Dual antiplatelet therapy following ACS percutaneous treatment: how long?

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DAPT exerts protection against ischaemic recurrences via a double mechanism of action

1. Reducing the risk of stent thrombosis

2. Mitigating the risk of subsequent MI in patients not previously treated with coronary stents or arising from non-previously stented coronary segments

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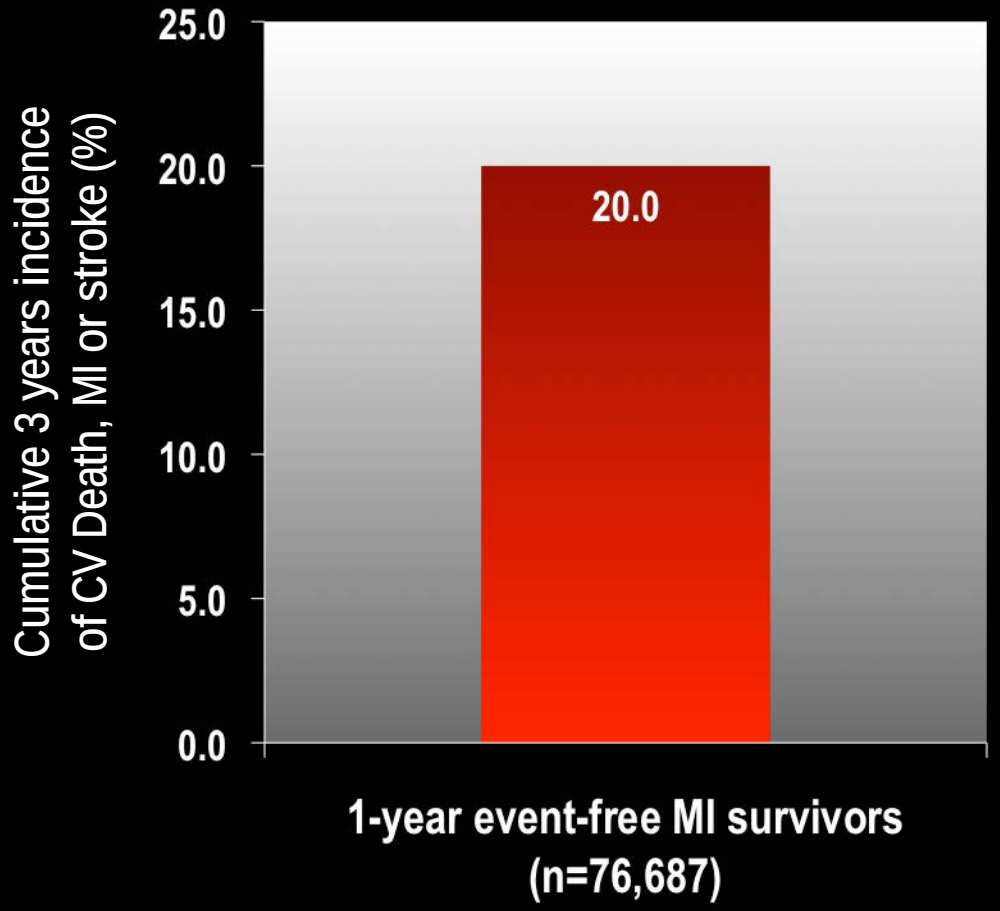
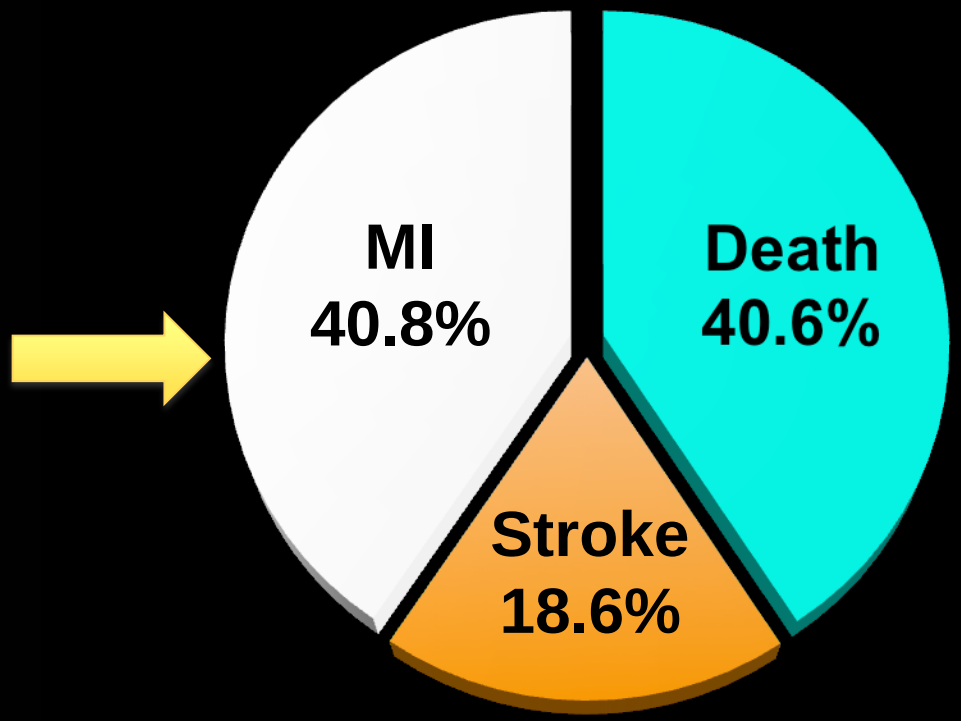
Results: CV Death, MI or stroke in the 1 year post-MI survivor population

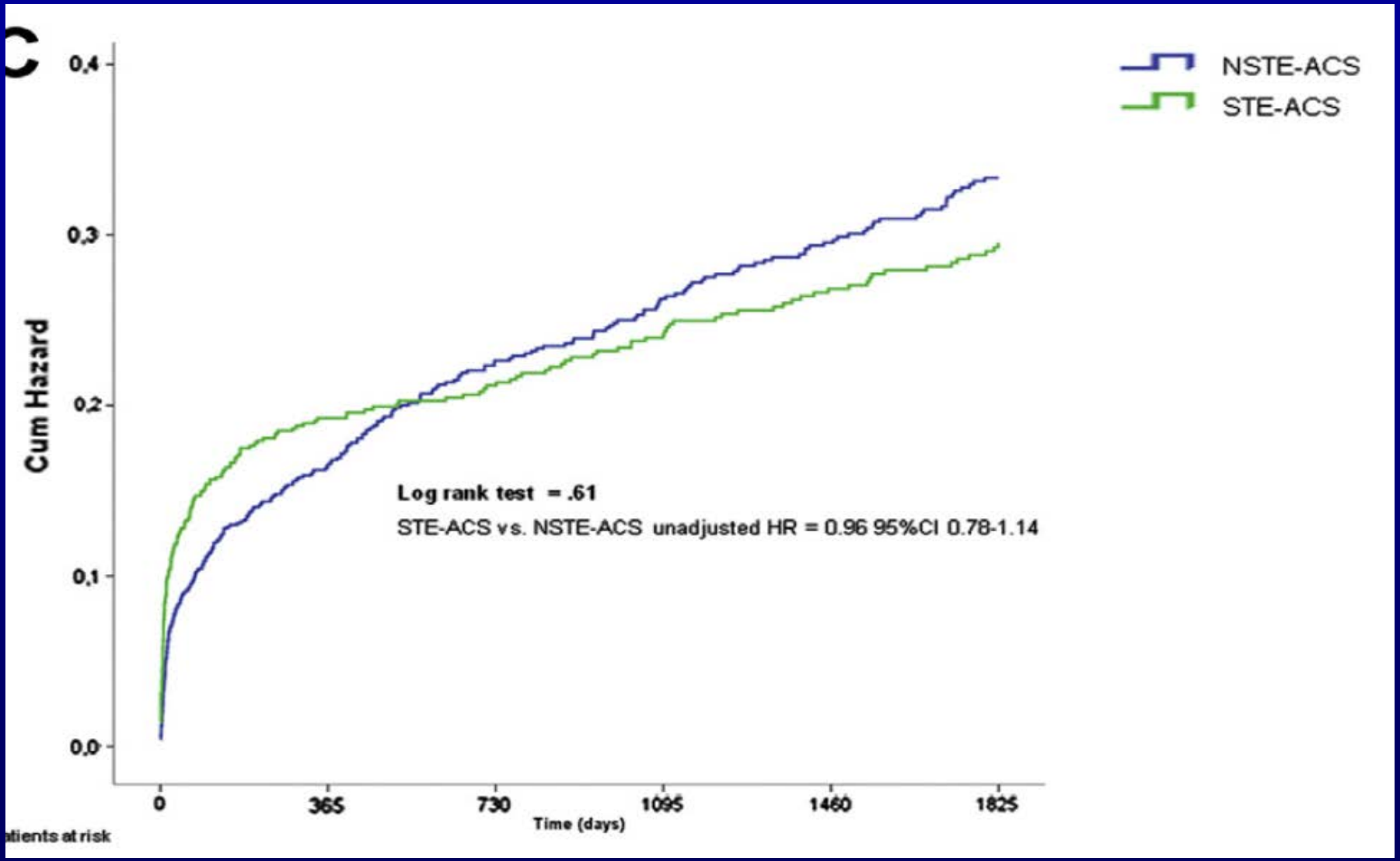
~1 in 5 patients, event-free for 1 year post-MI, suffered a MI, stroke or CV death within 3 years





Jernberg, T. et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehu505

5-Year CV Mortality After ACS



Vagnarelli F et al. Am J Cardiol 2015;115:171-7

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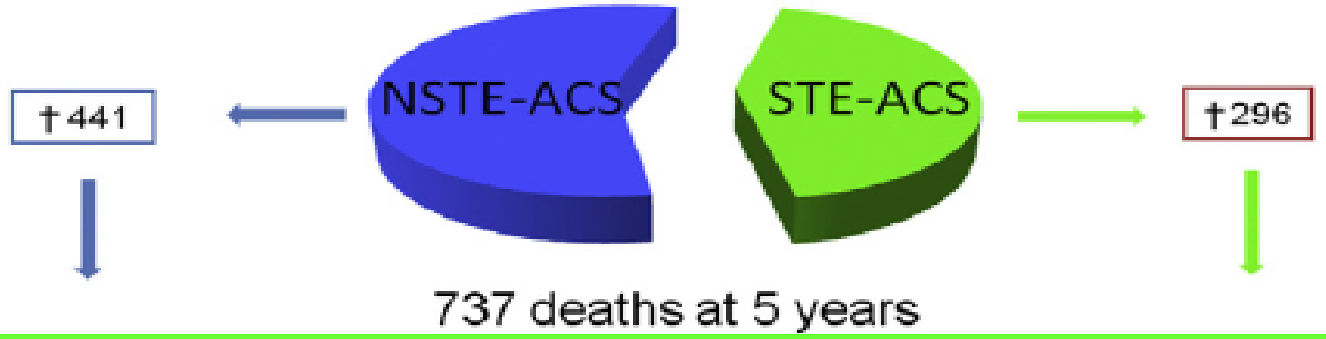
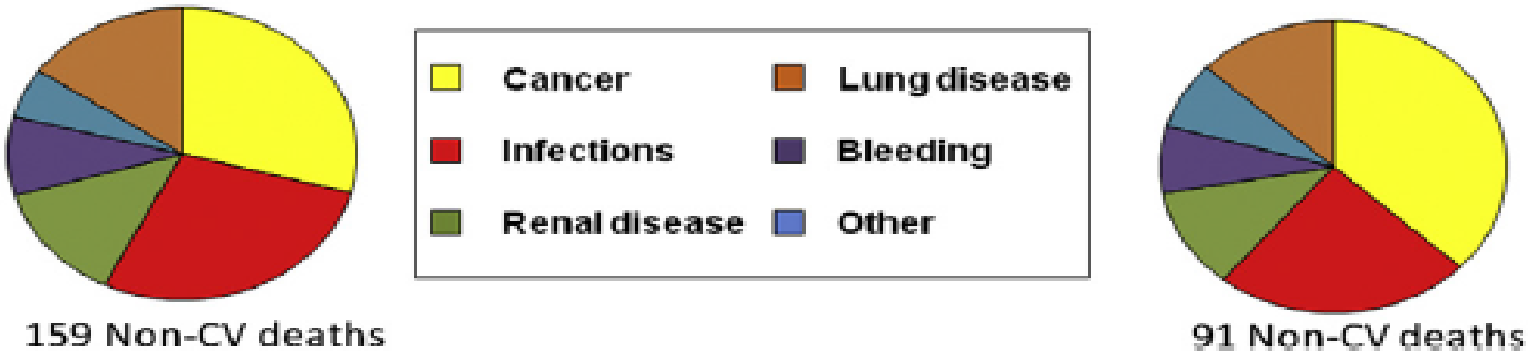
5-Year Mortality After ACS

The impact of nonCV Mortality



All-cause mortality therefore becomes central in assessing the long-term benefit/risk ratio



