

Antithrombotic Treatment from the Ambulance through the Cath Lab

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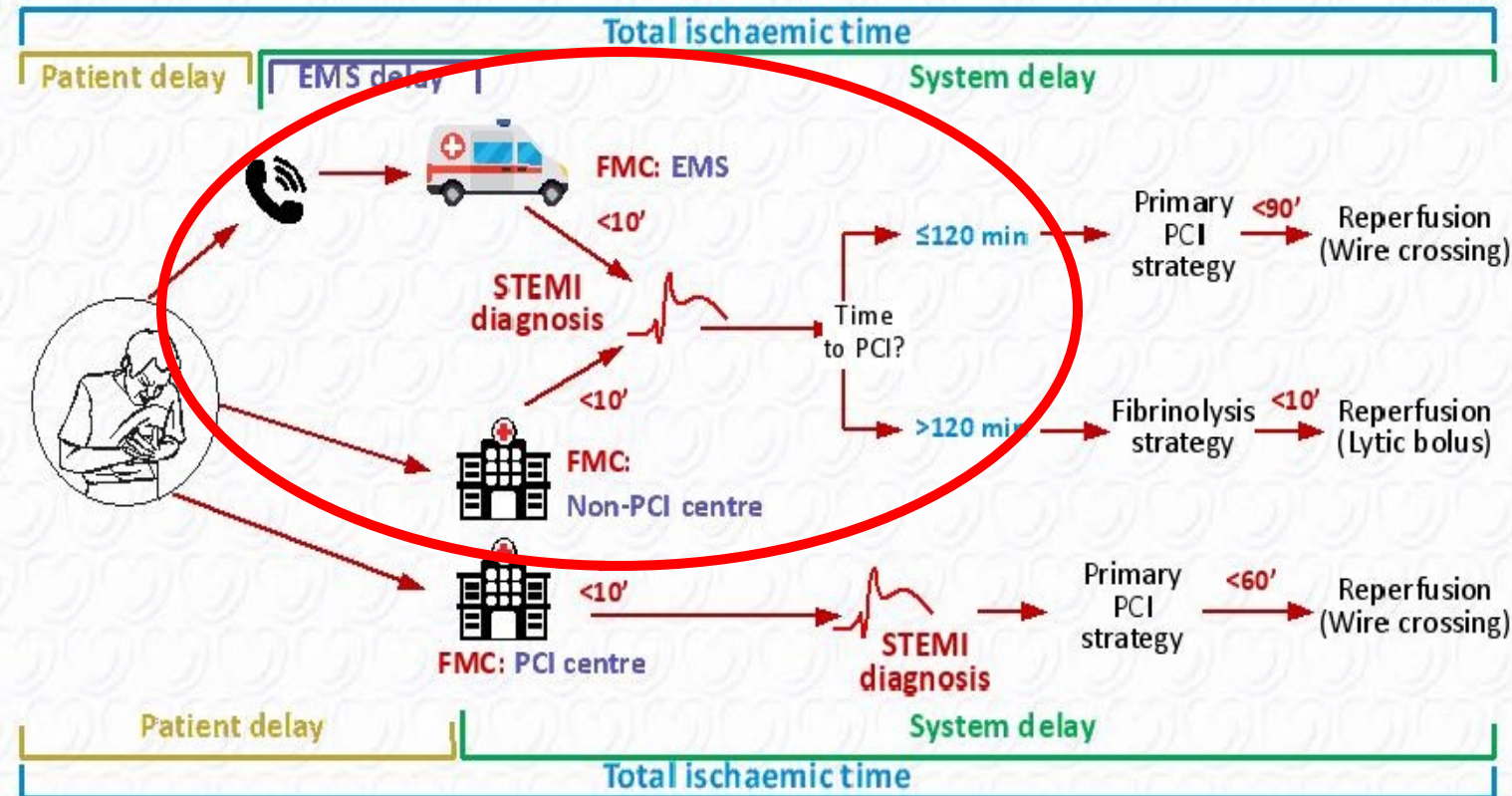
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Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (The presenter has previously or currently been involved in research contracts, consulting, speakers bureau or received research and educational grants from: Abbott, AstraZeneca, Aventis, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli-Lilly, Evolva, Fibrex, Janssen, Merck, Myogen, Medtronic, Mitsubishi Pharma, The Medicines Company, Nycomed, Organon, Pfizer, Pharmacia, Regado, Sanofi, Searle, Servier, ViFor Pharma, Zoll Medical Corporation)
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Modes of patient presentation, components of ischaemic time and flowchart for reperfusion strategy selection



STEMI Diagnosis & Treatment in the AMBULANCE

- 12 lead ECG →
- Treatment
 - Morphine
 - Oxygen
 - Nitro
 - Aspirin 150-300 mg
 - Heparin / Bivalirudin / Enoxaparin
 - Ticagrelor 180 mg
 - Prasugrel 60 mg
 - Clopidogrel 600 mg





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Anti-Thrombotics

Antiplatelets

Anticoagulation

2014 ESC Myocardial Revascularisation Guidelines: Primary PCI

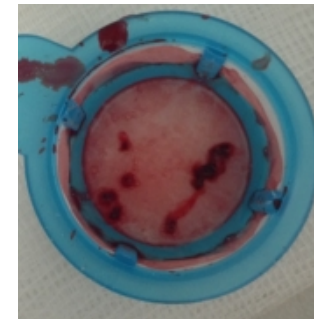
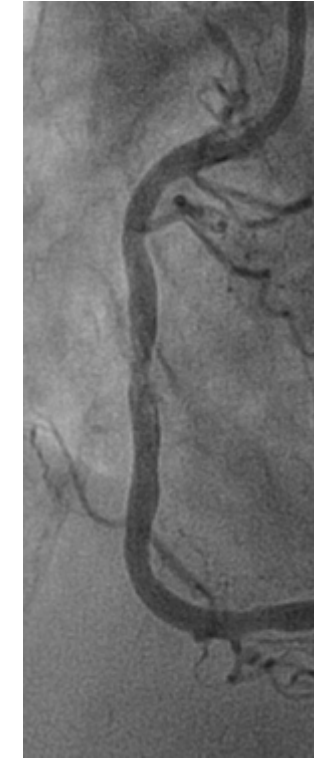
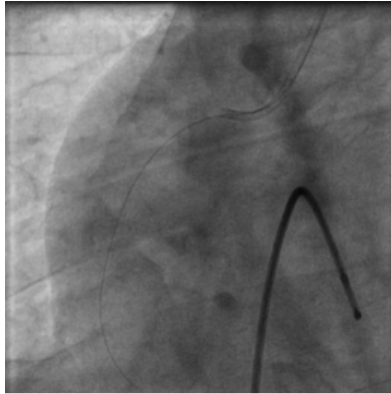
Patients undergoing primary PCI should receive a combination of DAPT with ASA and a P2Y₁₂ receptor blocker, as early as possible before angiography, and a parenteral anticoagulant.

Recommendations	Class ^a	Level ^b
Antiplatelet therapy		
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300mg (or 80–150mg i.v.) and at a maintenance dose of 75–100mg 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
P2Y₁₂ inhibitors should be given at time of first medical contact.	I	B

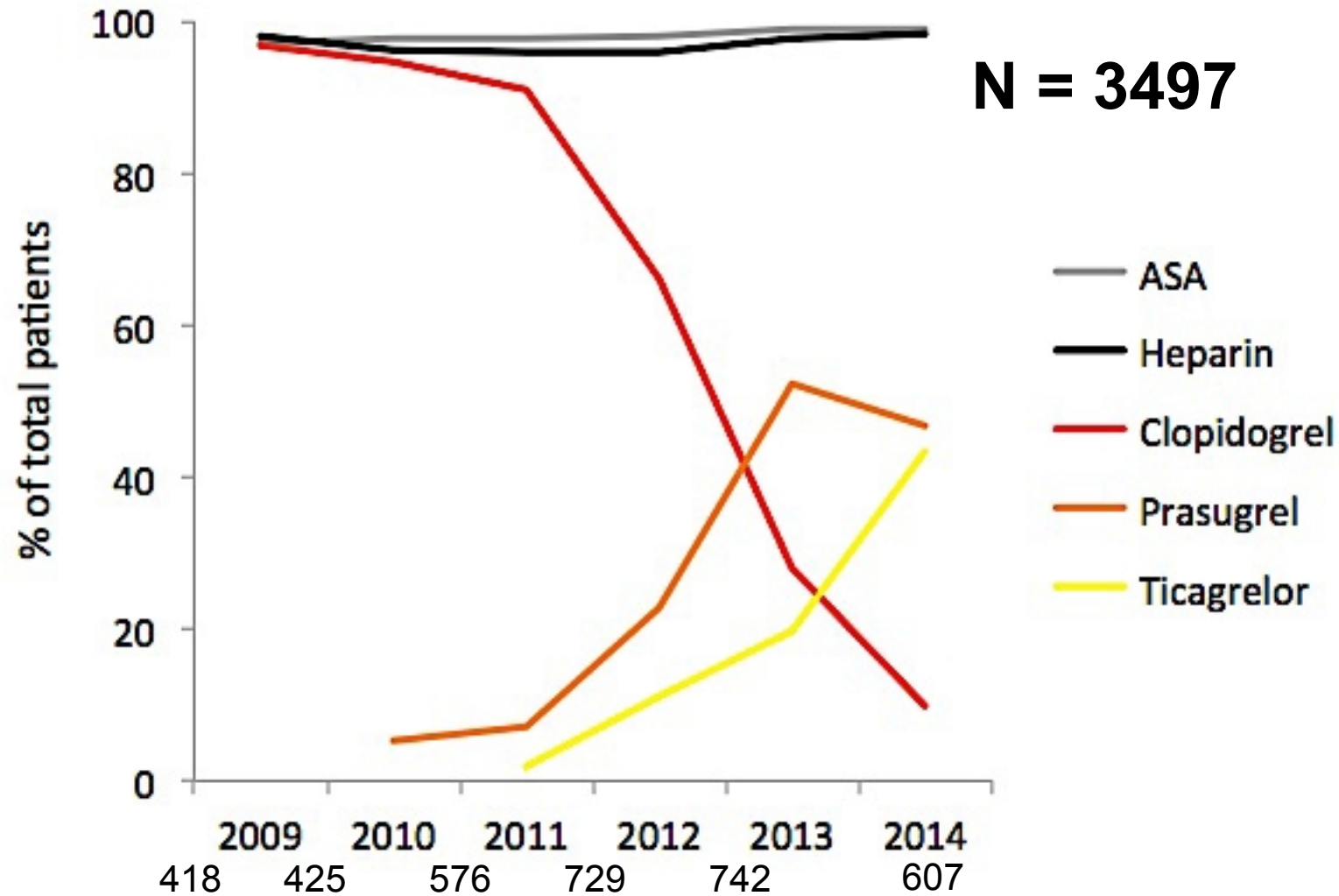


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Pre-Treatment = Before Cardiac Cath / PCI



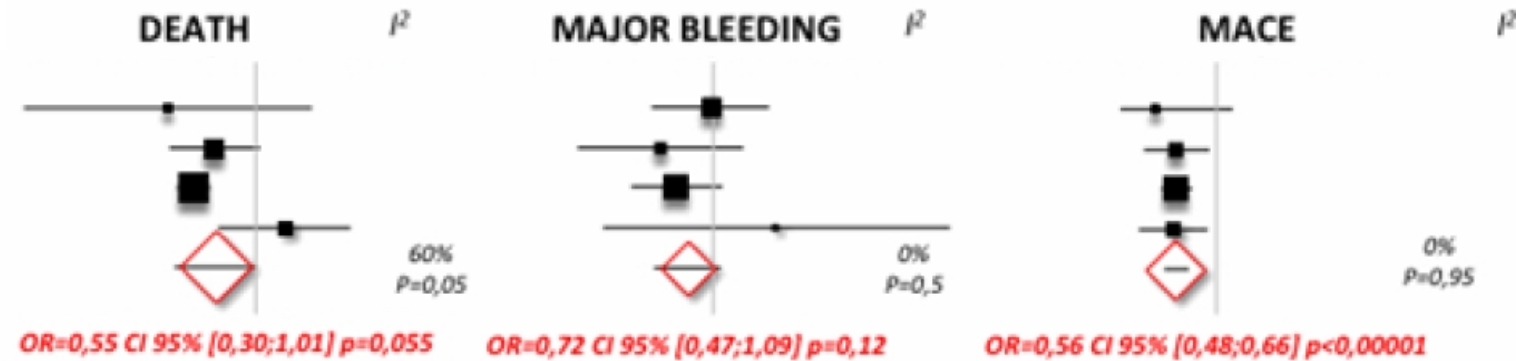
Prehospital Antithrombotics



of patients

Clopidogrel pretreatment

STEMI N=8 536
CIPAMI
CLARITY PCI
Dorler et al.
Fefer et al.
All STEMI



Bellemain-Apaix A et al. for the ACTION group, TCT 2013.



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Is Prehospital P2Y₁₂ Inhibition Useful ?



