Antiplatelet Therapy in Elderly & Post-Stroke Patients

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Disclosures

I have no financial disclosures for this topic

Investigator for antiplatelet trials, including TRITON – TIMI 38, PLATO, TRILOGY-ACS, CURRENT-ACS

No honoraria for this lecture

Agenda

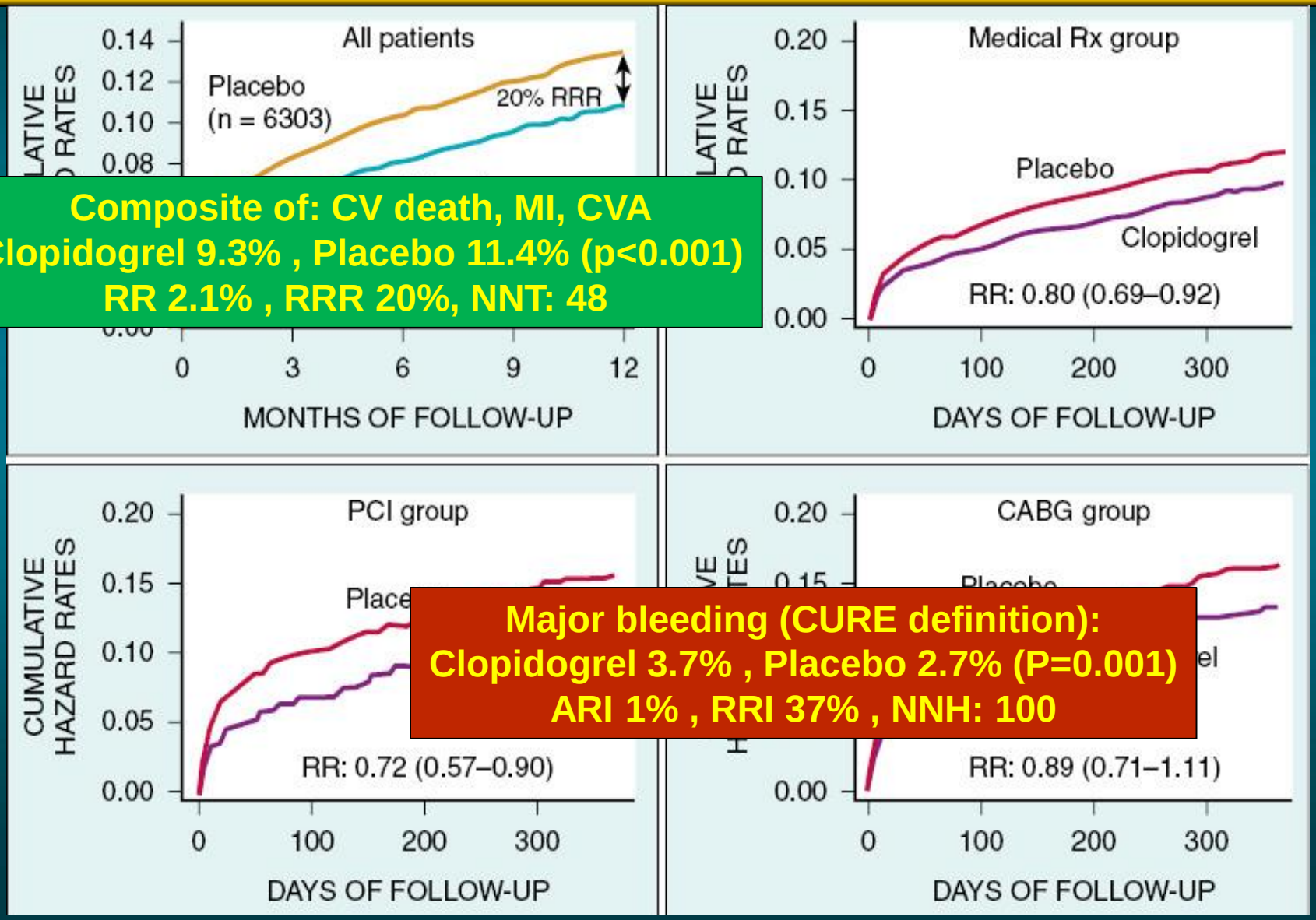
Reminders of older data:

Dual antiplatelet studies in ACS

Recent analyses on elderly and post-CVA patients in PLATO

Additional thoughts and open questions

Adding Clopidogrel to Aspirin in UA/NSTEMI (CURE, 2001)



Composite of: CV death, MI, CVA
Clopidogrel 9.3% , Placebo 11.4% (p<0.001)
RR 2.1% , RRR 20%, NNT: 48

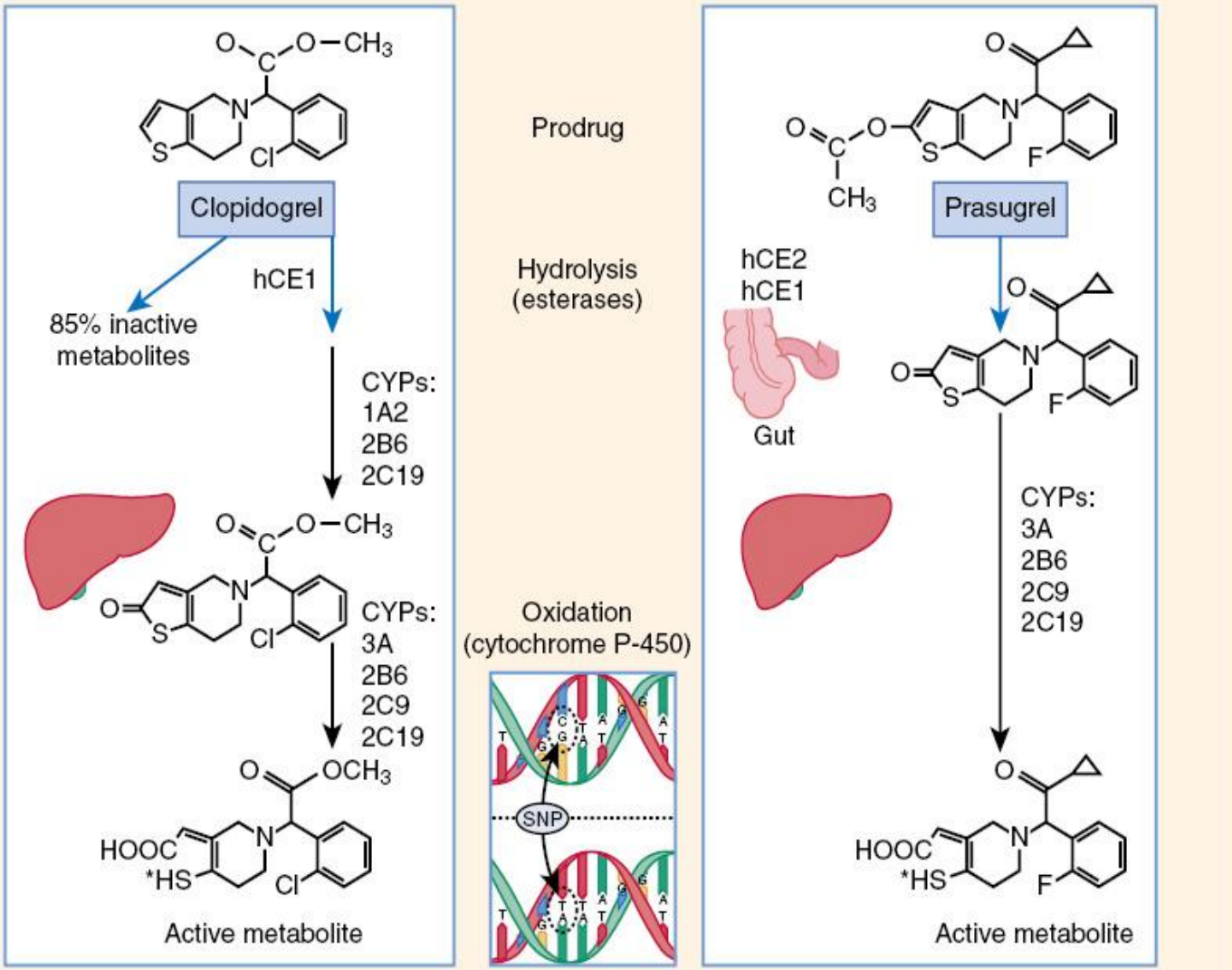
Major bleeding (CURE definition):
Clopidogrel 3.7% , Placebo 2.7% (P=0.001)
ARI 1% , RRI 37% , NNH: 100

Limitations of Clopidogrel

- Thienopyridines are pro-drugs requiring metabolism to an active metabolite.
- Clopidogrel has a delayed onset of effect (2-step metabolism).
- Clopidogrel has modest and variable platelet inhibition.
- There is marked inter- and intra-patient variability in response to clopidogrel.
- Variable PK / PD response to clopidogrel (e.g. CYP2C19) is associated with stent thrombosis, CV death, recurrent MI and stroke.

1. Gurbel PA and Bliden KP. *Am J Cardiol* 2003.
2. Angiolillo DJ et al. *Thromb Res* 2005.
3. Gurbel PA and Tantry US. *Thromb Res* 2006.
4. Matetzky S et al. *Circulation* 2004.
5. Lev EI et al. *JACC* 2006.

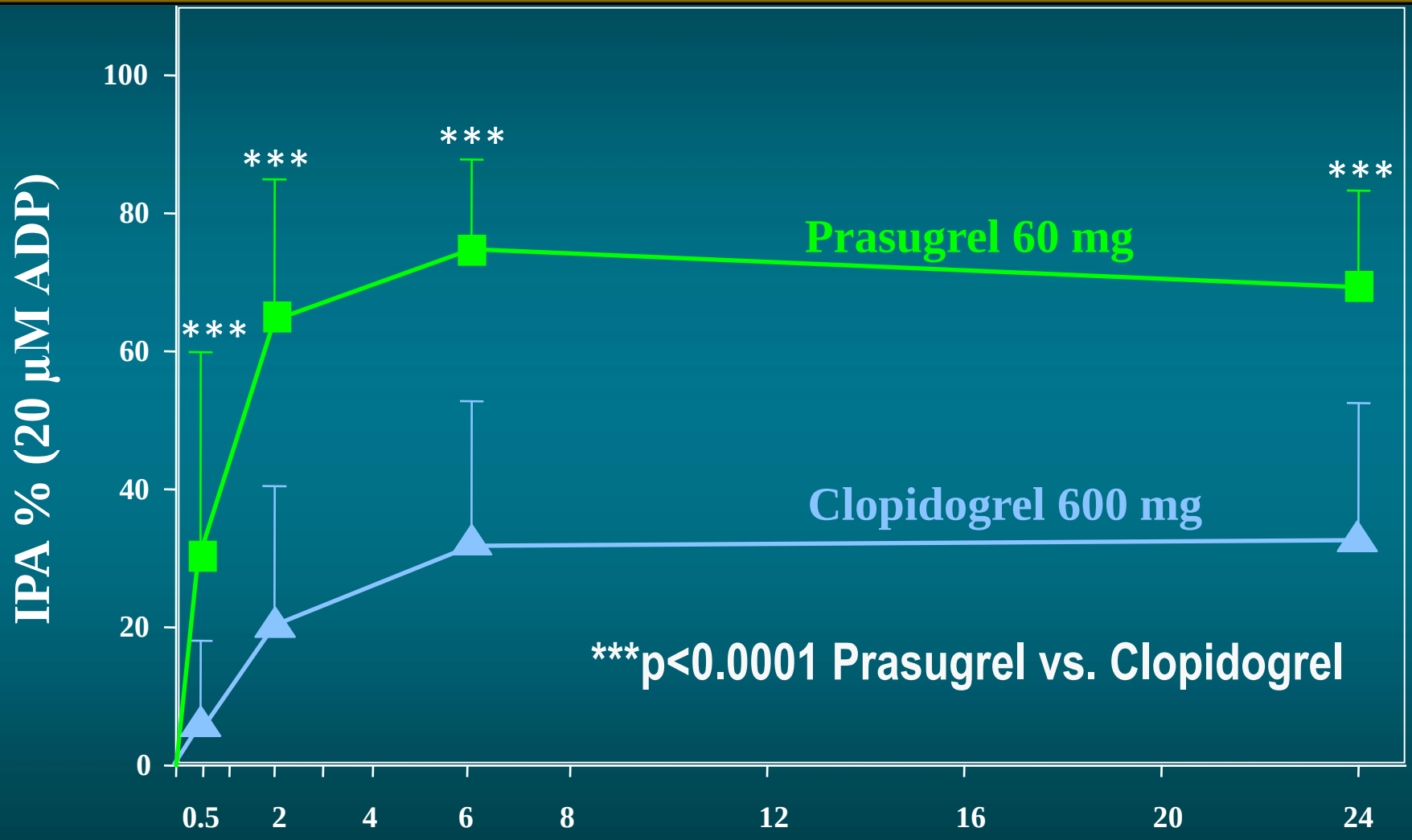
Clopidogrel and Prasugrel metabolism



Kurihara A. et al. Drug Metab. Rev. 37(S2): 99 (2005)
Tang M. et al. JPET 319: 1467–1476 (2006)

Farid N.A. et al. Drug Metab. Dispos. 35: 1096–1104 (2007)
Rehmel J.L.F. et al. Drug Metab. Dispos. 34: 600–607 (2006)
Williams E.T. et al. Drug Metab. Rev. 39(S1): 254 (2007)

