ALPIC, Motsovo 28th January 2012

"New reversible antagonists of the ADP receptor P2Y12: Clinical benefits & unanswered questions"

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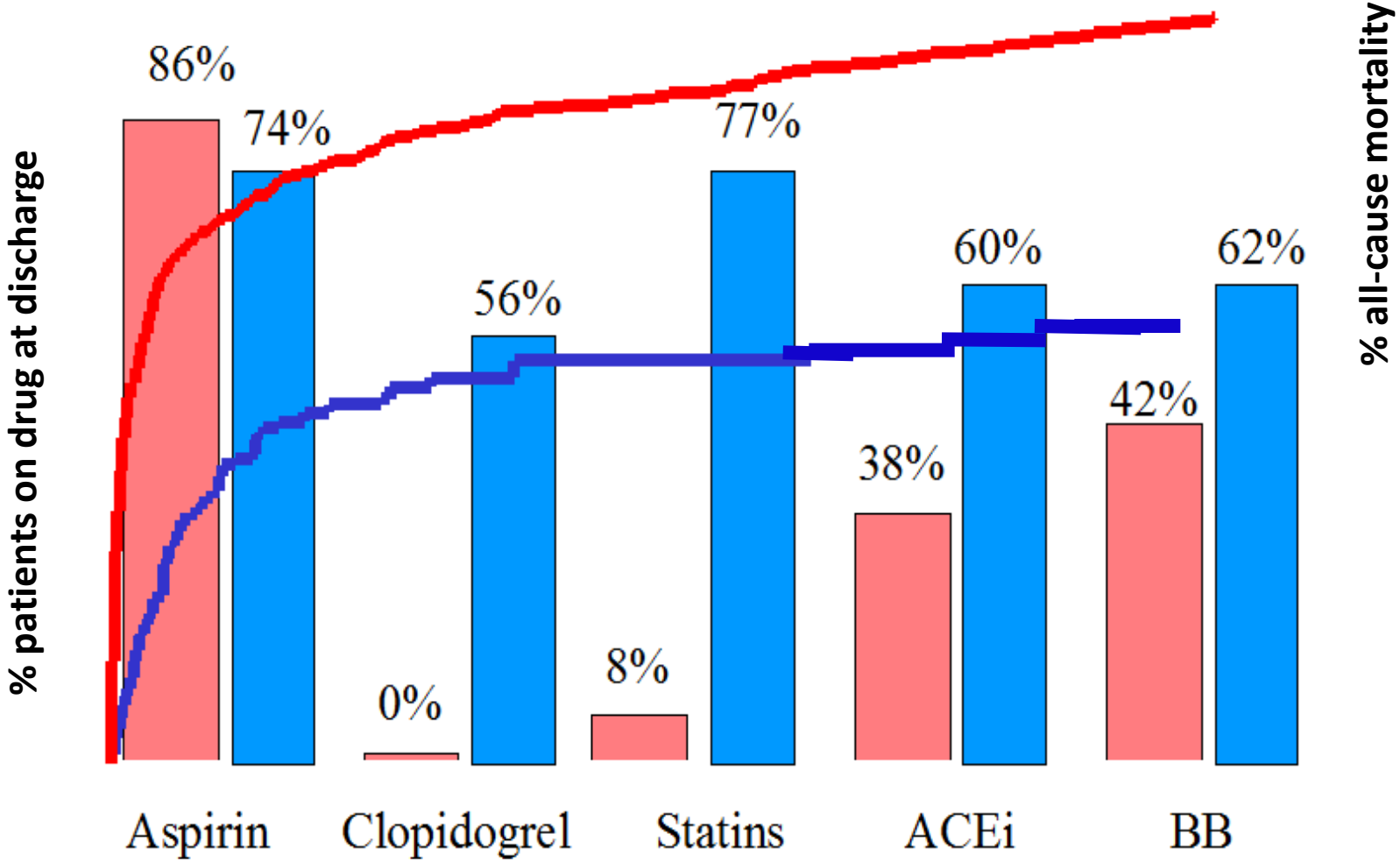
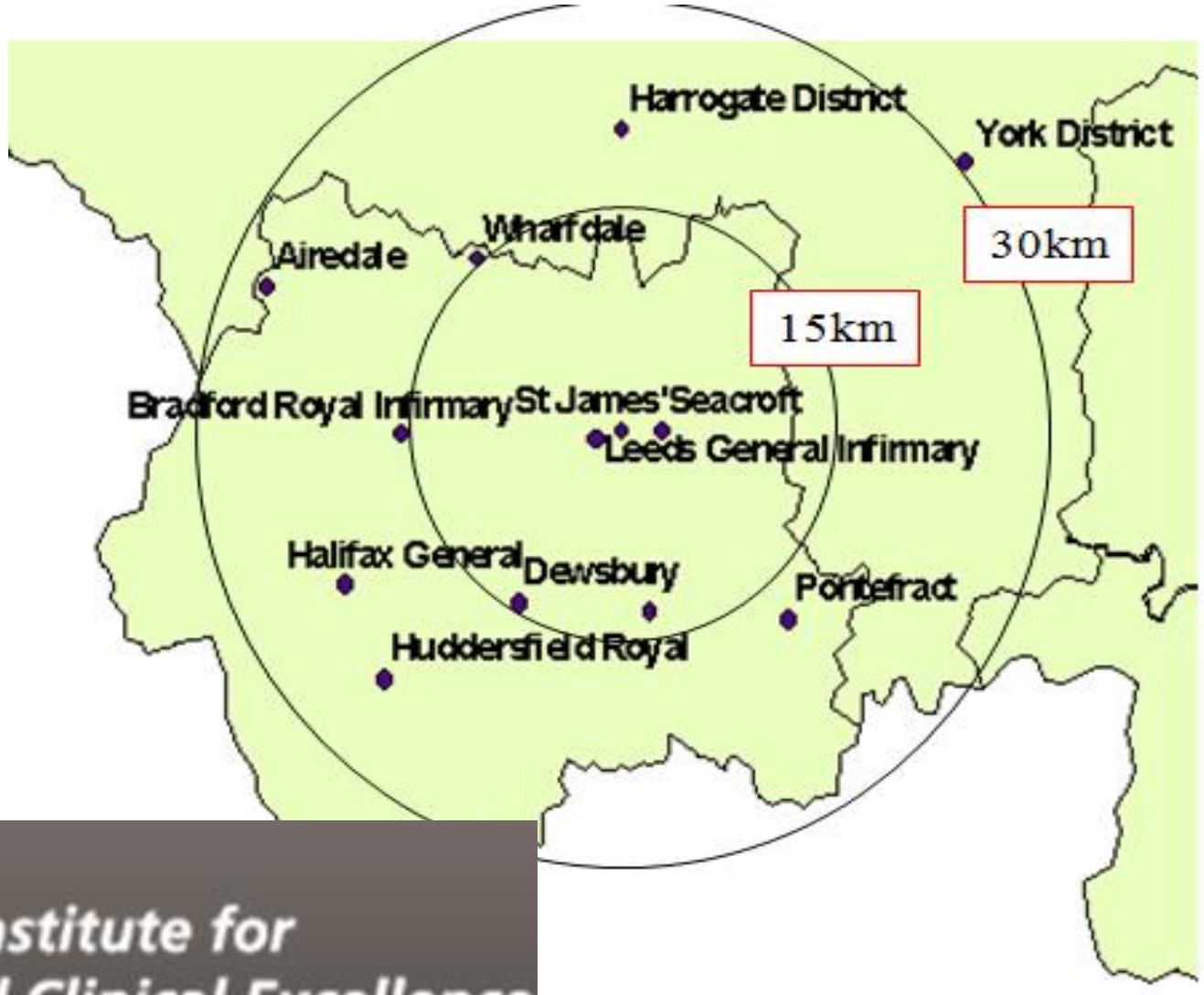
West Yorkshire Cardiovascular Network
Stroke and Cardiac Networks

Baseline secondary prevention use for myocardial infarction in 1996 vs 2006 & total mortality



West Yorkshire Region (UK)

Evaluation of Methods and Management of Acute Coronary Events
EMMACE-2



NHS
National Institute for
Health and Clinical Excellence

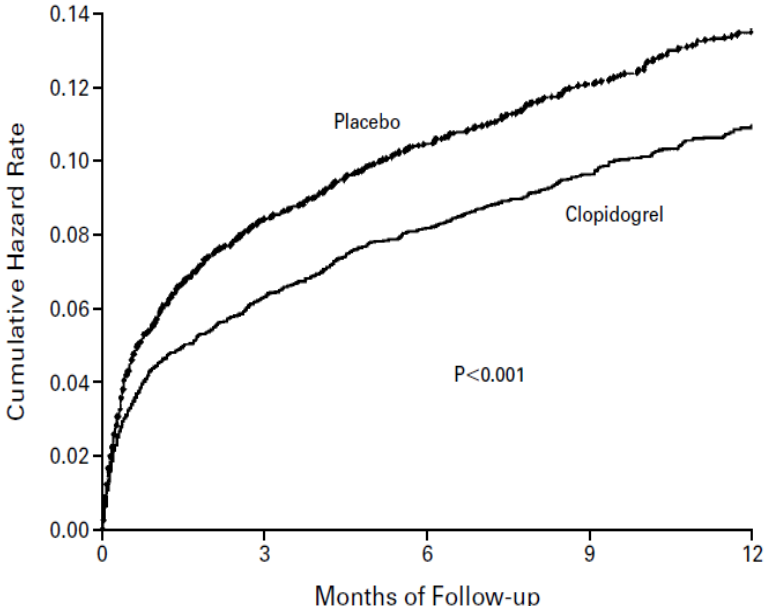
EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL INVESTIGATORS*

Study Patients

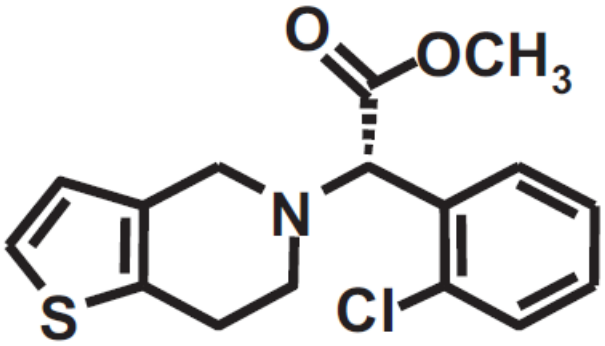
Patients were eligible for the study if they had been hospitalized within 24 hours after the onset of symptoms and did not have ST-segment elevation.

