Antiplatelet in ACS
Moving beyond clopidogrel

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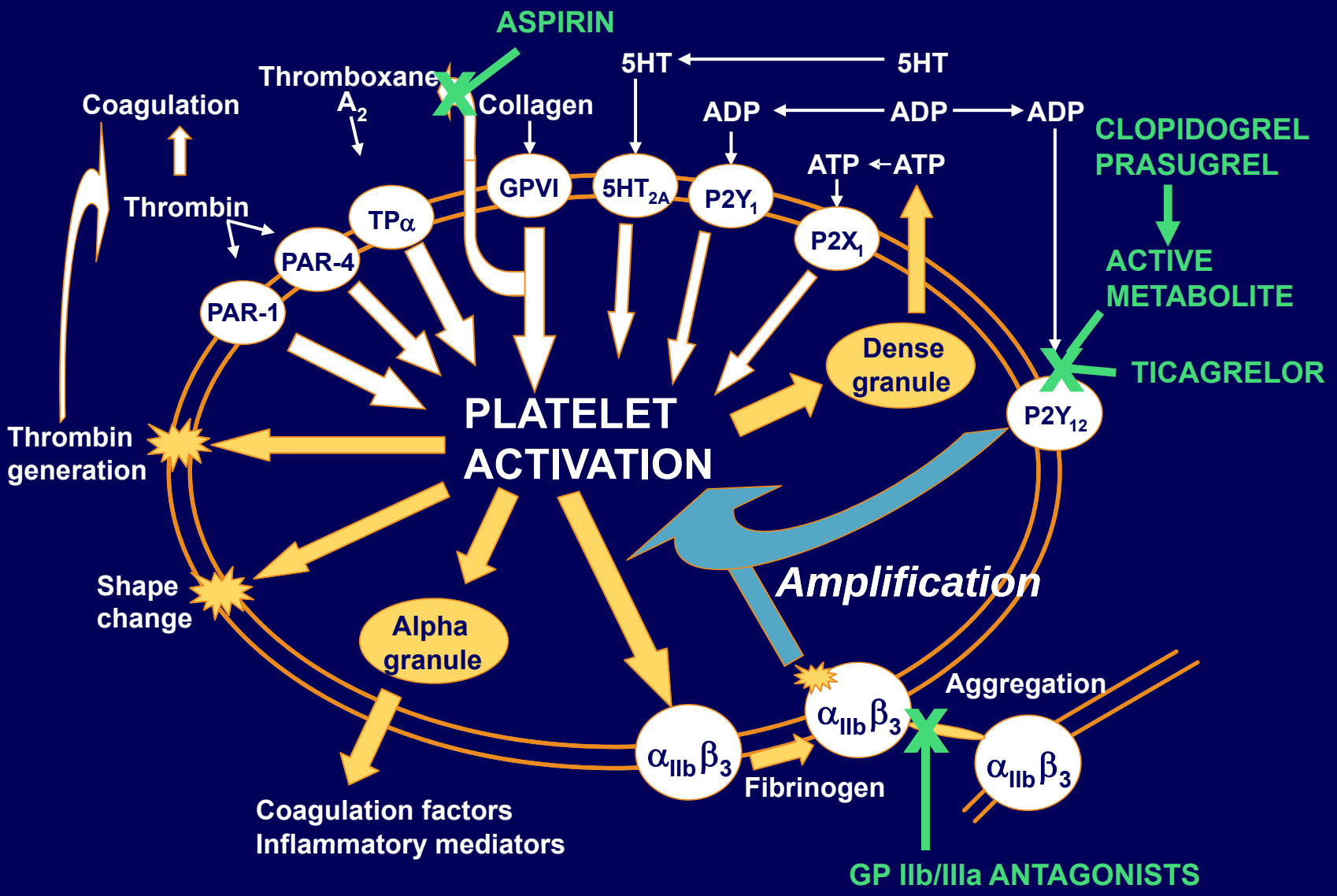
My Conflicts of Interest Are:

Company Name	Relationship
AstraZeneca	Research grant, honoraria, consultant
Eli Lilly / Daiichi Sankyo	Research/educational grants, honoraria, consultant
The Medicines Company	Consultant
Merck	Research grant, consultant
Novartis	Consultant
Sanofi aventis / BMS	Consultant
Eisai	Consultant
Medscape	Honoraria
Accumetrics	Educational grant, research consumables, consultant
Iroko	Honorarium

Mechanisms of Platelet Inhibition

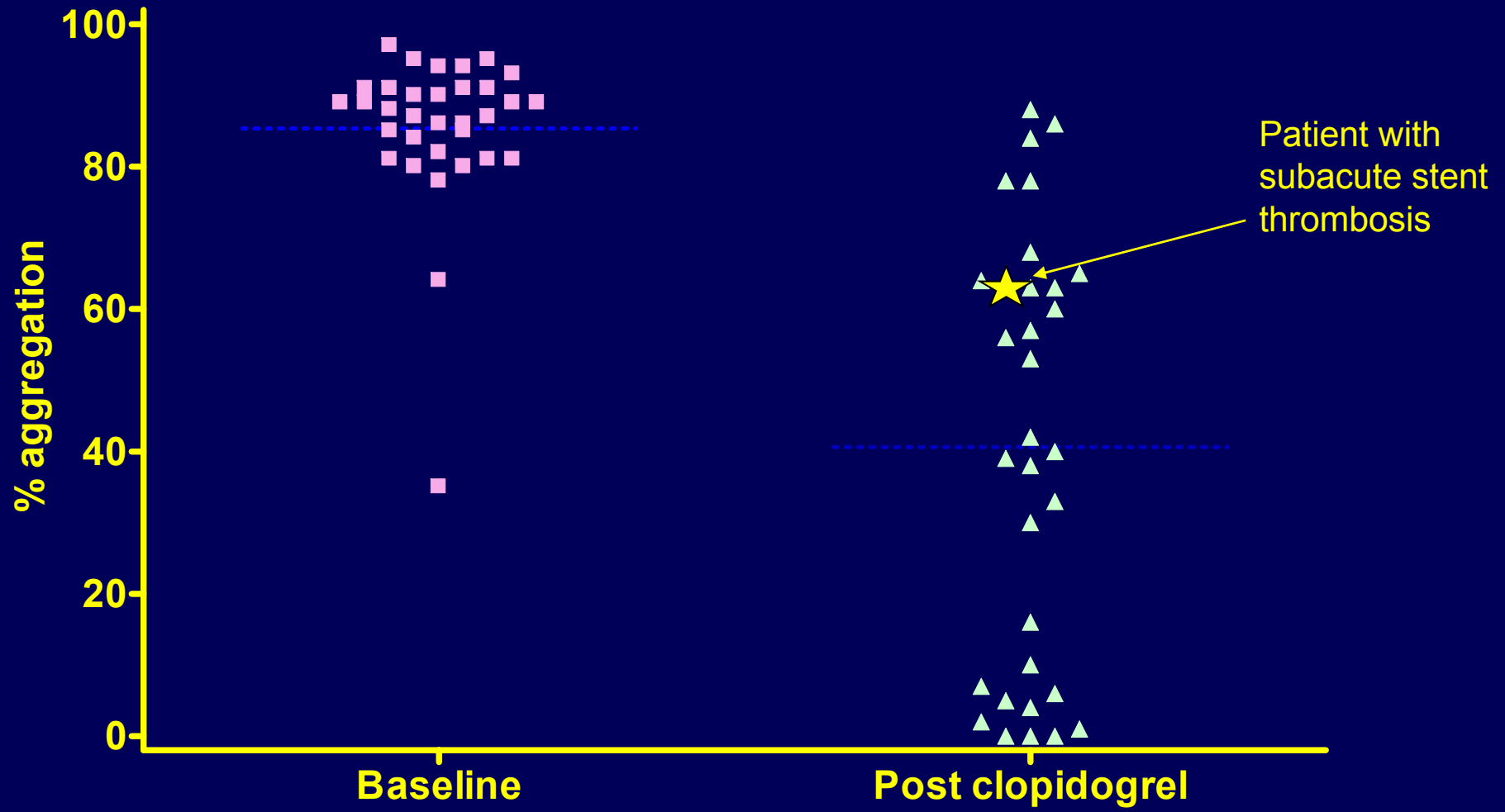


GP = glycoprotein; PAR = protease-activated receptor; TP = thromboxane A_2 / prostaglandin H_2.

Storey RF. *Curr Pharm Des*. 2006;12:1255-1259.

