The Role of New Anti-Platelet Agents: Will Prasugrel and Ticagrelor Change the DES Landscape?

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CARDIOVASCULAR RESEARCH FOUNDATION

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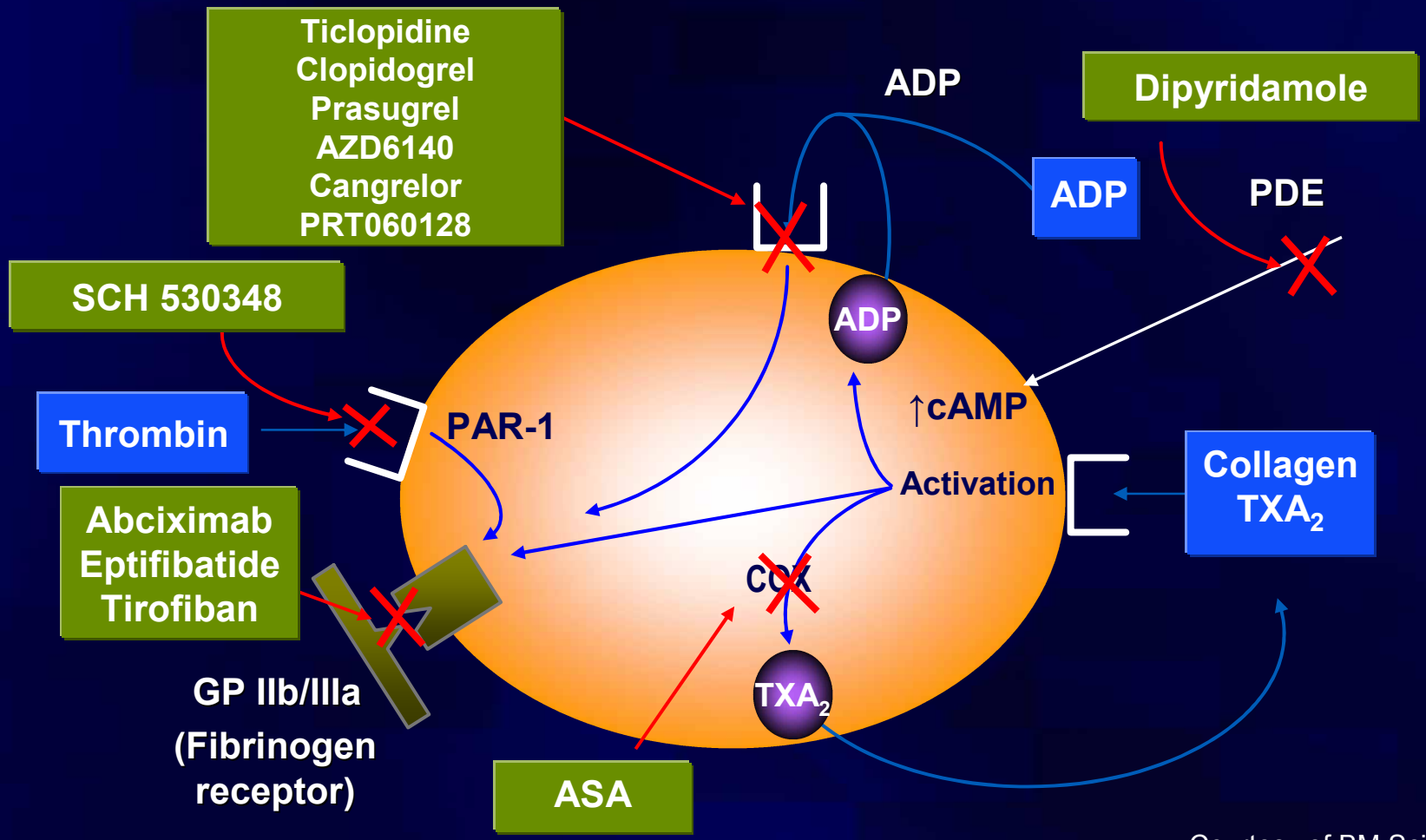
Disclosures: Roxana Mehran

Clinical Research Support to Columbia: Sanofi/Aventis, BMS, Bracco

Educational/Research Support to CRF: TMC, Boston Scientific, Abbott, Medtronic, Cordis, Lilly/Diachi Sankyo, BMS, AZ

Consultant/Honoraria: TMC, Sanofi/Aventis, Astra Zeneca, Cordis, Therox, Bracco, Guerbert, Regado, Gilead

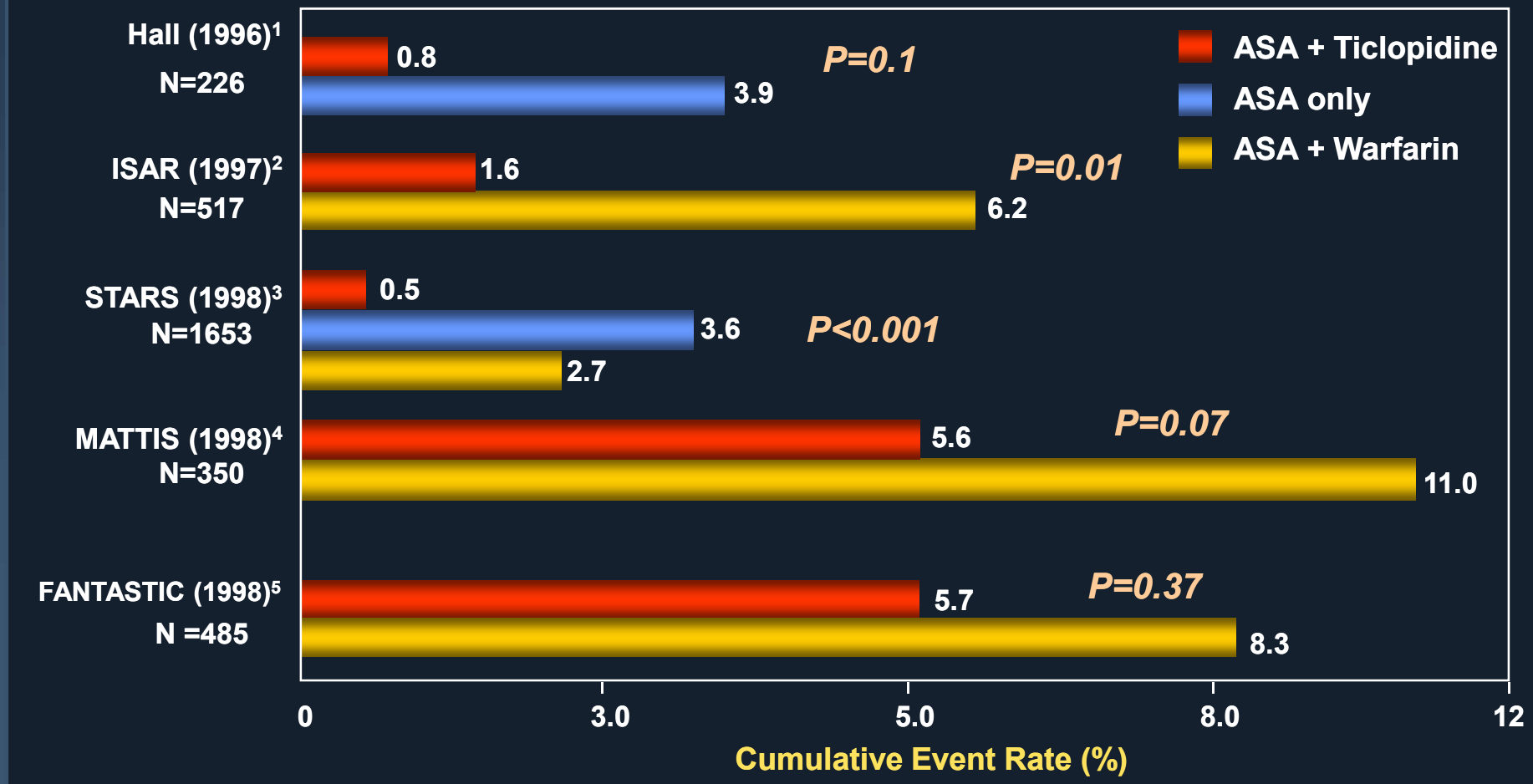
Targets for antiplatelet therapies



cAMP = cyclic adenosine monophosphate, COX = cyclooxygenase, PAR = protease-activated receptor, PDE = phosphodiesterase

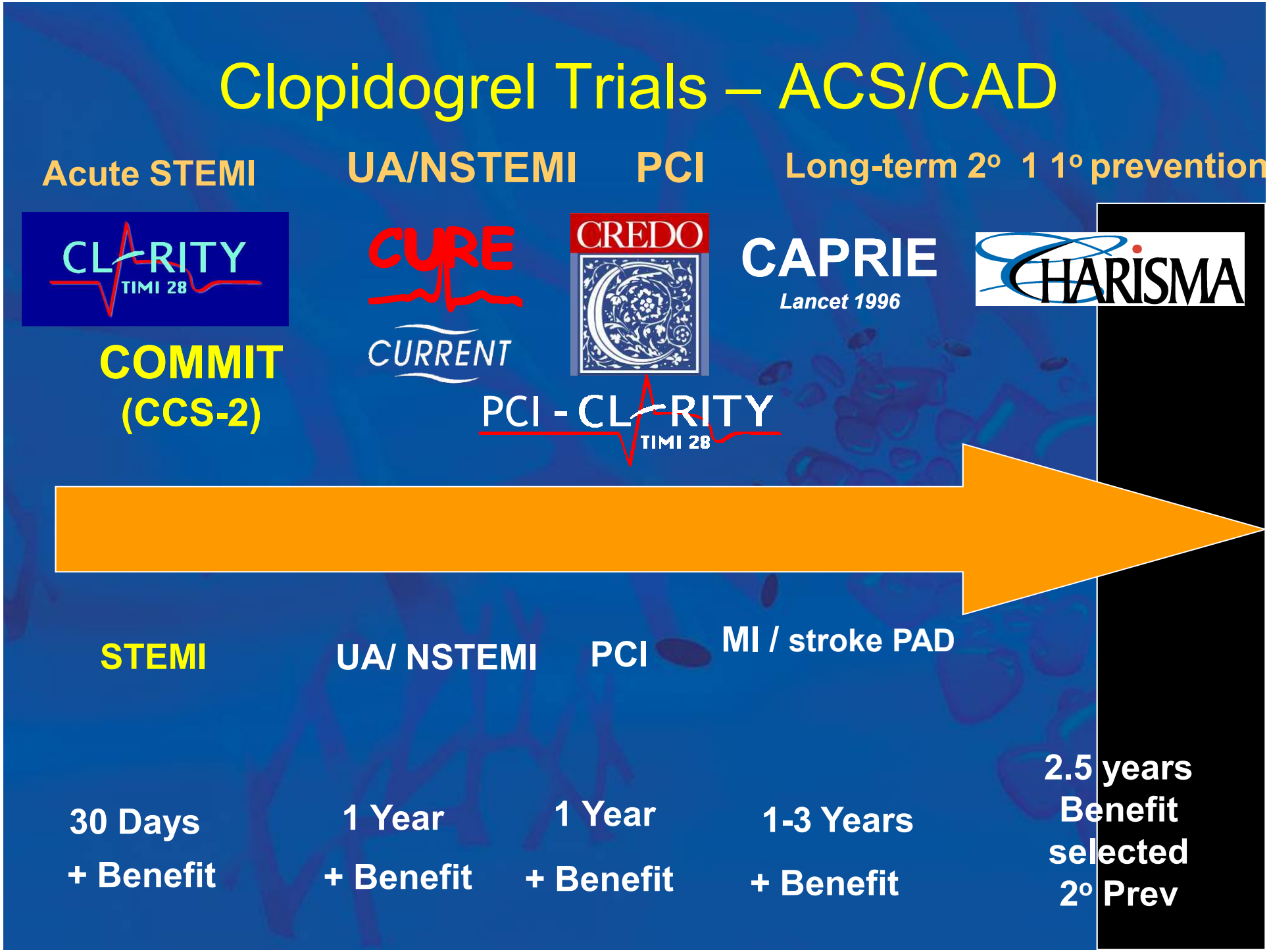
Courtesy of BM Scirica, MD.
Adapted from Schafer AI. *Am J Med*. 1996;101:199-209.

Combination Antiplatelet Therapy Reduces Coronary Events after Stenting



[1] Hall P, et al. *Circulation*. 1996;93:215-222.
[2] Schömig A, et al. *N Engl J Med*. 1996;335:1084-1089.
[3] Leon M, et al. *N Engl J Med*. 1998:339:1665-71.
[4] Urban P, et al. *Circulation*. 1998 98:2126-2132.
[5] Bertrand M, et al. *Circulation*. 1998;98:1597-1603. (Events include death, Q-wave or non-Q-wave MI).

Clopidogrel Trials – ACS/CAD



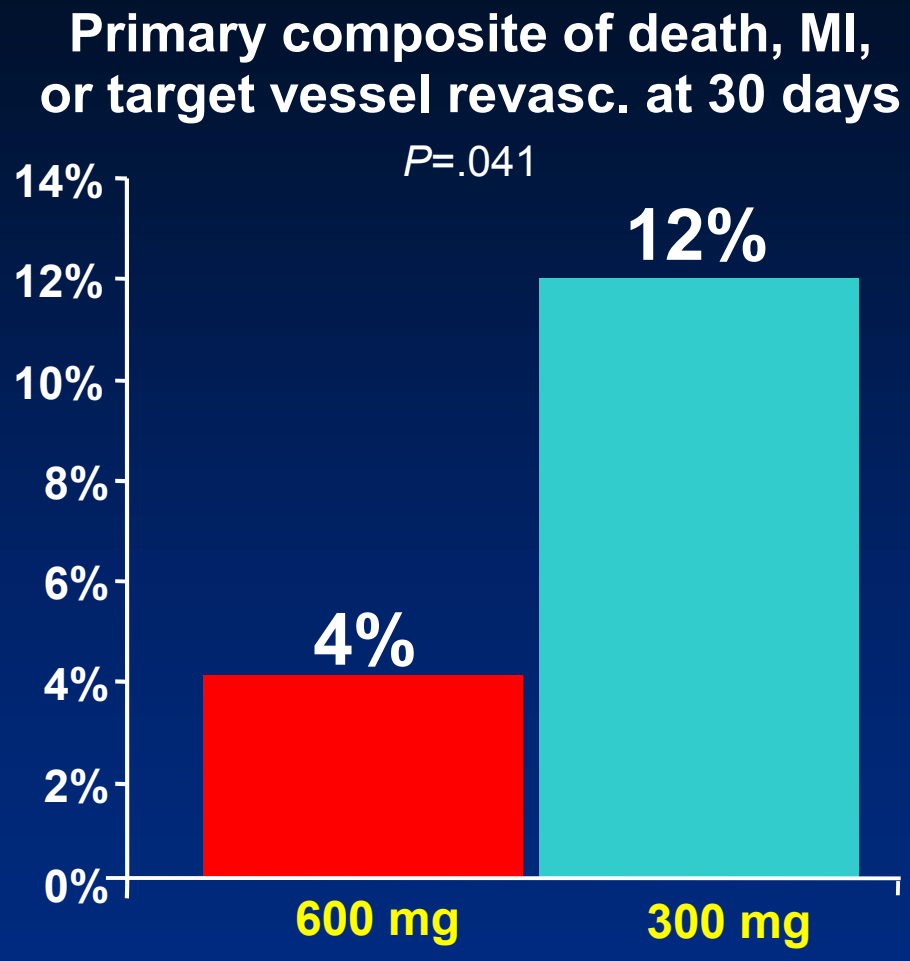
ARMYDA-2 Study: Design and Primary End Point

255 patients with stable CAD or NSTEMI prior to PCI
13% received GP IIb/IIIa inhibitors
20% received drug-eluting stents

Randomized 4-8 Hours Pre-PCI

High Loading Dose of Clopidogrel 600 mg Pre-PCI

Standard Loading Dose of Clopidogrel 300 mg Pre-PCI



ARMYDA-2, Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty.
Patti G, et al. *Circulation*. 2005;111(16):2099-2106.

