Antithrombotic Therapy for PCI

Michael S. Lee, MD, FSCAI
Associate Professor
UCLA Medical Center

Heartwire from Medscape

Stone and Stables Spar Over Heparin vs Bivalirudin in STEMI

Shelley Wood

September 22, 2014

WASHINGTON, DC — More than five months after the HEAT-PPCI STEMI trial of **heparin** monotherapy vs **bivalirudin** burst onto the radar of interventional cardiologists, the two men at opposite ends of this controversy took to the public stage to debate the issues.

In fact, at last week's TCT 2014 meeting, they did it not once, but twice.

On one side, **Dr Rod Stables** (Liverpool Heart and Chest Hospital, UK), the principal investigator for HEAT-PPCI, which first called into question bivalirudin's supremacy in primary PCI. The trial has since spurred a change to practice patterns and, at least in Europe, a

On the oth
NY). Stone
2007 trial t
course dir
outspoken
American
past April.

The first de
what do the data support? Stone, speaking first, landed the first jab with the provocative opener: "Heparin is a disgusting product," he proclaimed, showing a black and white photo of a chemist with dead swine dangling in the background and a recipe for concocting the drug. "It's made from pork intestines, it has pancreatic extract, ammonia, sodium hydroxide: this is how you made heparin [in the 1930s], and this is how you make it today. . . . It's inexpensive, yes, but it's a terrible drug."


Dr Gregg Stone

From there, Stone launched into the fast-paced clinical-trial review for which he is famous, slides flickering past like strobe lights, providing a sweeping recap of more than a decade's worth of research showing heparin monotherapy in STEMI care to be an inferior strategy.

"When did it become okay once again to use heparin only during primary PCI in STEMI?" Stone asked. "Heparin monotherapy is stepping back a decade."

Stone's most pointed remarks zeroed in on the three trials that have looked specifically at heparin monotherapy vs bivalirudin: BRIGHT (presented in the US for the first time at TCT), EUROMAX ,and HEAT-PPCI, saving his most blistering treatment for the last. The other two, he noted, were large multicenter trials, whereas HEAT-PPCI was a single-center trial, "so you've got to scrutinize the methods and the results."

> Heparin is a disgusting product.

"Heparin is a disgusting product. It's made from pork intestines. It has pancreatic extract, ammonia, sodium hydroxide. …it's a terrible drug"

"The problem with heparin is that there is no drug rep to take you out to an expensive dinner."

Saibal Kar, MD
Cedars-Sinai Medical Center

POINT #1

- **Acute stent thrombosis is higher with bivalirudin**

HORIZONS- AMI
30 Day Stent Thrombosis (N=3,124)

	UFH + GP IIb/IIIa (N=1553)	Bivalirudin (N=1571)	P Value
ARC definite or probable*	1.9%	2.5%	0.33
- definite	1.4%	2.2%	0.11
- probable	0.5%	0.3%	0.26
- acute (≤24 hrs)	0.3%	1.3%	0.0009
- subacute (>24 hrs – 30d)	1.7%	1.2%	0.30

*Protocol definition of stent thrombosis, CEC adjudicated

HEAT PPCI

- 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

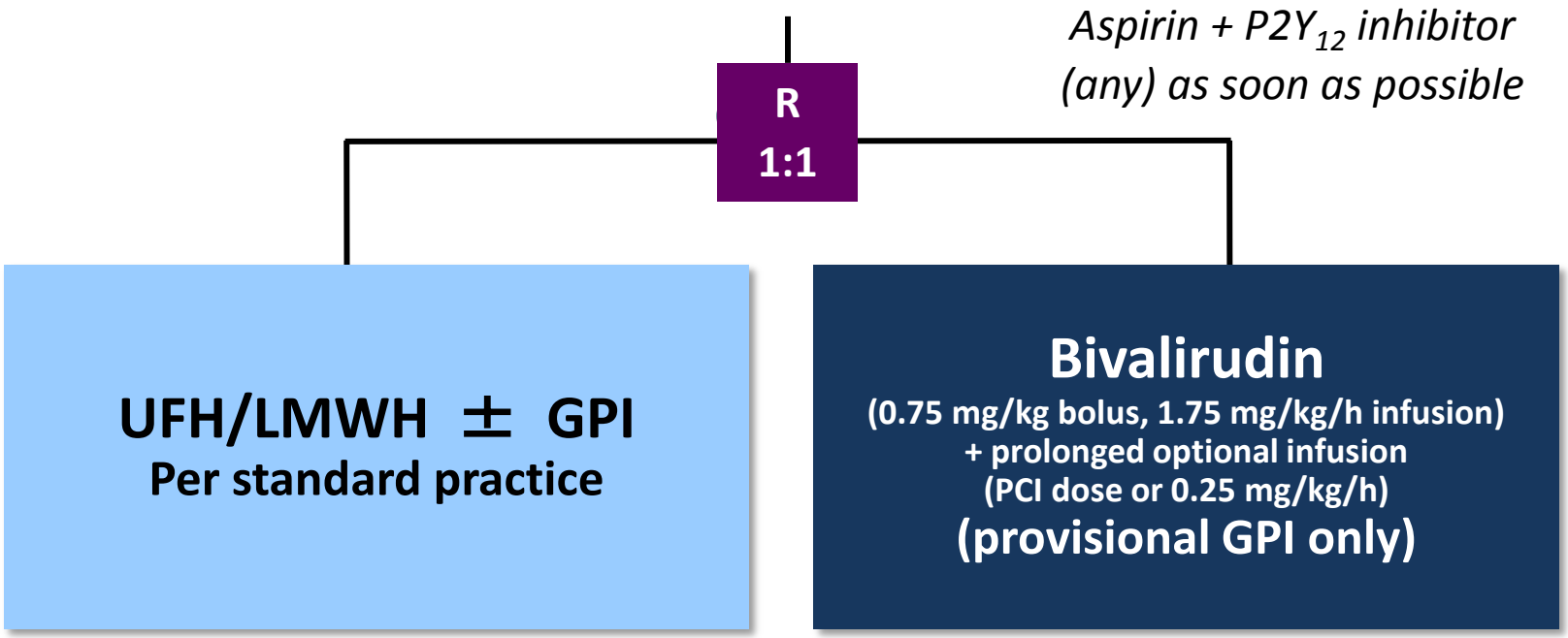
HEAT PPCI
Stent Thrombosis

	Bivalirudin		Heparin
	%		%
Definite*	3.3 %	v	0.7 %
Acute	2.9 %	v	0.9 %
Subacute	0.6%	v	0%

*p=0.001

EUROMAX 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

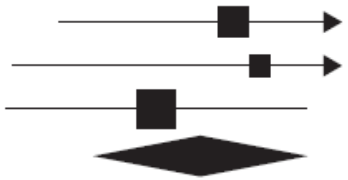
clinicaltrials.gov NCT01087723

EUROMAX Trial

	Bivalirudin (N=1089)	Heparins with optional GPI (N=1109)	Relative risk [95% CI]	P Value
Stent thrombosis (ARC definition)	17 (1.6)	6 (0.5)	2.89 (1.14–7.29)	0.02
Definite	17 (1.6)	6 (0.5)	2.89 (1.14–7.29)	0.02
Probable	0 (0)	0 (0)	–	n/a
Acute (≤24 hours)	12 (1.1)	2 (0.2)	6.11 (1.37–27.24)	0.007
Subacute (>24 hours to 30 days)	5 (0.5)	4 (0.4)	1.27 (0.34–4.73)	0.75

