Re-Evaluation of Antithrombotic Therapy in PCI

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

Antithrombotic Therapy for PCI

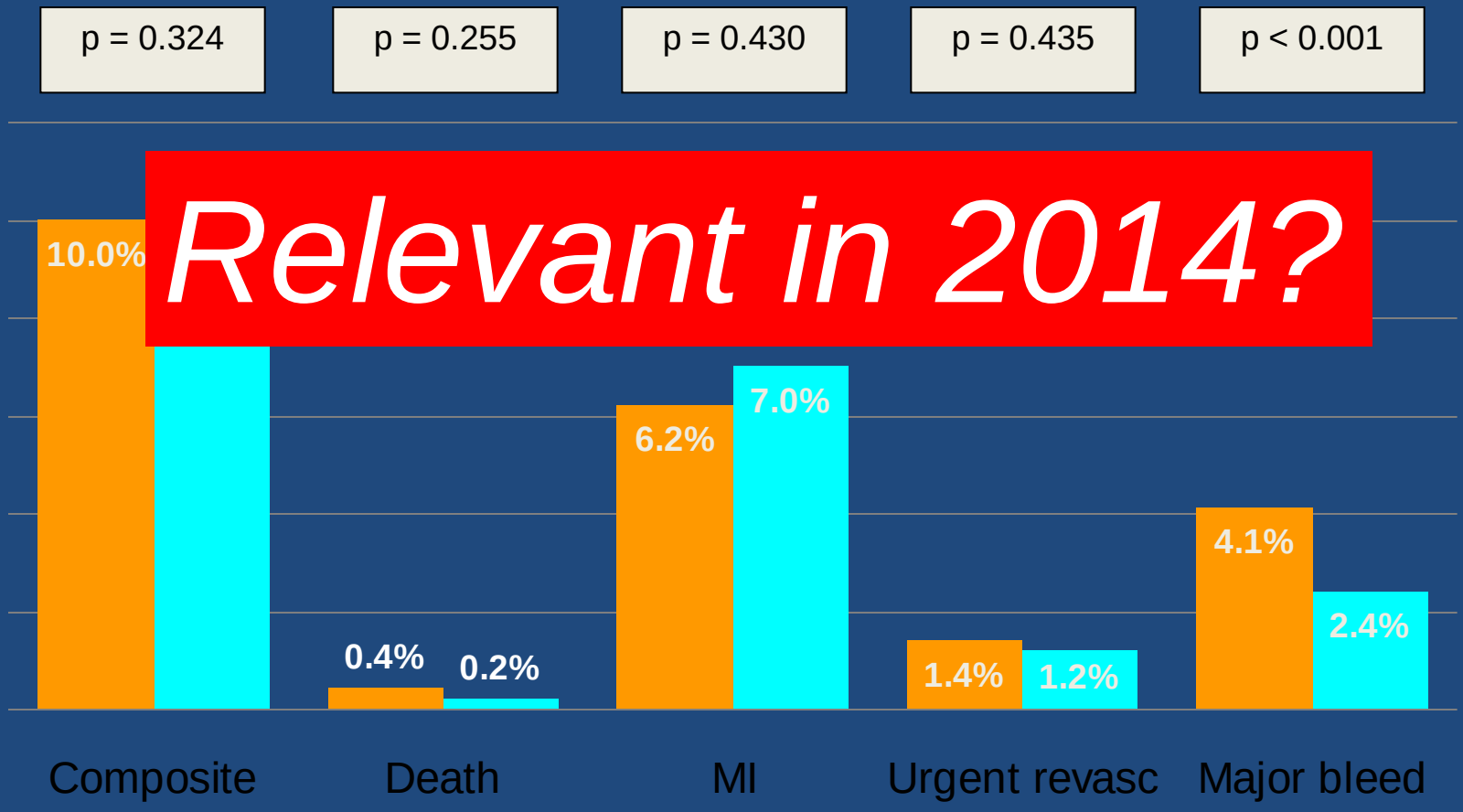
- **Heparin**
  - Unfractionated heparin
  - Enoxaparin
- **Synthetic pentasaccharides (indirect anti-Xa)**
  - Fondaparinux
- **Direct thrombin inhibitor**
  - Bivalirudin: most widely used agent in the US[1]

1. Dehmer GJ, et al. J Am Coll Cardiol 2012;60:2017-31.

REPLACE-2
Primary Endpoint

Angiomax® (bivalirudin) FOR INJECTION

- Intent-to-treat population



Relevant in 2014?

