

# PLATO



**Ticagrelor compared with clopidogrel  
in patients with acute coronary  
syndromes – the PLATO trial**

August 30, 2009 at 08.00 CET

*The* NEW ENGLAND  
JOURNAL *of* MEDICINE

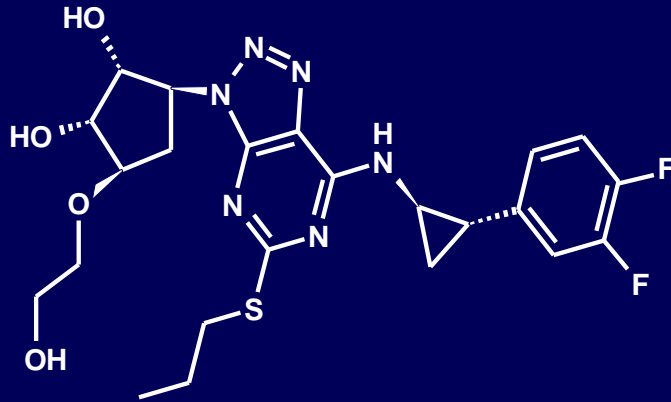
Ticagrelor versus Clopidogrel in Patients with Acute  
Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D.,  
Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc.,  
Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H.,  
Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D.,  
for the PLATO Investigators\*

- In NSTEMI-ACS and STEMI, current guidelines recommend 12 months aspirin and clopidogrel
- Efficacy of clopidogrel is hampered by
  - slow and variable transformation to the active metabolite
  - modest and variable platelet inhibition
  - increased risk of bleeding
  - risk of stent thrombosis and MI in poor responders

PLATO = **PLA**telet inhibition and patient **O**utcomes; NSTEMI = non-ST segment elevation; STEMI = ST segment elevation; ACS = acute coronary syndromes; MI = myocardial infarction

# Ticagrelor (AZD 6140): an oral reversible P2Y<sub>12</sub> antagonist



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

- **Direct acting**
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the P2Y<sub>12</sub> 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 all circulating platelets

**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 endpoint: Total major bleeding**

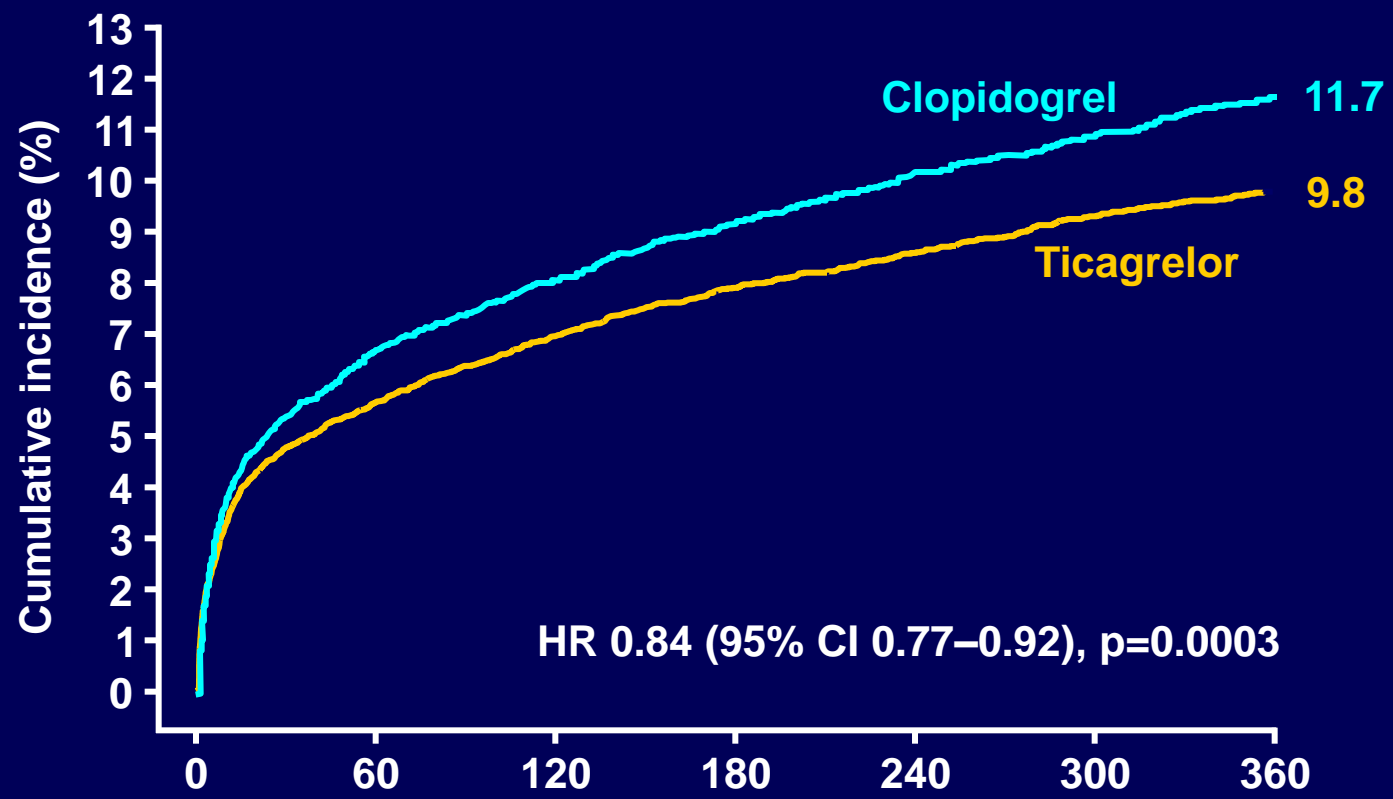
PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;  
CV = cardiovascular; TIA = transient ischaemic attack