Meta-Analysis
Acute Stent Thrombosis

	Bivalirudin	Heparin	Stent thrombosis risk ratio (95% CI)
Acute stent thrombosis			
HORIZONS-AMI[4]	21/1571 (1%)	4/1553 (<1%)	5·19 (1·79–15·08)
EUROMAX[7]	12/1089 (1%)	2/1109 (<1%)	6·11 (1·37–27·74)
HEAT PPCI[26]	20/697 (3%)	6/682 (1%)	3·26 (1·32–8·07)
Overall	53/3357 (2%)	12/3344 (<1%)	4·27 (2·28–8·00)
			p<0·0001



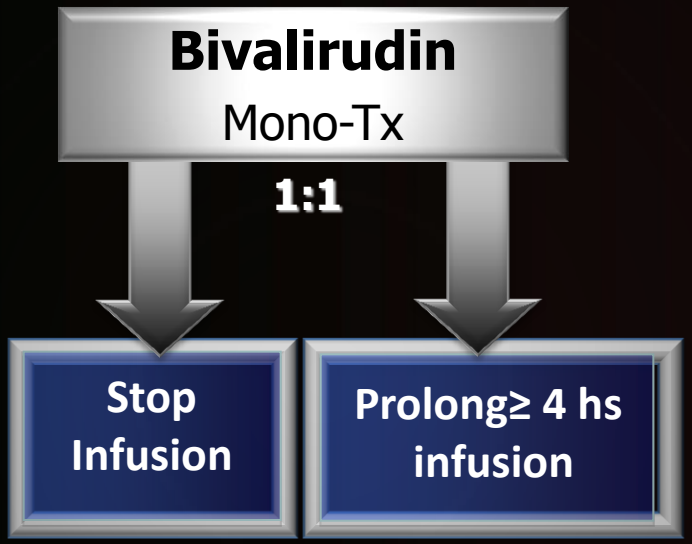
Lancet 2014

MATRIX Treatment duration

NSTEACS or STEMI with invasive management

Aspirin+P2Y12 blocker

NCT01433627

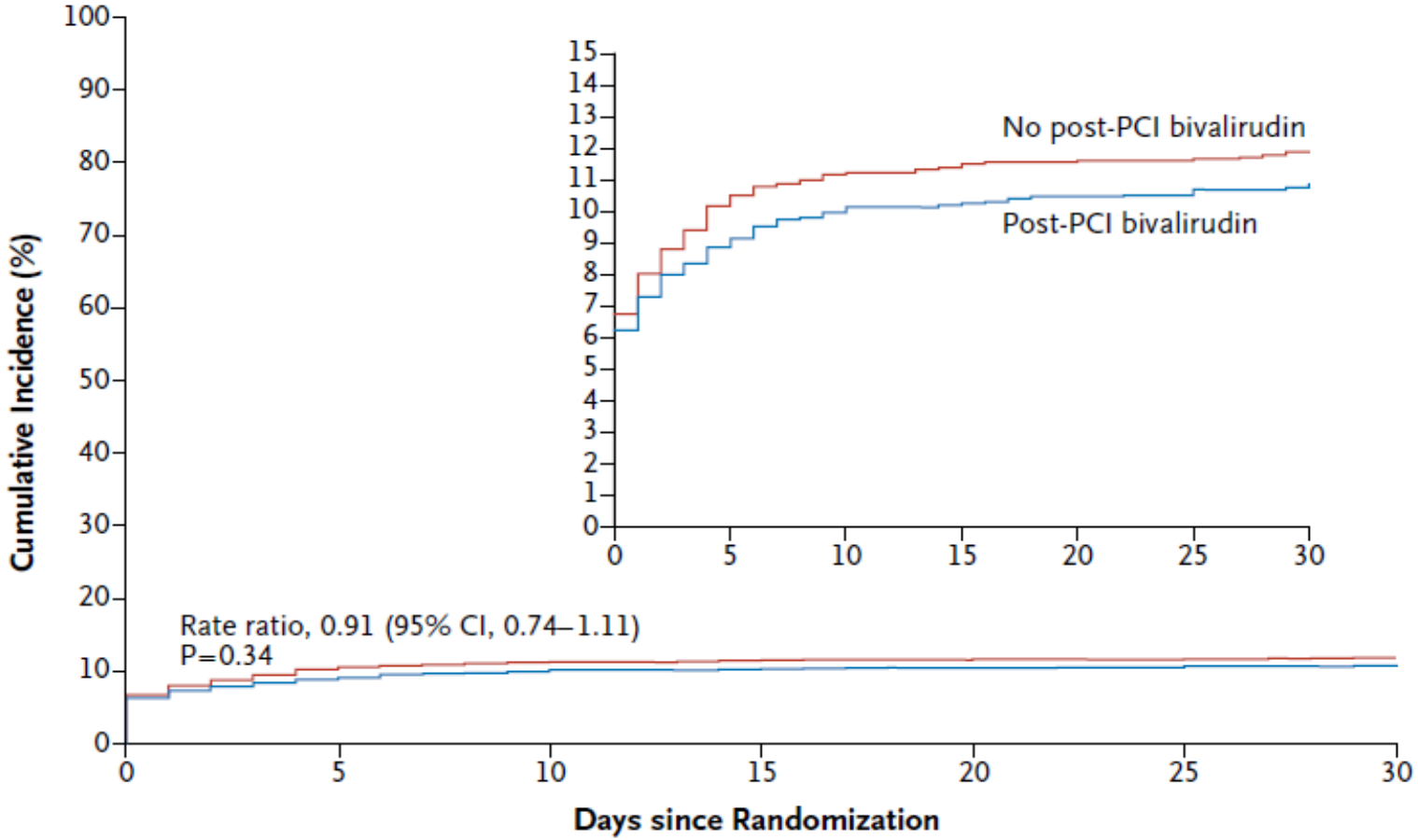


Primary Objective

To demonstrate that prolonged Bivalirudin infusion is associated to lower rate of the composite endpoint of Death, MI, Stroke, urgent TVR, Stent thrombosis or BARC bleeds V or III within the first 30 days