We excluded patients with contraindications to antithrombotic or antiplatelet therapy, those who were at high risk for bleeding or severe heart failure, those who were taking oral anticoagulants, and those who had undergone coronary revascularization in the previous three months or had received intravenous glycoprotein IIb/IIIa receptor inhibitors in the previous three days.

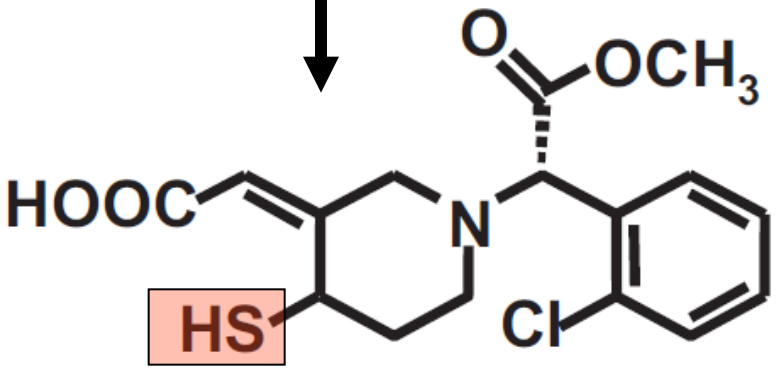


OUTCOME	CLOPIDOGREL GROUP (N=6259)	PLACEBO GROUP (N=6303)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
First primary outcome: nonfatal myocardial infarction, stroke, or death from cardiovascular causes	582 (9.3)	719 (11.4)	0.80 (0.72–0.90)	<0.001

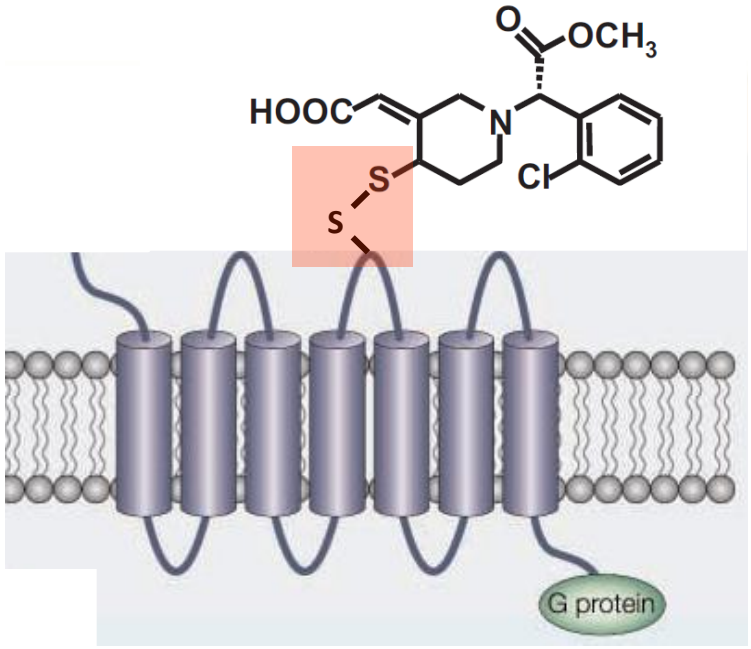
$P2Y_{12}$ ADP receptor inhibition by clopidogrel



Clopidogrel (prodrug)

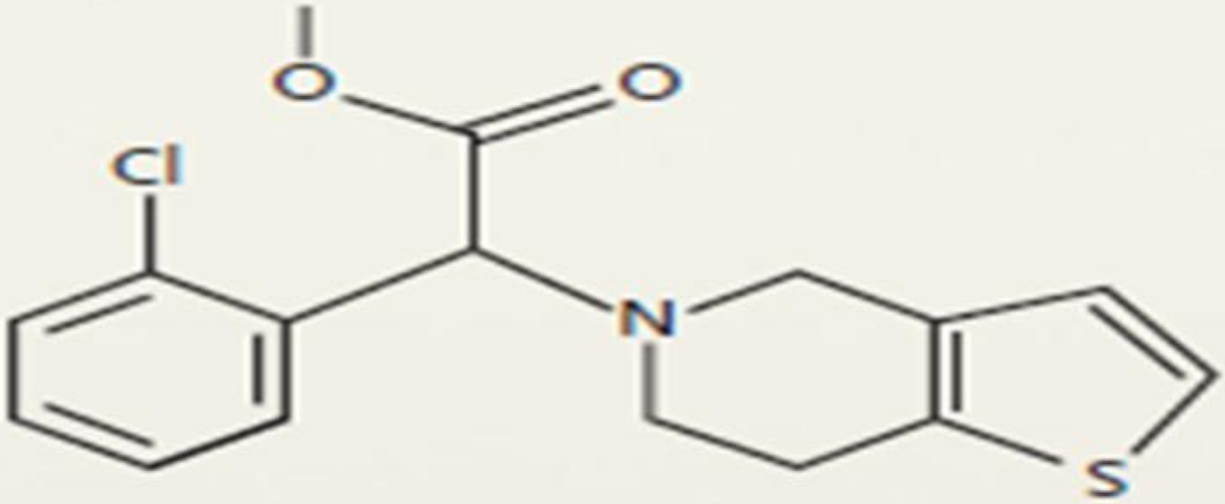


Clopidogrel (active metabolite)

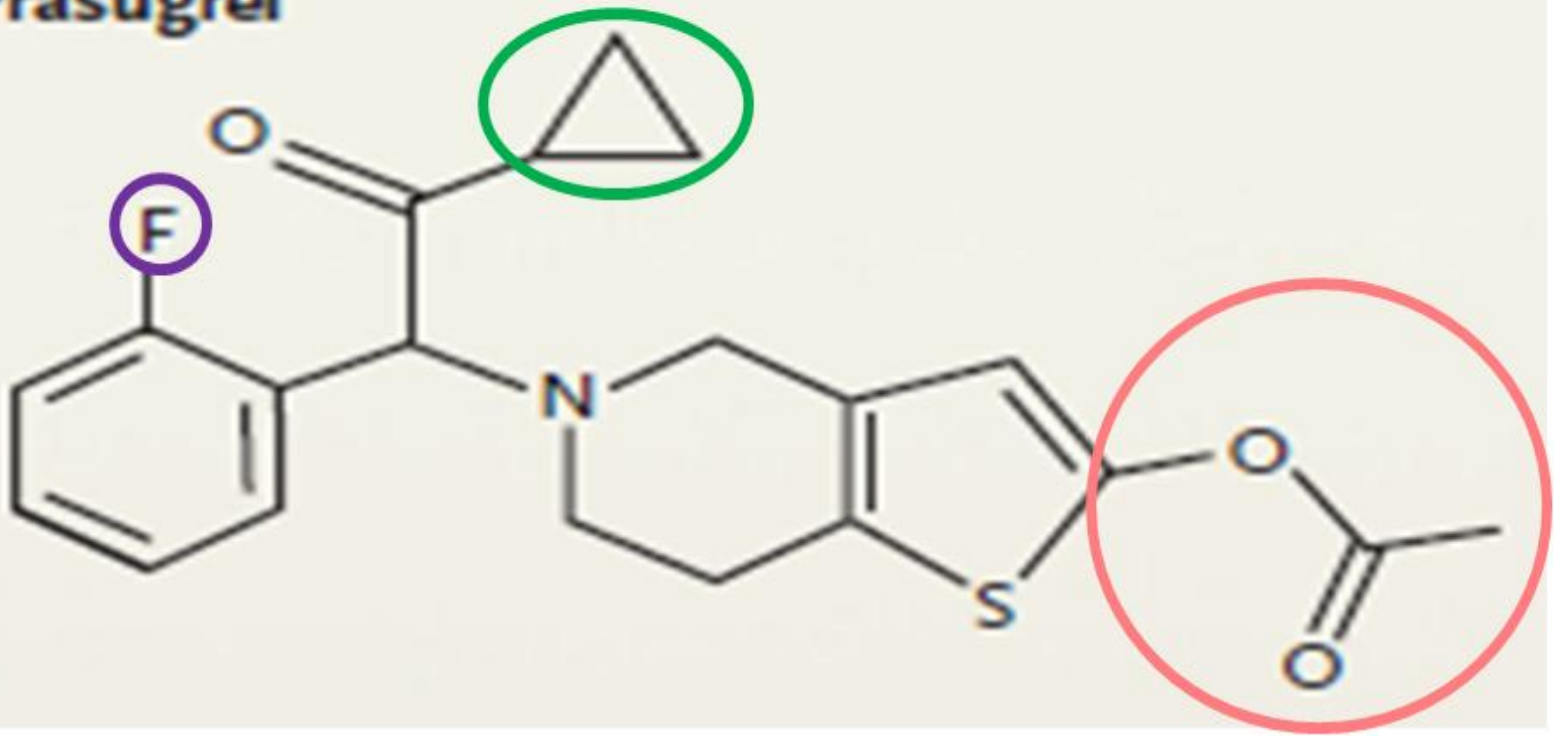


1. Irreversible inhibition of $P2Y_{12}$ receptor on platelet.
2. Requires synthesis of new platelets to overcome inhibition
3. Risk of bleeding

Clopidogrel



Prasugrel



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 15, 2007 VOL. 357 NO. 20

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

STUDY POPULATION

We enrolled 13,608 patients with acute coronary syndromes (representative of the entire spectrum of those syndromes) with scheduled PCI.

