New Insights Regarding the Safety and Efficacy of DAPT after Stenting

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Cardiovascular Research Foundation

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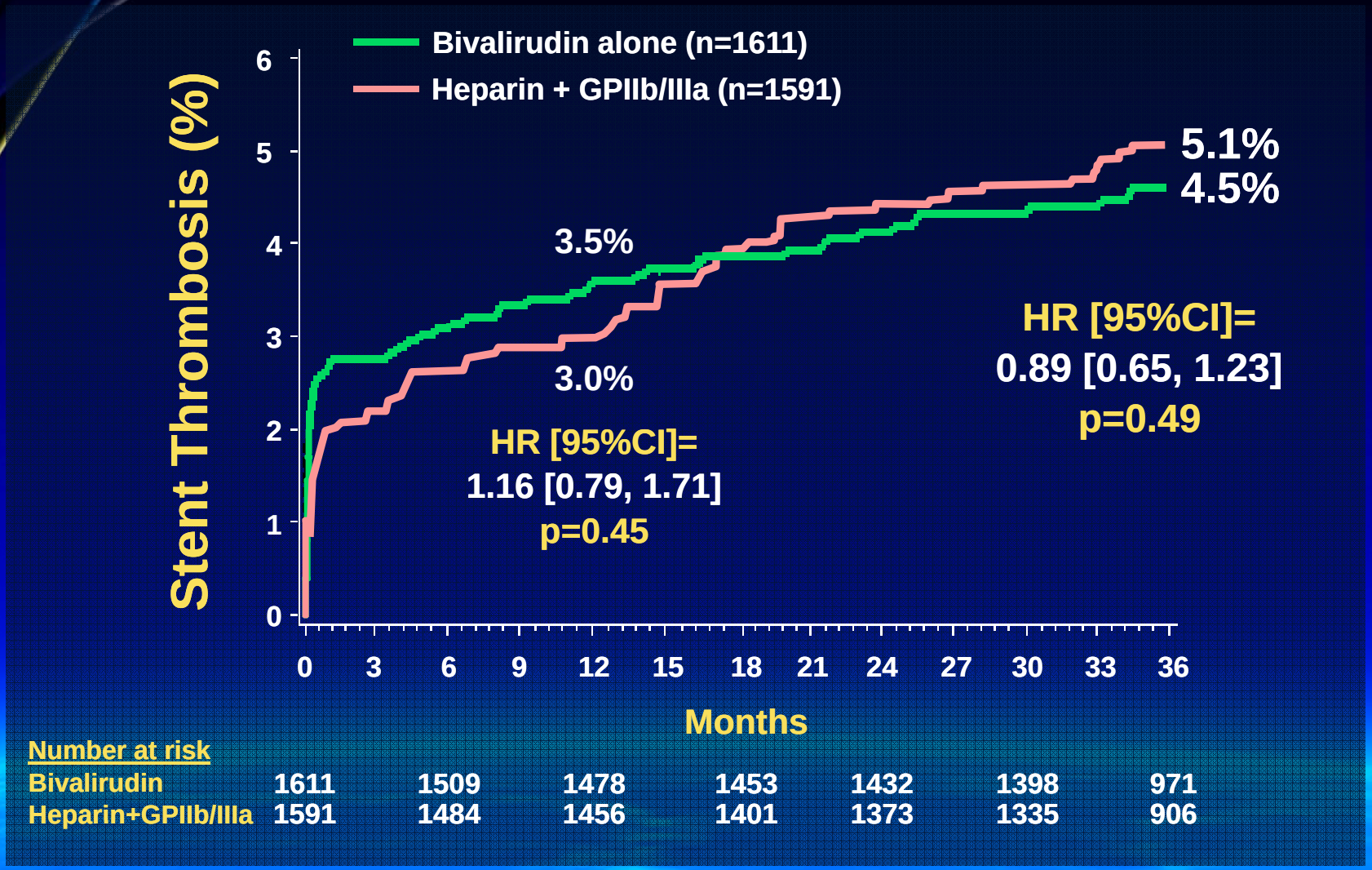
When considering the safety and efficacy of DAPT after DES

Must distinguish between:

1. **Acute coronary syndromes** (NSTEMI or STEMI; i.e. troponin positive pts)

2. **Stable ischemic heart disease** (troponin negative pts)

HORIZONS-AMI: 3-Year Stent Thrombosis (ARC Definite/Probable)

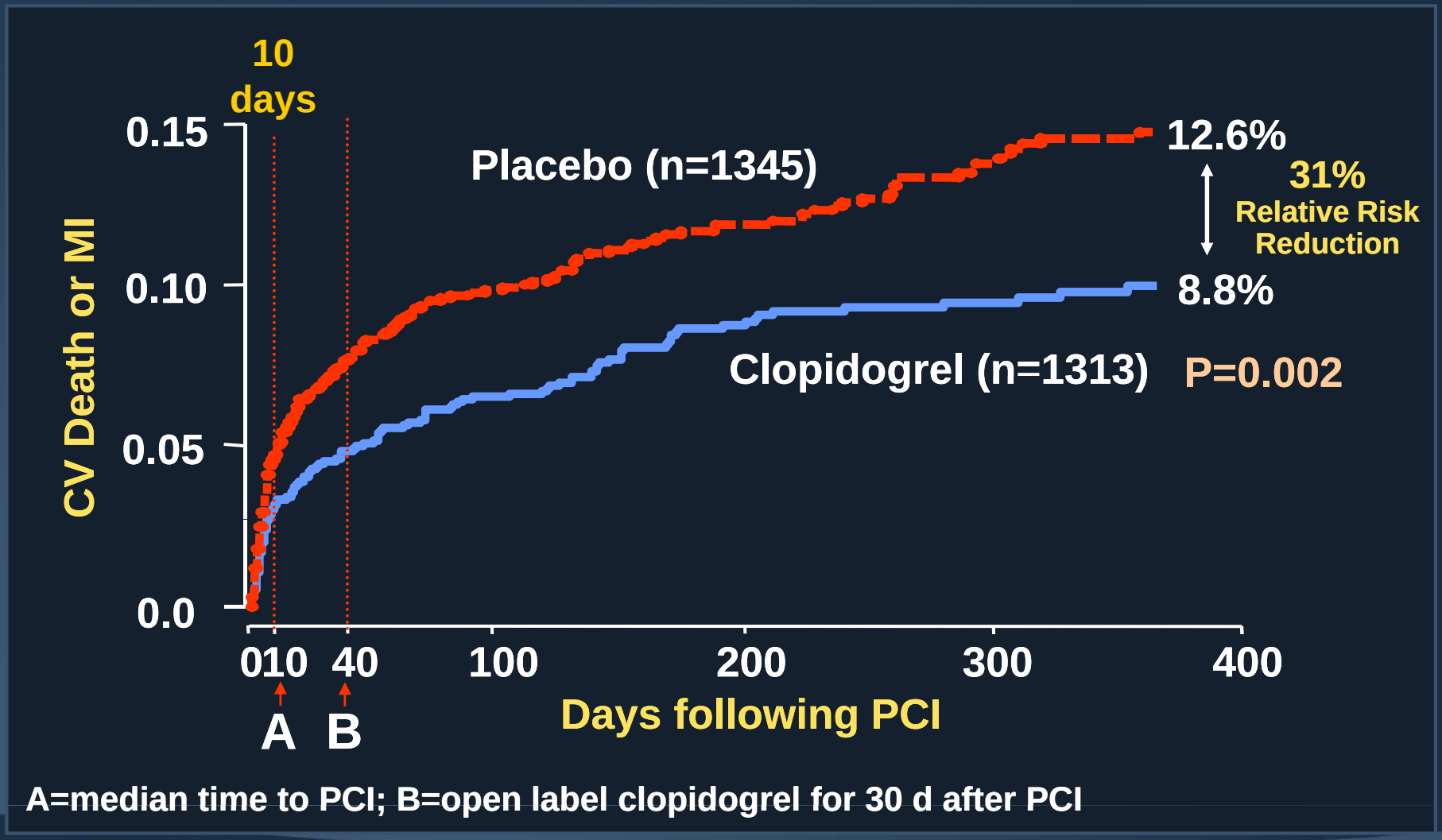


Stone GW et al. Lancet 2011;377:2193-204.

HORIZONS-AMI

PCI-CURE

PCI was performed in 2658 pts (21%): *1 Yr CV Death or MI*



A=median time to PCI; B=open label clopidogrel for 30 d after PCI

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Mehta, SR et al. *Lancet* 2001;21:2033–41

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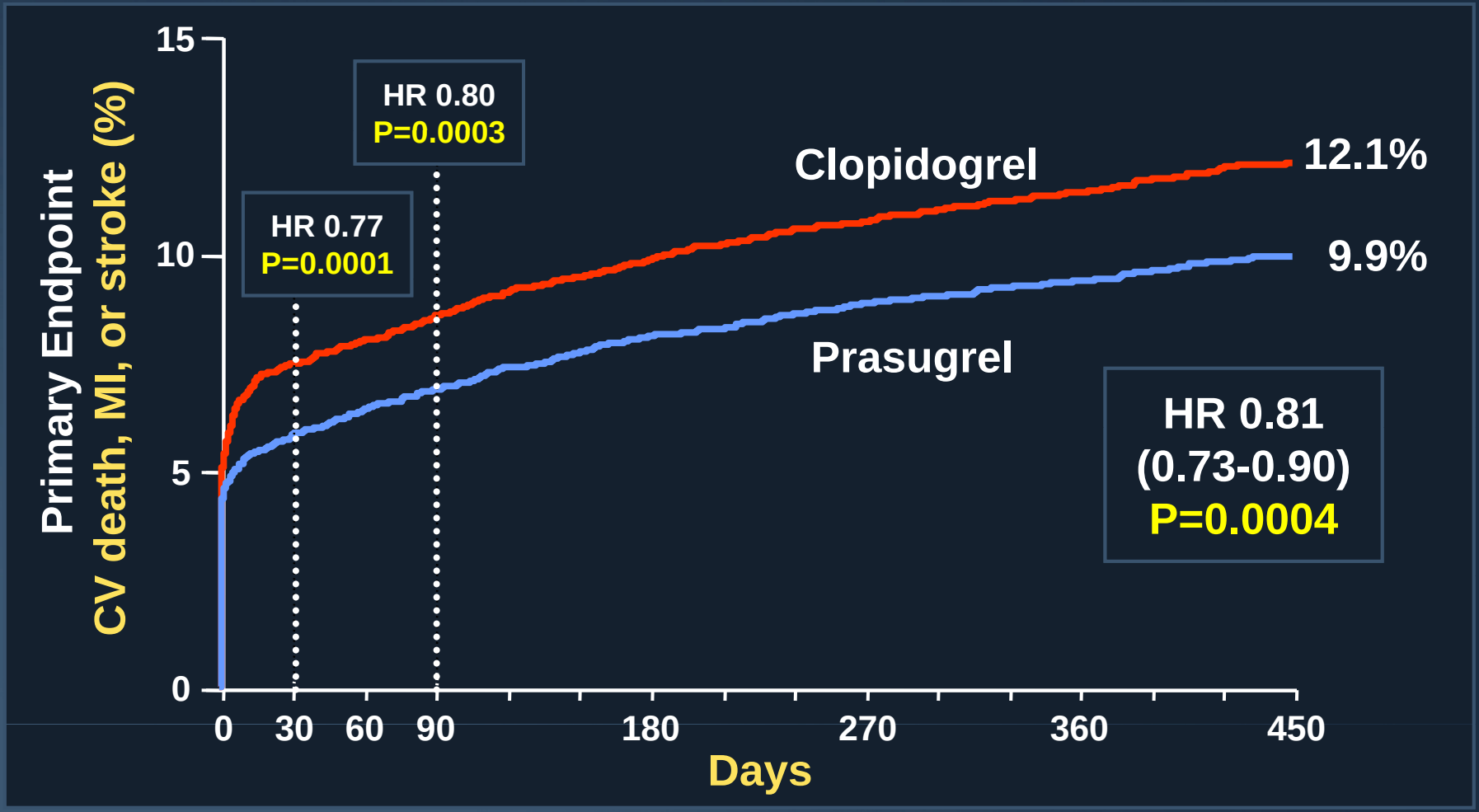
TRITON-TIMI-38

13,608 pts with ACS (unstable angina, NSTEMI, acute STEMI, or recent STEMI) undergoing PCI with known coronary anatomy (except for primary PCI pts) were treated with aspirin and randomized to clopidogrel 300 mg load + 75 mg qd vs. prasugrel 60 mg load + 10 mg qd and followed for 6-15 mos (median 12 mos)

