



Ticagrelor

Platelet Inhibition and Beyond ...

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Conflict of Interest – Disclosure

Christian W. Hamm

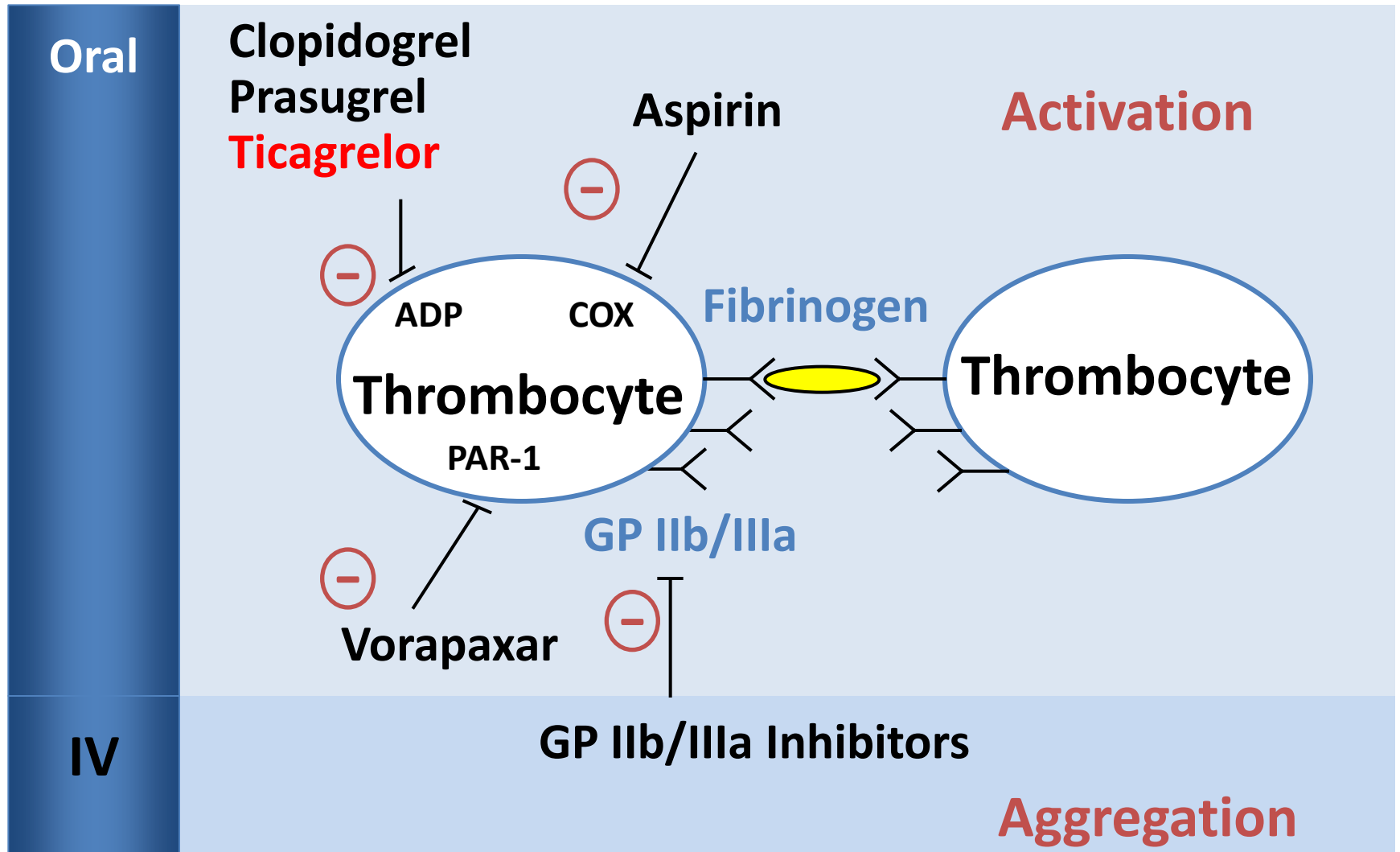
Affiliation/Financial Relationship

1. Honoraria for lectures
2. Honoraria for advisory board activities
3. Participation in clinical trials
4. Financial shares and options:

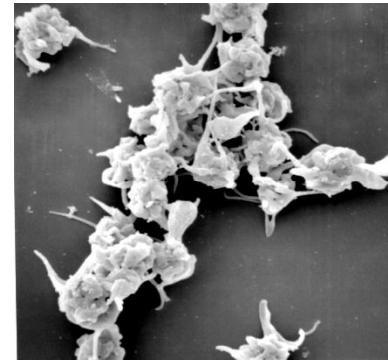
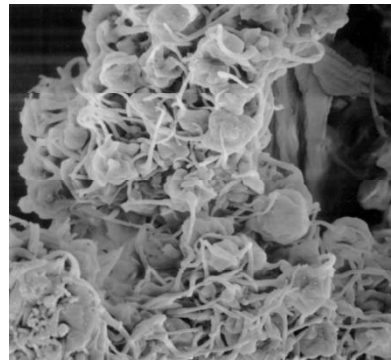
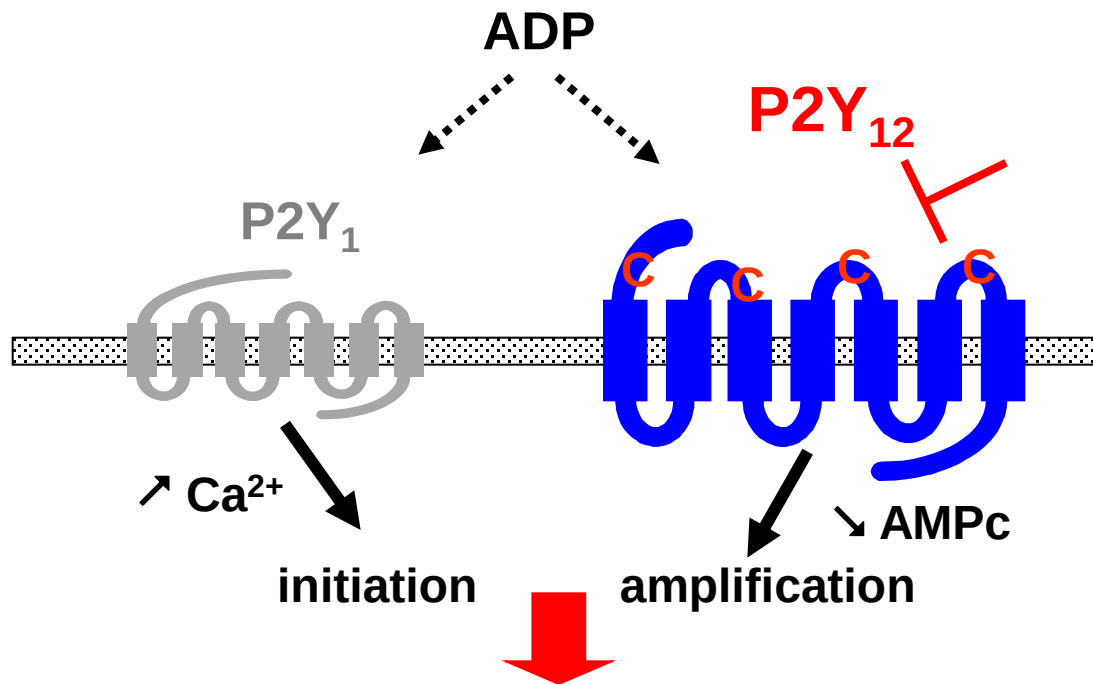
Company

Abbott, AstraZeneca , Berlin Chemie, Boehringer. MSD Ingelheim, BMS, Brahms, Daiichi Sankyo, Essex, GSK, Medtronic, Lilly, SanofiAventis, Iroko, Pfizer, Roche, AstraZeneca, BRAHMS, Boehringer Ingelheim, Medtronic AstraZeneca, MSD, Braun, Boston Scientific, Takeda, GSK, The Med. Comp. no

