The DAPT Duration Debate – Practical Synthesis and Clinical Recommendations

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Mount Sinai Heart

21st CardioVascular Summit
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Disclosure Statement of Financial Interest

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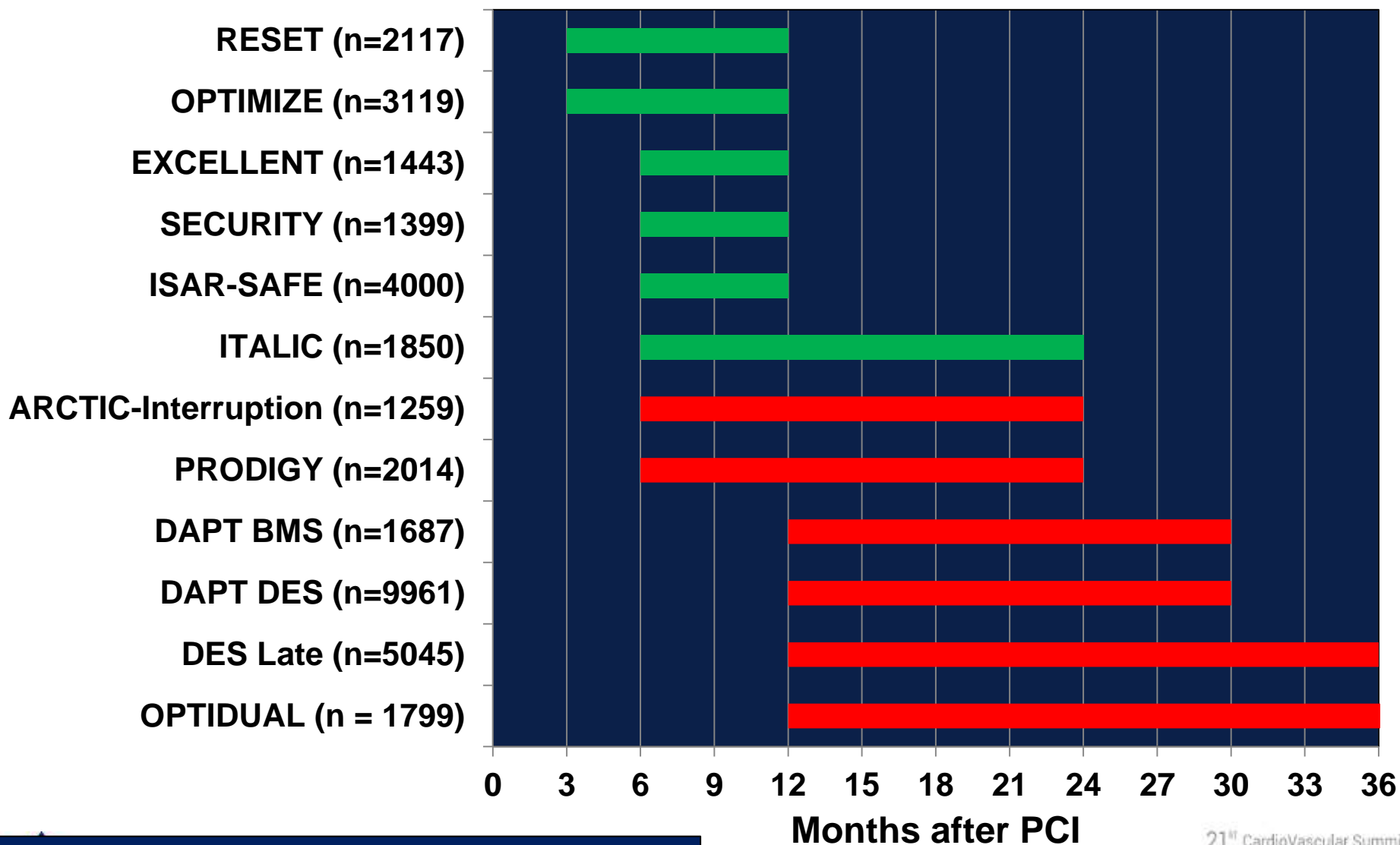
- Consulting Fees/Honoraria

Company

- The Medicines Co., AZ, BMS, Lilly/Daiichi Sankyo

- Janssen (J+J),

- Janssen (J+J), Maya Medical,

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

Timing of aspirin only vs. DAPT

Trial	Months after PCI
RESET (n=2117)	
OPTIMIZE (n=3119)	
EXCELLENT (n=1443)	
SECURITY (n=1399)	
ISAR-SAFE (n=4000)	
ITALIC (n=1850)	
ARCTIC-Interruption (n=1259)	
PRODIGY (n=2014)	
DAPT BMS (n=1687)	
DAPT DES (n=9961)	
DES Late (n=5045)	
OPTIDUAL (n = 1799)	

Months after PCI

0 3 6 9 12 15 18 21 24 27 30 33 36

More than 30,000 randomized patients!

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Is there a benefit in extending DAPT beyond one year?

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

Chart: Cumulative Incidence (%) comparing Thienopyridine (N=5020) vs Placebo (N=4941)

Endpoint	Thienopyridine	Placebo	p-value
ST (Definite/Probable)	0.4%	1.4%	<0.001
Definite ST	0.3%	1.2%	<0.001
Probable ST	0.1%	0.1%	0.55
MACCE	4.3%	5.9%	<0.001
Death	2.0%	1.5%	0.052
MI	2.1%	4.1%	<0.001
Ischemic stroke	0.5%	0.7%	0.16
Hemorrhagic stroke	0.3%	0.2%	0.68

