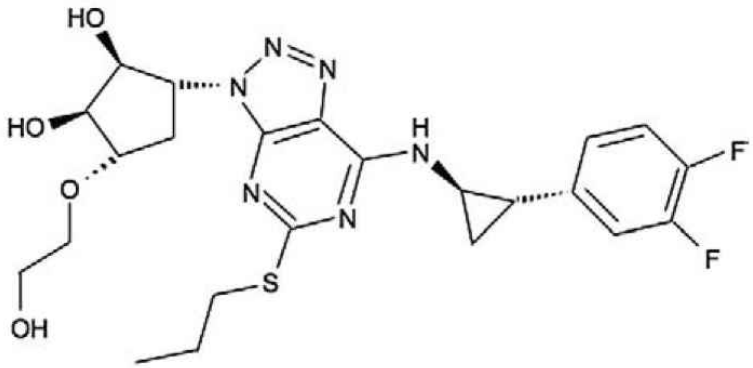
Ticagrelor: A New Chapter Opens

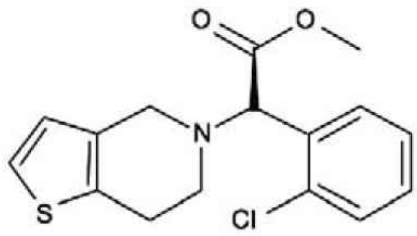
Matthew J. Price MD
Director, Cardiac Catheterization Laboratory,
Scripps Clinic, La Jolla, California, USA

Ticagrelor: Pharmacology

- **Class:** *Cyclopentyl-triazolo-pyrimidine (CPTP)*
- **Mechanism:** Direct inhibition of the P2Y12 receptor (no metabolic activation required).
- **Onset of action:** Rapid, max reached at < 2 hrs
- **Administration:** Oral
- **Plasma $t_{1/2}$** ≈10-12 hours (bid drug)



Ticagrelor



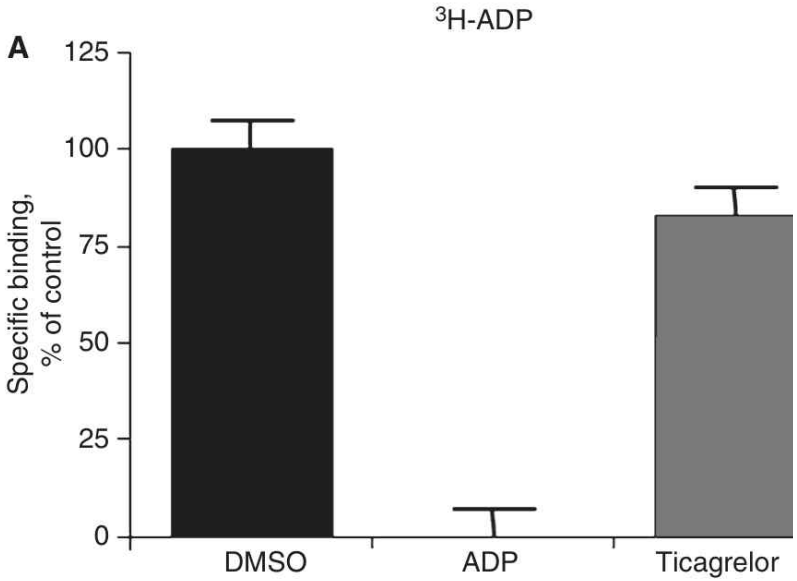
Clopidogrel

O'Donoghue M, Wiviott SD. Circulation. 2006;114:e600-e606;
Angiolillo DJ et al. Am J Cardiov Drugs. 2007.
Teng, Eur J Clin Pharmacol 2010;66:487-496

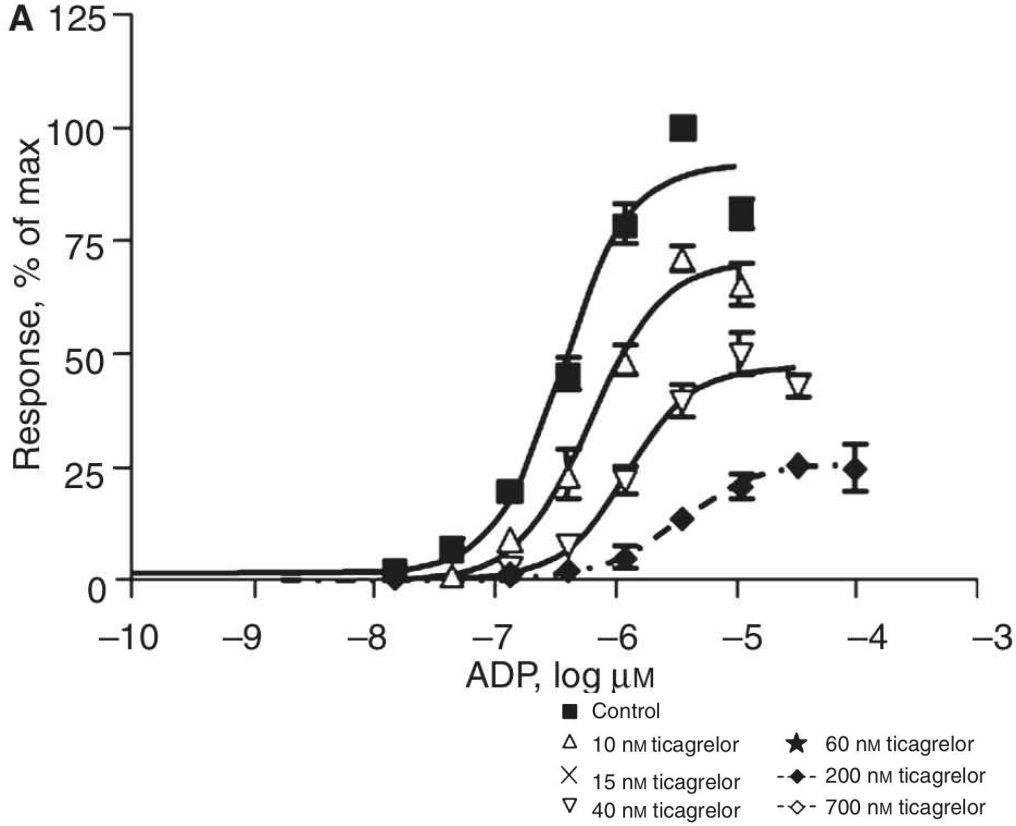
Ticagrelor Antagonizes the P2Y12 Receptor *Non-Competitively* With ADP

Receptor binding and concentration-response studies

Effect of Different Ligands on ADP-binding to the human P2Y12 receptor



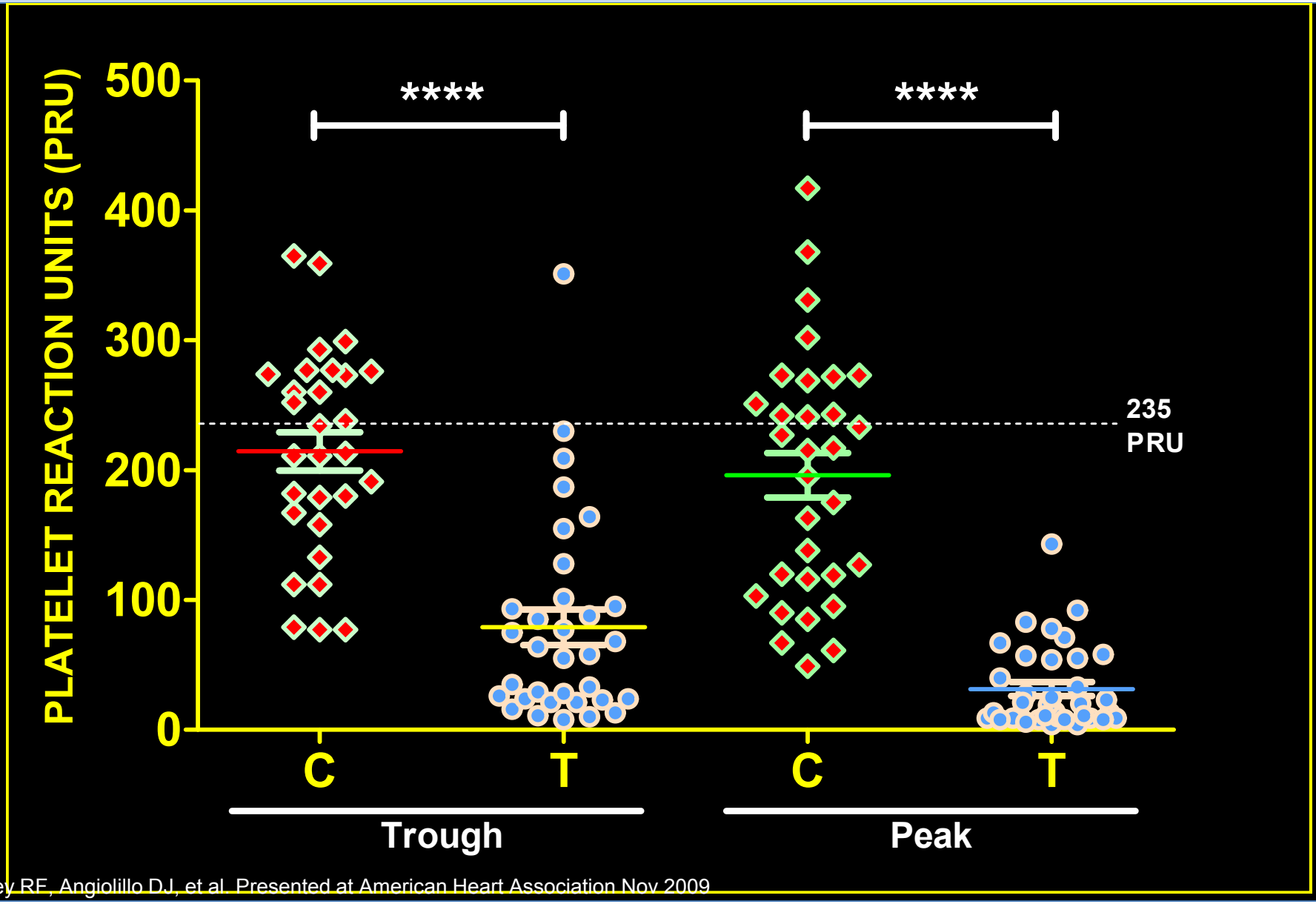
Concentration-response curve for ADP in the presence of increasing [ticagrelor]