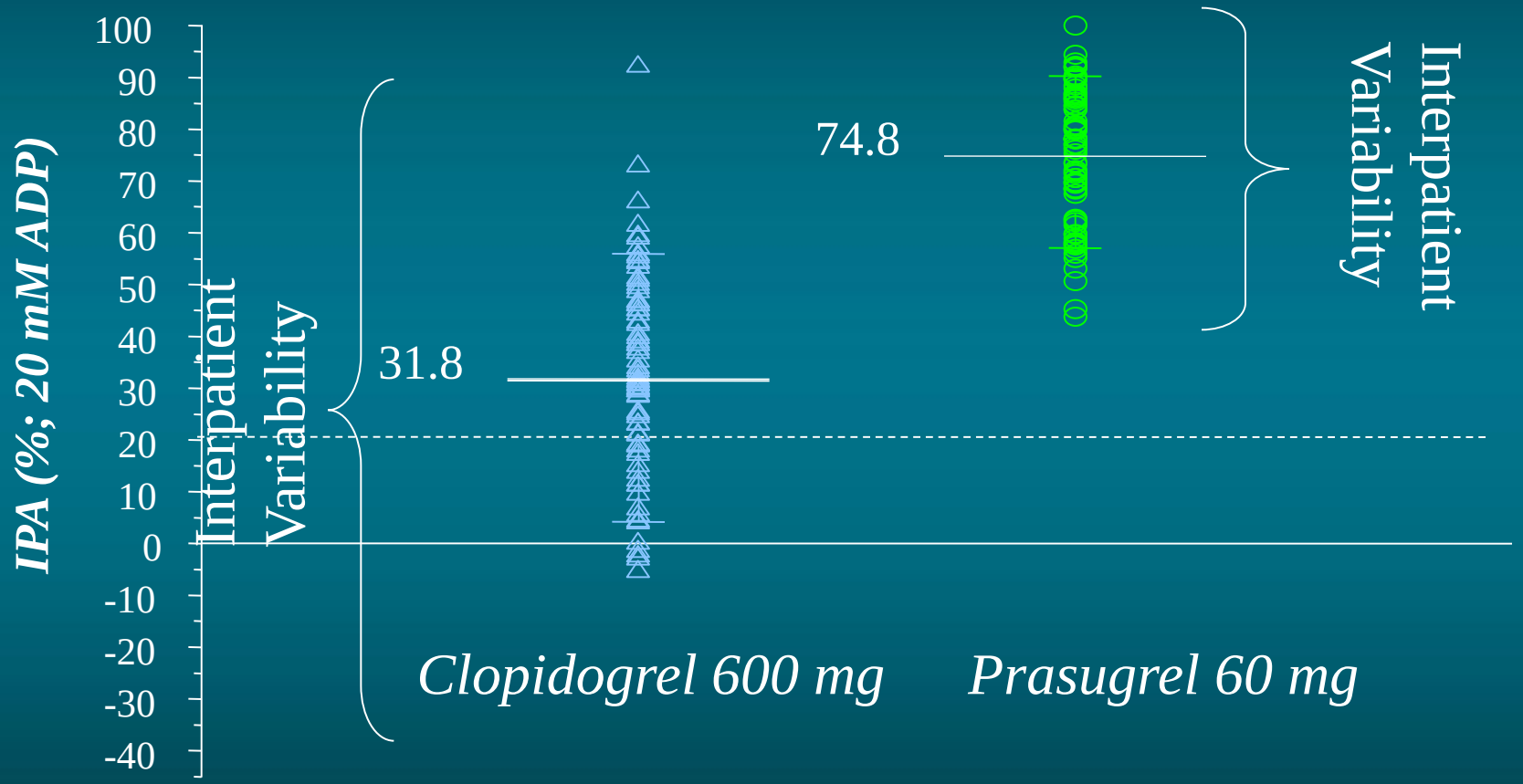
IPA after LD – elective PCI



IPA = inhibition of platelet aggregation;
PCI = percutaneous coronary intervention

Wiviott SD et al. Circulation 2007.

Individual IPA data 6h after LD

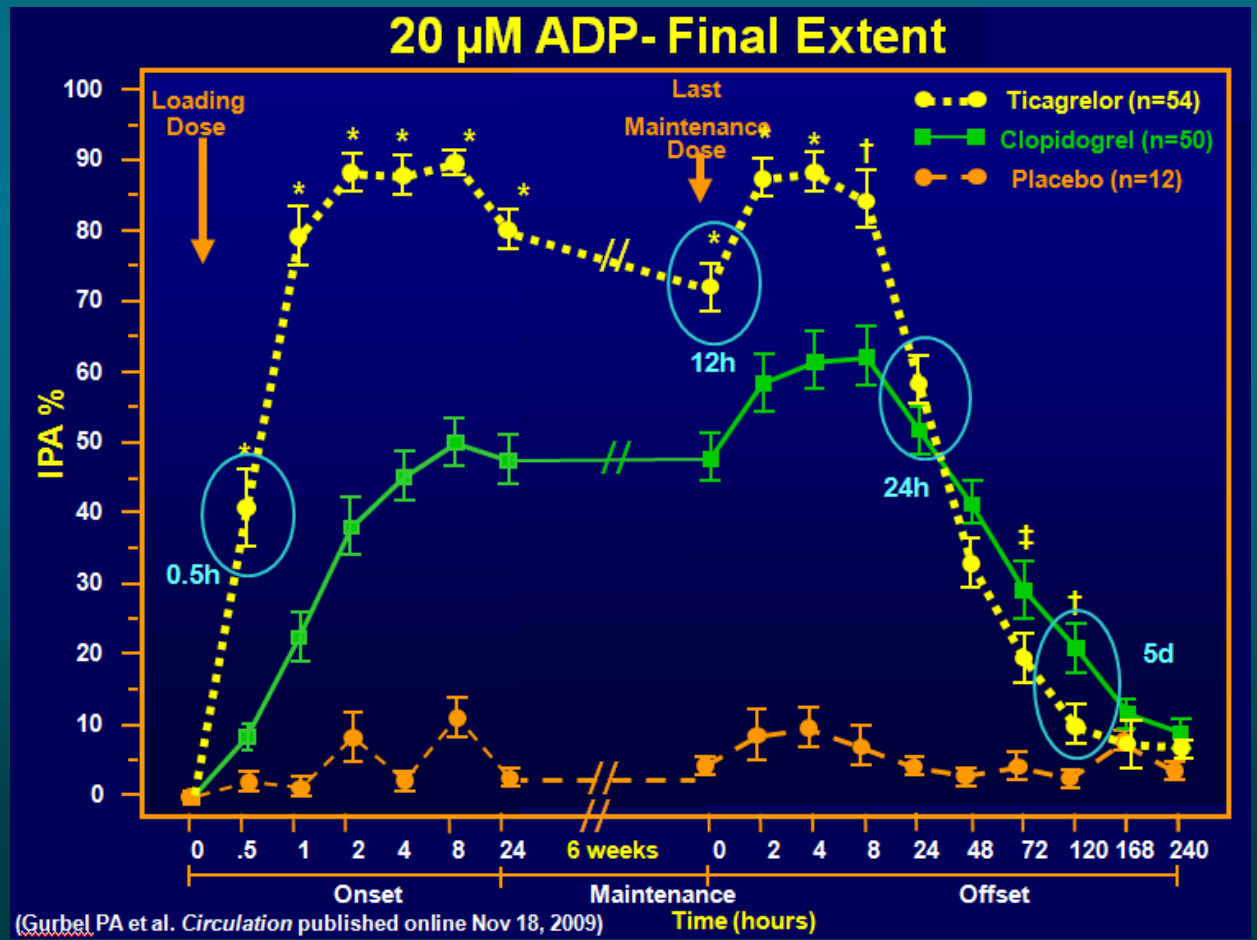


IPA=inhibition of platelet aggregation; LD=loading dose

Wiviott SD et al. Circulation 2007

Ticagrelor (AZD 6140)

- Direct acting (not pro-drug) & reversible binding to P2Y12
- Quicker onset and faster offset of effect vs. clopidogrel
- Greater and consistent inhibition of platelet aggregation vs. clopidogrel

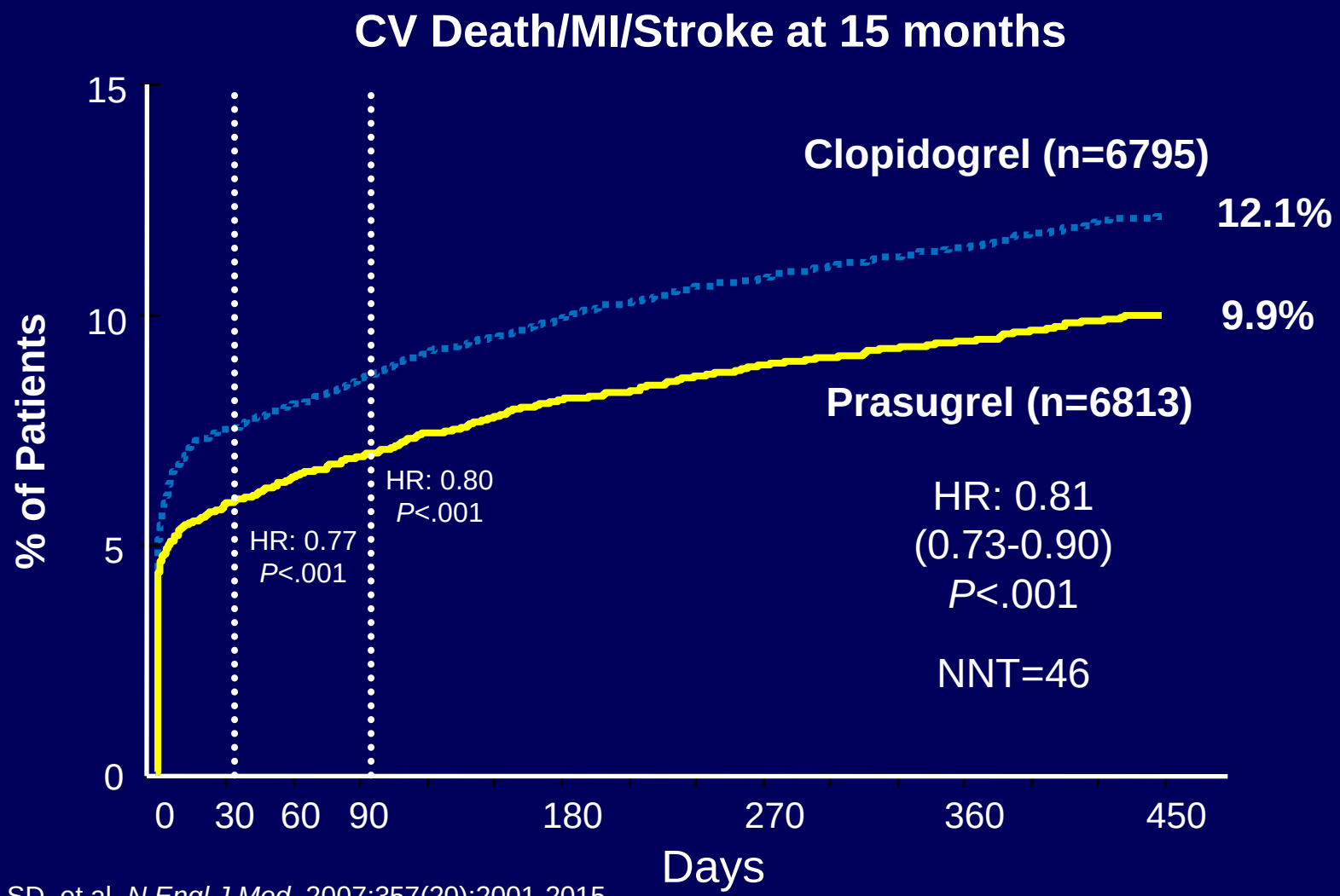


(Gurbel PA et al. *Circulation* published online Nov 18, 2009)

P2Y12 inhibitors

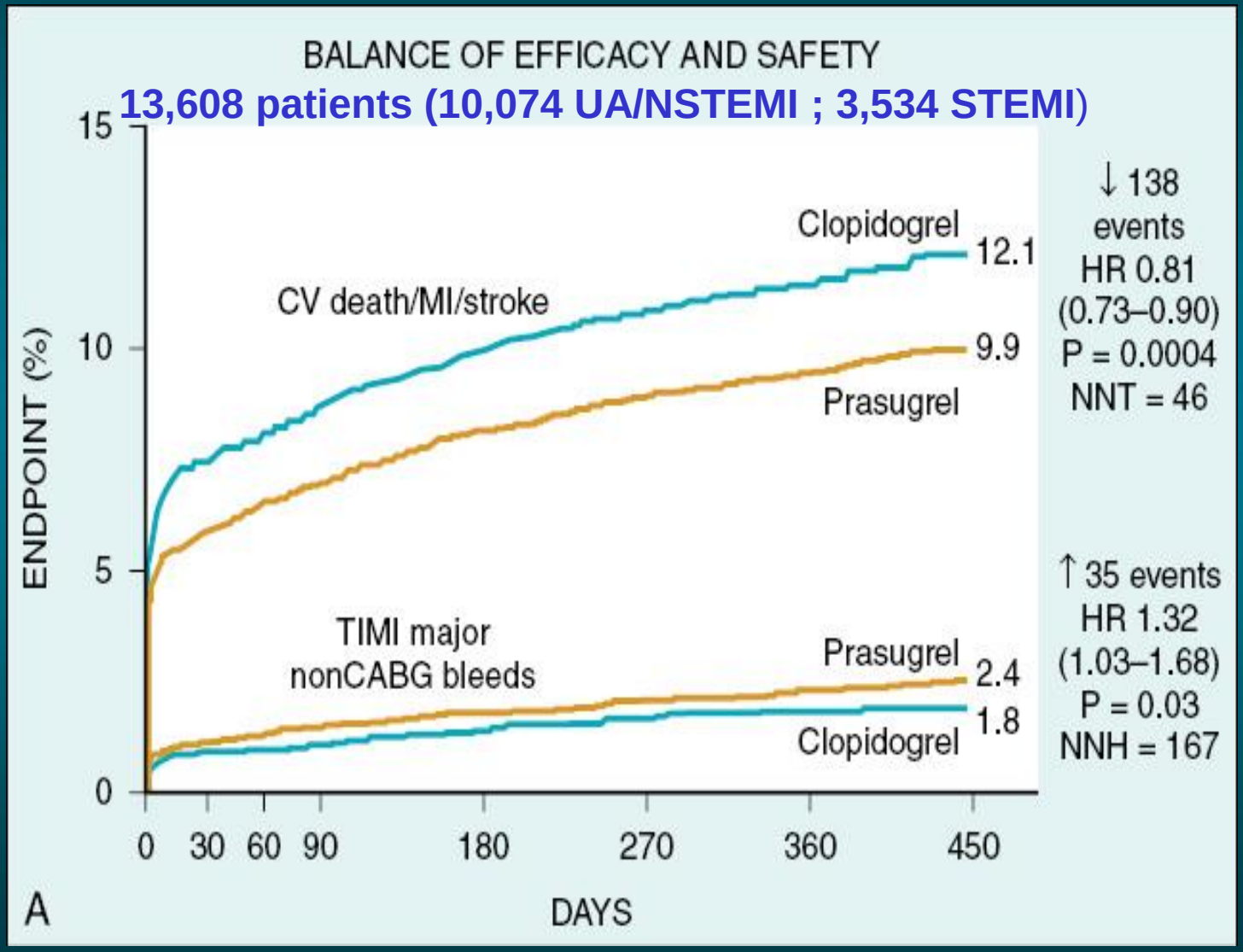
	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolization	Prodrug, not limited by metabolization	Active drug
Onset of effect	2-4 h	30 min	30 min
Duration of effect	3-10 days	5-10 days	3-4 days
Withdrawal before major surgery	5 days	7 days	5 days