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction

Gilles Montalescot, M.D., Ph.D., Arnoud W. van 't Hof, M.D., Ph.D.,
Frédéric Lapostolle, M.D., Ph.D., Johanne Silvain, M.D., Ph.D.,
Jens Flensted Lassen, M.D., Ph.D., Leonardo Bolognese, M.D.,
Warren J. Cantor, M.D., Ángel Cequier, M.D., Ph.D., Mohamed Chettibi, M.D., Ph.D.,
Shaun G. Goodman, M.D., Christopher J. Hammitt, M.B., Ch.B., M.D., Kurt Huber, M.D.,
Magnus Janzon, M.D., Ph.D., Béla Merkely, M.D., Ph.D., Robert F. Storey, M.D., D.M.,
Uwe Zeymer, M.D., Olivier Sibbe, M.D., Patrick Ecollan, M.D.,
Wim M.J.M. Heutz, M.D., Eva Swahn, M.D., Ph.D., Jean-Philippe Collet, M.D., Ph.D.,
Frank F. Willems, M.D., Ph.D., Caroline Baradat, M.Sc., Muriel Licour, M.Sc.,
Anne Tsatsaris, M.D., Eric Vicaut, M.D., Ph.D., and Christian W. Hamm, M.D., Ph.D.,
for the ATLANTIC Investigators*

ABSTRACT

BACKGROUND

The direct-acting platelet P2Y₁₂ receptor antagonist ticagrelor can reduce the incidence of major adverse cardiovascular events when administered at hospital admission to patients with ST-segment elevation myocardial infarction (STEMI). Whether prehospital administration of ticagrelor can improve coronary reperfusion and the clinical outcome is unknown.

METHODS

We conducted an international, multicenter, randomized, double-blind study involv-

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Montalescot at the Allies in Cardiovascular Trials Initiatives and Organized Networks (ACTION) Study Group, Institut de Cardiologie, Centre Hospitalier Universitaire Pitié-Salpêtrière, 47 Blvd. de l'Hôpital, 75013 Paris, France, or at gilles.montalescot@psl.aphp.fr.

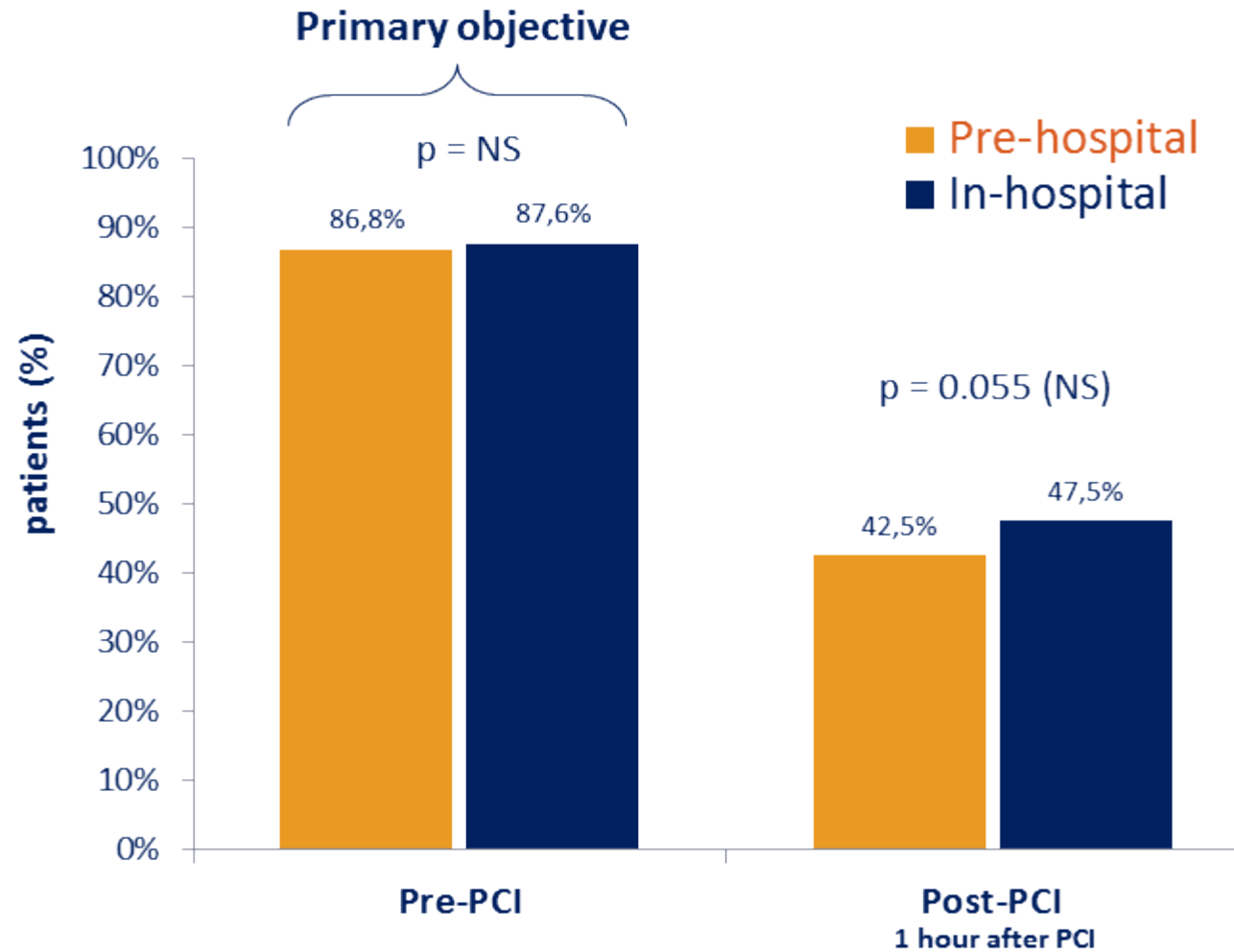


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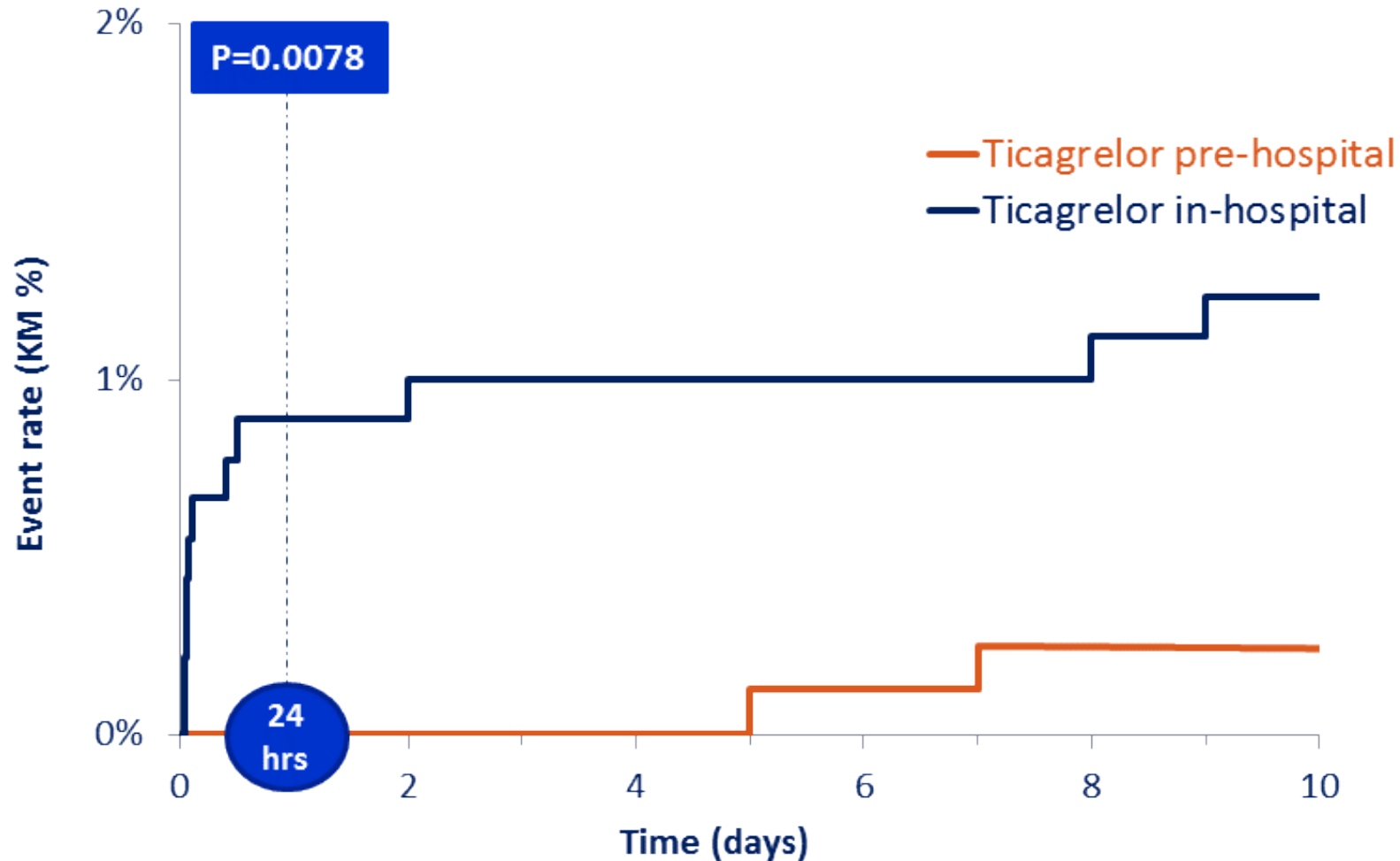
ATLANTIC 1st Co-primary endpoint

No ST-segment resolution ($\geq 70\%$)

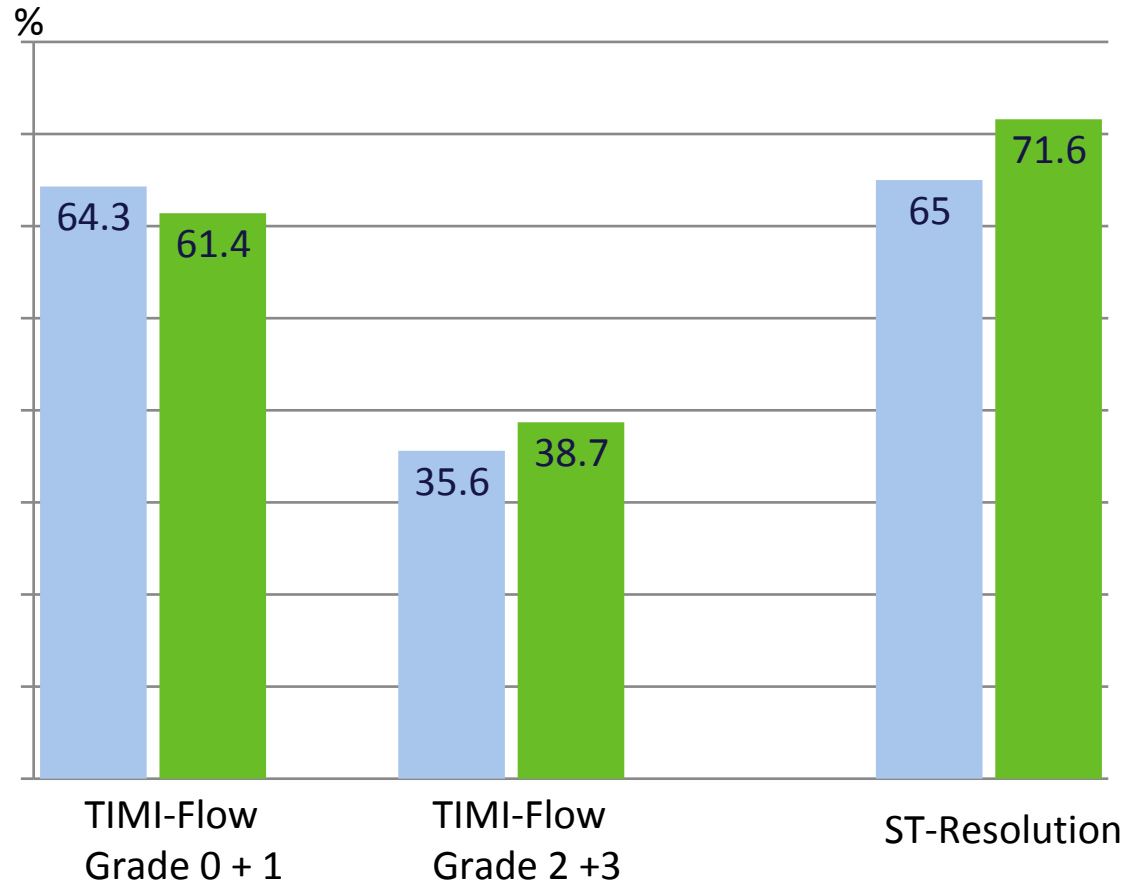




Definite stent thrombosis up to 10 days



TIMI flow and ST resolution by thienopyridine



 Pure clopidogrel  Pure prasugrel

TIMI-Flow 2-3 before pPCI

Odds ratio, [confidence interval]
1,138 [0,883-1,466], p=0,32

Adjusted by covariates:
1,170 [0,868-1,1585], p=0,31

ST-Resolution $\geq$ 50% within 60 min

Odds ratio, [confidence interval]
1,356 [1,050 -1,751], p=0,02*

Adjusted by covariates:
1,543 [1,138-2,093], p=0,01*

ON-TIME 2

The Lancet 2008; 372: 537-46

Articles

Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial



Arnoud WJ van't Hof, Jurriën ten Berg, Ton Heestermaas, Thorsten Dill, Reinhard C Funck, Wouter van Werkum, Jan-Henk E Dambrink, Harry Suryapranata, Gert van Houwelingen, Jan Paul Ottervanger, Pieter Stella, Evangelos Giannitsis, Christian Hamm, on behalf of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group*

