Antiplatelet Therapies in ACS

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• **Grant/Research Support to Institution**	• Sanofi/BMS- Significant • The Medicines Company
• **Consulting Fees/Honoraria**	• Astra Zeneca, Abbott Vascular, Regado Biosciences, Janssen

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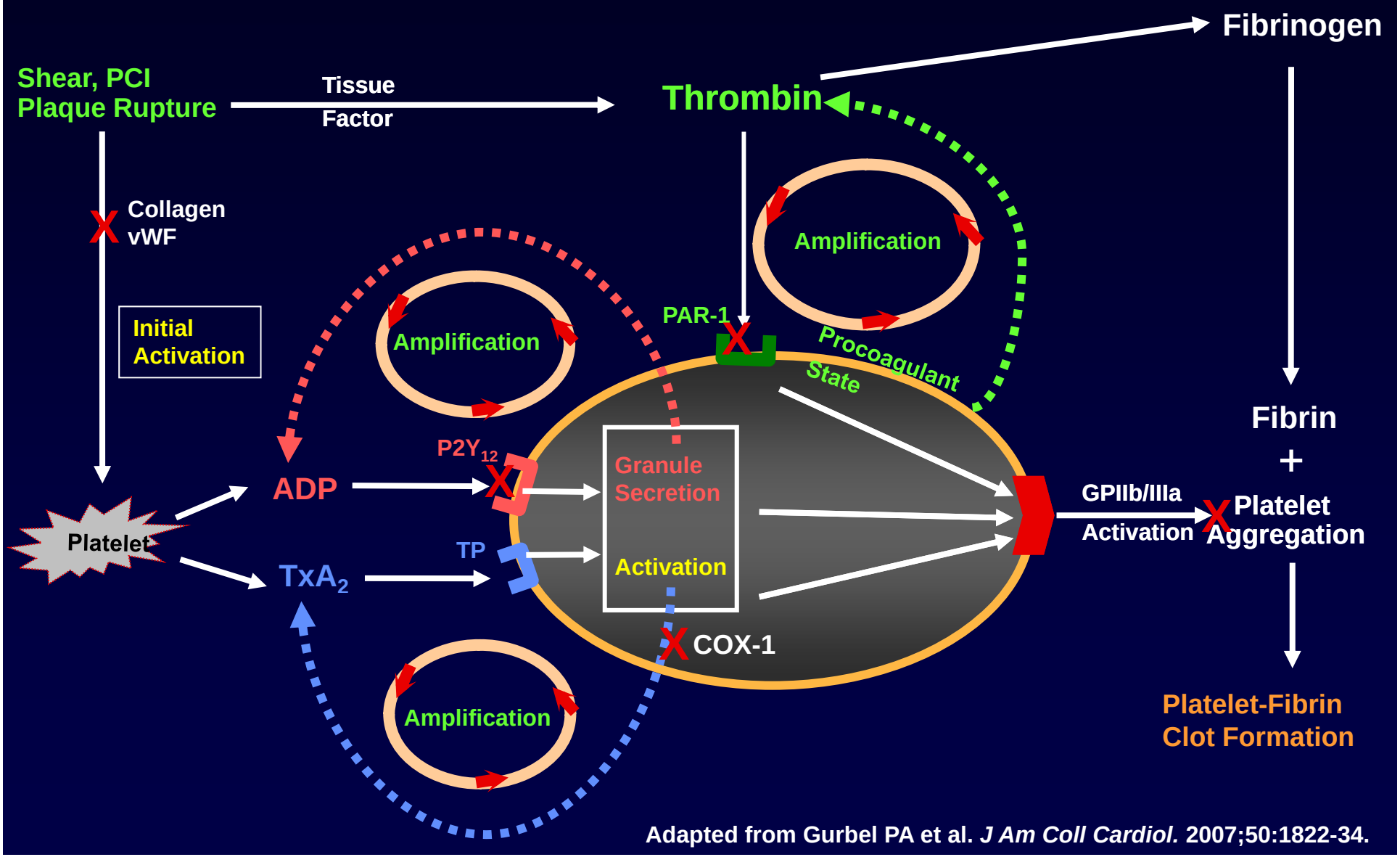
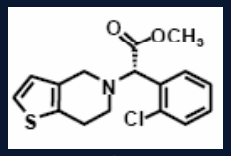
Central Role of Platelets and Interaction with Coagulation in the Genesis of Thrombosis



Adapted from Gurbel PA et al. *J Am Coll Cardiol.* 2007;50:1822-34.

Metabolism of $P2Y_{12}$ Blockers

Clopidogrel

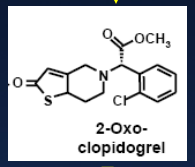


P-Glycoprotein-Absorption

h-Esterases

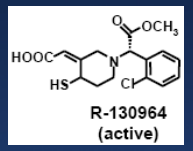
Inactive metabolite 90%

10%



2C19 (*2, *17)
1A2
2B6

2 Step Hepatic CYP Conversion

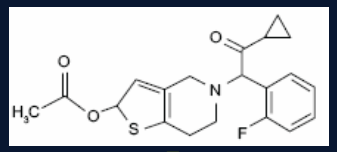


2C19 (*2, *17)
2C9
3A4
2B6

Variable and inefficient active metabolite generation

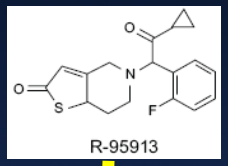
Slow, Variable/ Modest IPA

Prasugrel

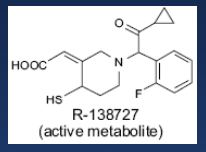


P-Glycoprotein-Absorption

Intestinal Esterases 85%



1 Step Intestinal/Hepatic CYP Conversion

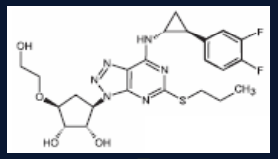


3A4
2B6
2C9
2C19

Efficient active metabolite generation

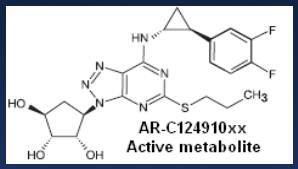
Rapid Consistent /Greater IPA

Ticagrelor



P-Glycoprotein-Absorption

Hepatic CYP3A4 30%



Rapid, Consistent/Greater IPA

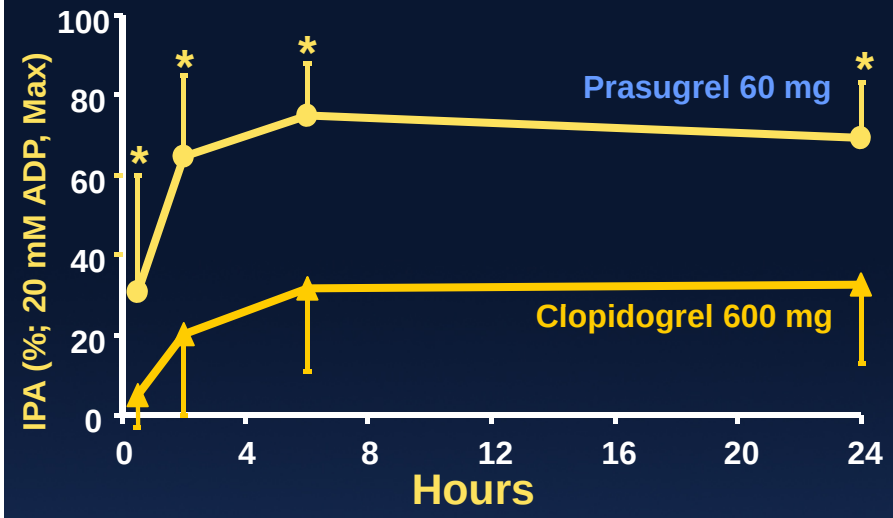
Farid NA et al. *J Clin Pharmacol*. 2010;50:126-142; Bouman HJ et al. *Nat Med.* 2011;17:110-6; Tantry US and Gurrbel PA et al.*Clin Inv.* 2011; 1:429-37

Pharmacodynamic Effects of High- Dose Clopidogrel vs. Prasugrel/Ticagrelor

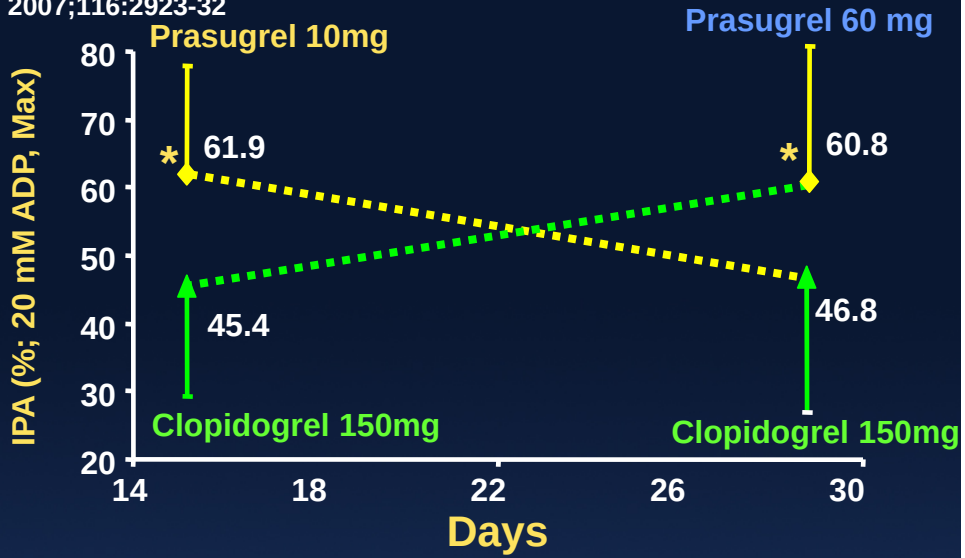
Loading

PRINCIPLE TIMI-44

Wiviott SD et al. *Circulation.* 2007;116:2923-32



Maintenance



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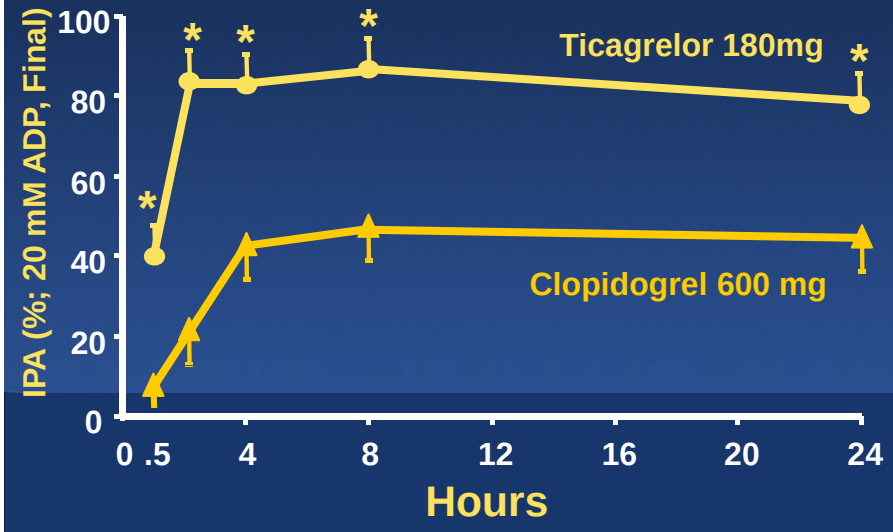
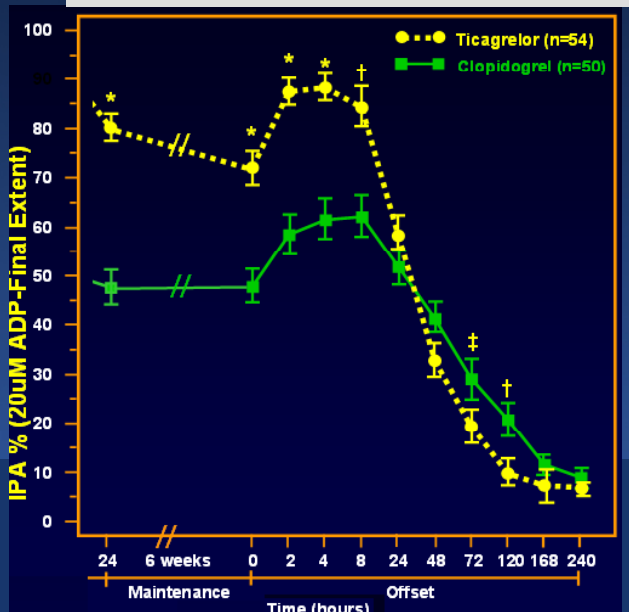
ONSET/OFFSET