# Baseline and index event characteristics

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

Medication	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)
<b>Start of randomised treatment</b>		
Time after start of chest pain, h, median	11.3	11.3
<b>Randomised treatment compliance, %</b>		
Premature discontinuation of study drug	23.4	21.5
<b>Clopidogrel start-up, %</b>		
Clopidogrel in hospital before randomisation	46.0	46.1
<b>Invasive procedures at index hospitalisation, %</b>		
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

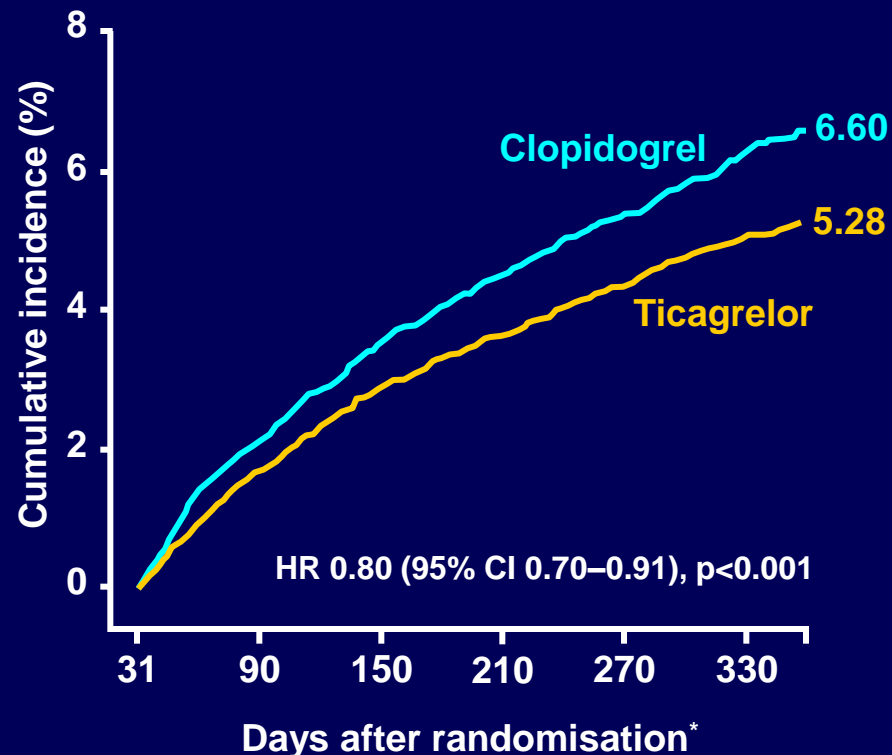
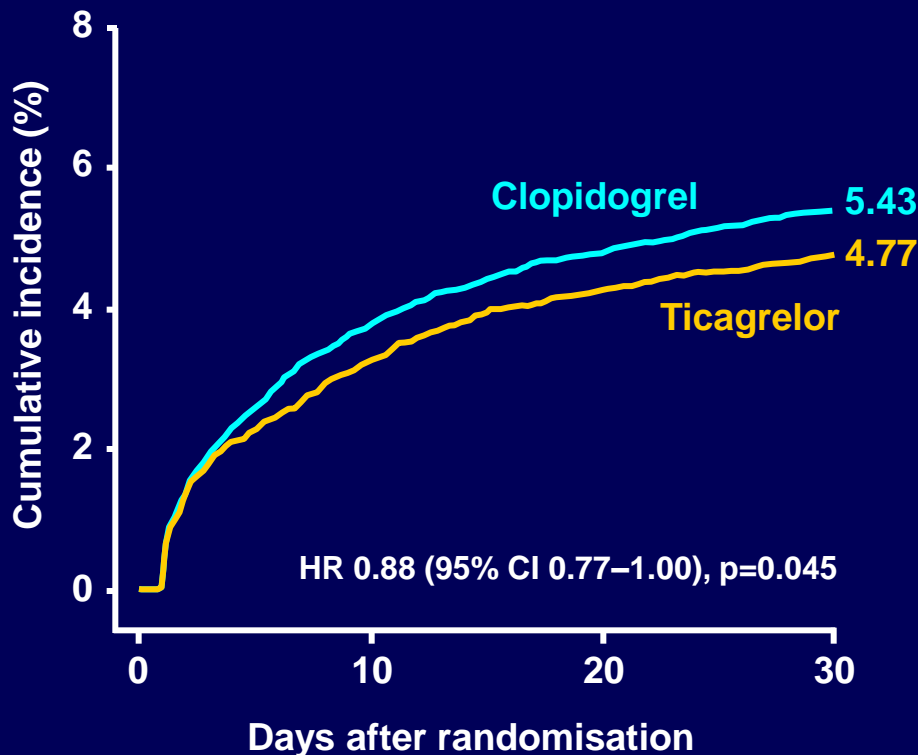
# K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)