Anti-Platelet Therapy



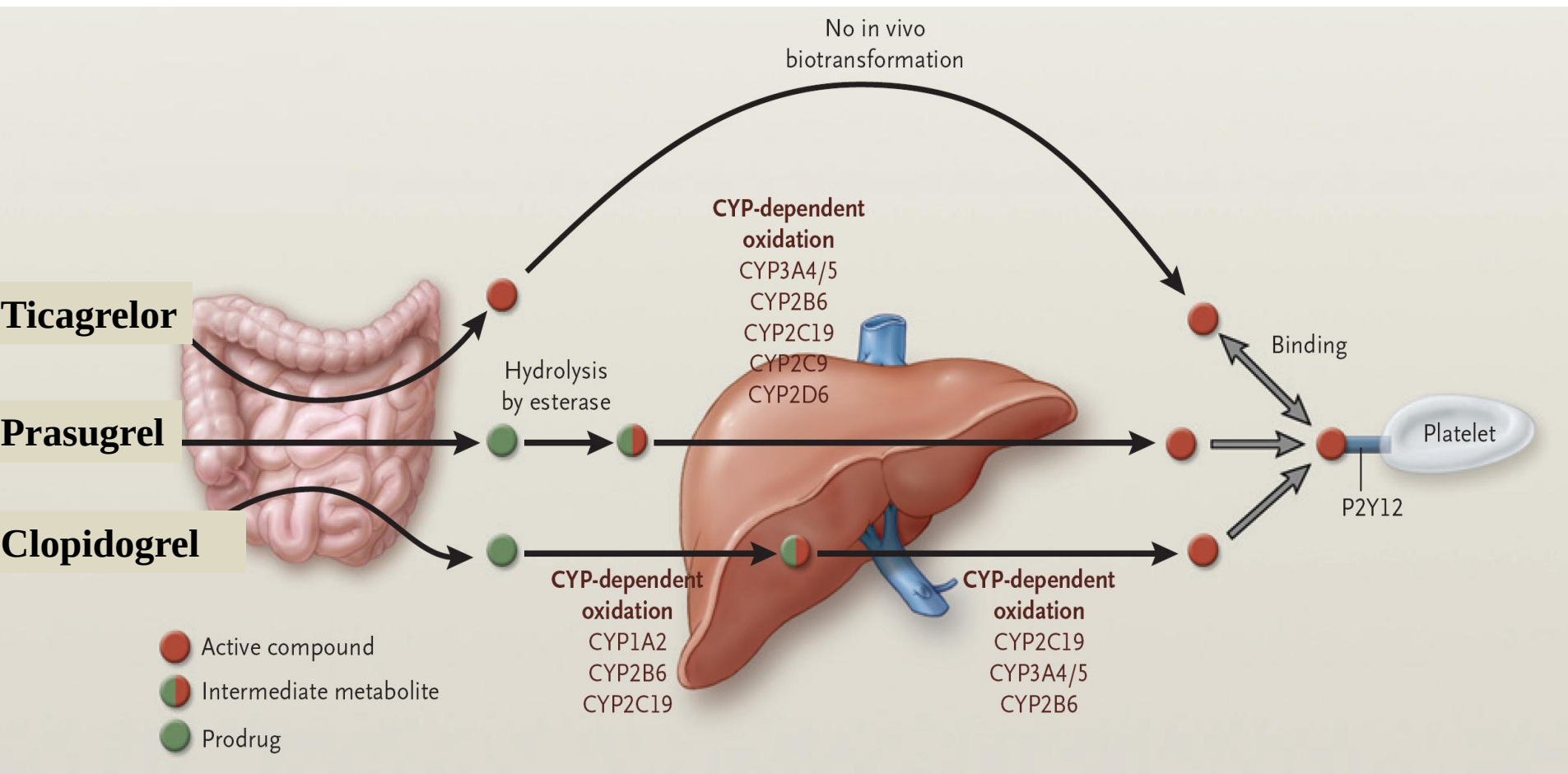
P2Y₁₂ Receptor Blockade



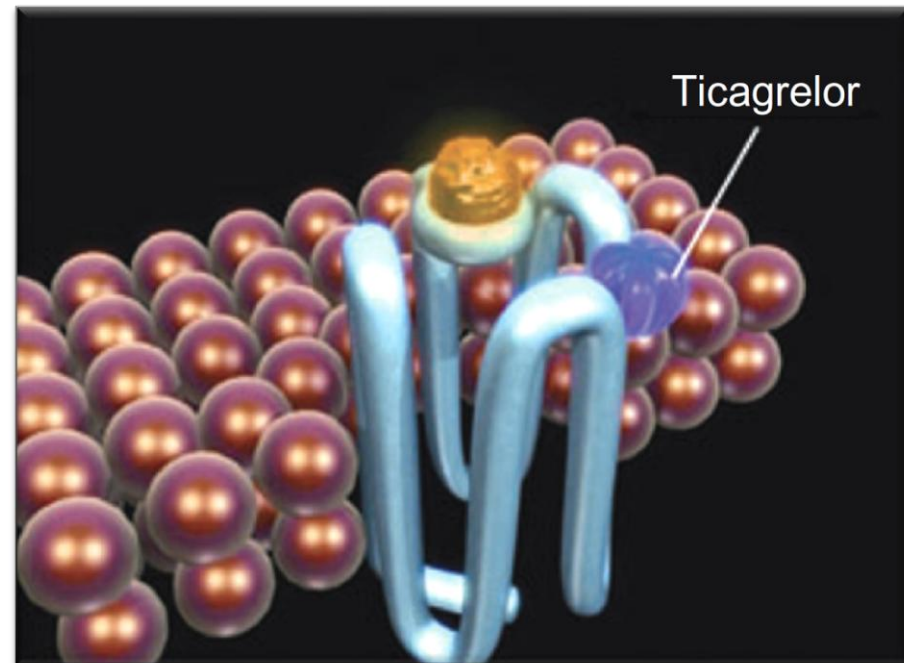
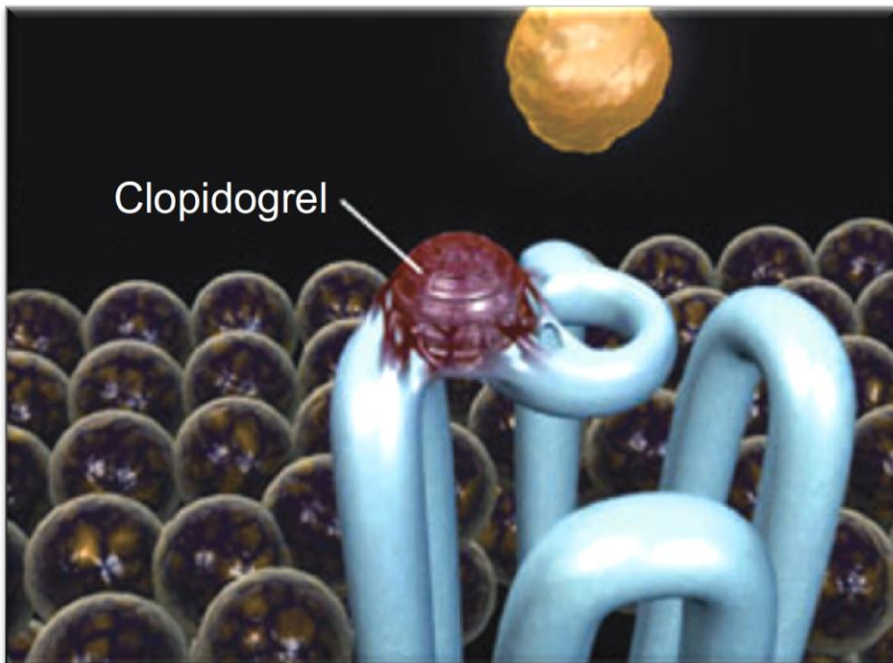
P2Y₁₂ Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Binding	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolism	Prodrug, not limited by metabolism	Active drug
Nonresponders	Yes	No	No
Onset of Effect	2–4 h	30 min	30 min
Duration of Effect	3–10 days	5–10 days	3–4 days
Withdrawal Before Major Surgery	5 days	7 days	5 days

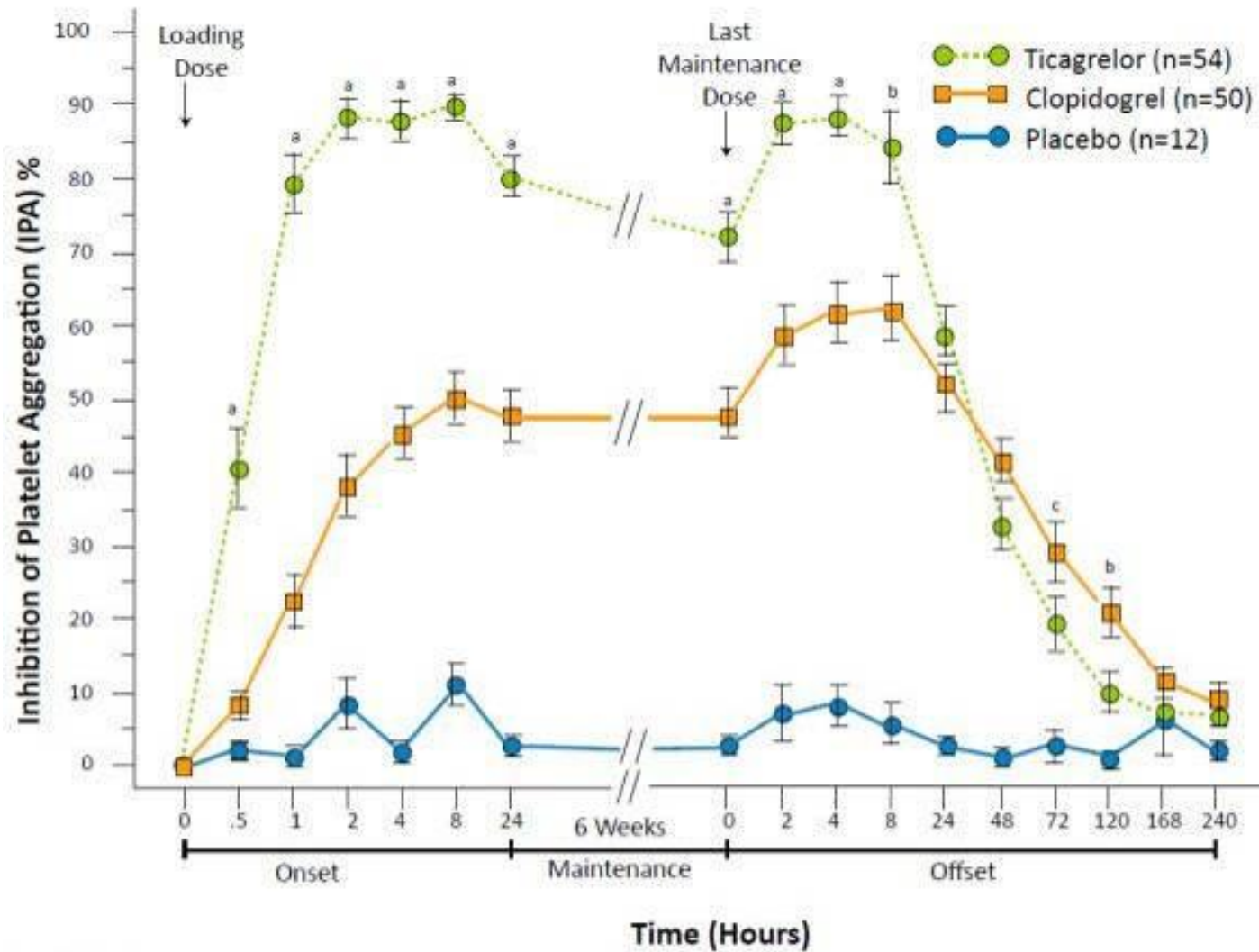
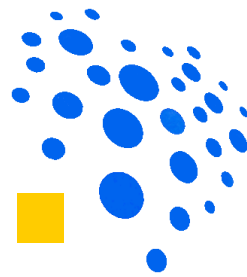
Metabolism of P2Y₁₂ Inhibitors



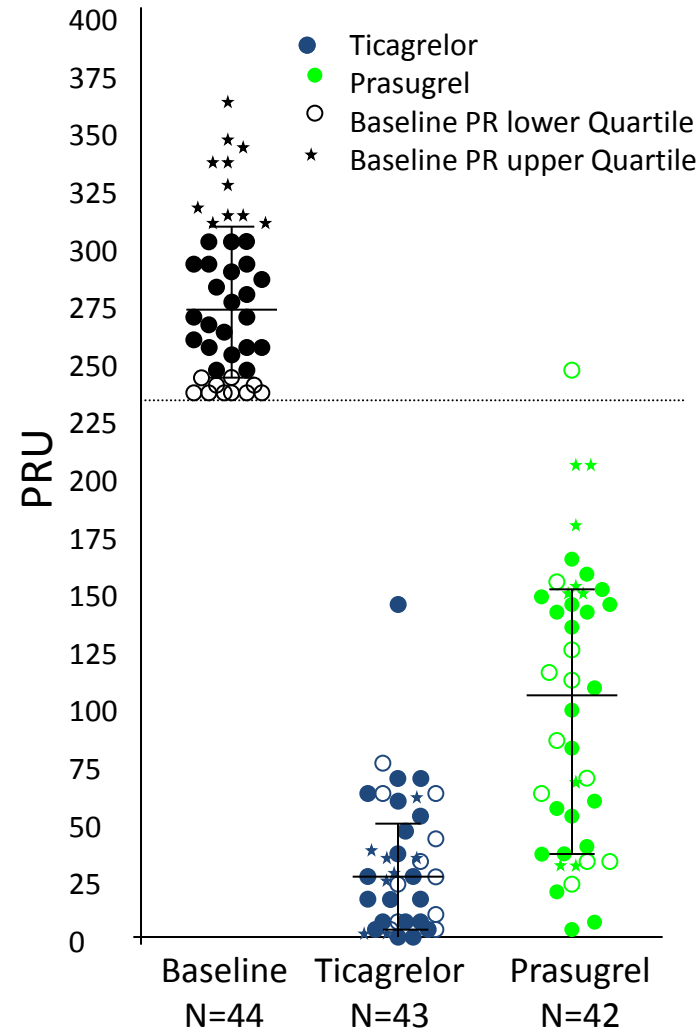
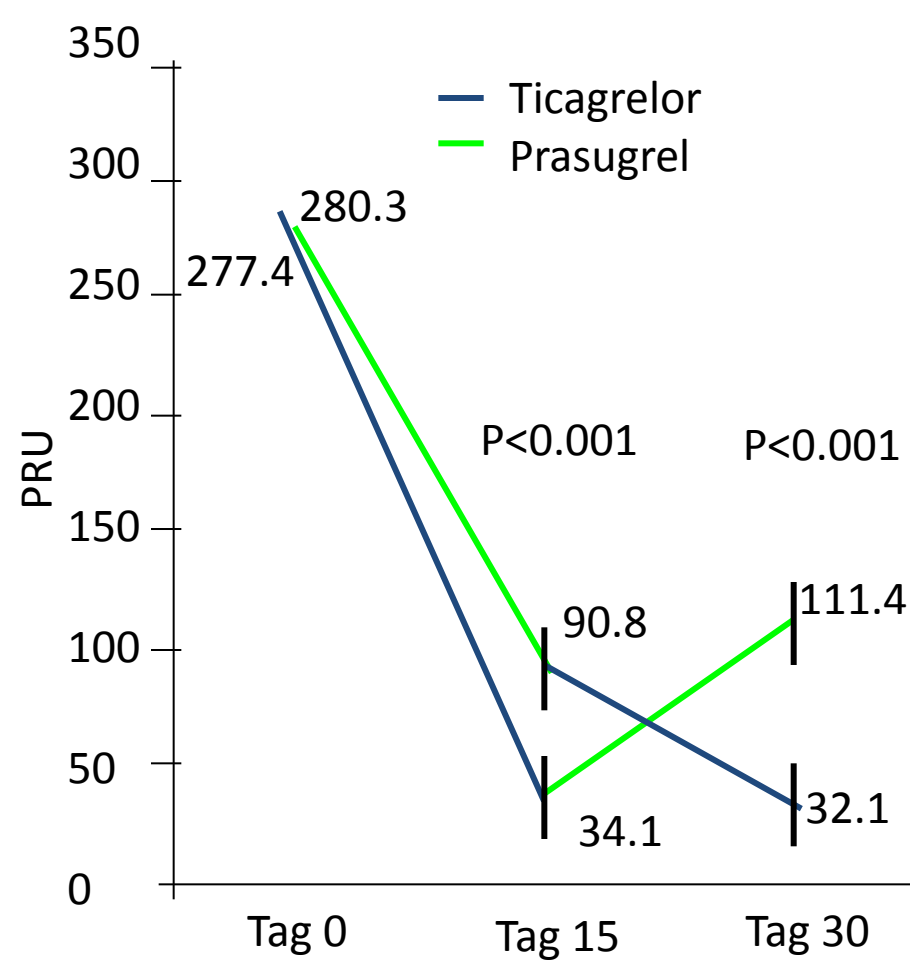
Binding Sites to P2Y₁₂