van Giezen JJ et al, J Thromb Haemost 2009; 7:1556-65

SCRIPPS CLINIC

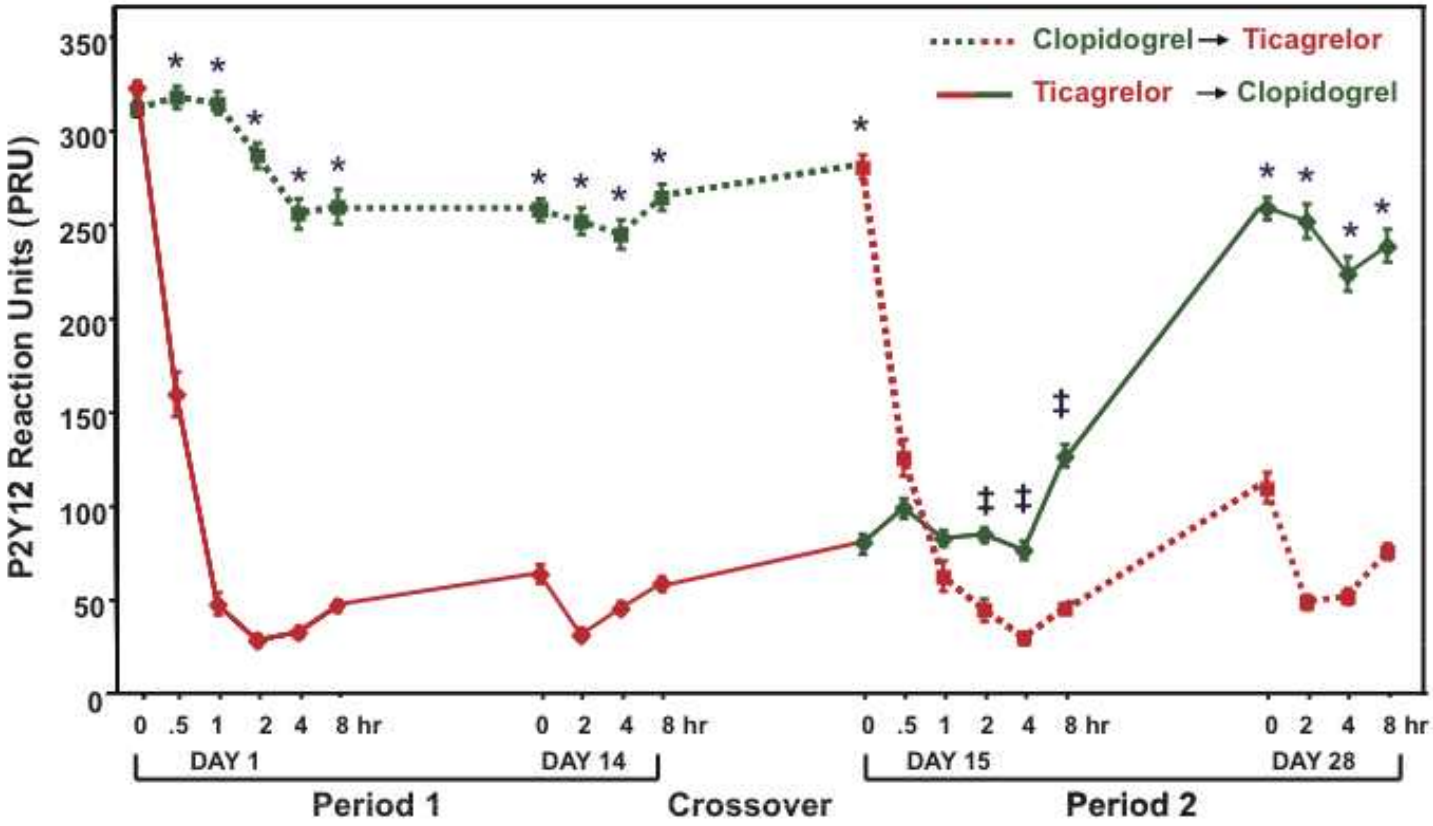
PLATO PLATELET – VerifyNow P2Y12 Assay Results on Maintenance therapy with clopidogrel (C) vs ticagrelor (T)



Storey RF, Angiolillo DJ, et al. Presented at American Heart Association Nov 2009

Antiplatelet Effect of Ticagrelor in CAD Patients with High On-Clopidogrel Platelet Reactivity

N=34



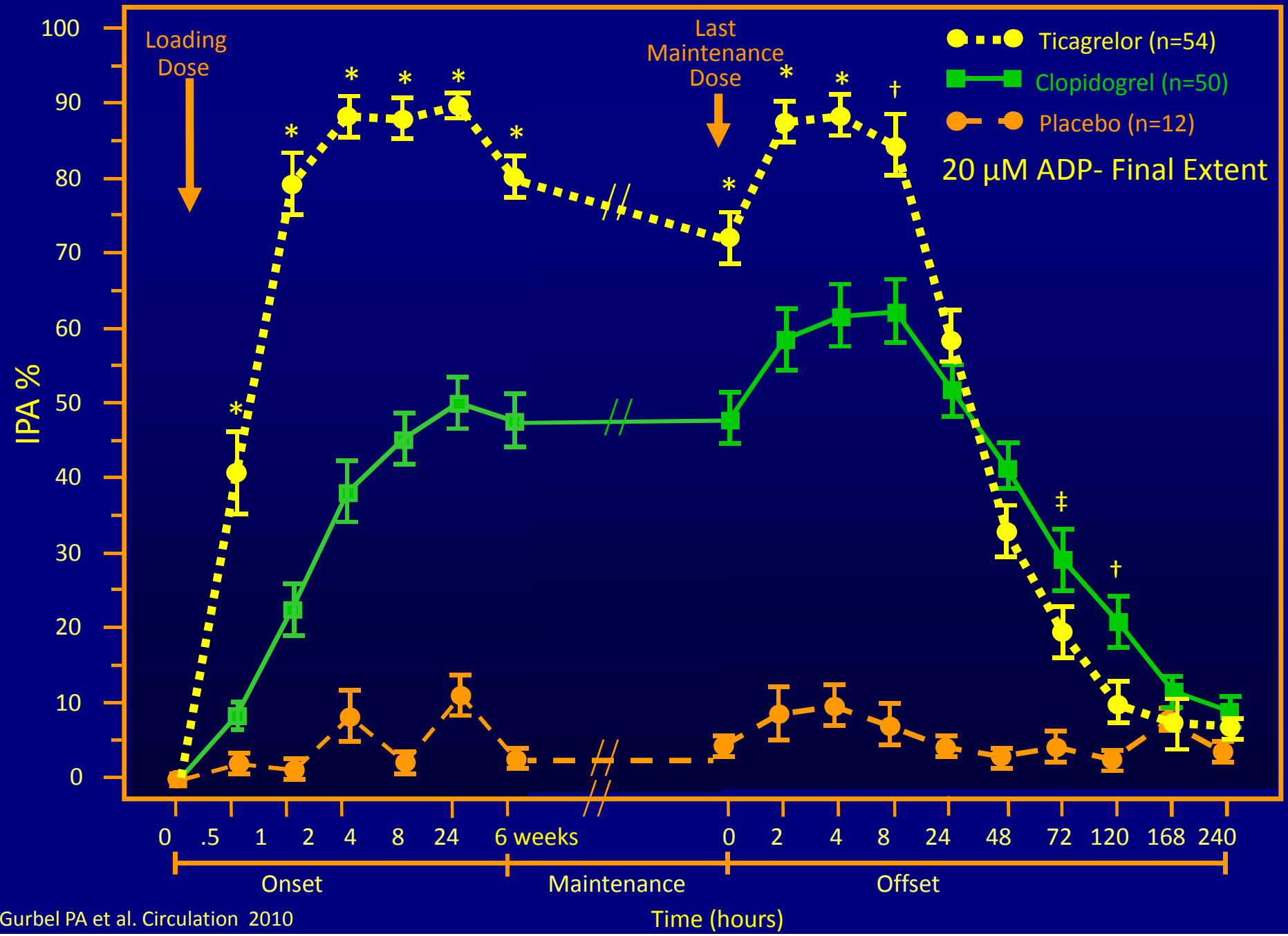
*P< 0.0001
‡ P<005

Subjects with CAD on aspirin

Gurbel et al, Circulation. 2010;121:1188-1199

SCRIPPS CLINIC

ONSET/OFFSET Study: Platelet Recovery after Ticagrelor vs. Clopidogrel



Gurbel PA et al. Circulation 2010

PLATO

PLATO – NSTE-ACS and STEMI (conservative/invasive)

- PLATO Invasive
- PLATO CABG – study drug d/c'd <7 days

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

Baseline and index event characteristics

PLATO

Characteristic	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)
Median age, years	62.0	62.0
Women, %	28.4	28.3
CV risk factors, %		
Habitual smoker	36.0	35.7
Hypertension	65.8	65.1
Dyslipidaemia	46.6	46.7
Diabetes mellitus	24.9	25.1
History, %		
Myocardial Infarction	20.4	20.7
Percutaneous coronary intervention	13.6	13.1
Coronary-artery bypass grafting	5.7	6.2
ECG at entry, %		
Persistent ST-segment elevation	37.5	37.8
ST-segment depression	50.7	51.2
Troponin-I positive,* %	85.3	86.0