Vagnarelli F et al. Am J Cardiol 2015;115:171-7

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The reasons why long-term prolongation of DAPT is debated are two-fold

1. Time-dependent risk of major and clinically relevant bleeding complications

2. The advent of DES has prompted attention to be paid to delayed healing and persistent polymer induced inflammation at the sites of stent placement, thereby potentially requiring long-standing DAPT continuation

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Yet, after multiple dedicated randomized controlled studies, the issue of the optimal duration of DAPT after ACS remains apparently unsettled

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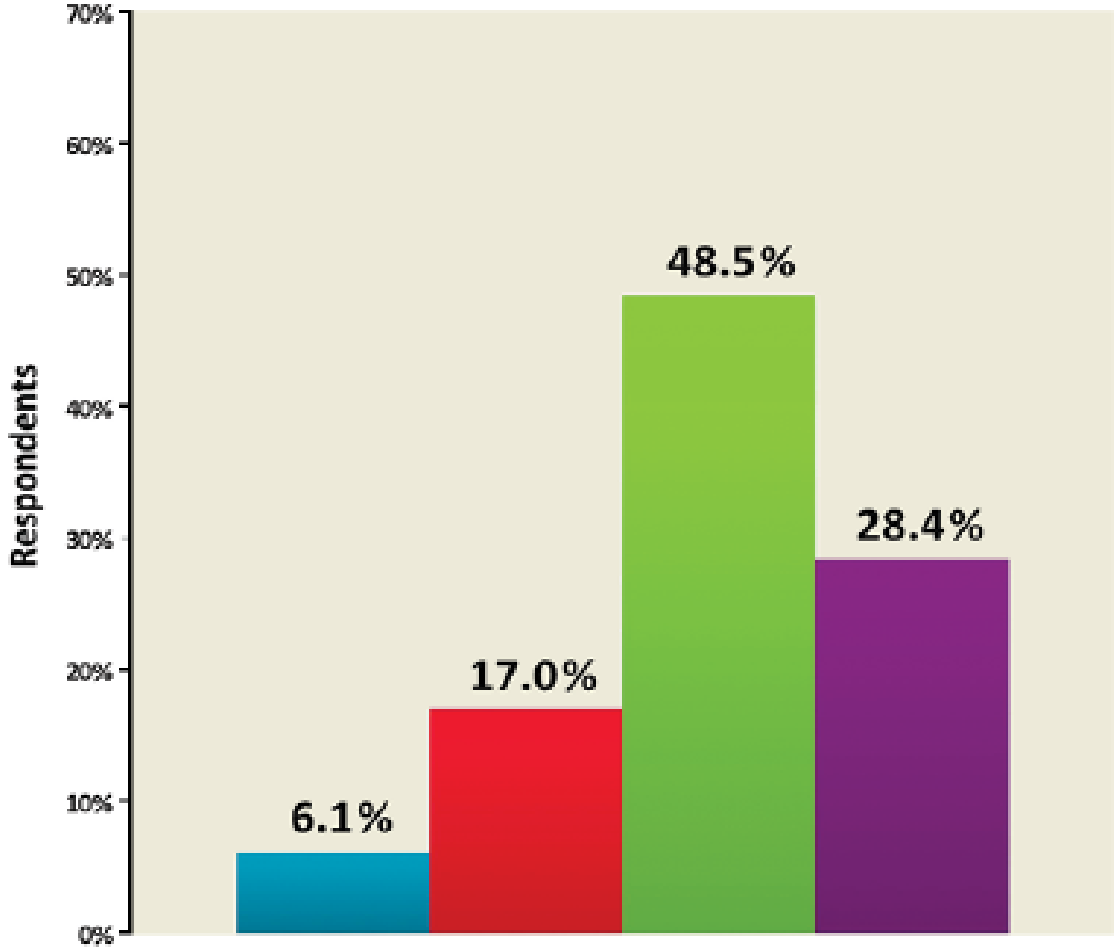
DAPT duration after coronary stenting in clinical practice: results of an EAPCI survey

What is your interpretation of the results of the DAPT trial ?



Valgimigli M et al. EuroIntervention 2015;11:68-74

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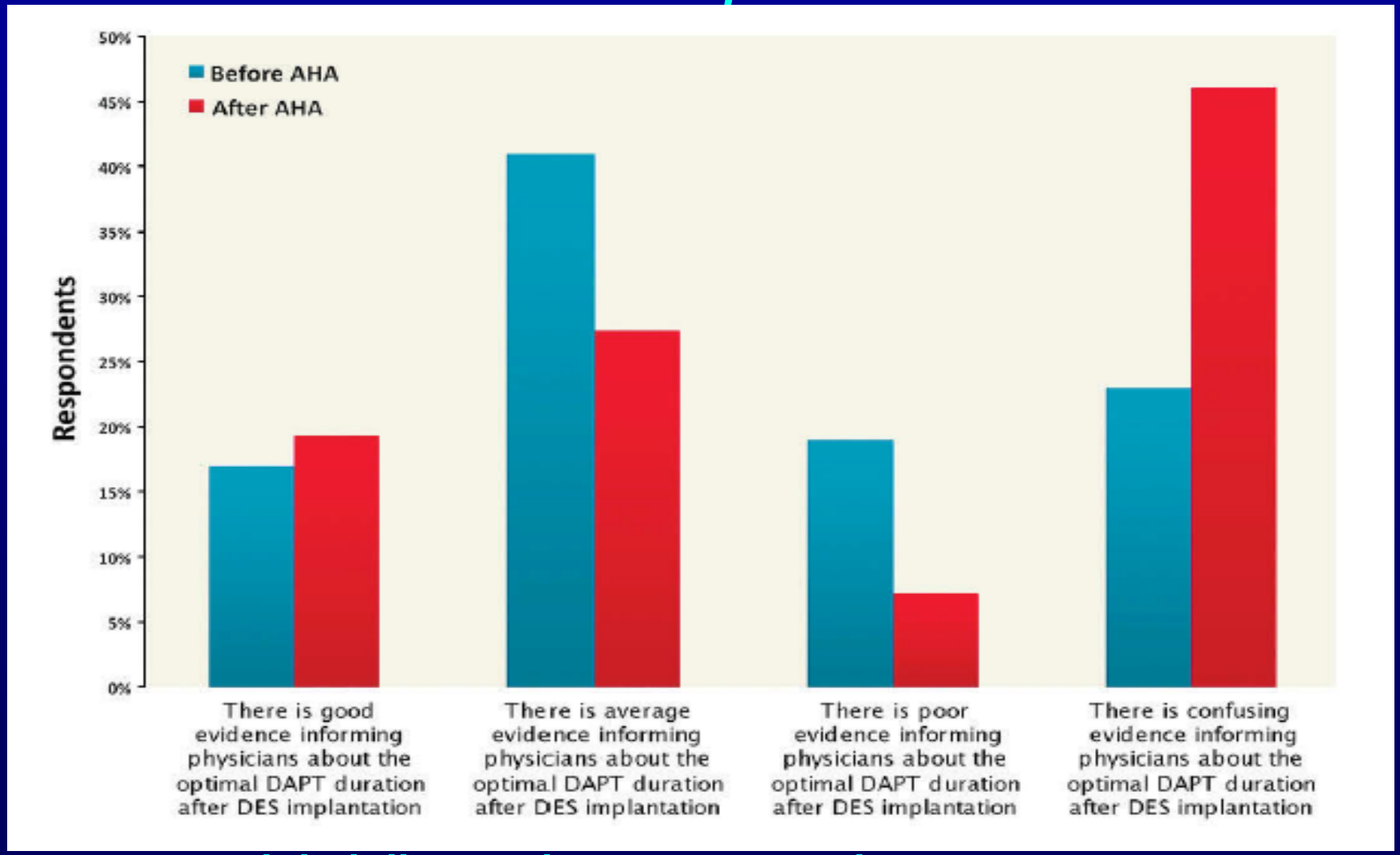
DAPT duration after coronary stenting in clinical practice: results of an EAPCI survey

How do you judge the evidence regarding DAPT duration after DES implantation?



Valgimigli M et al. EuroIntervention 2015;11:68-74

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The need for dual antiplatelet therapy

Premature discontinuation of DAPT would lead to an unacceptably high rate of ST

Mitigating the risk of recurrent ischemic events unrelated to previous PCI

EXCELLENT
RESET
SECURITY
ISAR SAFE
OPTIMIZE

PRODIGY
ITALIC

ARCTIC INTERRUPTION
DES-LATE
REAL/ZEST
DAPT
PEGASUS
TRA 2° P-TIMI 50

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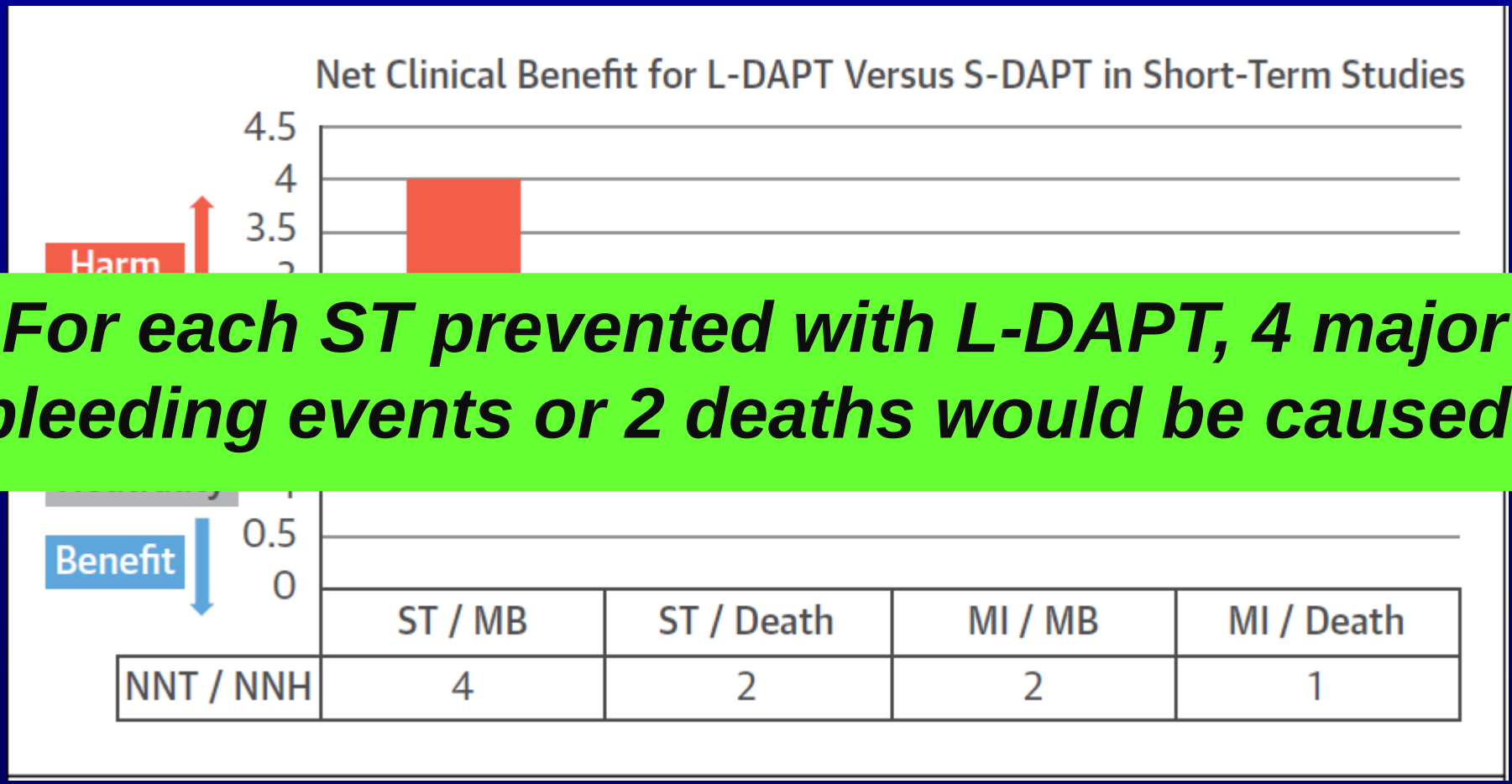
Net Clinical Benefit of Longer DAPT in Studies Evaluating a Period of DAPT ≤6 Months

EXCELLENT, RESET, SECURITY, ISAR SAFE, OPTIMIZE, PRODIGY, ITALIC



	ST / MB	ST / Death	MI / MB	MI / Death
NNT / NNH	4	2	2	1

For each ST prevented with L-DAPT, 4 major bleeding events or 2 deaths would be caused!