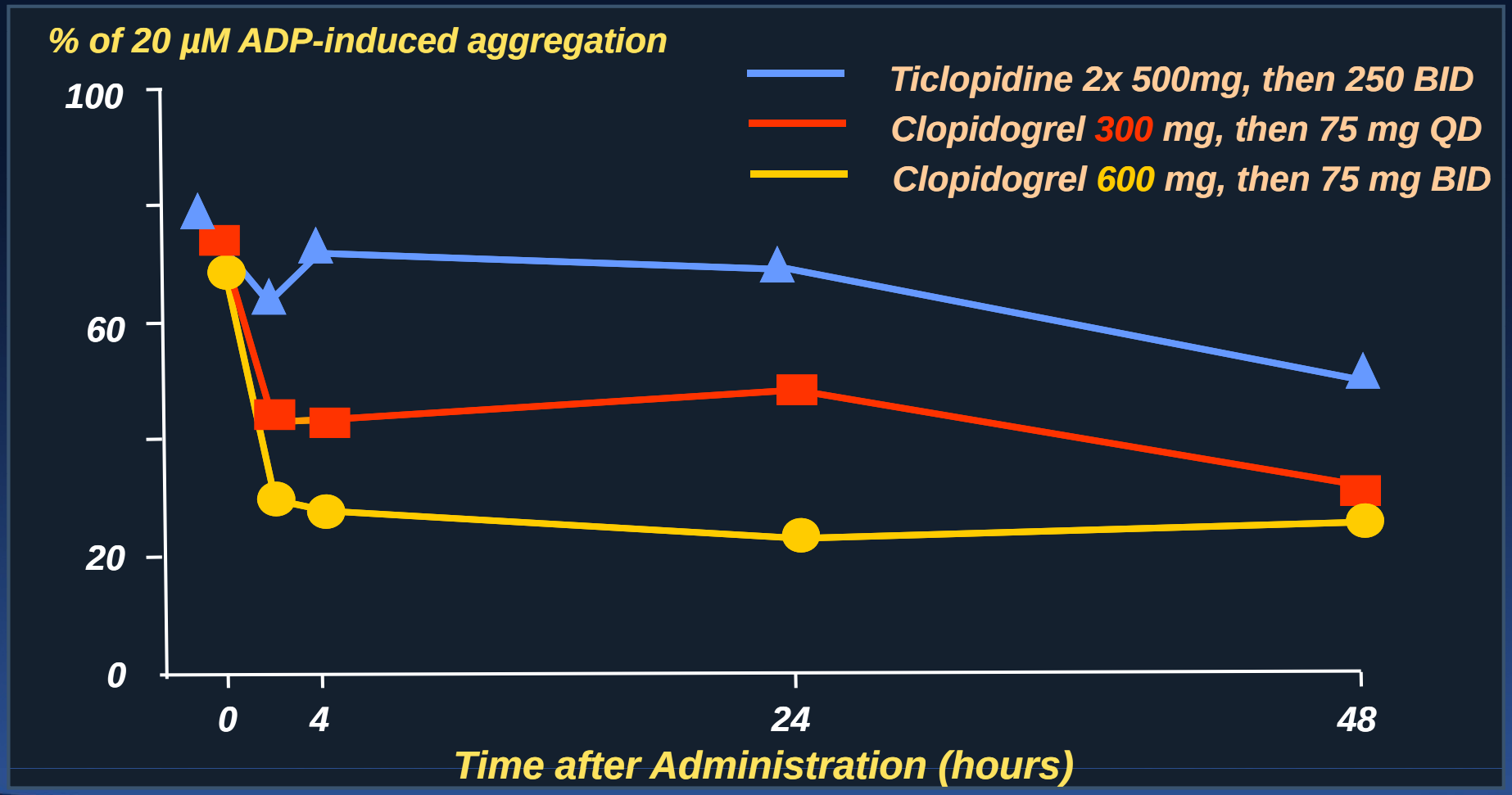
Gurbel PA et al. *Circulation.* 2009;120:2577-85



Maintenance and Offset



Clopidogrel LD: Is Higher Dosage Better?



Muller I. Heart 2001;85:92-3

CURRENT Study Design, Flow and Compliance

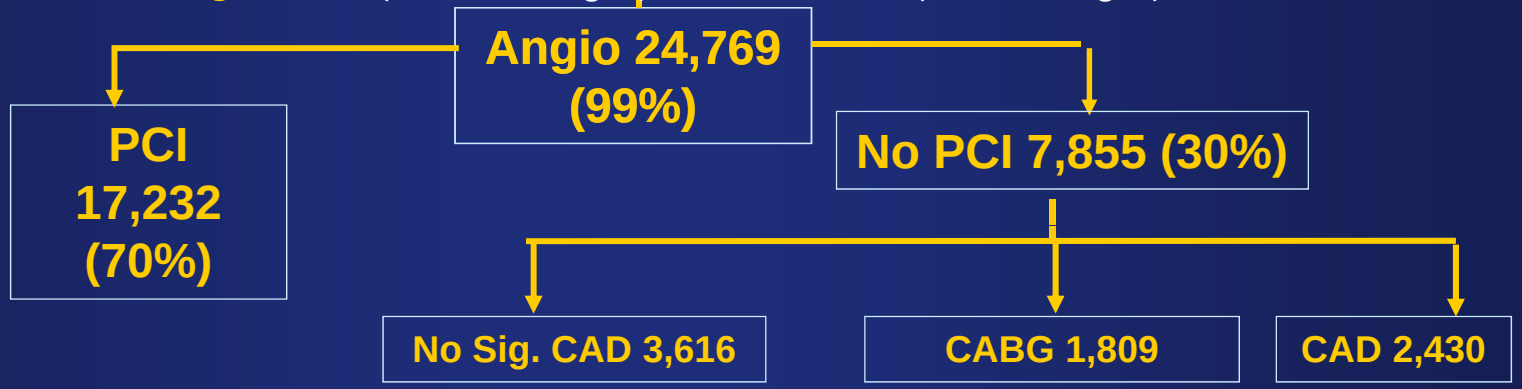
25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

- ✓ 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)



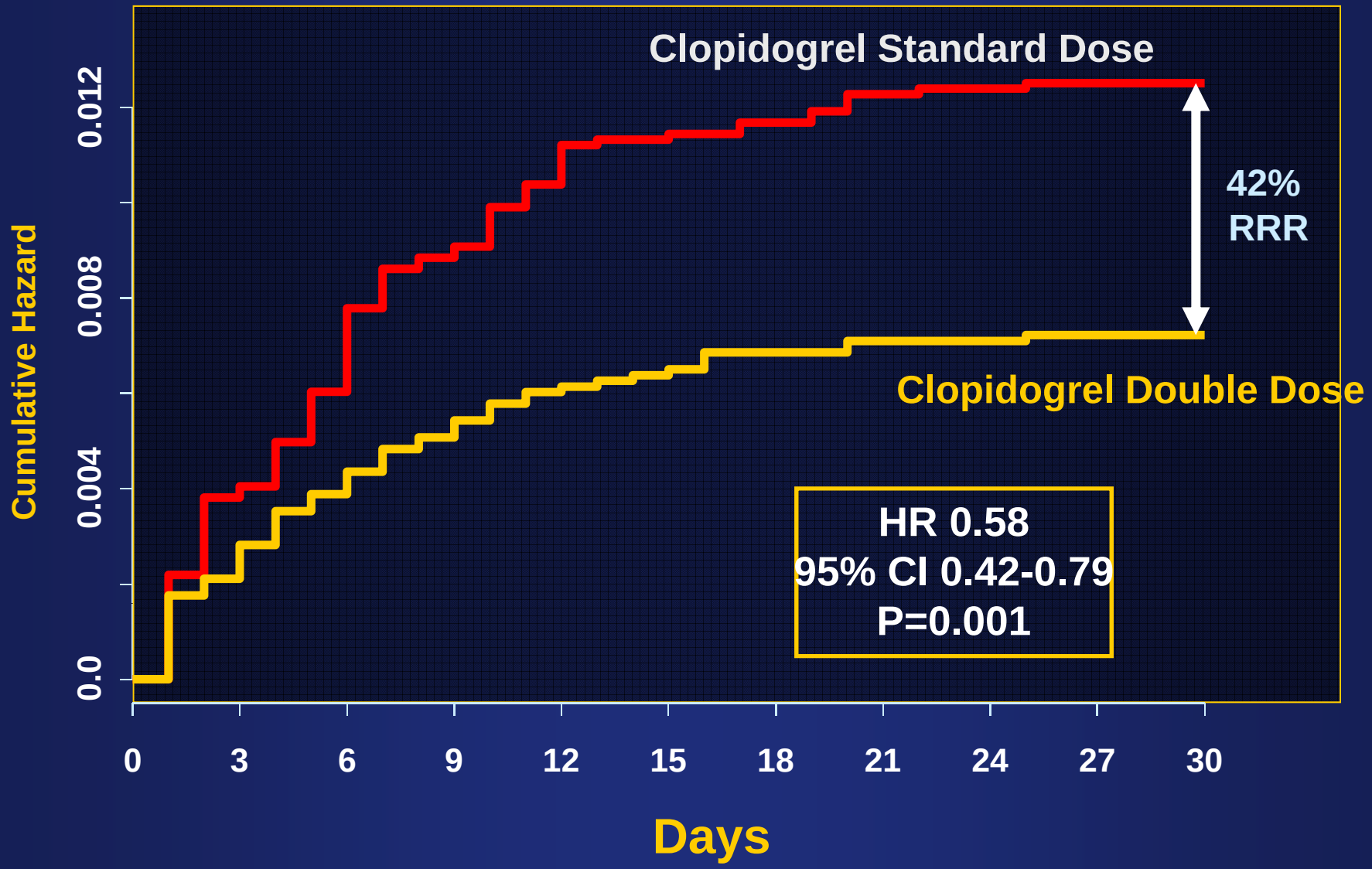
Efficacy Outcomes:	CV Death, MI or stroke at day 30 Stent Thrombosis at day 30
Safety Outcomes:	Bleeding (CURRENT defined Major/Severe and TIMI Major)
Key Subgroup:	PCI v No PCI