No. at risk	Days after randomisation						
	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

# Primary efficacy endpoint over time (composite of CV death, MI or stroke)



No. at risk

Ticagrelor	9,333	8,942	8,827	8,763	8,673	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

\*Excludes patients with any primary event during the first 30 days

# Hierarchical testing major efficacy endpoints

All patients*	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for (95% CI)	p value†
<b>Primary objective, n (%)</b>				
CV death + MI + stroke	<b>864 (9.8)</b>	<b>1,014 (11.7)</b>	<b>0.84 (0.77–0.92)</b>	<b>&lt;0.001</b>
<b>Secondary objectives, n (%)</b>				
Total death + MI + stroke				
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events				
Myocardial infarction				
CV death				
Stroke				
<b>Total death</b>				

The percentages are K-M estimates of the rate of the endpoint at 12 months.

# Hierarchical testing major efficacy endpoints

All patients*	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for (95% CI)	p value†
<b>Primary objective, n (%)</b>				
CV death + MI + stroke	<b>864 (9.8)</b>	<b>1,014 (11.7)</b>	<b>0.84 (0.77–0.92)</b>	<b>&lt;0.001</b>
<b>Secondary objectives, n (%)</b>				
Total death + MI + stroke	<b>901 (10.2)</b>	<b>1,065 (12.3)</b>	<b>0.84 (0.77–0.92)</b>	<b>&lt;0.001</b>
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	<b>1,290 (14.6)</b>	<b>1,456 (16.7)</b>	<b>0.88 (0.81–0.95)</b>	<b>&lt;0.001</b>
Myocardial infarction	<b>504 (5.8)</b>	<b>593 (6.9)</b>	<b>0.84 (0.75–0.95)</b>	<b>0.005</b>
CV death	<b>353 (4.0)</b>	<b>442 (5.1)</b>	<b>0.79 (0.69–0.91)</b>	<b>0.001</b>
Stroke	<b>125 (1.5)</b>	<b>106 (1.3)</b>	<b>1.17 (0.91–1.52)</b>	<b>0.22</b>
<b>Total death</b>				

The percentages are K-M estimates of the rate of the endpoint at 12 months.