CURRENT Study Design, Flow and Compliance

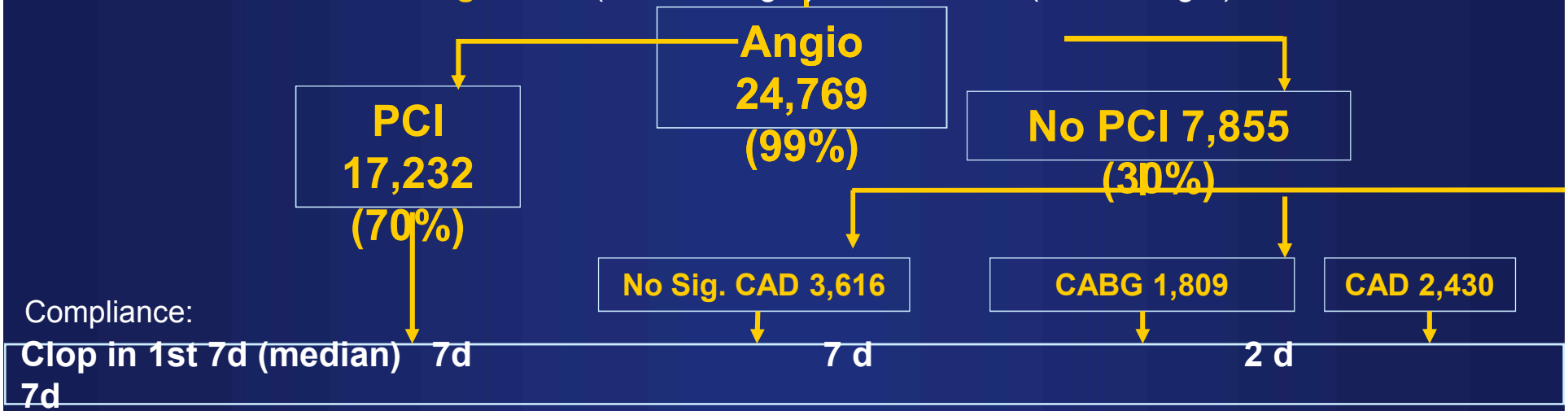
25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

- ✓ Planned Early (<24 h) Invasive Management with **intended PCI**
- ✓ Ischemic ECG Δ (80.8%) or ↑cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):

CLOPIDOGREL: Double-dose (600 mg then150 mg/d x 7d then 75 mg/d) **vs Standard dose** (300 mg then 75 mg/d)

ASA: High Dose (300-325 mg/d) **vs Low dose** (75-100 mg/d)

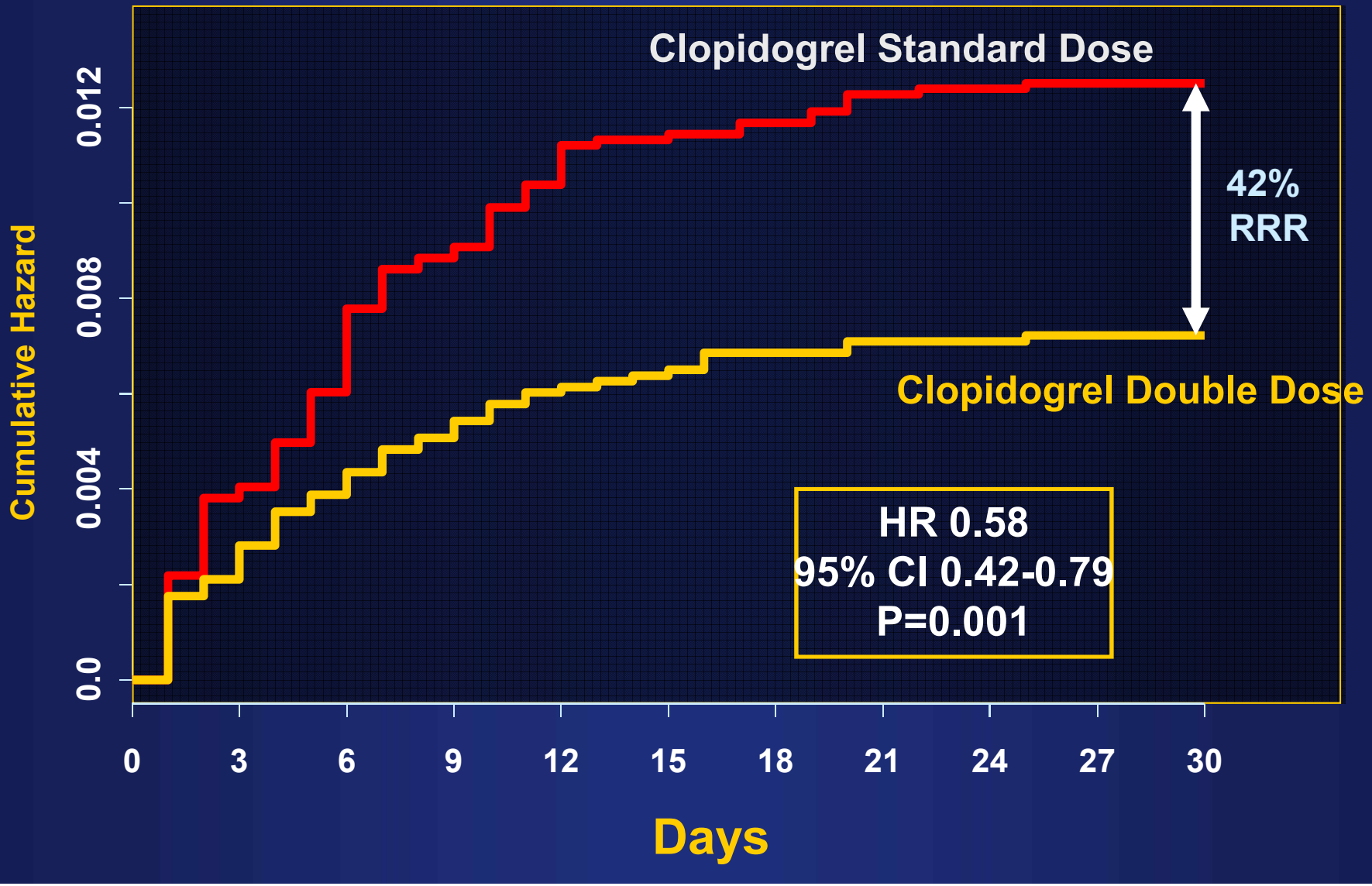


Efficacy Outcomes:	CV Death, MI or stroke at day 30 Stent Thrombosis at day 30
Safety Outcomes:	Bleeding (CURRENT defined Major/Severe and TIMI Major)
Key Subgroup:	PCI v No PCI

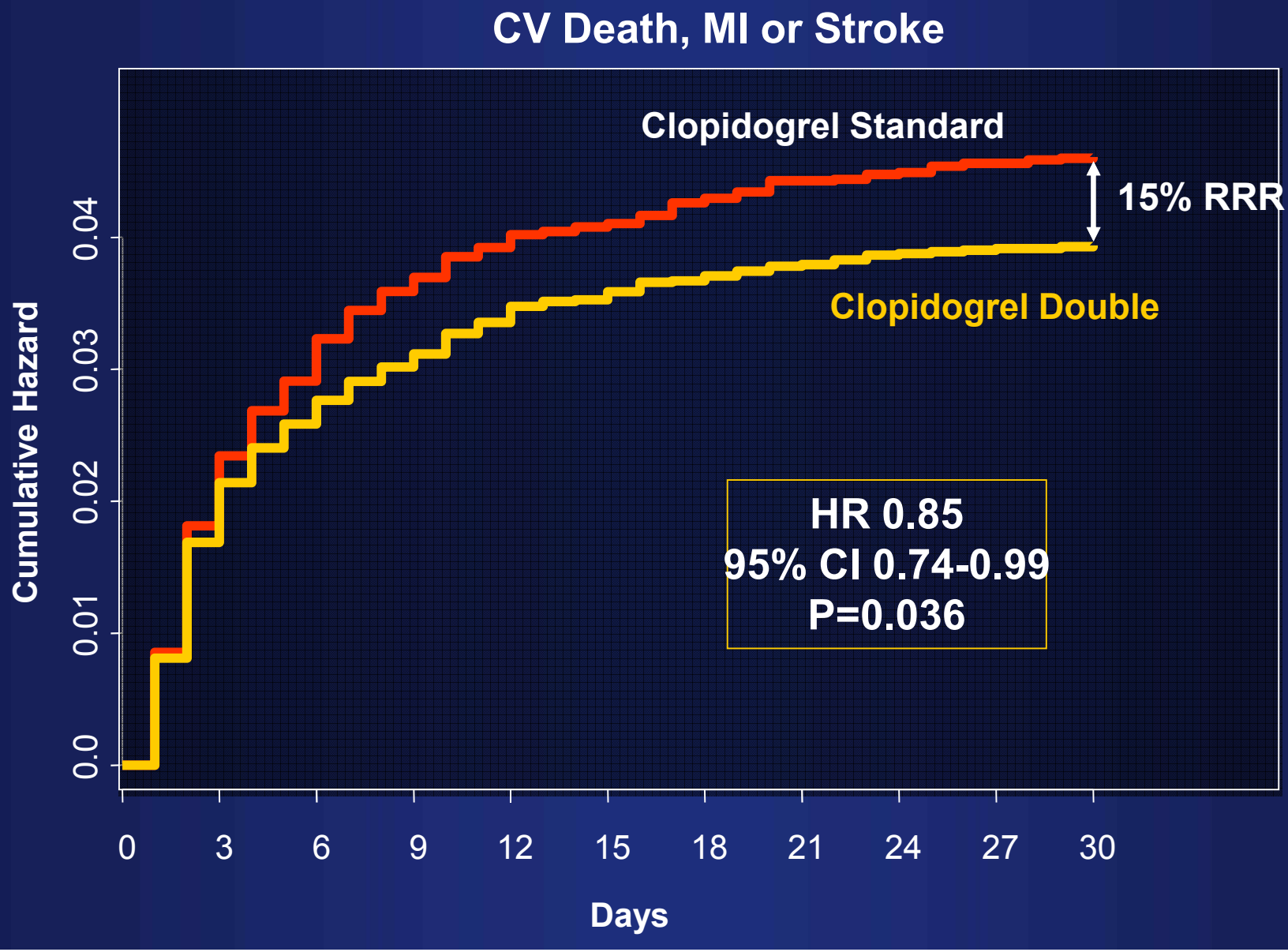
Complete Followup 99.8%

CURRENT

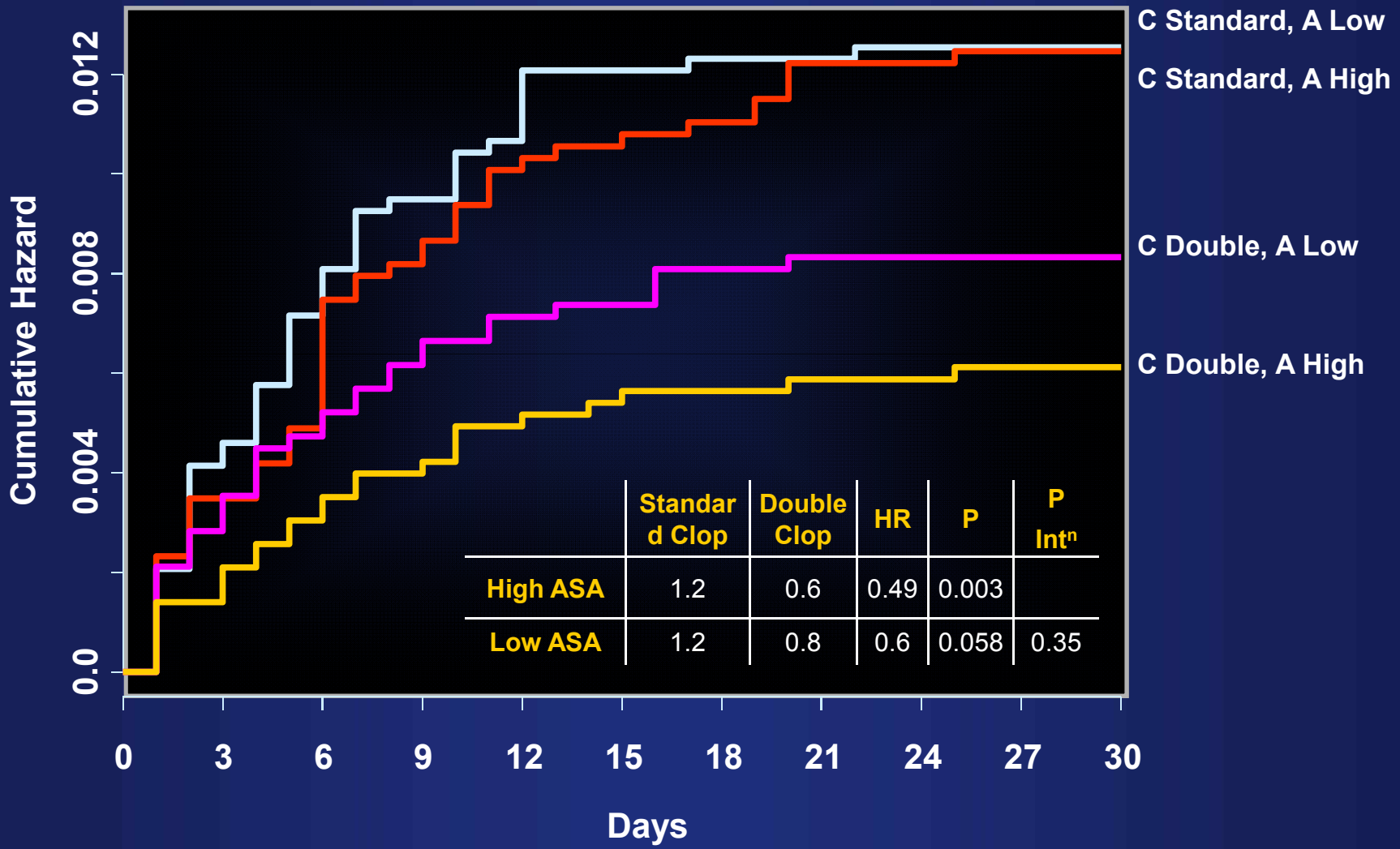
Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis (Angio confir