Montalescot et al. JACC 2015; 66: 832 – 47

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Studies Evaluating a Period of DAPT ≤6 Months: *CAVEATS*

- All studies were underpowered to detect differences in hard endpoints, including the composite primary EP
- All studies (except 1) were open-label trials
- Most of these trials had only 1 year of follow-up
- All studies had a noninferiority design with wide noninferiority margins
- Except for the PRODIGY trial, results from these studies lack external validity (generalizability), as high-risk patients were excluded from the majority
- Primary endpoint definitions were heterogeneous

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STUDIES EVALUATING A DURATION LONGER THAN 12 MONTHS

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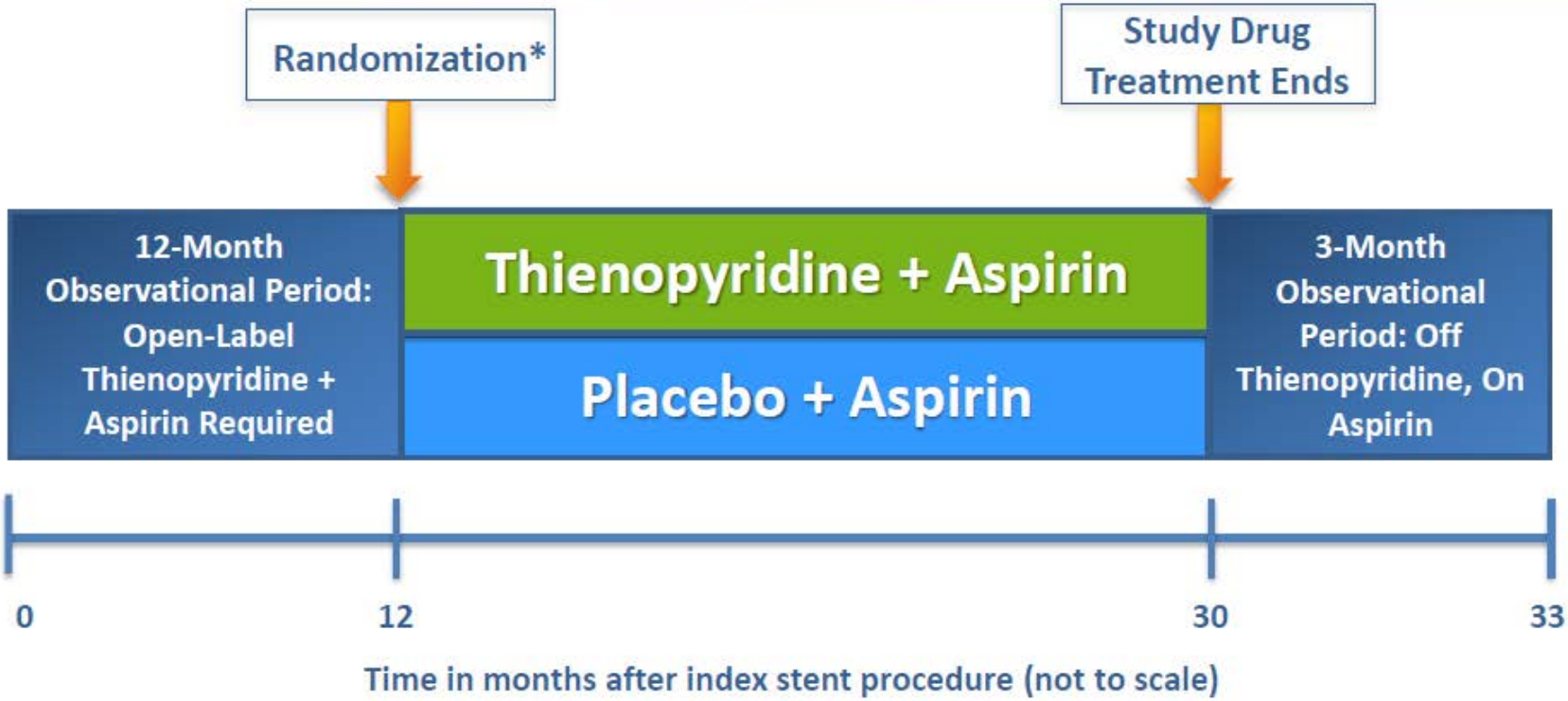
Design

DAPT STUDY



Enrolled: Subjects treated with FDA-approved DES or BMS. Subjects on oral anticoagulant therapy or with life expectancy < 3 years excluded.

Randomized: Free from MI, stroke, repeat revascularization, and moderate or severe bleeding, and adherent with thienopyridine (80% to 120% of doses taken and no interruption > 14 days).

Mauri, Kereiakes et al AHJ 2010; 160(6): 1035-1041

ClinicalTrials.gov number NCT00977938

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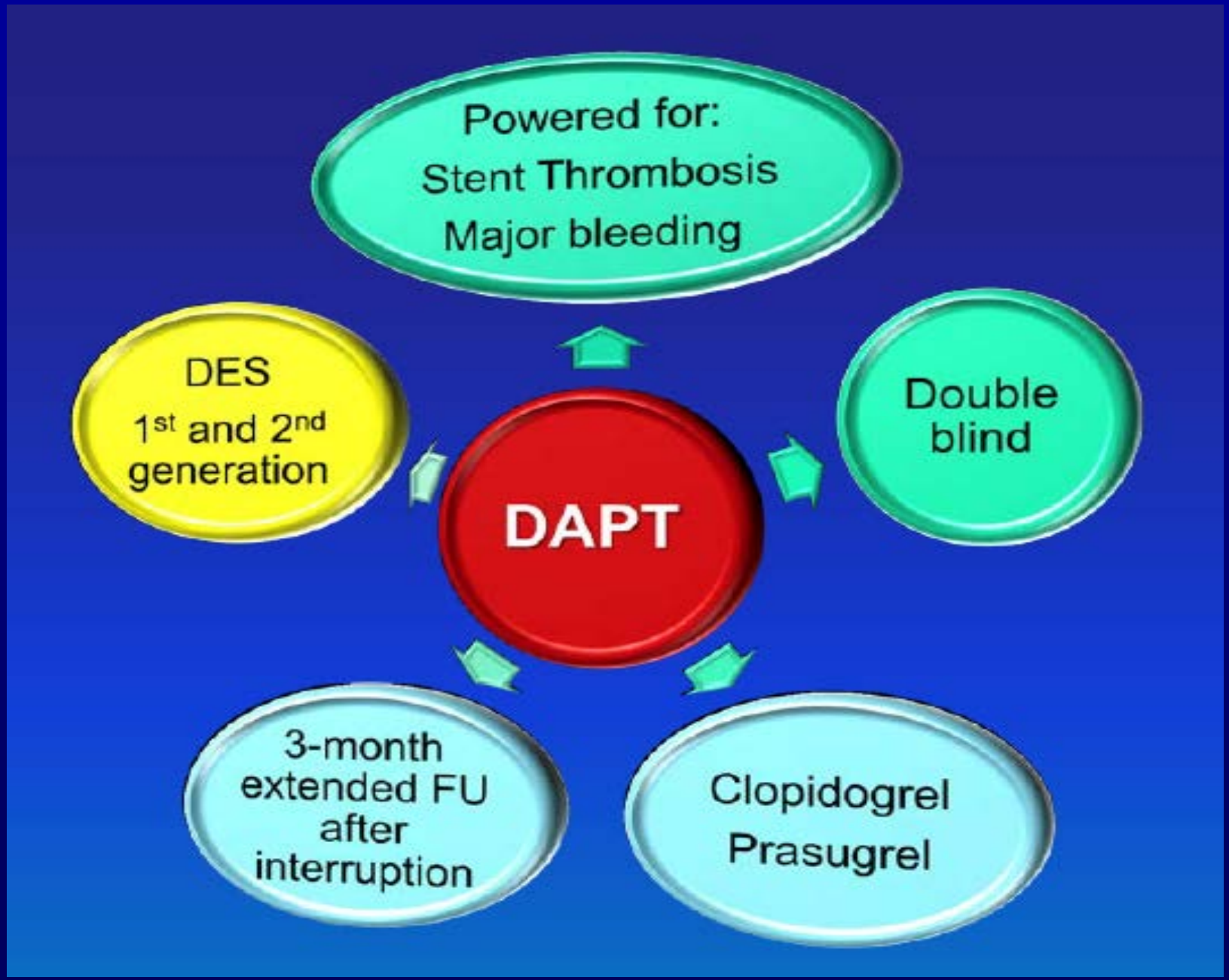
DAPT: unique characteristics of trial design and execution



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Baseline Demographics

DAPT STUDY

	Thienopyridine N=5020	Placebo N=4941	P-value
Age (years)	61.8	61.6	0.24
Female	24.7%	26.0%	0.15
Race – Non White	8.9%	8.6%	0.67
Ethnicity-Hispanic or Latino	3.2%	3.3%	0.91
Weight – kg	91.5	91.5	0.93
BMI	30.5	30.6	0.92
Diabetes Mellitus	31.1%	30.1%	0.28
Hypertension	75.8%	74.0%	0.03
Cigarette Smoker	24.6%	24.7%	0.91
Prior PCI	30.4%	31.0%	0.50
Prior CABG	11.3%	11.8%	0.49
NSTEMI	15.5%	15.5%	0.93
STEMI	10.6%	10.3%	0.65

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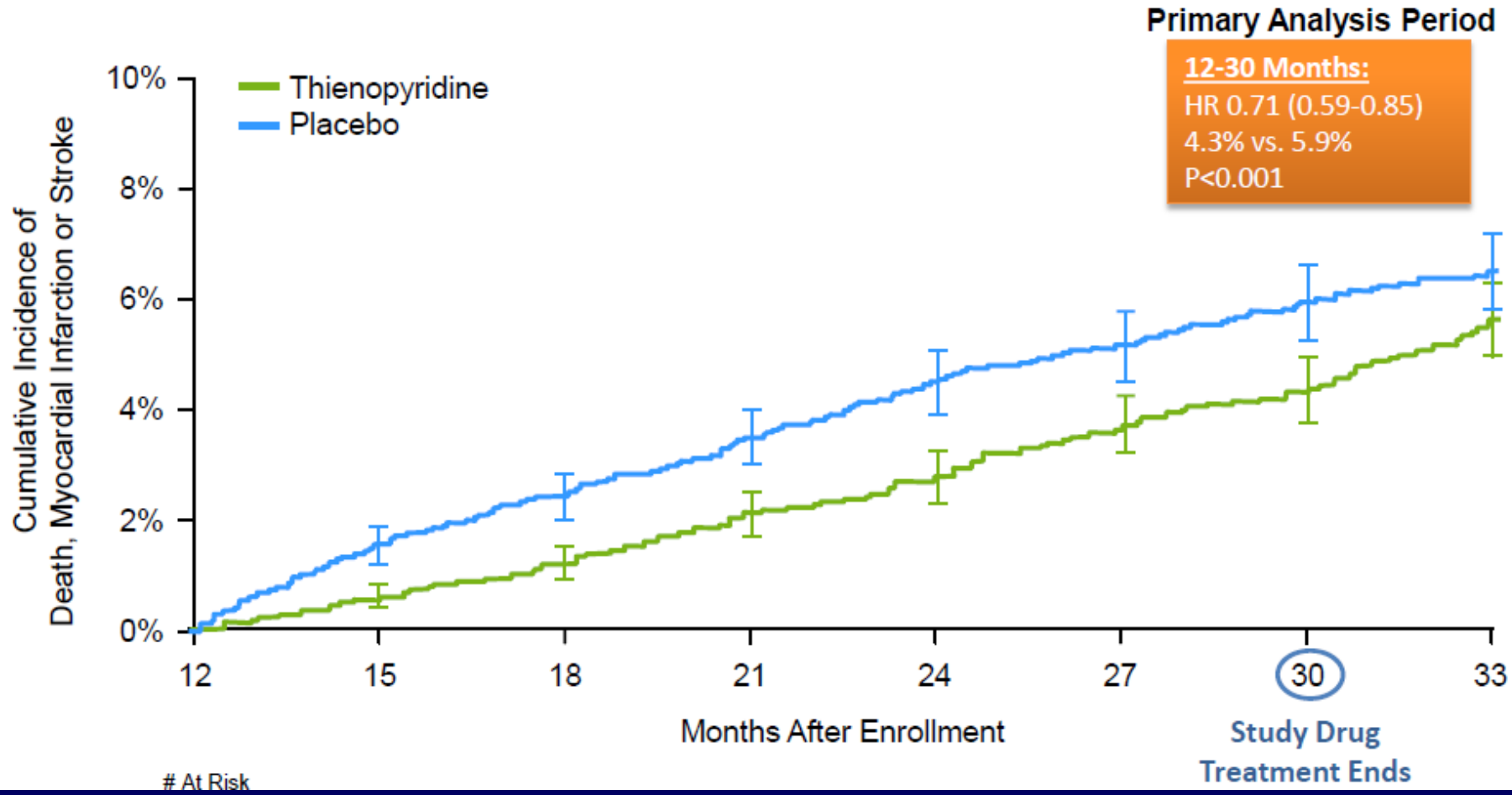
Co-Primary Effectiveness End Point MACCE

