PLATO STEMI

Ticagrelor compared with clopidogrel in patients with acute coronary syndromes
the PLATelet Inhibition and patient Outcomes trial

Outcomes in patients with STEMI and planned PCI

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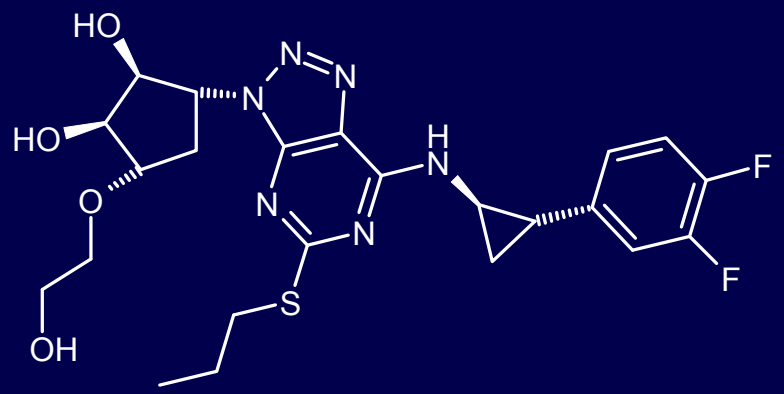
PG Steg: disclosures

PLATO STEMI

- Research Grant: Sanofi-aventis (1999-2008), Servier (2009–2014)
- Speaking: AstraZeneca, Boehringer-Ingelheim, BMS, GSK, Menarini, Medtronic, Nycomed, Pierre Fabre, sanofi-aventis, Servier, The Medicines Company
- Consulting/advisory board: Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi-Sankyo, Endotis, GSK, Medtronic, MSD, Nycomed, Sanofi-aventis, Servier, The Medicines Company
- Stockholding: Aterovax

Ticagrelor (AZD 6140): an oral reversible $P2Y_{12}$ antagonist

PLATO



Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**
  - Not a pro-drug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel
- **Reversibly bound**
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of circulating platelets within ~48 hours

PLATO study design

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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 (n=9291)
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 (n=9333)
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 endpoint: Total major bleeding

PLATO main endpoints

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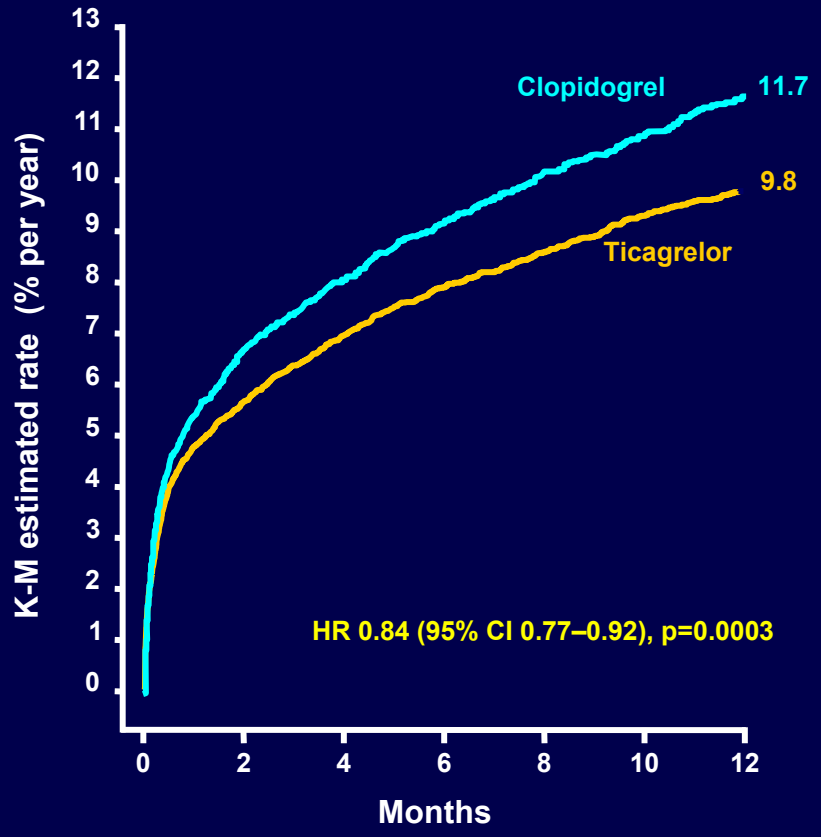
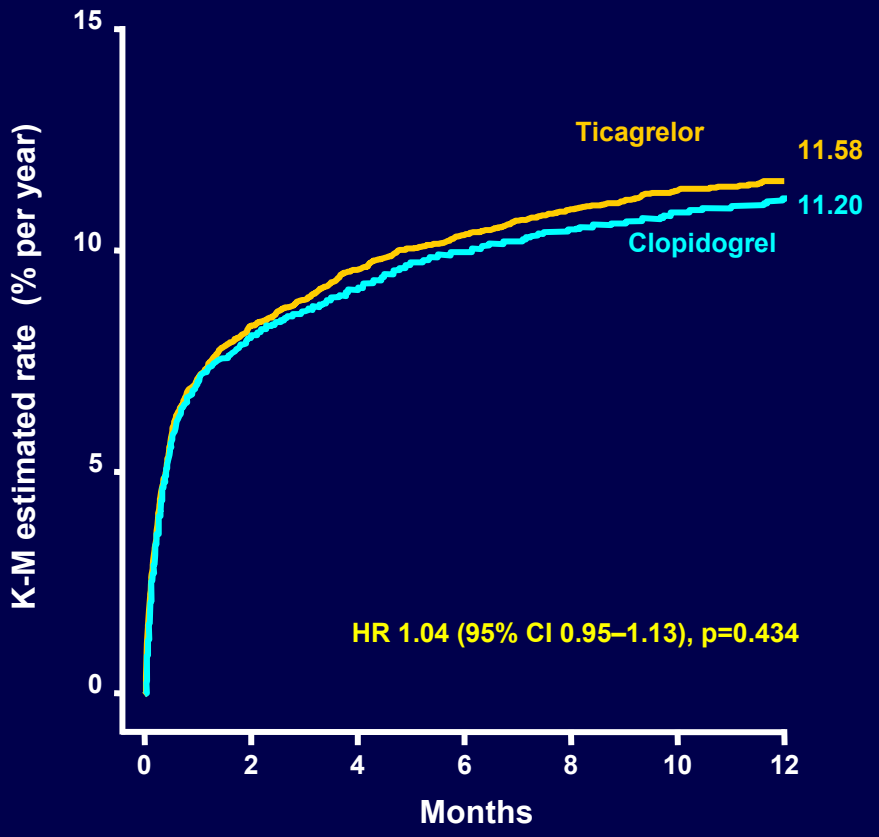
Primary efficacy endpoint