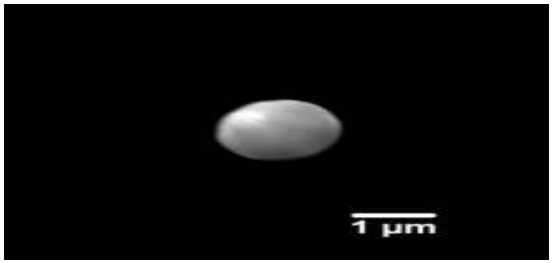
Angiomax® (bivalirudin) in PCI: An Overview

- Role of thrombin and heparin's shortcomings
- Angiomax is an ideal antithrombotic
  - Inhibits clot-bound and circulating thrombin
  - Inhibits platelet activation via thrombin
  - Short acting and reversible
  - Proven efficacy and safety, even in high-risk patients
    - Early trials: reduced ischemic events and bleeding
    - REPLACE-2: reduced bleeding and mortality
- REPLACE-2: Angiomax with provisional GP IIb/IIIa provides proven efficacy with less bleeding when compared with heparin + GP IIb/IIIa
- Angiomax provides cost savings

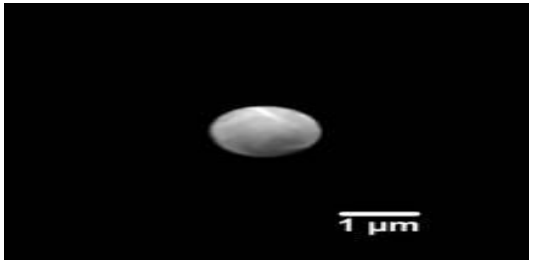
Replace heparin. Improve outcomes.

Angiomax® (bivalirudin): No Direct Platelet Activation

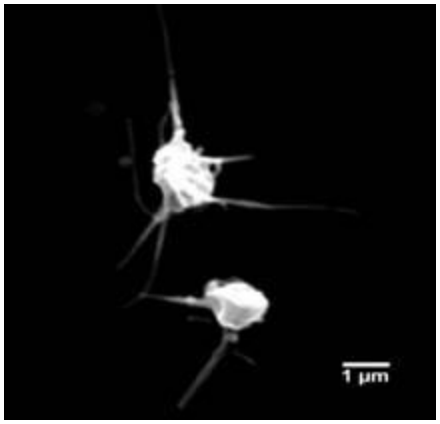
- Direct platelet activation by UFH but not Angiomax*



Control platelets



Platelets treated with Angiomax



Platelets treated with UFH

*All SEMs were acquired at a magnification of 4000X with the investigator blinded to treatment.