10% vs. 7%, β<4%, α:5%: 3,400 patients

MATRIX

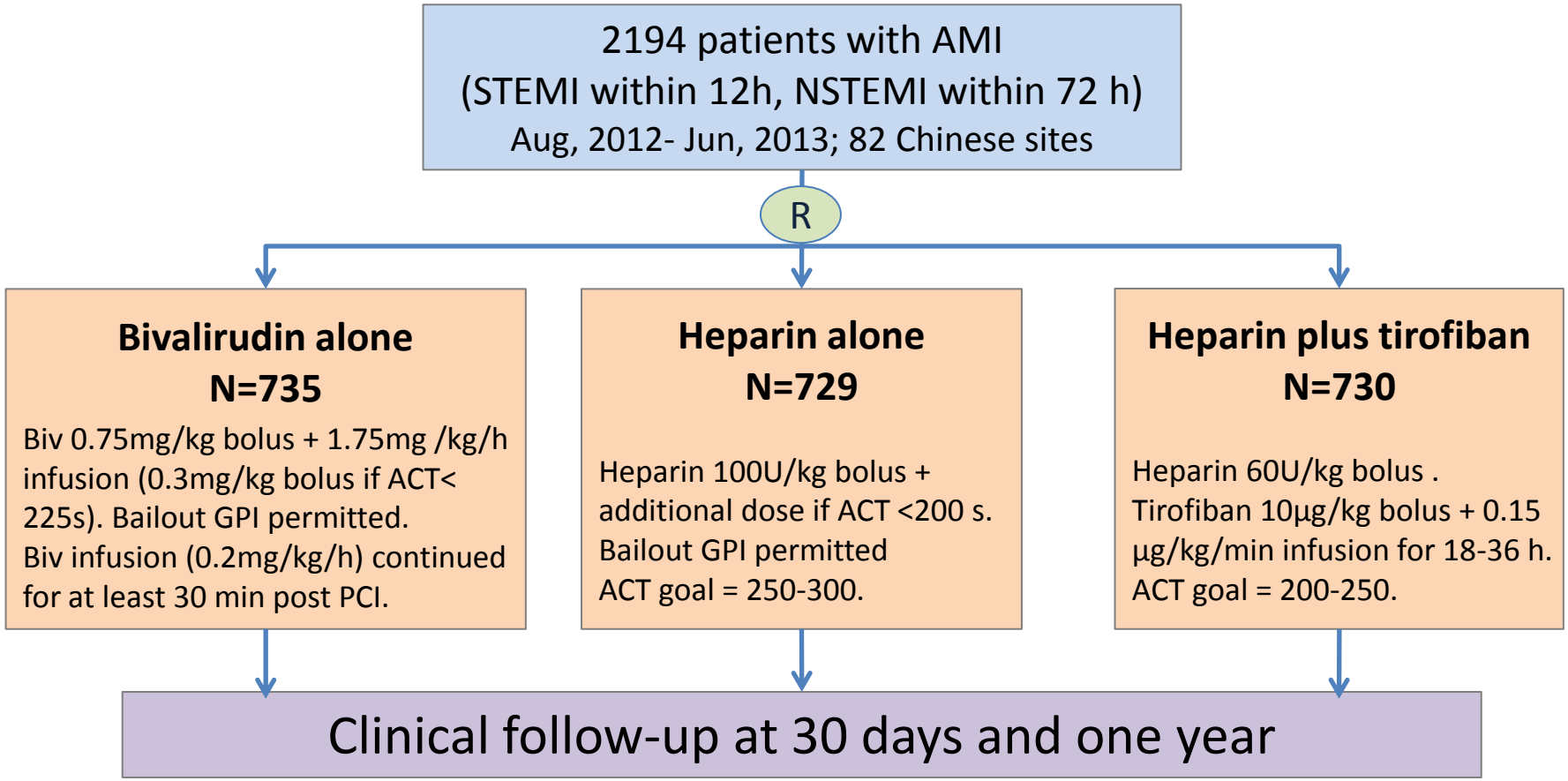


No. at Risk

No post-PCI bivalirudin	1811	1624	1606	1602	1599	1598	1592
Post-PCI bivalirudin	1799	1634	1611	1607	1602	1601	1597

BRIGHT Study Design

(clinicaltrials.gov number: NCT01696110)