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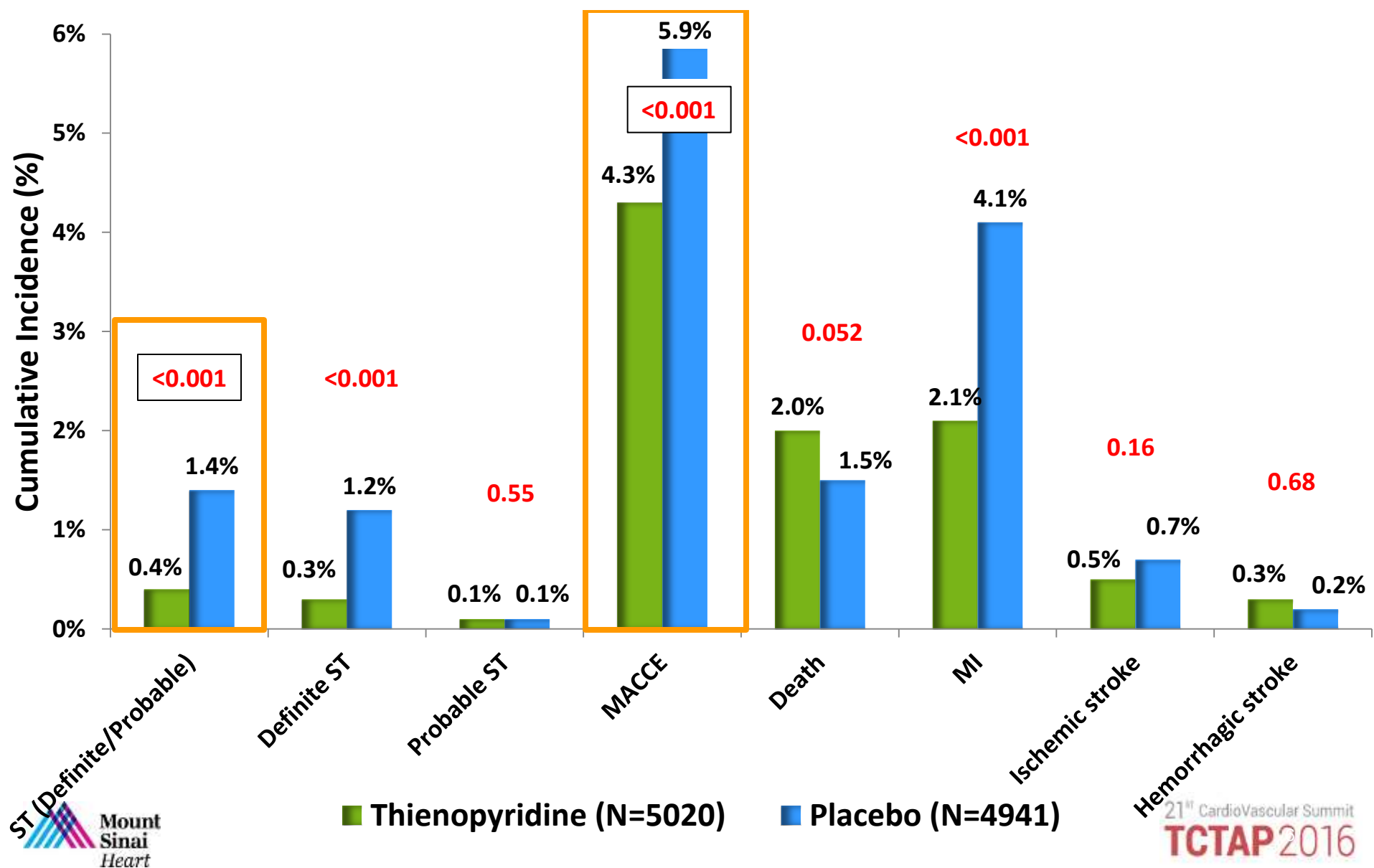
Non-Stent Thrombosis Myocardial Infarction
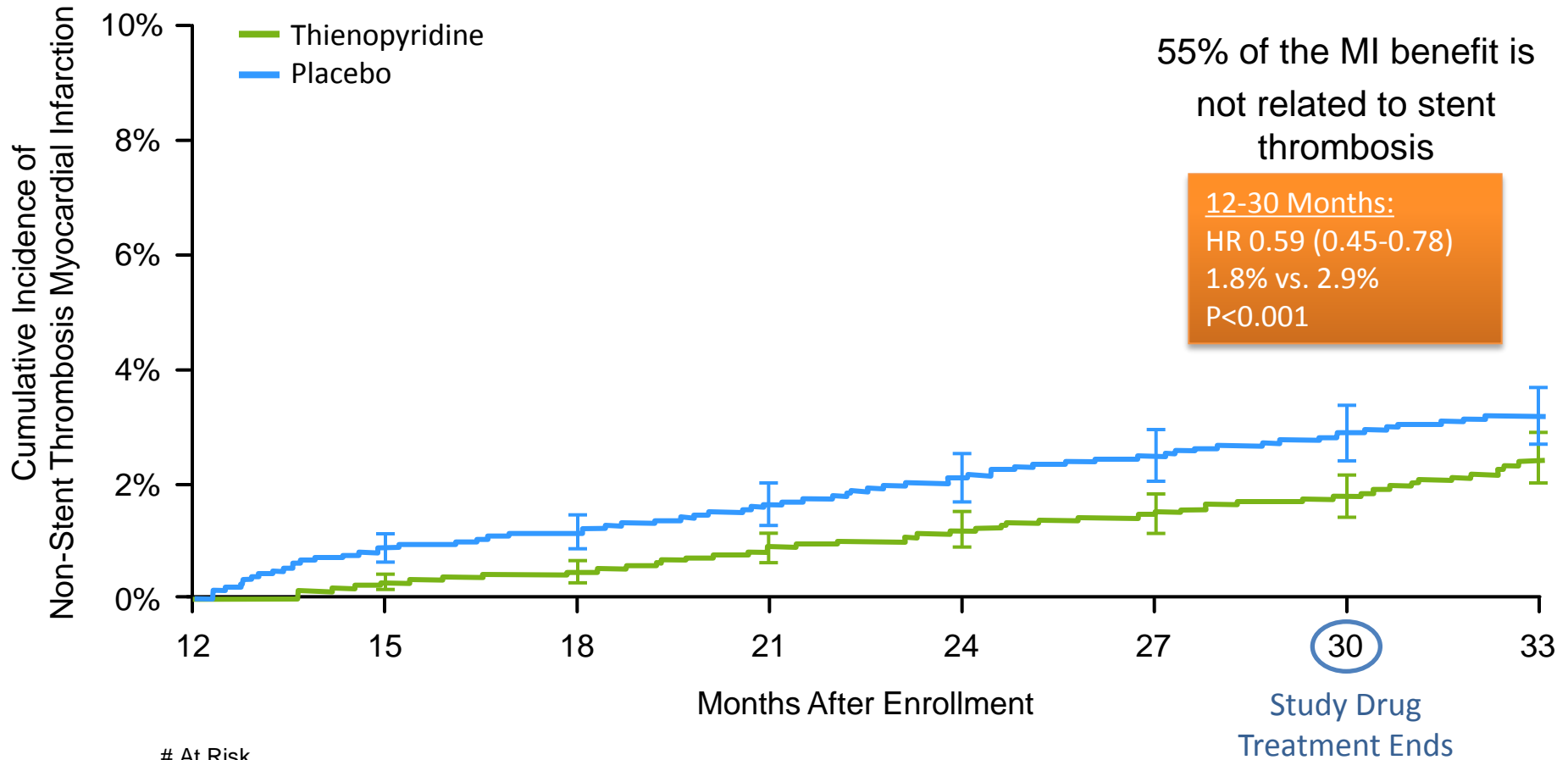
Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months

Cumulative Incidence (%) — bar chart

Category	Thienopyridine (N=4710)	Placebo (N=4649)	p-value
Moderate or Severe	2.5%	1.6%	0.001
Moderate	1.7%	1.0%	0.004
Severe	0.8%	0.6%	0.15
BARC Type 2	3.1%	1.5%	<0.001
BARC Type 3	2.6%	1.5%	<0.001
BARC Type 5	0.1%	0.1%	0.38