Primary safety endpoint



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

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

STEMI and primary PCI

PLATO STEMI

- Primary PCI is the optimal reperfusion therapy for STEMI
- Patients with STEMI and planned primary PCI particularly require urgent and effective blockade of the $P2Y_{12}$ platelet receptor and also are potentially at greater risk of side effects from new therapies
- Therefore, the objective of this predefined analysis of the PLATO trial was to investigate the efficacy and safety of ticagrelor versus clopidogrel in patients with STEMI intended for reperfusion with primary PCI

Patient disposition

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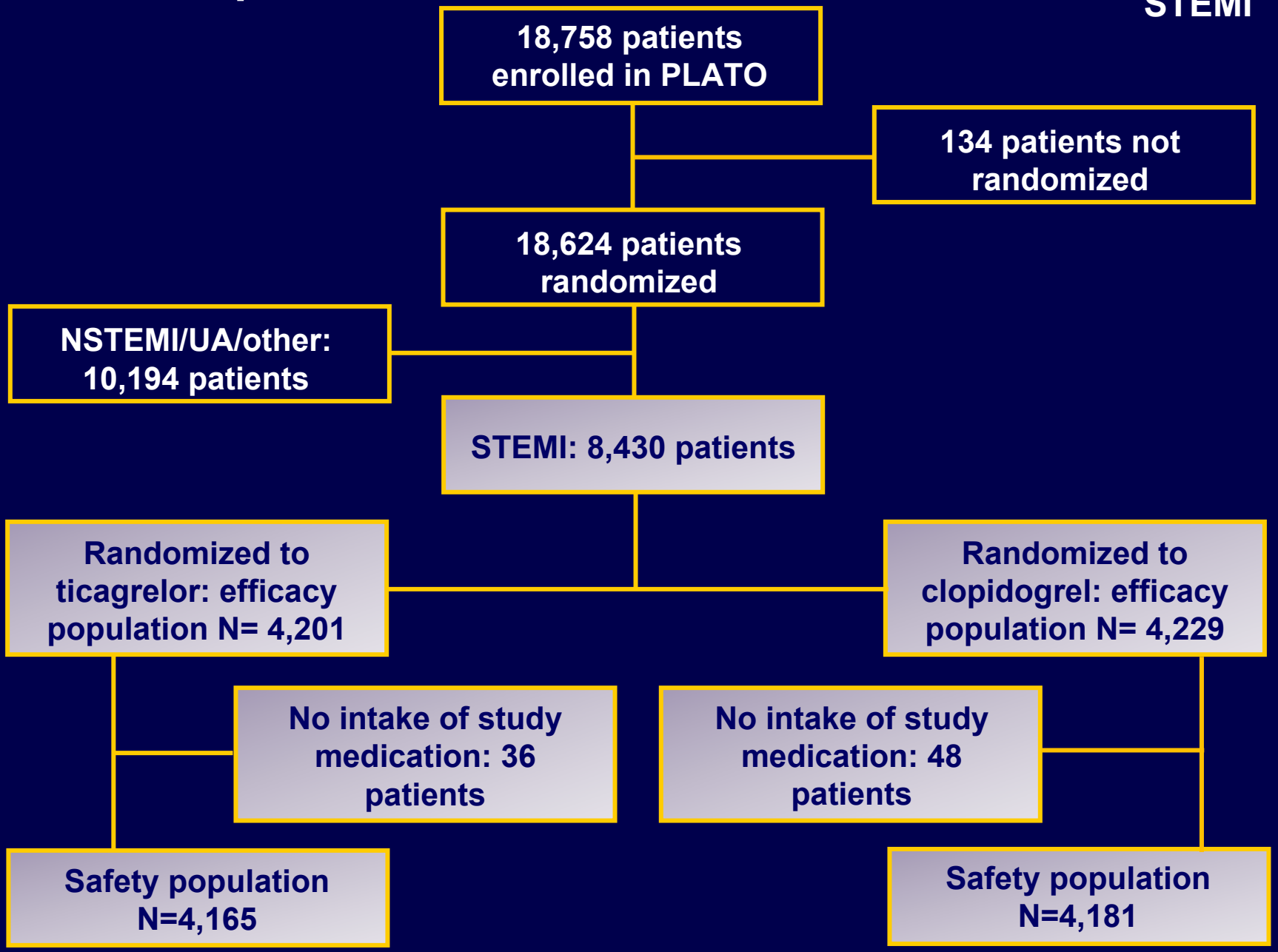

