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

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Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

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PLATO background

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- In NSTE-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 = **PLAT**elet 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 $P2Y_{12}$ antagonist

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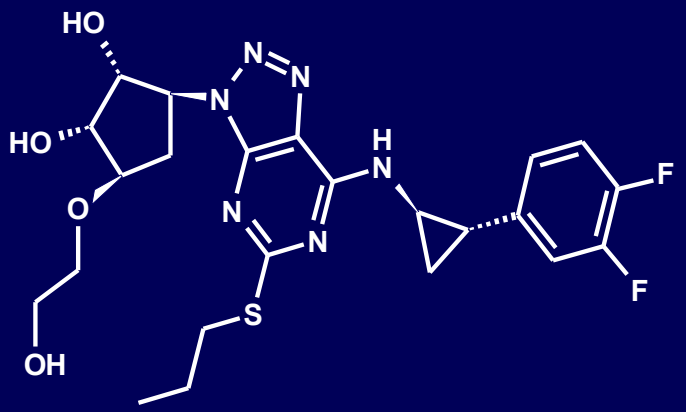

Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the $P2Y_{12}$ 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 all circulating platelets

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
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

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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

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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)

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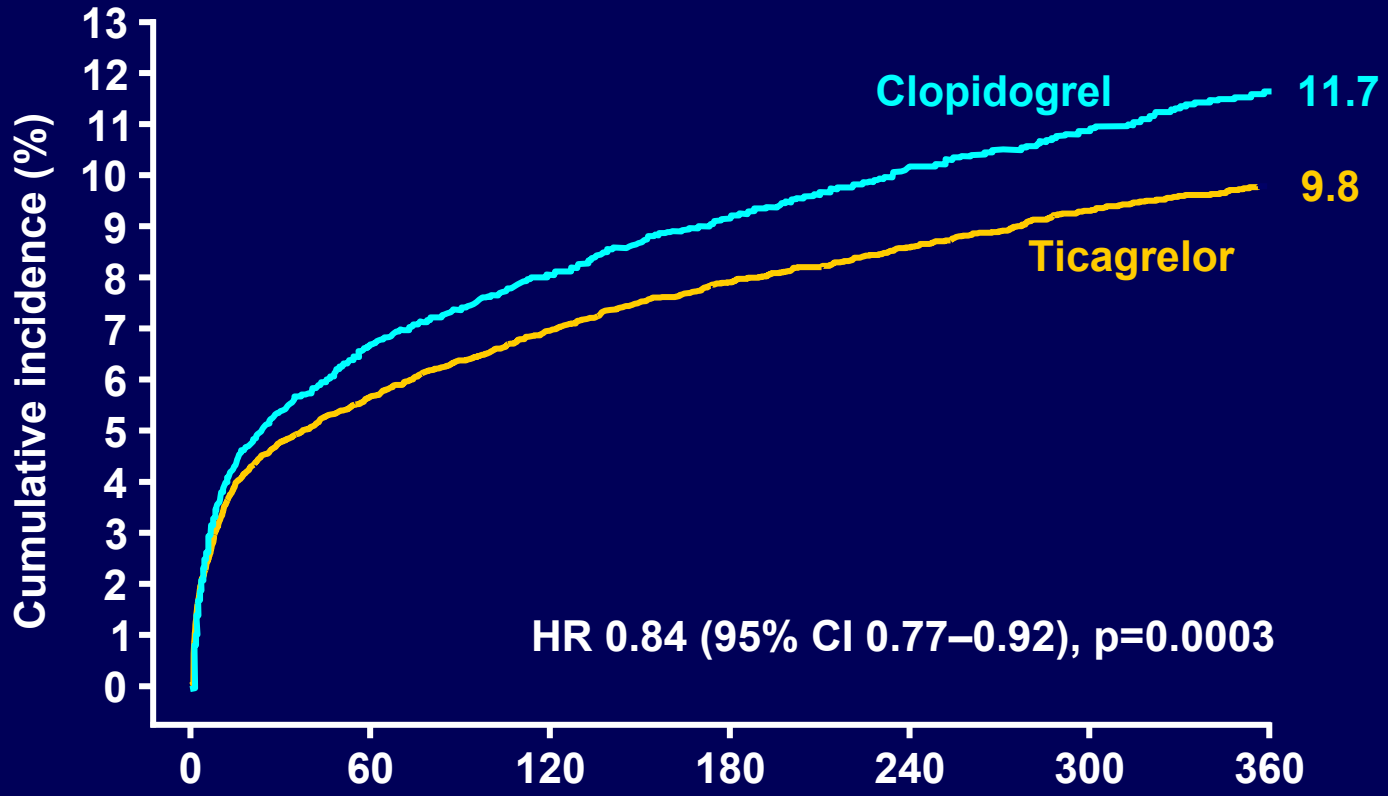