Legend: ■ Thienopyridine (N=4710) ■ Placebo (N=4649)
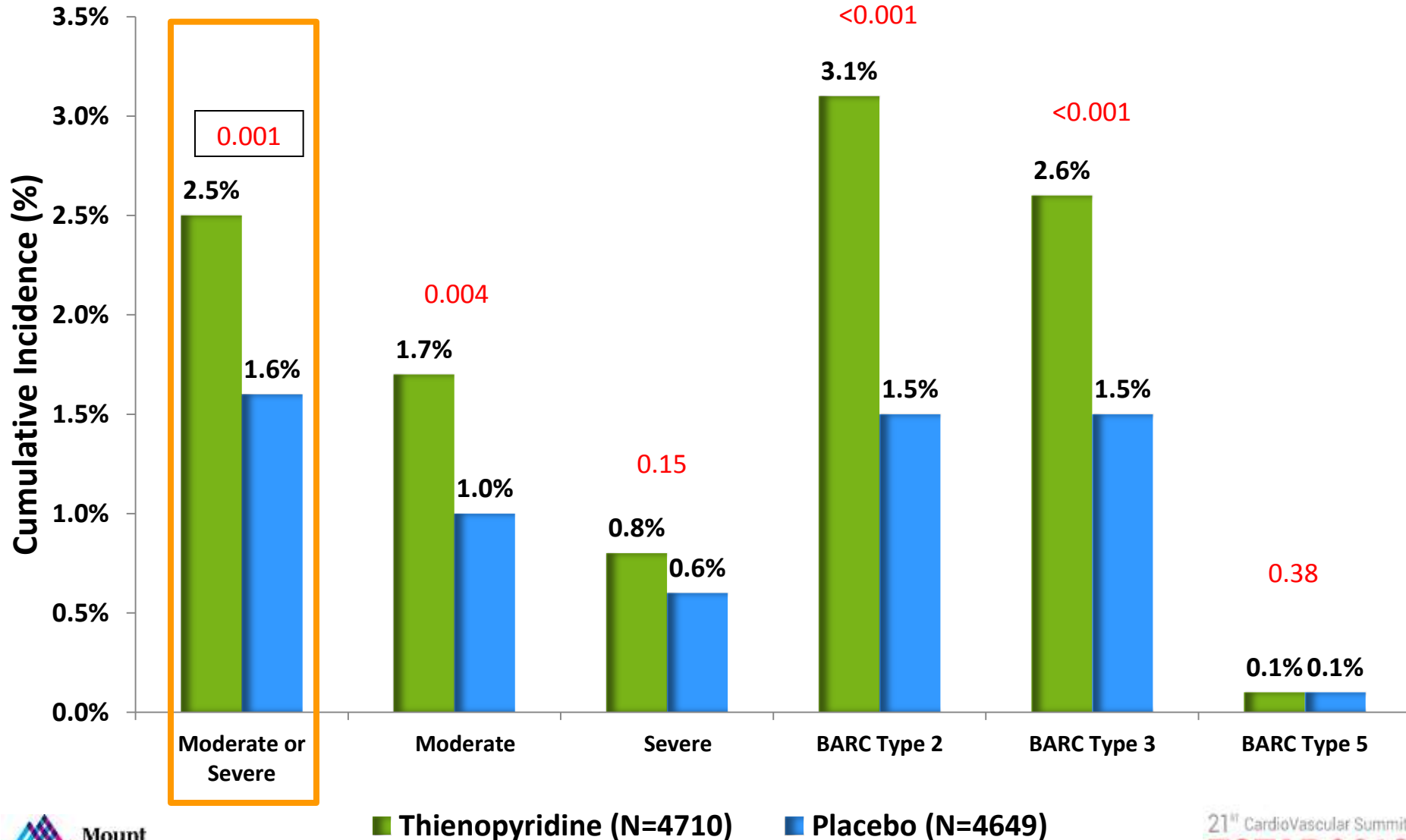
Longer DAPT is associated with lower risk of Stent Thrombosis and Myocardial Infarction
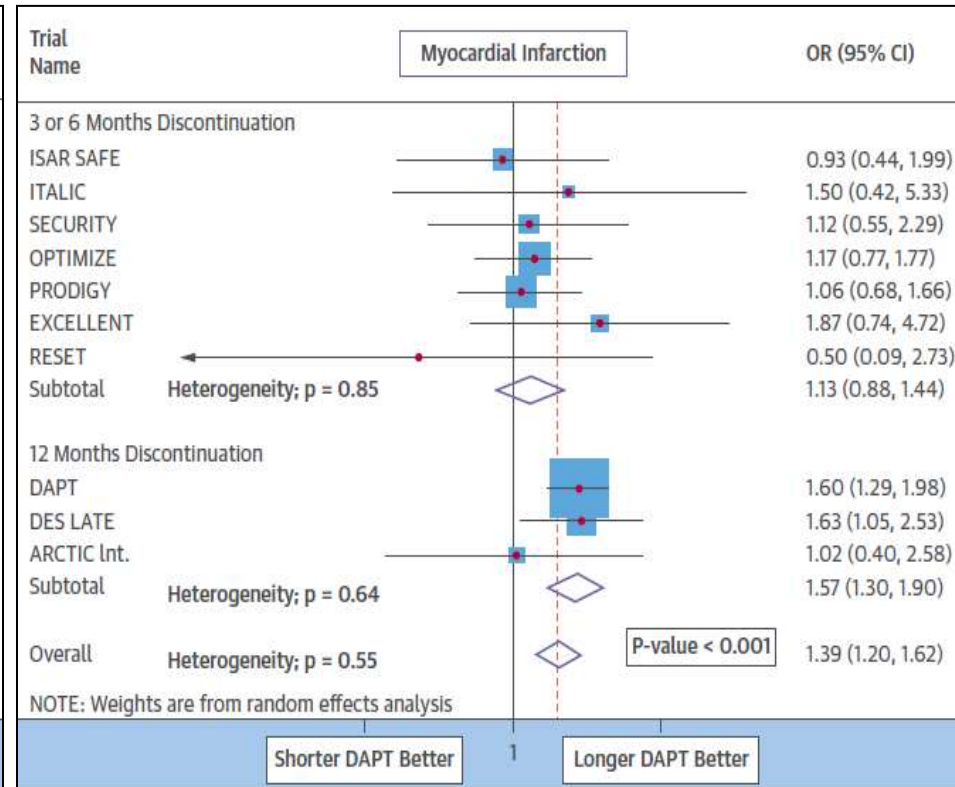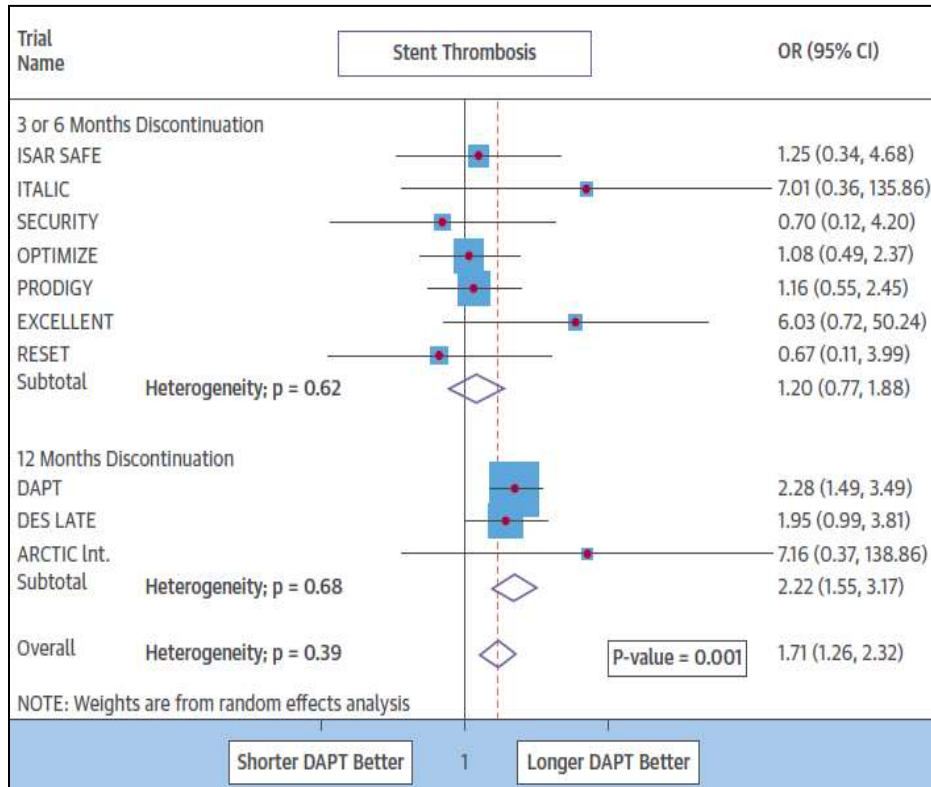
- **Mean weighted exposure time to DAPT within the S-DAPT and L-DAPT groups was 8.5 months and 23.2 months respectively.**