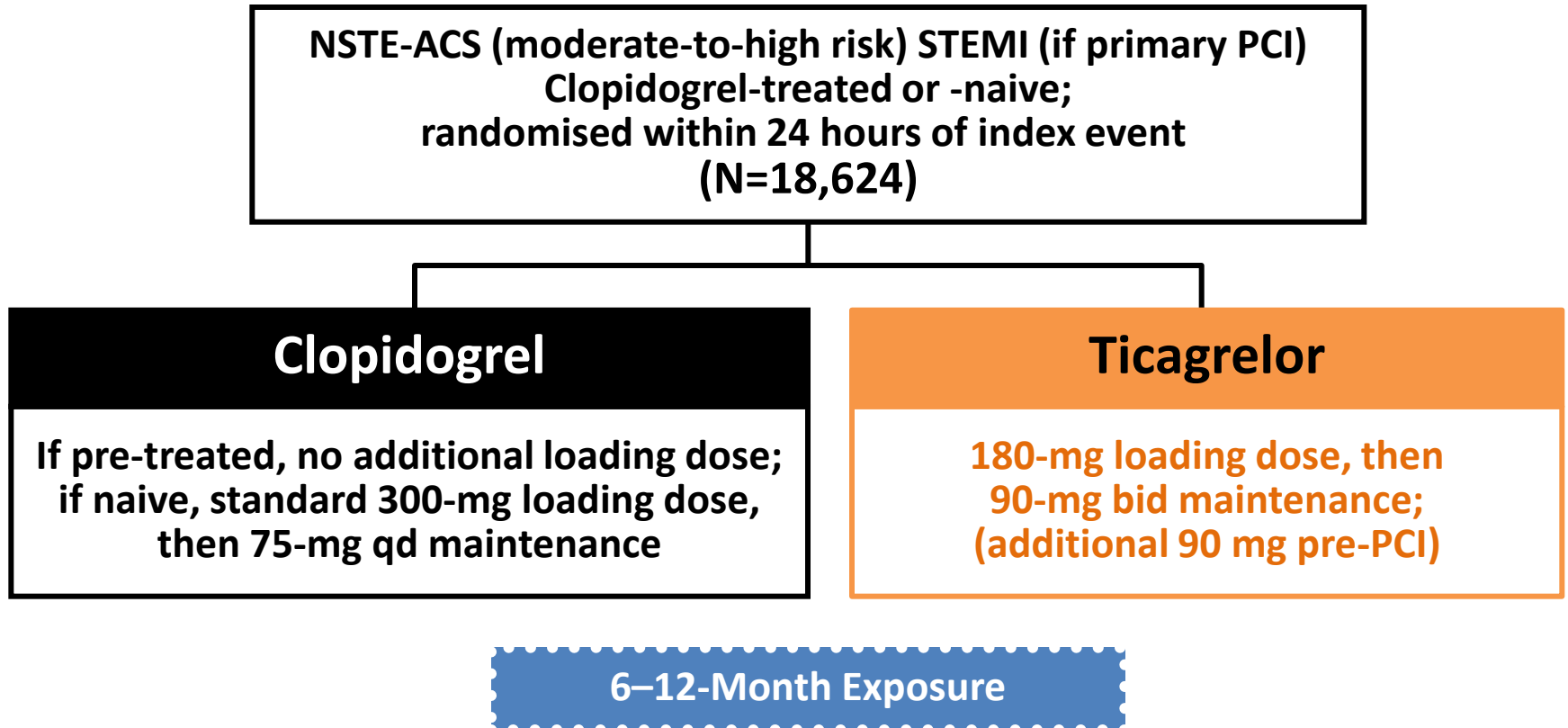
Antiplatelet Effect Clopidogrel vs. Ticagrelor



Prasugrel vs. Ticagrelor: Platelet Inhibition

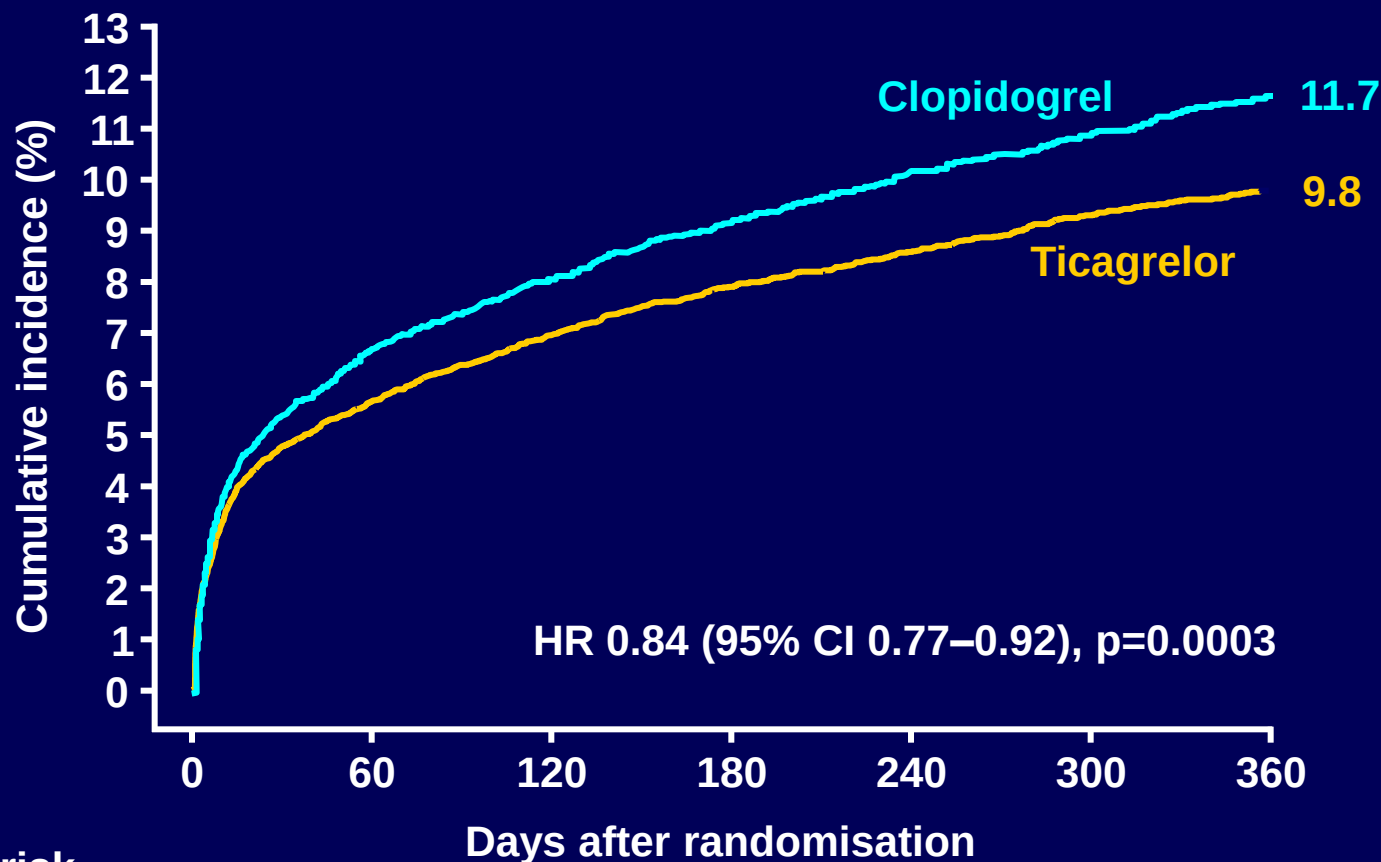


PLATO Study Design



Primary End Point: CV Death + MI + Stroke
Primary Safety End Point: Total major bleeding