No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

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

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

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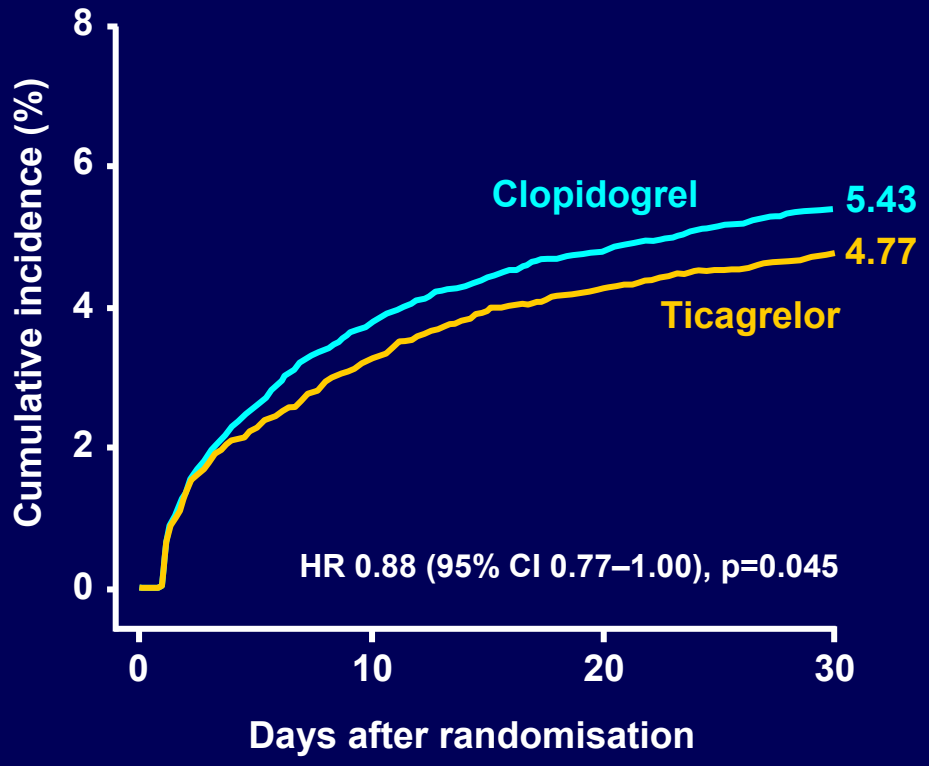