Giustino, Dangas et al; JACC 2015

Shorter DAPT is associated with lower risk of Clinically Significant Bleeding and All-Cause Mortality
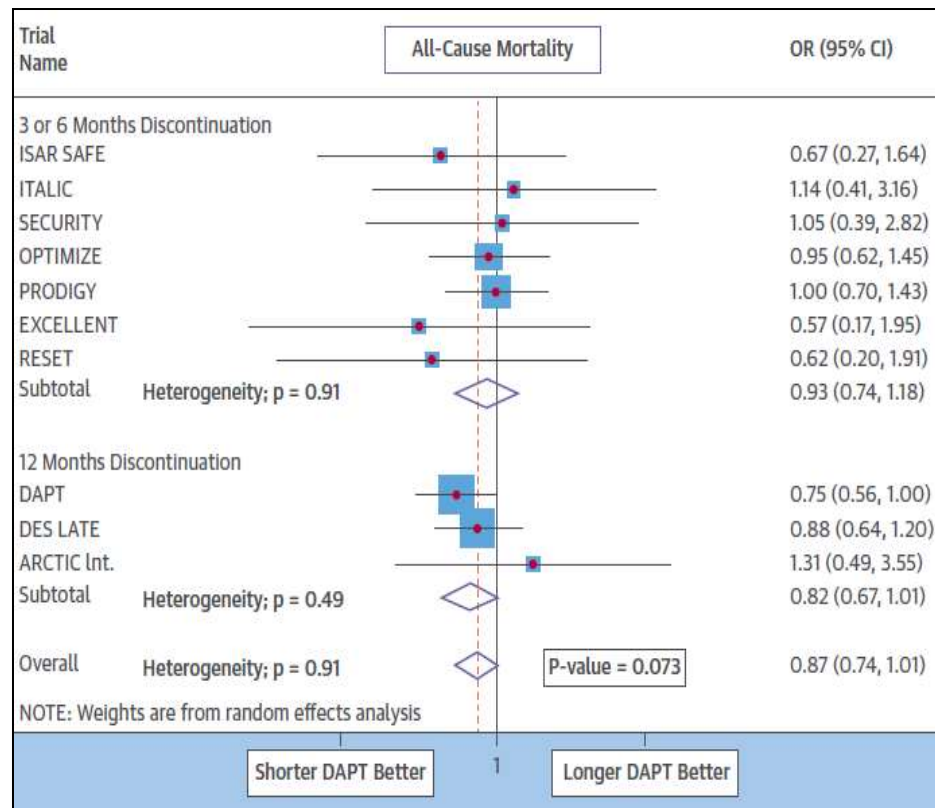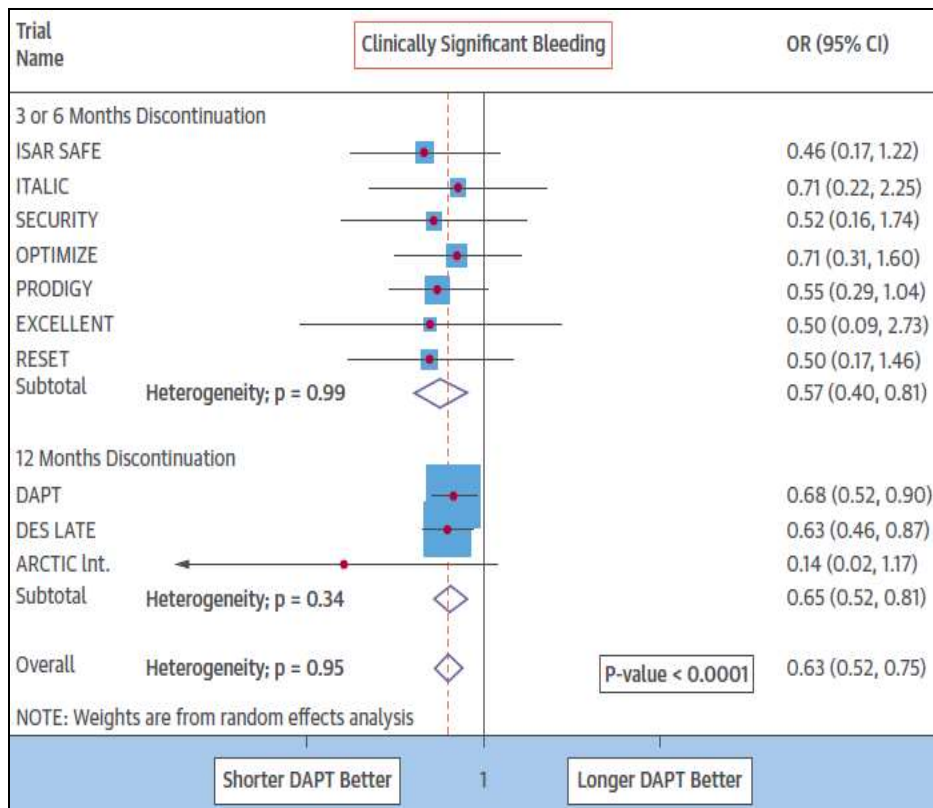
*CSB defined as a BARC 3 or 5, TIMI major or minor, GUSTO moderate or severe or STEEPLE major

Giustino, Dangas et al; JACC 2015

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

Palmerini, Stone, et al - Lancet 2015

ES=effect size

All-cause Death forest plot:

Study	HR (95% CI)	Weight (%)	Events Group 1	Events Group 2
ARTIC Interruption	1.32 (0.49, 3.55)	3.03	9/624	7/635
DAPT	0.75 (0.56, 1.02)	33.00	74/4941	98/5020
DES LATE	0.71 (0.45, 1.10)	14.85	32/2514	46/251
EXCELLENT	0.57 (0.17, 1.95)	1.99	4/722	7/721
ISAR SAFE	0.66 (0.27, 1.63)	3.67	8/1997	12/2003
ITALIC	1.14 (0.41, 3.15)	2.85	8/912	7/910
OPTIMIZE	0.95 (0.63, 1.45)	17.07	43/1563	45/1556
PRODIGY	0.91 (0.61, 1.37)	18.12	45/751	49/750
RESET	0.62 (0.20, 1.88)	2.36	5/1059	8/1058
SECURITY	1.00 (0.37, 2.66)	3.05	8/682	8/717
I-V (I²=0.0%, p=0.93); p value for ES=0.02	0.82 (0.69, 0.98)	100.00	236/	287/1590
D+L: p value for ES=0.02	0.82 (0.69, 0.98)	100.00	15765	

Shorter DAPT better   Longer DAPT better

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

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

Non-cardiac Death

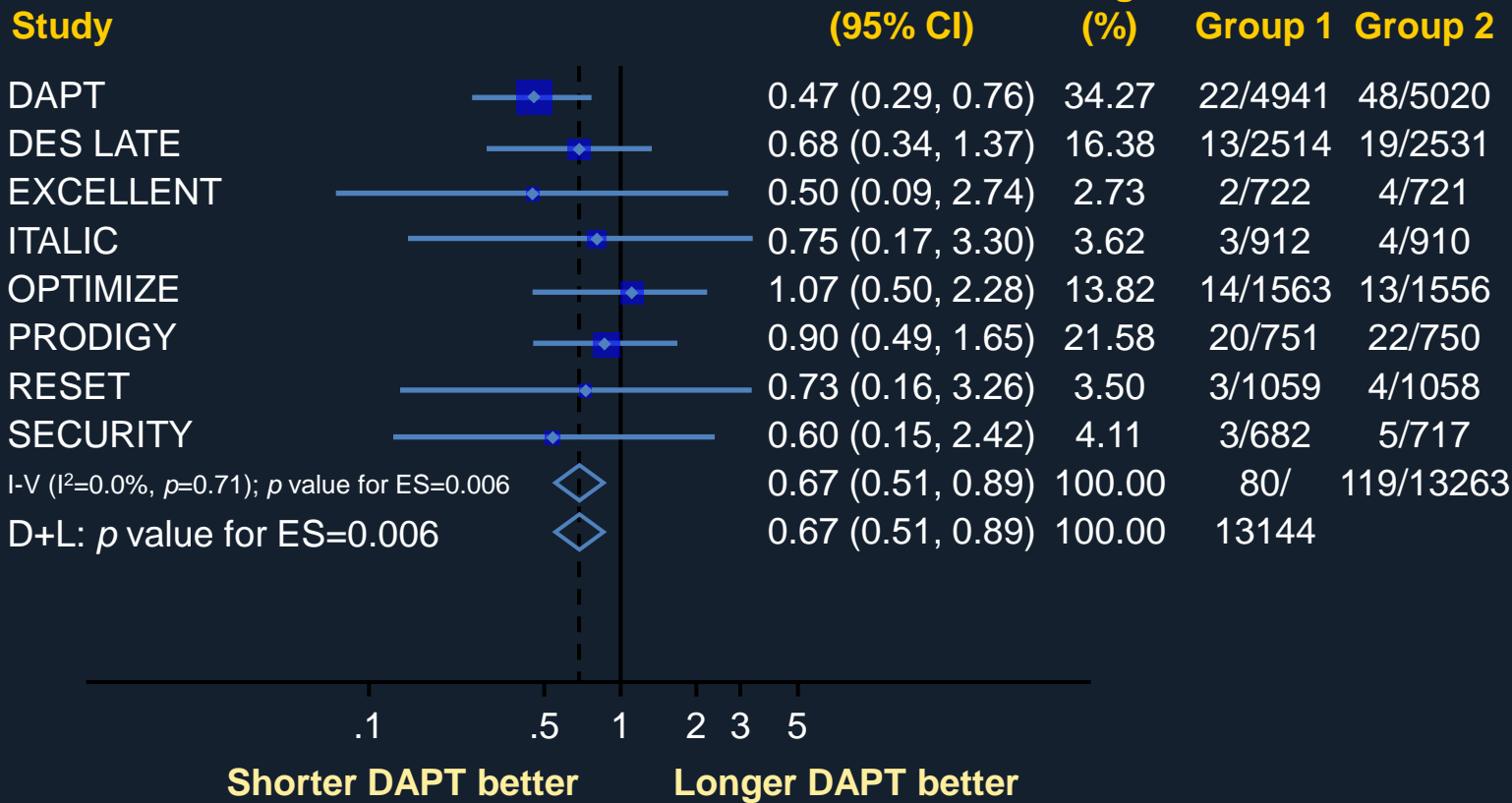| Study	HR (95% CI)	Weight (%)	Events Group 1	Events Group 2
DAPT	0.47 (0.29, 0.76)	34.27	22/4941	48/5020
DES LATE	0.68 (0.34, 1.37)	16.38	13/2514	19/2531
EXCELLENT	0.50 (0.09, 2.74)	2.73	2/722	4/721
ITALIC	0.75 (0.17, 3.30)	3.62	3/912	4/910
OPTIMIZE	1.07 (0.50, 2.28)	13.82	14/1563	13/1556
PRODIGY	0.90 (0.49, 1.65)	21.58	20/751	22/750
RESET	0.73 (0.16, 3.26)	3.50	3/1059	4/1058
SECURITY	0.60 (0.15, 2.42)	4.11	3/682	5/717
I-V (I^2=0.0%, p=0.71); p value for ES=0.006	0.67 (0.51, 0.89)	100.00	80/	119/13263
D+L: p value for ES=0.006	0.67 (0.51, 0.89)	100.00	13144	