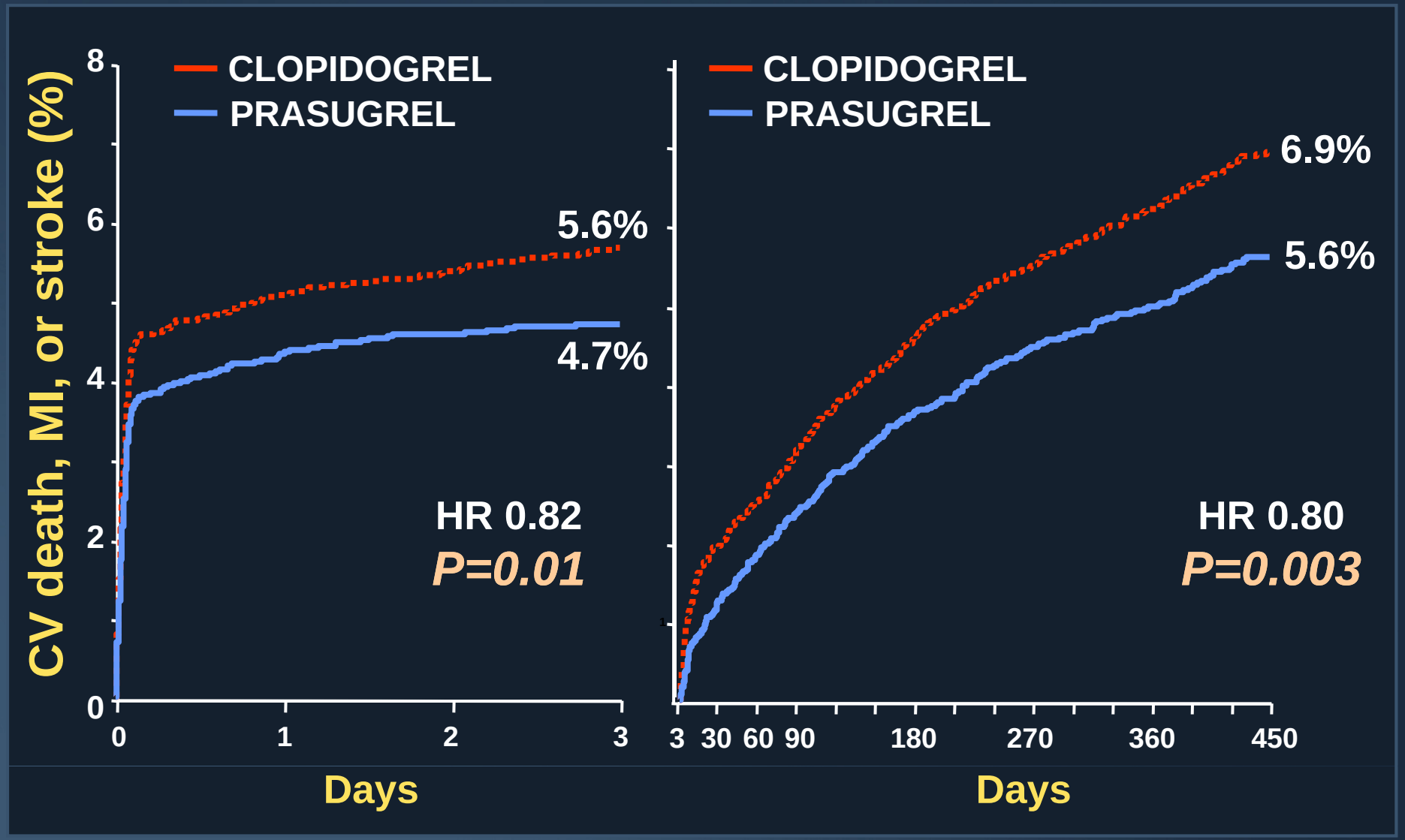


Wiviott SD et al. NEJM 2007;357:2001-15

TRÎTON TIMI-38

TRITON-TIMI-38

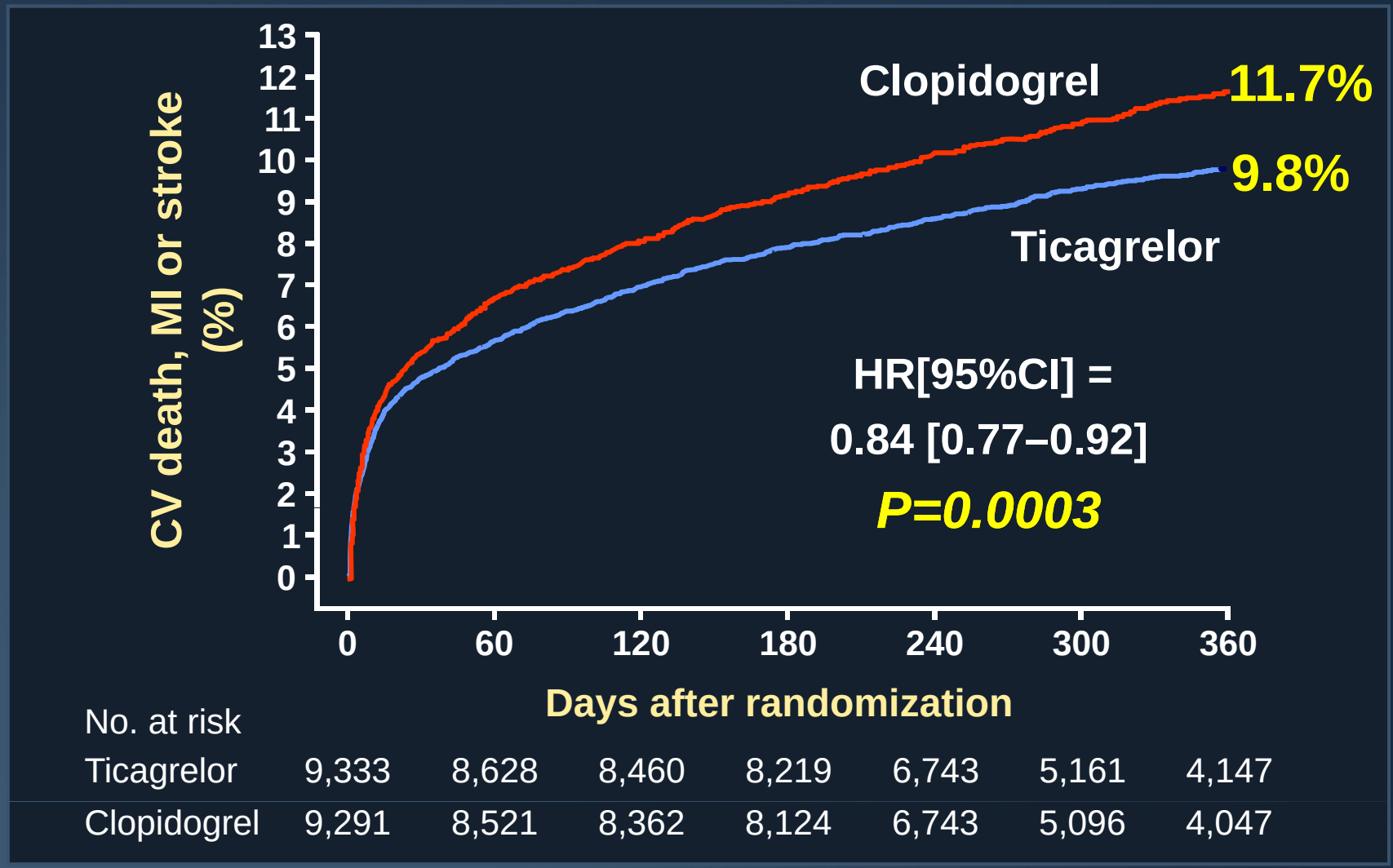
Timing of benefit (landmark analysis)



Wiviott SD et al. NEJM 2007;357:2001-15

Primary Efficacy Endpoint

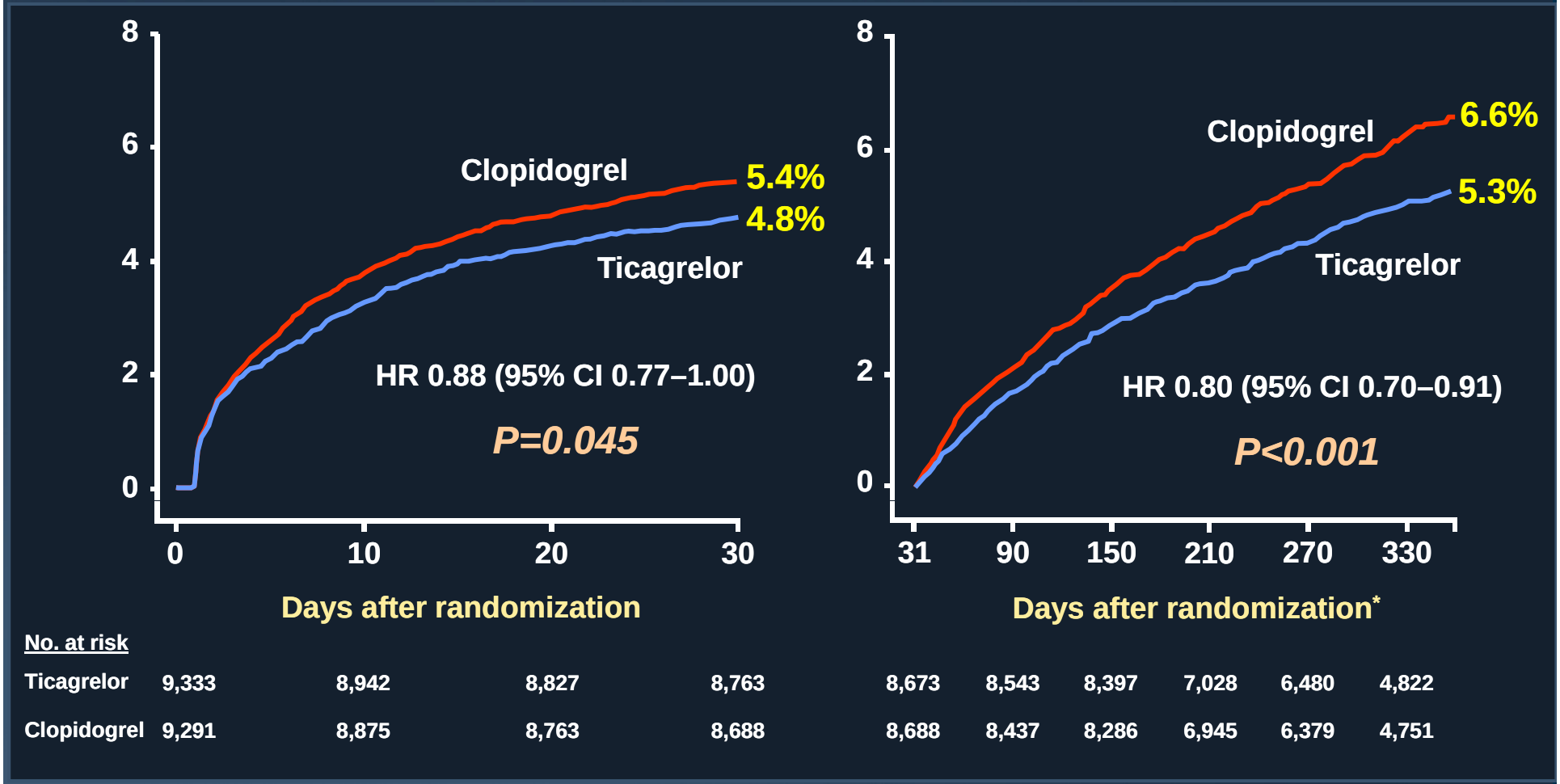
Composite of CV Death, MI or Stroke



No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

Wallentin L et al. *NEJM* 2009;361:1045-57

Primary Efficacy Endpoint (Composite of CV Death, MI or Stroke)



No. at risk										
Ticagrelor	9,333	8,942	8,827	8,763	8,673	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

* Excludes patients with any primary event during the first 30 days

Wallentin L et al. *NEJM* 2009;361:1045-57

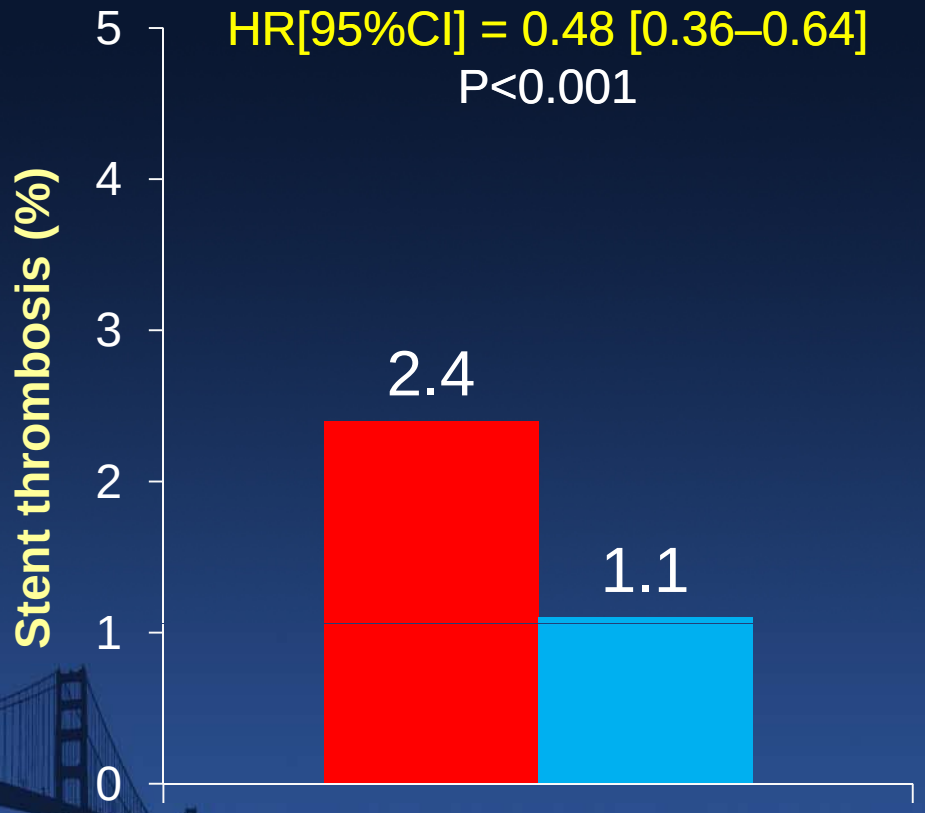
Prasugrel and Ticagrelor in ACS

Stent thrombosis

TRITON-TIMI-38 (n=13,608)
15 months

Clopidogrel (n=6795) Prasugrel (n=6813)

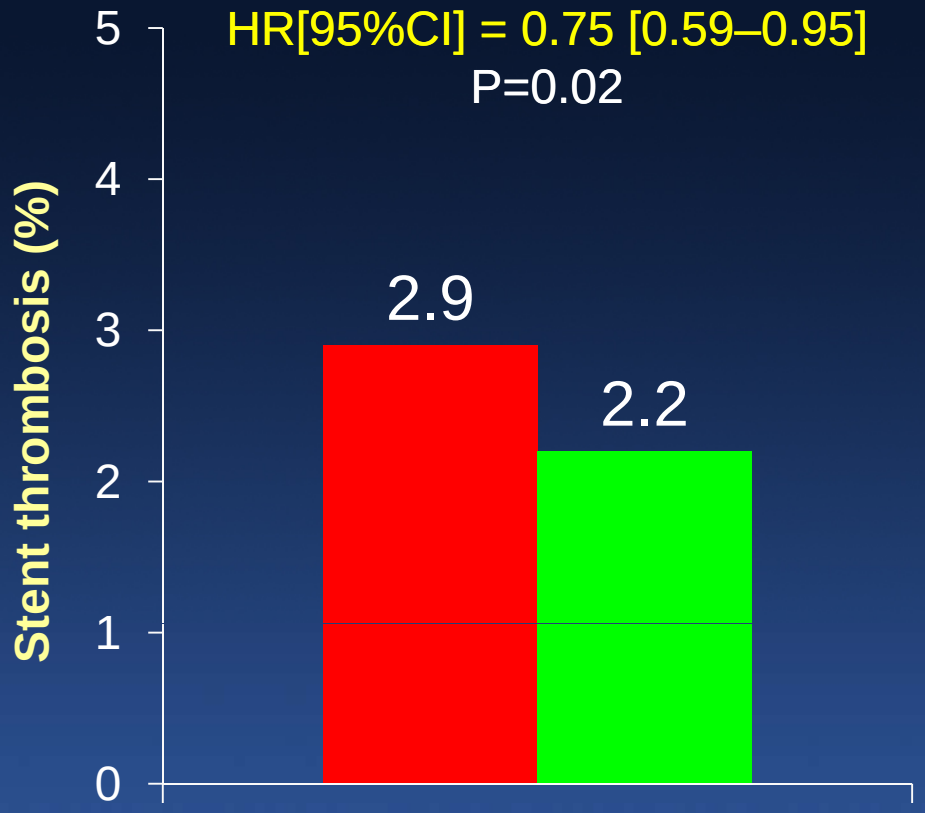
HR[95%CI] = 0.48 [0.36–0.64]
P<0.001



PLATO (n=18,624)
12 months

Clopidogrel (n=9291) Ticagrelor (n=9333)