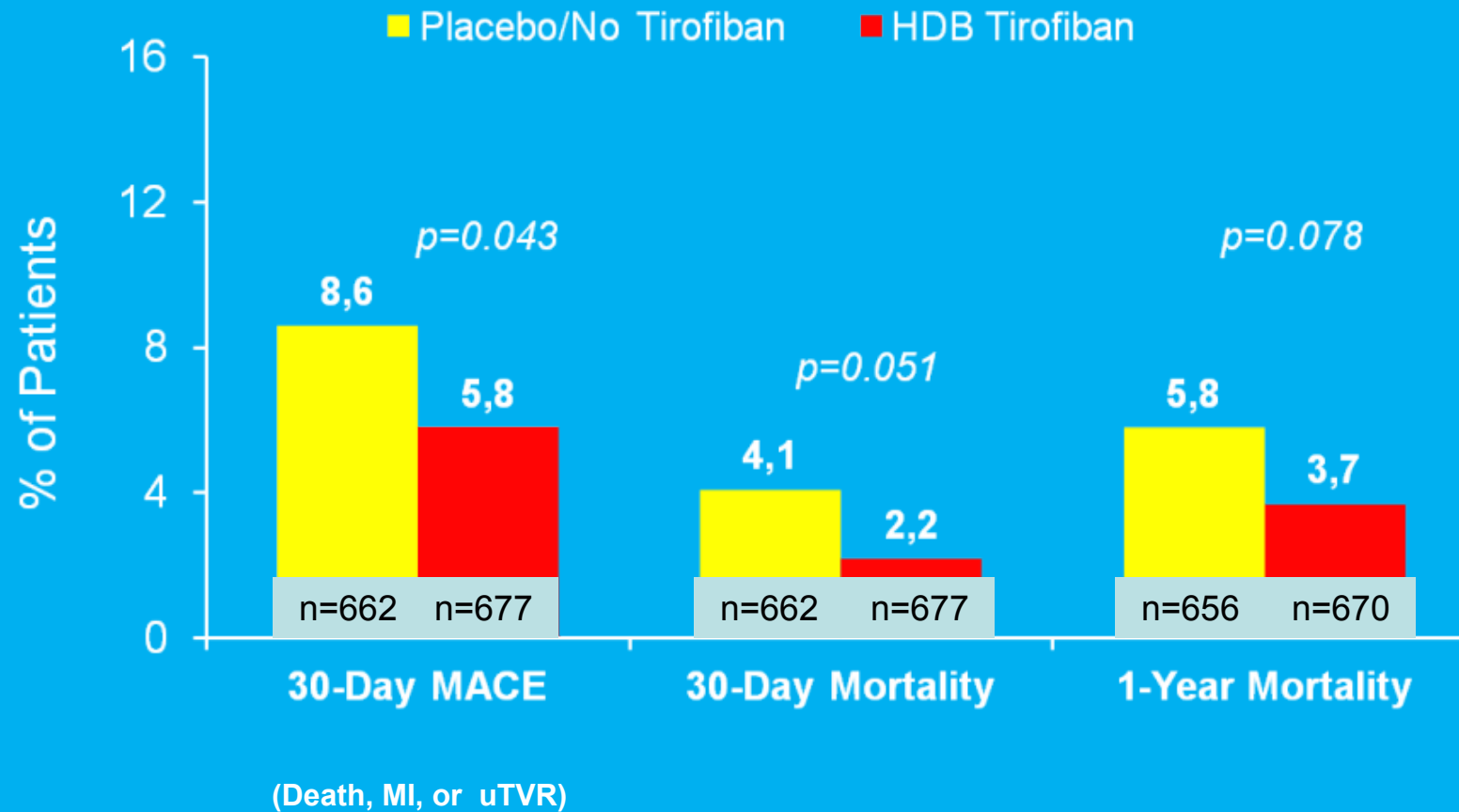
Summary

Background The most effective magnitude and timing of antiplatelet therapy is important in patients with acute *Lancet 2008; 372: 537-46*

Open and blinded study combined

Total Pooled Cohort (n=1398)

On-TIME 2
Pooled





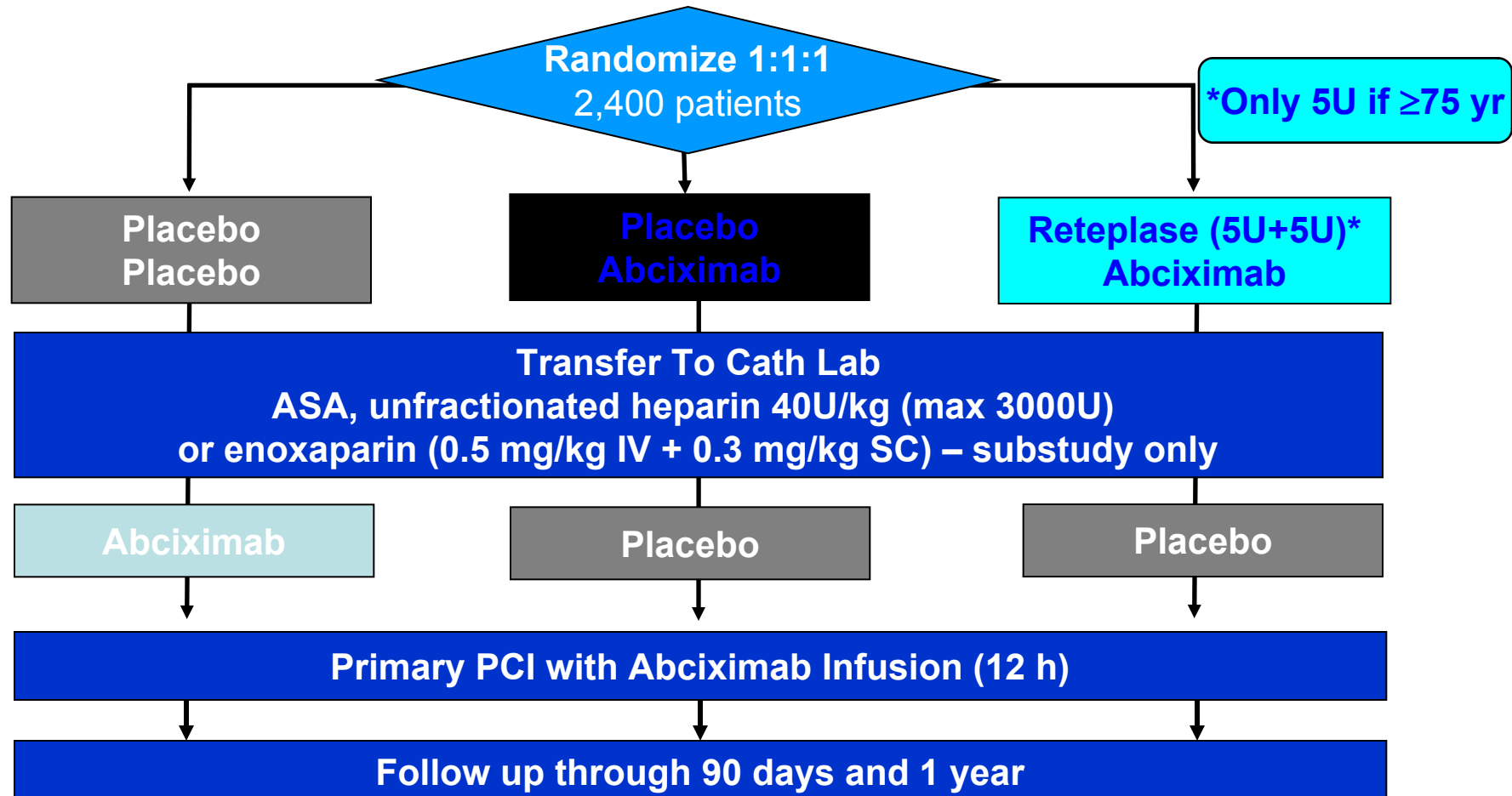
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FINESSE: Study Design

Acute ST Elevation MI (or New LBBB) within 6h pain onset

Presenting at Hub or Spoke with estimated time to Cath between 1
& 4h



Euromax Procedures, Medications

	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)
Initial anticoagulation — no. (%)		
Bivalirudin	1074 (98.6)	29 (2.6)
Unfractionated heparin	24 (2.2)	997 (89.9)
Enoxaparin	0	94 (8.5)
Time from initiating anticoagulation to angiography — median (IQR), min	50.0 (37–67)	50.0 (37–65)
Glycoprotein IIb/IIIa inhibitor use — no. (%)	125/1088 (11.5)	766/1109 (69.1)*
Routine	42/1088 (3.9)‡	649/1109 (58.5)*
Bailout [§]	83/1046 (7.9)	117/460 (25.4)*
Femoral access — no. (%)	558/1069 (52.2)	582/1084 (53.7)
Radial access — no. (%)	510/1069 (47.7)	502/1084 (46.3)

* P < 0.05 between groups

PG Steg et al NEJM 2014

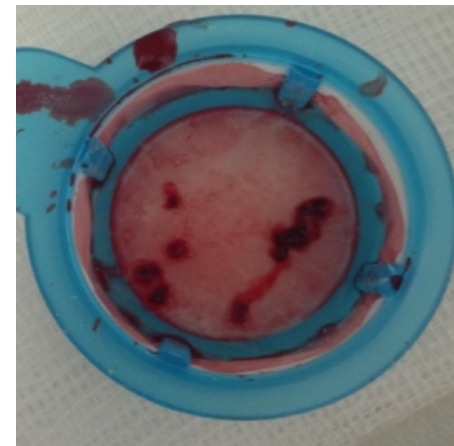
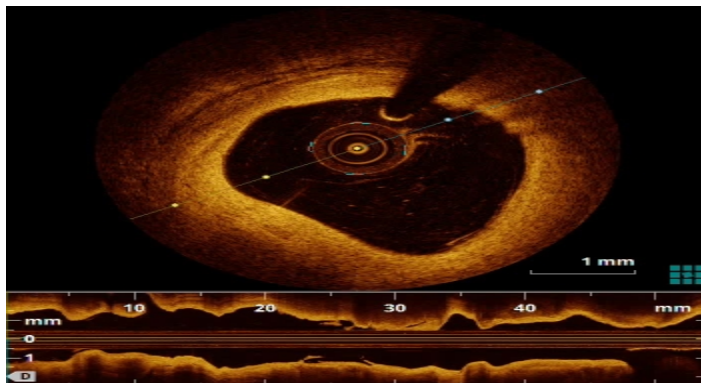
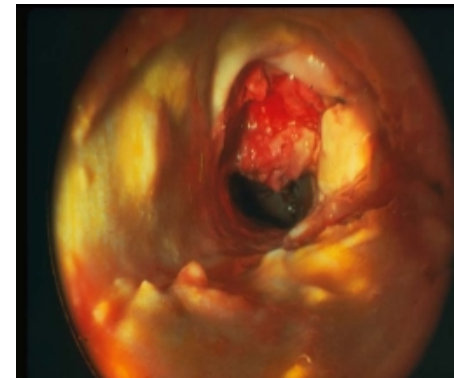
Periprocedural and postprocedural antithrombotic therapy in patients undergoing primary percutaneous coronary intervention

Recommendations	Class	Level
Antiplatelet therapy		
A potent P2Y ₁₂ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contra-indicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contra-indications such as excessive risk of bleeding.	I	A
Aspirin (oral or i.v, if unable to swallow) is recommended as soon as possible for all patients without contra-indications.	I	B
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received P2Y ₁₂ receptor inhibitors.	IIb	A

How to attack the Intracoronary Thrombus

- **Anticoagulation**

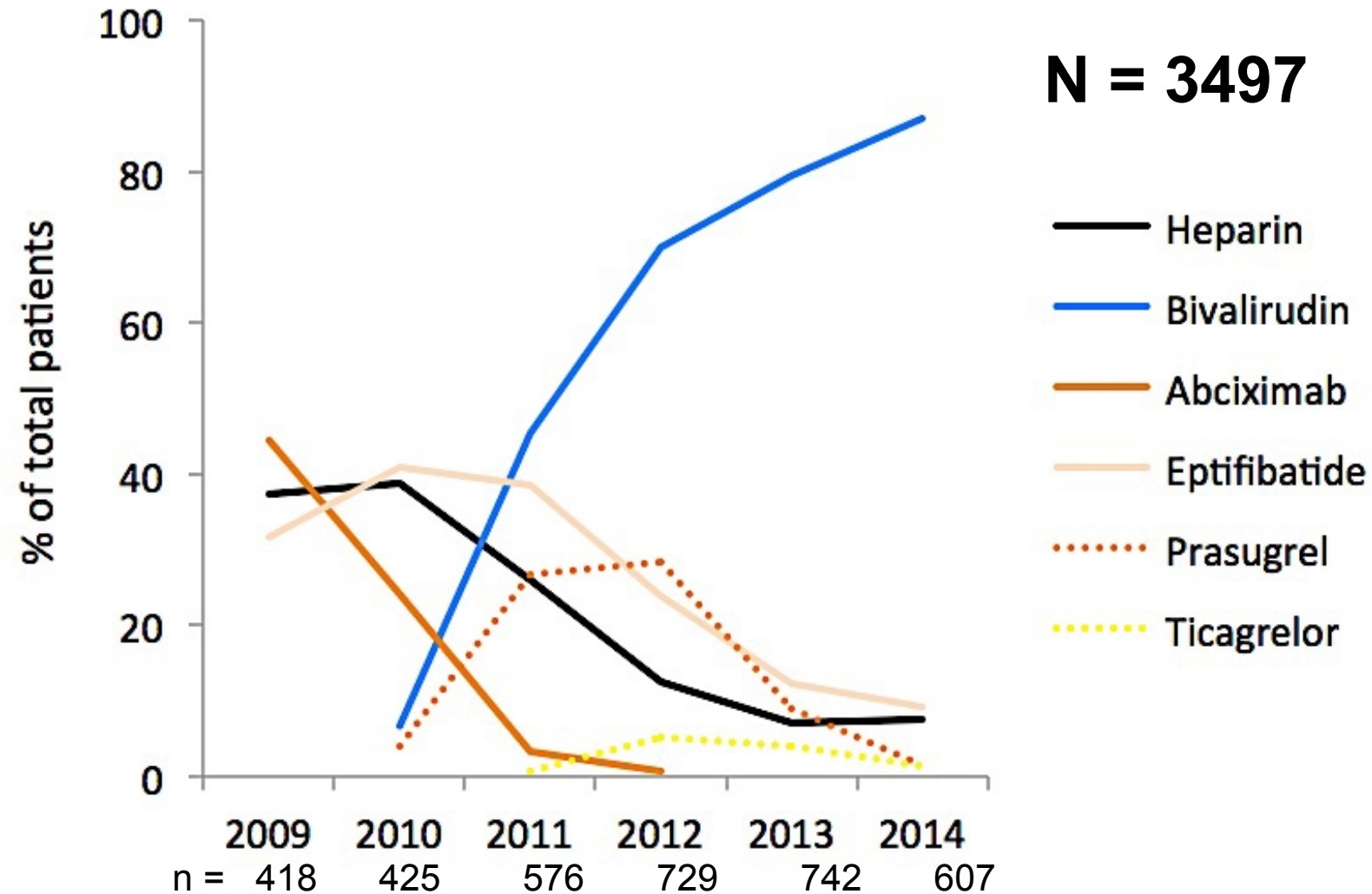
Antiplatelets



Periprocedural and postprocedural antithrombotic therapy in patients undergoing primary percutaneous coronary intervention