PLATO STEMI population

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- Inclusion criteria
  - Hospitalization for ST-segment elevation ACS, with onset during the previous 24 hours with either of the following
    - Persistent ST-elevation and planned primary PCI
    - New or presumed new LBBB and planned primary PCI
    - Or final diagnosis of STEMI

- Main exclusion criteria
  - Contraindication to clopidogrel
  - Fibrinolytic therapy within 24 hours prior to randomization
  - Need for oral anticoagulation therapy
  - STEMI as acute complication of PCI or PCI performed before the first study dose
  - Increased risk of bradycardic events (e.g. no pacemaker and known sick sinus syndrome, 2nd degree A-V block, 3rd degree A-V block or previous documented syncope suspected to be due to bradycardia)
  - Concomitant therapy with strong CYP3A inhibitors or inducers

Baseline and index event characteristics

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Characteristic	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)
Median age, years	59	59
Women, %	24.1	23.5
CV risk factors, %		
Habitual smoker	45.5	44.3
Hypertension	59.3	57.8
Dyslipidemia	38.7	39.2
Diabetes mellitus	19.6	21.1
History, %		
Myocardial infarction	13.5	13.8
Percutaneous coronary intervention	8.8	7.9
Coronary-artery bypass graft	2.6	2.7
ECG findings at entry, %		
Persistent ST-segment elevation ≥1mm	81.3	80.6
Left bundle branch block	8.0	9.0
Other*	10.7	10.3

+*Final diagnosis of STEMI

Study medication and procedures

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	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)
Start of randomized treatment		
Median time after start of chest pain, hours	5.6	5.8
Premature discontinuation of study drug, %	19.5	18.9
Invasive procedures at index hospitalization, %		
Coronary angiography	92.6	92.8
PCI during index hospitalization	80.6	80.0
CABG during index hospitalization	2.2	2.9
Received at least one stent, %	74.3	74.2
Bare metal stent only	57.9	57.6
Drug-eluting stent (at least one)	16.1	16.3
Open-label clopidogrel pre-randomization, %		
None	56.5	55.5
75 mg	4.8	5.1
300 mg	18.1	18.6
600 mg	20.7	20.8
Total clopidogrel (OL + IP)* pre-randomization to 24 h, %		
300 mg	65.2	65.4
600 mg	34.8	34.6