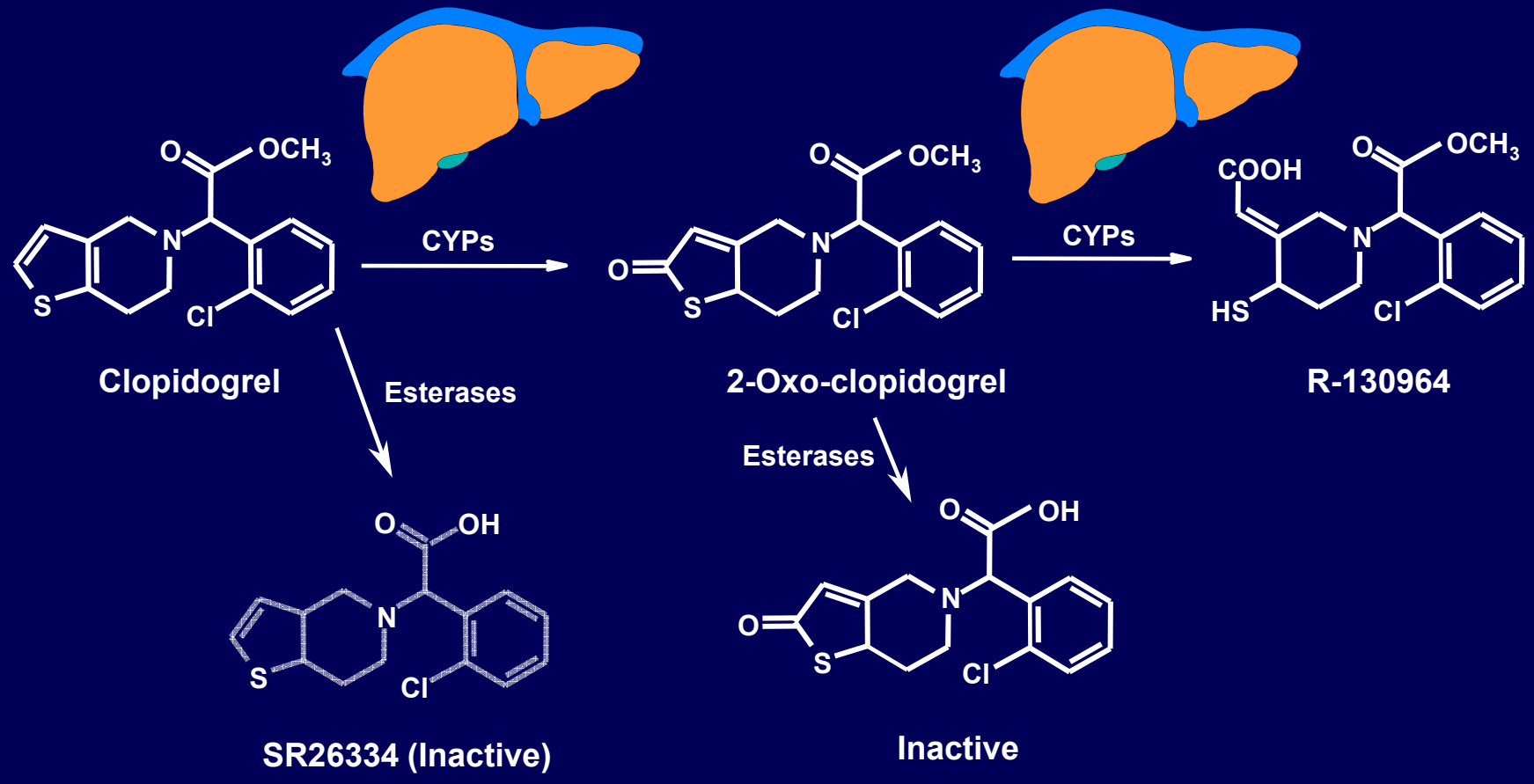
Platelet aggregation before and 4 hours after clopidogrel 600 mg in patients undergoing PCI

Whole blood single platelet counting in response to ADP 10 uM



Smith SMG et al. *Platelets* 2006; 17: 250-258

Activation/inactivation of clopidogrel



CYP = cytochrome P450.

Farid NA, et al. *Clin Pharmacol Ther.* 2007;81:735-741.

$P2Y_{12}$ inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolization	Prodrug, not limited by metabolization	Active drug
Onset of effect[a]	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

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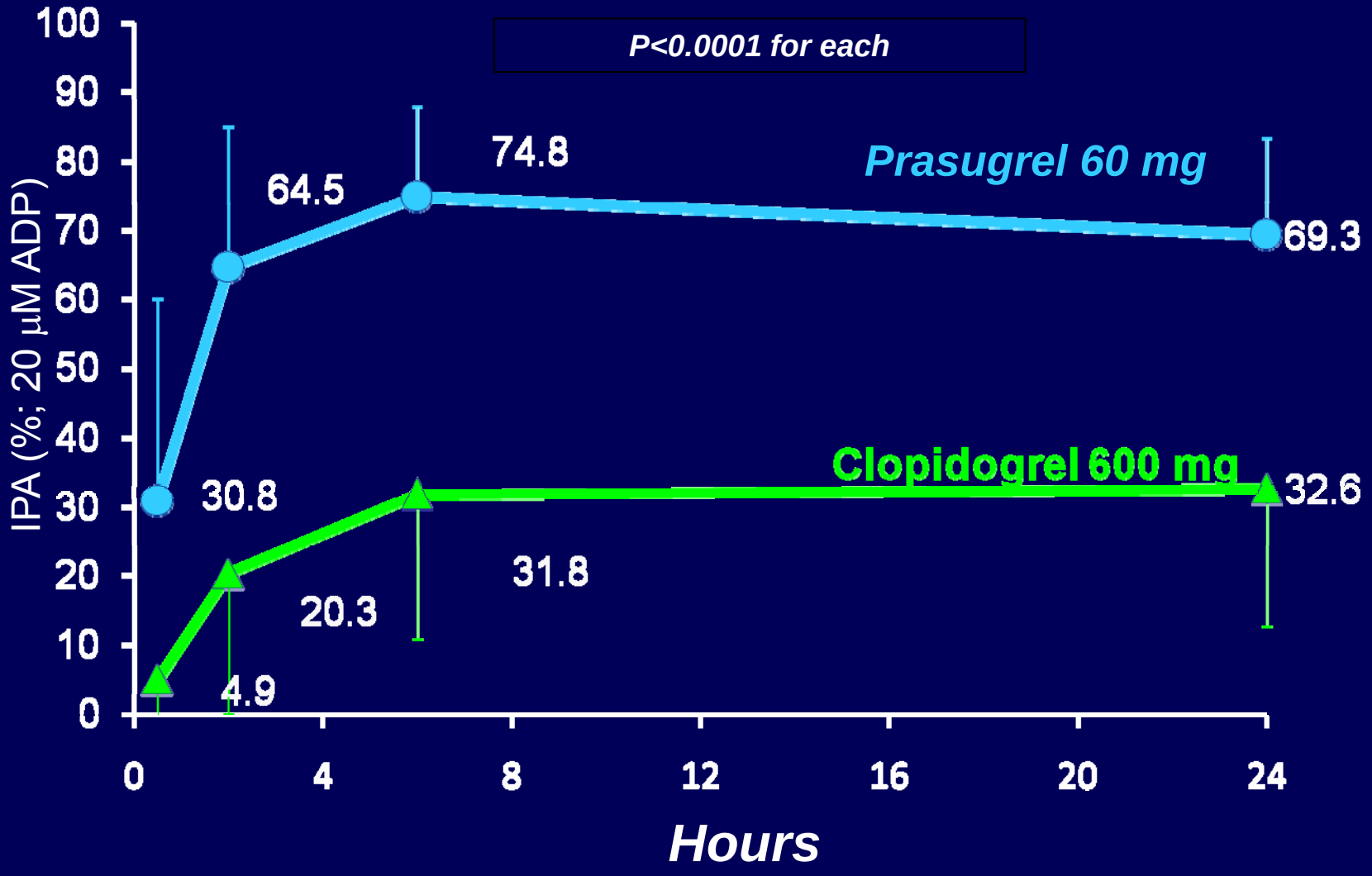
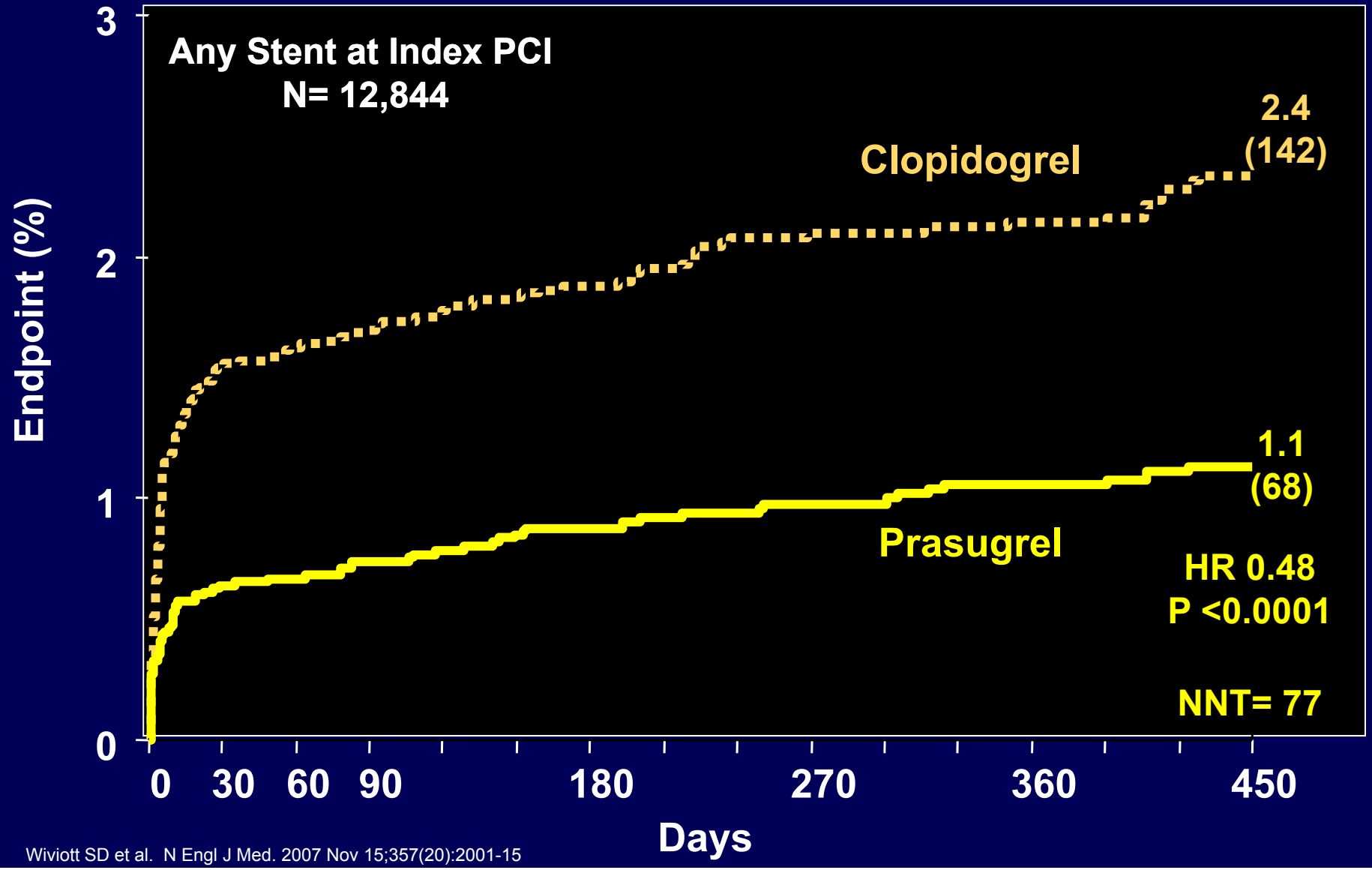
PRINCIPLE TIMI 44