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



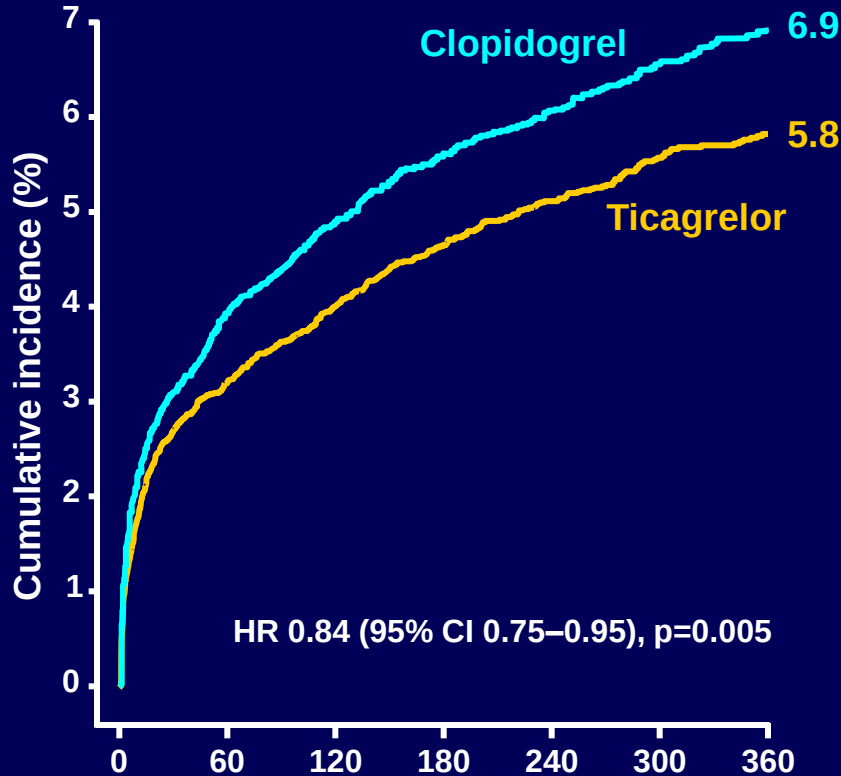
No. at risk

	0	60	120	180	240	300	360
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

Myocardial infarction

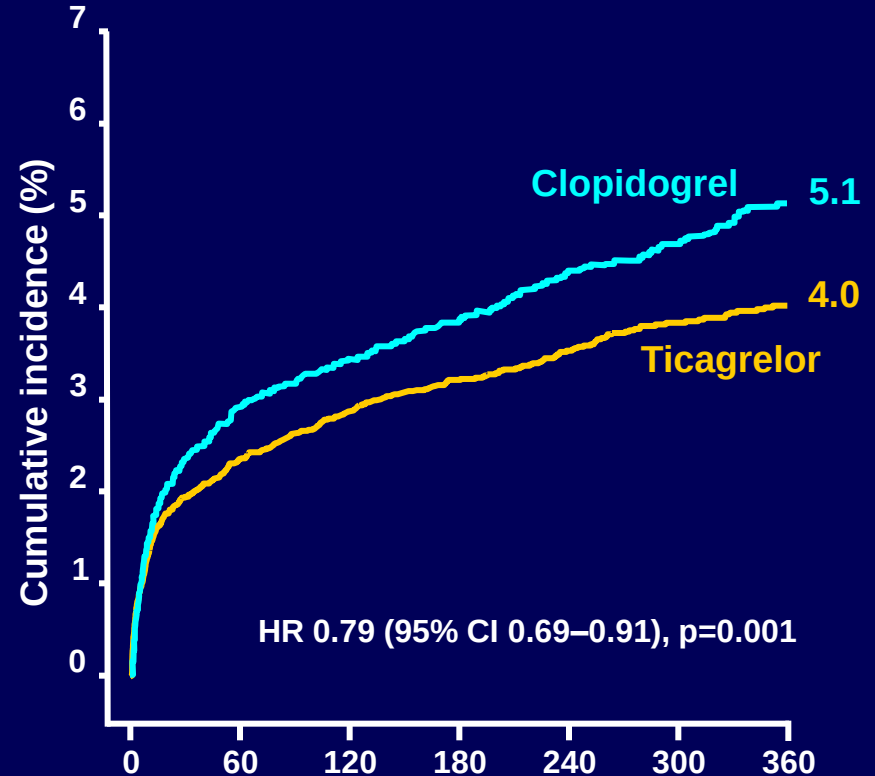


No. at risk

Days after randomisation

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

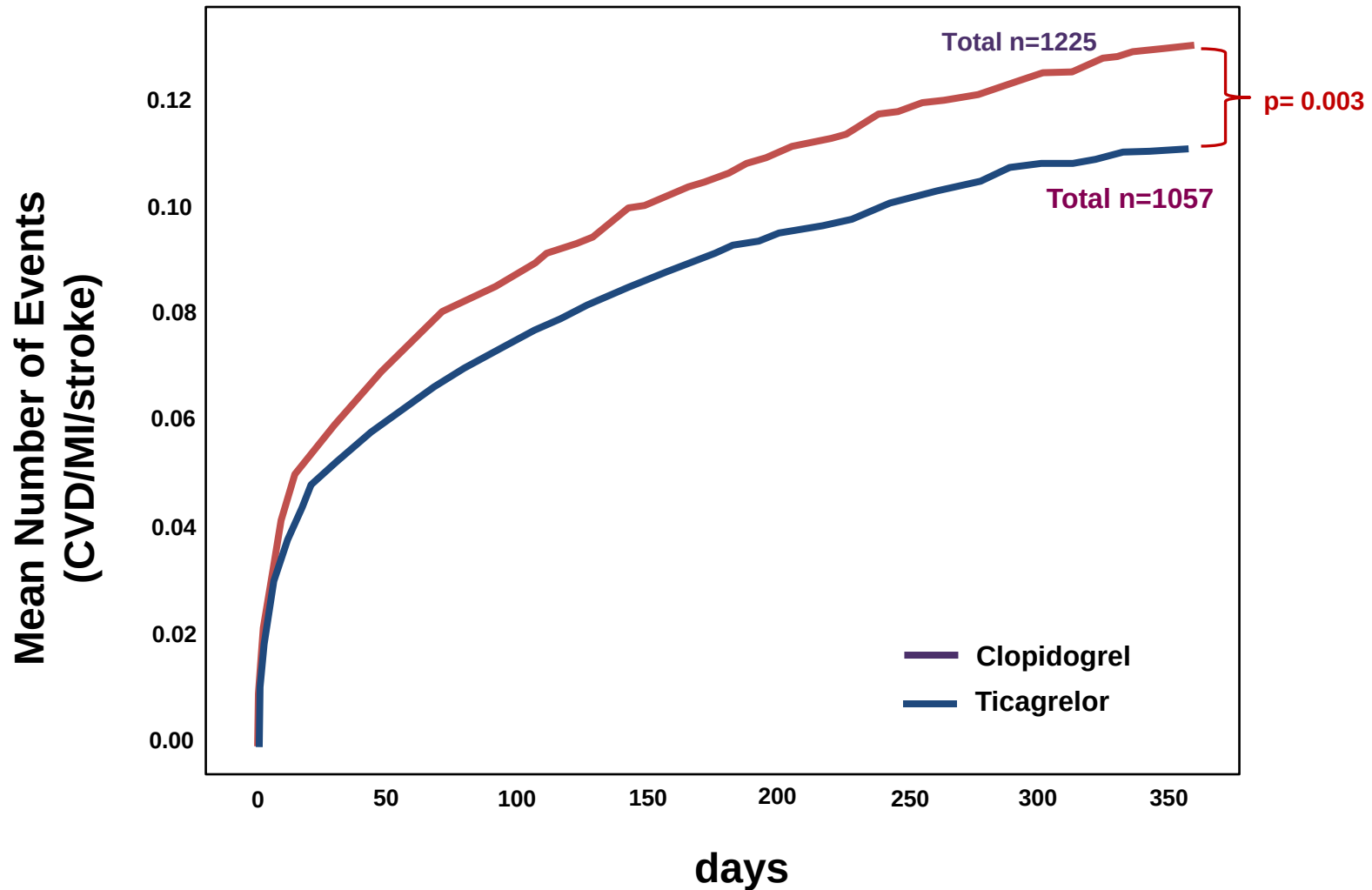
Cardiovascular death



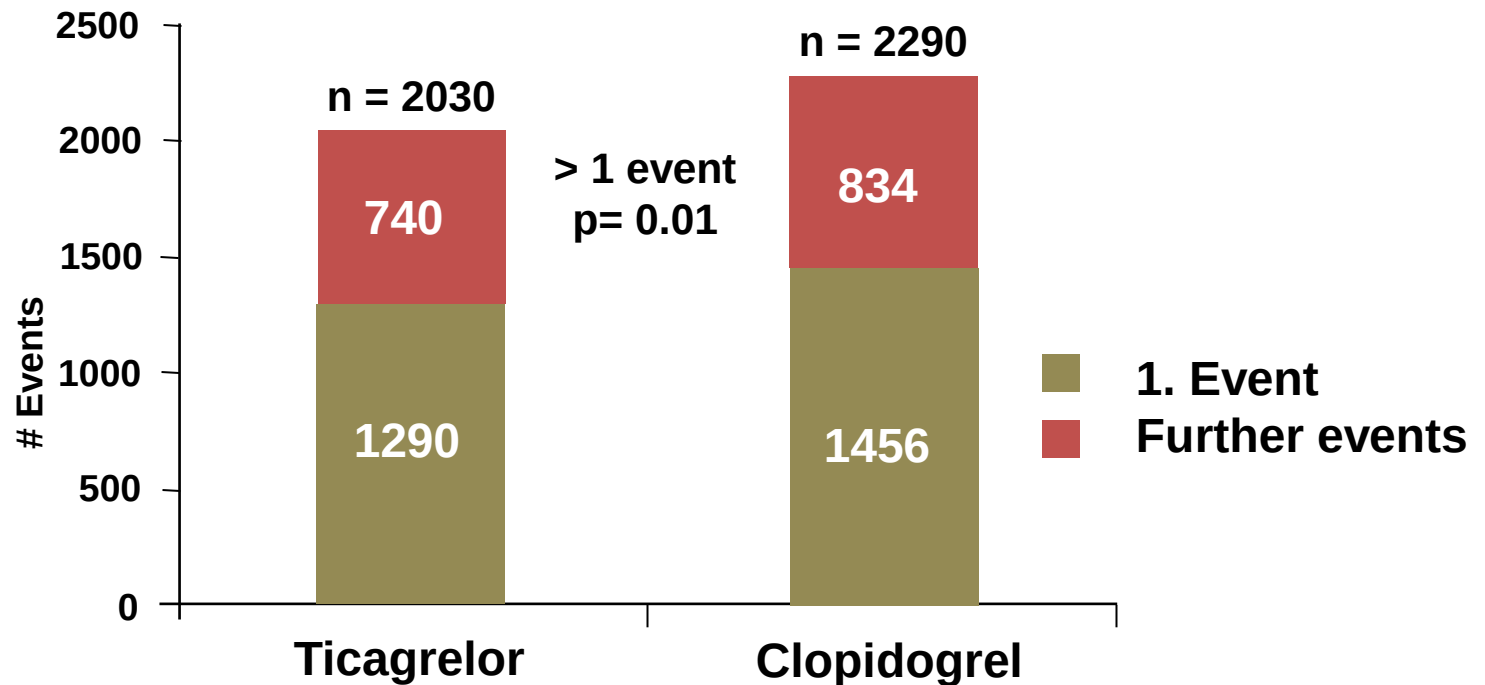
Days after randomisation

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

Clinical Events per Patient



Reduction of Clinical Events under Ticagrelor in PLATO

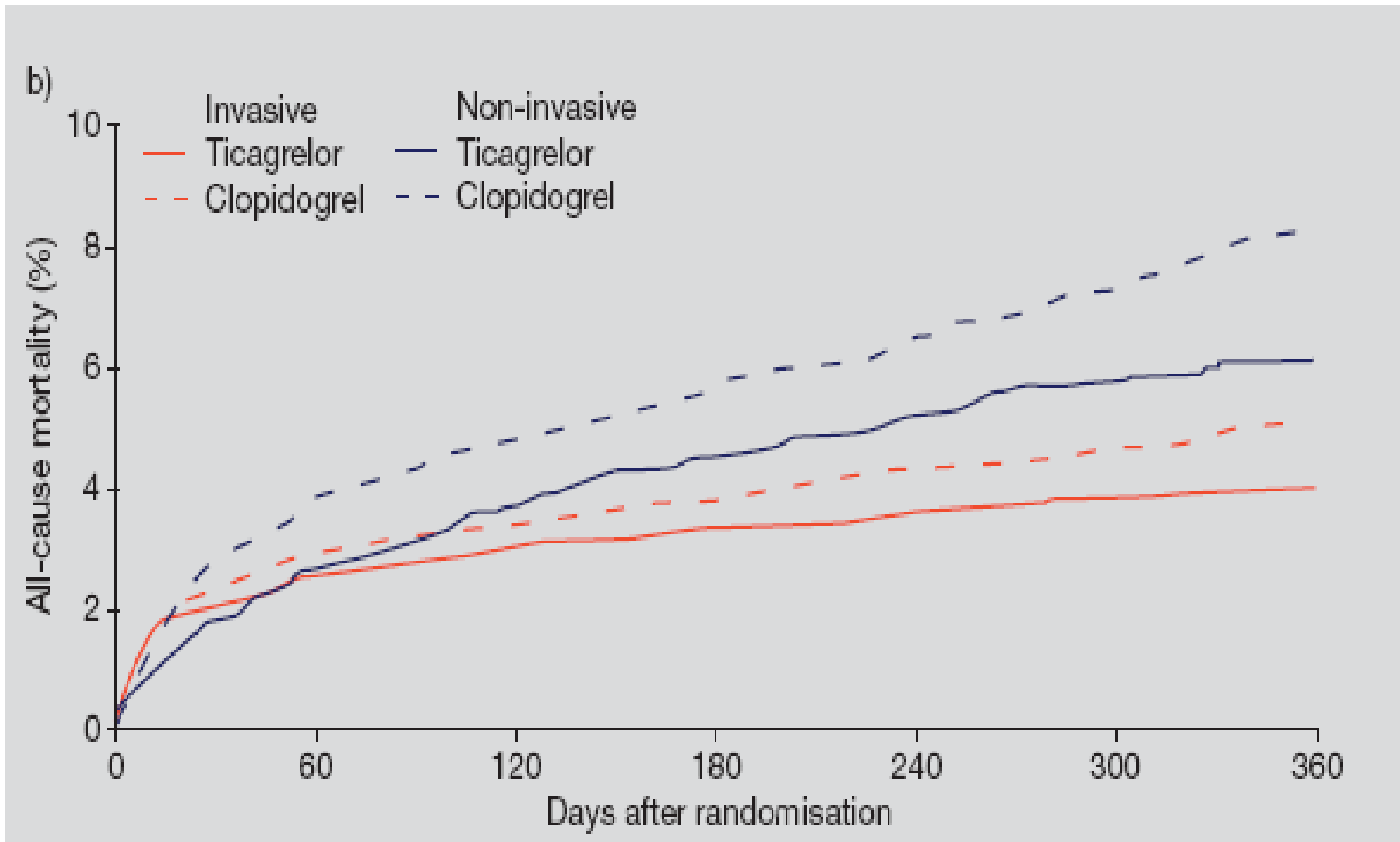


inkl. CV Death/MI/Stroke/SRI/RI/TIA/ATE
(severe) recurrent ischemia (SRI/RI), transient ischemic attack (TIA), arterial thromboses (ATE)

Ticagrelor versus Clopidogrel – Invasive/ Non-invasive

(sub-analysis of PLATO Trial)

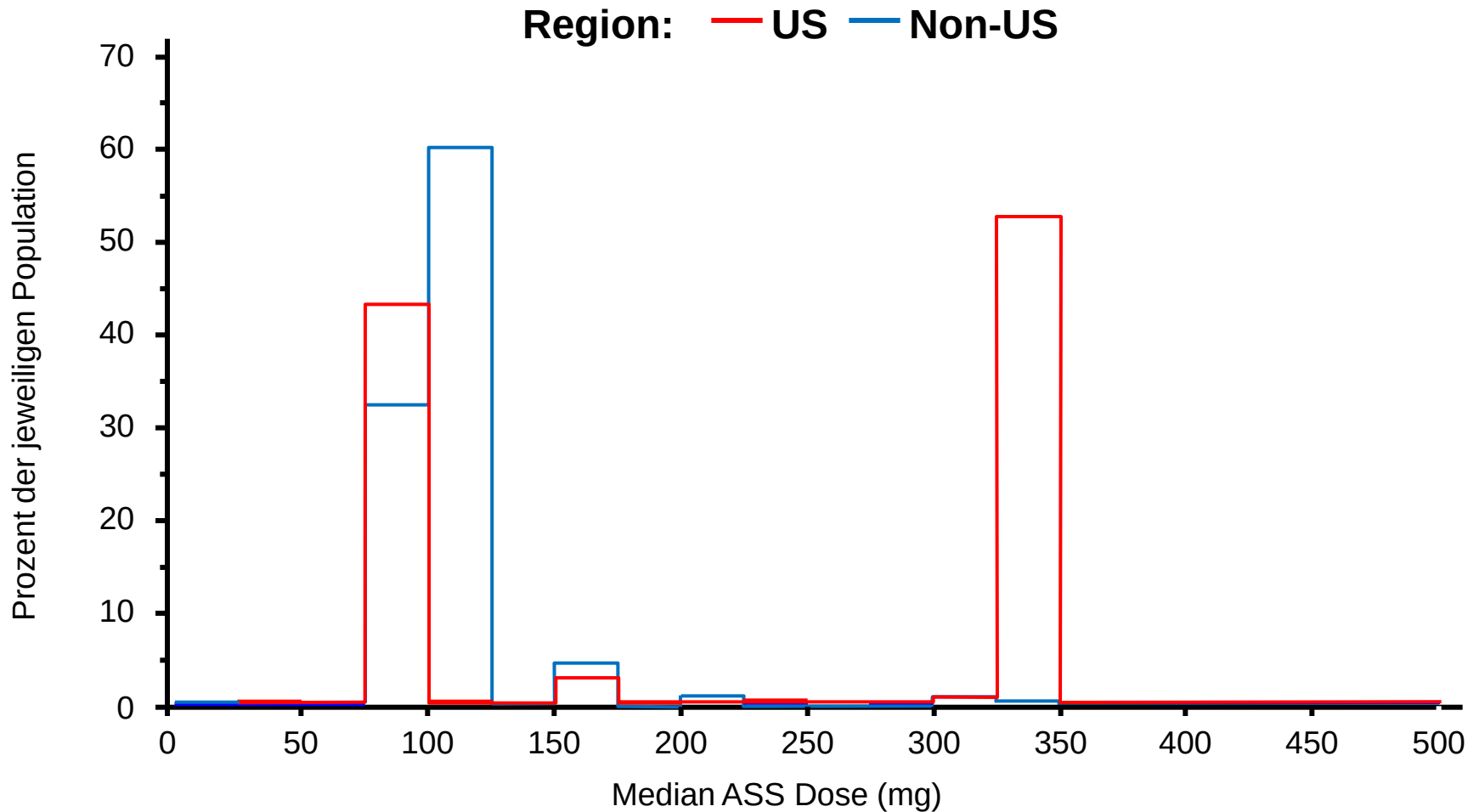
- Cumulative all-cause mortality in patients intended for invasive and non-invasive management.