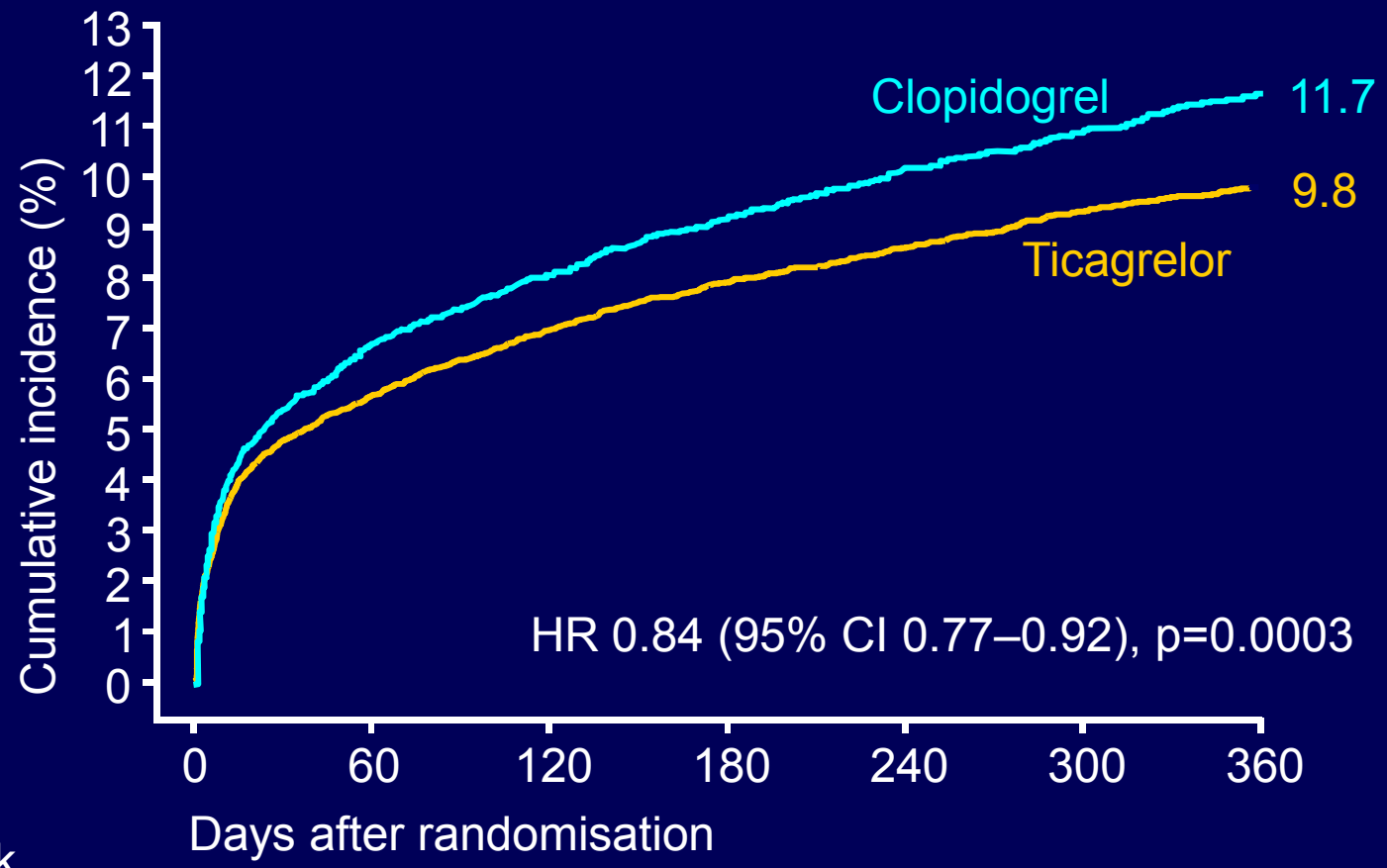
Study medication

PLATO

Medication	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)
Start of randomised treatment		
Time after start of chest pain, h, median	11.3	11.3
Randomised treatment compliance, %		
Premature discontinuation of study drug	23.4	21.5
Clopidogrel start-up, %		
Clopidogrel in hospital before randomisation	46.0	46.1
Invasive procedures at index hospitalisation, %		
Planned invasive treatment	72.1	71.9
Coronary angiography	81.4	81.5
PCI during index hospitalisation	60.9	61.1
Cardiac surgery	4.3	4.7

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

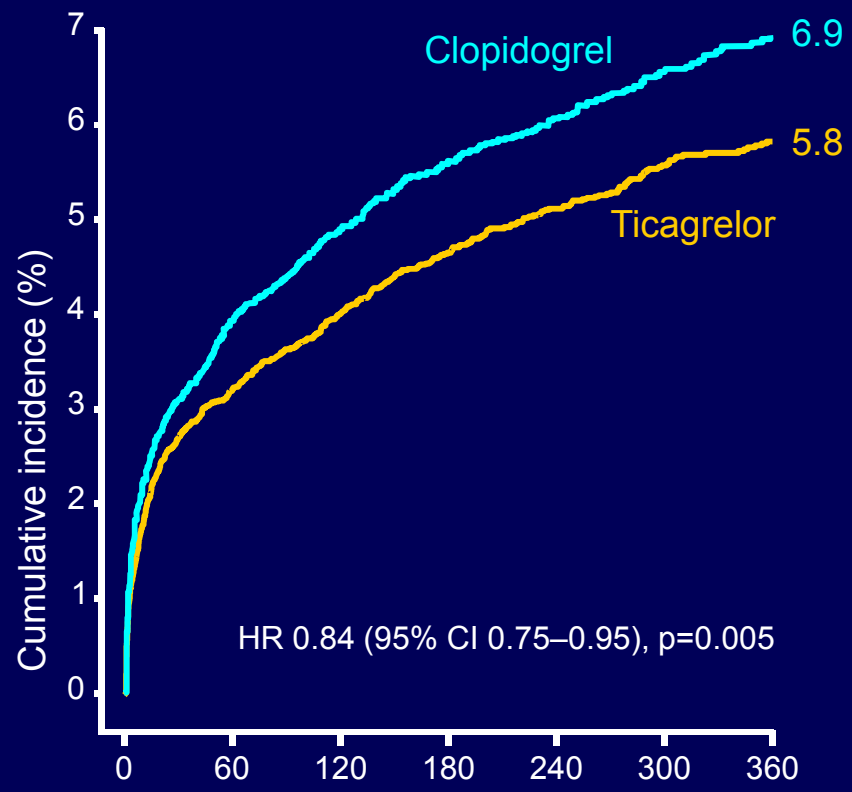
K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