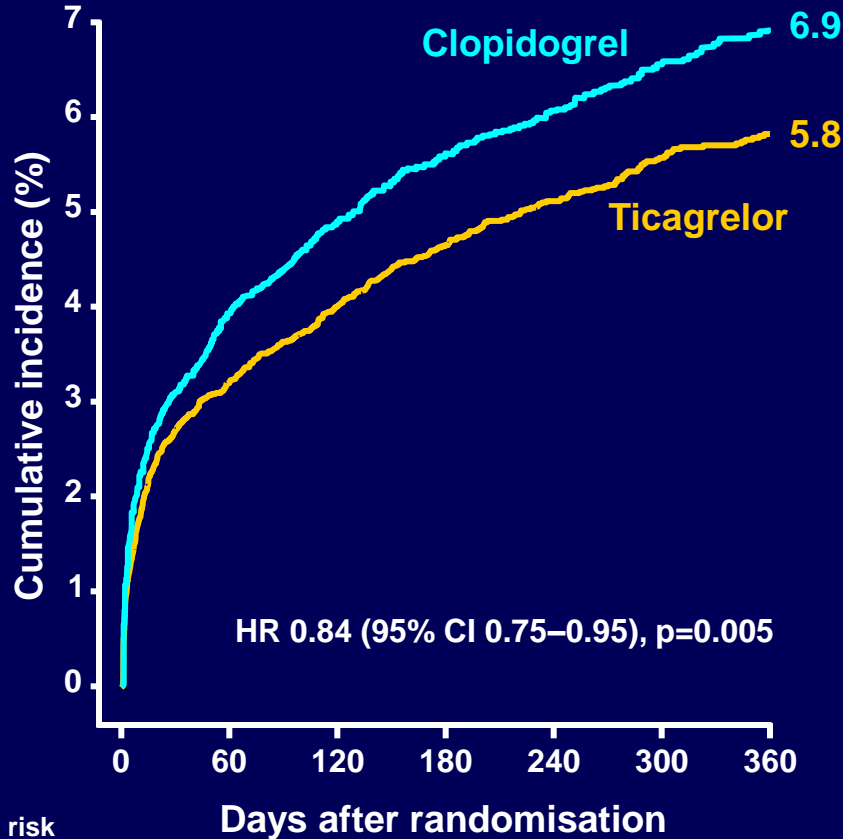
# Hierarchical testing major efficacy endpoints

All patients*	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for (95% CI)	p value†
<b>Primary objective, n (%)</b>				
CV death + MI + stroke	<b>864 (9.8)</b>	<b>1,014 (11.7)</b>	<b>0.84 (0.77–0.92)</b>	<b>&lt;0.001</b>
<b>Secondary objectives, n (%)</b>				
Total death + MI + stroke	<b>901 (10.2)</b>	<b>1,065 (12.3)</b>	<b>0.84 (0.77–0.92)</b>	<b>&lt;0.001</b>
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	<b>1,290 (14.6)</b>	<b>1,456 (16.7)</b>	<b>0.88 (0.81–0.95)</b>	<b>&lt;0.001</b>
Myocardial infarction	<b>504 (5.8)</b>	<b>593 (6.9)</b>	<b>0.84 (0.75–0.95)</b>	<b>0.005</b>
CV death	<b>353 (4.0)</b>	<b>442 (5.1)</b>	<b>0.79 (0.69–0.91)</b>	<b>0.001</b>
Stroke	<b>125 (1.5)</b>	<b>106 (1.3)</b>	<b>1.17 (0.91–1.52)</b>	<b>0.22</b>
<b>Total death</b>	<b>399 (4.5)</b>	<b>506 (5.9)</b>	<b>0.78 (0.69–0.89)</b>	<b>&lt;0.001</b>

