PALAIS DES CONGRES BIARRITZ 4 / 5 / 6 JUIN 2014

APPAC
ACTUALISATIONS ET PERSPECTIVES EN PATHOLOGIE CARDIOVASCULAIRE

Stratégie anti-thrombotique des SCA du pré-hospitalier à l'angioplastie coronaire

Etudes récentes sur la Bivalirudine

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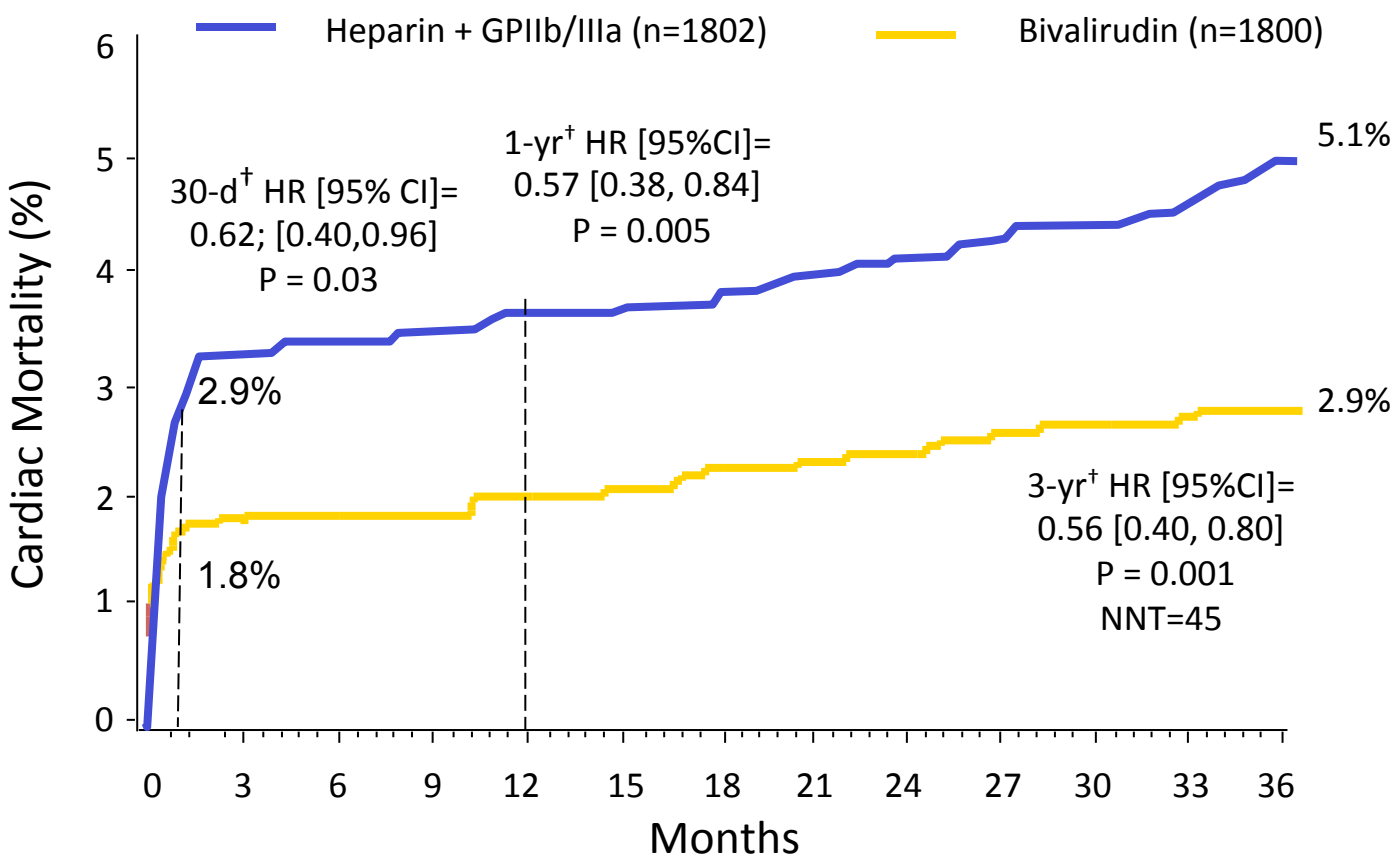
Angiox® (bivalirudine)

Etudes avec >26,000 patients

Study	REPLACE-2	B•A•T	ISAR - REACT 4 NEJM 2011	ACUITY	HORIZONS-AMI
Indication	Elective PCI	N-STEMI		N-STEMI	STEMI
Patients	6,002	4,312		13,819	3,602
Comparator	Heparin + GPIIb/ IIIa	High dose heparin		Heparin + GPIIb/ IIIa	Heparin + GPIIb/ IIIa
Principle publications	JAMA 2003; 289: 853-863 JAMA 2004; 292: 696-703	NEJM 1995; 333: 764-769 Am H. J. 2001;142:952-959		NEJM 2006; 355: 2203- 2216 JAMA. 2007; 297: 591-602 Lancet 2007; 369: 907–19 JAMA 2007; 298: 2497-2506	NEJM 2008; 358: 2218-30. Lancet 2009; 374: 1149–59 Lancet 2011; 377: 2193–204

Mortalité Cardiaque
30 jrs - 3 ans



*All cause mortality at 3 years was also consistently lower with bivalirudin (5·9% *vs* 7·7%), HR 0·75 [0·58–0·97]; p=0·03

†These timepoints were prespecified analyses

•Stone GW et al *NEJM* 2008;358:2218-30; Mehran R et al *Lancet.* 2009;374:1149-59; Stone GW et al. *Lancet* 2011;377:2193-204

Recommandations ESC 2012 ST+
Angioplastie primaire et anticoagulants

Recommandations	Classe	Preuve
Un anticoagulant injectable doit être utilisé pour une angioplastie primaire	I	C
Bivalirudine (avec l'utilisation d'un inhibiteur des GP IIb/IIIa restreinte au sauvetage) est recommandée préférentiellement à l'héparine non fractionnée et un inhibiteur des GP IIb/IIIa	I	B
Héparine non fractionnée avec ou sans inhibiteur des GP IIb/IIIa en routine doit être utilisée chez les patients ne recevant pas de bivalirudine ou d'enoxaparine	I	C
Enoxaparine (avec ou sans utilisation d'inhibiteur des GP IIb/IIIa en routine) peut être préférée par rapport à l'héparine non fractionnée	IIb	B
Fondaparinux est non recommandé pour l'angioplastie primaire	III	B
L'utilisation de fibrinolytiques avant une angioplastie primaire est non recommandée	III	A

Ph. Gabriel Steg, Stefan K. James, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC) *Eur Heart J ehs215 first published online August 24, 2012 doi:10.1093/eurheartj/ehs215*

HORIZONS et ses Limites

- Abord **fémoral 94%**
- 66 % patients bivalirudine pré HNF
- Utilisation **systématique** des **inh. des GPIIbIIIa /HNF**
- Clopidogrel seulement
- **Extension de l'utilisation en Pré-Hospitalier** ? (SAMU)

Etudes Récentes


ROUND
1
WWW.IFL.TV
IFL

***EURO**pean AM**b**ulance **A**CS Angio**X** Trial*

Steg PG et al *N Engl J Med* 2013;DOI:10.1056/NEJMoa1311096

EUROMAX was funded and conducted by The Medicines Company
ClinicalTrial.gov ID: NCT 01087723

EUROMAX - A European Trial

EUROMAX Trial Design

EUROMAX
EUROpean AMbulance ACS AngioX Trial

STEMI patients with symptoms >20 min & ≤12h randomized in ambulance or non-PCI hospital → primary PCI (**n=2218**)

Aspirin + $P2Y_{12}$ inhibitor (any) ASAP

R
1:1

UFH/LMWH ± GPI
Per standard practice

Bivalirudin
(0.75 mg/kg bolus, 1.75 mg/kg/h infusion)
+ prolonged optional infusion
(PCI dose or 0.25 mg/kg/h)
(provisional GPI only)

Primary endpoint: Death or non-CABG major bleeding at 30 days
Key Secondary endpoint: Death, Re-infarction or non-CABG major bleeding at 30 days
Vital Status at 1 year

Steg et al. Am Heart J. 2013;166:960-7

Exclusion criteria

1. Any bleeding diathesis or severe hematologic disease or history of intracerebral mass, aneurysm, arteriovenous malformation, hemorrhagic stroke, intracranial hemorrhage or gastrointestinal or genitourinary bleeding within the past 2 weeks.
2. Patients who have undergone recent surgery (including biopsy) within the past 2 weeks.
3. Patients on warfarin (not applicable if international normalized ratio known to be <1.5).
4. Patients who have received unfractionated heparin, low-molecular-weight heparin or bivalirudin immediately before randomization.
5. Thrombolytic therapy within the past 48 hours.
6. Absolute contraindications or allergy that cannot be premedicated to iodinated contrast or to any of the study medications, including aspirin or clopidogrel.
7. Contraindications to angiography, including but not limited to severe peripheral vascular disease.
8. If known, pregnant or nursing mothers. Women of childbearing age will be asked if they are pregnant or think that they may be pregnant.
9. If known, a creatinine clearance <30 mL/min or dialysis dependent.
10. Previous enrollment in this study.
11. Treatment with other investigational drugs or devices within the 30 days preceding randomization or planned use of other investigational drugs or devices in this trial.
12. Patients may not be enrolled if the duration of randomized investigational medicinal product antithrombin infusion is likely to be <30 minutes from the time of onset to the commencement of angiography.
13. Patients may not be enrolled within a primary-PCI–capable hospital (unless at the time of randomization the catheter laboratory is not available and the patient requires transfer to another primary-PCI–capable hospital).
14. Estimated body weight of >120 kg.

EUROMAX
EUROpean AMbulance ACS AngioX Trial

Procedures, Medications

50 % clopi et 50 % nouveaux anti-ADP

40 % clopi et 60 % nouveaux anti-ADP

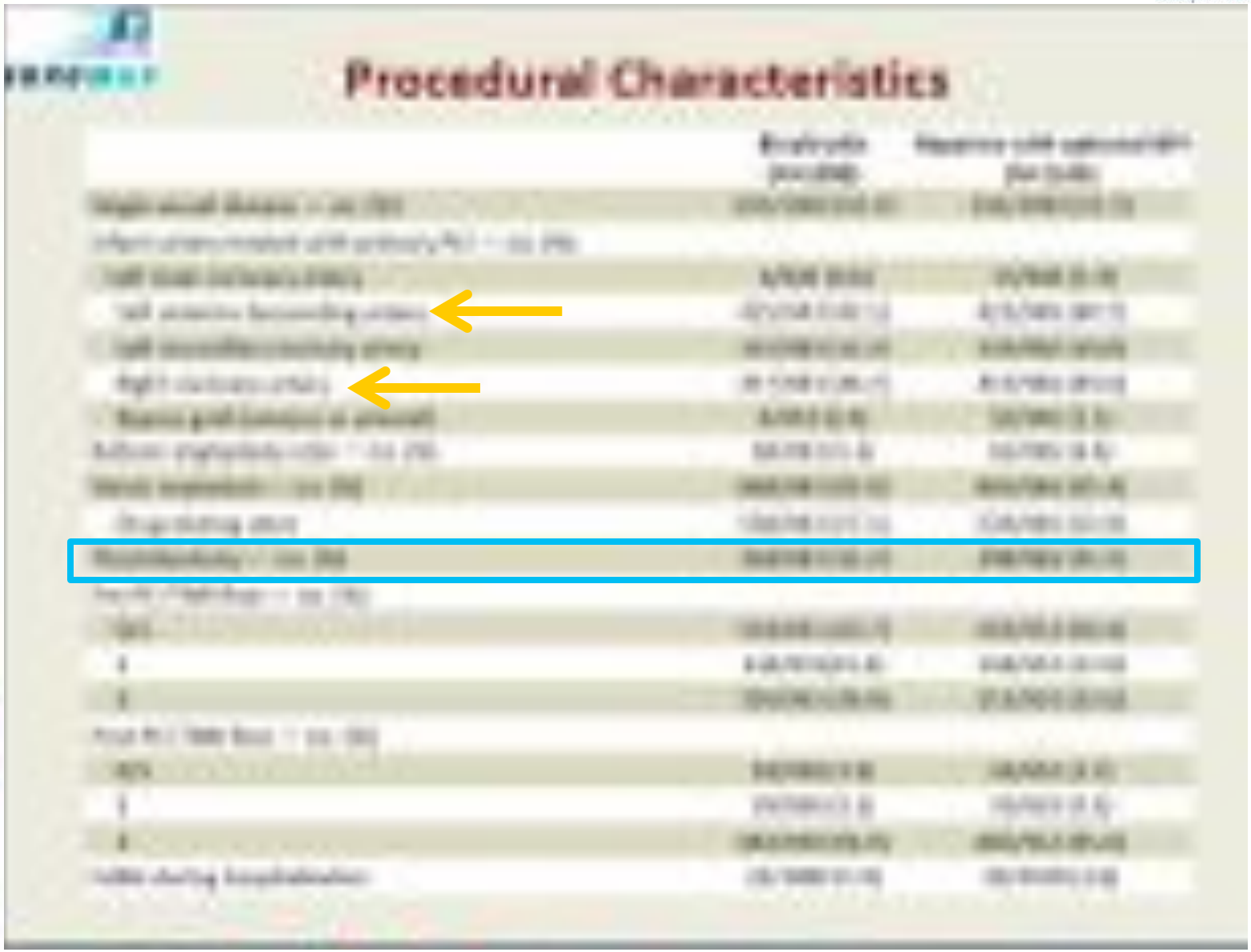
EUROMAX
EUROpean AMbulance ACS AngioX Trial