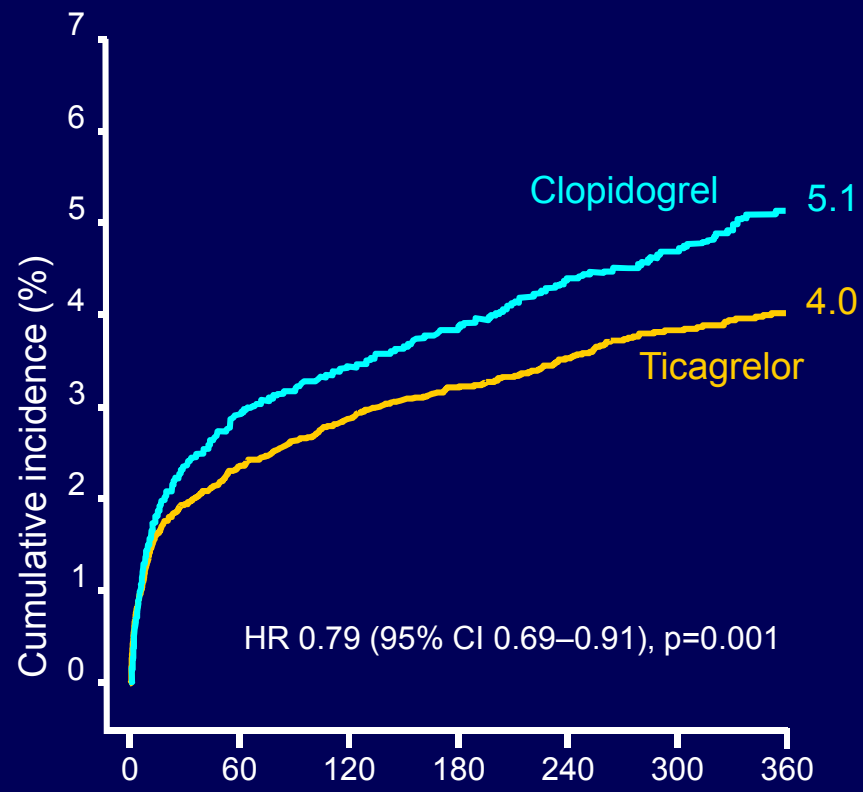
Duke Clinical Research Institute

UCR UPPSALA CLINICAL RESEARCH CENTER

Secondary efficacy endpoints over time

PLATO





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

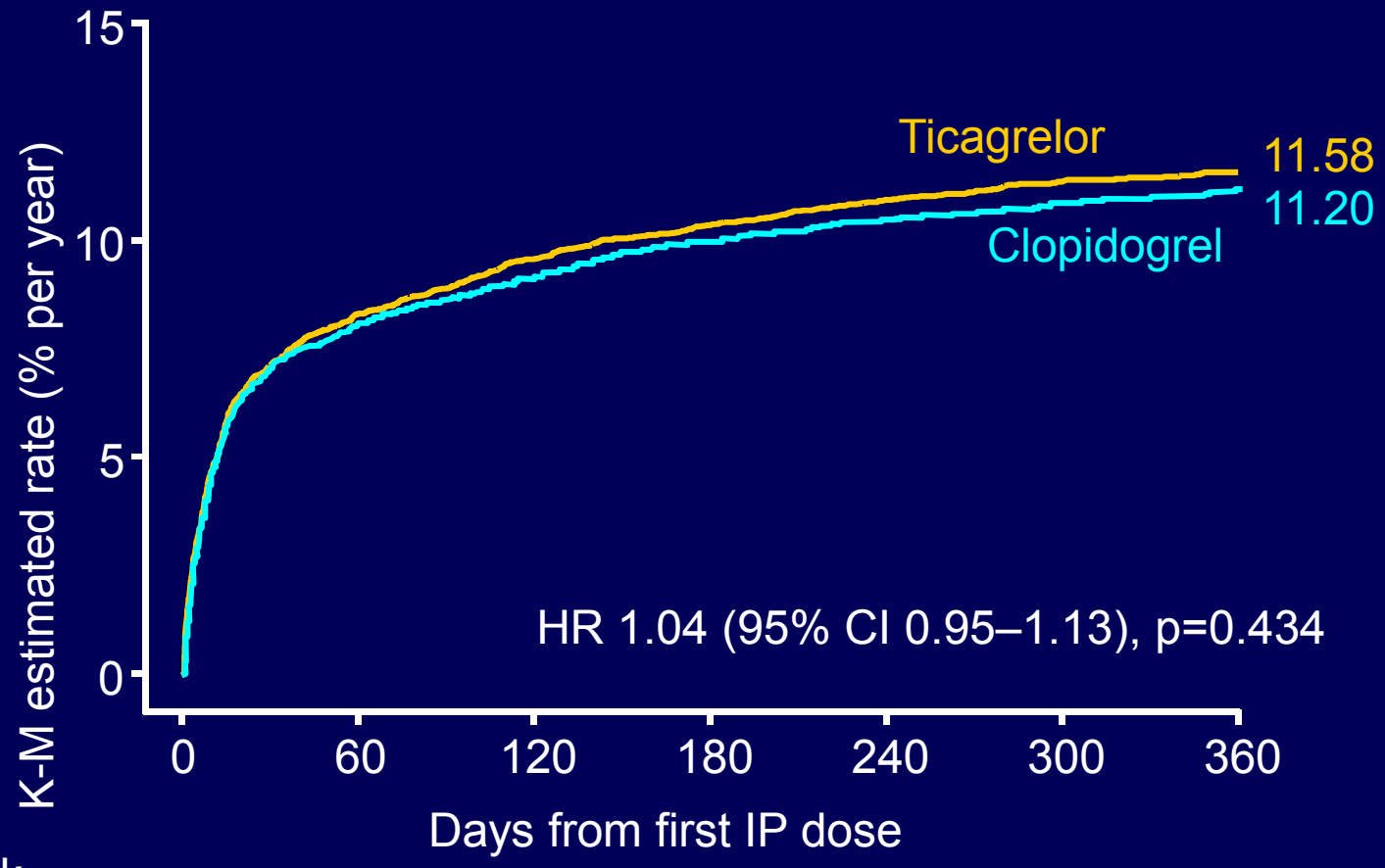
9,333	8,294	8,822	8,626	7119	5,482	4,419
9,291	8,865	8,780	8,589	7079	5,441	4,364

Duke Clinical Research Institute

UCR UPPSALA CLINICAL RESEARCH CENTER

Time to major bleeding – primary safety event

PLATO



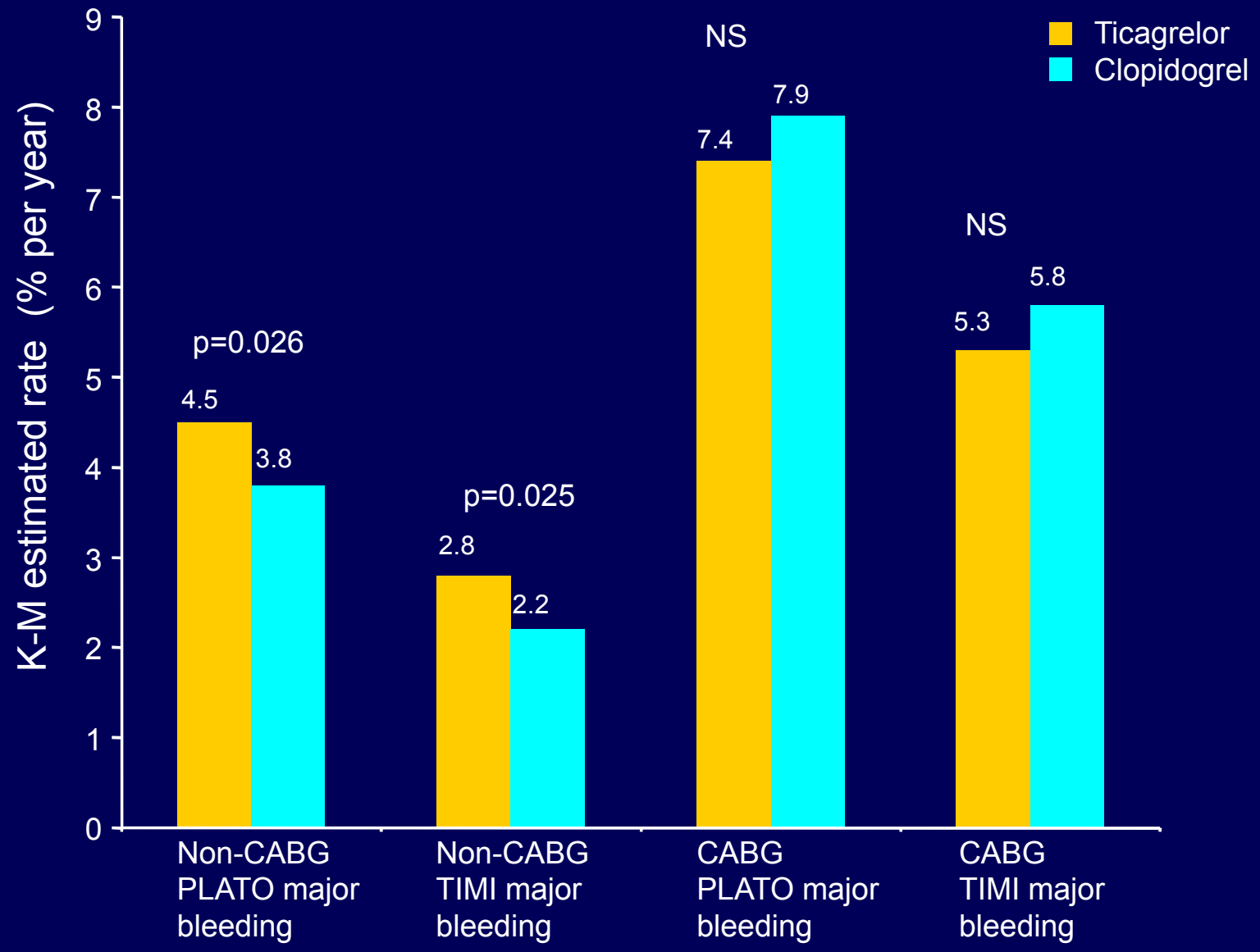
No. at risk							
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

Duke Clinical Research Institute

UCR UPPSALA CLINICAL RESEARCH CENTER

Non-CABG and CABG-related major bleeding

PLATO



Duke Clinical Research Institute

UCR UPPSALA CLINICAL RESEARCH CENTER

Holter monitoring & Bradycardia related events

PLATO

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

Holter monitoring at 30 days	Ticagrelor (n= 985)	Clopidogrel (n=1,006)	p value
Ventricular pauses ≥3 seconds, %	2.1	1.7	0.52
Ventricular pauses ≥5 seconds, %	0.8	0.6	0.60

Bradycardia-related event, %	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value
Pacemaker Insertion	0.9	0.9	0.87
Syncope	1.1	0.8	0.08
Bradycardia	4.4	4.0	0.21
Heart block	0.7	0.7	1.00

Other findings

PLATO

All patients	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value*
Dyspnoea, %			
Any	13.8	7.8	<0.001
With discontinuation of study treatment	0.9	0.1	<0.001
Neoplasms arising during treatment, %			
Any	1.4	1.7	0.17
Malignant	1.2	1.3	0.69
Benign	0.2	0.4	0.02

*p values were calculated using Fischer's exact test

Other findings – laboratory parameters

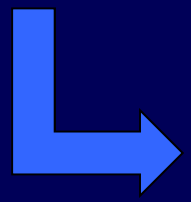
PLATO

All patients	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value*
% increase in creatinine from baseline			
At 1 month	10 ± 22	8 ± 21	<0.001
At 12 months	11 ± 22	9 ± 22	<0.001
Follow-up visit	10 ± 22	10 ± 22	0.59
% increase in uric acid from baseline			
At 1 month	14 ± 46	7 ± 44	<0.001
At 12 months	15 ± 52	7 ± 31	<0.001
Follow-up visit	7 ± 43	8 ± 48	0.56

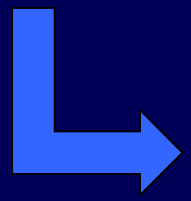
Values are mean % ± SD; *p values were calculated using Fisher's exact test

PLATO

PLATO – NSTE-ACS and STEMI (conservative/invasive)



