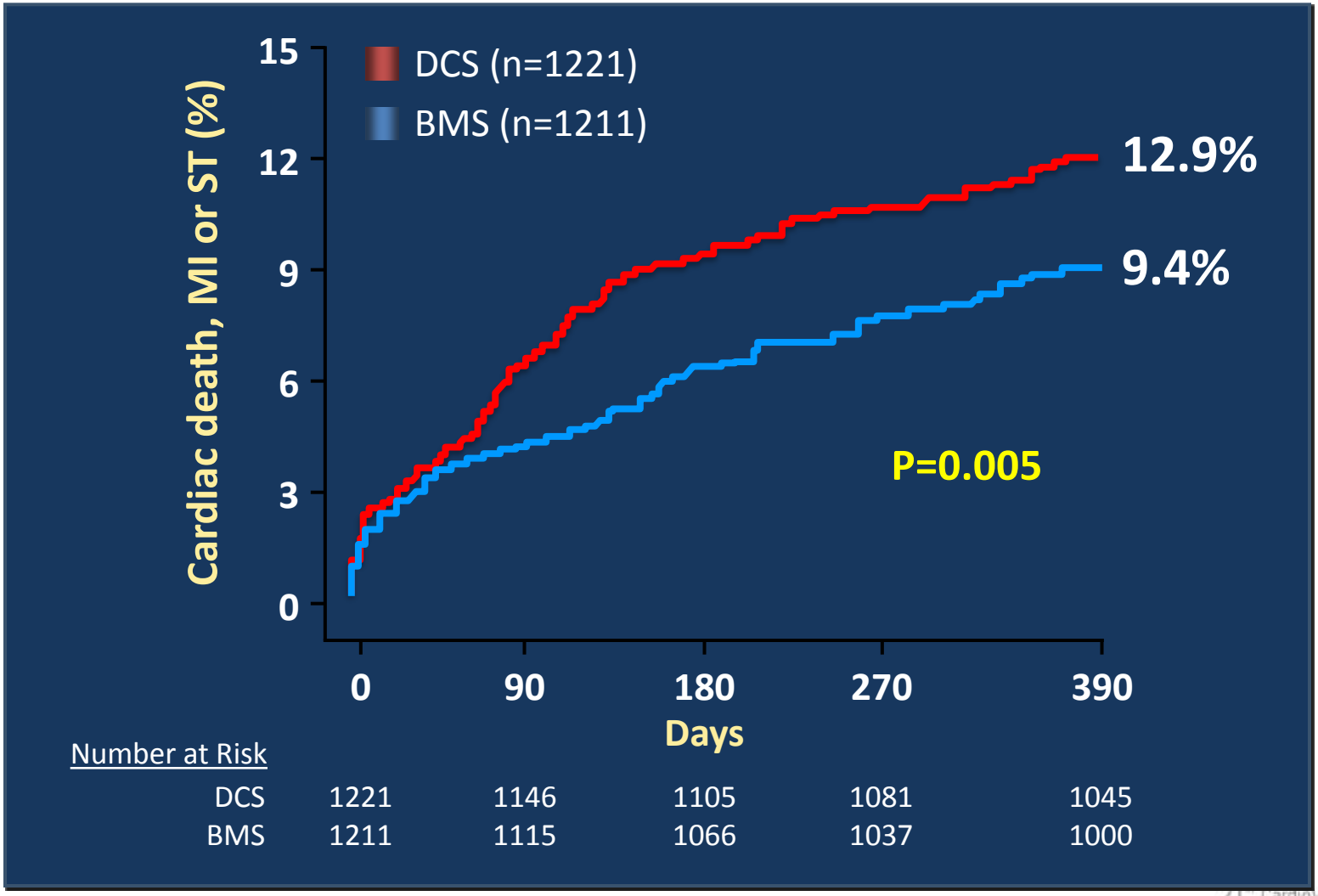
- **Primary efficacy endpoint:**
  Clinically-driven TLR at 1 year (superiority)
- **Primary safety endpoint:**
  Composite of cardiac death, MI, definite / probable stent thrombosis at 1 year (non-inferiority then superiority)

Leaders Free: Primary Efficacy Endpoint (Clinically-Driven TLR)