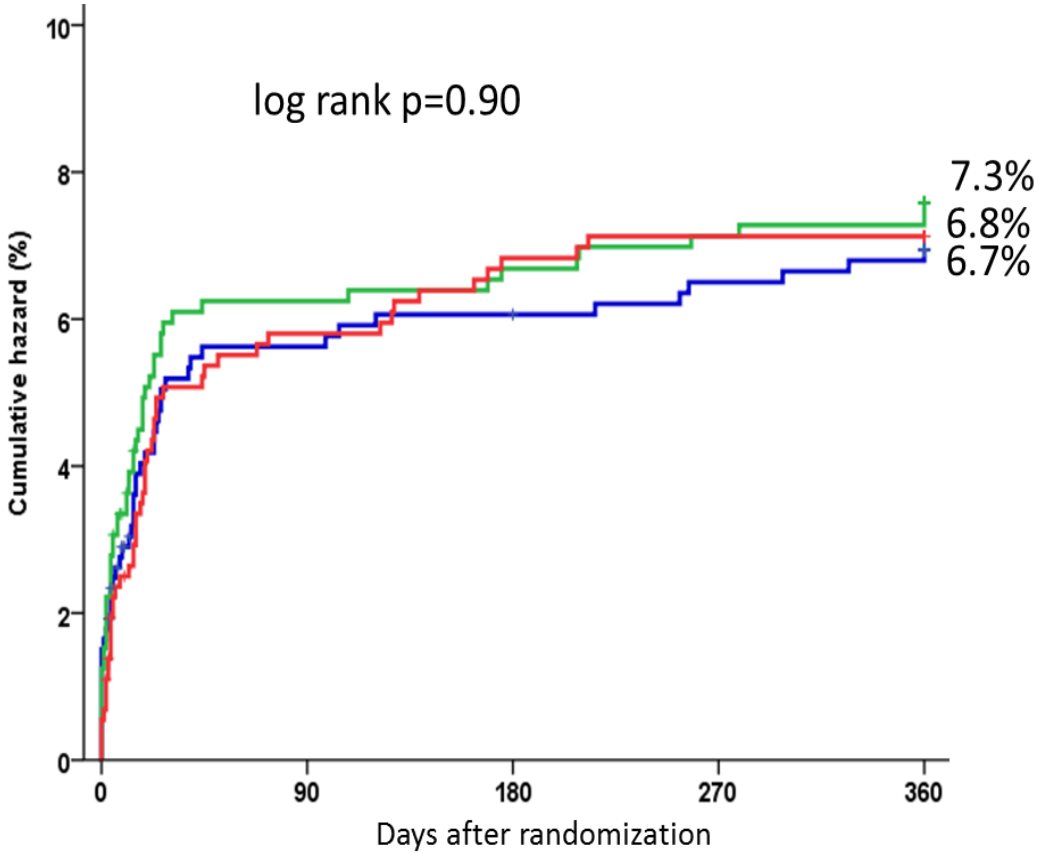


1° endpoint: NACE (death, MI, iTVR, stroke, any bleeding) @ 30 days

2° endpoints: NACE @ 1 year, MACCE & bleeding @ 30 days and 1 year

BRIGHT Trial
Time-to-Event Curves: 1 Year Outcomes

MACCE at 1 year

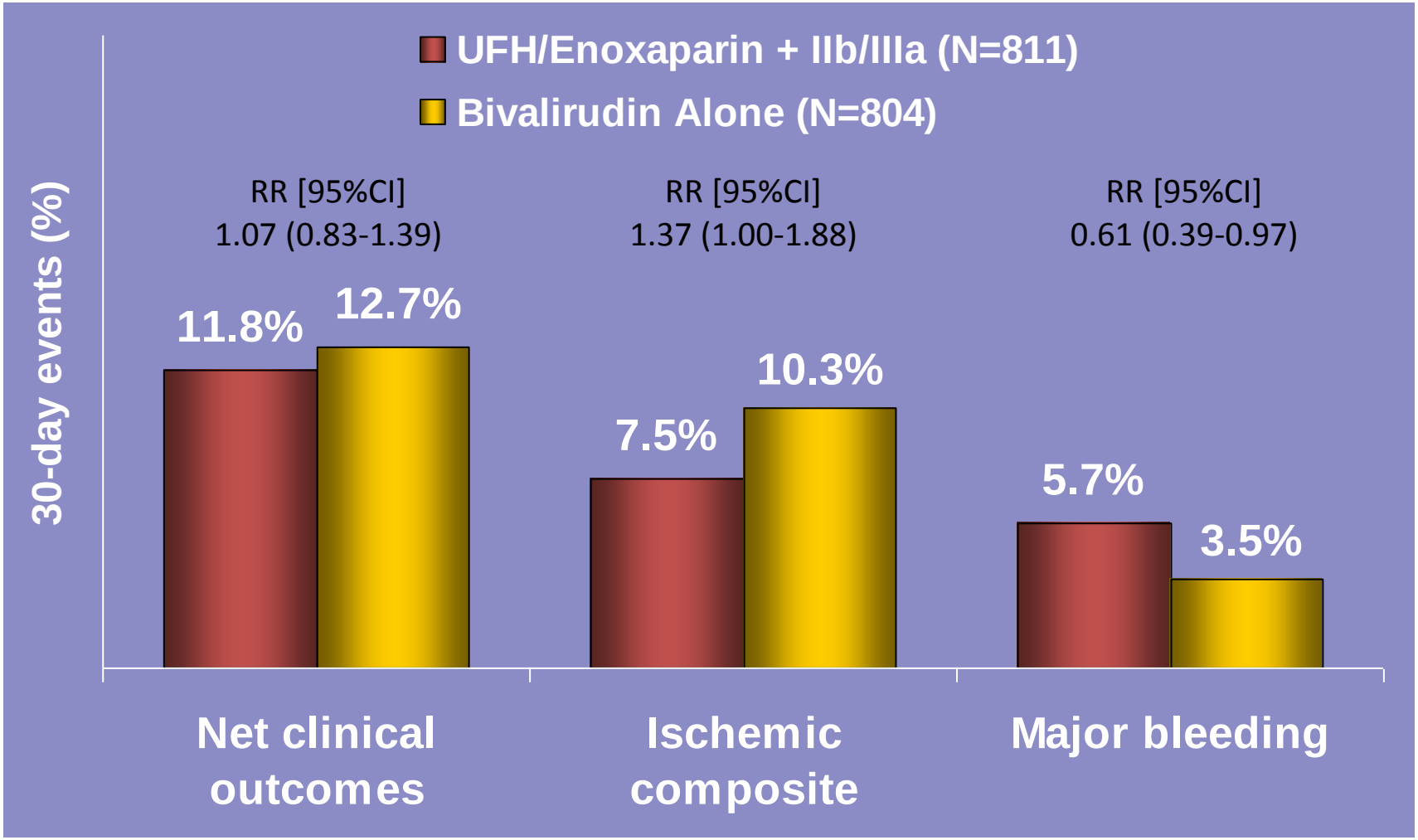


POINT #2

- **Ischemic events are higher with bivalirudin**

ACUITY Trial

No Thienopyridine Exposure – PCI pts*



ACUITY PCI as presented at TCT 2006.

*Thienopyridine at any time, any dose, up to time of PCI

International Journal of Cardiology 152 (2011) 369–374

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Comparison of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitors in patients undergoing an invasive strategy: A meta-analysis of randomized clinical trials

Michael S. Lee [a,b,c,*], Hsini Liao [d], Tae Yang [a,b,c], Jashdeep Dhoot [a,b,c], Jonathan Tobis [a,b,c], Gregg Fonarow [a,b,c], Ehtisham Mahmud [a,b,c]

[a] David Geffen School of Medicine at University of California, Los Angeles (Division of Cardiology), Los Angeles, CA, United States
[b] Boston Scientific Corporation, Maple Grove, MN, United States
[c] University of California, San Diego (Division of Cardiology), San Diego, CA, United States
[d] Boston Scientific Corporation, Marlborough, MA, United States

ARTICLE INFO

Article history:
Received 11 January 2010
Received in revised form 22 April 2010
Accepted 6 August 2010
Available online 16 September 2010

Keywords:
Percutaneous coronary intervention
Bivalirudin
Heparin
Glycoprotein IIb/IIIa inhibitors

ABSTRACT

Objective: This meta-analysis was performed to assess the efficacy and safety of bivalirudin compared with unfractionated heparin or enoxaparin plus glycoprotein (GP) IIb/IIIa inhibitors in patients undergoing percutaneous coronary intervention (PCI).

Background: Pharmacotherapy for patients undergoing PCI includes bivalirudin, heparin, and GP IIb/IIIa inhibitors. We sought to compare ischemic and bleeding outcomes with bivalirudin versus heparin plus GP IIb/IIIa inhibitors in patients undergoing PCI.

Methods: A literature search was conducted to identify fully published randomized trials that compared bivalirudin with heparin plus GP IIb/IIIa inhibitors in patients undergoing PCI.

Results: A total of 19,772 patients in 5 clinical trials were included in the analysis (9785 patients received bivalirudin and 9987 patients received heparin plus GP IIb/IIIa inhibitors during PCI). Anticoagulation with bivalirudin, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, results in no difference in major adverse cardiovascular events (odds ratio [OR] 1.07, 95% confidence interval [CI] 0.96 to 1.19), death (OR 0.93, 95% CI 0.72 to 1.21), or urgent revascularization (OR 1.06, 95% CI 0.86 to 1.30). There is a trend towards a higher risk of myocardial infarction (OR 1.12, 95% CI 0.99 to 1.28) but a significantly lower risk of TIMI major bleeding with bivalirudin (OR 0.55, 95% CI 0.44 to 0.69).

Conclusion: In patients who undergo PCI, anticoagulation with bivalirudin as compared with unfractionated heparin or enoxaparin plus GP IIb/IIIa inhibitors results in similar ischemic adverse events but a reduction in major bleeding.

In conjunction with contemporary pharmacologic therapy, percutaneous coronary intervention (PCI) results in excellent clinical outcomes in patients with coronary artery disease. However, adverse events associated with PCI include periprocedural ischemic events, recurrent revascularization and bleeding [1]. Unfractionated heparin was the traditional antithrombin agent used during PCI to prevent ischemic complications [2]. The administration of glycoprotein (GP) IIb/IIIa inhibitors in addition to heparin results in additional reduction of periprocedural ischemic events but also increases the risk of bleeding complications [3,4]. Recent data have shown that bleeding complications at the time of PCI have been associated with higher mortality after PCI [5–7]. This has resulted in continued investigation into alternative pharmacologic agents for optimal ischemic efficacy during PCI while decreasing hemorrhagic complications.

The direct thrombin inhibitor, bivalirudin (Angiomax, the Medicines Company, Fort Lee, NJ), a synthetic polypeptide derived from the native anticoagulant hirudin, is an attractive alternative to heparin in patients who undergo PCI [8]. Randomized clinical trials comparing bivalirudin with heparin plus GP IIb/IIIa inhibitors in patients who undergo PCI demonstrated that bivalirudin had comparable rates of ischemic complications with lower rates of major bleeding compared

Abbreviations: ACT, activated clotting time; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; CACHET, Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial; GP, glycoprotein; HORIZONS-AMI, Harmonizing Outcomes with RevascularizatiON and Stents in Acute Myocardial Infarction; PCI, percutaneous coronary intervention; PROTECT-TIMI-30, Randomized Trial to Evaluate the Relative PROTECTion against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Anti-Platelet and Anti-Thrombotic Agents—Thrombolysis in Myocardial Infarction-30; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; TIMI, Thrombolysis in Myocardial Infarction.

* Corresponding author. UCLA Medical Center, Adult Cardiac Catheterization Laboratory, 10833 Le Conte Avenue, Rm A2-237 CHS, Los Angeles, CA 90095-1679, United States. Tel.: +1 310 696 9523.
E-mail address: mslee@mednet.ucla.edu (M.S. Lee).