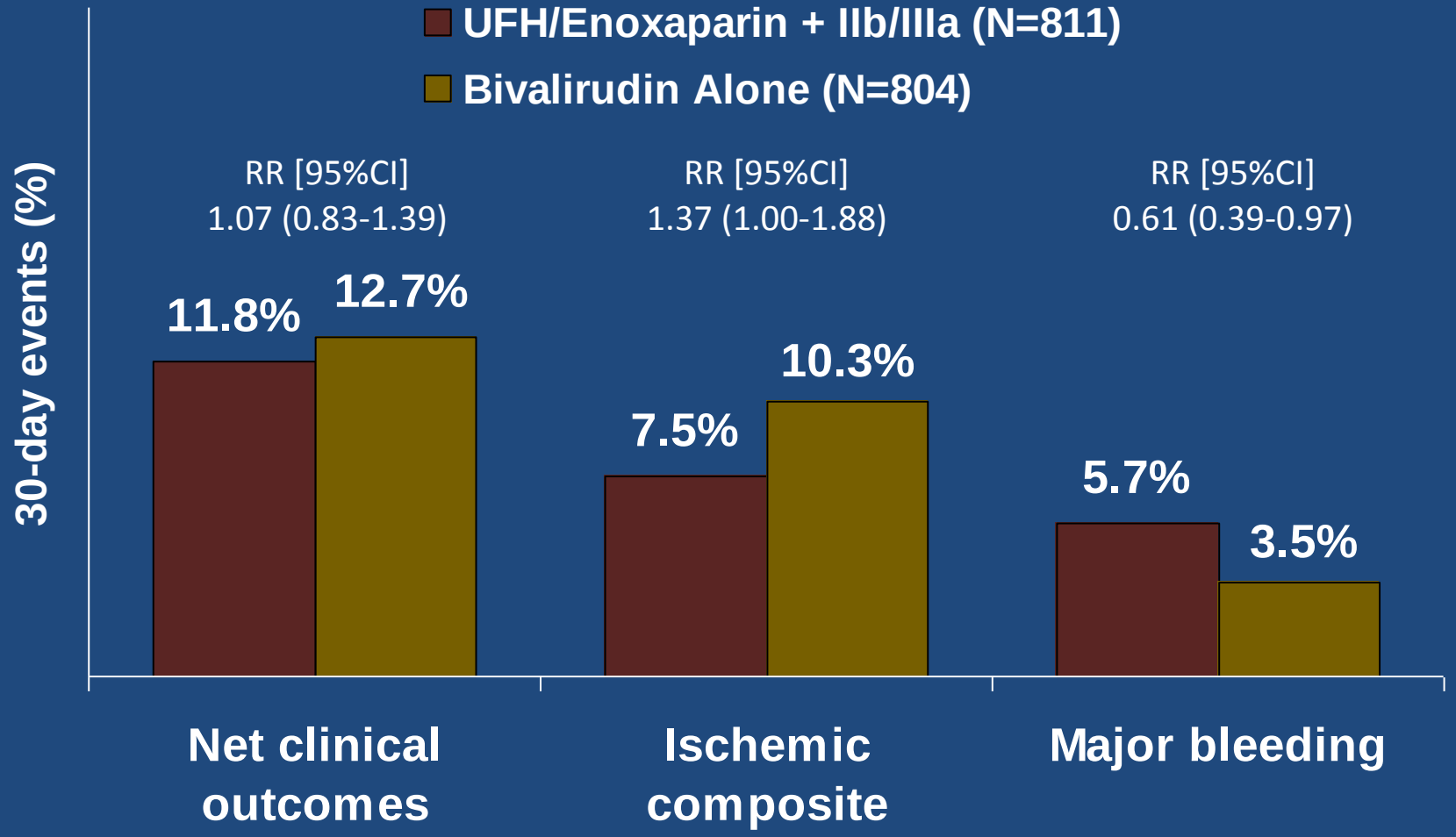
SEM=scanning electron micrograph.

Data on file, The Medicines Company.

ACUITY Trial

No Thienopyridine Exposure – PCI pts*

30-Day Primary Endpoint Adverse Events



ACUITY PCI as presented at TCT 2006.

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

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

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

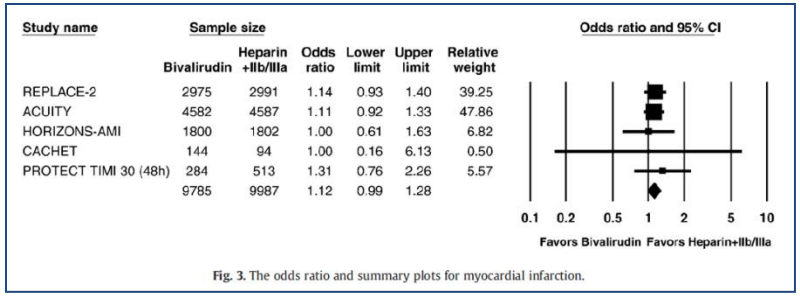


Fig. 3. The odds ratio and summary plots for myocardial infarction.

UCLA Experience

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

- 300 patients
- 40 U/kg
- Mean ACT 233
- Cardiac death 0.3%
- MI 2.3%
- No stent thrombosis
- Major bleeding 0.3%

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

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

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

HEAT PPCI
Safety Outcomes

	Bivalirudin		Heparin
	%		%
Minor Bleed	9.2 %	v	10.8 %
Major or Minor	12.5 %	v	13.5 %