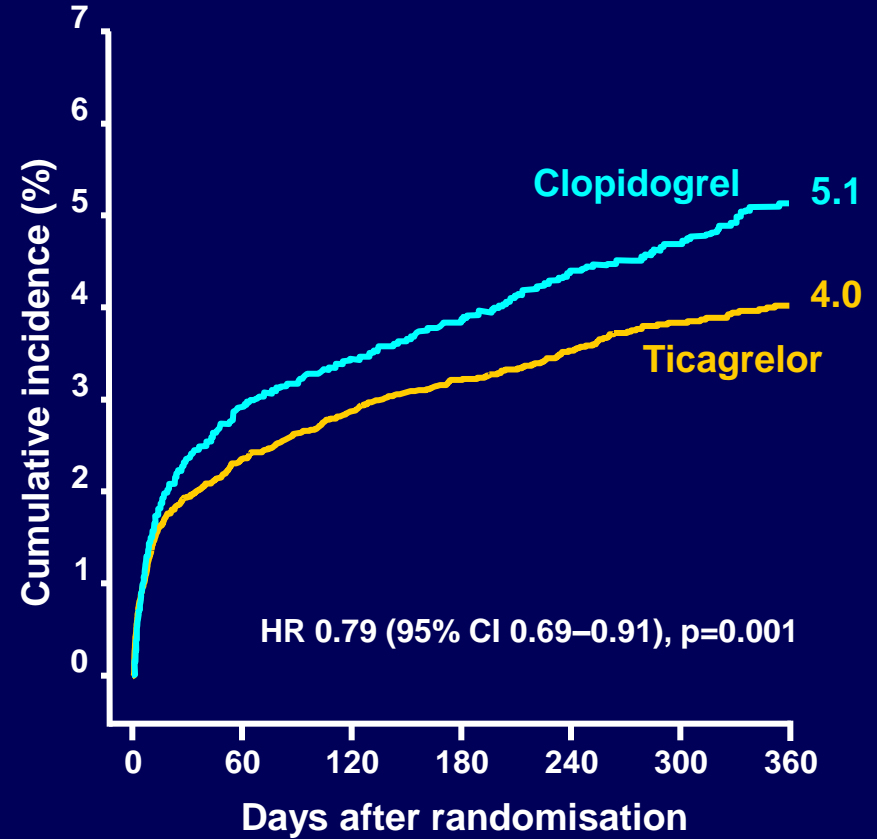
The percentages are K-M estimates of the rate of the endpoint at 12 months.

# Secondary efficacy endpoints over time

## Myocardial infarction



## Cardiovascular death



No. at risk

	0	60	120	180	240	300	360
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

	0	60	120	180	240	300	360
Clopidogrel	9,333	8,294	8,822	8,626	7,119	5,482	4,419
Ticagrelor	9,291	8,865	8,780	8,589	7,079	5,441	4,364