TRITON-TIMI 38: Primary Endpoint



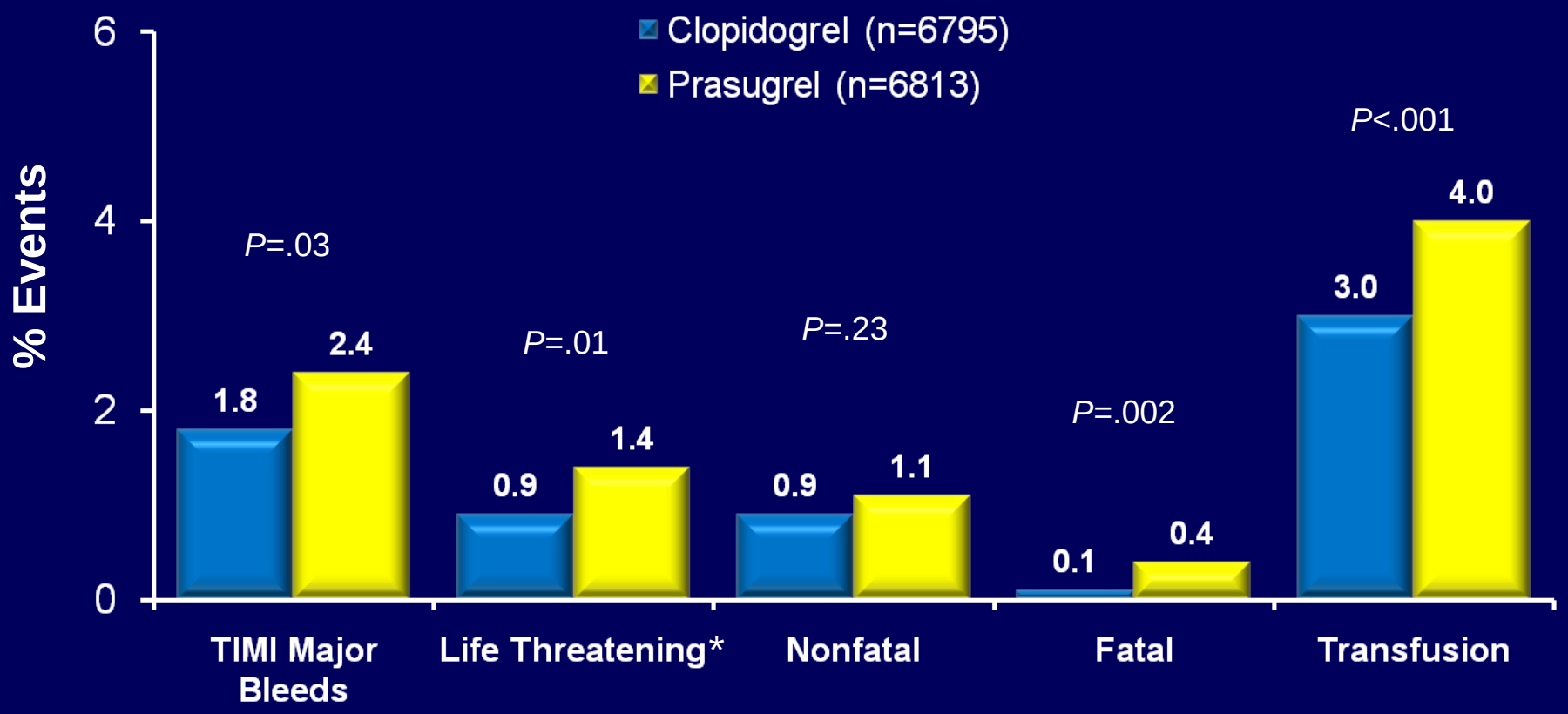
Wiviott SD, et al. *N Engl J Med.* 2007;357(20):2001-2015.

TRITON – TIMI 38: patients with ACS undergoing PCI



Wiviott SD. TRITON – TIMI 38. N Engl J Med 2007;357:2001

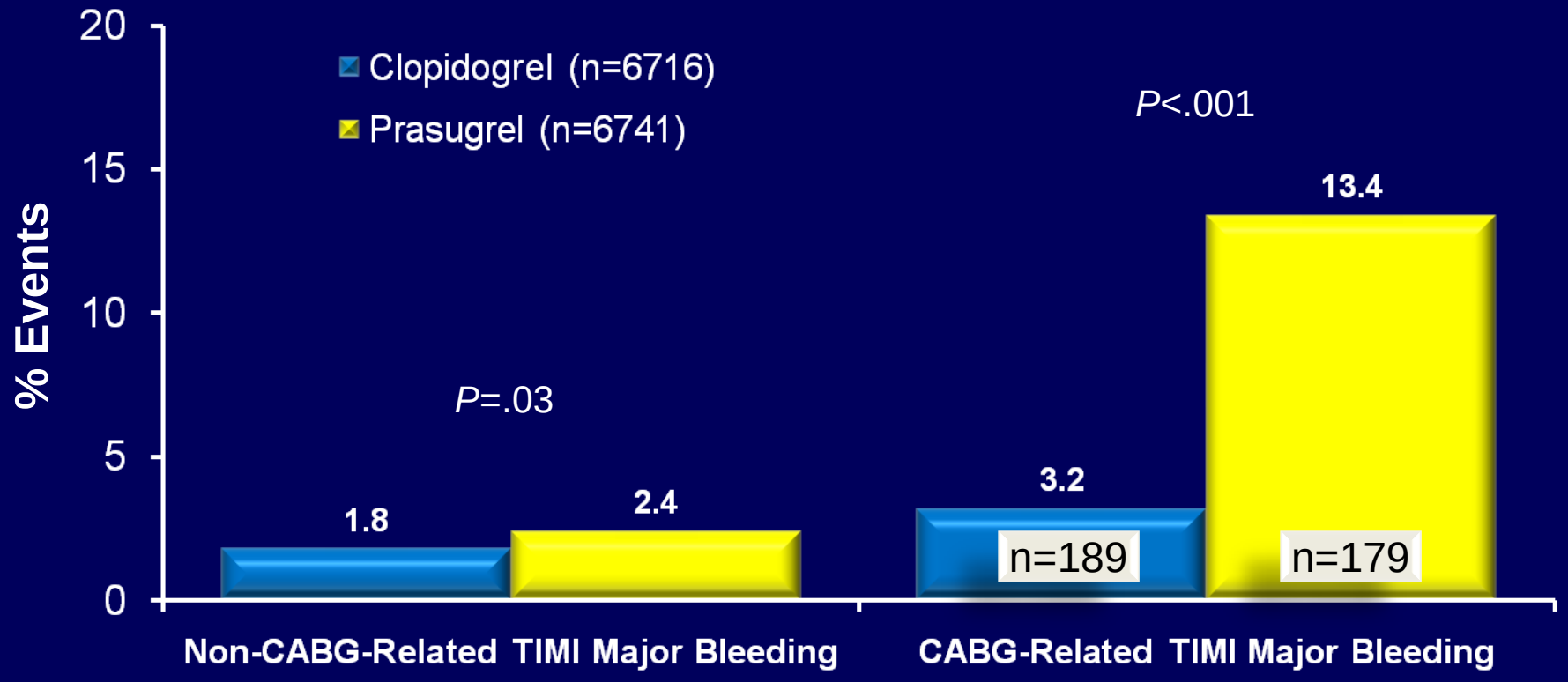
TRITON-TIMI 38: Safety at 15 Months



*Most frequent sites of life-threatening bleeding: Gastrointestinal, intracranial, puncture, and retroperitoneal.

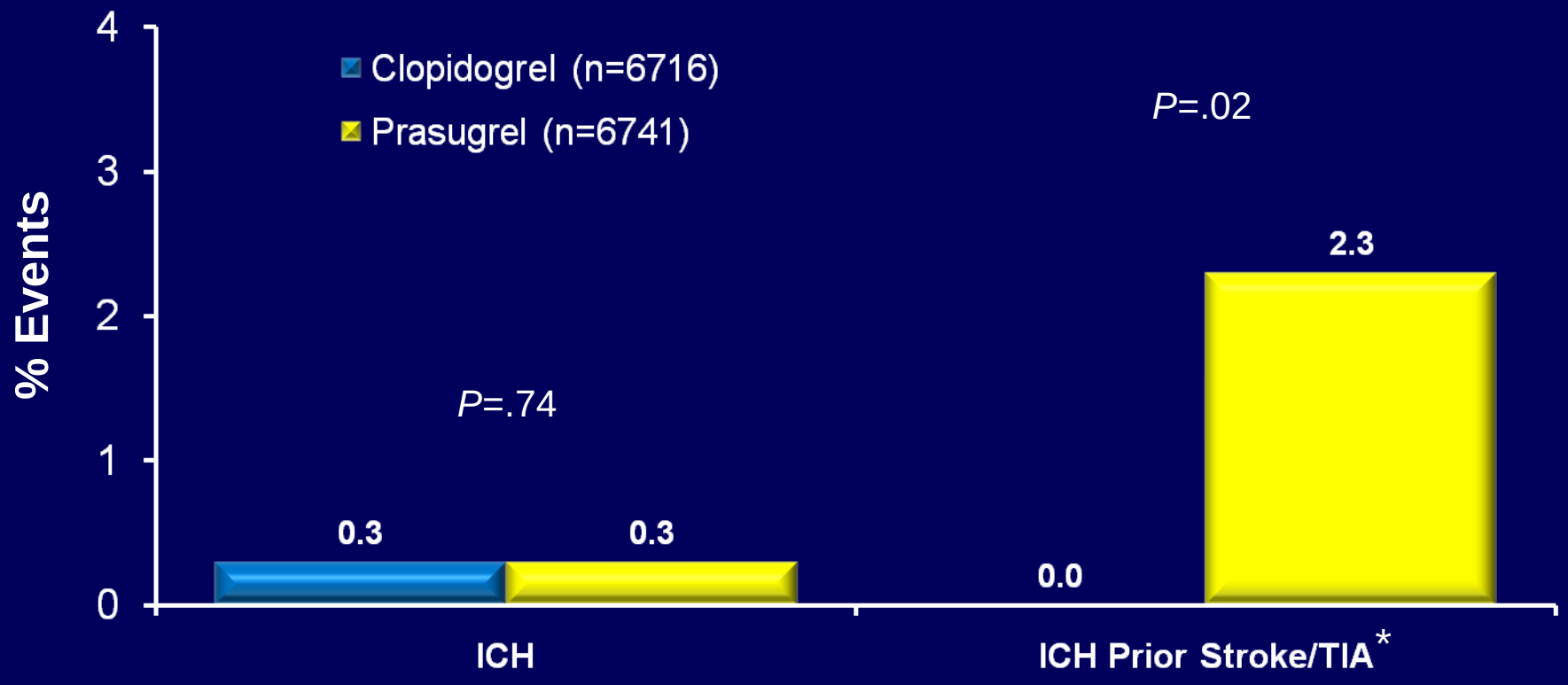
Wiviott SD, et al. *N Engl J Med.* 2007;357(20):2001-2015.

TRITON-TIMI 38: Safety at 15 Months



Wiviott SD, et al. *N Engl J Med.* 2007;357(20):2001-2015.