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Shorter DAPT better   **Longer DAPT better**

49% ↑ Non-cardiac mortality with prolonged DAPT (p=0.006)

ES=effect size

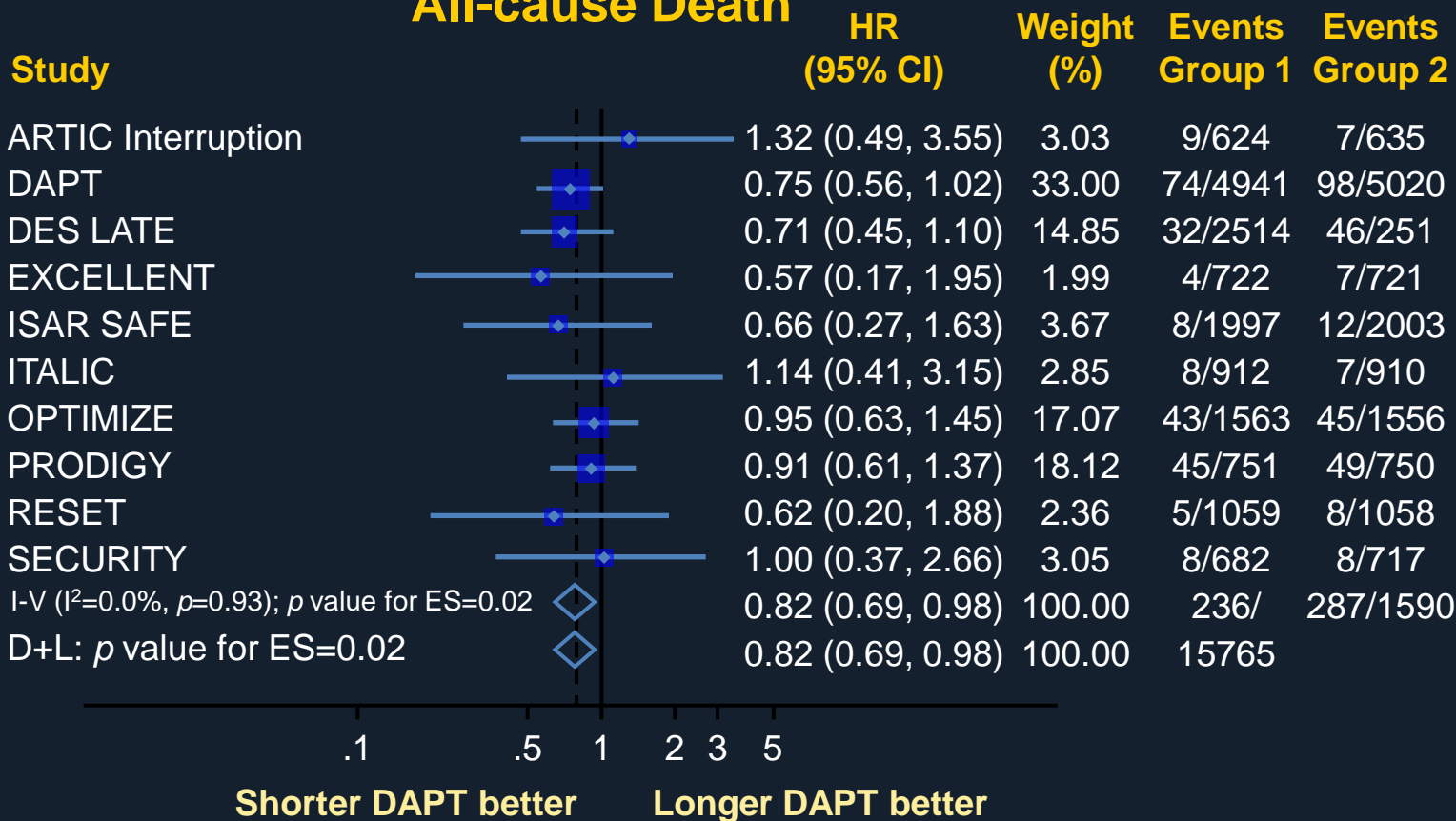Palmerini T, Stone GW, et al - Lancet 2015

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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

All-cause Death

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Palmerini, Stone, et al - Lancet 2015

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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

| Study (Ref. #) | Stent Thrombosis | | | | | | Clinically Significant Bleeding | | | | | |
| | S-DAPT | | L-DAPT | | | | S-DAPT | | L-DAPT | | | |
	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).

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
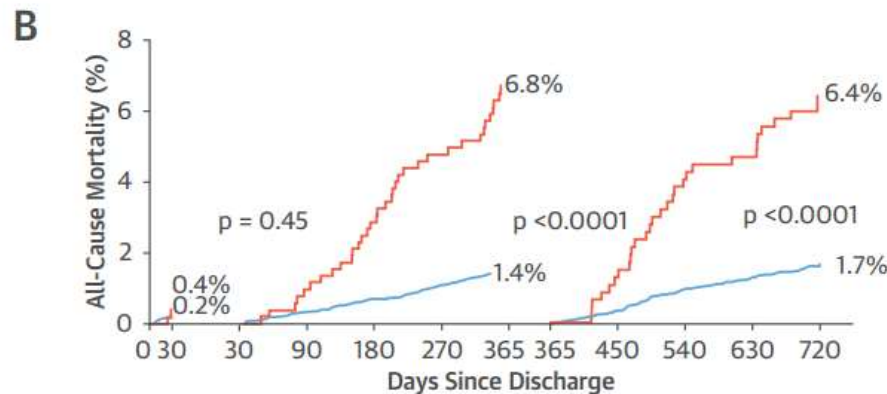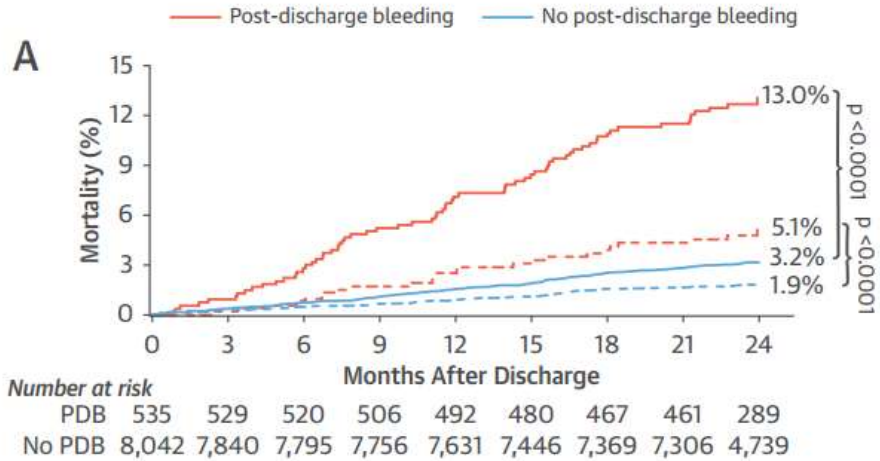
PD bleeding Vs. PD MI