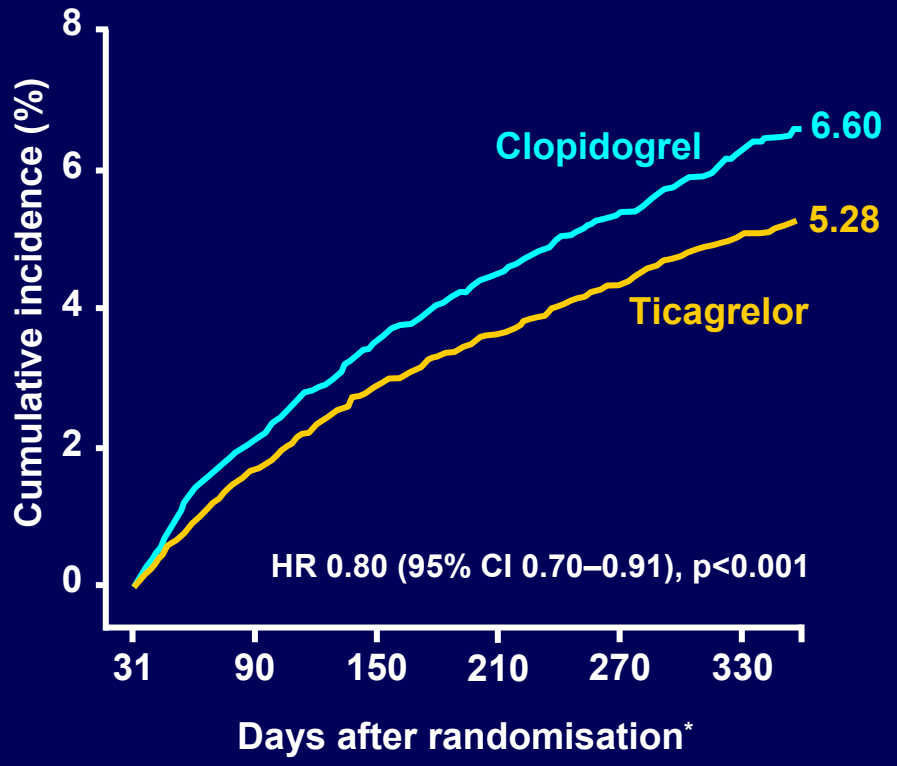

No. at risk										
Ticagrelor	9,333	8,942	8,827	8,763	8,673	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

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

Hierarchical testing major efficacy endpoints

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All patients*	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for (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 + stroke				
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events				
Myocardial infarction				
CV death				
Stroke				
Total death				

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

Hierarchical testing major efficacy endpoints

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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 + stroke	901 (10.2)	1,065 (12.3)	0.84 (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
Total death				

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

Hierarchical testing major efficacy endpoints

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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
Total death	399 (4.5)	506 (5.9)	0.78 (0.69–0.89)	<0.001

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

Secondary efficacy endpoints over time

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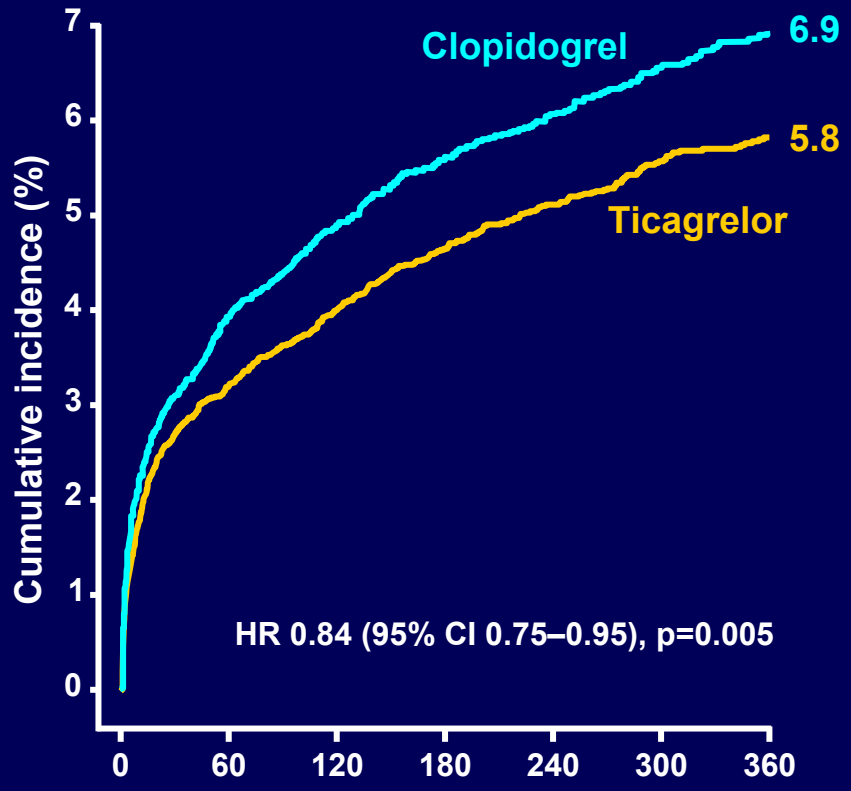
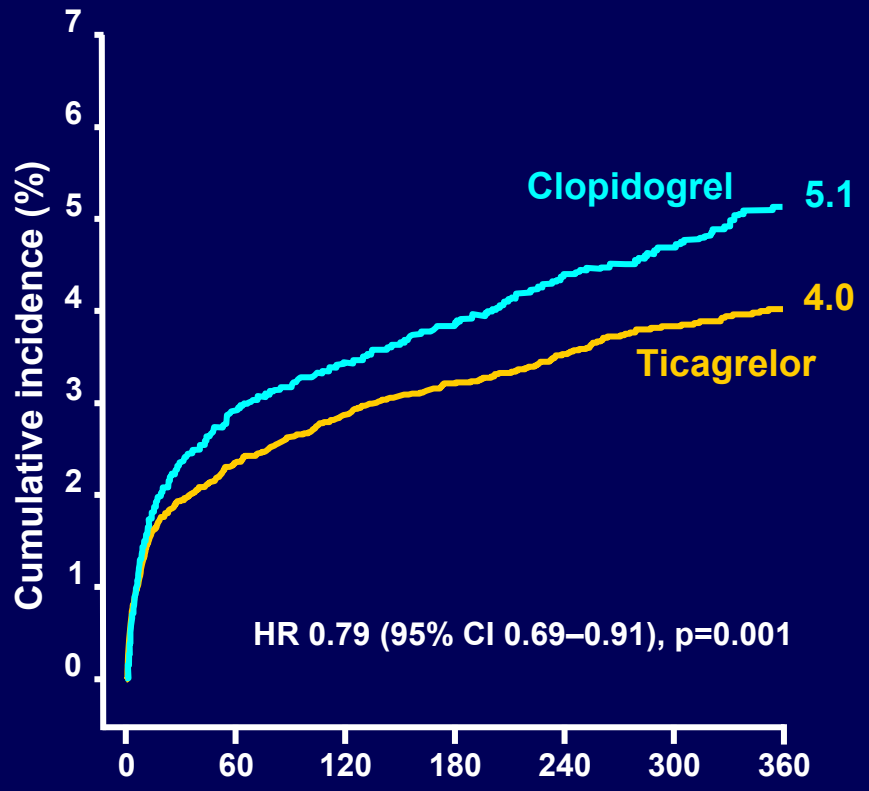
Myocardial infarction