PLATO Invasive



PLATO CABG – study drug d/c'd <7 days

PLATO INVASIVE: Procedures and timing*

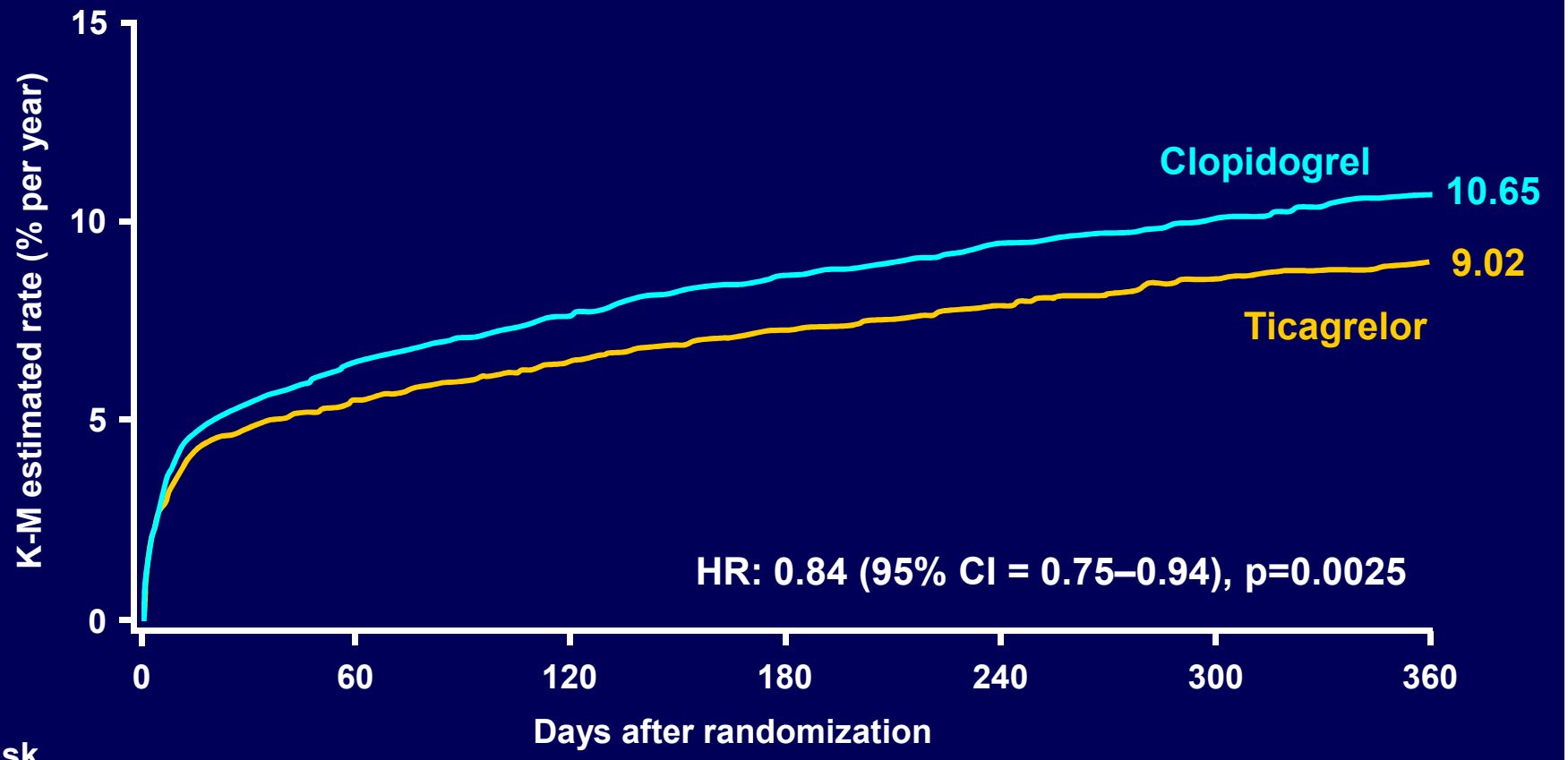
PLATO Invasive

Procedure	Ticagrelor (n=6,732)	Clopidogrel (n=6,676)
Invasive procedures at index hospitalization, % (n)		
Coronary angiography	96.8 (6514)	96.9 (6471)
Median (IQR), hours	0.62 (0.10, 3.70)	0.62 (0.12, 3.65)
PCI during index hospitalization % (n)	76.7 (5166)	77.1 (5148)
Median (IQR), hours	0.77 (0.30, 2.75)	0.78 (0.32, 2.65)
UA/NSTEMI – PCI % (n)	63.8 (1882)	64.8 (1854)
Median (IQR), hours	2.63 (0.78, 21.10)	2.60 (0.87, 21.30)
STEMI - Primary PCI % (n)	83.2 (3138)	82.7 (3149)
Median (IQR), hours	0.47 (0.23, 0.95)	0.48 (0.23, 0.95)
Coronary by-pass surgery pre-discharge % (n)	5.5 (372)	6.1 (410)
Median (IQR), hours	117 (47, 216)	121 (48, 218)

* Time between randomization and first procedure

Primary endpoint: CV death, MI or stroke

PLATO Invasive



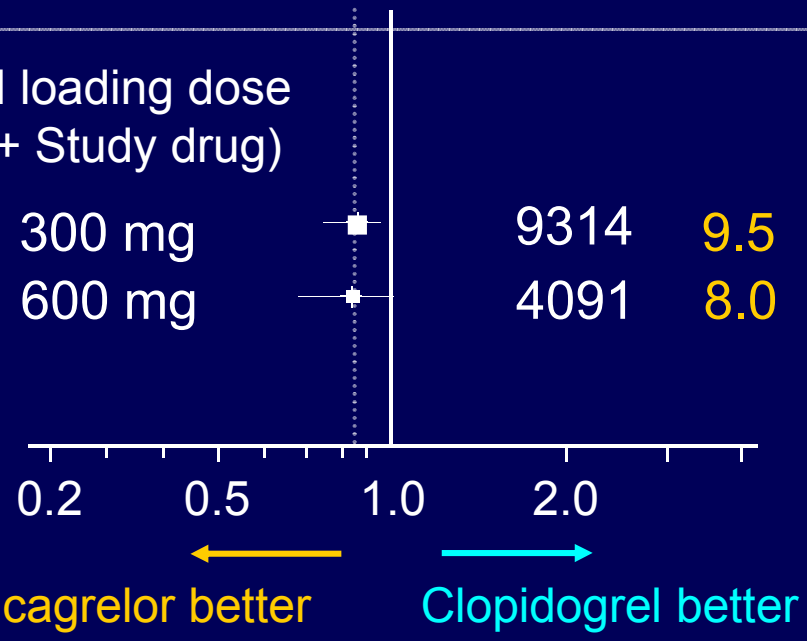
No. at risk							
Ticagrelor	6,732	6,236	6,134	5,972	4,889	3,735	3,048
Clopidogrel	6,676	6,129	6,034	5,881	4,815	3,680	2,965

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

Primary efficacy endpoint by clopidogrel loading dose

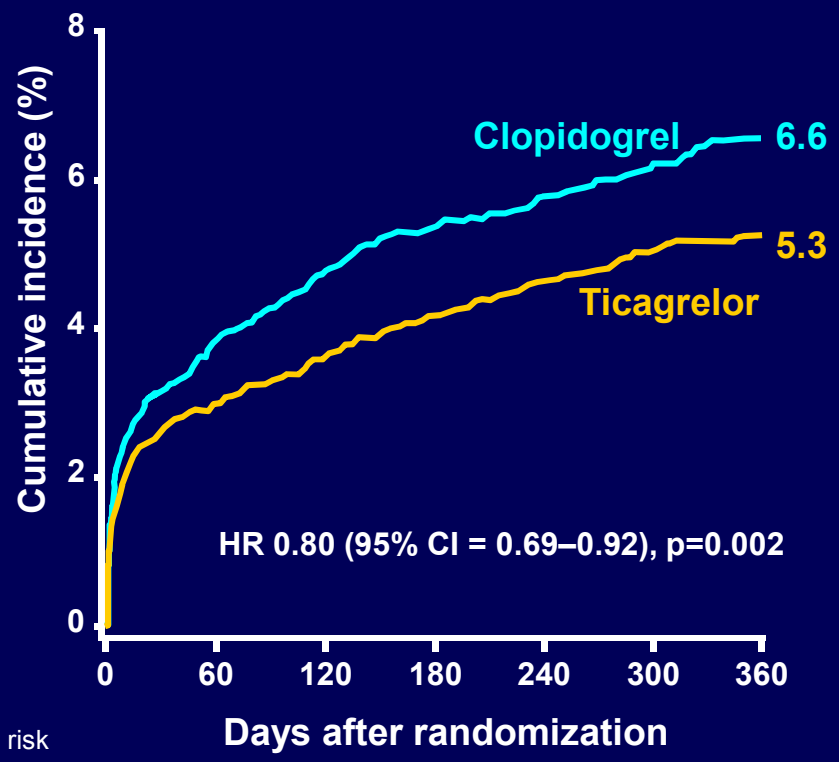
PLATO Invasive

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)	p value (Interaction)
Clopidogrel loading dose (Pre-rand. + Study drug)						0.917
300 mg		9314	9.5	11.2	0.85 (0.74, 0.96)	
600 mg		4091	8.0	9.5	0.83 (0.67, 1.03)	