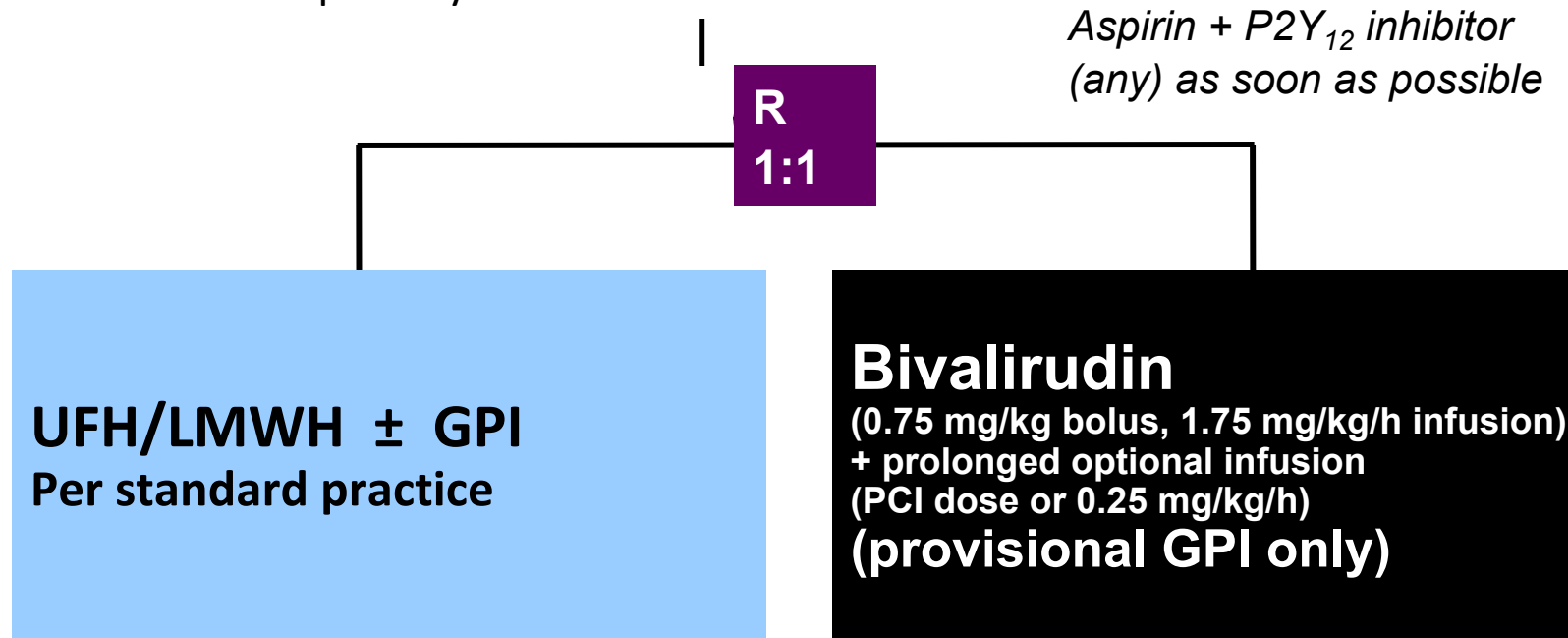
Recommendations	Class	Level
Anticoagulant therapy		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI.	I	C
Routine use of UFH is recommended.	I	C
In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI.	I	C
Routine use of enoxaparin i.v. should be considered.	IIa	A
Routine use of bivalirudin should be considered.	IIa	A
Fondaparinux is not recommended for primary PCI.	III	B

In-Hospital Antithrombotics



Trial Design

2218 patients with STEMI with symptom onset >20 min and ≤12h
Randomized in ambulance or non-PCI hospital
Intent for primary PCI



Primary endpoint: 30-day death or non-CABG related major bleeding

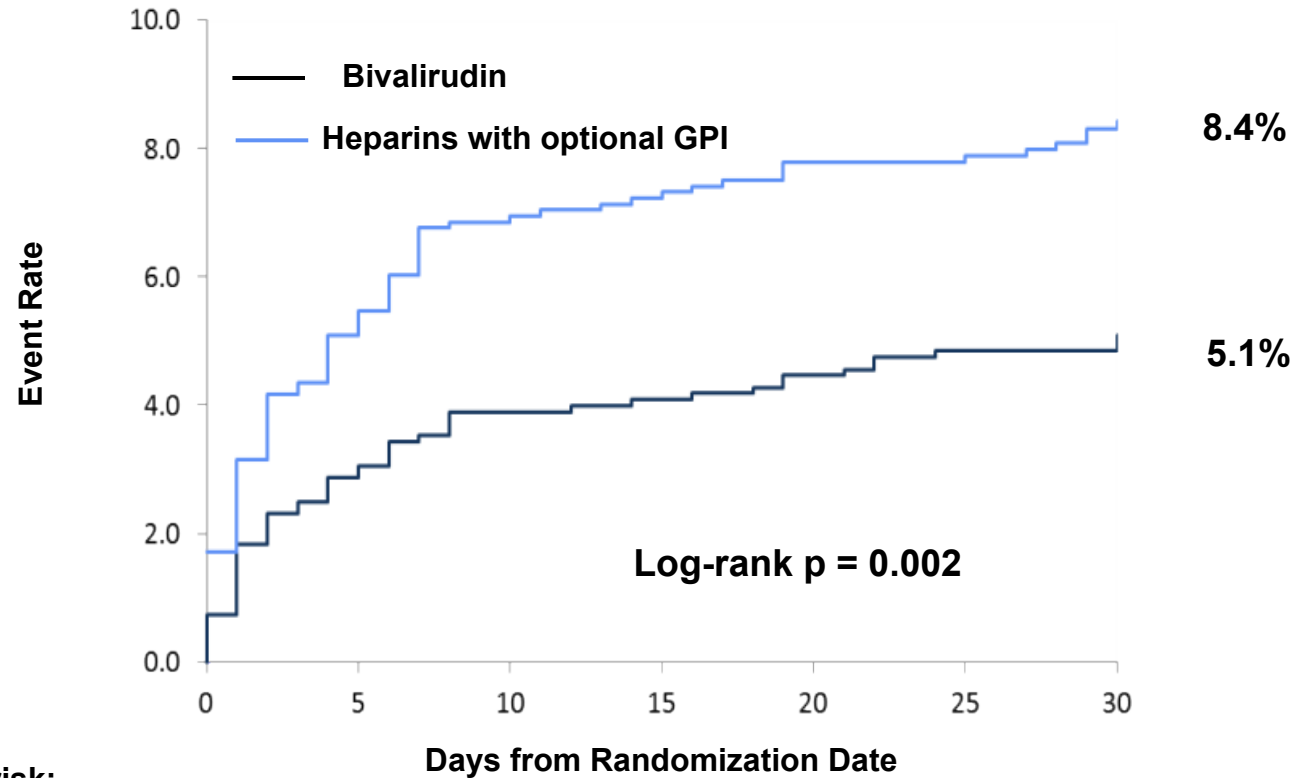
Key Secondary endpoint: Death, Re-infarction or non-CABG major bleeding at 30 days

Clinical FU at 30 days and 1 year



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Primary Endpoint: Death/Major Bleed, 30 day



Patients at risk:

Bivalirudin	1089	1038	1024	1020	1007	988	791
Heparins with optional GPI	1109	1024	1003	998	984	958	765



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Bivalirudin vs Heparin

Which price are you willing to pay for less bleeds

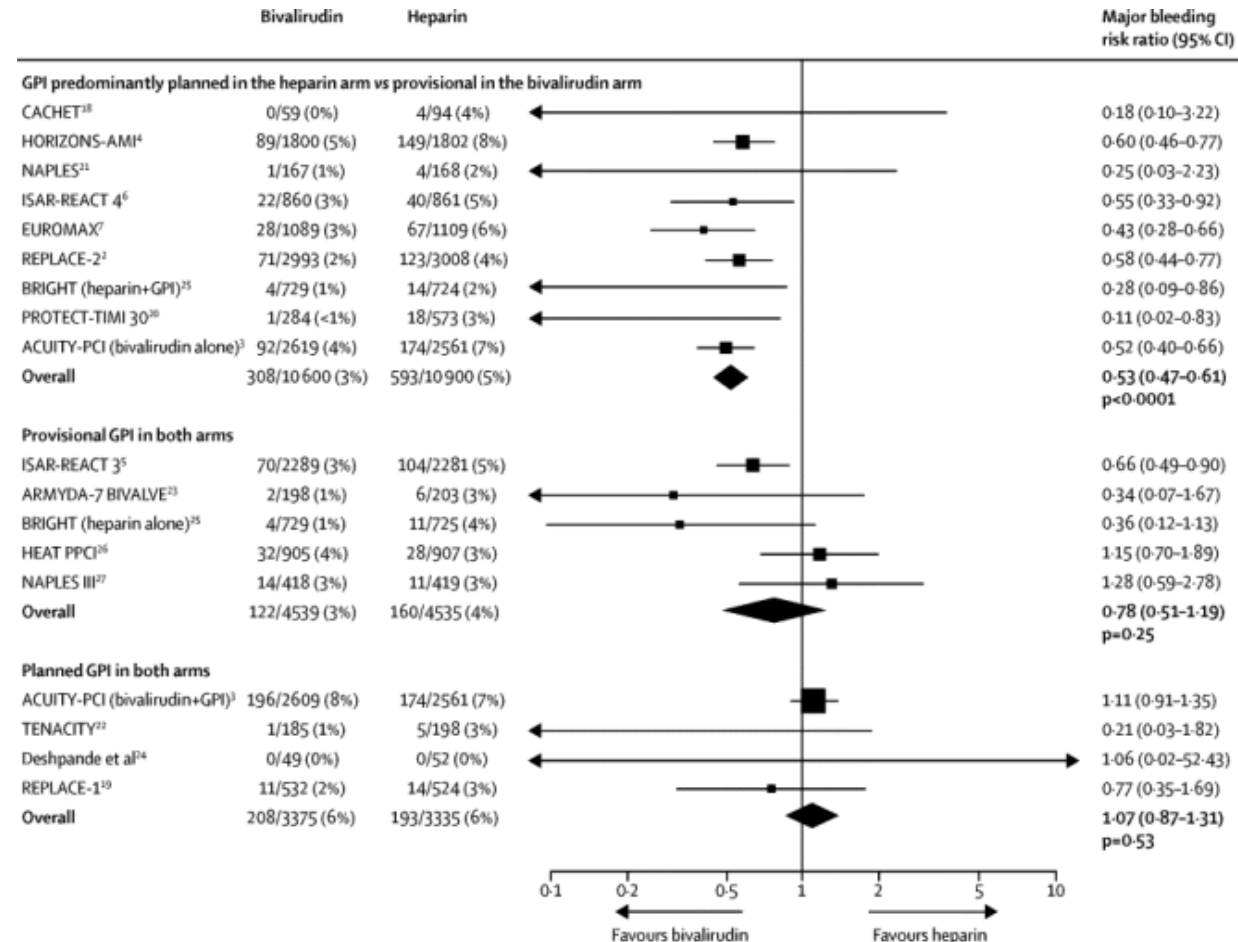
Conflicting trial results on mortality

Understanding Stent Thrombosis

Bivalirudin vs Heparin

Major bleeding

Patients planned for percutaneous coronary intervention:
Meta-analysis stratified by use of glycoprotein IIb/IIIa inhibitors