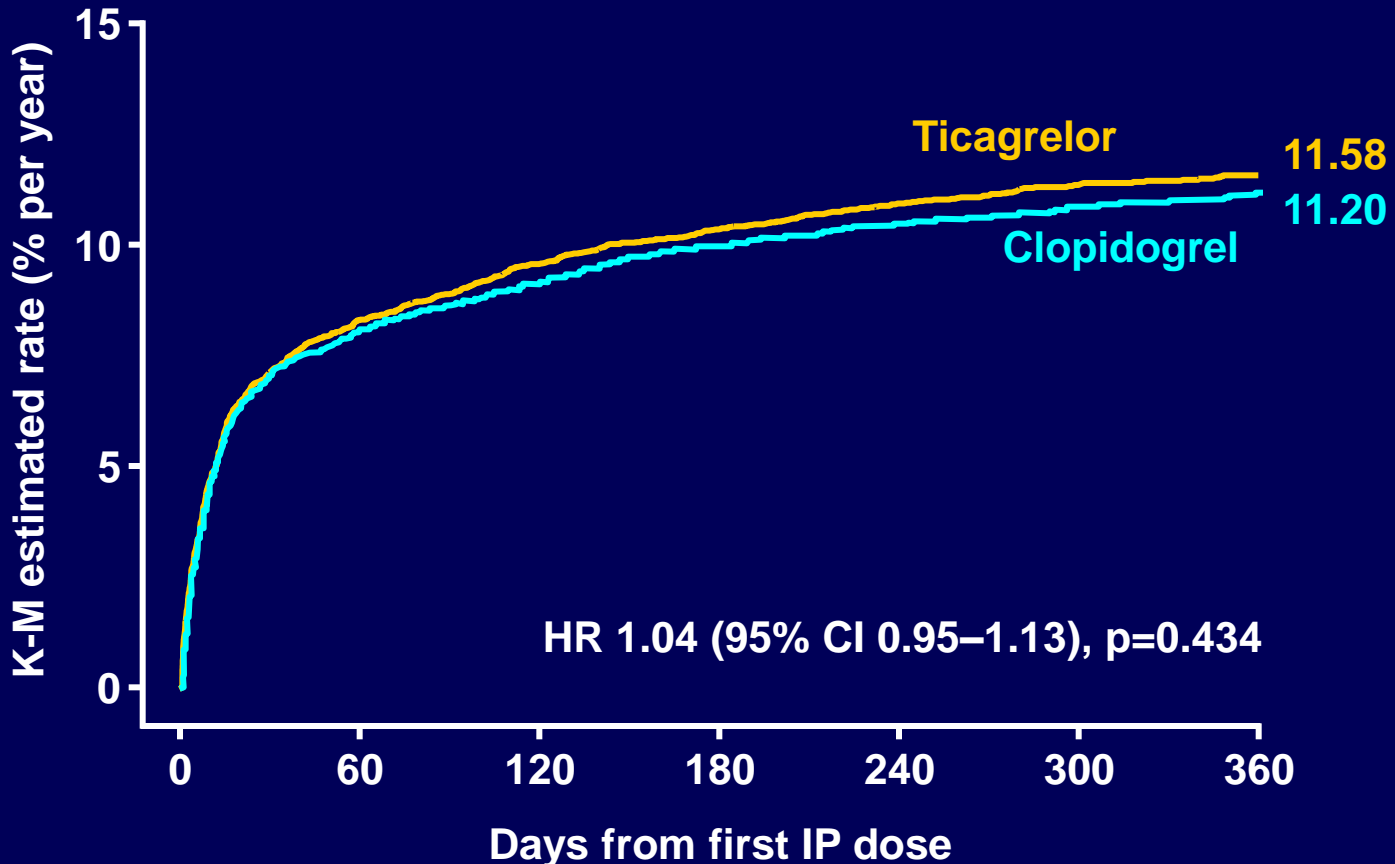
# Stent thrombosis

(evaluated in patients with any stent during the study)

	<b>Ticagrelor (n=5,640)</b>	<b>Clopidogrel (n=5,649)</b>	<b>HR (95% CI)</b>	<b>p value</b>
<b>Stent thrombosis, n (%)</b>				
<b>Definite</b>	<b>71 (1.3)</b>	<b>106 (1.9)</b>	<b>0.67 (0.50–0.91)</b>	<b>0.009</b>
<b>Probable or definite</b>	<b>118 (2.1)</b>	<b>158 (2.8)</b>	<b>0.75 (0.59–0.95)</b>	<b>0.02</b>
<b>Possible, probable, definite</b>	<b>155 (2.8)</b>	<b>202 (3.6)</b>	<b>0.77 (0.62–0.95)</b>	<b>0.01</b>