* Includes placebo in the Ticagrelor arm

Co-medication

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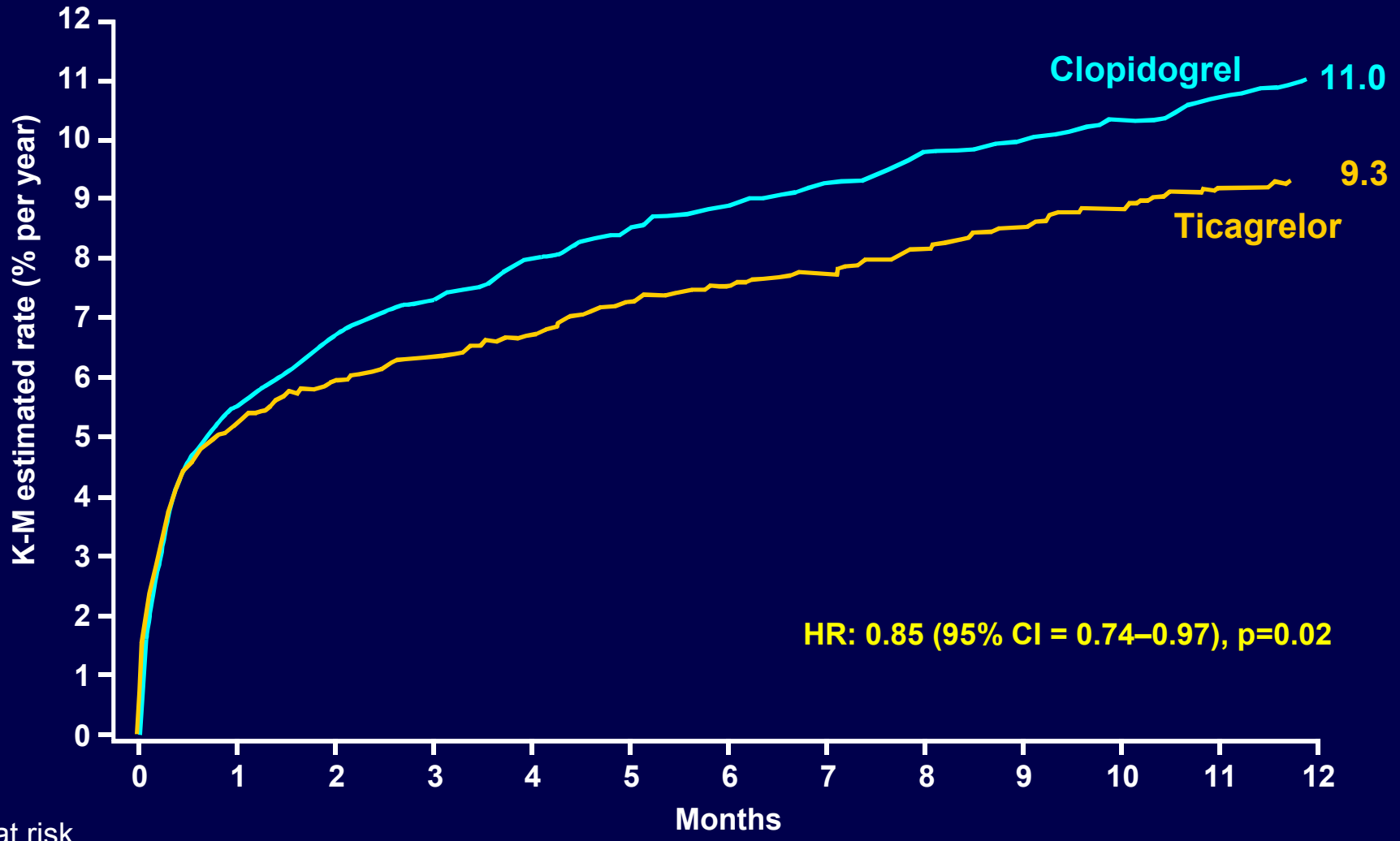
Medication	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)
Anti-thrombotic treatment in hospital, %		
Aspirin prior to index event	21.4	20.7
Aspirin from index event to discharge	99.0	98.8
Unfractionated heparin	66.3	65.8
Low molecular weight heparin	45.8	46.1
Fondaparinux	1.8	1.7
Bivalirudin	1.3	1.4
GPIIb/IIIa inhibitor from index event to randomization	34.7	35.2
Other medication in hospital or at discharge, %		
Beta-blockade	85.8	86.2
ACE inhibition and/or angiotensin-II receptor blocker	86.0	85.9
Cholesterol lowering (statin)	94.8	95.1
Calcium-channel blocker	17.1	17.1
Diuretic	36.2	35.4
Proton pump inhibitor	49.1	49.1

Primary endpoint: CV death, MI or stroke

PLATO
STEMI

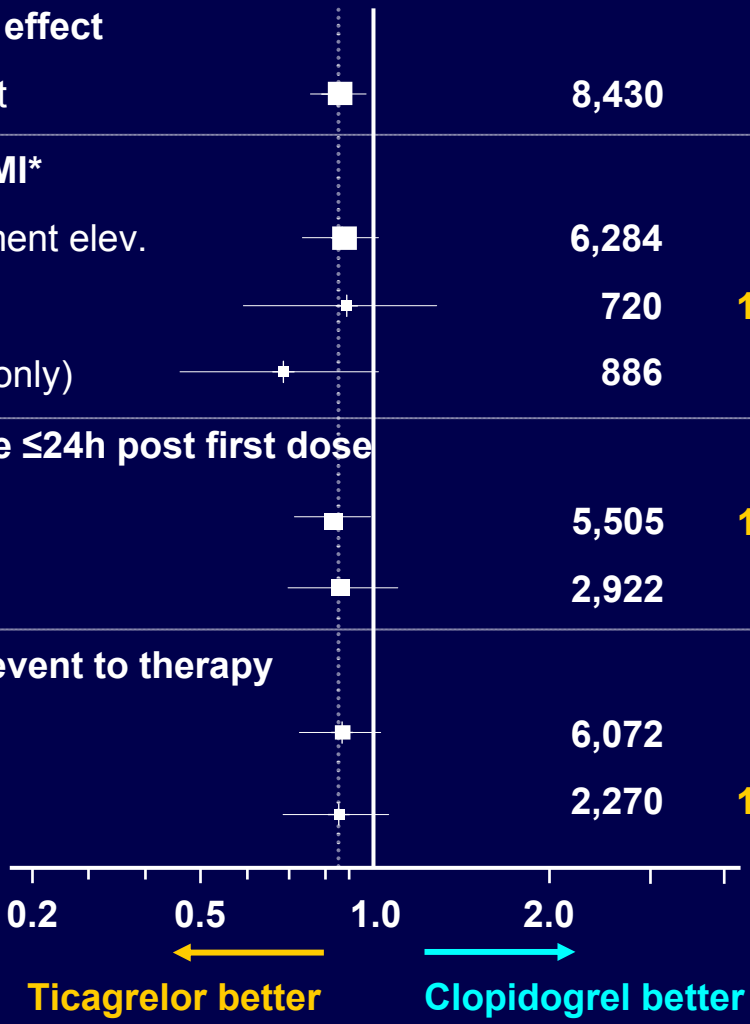


No. at risk							
Ticagrelor	4,201	3,887	3,834	3,732	3,011	2,297	1,891
Clopidogrel	4,229	3,892	3,823	3,730	3,022	2,333	1,868