Use of aspirin was required, and a daily dose of 75 to 162 mg was recommended.

Key exclusion criteria included an increased risk of bleeding, anemia, thrombocytopenia, a history of pathologic intracranial findings, or the use of any thienopyridine within 5 days before enrollment.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Prasugrel (N=6813)	Clopidogrel (N=6795)
Unstable angina or NSTEMI (%)	74	74
STEMI (%)	26	26
Index procedure (%)		
PCI	99	99
CABG	1	1
Timing of study-drug administration (%)¶		
Before PCI	26	25
During PCI	73	74
After PCI	1	1

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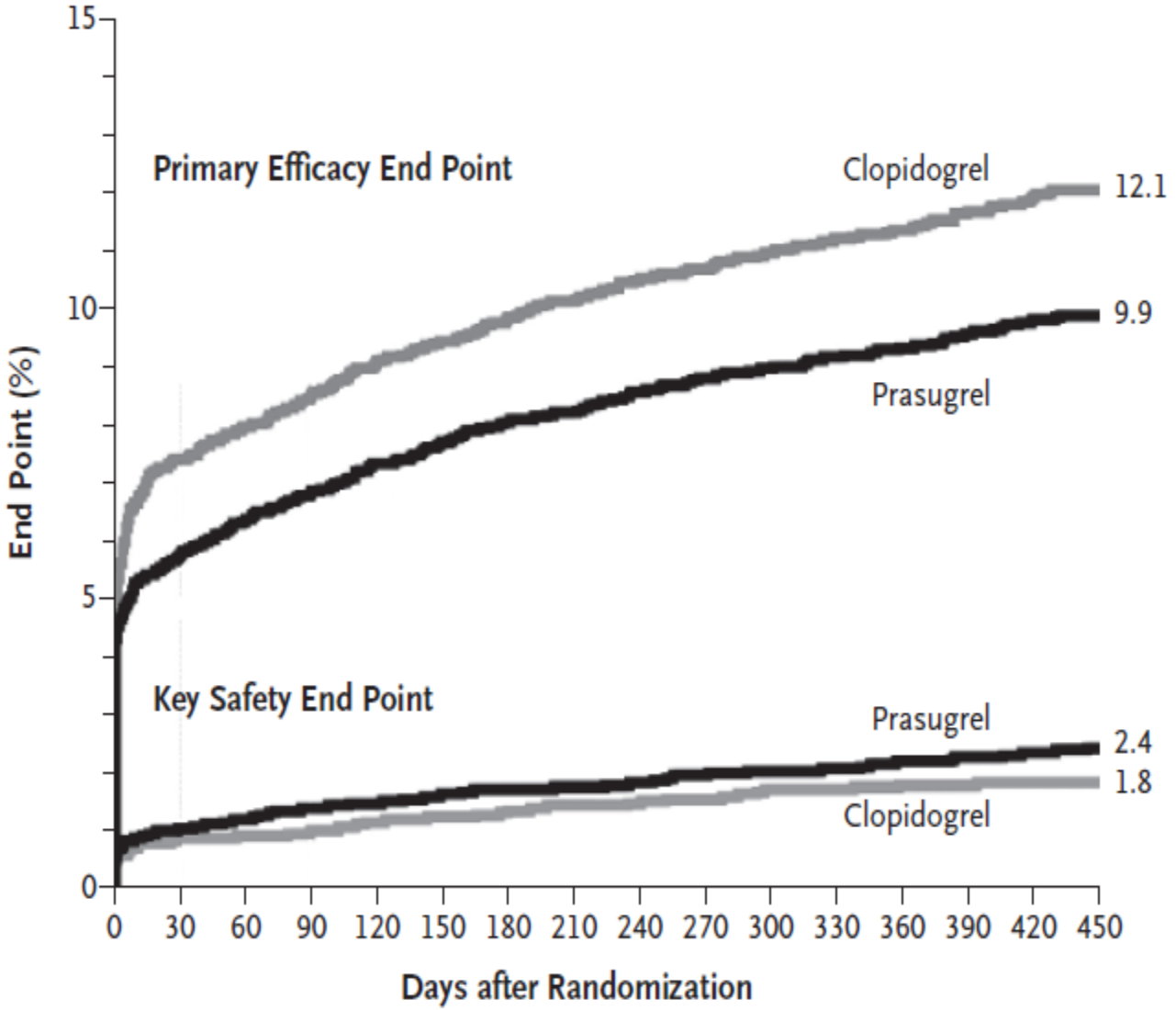


↓ 138 Events

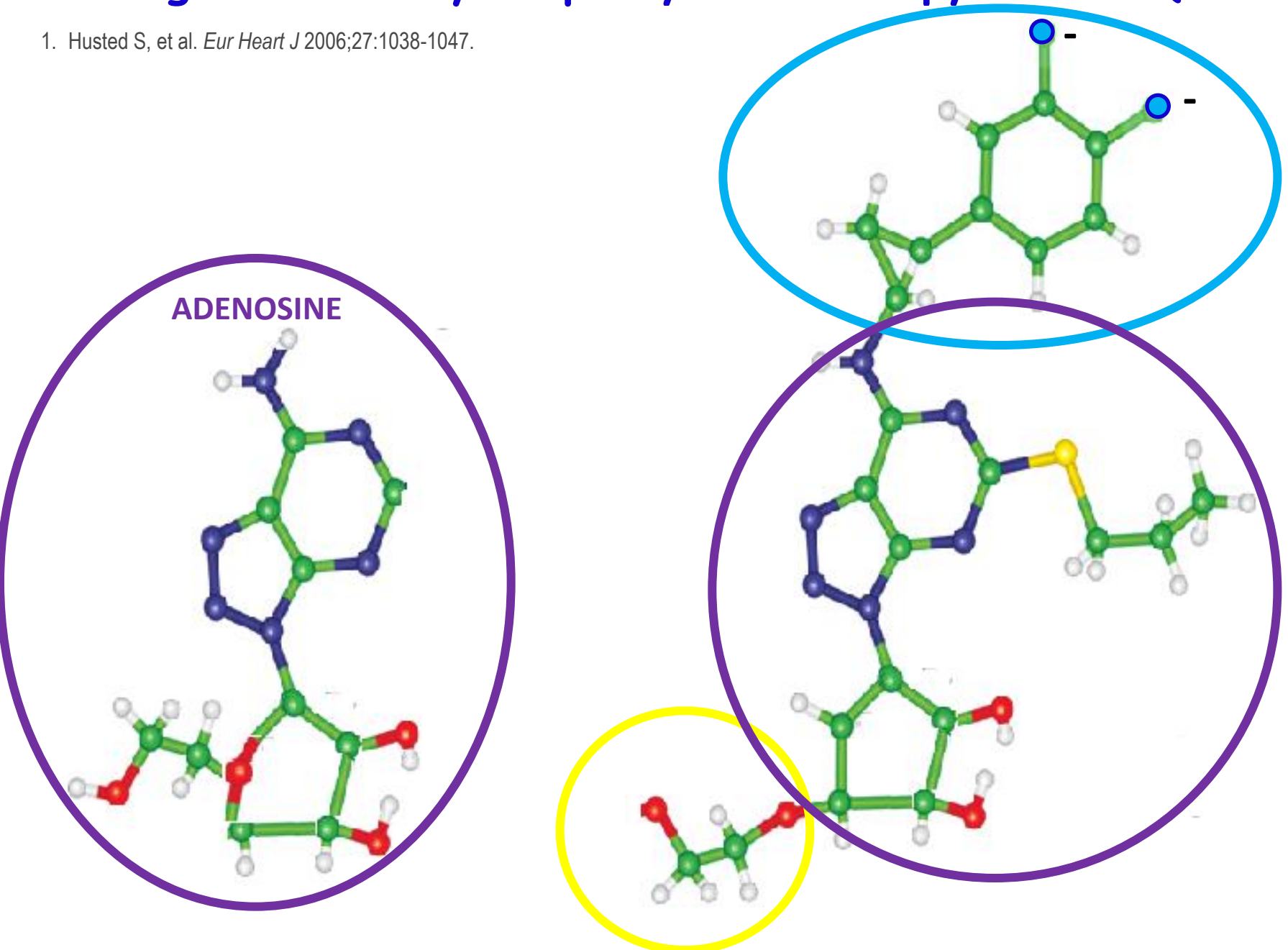
Hazard ratio, 0.81;
95% CI, 0.73–0.90;
P<0.001

↑ 35 Events

Hazard ratio, 1.32;
95% CI, 1.03–1.68;
P=0.03

Ticagrelor is a Cyclo-pentyl-triazolo-pyrimidine (CPTP)[1]