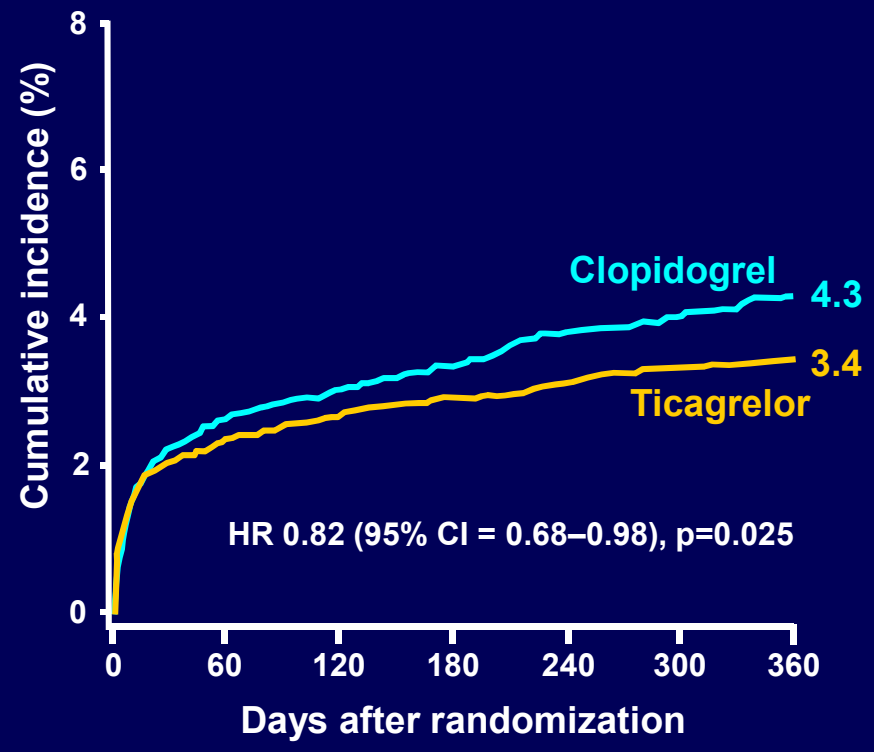


PLATO Invasive

Myocardial infarction



Cardiovascular death



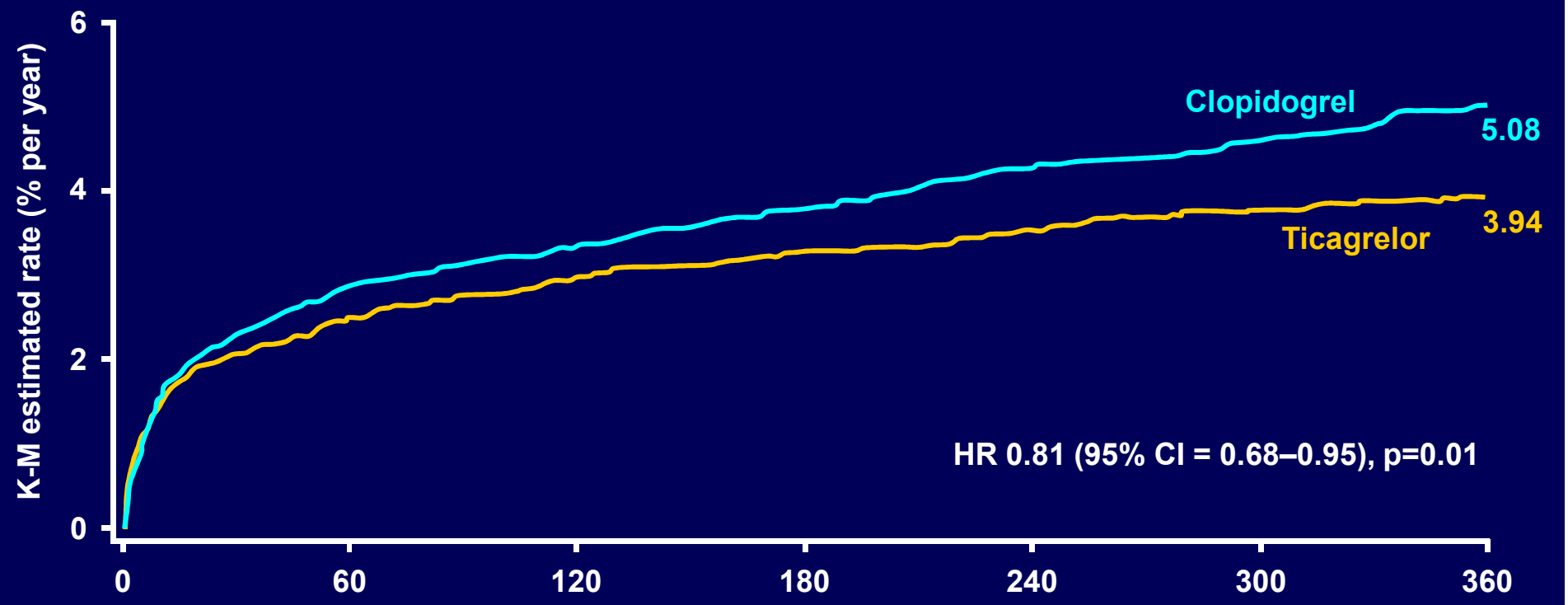
No. at risk

Ticagrelor	6,732	6,268	6,173	6,010	4,924	3,766	3,078
Clopidogrel	6,676	6,157	6,062	5,917	4,849	3,706	2,987

	6,732	6,439	6,375	6,241	5,141	3,591	3,233
	6,676	6,376	6,332	6,209	5,114	3,917	3,164

All-cause mortality

PLATO Invasive



No. at risk							
Ticagrelor	6,732	6,439	6,375	6,241	5,141	3,951	3,233
Clopidogrel	6,676	6,376	6,331	6,209	5,114	3,917	3,164

Stent thrombosis

PLATO Invasive

	Ticagrelor (n=6,732)	Clopidogrel (n=6,676)	HR for ticagrelor (95% CI)	p value*
Stent thrombosis, %				
Definite	1.0	1.6	0.62 (0.45–0.85)	0.003
Probable or definite	1.7	2.3	0.72 (0.56–0.93)	0.01
Possible, probable, or definite	2.2	3.1	0.72 (0.58–0.90)	0.003

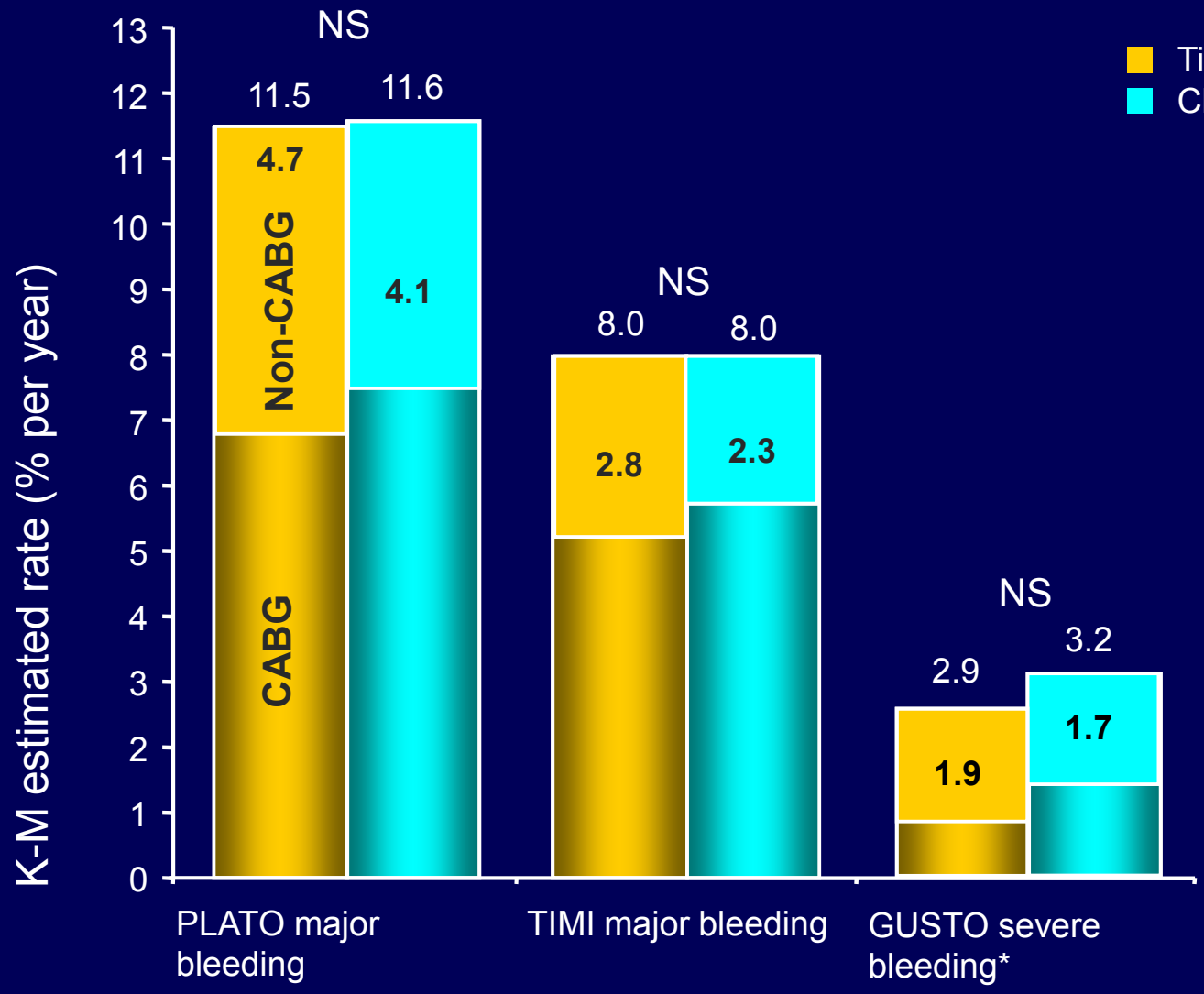
¶ Evaluated in patients with any stent during the study