Procedures, Medications, con't

Dose médiane HNF
62 UI/Kg

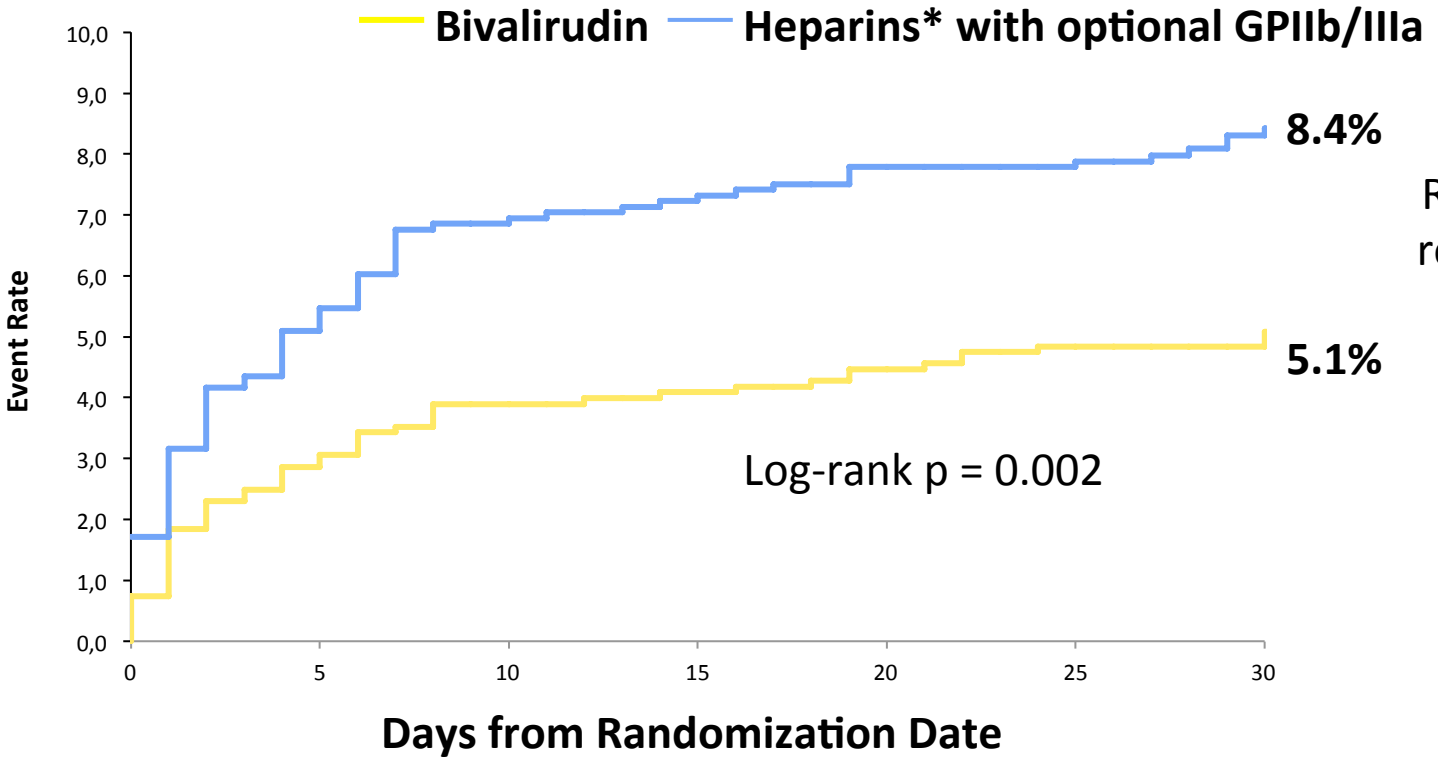
EUROMAX
EUROpean AMbulance ACS AngioX Trial

Procedural Characteristics



Critère primaire

- 30-Day Death or Non-CABG Major Bleeding



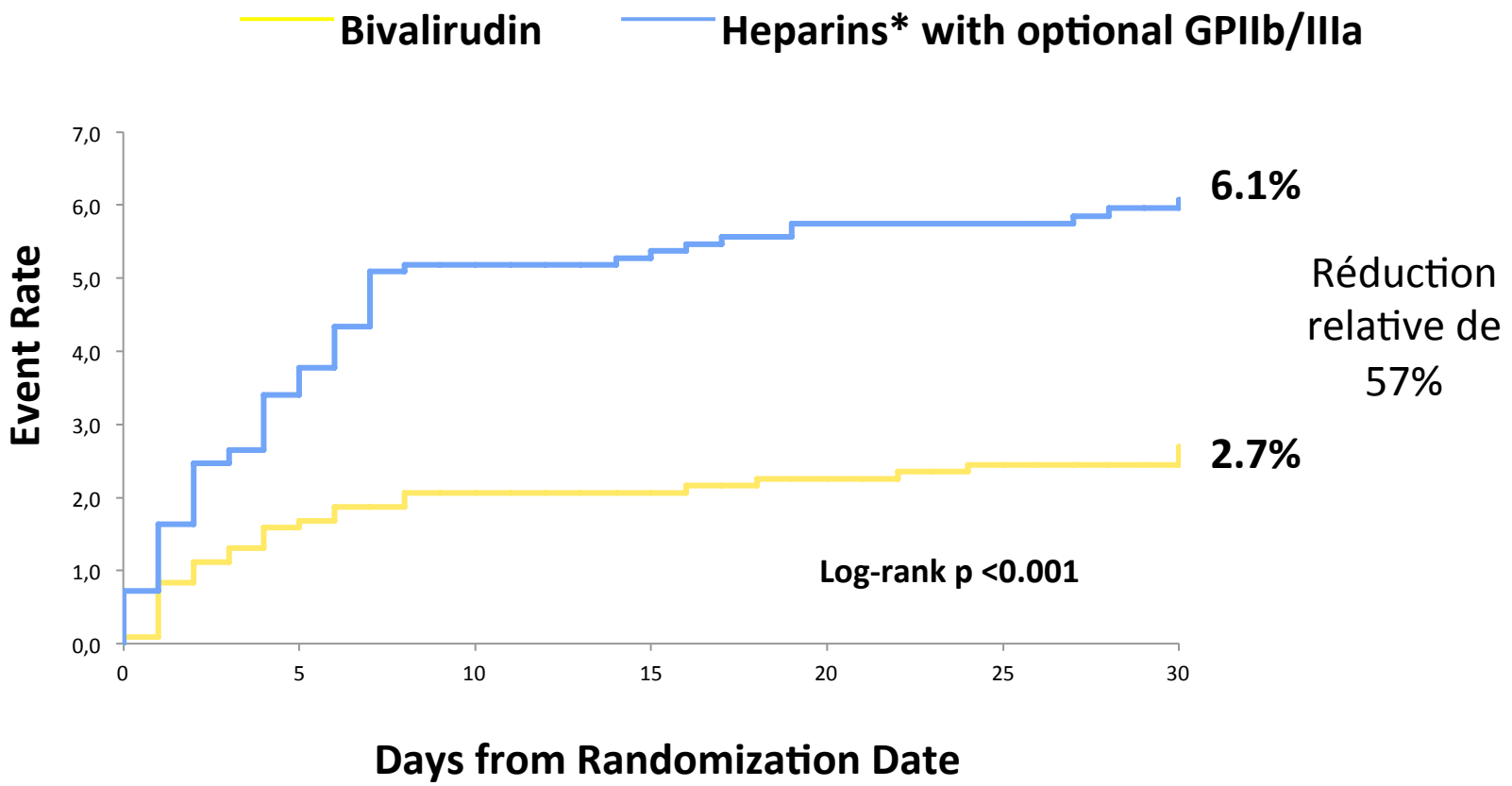
Réduction relative de 40%

*unfractionated or low molecular weight

Steg PG et al *N Engl J Med* 2013;DOI:10.1056/NEJMoa1311096

Saignement Majeurs (Hors PAC) 30 Jrs

EUROMAX
EUROpean AMbulance ACS AngioX Trial



Réduction relative de 57%

*unfractionated or low molecular weight

Steg PG et al *N Engl J Med* 2013;DOI:10.1056/NEJMoa1311096

Saignements, 30 Jrs

EUROMAX
EUROpean AMbulance ACS AngioX Trial

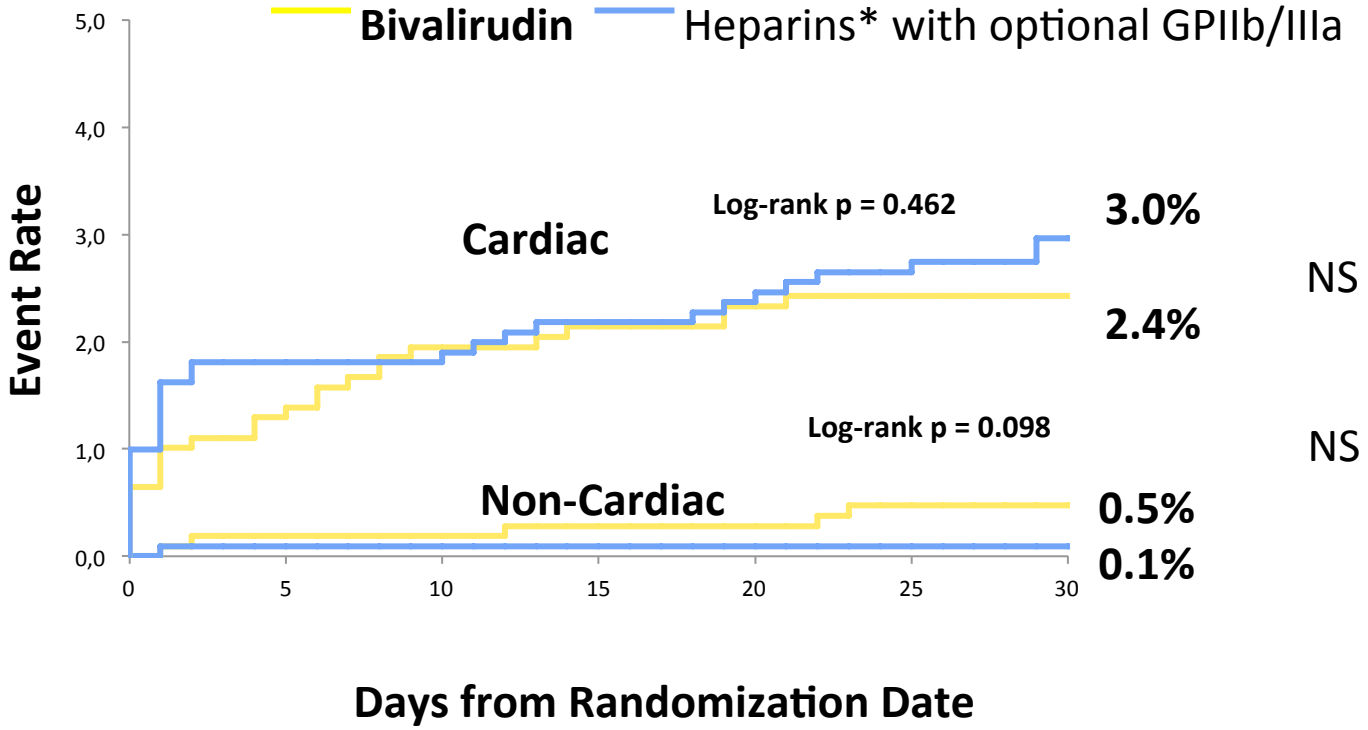
	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)	Relative risk [95% CI]	P Value
Major bleeding (non-CABG)	28 (2.6)	67 (6.0)	0.43 (0.28–0.66)	<0.001 ↘57%
Major or minor bleeding (non-CABG)	85 (7.8)	149 (13.4)	0.58 (0.45–0.75)	<0.001
TIMI major bleeding (non-CABG)	14 (1.3)	23 (2.1)	0.62 (0.32–1.20)	0.15
TIMI major/minor bleeding (non-CABG)	85 (7.8)	146 (13.2)	0.59 (0.46–0.76)	<0.001
GUSTO severe/life-threatening bleeding (non-CABG)	6 (0.6)	10 (0.9)	0.61 (0.22–1.68)	0.33
GUSTO severe/life-threatening or moderate bleeding (non-CABG)	14 (1.3)	26 (2.3)	0.55 (0.29–1.04)	0.06
GUSTO any bleeding (non-CABG)	85 (7.8)	148 (13.3)	0.58 (0.45–0.75)	<0.001
Blood transfusion	23 (2.1)	43 (3.9)	0.54 (0.33–0.90)	0.02

* Patients may have experienced more than one event.
CI denotes confidence interval, GPI glycoprotein inhibitor, and NA not applicable.