1. Husted S, et al. *Eur Heart J* 2006;27:1038-1047.



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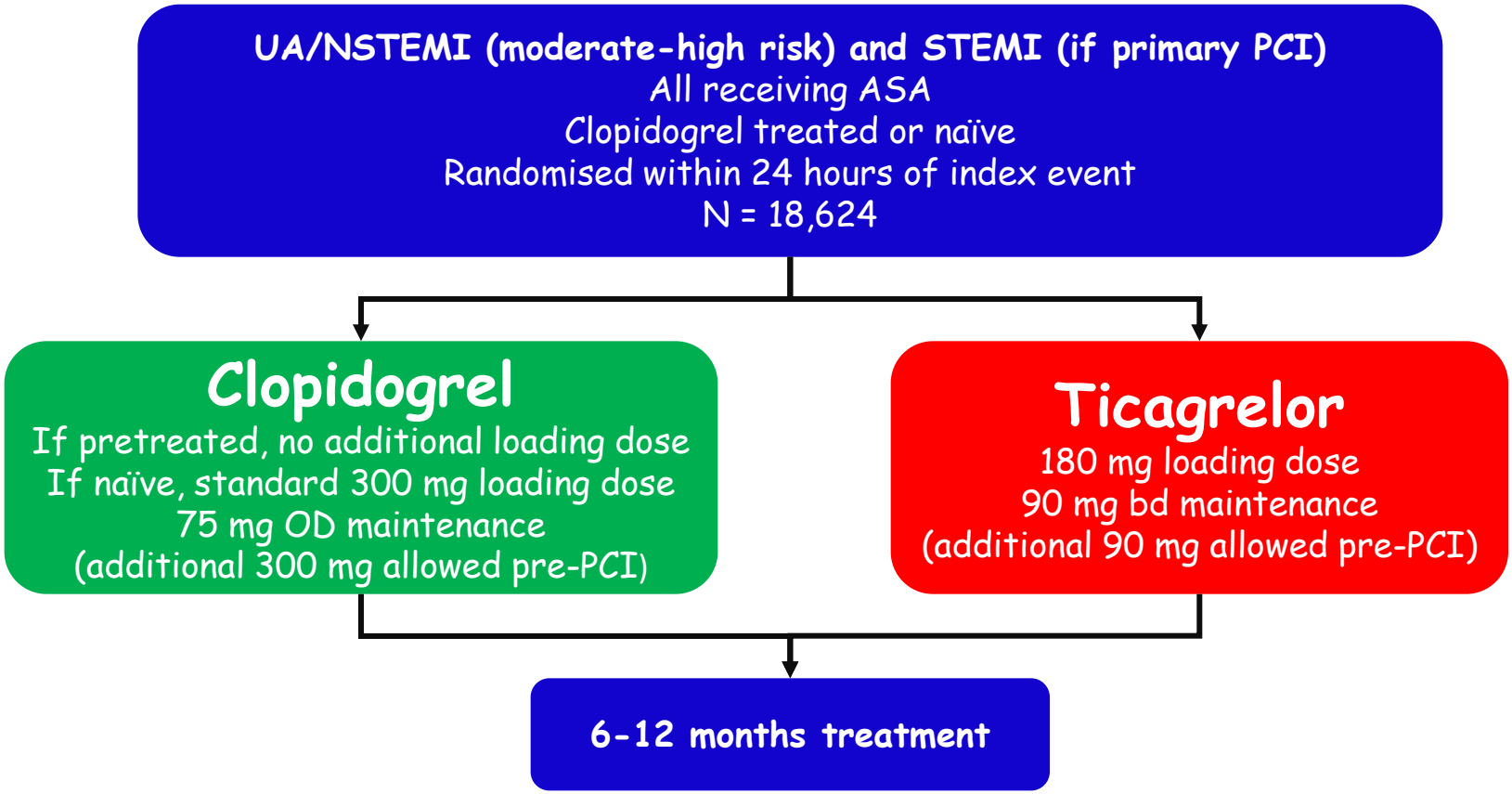
Platelet inhibition and patient Outcomes: Study design



1. Adapted from James S, et al. *Am Heart J* 2009;157:599-605.
2. Adapted from Wallentin L, et al. *N Eng J Med* 2009; 361(11):1045-1057.

PLATO study
Primary efficacy and safety endpoints

Primary efficacy endpoint

Time to first occurrence of **death from vascular causes, stroke or MI**

Primary safety endpoint

Time to first occurrence of any **major bleeding**

1.James S, et al. *Am Heart J* 2009;157:599-605.

PLATO: Inclusion Criteria

ACS without ST-segment elevation,

- ST-segment changes on electrocardiography, indicating ischaemia
- A positive test of a biomarker, indicating myocardial necrosis
- Or one of several risk factors

ACS with ST-segment elevation,

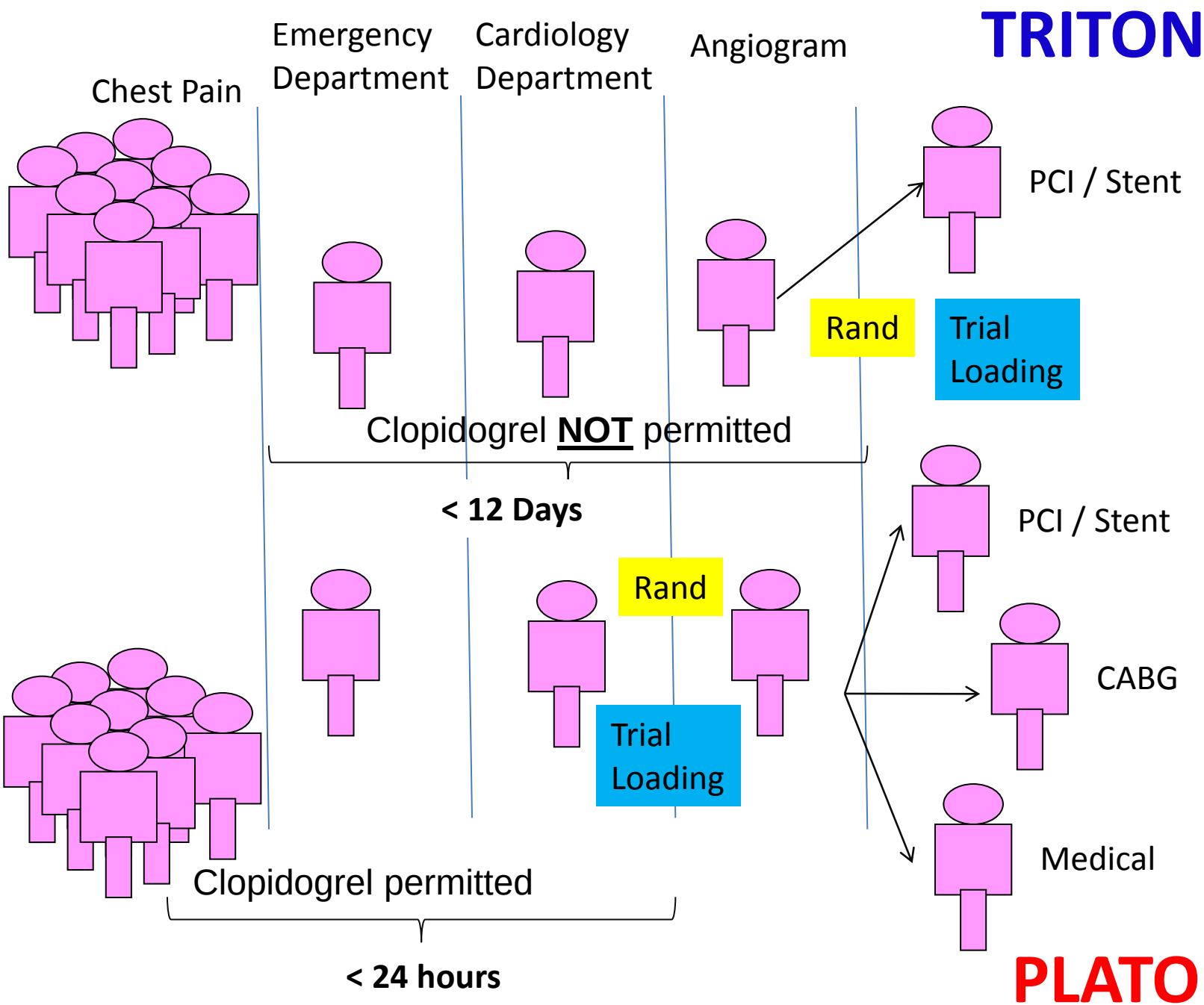
- Persistent ST-segment elevation of at least 0.1 mV in at least two contiguous leads or a new left bundle-branch block
- The intention to perform primary PCI