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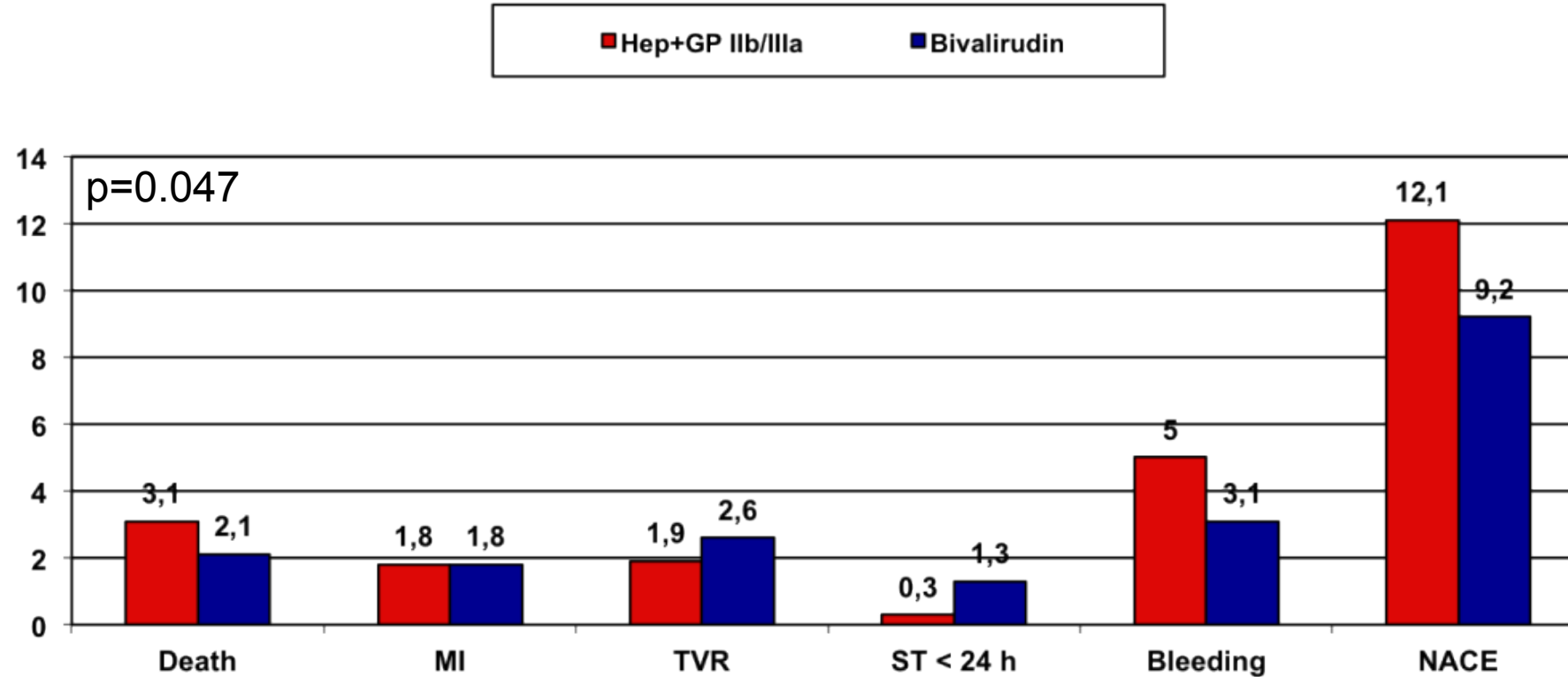
Bivalirudin vs Heparin