0167-5273/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2010.08.007

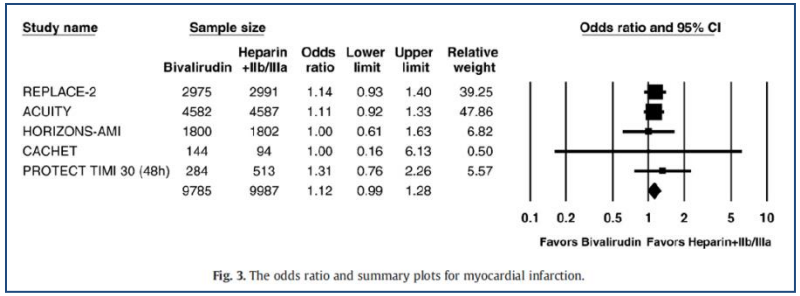


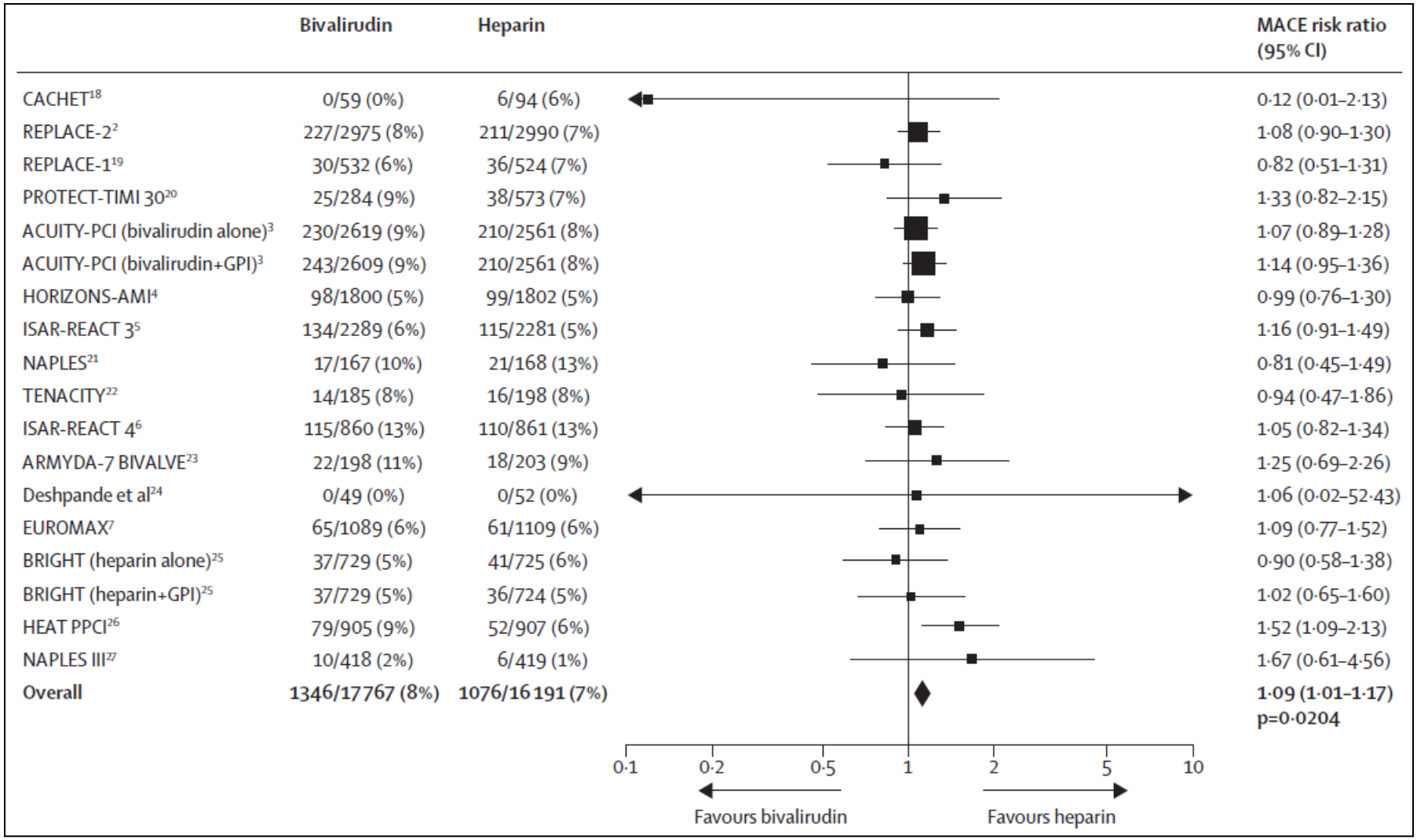
Fig. 3. The odds ratio and summary plots for myocardial infarction.

HEAT PPCI
MACE Outcomes at 28 days

	Bivalirudin		Heparin
	%		%
Death	5.1 %	V	4.3 %
CVA	1.6%	v	1.2%
Reinfarction	2.7%	v	0.9%
TLR	2.7%	v	0.7%
Any MACE*	8.7 %	v	5.7 %