HR[95%CI] = 0.75 [0.59–0.95]
P=0.02



TCT2011

Wiviott SD et al. N Engl J Med 2007;357:2001-15
Wallentin L et al. N Engl J Med 2009;361:1045-57

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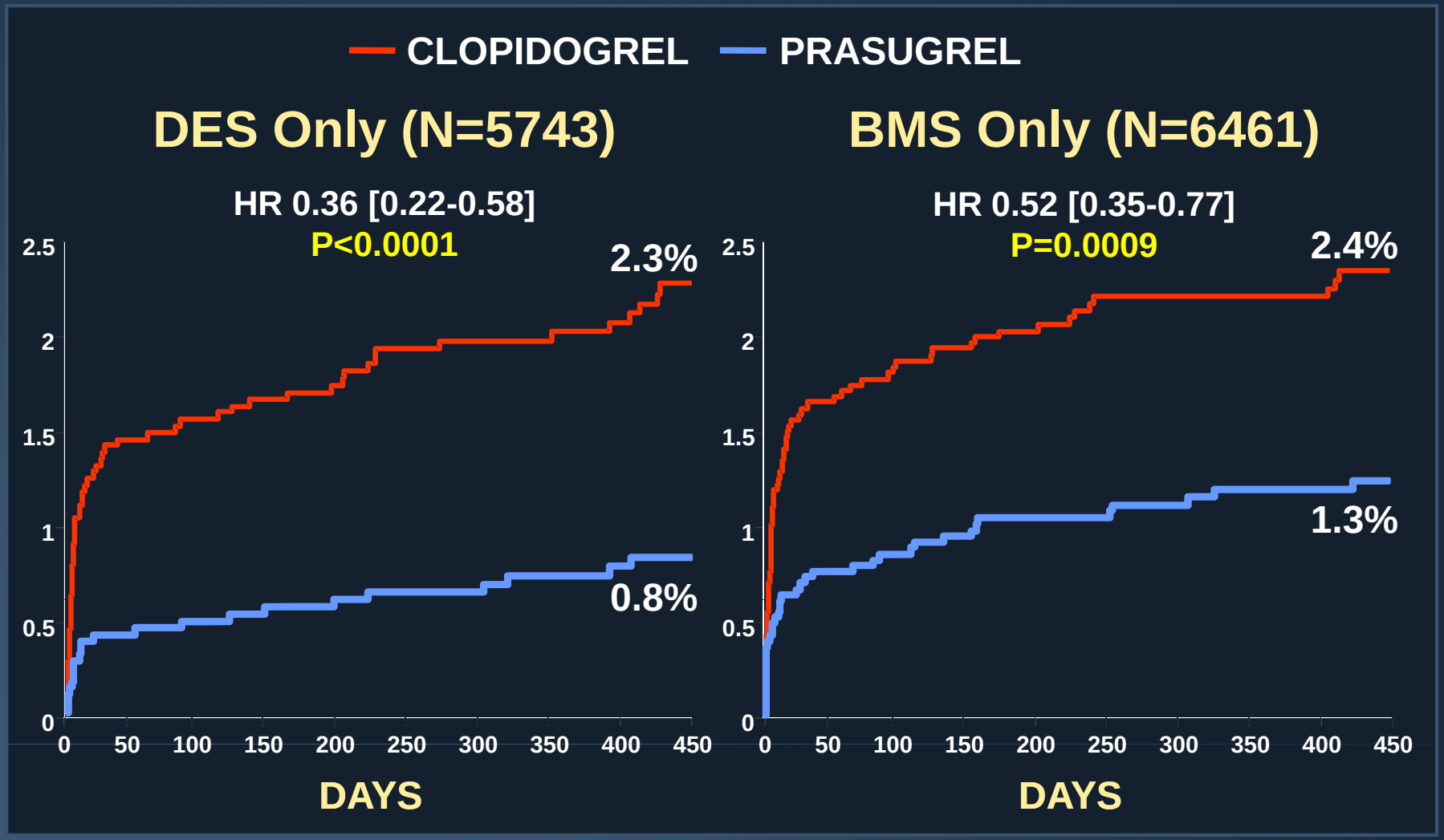
TRÎTON TIMI-38

TRITON-TIMI-38

Definite or probable stent thrombosis in 12,844 pts receiving any stent



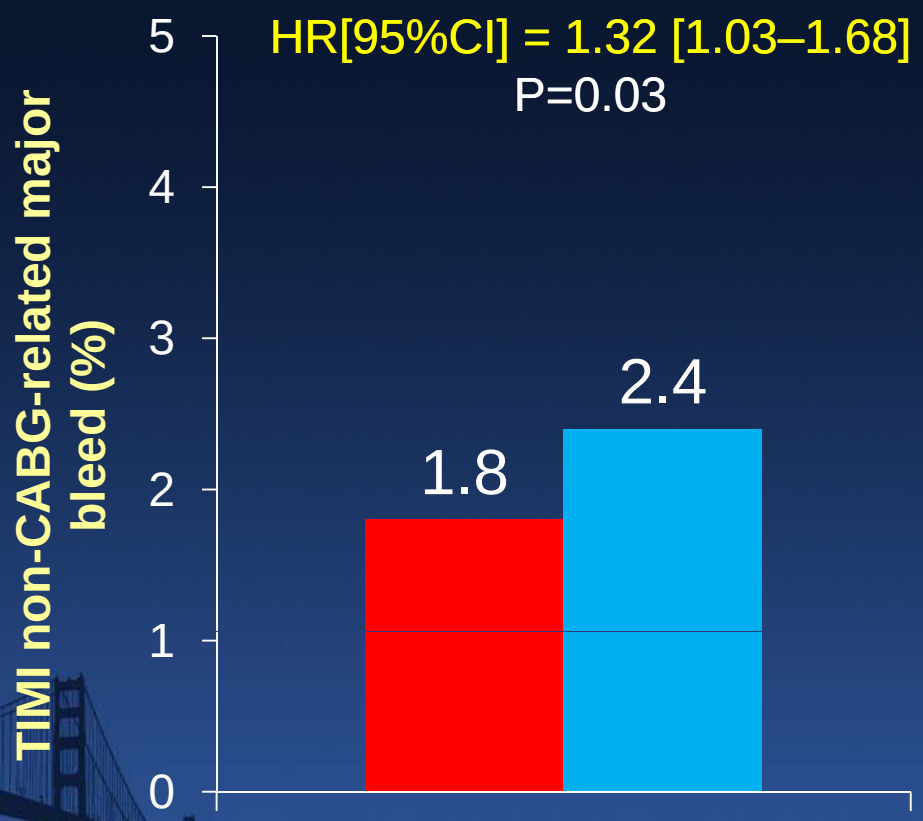
Wiviott SD et al. Lancet. 2008;371:1353-63

Prasugrel and Ticagrelor in ACS

TIMI non-CABG-related major bleeding

TRITON-TIMI-38 (n=13,608)

15 months



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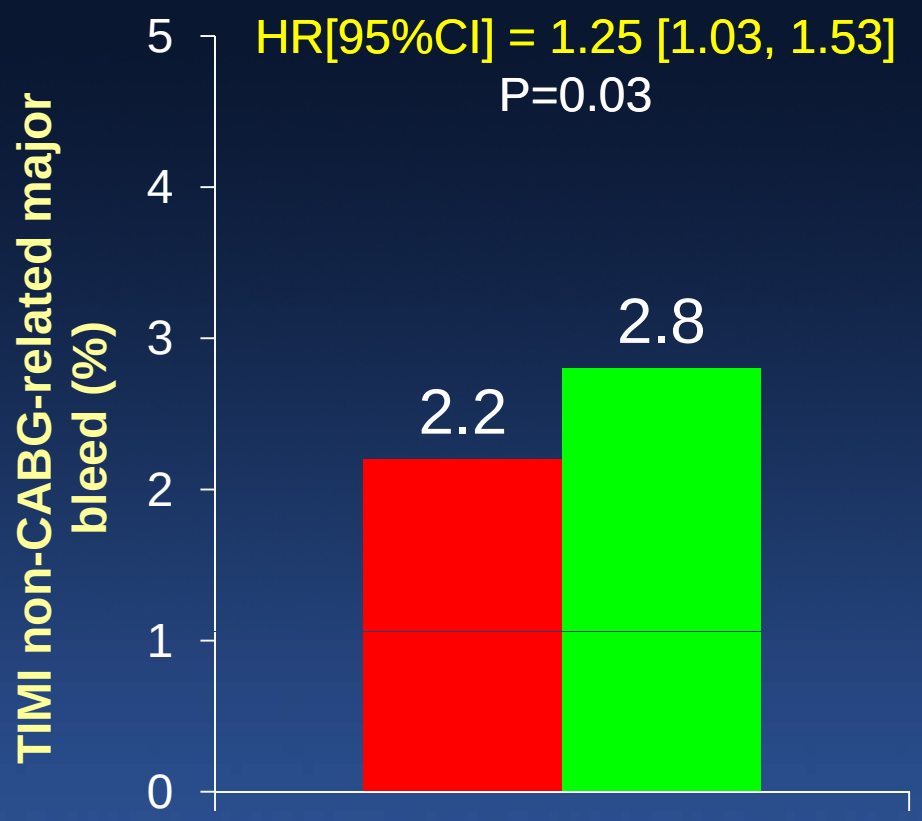

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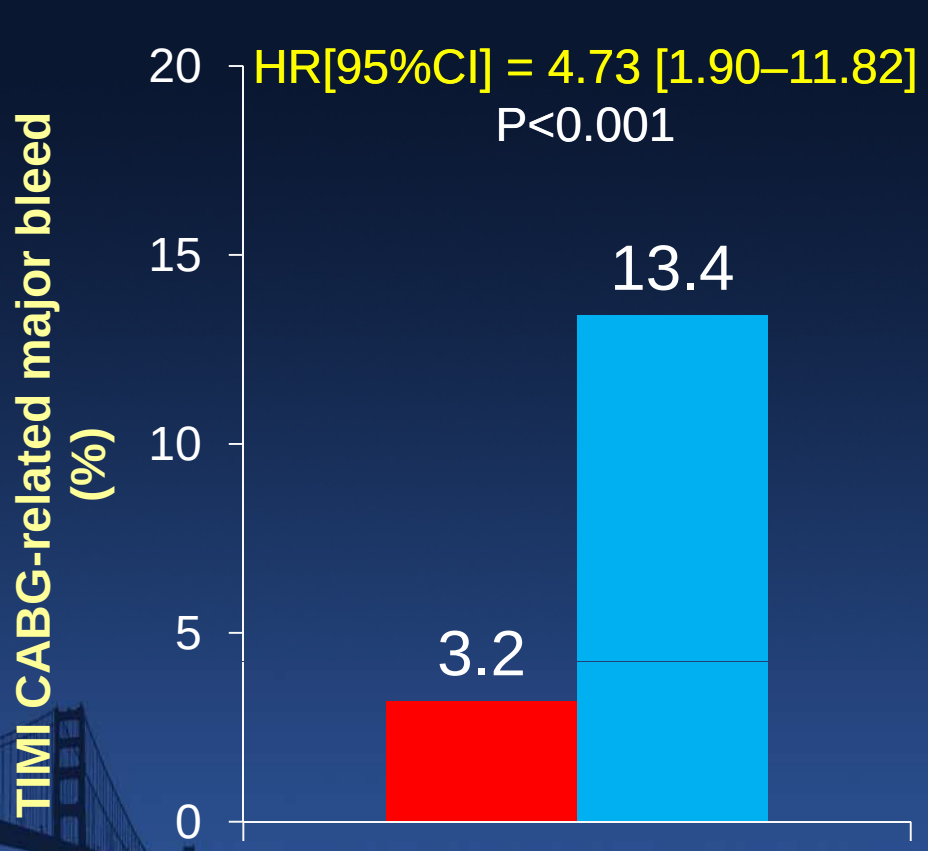
Prasugrel and Ticagrelor in ACS

TIMI CABG-related major bleeding

TRITON-TIMI-38 (n=13,608)

15 months



PLATO (n=18,624)

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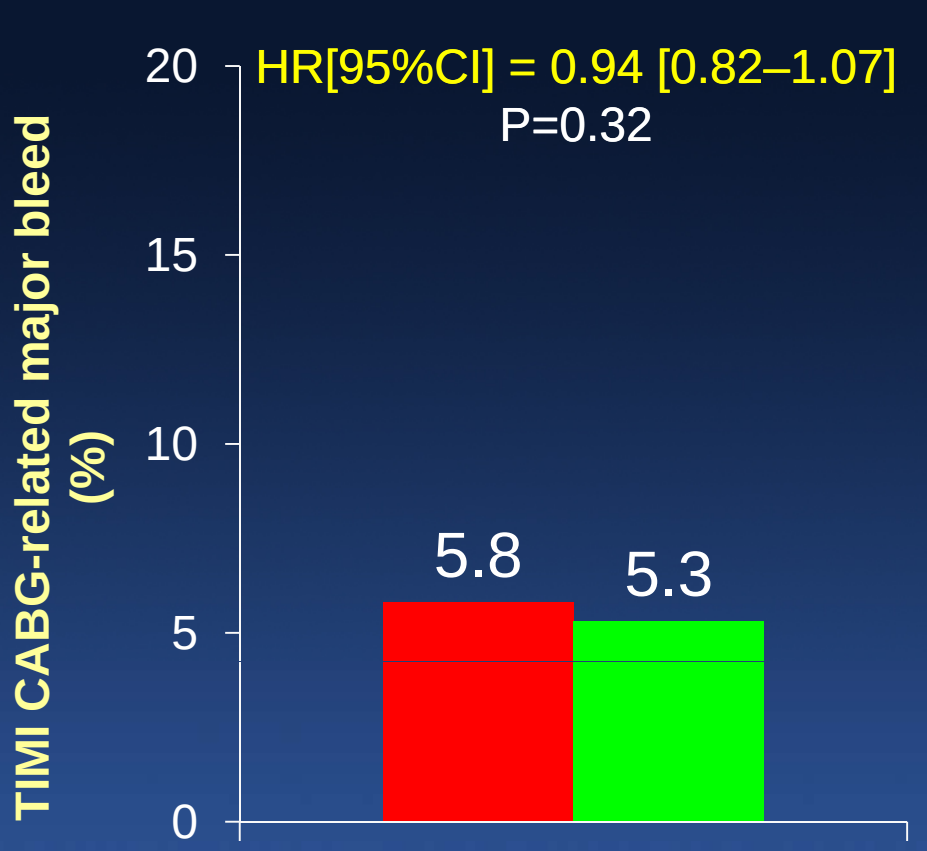