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

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!**

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

1st-generation DES

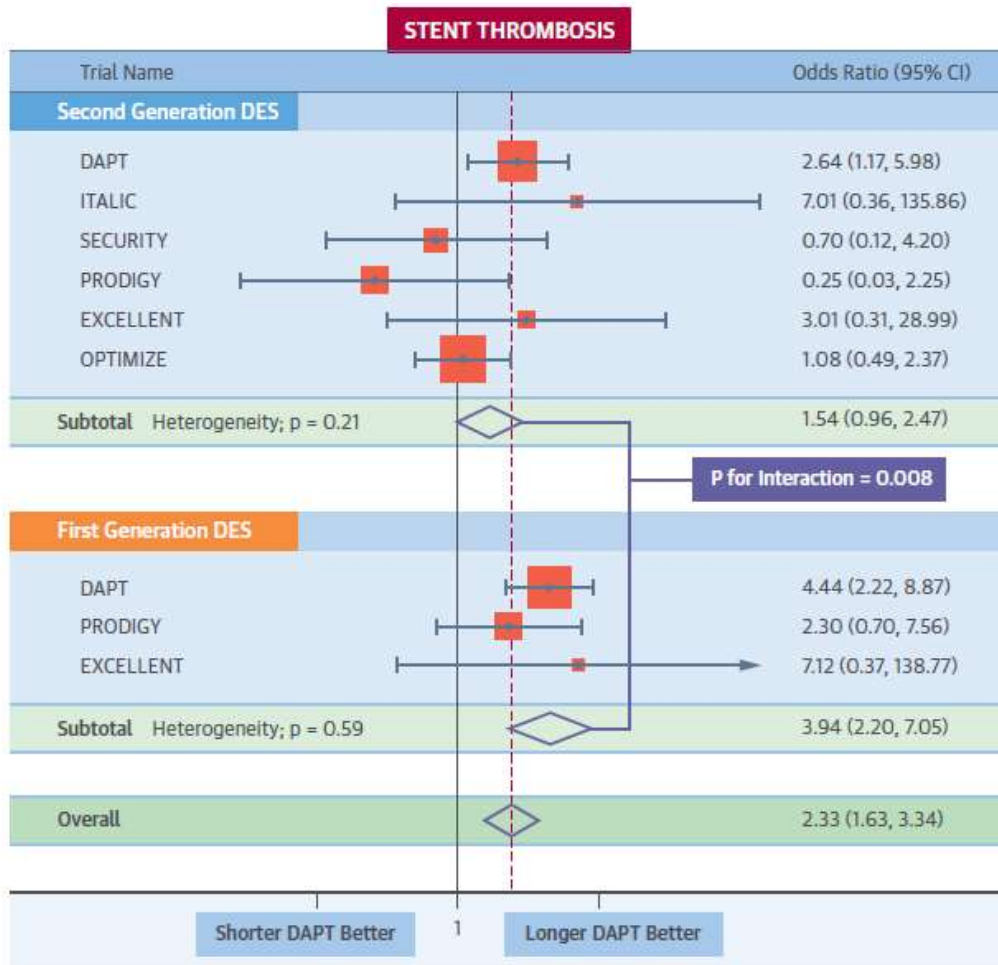**2nd-generation DES**
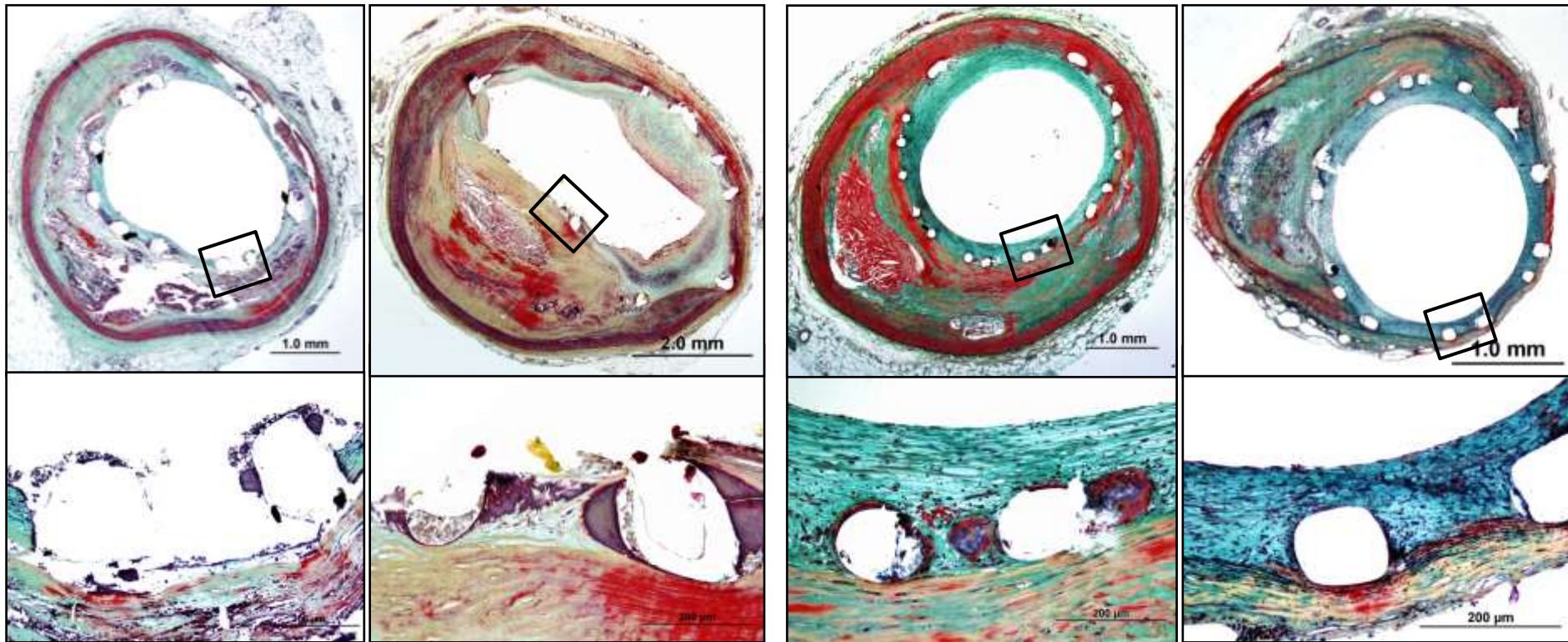
Representative Images of 2nd- vs. 1st-generation DES in Human Coronary Arteries

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.