Clopidogrel: Double vs Standard Dose
Primary Outcome: PCI Patients



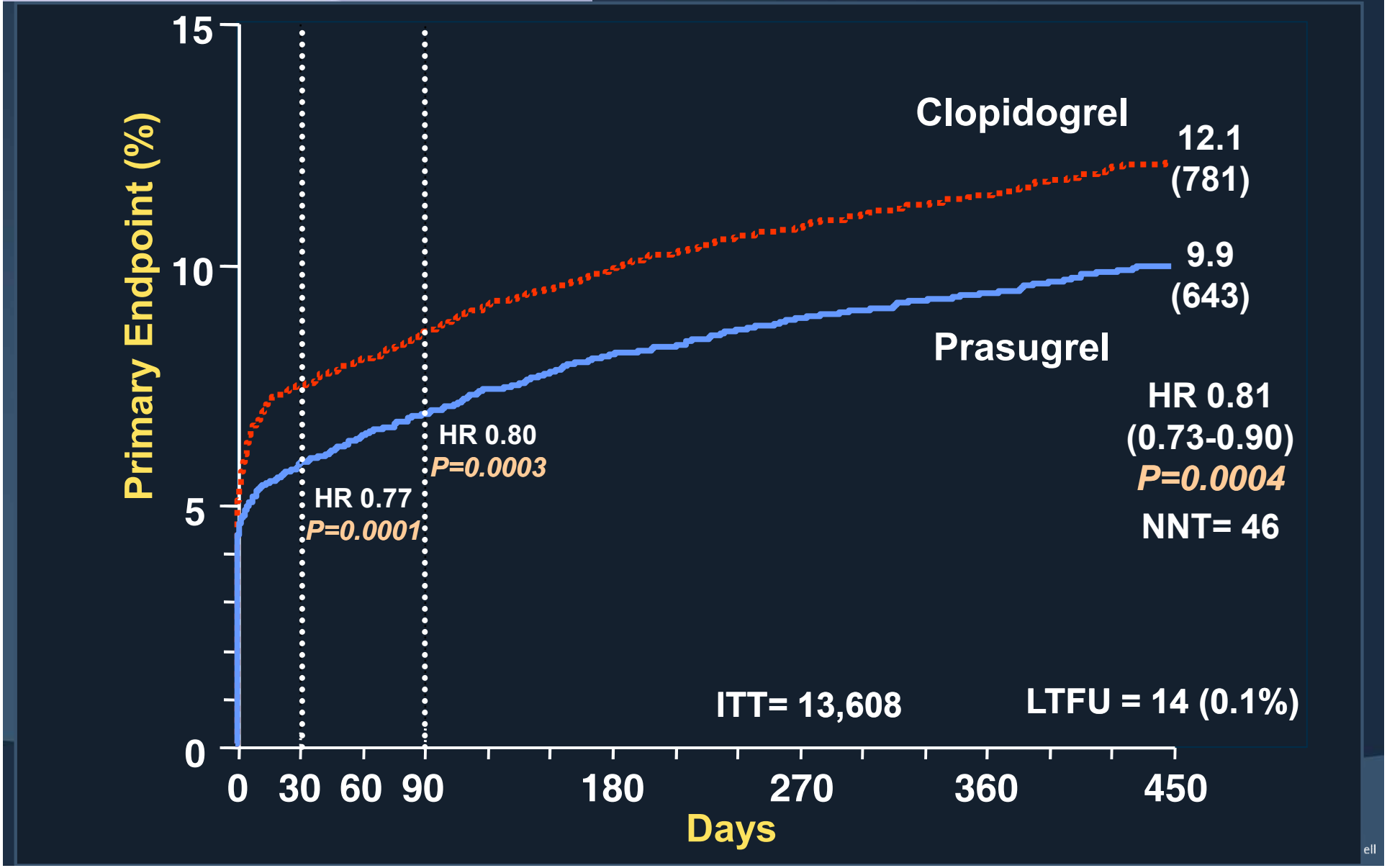
Definite Stent Thrombosis in 4 Groups (Angiographically Proven)



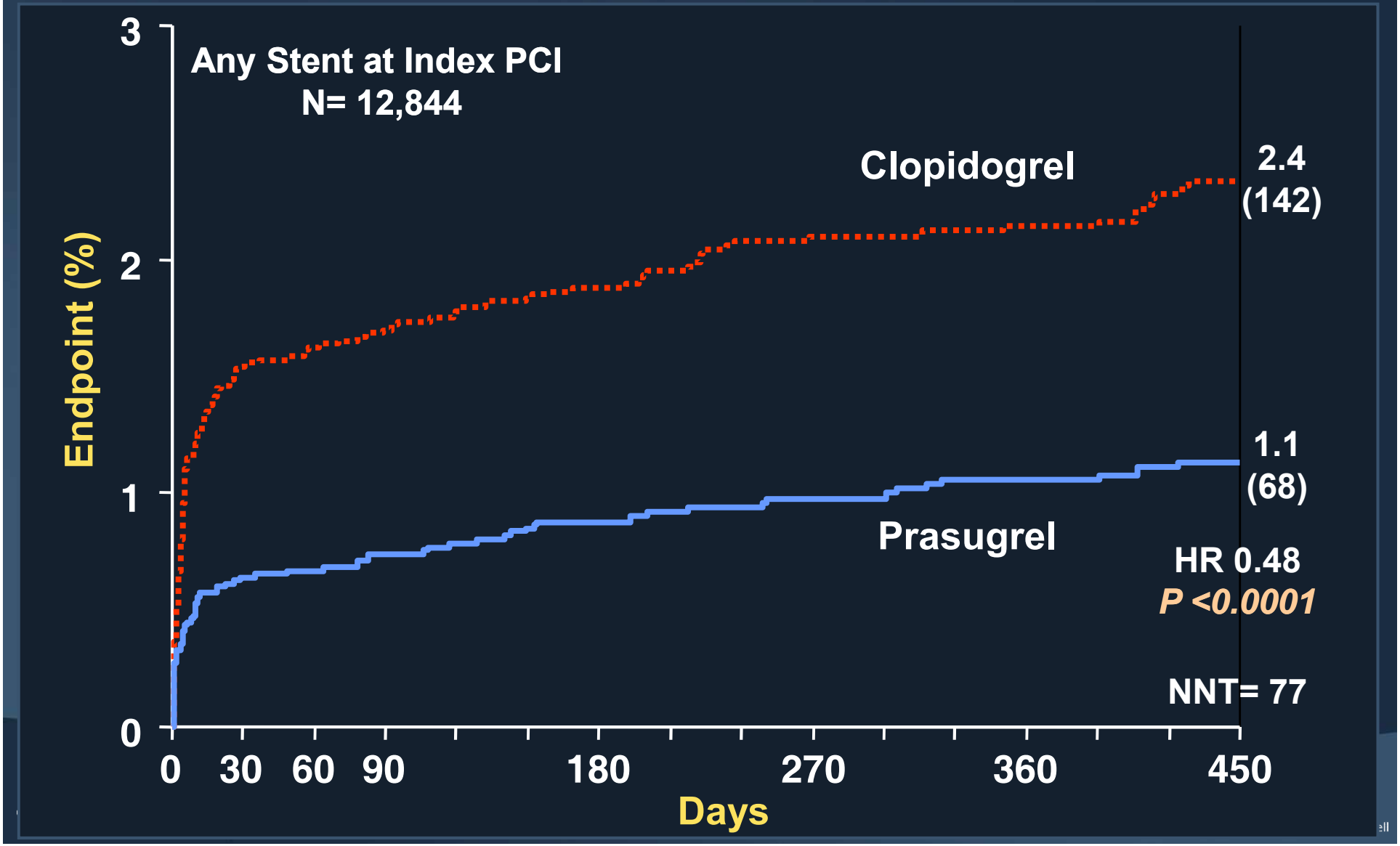
	Standard Clop	Double Clop	HR	P	P Int^n
High ASA	1.2	0.6	0.49	0.003	
Low ASA	1.2	0.8	0.6	0.058	0.35

TRITON TIMI-38

Primary Endpoint CV Death,MI,Stroke



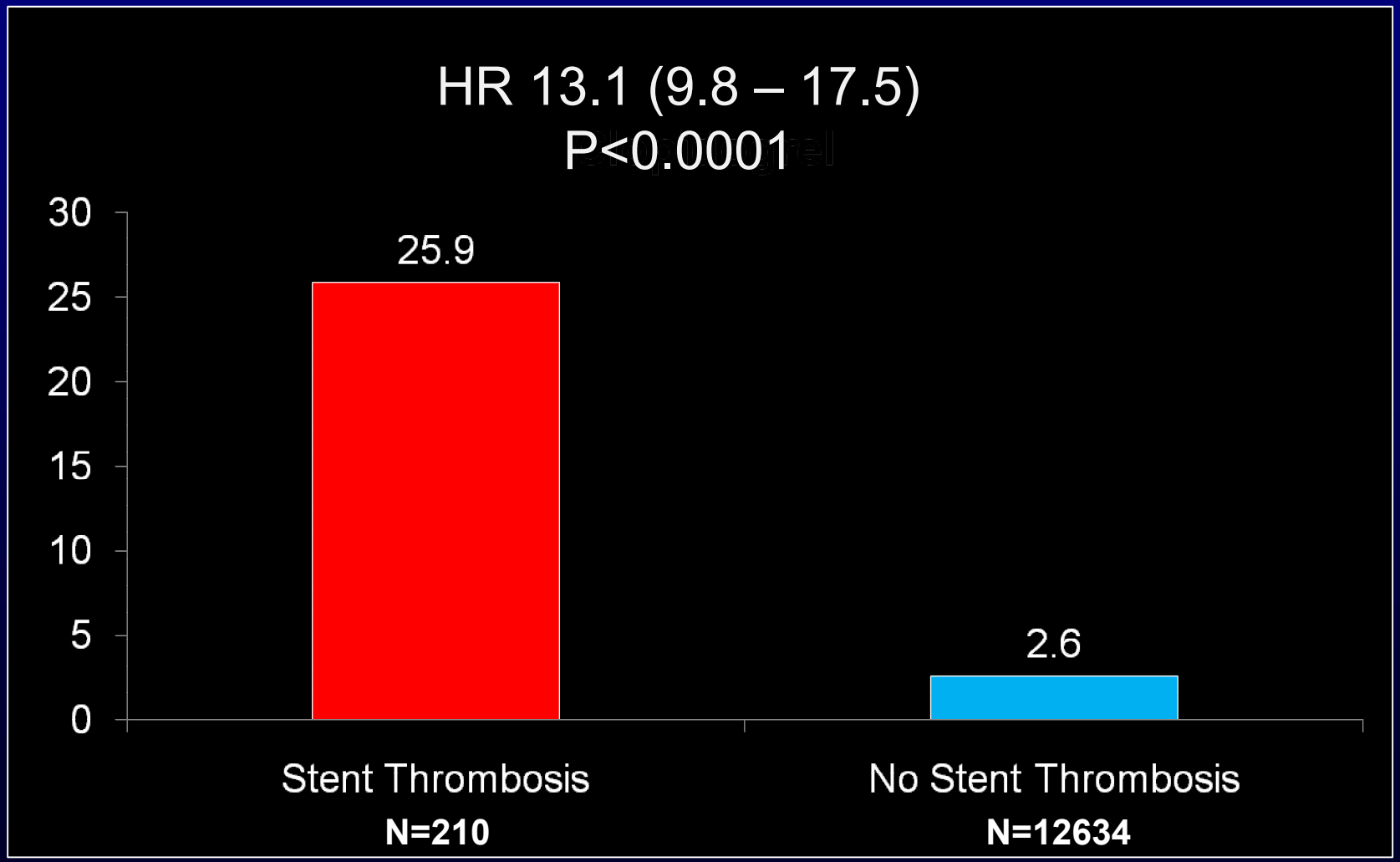
Stent Thrombosis (ARC Definite + Probable)



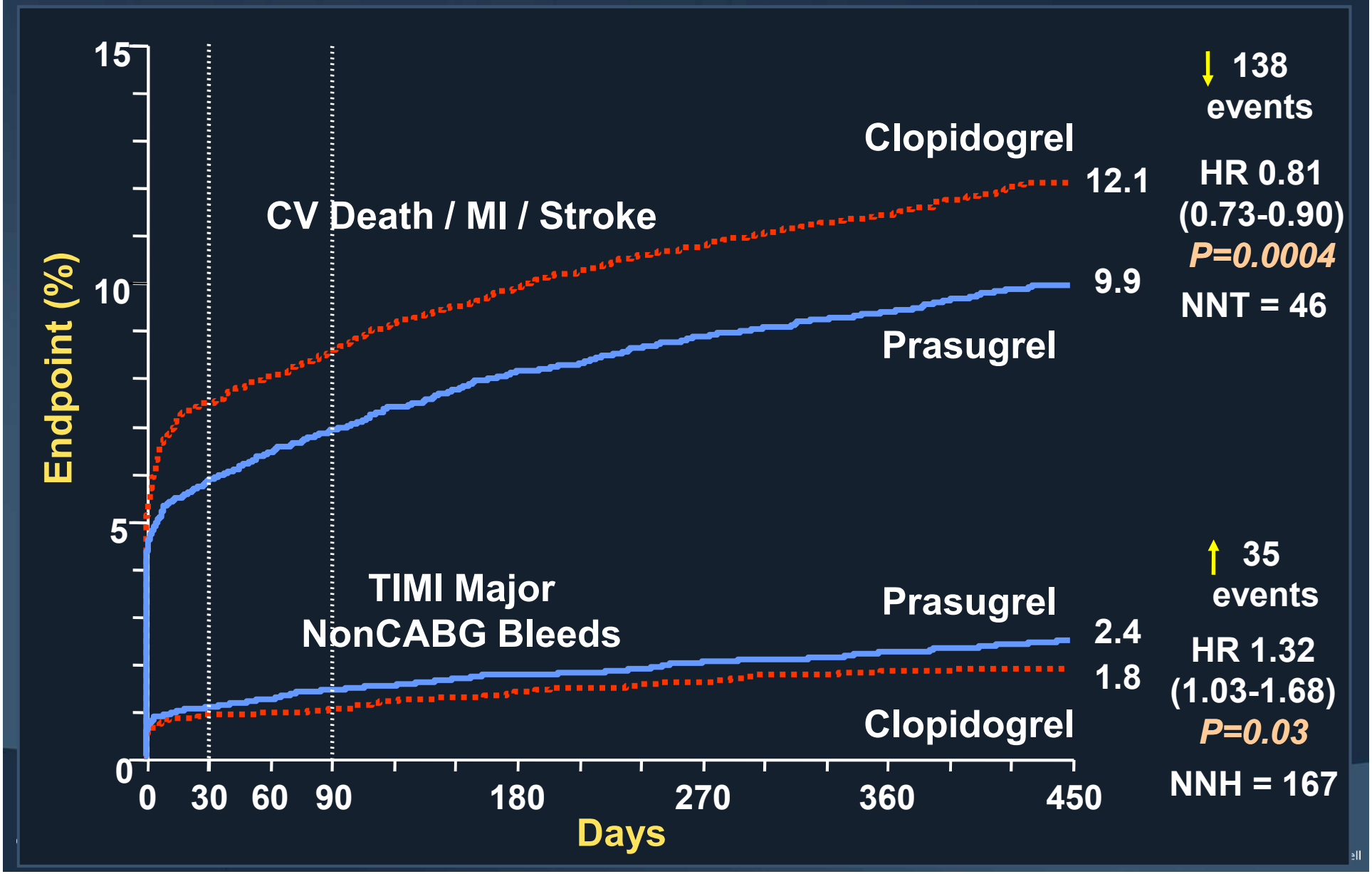
TRÎTON TIMI·38
STENT ANALYSIS

Death Following ST

Mortality During Follow up (%) Post-Stent Thrombosis

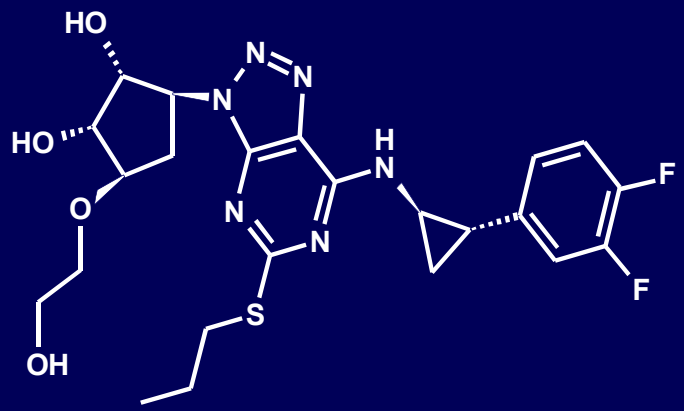


Balance of Efficacy and Safety



Ticagrelor (AZD 6140): an oral reversible $P2Y_{12}$ antagonist

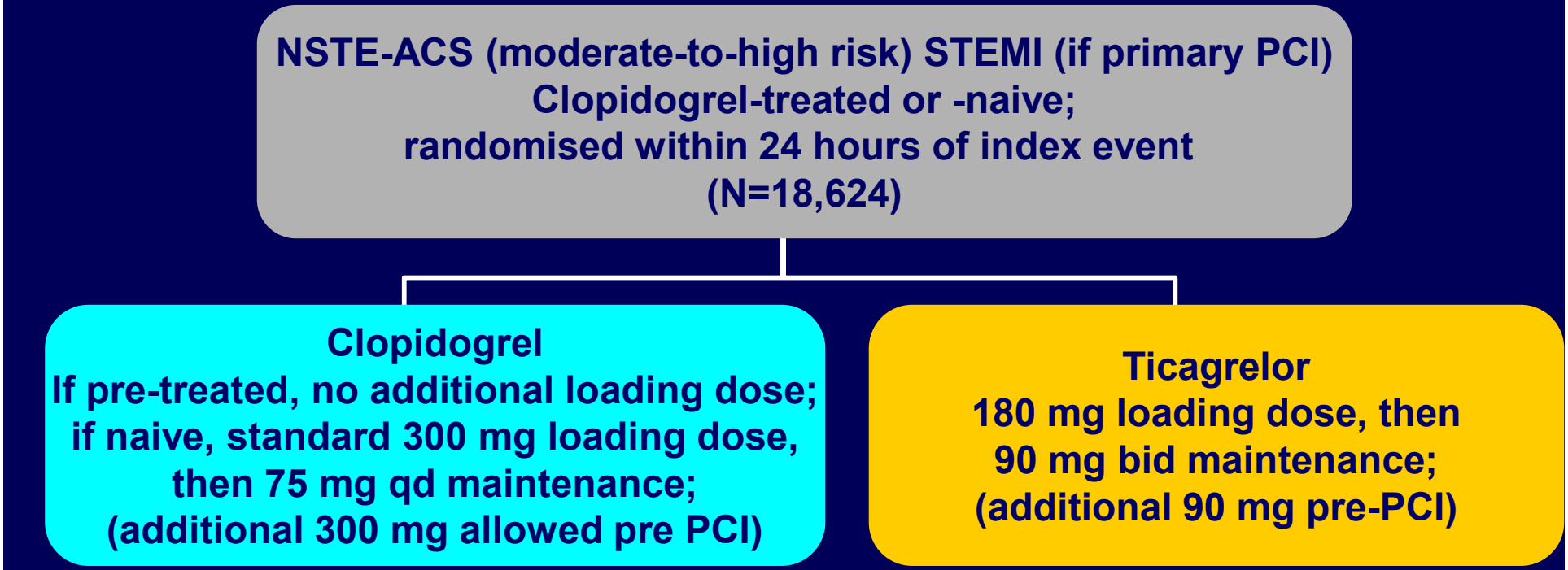
PLATO



Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel
- **Reversibly bound**
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets

PLATO study design



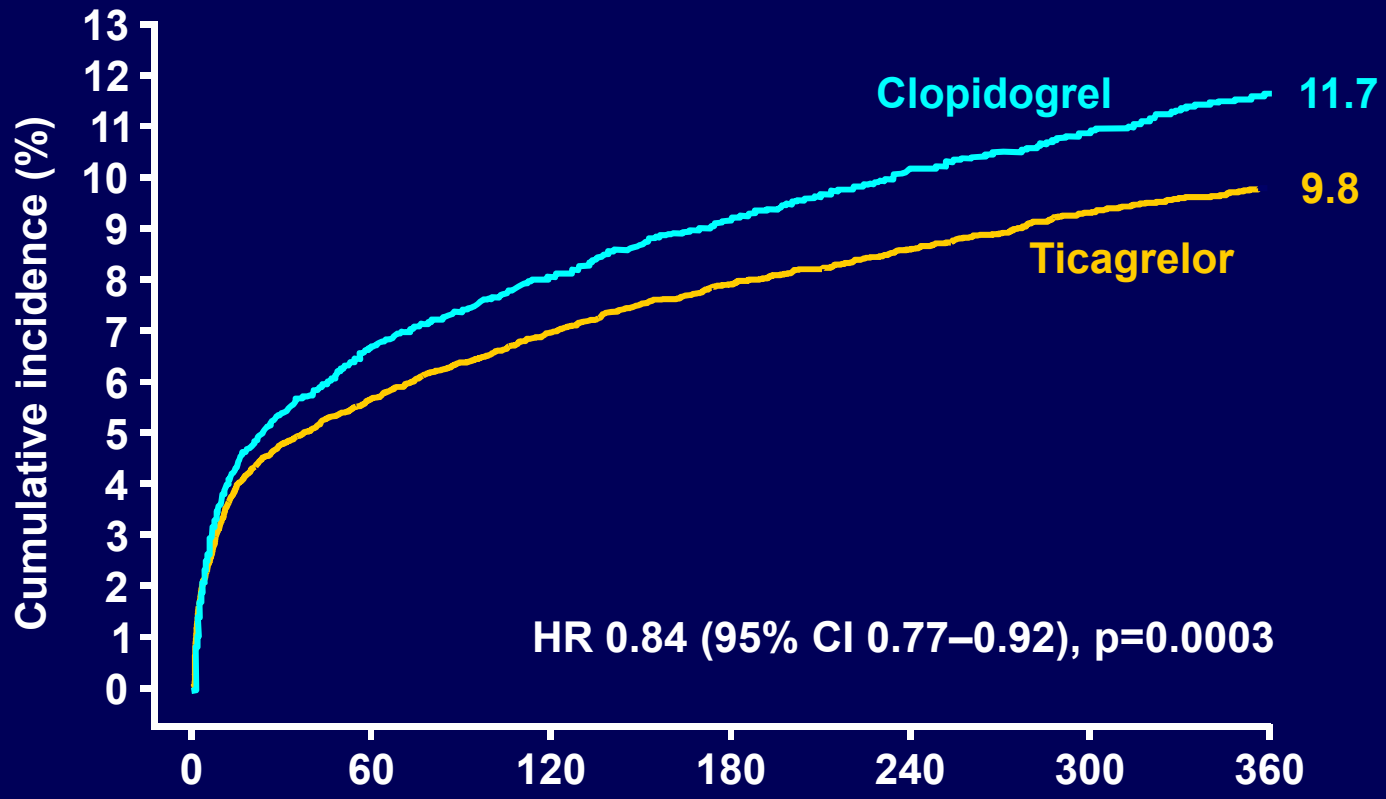
6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack

K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

PLATO



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

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Secondary efficacy endpoints over time

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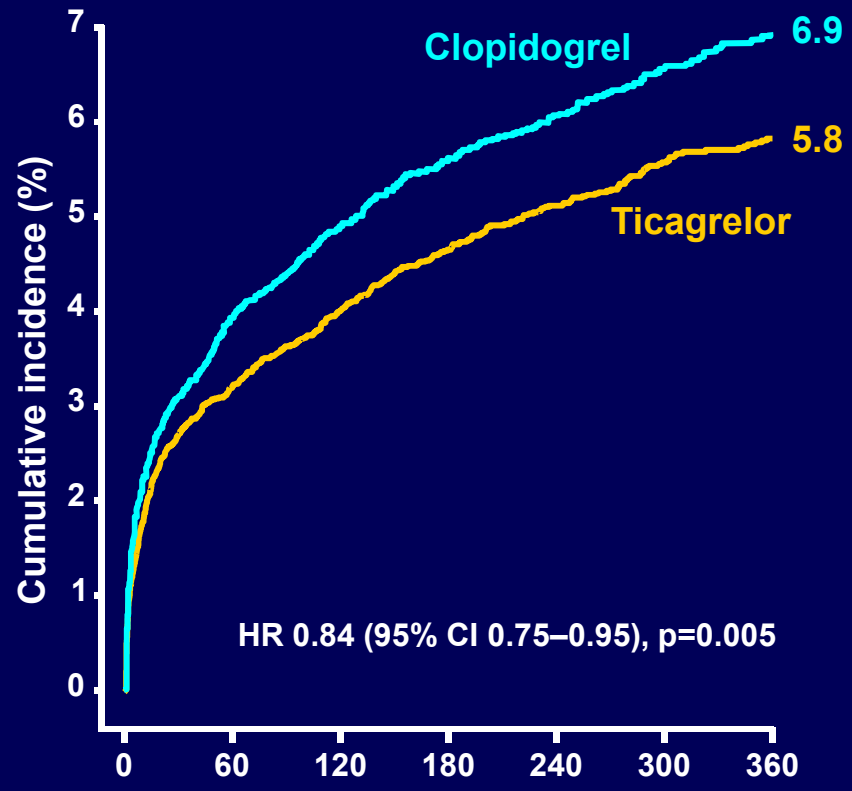
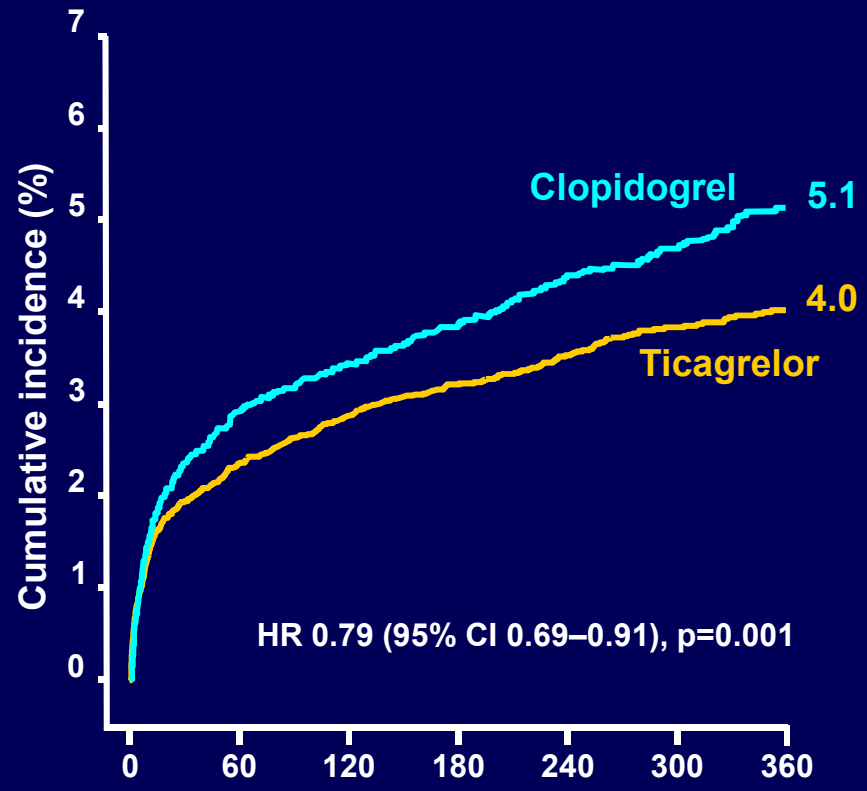
Myocardial infarction



No. at risk

Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

Cardiovascular death



	9,333	8,294	8,822	8,626	7119	5,482	4,419
	9,291	8,865	8,780	8,589	7079	5,441	4,364

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Stent thrombosis

(evaluated in patients with any stent during the study)

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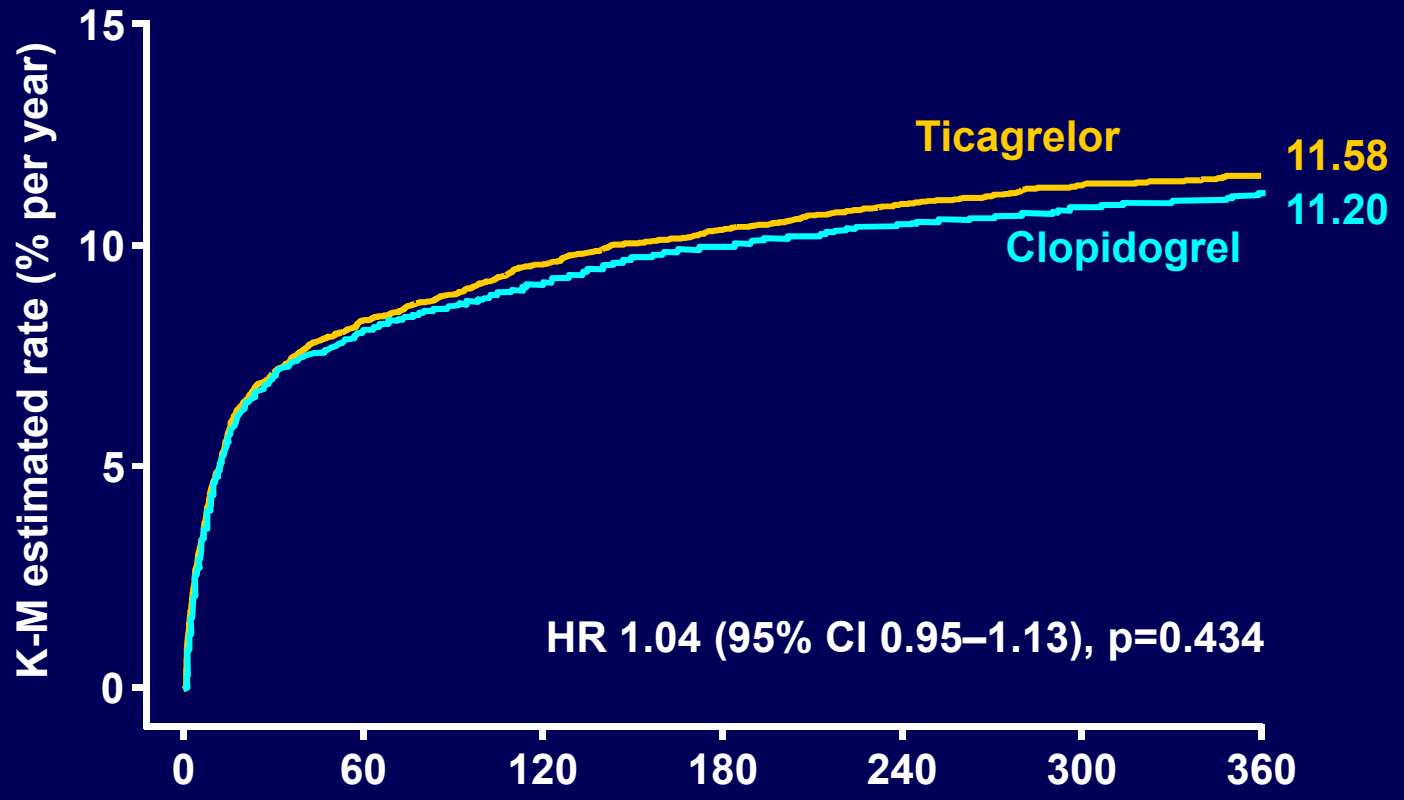
	Ticagrelor (n=5,640)	Clopidogrel (n=5,649)	HR (95% CI)	p value
Stent thrombosis, n (%)				
Definite	71 (1.3)	106 (1.9)	0.67 (0.50–0.91)	0.009
Probable or definite	118 (2.1)	158 (2.8)	0.75 (0.59–0.95)	0.02
Possible, probable, definite	155 (2.8)	202 (3.6)	0.77 (0.62–0.95)	0.01

*Time-at-risk is calculated from first stent insertion in the study or date of randomisation