DAPT STUDY



Mauri L et al. N Engl J Med 2014;371:2155-66

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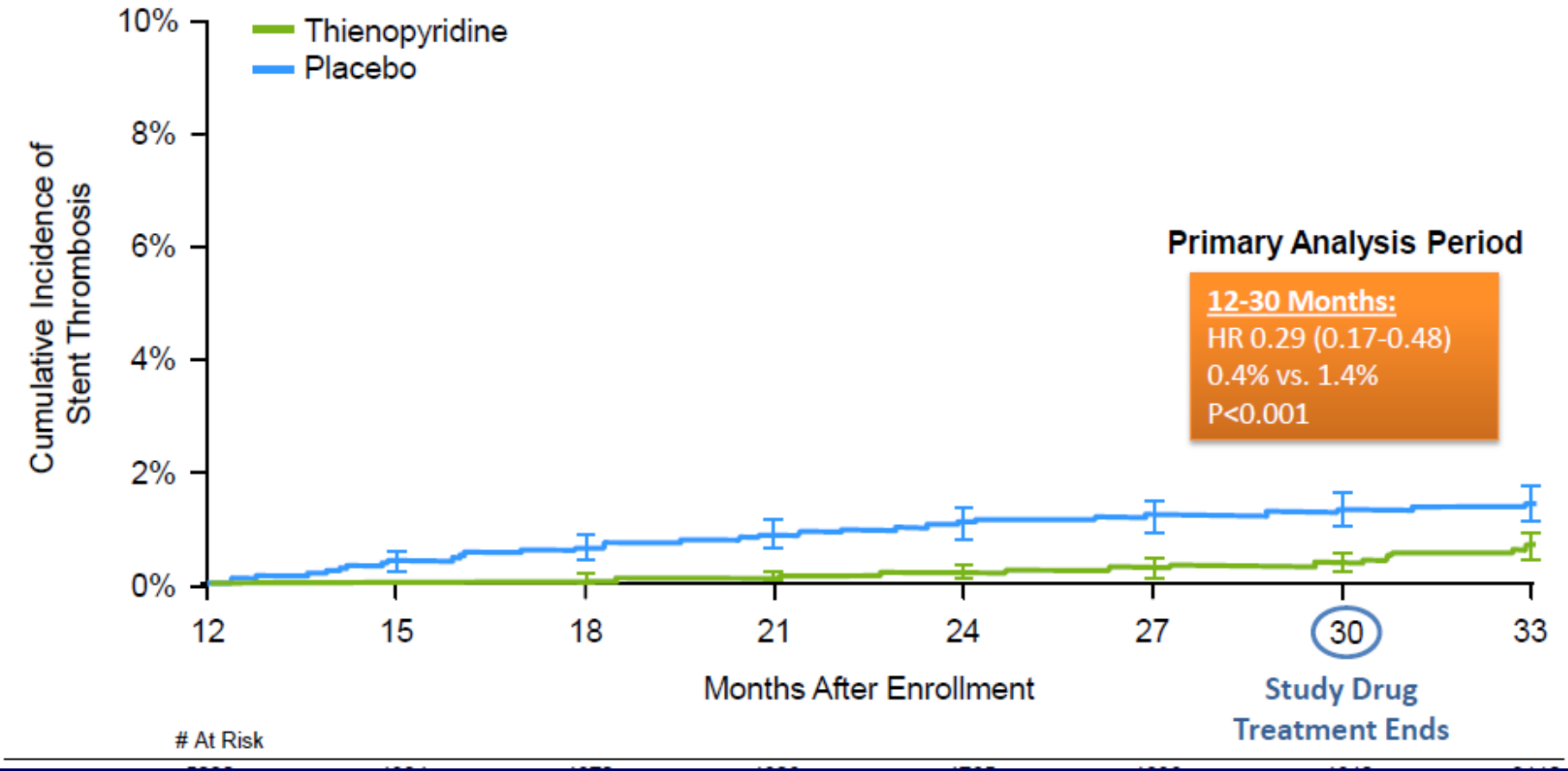
Co-Primary Effectiveness End Point
Stent Thrombosis

DAPT STUDY



Mauri L et al. N Engl J Med 2014;371:2155-66

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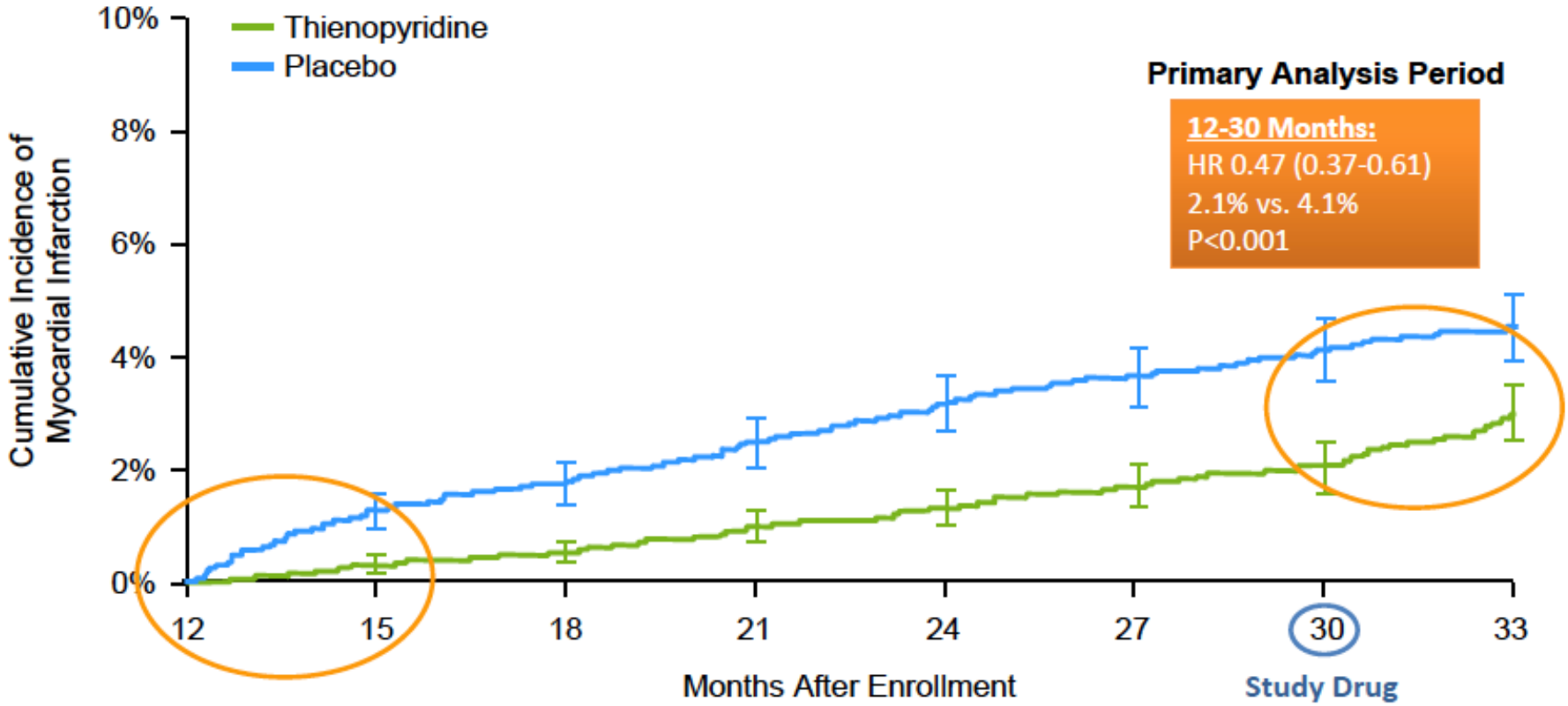
Myocardial Infarction

DAPT STUDY



# At Risk								
Thienopyridine	5020	4920	4849	4789	4717	4634	4580	3051
Placebo	4941	4804	4727	4653	4565	4501	4440	3012

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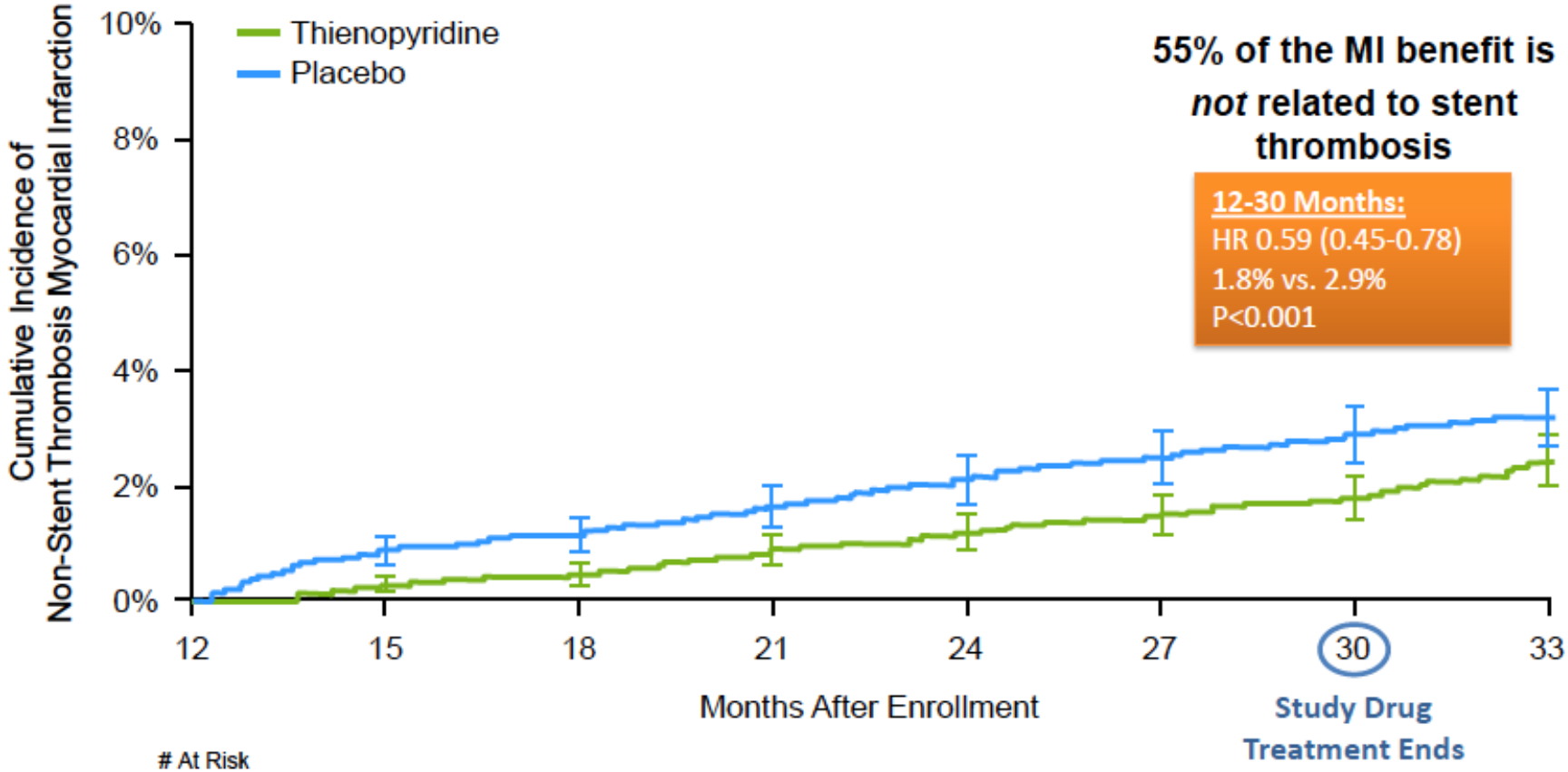
Mauri L et al. N Engl J Med 2014;371:2155-66

