Ранната, агресивна и продължителна антиагрегантна терапия благоприятства всички пациенти с ОКС

Против

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А. Постаджиян, дм

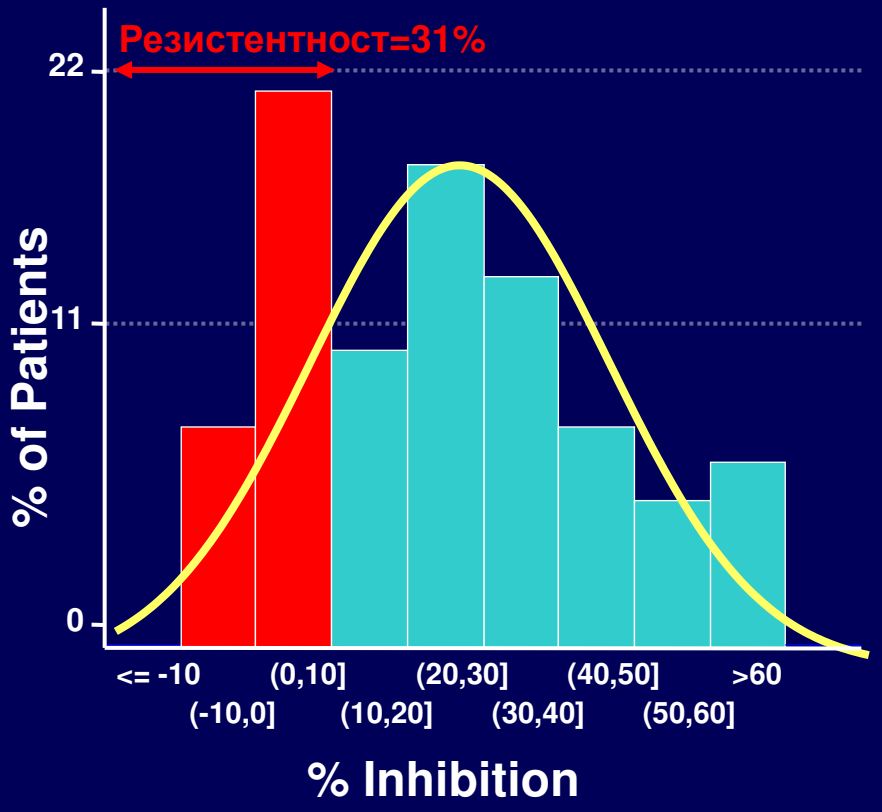
През последните 5 години
съм бил консултант/лектор
на следните фармацевтични
фирми

AstraZeneca,
Amgen,
Actavis
Bayer
Merck
Boehringer Ingelheim
Servier
Berlin Chemie
Sanofi Aventis
Pfizer
Gedeon Richter

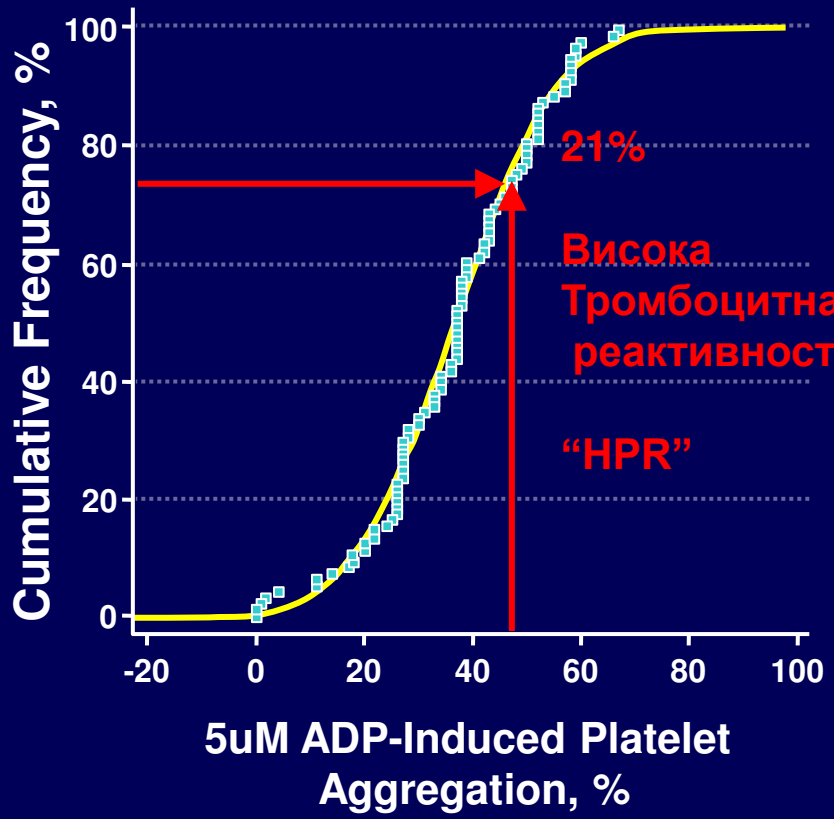
1) Тромбоцитната инхибиция с Clopidogrel е непредсказуема

2) Тромбоцитната реактивност в хода на терапия с Clopidogrel е непредсказуема

LTA at 5 Days[1]



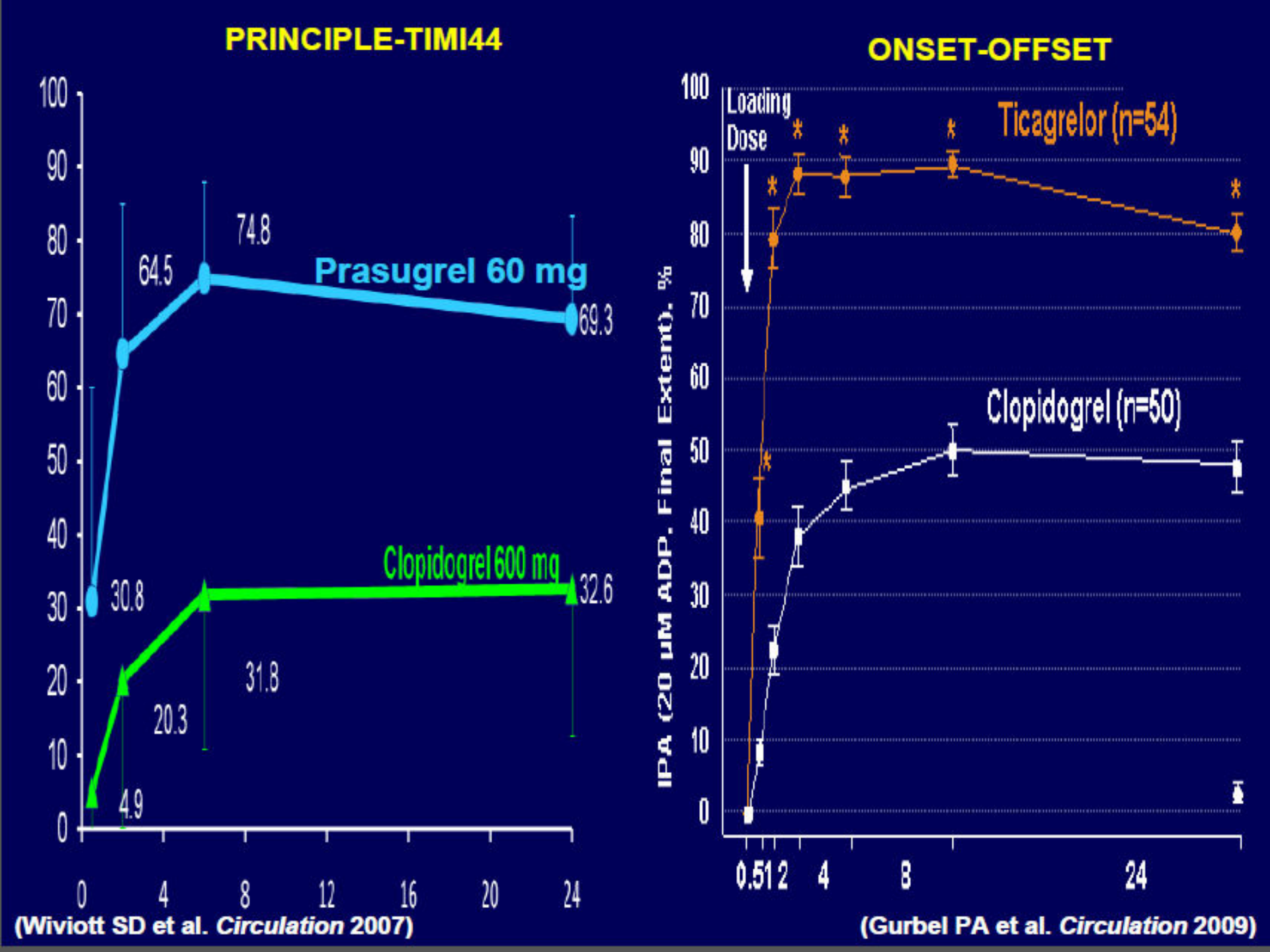
LTA on Chronic MD (75 mg)[2]



Clopidogrel има нищожен антиагрегантен ефект при ~1/3 от пациентите

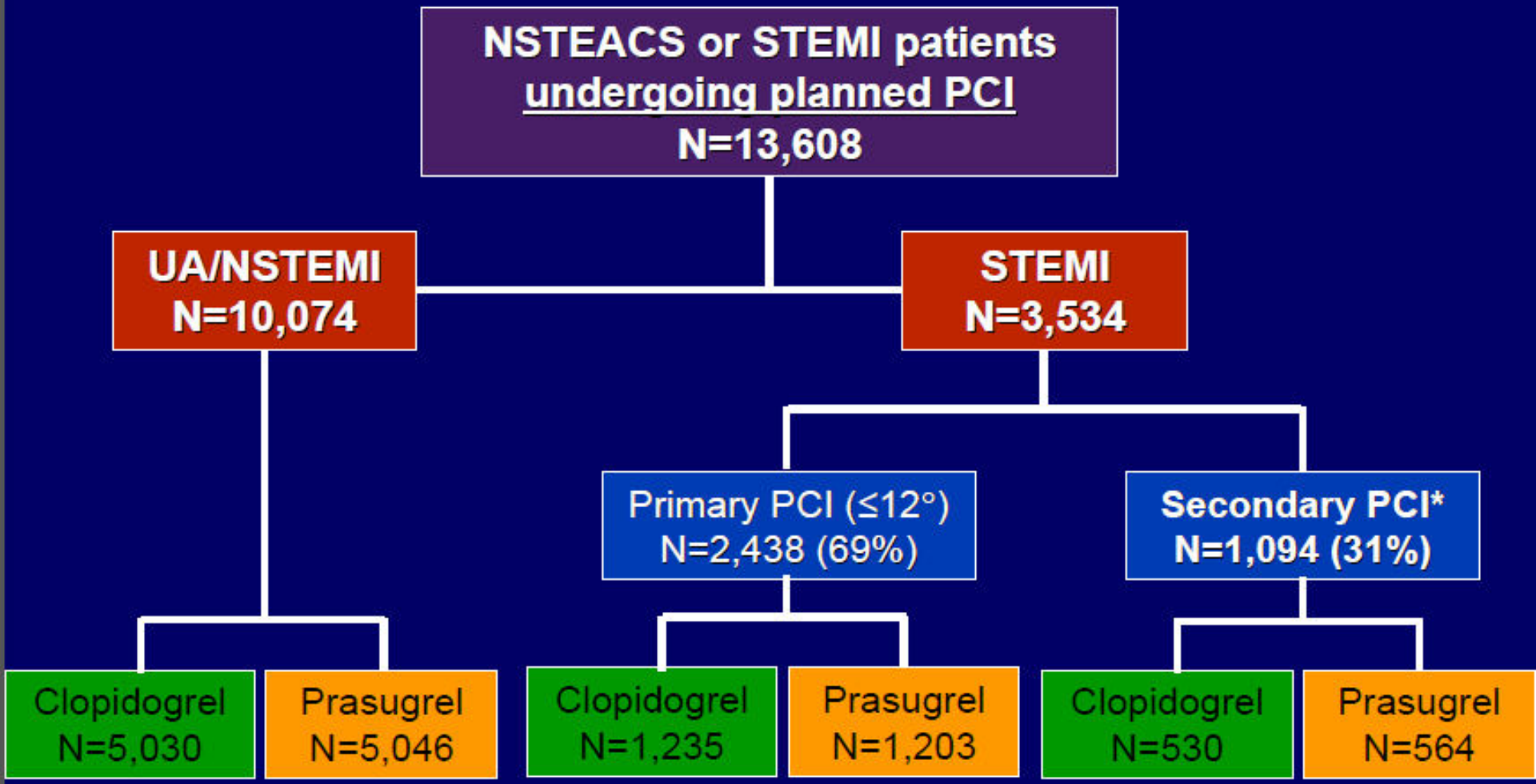
HPR, high-platelet reactivity; LTA, light transmission aggregometry.

1. Gurbel PA, et al. *Circulation*. 2003;107: 2908-13. 2. Adapted from Bliden KP, et al. *J Am Coll Cardiol*. 2007;49:657-66.


PRINCIPLE-TIMI44
100
90
80
70
60
50
40
30
20
10
0
64.5
74.8
Prasugrel 60 mg
69.3
Clopidogrel 600 mg
30.8
32.6
31.8
20.3
4.9
0
4
8
12
16
20
24
(Wiviott SD et al. Circulation 2007)
ONSET-OFFSET
IPA (20 µM ADP, Final Extent), %
Loading Dose
Ticagrelor (n=54)
Clopidogrel (n=50)
0.5
1
2
4
8
24
(Gurbel PA et al. Circulation 2009)

TRITON TIMI-38

Patient Flow

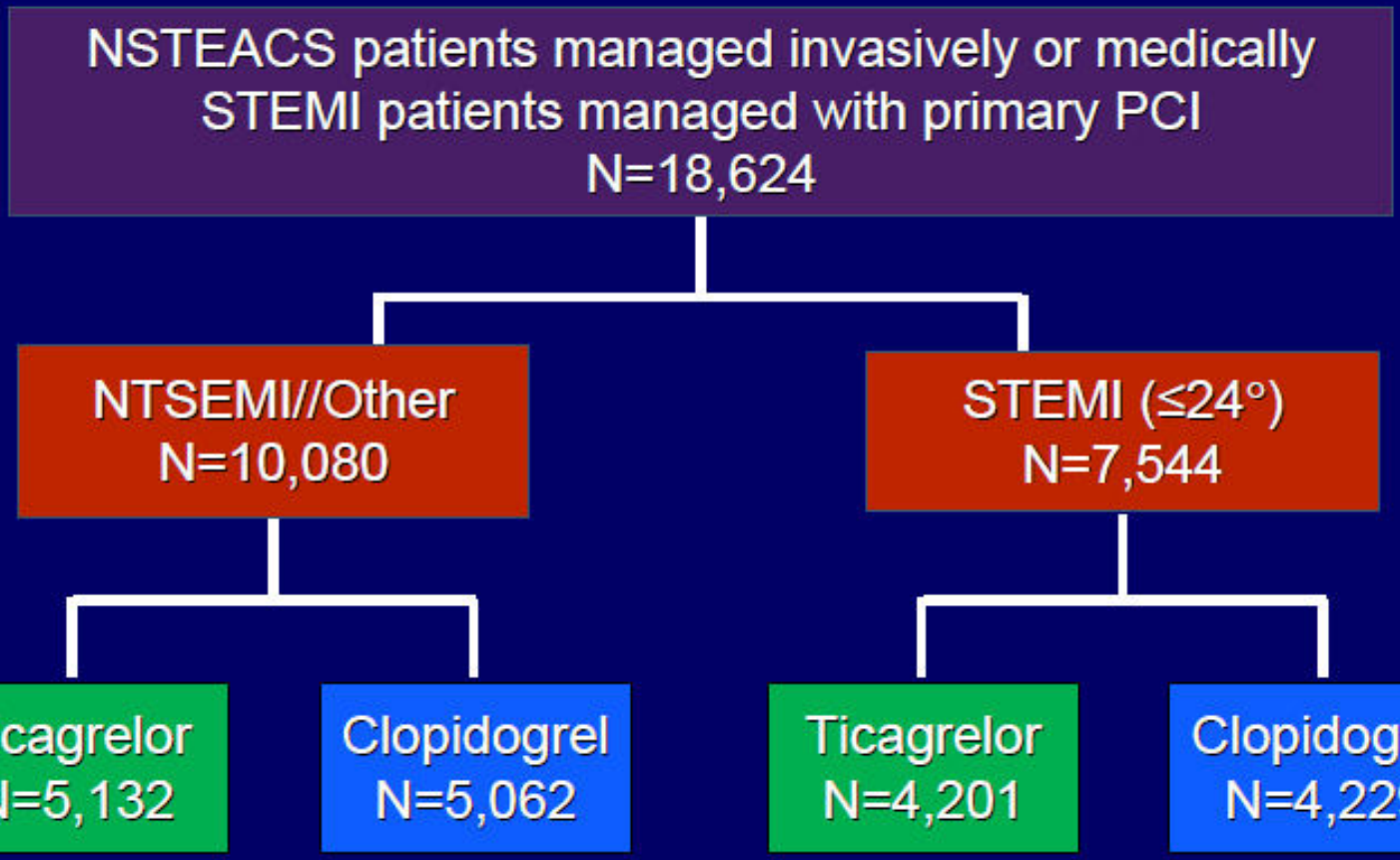


*enrolled between 12 h and 14 days after symptom onset

Note: Pts were not pre-loaded prior to angiography, except a minority with primary PCI