Time to major bleeding – primary safety event

PLATO



No. at risk							
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

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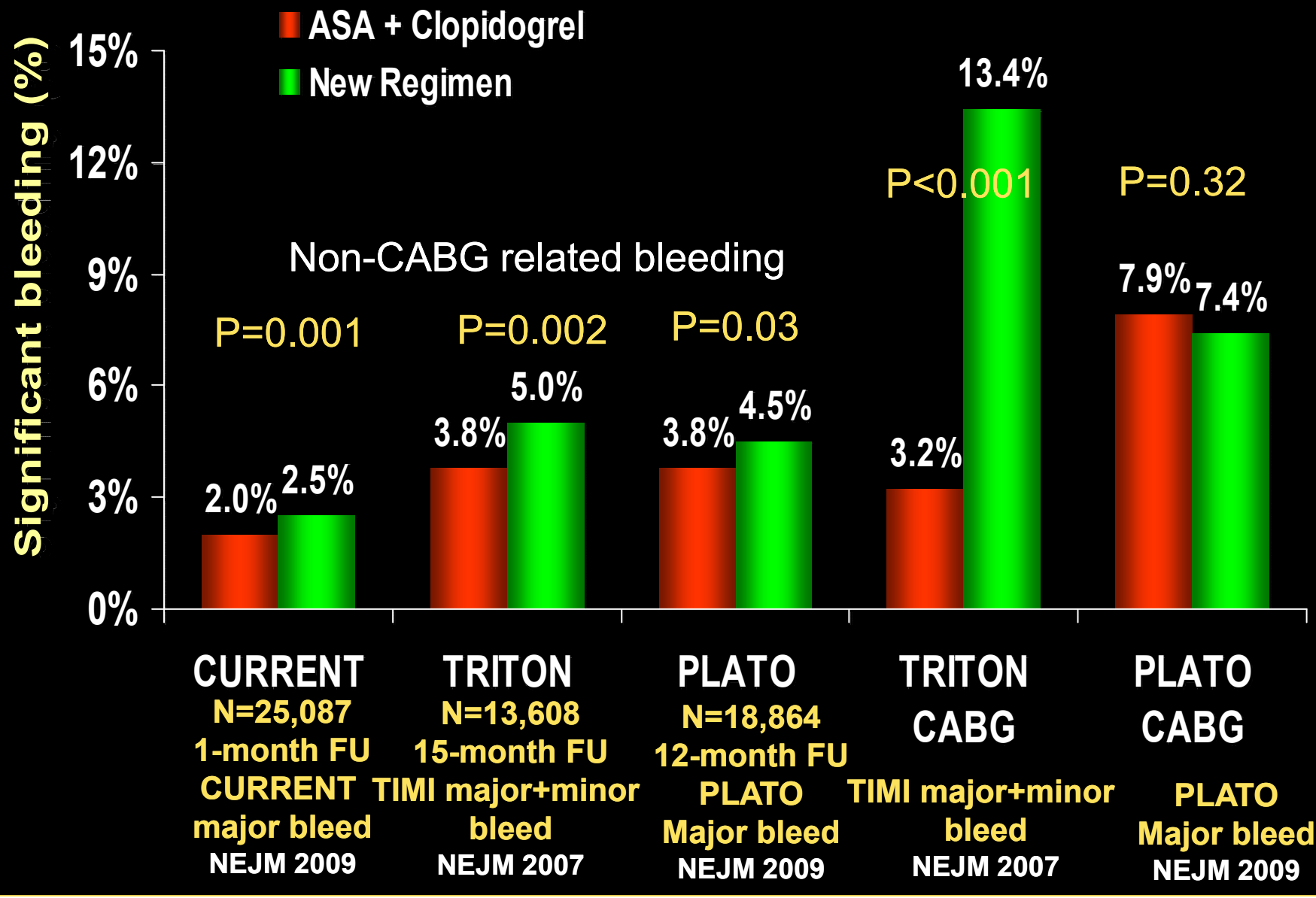
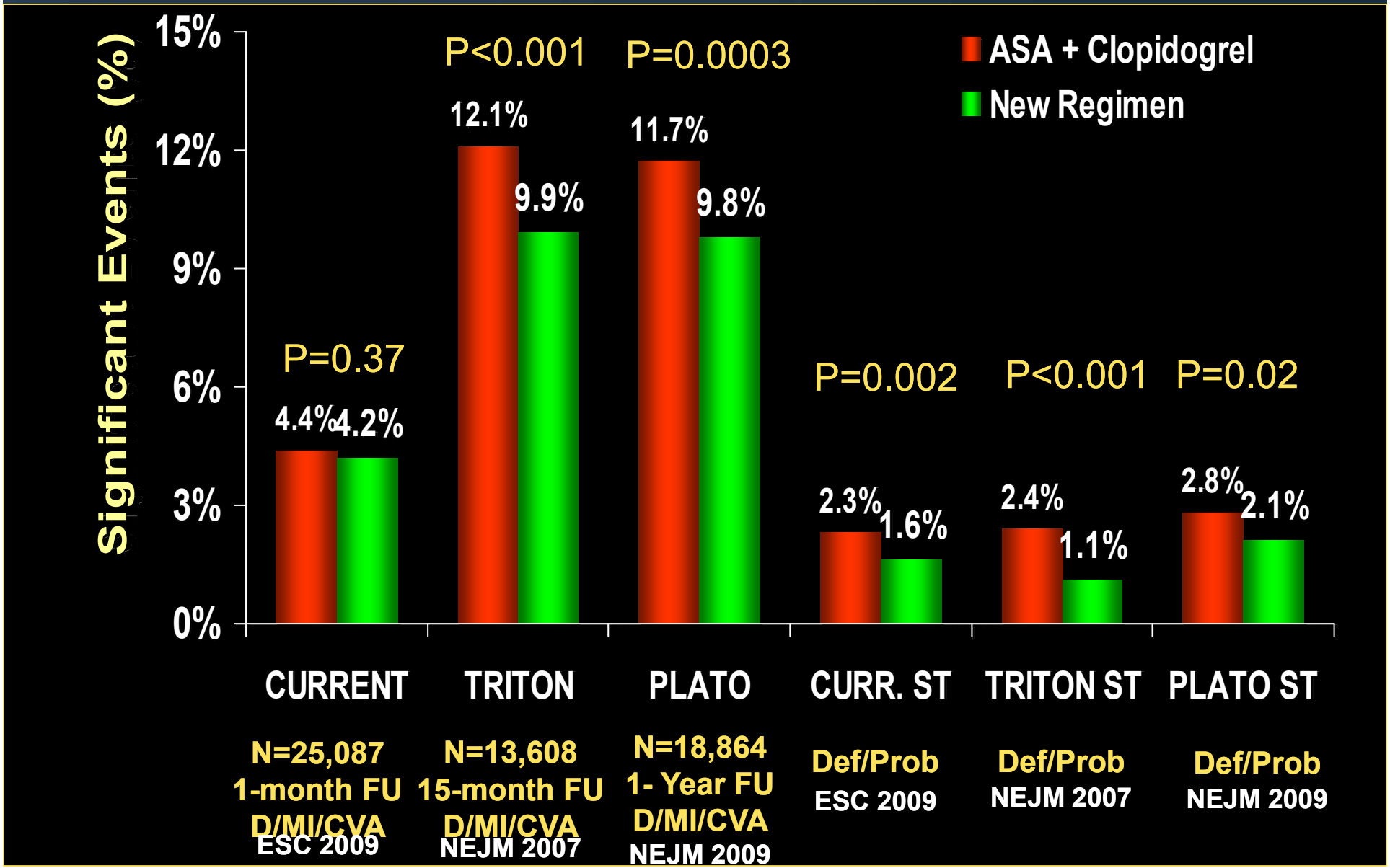
Safety of New DAPT Regimens

3 Active Controlled Trials (vs Standard Clop)



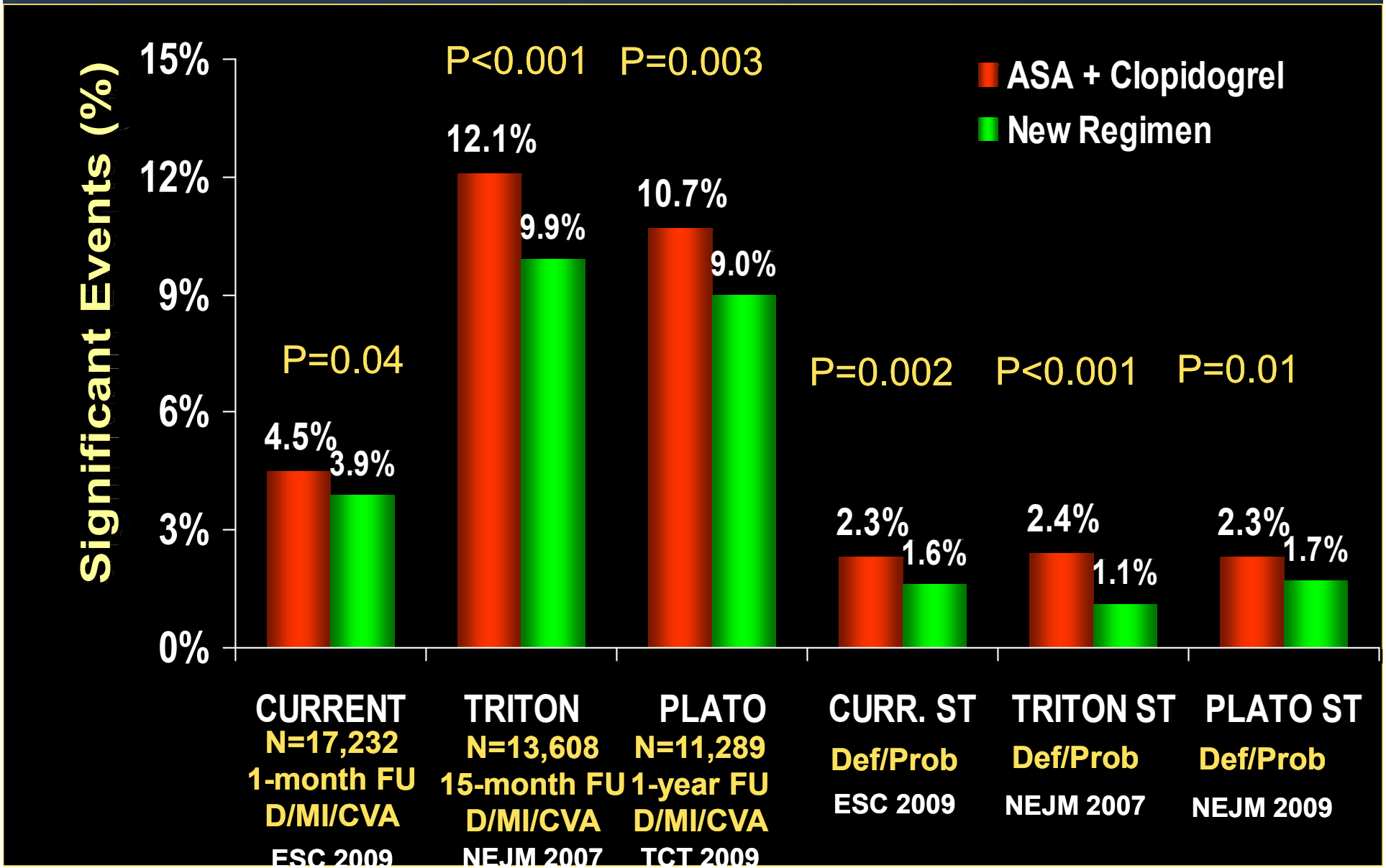
Efficacy of New DAPT Rx in ACS

3 Active Controlled Trials (vs Standard Clop)

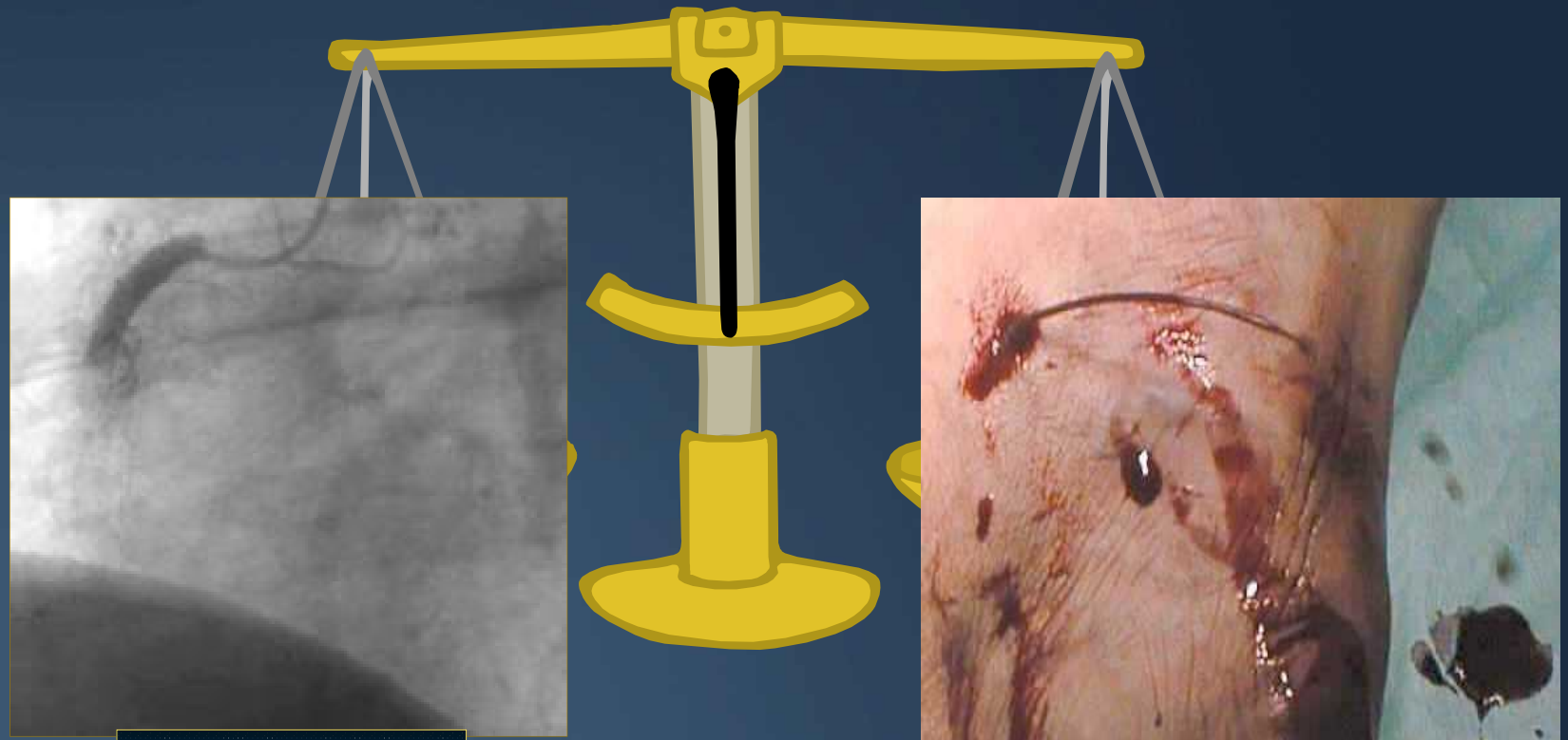


Efficacy of New DAPT Rx: ACS+PCI

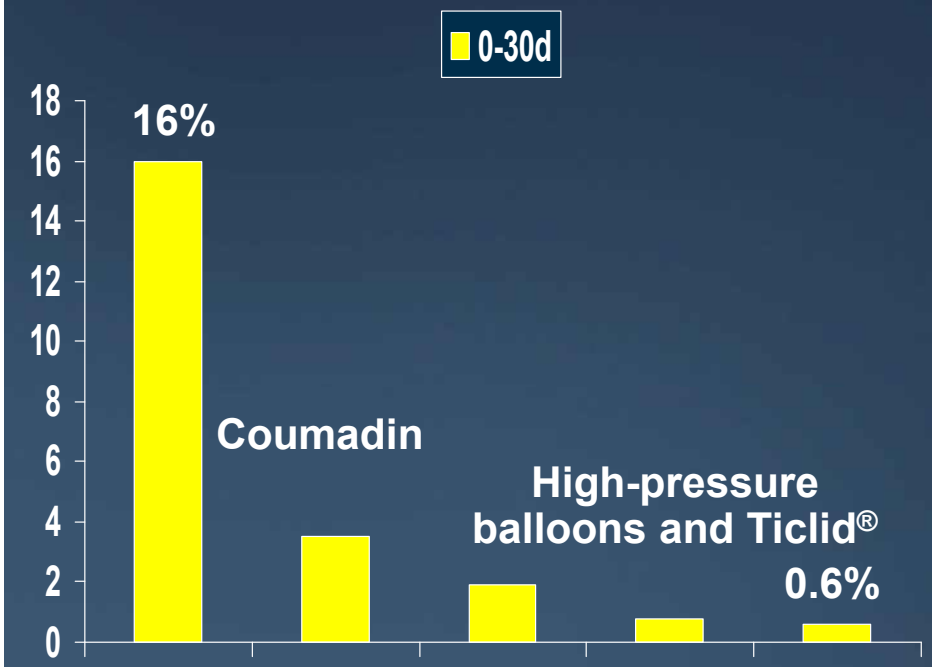
3 Active Controlled Trials (vs Standard Clop)



