



Antithrombotic therapy in STEMI: Is Bivalirudin or Heparin the agent of choice

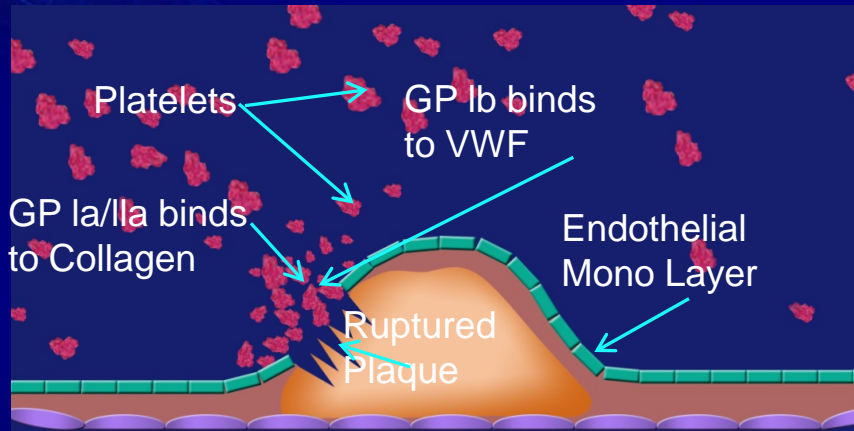


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Associate Professor of Medicine
Director, Cardiac and Vascular Cath Lab
University of Florida College of Medicine - Jacksonville

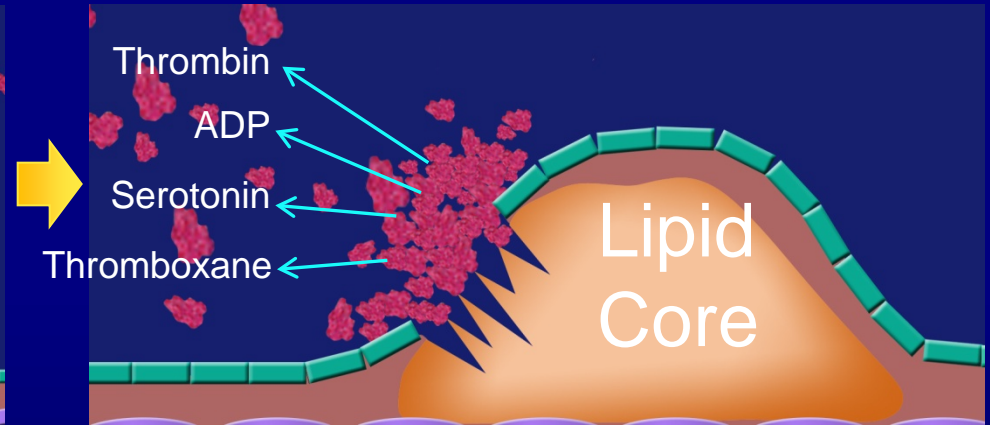


ACS Pathophysiology

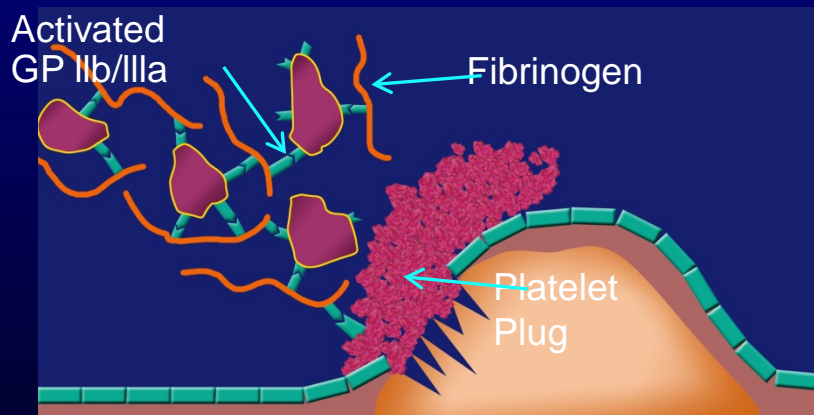
Adhesion



Activation



Aggregation



VWF= von Willebrand Factor;
 ADP=adenosine diphosphate;
 GP=glycoprotein.