Montalescot G et al. Lancet 2009;373:723-31

Patient Flow

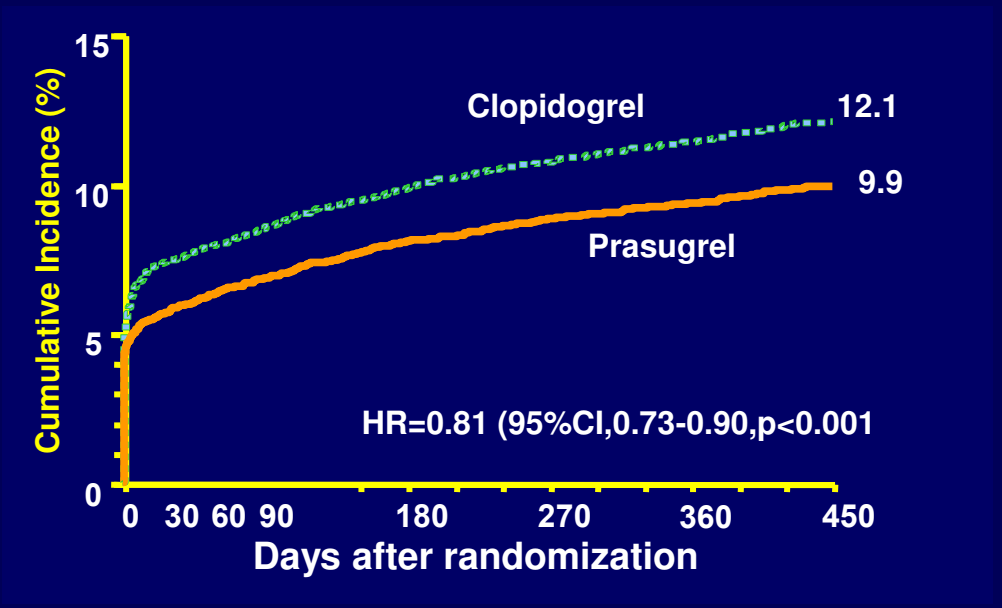


Note: Pts were pre-loaded with 300-600 mg clopidogrel or 180 mg ticagrelor prior to angiography

Steg PG et al. Circulation. 2010;122:2131-2141

3) Prasugrel and Ticagrelor неопровержимо редуцират тромботичните инциденти при високорискови пациенти (n~32,000)

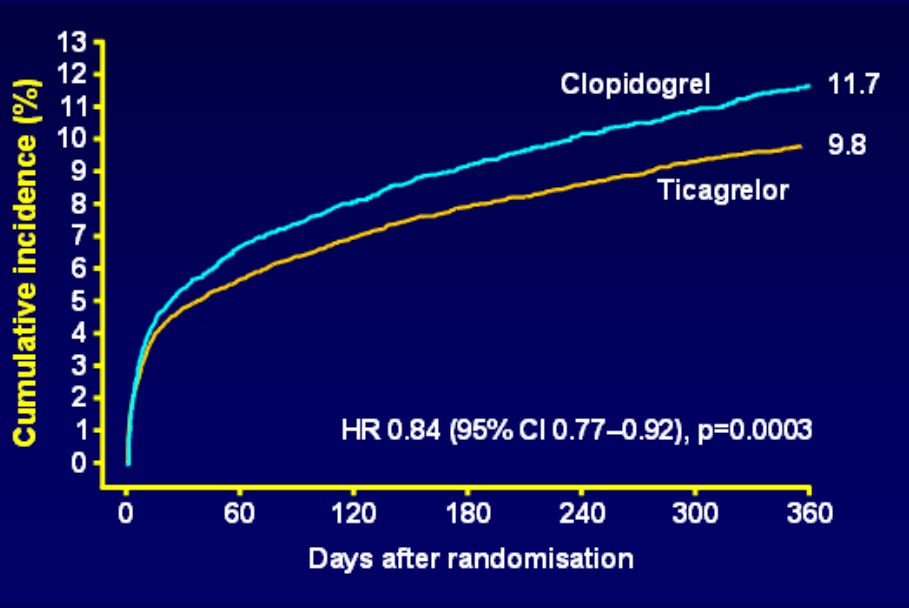
TRITON TIMI-38 n=13,608



Wiviott SD, et al. *N Engl J Med.* 2007;357:2001-15

Thienopyridine-Naïve ACS Patients Undergoing Planned PCI, Coroanry Anatomy Defined

PLATO n=18,624

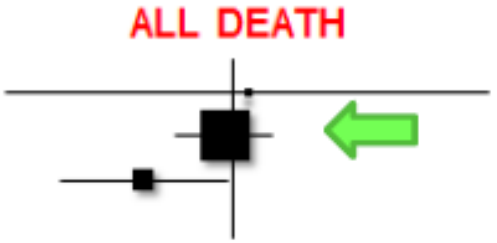


Wallentin L, et al. *N Engl J Med.* 2009;36:1045-57

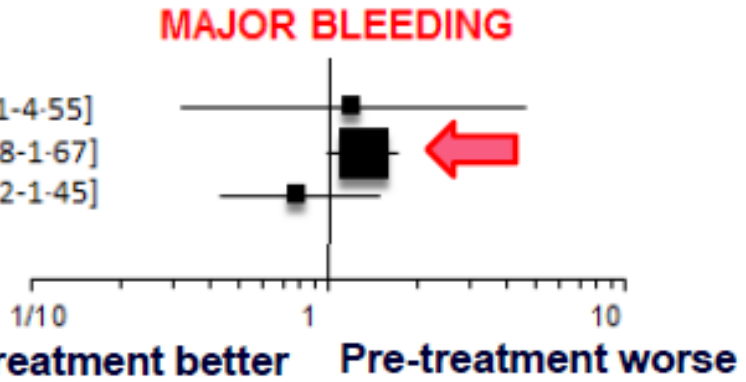
All comers ACS, Clopidogrel possible

Претретиране с Clopidogrel STEMI

		Events / Size, Clopidogrel		OR [CI 95%] *
		Pretreatment	*No Pretreat*	
Presenting feature	Elective PCI	2/820	2/816	1·12 [0·17-7·27]
	NSTE ACS	50/2366	55/2408	0·93 [0·63-1·36]
	STEMI	14/1097	28/1101	0·50 [0·26-0·96]



Presenting feature	Elective PCI	5/820	4/816	1·18 [0·31-4·55]
	NSTE ACS	129/2366	104/2408	1·28 [0·98-1·67]
	STEMI	19/1097	25/1101	0·78 [0·42-1·45]

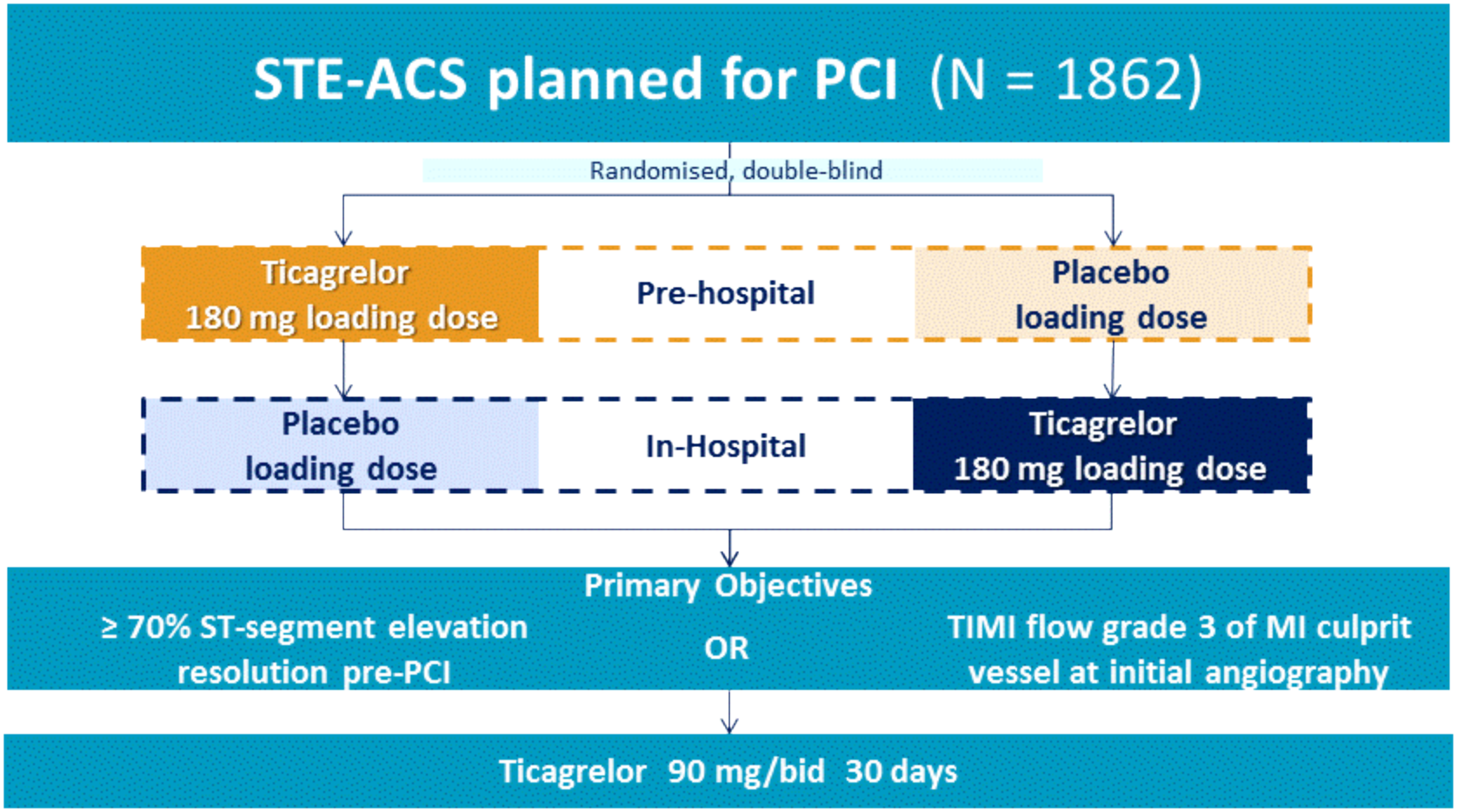


Претретиране при ОКС – Лечение, дадено <u>преди коронарната ангиография</u>, когато е използвана <u>инвазивна стратегия</u>

ATLANTIC

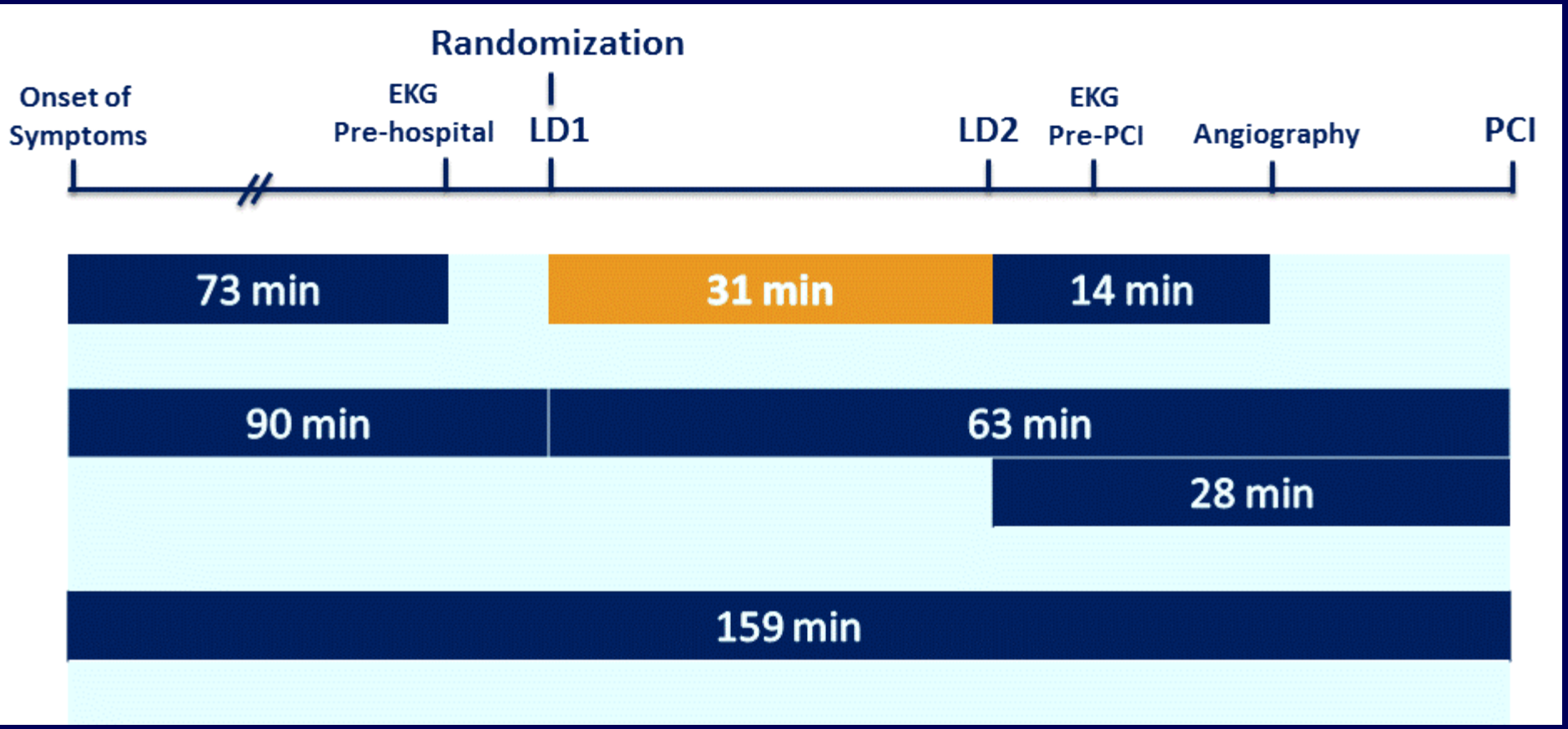
Atlantic Population

- Documented evidence of **STEMI**
- Planned for **angioplasty (PCI)**
- **onset of ischaemic symptoms within 6 h**
- **initially managed by ambulance physician/personnel**; also concerning patients not pre-treated for STEMI in **emergency rooms of non-PCI hospitals**

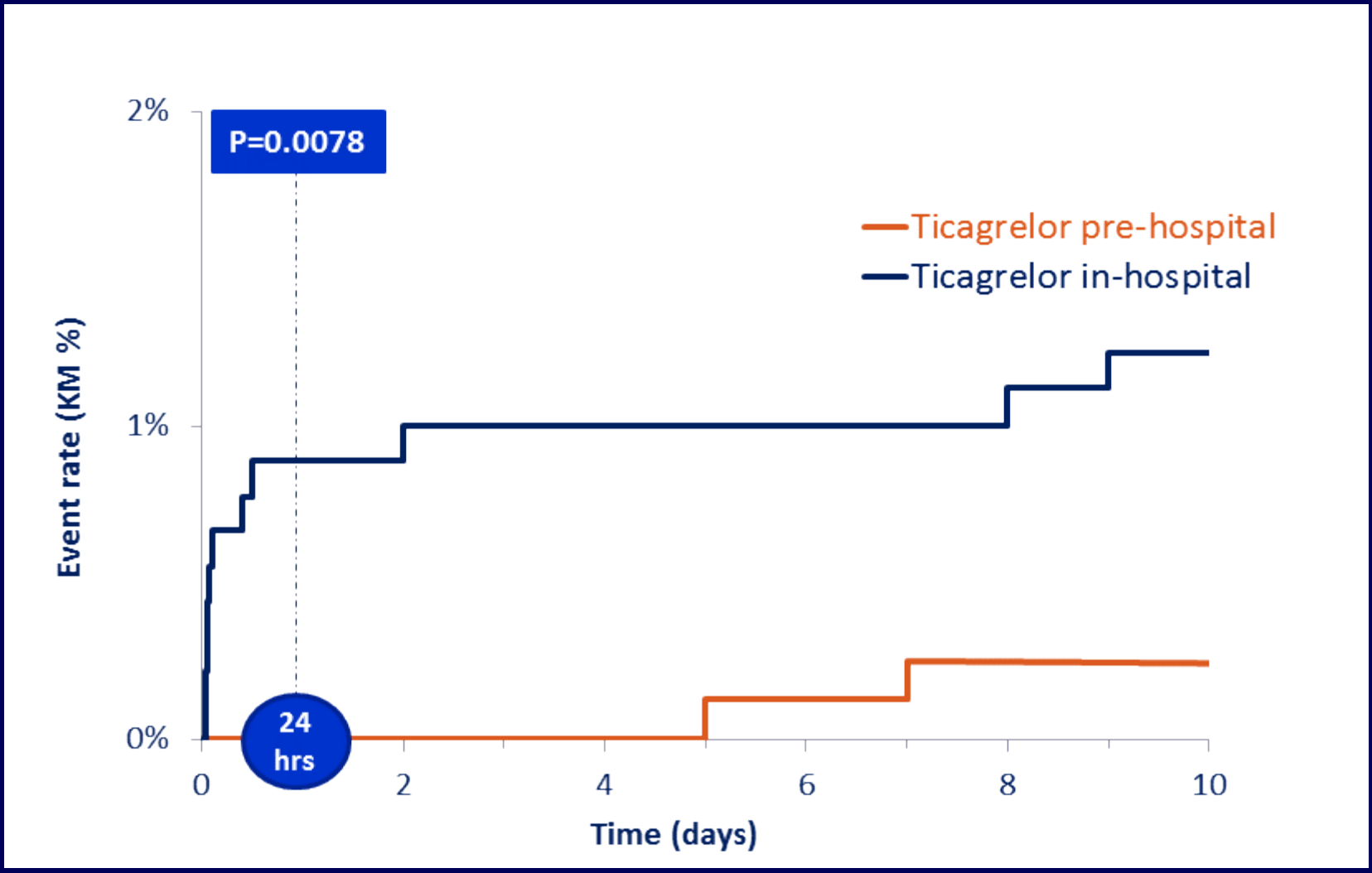


Montalescot G et al. *Am Heart J.* 2013;165:515–522.