P=0.01

Meta-Analysis
Major Adverse Cardiac Events

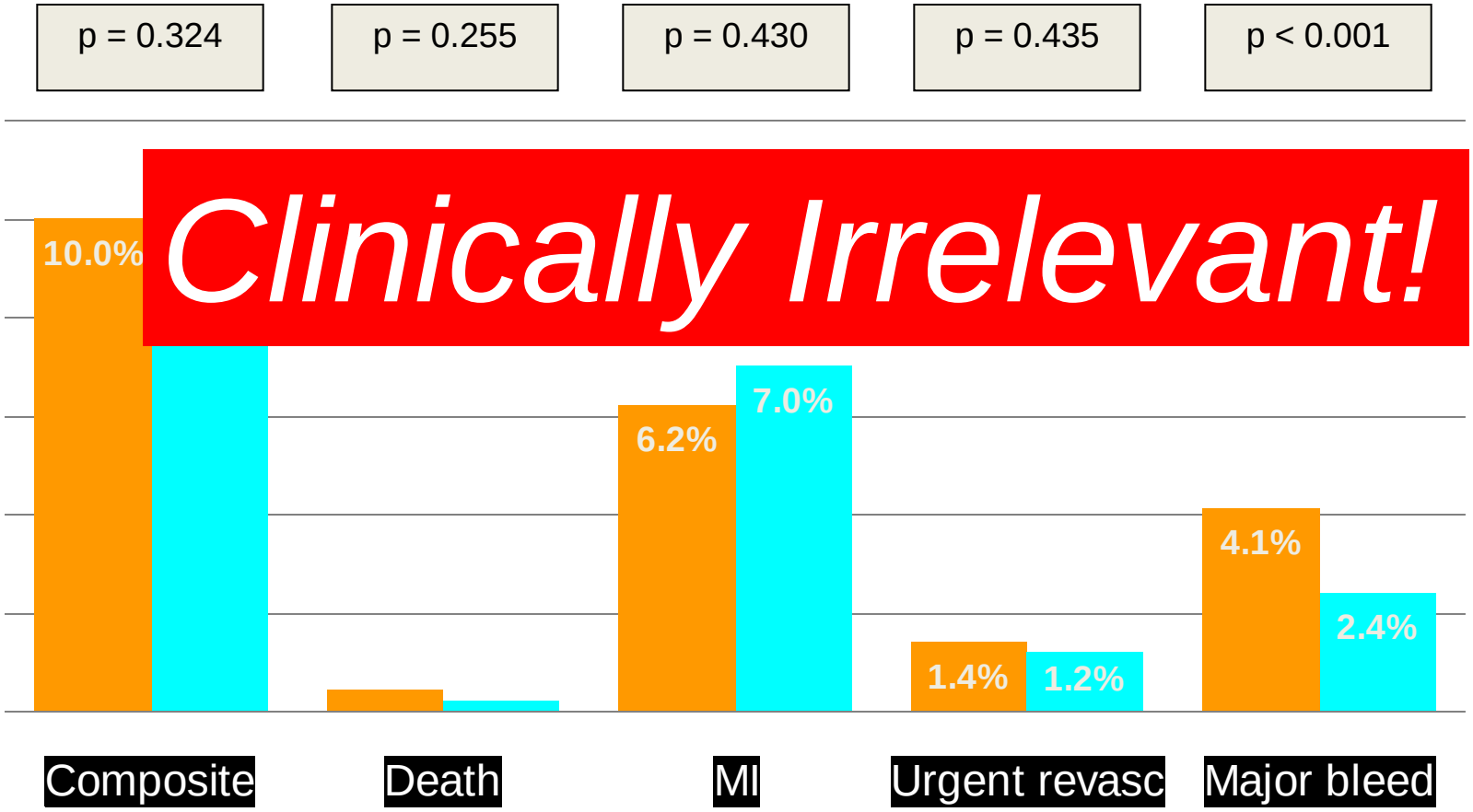


Lancet 2014

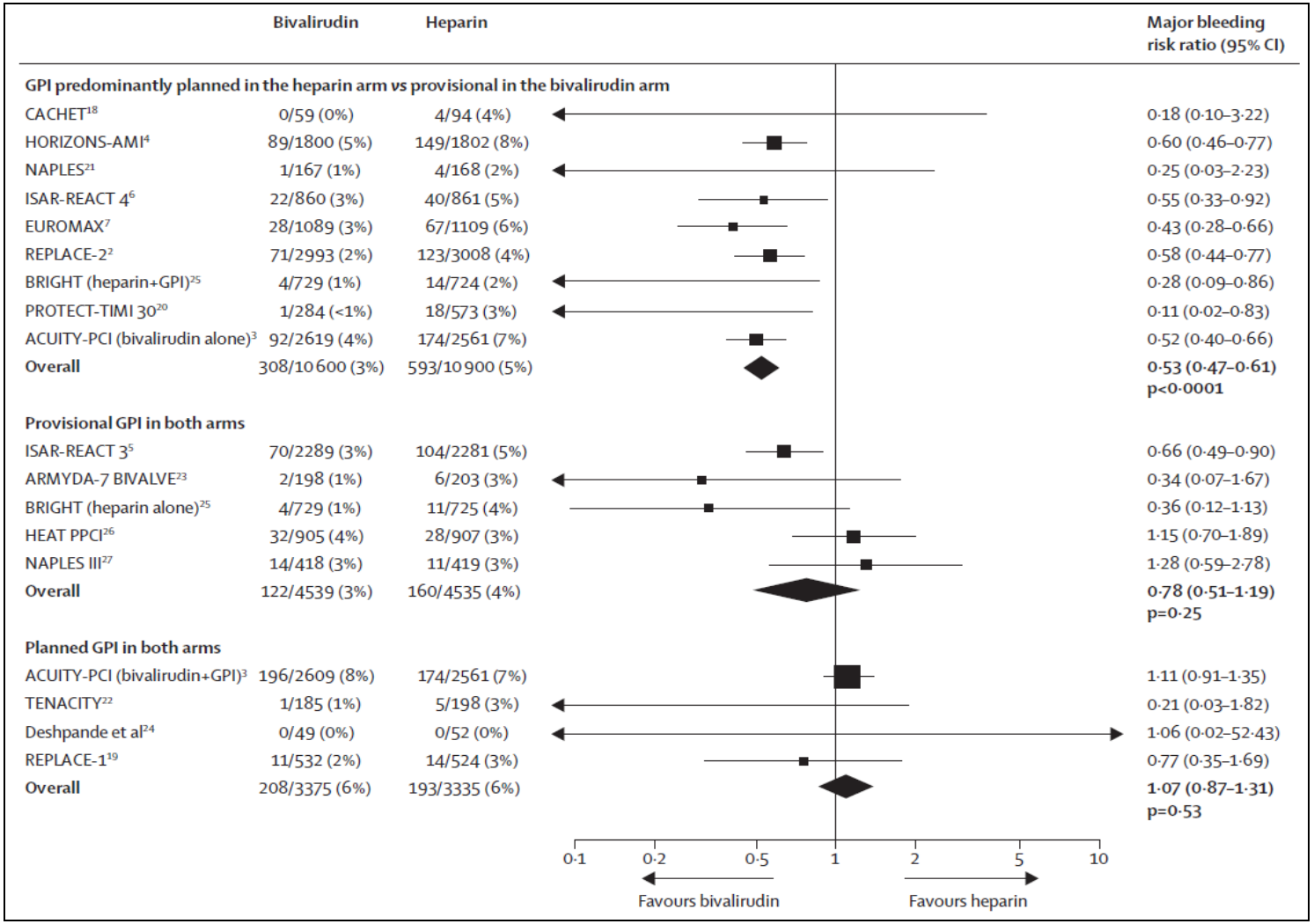
POINT #3

- **If GP IIb/IIIa inhibitor is not used, heparin and bivalirudin have similar bleeding rates**

REPLACE-2 Trial



Major Bleeding Stratified by GP IIb/IIIa Inhibitor Use



Lancet 2014

NAPLES III trial

Elective PCI in biomarker negative patients at high risk of bleeding

UFH group

↓

70 U/Kg i.v. prior to start the procedure

Additional bolus 20 U/Kg in case ACT <250 sec

Bivalirudin group

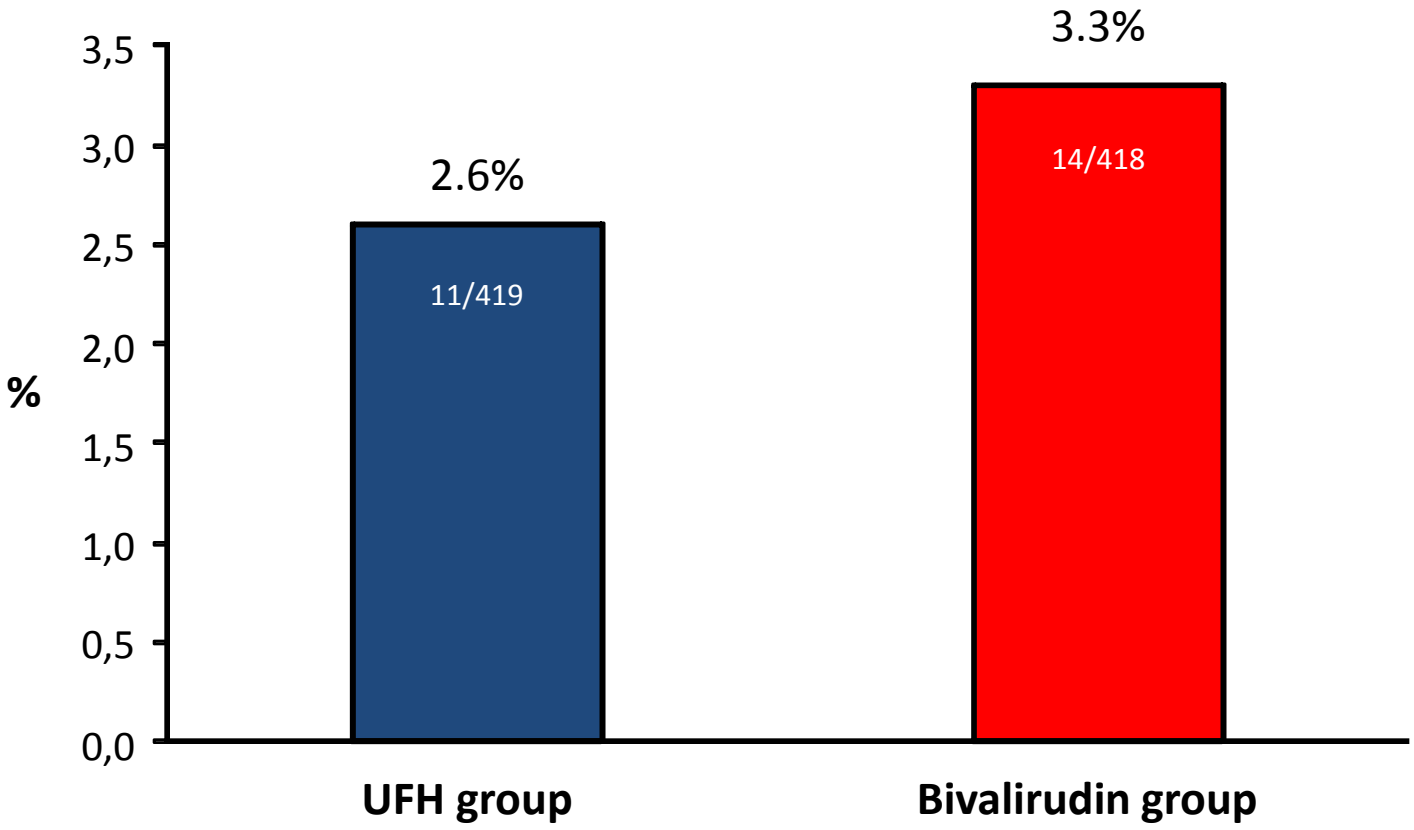
↓

Bolus of 0.75 mg/kg i.v. prior to the start of the procedure, followed by infusion of 1.75 mg/kg per hour for the duration of the procedure