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Wallentin L et al. N Engl J Med 2009;361:1045-57

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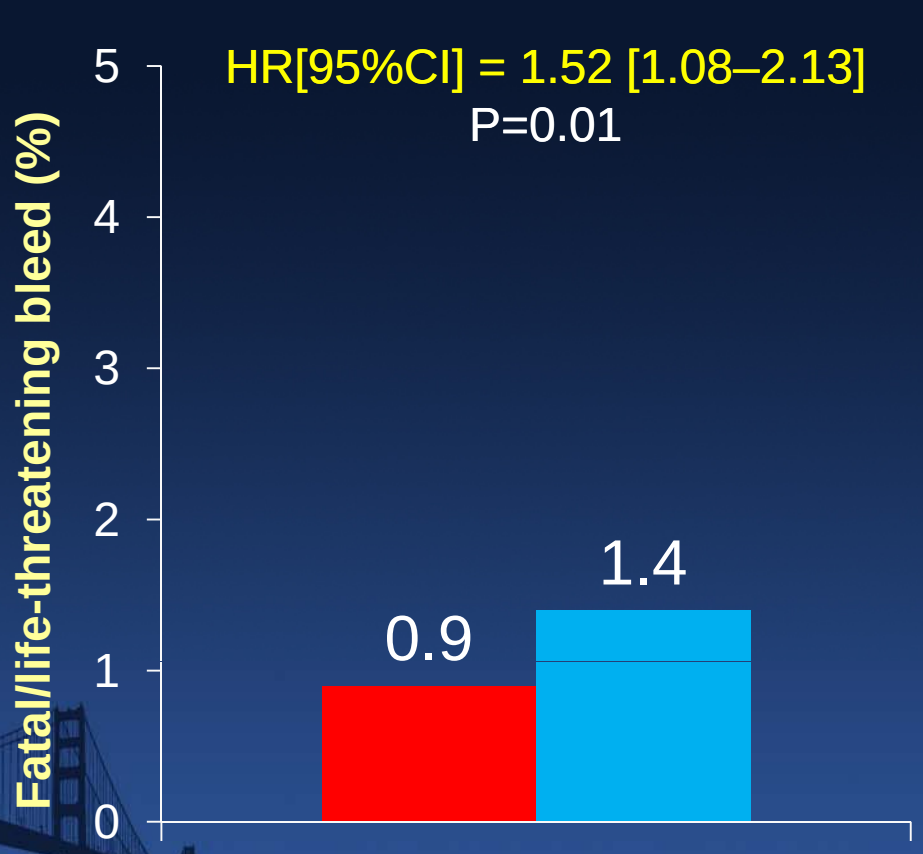
Prasugrel and Ticagrelor in ACS

Fatal or life-threatening bleeding

TRITON-TIMI-38 (n=13,608)

15 months



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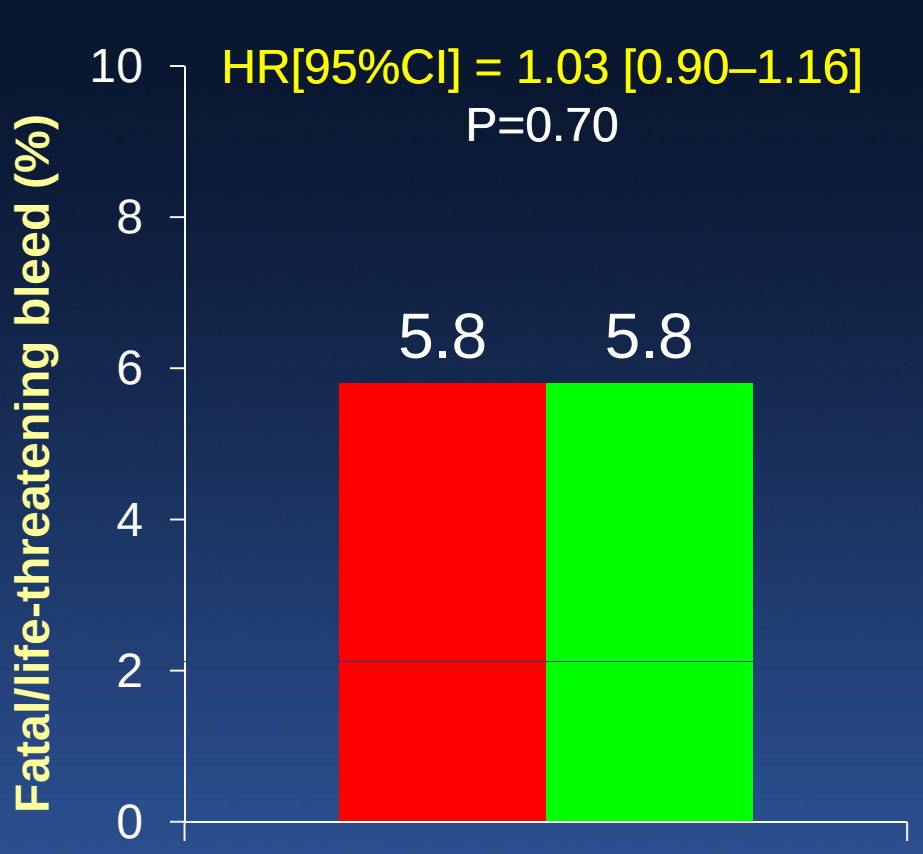
12 months



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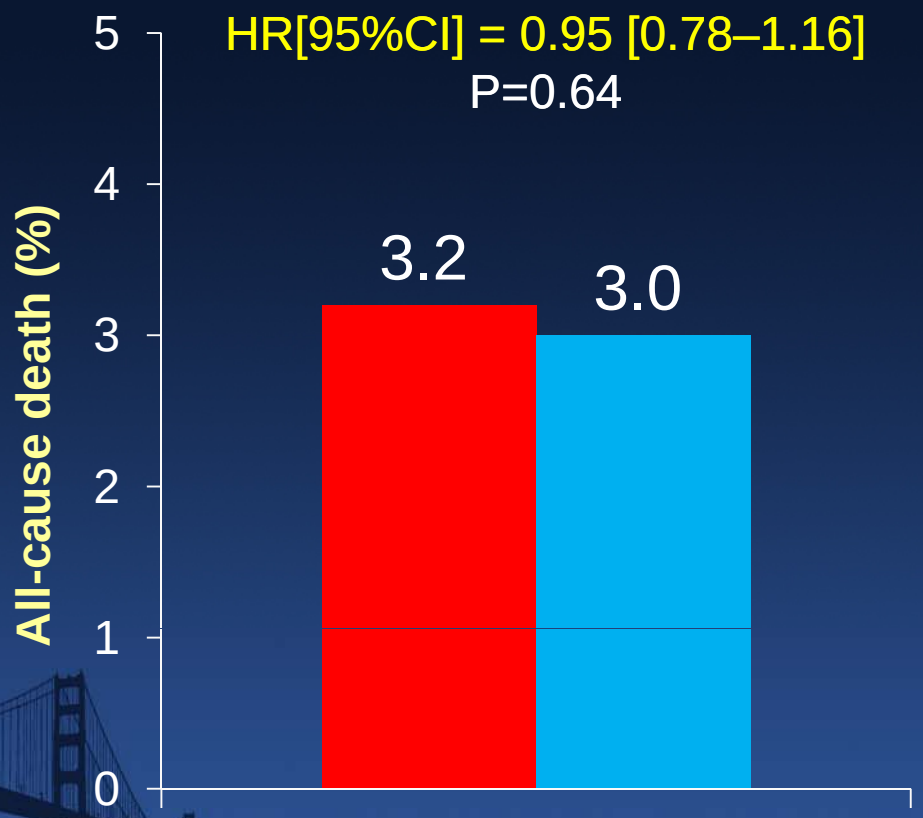
Prasugrel and Ticagrelor in ACS

All-cause mortality

TRITON-TIMI-38 (n=13,608)

15 months



PLATO (n=18,624)

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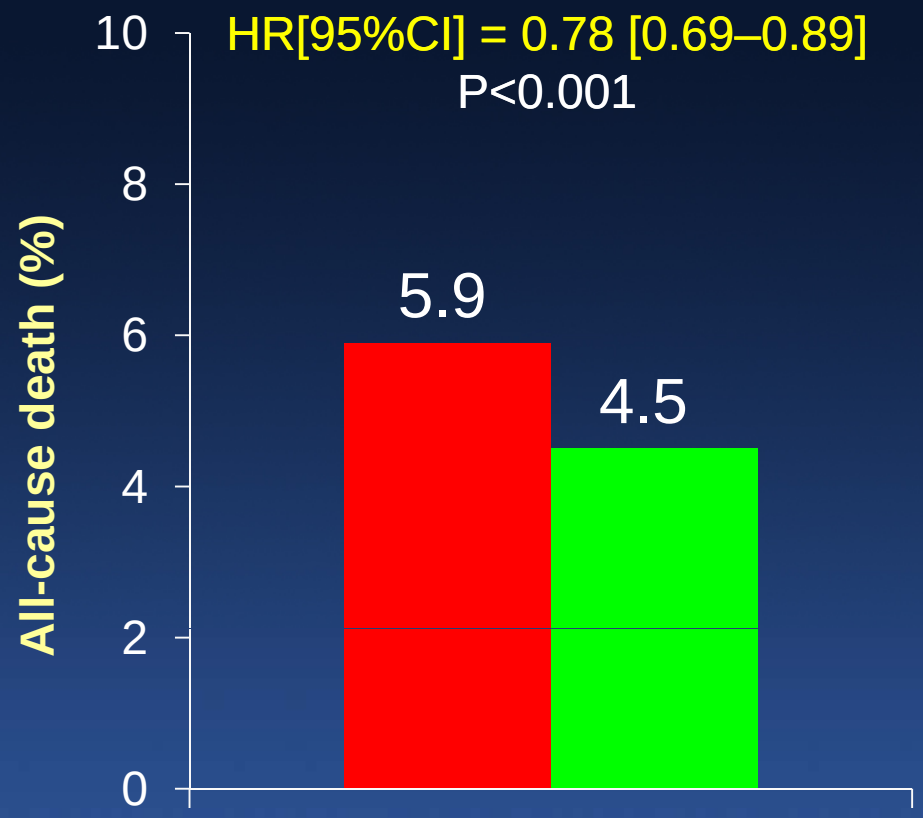

TCT2011

Wiviott SD et al. N Engl J Med 2007;357:2001-15
Wallentin L et al. N Engl J Med 2009;361:1045-57

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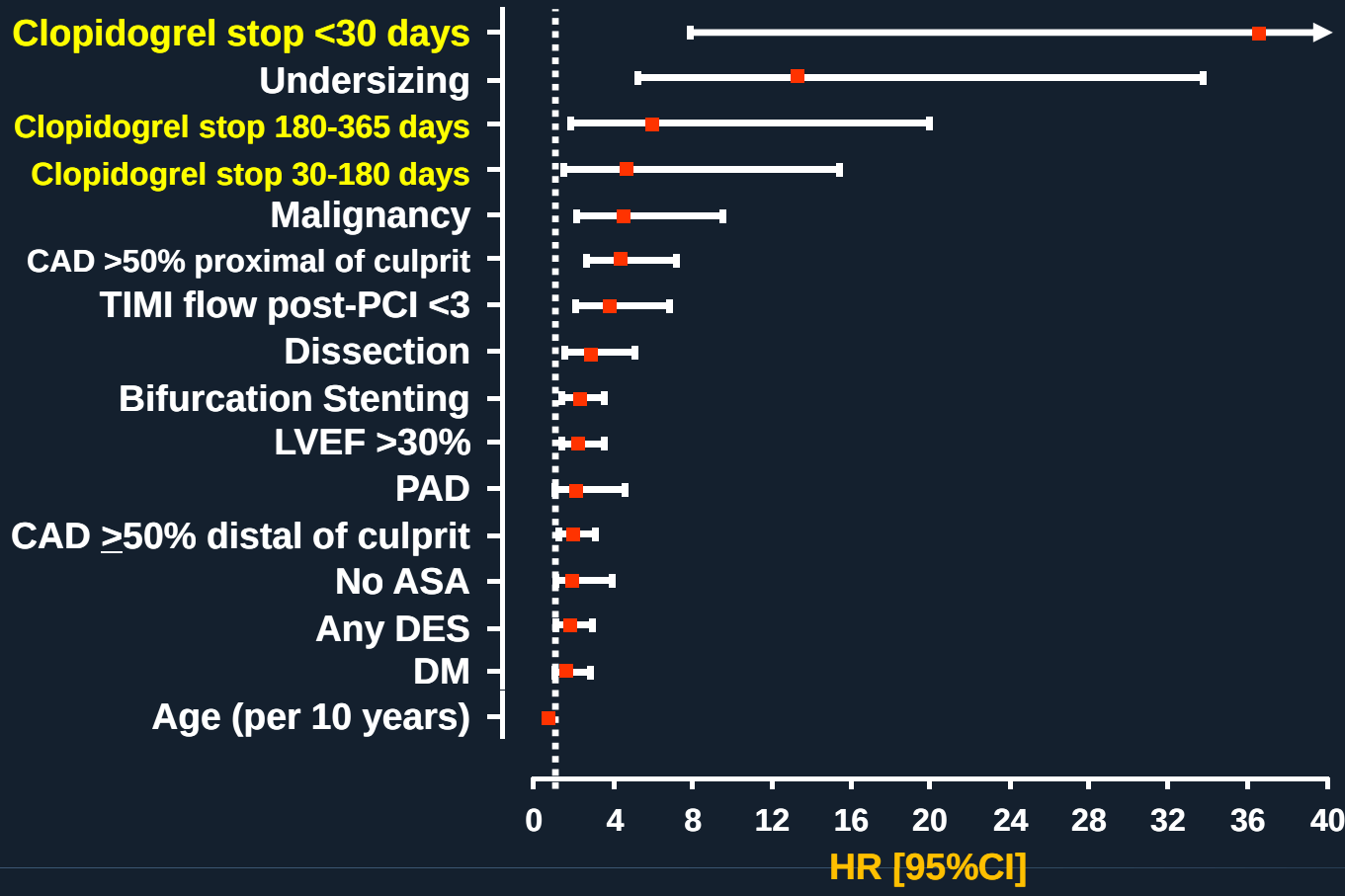
Independent Predictors of Stent Thrombosis: Dutch Registry (n=21,009 with DES or BMS)