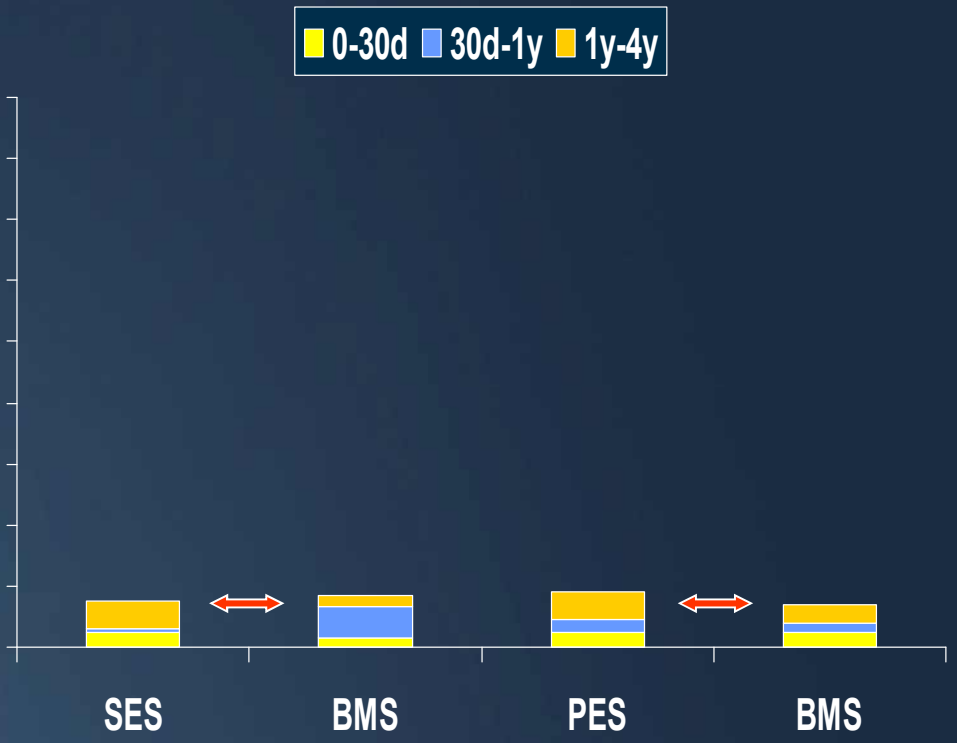
How will these results change the landscape?



Stent thrombosis:
Past and present trial results



30 day results
BMS Trials 1991-1997

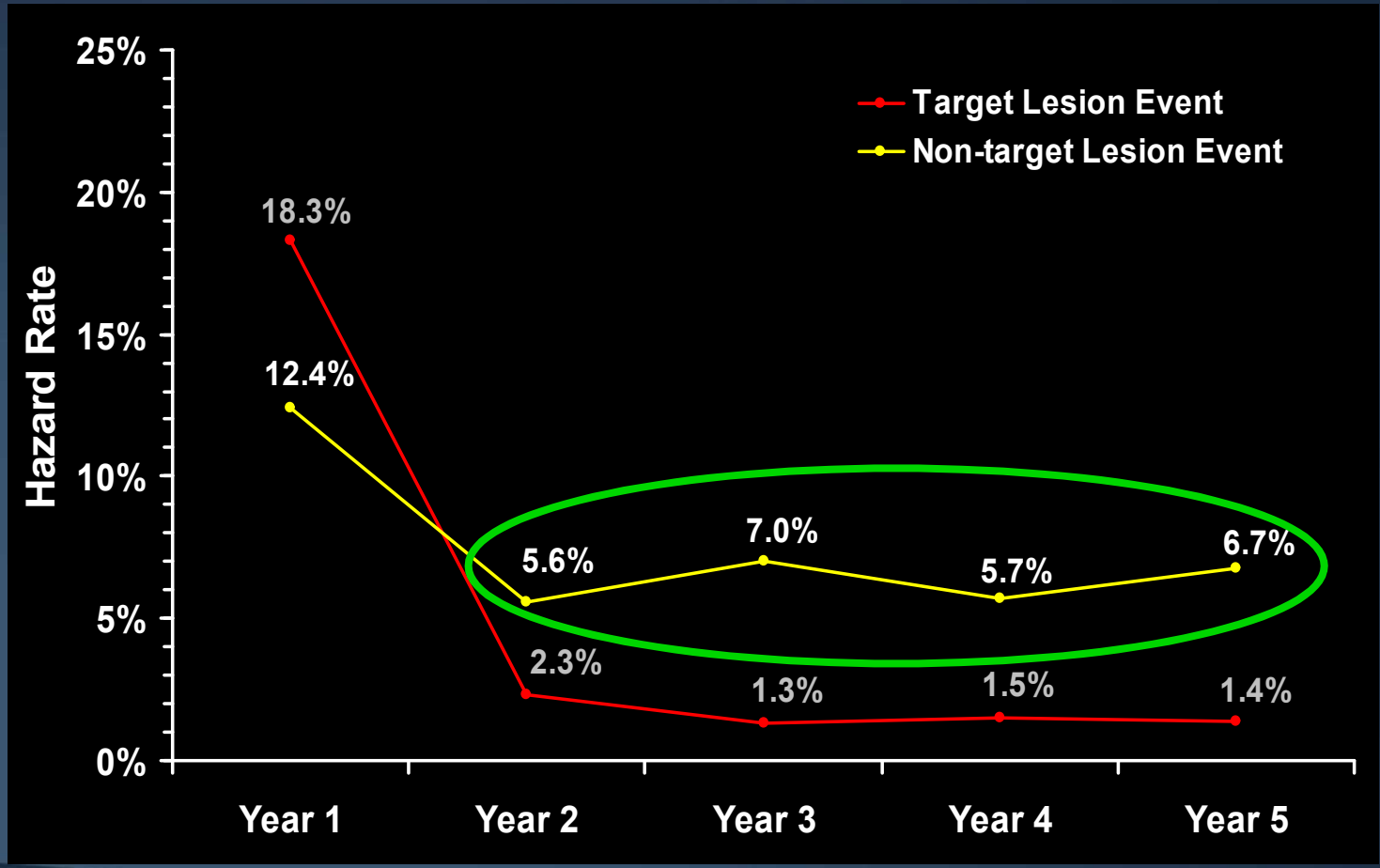


4 year results definite and probable ARC
Pooled DES vs BMS Trials 2002-2006

Schatz et al. *Circulation*.1991;83:148; Fischman et al. *N Engl J Med.* 1994;331496; Colombo et al. *Circulation*. 1995;91:1676; Schömig et al *Circulation*.1994,90:2716; Leon et al. *N Engl J Med*. 1998;339:1665; Mauri et al *N Engl J Med*. 2007;356:1020

Non Target Lesion Events outnumber stent specific outcomes in long term follow up

HCRI database N=6186 with complete 5y follow up



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Cutlip et al. Circulation 2004; 110: 1226–1230.

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NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Stent thrombosis accounts for a minority of clinical events

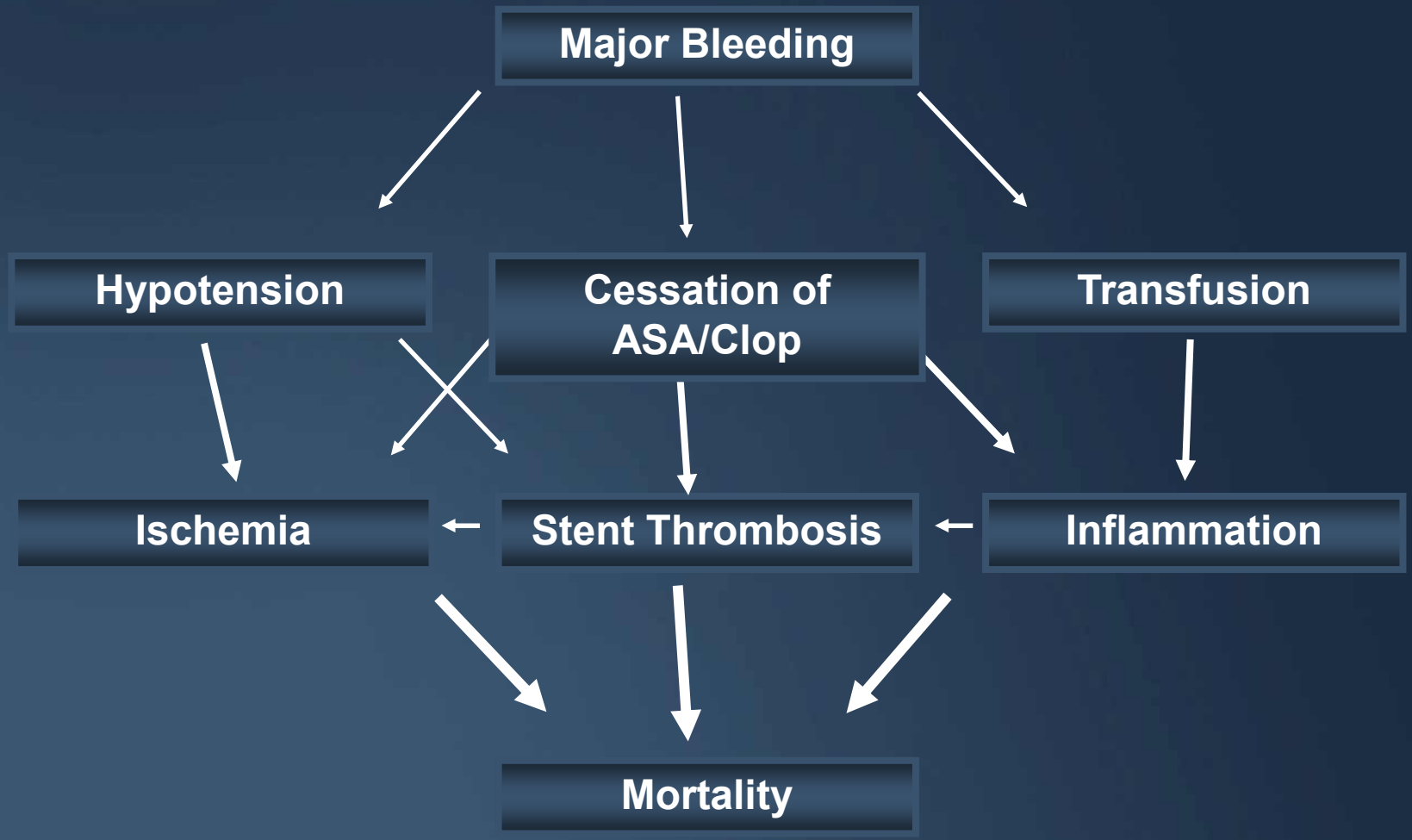
	SES	BMS	PES	BMS
Death	57 (6.7%)	45 (5.3%)	86 (6.1%)	92 (6.6%)
ST Death	4 (0.5%)	5 (0.6%)	7 (0.5%)	5 (0.4%)
ST death/ total death	**7%**	**11%**	**8%**	**6 %**

ST represents less about 10% of mortality, and a smaller proportion of death/MI composite.

Clinical endpoints may not distinguish differences in ST

Mauri, L. N Engl J Med 2007;356:1020-9.

Bleeding and Mortality

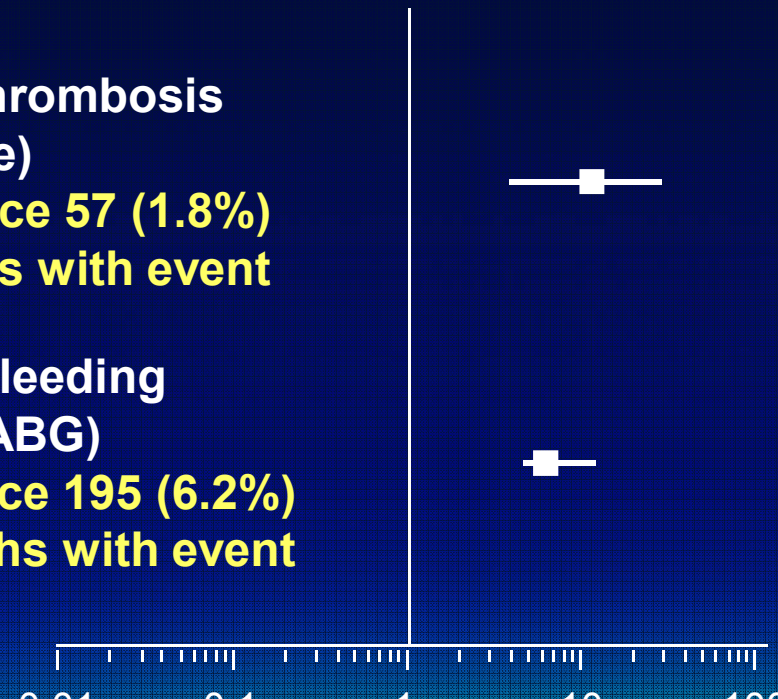


Bhatt DL. In Braunwald EB, Harrison's Online. 2005.

Time-updated covariate adjusted Cox model relating 30-day events to 30-day mortality

- Complete model in 3,124 pts with successfully implanted stents -

Risk Factor	HR [95% CI]	P-value	Attributable Deaths
Stent thrombosis (definite) Incidence 57 (1.8%) 5 deaths with event	10.62 [3.96, 28.48]	<0.001	4.5* [3.7, 4.8]
Major bleeding (non CABG) Incidence 195 (6.2%) 18 deaths with event	6.22 [3.33, 11.60]	<0.001	15.1** [12.6, 16.4]



*8.3% of 54 total deaths

**28.0% of 54 total deaths

C-statistic = 0.87. Attributable deaths = N deaths among pts with the time updated event (attribute) X (adj. HR – 1)/adj. HR

HORIZONSAMI

Definitions of Major/Severe Bleeding in Randomized Controlled Clinical Trials

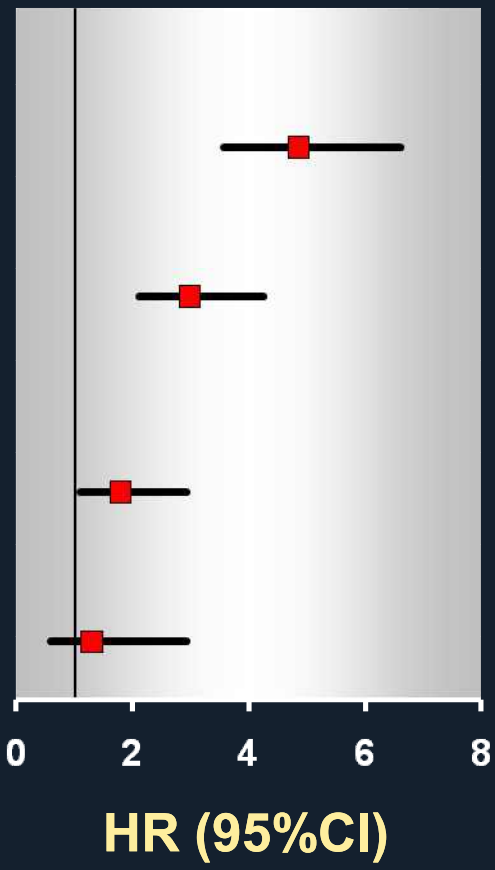
Type of bleeding	GUSTO	TIMI phase I	TIMI phase II	REPLACE-2	OASIS-5 ESSENCE	CURE	STEEPLE	ACUITY HORIZONS	PLATO
Intracranial/intracerebral	+	+	+	+	+	+	+	+	+
Intraocular	-	-	-	+	+	+	+	+	+
Retroperitoneal	-	-	-	+	+	+	+	+	-
Bleeding causing hemodynamic compromise	+	-	-	-	-	+	+	-	+
Cardiac tamponade	-	+	+	-	-	-	-	-	+
Bleeding requiring surgical intervention	-	-	-	-	-	+	+	+	+
Hematoma >5cm at the puncture site	-	-	-	-	-	-	-	+	-
Transfusion, units	≥1	≥1	≥1	≥2	≥2	≥2	≥1	≥1	≥4
Decrease in Hgb *with* overt bleeding, g/dL	-	≥5.0*	≥3.0	≥3.0	≥3.0	-	≥3.0	≥3.0	≥5.0
Decrease in Hgb *without* overt bleeding, g/dL	-	-	-	≥4.0	-	≥5.0	-	≥4.0	-