CURRENT Clopidogrel: Double vs Standard Dose Primary Outcome and Components

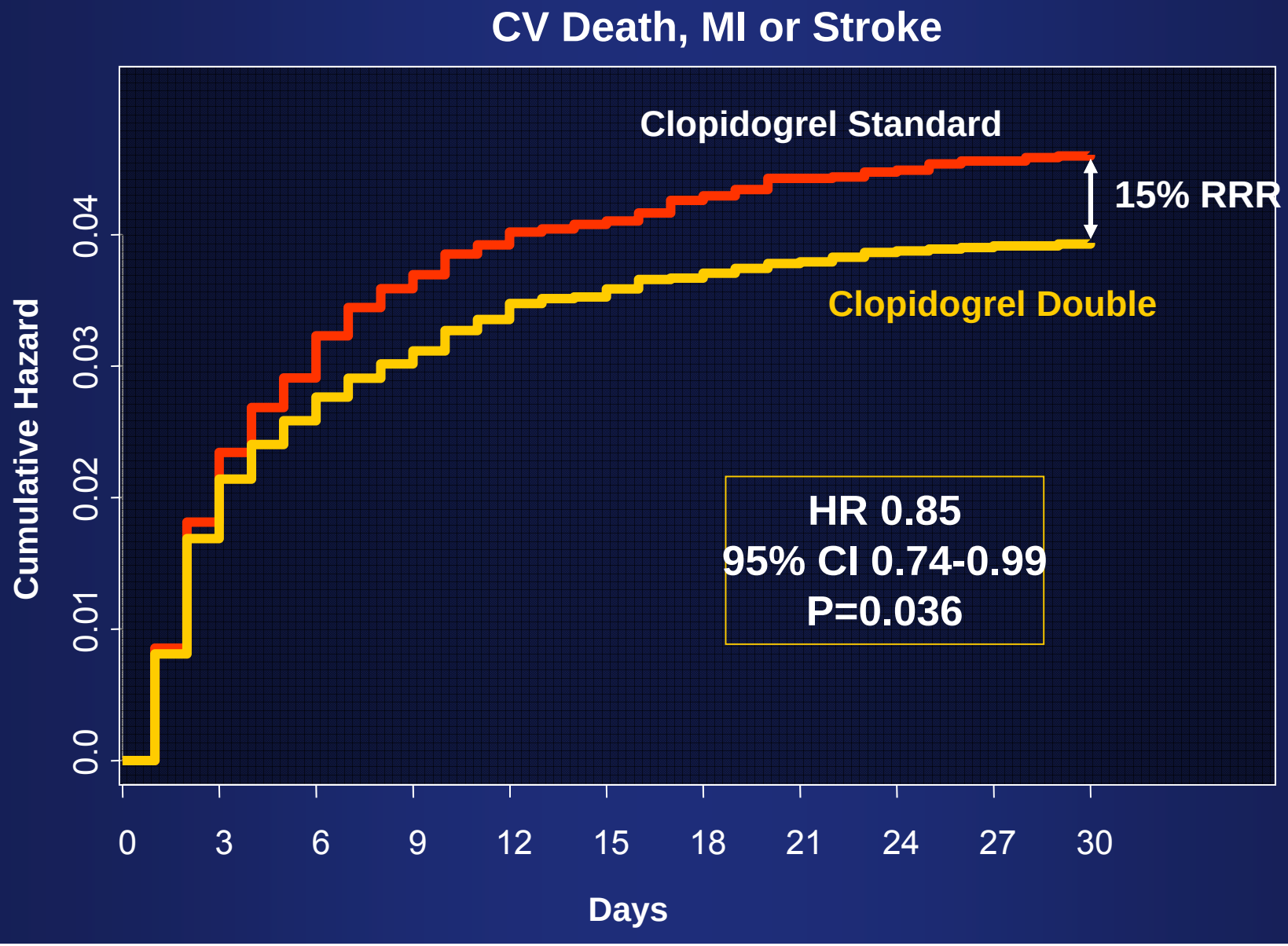
	Standard	Double	HR	95% CI	P	Intn P
CV Death/MI/Stroke						
PCI (2N=17,232)	4.5	3.9	0.85	0.74-0.99	0.036	0.016
No PCI (2N=7855)	4.2	4.9	1.17	0.95-1.44	0.14	
Overall (2N=25,087)	4.4	4.2	0.95	0.84-1.07	0.370	
MI						
PCI (2N=17,232)	2.6	2.0	0.78	0.64-0.95	0.012	0.025
No PCI (2N=7855)	1.4	1.7	1.25	0.87-1.79	0.23	
Overall (2N=25,087)	2.2	1.9	0.86	0.73-1.03	0.097	
CV Death						
PCI (2N=17,232)	1.9	1.9	0.96	0.77-1.19	0.68	1.0
No PCI (2N=7855)	2.8	2.7	0.96	0.74-1.26	0.77	
Overall (2N=25,087)	2.2	2.1	0.96	0.81-1.14	0.628	
Stroke						
PCI (2N=17,232)	0.4	0.4	0.88	0.55-1.41	0.59	0.50
No PCI (2N=7855)	0.8	0.9	1.11	0.68-1.82	0.67	
Overall (2N=25,087)	0.5	0.5	0.99	0.70-1.39	0.950	

CURRENT

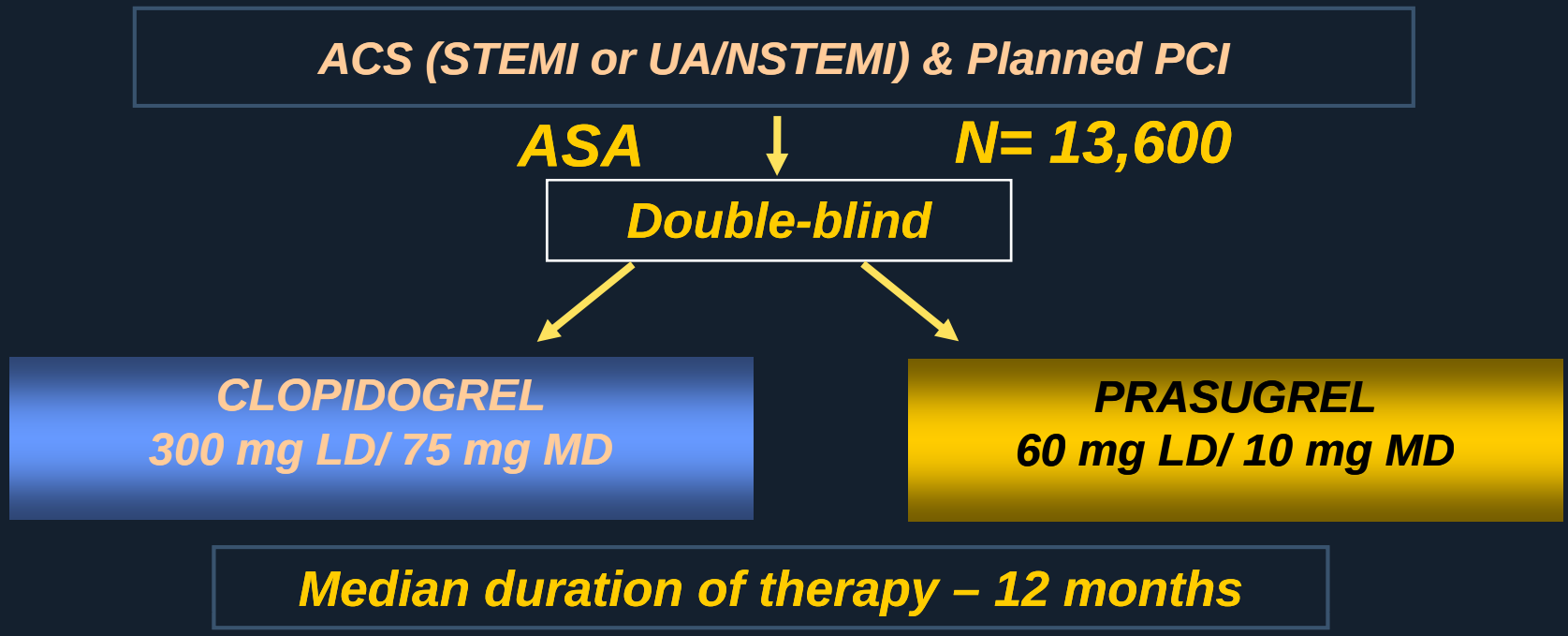
Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis (Angio confir



Clopidogrel: Double vs Standard Dose
Primary Outcome: PCI Patients



TRITON-Study Design

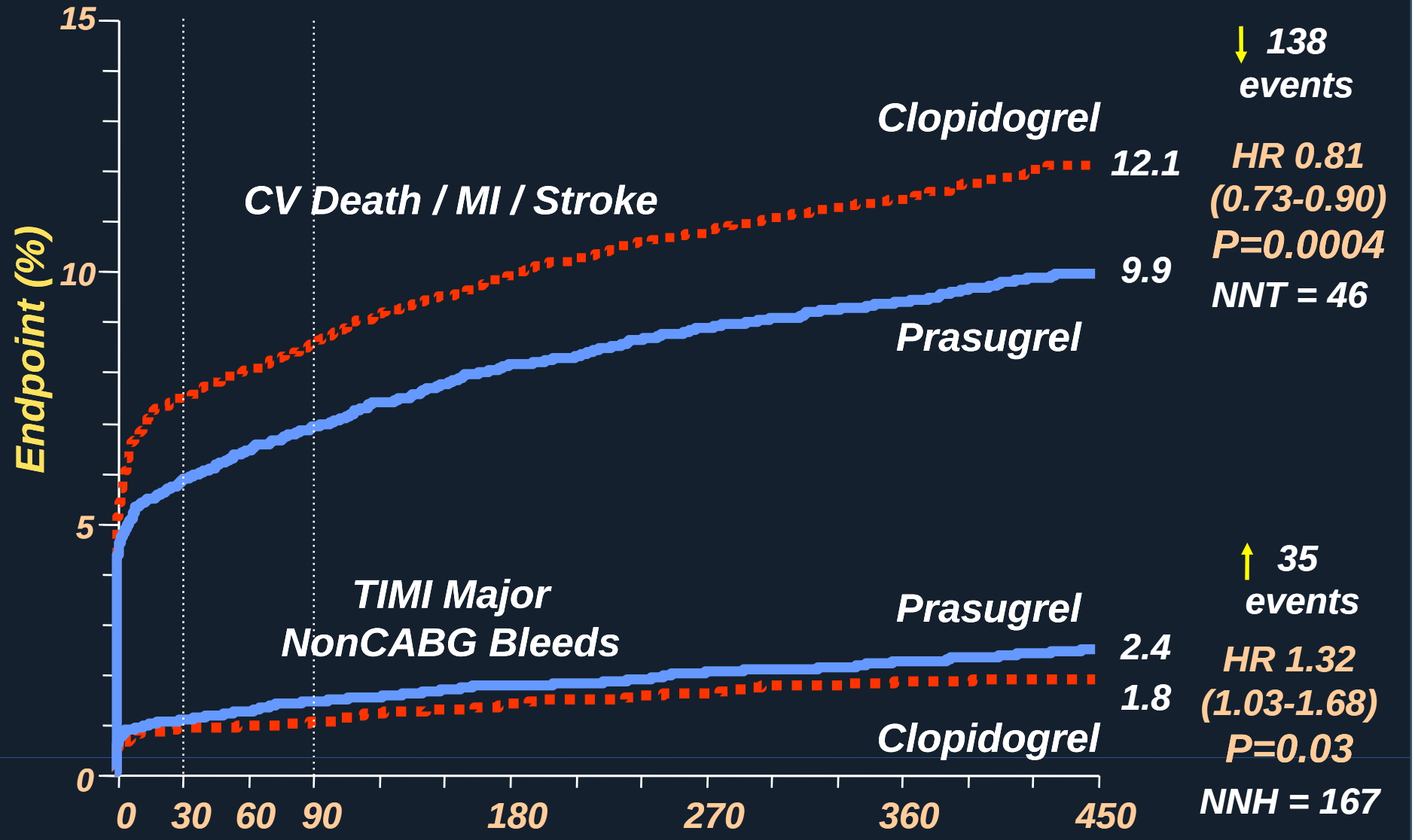


Median duration of therapy – 12 months

1º endpoint: ***CV death, MI, Stroke***
2º endpoints: ***CV death, MI, Stroke, Rehosp-Rec Isch, CV death, MI, UTVR***
Stent Thrombosis (ARC definite/prob.)