Additional bolus 0.3mg/Kg in case ACT <250 sec

NAPLES III:
Primary endpoint: Major Bleeding

Odds ratio = 1.28; 95% CI= 0.58-2.86
p = 0.54



NAPLES 4
Secondary endpoint30-day MACE

	Bivalirudin group (N= 418)	UFH Group (N=419)	P
Major bleeding	14 (3.3%)	11 (2.6%)	0.58
Death	10 (2.4%)	6 (1.4%)	0.31
Myocardial infarction	1 (0.2%)	0	0.50
Revascularization	5 (1.2%)	3 (0.7%)	0.47
Stent thrombosis	2 (0.5%)	2 (0.5%)	0.99
Composite	27 (6.5%)	18 (4.3%)	0.17

DOI: 10.1111/joic.12081

ORIGINAL INVESTIGATION

Low-Dose Heparin for Elective Percutaneous Coronary Intervention

MICHAEL S. LEE, M.D.,[1] JARED OYAMA, M.D.,[1] ZAHID IQBAL, M.D.,[2] and GIUSEPPE TARANTINI, M.D.[3]

From the [1]UCLA Medical Center, Los Angeles, California; [2]UC Davis Medical Center, Davis, California; and [3]Padova University Hospital, Padova, Italy

Objectives: *We evaluated the safety and efficacy of low-dose heparin (40 IU/kg) for elective percutaneous coronary intervention (PCI).*

Background: *Current guidelines recommend a 70–100 IU/kg bolus of heparin for elective PCI, but this dose may be associated with increased bleeding risk. Low-dose heparin may have an advantage in this regard, but has not been well studied.*

Methods: *From January 2008 to October 2012, 300 patients underwent elective transfemoral PCI and were treated with an initial bolus of 40 IU/kg of heparin at the UCLA Medical Center. Dual antiplatelet therapy with clopidogrel and aspirin was administered prior to or just after diagnostic coronary angiography. The primary end-point was the composite of cardiac death, myocardial infarction, urgent target vessel revascularization for ischemia, or major bleeding within 30 days after PCI.*

Results: *The mean activating clotting time was 233 ± 28 seconds. The primary end-point occurred in 2.3%. The cardiac death rate was 0.3% but was not related to the PCI. The myocardial infarction rate was 1.3%. Urgent target vessel revascularization occurred in 1 patient (0.3%). The major bleeding rate was 0.3%. No stent thrombosis occurred.*

Conclusion: *Using a lower dose of heparin with dual antiplatelet therapy is safe and is associated with a low bleeding risk after transfemoral PCI while providing suppression of ischemic events. This may also represent a cost savings compared with other antithrombotic strategies. A randomized clinical trial comparing low-dose heparin with bivalirudin in patients is required to determine the optimal anticoagulation strategy.* (J Interven Cardiol 2013;9999:1–5)

Background

Unfractionated heparin remains a commonly used anticoagulant to minimize acute thrombotic complications during percutaneous coronary intervention (PCI). When glycoprotein IIb/IIIa inhibitors are not planned, the American College of Cardiology Foundation/American Heart Association/Society of Coronary Angiography and Interventions guidelines recommend a 70–100 IU/kg bolus of heparin to achieve an activated clotting time (ACT) of 250–300 seconds for Hemotec and 300–350 seconds for Hemochron systems.[1] However, the optimal dosing regimen of heparin during elective PCI is unknown. Previously, large doses of heparin, often in the range of 10,000 to 15,000 IU, were given prior to PCI. However, subsequent prospective and randomized studies have demonstrated the feasibility and safety of using heparin at lower fixed (5,000 IU)[2–5] or weight-based (100 IU/kg) doses.[6]

An individual patient's response to heparin remains difficult to predict. Previous studies have demonstrated an association between bleeding frequency and high ACT as well as increased ischemic complications with low ACT.[7–9] A pooled analysis of 6 randomized trials revealed fewer ischemic complications but more bleeding with higher doses of heparin.[8] However, ischemic complications did not increase at the lowest ACT levels, whereas bleeding complications were reduced at lower ACT levels.[10] Anticoagulation strategies must be designed to avoid major bleeding complications as they are associated with increased 1-year mortality.[11,12]

Address for reprints: Michael S. Lee, M.D., 100 Medical Plaza, Suite 630, Los Angeles, CA 90095. Fax: 310-825-9012; e-mail: mslee@mednet.ucla.edu

UCLA Experience

- 300 patients
- 40 U/kg initial dose
- Pretreat with DAPT
- Mean ACT 233
- Cardiac death: 0.3%
- MI: 2.3%
- No stent thrombosis
- Major bleeding: 0.3%

MATRIX Anti-thombin

NCT01433627

NSTEACS or STEMI with invasive management

Aspirin+P2Y12 blocker

1:1

Bivalirudin	**Heparin**
Mono-Tx	±GPI

1° co-Primary Objective

To demonstrate that Bivalirudin as compared to UFH plus provisional GPI is associated to lower rate of the composite endpoint of Death, MI or Stroke within the first 30 days