James S, et al. *Am Heart J* 2009;157:599-605

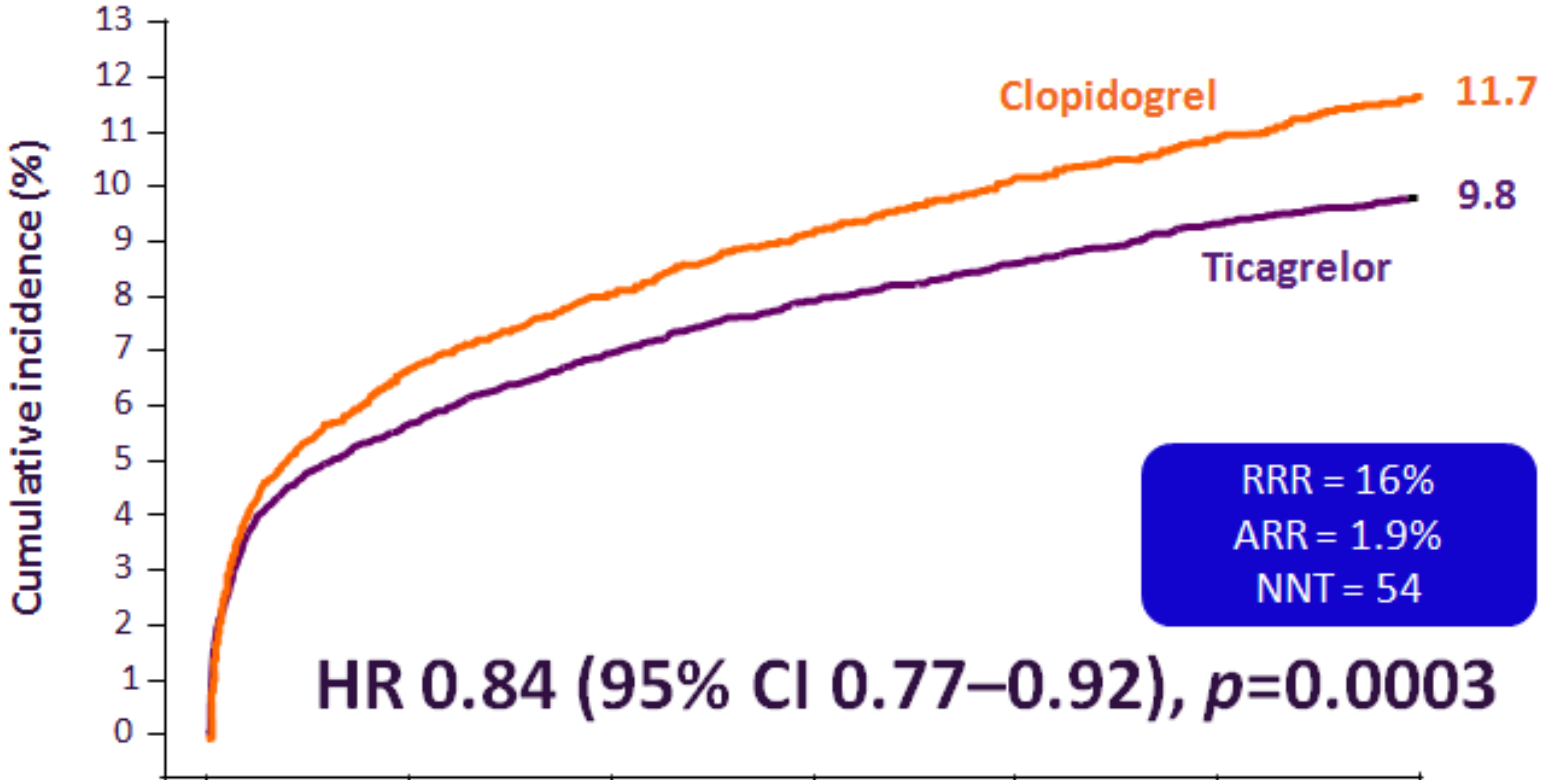
PLATO: Exclusion Criteria

- **Major exclusion criteria were:**[1]
  - Any contraindication to the use of clopidogrel
  - Fibrinolytic therapy within the previous 24 hours before randomisation
  - A need for oral anticoagulation therapy
  - An increased risk of bradycardia
  - Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer

James S, et al. *Am Heart J* 2009;157:599-605.


TRITON Trial
Chest Pain
Emergency Department
Cardiology Department
Angiogram
PCI / Stent
Rand
Trial Loading
Clopidogrel NOT permitted
< 12 Days
PCI / Stent
Rand
CABG
Trial Loading
Medical
Clopidogrel permitted
< 24 hours
PLATO Trial

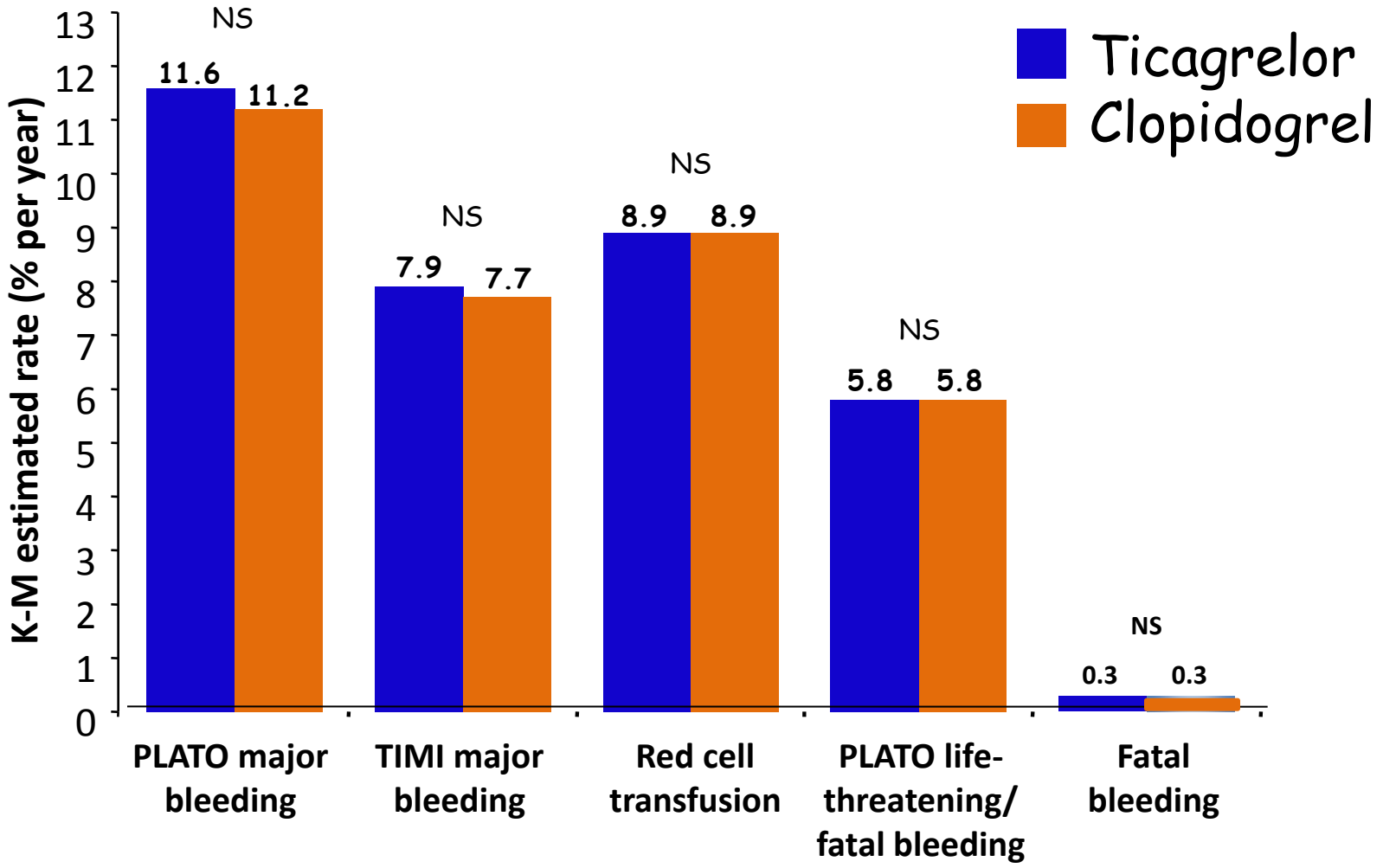
Kaplan-Meier estimate of time to first primary efficacy endpoint (composite of CV death, MI or stroke)[1]



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

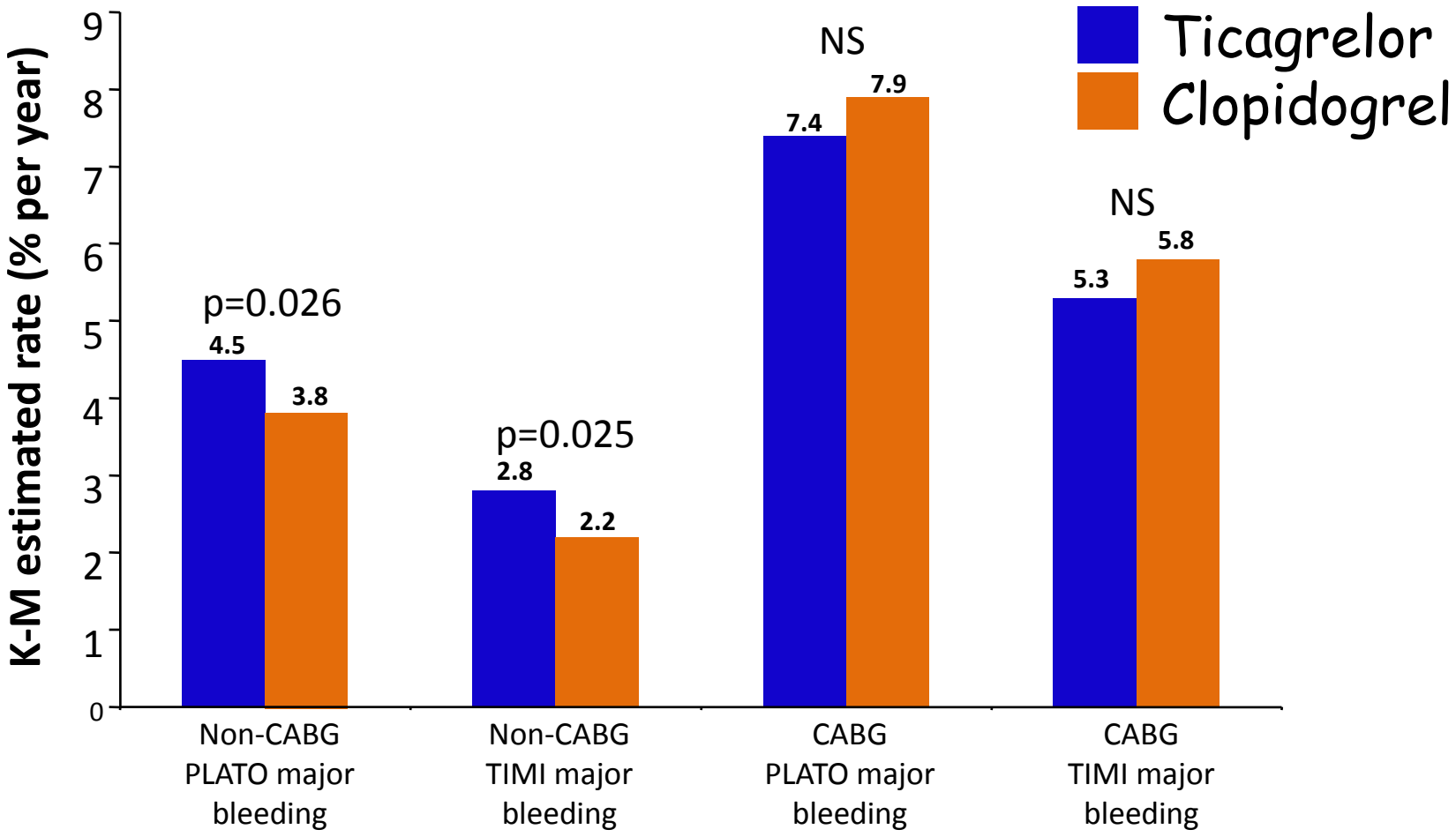
Wallentin L, et al. *N Engl J Med* 2009;361:1045-1057.