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

Cardiovascular death



	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

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Stent thrombosis

(evaluated in patients with any stent during the study)

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

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

Time to major bleeding – primary safety event

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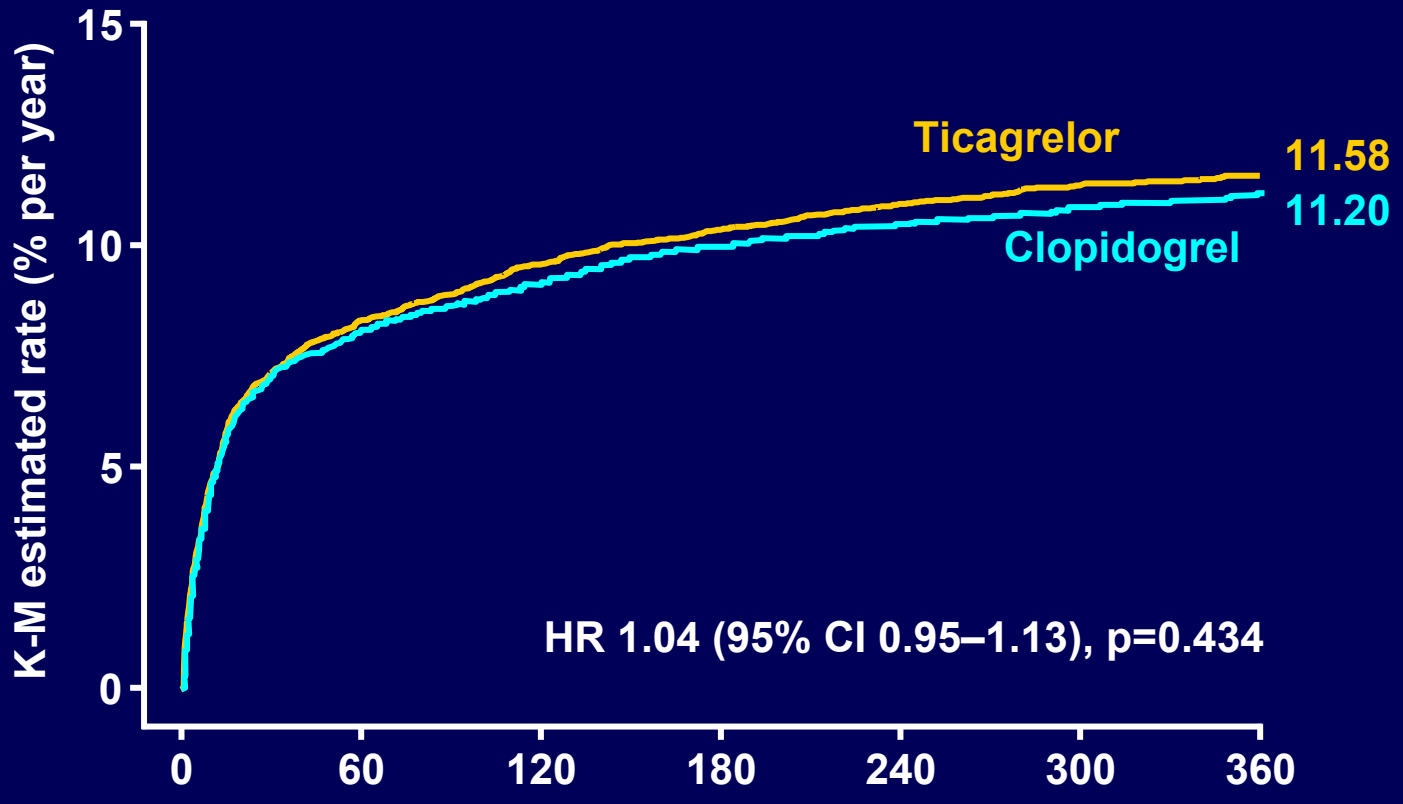