Definite stent thrombosis occurred in 437 (2.1%) pts



	HR	95% CI	*P* Value
Clopidogrel stop <30 days	36.53	[7.96-167.77]	*P*<0.0001
Undersizing	13.39	[5.27-34.04]	*P*<0.0001
Clopidogrel stop 180-365 days	5.87	[1.74-19.80]	*P*=0.004
Clopidogrel stop 30-180 days	4.63	[1.40-15.35]	*P*=0.01
Malignancy	4.50	[2.14-9.49]	*P*<0.0001
CAD >50% proximal of culprit	4.40	[2.71-7.16]	*P*<0.0001
TIMI flow post-PCI <3	3.77	[2.09-6.80]	*P*<0.0001
Dissection	2.88	[1.67-5.00]	*P*=0.0002
Bifurcation Stenting	2.27	[1.48-3.47]	*P*=0.0002
LVEF >30%	2.27	[1.43-3.60]	*P*=0.0005
PAD	2.13	[1.01-4.51]	*P*=0.048
CAD ≥50% distal of culprit	1.98	[1.32-2.95]	*P*=0.0009
No ASA	1.91	[1.01-3.88]	*P*=0.049
Any DES	1.88	[1.21-2.94]	*P*=0.005
DM	1.66	[1.02-2.70]	*P*=0.04
Age (per 10 years)	0.80	[0.68-0.94]	*P*=0.007

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van Werkum JW et al. *JACC* 2009;53:1399–409

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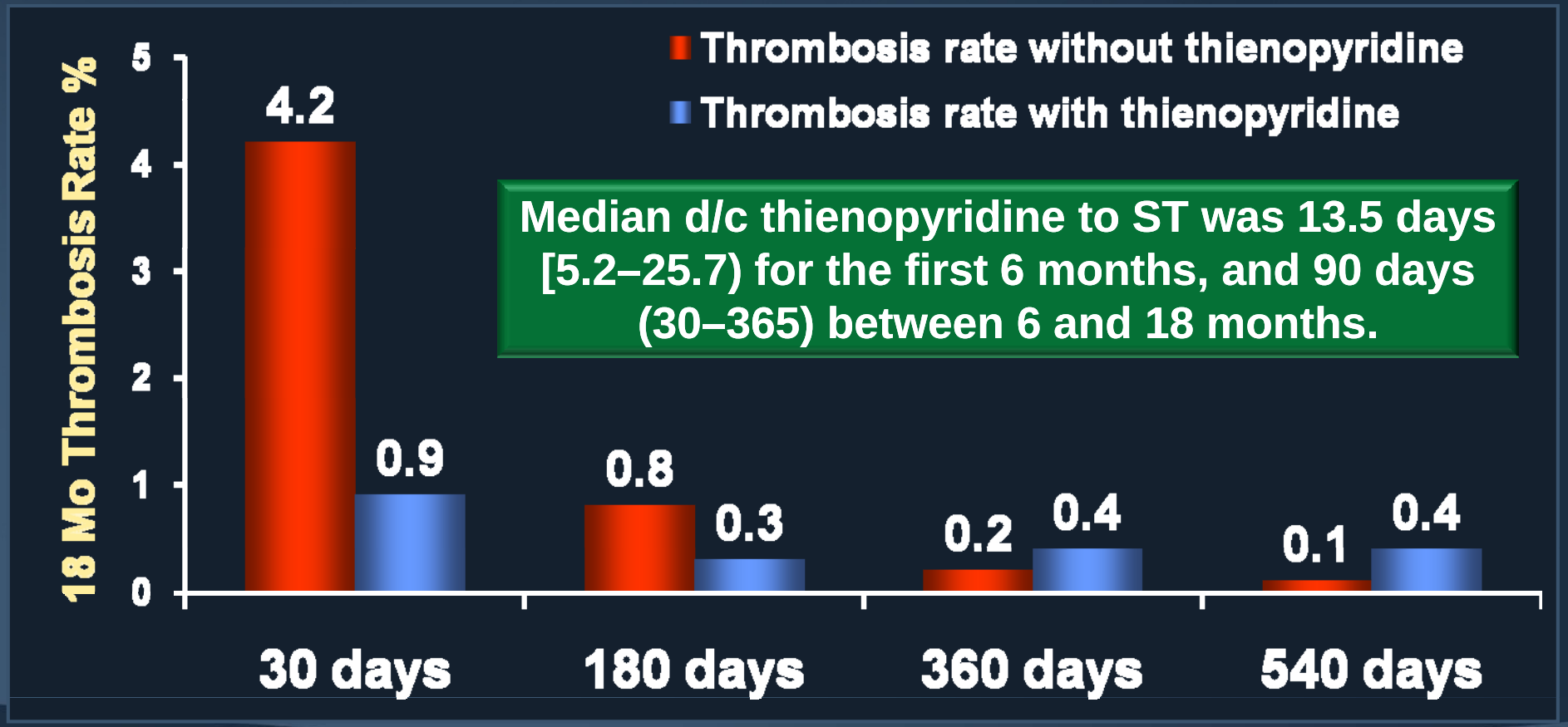
Milan Stent Thrombosis Experience

3,021 Consecutive Pts with DES in 5389 Lesions

Stent thrombosis occurred in 58 pts (1.9%) at 18 months;
42 episodes (72%) occurred within 6 months



Median d/c thienopyridine to ST was 13.5 days [5.2–25.7) for the first 6 months, and 90 days (30–365) between 6 and 18 months.

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Airoldi F et al. *Circulation* 2007;116:745-54

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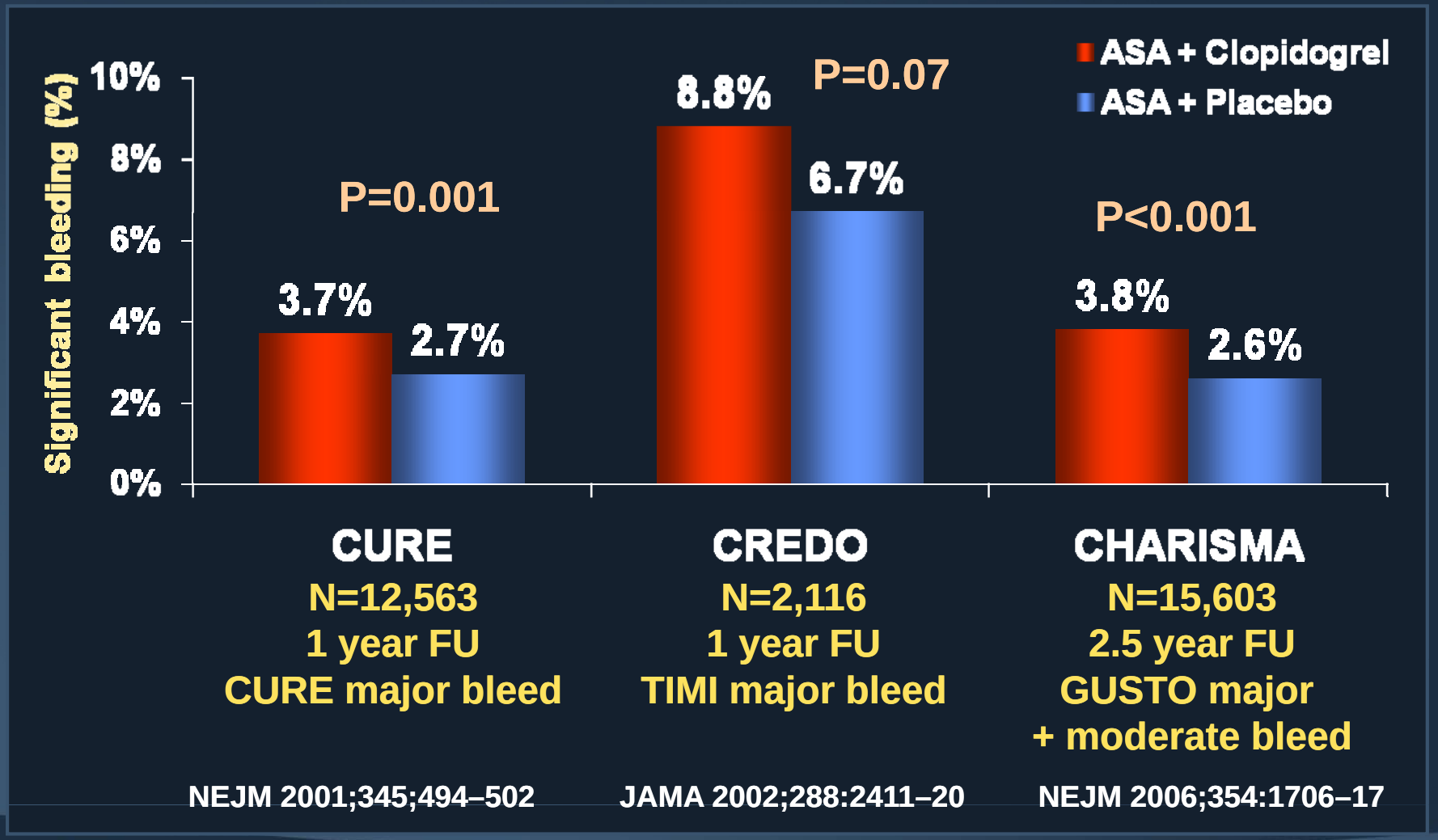
Safety of Long-term Clopidogrel

3 Placebo Controlled Trials



Randomized Trials of DAPT Duration

Trial	Pts	Test	Randomization	1° EP
Prolonged DAPT studies				
REAL/ZEST Late	2,701 DES	1 vs. 3 yrs	A vs. A+C Superiority	D/MI 2 yrs after rand
DAPT	N=20,645 (15,245 DES) (5,400 BMS)	1 vs. 2.5 yrs*	A+P vs DAPT (clop or pras) NI and Sup	D/MI/CVA ST, Bleeding
Abbreviated DAPT studies				
PRODIGY	N=1,800 DES, BMS	6 mos vs. 2 yrs	A vs. A+C Superiority	D/MI/CVA
EXCELLENT	N=1443 SES and EES	6 vs. 12 mos	A vs. A+C Noninferiority	D/MI/TVR
ISAR- SAFE	N=6,000 DES	6 vs. 12 mos*	A+P vs. A+C Noninferiority	D/MI/CVA/ ST/TIMI MB
ITALIC	N=3,700 EES	6 vs. 12 mos	A vs. A+C Noninferiority	D/MI/CVA/ Urg Revasc/MB
OPTIMIZE	N=3,120 ZES	3 vs. 12 mos	A vs. A+C Noninferiority	D/MI/CVA/MB

*Plus a 3 month washout period

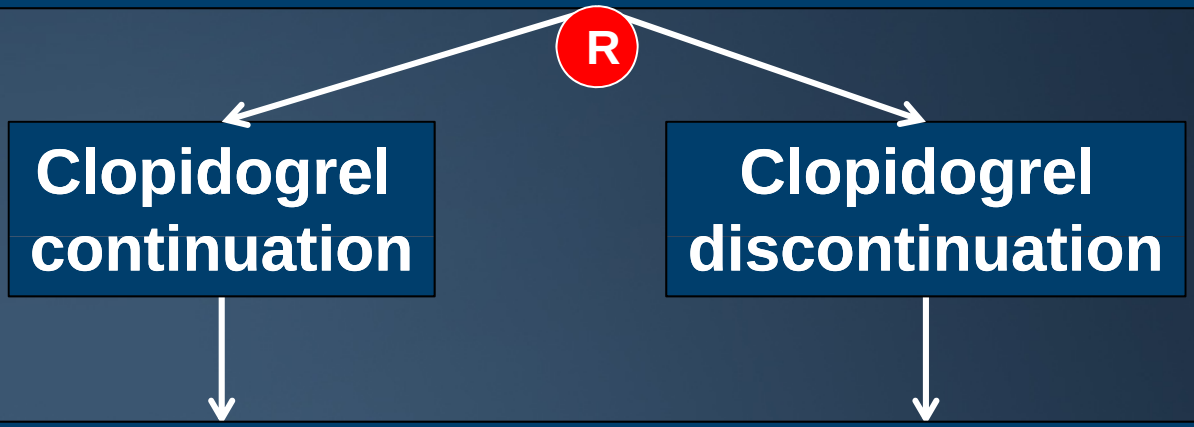
Optimal Duration of Dual Antiplatelet Therapy after Drug-Eluting Stents Implantation: The REAL-LATE and ZEST-LATE RCTs (pooled)

2701 pts MACE-free 1 year after DES (SES, PES or ZES)

Consecutive pts, all-comers

26% diabetes; 62% ACS

Mean 1.4 stents/pt



Primary endpoint: Death or MI at additional 2 year FU

Secondary endpoints: Stent thrombosis, MACCE, major bleeding

80% power for a 50% reduction from 5% control rate

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Park SJ et al. NEJM 2010:on-line