TRITON-TIMI38: Intracranial Bleeding at 15 Months

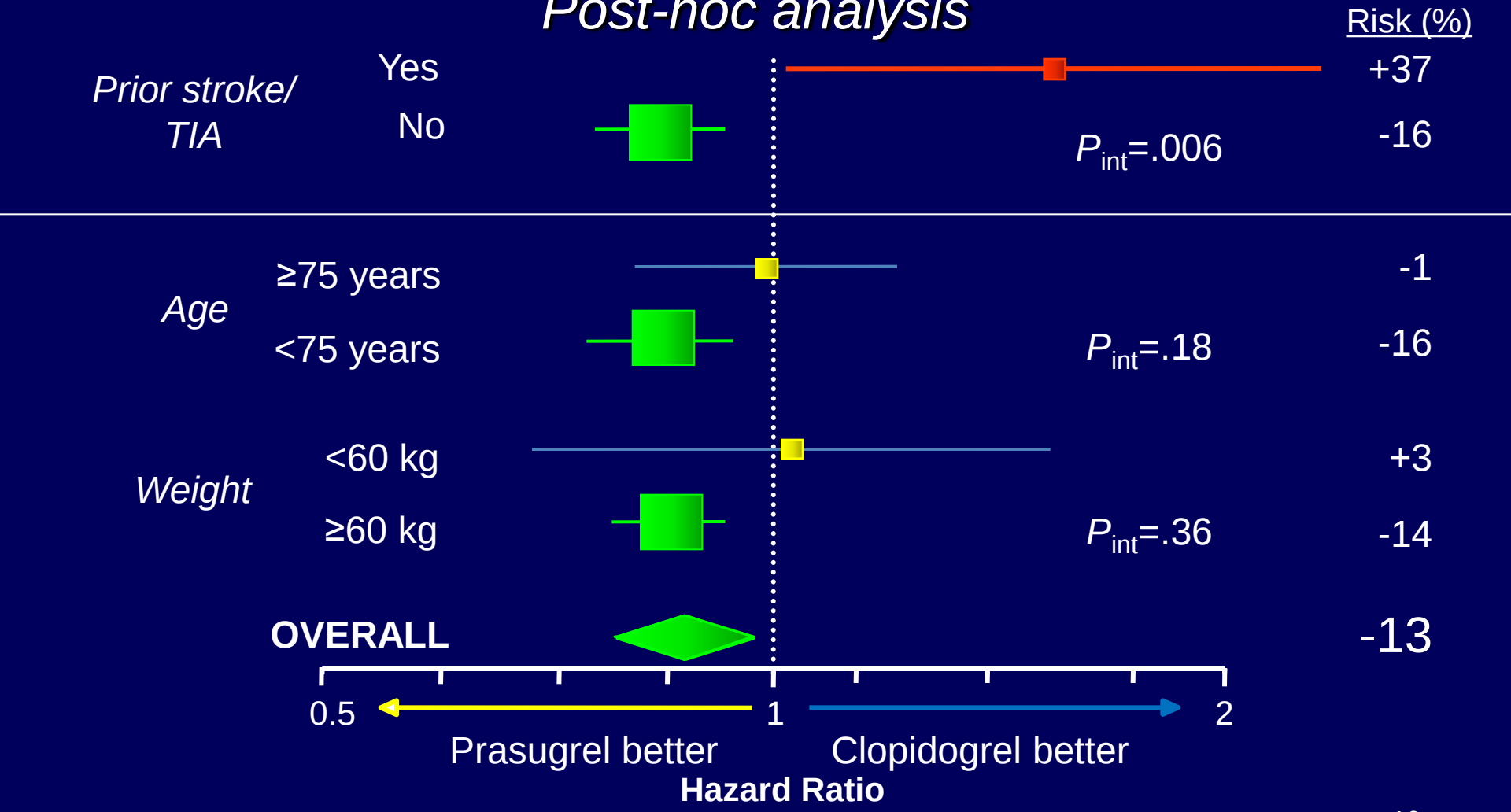


*ICH in patients with prior stroke/TIA (n=518)

Wiviott SD, et al. *N Engl J Med.* 2007;357(20):2001-2015.

TRITON-TIMI 38: Net Clinical Benefit in Subgroups at Risk for Bleeding

Post-hoc analysis

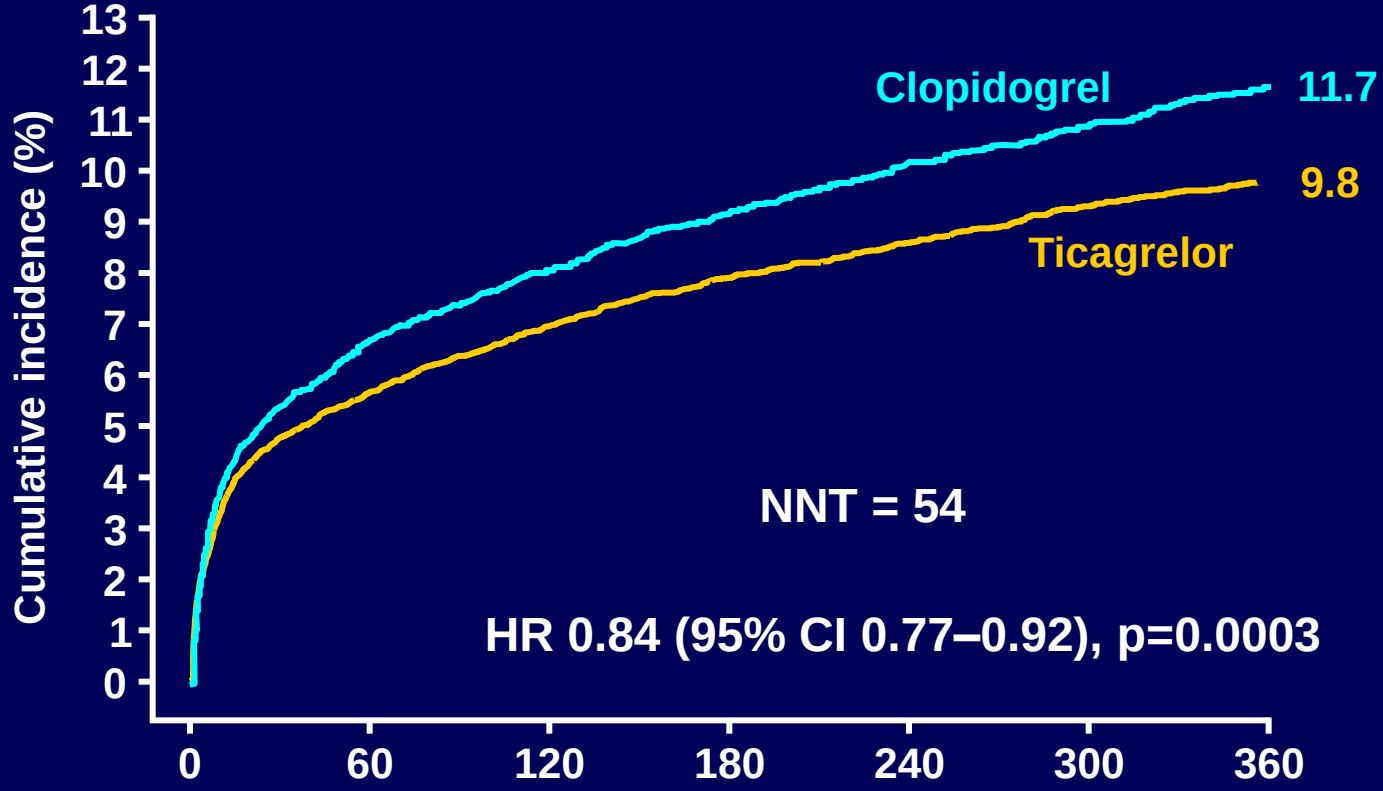


Wiviott SD, et al. *N Engl J Med.* 2007;357(20):2001-2015.

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

PLATO

18,624 patients (10,174 UA/NSTEMI ; 8,430 STEMI)



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

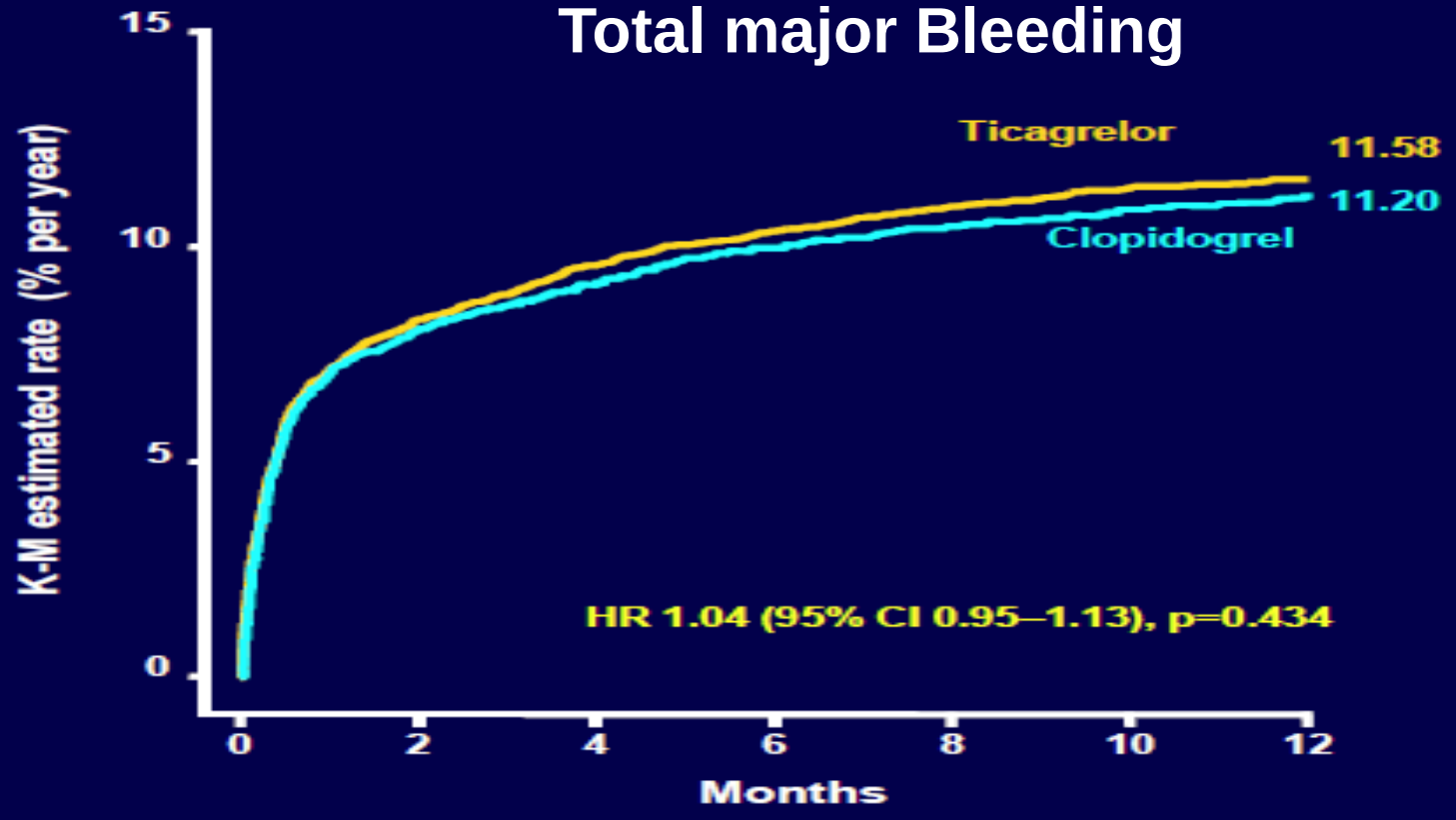
K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Wallentin et al. NEJM 2009;361:1045-57

PLATO

Primary safety endpoint

Total major Bleeding



9,235	7,246	6,826	6,545	5,129	3,783	3,433
9,186	7,305	6,930	6,670	5,209	3,841	3,479

Wallentin et al., New Eng J Med. 2009;361:1045–1057

Hierarchical testing of major efficacy endpoints

PLATO

All patients*	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for ticagrelor (95% CI)	p value†
Primary objective, n (%)				
CV death + MI + stroke	864 (9.8)	1,014 (11.7)	0.84 (0.77–0.92)	<0.001
Secondary objectives, n				
Total death + MI + strok			84 (0.77–0.92)	<0.001
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	1,290 (14.6)	1,456 (16.7)	0.88 (0.81–0.95)	<0.001
Myocardial infarction	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	0.005
CV death	353 (4.0)	442 (5.1)	0.79 (0.69–0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	0.22

All-cause mortality reduction

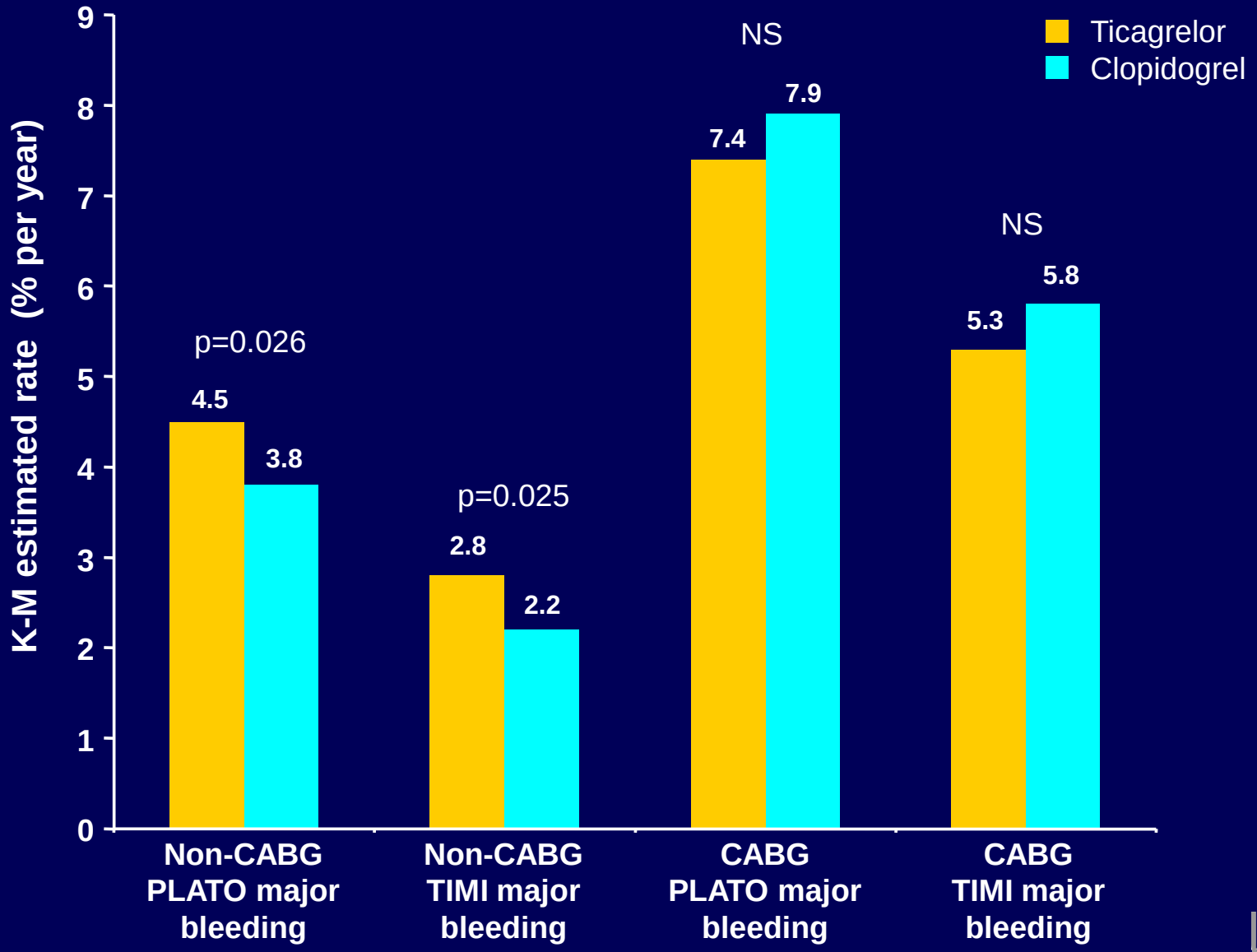
-22%

*The percentages are K-M estimates of the rate of the endpoint at 12 months. Patients could have had more than one type of endpoint. Death from CV causes included fatal bleeding and only traumatic fatal bleeds were excluded from the CV death category; †By Cox regression analysis