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

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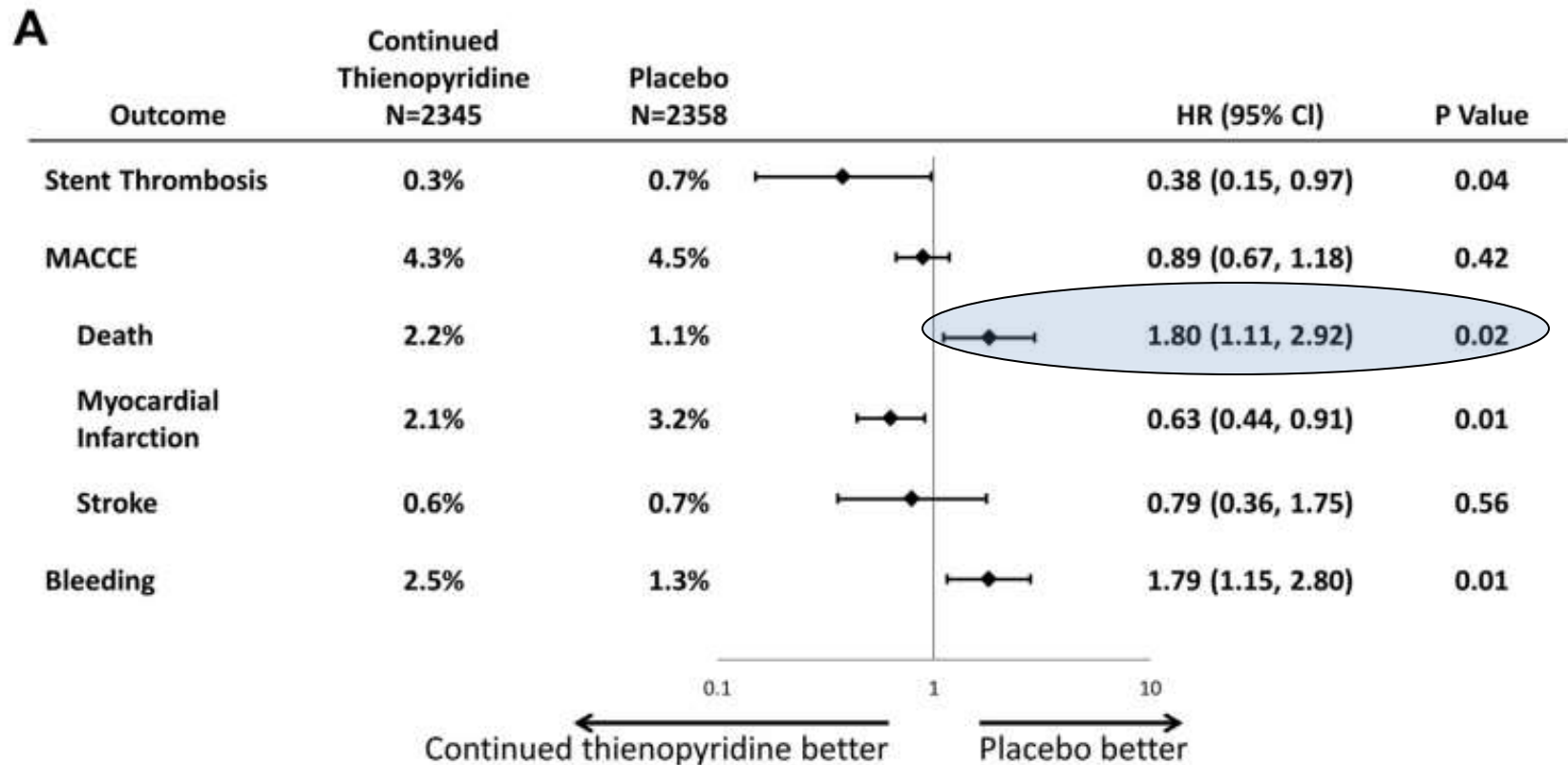
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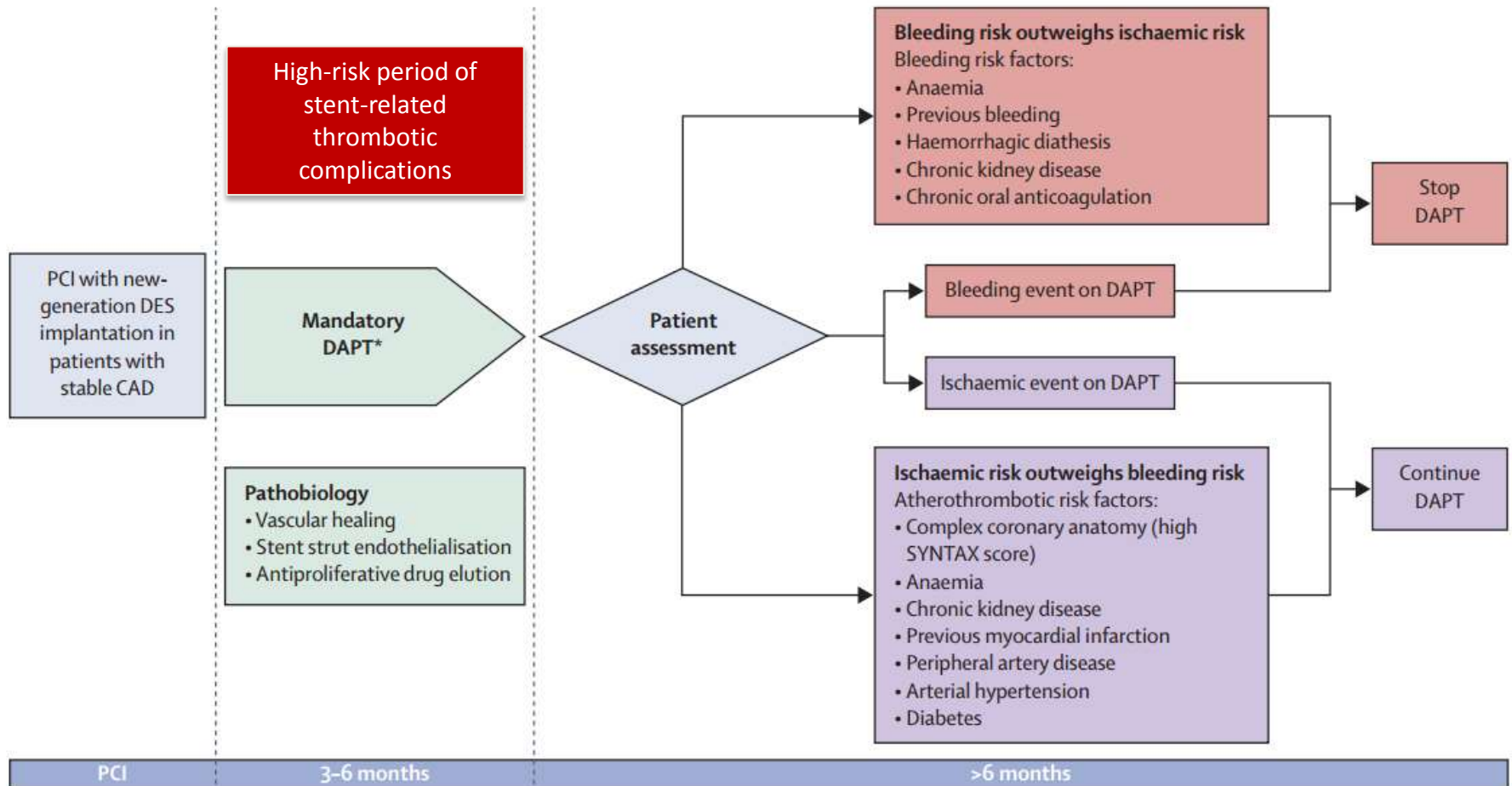# Algorithm for the management of dual antiplatelet therapy after new-generation drug-eluting stent implantation in patients with stable coronary artery disease

High-risk period of stent-related thrombotic complications

PCI with new-generation DES implantation in patients with stable CAD

Mandatory DAPT*

Pathobiology
• Vascular healing
• Stent strut endothelialisation
• Antiproliferative drug elution

Patient assessment

Bleeding risk outweighs ischaemic risk
Bleeding risk factors:
• Anaemia
• Previous bleeding
• Haemorrhagic diathesis
• Chronic kidney disease
• Chronic oral anticoagulation

Bleeding event on DAPT

Ischaemic event on DAPT

Ischaemic risk outweighs bleeding risk
Atherothrombotic risk factors:
• Complex coronary anatomy (high SYNTAX score)
• Anaemia
• Chronic kidney disease
• Previous myocardial infarction
• Peripheral artery disease
• Arterial hypertension
• Diabetes