Minor Bleed P=0.25 Major or Minor P=0.54

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

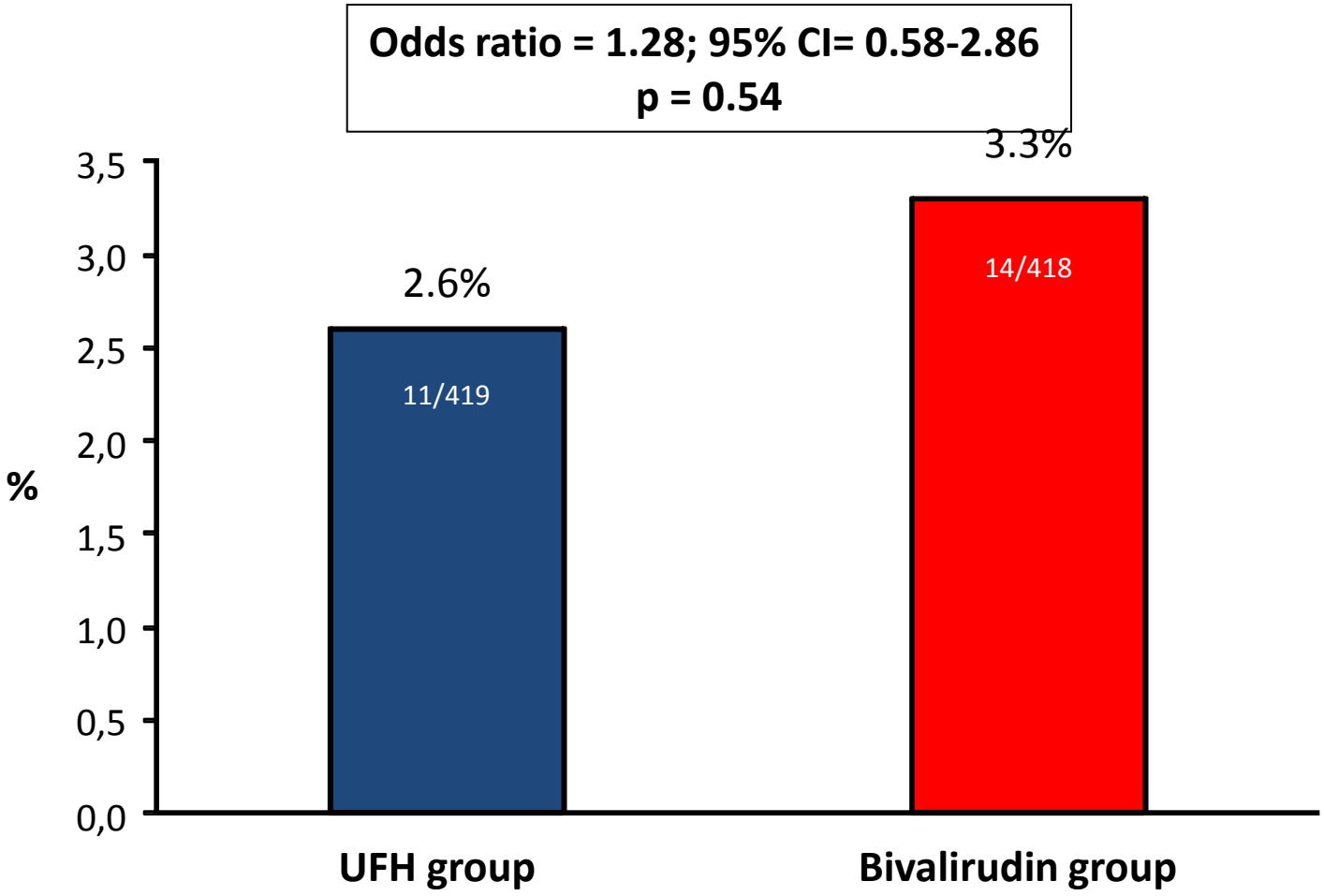
Additional bolus 20 U/Kg in case ACT <250 sec

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



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

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
- Improvements in medical practice can reinvigorate old drugs
- Despite its mechanistic disadvantages, heparin, with appropriate dosing, optimal P2Y12 inhibitors, and selective use of GP IIb/IIIa inhibitors, is a safe and cost-effective anticoagulant for PCI

Editorial

- Recent trials suggest that when GP IIb/IIIa inhibitor is selectively used, heparin, when appropriately dosed, is a cost-effective antithrombotic agent with significant cost savings.
- The higher risk of bleeding observed in the previous trials may be attributed to high doses of heparin and the use of GP IIb/IIIa inhibitor

Lee MS, et al. JACC Interv 2015 (in press)

John Wooden

"Failing to prepare is preparing to fail."

Thank You!