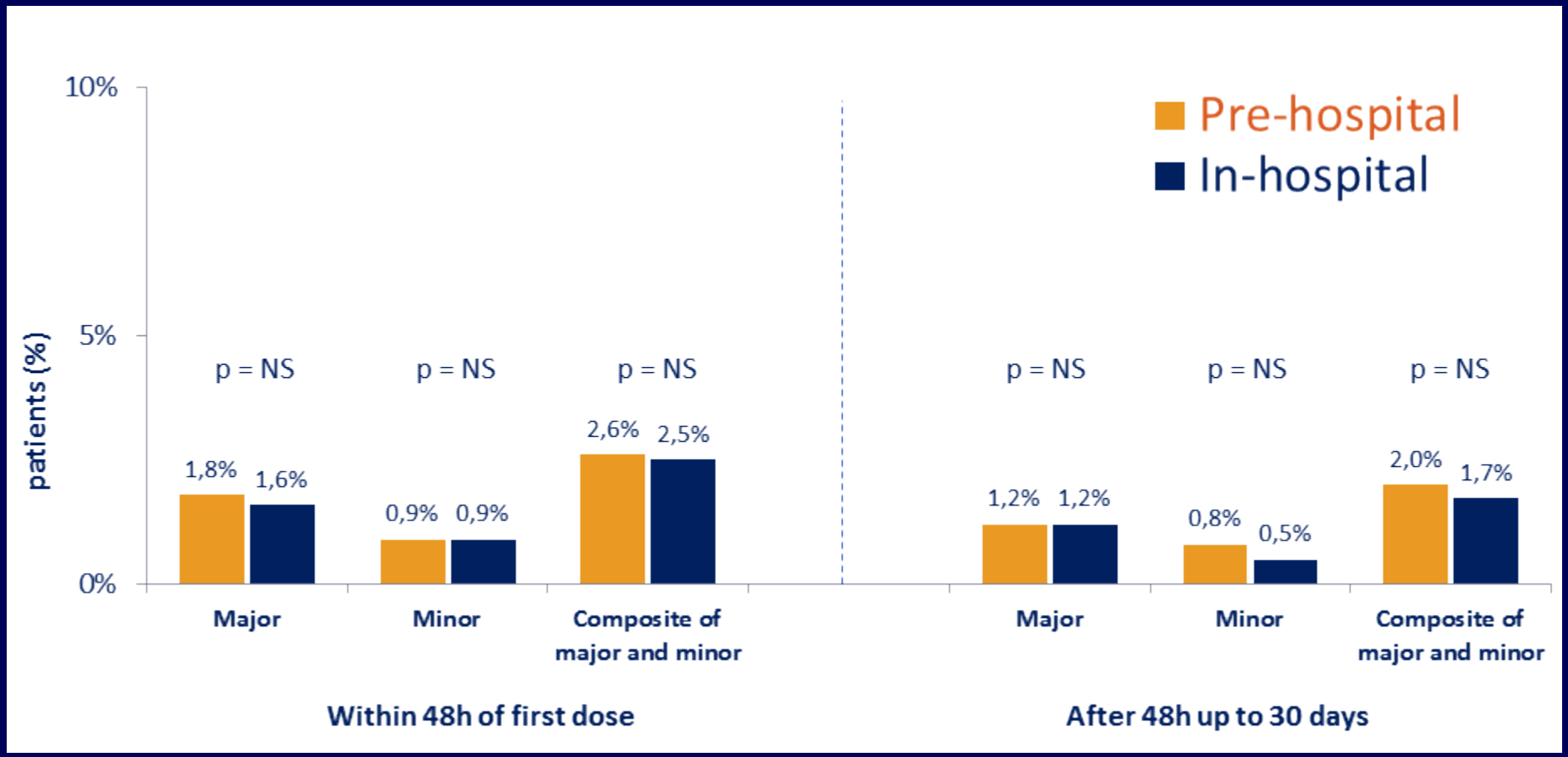
Времеви интервали в двете рамена



Дефинитивна стент тромбоза



Кървене в хода на терапията

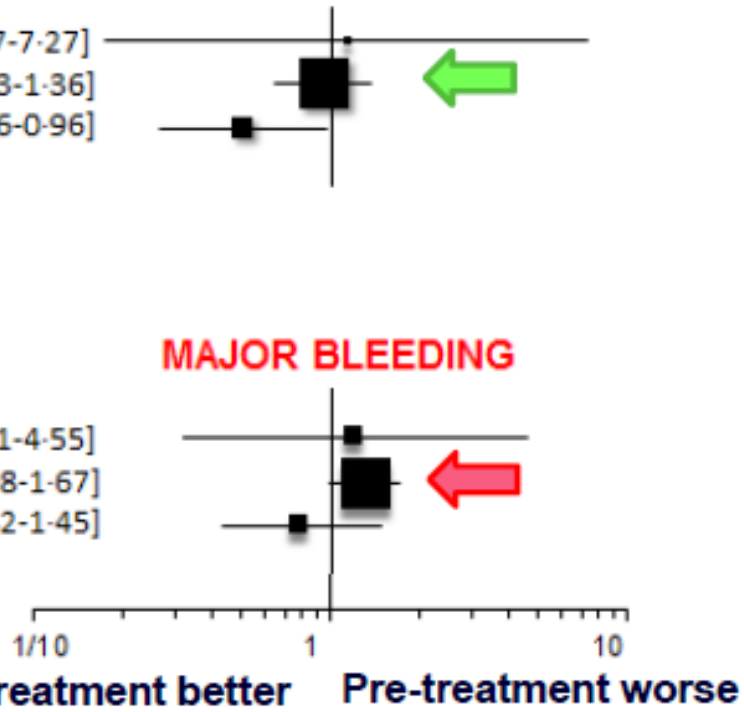


Antithrombotic therapy in STEMI patients undergoing primary PCI

Recommendations	Class[a]	Level[b]
Antiplatelet therapy		
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.) and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A
• Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication	I	B
• Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B
It is recommended to give $P2Y_{12}$ inhibitors at the time of first medical contact.	I	B
GP IIb/IIIa inhibitors should be considered for bail-out or evidence of no-reflow or a thrombotic complication.	IIa	C
Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.	IIb	B
Anticoagulants		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI.	I	A
The anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent.	I	C
Unfractionated heparin: 70–100 U/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned 50–70 U/kg i.v. bolus with GPIIb/IIIa inhibitor	I	C
Bivalirudin 0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/h for up to 4 hours after the procedure	IIa	A
Enoxaparin i.v. 0.5 mg/kg with or without GP IIb/IIIa inhibitor.	IIa	B

Претретиране с Clopidogrel NSTEMI

		Events / Size, Clopidogrel *Pretreatment*	*No Pretreat*	OR [CI 95%] *
ALL DEATH				
Presenting feature	Elective PCI	2/820	2/816	1·12 [0·17-7·27]
	NSTE ACS	50/2366	55/2408	0·93 [0·63-1·36]
	STEMI	14/1097	28/1101	0·50 [0·26-0·96]
MAJOR BLEEDING				
Presenting feature	Elective PCI	5/820	4/816	1·18 [0·31-4·55]
	NSTE ACS	129/2366	104/2408	1·28 [0·98-1·67]
	STEMI	19/1097	25/1101	0·78 [0·42-1·45]



Претретиране при ОКС – Лечение, дадено <u>преди коронарната ангиография</u>, когато е използвана <u>инвазивна стратегия</u>

Recommendations for oral antiplatelet agents (1)

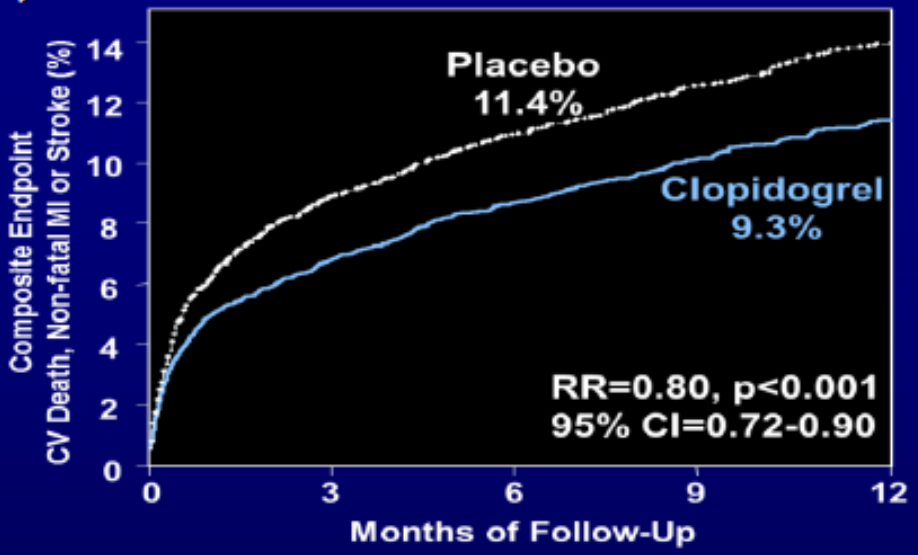
Recommendations	Class	Level
Aspirin should be given to all patients without contraindications at an initial loading dose of 150-300 mg, and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*H. elicobacter pylori* infection, age ≥ 65 years, concurrent use of anticoagulants or steroids).	I	A
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C
Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.	I	B

European Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236

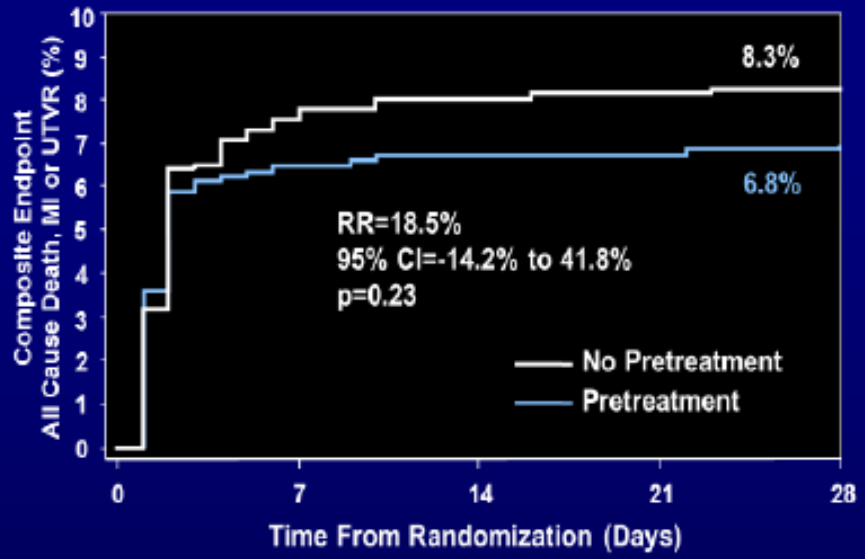
ACS

PCI

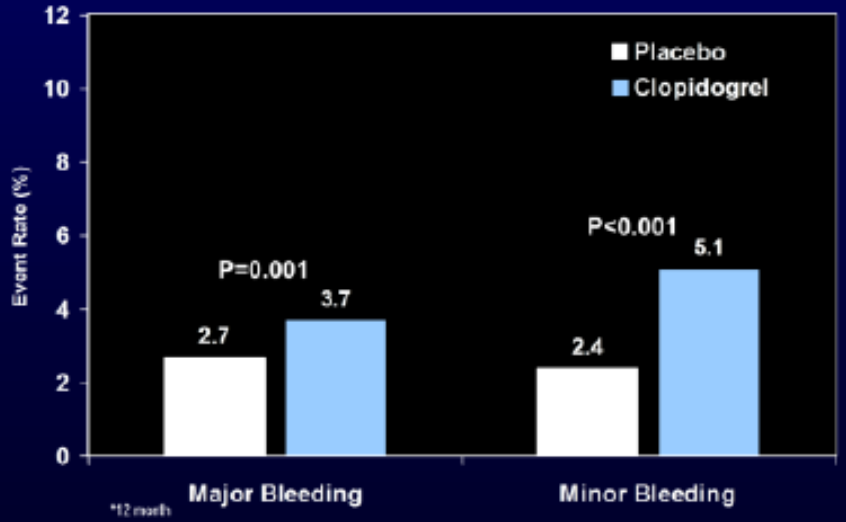
CURE Efficacy



CREDO Efficacy

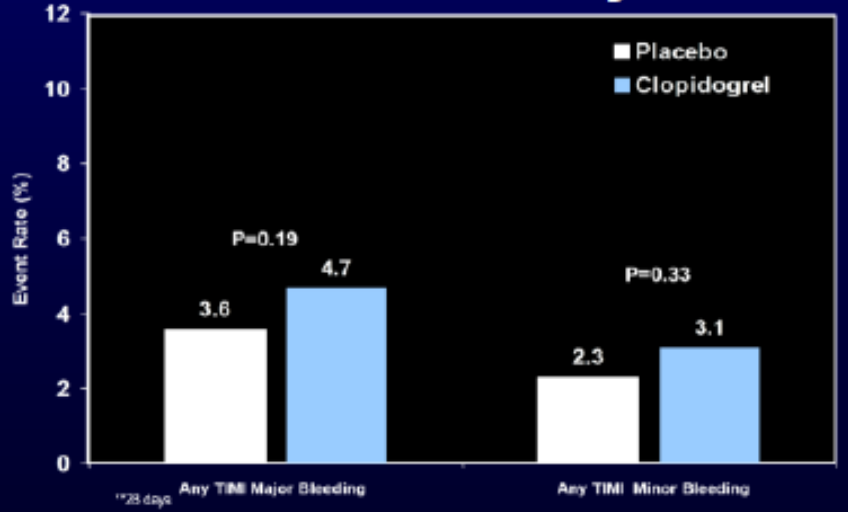


CURE Safety*



Yusuf S, et al. *N Engl J Med* 2001;345:494-502

CREDO Safety**



Steinhubl SR, et al. *JAMA* 2002;288:2411-2420

The New England Journal of Medicine

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*

ABSTRACT

Background Despite current treatments, patients who have acute coronary syndromes without ST-segment elevation have high rates of major vascular events. We evaluated the efficacy and safety of the antiplatelet agent clopidogrel when given with aspirin in such patients.

Methods We randomly assigned 12,562 patients who had presented within 24 hours after the onset of symptoms to receive clopidogrel (300 mg immediately, followed by 75 mg once daily) (6259 patients) or placebo (6303 patients) in addition to aspirin for 3 to 12 months.

Results The first primary outcome — a composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke — occurred in 9.3 percent of the patients in the clopidogrel group and 11.4 percent of the patients in the placebo group (relative risk with clopidogrel as compared with placebo, 0.80; 95 percent confidence interval, 0.72 to 0.90; P<0.001). The second primary outcome — the first primary outcome or refractory ischemia — occurred in 16.5 percent of the patients in the clopidogrel group and 18.8 percent of the patients in the placebo group (relative risk, 0.86, P<0.001). The percentages of patients with in-hospital refractory or severe ischemia, heart failure, and revascularization procedures were also significantly lower with clopidogrel. There were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7 percent vs. 2.7 percent; relative risk, 1.38; P=0.001), but there were not significantly more patients with episodes of life-threatening bleeding (2.1 percent vs. 1.8 percent, P=0.13) or hemorrhagic strokes.

Conclusions The antiplatelet agent clopidogrel has beneficial effects in patients with acute coronary syndromes without ST-segment elevation. However, the risk of major bleeding is increased among patients treated with clopidogrel. (N Engl J Med 2001;345:494-502.)

THROMBOSIS caused by a ruptured or eroded atherosclerotic plaque is the usual underlying mechanism of acute coronary syndromes.[1] Aspirin and heparin reduce the risk of death from cardiovascular causes, new myocardial infarction, and recurrent ischemia,[2,3] but there is still a substantial risk of such events in both the short term and the long term. Intravenous glycoprotein IIb/IIIa receptor blockers have been shown to reduce the incidence of early events, mainly among patients who are treated according to an invasive strategy,[4,5] but long-term oral therapy with glycoprotein IIb/IIIa receptor blockers is not beneficial and may even increase mortality.[6] Similarly, continuing treatment with low-molecular-weight heparin beyond one week has not been shown to be effective.[7] Although the long-term use of oral anticoagulants may be useful, no convincing evidence of their benefit is yet available.[8] Therefore, there is a need to reduce further the risk of ischemic events in a broad spectrum of patients both when they first present with acute coronary syndromes and in the long term.

The thienopyridine derivatives, ticlopidine and clopidogrel, are antiplatelet agents that inhibit the platelet aggregation induced by adenosine diphosphate, thereby reducing ischemic events.[9] Combining one of these drugs with aspirin, which blocks the thromboxane-mediated pathway, may have an additive effect. In patients who are undergoing percutaneous transluminal coronary angioplasty (PTCA) with stenting, short-term aspirin treatment plus a thienopyridine derivative results in a substantially lower rate of myocardial infarction than does either aspirin alone or warfarin.[10] However, the role of long-term combined therapy with aspirin and an antiplatelet agent in a broader group of patients at high risk for cardiovascular events is unknown. We therefore designed the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial to compare the efficacy and safety of the early and long-term use of clopidogrel plus aspirin with those of aspirin alone in patients with acute coronary syndromes and no ST-segment elevation.

METHODS

Study Design

We undertook a randomized, double-blind, placebo-controlled trial comparing clopidogrel with placebo in patients who presented with acute coronary syndromes without ST-segment elevation. The design and rationale of the study have been reported previously.[9]

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. Initially, patients older than 60 years

The Manuscript Writing Committee (Salim Yusuf, D.Phil., F.R.C.P.C., Feng Zhao, M.Sc., Shamir R. Mehta, M.D., F.R.C.P.C., Sonia Chrolavicius, B.Sc., Gianni Tognoni, M.D., and Keith K. Fox, M.D., F.R.C.P.) assumes responsibility for the overall content of the manuscript. Address reprint requests to Dr. Yusuf at the Canadian Cardiovascular Collaboration Project Office, Population Health Research Institute, McMaster University, Hamilton General Hospital, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at yusuf@mcmaster.ca.

*The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial investigators are listed in the Appendix.