Non-Stent Thrombosis Myocardial Infarction

DAPT STUDY



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

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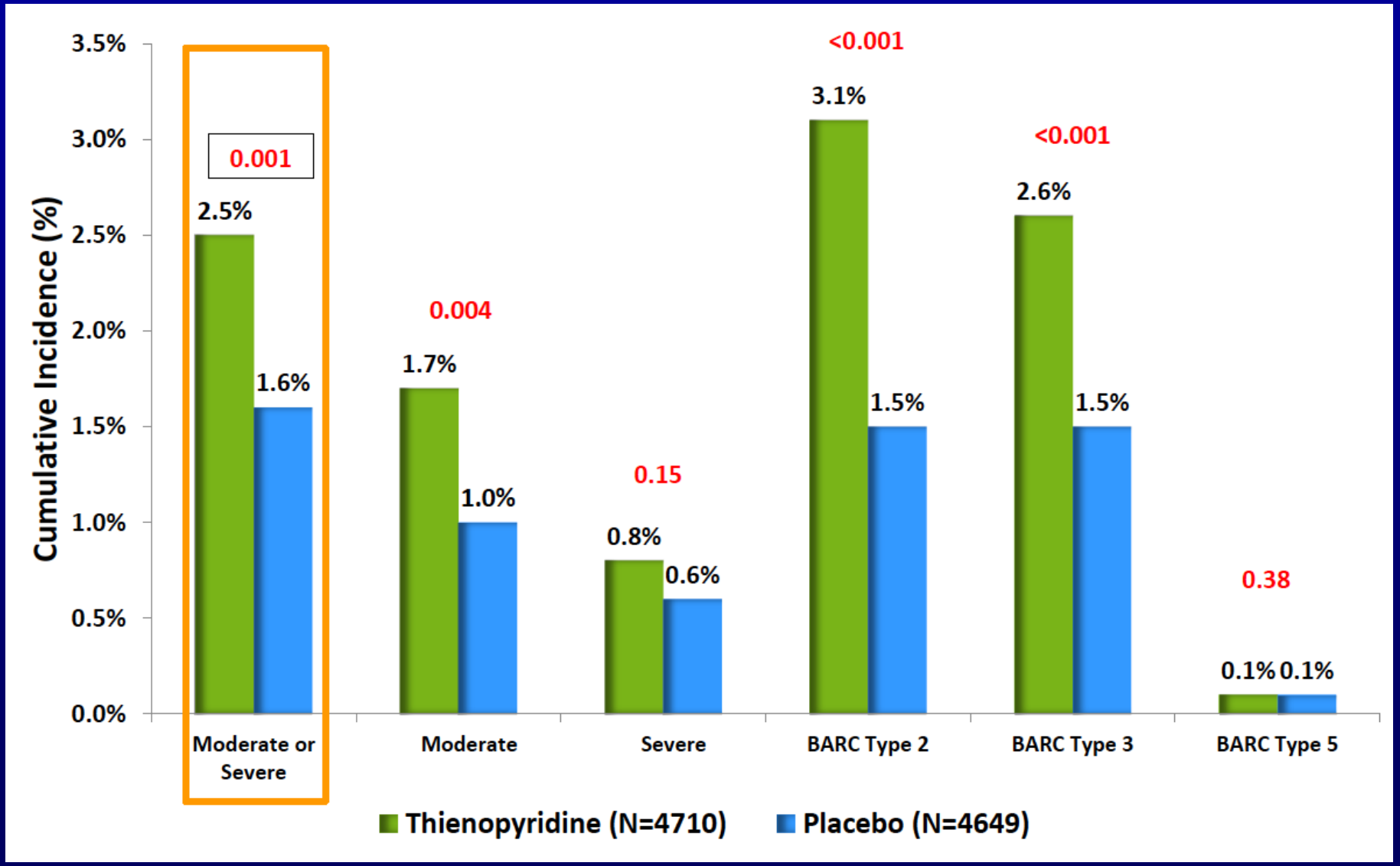
Mauri L et al. N Engl J Med 2014;371:2155-66

Bleeding End Point during Month 12 to Month 30



Mauri L et al. N Engl J Med 2014;371:2155-66

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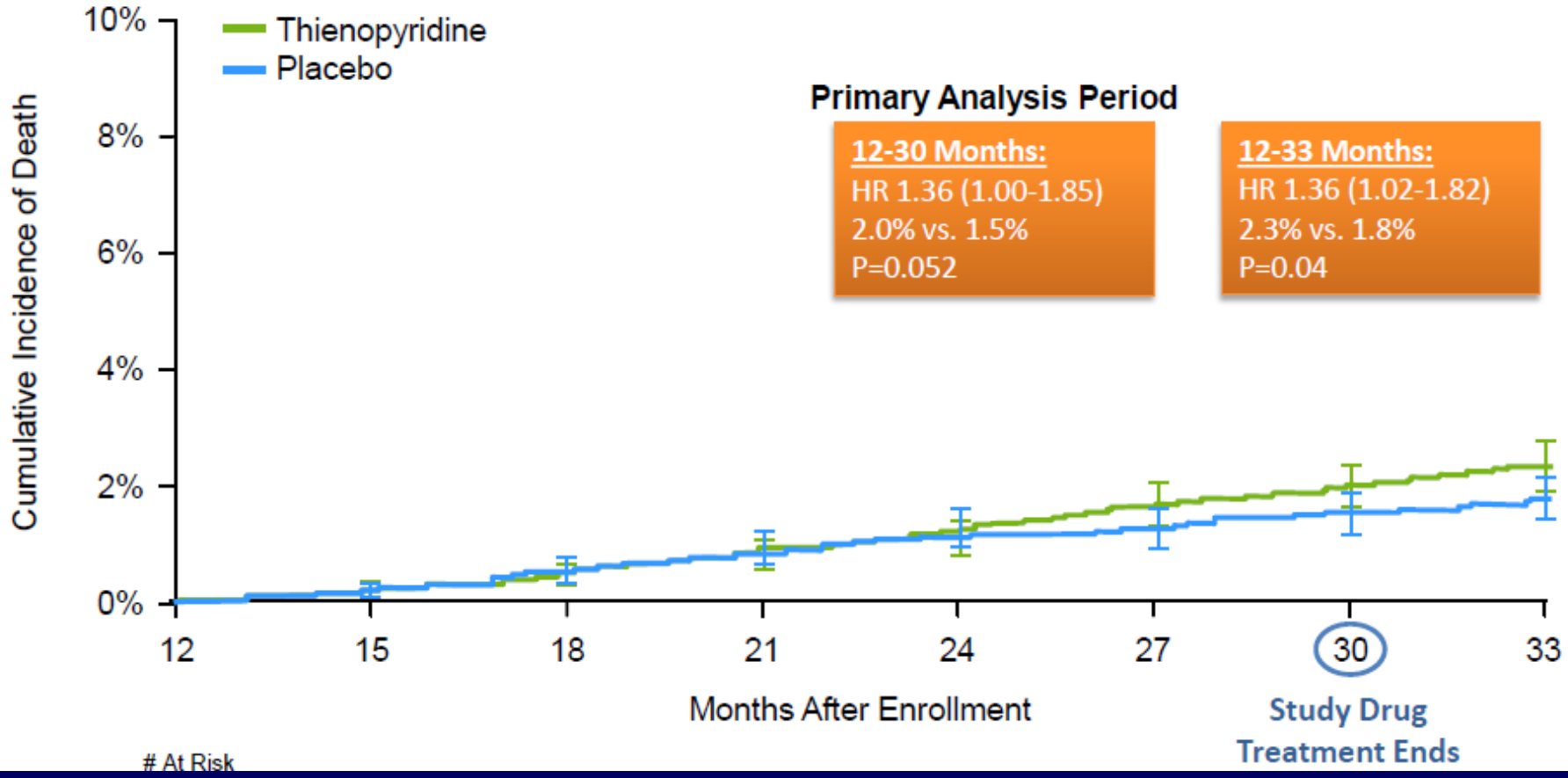
All-Cause Mortality

DAPT STUDY



Mauri L et al. N Engl J Med 2014;371:2155-66

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All-Cause Mortality

DAPT STUDY

	12-30 Months			
	Thienopyridine N=5020	Placebo N=4941	P-Value	Absolute Difference
All-Cause Mortality	**98 (2.0%)**	**74 (1.5%)**	**0.052**	**24 (0.5%)**
Cardiac	45 (0.9%)	47 (1.0%)	0.98	-2 (-0.1%)
Vascular	5 (0.1%)	5 (0.1%)	0.98	0 (-)
Non-Cardiovascular	48 (1.0%)	22 (0.5%)	0.002	26 (0.5%)

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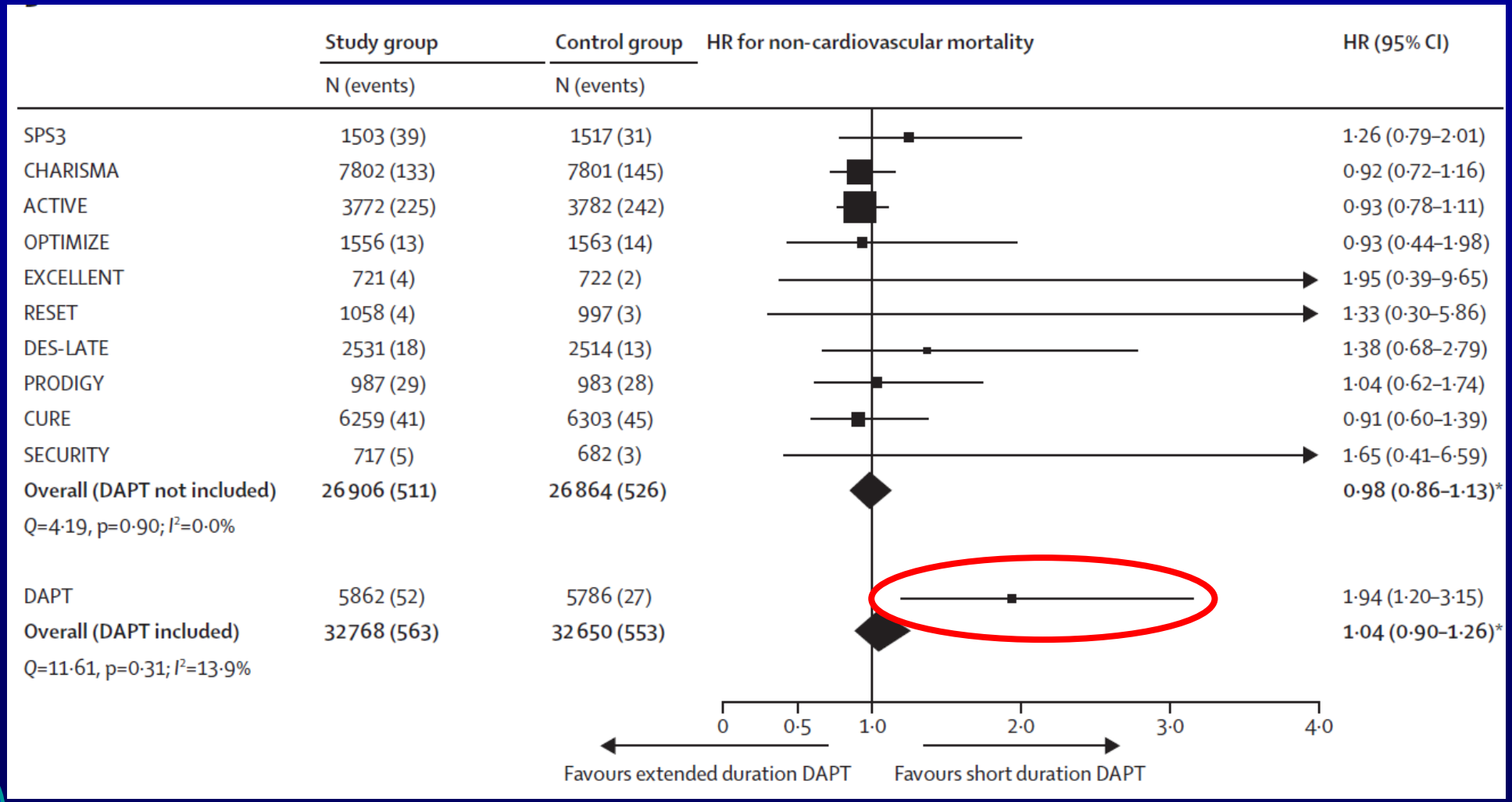
Mauri L et al. N Engl J Med 2014;371:2155-66