PLATO Major Bleeding



Wallentin L, et al. *N Engl J Med* 2009;361:1045-1057.

Non-CABG & CABG related bleeding



Wallentin L, et al. *N Engl J Med* 2009;361:1045-1057.

Major secondary efficacy endpoints

	Ticagrelor (n = 9333)	Clopidogrel (n = 9291)	HR (95% CI)	*p* value
Primary endpoint, n (%)*				
CV death + MI + stroke	864 (9.8)	1014 (11.7)	0.84 (0.77-0.92)	<0.001
Secondary endpoints, n (%)				
Total death + MI + stroke	901 (10.2)	1065 (12.3)	0.84 (0.77-0.92)	< 0.001
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	1290 (14.6)	1456 (16.7)	0.88 (0.81-0.95)	< 0.001
MI	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 (0.91-1.25)	0.22
Total death	399 (4.5)	506 (5.9)	0.78 (0.69-0.89)	<0.001†

* Percentages are Kaplan-Meier estimates of the endpoint at 12 months

† Nominal *p* value

Wallentin L, et al. *N Engl J Med* 2009;361:1045-1057.

Dyspnoea more frequent with ticagrelor treatment compared with clopidogrel

Dyspnoea[†], % [†] Most episodes of dyspnoea lasted less than a week	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	*p* value
Any	13.8	7.8	< 0.001
With discontinuation of study treatment	0.9	0.1	< 0.001

- Dyspnoea in patients receiving ticagrelor is usually mild or moderate in intensity and often resolves without the need for treatment discontinuation[2,3]
- Dyspnoea during ticagrelor treatment does not appear to be associated with any differences in efficacy or bleeding-related clinical outcomes compared with clopidogrel[2]
- In a pulmonary substudy (n = 199) of the PLATO trial, ticagrelor was not associated with any detectable detrimental effect on pulmonary function compared with clopidogrel[1]

1. Wallentin L, et al. *N Engl J Med* 2009;361:1045-1057
2. Storey RF, et al. Poster presented at European Society of Cardiology, Stockholm, Sweden, 28 August–1 September 2010.
3. Ticagrelor. Summary of product characteristics. 2010.

Holter monitoring and bradycardia-related events

	Ticagrelor (n = 1451)	Clopidogrel (n = 1415)	*p* value
Holter monitoring at first week, %			
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 = 1006)**	
Ventricular pauses ≥ 3 seconds	**2.1**	**1.7**	**0.52**
Ventricular pauses ≥ 5 seconds	**0.8**	**0.6**	**0.60**
Bradycardia-related events, %	**Ticagrelor (n = 9235)**	**Clopidogrel (n = 9186)**	
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**

1. Wallentin L, et al. *N Engl J Med* 2009;361:1045-1057.

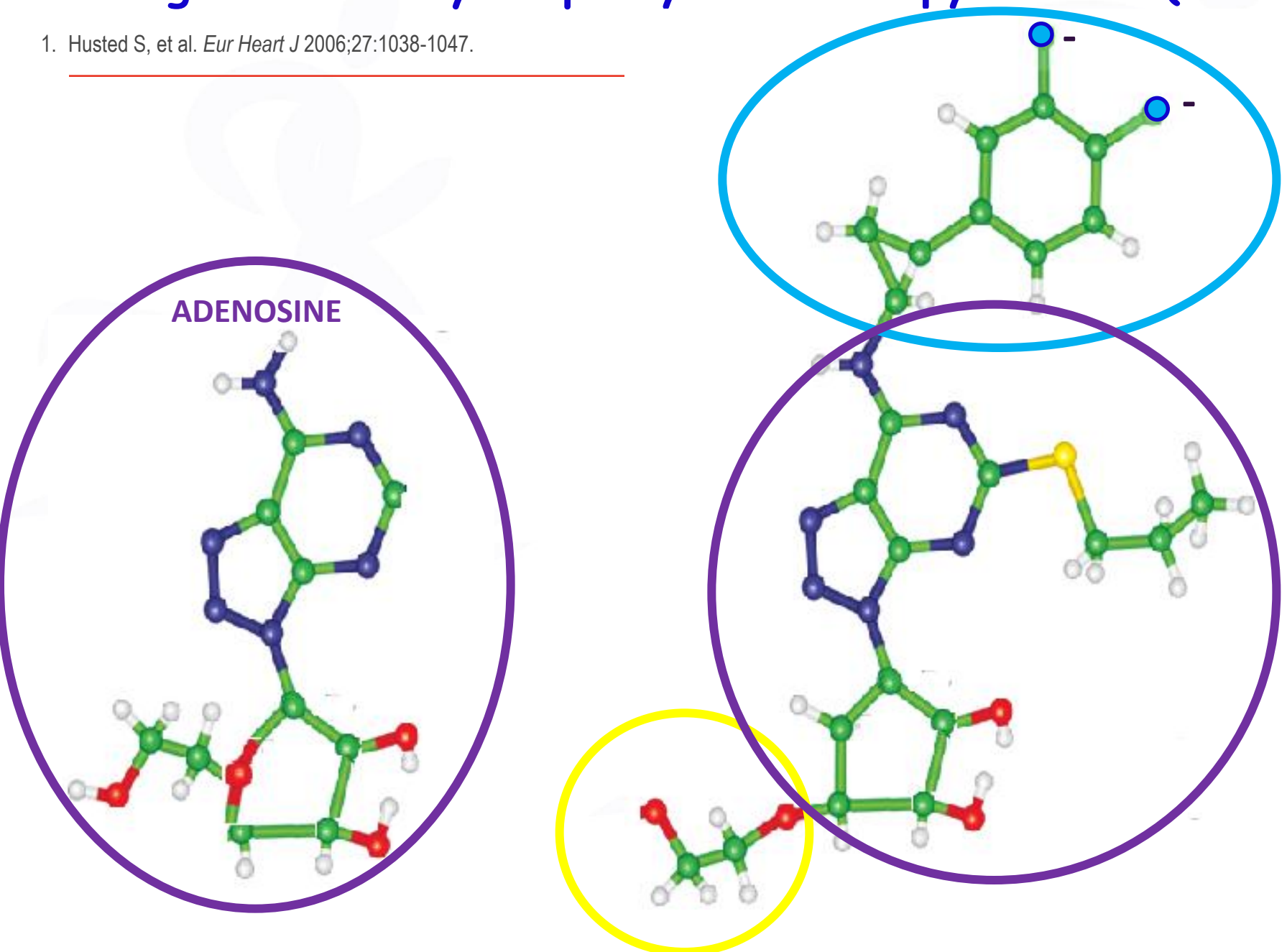
Other secondary safety endpoints

Endpoint	Ticagrelor (n = 9235)	Clopidogrel (n = 9186)	*p* value
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
Increases in serum uric acid from baseline value, %			
At 1 month	14 ± 46	7 ± 44	< 0.001
At 12 months	15 ± 52	7 ± 31	< 0.001
1 month after end of treatment	7 ± 43	8 ± 48	0.56
Increases in serum creatinine from baseline value, %			
At 1 month	10 ± 22	8 ± 21	< 0.001
At 12 months	11 ± 22	9 ± 22	< 0.001
1 month after end of treatment	10 ± 22	10 ± 22	0.59

1. Wallentin L, et al. *N Engl J Med* 2009;361:1045-1057.

Ticagrelor is a Cyclo-pentyl-triazolo-pyrimidine (CPTP)[1]

1. Husted S, et al. *Eur Heart J* 2006;27:1038-1047.



ESC Guidelines recommend ticagrelor as a 1st line therapy in patients with NSTE-ACS at moderate-to-high risk of an ischemic event

ESC Guidelines for management of patients with NSTE-ACS

OAP	Recommendation	Class†	Level†
Ticagrelor	Recommended for all patients at moderate-to-high risk of ischemic events, regardless of initial treatment strategy and including those pre-treated with clopidogrel	1	B
Clopidogrel (300-mg LD, 75-mg MD)	Recommended for patients who cannot receive ticagrelor or prasugrel	1	A
Clopidogrel 600-mg LD (or supplementary 300-mg dose at PCI following initial 300-mg LD)	Recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option	1	B
Prasugrel	Recommended for $P2Y_{12}$-inhibitor-naive patients (esp. diabetics) with known coronary anatomy and who are proceeding to PCI bb unless there is a high-risk of life-threatening bleeding or other contraindicatIons	1	B
Ticagrelor and clopidogrel	Should be considered to be (re)started after CABG surgery as soon as considered safe	2a	B

*Class I recognizes "evidence and/or general agreement that given the treatment or procedure is beneficial, useful, and effective" treatment option for first-line use in these patients.
Class 2a indicates the weight of evidence/opinion is in favour of usefulness/efficacy.

†Level A is based on data derived from multiple randomized clinical trials or meta-analyses. Level B is based on data derived from a single randomized clinical trial or large non-
randomized studies. Level C is based on the consensus of opinion of the experts and/or small studies, retrospective studies,registries.

Eur Heart J. doi:10.1093/eurheartj/ehr236.

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UK NICE GUIDANCE

Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option **in adults with acute coronary syndromes** (ACS) that is, people:

with ST-segment-elevation myocardial infarction **(STEMI)** – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary percutaneous coronary intervention (PCI) or

with non-ST-segment-elevation myocardial infarction (NSTEMI) or
admitted to hospital with *unstable angina* – defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus one of the characteristics defined in section 1.2

Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist.