Steg PG et al *N Engl J Med* 2013;DOI:10.1056/NEJMoa1311096

EUROMAX
EUROpean AMbulance ACS AngioX Trial

Mortalité Cardiaque / Non Cardiaque 30 Jrs



*unfractionated or low molecular weight

Steg PG et al *N Engl J Med* 2013;DOI:10.1056/NEJMoa1311096

30-day Outcomes

	Bivalirudin (N=1089) n (%)	Heparins*+ optional GPIIb/IIIa (N=1109) (n (%)	Relative risk (95% CI)	P Value
Primary: Death / major bleeding (non-CABG)	**55 (5.1)**	**94 (8.5)**	**0.60 (0.43–0.82)**	**0.001**
Death/ reinfarction/major bleeding	72 (6.6)	102 (9.2)	0.72 (0.54–0.96)	0.025
Death	32 (2.9)	34 (3.1)	0.96 (0.60–1.54)	0.86
Cardiac causes	27 (2.5)	33 (3.0)	0.83 (0.50–1.38)	0.48
Noncardiac causes	5 (0.5)	1 (0.1)	5.09 (0.60–43.51)	0.12
Major bleeding (non-CABG)	28 (2.6)	67 (6.0)	0.43 (0.28–0.66)	<0.0001
Blood transfusion	23 (2.1)	43 (3.9)	0.54 (0.33–0.90)	0.02
Reinfarction	19 (1.7)	10 (0.9)	1.93 (0.90–4.14)	0.08
Stent thrombosis (ARC definition)	**17 (1.6)**	**6 (0.5)**	**2.89 (1.14–7.29)**	**0.02**
Acute (≤24 h)	**12 (1.1)**	**2 (0.2)**	**6.11 (1.37–27.24)**	**0.007**
Subacute (>24 h to 30 d)	5 (0.5)	4 (0.4)	1.27 (0.34–4.73)	0.75
Ischemia-driven revascularization	24 (2.2)	17 (1.5)	1.44 (0.78–2.66)	0.25
Stroke	6 (0.6)	11 (1.0)	0.56 (0.21–1.50)	0.24
Acquired thrombocytopenia	7 (0.7)	14 (1.4)	0.50 (0.20–1.24)	0.13
MACE	65 (6.0)	61 (5.5)	1.09 (0.77–1.52)	0.64
NACE	85 (7.8)	118 (10.6)	0.73 (0.56–0.96)	0.02

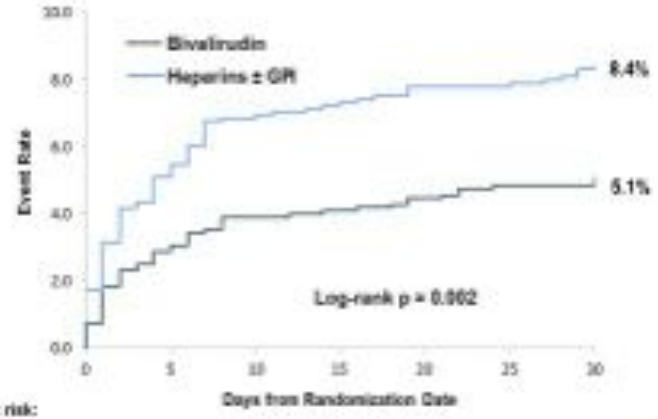
*unfractionated or low molecular weight. CABG= coronary artery bypass graft ; ARC= Academic Research Consortium; MACE=death, reinfarction, ischemia-driven revascularization or stroke; NACE= MACE or non–CABG major bleeding

Steg PG et al *N Engl J Med* 2013;DOI:10.1056/NEJMoa1311096

Résultats à 30 Jrs: Résumé

EUROMAX
EUROpean AMbulance ACS AngioX Trial

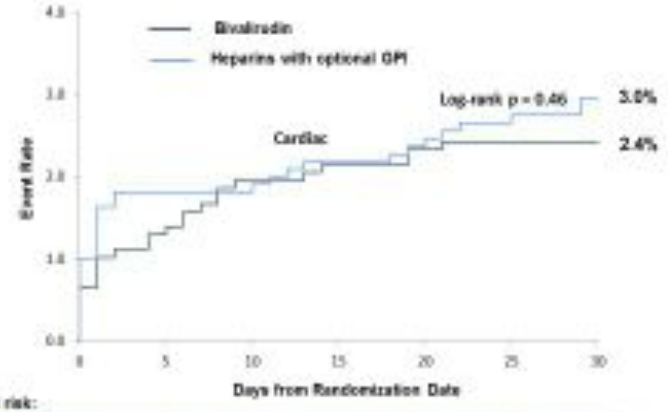
Death or Major Bleed



Patients at risk:

Bivalirudin	1088	1038	1024	1020	1007	986	791
Heparins ± GPI	1109	1024	1003	996	984	956	765

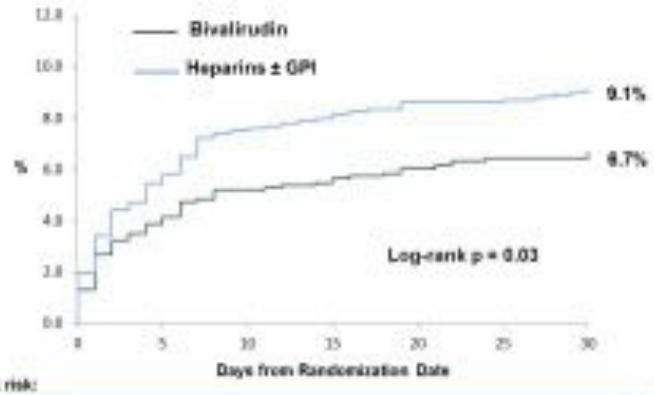
Cardiac Mortality



Patients at risk:

Bivalirudin	1089	1057	1048	1046	1039	1036	1034
Heparins with optional GPI	1109	1062	1061	1056	1050	1043	1037

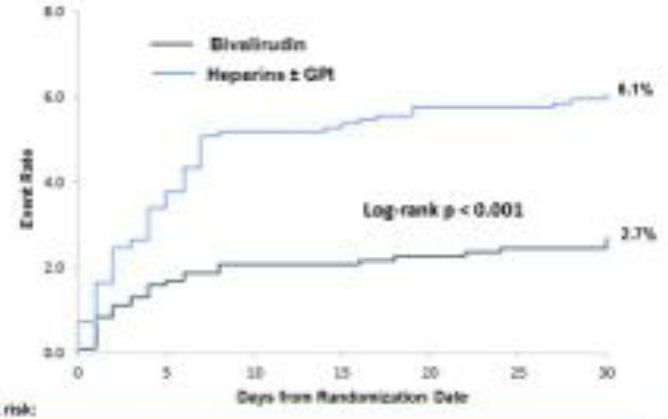
Death/MI or Major Bleed



Patients at risk:

Bivalirudin	1089	1027	1010	1005	989	871	779
Heparins ± GPI	1109	1028	996	986	975	949	780

Major Bleed

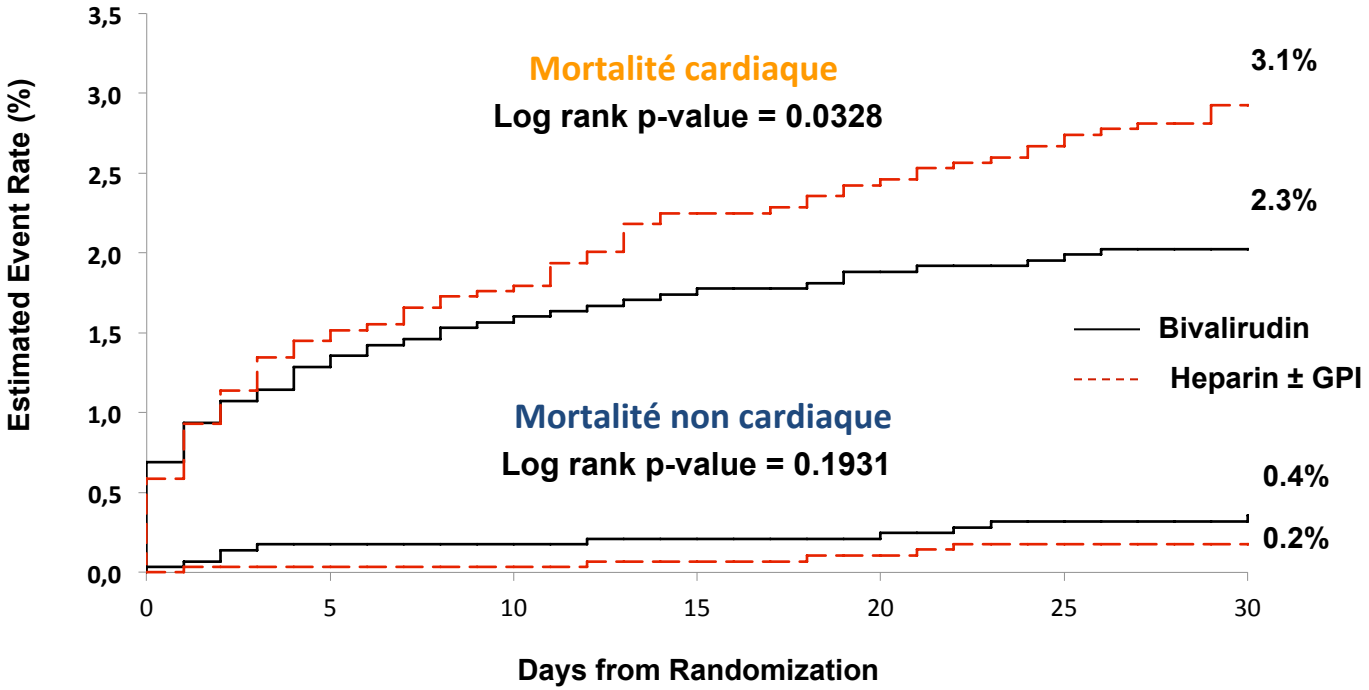


Patients at risk:

Bivalirudin	1089	1040	1025	1022	1010	891	794
Heparins ± GPI	1109	1030	1009	1005	986	864	773

Steg et al. *NEJM*. 2013;369;2207-17

Analyse poolée
Mortalité Cardiaque et non-Cardiaque



Patients at Risk:

Bivalirudin:	**2889**	**2822**	**2810**	**2802**	**2794**	**2789**	**2781**
Heparin:	**2911**	**2836**	**2825**	**2808**	**2796**	**2780**	**2766**

ACC, Washington mars 2013

Résultats poolés

	Bivalirudin (N=2889) n (%)	Heparin ± GPI (N=2911) n (%)	Relative risk (95% Confidence Interval)	P Value*
Death	69 (2.4)	90 (3.1)	0.77 (0.57-1.05)	0.102
Cardiac causes	59 (2.0)	85 (2.9)	0.70 (0.50-0.97)	0.0320
Non-cardiac causes	10 (0.4)	5 (0.2)	2.01 (0.69-5.88)	0.19
Protocol major bleeding (non-CABG)	120 (4.2)	226 (7.8)	0.53 (0.43-0.66)	<0.0001
TIMI major bleeding (non-CABG)	47 (1.6)	81 (2.8)	0.58 (0.41-0.83)	0.0027
TIMI major/minor bleeding (non-CABG)	160 (5.5)	281 (9.6)	0.58 (0.48-0.69)	<0.0001
Blood transfusion	62 (2.1)	110 (3.8)	0.57 (0.42-0.77)	0.0002
Reinfarction	53 (1.8)	42 (1.4)	1.27 (0.85-1.90)	0.24
Stent thrombosis (ARC)	60 (2.1)	40 (1.4)	1.51 (1.01-2.24)	0.041
Acute	36 (1.2)	6 (0.2)	6.04 (2.55-14.31)	<0.0001
Sub-acute	25 (0.9)	34 (1.2)	0.74 (0.44-1.23)	0.24
MACE°	163 (5.6)	161 (5.5)	1.02 (0.83-1.26)	0.85
NACE°°	253 (8.8)	346 (11.9)	0.74 (0.63-0.86)	<0.0001
Ischemia-driven revascularization	69 (2.4)	52 (1.8)	1.34 (0.94-1.91)	0.1096
Any stroke	20 (0.7)	23 (0.8)	0.88 (0.48-1.59)	0.66
Acquired thrombocytopenia	37 (1.4)	77 (2.9)	0.48 (0.33-0.71)	0.0002
Death/Major Bleed	176 (6.1)	290 (10.0)	0.61 (0.51-0.73)	<0.0001
Death/MI/Major Bleed	216 (7.5)	317 (10.9)	0.69 (0.58-0.81)	<0.0001

*Cochran-Mantel-Haenszel Test

° MACE: Death/MI/Stroke/IDR
°°NACE: Death/MI/Stroke/IDR/non-CABG major bleeding

Breslow-Day test for study heterogeneity non-significant p≥0.11 for all variables

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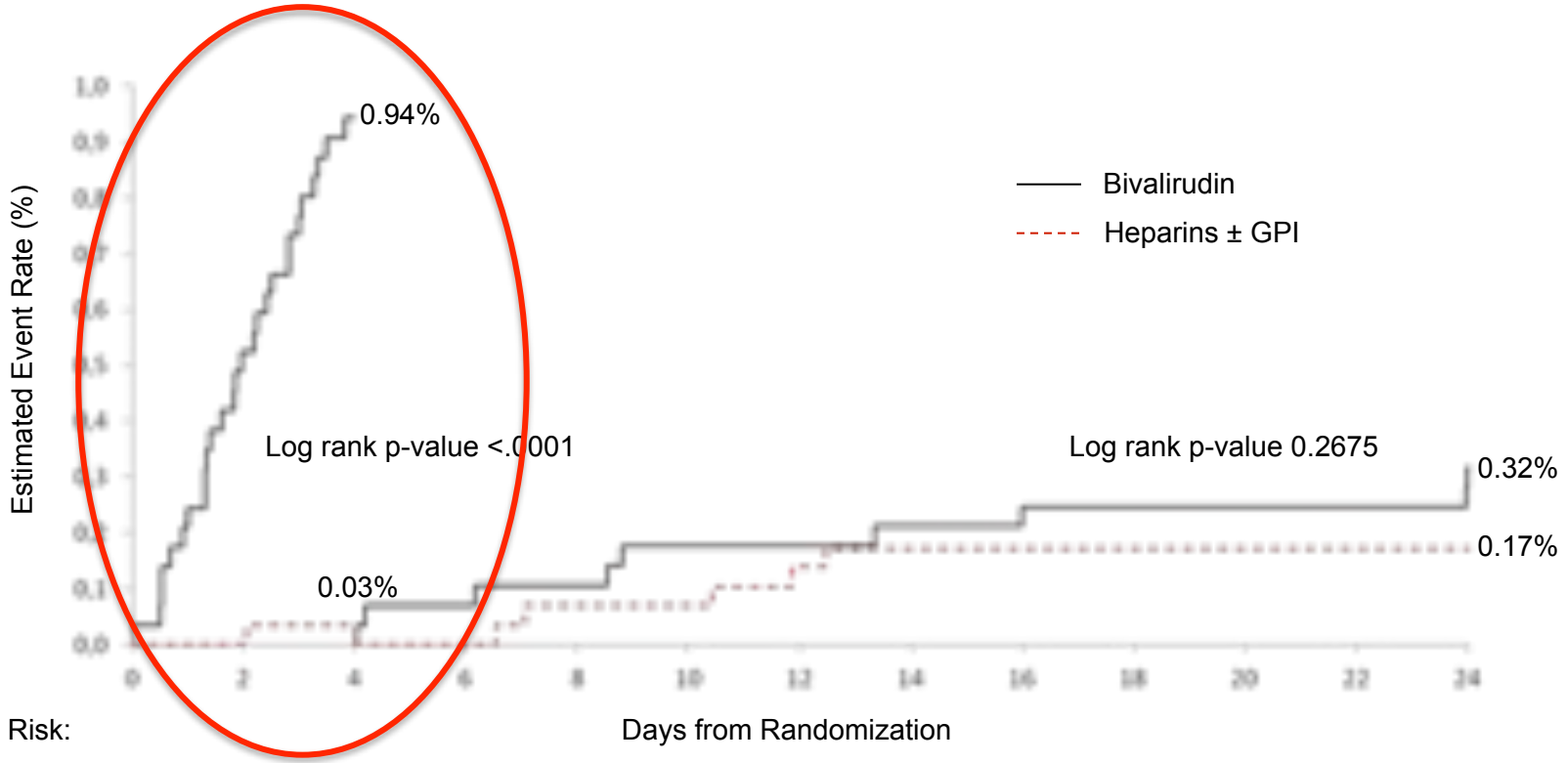
Analyse poolée
Acute Stent Thrombosis
Landmark analysis: 0 to 4 h – 4 h to 24 h