Stop DAPT

Continue DAPT

PCI | 3–6 months | >6 months

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

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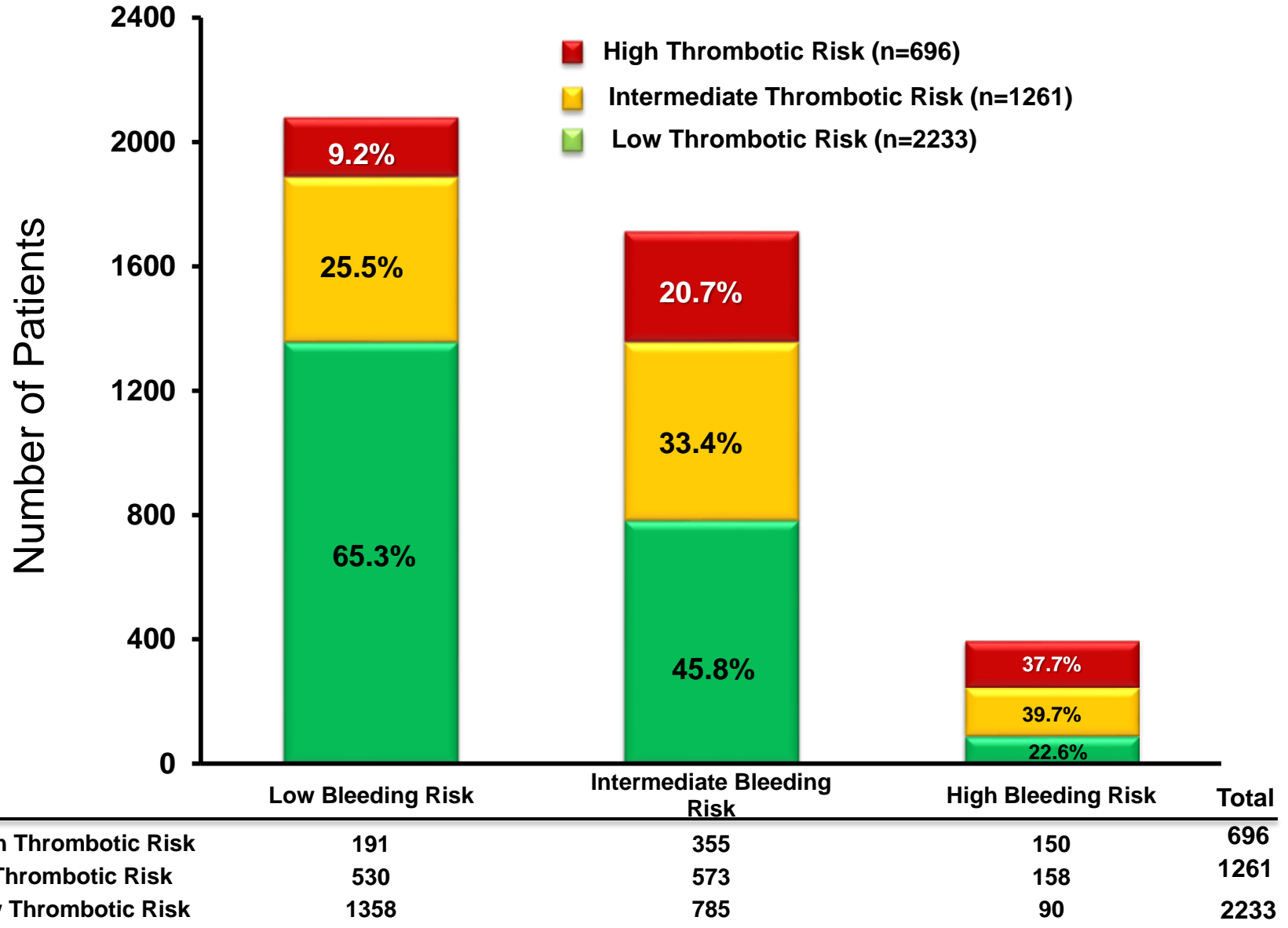
Integer Risk Score for Major Bleeding

Parameter	Score				
Age, years	< 50	50-59	60-69	70-79	>80
	0	+1	+2	+3	+4
BMI, kg/m²	<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	

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

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

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

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Cross-Classification by Thrombotic and Bleeding PARIS Risk Score Categories

Legend:
- High Thrombotic Risk (n=696)
- Intermediate Thrombotic Risk (n=1261)
- Low Thrombotic Risk (n=2233)

Y-axis: Number of Patients (0 – 2400)

Low Bleeding Risk:
- High Thrombotic Risk: 9.2%
- Intermediate Thrombotic Risk: 25.5%
- Low Thrombotic Risk: 65.3%

Intermediate Bleeding Risk:
- High Thrombotic Risk: 20.7%
- Intermediate Thrombotic Risk: 33.4%
- Low Thrombotic Risk: 45.8%

High Bleeding Risk:
- High Thrombotic Risk: 37.7%
- Intermediate Thrombotic Risk: 39.7%
- Low Thrombotic Risk: 22.6%

	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

Baber, Mehran et al – JACC 2016 in press

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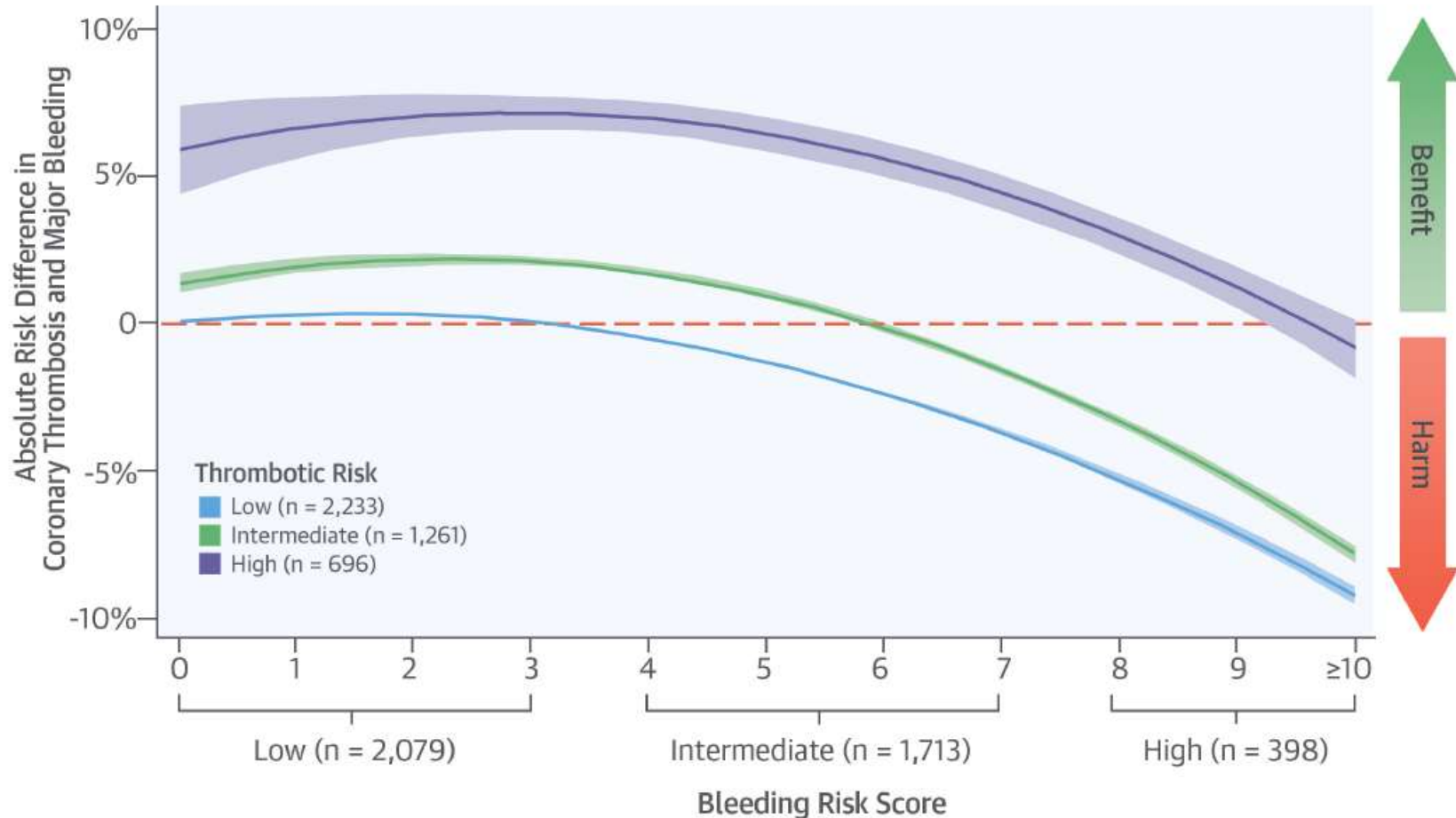
Conclusions

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