*Or decrease in Hct ≥15%

Influence of Bleeding Severity within 30 Days After PCI on the Risk of Death Over 1 Year

Baseline covariate-adjusted time-updated Cox multivariable model

Type of Bleed	HR (95% CI)	P-value	Attributable deaths within 1 yr
TIMI major bleed	4.85 (3.56-6.60)	<0.001	53
ACUITY major (non TIMI major) bleed with transfusion*	2.98 (2.10-4.24)	<0.001	40
ACUITY major (non TIMI major) bleed without transfusion*	1.79 (1.09-2.93)	0.02	17
Hematoma ≥5 cm only	1.30 (0.58-2.92)	0.53	6



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* Excluding hematomas if the only criteria
Each patient is represented only once according to their most severe bleed

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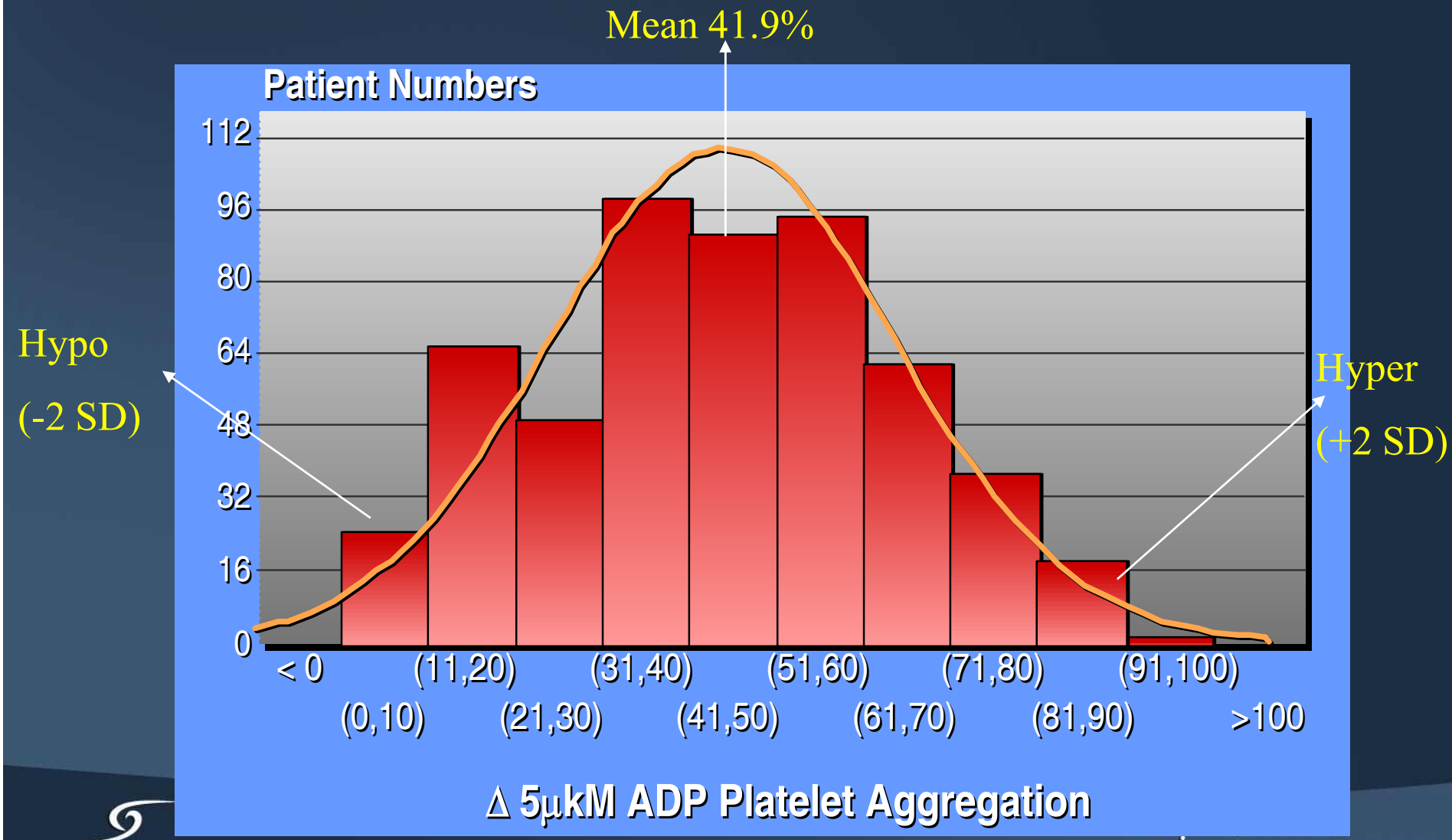
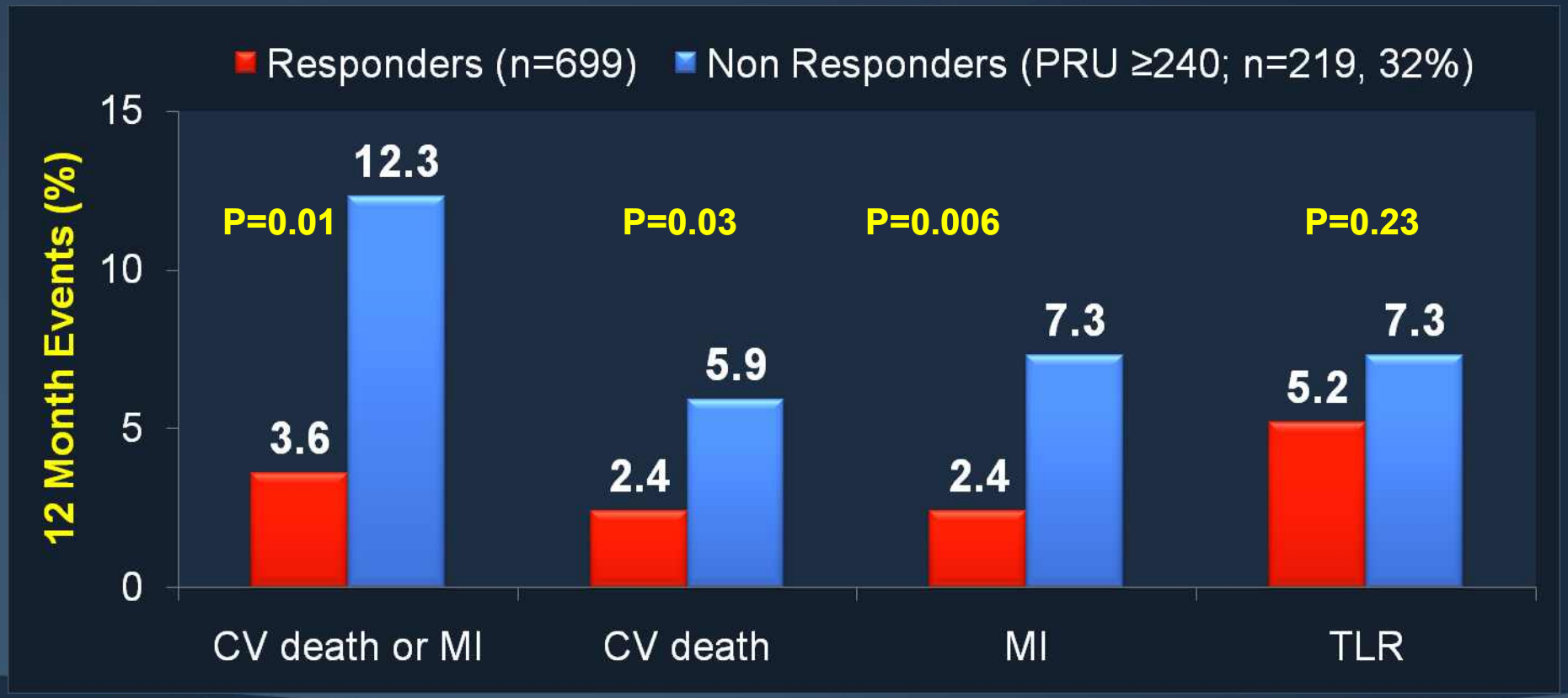
Change in Platelet Aggregation between Pre- and Post-Clopidogrel Time Points: Distribution



From Serebruany, et al. JACC 2005;45:246-251

Impact of clopidogrel hyporesponsiveness after stents: 683 pts with ACS after BMS or DES were tested by the VerifyNow P2Y12 assay within 24 hrs after 600 mg clopidogrel load. By ROC, pts with PRU ≥240 defined as nonresponders.



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Marcucci R et al. Circulation 2009;119:237-242

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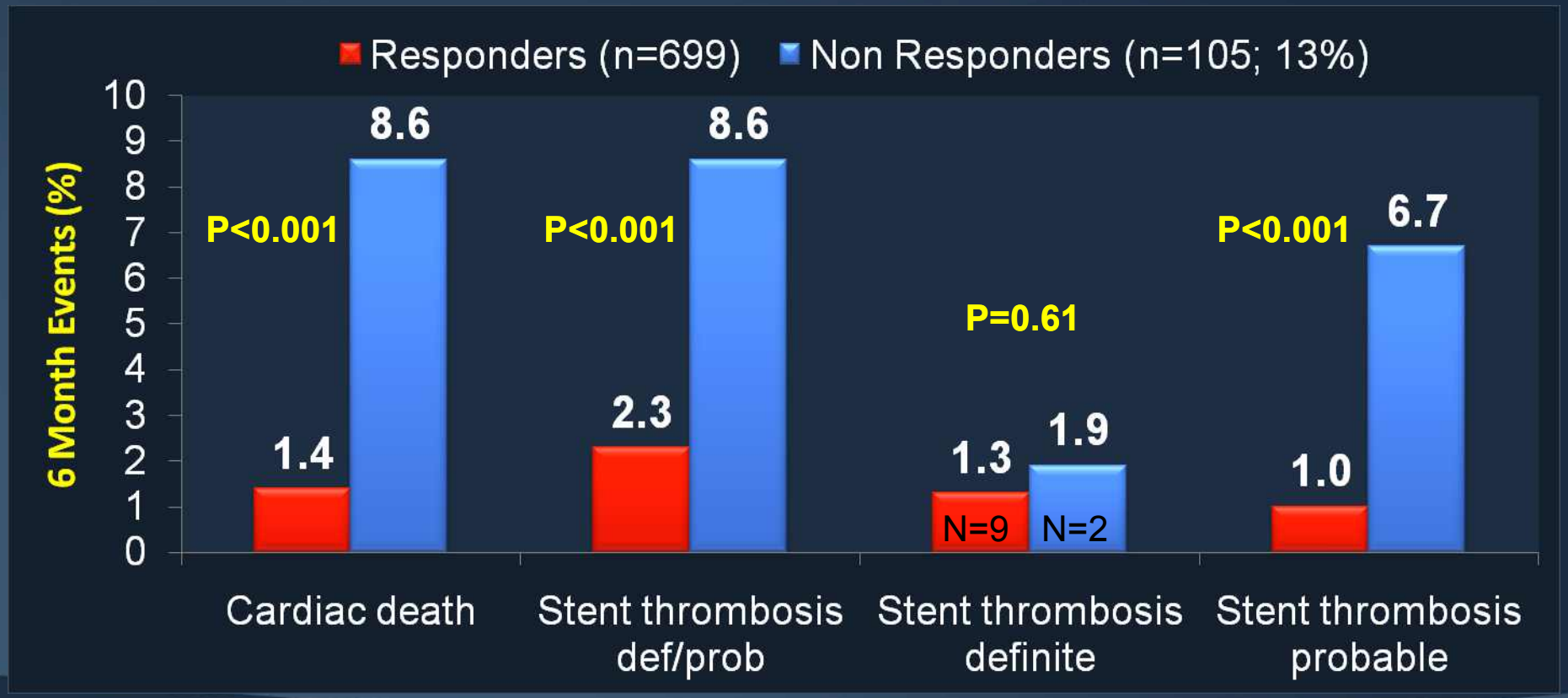
The University Hospital of Columbia and Cornell

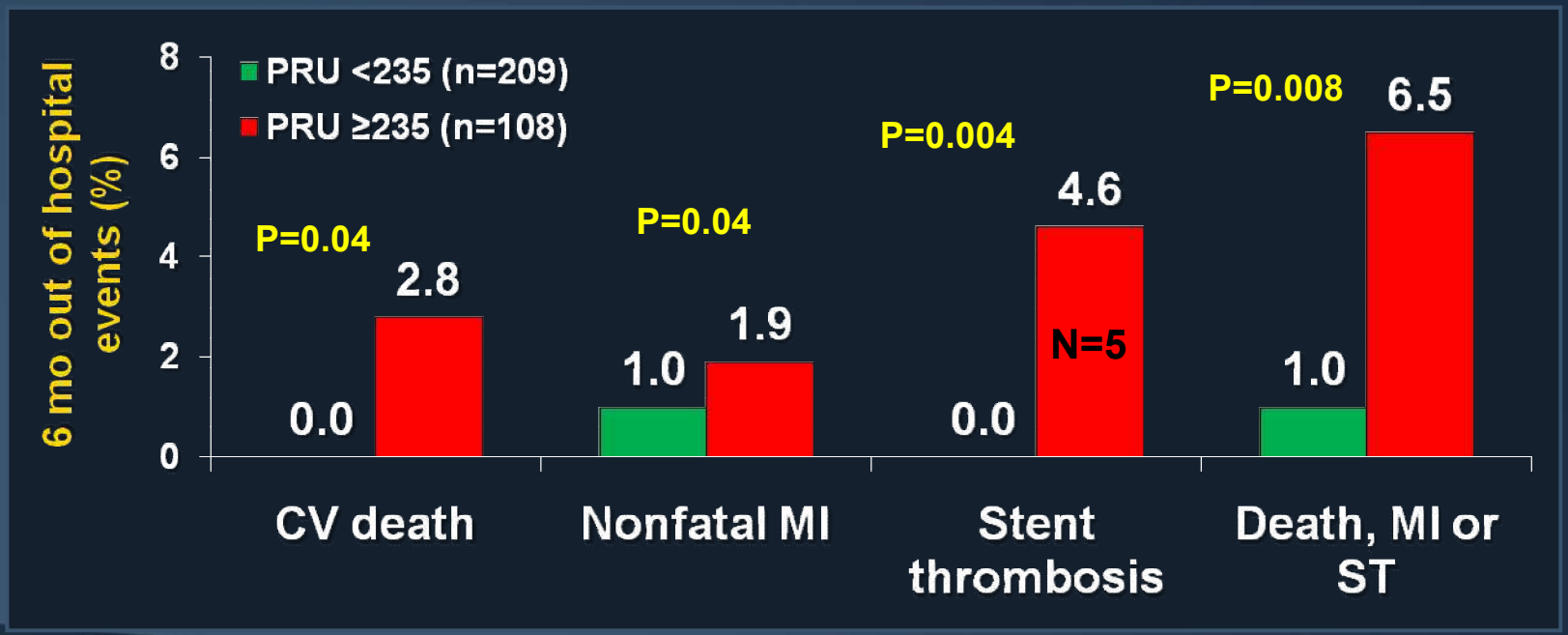
Impact of clopidogrel hyporesponsiveness after DES: 804 pts after PES or SES were tested by LTA 12-18 hrs after 600 mg clopidogrel load. Pts with platelet aggregation by 10 umol ADP ≥90th percentile of controls (70%) were defined as non responders.