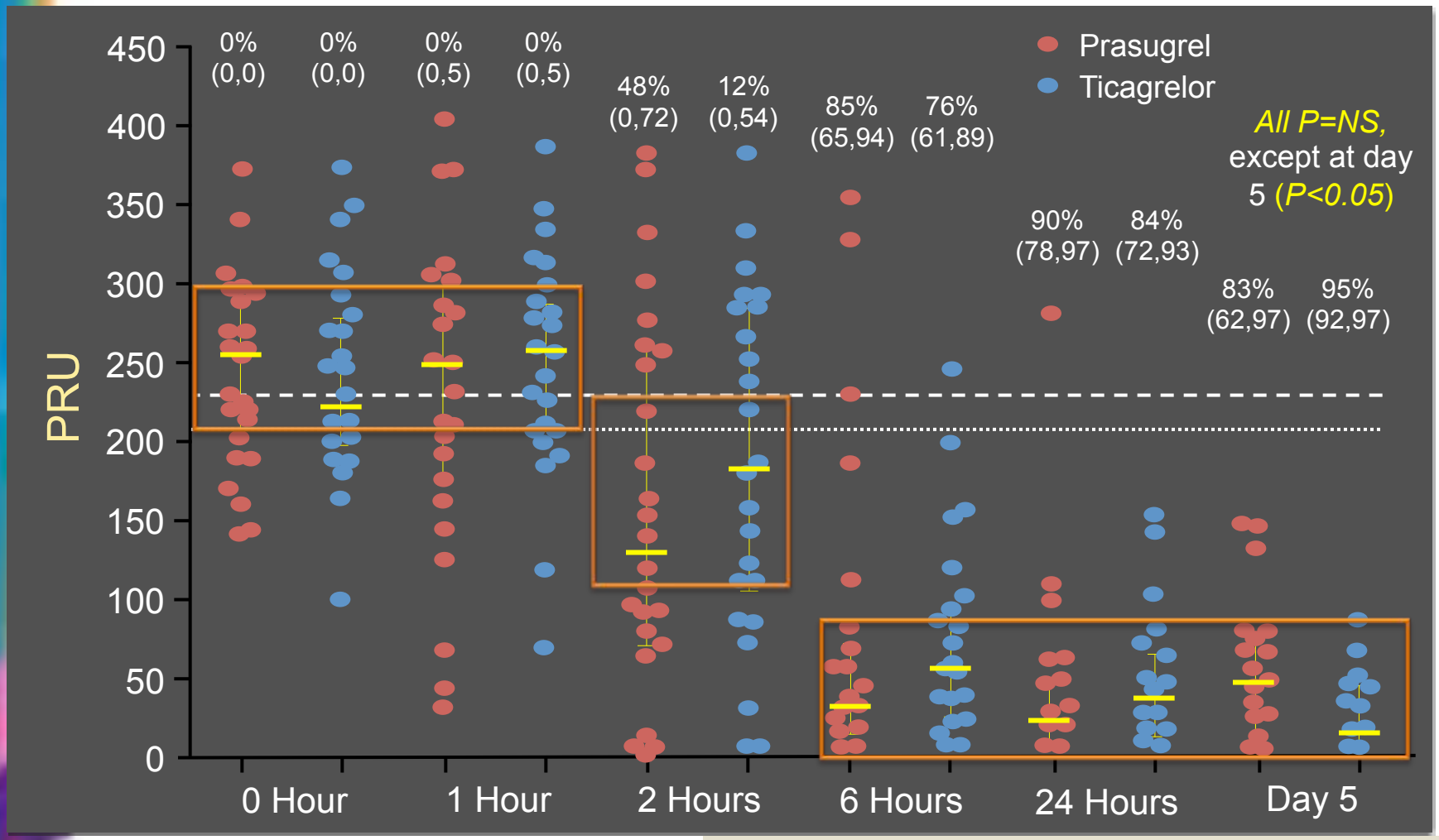
Patients at Risk:

Bivalirudin:	2889	2846	2834	2832	2831	2829	2829	2828	2828	2827	2827	2827	2826
Heparin:	2911	2894	2893	2893	2891	2891	2889	2888	2888	2888	2888	2888	2888

ACC, Washington mars 2013

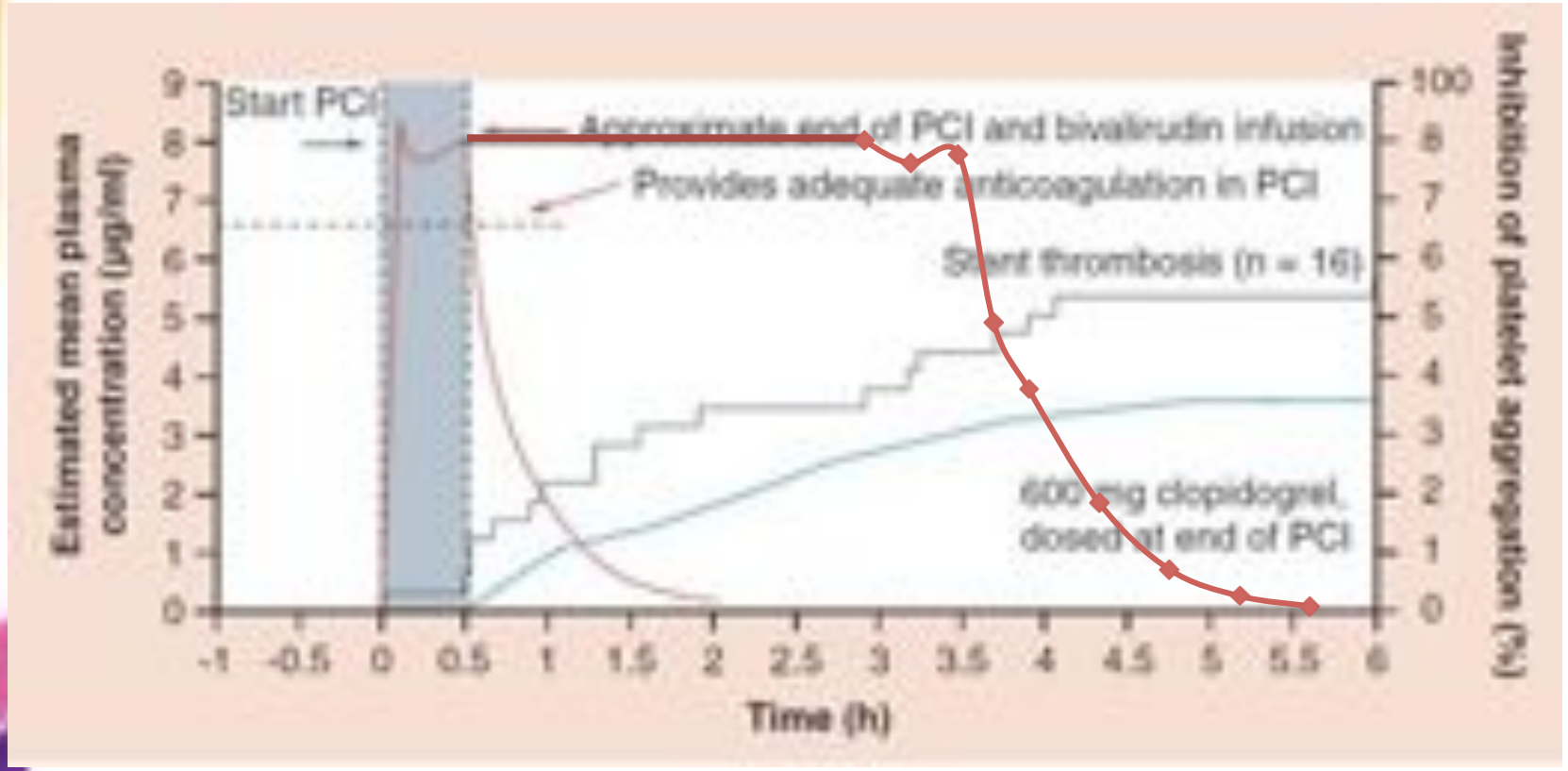
Ticagrelor and Prasugrel PD in STEMI

VerifyNow P2Y12 at 0, 1, 2, 6, 24 hrs, and 5 days post randomization in 55 STEMI pts (standard dosing). % inhibited:



Alexopoulos D et al. *Circ Cardiovasc Interv.* 2012;5:797-804

Representation of potential postprocedural period of increased **thrombotic risk.**



Capranzano *Expert Rev. Cardiovasc. Ther.* 10(4), 411–422 (2012)

Predictors Associated With Acute Stent Thrombosis After Primary PCI: Insights from The EUROMAX Trial

Peter Clemmensen, Arnoud van't Hof, Efthymios Deliargyris, Pierre Coste, Jurrien ten Berg, Sebastian Wiberg, Claudio Cavallini, Martial Hamon, Dariusz Dudek, Uwe Zeymer, Xavier Tabone, Steen Dalby Christensen, Tim Clayton, Debra Bernstein, Jayne Prats, Philippe Gabriel Steg on behalf of the EUROMAX investigators

EUROMAX

EUROpean AMbulance ACS AngioX Trial

Acute ST Analysis: Results

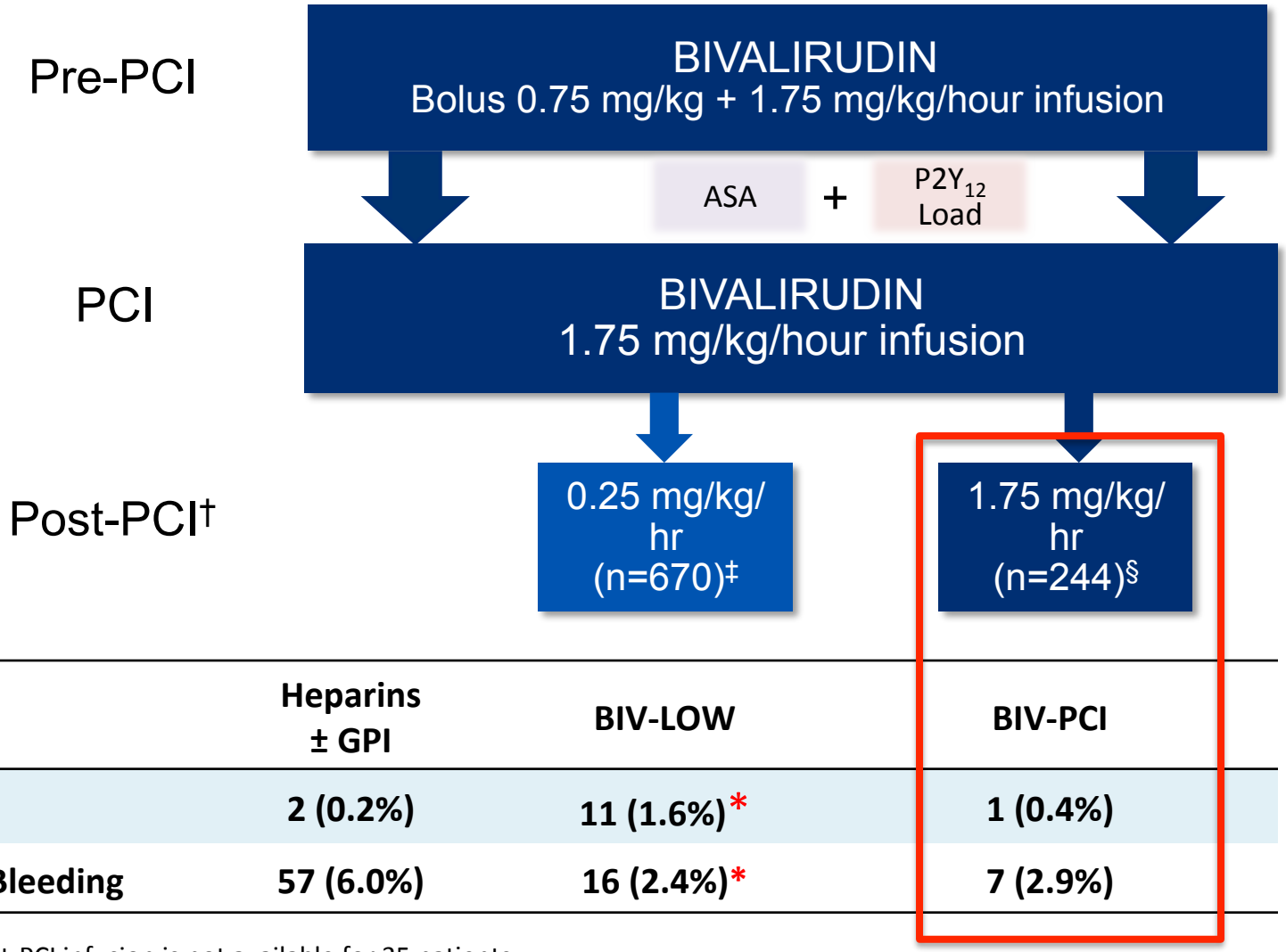
EUROMAX
EUROpean AMbulance ACS AngioX Trial