Safety endpoints: ***TIMI major bleeds, Life-threatening bleeds***
Key Substudies: ***Pharmacokinetic, Genomic***

Balance of Efficacy and Safety



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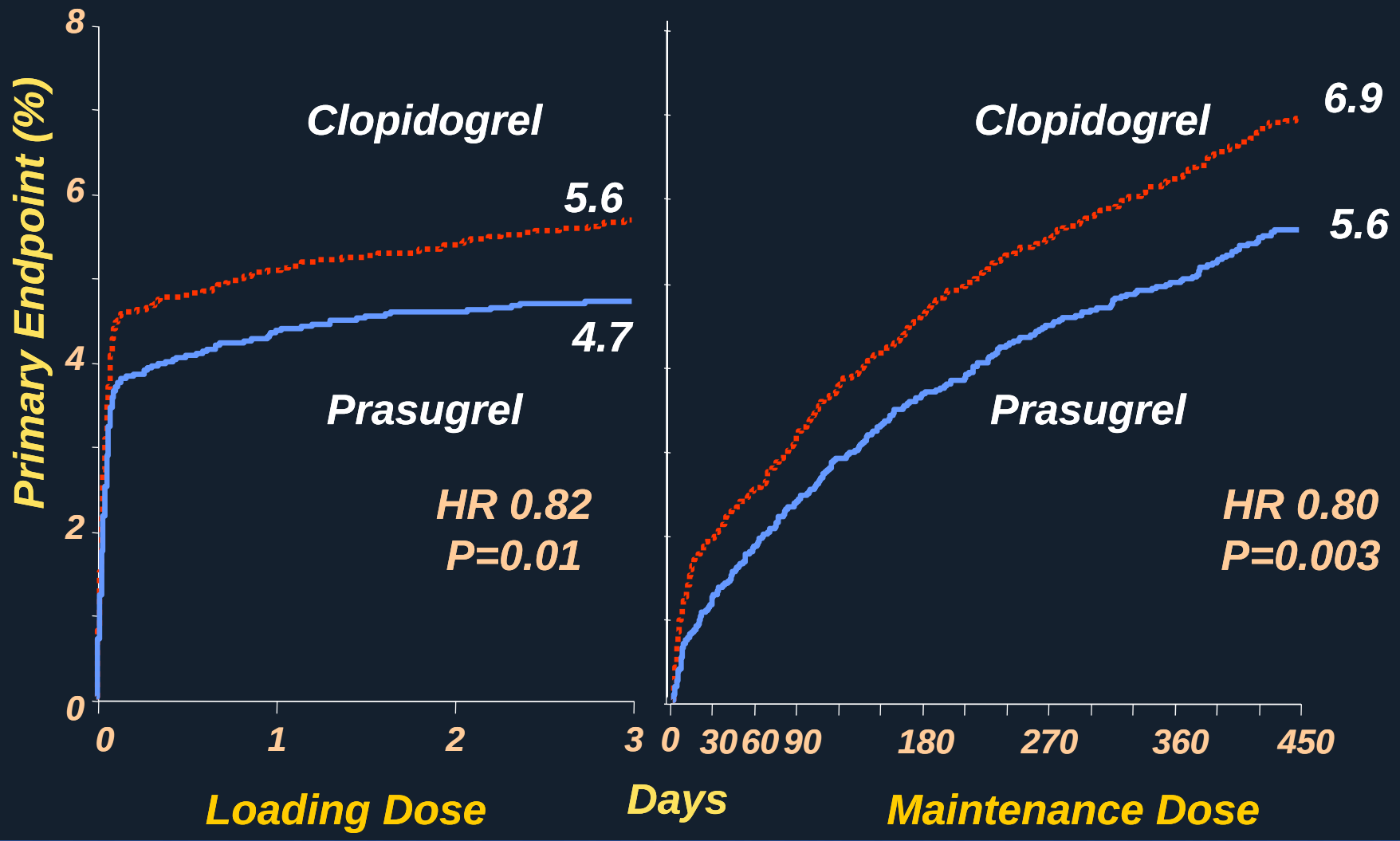
Wiviott SD, et al. N Engl J Med. 2007;357:2001-2015.

Timing of Benefit (Landmark Analysis)



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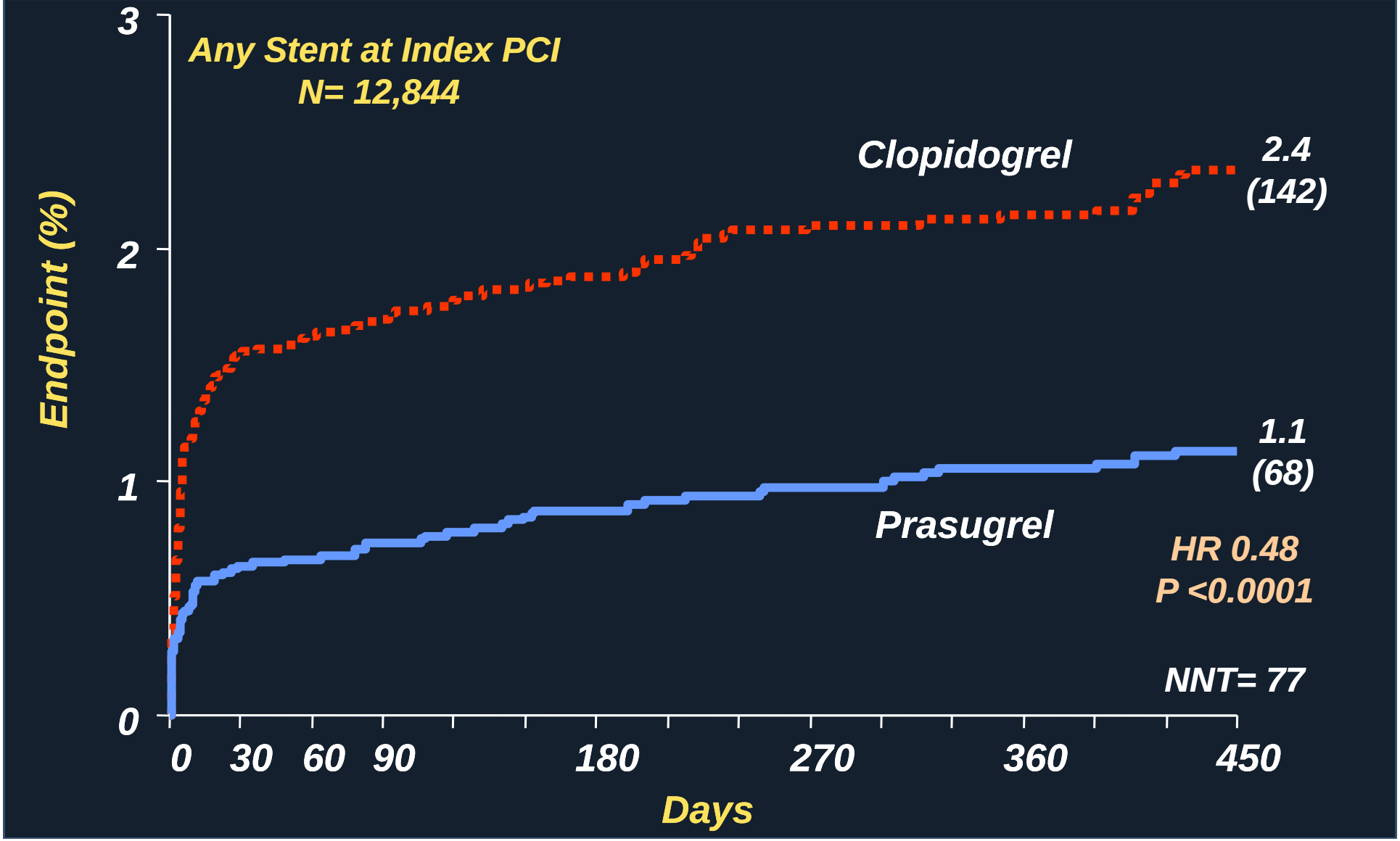
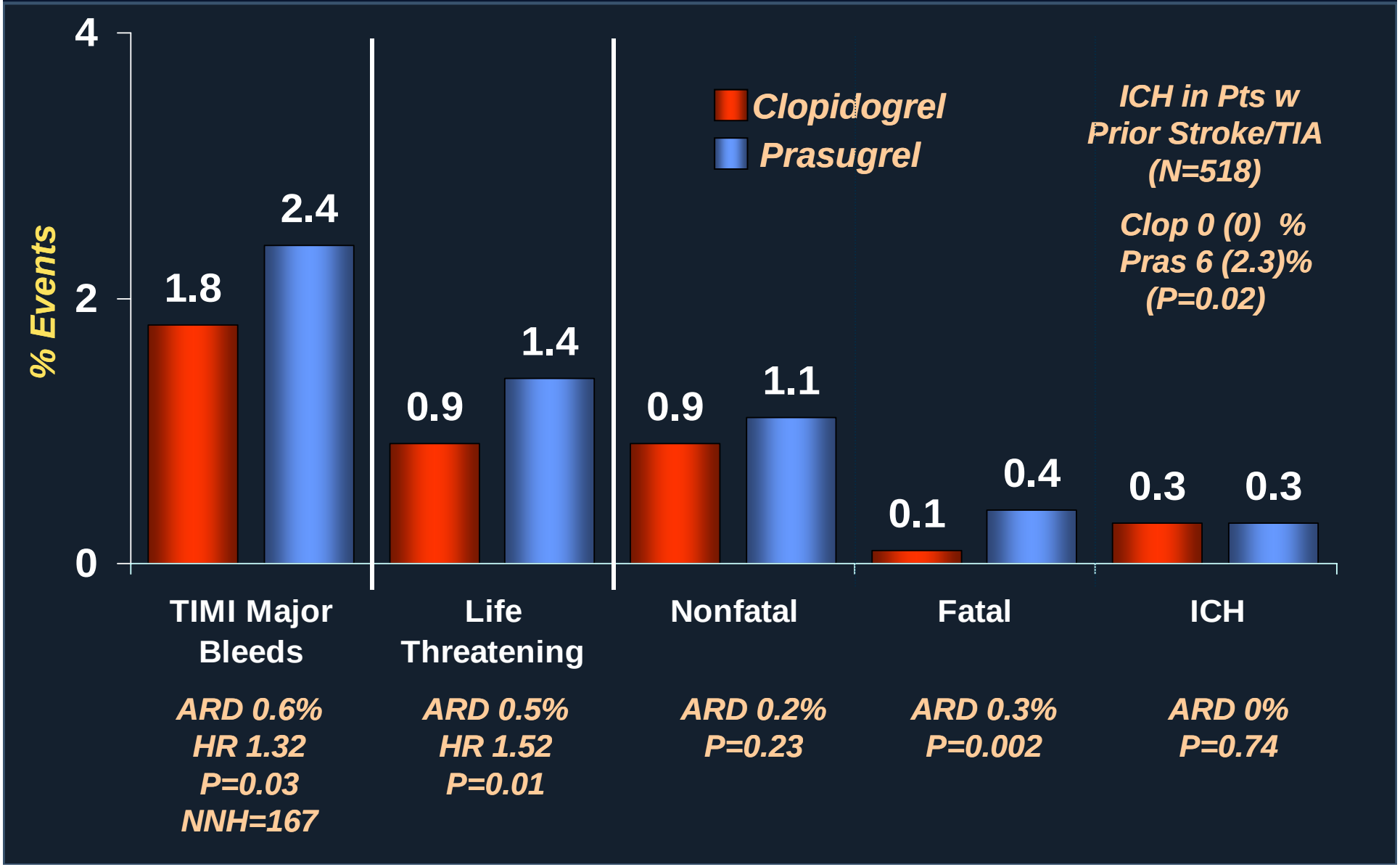
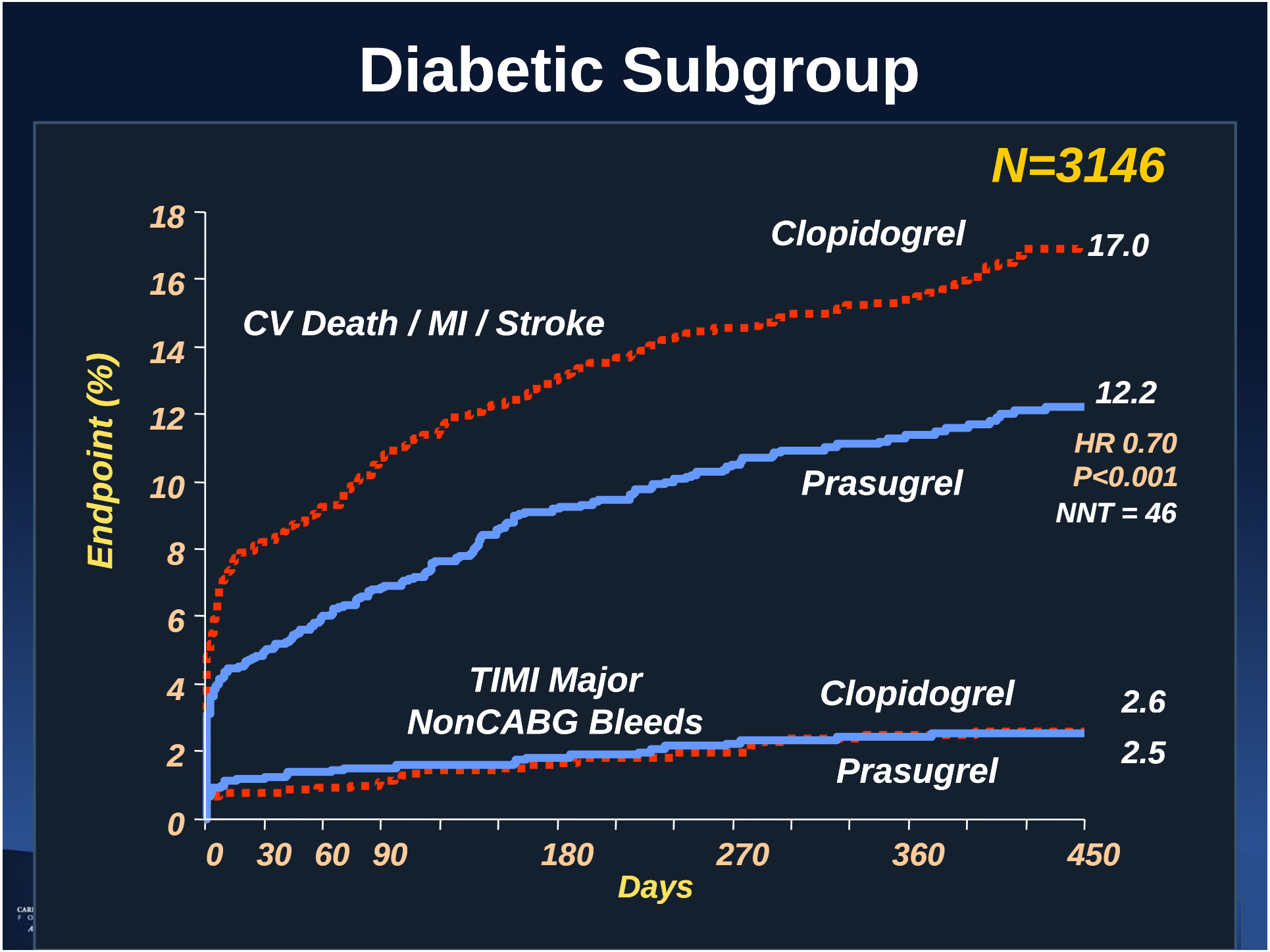
Stent Thrombosis (ARC Definite + Probable)