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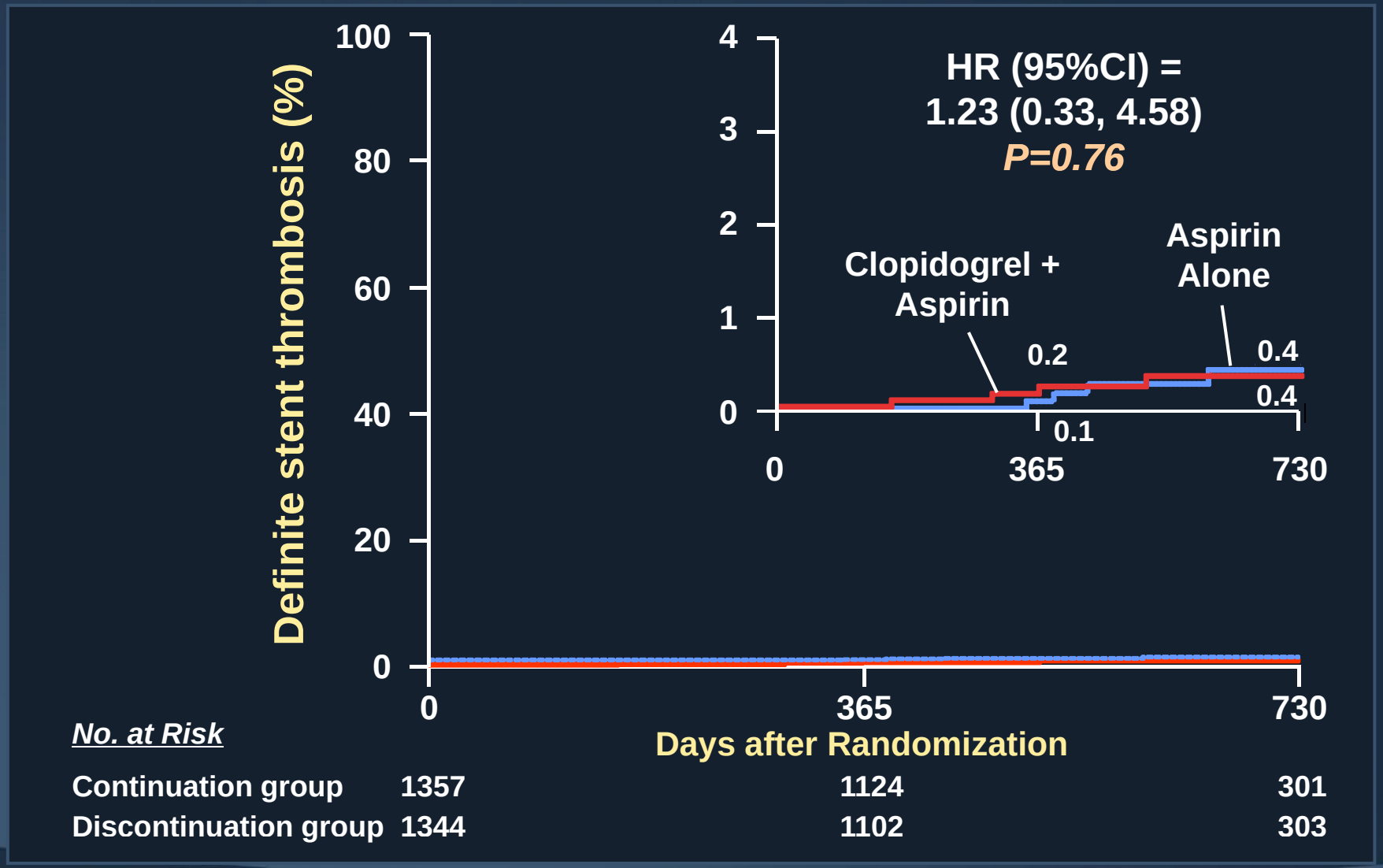
REAL-LATE and ZEST-LATE RCT

Definite Stent Thrombosis



Park SJ et al. *NEJM* 2010:0m-line

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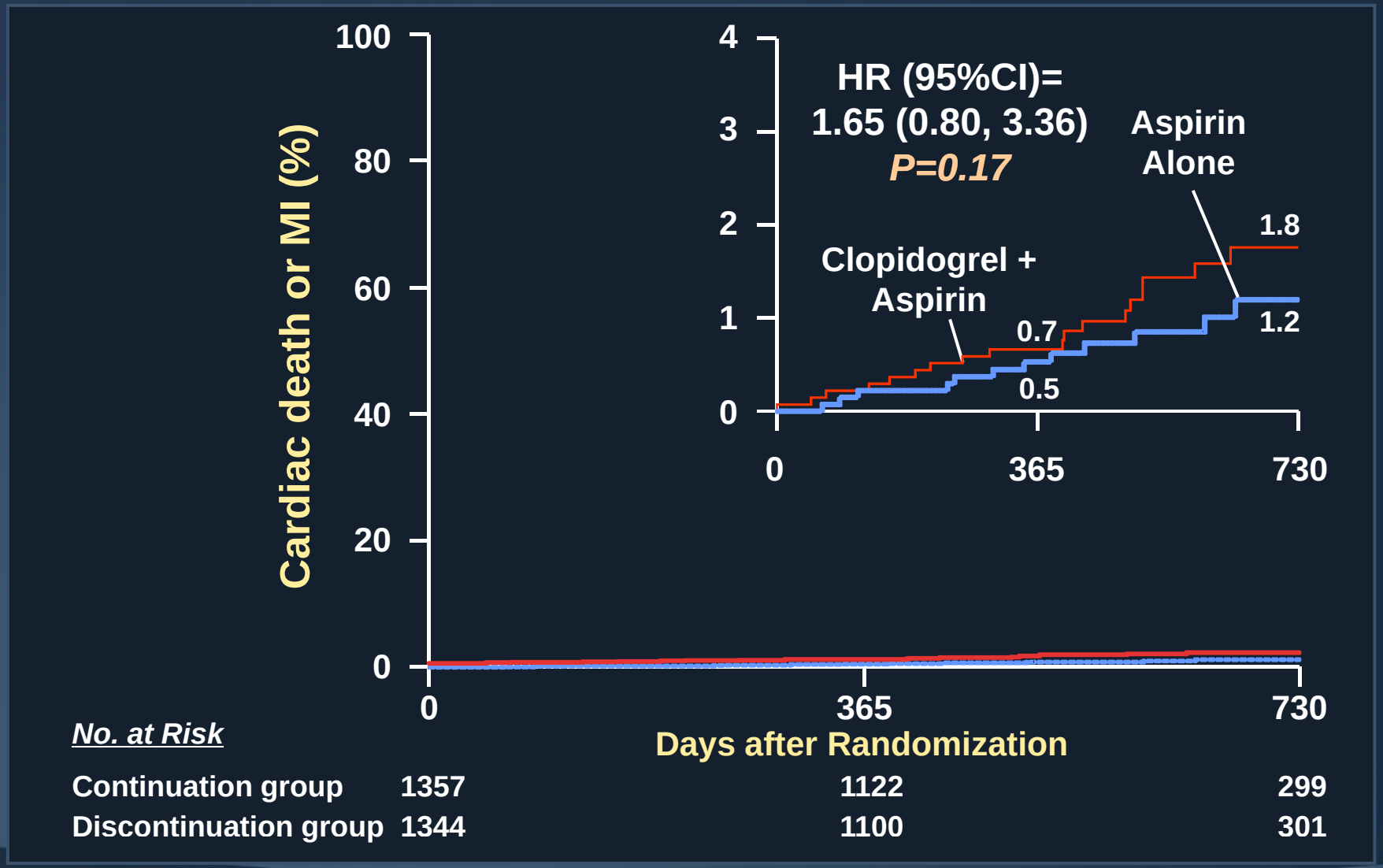
The University Hospital of Columbia and Cornell

REAL-LATE and ZEST-LATE RCT

Primary End Point: Cardiac Death or MI



No. at Risk

Continuation group	1357	1122	299
Discontinuation group	1344	1100	301

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Park SJ et al. *NEJM* 2010:on-line

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NewYork-Presbyterian
The University Hospital of Columbia and Cornell

PRODIGY Selection Criteria and Endpoints

Valgimigli M et al. ESC 2011

Eligibility Criteria

Inclusion Criteria

Any indication to PCI
(Stable, ACS, STEMI)
Intent to Stent

Exclusion Criteria

Known allergy to ASA or clopidogrel
Planned major surgery w/I 24 mos
Major surgery within 15 days
Bleeding diathesis
Previous stroke in the last 6 months
Concomitant oral anticoagulation

EFFICACY

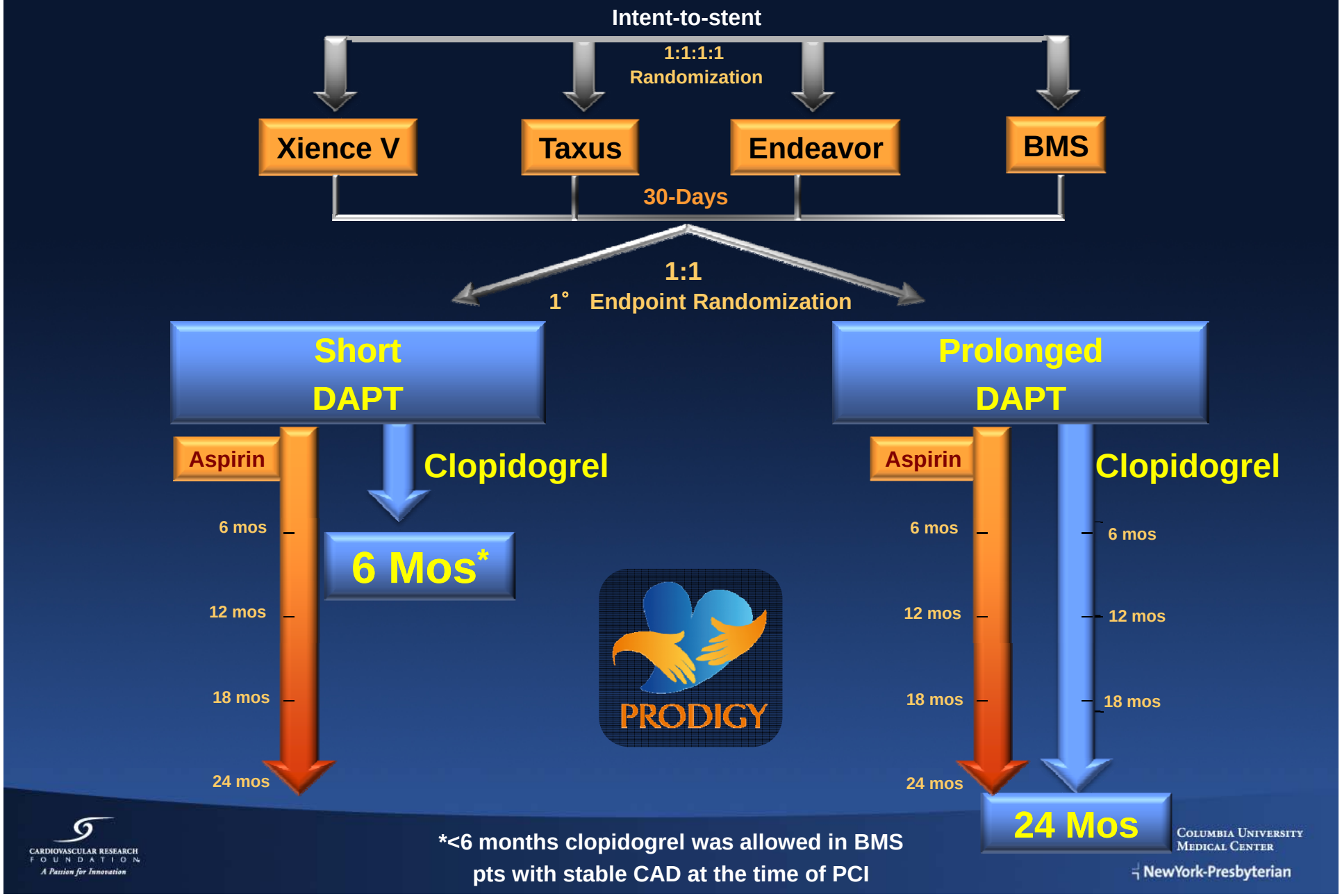
Death, MI, Stroke or Stent Thrombosis (ARC)

SAFETY

TIMI and Bleedscore,[1] Type 2, 3 and 5 BARC[2]

[1] Serebruany VL et al. *Am J Cardiol*. Jan 15 2007;99(2):288-290;
[2] Mehran R et al. *Circ*. Jun 14 2011;123 (23):2736-2747

PRODIGY Study Flow (N=1,970)