Wallentin et al. NEJM 2009;361:1045-57

Non-CABG and CABG-related major bleeding

PLATO



Caveats of Tricagrelor

All patients	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value*
Dyspnoea, %			
Any	13.8	7.8	<0.001
Requiring discontinuation of study treatment	0.9	0.1	<0.001

Holter monitoring at first week	Ticagrelor (n=1,451)	Clopidogrel (n=1,415)	p value
Ventricular pauses ≥3 seconds, %	5.8	3.6	0.01
Ventricular pauses ≥5 seconds, %	2.0	1.2	0.10

Drug interactions: strong CYP3A inhibitors should be avoided (Erythromycin, Clarithromycine, Cyclosporine, Amiodarone, Diltiazem, Amlodipine, Bosentan, Grapefruit juice…)

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 recommendations for oral antiplatelet agents in UA/NSTEMI

Recommendations	Class [a]	Level [b]
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
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*H. elicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids).	I	A
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C
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).	I	B
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 life-threatening bleeding or other contraindications.[d]	I	B
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	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.	I	B

Table 13 Checklist of treatments when an ACS diagnosis appears likely

Aspirin	Initial dose of 150–300 mg non-enteric formulation followed by 75–100 mg/day (i.v. administration is acceptable)
$P2Y_{12}$ inhibitor	Loading dose of ticagrelor or clopidogrel[a]
Anticoagulation	Choice between different options depends on strategy: • Fondaparinux 2.5 mg/daily subcutaneously • Enoxaparin 1 mg/kg twice daily subcutaneously • UFH i.v. bolus 60–70 IU/kg (maximum 5000 IU) followed by infusion of 12–15 IU/kg/h (maximum 1000 IU/h) titrated to aPTT 1.5–2.5 × control • Bivalirudin is indicated only in patients with a planned invasive strategy
Oral ß-Blocker	If tachycardic or hypertensive without signs of heart failure

aPTT = activated partial thromboplastin time; IU = international units; i.v. = intravenous; UFH = unfractionated heparin.

[a]Prasugrel is not mentioned as it is not approved as medical therapy before invasive strategy, but only after angiography when anatomy is known.

Table 14 Checklist of antithrombotic treatments prior to PCI

Aspirin	Confirm loading dose prior to PCI.
$P2Y_{12}$ inhibitor	Confirm loading dose of ticagrelor or clopidogrel prior to PCI. If $P2Y_{12}$ naïve, consider prasugrel (if <75 years age, >60 kg, no prior stroke or TIA)
Anticoagulation	• Fondaparinux pre-treated: add UFH for PCI • Enoxaparin pre-treated: add if indicated • UFH pre-treated: titrate to ACT >250 s, or switch to bivalirudin (0.1 mg/kg bolus followed by 0.25 mg/kg/h)
GP IIb/IIIa receptor inhibitor	• Consider tirofiban or eptifibatide in patients with high-risk anatomy or troponin elevation • Abciximab only prior to PCI in high-risk patients.

ACT = activated clotting time; GP, glycoprotein; PCI = percutaneous coronary intervention; TIA = transient ischaemic attack; UFH = unfractionated heparin.

Remarks

Ticagrelor – drug interactions related to CYP3A (FDA table)

CYP Enzymes	Strong Inhibitors ≥ 5-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL
CYP3A	Boceprevir, **clarithromycin**, conivaptan, **grapefruit juice**,(11) indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, (12) nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, **ciprofloxacin**, darunavir/ritonavir, **diltiazem**, **erythromycin**, fluconazole, fosamprenavir, **grapefruit juice**,(11) imatinib, **verapamil**	Alprazolam, **amiodarone**, **amlodipine**, **atorvastatin**, bicalutamide, cilostazol, **cimetidine**, cyclosporine, **fluoxetine**, fluvoxamine, ginkgo,(5) goldenseal,(5) isoniazid, nilotinib, oral contraceptives, **ranitidine**, **ranolazine**, tipranavir/ritonavir, zileuton

What do we fear?

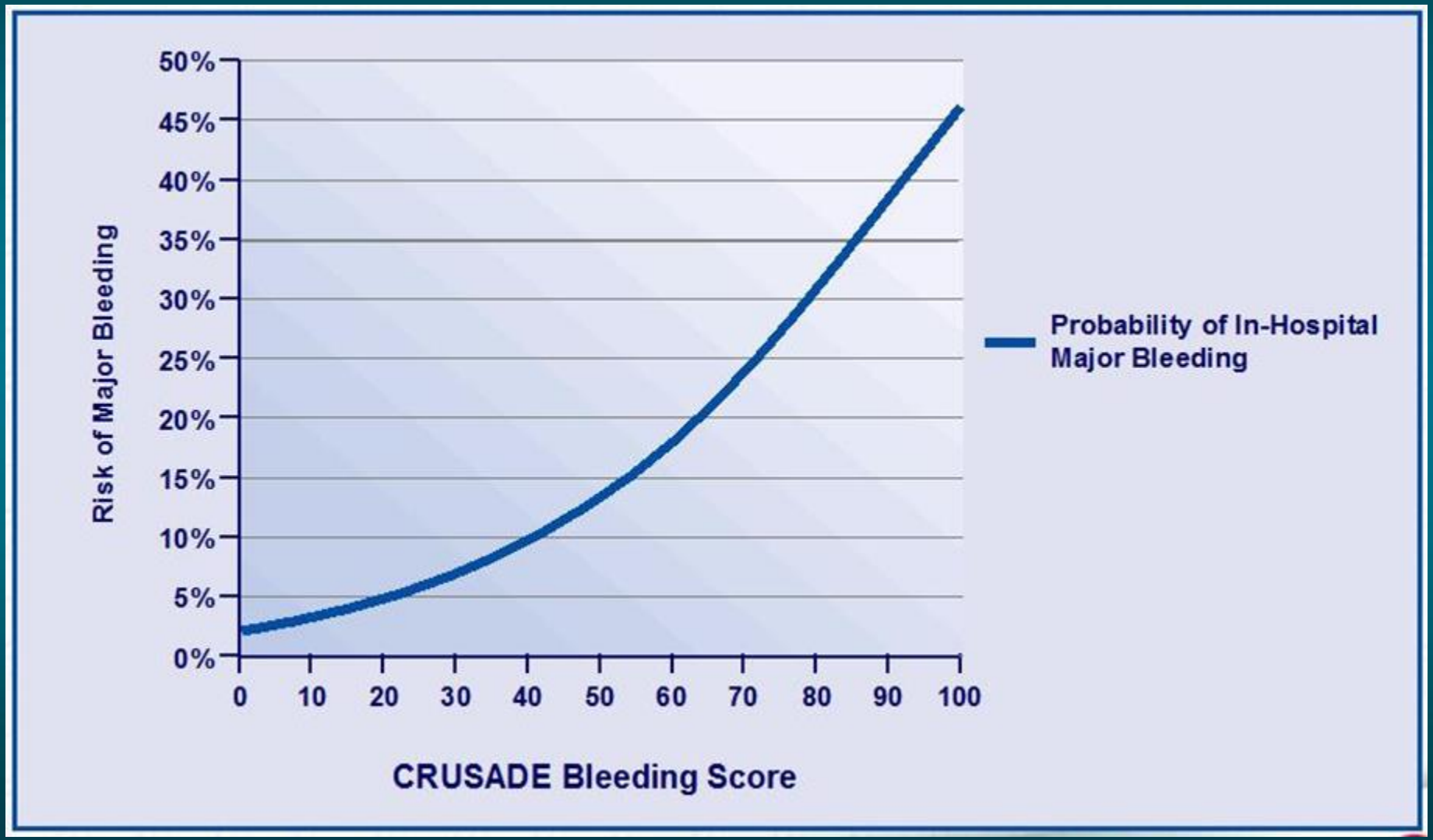
Bleeding… (tightly related to ACS outcome and mortality

…especially intracranial bleeding (disability and mortality)

Elderly – increased risk

Post CVA or TIA – increased risk

CRUSADE major bleeding risk in ACS



Bleeding is strongly related to ACS prognosis and mortality

CRUSADE bleeding risk score

Predictor	Score
Baseline haematocrit, %	
< 31	9
31-33.9	7
34-36.9	3
37-39.9	2
≥ 40	0
Creatinine clearance, mL/min	
≤ 15	39
> 15-30	35
> 30-60	28
> 60-90	17
> 90-120	7
> 120	0

Predictor	Score
Heart rate (b.p.m.)	
≤ 70	0
71-80	1
81-90	3
91-100	6
101-110	8
111-120	10
≥ 121	11
Male	0
Female	8
Sex	
Male	0
Female	8
Signs of CHF at presentation	
No	0
Yes	7

Predictor	Score
Prior vascular disease	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure, mmHg	
≤ 90	10
91-100	8
101-120	5
121-180	1
181-200	3
≥ 201	5

AGE not a factor!

Previous Stroke not a factor!

Bleeding is strongly related to ACS prognosis and mortality

Ticagrelor Versus Clopidogrel in Elderly Patients With Acute Coronary Syndromes

A Substudy From the Prospective Randomized PLATelet Inhibition and Patient Outcomes (PLATO) Trial

Steen Husted, MD, DSc; Stefan James, MD, PhD; Richard C. Becker, MD; Jay Horrow, MD; Hugo Katus, MD; Robert F. Storey, MD, DM; Christopher P. Cannon, MD; Magda Heras, MD; Renato D. Lopes, MD, PhD; Joao Morais, MD, FESC; Kenneth W. Mahaffey, MD; Richard G. Bach, MD; Daniel Wojdyla, MSc; Lars Wallentin, MD, PhD; for the PLATO study group

(*Circ Cardiovasc Qual Outcomes*. 2012;5:680-688.)

What is known?

PLATO Elderly

- Elderly patients with acute coronary syndrome have a high prevalence of cardiovascular risk factors and are at high risk of recurrent ischemic events and death.

- Elderly patients have a high risk of complications during antithrombotic therapy and revascularization.

- The increased risk of bleeding in elderly as compared with younger patients using some antiplatelet and anticoagulant therapies reduces the net clinical benefit of these therapies.

PLATO
Elderly

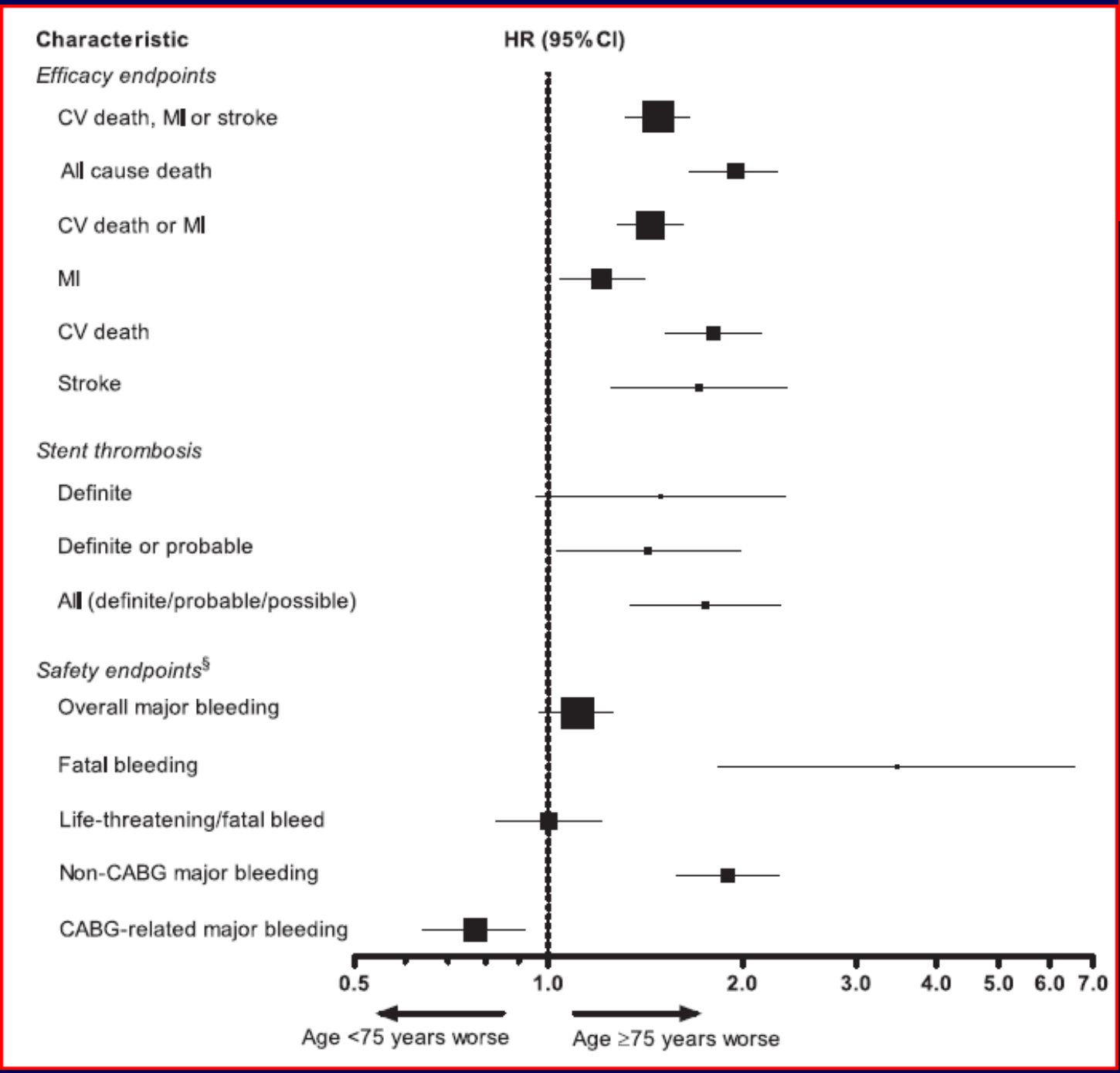


Figure 1. Association of age (<75 vs ≥75 years) with clinical outcome. *n=2878; †n=15 744; ‡See methods for adjustment variables; §PLATelet inhibition and patient Outcomes (PLATO)-defined.22 CABG indicates coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; KM, Kaplan-Meier estimate; and MI, myocardial infarction.