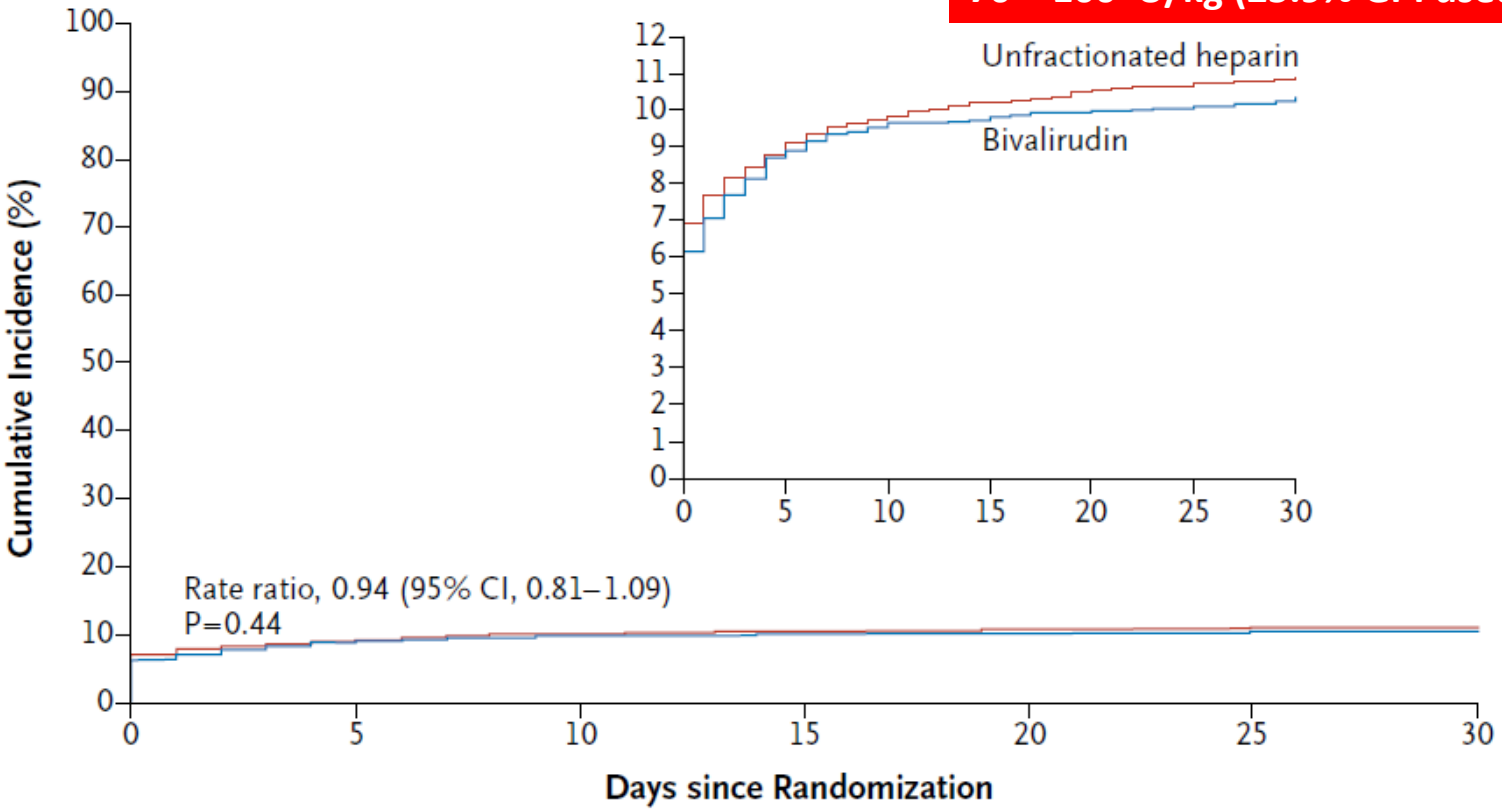
6% vs. 4.2%, β<15%, α: 2.5%: 6,800 patients

Adaptive study Design: sample size (SS) will be increased by the cross-over rate at 70% of planned SS

MATRIX

A Major Adverse Cardiovascular Events

70 – 100 U/kg (25.9% GPI used)



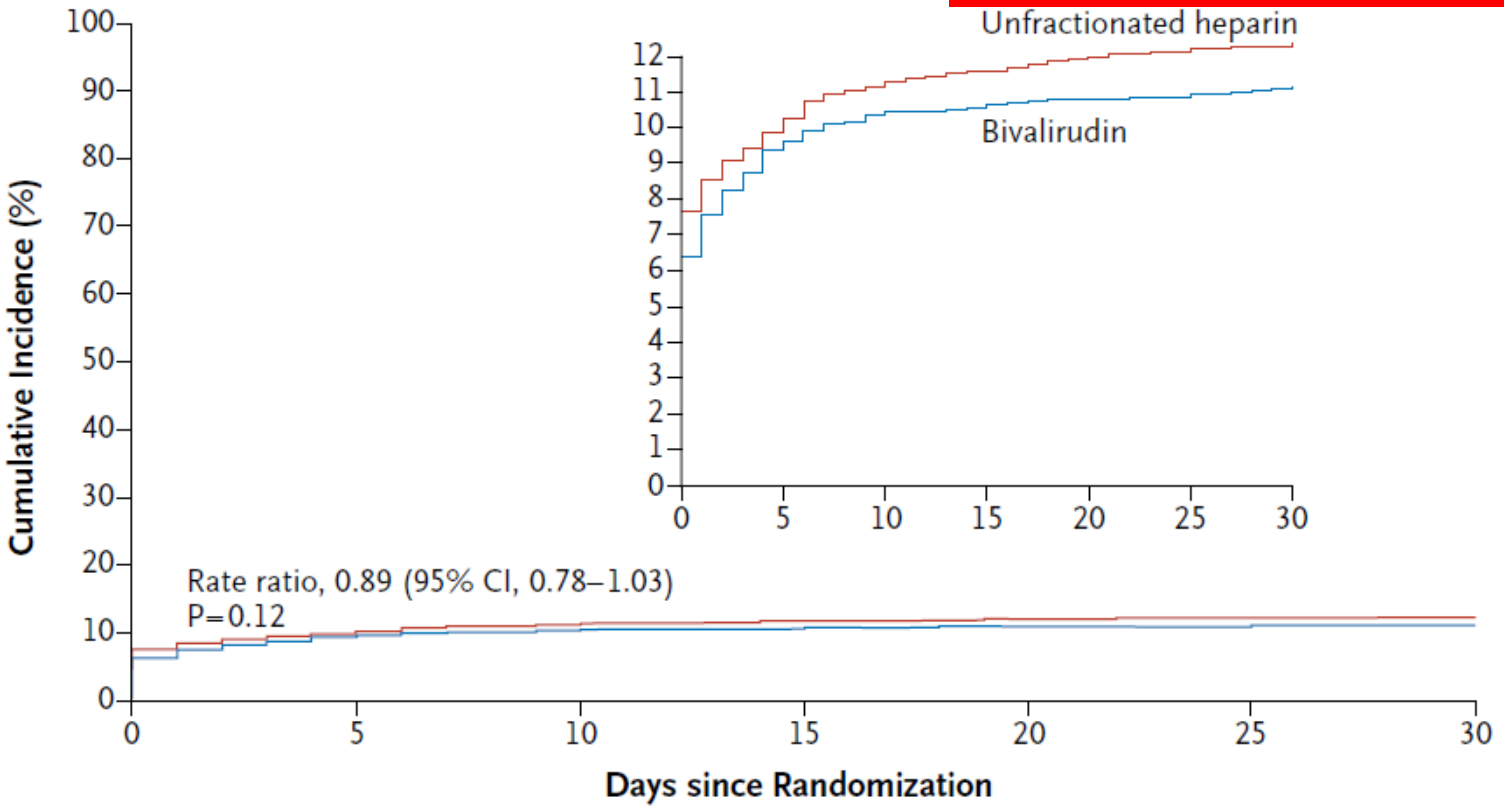
No. at Risk

Unfractionated heparin	3603	3277	3240	3223	3212	3207	3200
Bivalirudin	3610	3287	3254	3247	3239	3236	3227

MATRIX

70 – 100 U/kg (25.9% GPI used)

B **Net Adverse Clinical Events**



No. at Risk

Unfractionated heparin	3603	3238	3189	3172	3159	3153	3147
Bivalirudin	3610	3264	3226	3218	3210	3208	3198

POINT #4

- Bivalirudin is more expensive than heparin
  - Bivalirudin $400
  - Heparin $5

$400 saved per case

Unfractionated Heparin
Limitations

- Variability of preparations
- Unpredictable neutralization by PF-4
- Binds to endothelial cells, plasma proteins, m
- P
- In
structure
- Stimulates platelet aggregation
- HIT (TS)
- Made of beef and pork (and sausage, manure)

Clinically Relevant?

Conclusions

- Sometimes old and inexpensive drugs are good drugs.[1]
- Despite its mechanistic disadvantages, heparin, with ***appropriate dosing***, ***optimal P2Y12 inhibition*****,** and ***selective use of GP IIb/IIIa inhibitors***, is a safe and cost-effective anticoagulant

1. Lincoff AM. Lancet

John Wooden

"Failing to prepare is preparing to fail."

Thank You!