*<6 months clopidogrel was allowed in BMS pts with stable CAD at the time of PCI

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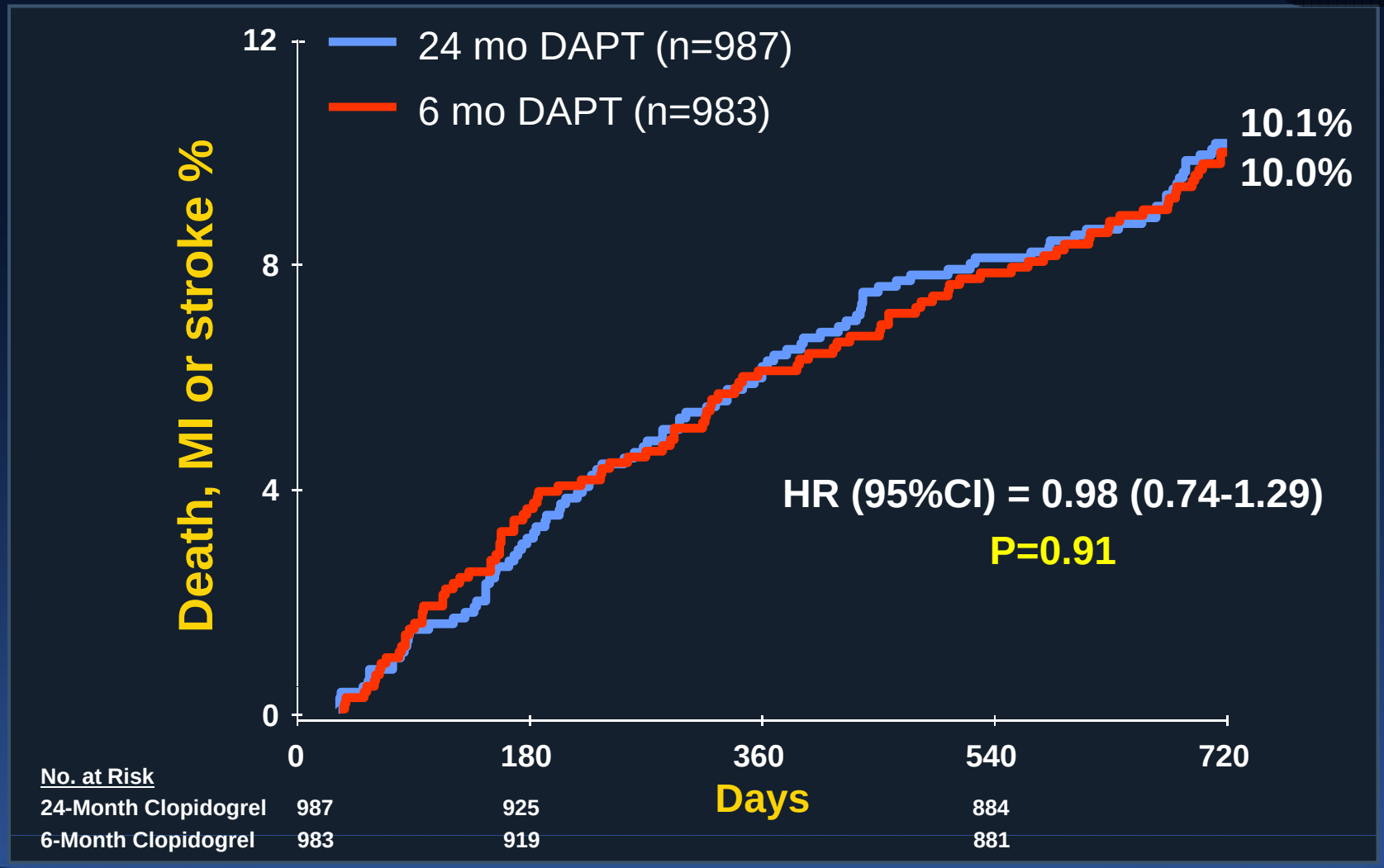
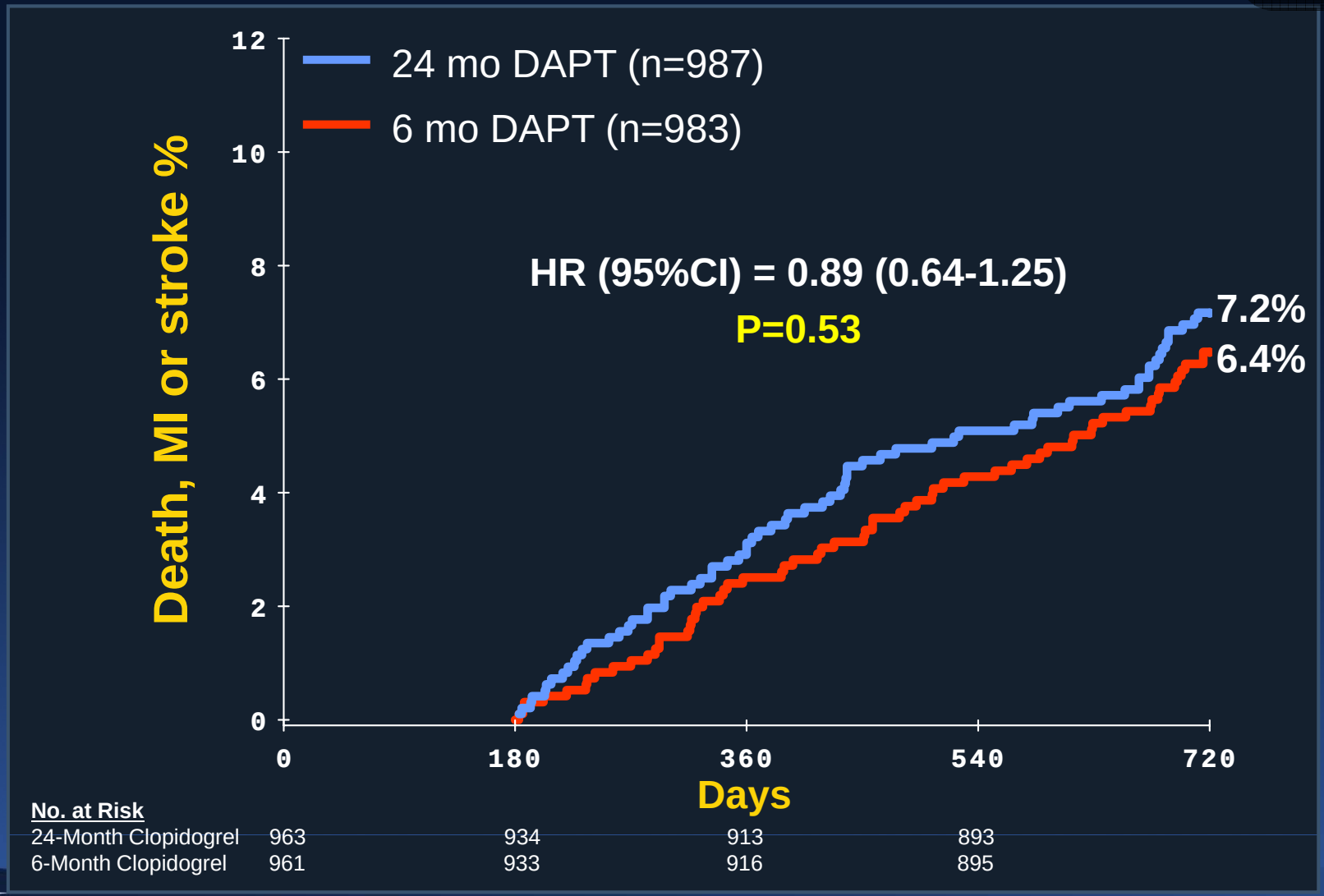
NewYork-Presbyterian

1° Endpoint:
Death, MI or Stroke



Valgimigli M et al. ESC 2011

Landmark Analysis: Death, MI, or Stroke after 6 Months



Valgimigli M et al. ESC 2011

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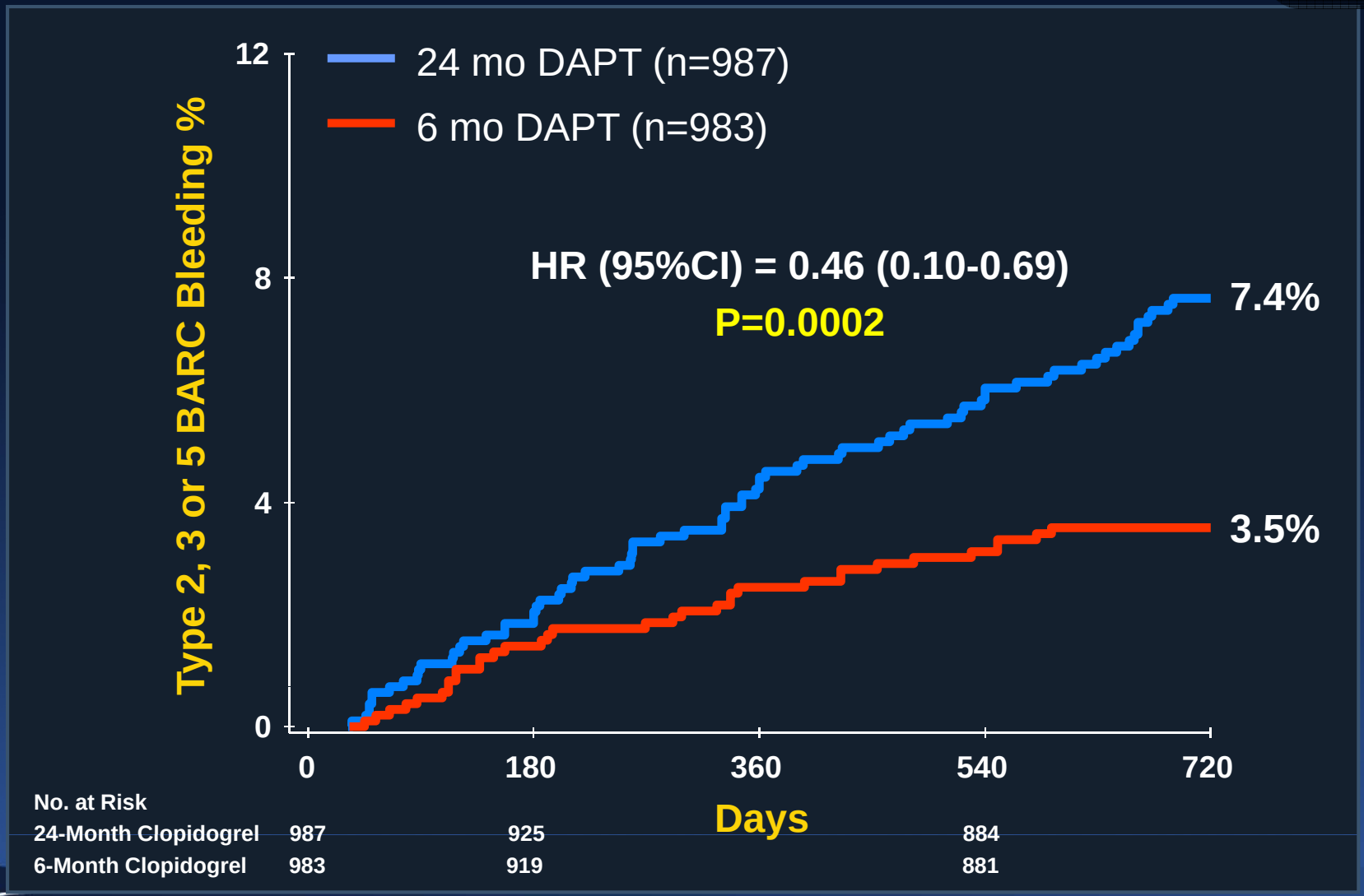
Key Safety Endpoint:
Type 2, 3 or 5 BARC Bleeding



Valgimigli M et al. ESC 2011

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THE LANCET

Articles

Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis

Tullio Palmerini, Giuseppe Biondi-Zoccai, Diego Della Riva, Christoph Stettler, Diego Sangiorgi, Fabrizio D'Ascenzo, Takeshi Kimura, Carlo Briguori, Manel Sabatè, Hyo-Soo Kim, Antoinette De Waha, Elvin Kedhi, Pieter C Smits, Christoph Kaiser, Gennaro Sardella, Antonino Marullo, Ajay J Kirtane, Martin B Leon, Gregg W Stone

Palmerini T et al. *Lancet* 2012:On-line

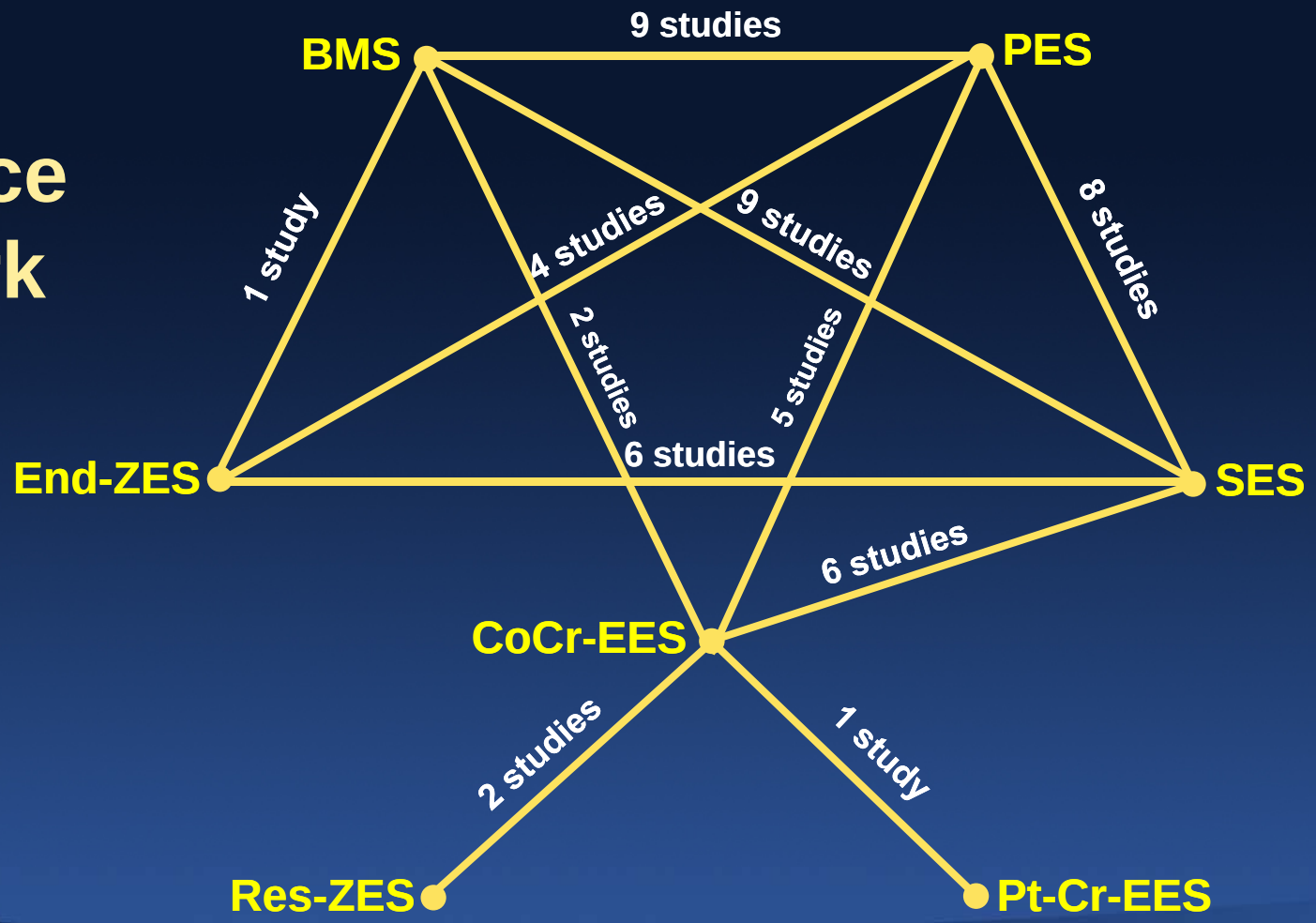
DOI:10.1016/S0140-6736(12)60324-9

Stent Thrombosis Network Meta-analysis

Primary EP: ARC Definite ST (FU through 2 years)