Prolonged DAPT and non-CV Mortality



Elmariah S et al. Lancet 2015; 385: 792–98

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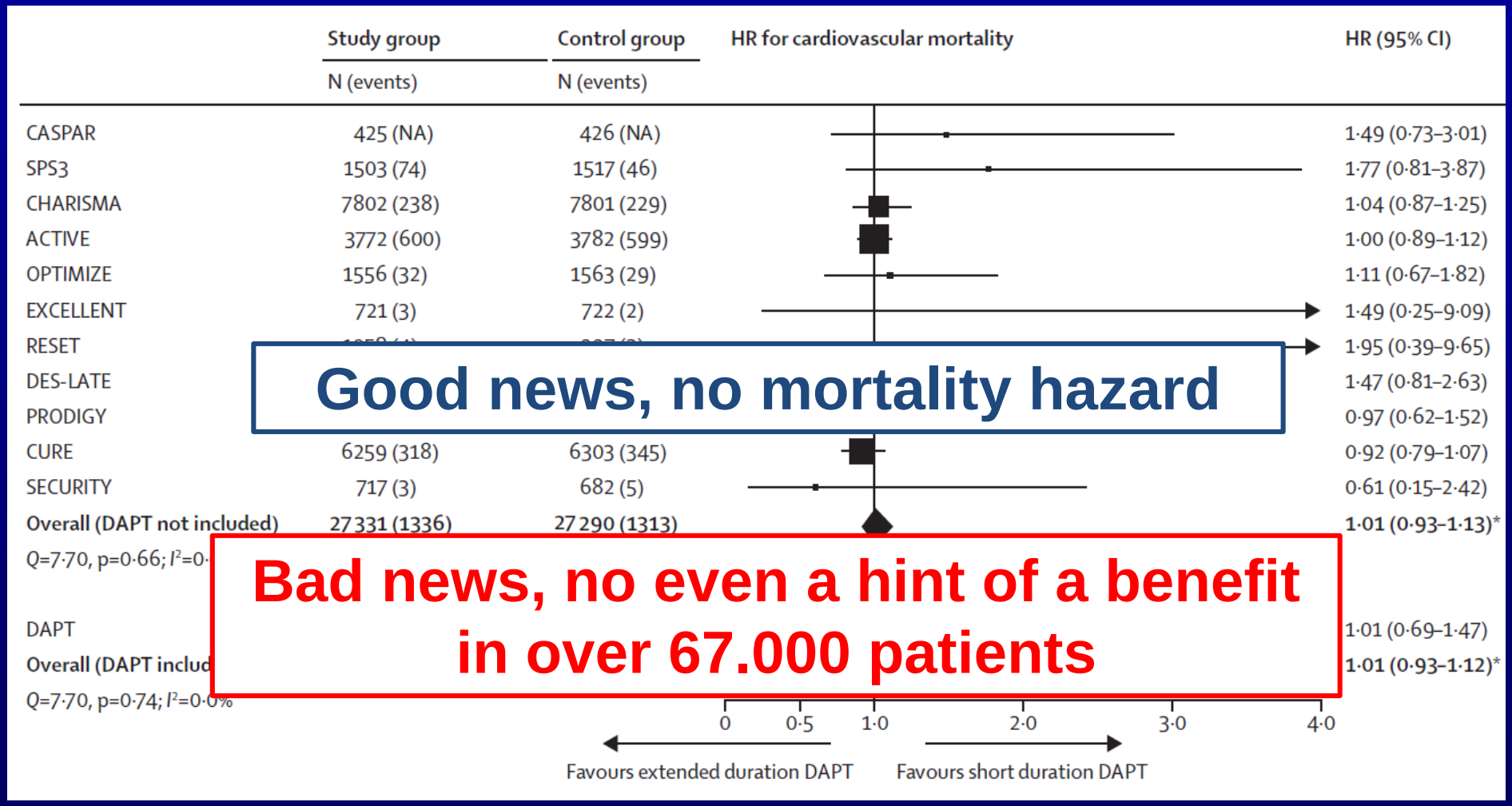
Prolonged DAPT and CV Mortality



Good news, no mortality hazard

Bad news, no even a hint of a benefit in over 67.000 patients

Elmariah S et al. Lancet 2015; 385: 792–98

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DAPT Trial: Summary of Efficacy/Harm

DAPT Relative Risk	DAPT Absolute Risk	DAPT NNT/NNH
• MACE 29% RR ↓	• MACE 1.6%↓	• MACE 62
• ST 71% RR ↓	• ST 1.0% ↓	• ST 100
• MI 53% RR ↓	• MI 2.0%↓	• MI 50
• Bleeding 61% ↑	• Bleeding 0.9% ↑	• Bleeding 111

Definite / Probable Stent Thrombosis

	ARR	NNT
Sirolimus	N/A	N/A
Zotarolimus	0.5%	200
Paclitaxel	2.2%	45
Everolimus	0.4%	250

Over 18 months treatment

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DAPT Trial: *Caveats*

- Selected group of pts who were event-free at 12 mth
- Only 47% of DES-treated pts received newer-generation DES
- The overall reduction in MI events is modest on an absolute scale, with 2 events prevented per 100 pts treated with prolonged DAPT in the overall study cohort (only 1.1 event prevented per 100 newer-generation stent pts treated with prolonged DAPT)
- Disturbing mortality signal

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FDA Drug Safety Communication: long-term antiplatelet therapy

Health care professionals should not change the way they prescribe these drugs at this time

http://www.fda.gov/Drugs/DrugSafety/ucm423079. htm

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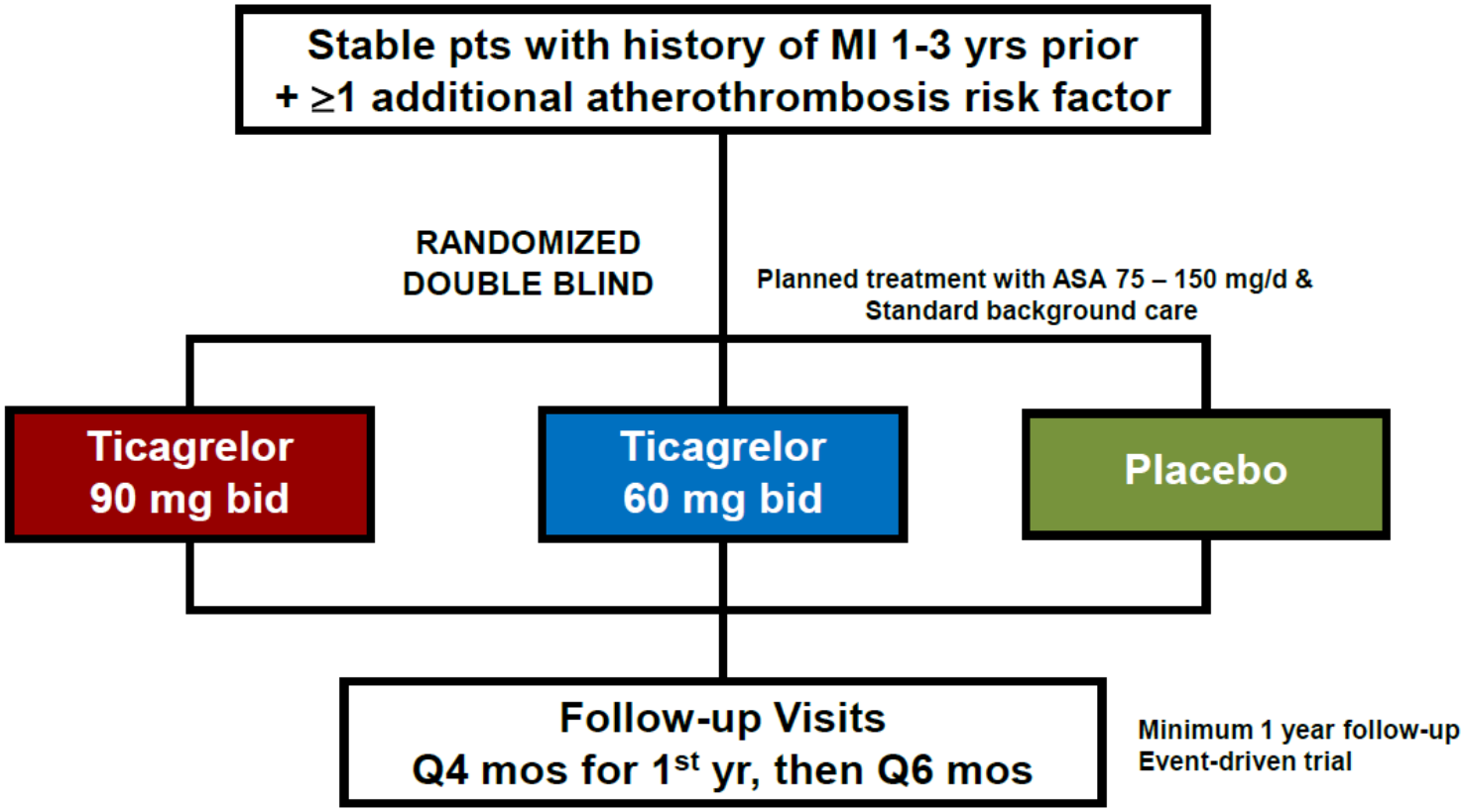
Trial Design

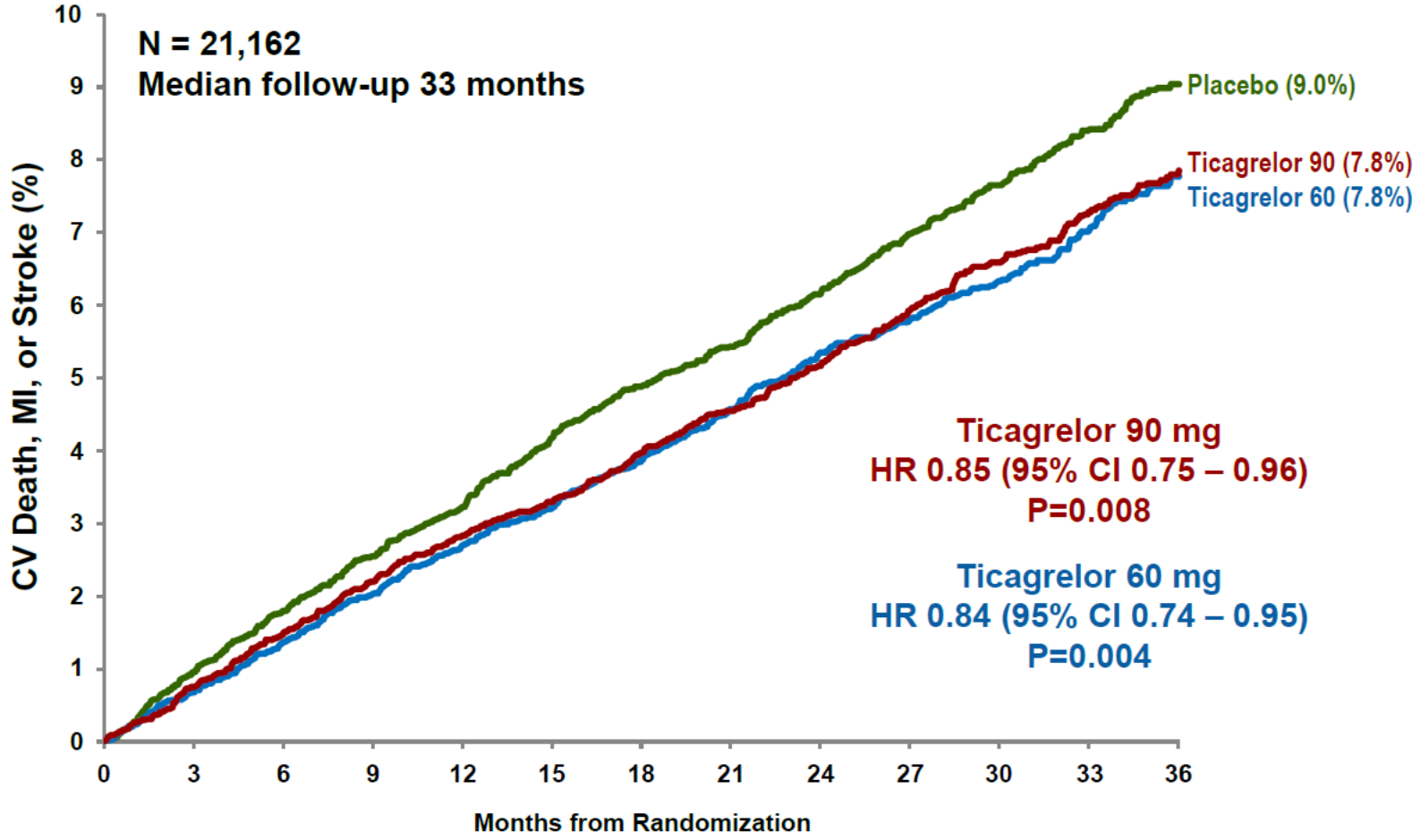


An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Bonaca MP et al. *Am Heart J* 2014;167:437-44

Bonaca MP et al. N Engl J Med 2015 March 14

Primary Endpoint



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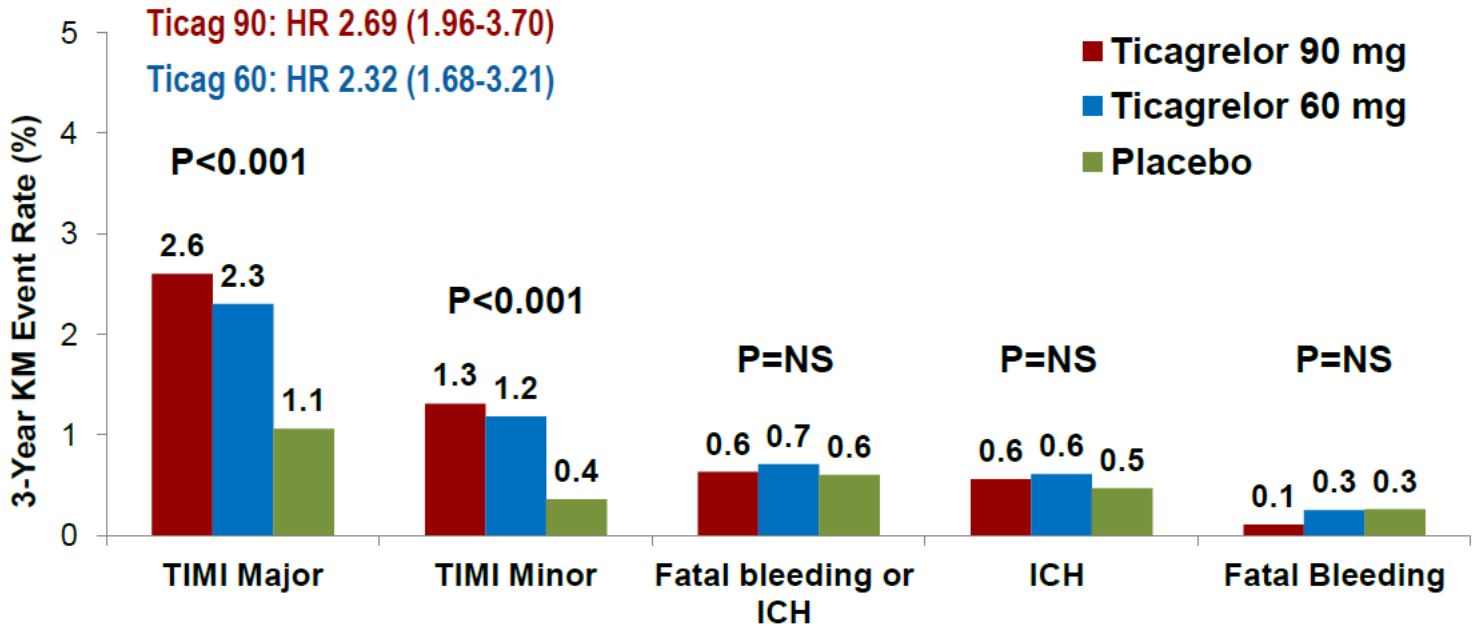
Bonaca MP et al. N Engl J Med 2015 March 14