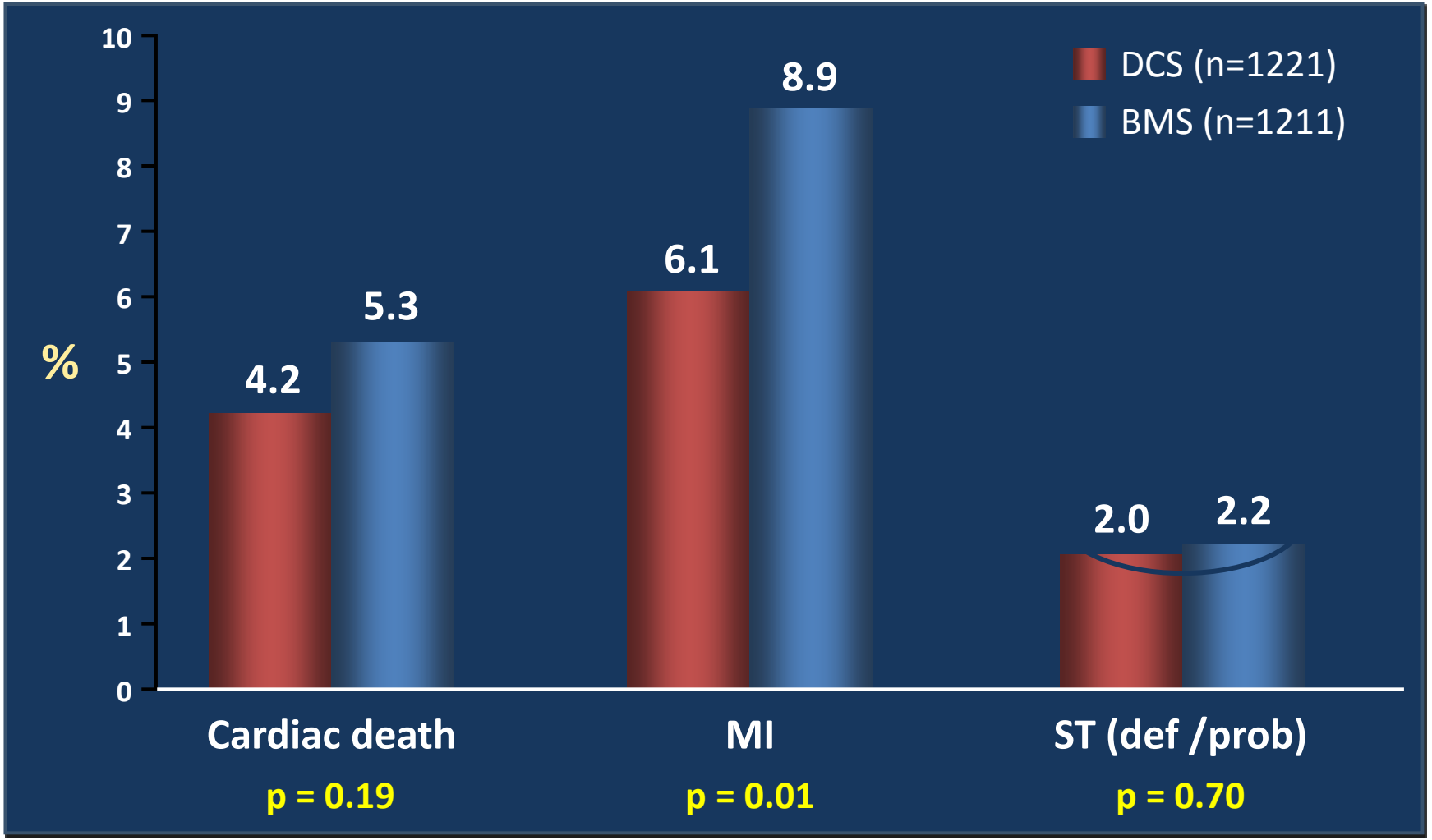
Leaders Free: Primary Safety Endpoint

(Cardiac Death, MI, ST)



Leaders Free:

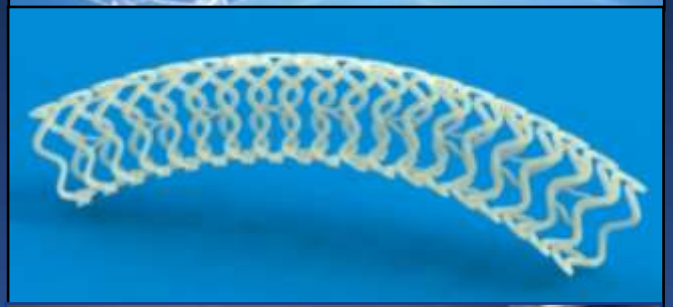
Components of the Safety Endpoint (1-year)



Mount Sinai Heart

21st CardioVascular Summit TCTAP 2016

Bioresorbable Vascular Scaffolds (BRS)

Igaki-Tamai		*PLLA*
Abbott Absorb		*PLLA (eluting everolimus)*
Elixir DESolve		*PLLA (eluting novolimus)*
Reva Fantom		*Iodinated tyrosine-derivative (eluting sirolimus)*
Biotronik Dreams		*Magnesium (eluting sirolimus)*

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Optimal Duration of DAPT with BVS:

1. Current trials have recommended at least 12 months of DAPT for patients.

2. BVS available is only first generation

3. Optimal duration is unknown

Conclusions

1. After DES, longer DAPT is associated with protection against ischemic events but increases the risk of bleeding significantly as well as possibly all-cause mortality!

2. Spontaneous bleeding events are strongly and consistently associated with increased risk of mortality. These parameters are difficult to capture in clinical trials, but extremely important to the patient.

3. New-generation DES have significantly improved the stent-related thrombotic events thus attenuating the benefit of prolonged DAPT in this population- the math just doesn't work for most patients!

4. Prolongation of DAPT **after the mandatory DAPT period** for protection against **non-stent related thrombotic events** might be applied judiciously after careful evaluation of the individual atherothrombotic (stent-related and non-stent-related) and hemorrhagic risk.

The Optimal duration of DAPT in most DES patients should be shorter rather than longer, but should be customized based on the ischemic benefit and bleeding risk for each patient