NHS
National Institute for
Health and Clinical Excellence

UK NICE GUIDANCE

For the purposes of this guidance, characteristics to be used in defining treatment with ticagrelor for unstable angina are:

- age 60 years or older;
- previous myocardial infarction or previous coronary artery bypass grafting (CABG);
- coronary artery disease with stenosis of 50% or more in at least two vessels;
- previous ischaemic stroke;
- previous transient ischaemic attack, carotid stenosis of at least 50%, or cerebral revascularisation;
- diabetes mellitus;
- peripheral arterial disease;
- or chronic renal dysfunction, defined as a creatinine clearance of less than 60 ml per minute per 1.73 m^2 of body-surface area.

"Future of antiplatelet therapy in cardiology ?"

SUMMARY-1

Characteristics	Clopidogrel	Prasugrel	Ticagrelor
Direct acting	✗	✗	✓
Reversible binding to $P2Y_{12}$ receptor	✗	✗	✓
Rapid onset of action	✗	✓	✓
> 60% IPA (mean steady state)	✗	✓	✓
Consistent Response	✗	✓	✓

"Future of antiplatelet therapy in cardiology ?"

SUMMARY-2

PATIENTS INCLUDED	CURE Trial	TRITON TIMI-38	PLATO Trial
UA	✓	✓	✓
NSTEMI	✓	✓	✓
STEMI	✗	✓	✓
Managed medically	✓	✗	✓
Managed with PCI	✗	✓	✓
Managed with CABG	✗	✗	✓

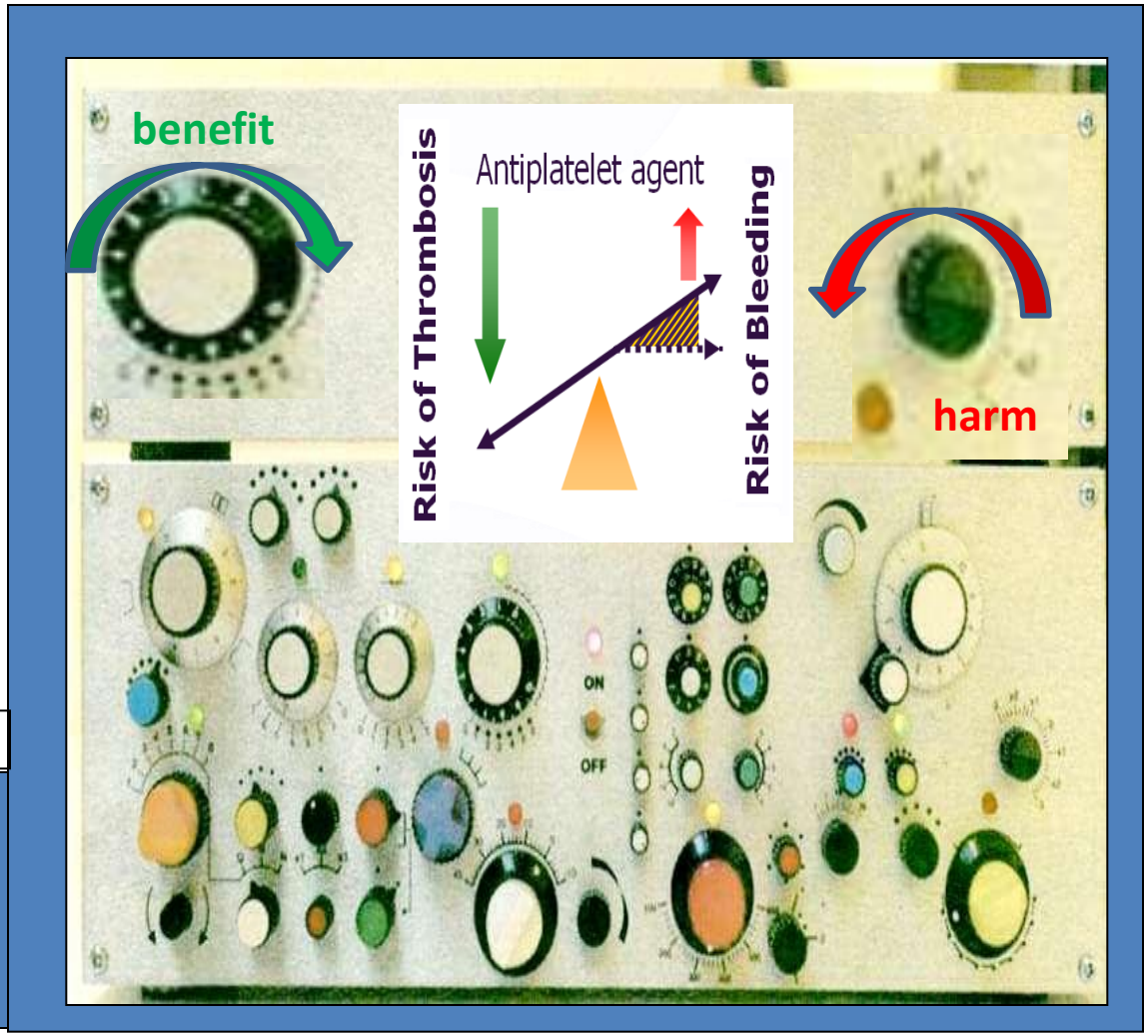
Note: Ticagrelor was not studied against prasugrel.

"Future of antiplatelet therapy in cardiology ?"

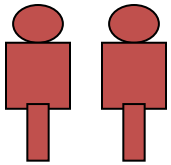
SUMMARY-3

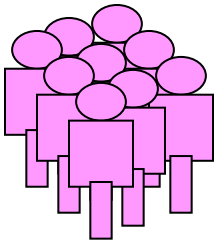
EFFICACY	CURE Trial	TRITON TIMI-38	PLATO Trial
All Death	✗	✗	✓
CV Death	✗	✗	✓
Myocardial Infarct	✓	✓	✓
Stroke	✗	✗	✗
CV Death / MI / Stroke	✓	✓	✓
SAFETY			
Major Bleeding	✗	✗	✓

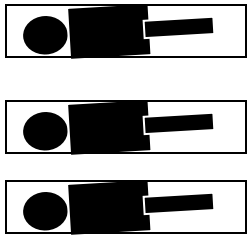
Note: Ticagrelor was not studied against prasugrel.


benefit
Antiplatelet agent
Risk of Thrombosis
Risk of Bleeding
harm
ON
OFF

Hospital





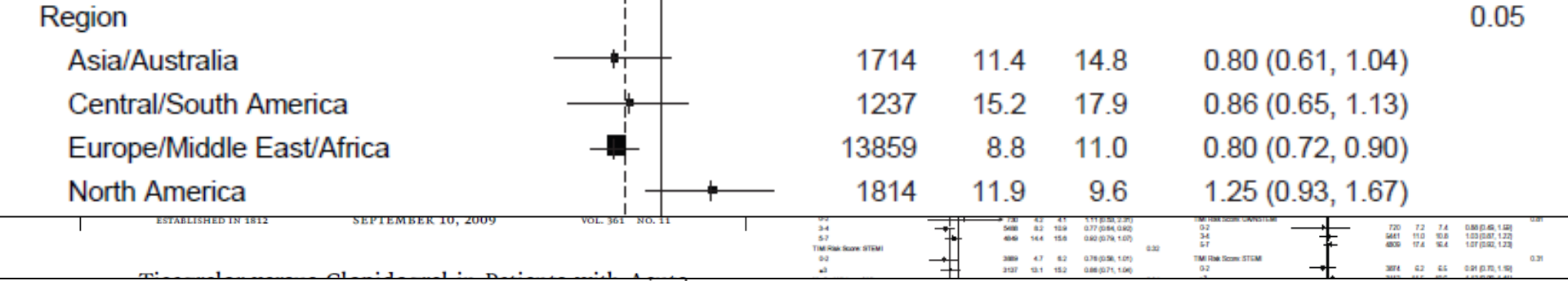


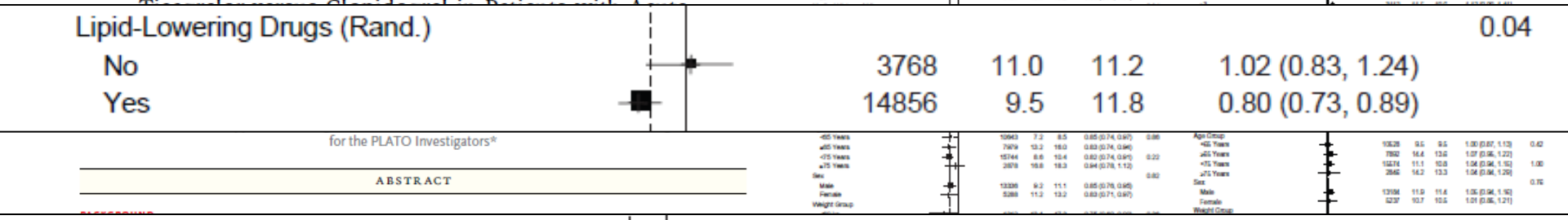
ALPIC, Motsovo 28th January 2012

"New reversible antagonists of the ADP receptor P2Y12: Clinical benefits & unanswered questions"

Alistair S Hall
MB ChB PhD FRCP
Professor of Clinical Cardiology
Head of Division of Epidemiology
Cardiovascular Research Lead for West Yorkshire, UK