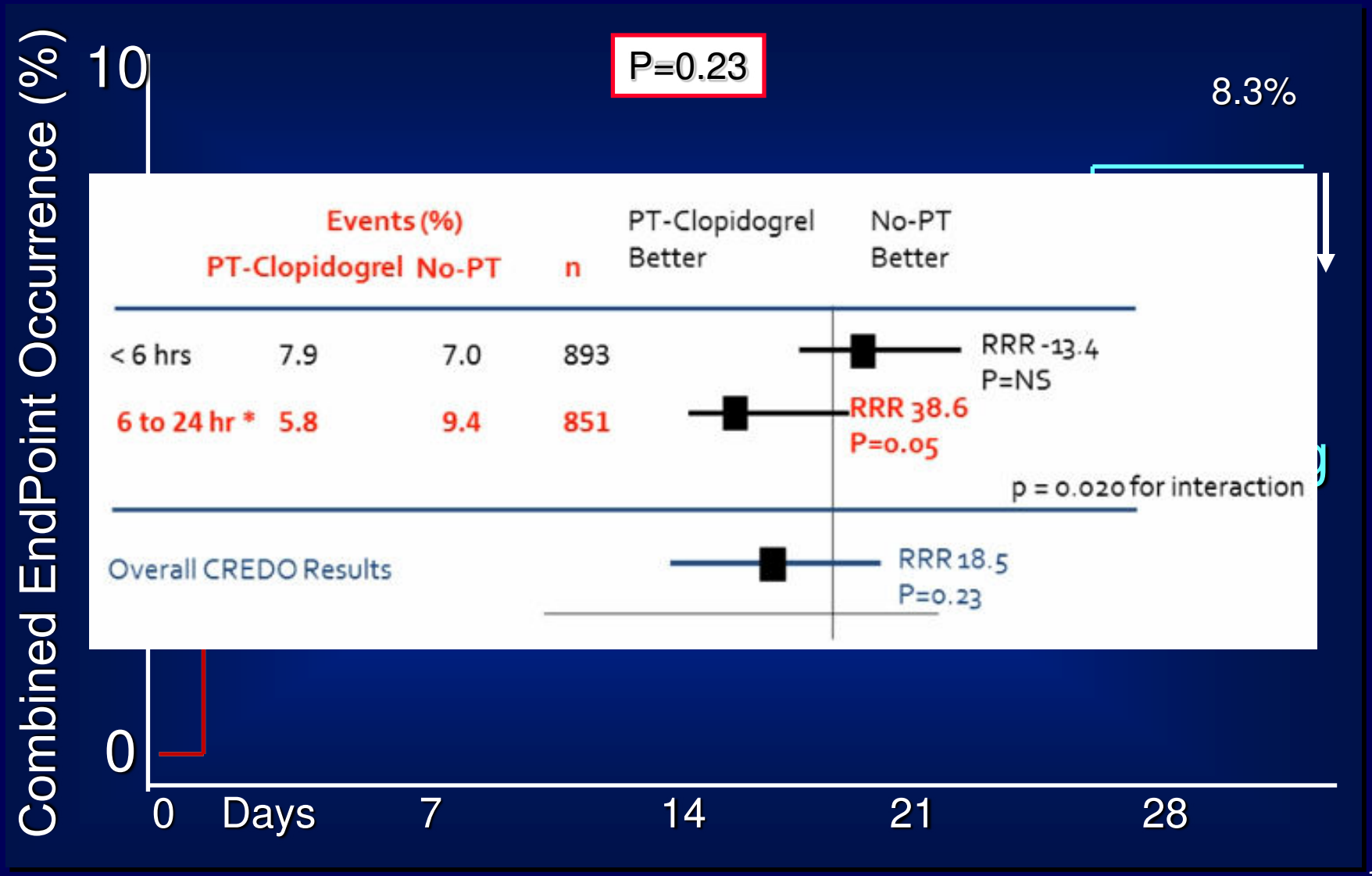
Our study primarily included centers in which there was no routine policy of early use of invasive procedures, since such a policy would have led to a high rate

A total of 71 patients in the clopidogrel group (1.1 percent) and 126 patients in the placebo group (2.0 percent) received thrombolytic therapy (relative risk, 0.57; 95 percent confidence interval, 0.43 to 0.76; P<0.001); 369 patients in the clopidogrel group (5.9

- 57% без ангиография
- Осъществена 10 ден
- 20% PCI

C.R.E.D.O.

Death, MI and Urgent TVR at 28 Days



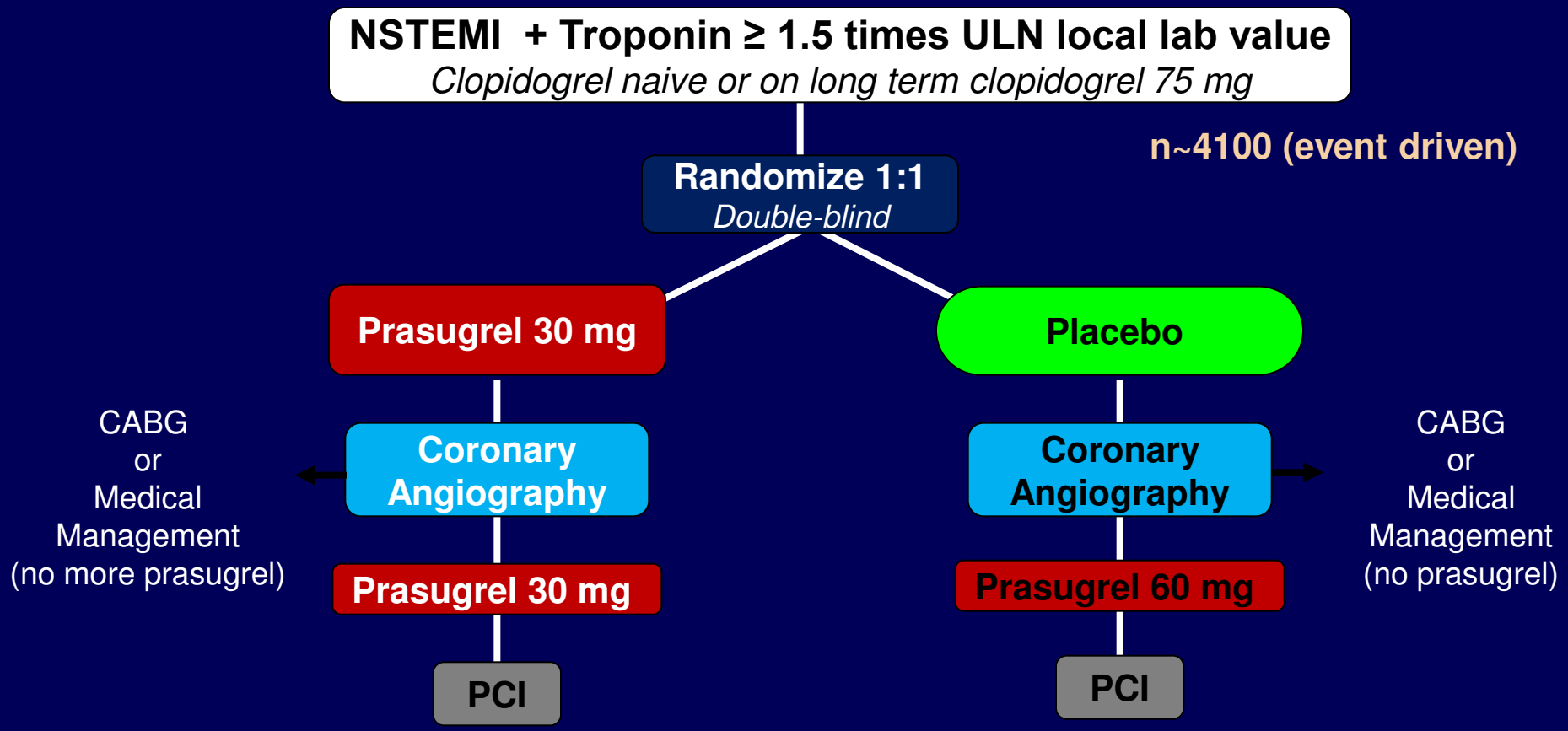
Steinhubl et al, JAMA 2002;228:2411-20


SABRINA
BOYS


36-76 МКЖ


НАЦИОНАЛНА КАРДИОЛОГИЧНА БОЛНИЦА

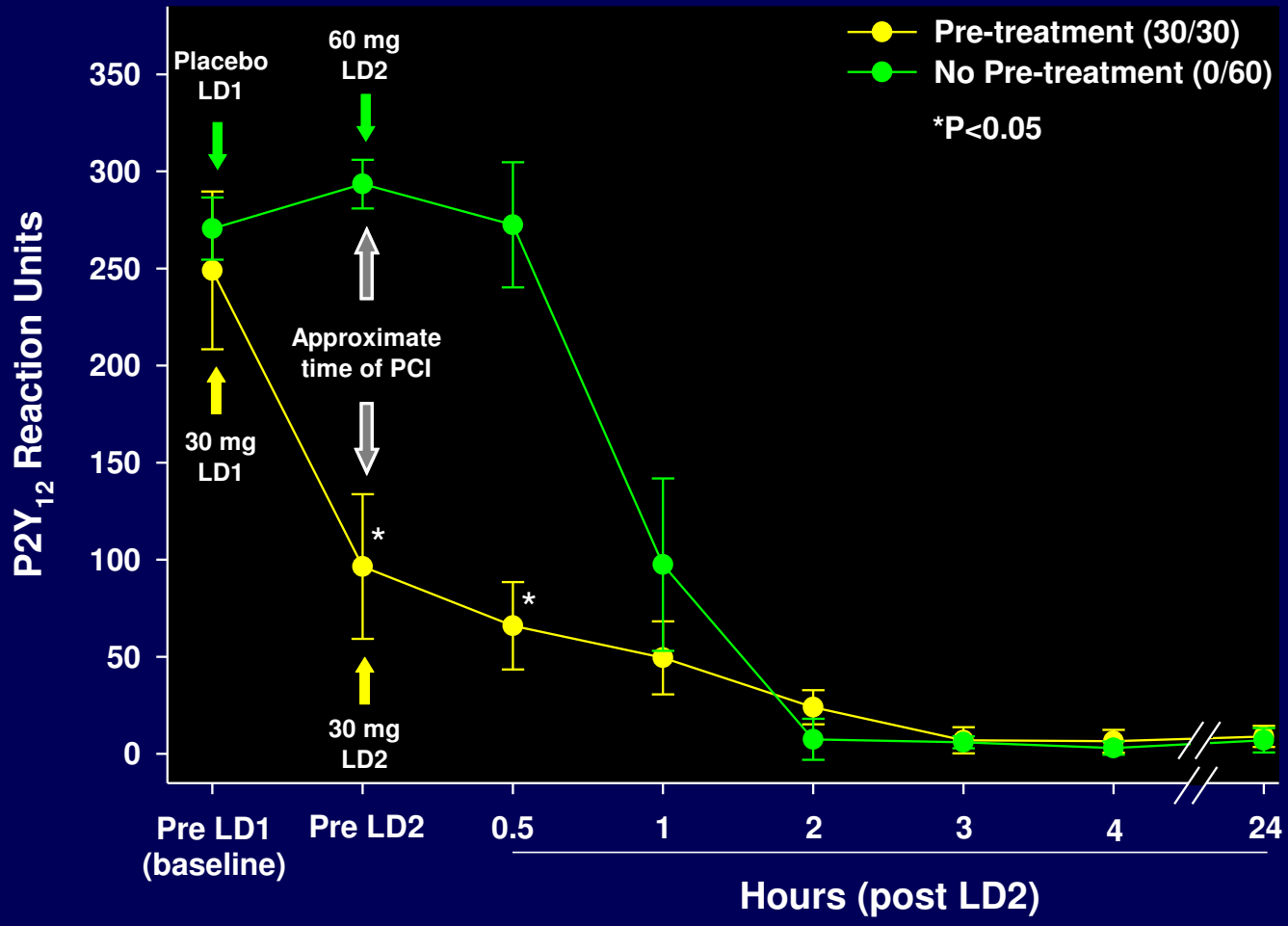
ACCOAST



1° Endpoint: CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout, at 7 days

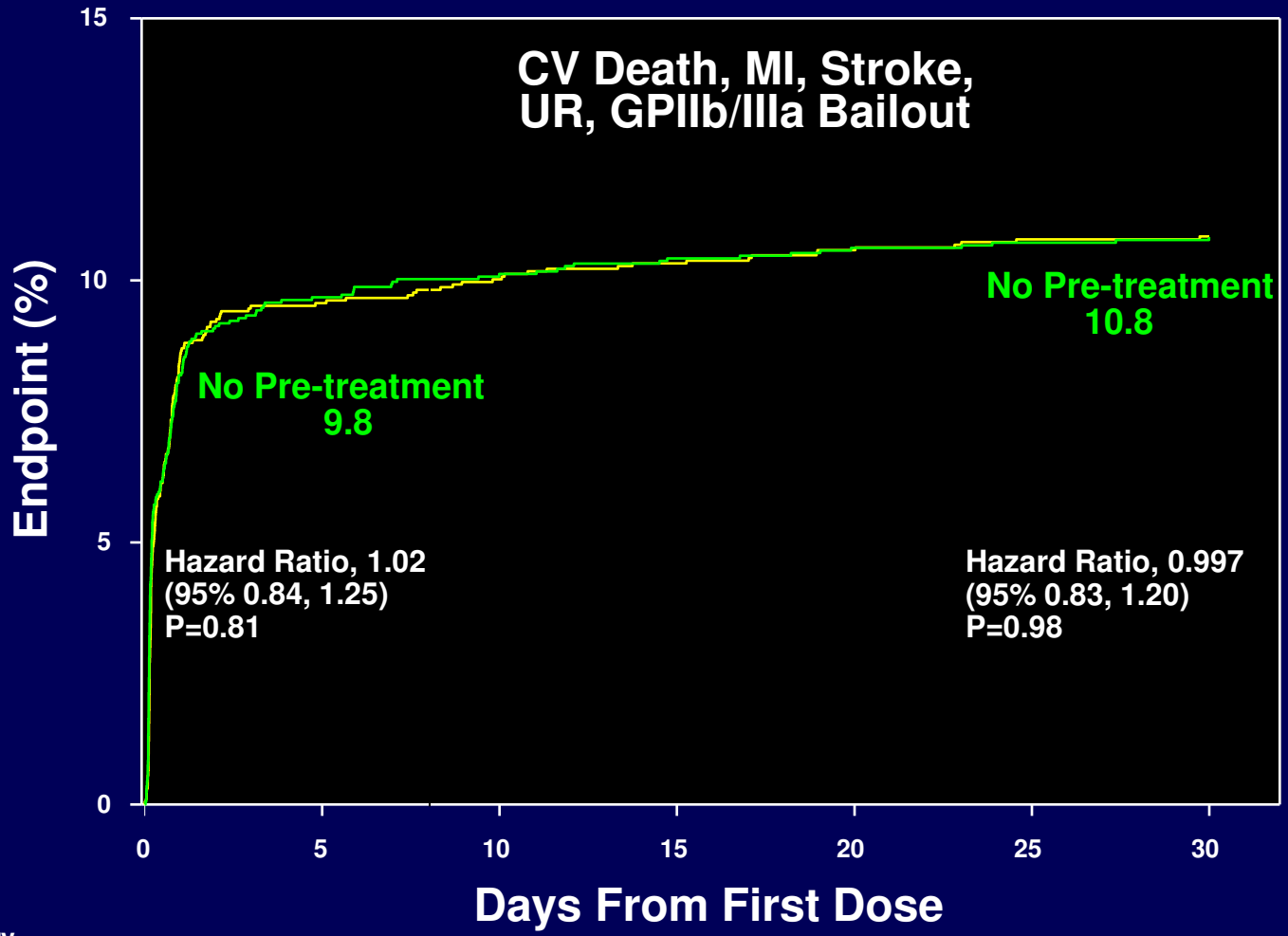
Montalescot G et al. *Am Heart J* 2011;161:650-656

Тромбоцитна реактивност



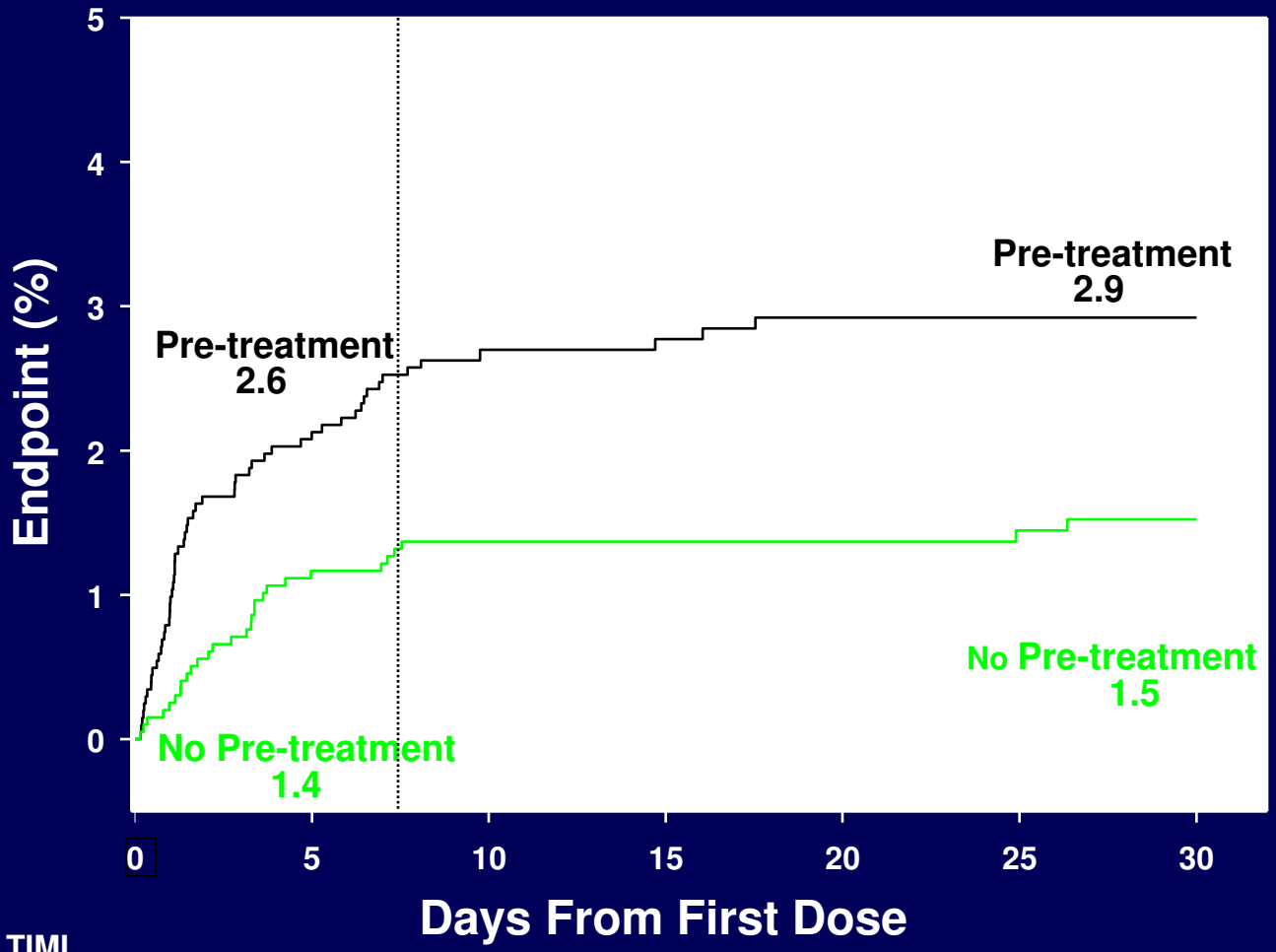
Data presented as median ± SEM. * p<0.05 relative to the No pre-treatment group. LD = loading dose.
Pretreatment=Prasugrel 30 mg/Prasugrel 30 mg; No Pre-treatment=Placebo/Prasugrel 60 mg