Inhibition of ADP-induced platelet aggregation



Wiviott SD et al. Circulation 2007

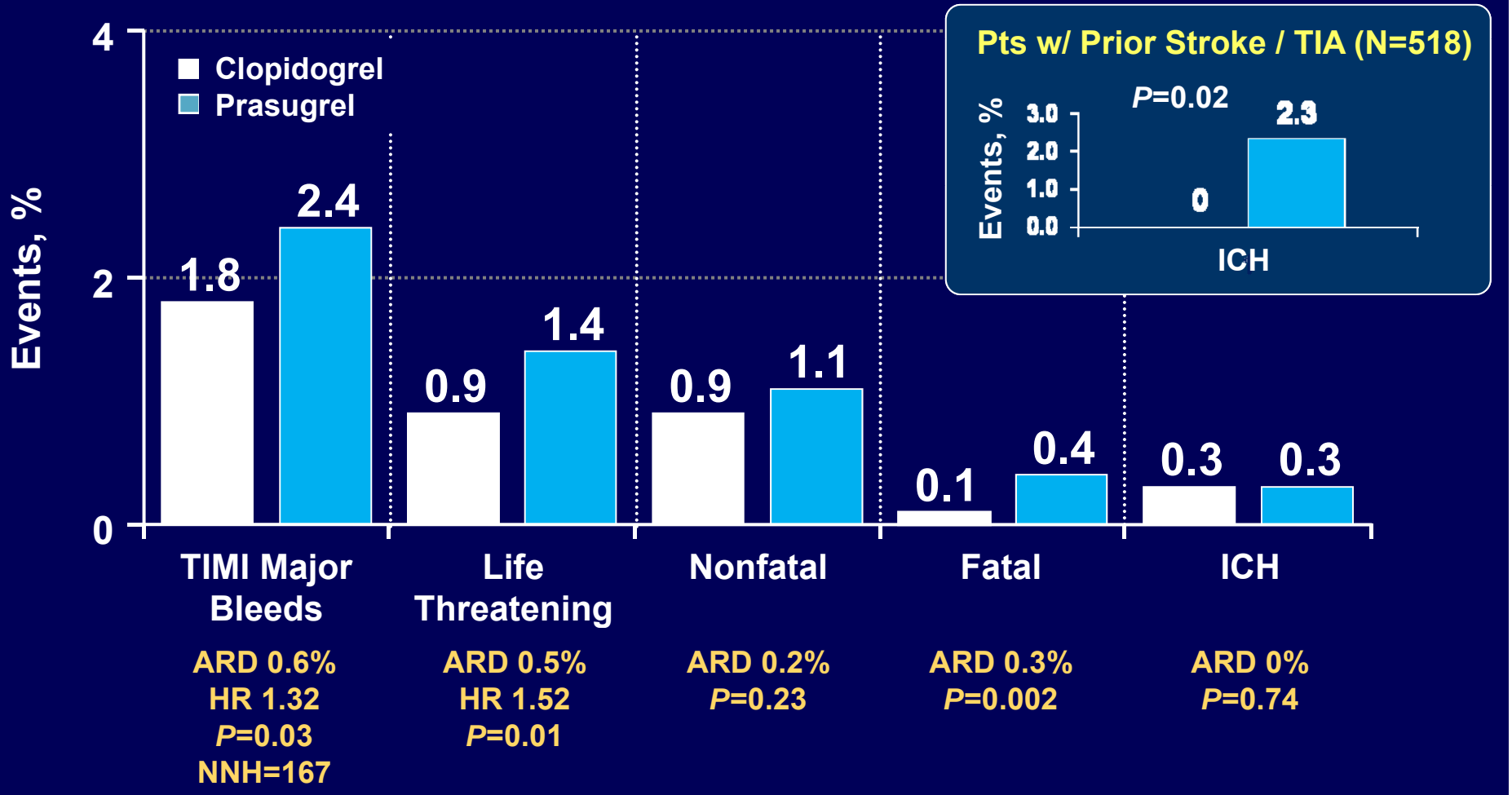
TRITON Stent Thrombosis
(ARC Definite + Probable)