Primary efficacy endpoint in selected pre-defined subgroups

PLATO STEMI

Characteristic	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)	p-value (Interaction)
Overall treatment effect					
Primary Endpoint	8,430	9.3	11.0	0.85 (0.74, 0.97)	
Definition of STEMI*					0.49
Persist. ST-segment elev.	6,284	8.9	10.4	0.87 (0.74, 1.02)	
LBBB	720	14.5	14.5	0.89 (0.59, 1.34)	
Final diagnosis (only)	886	8.4	12.5	0.67 (0.44, 1.02)	
Intended clop dose ≤24h post first dose					0.90
300 mg	5,505	10.1	11.9	0.84 (0.71, 0.99)	
600 mg	2,922	7.9	9.3	0.86 (0.67, 1.11)	
Time from index event to therapy					0.89
<12 hours	6,072	8.3	9.5	0.86 (0.73, 1.03)	
≥12 hours	2,270	12.0	14.2	0.85 (0.67, 1.07)	



*Patients with LBBB and ST-elevation were classified as LBBB

Hierarchical testing of major efficacy endpoints

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Endpoint*	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)	HR for ticagrelor (95% CI)	p-value†
Primary endpoint, %				
CV death + MI + stroke	9.3	11.0	0.85 (0.74–0.97)	0.02
Secondary endpoints, %				
Total death + MI + stroke	9.7	11.5	0.84 (0.73–0.96)	0.01
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	13.4	15.4	0.86 (0.76–0.96)	0.01
MI	4.7	6.1	0.77 (0.63–0.93)	0.01
CV death	4.5	5.4	0.84 (0.69–1.03)	0.09
Stroke	1.6	1.0	1.45 (0.98–2.17)	0.07
All-cause mortality	4.9	6.0	0.82 (0.68–0.99)	0.04

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.

†By univariate Cox model

CV death/total MI

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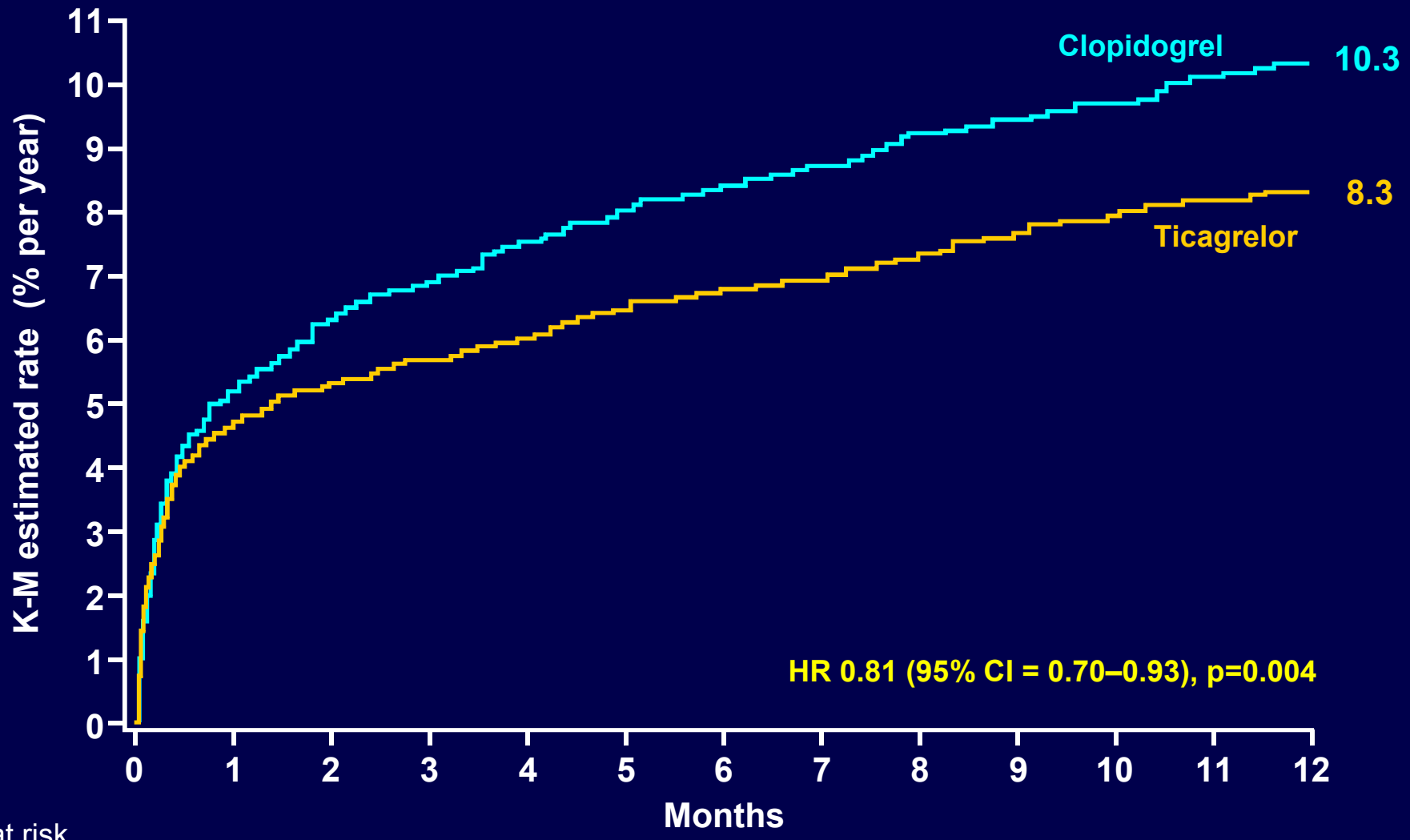
STEMI