Първична точка за ефикасност @ 7 + 30 days



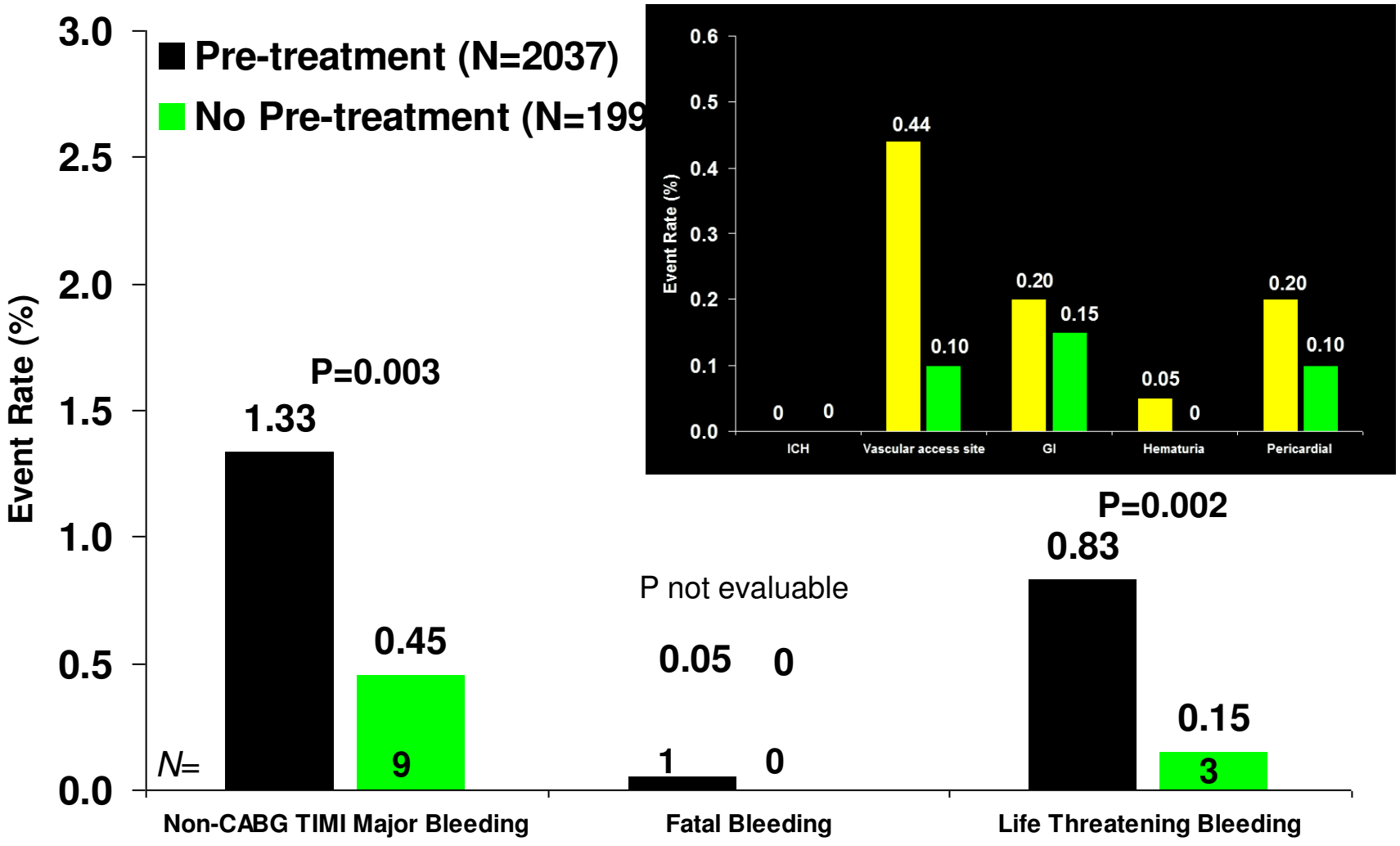
No. at Risk, Primary Efficacy End Point:							
No pre-treatment	1996	1788	1775	1769	1762	1752	1621
Pre-treatment	2037	1821	1809	1802	1797	1791	1616

TIMI (CABG or non-CABG) голямо кървене (All Treated patients)

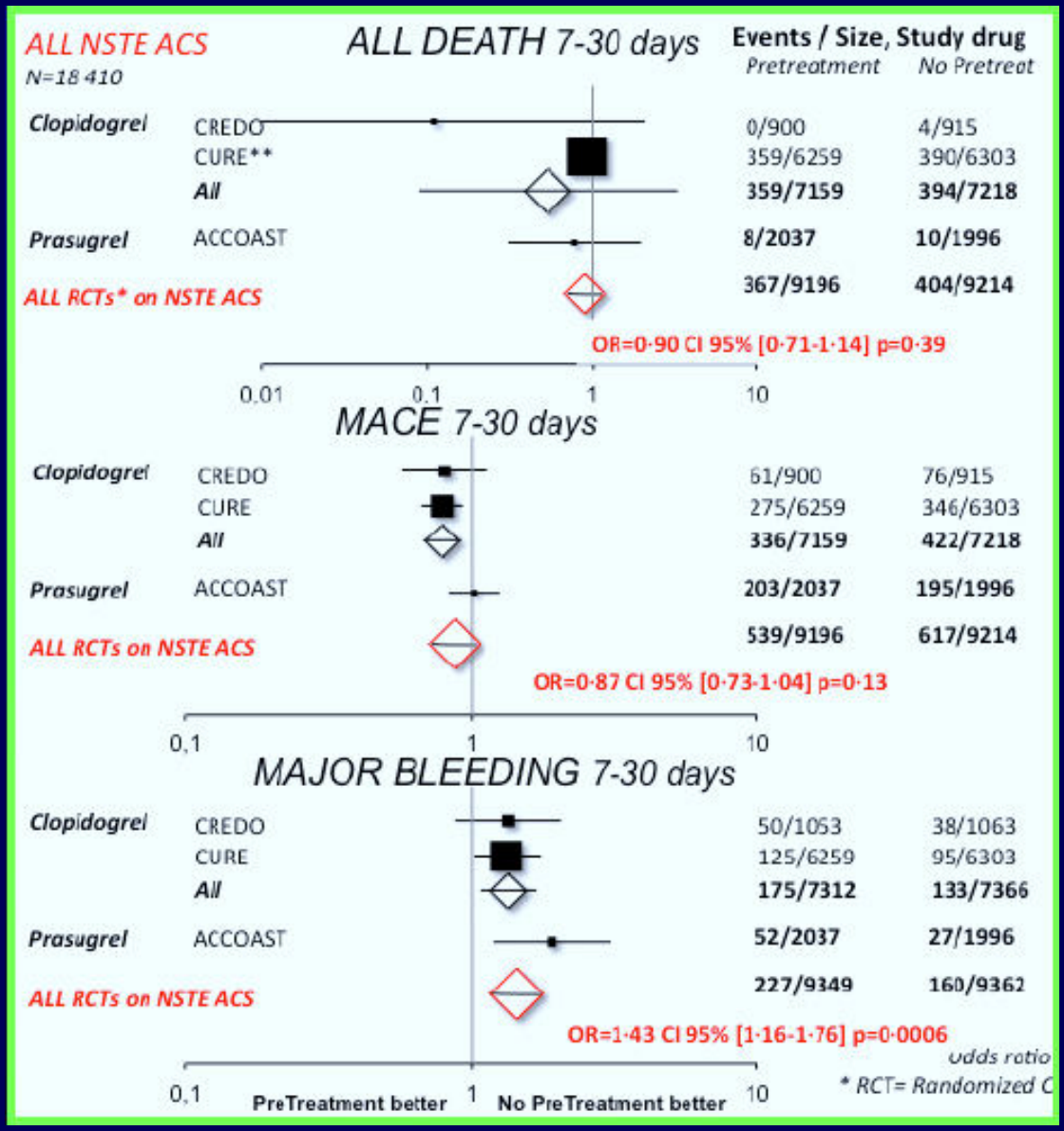


No. at Risk, All TIMI Major Bleeding:							
No pre-treatment	1996	1947	1328	1297	1288	1284	1263
Pre-treatment	2037	1972	1339	1310	1299	1297	1280

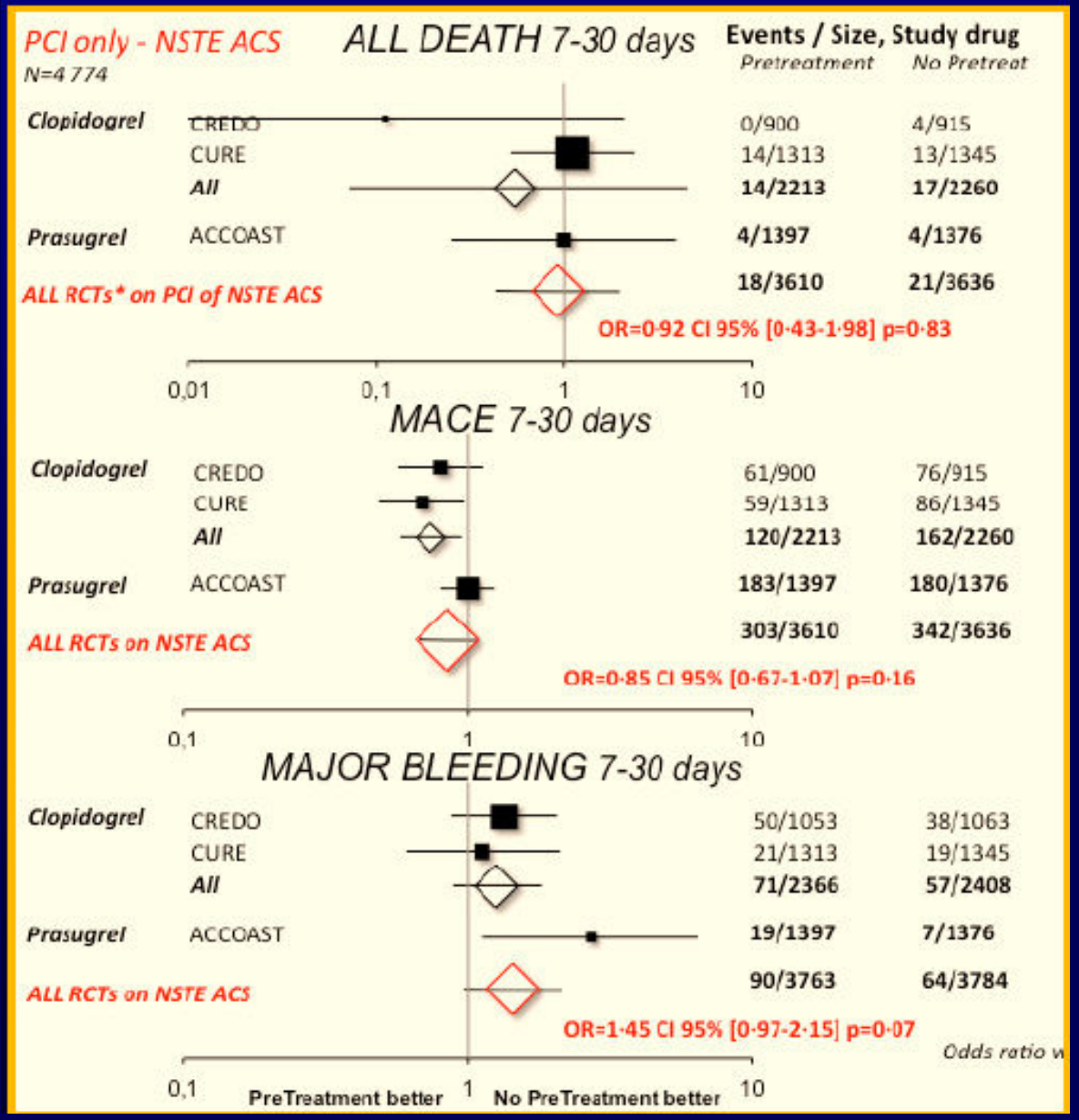
Видове кървене



Претретиране при NSTEMI



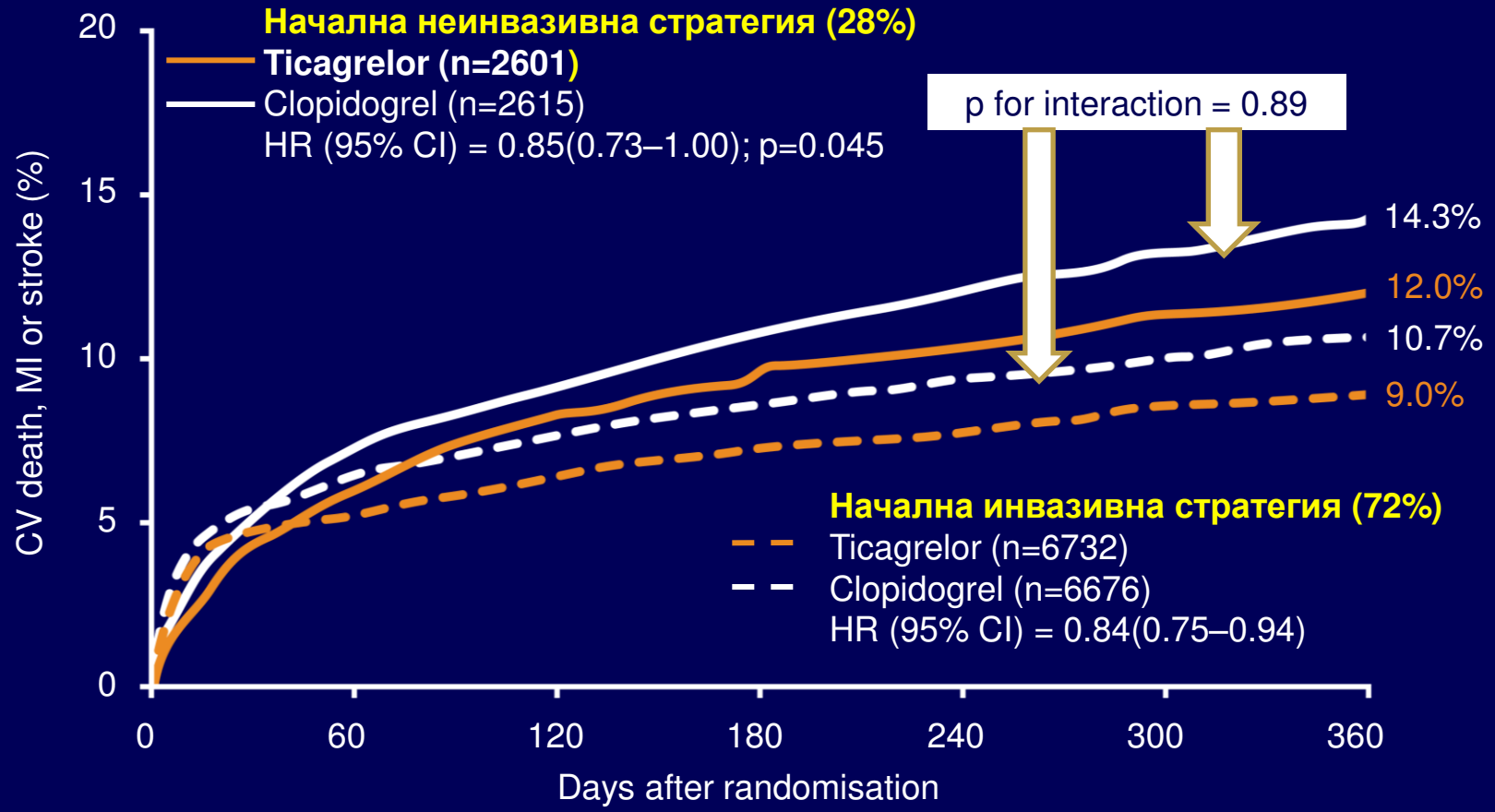
Претретиране при NSTEMI + PCI



Antithrombotic therapy in NSTE-ACS patients undergoing PCI

Antiplatelet therapy		
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to ASA, and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A
• Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication.	I	B
• Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication.	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B
GP IIb/IIIa antagonists should be considered for bail-out situation or thrombotic complications.	IIa	C
Pre-treatment with prasugrel in patients in whom coronary anatomy is not known is not recommended.	III	B
Pre-treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known is not recommended.	III	A

Първична крайна точка в PLATO в зависимост от типа приложена стратегия



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; NSTEMI, non-ST-segment elevated MI; UA, unstable angina.
James S, et al. *BMJ* 2011;342:d3527.

Време от първата доза на медикамента до PCI - PLATO

Time, hours	Ticagrelor (n=9333)	Clopidogrel (n=9291)
Patients with STEMI		
Median	0.25	0.25
IQR	0.05–0.75	0.05–0.72
Patients with NSTEMI		
Median	3.93	3.65
IQR	0.48–46.9	0.45–50.8

IQR, interquartile range; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
Wallentin L, et al. *N Engl J Med* 2009;361:1045–1057.