Bleeding Events *Safety Cohort* (N=13,457)



Diabetic Subgroup



PLATO study design

PLATO

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

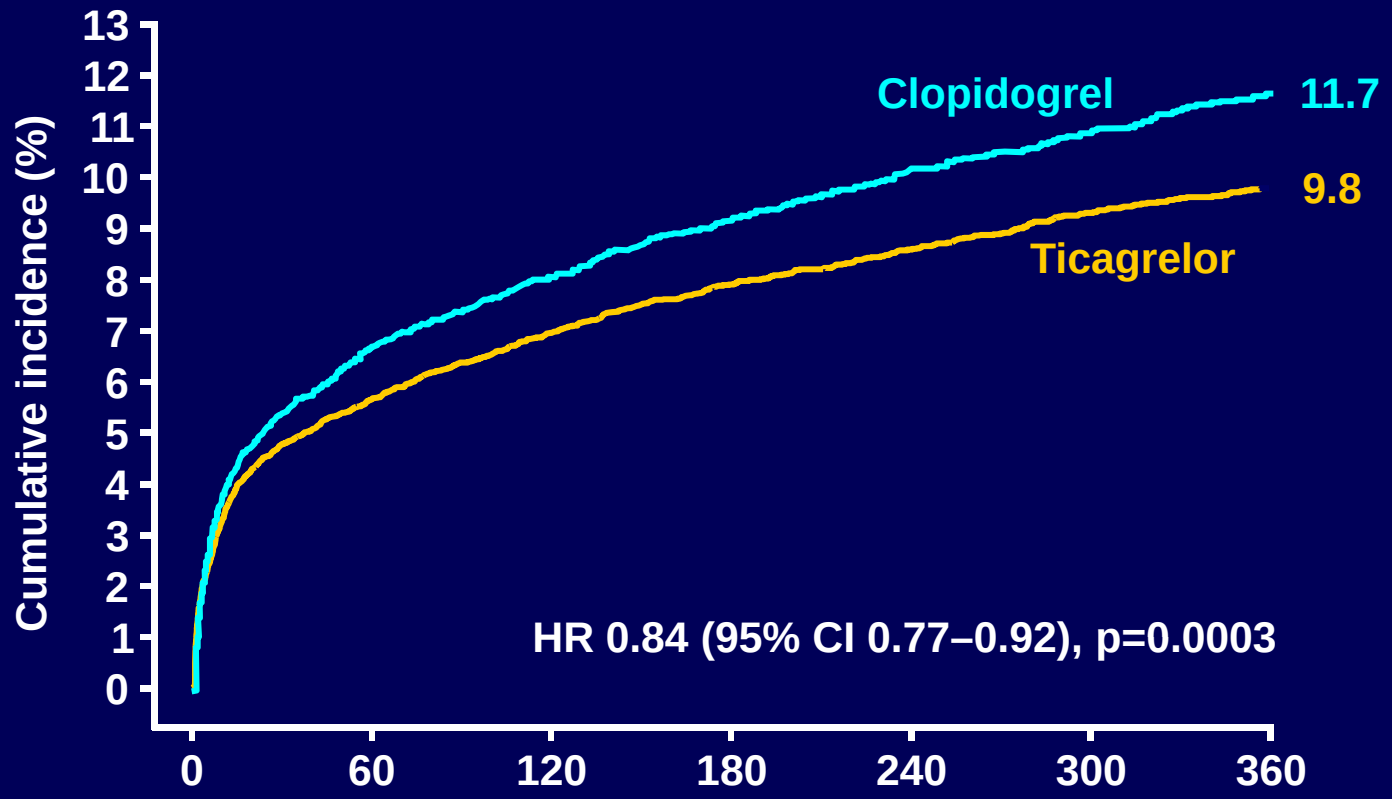
6–12-month exposure

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

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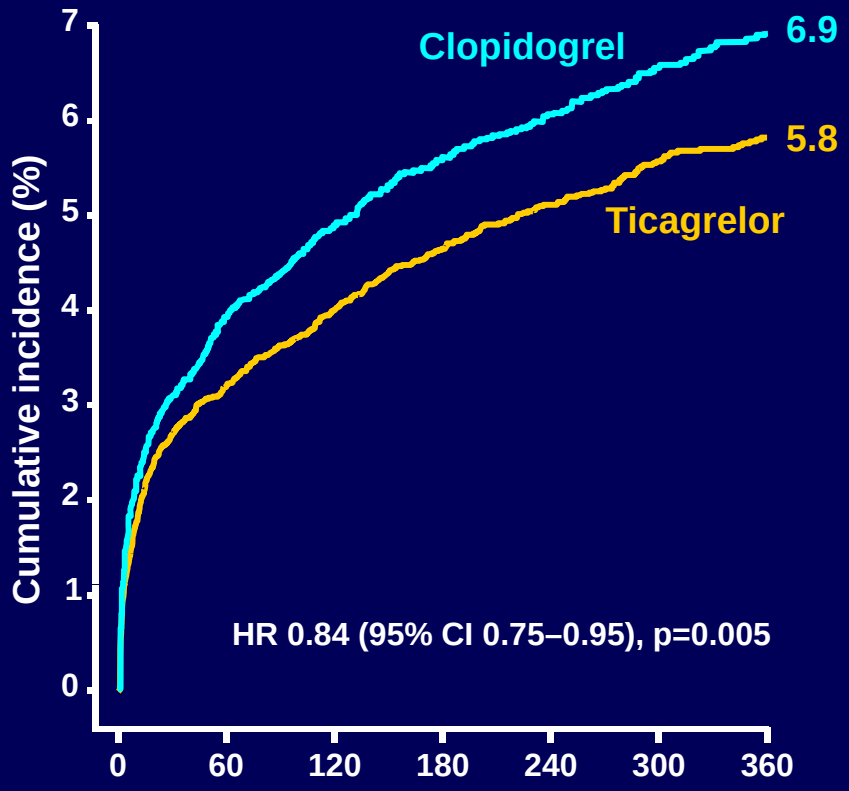
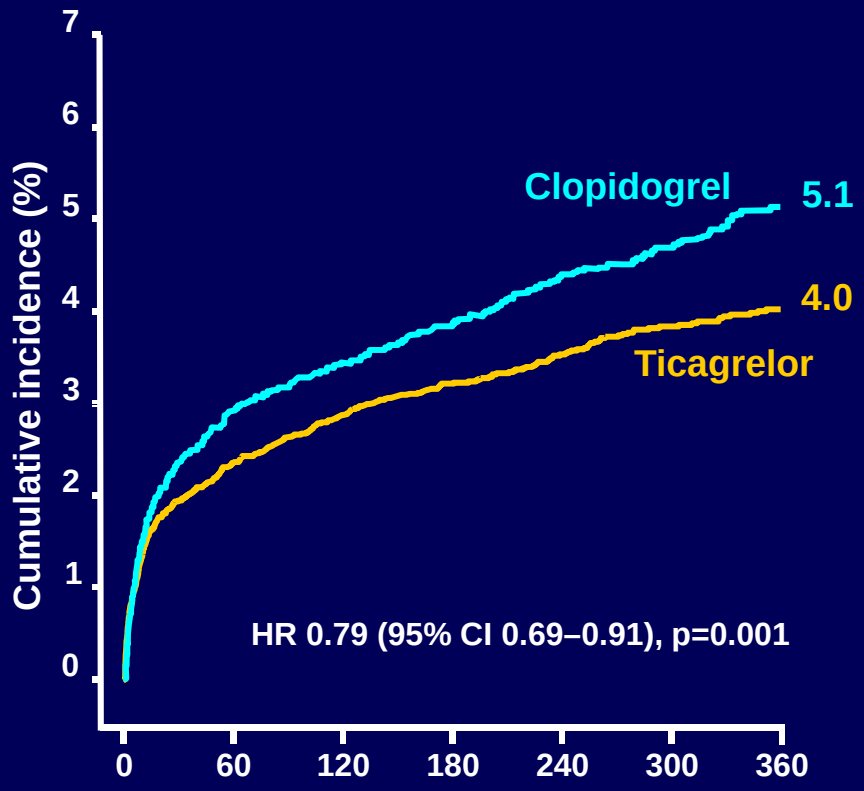
Secondary efficacy endpoints over time

PLATO

Myocardial infarction



Cardiovascular death



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

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)

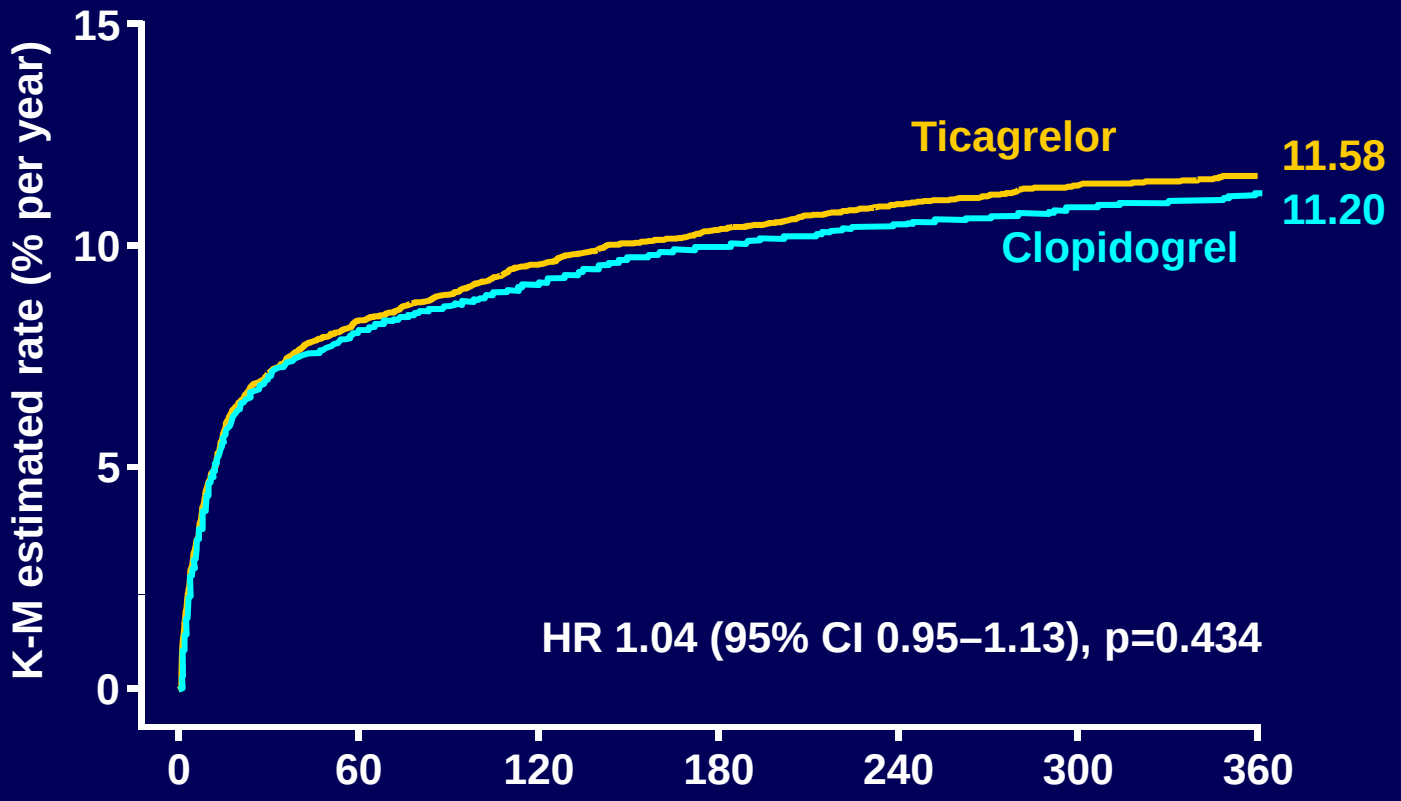
PLATO

	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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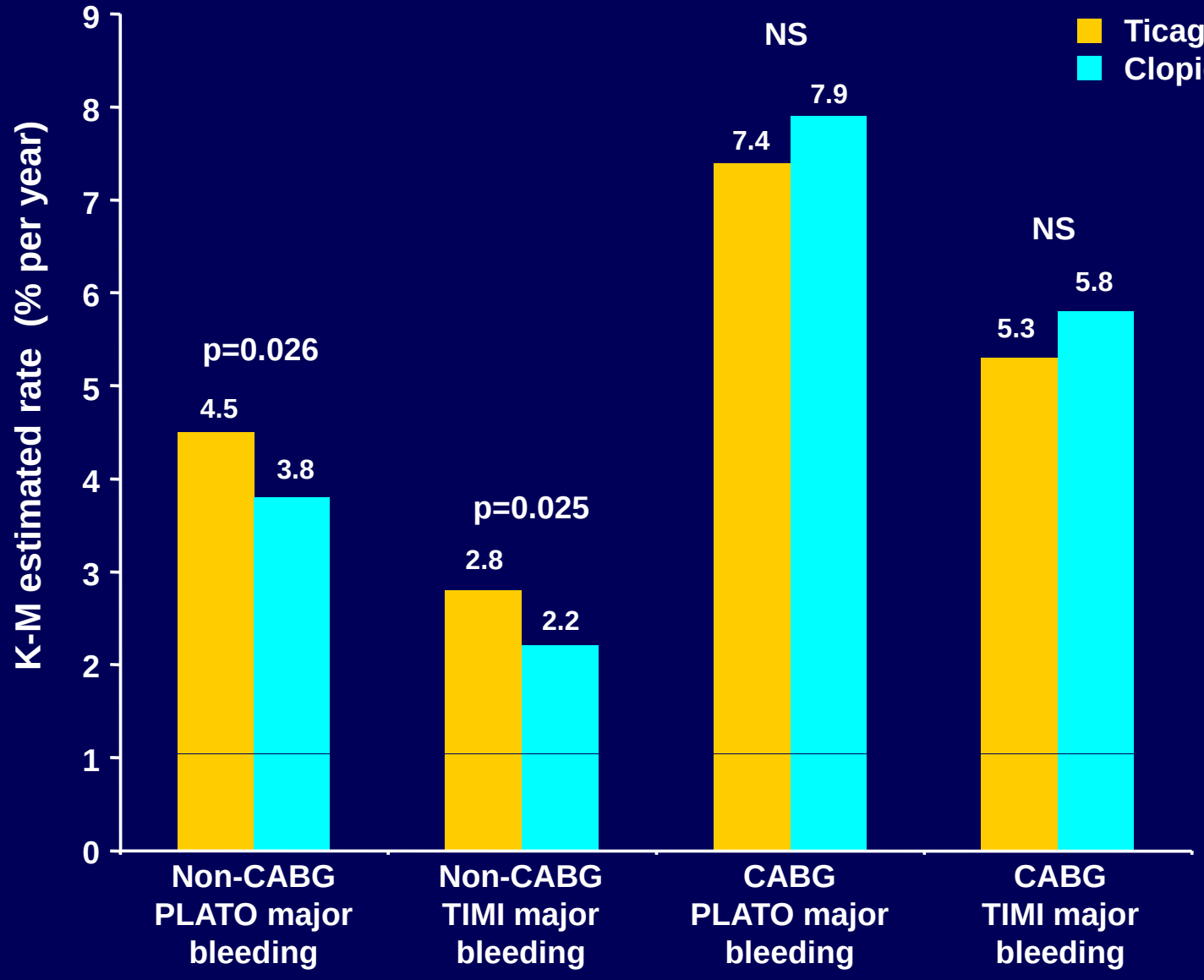
Non-CABG and CABG-related major bleeding

PLATO



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TRA·CER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes