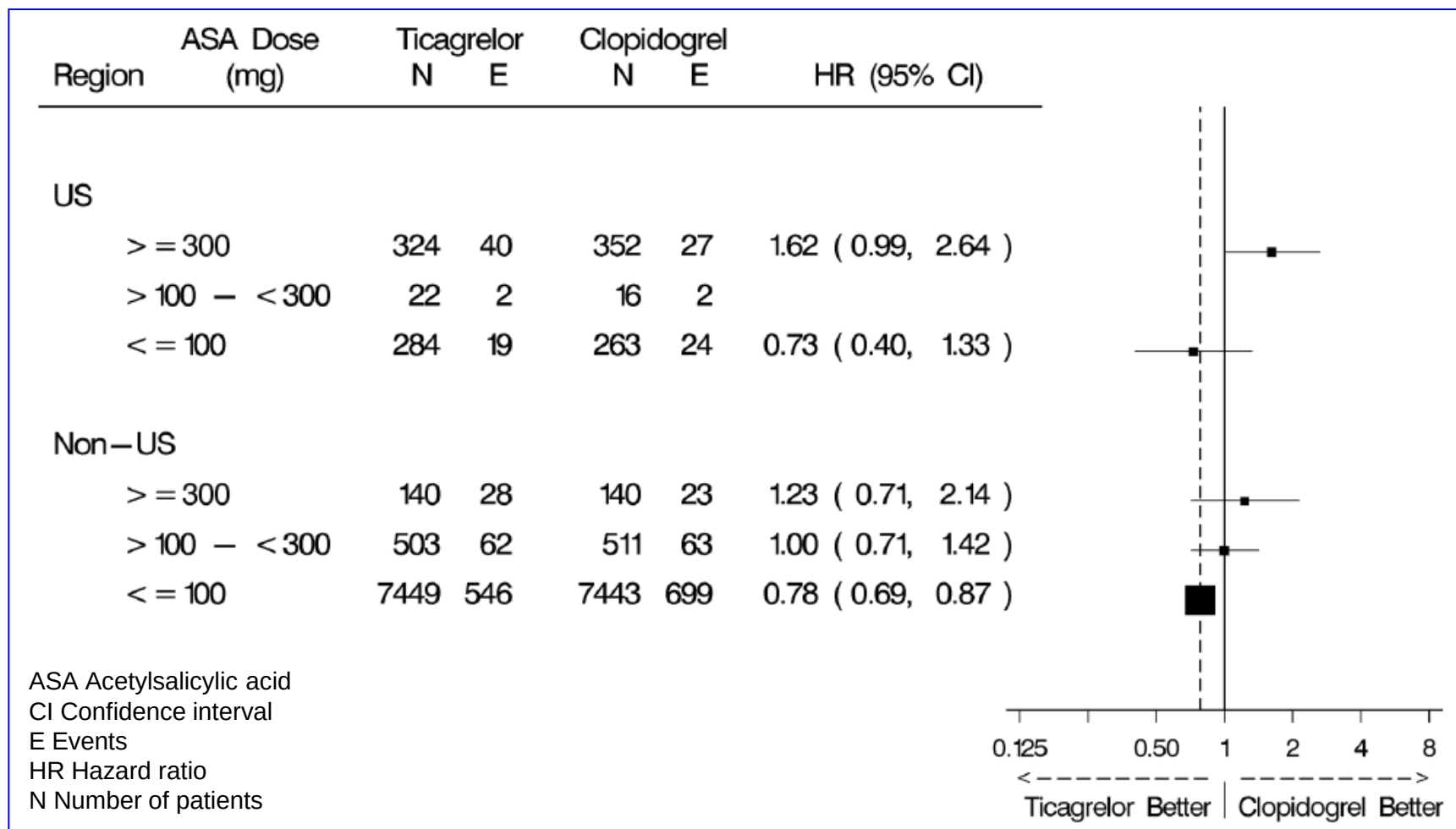
Hazard Ratios and Rates of Primary End Point in Predefined Subgroups of Study Patients

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12		HR (95% CI)	P value (Interaction)
			Ti.	CI.		
Region						0.05
Asia/Australia		1714	11.4	14.8	0.80 (0.61, 1.04)	
Central/South America		1237	15.2	17.9	0.86 (0.65, 1.13)	
Europe/Middle East/Africa		13859	8.8	11.0	0.80 (0.72, 0.90)	
North America		1814	11.9	9.6	1.25 (0.93, 1.67)	

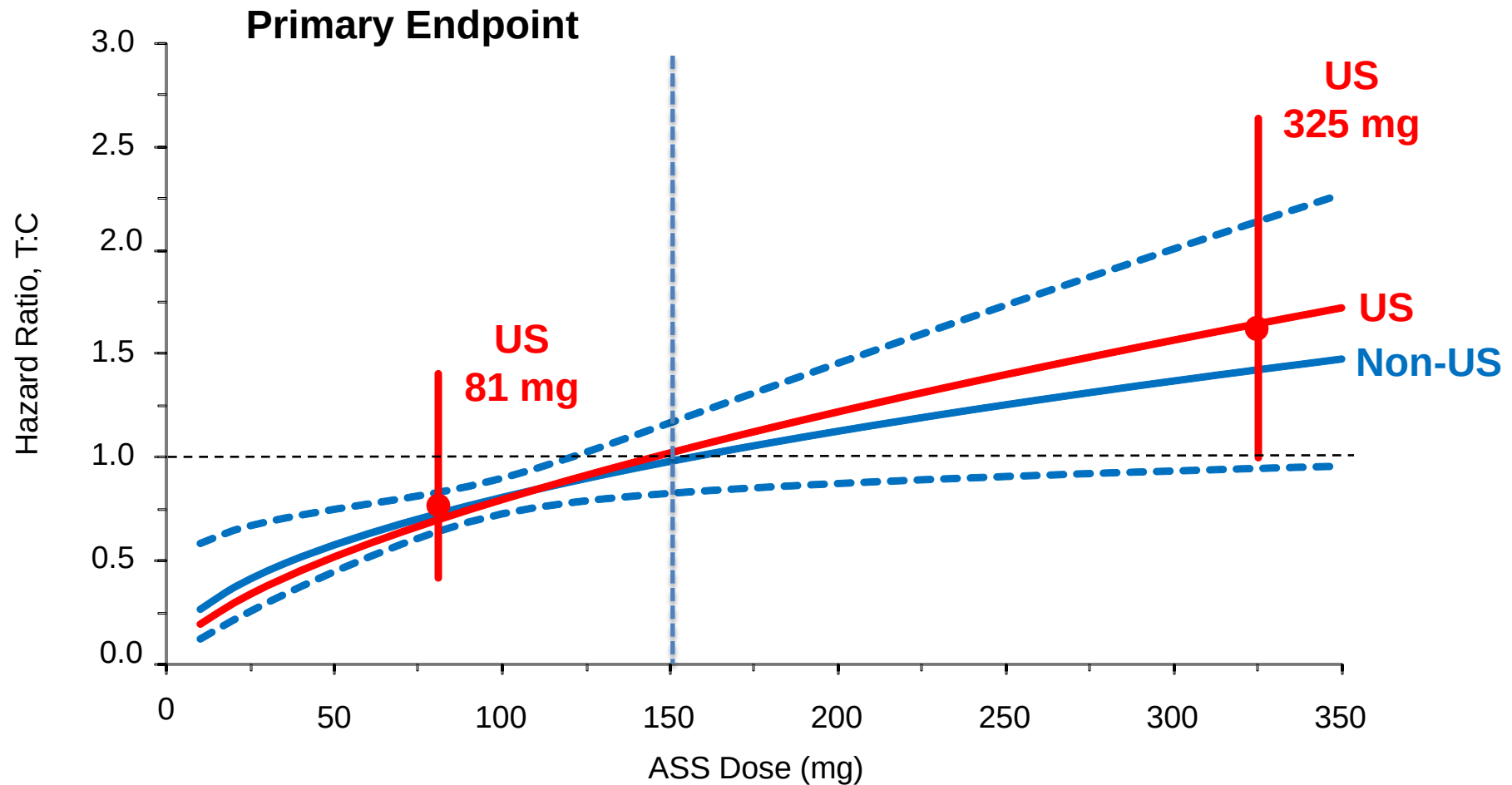
PLATO: Distribution of ASA Dose



ICAC-adjudicated primary endpoint by ASA dose category and treatment for US and non-US