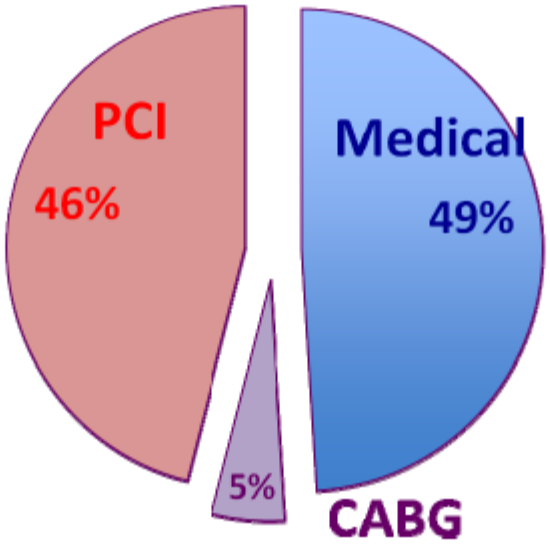
Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial

PLATO NSTE-ACS

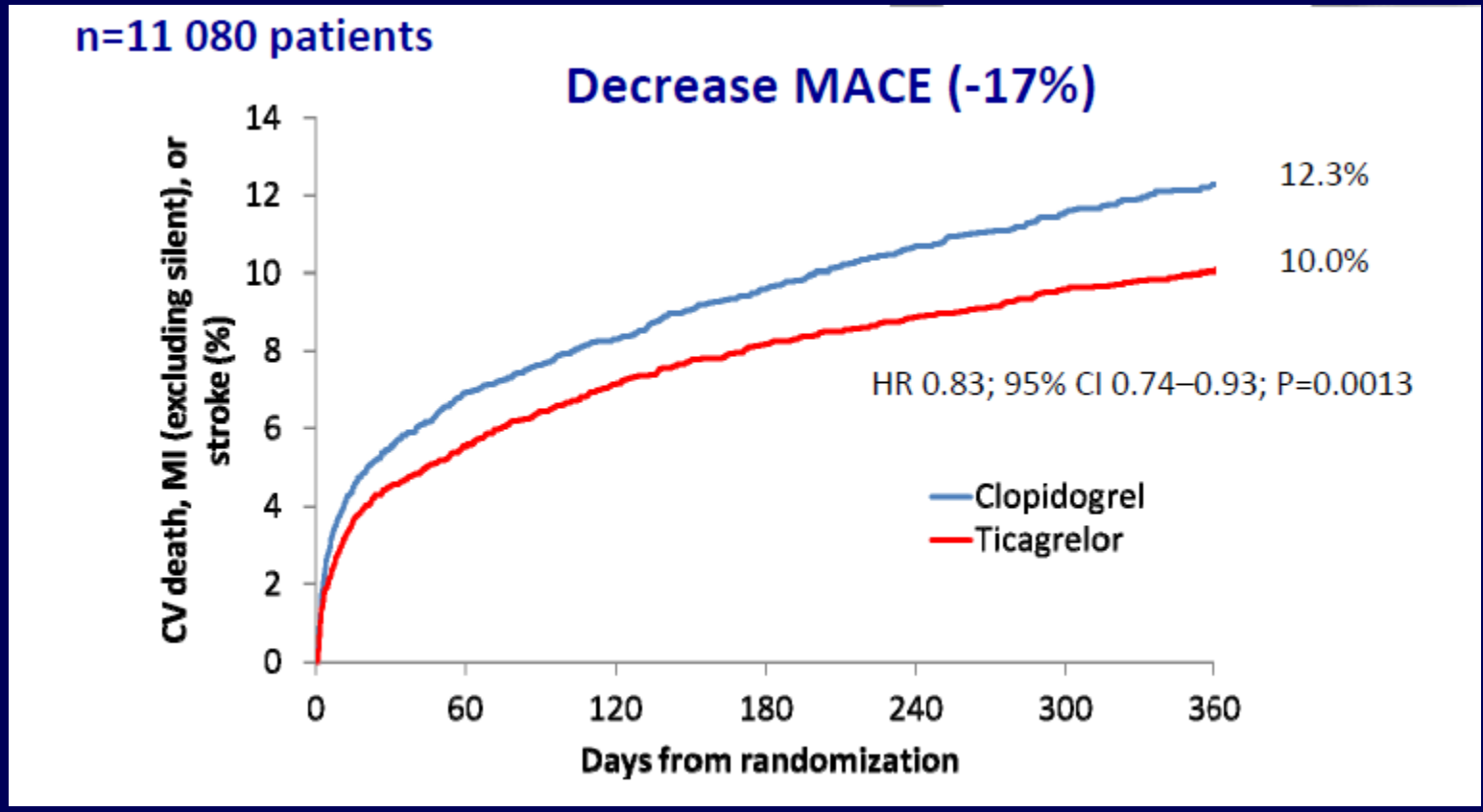
Among 18 624 PLATO patients, 11 080 (59%) were categorized as NSTE-ACS at randomization

Strategy during the First 10 days

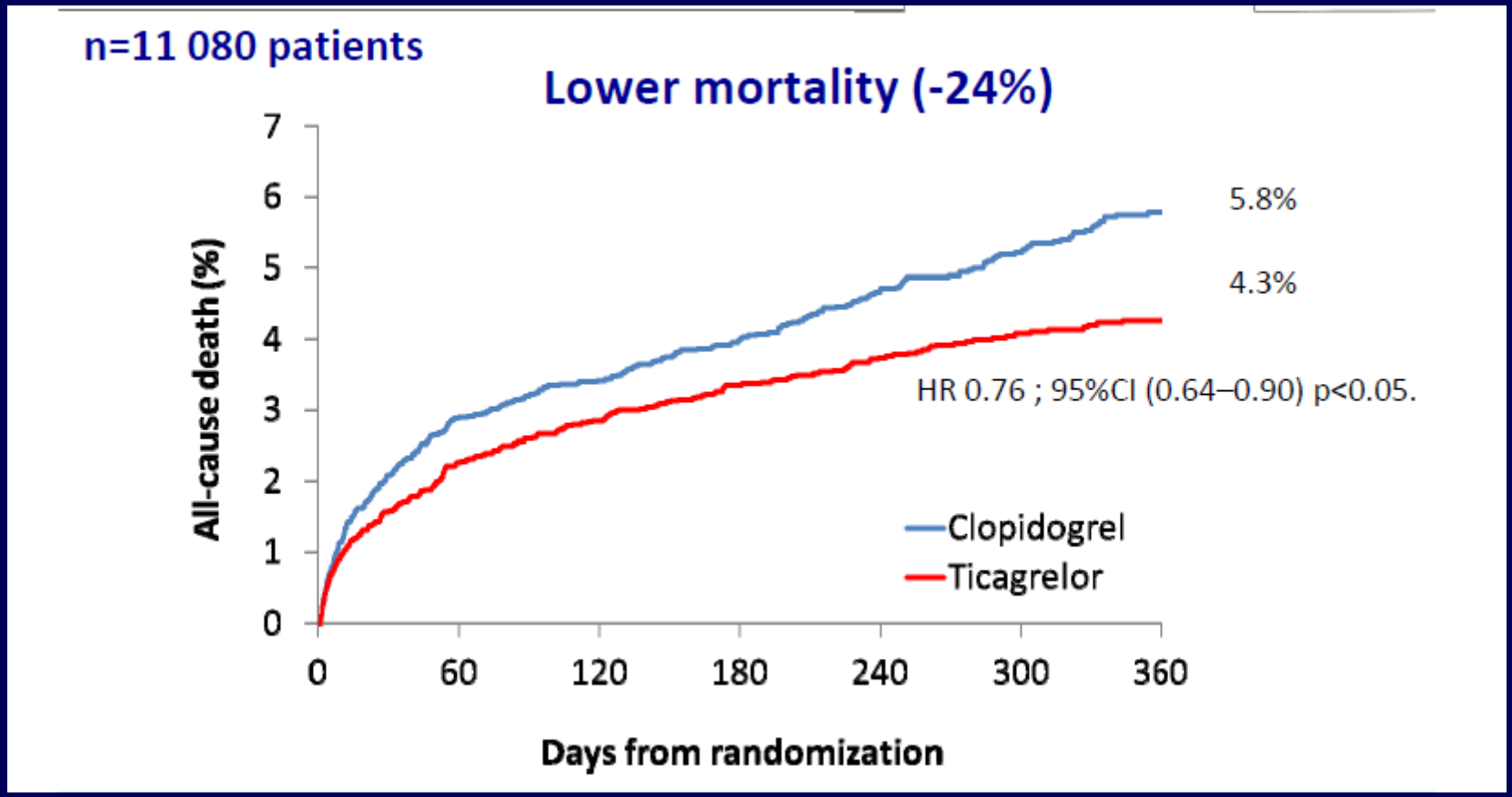
Angio 74%



Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial

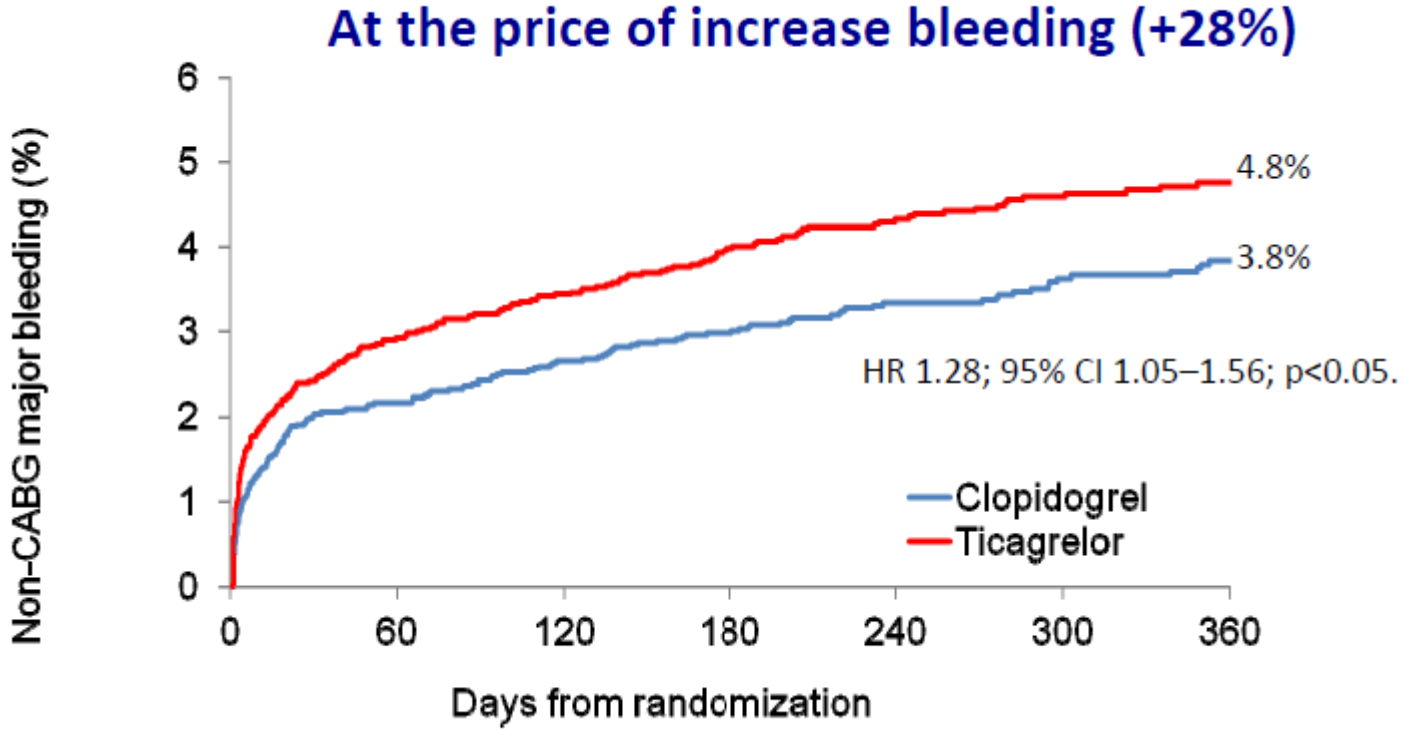


Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial

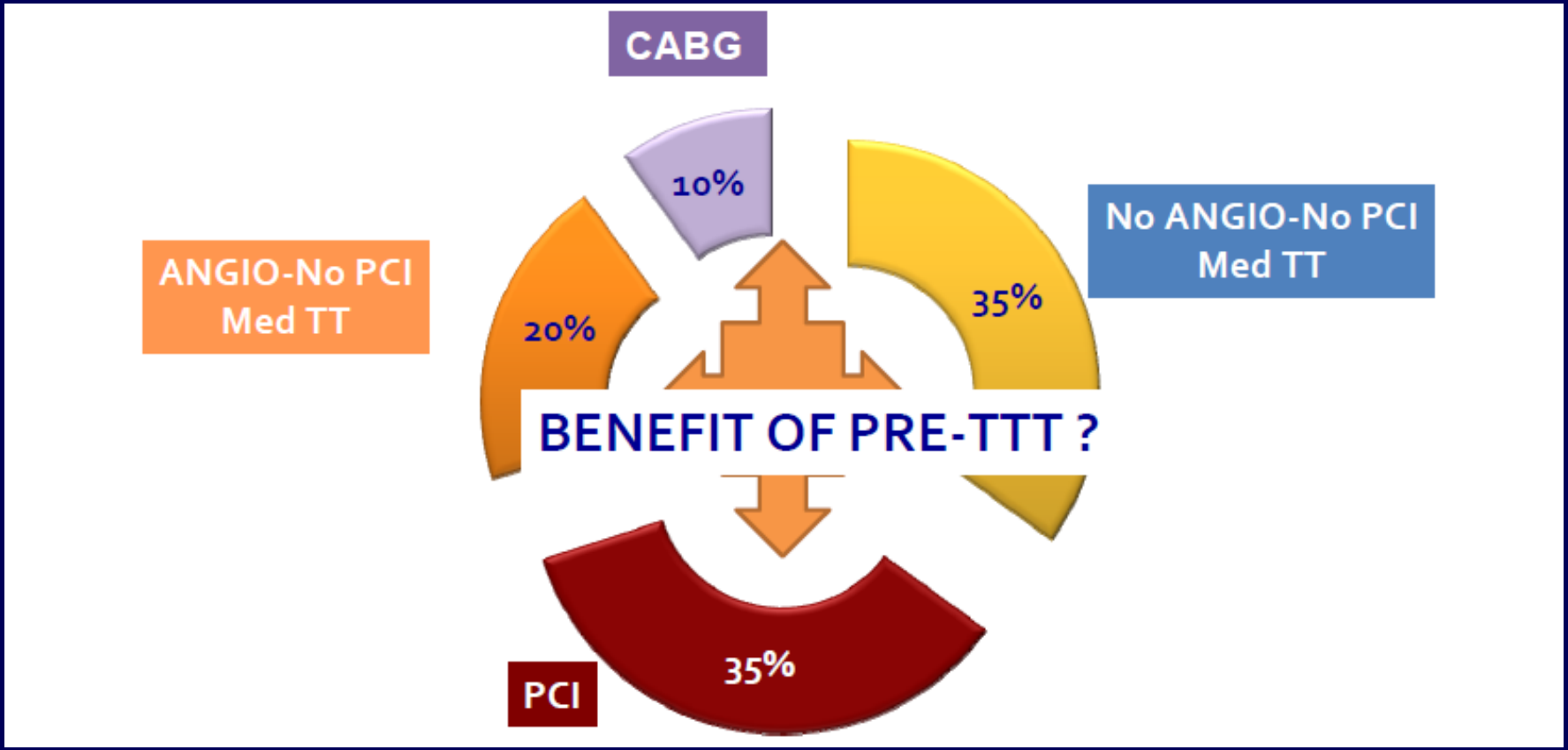


Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial

n=11 080 patients



NSTEMI пациенти в реалната практика



Collet, Circulation 2014

NSTEMI-ACS*

*Excluding STEMI Like

Aspirin 500 mg IV
Anticoagulation

- Fast Track to cathlab possible ?

NO

Delayed Angiography (24h to 72h or more ....)
+ No doubt on alternative diagnostic