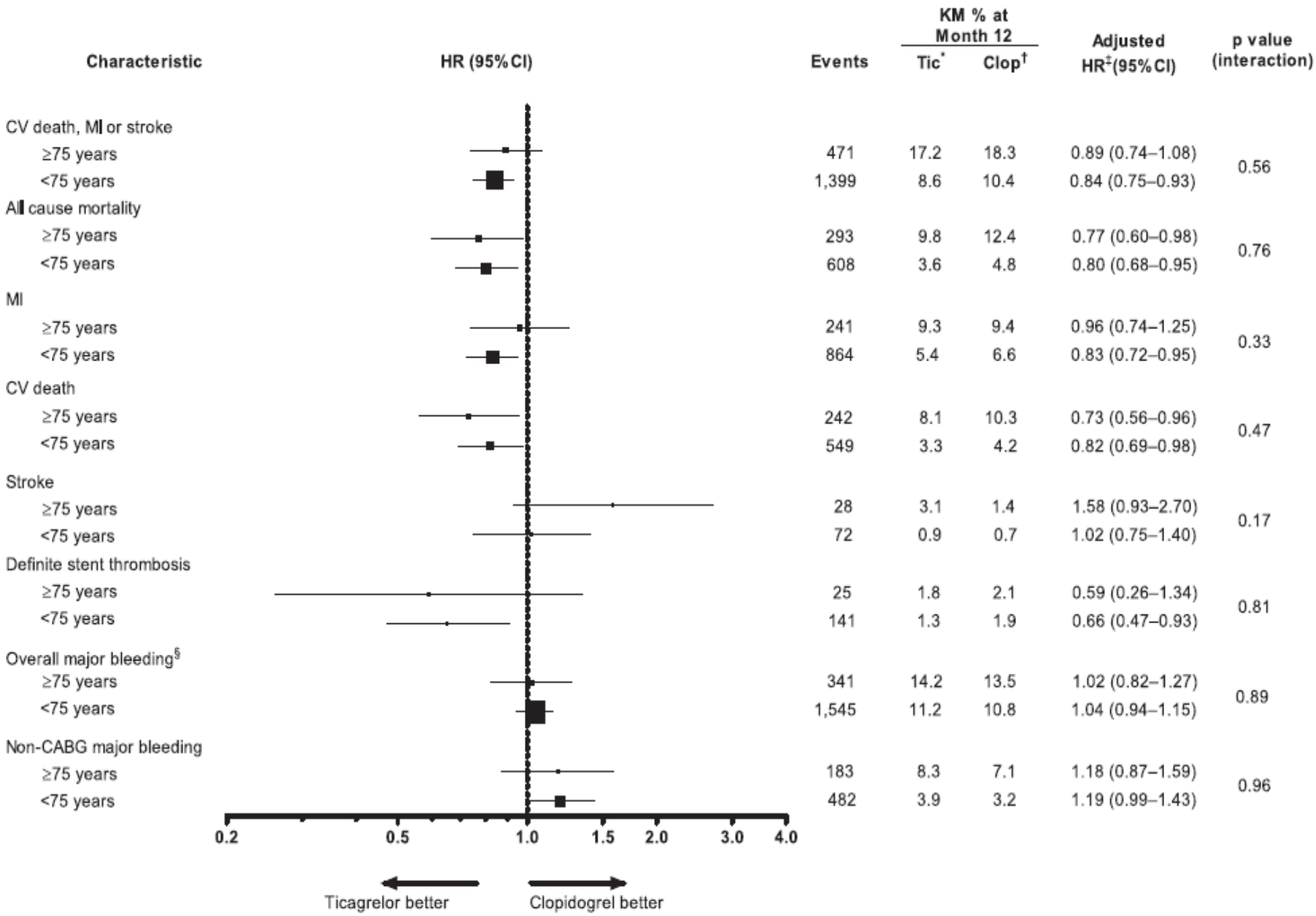


Figure 2. Association of age (<75 vs ≥75 years) and treatment with outcome. *Tic = ticagrelor (n=9333); †Clop = clopidogrel (n=9291); ‡See methods for adjustment variables; §PLATelet inhibition and patient Outcomes (PLATO)-defined;[22] CABG indicates coronary artery bypass graft; CV, cardiovascular; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; and MI, myocardial infarction.

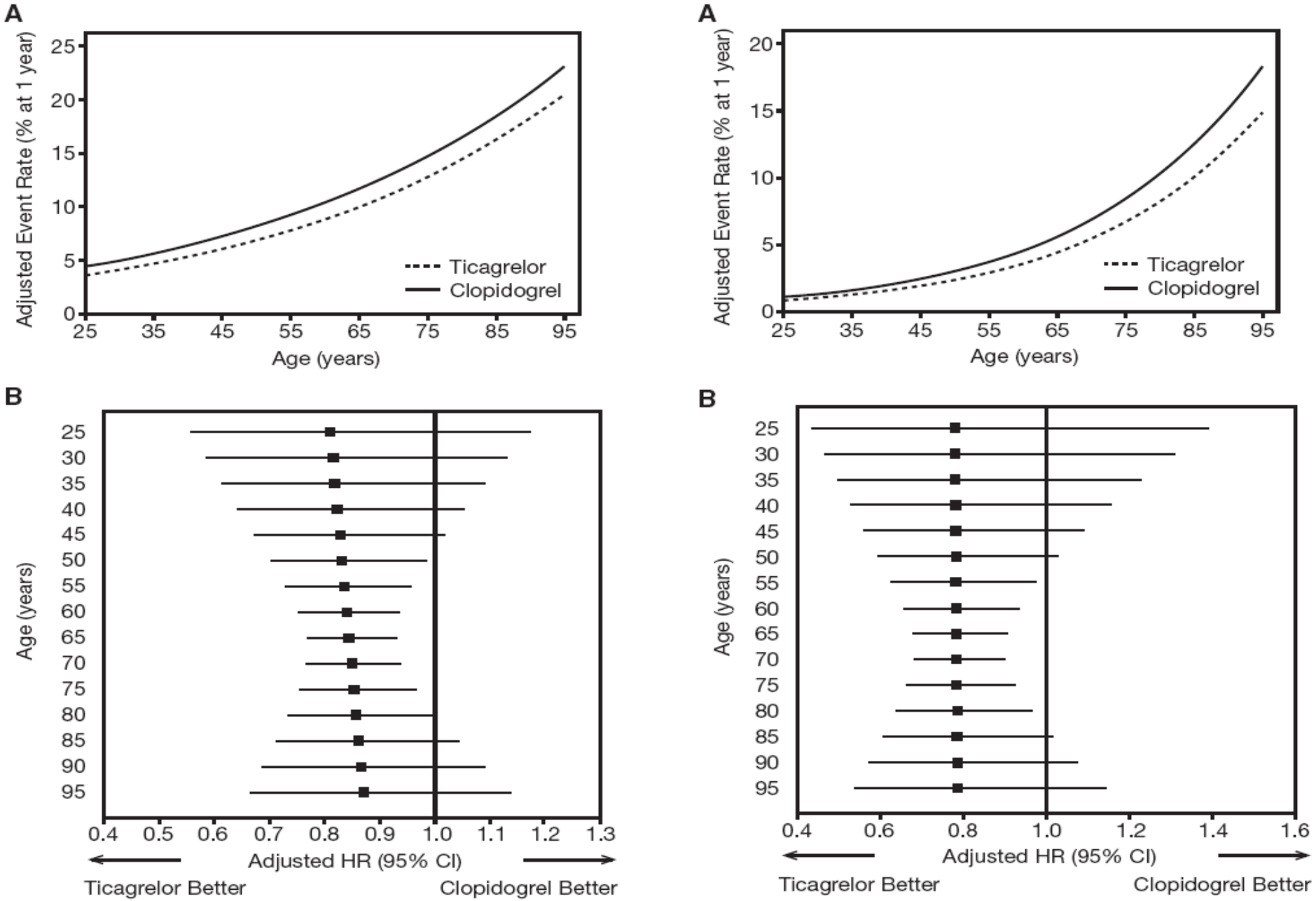


Figure 3. Primary composite outcome—cardiovascular death/MI/stroke according to age. **A**, Estimated event rate at 12 months, ticagrelor vs clopidogrel. **B**, treatment effect by patient age. HR indicates hazard ratio; CI, confidence interval.

Figure 4. All-cause mortality according to age. **A**, Estimated event rate at 12 months, ticagrelor vs clopidogrel. **B**, treatment effect by patient age. HR indicates hazard ratio; CI, confidence interval.

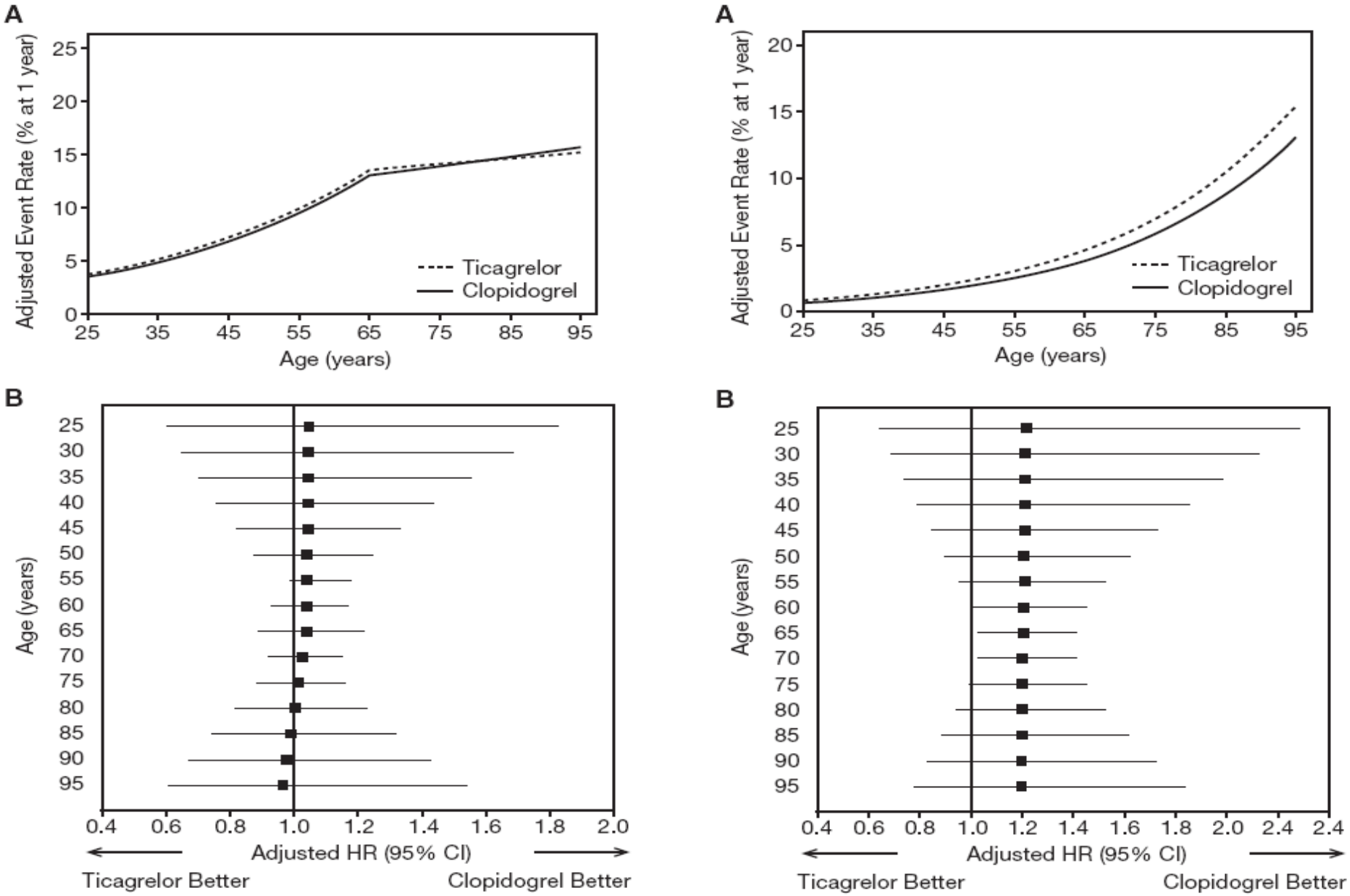


Figure 5. Overall major bleeding (PLATelet inhibition and patient Outcomes (PLATO)-defined)[22] according to age*. **A**, Estimated event rate at 12 months, ticagrelor vs clopidogrel. **B**, treatment effect by patient age. *As the relationship between age and major bleeding was not linear, age was considered as 2 linear splines. HR indicates hazard ratio; CI, confidence interval.