Wiviott SD et al. N Engl J Med. 2007 Nov 15;357(20):2001-15

TRITON-TIMI 38: Bleeding Events

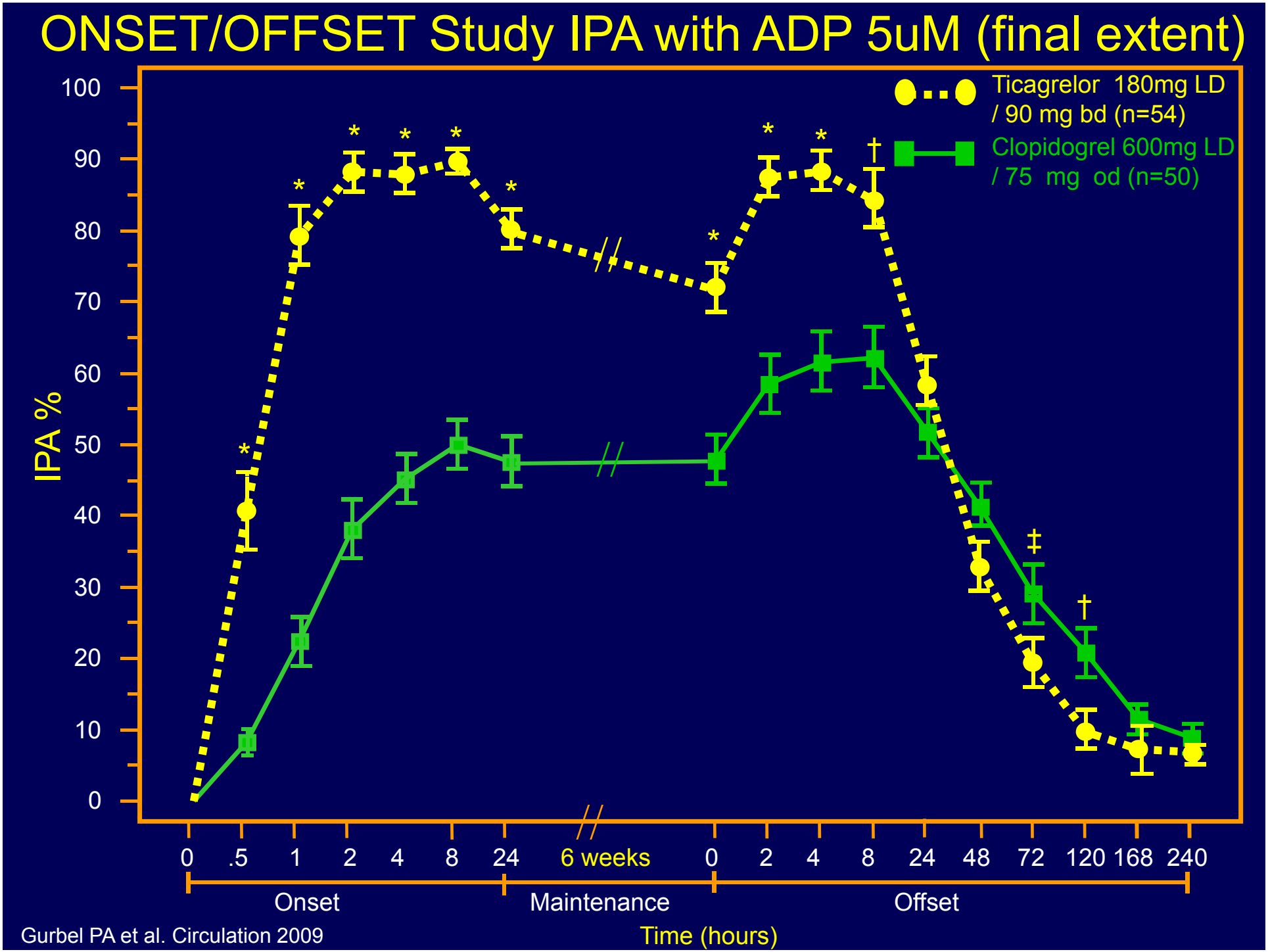
Safety Cohort (N=13,457)



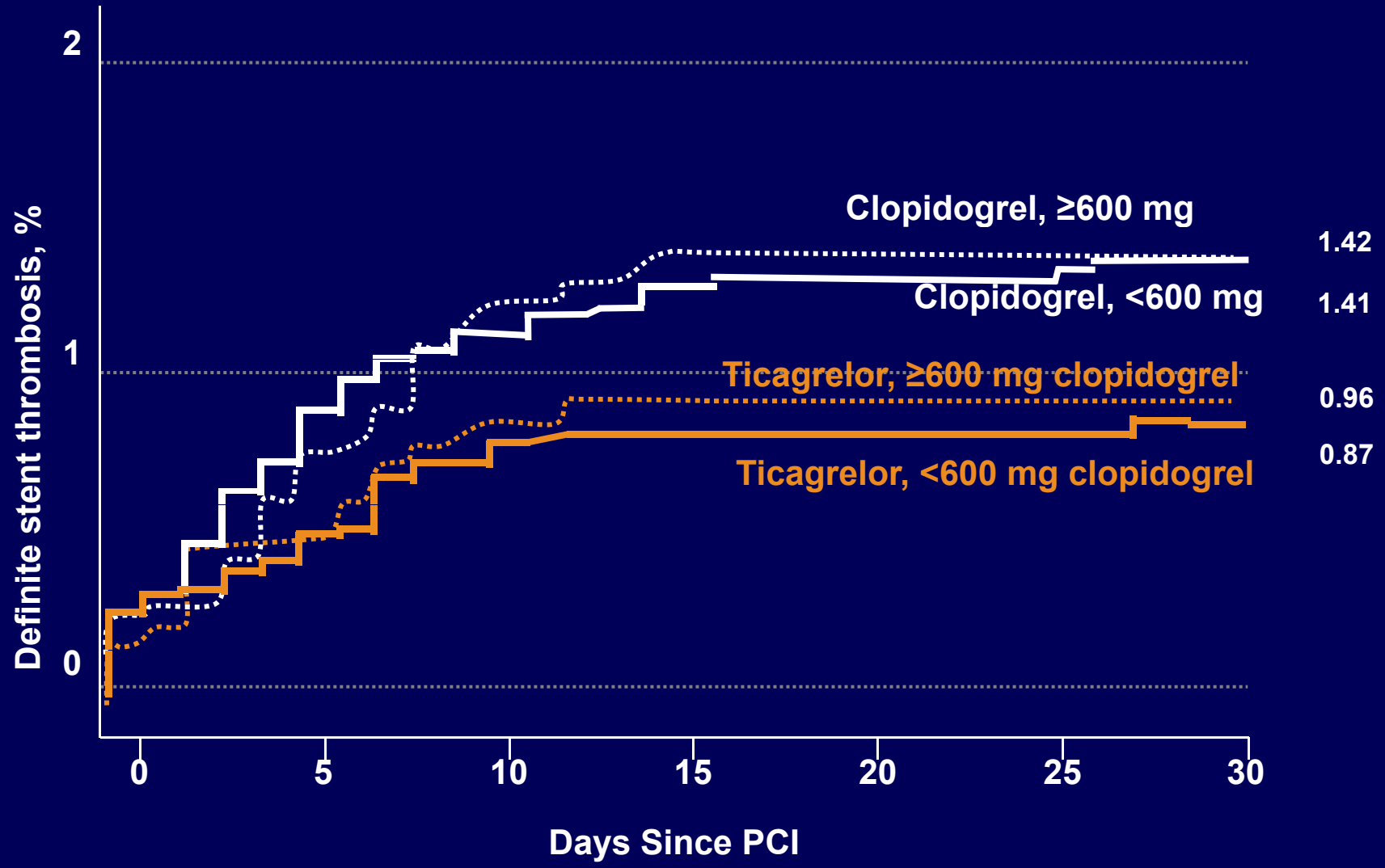
ARD = absolute risk difference; HR = hazard ratio; ICH = intracranial haemorrhage; NNH = number needed to harm; TIA = transient ischemic attack; TIMI = Thrombolysis in Myocardial Infarction.

Adapted from Wiviott SD, et al. Presented at: American Heart Association Scientific Sessions 2007; 4-7 November, 2007; Orlando, FL.