49 RCTs, 50,844 pts

Evidence network



Palmerini T et al. *Lancet* 2012:On-line

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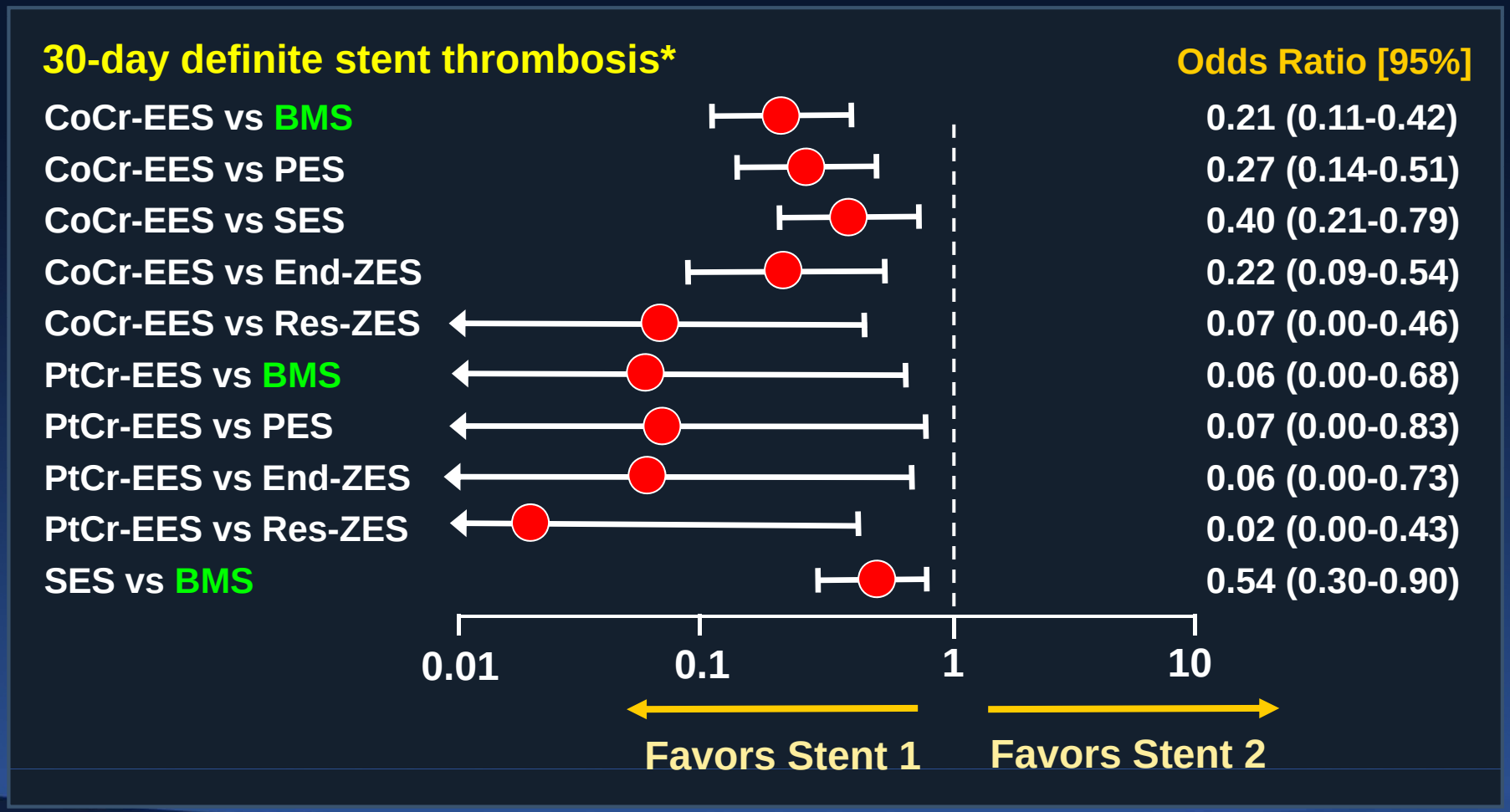

*Only statistically significant results are shown

Palmerini T et al. *Lancet* 2012:On-line

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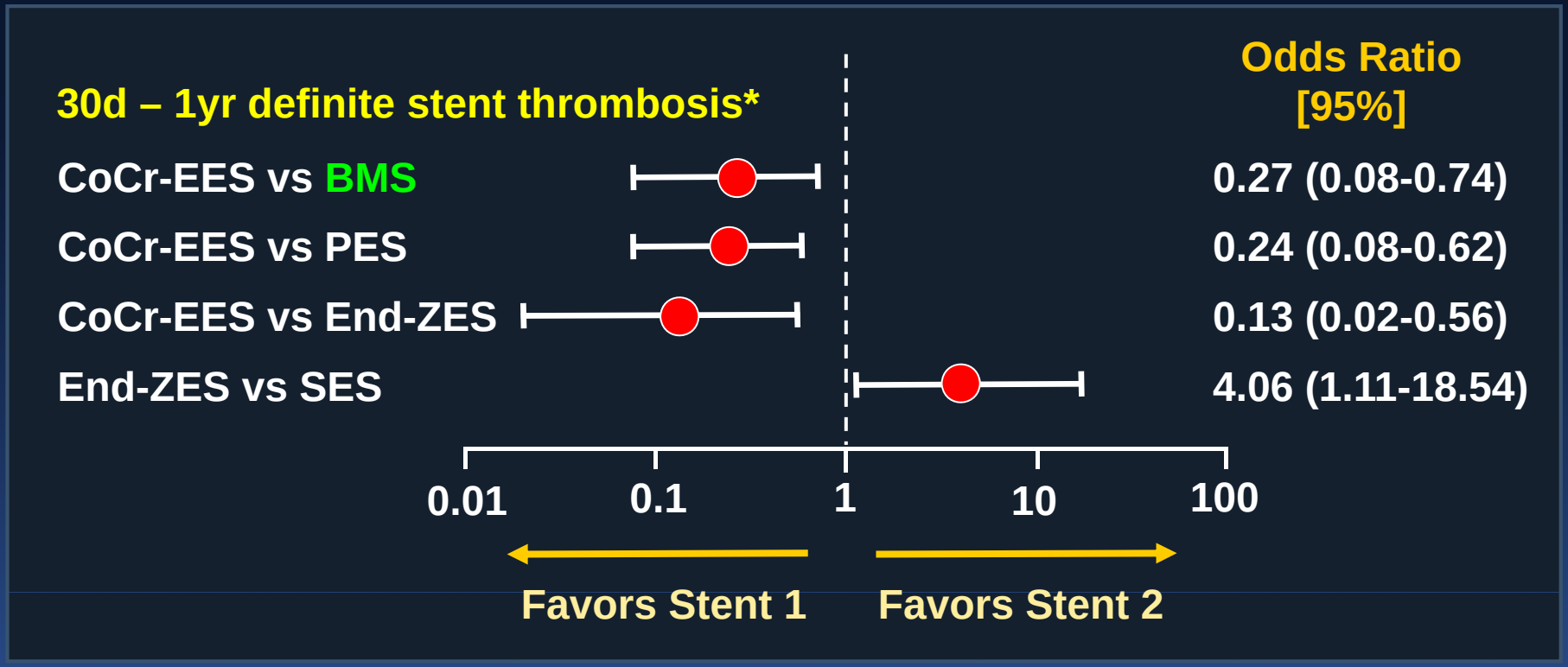

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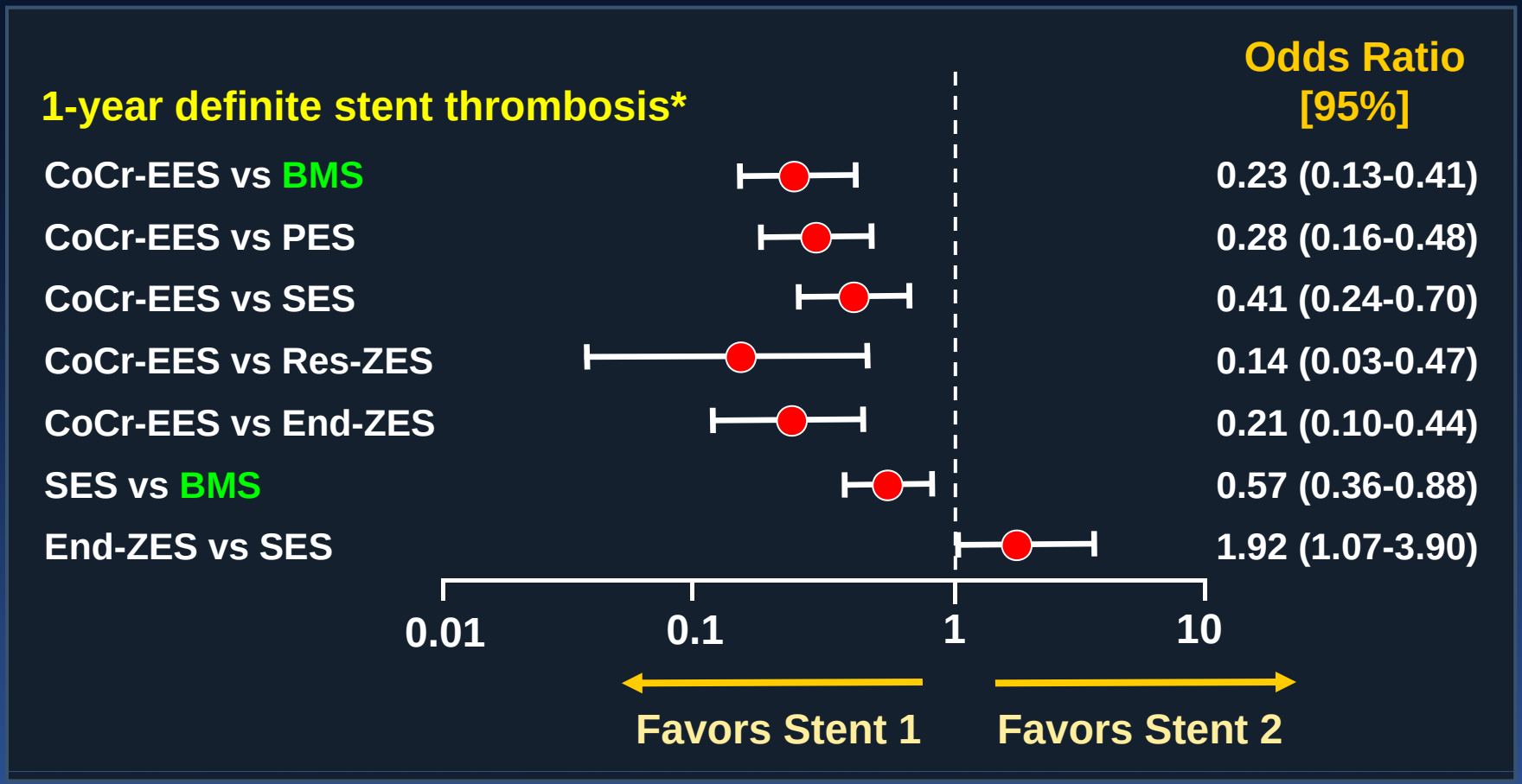

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Palmerini T et al. *Lancet* 2012:On-line

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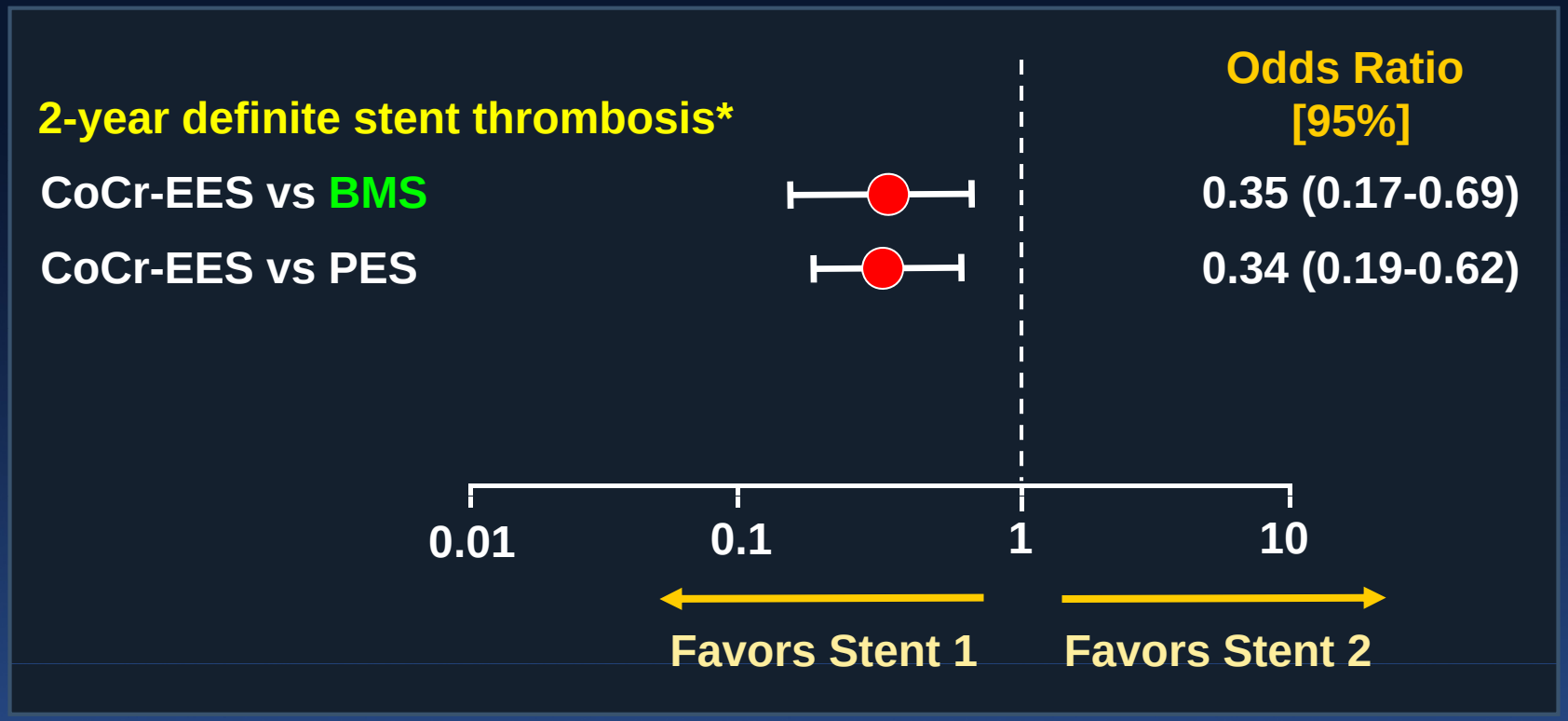
Primary EP: ARC Definite ST

49 RCTs, 50,844 pts



*Only statistically significant results are shown

Palmerini T et al. *Lancet* 2012:On-line

Conclusions: DAPT Duration after DES

1. Stable ischemic heart disease (troponin- pts)

- Randomized trial results to date suggest that prolonged clopidogrel use after DES implantation in stable IHD results in excessive bleeding without benefit
- Therefore, pending the results of additional trials, 1 year of DAPT is currently recommended with DES in pts not at increased risk of bleeding (in which case 6 months is recommended)
- Current data suggests 6 (or even 3) months of DAPT after EES in stable IHD may be safe

Conclusions: DAPT Duration after DES

2. Acute coronary syndromes (NSTEMI, STEMI; troponin+ pts)

- Randomized trial results to date suggest that DAPT should be used for at least 12-15 months after DES implantation in ACS (? longer)
- Prasugrel or ticagrelor are preferred over clopidogrel in patients not at high risk for bleeding
- Sufficient evidence does not at present exist to consider a shorter duration of DAPT in pts with ACS after EES, although further study in this regard is warranted