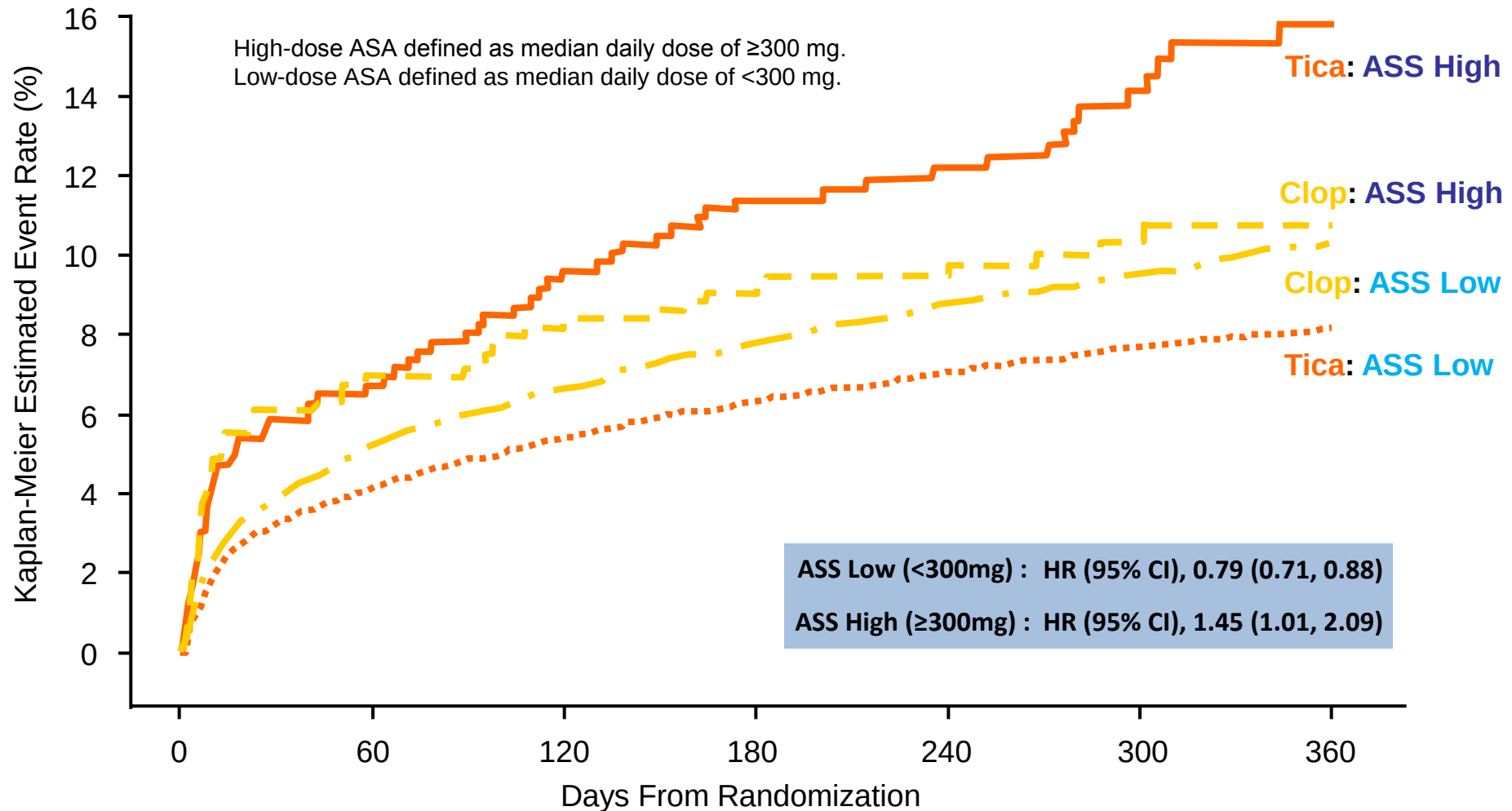


Optimal ASA Dose

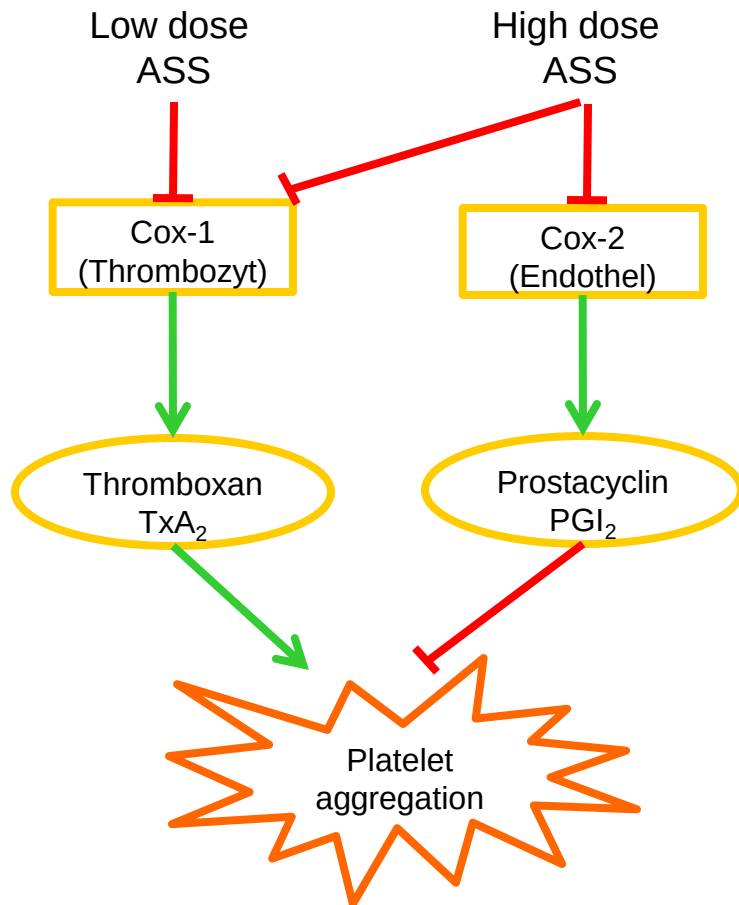


KAPLAN-MEIER PLOT OF ICAC-ADJUDICATED PRIMARY ENDPOINT BY TREATMENT GROUP AND ASA DOSE CATEGORY

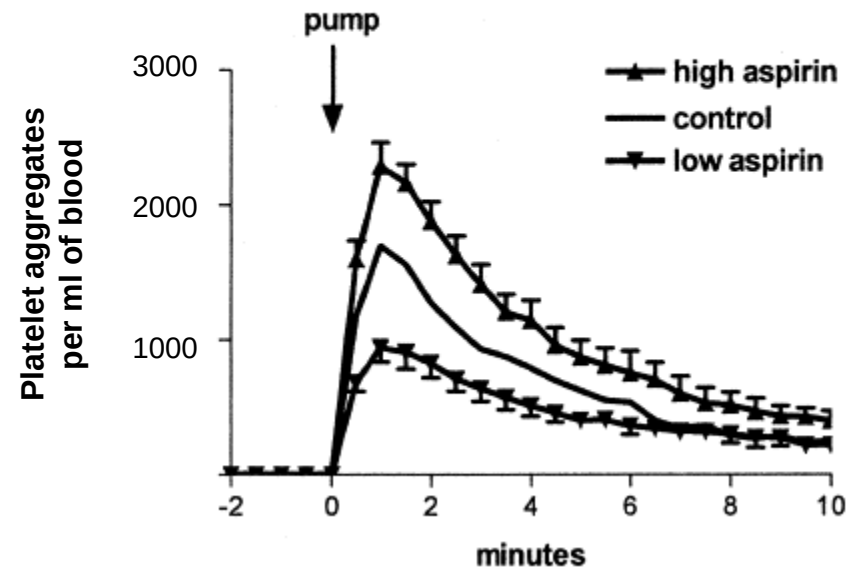
– PLATO FULL ANALYSIS SET



ASA-Hypothesis: High dose ASA blocks PGI₂-Production



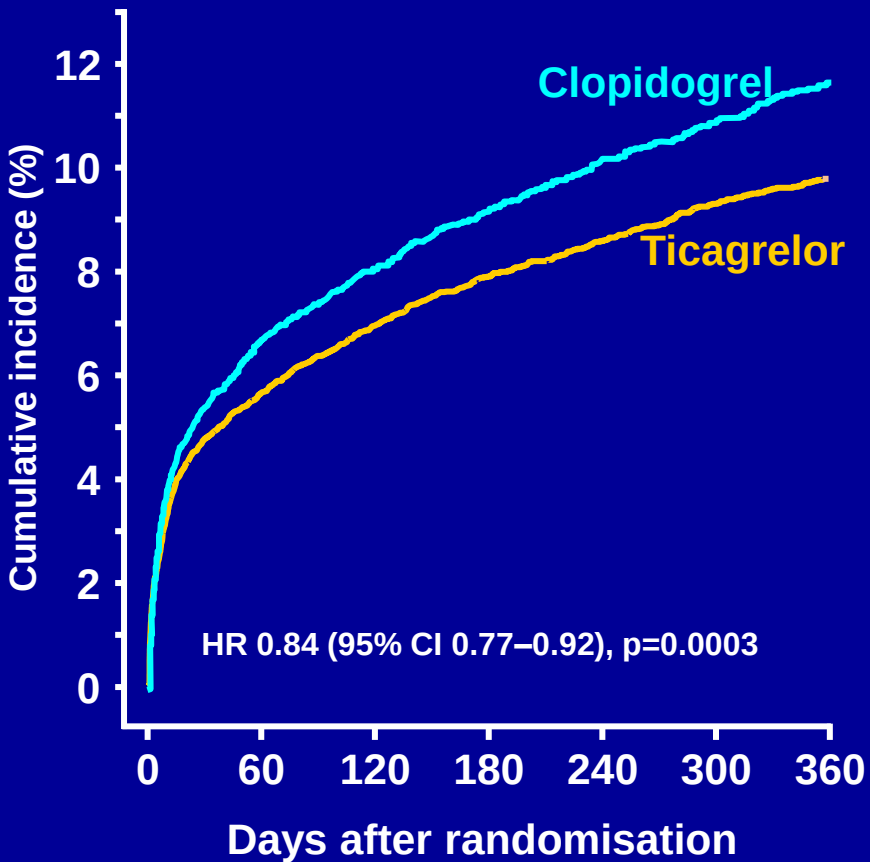
Dose dependent Platelet aggregation¹



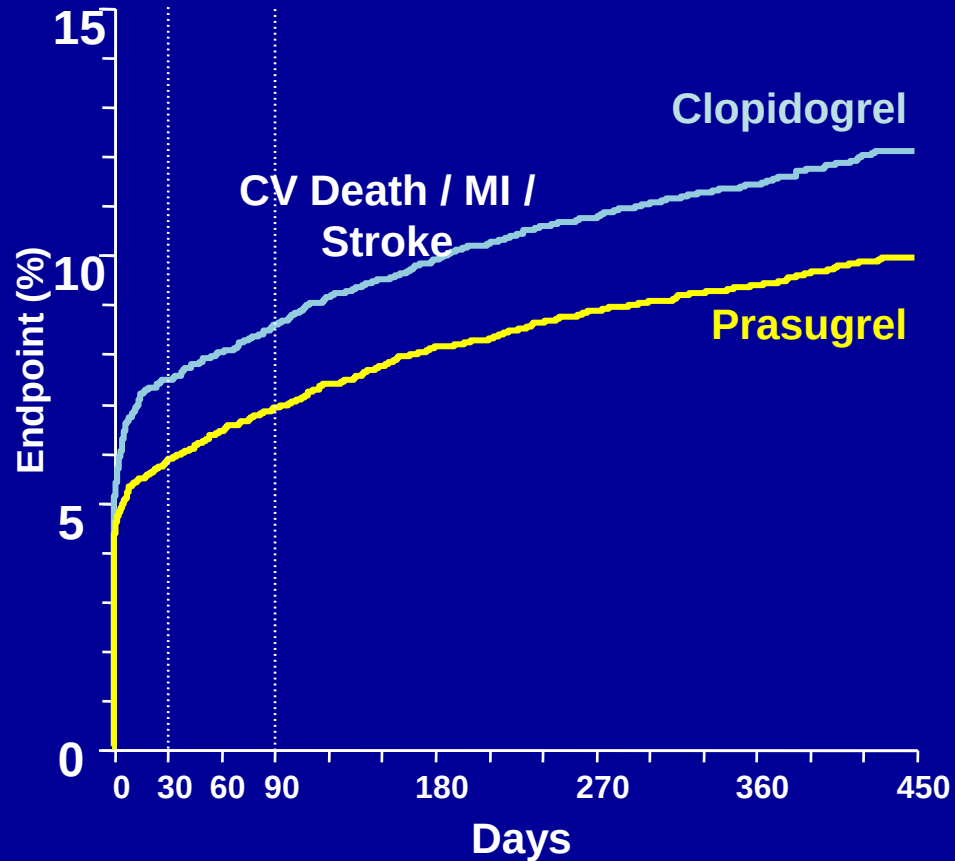
Warner TD et al. Br J Clin Pharmacol. **2011** Feb 15.

Mahaffey KW et al. Circulation 2011; Jun 27.

Mod. Borgdorff P. et al. Journal of the American College of Cardiology 2006 48:4 (817-823)