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

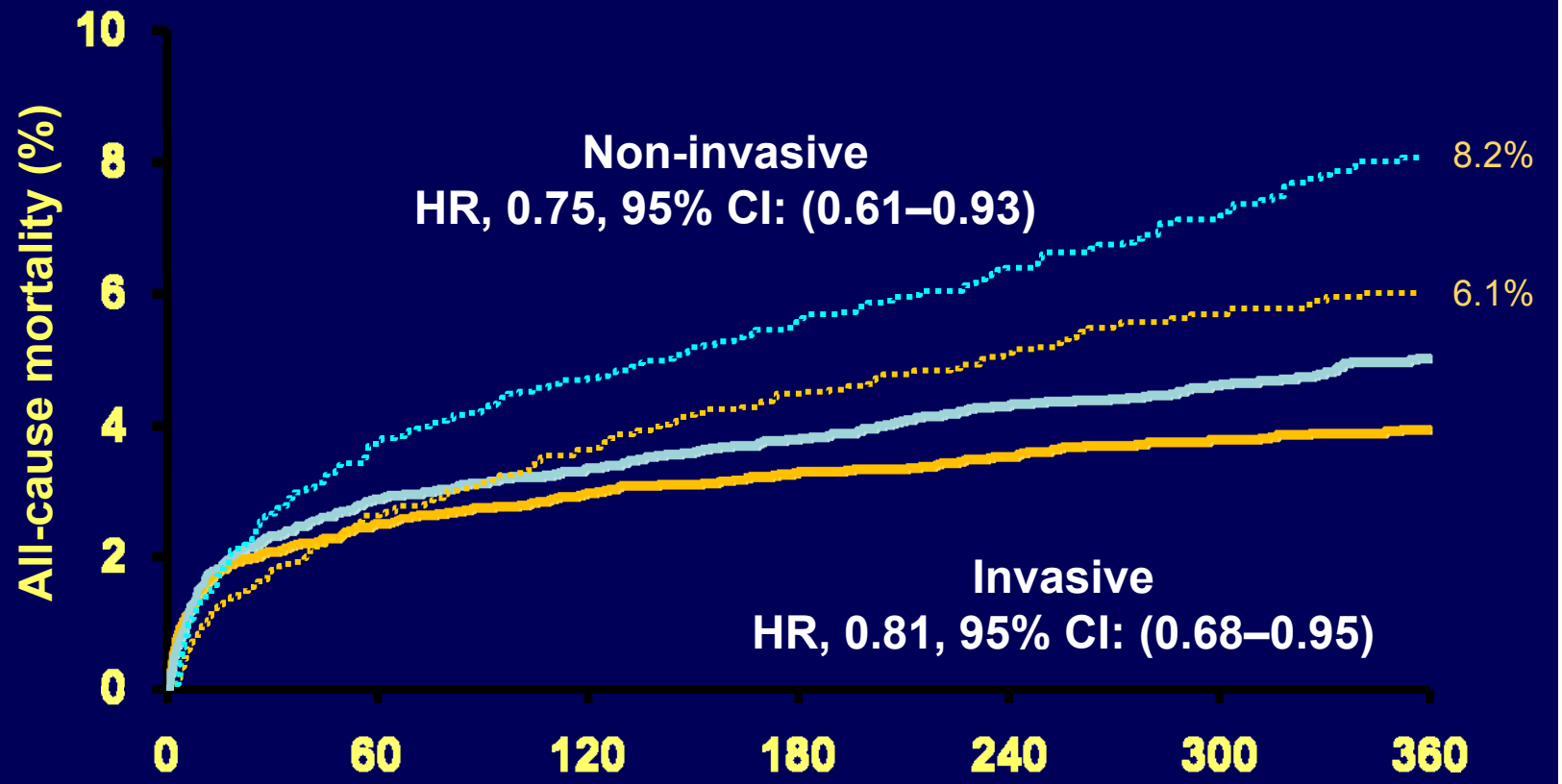

ONSET/OFFSET Study IPA with ADP 5uM (final extent)
Ticagrelor 180mg LD / 90 mg bd (n=54)
Clopidogrel 600mg LD / 75 mg od (n=50)
IPA %
100
90
80
70
60
50
40
30
20
10
0
0 .5 1 2 4 8 24 6 weeks 0 2 4 8 24 48 72 120 168 240
Onset
Maintenance
Offset
Time (hours)
Gurbel PA et al. Circulation 2009

PLATO Invasive
Definite Stent Thrombosis



Cannon CP, et al. *Lancet.* 2010;375:283-293.

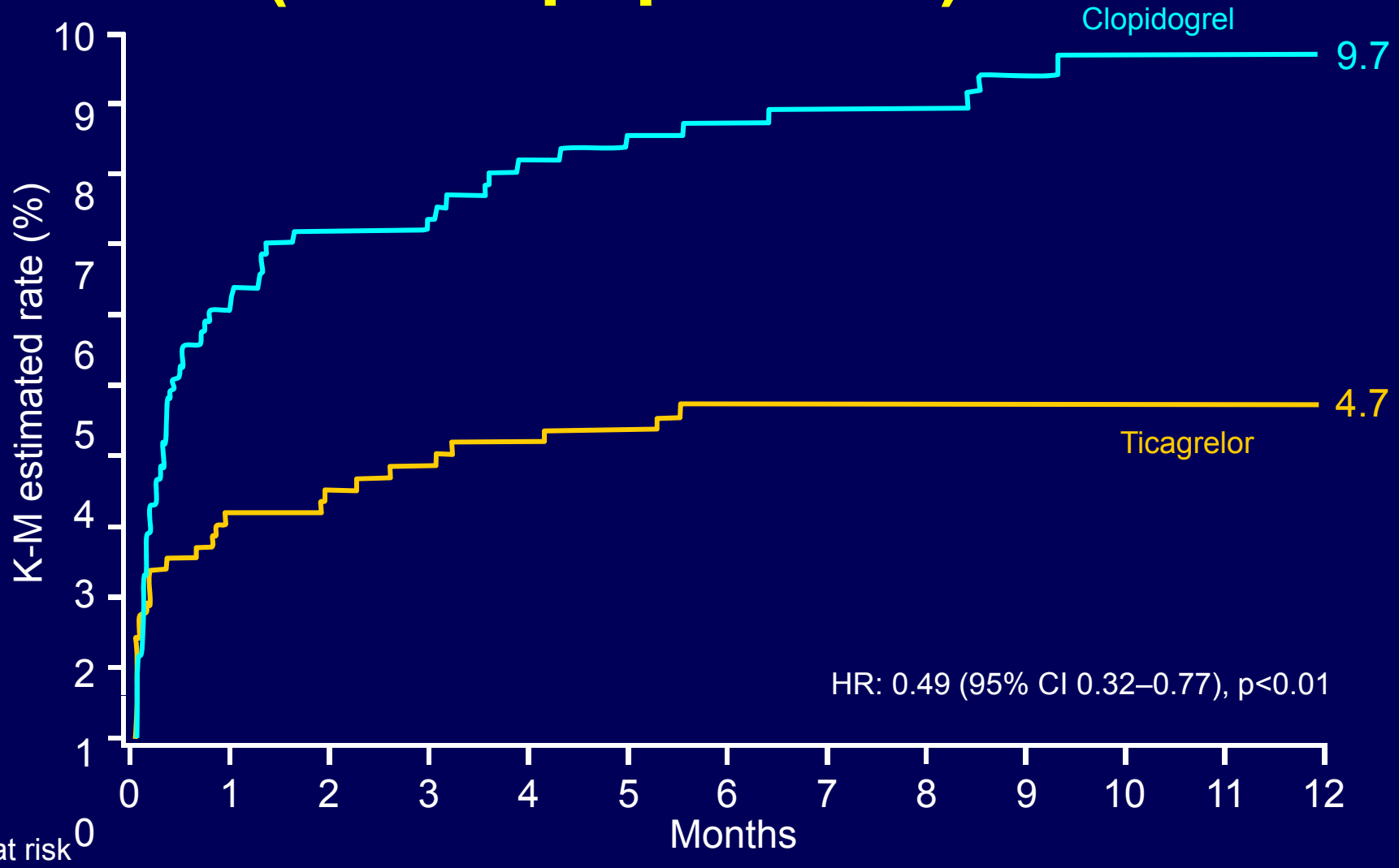
PLATO All-cause mortality – planned invasive vs non-invasive strategy



Number at risk							
Invasive							
Ticagrelor	6732	6439	6375	6241	5141	3951	3233
Clopidogrel	6676	6376	6331	6209	5114	3917	3164
Non-invasive							
Ticagrelor	2601	2485	2447	2385	1978	1531	1186
Clopidogrel	2615	2488	2448	2380	1965	1524	1200

James S et al. Brit Med J 2011

Time from CABG to any death (CABG population)