Which price are you willing to pay for less bleeds

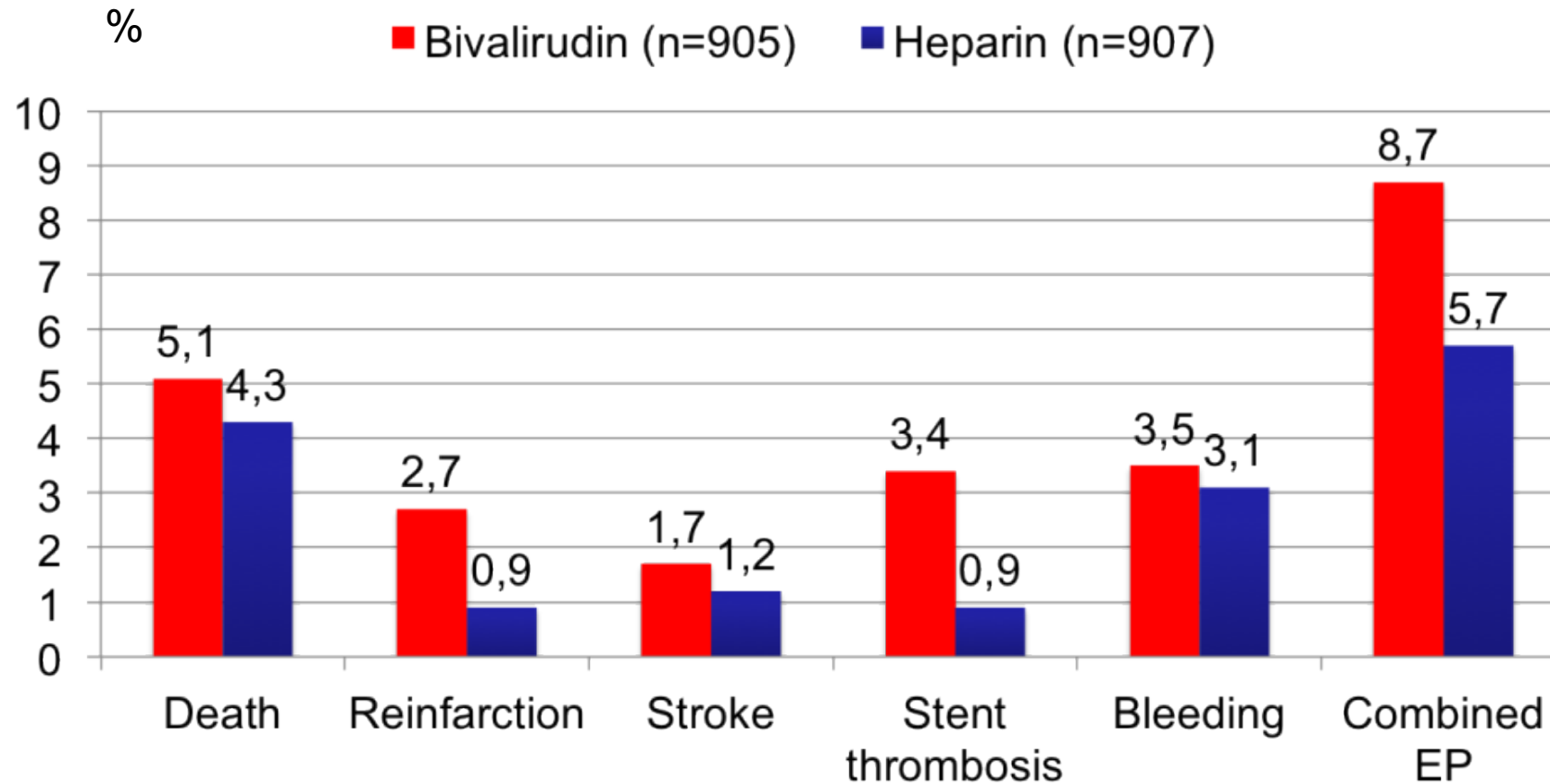
Conflicting trial results on mortality

Understanding Stent Thrombosis

HORIZONS-AMI 30-day results



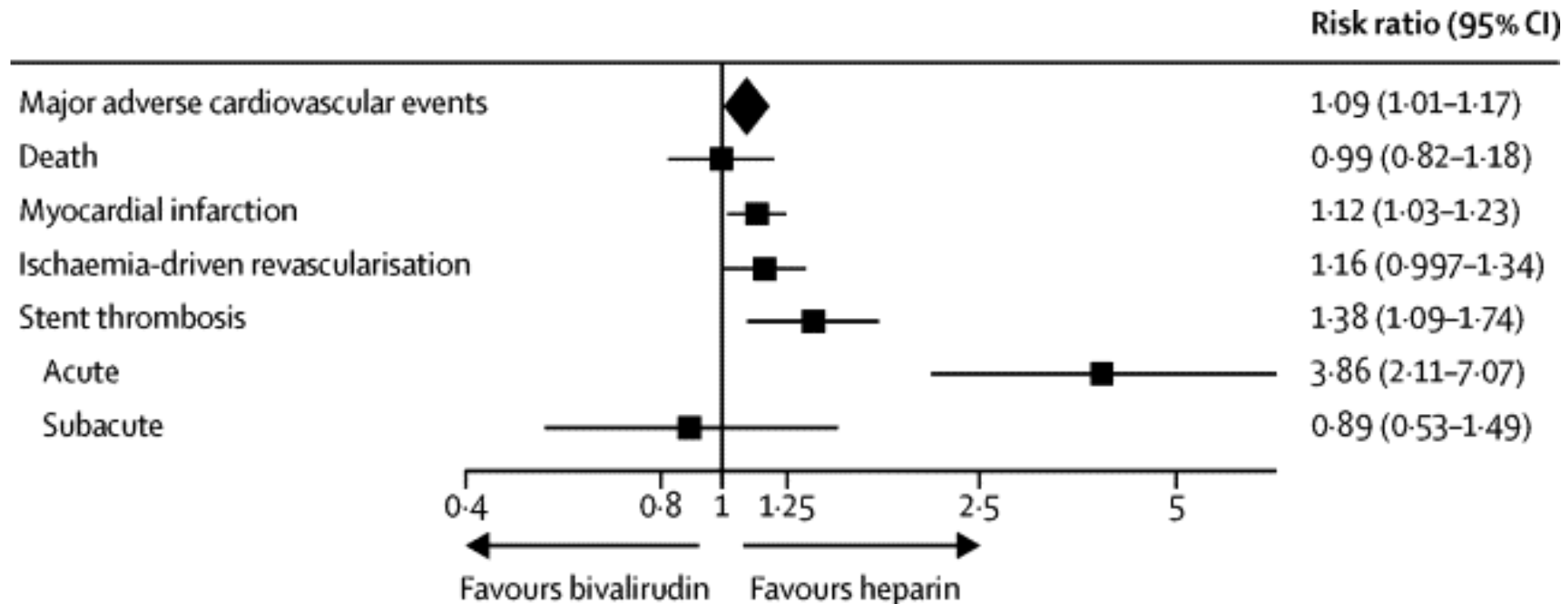
HEAT-PPCI 28-day results



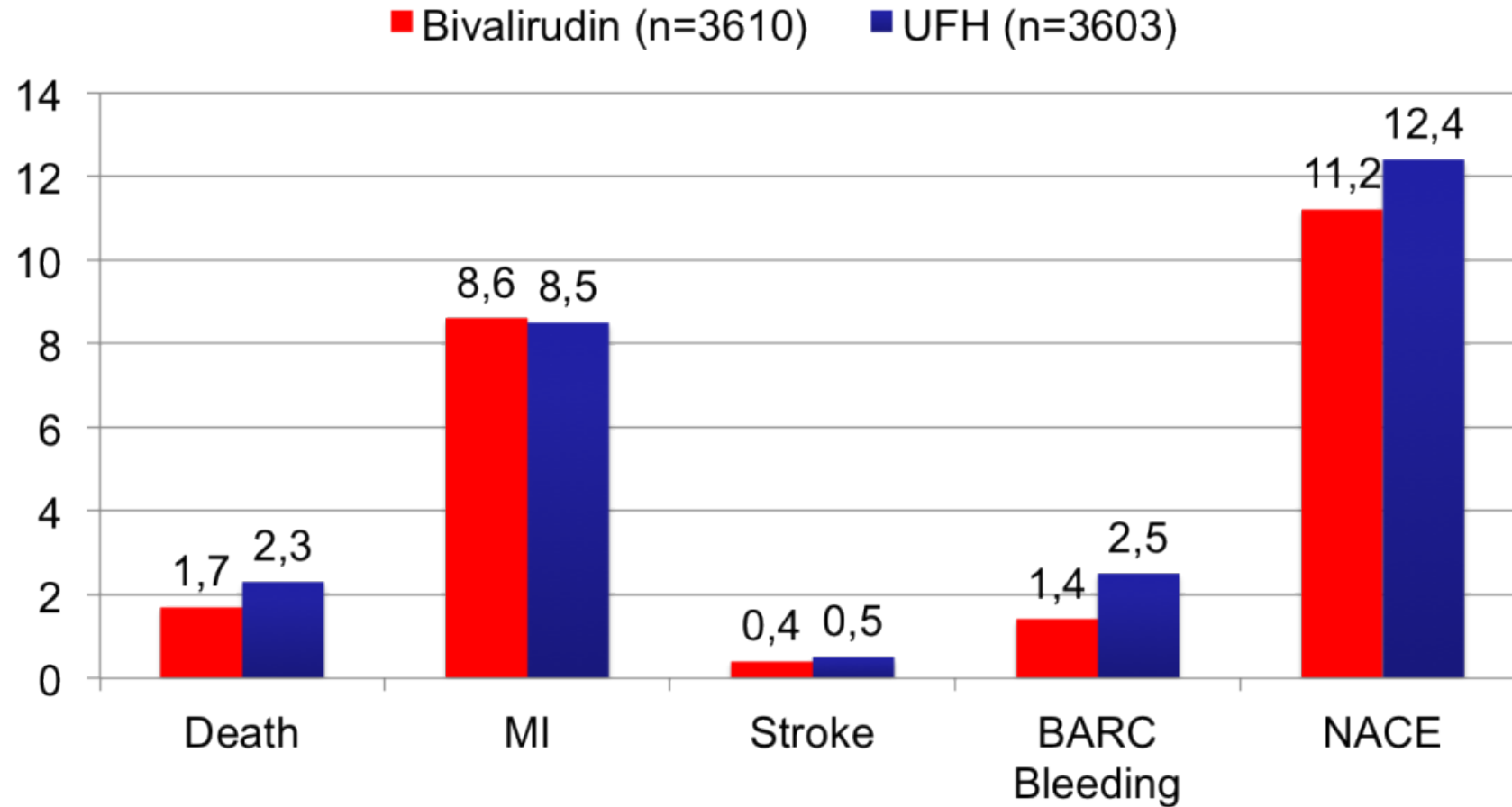
Bivalirudin vs Heparin

Major CV Events

Patients planned for PCI - Meta-analysis



MATRIX-Trial





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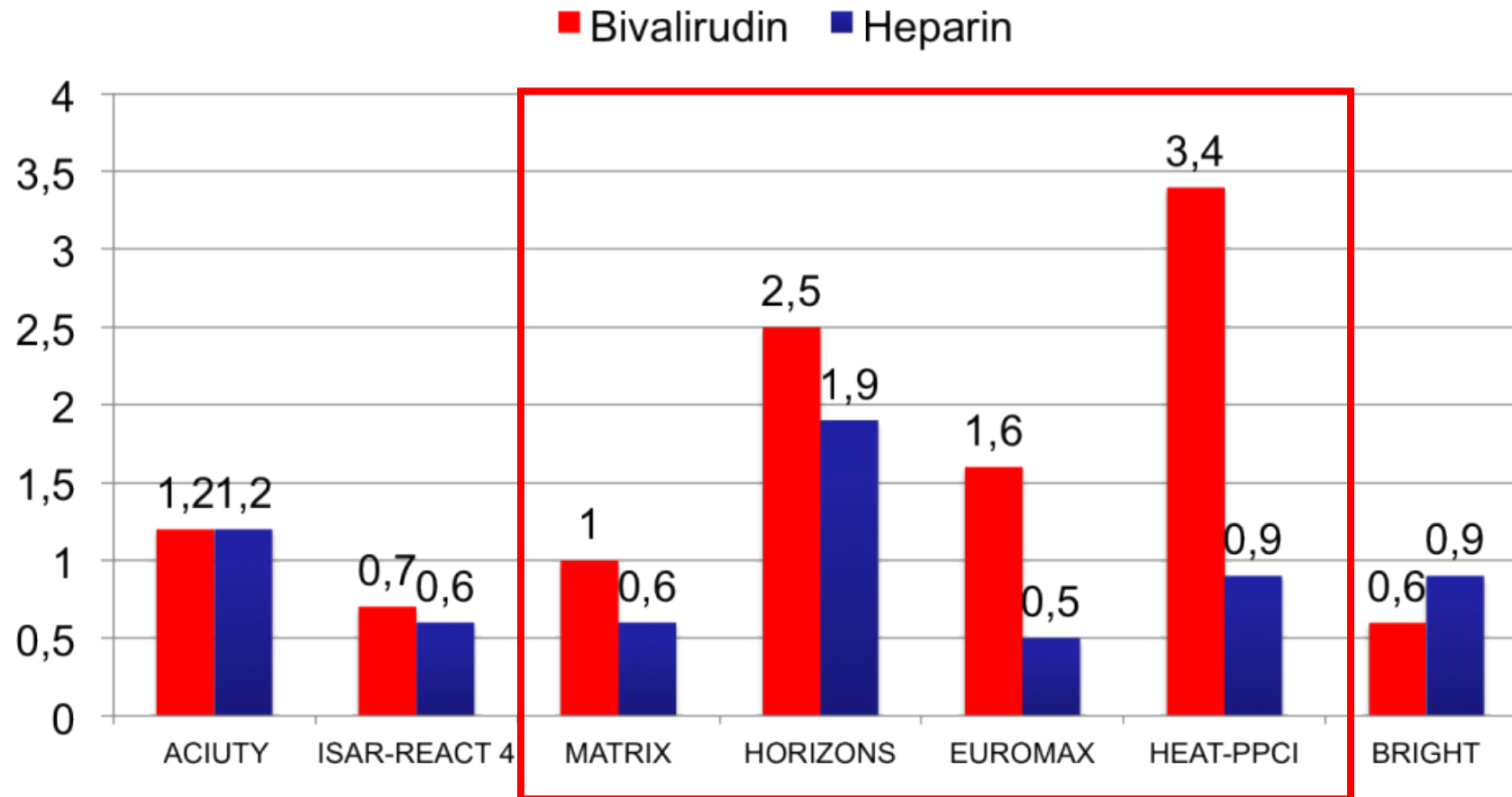
Bivalirudin vs Heparin

Which price are you willing to pay for less bleeds

Conflicting trial results on mortality

Understanding Stent Thrombosis

Stent thrombosis in RCTs

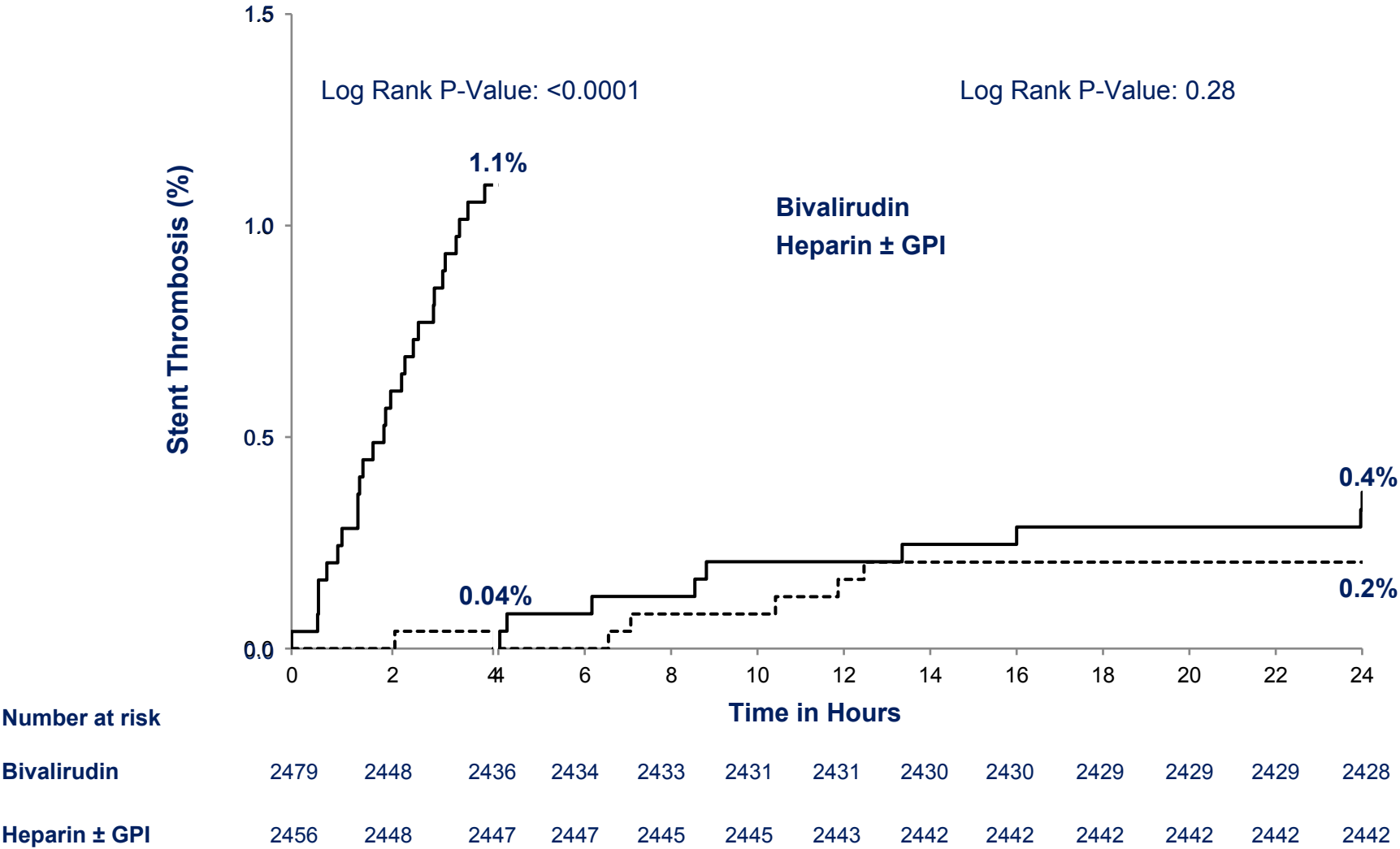


Early Stent Thrombosis and Mortality After Primary Percutaneous Coronary Intervention in ST-Segment–Elevation Myocardial Infarction

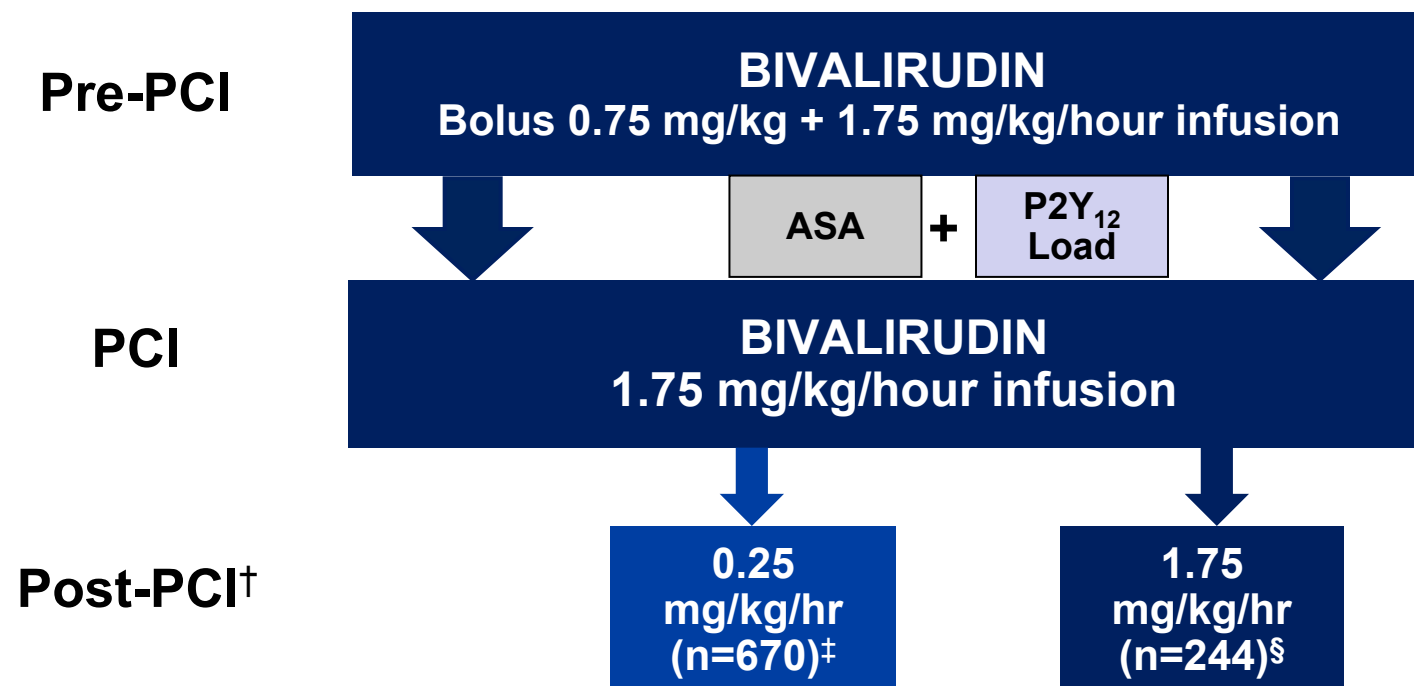
A Patient-Level Analysis of 2 Randomized Trials

George D. Dangas, MD, PhD; Mikkel M. Schoos, MD, PhD; Philippe Gabriel Steg, MD; Roxana Mehran, MD; Peter Clemmensen, MD, DMSc; Arnoud van 't Hof, MD, PhD; Jayne Prats, PhD; Debra Bernstein, PhD; Efthymios N. Deliargyris, MD; Gregg W. Stone, MD

Time-to-event Curves for Acute Stent Thrombosis (Within 24 hours of PCI) With a 4-hour Landmark Analysis