Figure 6. Overall non–coronary artery bypass graft-related bleeding (PLATelet inhibition and patient Outcomes (PLATO)-defined)[22] according to age. **A**, Estimated event rate at 12 months, ticagrelor vs clopidogrel. **B**, treatment effect by patient age. HR indicates hazard ratio; CI, confidence interval.

PLATO
Elderly

Table 2. Side Effects: Dyspnea and Holter Monitoring

	Ticagrelor (n=9333)	Clopidogrel (n=9291)		Interaction
	KM %	KM %	HR (95% CI)	*P*
Dyspnea				
≥75 y	18.8	12.2	1.63 (1.33–1.90)	0.21
<75 y	14.2	7.8	1.89 (1.70–2.09)	
Ventricular pauses				
First week	% (n=1461)	% (n=1432)	OR (95% CI)	
≥3 s				
≥75 y	7.2	6.9	1.06 (0.54–2.08)	0.14
<75 y	5.5	2.9	1.92 (1.26–2.93)	
≥5 s				
≥75 y	2.8	2.7	1.05 (0.36–3.05)	0.28
<75 y	1.8	0.9	2.14 (1.01–4.55)	
At 30 days	% (n=992)	% (n=1012)	OR (95% CI)	
≥3 s				
≥75 y	2.4	3.4	0.70 (0.20–2.54)	0.29
<75 y	2.1	1.3	1.57 (0.73–3.38)	
≥5 s				
≥75 y	0.0	1.1	—	—
<75 y	1.0	0.5	2.03 (0.61–6.77)	

KM indicates Kaplan–Meier estimate; HR, hazard ratio; and CI, confidence interval; OR, odds ratio.

What the study adds

PLATO Elderly

- The clinical benefit of ticagrelor over clopidogrel in patients with ACS with respect to the composite end point; myocardial infarction; cardiovascular death; stent thrombosis or all-cause mortality, was not significantly different between patients aged ≥75 and those aged <75 years.
- No increased risk of major bleeding complications with ticagrelor versus clopidogrel was observed in patients aged ≥75 years or patients aged <75 years.
- Side-effects dyspnea and ventricular pauses were more common during treatment with ticagrelor than clopidogrel, with no evidence of an age-by-treatment interaction.

Conclusions

PLATO Elderly

This **predefined subanalysis** assessed clinical outcomes in elderly (≥75 years of age) versus younger (*<75 years of age) patients in the PLATO trial*

It showes that ticagrelor compared with clopidogrel ***reduced ischemic outcomes and mortality .***

The present findings are consistent with the overall results of the PLATO trial, and suggest that the antithrombotic benefits of ticagrelor also apply to the age group >75 years.

Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes and a History of Stroke or Transient Ischemic Attack

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(*Circulation*. 2012;125:2914-2921.)

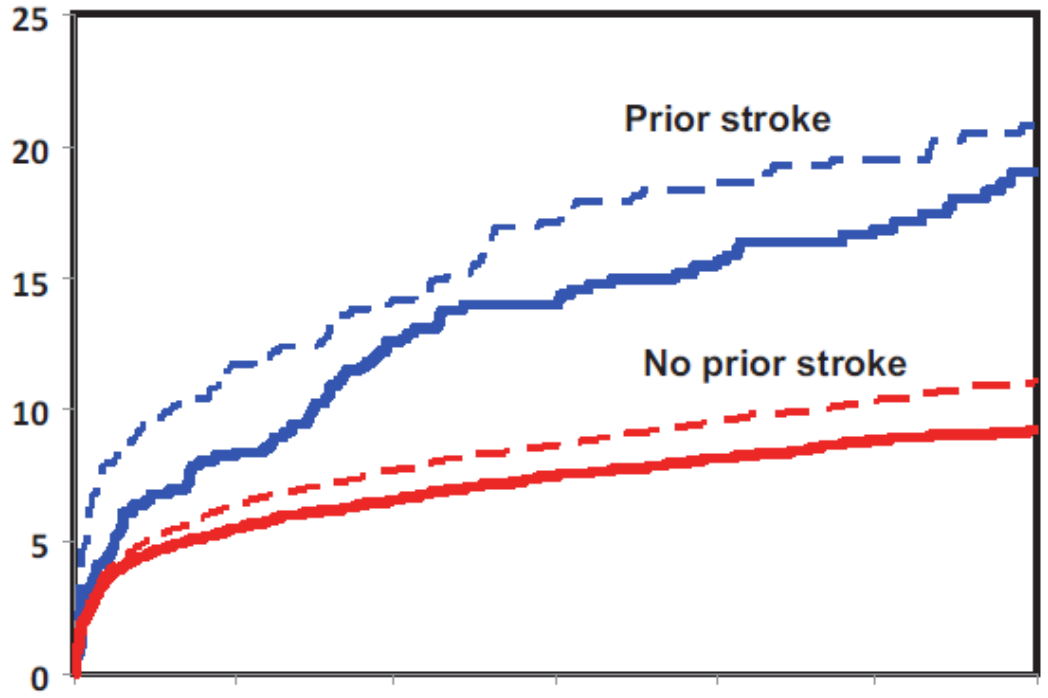
Table 3. Association of Prior Stroke With End Point

End Point	Prior Stroke or TIA (n=1152)	No Prior Stroke or TIA (n=17 460)	Unadjusted			Adjusted		
			HR (95% CI)	χ^2	*P*	HR (95% CI)	χ^2	*P*
Primary outcome: CV death/MI (excluding silent)/stroke	19.9 (215)	10.1 (1663)	2.06 (1.78–2.37)	98.9672	<0.0001	1.65 (1.40–1.93)	36.7953	<0.0001
CV death (includes vascular and unknown deaths)	9.7 (102)	4.2 (693)	2.29 (1.86–2.82)	61.1987	<0.0001			
All-cause death	10.5 (111)	4.9 (794)	2.18 (1.79–2.66)	59.1666	<0.0001	1.68 (1.33–2.11)	19.7284	<0.0001
MI (excluding silent)	11.5 (119)	6.0 (978)	1.92 (1.59–2.33)	45.3974	<0.0001			
Major bleeding (study criteria)	14.8 (144)	11.2 (1746)	1.31 (1.10–1.55)	9.5022	0.0021	1.18 (0.98–1.43)	2.9463	0.0861
Non–CABG-related major bleeding (study criteria)	6.3 (60)	4.0 (608)	1.56 (1.20–2.04)	10.8716	0.0010	1.38 (1.03–1.85)	4.5464	0.0330
Stroke	3.4 (36)	1.2 (195)	2.90 (2.03–4.14)	34.4170	<0.0001			
Intracranial bleeding	0.8 (8)	0.2 (33)	3.95 (1.82–8.55)	12.1333	0.0005			

TIA indicates transient ischemic attack; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; and CABG, coronary artery bypass graft surgery.

Event rates are presented as Kaplan-Meier rate at 360 days (total number of events during the trial). Variables included in the multivariable model were age, sex, prior myocardial infarction, heart failure, hypertension, smoking, height, weight, previous percutaneous coronary intervention, coronary artery bypass surgery, ST elevation or left bundle-branch block on ECG at entry, estimated creatinine clearance, heart rate, peripheral artery disease, prior tachyarrhythmia, blood pressure, and prior angina pectoris.

A Primary endpoint



Clopidogrel

Ticagrelor

HR 0.87
(HR 0.97 MV)

Clopidogrel

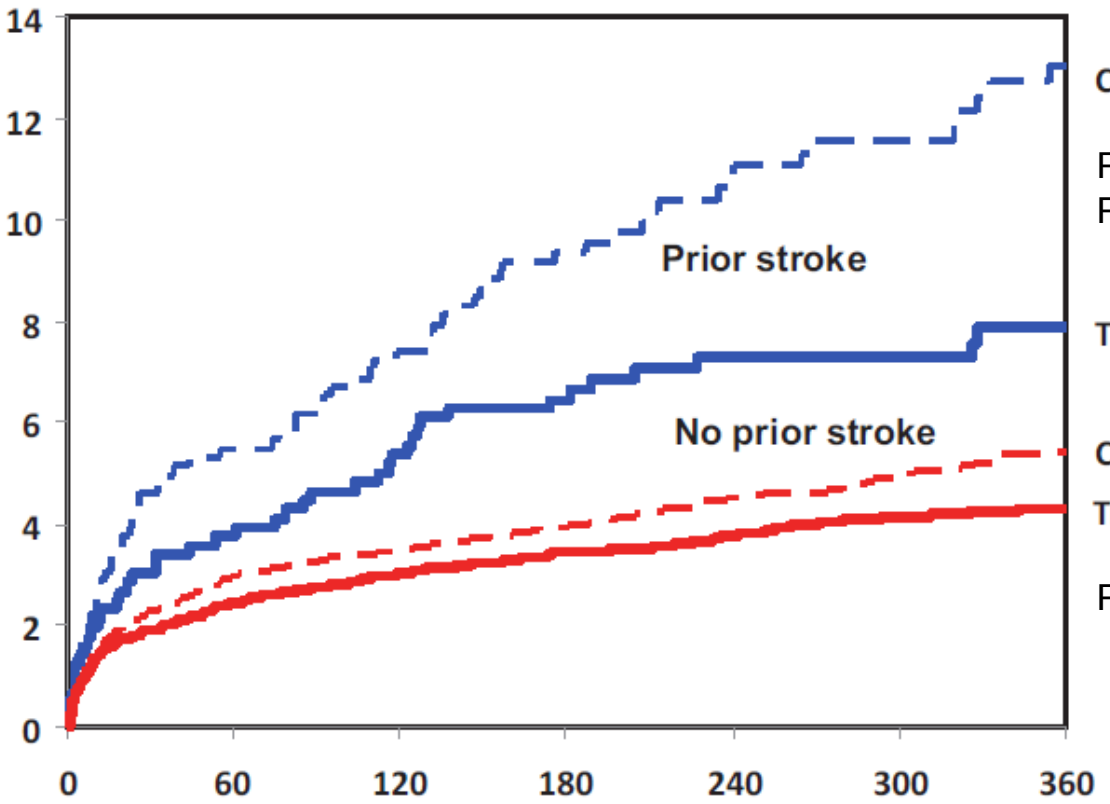
Ticagrelor

HR 0.84

Patient at risk

Prior stroke	Clopidogrel	588	505	488	458	357	280	218
	Ticagrelor	564	509	485	470	379	300	225
No prior stroke	Clopidogrel	8699	8012	7870	7662	6290	4813	3853
	Ticagrelor	8761	8111	7967	7741	6357	4854	3919

B Total mortality



Clopidogrel

RRR 38%
RRR 15% MV

Ticagrelor

Clopidogrel

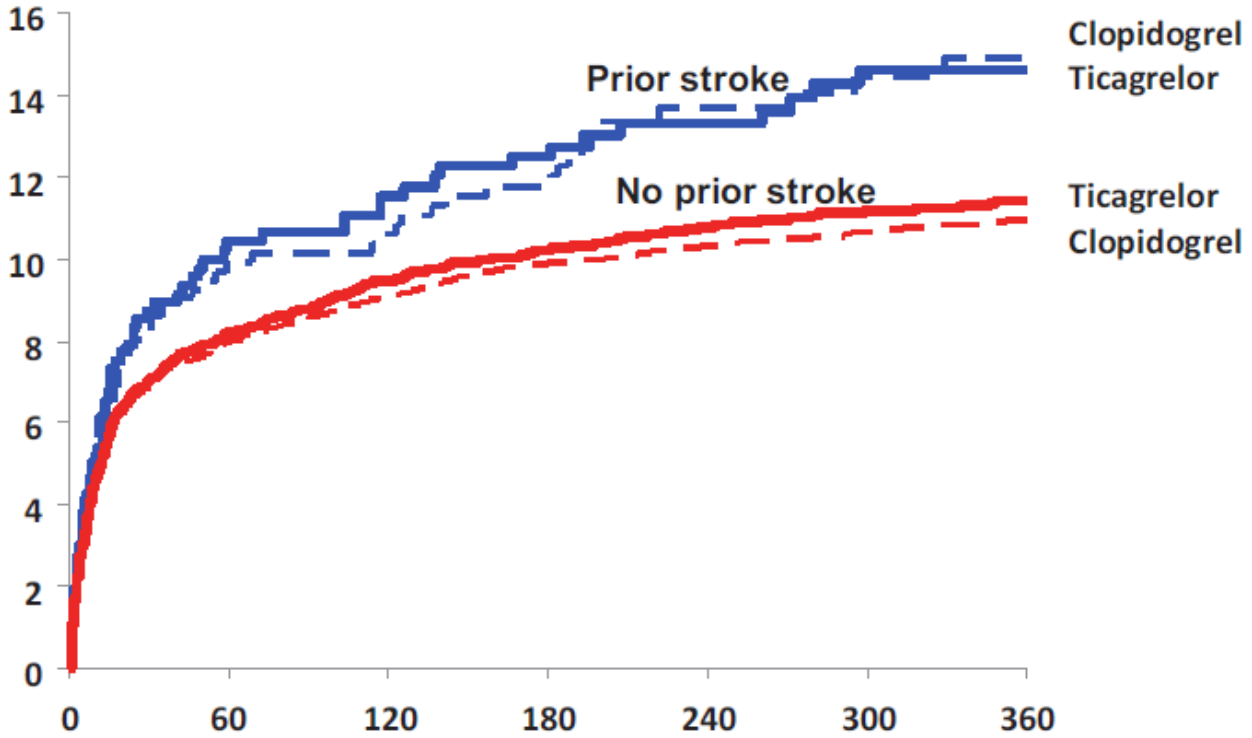
Ticagrelor

RRR 19%

Patient at risk								
Prior stroke	Clopidogrel	588	542	530	507	397	314	246
	Ticagrelor	564	534	525	511	411	332	254
No prior stroke	Clopidogrel	8699	8318	8245	8078	6679	5124	4115
	Ticagrelor	8761	8382	8289	8107	6701	5143	4162

C

Major bleeding



Patient at risk								
Prior stroke	Clopidogrel	578	412	387	358	270	198	179
	Ticagrelor	558	415	383	364	282	222	190
No prior stroke	Clopidogrel	8607	6892	6542	6311	4938	3642	3299
	Ticagrelor	8675	6830	6442	6180	4846	3560	3243

Editorial

Beware of Novel Antiplatelet Therapy in Acute Coronary Syndrome Patients With Previous Stroke

Freek W.A. Verheugt, MD, FACC, FESC

(*Circulation*. 2012;125:2821-2823.)