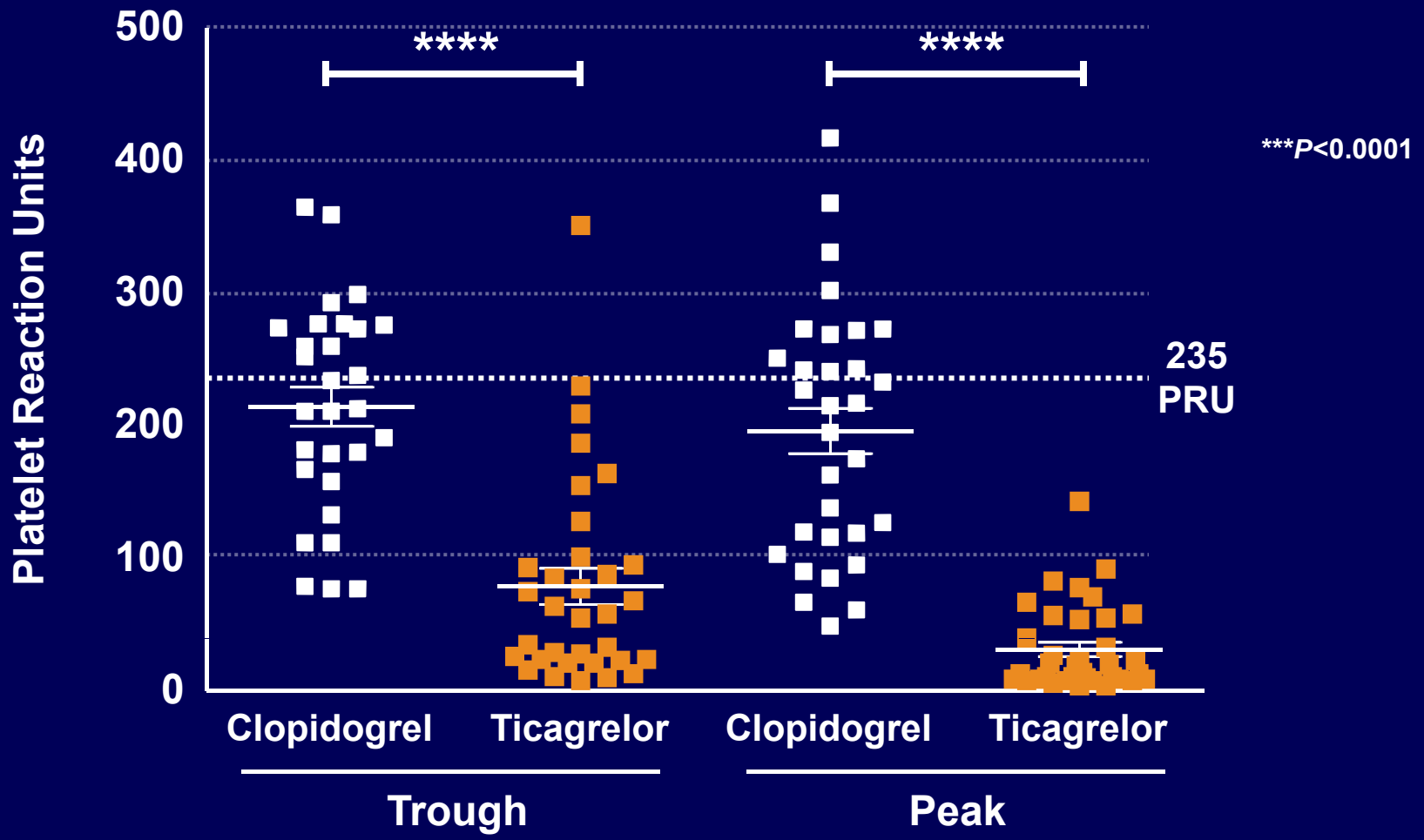


No. at risk							
Ticagrelor	629	583	557	491	415	291	119
Clopidogrel	629	565	539	472	404	269	130

Held C. J Am Coll Cardiol 2011

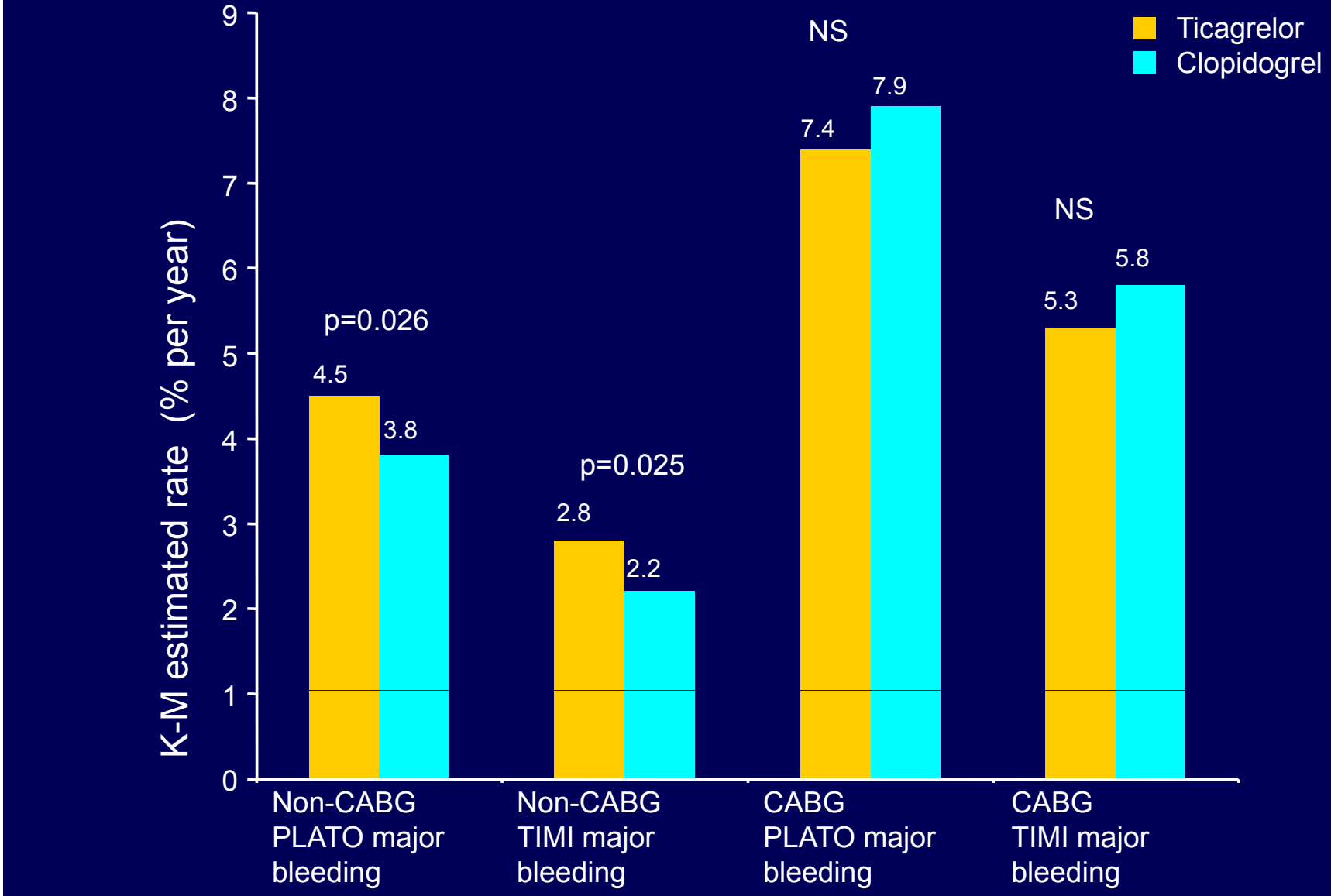
PLATO PLATELET: VerifyNow $P2Y_{12}$ Assay