Treatment Breakdown and Outcomes by Bivalirudin Post-PCI Infusion Dose

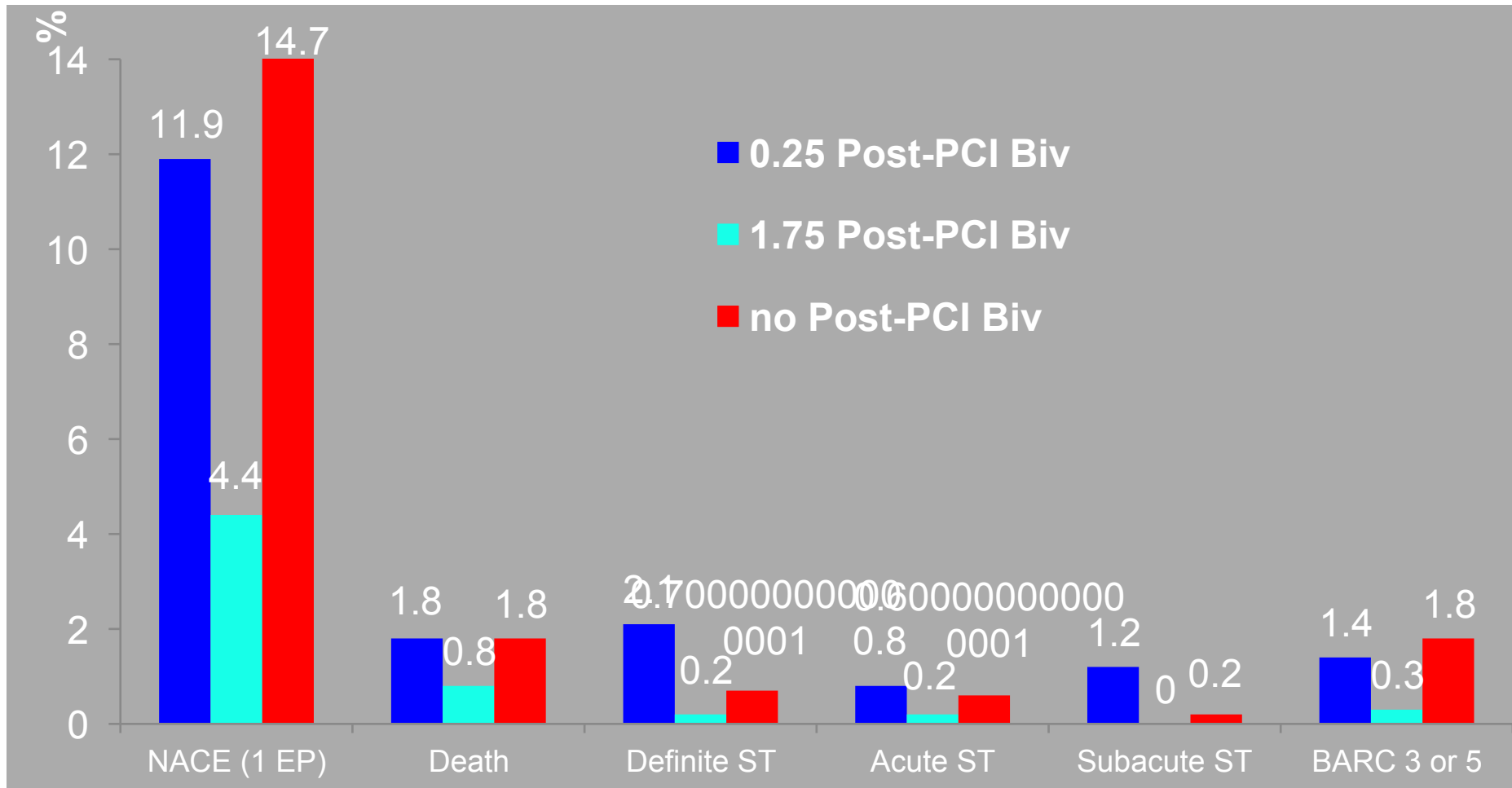


	Heparins ± GPI	BIV-LOW	BIV-PCI
AST	2 (0.2%)	11 (1.6%)*	1 (0.4%)
Major Bleeding	57 (6.0%)	16 (2.4%)*	7 (2.9%)

[‡]data on a post-PCI infusion is not available for 35 patients
[‡]659 of these received at least 2 hours infusion post-PCI ;
[§]191 of these received at least 2 hours infusion post-PCI

***p < 0.05 vs. Heparins ± GPI**

Ischemic and Bleeding EPs according to bivalirudin regimen in the post-PCI bivalirudin arm



What is new in 2017 Guidelines on AMI-STEMI

2012	CHANGE IN RECOMMENDATIONS	2017
	Radial access	MATRIX
	DES over BMS	EXAMINATION, COMFORTABLE-AMI, NORSTENT
	Complete Revascularisation	PRAMI, DANAMI-3-PRIMULTI, CVLPRIT, Compare-Acute
	Thrombus Aspiration	TOTAL, TASTE
	Bivalirudin	MATRIX, HEAT-PPCI
	Enoxaparin	AT OLL, Meta-analysis
	Early Hospital Discharge	Small trials & observational data
Oxygen when SaO ₂ <95%	OXYGEN	Oxygen when SaO ₂ <90% AVOID, DETO2X
Same dose i.v. in all patients	TNK-tPA	Half dose i.v. in Pts ≥75 years STREAM



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Bivalirudin vs Heparin

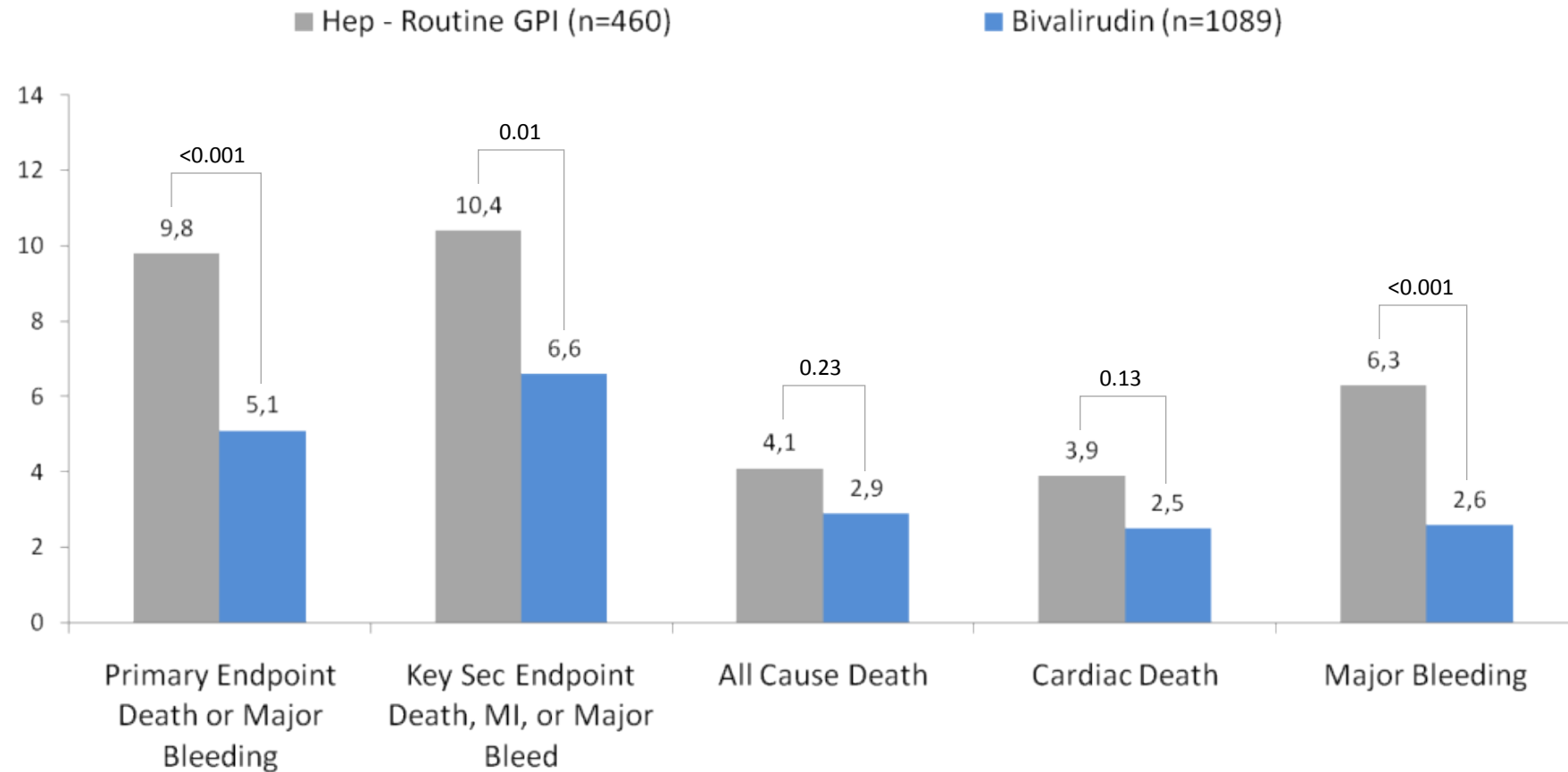
Which price are you willing to pay for less bleeds

Conflicting trial results on mortality

Understanding Stent Thrombosis

What happens in a world without bivalirudin ?

Bivalirudin vs. Heparins Without Routine GPI





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Validate-Swedeheart

Enrollment: 6012
Study Start Date: June 2014
Estimated Study Completion Date: March 2017
Estimated Primary Completion Date: March 2017 (Final data)

Arms

Experimental: bivalirudin

bivalirudin as intravenous bolus of 0,75 mg per kilogram
followed by an infusion of 1,75 mg per kilogram per hour

Active Comparator: heparin

unfractionated Heparin 5 000 IU/ml as intravenous bolus
according to local practice

Special Subgroups

- Fibrinolysis
- Resuscitated cardiac arrest
- Cardiogenic Shock



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STREAM STUDY PROTOCOL

STEMI <3 hrs from onset symptoms, PPCI <60 min not possible, 2 mm ST-elevation in 2 leads

RANDOMIZATION 1:1 by IVRS, OPEN LABEL

Strategy A: pharmaco-invasive

Strategy B: primary PCI

<75y: full dose

≥75y: ½ dose TNK

no lytic

Aspirin
Clopidogrel:
LD 300 mg + 75 mg QD
Enoxaparin:
30 mg IV + 1 mg/kg SC
Q12h

After 20% of the
planned recruitment,
the TNK dose was
reduced by 50%
among patients ≥75
years of age.

Antiplatelet and
antithrombin treatment
according to local standards

ECG at 90 min: S

YES

angio >6 to 24 hrs
PCI/CABG if indicated

Immediate angio +
rescue PCI if indicated

Standard primary PCI

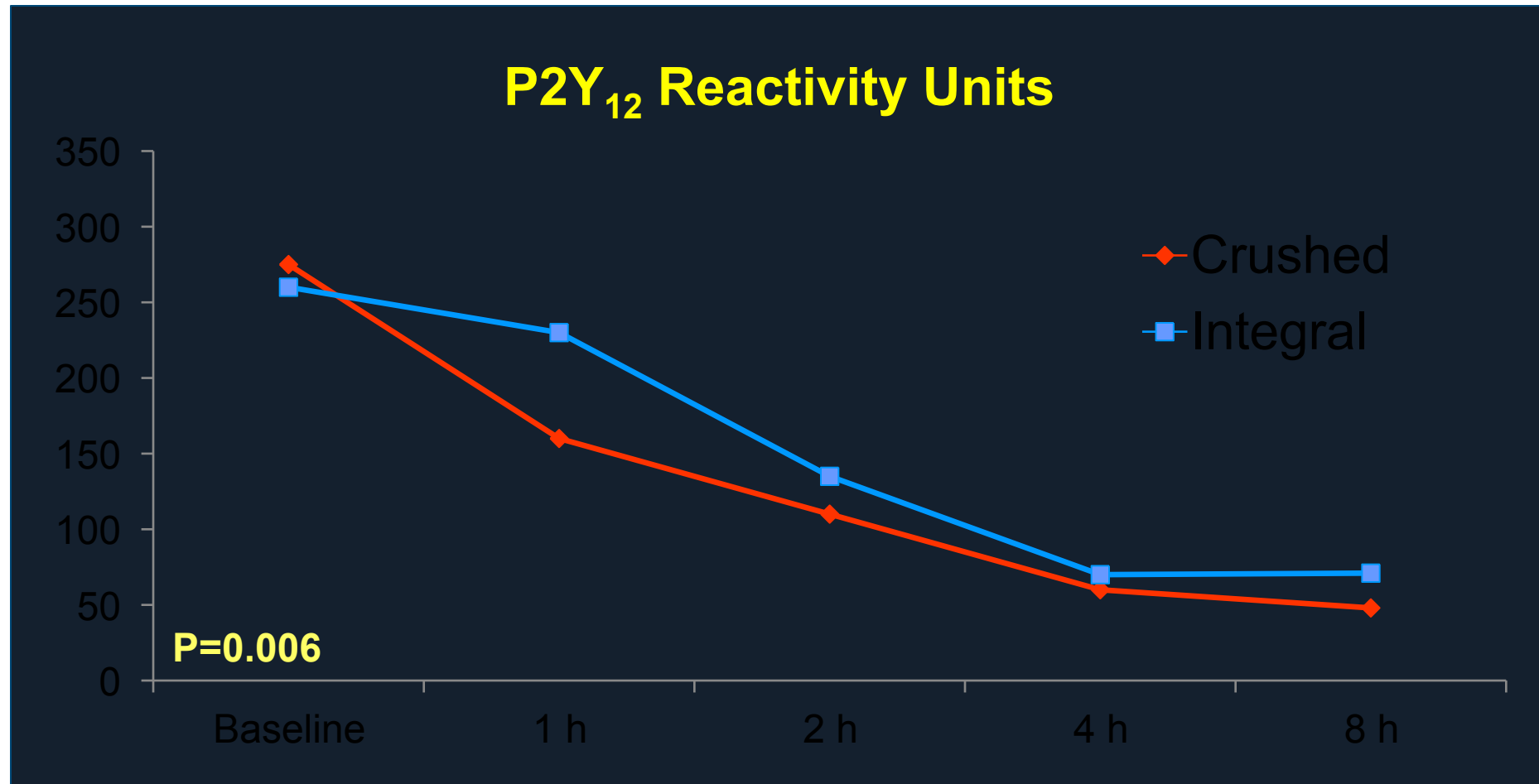
Ambulance/ER

PCI Hospital

Primary endpoint: composite of all cause death or shock or CHF or reinfarction up to day 30