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

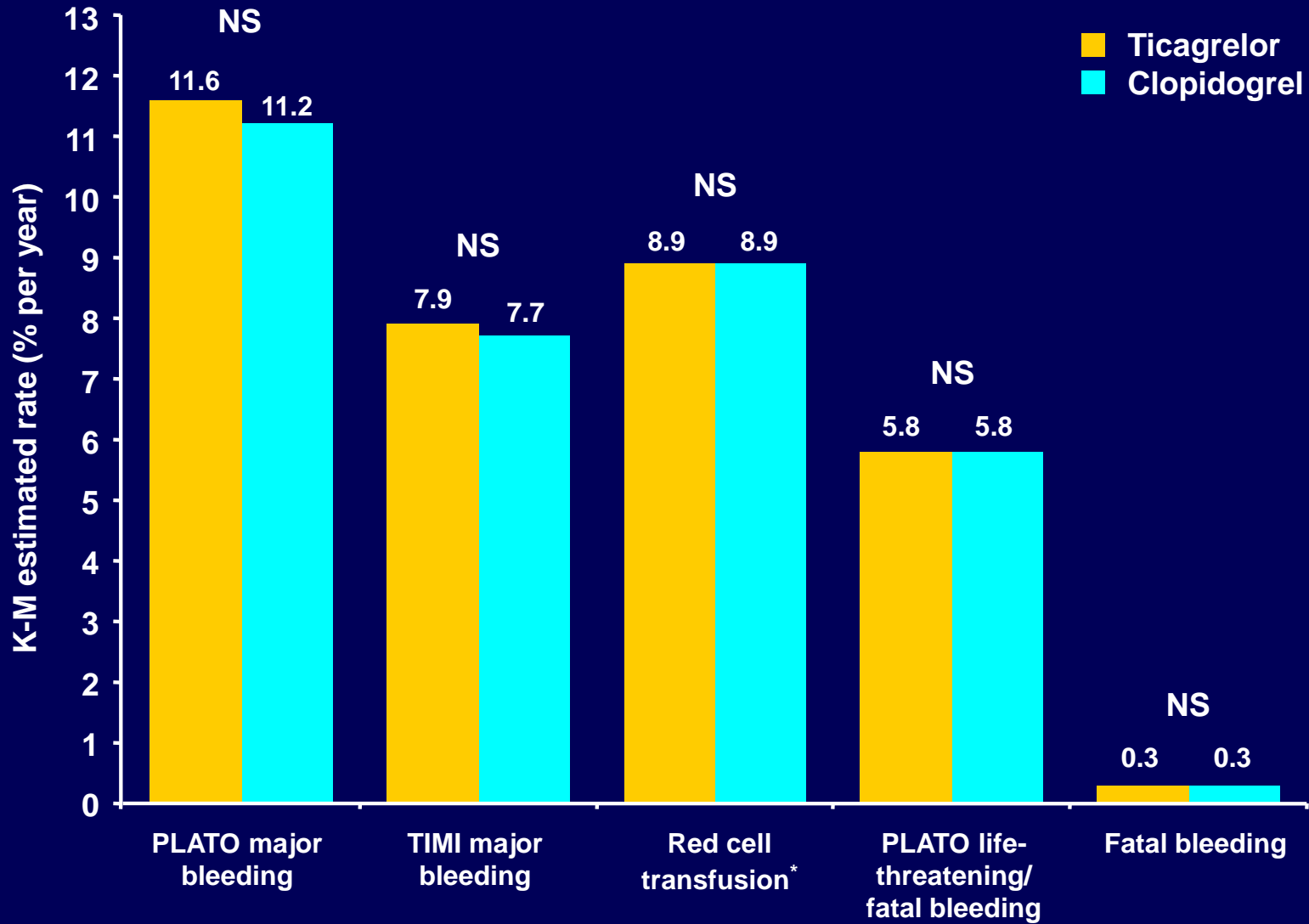
# Time to major bleeding – primary safety event