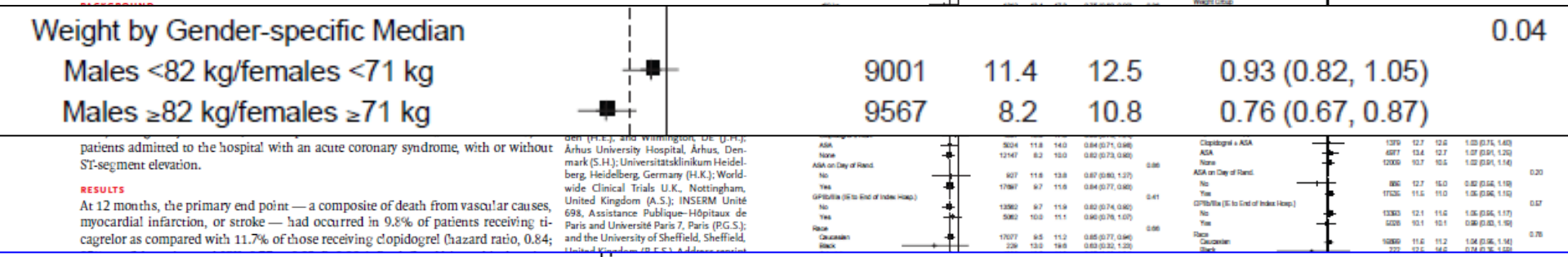
West Yorkshire Cardiovascular Network
Stroke and Cardiac Networks





for the PLATO Investigators*

ABSTRACT

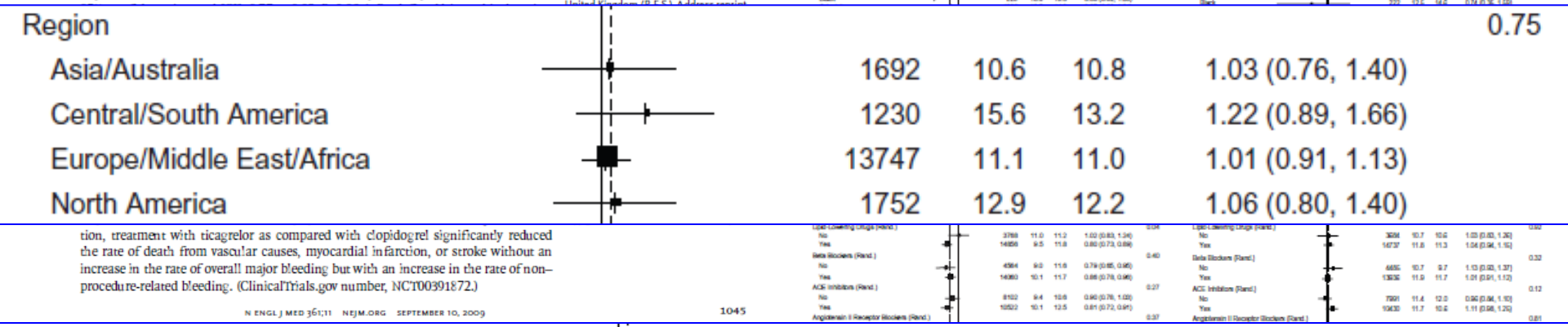


patients admitted to the hospital with an acute coronary syndrome, with or without ST-segment elevation.

RESULTS

At 12 months, the primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (hazard ratio, 0.84;

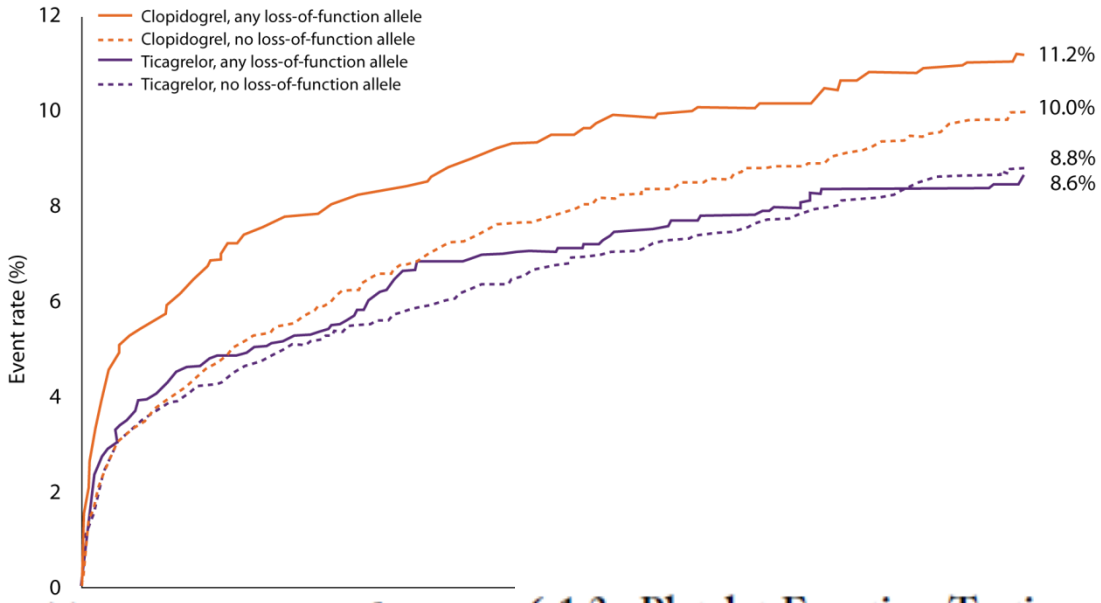
ben (H.E.), and Wiltshire, UK (J.H.); Århus University Hospital, Århus, Denmark (S.H.); Universitätsklinikum Heidelberg, Heidelberg, Germany (H.K.); Worldwide Clinical Trials U.K., Nottingham, United Kingdom (A.S.); INSERM Unité 698, Assistance Publique–Hôpitaux de Paris and Université Paris 7, Paris (P.G.S.); and the University of Sheffield, Sheffield,



tion, treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non–procedure-related bleeding. (ClinicalTrials.gov number, NCT00391872.)

PLATO substudy - Ticagrelor reduction in primary end point regardless of genetic variability

Kaplan-Meier estimates of events of the primary efficacy outcome in relation to the *CYP2C19* genotype[1]



6.1.2. Clopidogrel Genetic Testing: Recommendations

CLASS IIb

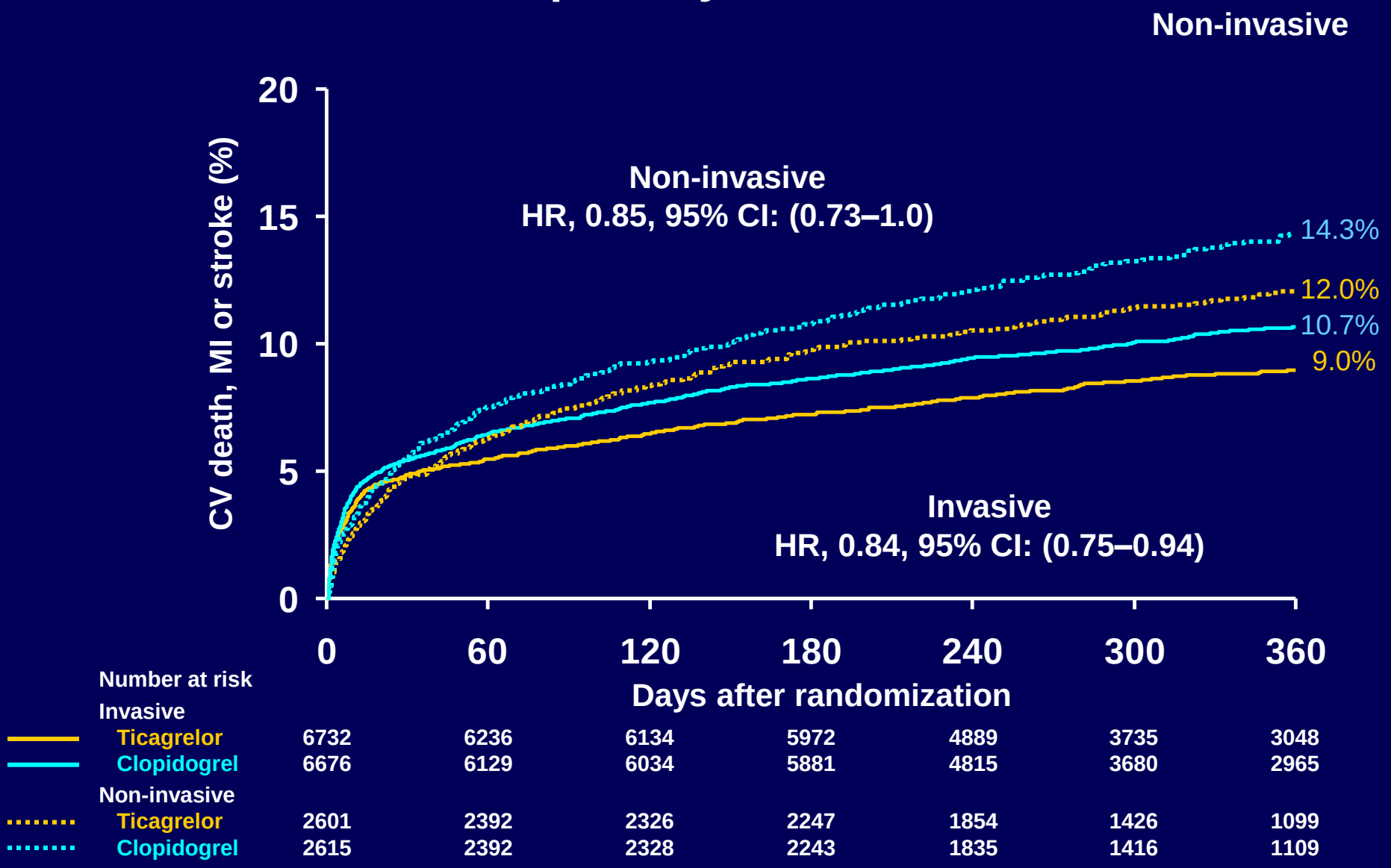
1. Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel (829). *(Level of Evidence: C)*
2. When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternate $P2Y_{12}$ inhibitor (e.g., prasugrel or ticagrelor) might be considered (829). *(Level of Evidence: C)*

6.1.3. Platelet Function Testing: Recommendations

CLASS IIb

1. Platelet function testing may be considered in patients at high risk for poor clinical outcomes (829). *(Level of Evidence: C)*
2. In patients treated with clopidogrel with high platelet reactivity, alternative agents, such as prasugrel or ticagrelor, might be considered (829). *(Level of Evidence: C)*

PLATO Non-invasive: primary outcome



James S et al. ESC abstract 2010