No. at risk							
Ticagrelor	4,201	3,912	3,862	3,759	3,038	2,321	1,914
Clopidogrel	4,229	3,908	3,841	3,751	3,043	2,350	1,881

All cause mortality

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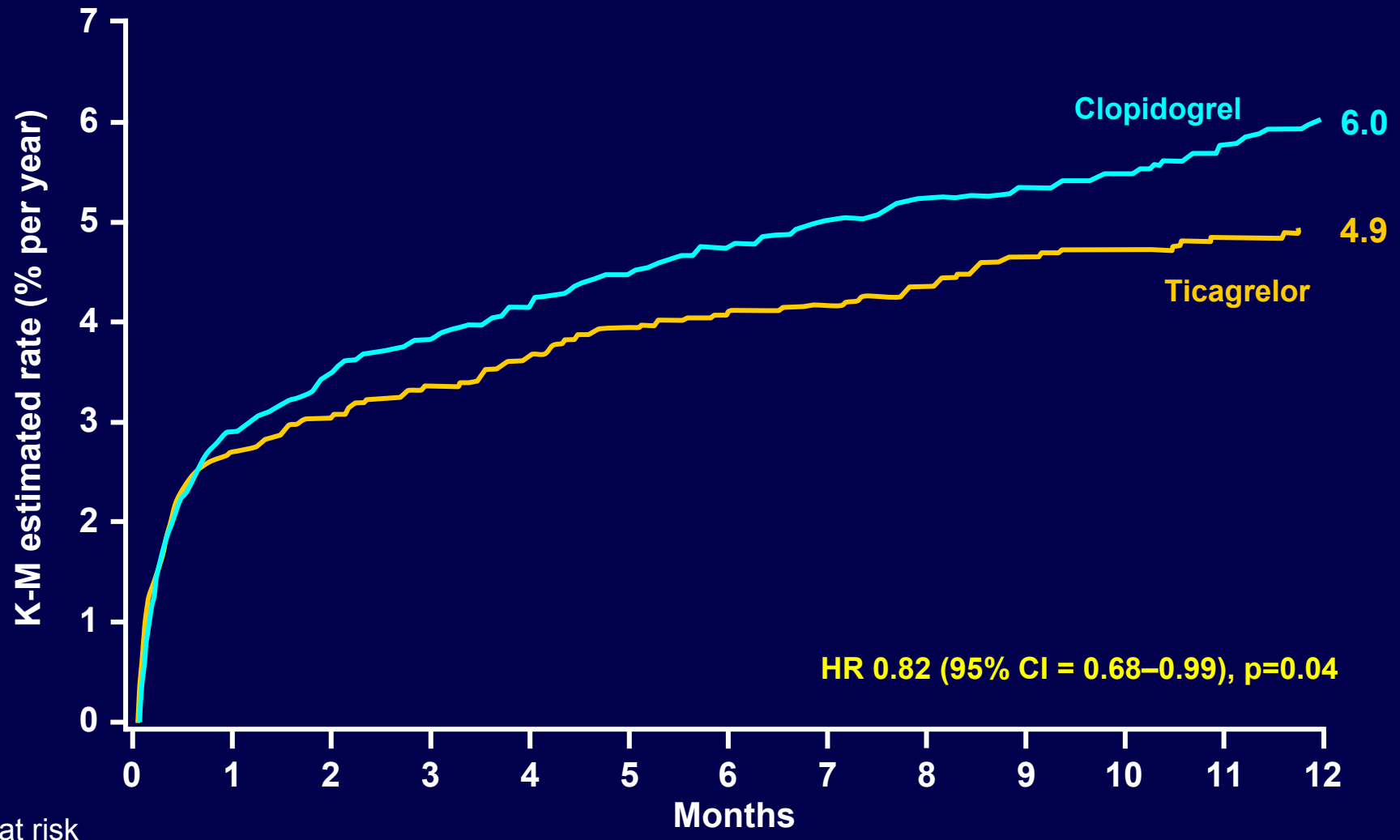