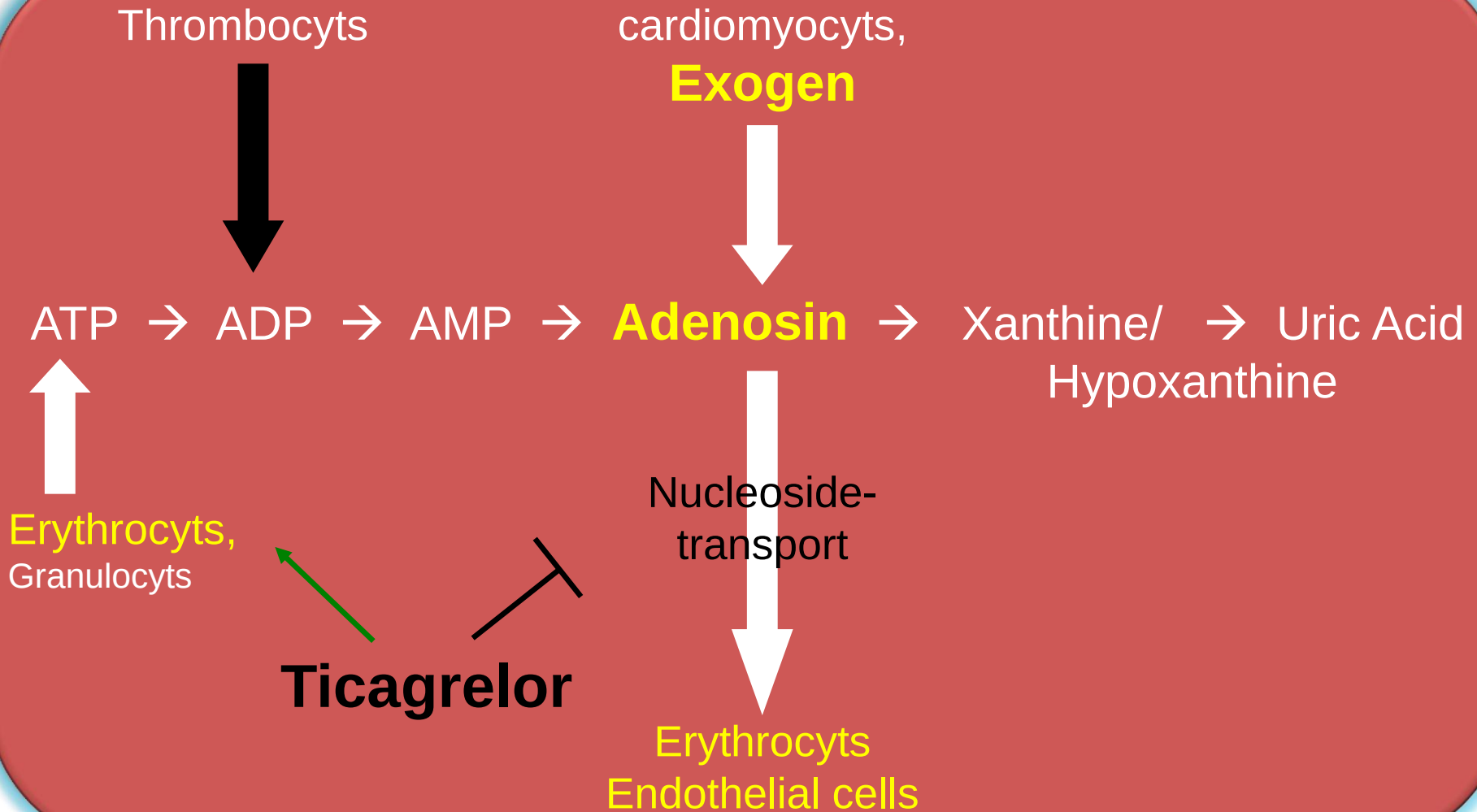


PLATO

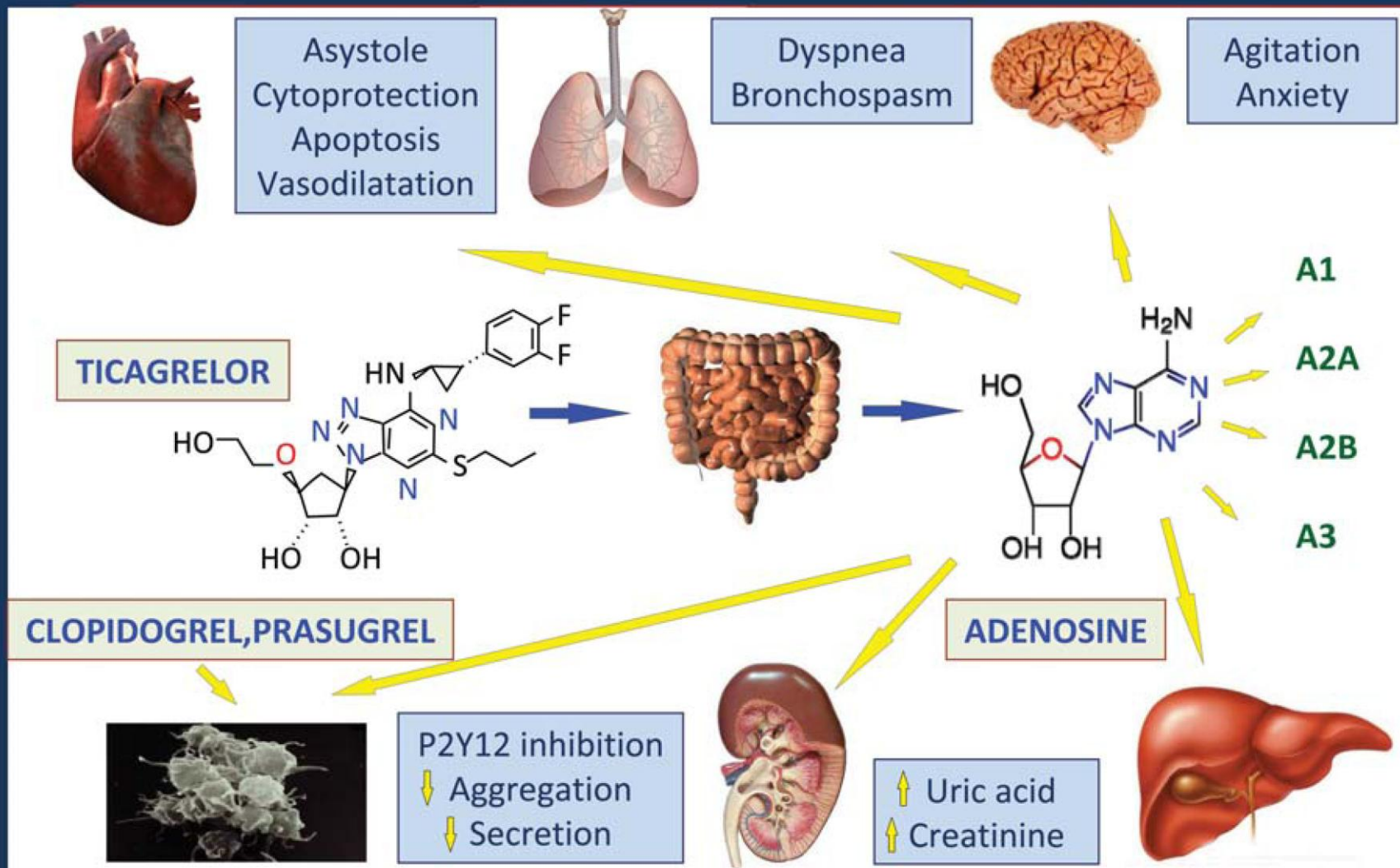


TRITON

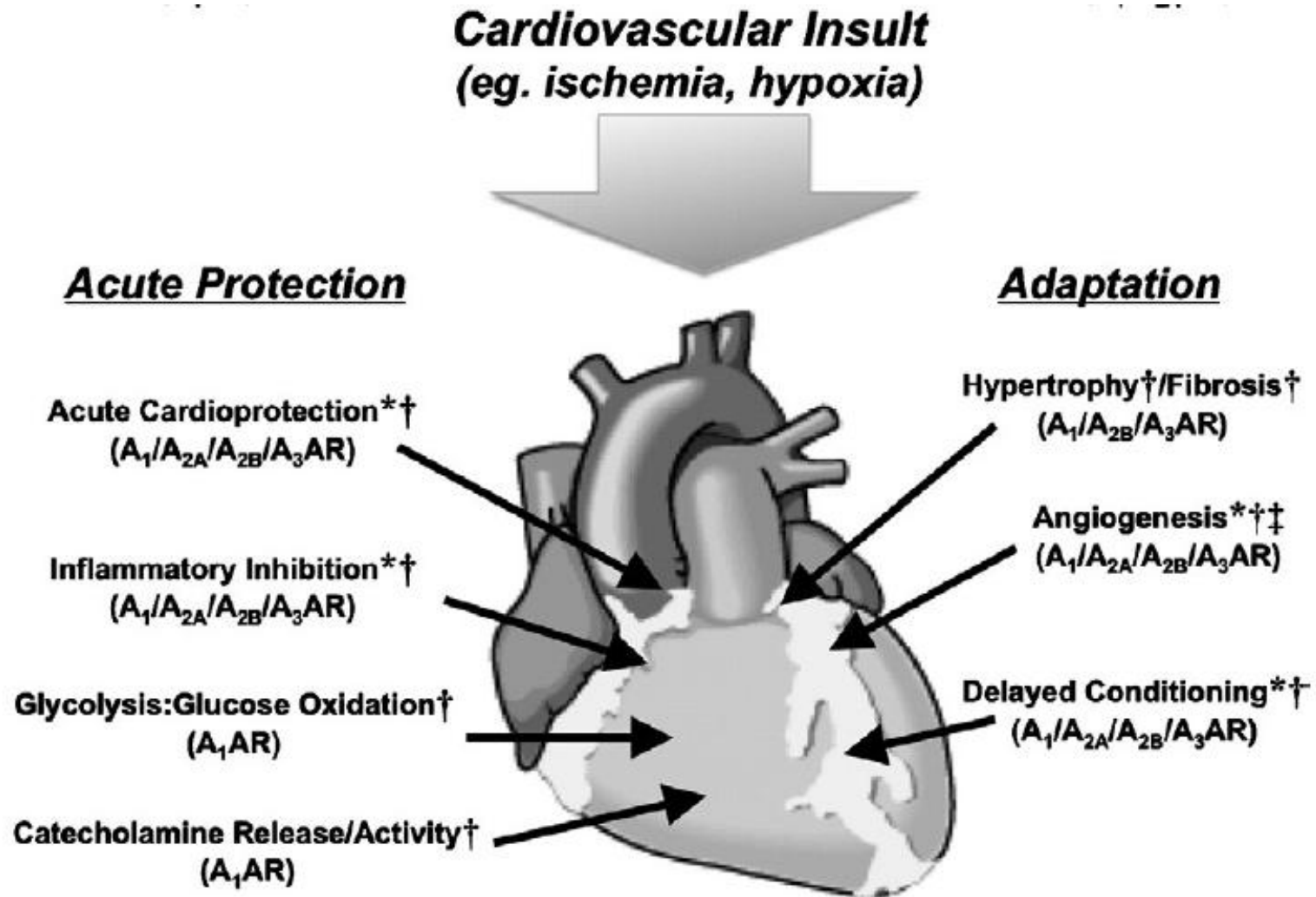
Adenosine Metabolism



Ticagrelor: Potential Mechanism of Action

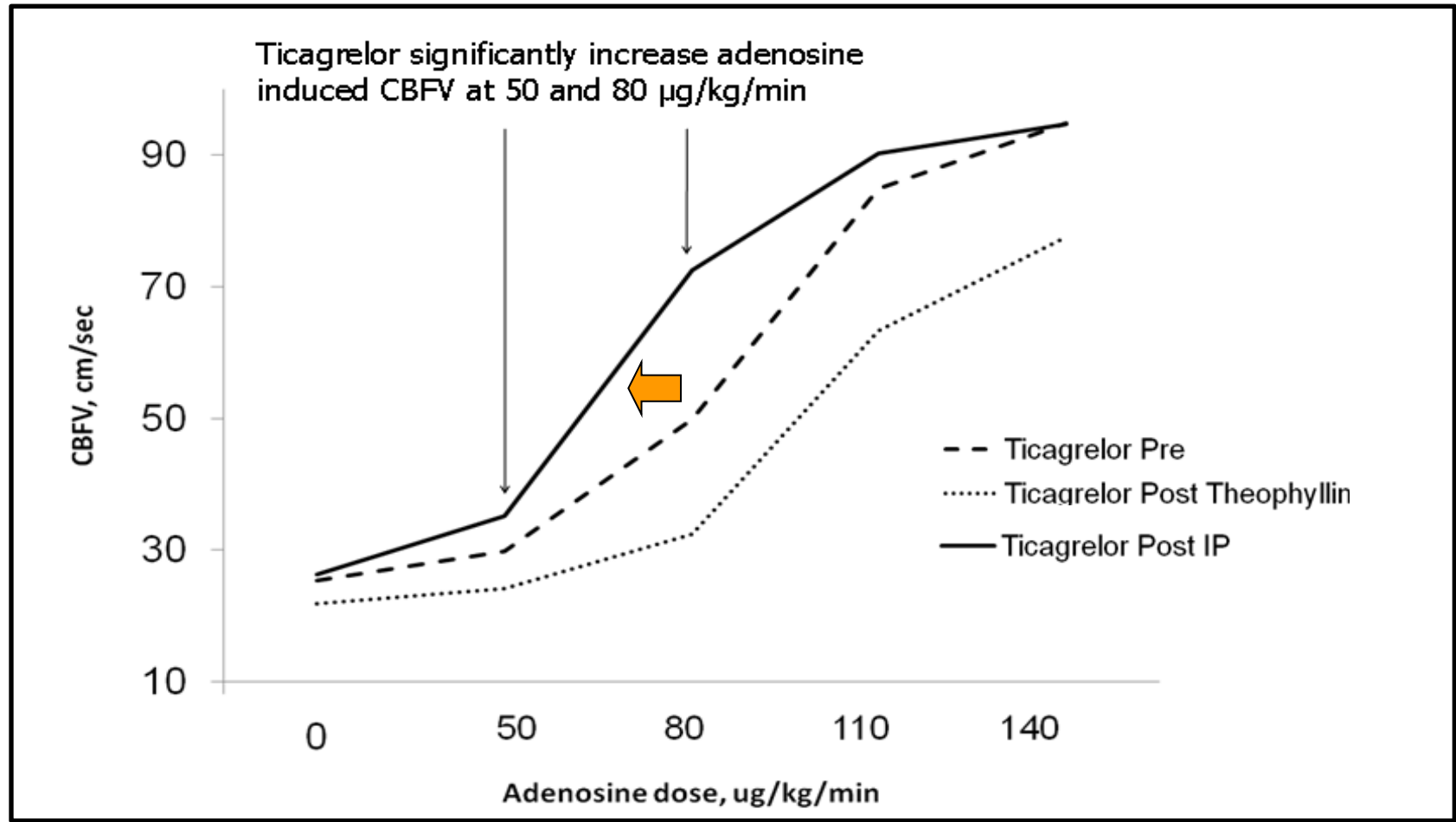


Adenosine Effects on Myocardium



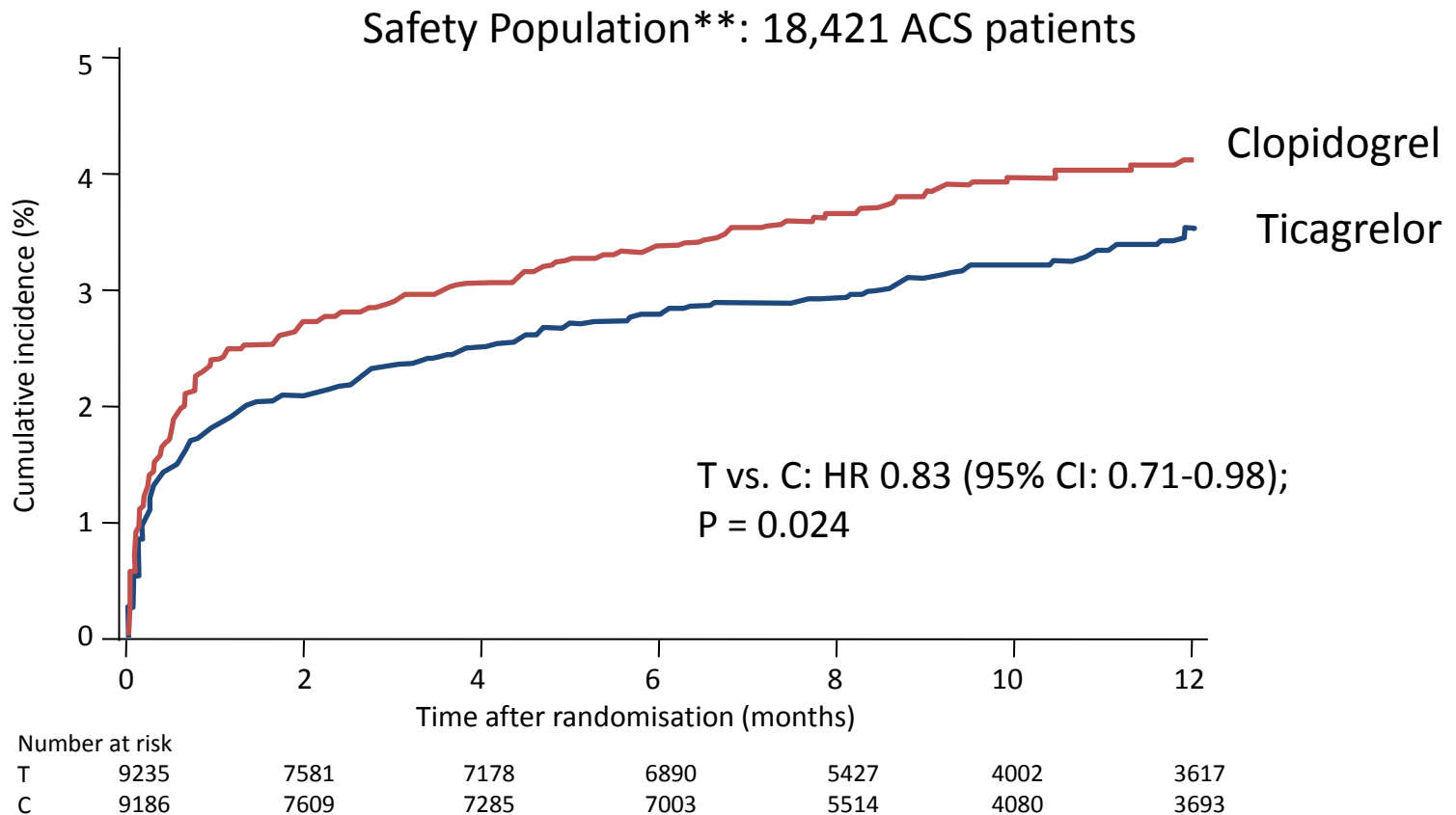
* - support from human tissue studies; † - supported from animal models; ‡ - speculative/debated

Ticagrelor Increases Blood Flow



Time to Pulmonary AE on Treatment*

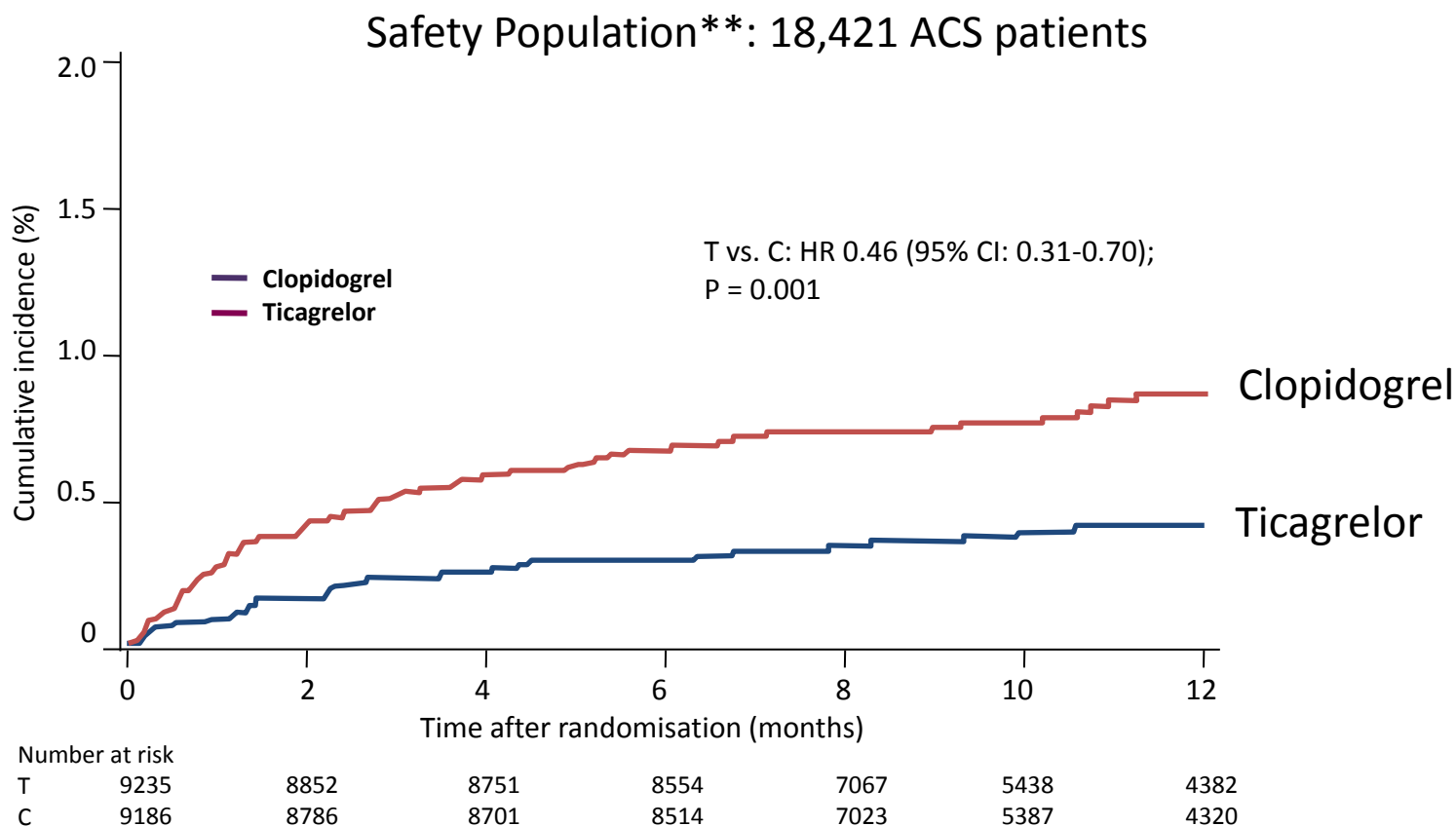
Pulmonary Infection or Sepsis



* Within 7 days of last intake of study drug

** received at least one dose of study medication

Time to death following pulmonary AE on-treatment* – an exploratory post-hoc analysis



* Within 7 days of last intake of study drug

** received at least one dose of study medication





Thank you !

What do the Guidelines Recommend?



KERCKHOFF
KLINIK



European Heart Journal (2008) 29, 2909–2945
doi:10.1093/eurheartj/ehn416

ESC GUIDELINES

Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation

The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology:

Authors/Task Force Members: Frans Van de Werf, Chairperson (Belgium), Jeroen Bax (The Netherlands), Amadeo Betriu (Spain), Carina Blomstrom-Lundqvist (Sweden), Filippo Crea (Italy), (Germany), Gerasimos Filippatos (Greece), Keith Fox (Germany), Adnan Kastrati (Germany), Annika Rosengren (Sweden), Marco Tubaro (Italy), Freek Verheugt (The Netherlands), Michael Weis (Germany)

ESC/EACTS GUIDELINES

Guidelines on myocardial revascularization
The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)
Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI)



European Heart Journal
doi:10.1093/eurheartj/ehq277



European Heart Journal
doi:10.1093/eurheartj/ehr236

ESC GUIDELINES