Comparing Maintenance Therapy with Clopidogrel vs Ticagrelor



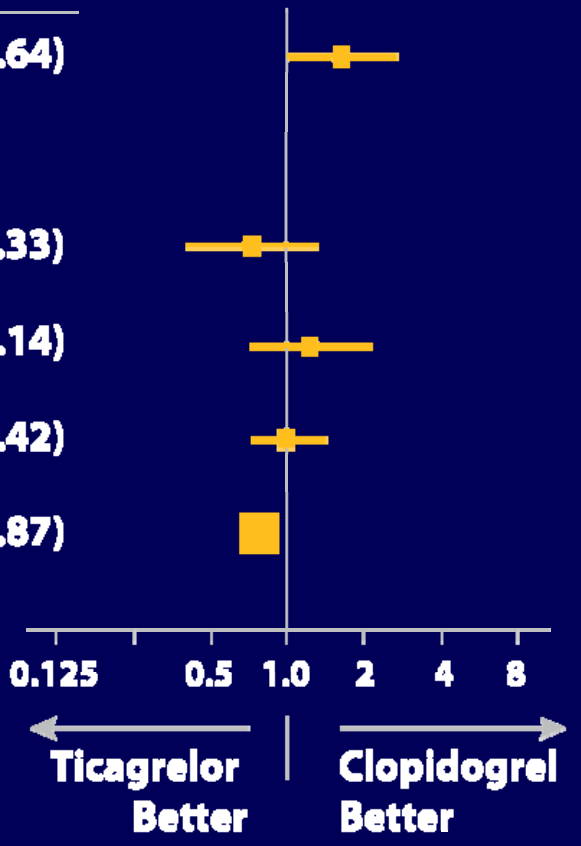
Storey RF et al. J Am Coll Cardiol 2010

PLATO
Non-CABG and CABG-related major bleeding



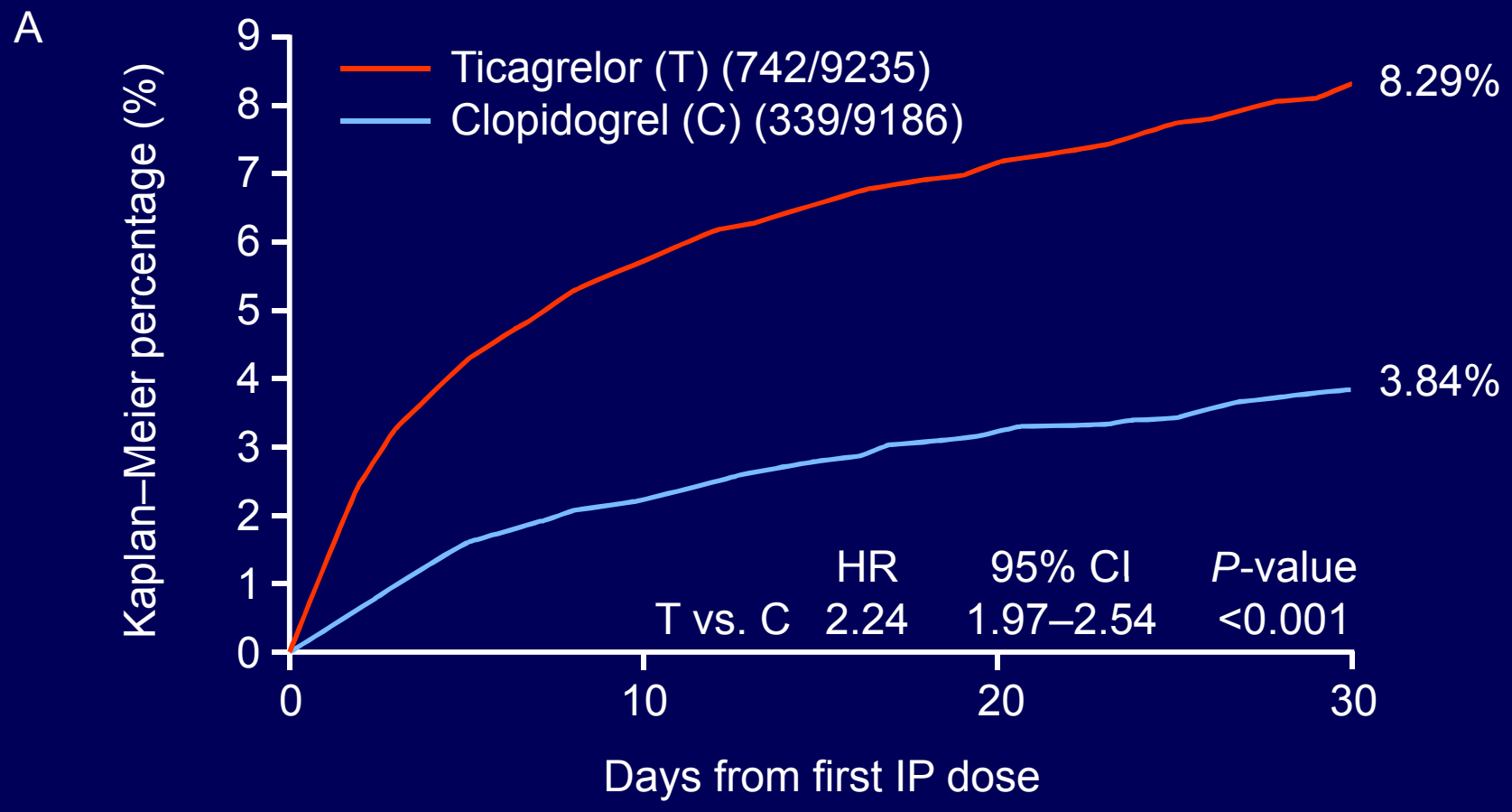
Primary Efficacy Outcome
US and Non-US and by ASA Dose

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
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)



**Hazard ratio not calculated due to small number of events.*

PLATO: Any dyspnoea AE (≤30 days)



n at risk

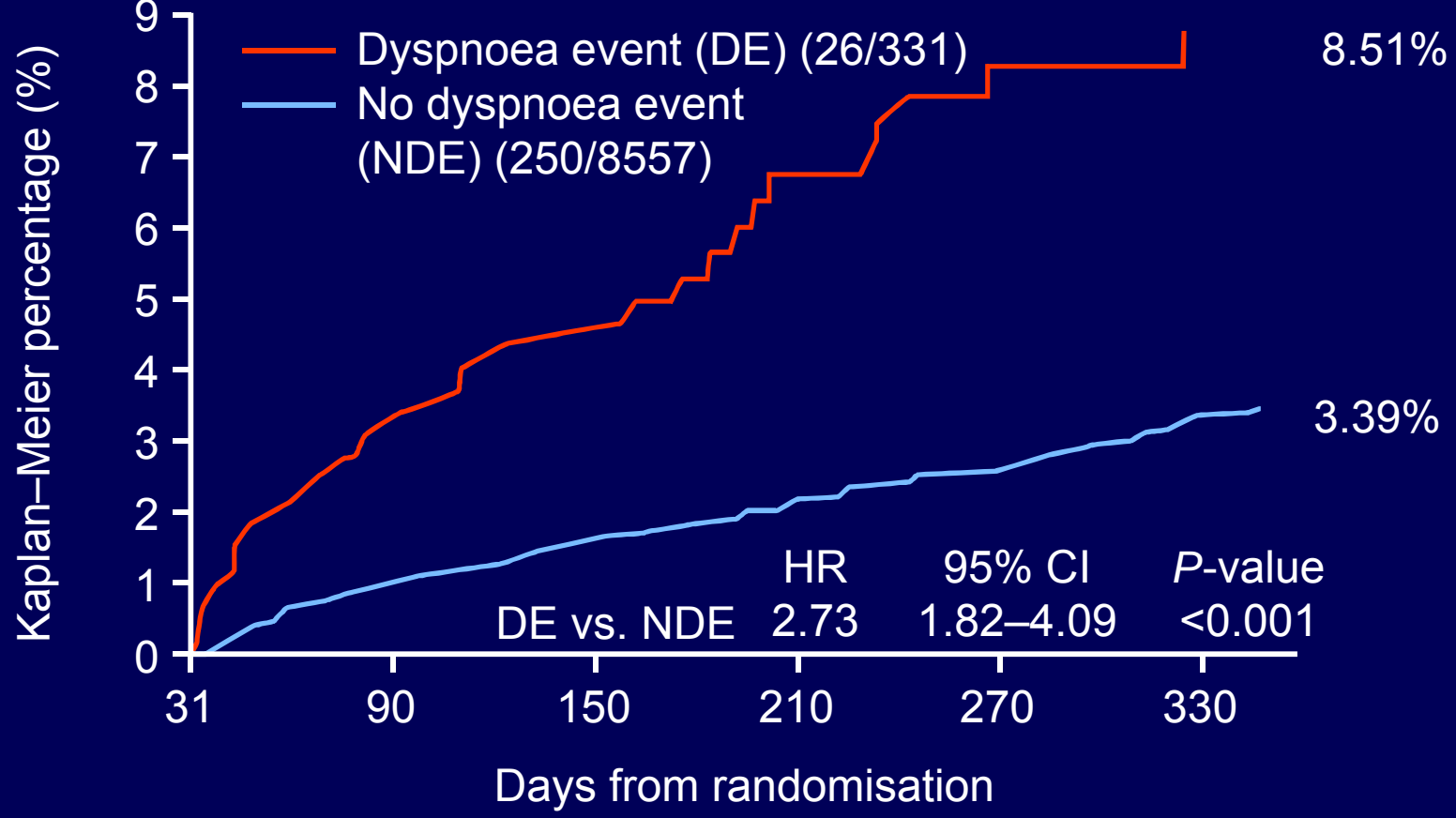
T	9235	8380	7740	7470
C	9186	8644	8053	7844

Storey RF et al. Eur Heart J 2011.

AE = adverse event; CI = confidence interval; HR = hazard ratio; IP = investigational product.