No. at risk							
Ticagrelor	4,201	4,005	3,962	3,876	3,150	2,413	1,993
Clopidogrel	4,229	4,029	3,989	3,912	3,195	2,471	1,980

Stent thrombosis (as per ARC definitions)*

PLATO STEMI

	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)	HR for ticagrelor (95% CI)	p-value†
Definite	1.6	2.5	0.61 (0.42–0.87)	0.01
Probable or definite	2.5	3.6	0.69 (0.52–0.92)	0.01
Possible, probable, or definite	3.2	4.4	0.73 (0.56–0.94)	0.02

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

*Cutlip et. al., Circulation. 2007;115:2344–2351

†By univariate Cox model

Primary safety event: major bleeding

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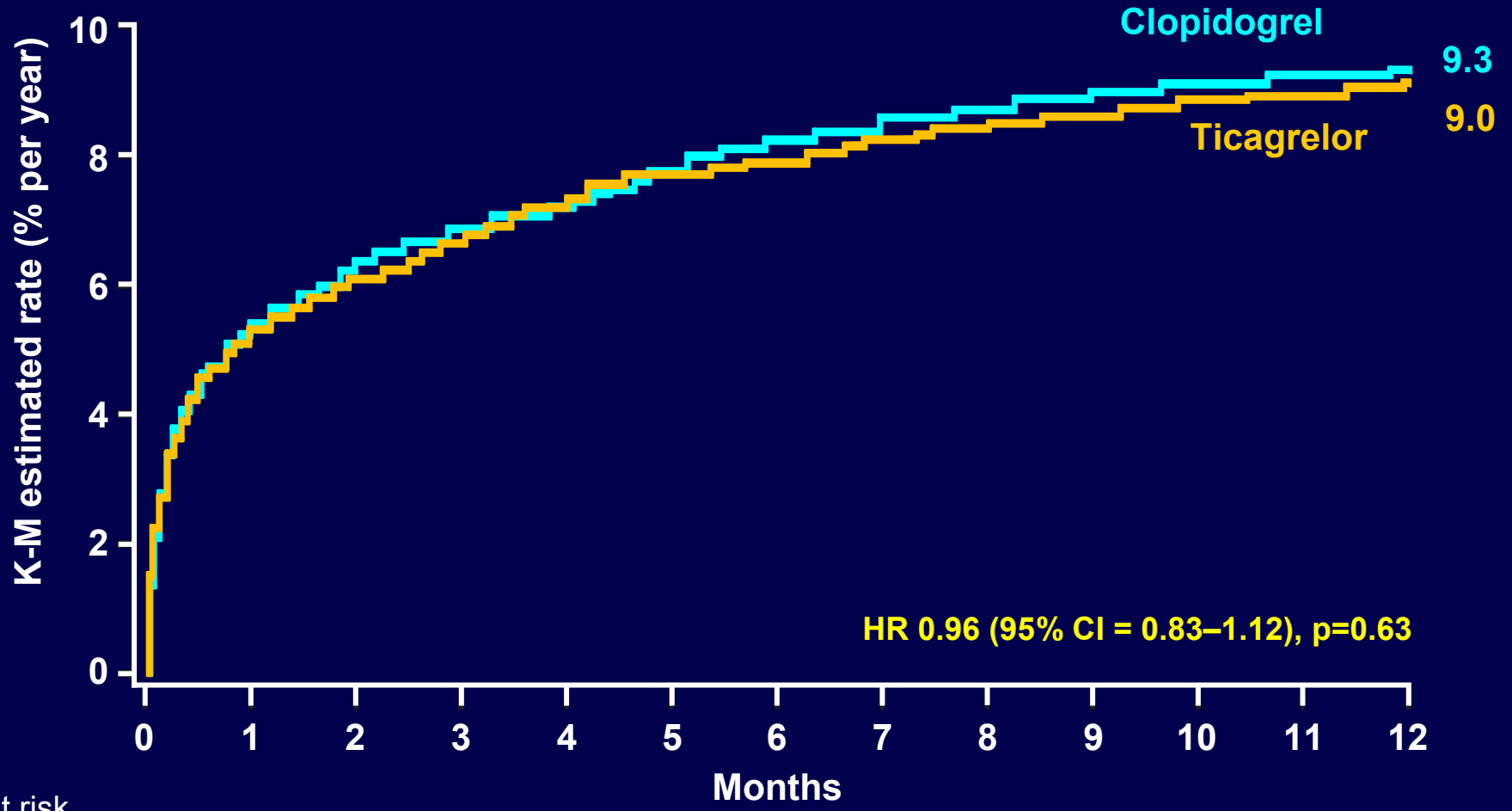

No. at risk							
Ticagrelor	4,165	3,431	3,254	3,137	2,440	1,786	1,640
Clopidogrel	4,181	3,430	3,297	3,159	2,441	1,804	1,635