No. at risk							
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

Total major bleeding

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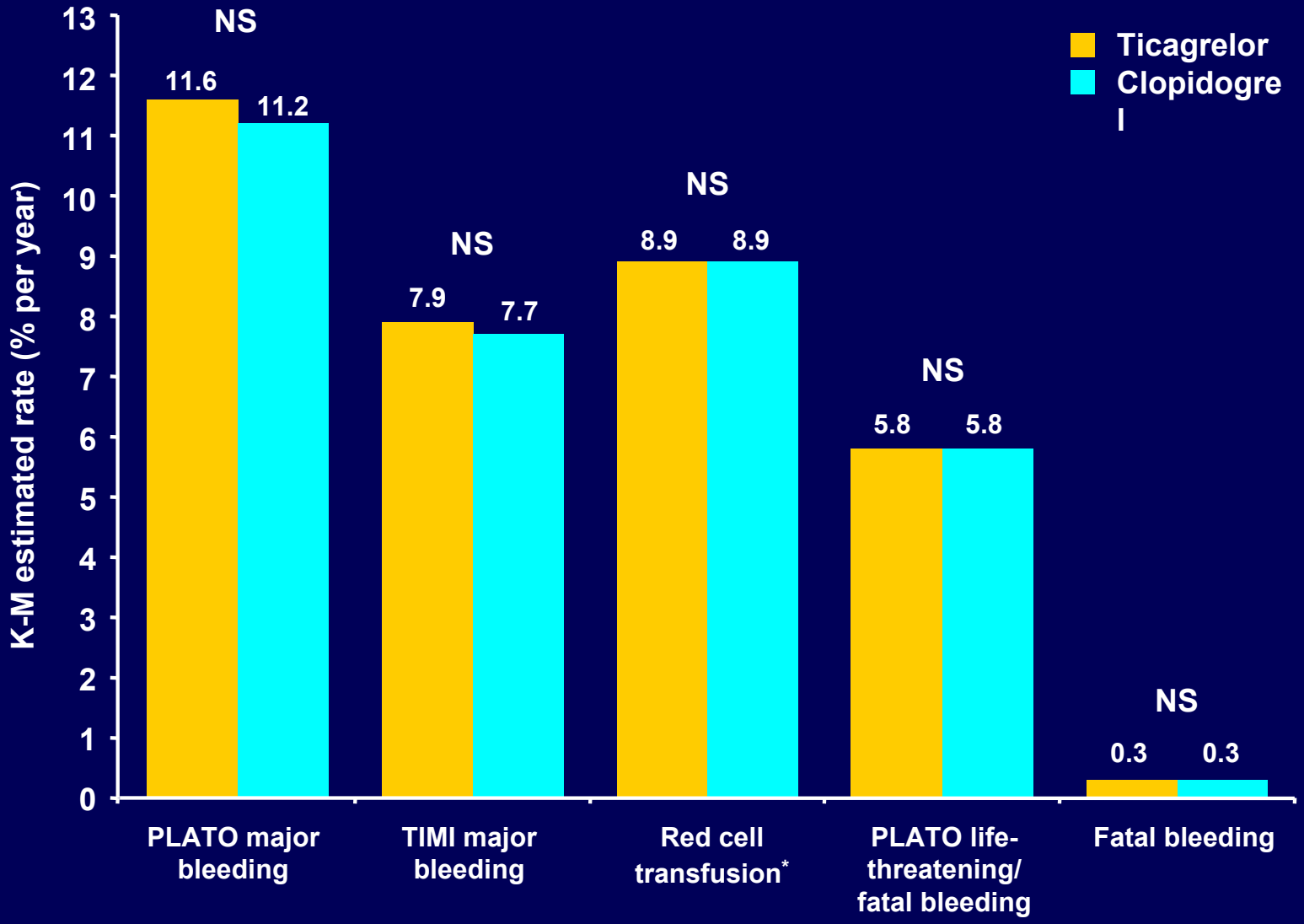

Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. NEJM 2007;357:2001–15;
*Proportion of patients (%); NS = not significant

Non-CABG and CABG-related major bleeding

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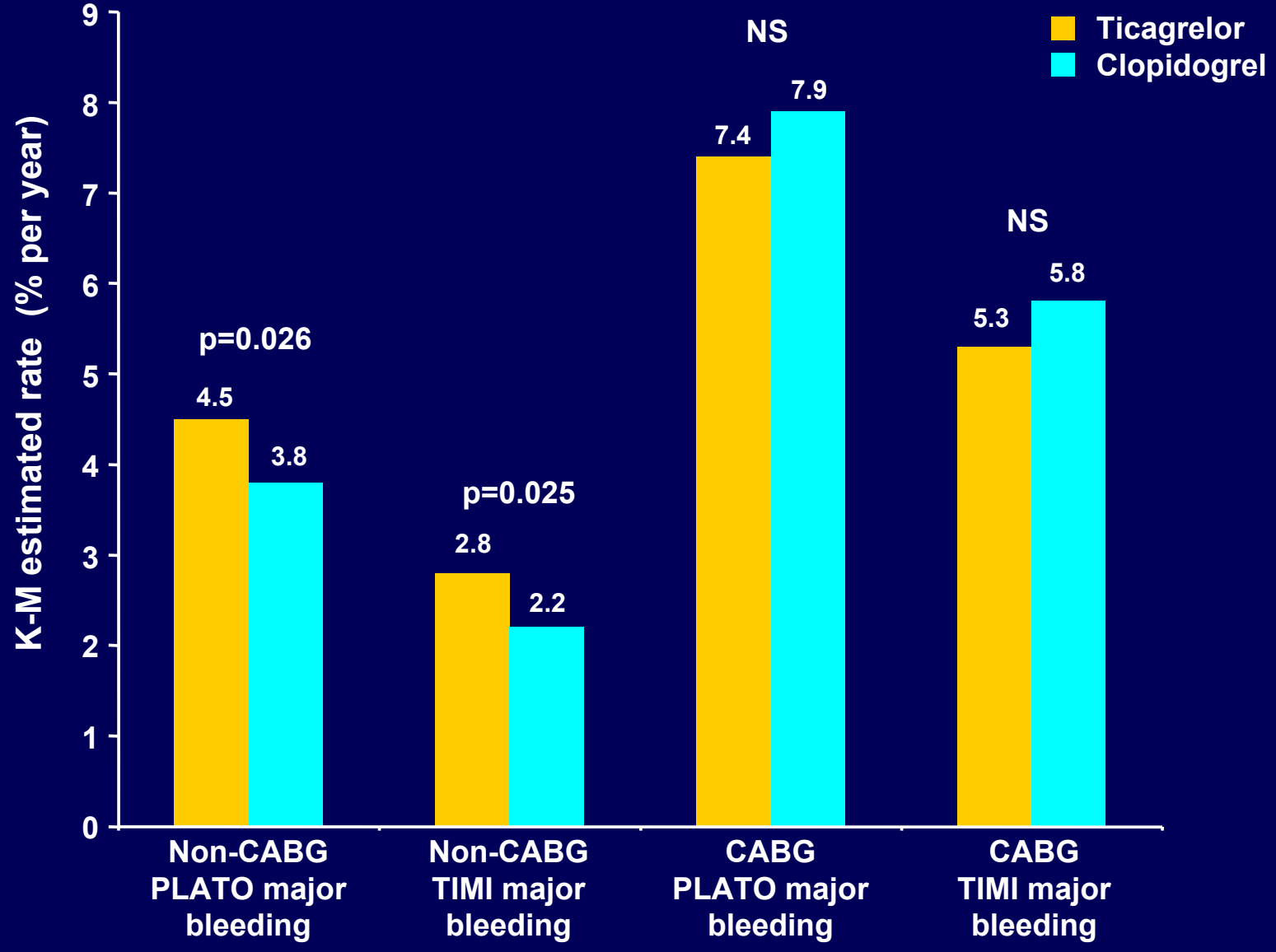