Words of caution…

Table 1. Intracranial Bleeding With Dual Versus Single Antiplatelet Therapy in Large Randomized Controlled Trials With Previous Stroke/TIA Patients

Trial	Indication	No. of Patients	% of Patients With Prior Stroke or TIA	Intracranial Bleeding		RR (95% CI)	*P*
				Dual Antiplatelet Therapy	Single Antiplatelet Therapy		
Thrombin Receptor Antagonist in Secondary Prevention of. Atherothrombotic Ischemic Events (TRA-2P)[10]*	Post stroke/TIA	5746	100	51/2870 (2.4%)	20/2876 (0.9%)	2.55 (1.52–4.28)	0.001
Management of Atherothrombosis with Clopidogrel in High-Risk Patients With Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH)[11]	Post stroke/TIA	7540	100	32/3759 (0.9%)	17/3781 (0.5%)	1.31 (1.07–1.61)	0.03
Prevention Regimen For Effectively Avoiding Second Strokes (PROFESS)[12]	Post stroke/TIA	21 332	100	147/10 181 (1.4%)	103/10 151 (1.0%)	1.42 (1.11–1.83)	0.006
Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events a (ACTIVE-A)[13]	SPAF†	7554	13	54/3772 (0.4%)	29/3782 (0.2%)	1.87 (1.19–2.94)	0.006

RR indicates risk ratio; CI, confidence interval.
*8% of patients of patients were also on clopidogrel.
†Stroke prevention in atrial fibrillation.

Verheugt FWA. Editorial. Circulation 2012;125:2821-2823

Words of caution…

Table 2. Intracranial Bleeding With Novel Versus Conventional Dual Antiplatelet Therapy in ACS Patients With Previous Stroke/TIA

Trial	Intervention	No. of Patients	% of Patients With Prior Stroke or TIA	Intracranial Bleeding		RR (95% CI)	*P*
				Novel Antiplatelet Therapy	Clopidogrel		
Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With prasugrel (TRITON)[8]	Prasugrel vs clopidogrel	13 608	3.8	6/262 (2.3%)	0/256 (0.0%)	…	0.02
PLATelet Inhibition and Patient Outcomes (PLATO)[14]*	Ticagrelor vs clopidogrel	18 624	6.2	4/564 (0.9%)	4/588 (0.7%)	1.00 (0.25–3.99)	0.96

RR indicates risk ratio; CI, confidence interval.
*Present study.

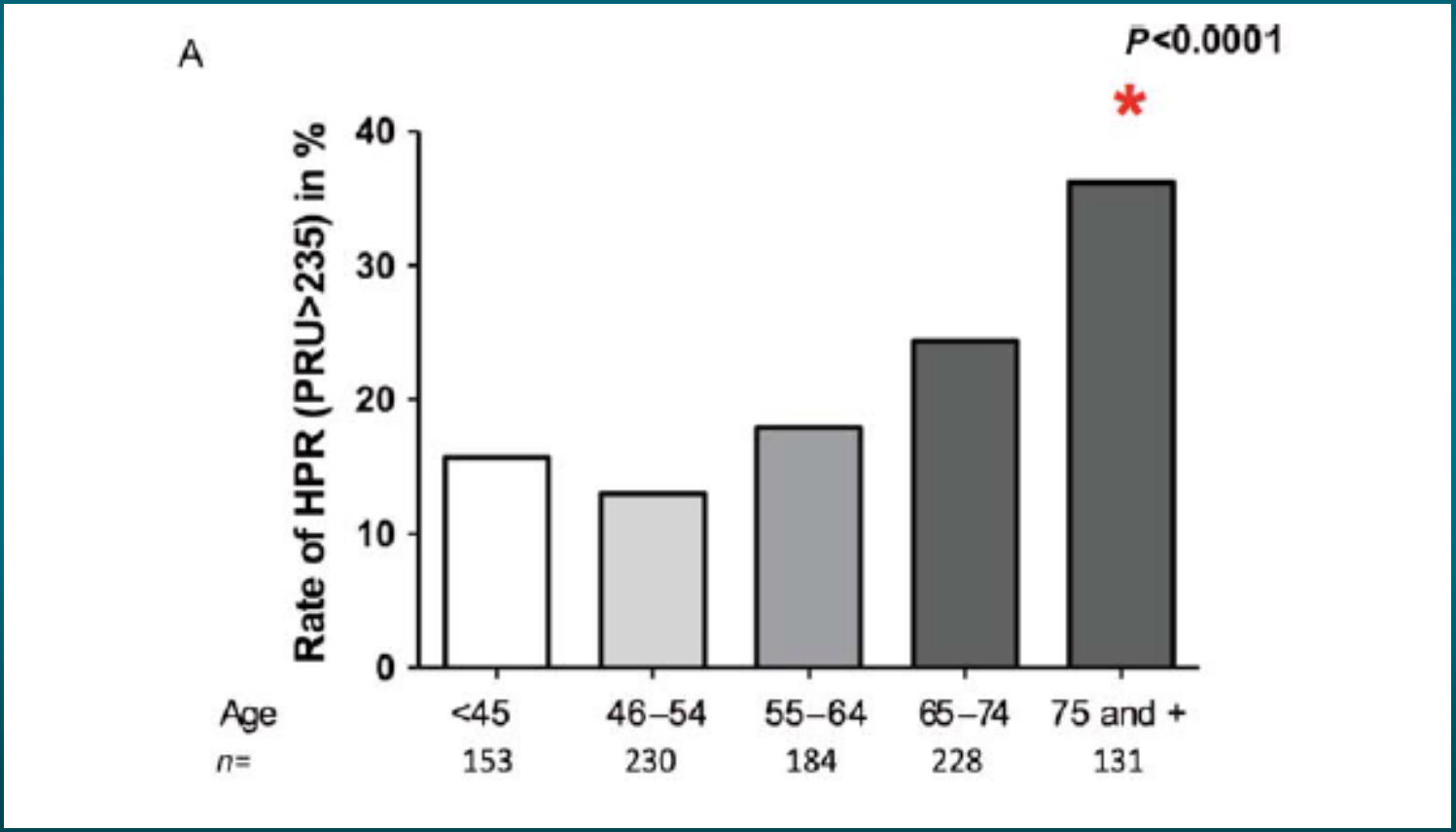
The number of patients with previous stroke in these ACS trials is low (4%-6%), and the number of excess intracranial bleedings by novel dual antiplatelet therapy even lower (1%-2% of that subpopulation). Therefore, in the case of ticagrelor the test for interaction is not statistically significant, but given the insufficient data an interaction cannot be excluded either.

Given the above, there is no safe ground to treat ACS patients with a previous stroke or TIA routinely with novel the platelet P2Y12 receptor antagonists, prasugrel or ticagrelor, rather than with clopidogrel

Verheugt FWA. Editorial. Circulation 2012;125:2821-2823

The SENIOR-PLATELET study

1331 coronary patients chronically (>14 days) treated with ASA & thienopyridine
Rate of high platelet reactivity in pts treated with 75 mg clopidogrel by age

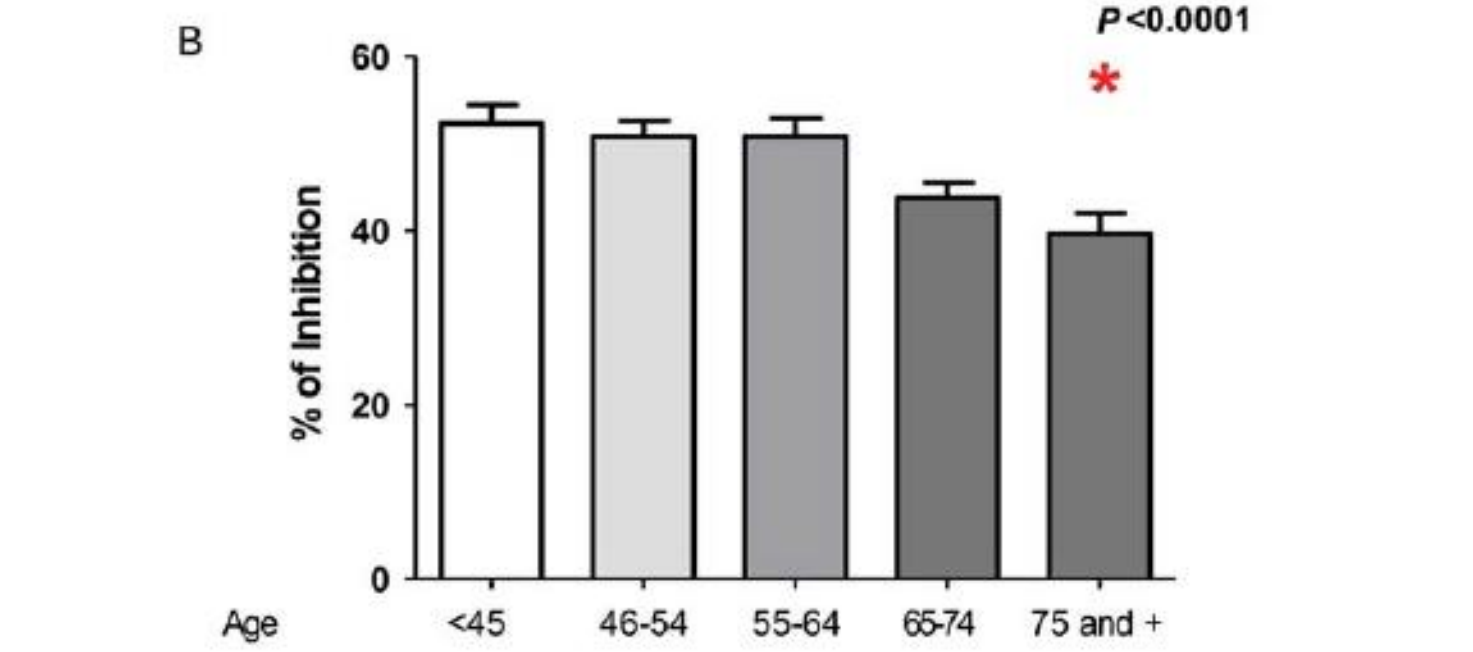


HPR=High Platelet Reactivity

Silvain J, et al. European Heart Journal 2012;33:1241-1250

The SENIOR-PLATELET study

1331 coronary patients chronically (>14 days) treated with ASA & thienopyridine
Mean platelet inhibition in pts treated with 75 mg clopidogrel by age



PRU Iso-TRAP	289±60	295±54	297±62	311±65	327±50	P<0.0001*
PRU ADP-PGE$_1$	142±84	142±81	149±87	177±86	200±86	P<0.0001*

Silvain J, et al. European Heart Journal 2012;33:1241-1250

In an editorial to this trial, Dr. Gurbel stated that the elderly have high ischemic event rates even during treatment with the more potent P2Y12 receptor blockers. The elderly also have more frequent serious bleeding. Personalized antiplatelet therapy may have a significant clinical impact in the elderly given their overall high prevalence of treatment failure (ischemia + bleeding). Could we give a reduced dose of a novel antiplatelet in selected patients?
But the Trilogy-ACS trial disappointed us…

How to tailor DAPT with elderly / post stroke patients in need for anticoagulation?
How to tailor ticagrelor use in elderly in view of multiple drug interactions?

Thank you

View of the Hadassah – Hebrew University Medical Center

Remarks

- **Prasugrel**

  Contraindications:

  1. History of stroke or TIA; discontinue if stroke or TIA occurs with therapy

  Precautions:

  1. Elderly (75 years of age and older)
  2. Severe hepatic impairment
  3. Patient's weight < 60 kg
  4. Surgery

- **Ticagrelor**

  Contraindications:

  1. Severe hepatic impairment

  Precautions:

  1. Strong CYP3A inhibitors should be avoided
  2. Potent CYP3A inducers should be avoided
  3. Older age – increased risk of bleeding
  4. Moderate CYP3A inhibitors? Bradyarrhythmias?

Remarks

Ticagrelor – drug interactions related to CYP3A (AstraZeneca tab

strong CYP3A inhibitors עליה בריכוזי ticagrelor	moderate CYP3A inhibitors עליה בריכוזי ticagrelor	potent CYP3A inducers ירידה בריכוזי ticagrelor	עליה בריכוזי תרופות אחרות
atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole imatinib isiniazid propofol verapamil	Amiodarone Cyclosporin Diltiazem Erythromycin Fluconazole Grapefruit juice Bosentan Amlodipine	rifampin, dexamethasone, phenytoin, carbamazepine, , phenobarbital	**Simvastatin-** לא לעלות מעבר ל-40 מ"ג **Digoxin** – לנטר **Cyclosporin** – לנטר **? Bosentan** **? Carbamazepine** **? Colchicines** **? Tacrolimus**