- Variables in the logistic regression model included
  - demographic/baseline characteristics (age, sex, anemia, renal function, diabetes, hypertension, hyperlipidemia, smoker, prior PCI, MI, CABG)
  - choice of $P2Y_{12}$ inhibition (clopidogrel vs. newer agents), occurrence of procedural complications
  - pre-PCI TIMI flow (0/1 vs. 2/3)
  - single or multi-vessel disease
  - Killip class II – IV or I
  - Access site
  - Drug-eluting stents
  - anticoagulant strategy: BIV-LOW vs. heparin standard of care, BIV-PCI vs. heparin standard of care

- Final model
  - age>65 (OR 2.1 [95% CI 0.69, 6.46], p=0.19);
  - hypertension (OR 0.21 [95% CI 0.04-0.95], p=0.04)
  - BIV-PCI (OR 2.06 [95% CI 0.19,22.9, p=0.55)
  - BIV-LOW (OR 6.9 [95% CI 1.5,31.8], p=0.013)

Treatment Breakdown and Outcomes by Bivalirudin Post-PCI Infusion Dose

EUROMAX
EUROpean AMbulance ACS AngioX Trial



	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

LIMITES

- **Analyse Post-Hoc**
  - Faible Taux de thrombose aigue de stent: **14 patients** (0.6%)
  - Liste des variables: réalisée post-Hoc
  - Seulement 27% (n=244) du bras Biva avec Perfusion à dose ATL en post procédure.

Conclusions sur la thrombose aigue de stent

EUROMAX
EUROpean AMbulance ACS AngioX Trial

- **Survenue limitée aux premières heures post-procédure (<4h)**
- **Pas de protection**
  - **avec nouveaux AAP** (prasugrel / ticagrélor)
  - **avec perfusion prolongée de bivalirudine à faible dose** (0.25 mg/kg/h) en post-procédure (4h)

- **Perfusion prolongée à dose d'ATL (1.75 mg/kg/h)**: n'est pas associée à un surrisque de thrombose aigue de stent ou une augmentation des saignements

- Cette stratégie devra être confirmée par une étude plus large

European Heart Journal Advance Access published May 9, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu183

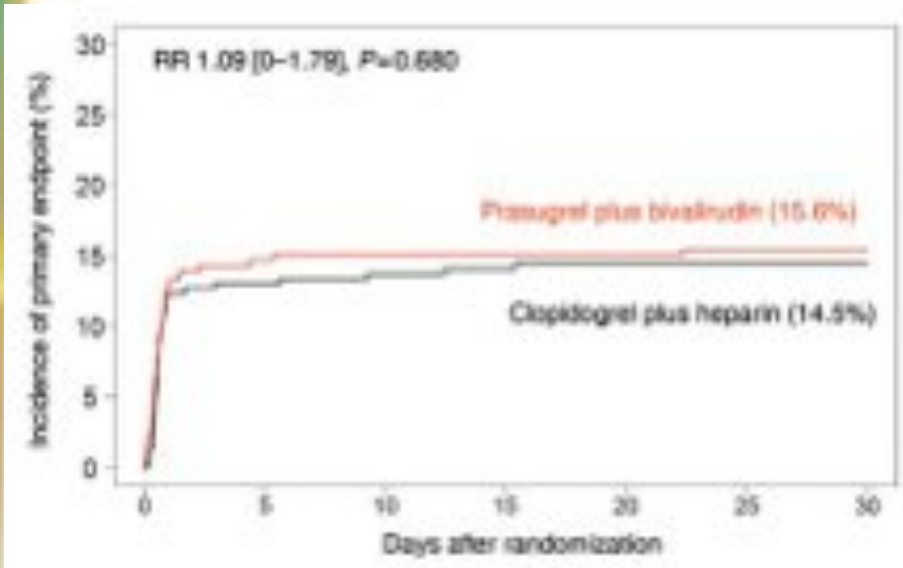
FASTTRACK CLINICAL RESEARCH
Acute coronary syndromes

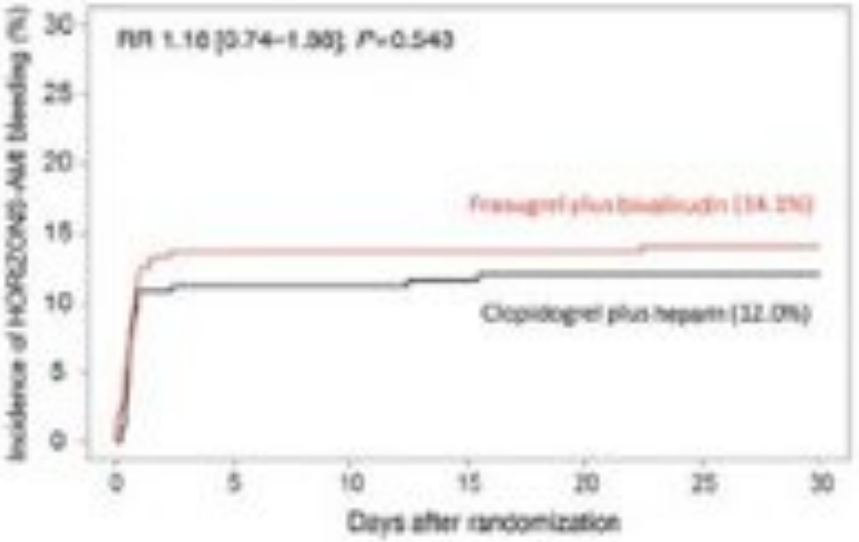
Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction

Stefanie Schulz[1,2*], Gert Richardt[3], Karl-Ludwig Laugwitz[2,4], Tanja Morath[1], Julia Neudecker[1], Petra Hoppmann[4], Roxana Mehran[5], Anthony H. Gershlick[6], Ralph Tölg[1], K. Anette Fiedler[1], Mohamed Abdel-Wahab[3], Sebastian Kufner[1], Simon Schneider[4], Heribert Schunkert[1,2], Tareq Ibrahim[4], Julinda Mehilli[2,7], Adnan Kastrati[1,2], and for the Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 Investigators

- Arrêt prématuré (défaut de recrutement)
- 548 /1240 patients

BRAVE-4


RR 1.09 [0–1.79], P=0.680
Prasugrel plus bivalirudin (15.6%)
Clopidogrel plus heparin (14.5%)
Incidence of primary endpoint (%)
Days after randomization


RR 1.16 [0.74–1.88], P=0.543
Clopidogrel plus heparin (12.0%)
Days after randomization


UFC
2

HEAT-PPCI
Le pavé dans la mare ?

HEAT PPCI

How Effective are
Antithrombotic Therapies in PPCI

Heparin versus Bivalirudin in PPCI

Dr Adeel Shahzad
Dr Rod Stables (PI)
Liverpool Heart and Chest Hospital
Liverpool, UK

Study Population

Inclusion Criterion

- All STEMI patients activating PPCI pathway

Exclusion Criteria

- Active bleeding at presentation
- Factors precluding administration of oral A-P therapy
- Known intolerance / contraindication to trial medication
- Previous enrolment in this trial

Study Medication

- Dual oral anti-platelet therapy pre-procedure
- Heparin: 70 units/kg body weight pre-procedure
- Bivalirudin: Bolus 0.75 mg/kg

  Infusion 1.75 mg/kg/hr - procedure duration

- GPI - Abciximab
  - Selective ('bailout') use in both groups
  - ESC guideline indications

Outcome Measures

At 28 days

Primary Efficacy Outcome Measure

- Major Adverse Cardiac Events (MACE)

Primary Safety Outcome Measure

- Major bleeding -
  - Type 3-5 bleeding as per BARC definitions

Results - Population

1917 patients scheduled for emergency angiography

29 (1.5%) already randomised in the trial
59 (3.0%) met one or more other exclusion criteria

1829 eligible for recruitment

1829 Randomised

Representative 'Real-World' Population

HEAT PPCI

Procedural Information

Characteristic	Bivalirudin (%)	Heparin (%)
P2Y12 use - Any	99.6	99.5
- Clopidogrel	11.8	10.0
- Prasugrel	27.3	27.6
- Ticagrelor	61.2	62.7
GPI use	13.5	15.5
Radial arterial access	80.3	82.0
PCI performed	83.0	81.6

Primary Efficacy Outcome

	Bivalirudin			Heparin	
	n	%		%	n
MACE	79	8.7 %	v	5.7 %	52

Absolute risk increase = 3.0% (95% CI 0.6, 5.4)

Relative risk = 1.52 (95% CI 1.1 – 2.1) P=0.01

HEAT PPCI

MACE Outcome - All Events

	Bivalirudin			Heparin	
	n	%		%	n
Death	46	5.1 %	v	4.3 %	39
CVA	15	1.6%	v	1.2%	11
Reinfarction	24	2.7%	v	0.9%	8
TLR	24	2.7%	v	0.7%	6
Any MACE	79	8.7 %	v	5.7 %	52

HEAT PPCI

Stent Thrombosis

ARC definite or probable stent thrombosis events

	Bivalirudin			Heparin	
	n	%		%	n
Definite	23	3.3 %	v	0.7 %	5
Probable	1	0.1 %	v	0.1 %	1
Acute	20	2.9 %	v	0.9 %	6
Subacute	4	0.6%	v	0%	0

HEAT PPCI

Primary Safety Outcomes

Major Bleed BARC grade 3-5

	Bivalirudin			Heparin	
	n	%		%	n
Major Bleed	32	3.5 %	v	3.1 %	28

Relative risk = 1.15 (95% CI 0.7 - 1.9) P=0.59

HEAT PPCI

- **Limites**
  - Etude monocentrique
  - Manque d'info: en attente de publications
  - Pas de poursuite de la bivalirudine en post-procédure
  - Seulement 80 % d'angioplastie !
- **Points Forts**
  - 1829 patients: peu de critère d'exclusion: **VRAIE VIE**


ROUND
3

ClinicalTrials.gov ID: NCT01696110

Bivalirudin versus Heparin Monotherapy and Glycoprotein IIb/IIIa Plus Heparin for Patients with AMI Undergoing Coronary Stenting