Pierluigi Tricoci, M.D., Ph.D., Zhen Huang, M.S., Claes Held, M.D., Ph.D., David J. Moliterno, M.D., Paul W. Armstrong, M.D., Frans Van de Werf, M.D., Harvey D. White, D.Sc., Philip E. Aylward, M.D., Lars Wallentin, M.D., Ph.D., Edmond Chen, M.D., Yuliya Lokhnygina, Ph.D., Jinglan Pei, M.S., Sergio Leonardi, M.D., Tyrus L. Rorick, R.N., Ann M. Kilian, B.S., Lisa H.K. Jennings, Ph.D., Giuseppe Ambrosio, M.D., Ph.D., Christoph Bode, M.D., Angel Cequier, M.D., Jan H. Cornel, M.D., Rafael Diaz, M.D., Aycan Erkan, M.D., Ph.D., Kurt Huber, M.D., Michael P. Hudson, M.D., Lixin Jiang, M.D., J. Wouter Jukema, M.D., Ph.D., Basil S. Lewis, M.D., A. Michael Lincoff, M.D., Gilles Montalescot, M.D., José Carlos Nicolau, M.D., Ph.D., Hisao Ogawa, M.D., Matthias Pfisterer, M.D., Juan Carlos Prieto, M.D., Witold Ruzyllo, M.D., Peter R. Sinnaeve, M.D., Ph.D., Robert F. Storey, M.D., D.M., Marco Valgimigli, M.D., Ph.D., David J. Whellan, M.D., Petr Widimsky, M.D., Dr.Sc., John Strony, M.D., Robert A. Harrington, M.D., and Kenneth W. Mahaffey, M.D., for the TRACER Investigators*