Total major bleeding

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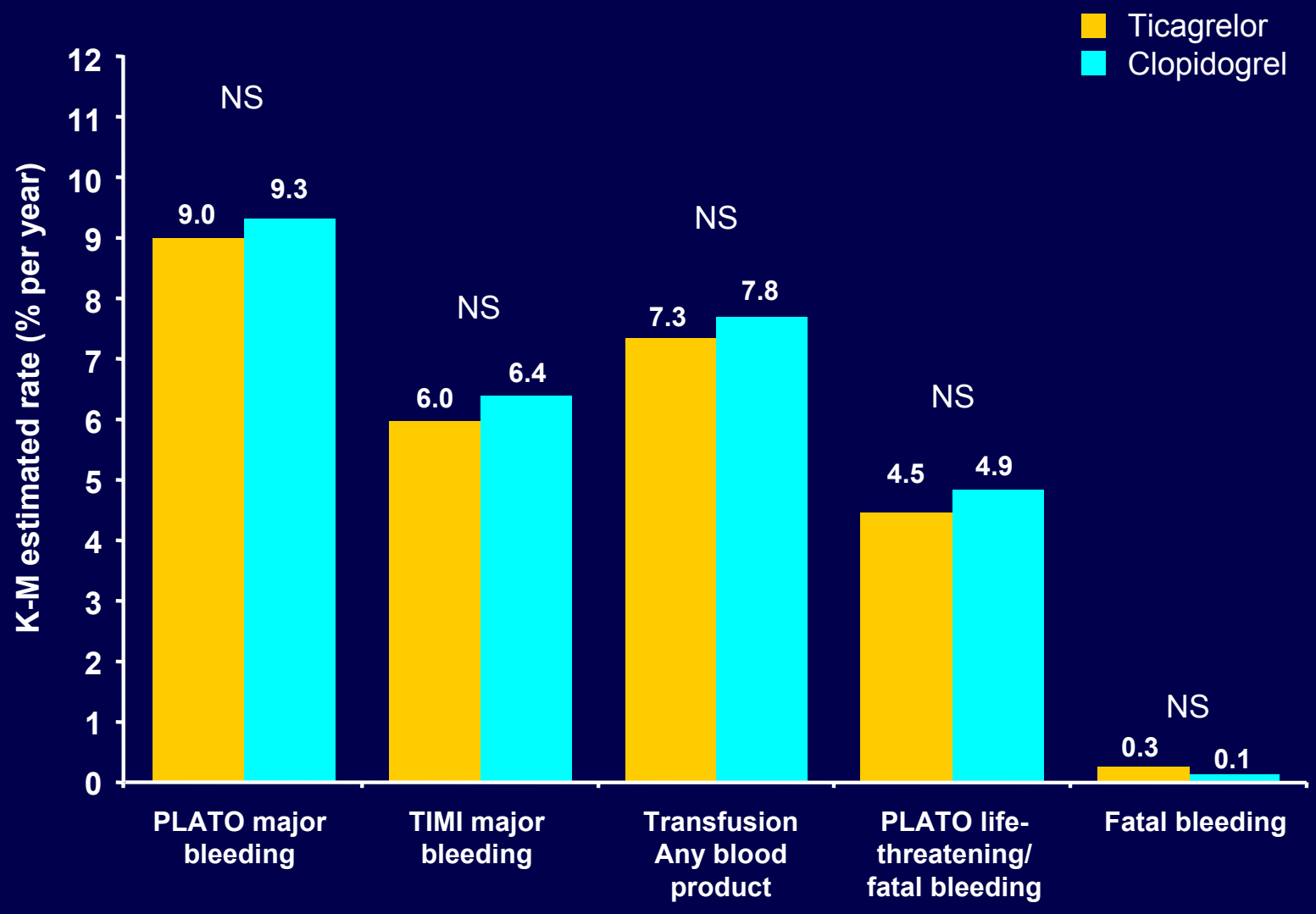

Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. New Eng J Med. 2007;357:2001–15;
NS = not significant

Other findings

PLATO STEMI

All patients	Ticagrelor (n=4,165)	Clopidogrel (n=4,181)	p-value*
Dyspnoea, %			
Any	12.9	8.3	<0.0001
Requiring discontinuation of study treatment	0.5	0.1	0.0003
Bradycardia-related events, %			
Bradycardia	4.6	4.9	0.57
Pacemaker placement	1.2	1.0	0.35
Syncope	1.0	0.8	0.35
Heart block	1.0	0.9	0.82

* Fisher's exact test

Conclusions

PLATO STEMI

- Reversible, more intense $P2Y_{12}$ receptor inhibition for one year with ticagrelor in comparison with clopidogrel in patients with STEMI intended for reperfusion with primary PCI provides
  - Reduction in composite of CV death, MI or stroke
  - Reduction in MI and stent thrombosis
  - Reduction in total mortality
  - No increase in the risk of major bleeding
- The NNT (number needed to treat) to avoid one primary endpoint (CV death, MI or stroke) is 59
- The mortality reduction is afforded on top of modern care

Ticagrelor may become a new standard of care for the management of patients with STEMI intended for primary PCI