Clopidogrel: total death in patients with dyspnoea AE within 30 days

D



n at risk

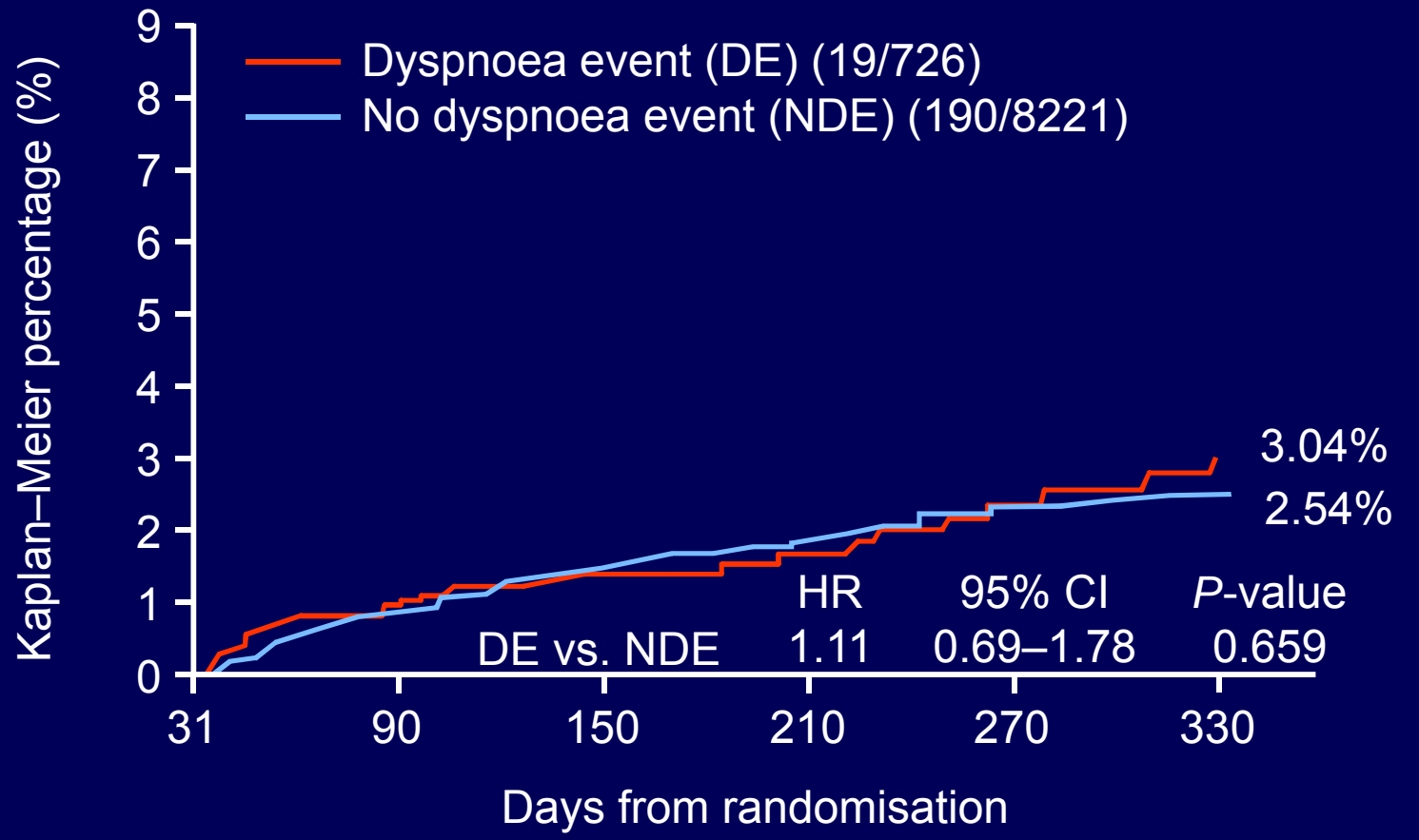
DE	331	319	314	264	240	191
NDE	8557	8419	8344	7036	6608	4853

Storey RF et al. Eur Heart J 2011.

CI = confidence interval; HR = hazard ratio.

Ticagrelor: total death in patients with dyspnoea AE within 30 days

C



n at risk

DE	726	717	713	628	582	431
NDE	8221	8089	8004	6711	6220	4666

Storey RF et al. Eur Heart J 2011.

CI = confidence interval; HR = hazard ratio.

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

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)

Class	Level
I	B

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

Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of lifethreatening bleeding or other contraindications

Class	Level
I	B

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

Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel

Class	Level
I	A

A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option

Class	Level
I	B

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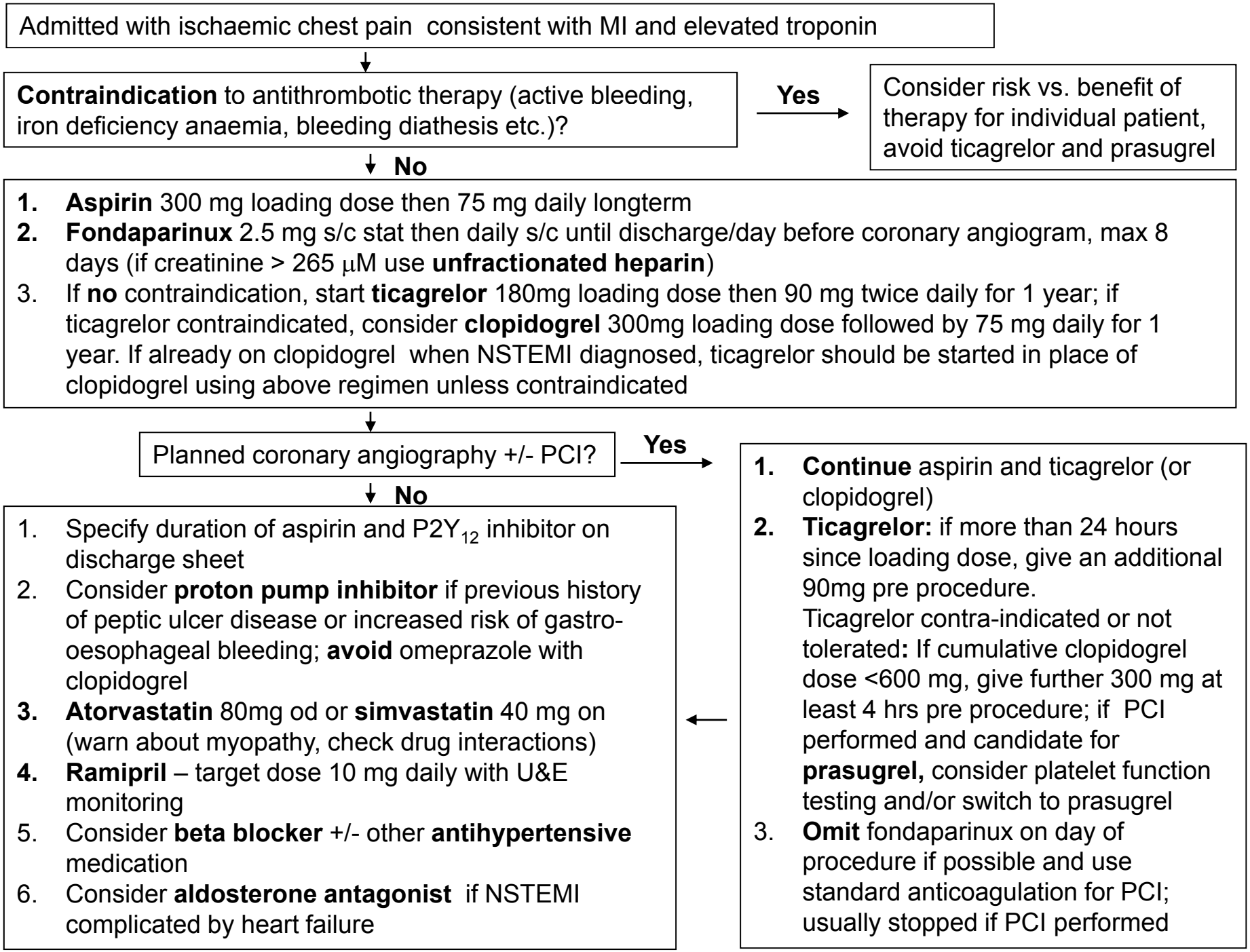
Sheffield NSTEMI protocol


Admitted with ischaemic chest pain consistent with MI and elevated troponin
Contraindication to antithrombotic therapy (active bleeding, iron deficiency anaemia, bleeding diathesis etc.)?
Yes
Consider risk vs. benefit of therapy for individual patient, avoid ticagrelor and prasugrel
No
1. Aspirin 300 mg loading dose then 75 mg daily longterm
2. Fondaparinux 2.5 mg s/c stat then daily s/c until discharge/day before coronary angiogram, max 8 days (if creatinine > 265 μM use unfractionated heparin)
3. If no contraindication, start ticagrelor 180mg loading dose then 90 mg twice daily for 1 year; if ticagrelor contraindicated, consider clopidogrel 300mg loading dose followed by 75 mg daily for 1 year. If already on clopidogrel when NSTEMI diagnosed, ticagrelor should be started in place of clopidogrel using above regimen unless contraindicated
Planned coronary angiography +/- PCI?
Yes
No
1. Continue aspirin and ticagrelor (or clopidogrel)
2. Ticagrelor: if more than 24 hours since loading dose, give an additional 90mg pre procedure.
Ticagrelor contra-indicated or not tolerated: If cumulative clopidogrel dose <600 mg, give further 300 mg at least 4 hrs pre procedure; if PCI performed and candidate for prasugrel, consider platelet function testing and/or switch to prasugrel
3. Omit fondaparinux on day of procedure if possible and use standard anticoagulation for PCI; usually stopped if PCI performed
1. Specify duration of aspirin and P2Y12 inhibitor on discharge sheet
2. Consider proton pump inhibitor if previous history of peptic ulcer disease or increased risk of gastro-oesophageal bleeding; avoid omeprazole with clopidogrel
3. Atorvastatin 80mg od or simvastatin 40 mg on (warn about myopathy, check drug interactions)
4. Ramipril – target dose 10 mg daily with U&E monitoring
5. Consider beta blocker +/- other antihypertensive medication
6. Consider aldosterone antagonist if NSTEMI complicated by heart failure

Thank you for listening!