Bleeding



An Academic Research Organization of
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Bonaca MP et al. N Engl J Med 2015 March 14

Outcomes over 1 Year for 10,000 Patients with Prior MI Initiated on Ticagrelor

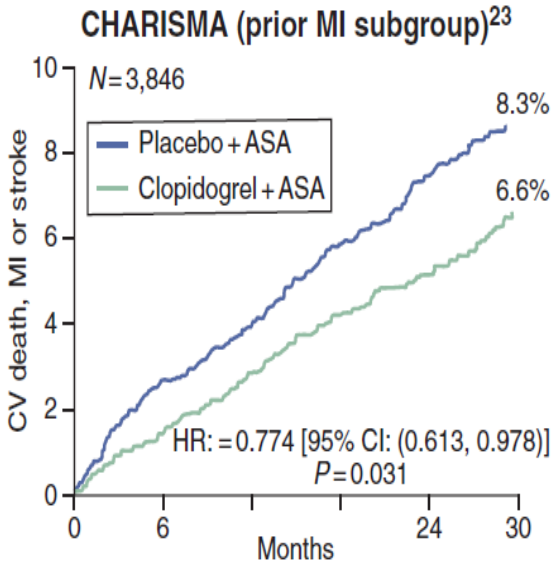
Using ticagrelor 90 mg twice daily in 10,000 post-MI patients each year resulted in:

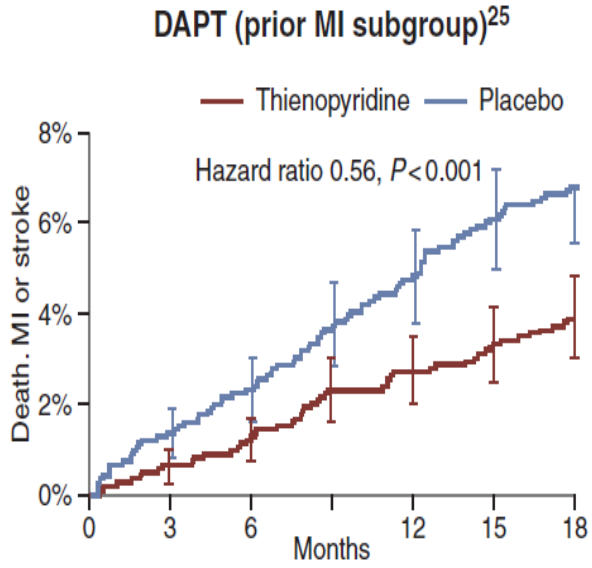
- **40 fewer ischemic events**
- **41 more TIMI Major bleeding events**

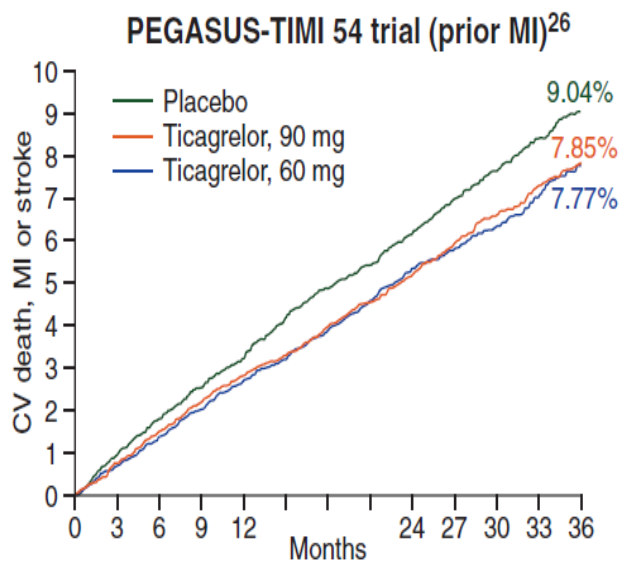
Using ticagrelor 60 mg twice daily in 10,000 patients each year resulted:

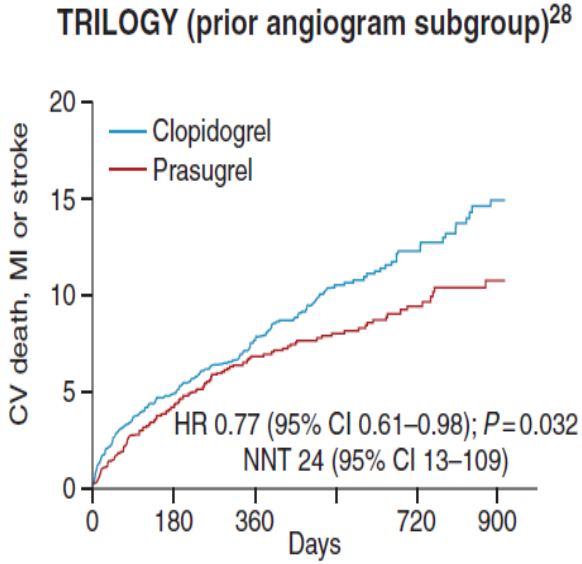
- **42 fewer ischemic events**
- **31 more TIMI Major bleeding events**

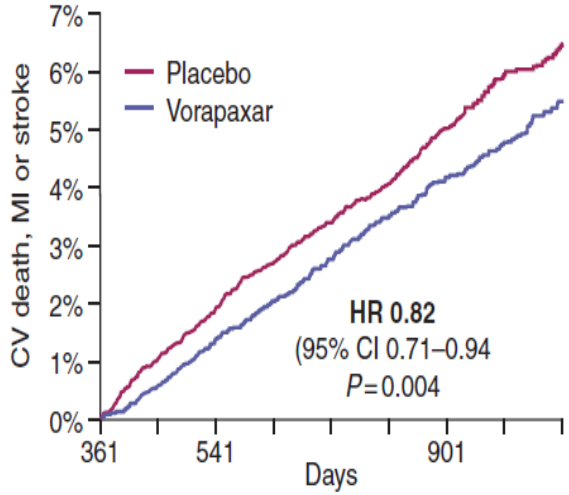
Results of the 5 studies which tested stronger antiplatelet Rx beyond 1 year vs. standard of care, in pts with proven CAD











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Mortality Benefit of Prolonged Platelet Inhibition in Pts w/ Prior MI

Trial	CV Mortality	All-cause Mortality
CHARISMA MI	0.82 (0.57-1.18)	0.84 (0.62-1.12)
TRA2P-TIMI 50 MI	0.84 (0.68-1.05)	0.92 (0.78-1.09)
DAPT MI	0.67 (0.31-1.44)	0.87 (0.50-1.50)
PEGASUS-TIMI 54 60 mg	0.83 (0.68-1.01)	0.89 (0.76-1.04)
TOTAL	**0.81 (0.69-0.95) P=0.010**	**0.89 (0.81-0.99) P=0.037**

Sabatine MS ESC 2015

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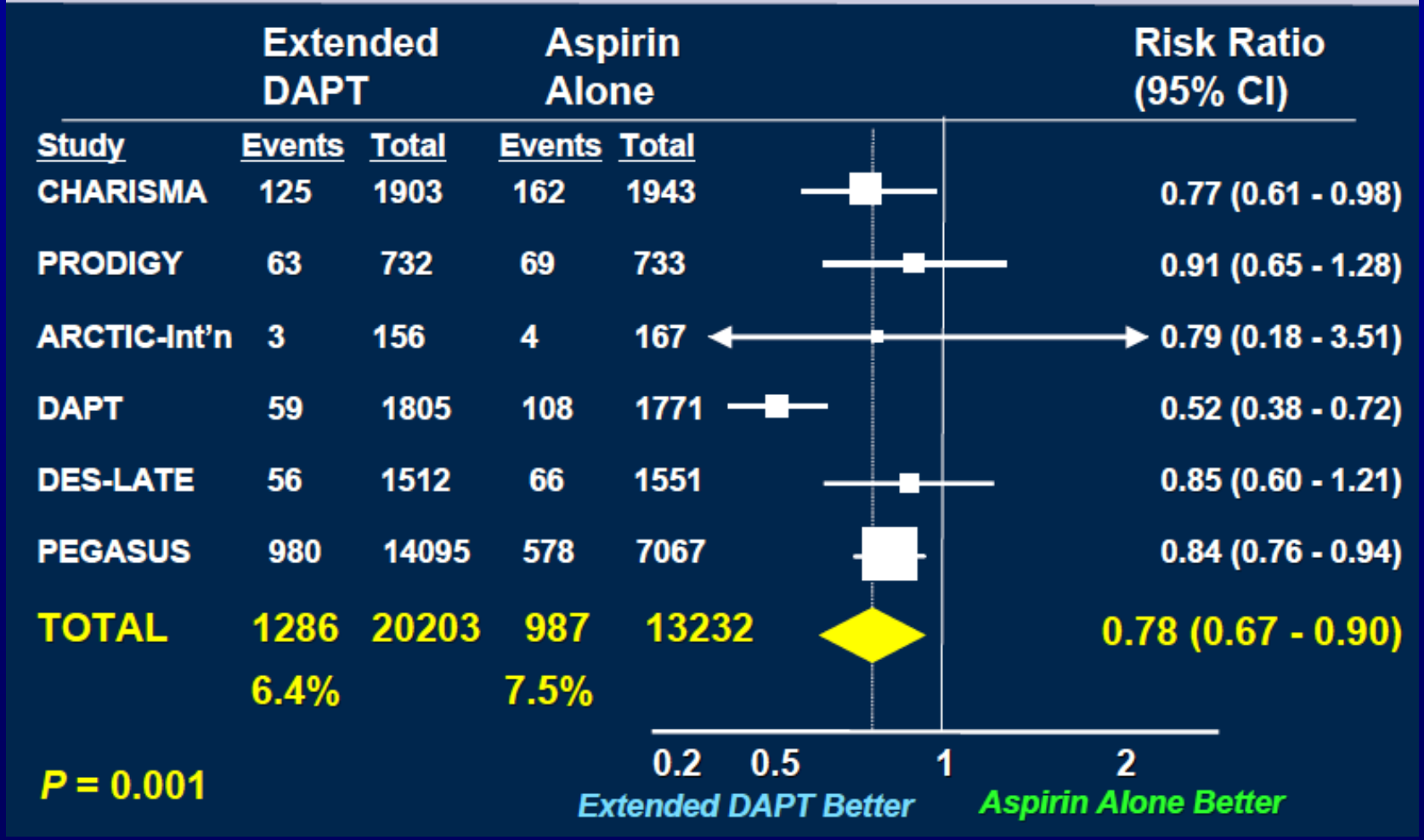
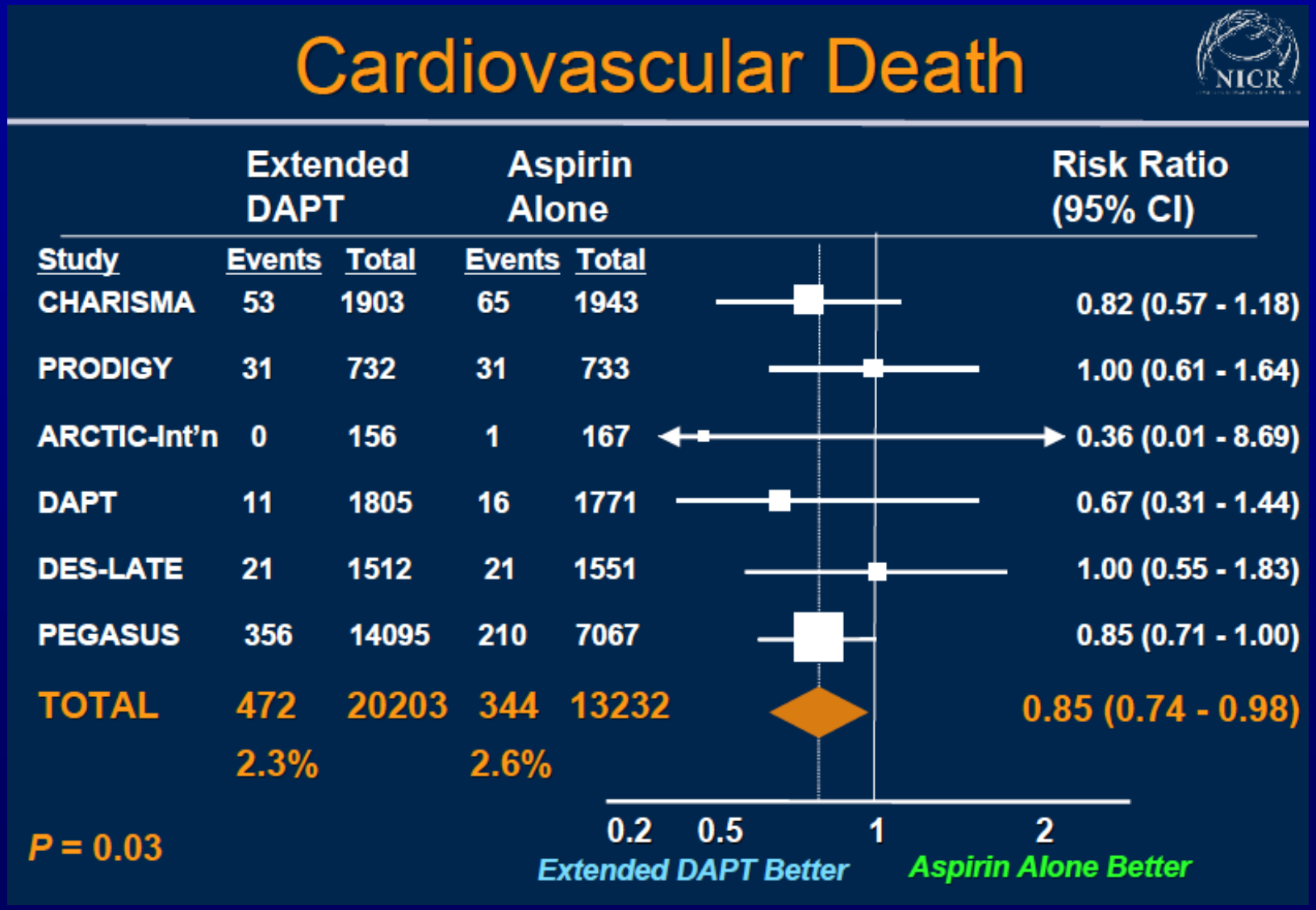
Benefit of Prolonged Platelet Inhibition in Pts with Prior MI: a Metaanalysis