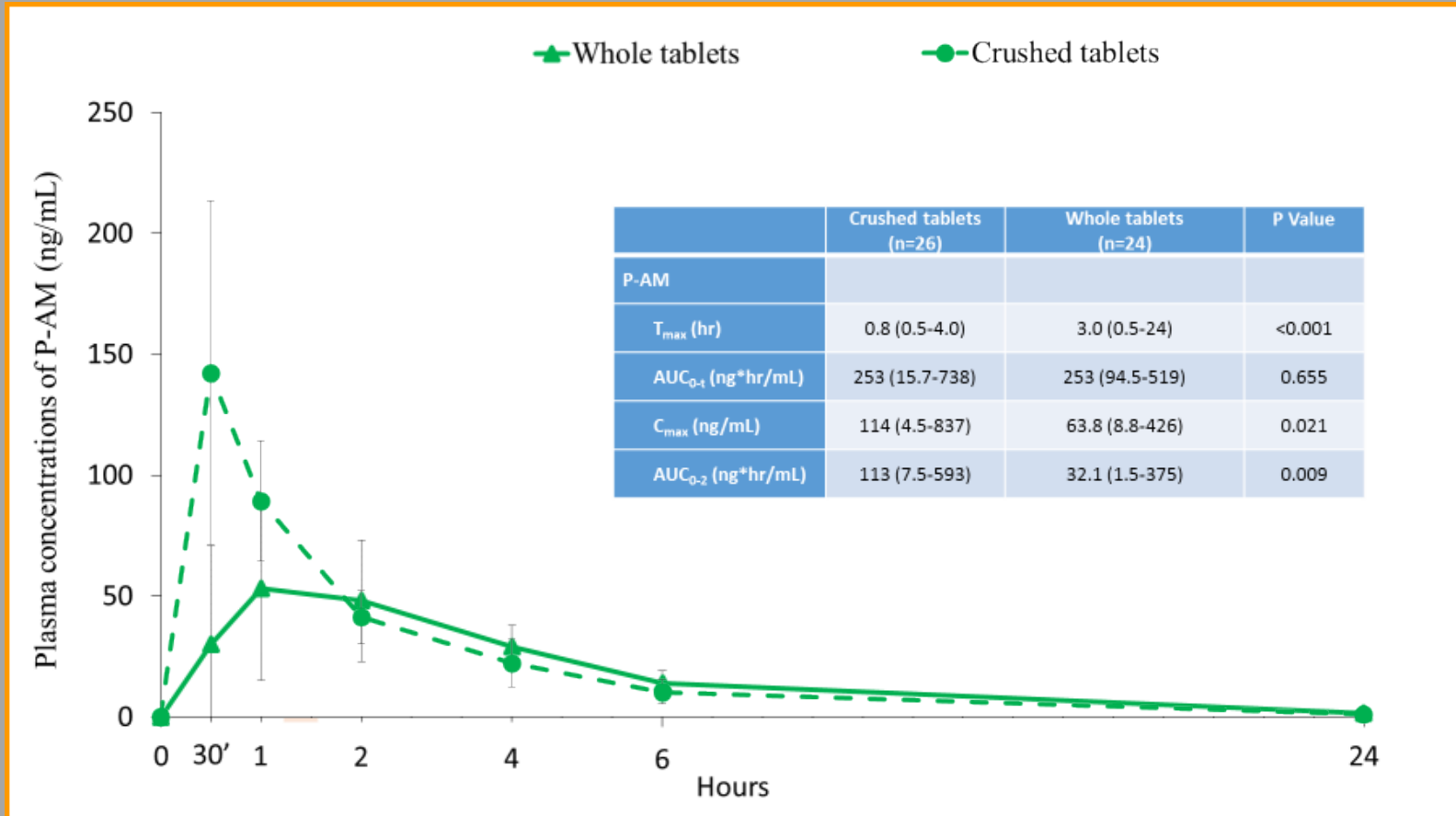
The MOJITO Study

82 STEMI patients randomized to crushed or integral ticagrelor 180-mg LD



The CRUSH Study: A prospective, randomized PD and PK comparison of standard versus crushed prasugrel tablets in STEMI-PPCI

Pharmacokinetic profile





Cangrelor

- Cangrelor is an intravenous ADP receptor antagonist that is rapidly acting, potent, and reversible, with return of normal platelet function within an hour.
- Cangrelor was studied previously in two large Phase 3 PCI trials, CHAMPION PCI and CHAMPION PLATFORM. Neither study met its primary endpoint, but the secondary endpoint of stent thrombosis at 48 hours was significantly reduced in CHAMPION PLATFORM and in a prespecified pooled analysis of the two trials. There was no excess in severe bleeding.
- The potential efficacy signal prompted us to launch the CHAMPION PHOENIX trial.

Harrington RA, et al. CHAMPION PCI. NEJM 2009

Bhatt DL, et al. CHAMPION PLATFORM. NEJM 2009

White HD, et al. Meta-Analysis of CHAMPION PCI and PLATFORM. AHJ 2012



Efficacy Outcomes at 30 Days, MITT

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR (95% CI)	P Value
Death/MI/IDR/ST (primary endpoint, adjusted)	326/5462 (6.0%)	380/5457 (7.0%)	0.85 (0.73,0.99)	0.03
Stent thrombosis	71/5462 (1.3%)	104/5457 (1.9%)	0.68 (0.50,0.92)	0.01
MI	225/5462 (4.1%)	272/5457 (5.0%)	0.82 (0.68,0.98)	0.03
Q-wave MI	14/5462 (0.3%)	22/5457 (0.4%)	0.63 (0.32,1.24)	0.18
IDR	56/5462 (1.0%)	66/5457 (1.2%)	0.85 (0.59,1.21)	0.36
Death	60/5462 (1.1%)	55/5457 (1.0%)	1.09 (0.76,1.58)	0.64
CV Death	48/5462 (0.9%)	46/5457 (0.8%)	1.04 (0.69,1.57)	0.84

STEMI Antithrombotics

"Work horses" first 120 min.

- Ambulance



Cath Lab

PCI

Aspirin 150-300 mg Oral or IV

Heparin 70-100 IU/kg IV

Ticagrelor 180 mg

or Prasugrel 60 mg

Measure ACT
(GPI or Bival)

Fibrinolysis

Clopidogrel 300 mg

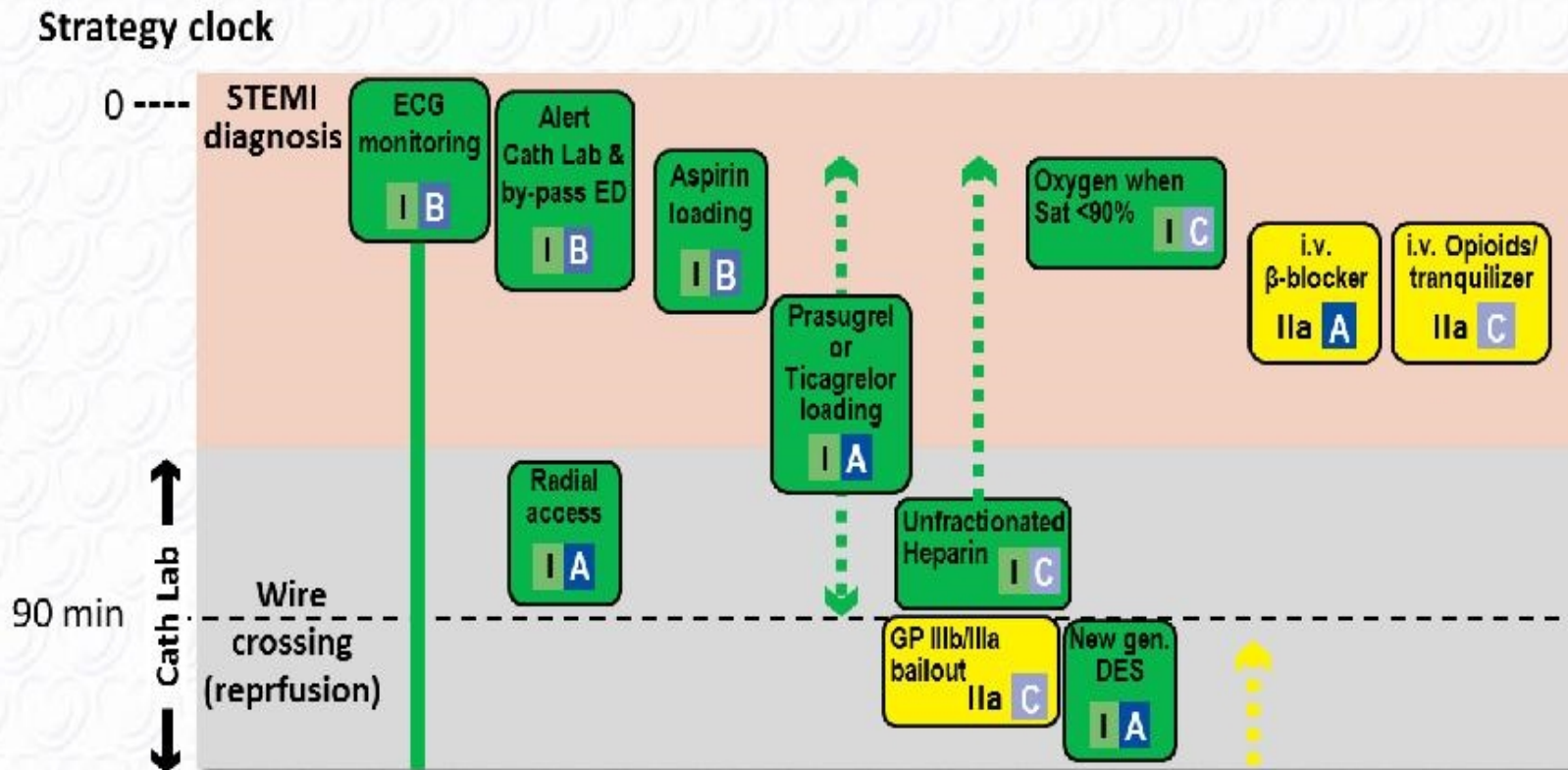
Vomiting/OHCA/Shock

Cangrelor IV

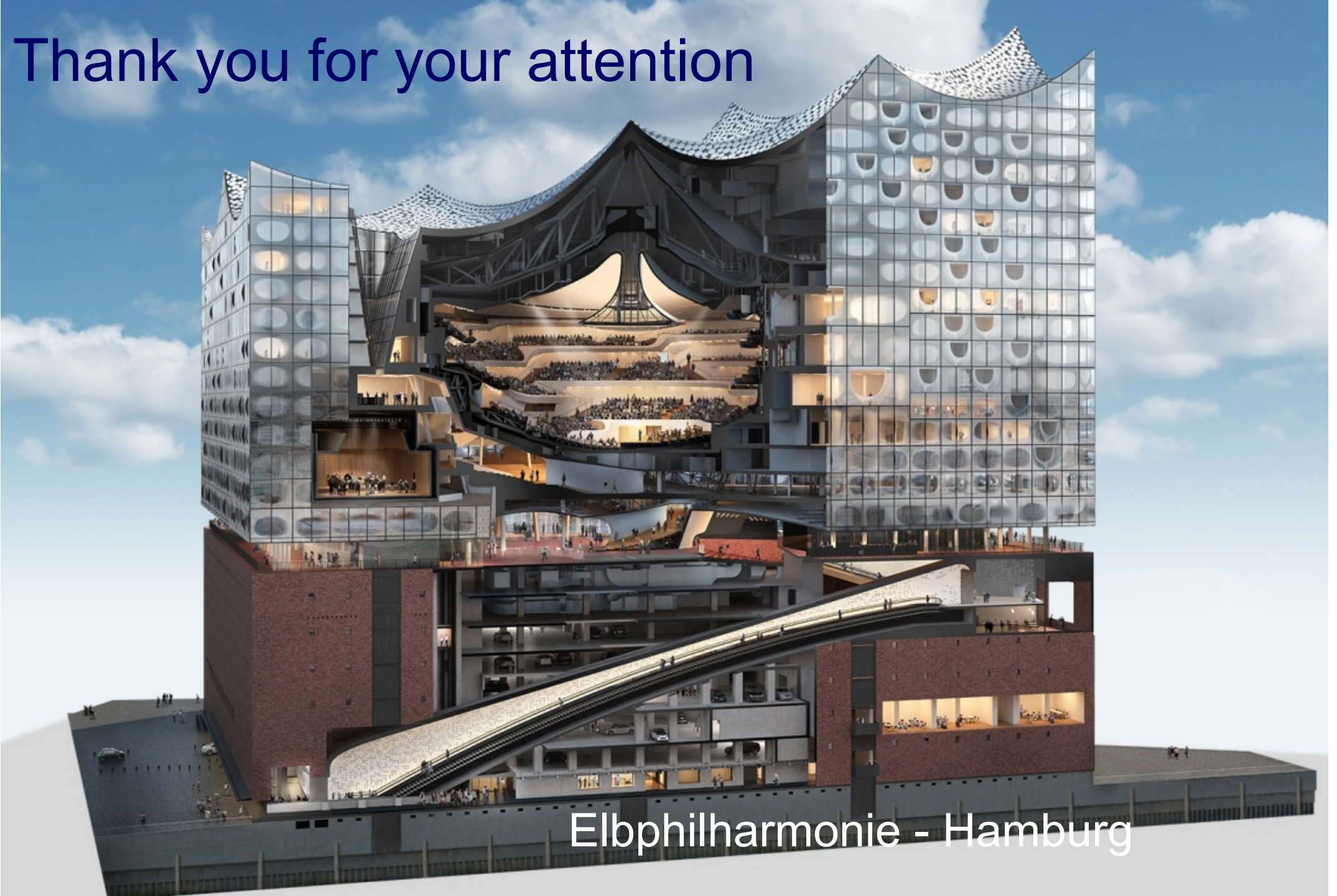
- ✓ High bleeding risk: bivalirudin
- ✓ High ischemic and low bleeding risk, early presentation, or bail-out: GP IIb/IIIa inhibitor
- ✓ Low ischemic risk: enoxaparin+prasugrel/ticagrelor

Acute Stent Thrombosis is mitigated by continuing Bivalirudin PCI dose 4 hrs post PCI

“Do not forget” interventions in STEMI patients undergoing a primary PCI strategy



Thank you for your attention



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