Ticagrelor **Clopidogrel**

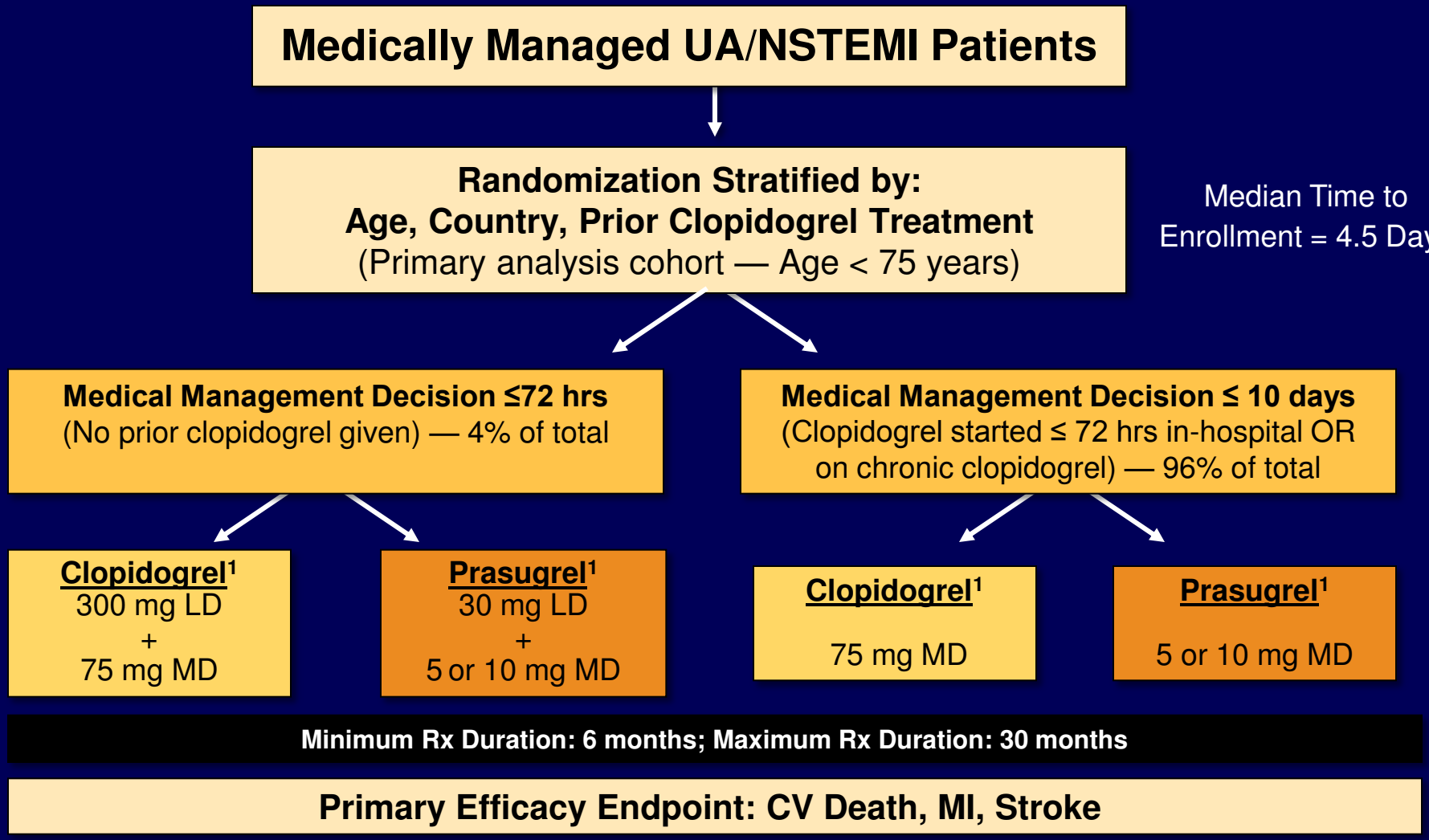
Cath **Cath**

YES

same day cath

In lab loading of
prasugrel/ticagrelor
post angio if PCI

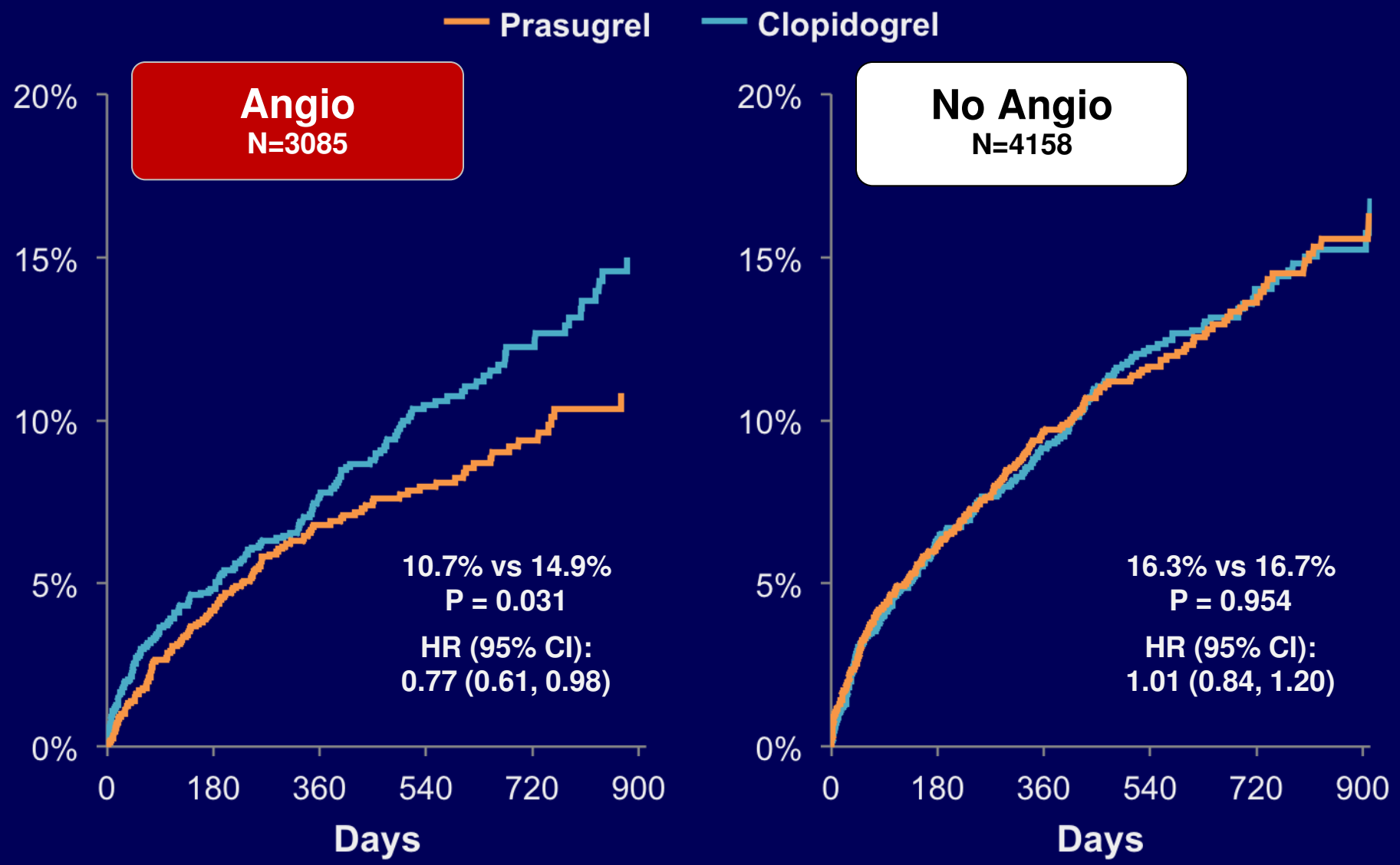
TRILOGY ACS



1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients <60 kg or ≥75 years, 5 mg MD of prasugrel was given. Adapted from Chin CT et al. *Am Heart J* 2010;160:16-22.e1.

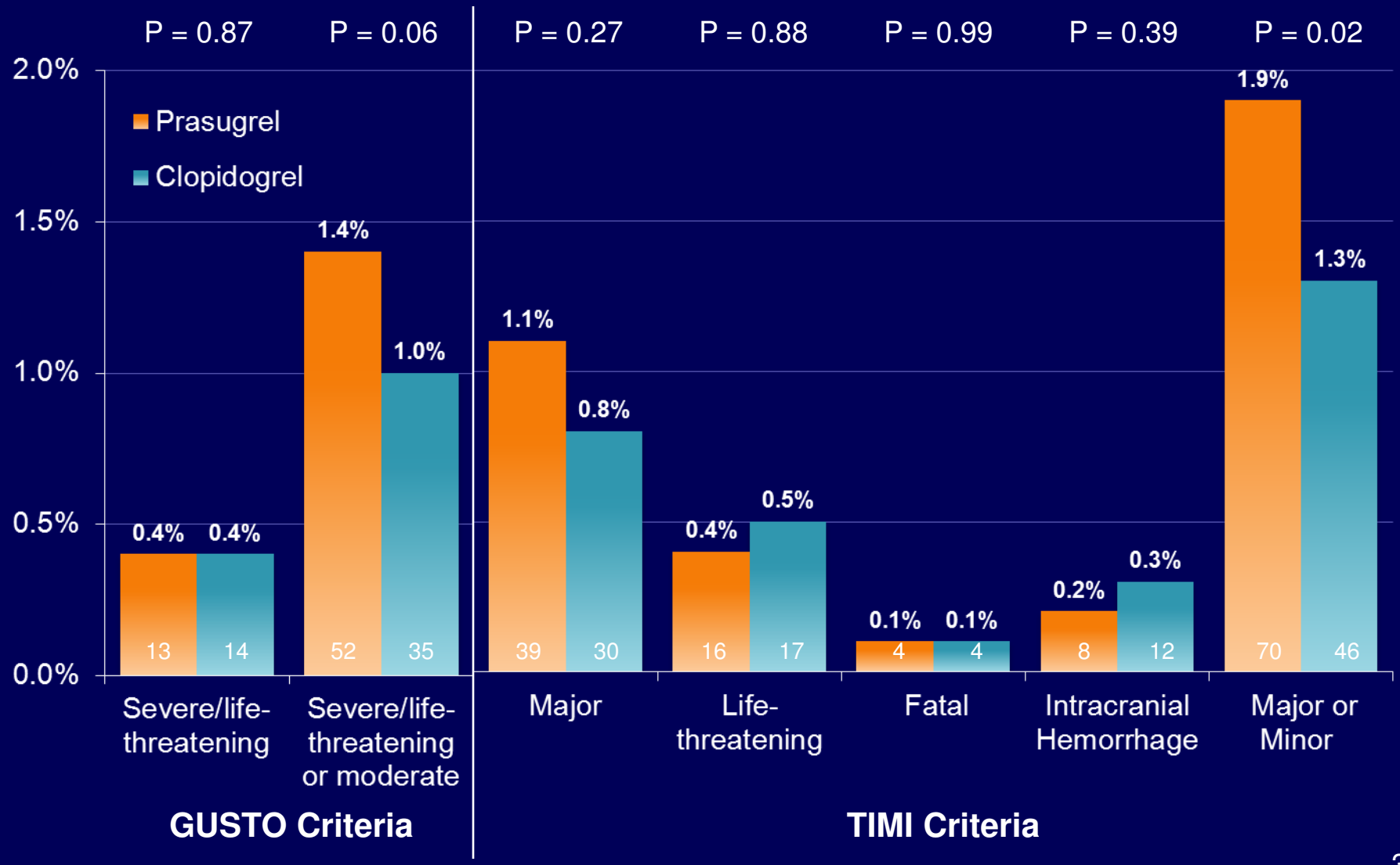
CC смърт, МИ, инсулт – 30 месеца

(Възраст < 75 years)

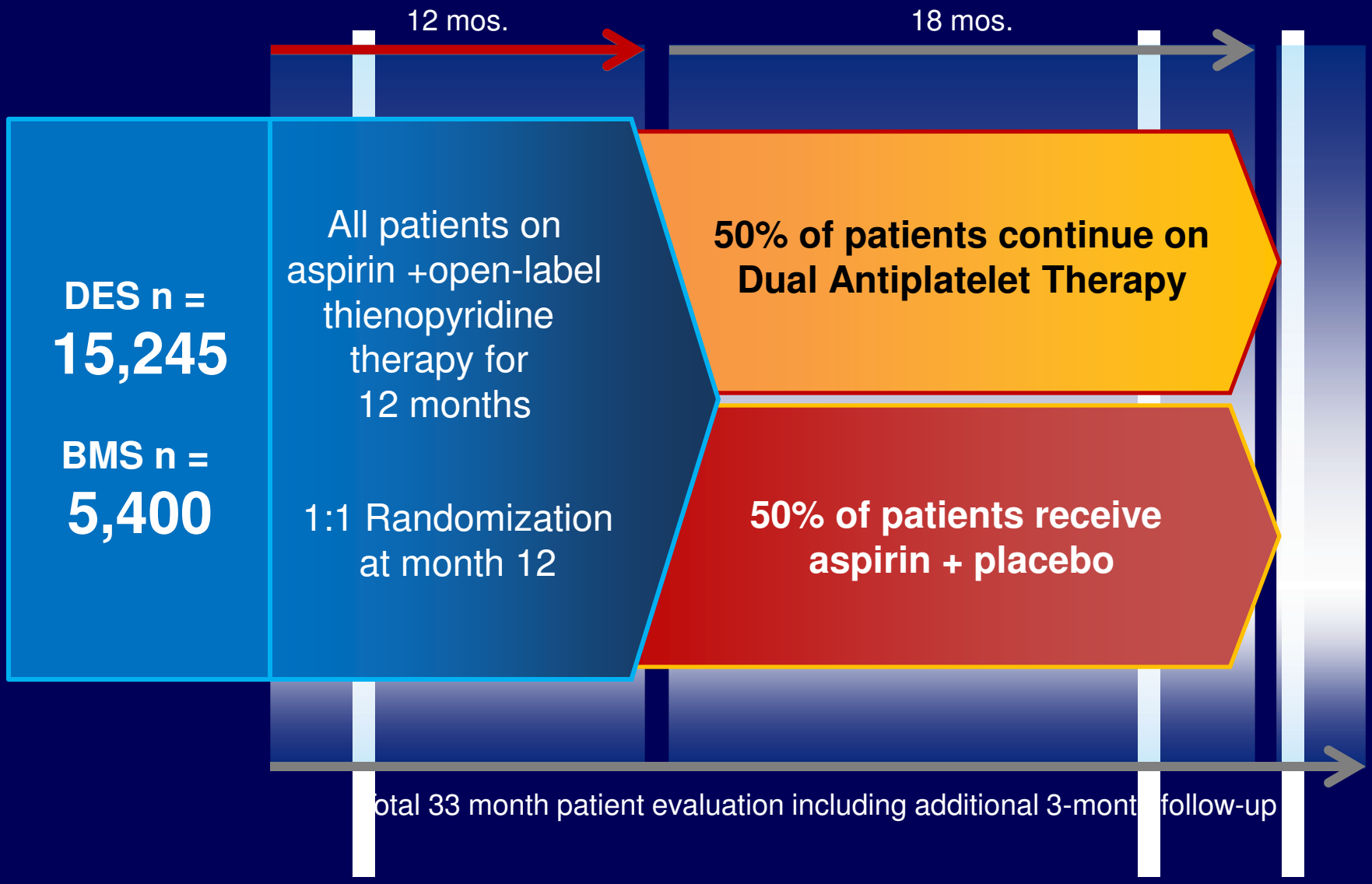


P interaction = 0.08

Кървене

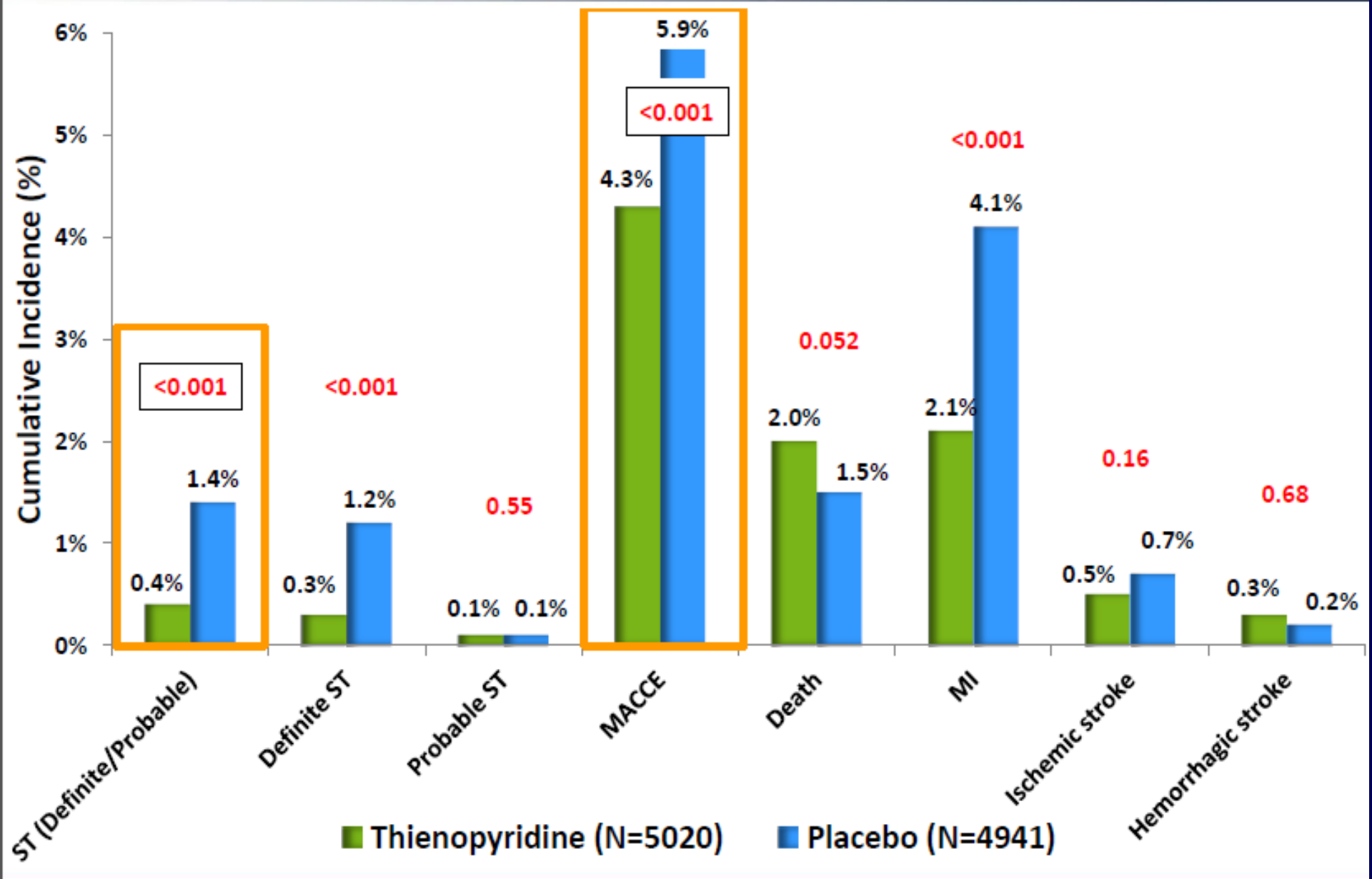

P = 0.87
P = 0.06
P = 0.27
P = 0.88
P = 0.99
P = 0.39
P = 0.02
2.0%
1.5%
1.0%
0.5%
0.0%
Prasugrel
Clopidogrel
0.4%
0.4%
1.4%
1.0%
1.1%
0.8%
0.4%
0.5%
0.1%
0.1%
0.2%
0.3%
1.9%
1.3%
13
14
52
35
39
30
16
17
4
4
8
12
70
46
Severe/life-threatening
Severe/life-threatening or moderate
Major
Life-threatening
Fatal
Intracranial Hemorrhage
Major or Minor
GUSTO Criteria
TIMI Criteria

Dual Antiplatelet Therapy (DAPT) Study



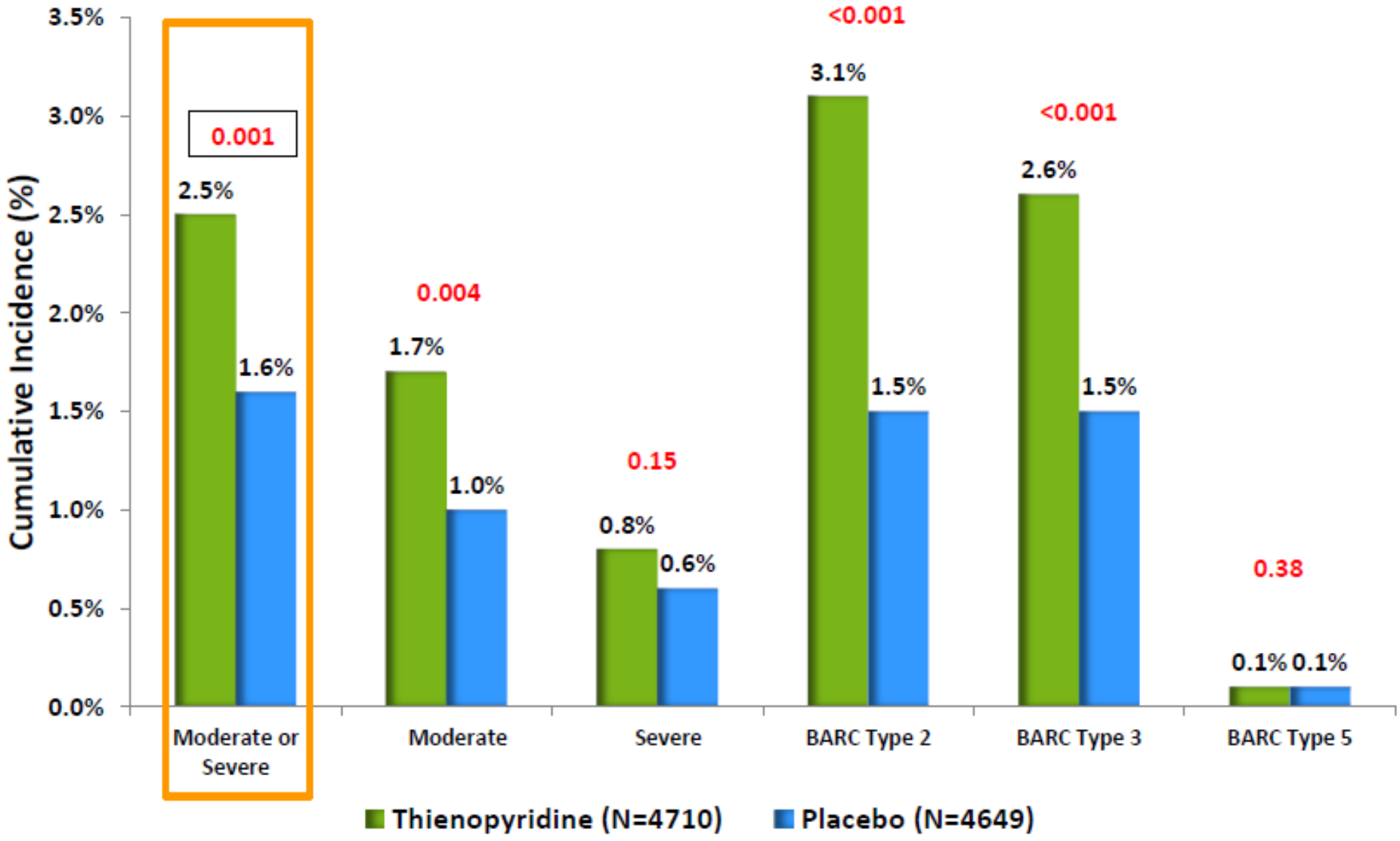
Co-Primary Effectiveness End Points & Components: 12-30 Months