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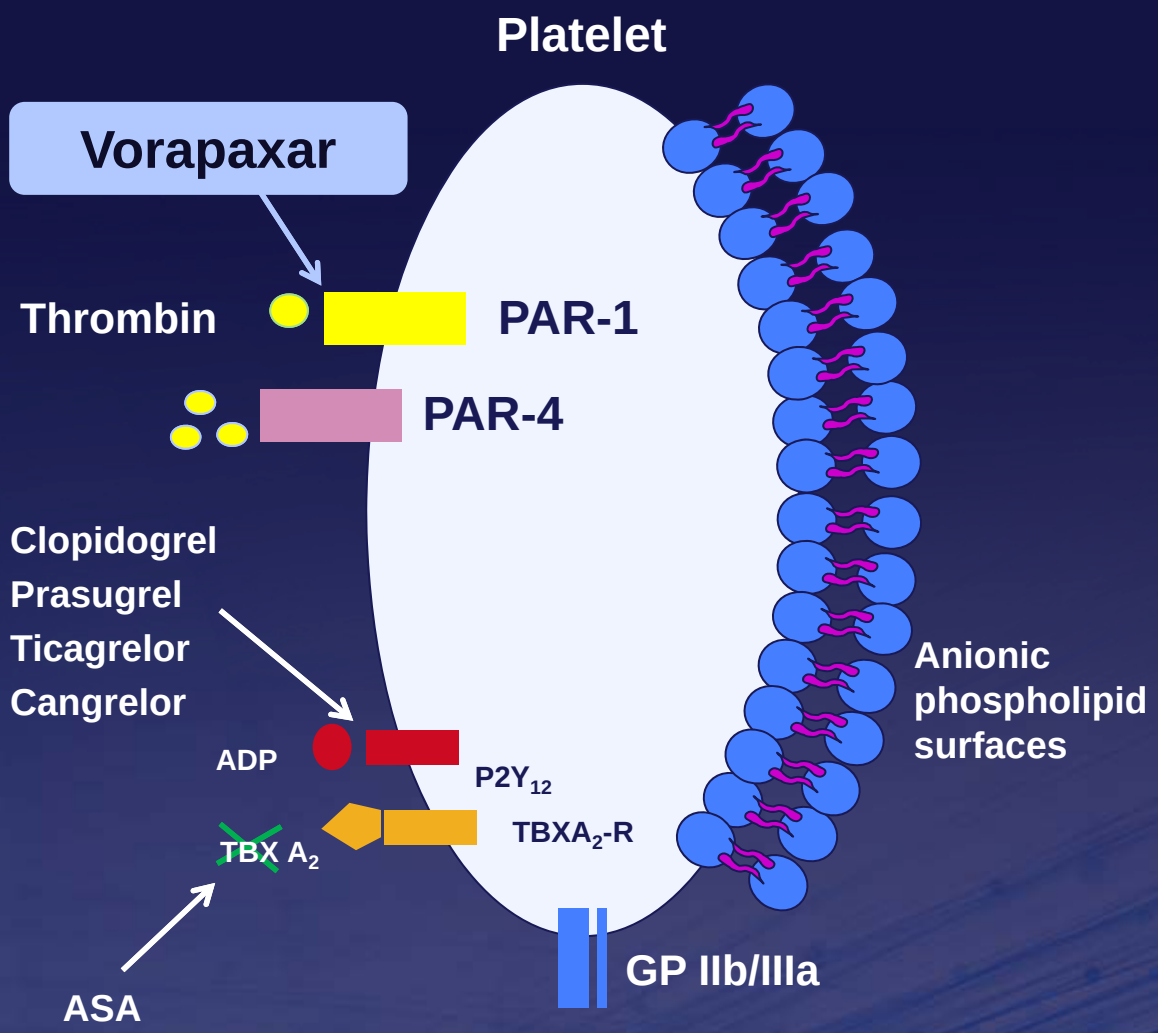

- Vorapaxar:
  - First-in-class
  - Oral PAR-1 inhibitor
- Metabolism:
  - Primarily hepatic via CYP 3A4
  - Terminal half-life: ~126–269 hrs
- Prior trials:
  - No increase in bleeding and fewer MIs

Chackalamannil S, J Med Chem, 2006

Trial Design

NSTE Acute Coronary Syndromes

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Key inclusion criteria
- Within 24 hrs of symptoms
- ↑ biomarkers or ECG changes
- 1 other high-risk feature

1:1
Randomized
Double-blind

Placebo

Vorapaxar

Loading: 40 mg
Maintenance: 2.5 mg daily

Follow-up: 1, 4, 8, 12 months, then every 6 months
Standard of care based on practice guidelines

Efficacy Endpoints
Primary: CV death, MI, stroke, hospitalization for ischemia, urgent revascularization
Key Secondary: CV death, MI, stroke
Bleeding Endpoints: GUSTO moderate or severe and clinically significant TIMI bleeding

Primary Endpoint

CV Death, MI, Stroke, Hospitalization for Ischemia, Urgent Revascularization

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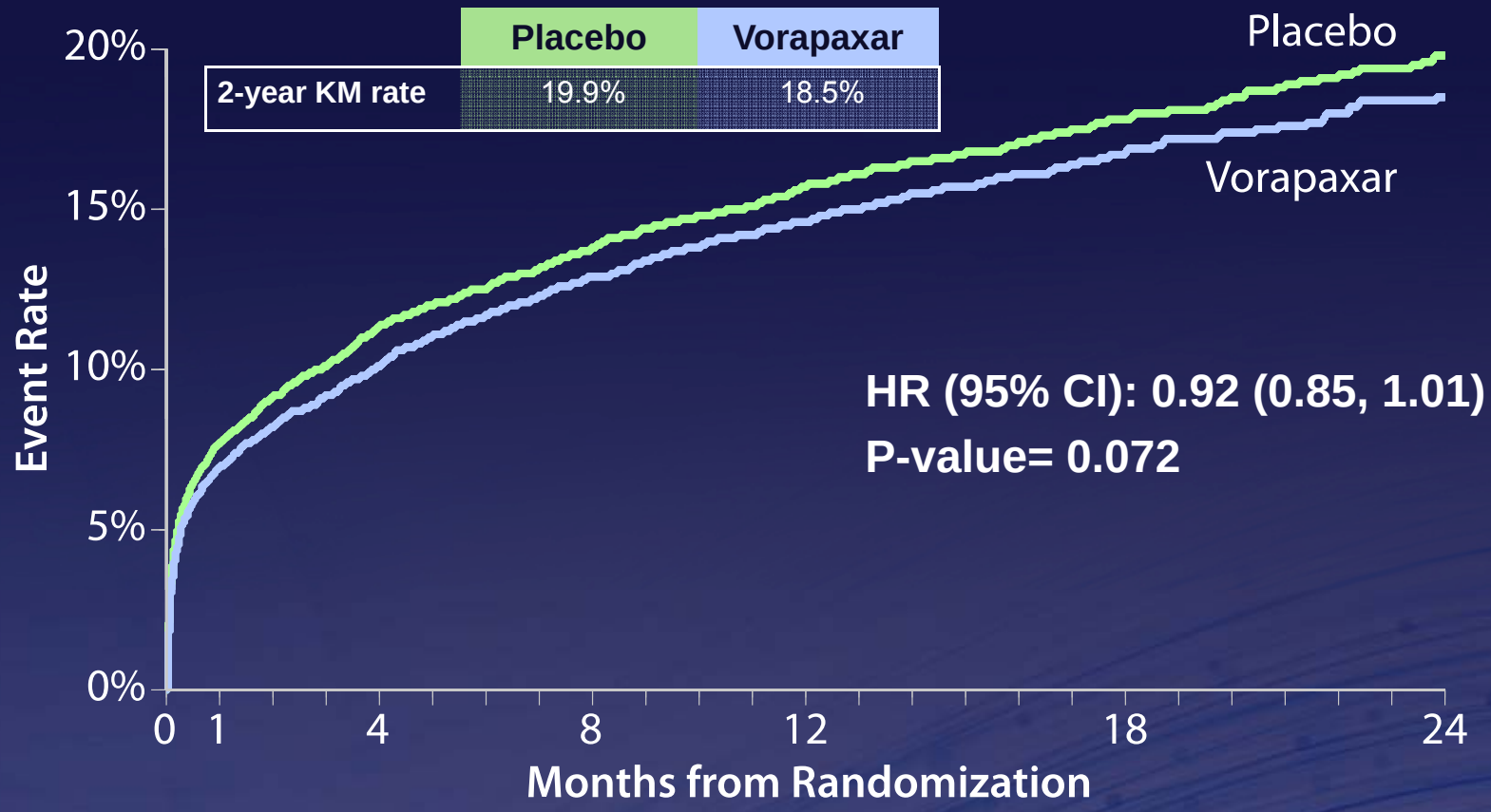

No. at risk							
Placebo	6471	5844	5468	5121	3794	2291	795
Vorapaxar	6473	5897	5570	5199	3881	2318	832