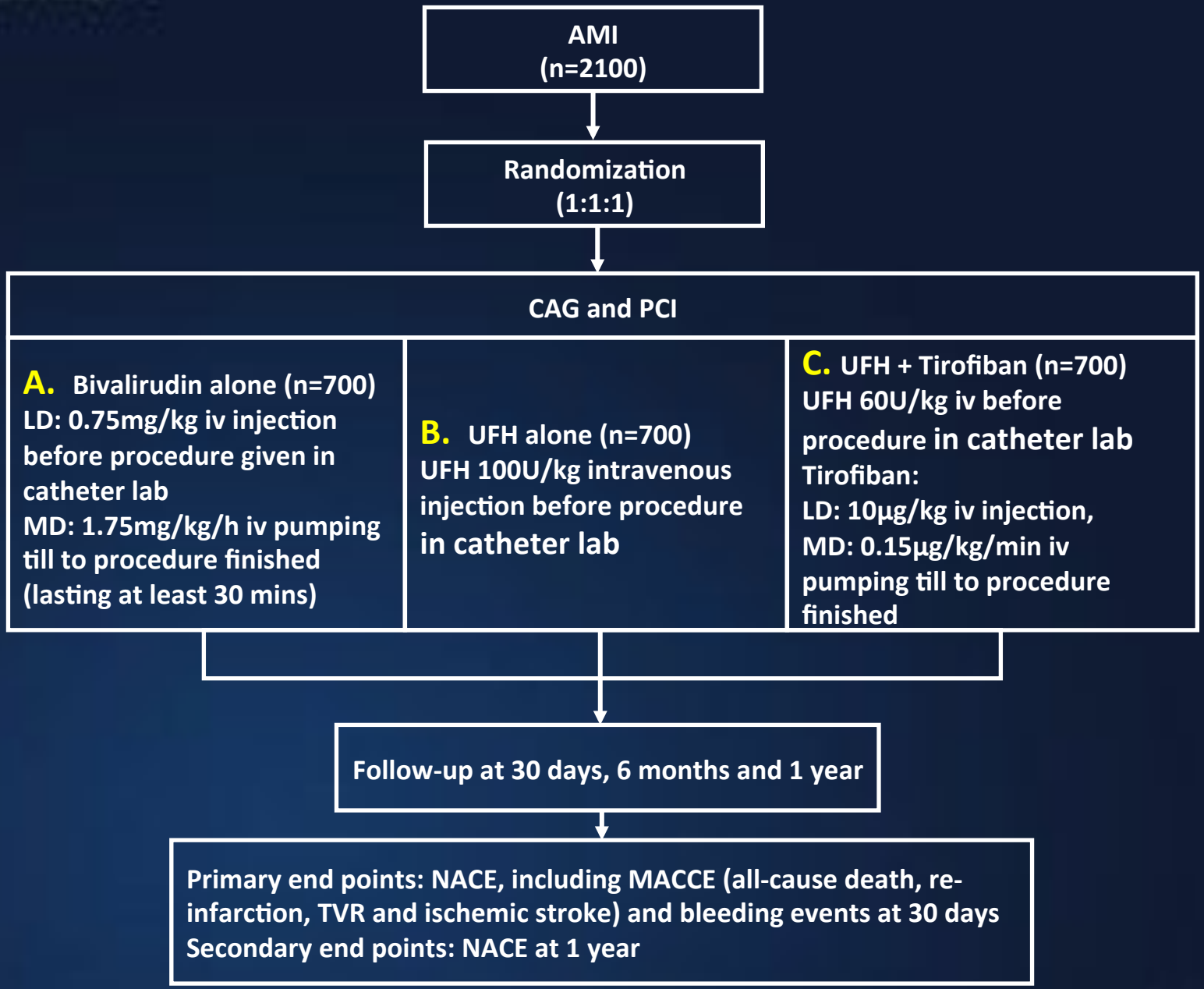
--Six-month results of the BRIGHT study

Yaling Han , MD, PhD, FACC

Shenyang Northern Hospital, China

Shanghai, 21st Mar, 2014

Study Flowchart



Endpoints

Primary end point

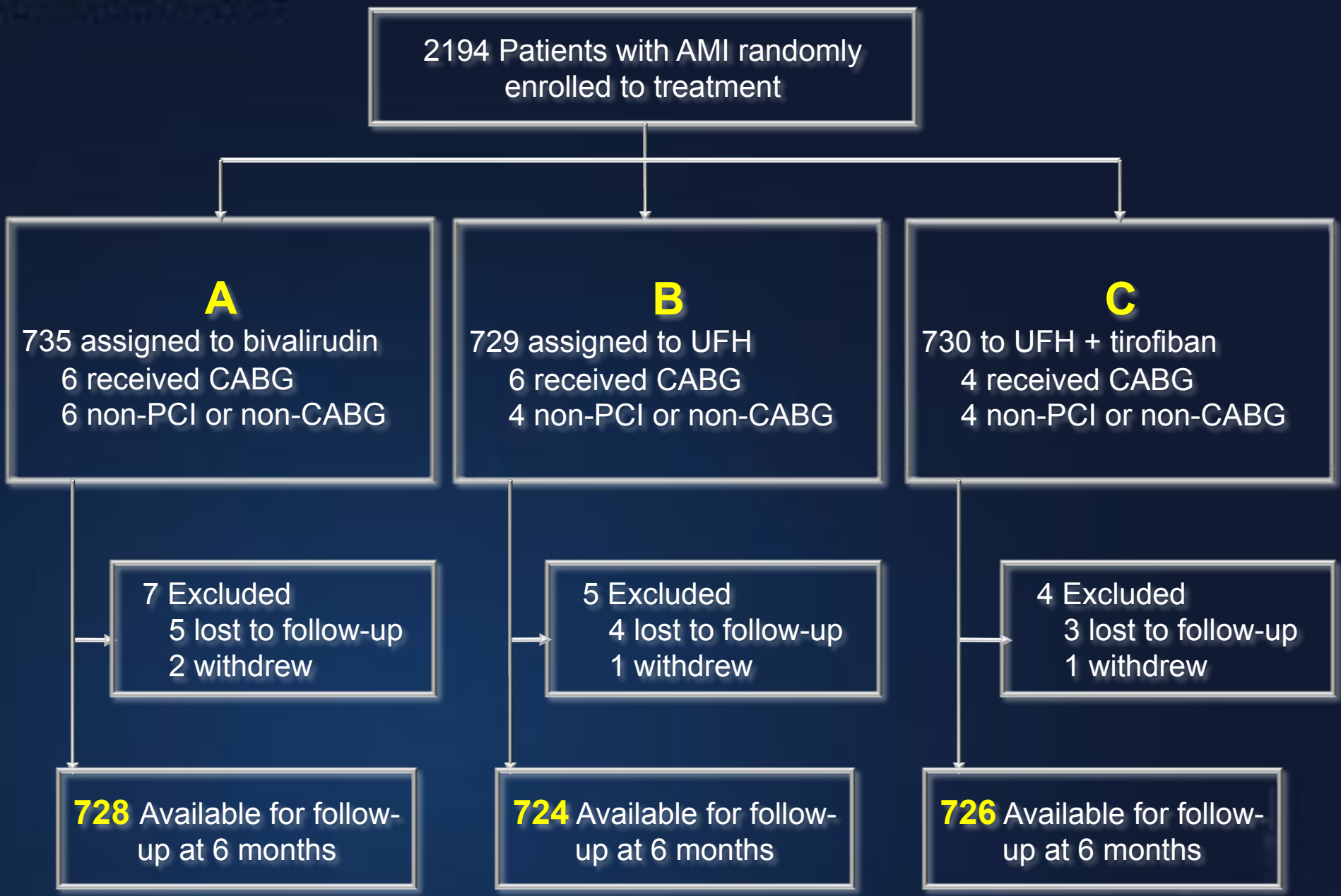
NACE at 30 days, including MACCE (all-cause death, re-infarction, TVR and ischemic stroke) and bleeding events

Secondary end point

NACE at 1 year follow-up

NACE = net adverse clinical events.

Analyzed Patient Set



Baseline Characteristics (1/2)

All p-value>0.05

Characteristic	All enrolled (N=2178)	Bivalirudin (N = 728)	UFH (N = 724)	UFH + Tirofiban (N = 726)
Age(years, median)	57.8±14.0	57.2±14.2	58.1±13.7	58.2±14.1
Male, n(%)	1791(82.2)	603(82.7)	592(81.6)	596(82.3)
Weight, kg	72.0±14.0	72.5±14.1	71.9±13.9	71.4±14.1
Medical history, no./total no.(%)				
Diabetes	462(21.1)	166(22.6)	136(18.7)	160(21.9)
Hypertension	913(41.6)	296(40.3)	309(42.4)	308(42.2)
Hyperlipidemia	810(37.2)	266(36.5)	275(38.1)	267(36.9)
Current smoker	1354(61.7)	470(63.9)	432(59.3)	452(61.9)
Previous myocardial infarction	98(4.5)	32(4.4)	33(4.5)	33(4.5)
Previous PCI	109(5.0)	37(5.1)	35(4.8)	37(5.1)
Previous stroke	175(8.0)	62(8.4)	60(8.2)	53(7.3)
Type of AMI, no./total no.(%)				
STEMI	1901(87.1)	651(88.6)	637(87.4)	625(86.3)
Non-STEMI	277(12.9)	78(11.4)	88(12.6)	99(14.7)
Antithromboic or antiplatelet medications				
Unfractionated heparin		2(0.3)	ND	ND
Low-molecular-weight heparin		47(6.4)	59(8.1)	32(4.4)
Bivalirudin		ND	2(0.3)	1(0.1)
GP IIb/IIIa inhibitor		32(4.4)	41(5.7)	ND
Aspirin	2173(99.8)	728(99.9)	724(99.9)	721(99.6)
Clopidogrel	2176(99.9)	729(100)	724(99.9)	723(99.9)

Baseline Characteristics(2/2)

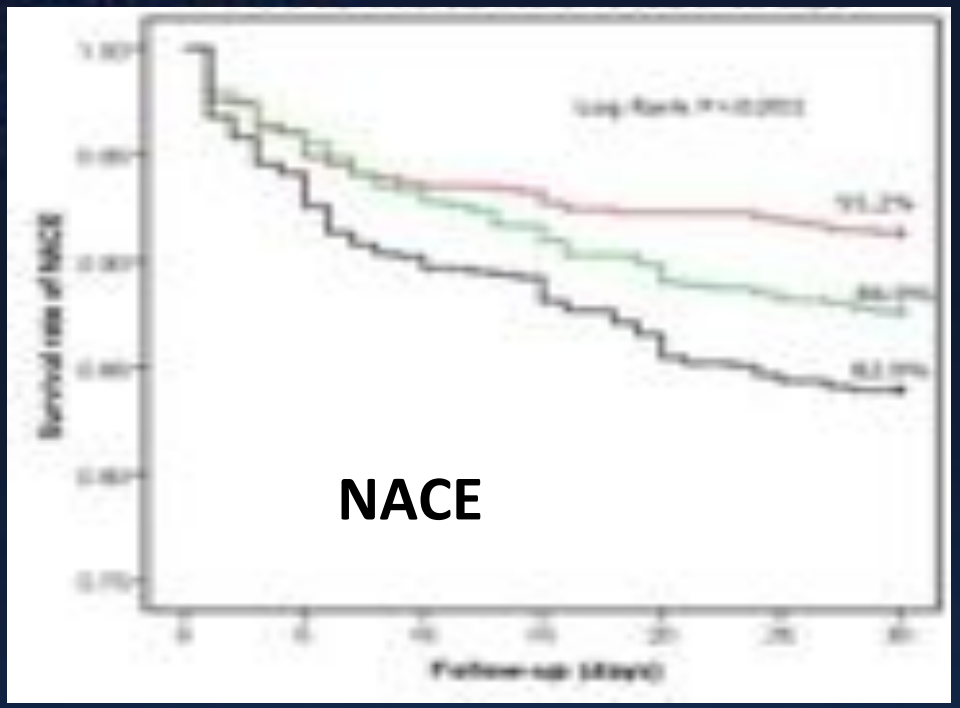
All p-value>0.05

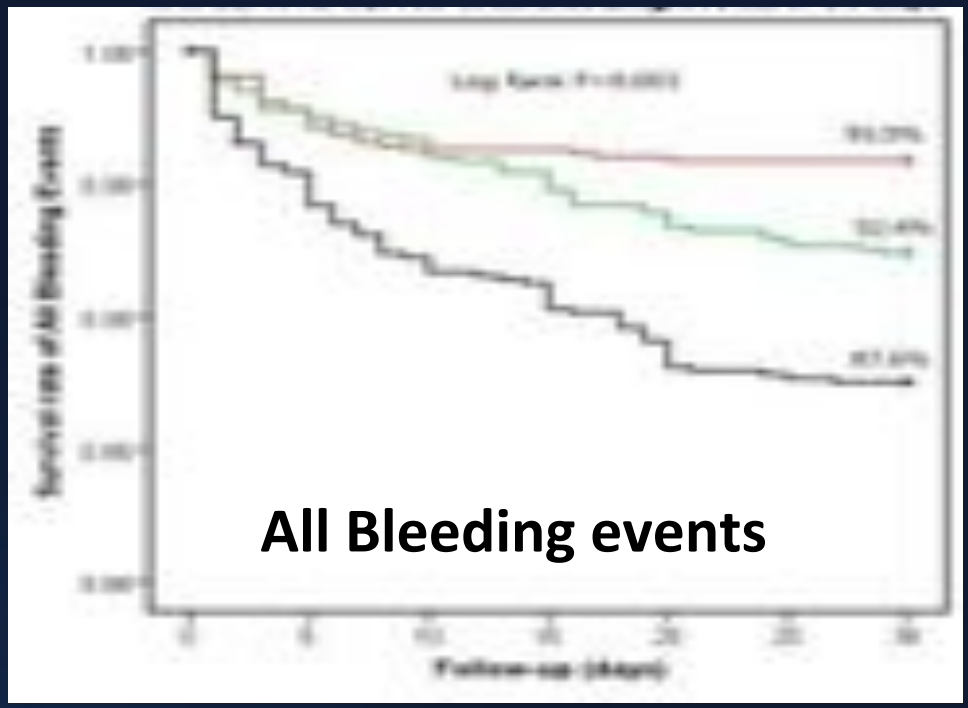
Characteristic	All enrolled (N=2178)	Bivalirudin (N = 728)	UFH (N = 724)	UFH + Tirofiban (N = 726)
Index procedure				
TF (trans femoral approach)	464(21.3)	157(21.5)	153(21.1)	154(21.3)
TR (trans radial approach)	**1714(78.7)**	**572(78.5)**	**572(78.9)**	**570(78.7)**
No. of stent implantation				
0 stent	71(3.3)	21(2.9)	23(3.2)	17(2.3)
1 stent	1727(79.3)	575(78.9)	563(77.7)	589(81.4)
2 stents	306(14.0)	106(14.5)	102(14.1)	98(13.5)
≥3 stents	26(1.2)	10(1.4)	10(1.4)	6(0.8)
Length of stented segment, mm	28.9±12.6	27.8±11.9	29.5±13.2	29.2±12.5
Vessel diameter, mm	3.1±1.3	3.0±1.2	3.1±1.2	3.2±1.4
Target vessel				
LM	15(0.7)	7(1.0)	4(0.6)	4(0.6)
LAD	1161(53.3)	389(53.3)	390(53.8)	382(52.8)
LCX	468(21.5)	152(20.9)	147(20.3)	169(23.3)
RCA	534(24.5)	188(25.8)	184(25.4)	169(23.3)
After hospital discharge through 30 days				
Aspirin	2150(98.7)	719(98.6)	720(98.8)	711(98.2)
Clopidogrel	2167(99.5)	725(99.5)	721(99.4)	721(99.6)
Statin	1943(89.2)	644(88.3)	653(87.6)	646(89.2)
Beta-blocker	1603(73.6)	537(73.7)	526(72.6)	540(74.6)