Holter monitoring & Bradycardia related events

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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

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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

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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

Therapeutic considerations

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- 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

Conclusions

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- Reversible, more intense $P2Y_{12}$ 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

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Thanks to all PLATO leaders, committees, investigators and patients

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PLATO – a global trial

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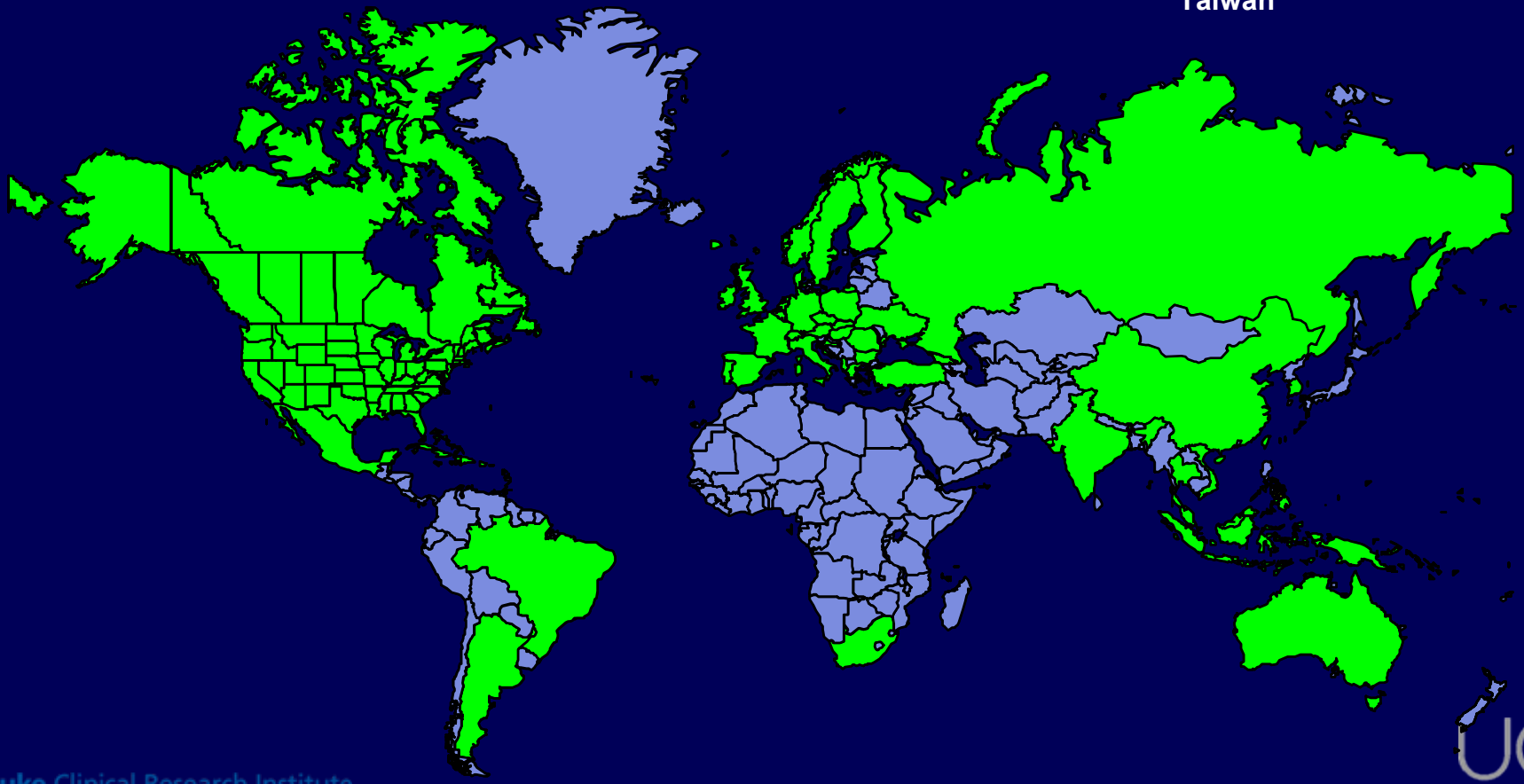

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