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

* By univariate Cox model

Non-CABG and CABG-related major bleeding

PLATO Invasive



*Preliminary – from eCRF

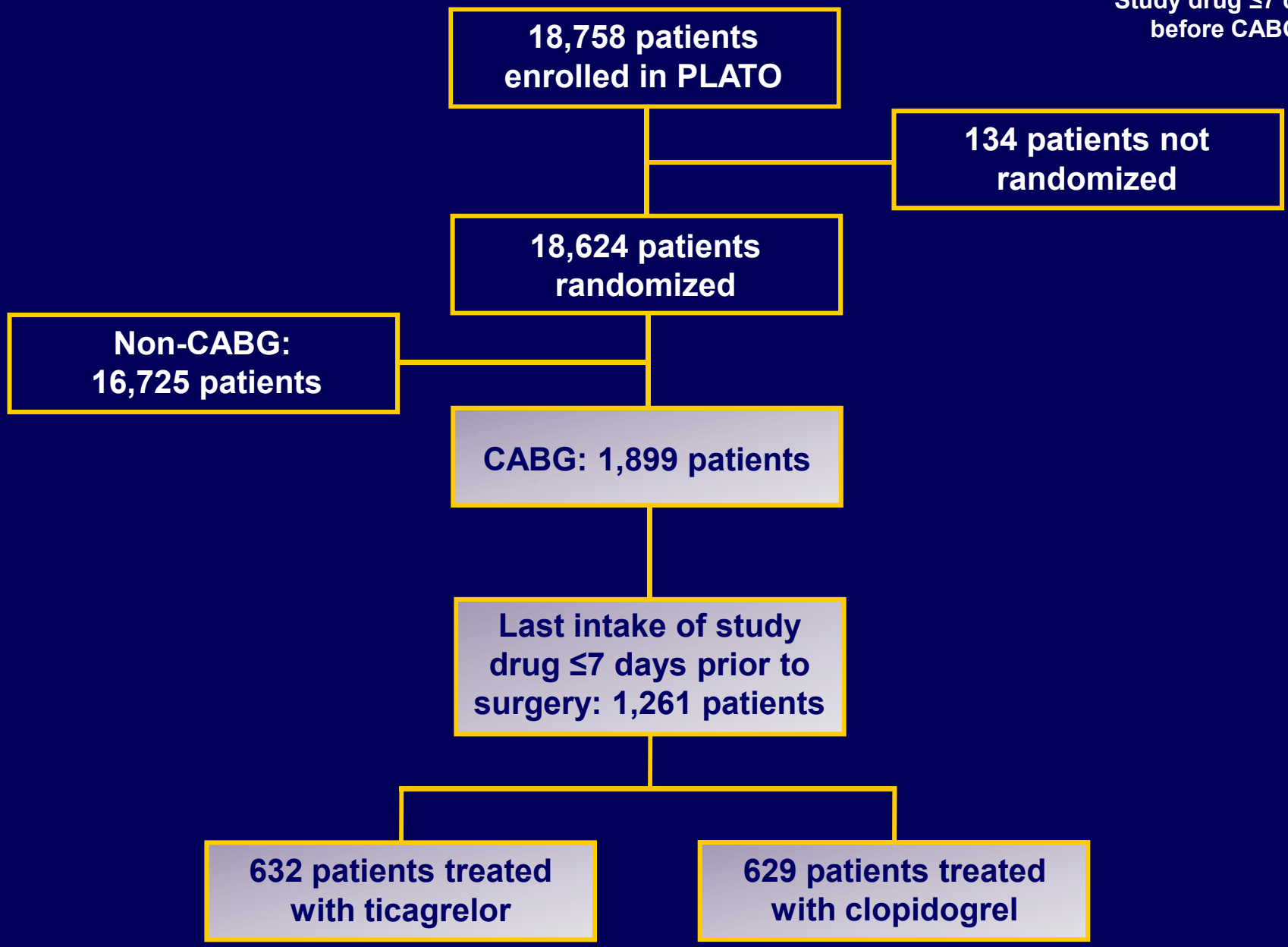
PLATO

PLATO – NSTE-ACS and STEMI (conservative/invasive)

- PLATO Invasive
- PLATO CABG – study drug d/c'd <7 days

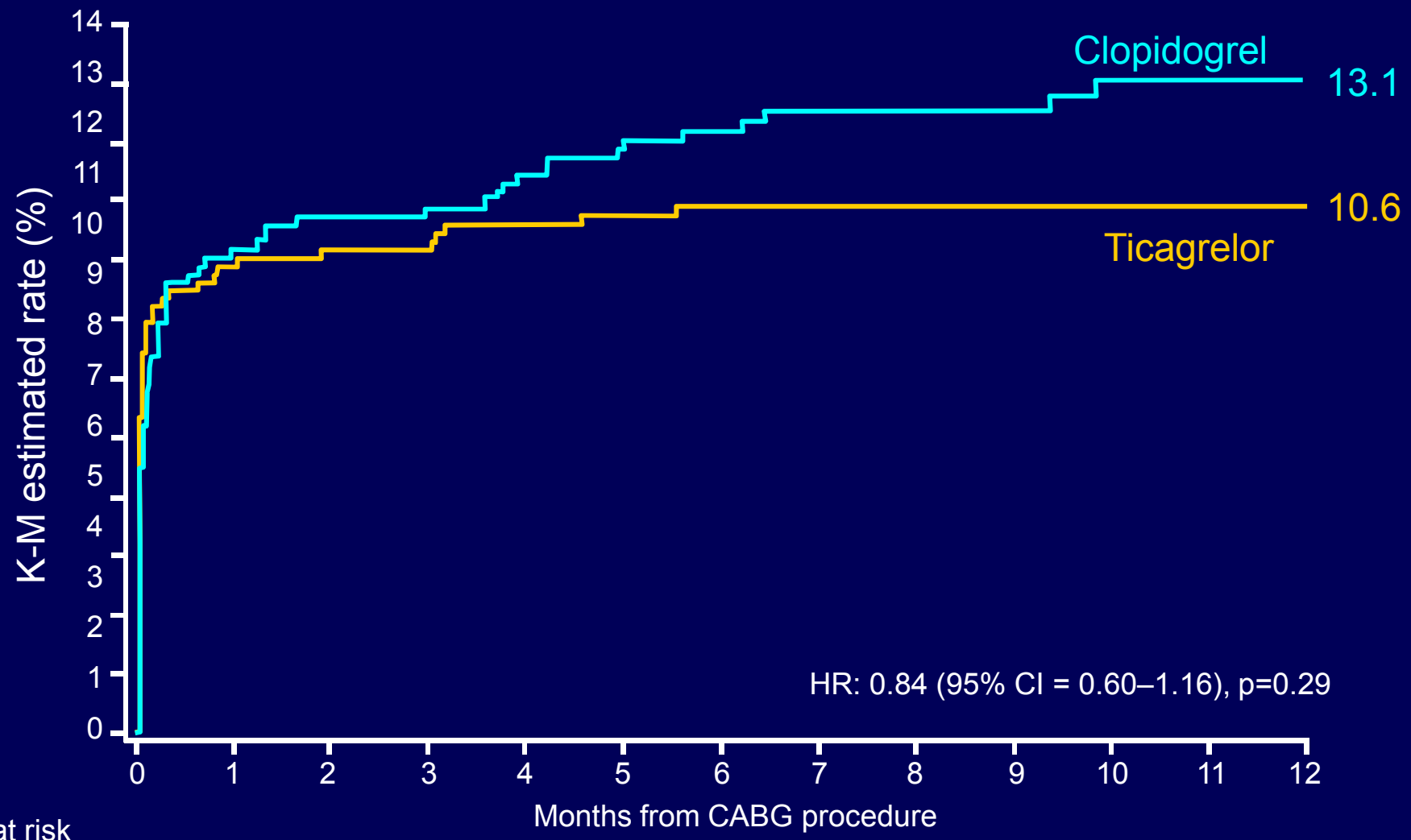
Patient disposition

PLATO
Study drug ≤7 days before CABG



Primary endpoint: CV death, MI or stroke

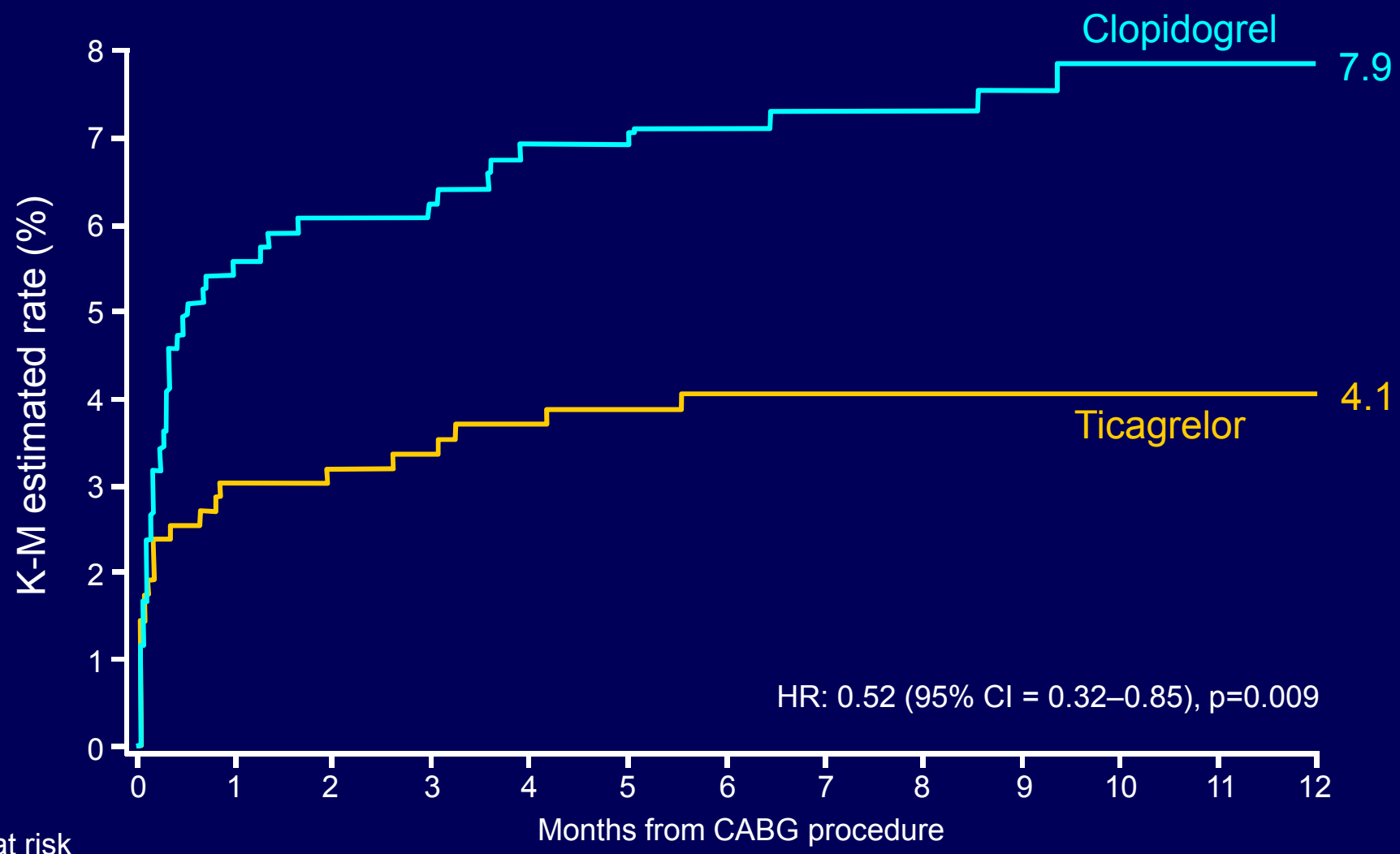
PLATO
Study drug ≤7 days before CABG



No. at risk							
Ticagrelor	629	543	519	458	386	268	108
Clopidogrel	629	541	516	448	386	255	125