Primary end points at 30 days

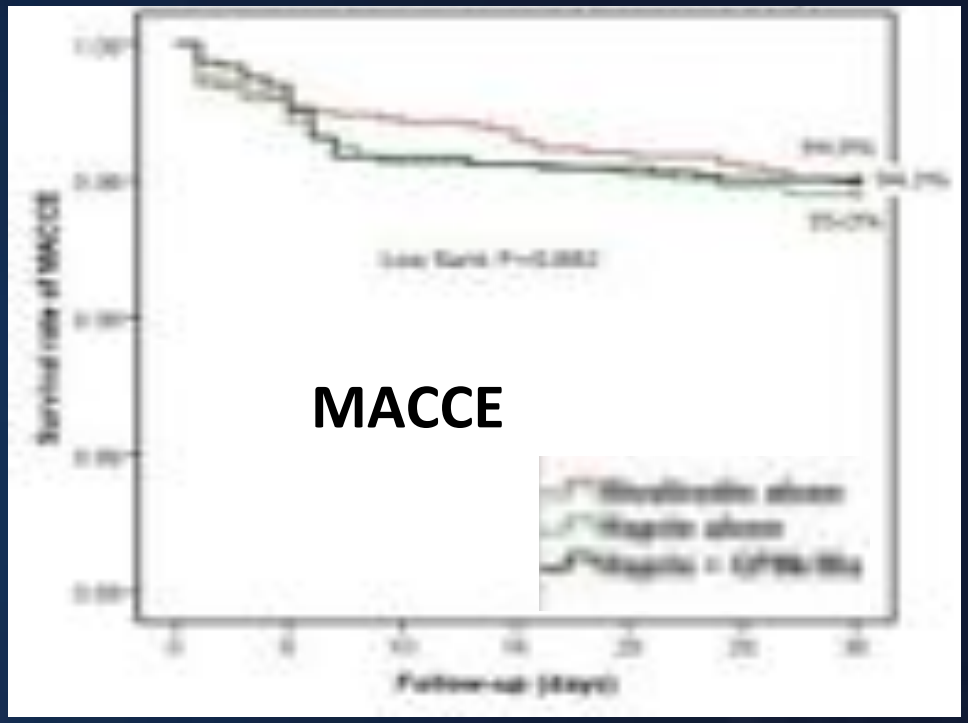
Endpoints, n(%)	All enrolled (N=2178)	A group Bivalirudin (N = 729)	B group UFH (N = 725)	C group UFH +Tirofiban (N = 724)	p-value(log-rank)		
					A vs B	A vs C	B vs C
NACE	283(13.0)	64(8.8)	95(13.1)	124(17.1)	**.045**	**.012**	.373
Bleeding endpoints	175(8.0)	30(4.1)	55(7.6)	90(12.4)	**.041**	**.001**	**.032**
BARC 3 or 5	29(1.3)	4(0.5)	11(1.5)	14(1.9)	**.047**	**.003**	.177
BARC 1-2	146(6.7)	26(3.6)	44(6.1)	76(10.5)	**.021**	**.009**	**.038**
MACCE	114(5.2)	37(5.1)	41(5.7)	36(5.0)	.612	.745	.103
Death, all-cause	40(1.8)	13(1.8)	12(1.7)	15(2.1)	.322	.110	.453
Reinfarction	22(1.0)	7(1.0)	9(1.2)	6(0.8)	.118	.521	.652
Ischemic TVR	34(1.6)	12(1.6)	13(1.8)	9(1.2)	.479	.342	.730
Ischemic stroke	18(0.8)	5(0.7)	7(1.0)	6(0.8)	.273	.831	.239

NACE = net adverse clinical events.





Survival curves of endpoints at 30 days



Conclusions

- 100% sous Clopidogrel
- Pas encore publiée
- Pas de détails sur les thromboses de stent
- SCA à Haut-risque traité par ATL ds la population chinoise:
- Efficacité et sécurité de la bivalirudine
- Bivalirudine / HNF ou HNF+ Tirofiban
    - Efficacité comprarable sur events ischémiques
    - Incidence plus faible de complications hémorragiques
- Résultats concordants avec EUROMAX

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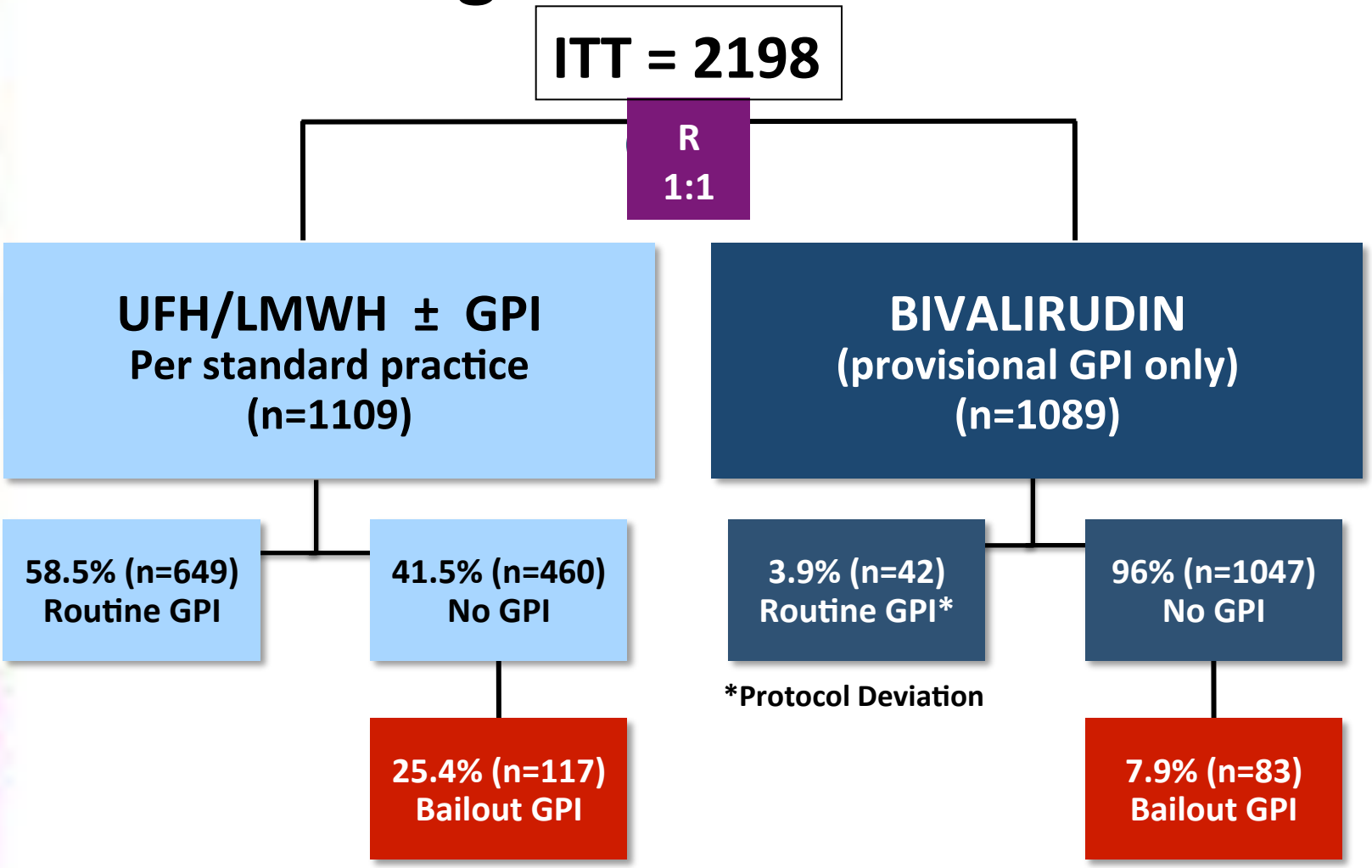
European Heart Journal
doi:10.1093/eurheartj/ehu214

Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a pre-specified analysis from the EUROMAX trial

Uwe Zeymer[1*], Arnoud van 't Hof[2], Jennifer Adgey[3], Lutz Nibbe[4], Peter Clemmensen[5], Claudio Cavallini[6], Jurrien ten Berg[7], Pierre Coste[8], Kurt Huber[9], Efthymios N. Deliargyris[10], Jonathan Day[10], Debra Bernstein[10], Patrick Goldstein[11], Christian Hamm[12], and Philippe Gabriel Steg[13,14,15]

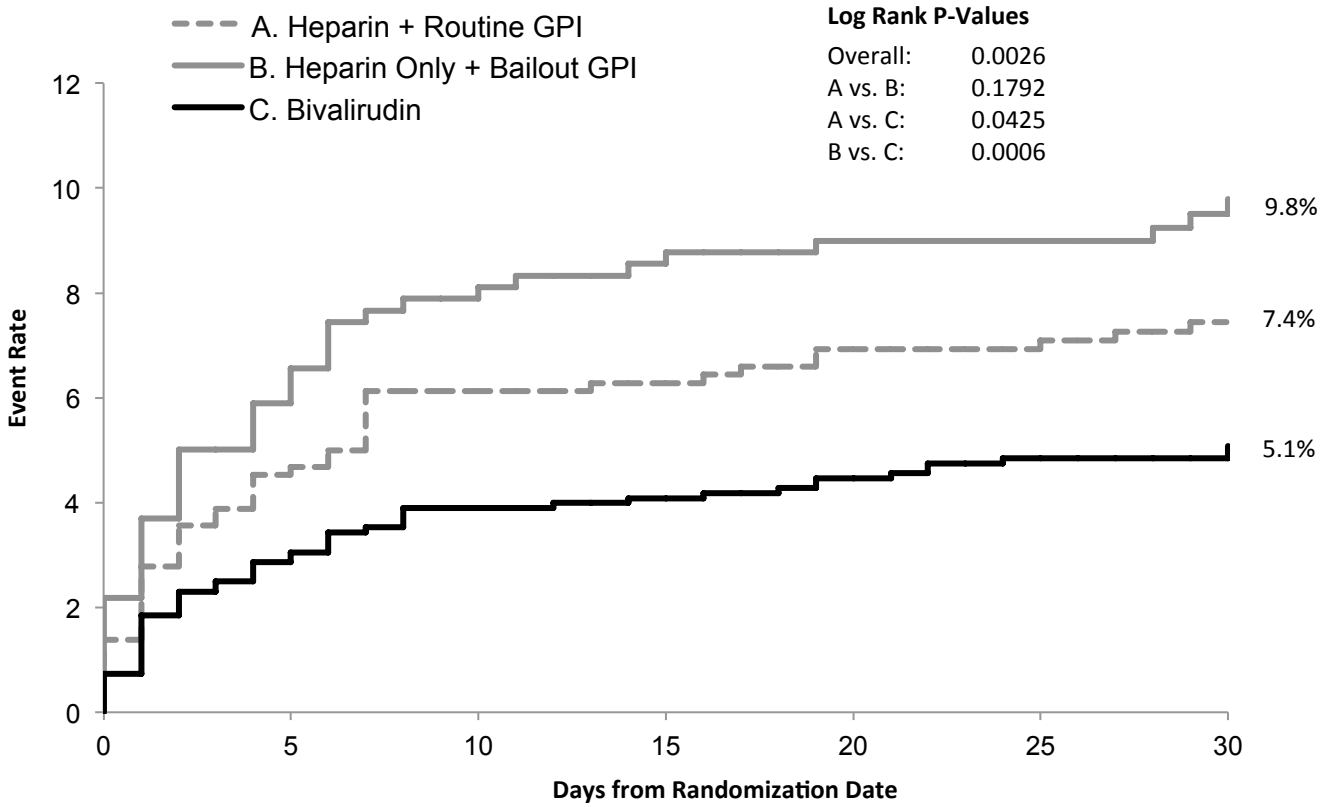
Treatment Breakdown According to Routine GPI use

EUROMAX
EUROpean AMbulance ACS AngioX Trial



Steg et al, N Engl J Med 2013

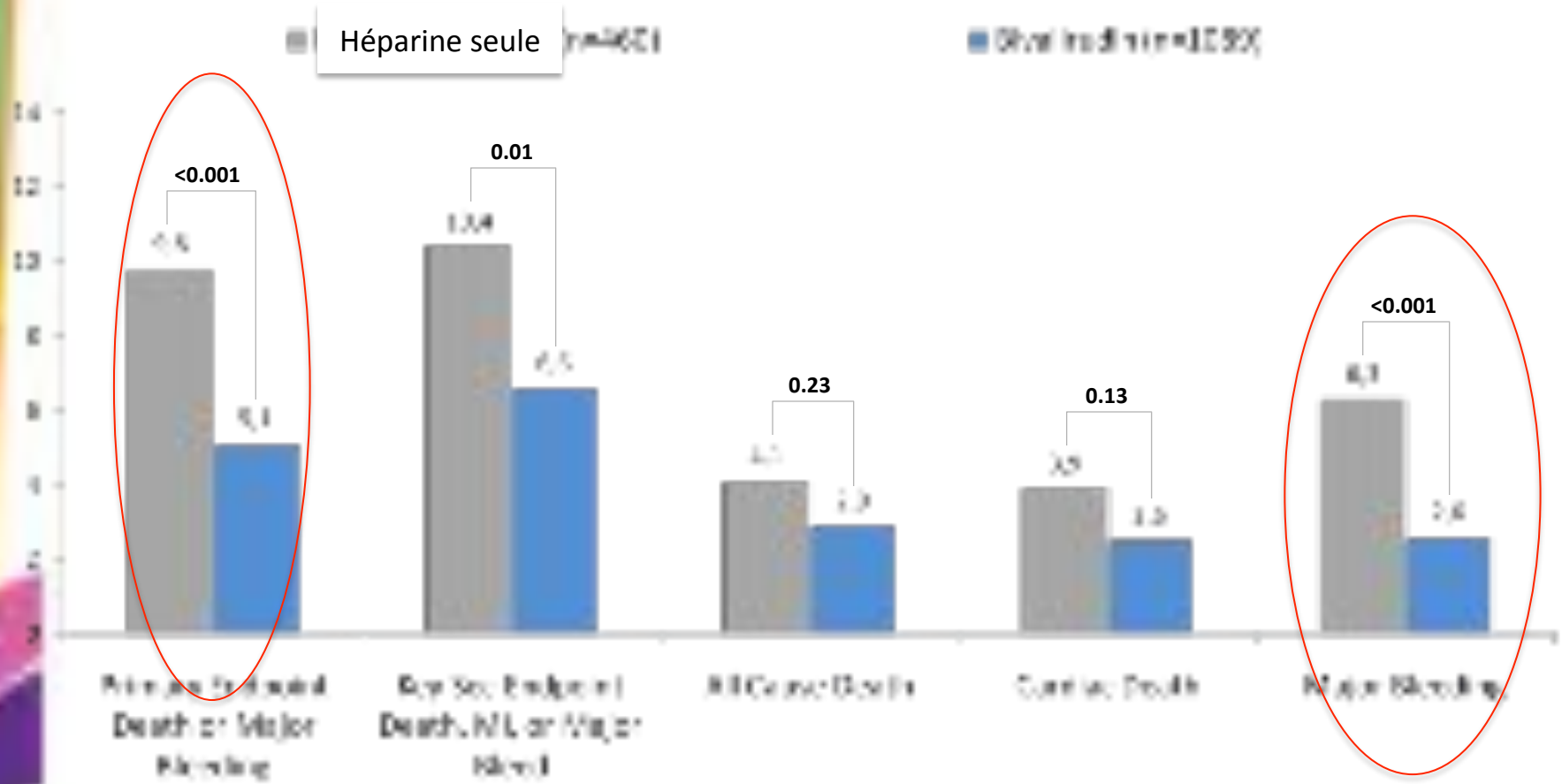
Critaire primaire
Mortalité et Saignement majeur