## 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

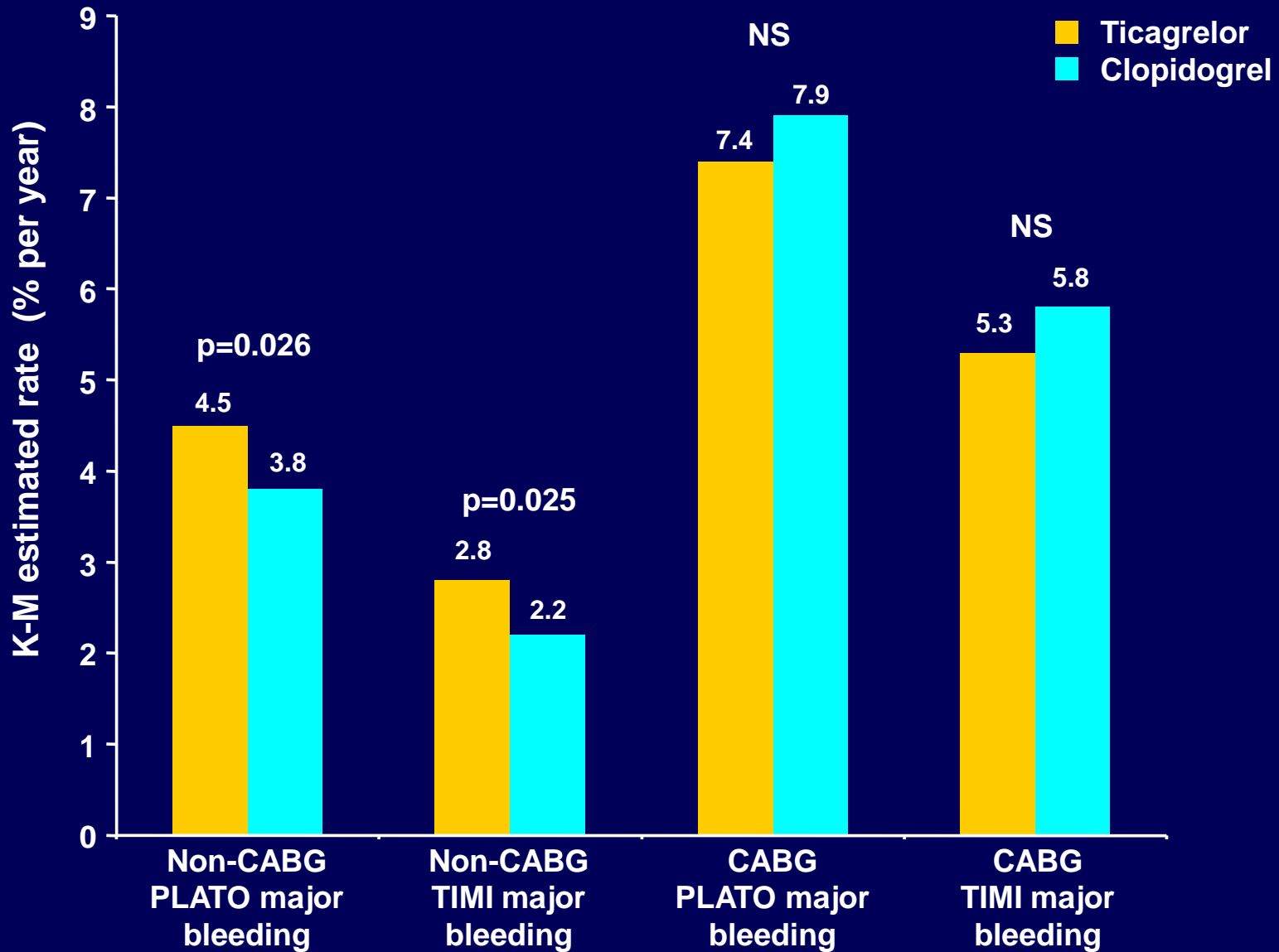
# Total major bleeding



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. NEJM 2007;357:2001-15;

\*Proportion of patients (%); NS = not significant

# Non-CABG and CABG-related major bleeding



# Holter monitoring & Bradycardia related events

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

Holter monitoring at 30 days	Ticagrelor (n= 985)	Clopidogrel (n=1,006)	p value
Ventricular pauses $\geq 3$ seconds, %	2.1	1.7	0.52
Ventricular pauses $\geq 5$ 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

All patients	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value*
<b>Dyspnoea, %</b>			
Any	13.8	7.8	<0.001
With discontinuation of study treatment	0.9	0.1	<0.001
<b>Neoplasms arising during treatment, %</b>			
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

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

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

- **Based on 1,000 patients admitted to hospital for ACS, using ticagrelor instead of clopidogrel for 12 months resulted in**
  - **14 fewer deaths**
  - **11 fewer myocardial infarctions**
  - **6–8 fewer cases with stent thrombosis**
  - **No increase in bleedings requiring transfusion**
  - **9 patients may switch to thienopyridine treatment because of reversible symptoms of dyspnoea**
- **Treating 54 patients with ticagrelor instead of with clopidogrel for one year will prevent one event of CV death, MI or stroke**

- **Reversible, more intense P2Y<sub>12</sub> receptor inhibition for one year with ticagrelor in comparison with clopidogrel in a broad population with ST- and non-ST-elevation ACS provides**
  - **Reduction in myocardial infarction and stent thrombosis**
  - **Reduction in cardiovascular and total mortality**
  - **No change in the overall risk of major bleeding**

**Ticagrelor is a more effective alternative than clopidogrel for the continuous prevention of ischaemic events, stent thrombosis and death in the acute and long-term treatment of patients with ACS**

**Thanks to all PLATO  
leaders,  
committees,  
investigators  
and patients**

# PLATO – a global trial

Argentina	Canada	Finland	Hong Kong	Malaysia	Philippines	Slovakia	Thailand
Australia	China	France	Hungary	Mexico	Poland	Spain	Turkey
Austria	Czech Republic	Georgia	India	The Netherlands	Portugal	Sweden	Ukraine
Belgium	Denmark	Germany	Indonesia	Norway	Romania	Switzerland	United Kingdom
Brazil		Greece	Israel		Russia	South Africa	United States
Bulgaria			Italy		Singapore	South Korea	
						Taiwan	