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Key Secondary Endpoint

CV Death, MI, Stroke

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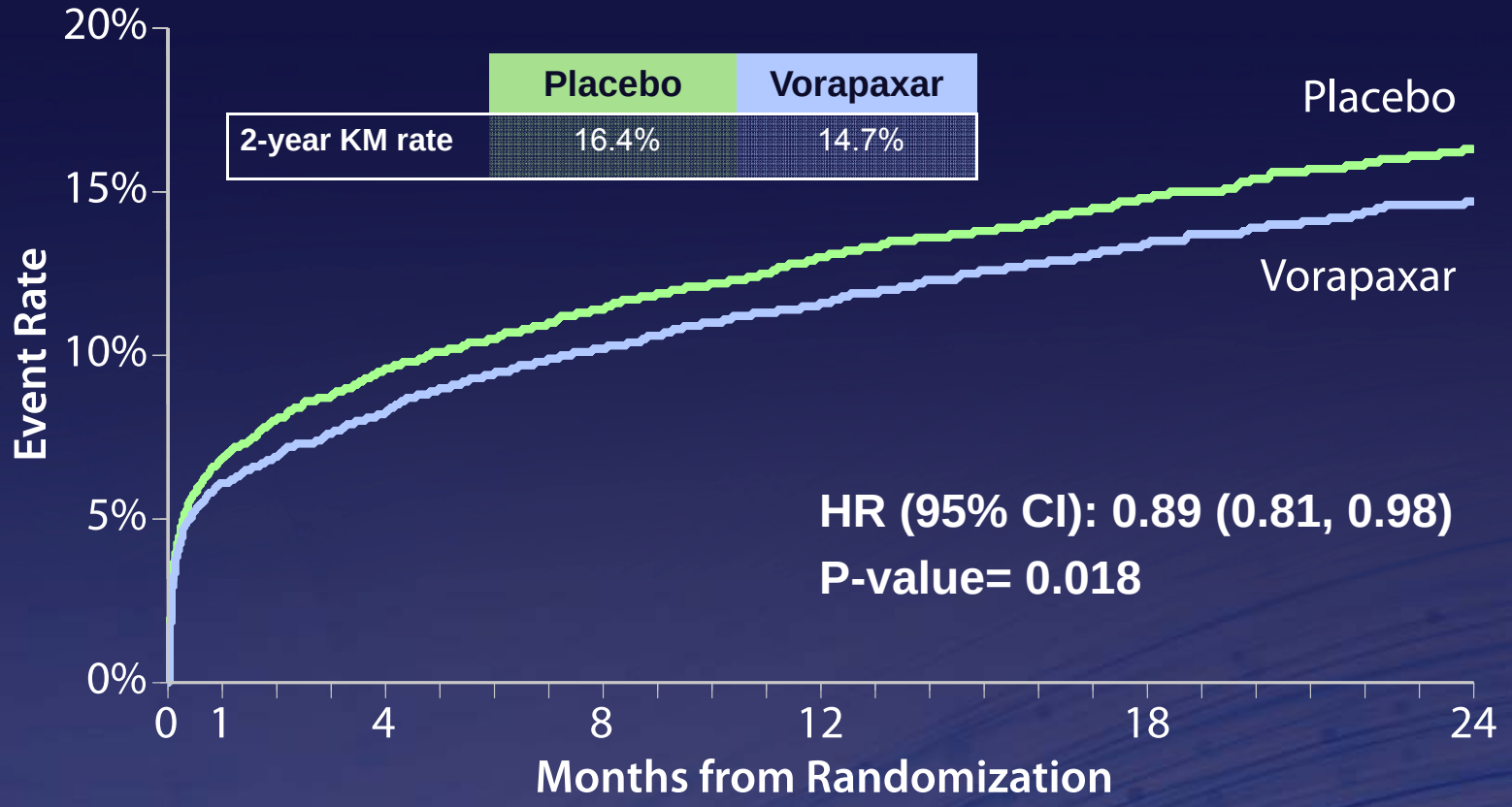

No. at risk							
Placebo	6471	5895	5575	5263	3922	2383	830
Vorapaxar	6473	5949	5684	5356	4023	2427	868

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Bleeding Outcomes

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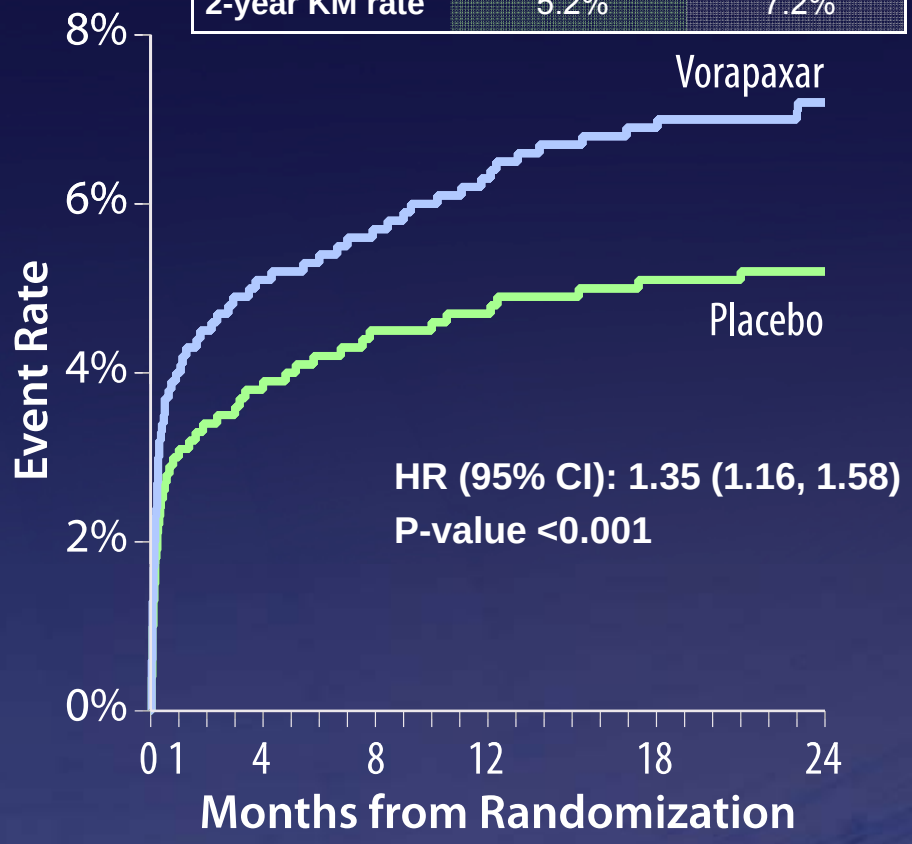
GUSTO Moderate/Severe

	Placebo	Vorapaxar
2-year KM rate	5.2%	7.2%

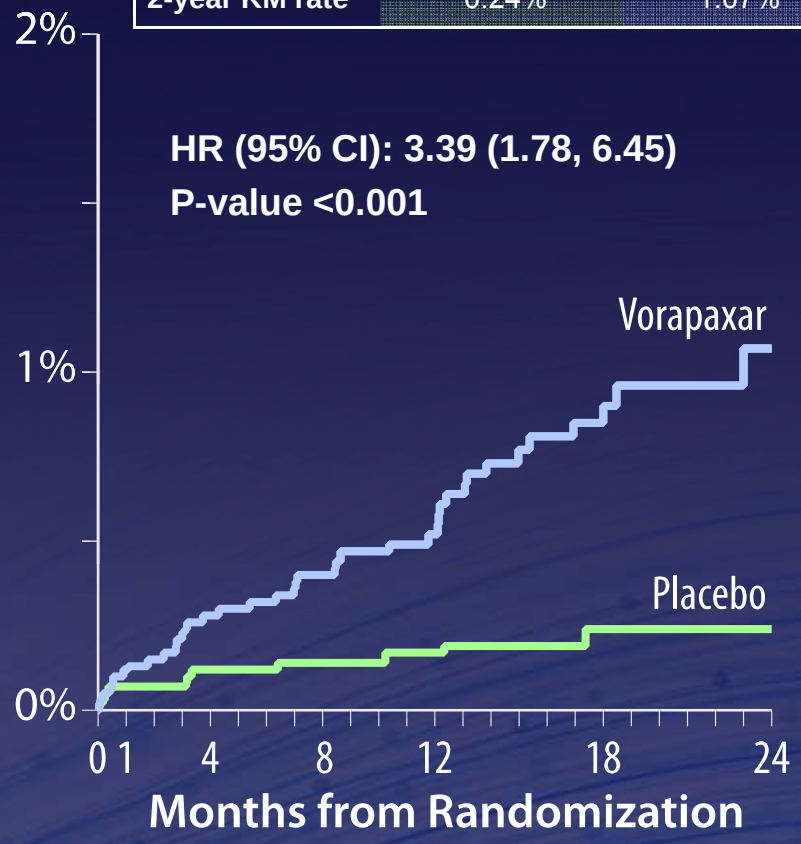


No. at risk

6441	5536	5137	4674	3393	1972	650
6446	5529	5108	4598	3278	1883	625

ICH

	Placebo	Vorapaxar
2-year KM rate	0.24%	1.07%



No. at risk

6441	5673	5281	4823	3511	2038	678
6446	5694	5272	4760	3411	1965	657

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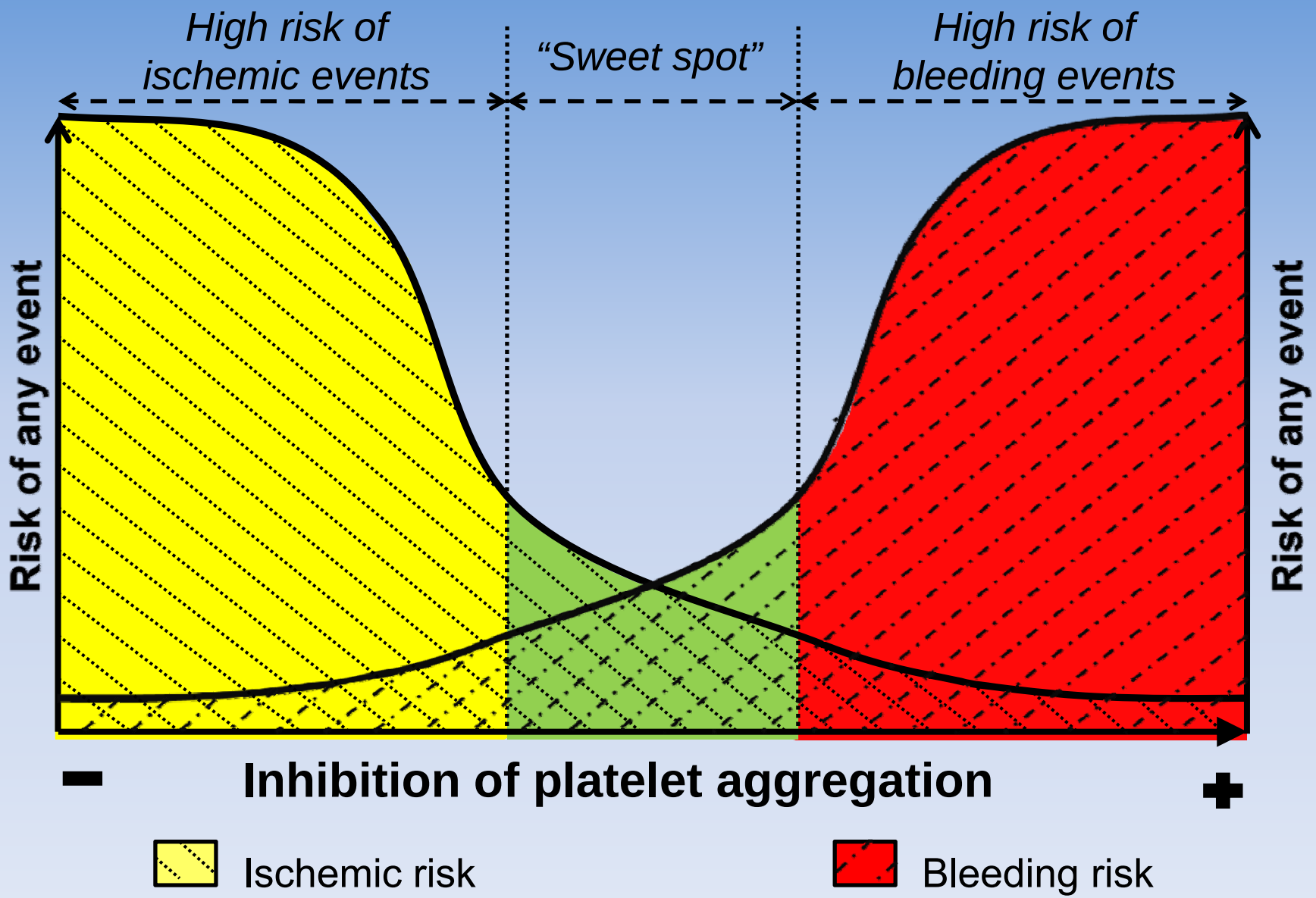
Balancing Safety and Efficacy



Ferreiro & Angiolillo. Thromb Haemost 2010 (in press)