Primary Endpoint – CV Death, MI, or Stroke



Udell JA et al. Eur Heart J 2015 doi:10.1093/eurheartj/ehv443

Benefit of Prolonged Platelet Inhibition in Pts with Prior MI: a Metaanalysis



Udell JA et al. Eur Heart J 2015 doi:10.1093/eurheartj/ehv443

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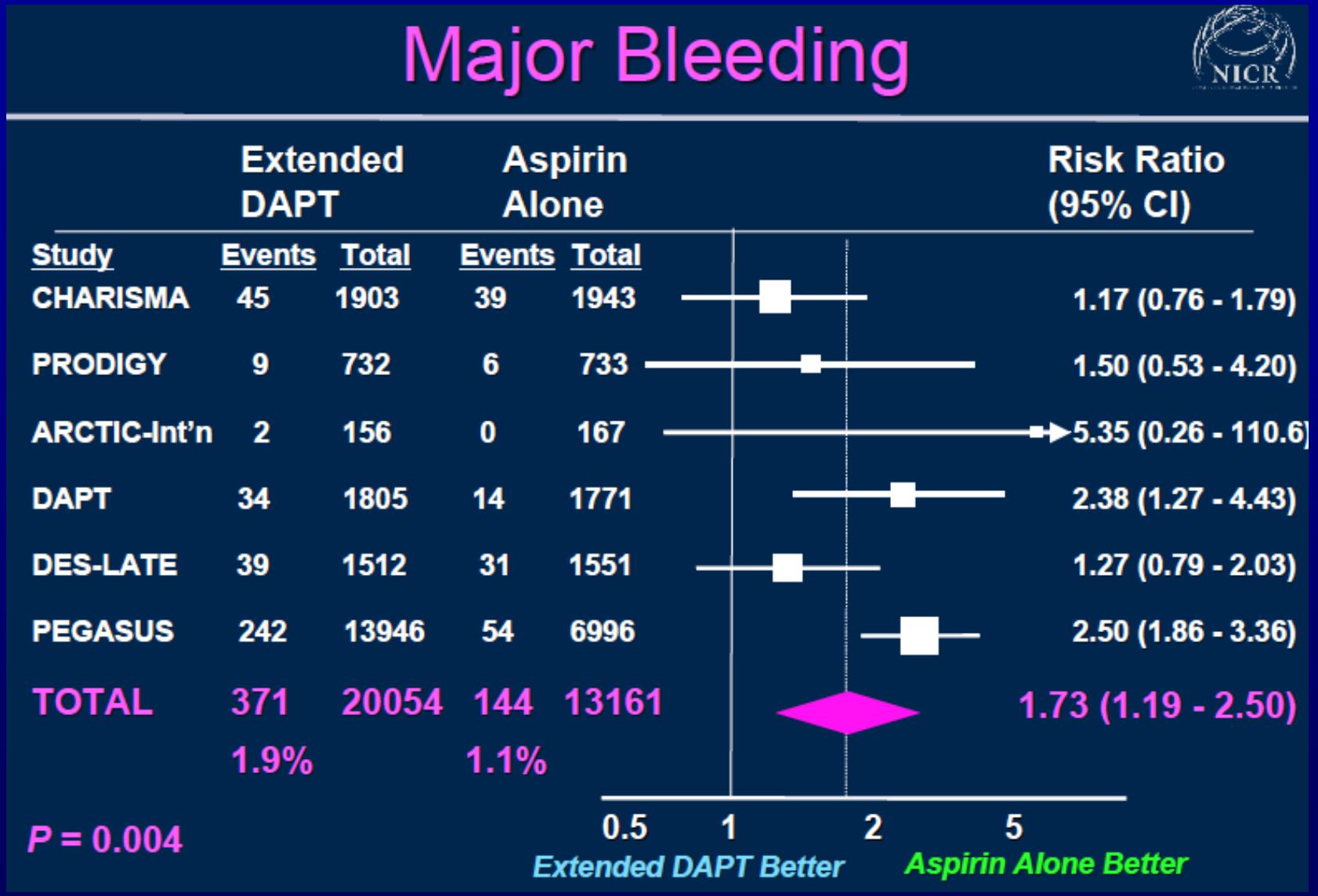
Benefit of Prolonged Platelet Inhibition in Pts with Prior MI: a Metaanalysis



Udell JA et al. Eur Heart J 2015 doi:10.1093/eurheartj/ehv443

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New 2015 ESC guidelines for the management of NSTEMI

DAPT Duration

Evidence to support the extension of DAPT after DES beyond 1 year in NSTE-ACS patients is limited (Page 20; 5.2.6)

Recommendations	Class[a]	Level[b]	
Oral antiplatelet therapy			
$P2Y_{12}$ inhibitor adm… DES implantation … risk.		A	NEW
Long-term $P2Y_{12}$ in…			
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	IIb	A	NEW

Personalized options for DAPT duration

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Ongoing Studies Examining Abbreviated Duration of DAPT

Study (Ref. #)	Design	Size	Active (Months)	Control (Months)	Population	Primary EP	Expected Completion Date
GLOBAL LEADERS (NCT01813435)	RCT (Biomatrix stent)	16,000	1	12	DES	Composite of all-cause mortality or nonfatal new Q-wave MI up to 2 yrs post-randomization	June 2016
REDUCE (NCT02118870)	RCT (COMBO dual therapy stent)	1,500	3	12	ACS	Composite of all-cause mortality, MI, ST, stroke, or bleeding at 12 months	March 2017
SMART-CHOICE (NCT02079194)	RCT	5,100	3	12	DES	Composite of death, MI, cerebrovascular events, or bleeding over 3-12 months after the index procedure	February 2020
SMART-DATE (NCT01701453)	RCT	3,000	6	12	ACS	Composite of death, MI, CVA, ST, or major bleeding over 6-18 months post-hospitalization	August 2016
DAPT-STEMI (NCT01459627)	RCT	1,100	6	12	STEMI	Composite of death, MI, revascularization, CVA, or bleeding at 18 months post-randomization	December 2017
TWILIGHT (NCT02270242)	RCT	8,000	3	12	complex PCI with DES	Major bleeding at 15 months post-PCI	March 2017

Montalescot et al. JACC 2015; 66: 832 – 47

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Revival of clopidogrel in long term treatment for ACS?

Starting with new ADP-receptor blockers, but…

- **WUPPER**: switching to clopidogrel after 1 week
- **HORIZONS II-AMI**: switching to clopidogrel after 30 days
- **TROPICAL-ACS**

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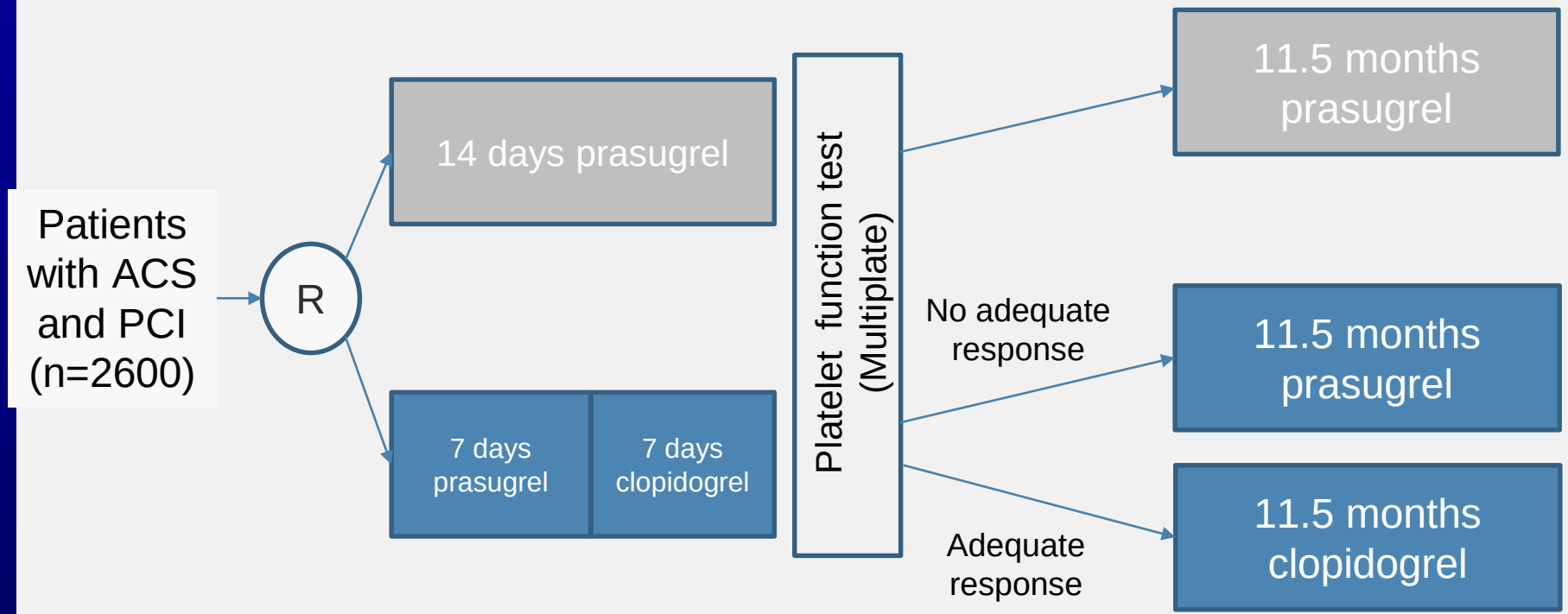
Revival of clopidogrel in long term treatment for ACS?

TROPICAL ACS trial



Courtesy of Dr. Sibbing

ACS Secondary Prevention: Unmet Needs

Tailoring therapy to risk

The challenge:

Develop a model that will account for variation of risk over time in a specific patient

There is significant overlap in risk factors for bleeding and MI (e.g., age and chronic kidney disease); therefore, clinical judgment is still important to avoid undertreating patients whose ischemic risk outweighs bleeding risk

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Is prolonged DAPT the new gold standard?

"Not for most patients."

- The robustness of existing data are weak and the selected populations included in the studies might not be representative of current practice in patients with ACS
- The bleeding risks of prolonged DAPT combined with the neutral/negative effect of prolonged DAPT on all-cause mortality should give us pause before widely advocating prolonged DAPT to all ACS pts.
- Among certain groups for whom the absolute risk of ischemic events is greatest, we ought to strongly consider extension of DAPT.

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