DAPT STUDY



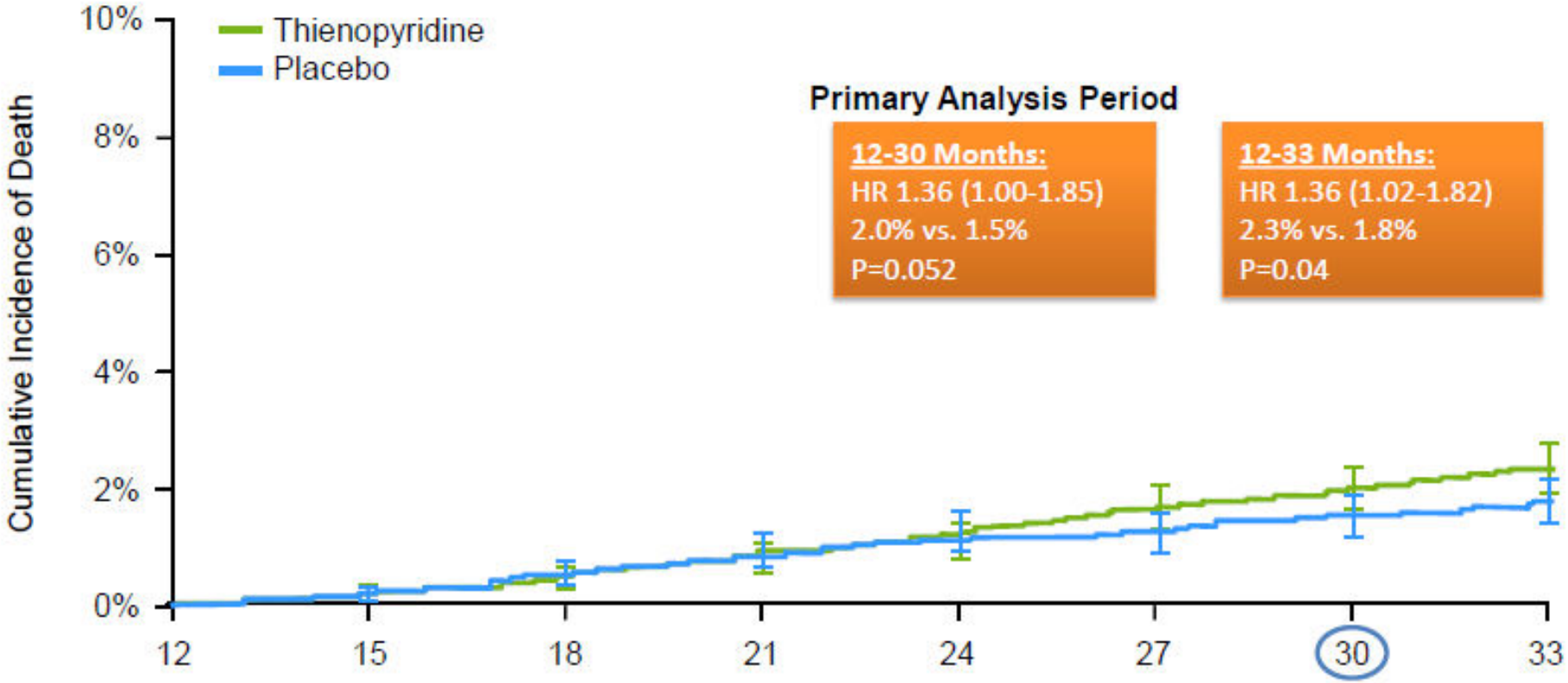
Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months

DAPT STUDY



All-Cause Mortality

DAPT STUDY



Primary Analysis Period

12-30 Months:
HR 1.36 (1.00-1.85)
2.0% vs. 1.5%
P=0.052

12-33 Months:
HR 1.36 (1.02-1.82)
2.3% vs. 1.8%
P=0.04

# At Risk								
Thienopyridine	5020	4936	4875	4835	4777	4703	4663	3139
Placebo	4941	4866	4805	4761	4700	4659	4618	3159

All-Cause Mortality

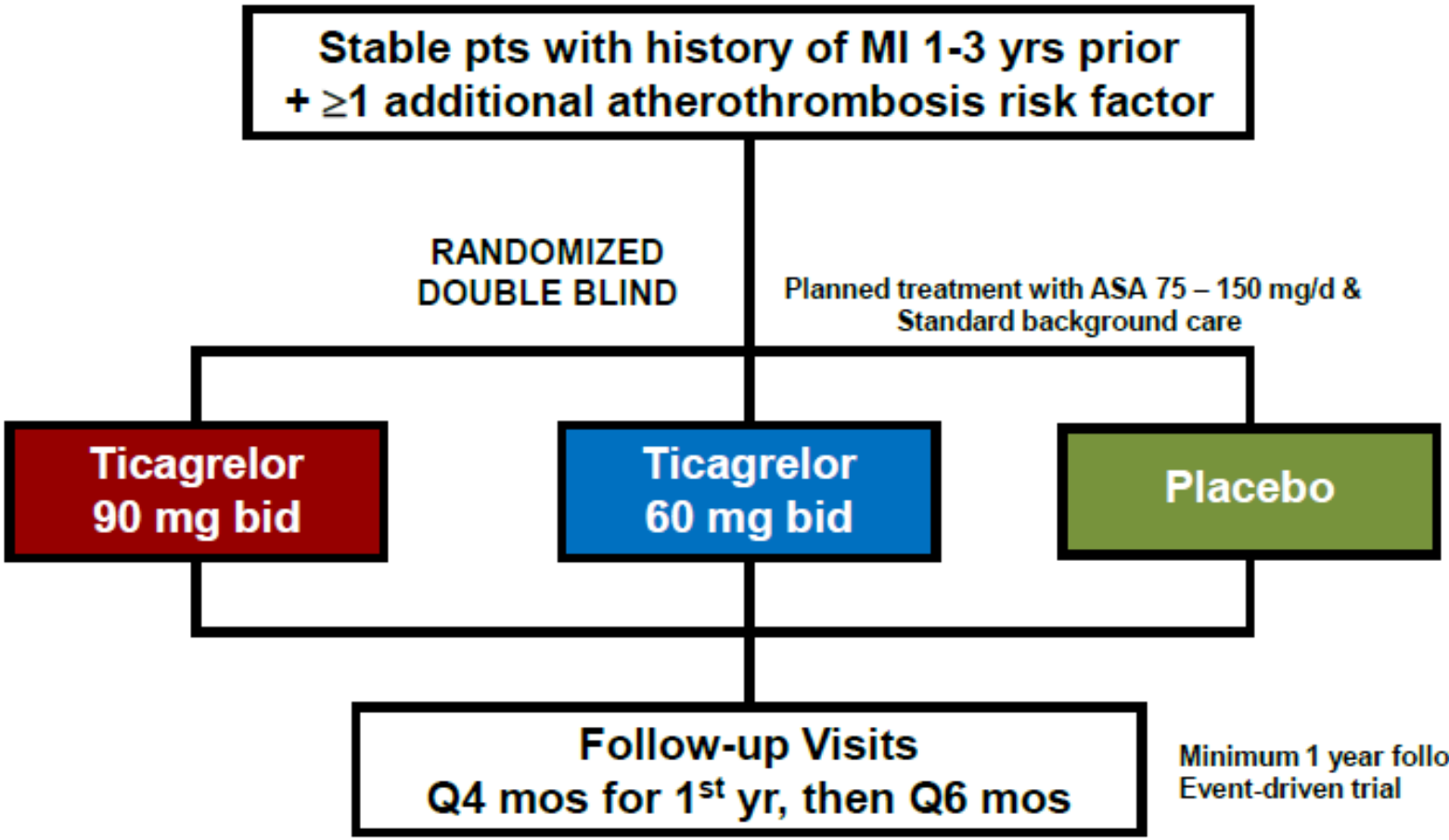
DAPT STUDY

12-30 Months				
	Thienopyridine N=5020	Placebo N=4941	P-Value	Absolute Difference
All-Cause Mortality	**98 (2.0%)**	**74 (1.5%)**	**0.052**	**24 (0.5%)**
Cardiac	45 (0.9%)	47 (1.0%)	0.98	-2 (-0.1%)
Vascular	5 (0.1%)	5 (0.1%)	0.98	0 (-)
Non-Cardiovascular	48 (1.0%)	22 (0.5%)	0.002	26 (0.5%)

Non-Cardiovascular Deaths, 12-33 Months			
Relatedness for Deaths*	Thienopyridine N=5020	Placebo N=4941	P-value
Bleeding-Related Death	11 (0.22%)	3 (0.06%)	0.057
Trauma-Related Death	9 (0.18%)	2 (0.04%)	0.07
Cancer-Related Death	31 (0.62%)	14 (0.28%)	0.02

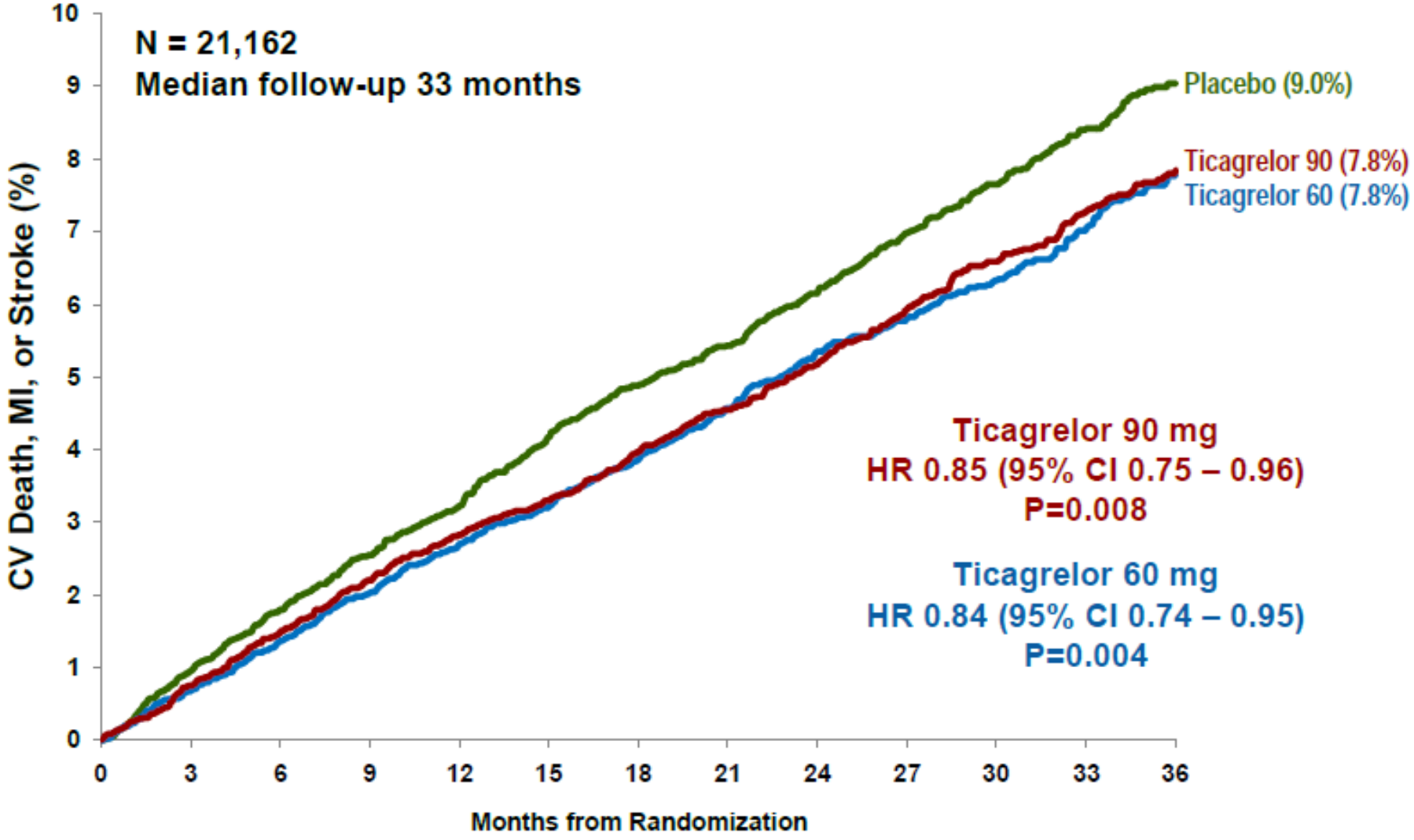
Cumulative incidence is presented according to Kaplan-Meier method

Trial Design

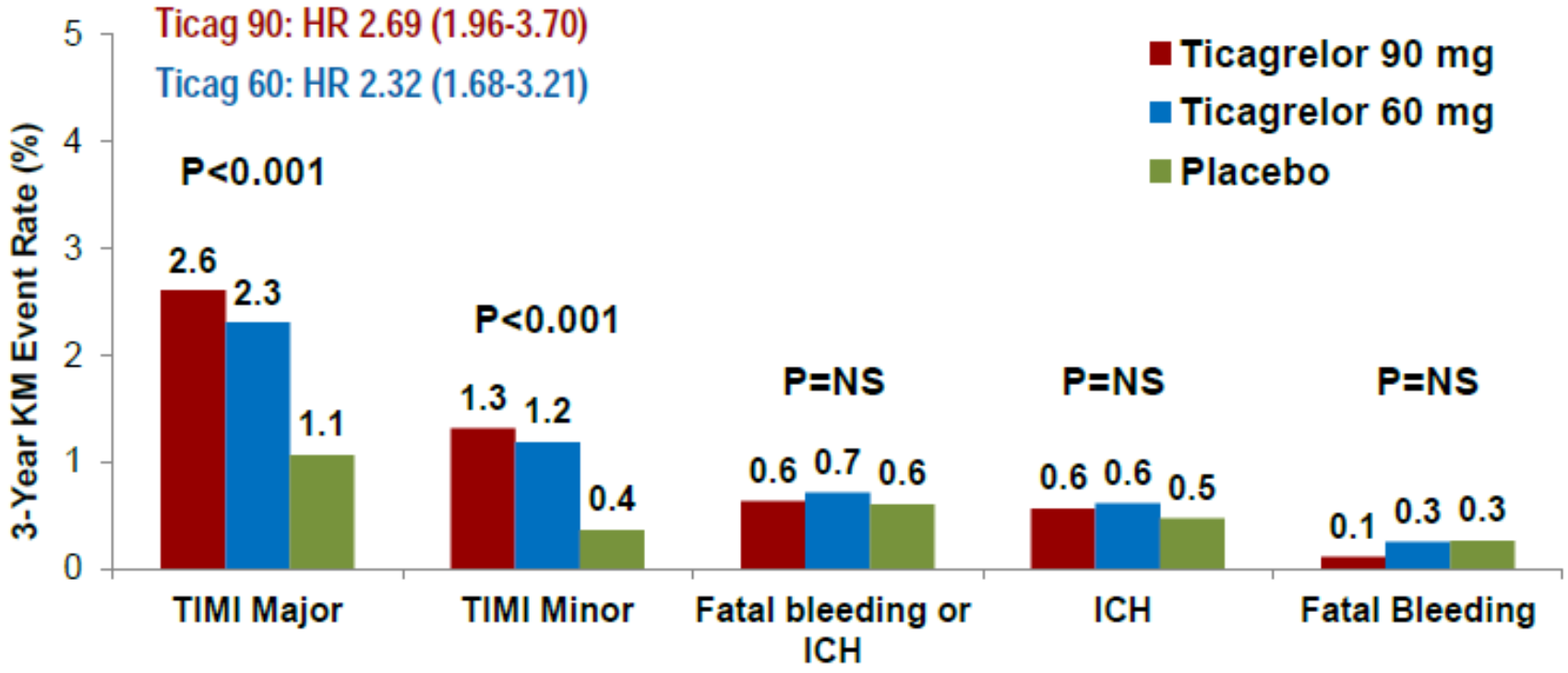


Bonaca MP et al. *Am Heart J* 2014;167:437-44

Primary Endpoint



Bleeding


Ticag 90: HR 2.69 (1.96-3.70)
Ticag 60: HR 2.32 (1.68-3.21)
Ticagrelor 90 mg
Ticagrelor 60 mg
Placebo
3-Year KM Event Rate (%)
0
1
2
3
4
5
P<0.001
2.6
2.3
1.1
P<0.001
1.3
1.2
0.4
P=NS
0.6
0.7
0.6
P=NS
0.6
0.6
0.5
P=NS
0.1
0.3
0.3
TIMI Major
TIMI Minor
Fatal bleeding or ICH
ICH
Fatal Bleeding