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Christian W. Hamm (Chairperson) (Germany)*, Jean-Pierre Bassand (Co-Chairperson)*, (France), Stefan Agewall (Norway), Jeroen Bax (The Netherlands), Eric Boersma (The Netherlands), Hector Bueno (Spain), Pio Caso (Italy), Dariusz Dudek (Poland), Stephan Gielen (Germany), Kurt Huber (Austria), Magnus Ohman (USA), Mark C. Petrie (UK), Frank Sonntag (Germany), Miguel Sousa Uva (Portugal), Robert F. Storey (UK), William Wijns (Belgium), Doron Zahger (Israel).

ESC Committee for Practice Guidelines: Jeroen J. Bax (Chairperson) (The Netherlands), Angelo Auricchio (Switzerland), Helmut Baumgartner (Germany), Claudio Ceconi (Italy), Veronica Dean (France), Christi Deaton (UK), Robert Fagard (Belgium), Christian Funck-Brentano (France), David Hasdai (Israel), Arno Hoes (The Netherlands), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Theresa McDonagh (UK), Cyril Moulin (France), Don Poldermans (The Netherlands), Bogdan A. Popescu (Romania), Željko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Adam Torbicki (Poland), Alec Vahanian (France), Stephan Windecker (Switzerland).

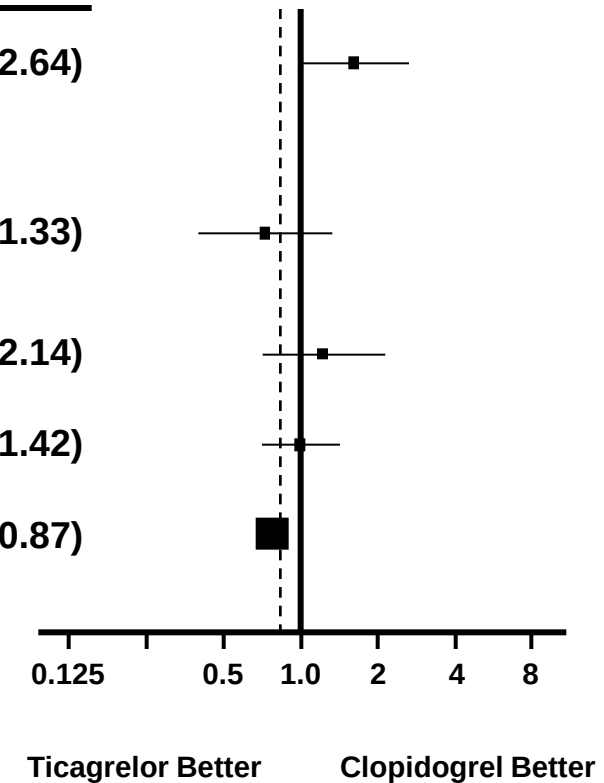
2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline)

A Report of the American College of Cardiology Foundation/
American Heart Association Task Force on Practice Guidelines

Ticagrelor vs. Clopidogrel nach Region und ASS-Dosis in PLATO

PLATO: Primärer Endpunkt (CV-Mortalität, MI, Schlaganfall)

Region	ASS Dosis (mg)	Ticagrelor		Clopidogrel		HR (95% CI)
		N	E	N	E	
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100 – <300	22	2	16	2	
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100 – <300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7449	546	7443	699	0.78 (0.69, 0.87)



N = Anzahl Patienten; E = primäre Endpunkt Ereignisse

Recommendations for Oral Antiplatelet Agents (1)

Recommendations	Class	Level
Aspirin should be given to all patients without contraindications at an initial loading dose of 150-300 mg, and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy.	I	A
A P2Y ₁₂ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A

Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).

P2Y ₁₂ -inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.	I	B