Buonamici P et al. JACC 2007;49:2312–7

Impact of clopidogrel hyporesponsiveness after DES

Clopidogrel responsiveness in loaded pts was assessed in 380 pts receiving SES by the Accumetrics VerifyNow P2Y12 assay. Hyporesponsiveness was defined as post-treatment reactivity PRU ≥235 (~ the upper tertile) by ROC analysis to optimize prediction of 6 month MACE.



Price MJ et al. EHJ 2008;29:992–1000

ADAPT-DES

Assessment of **D**ual **A**nti**P**latelet **T**herapy with **D**rug-**E**luting **S**tents

11,000 – 15,000 pts

10-15 sites in US, Germany, Italy

↓

Aspirin: ≥300 mg oral ≥6 hrs or 324 mg chewed or 250 mg IV ≥30 mins prior to PCI

Clopidogrel: Assess ≥6' after 600 mg or ≥12' after 300 mg or ≥5d after 75 mg qd

GP IIb/IIIa inhibitor: Optional per standard of care, but washout required

↓

PCI with non investigational DES

(IVUS/VH substudy; n=3000)

↓

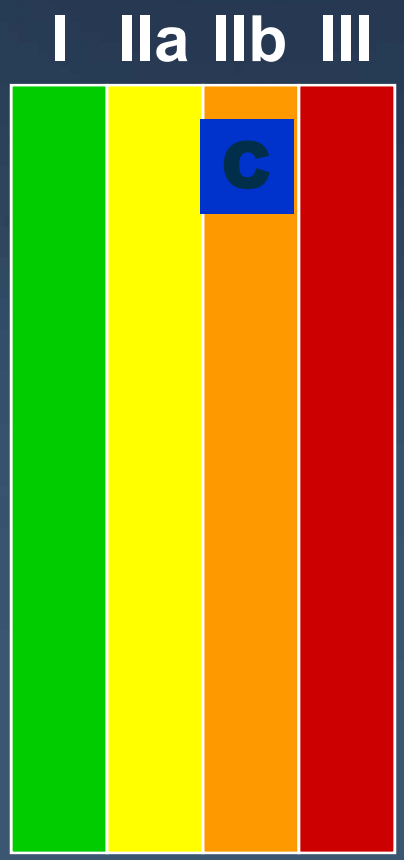
Assessment of platelet function: Accumetrics VerifyNow Aspirin, VerifyNow P2Y12, and VerifyNow IIb/IIIa assays (results blinded to investigators)

↓

Clinical FU ≥2 yrs (5 yrs max)

Angio core lab assessment all STs w/1:3 matching controls

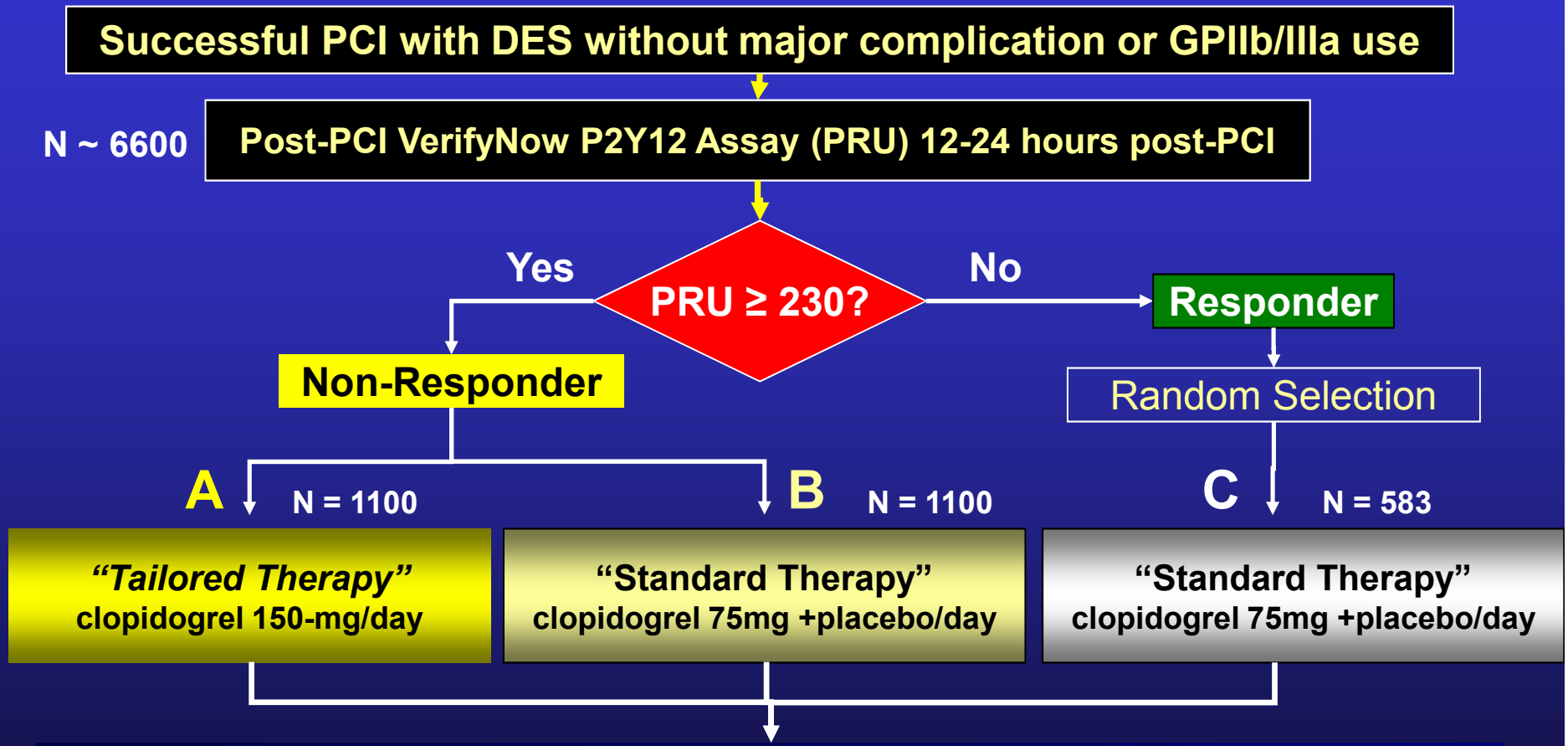
ACC/AHA/SCAI 2005 Guideline Update for PCI
Oral Anti-platelet Adjunctive Therapies



In patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcating left main, or last patent coronary vessel), platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg per day if less than 50% inhibition of platelet aggregation is demonstrated.

Adapted from Smith SC Jr, et al. Available at: www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf

GRAVITAS



Primary Endpt: 6 month CV Death, Non-Fatal MI, ARC Def/Prob Stent Thrombosis

Study PI: Matthew J. Price, MD

Coordinating Center: Scripps Advanced Clinical Trials

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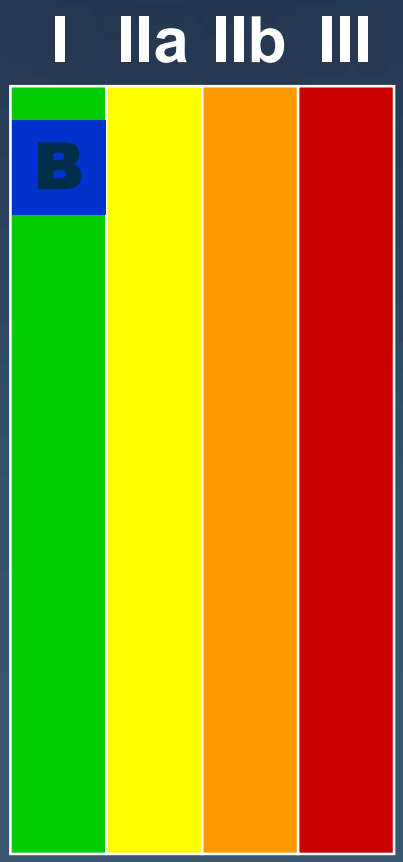


Clopidogrel

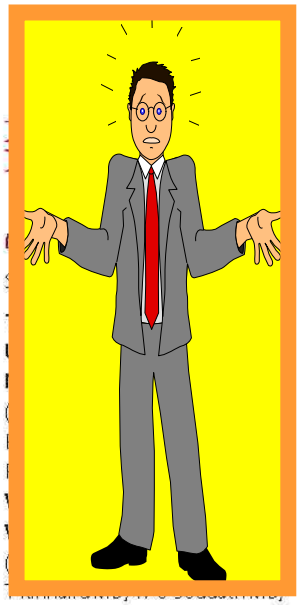
In patients who have undergone PCI, clopidogrel 75 mg daily should be given for at least 1 month after bare-metal stent implantation (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks), 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, and ideally up to 12 months in patients who are not at high risk of bleeding.

Adapted from Smith SC Jr, et al. Available at:
www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf

Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

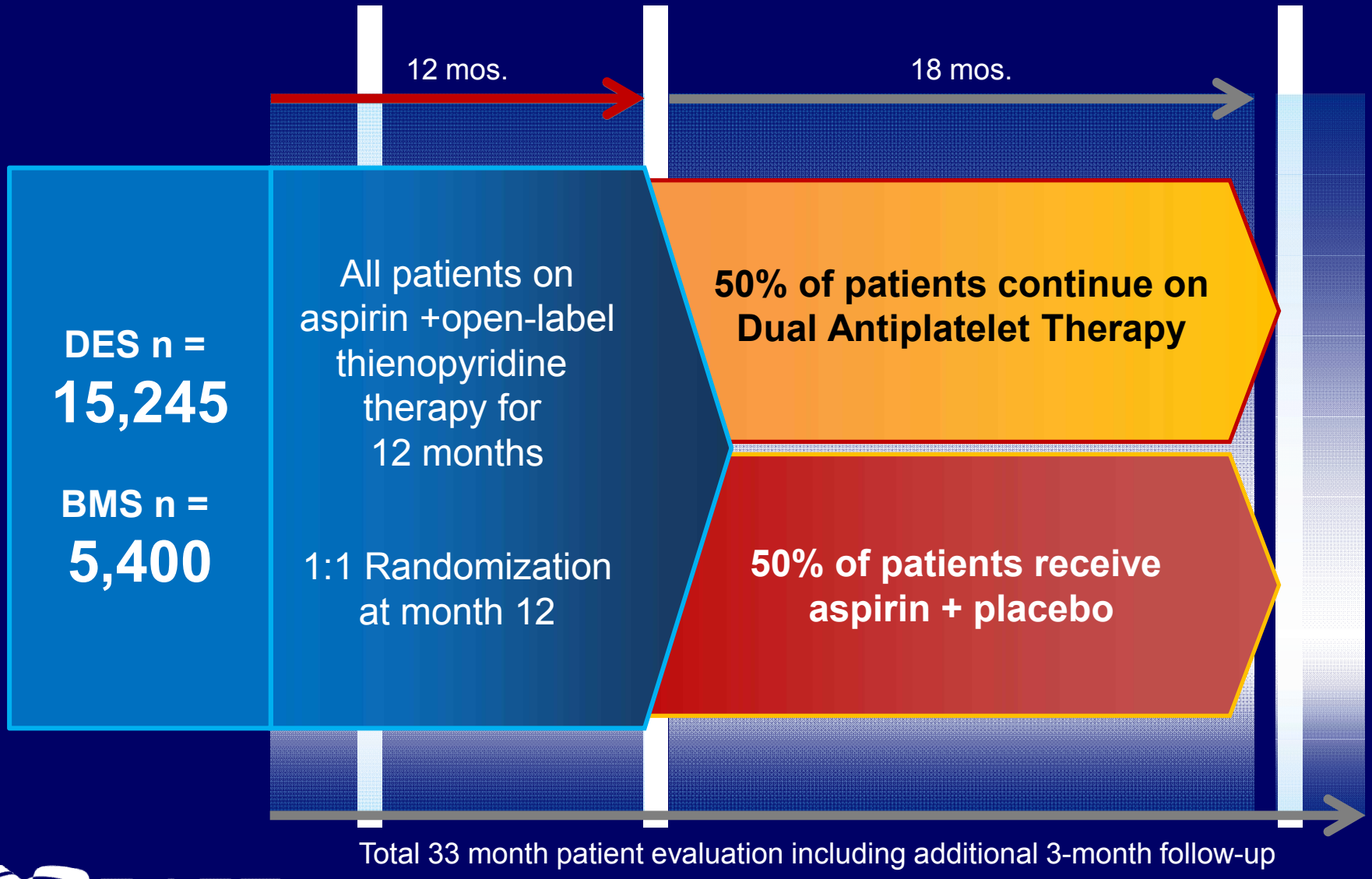
Eugène P McFadden, Eugenio Stabile, Evelyn Regar, Edouard Cheneau, Andrew T L Ong, Timothy Kinnaird, William O Suddath, Neil J Weissman, Rebecca Torguson, Kenneth M Kent, August D Pichard, Lowell F Satler, Ron Waksman, Patrick W Serruys

Although the safety profiles of coronary stents eluting sirolimus or paclitaxel do not seem to differ from those of bare metal stents in the short-to-medium term, concern has arisen about the potential for late stent thromboses related to delayed endothelialisation of the stent struts. We report four cases of angiographically-confirmed stent thrombosis that occurred late after elective implantation of polymer-based paxlitaxel-eluting (343 and 442 days) or sirolimus-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted. If confirmed in systematic long-term follow-up studies, our findings have potentially serious clinical implications.



Clopidogrel for >1-year?

DAPT Study Design



DAPT STUDY

MI, Bleeding and All-Cause Mortality

Large RCTs with significant reductions in death

Trial	MI	Major bleed*	Death (time)
OASIS-5 (n=20,078)			**6 months**
- Enoxaparin	4.1%	5.0%	6.5%
- Fondaparinux	3.9% -	3.1% ↓	5.8% ↓
HORIZONS (n=3,602)			**1 year**
- UFH/GPI	1.8%	10.8%	4.8%
- Bivalirudin	1.8% -	6.8% ↓↓	3.5% ↓
PLATO (n=18,624)			**1 year**
- Clopidogrel	6.9%	11.2%	5.9%
- Ticagrelor	5.8% ↓	11.6% -	4.5% ↓

Stone, GW NEJM 2010

*TIMI major + minor or protocol major

MI, Bleeding and All-Cause Mortality

Large RCTs without significant reductions in death

Trial	MI	Major bleed*	Death (time)
CHARISMA (n=15,603)			28 mos
- Placebo	2.0%	1.3%	4.8%
- Clopidogrel	1.9% -	1.7% -	4.8% -
CURRENT (n=25,807)			30 days (CV)
- LD Clopidogrel	2.2%	2.0%	2.2%
- HD Clopidogrel	1.9% -	2.5% -↑	2.1% -
SYNERGY (n=10,027)			1 year
- UFH	12.7%	7.6% ↑	7.3%
- Enoxaparin	11.7% -↓	9.1%	7.7% -
REPLACE-2 (n=6,010)			1 year
- UFH/GPI	6.2%	4.1% ↓	1.4%
- Bivalirudin	7.0% -↑	2.4%	1.0% -
ACUITY (n=9,215)			1 year
- UFH/GPI	4.9%	11.8% ↓	3.9%
- Bivalirudin	5.4% -↑	9.1%	3.8% -
CURE (N=12,562)			1 year
- Placebo	6.7% ↓	2.7% ↑	6.2%
- Clopidogrel	5.2%	3.7%	5.8% -
TRITON (n=13,608)			15 mos
- Clopidogrel	9.5% ↓	3.8% ↑	3.2%
- Prasugrel	7.3%	5.0%	3.0% -

Conclusions

- Pharmacologic treatment of patients undergoing PCI has improved over the years to decrease ischemic and bleeding complications
- As most drugs which ↓ ischemia also ↑ bleeding, the offsetting impact of adverse ischemic and hemorrhagic events must be carefully examined
- The net balance of ischemia and bleeding should be strongly considered when choosing APT for individual pts in an attempt to minimize complications