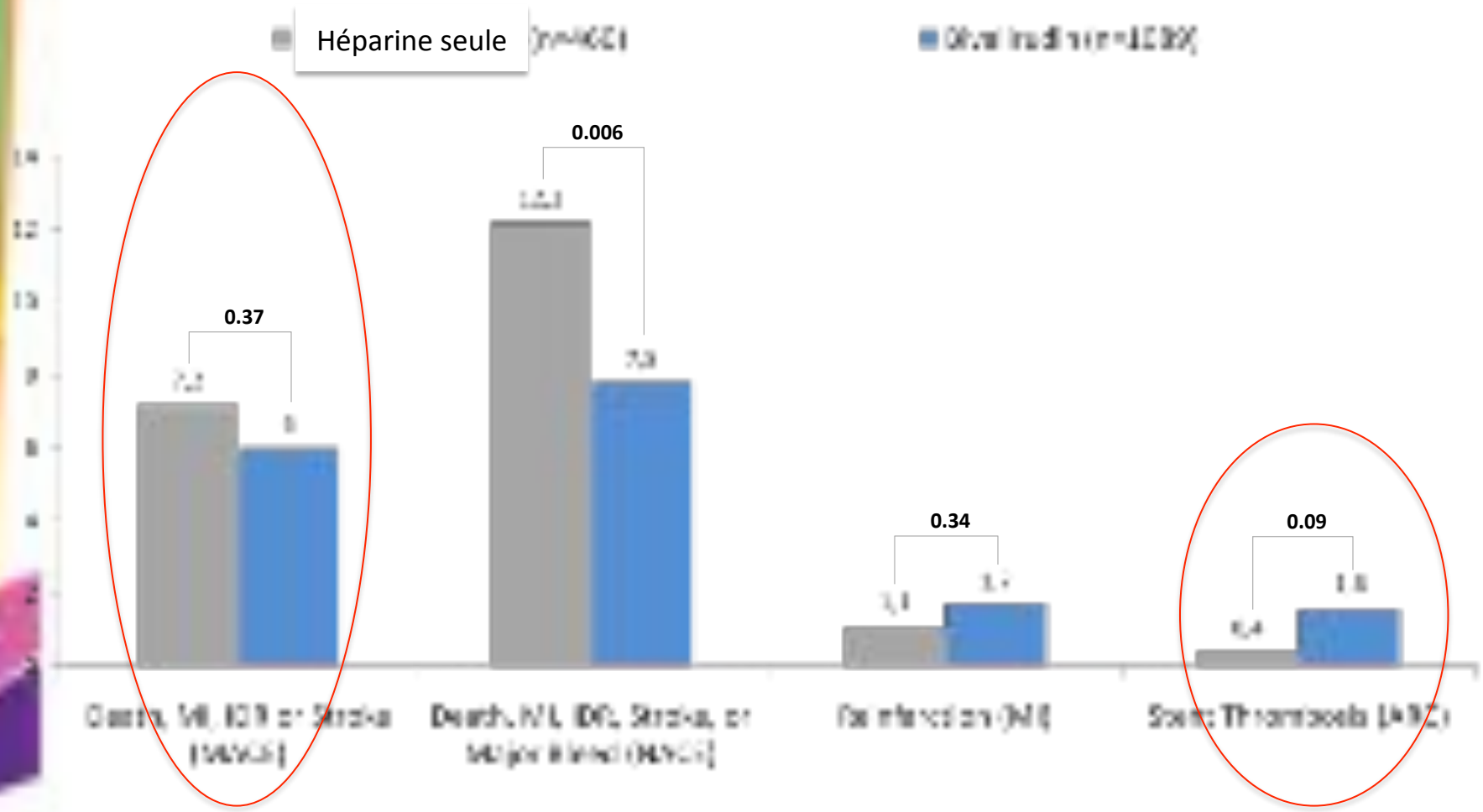
Patients at risk:

A. Heparin + Routine GPI	649	598	588	586	577	563	445
B. Heparin Only + Bailout GPI	460	426	415	412	407	395	320
C. Bivalirudin	1089	1038	1024	1020	1007	899	791

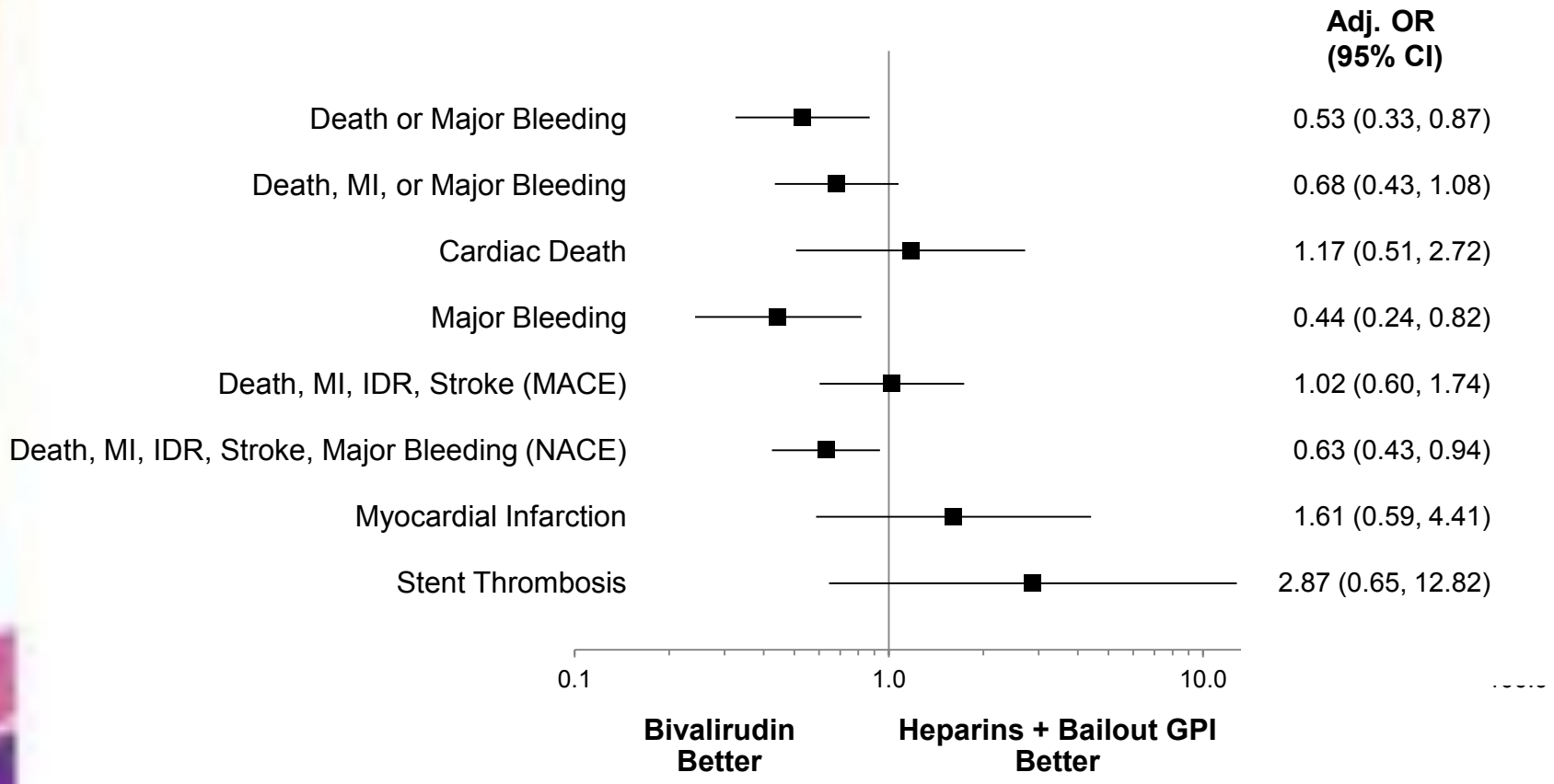
Bivalirudin vs. Heparins Without Routine GPI



Bivalirudin vs. Heparins Without Routine GPI



Analyse Multivariée



	Bivalirudine				HNF seule			
	EUROMAX (n=1047)	HEAT-PPCI (n=905)	BRAVE-4 (n=271)	BRIGHT (n=729)	EUROMAX (n=460)	HEAT-PPCI (n=907)	BRAVE-4 (n=277)	BRIGHT (n=725)
TTT Antiagrégants, %								
Clopidogrel	50	11.8	3.7	100	51	10	90.2	99.9
Nouveaux Inhi-bP2Y12	50	88.2	94.6	_	49	90	7.1	_
Anti-GP Routine	_	_	_	_	_	_	_	_
Anti-Gp Bail-out	7.9	13.5	3	4.4	25.4	15.5	6.1	5.7
Héparine, %								
Dose HNF	_	_	_	_	60Ui/Kg Pré-PCI	70Ui/Kg	70-100Ui/Kg	100Ui/Kg Pré-PCI
Contrôle ACT	_	_	_	_	0		1	
Nouveau bolus HNF	_	_	_	_	0	34		?
Bivalirudine, %								
Perfusion poursuivie à 0.25	63.9	0	0	0	_	_	_	_
Pefusion poursuivie à 1.25	23.3	0	0	0	_	_	_	_
Interventionnel, %								
Radial	47.7	80.3	0	78.5	54.1	82	0	78.9
Angioplastie	97.1	83	91.1		95.8	81.6	92.8	
Thrombectomie	32.2	59.1			33.5	57.6		
Stent	92	92.8	88.6	97.1	91.4	92.2	86.6	96.8
Ballon seul	5.1	7.2	2.2	2.9	3.9	7.8	5.8	3.2
Décès	2.9	5.1	2.6	1.8	3.5	4.3	2.5	1.7
Saignement Majeur	2.7	3.5	2.6	0.5	6.1	3.1	2.9	1.5
Thrombose aigue de stent	1.6	2.9	1.1	1.1	0.4	0.9	1.5	1.5

Conclusion

- **ANGIOX en préhospitalier de STEMI**
  - Faisable, efficacité égale / HNF
  - Fait moins saigner (-60% de saignts majeurs)

- **Sur-risque de thrombose de stent aigue (<24h)**
  - Trou entre arrêt ANGIOX et effet des anti-P2Y12 (retardé) ?
  - Pas d'effet protecteur
    - Nouveaux anti-P2Y12 en préhospitalier
    - Poursuite de la perfusion lente de Biva sur 2-4h après ATL
  - Solution?
    - Poursuite d'une perfusion de biva à dose d'angioplastie sur 2 à 4h
    - Surcout : 2 flacons de Biva
    - +/- Cangrelor ? (HORIZONS 2)

Conclusion

- Résultats contradictoires de HEAT-PPCI

- **Etudes EUROMAX et BRIGHT**
  - Protection thrombotique (MACE): Biva=HNF
  - Protection hémorragique: Biva>HNF
- **Etude HEAT-PPCI**
  - Protection thrombotique (MACE): Biva<HNF
  - Protection hémorragique: Biva=HNF

- HEAT-PPCI = Belle étude

- Bras HNF optimisé
  - contrôle ACT (nouveau bolus pour 30% des patients)
- Bras Bivalirudine Non optimisé
  - Pas de poursuite de perfusion à haute dose en post-procédure
- Seulement 80% d'angioplastie !

Alors, que fait-on ?

De façon pratique…

De façon pratique…

- **Bivalirudine (ANGIOX) ds le STEMI**
  - Molécule efficace et sure en préhospitalier Courbe d'apprentissage de son utilisation (Thrombose de stent)
  - Molécule chère / HNF +++ : mais bientôt génériquée
  - Reco ESC 2012: IB
- **Pas de changement immédiat dans nos pratiques**
  (Biva en préhospitalier)
- **Dans l'Attente de**
  - Publication de HEAT-PPCI
  - Méta-analyse
  - Etude ou registre de grand volume: Biva vs HNF
  - Reco ESC 2014: modifications ? Probabes…

MERCI