CV death post-CABG

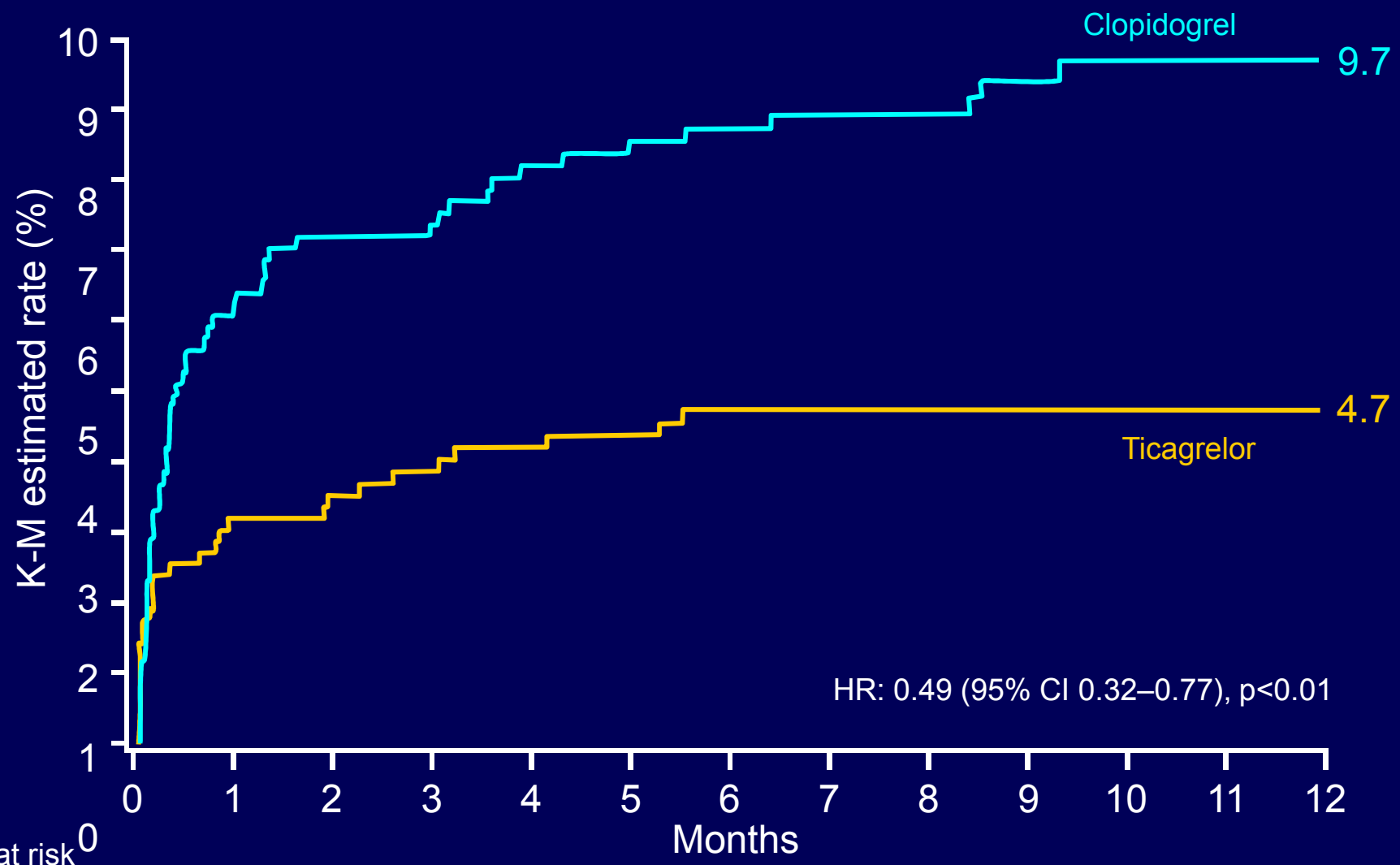
PLATO
Study drug ≤7 days before CABG



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

All cause mortality post-CABG

PLATO
Study drug ≤7 days before CABG

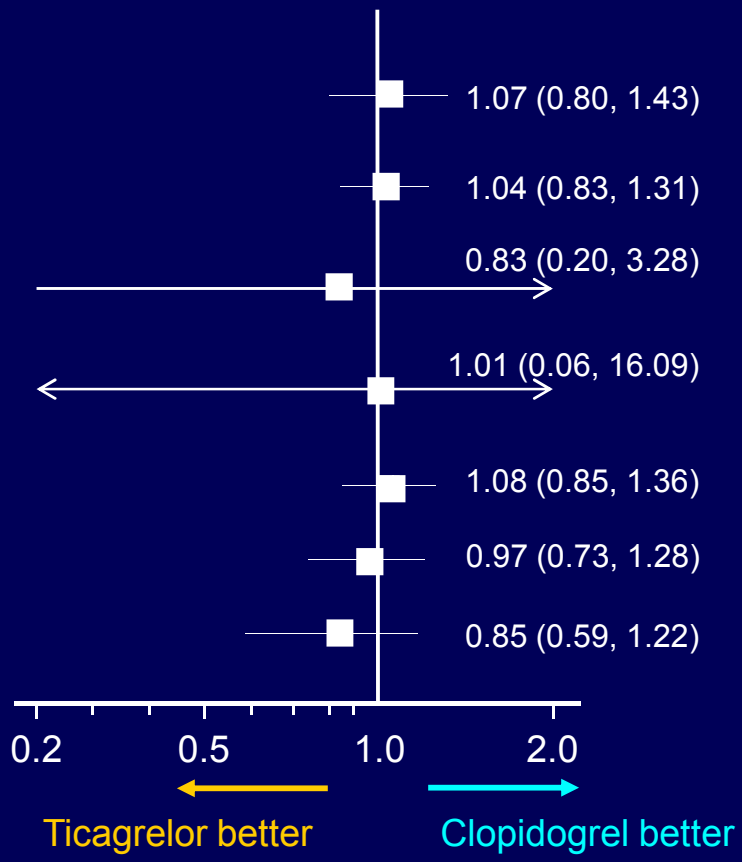


No. at risk							
Ticagrelor	629	583	557	491	415	291	119
Clopidogrel	629	565	539	472	404	269	130

Safety: bleeding post-CABG

PLATO
Study drug ≤7 days before CABG

Characteristic	Ticagrelor (n=631)	Clopidogrel (n=629)	Odds Ratio (95% CI)	p-value
CABG-related bleeding				
Major bleeding	81.2	80.1	1.07 (0.80, 1.43)	0.67
Life-threatening/ fatal bleeding	43.7	42.6	1.04 (0.83, 1.31)	0.73
Fatal bleeding	0.8	1.0	0.83 (0.20, 3.28)	0.77
All intracranial bleeding post-CABG*	0.2	0.2	1.01 (0.06, 16.09)	1.00
TIMI major bleeding	59.3	57.6	1.08 (0.85, 1.36)	0.53
TIMI minor bleeding	21.0	21.6	0.97 (0.73, 1.28)	0.84
GUSTO severe bleeding	10.6	12.2	0.85 (0.59, 1.22)	0.38



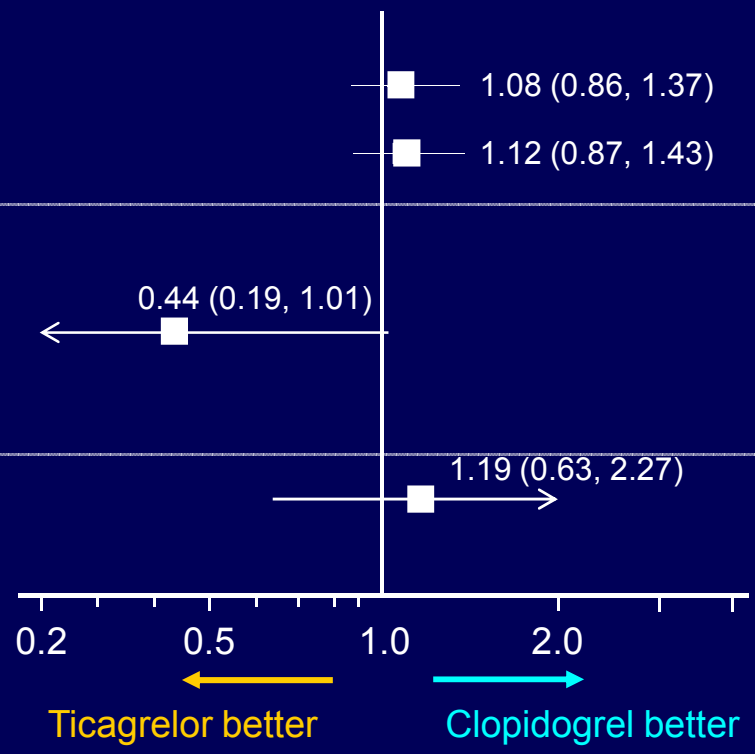
All event rates are number of events divided by n

*Hazard ratio Kaplan-Meier estimates. Both CABG-related and non-related

Safety: bleeding post-CABG (cont'd)

PLATO
Study drug ≤7 days before CABG

Characteristic	Ticagrelor (n=631)	Clopidogrel (n=629)	Hazard/Odds Ratio (95% CI)	p value
Hemoglobin decrease*				
>50 g/L	38.1	36.2	1.08 (0.86, 1.37)	0.52
>30 g/L	69.9	67.6	1.12 (0.87, 1.43)	0.40
Major/life-threatening CABG-related bleeding resulting in death within 7 days of CABG†	1.3	2.9	0.44 (0.19, 1.01)	0.05
Re-operation due to bleeding*	4.0	3.3	1.19 (0.63, 2.27)	0.65



*Odds ratio and p-value from Fisher's exact test

†Hazard ratio

Event rate is number of events divided by n

Summary

- Ticagrelor, a non-thienoypridine, is a non-competitive, reversible, P2Y12 receptor antagonist.
- In PLATO, ticagrelor significantly reduced CV death, MI, and stroke compared with clopidogrel in patients presenting with NSTE-ACS and STEMI.
- While non-CABG related bleeding was increased with ticagrelor, there was no increase in fatal bleeding or CABG-related bleeding.

Summary (2)

- Furthermore, in patients treated with a planned invasive strategy, ticagrelor provided significant ischemic benefit without an increase in all-cause major bleeding.
- The observed reduction in mortality in the overall trial, invasively-managed patients, and in patients undergoing CABG is provocative and requires further mechanistic evaluation.


A new chapter in antiplatelet therapy is on the horizon….
…thank you!