¹Konkle, BA. Bleeding and thrombosis. In: Fauci AS, Braunwald E, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*. 17th ed. New York, NY: McGraw-Hill; 2008: 355-362/ Available at: <http://www.accessmedicine.com/resourceTOC.aspx?resourceID=4>.

²Schafer AI. *Am J Med*. 1996;101(2):199-209.

ANTITHROMBOTIC DRUGS USED IN ACS/PCI

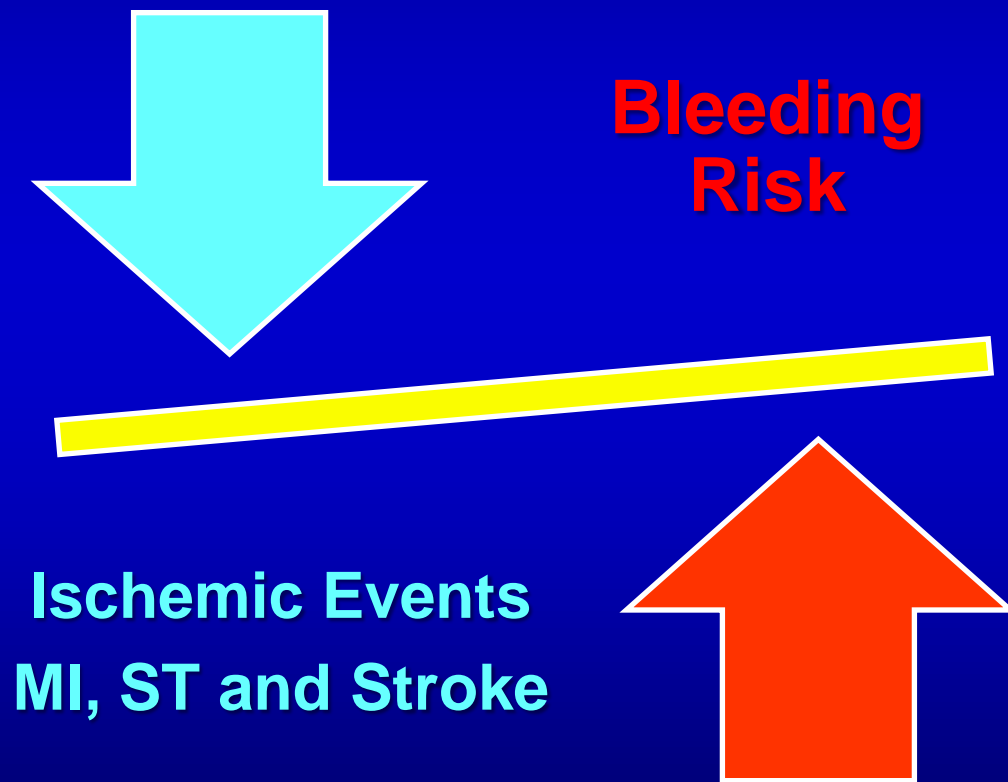
I. ANTIPLATELET DRUGS

- COX-1 inhibitor (aspirin)
- P2Y₁₂ inhibitors (ticlopidine; clopidogrel; prasugrel; ticagrelor)
- Glycoprotein IIb/IIIa inhibitors (abciximab; eptifibatide; tirofiban)

II. ANTICOAGULANT DRUGS

- Anti-Factor II (anti-thrombins)
 - Indirect Thrombin Inhibitors (UFH & LMWH)
 - Direct Thrombin Inhibitors (Bivalirudin)
- Anti-Factor X
 - Fondaparinux

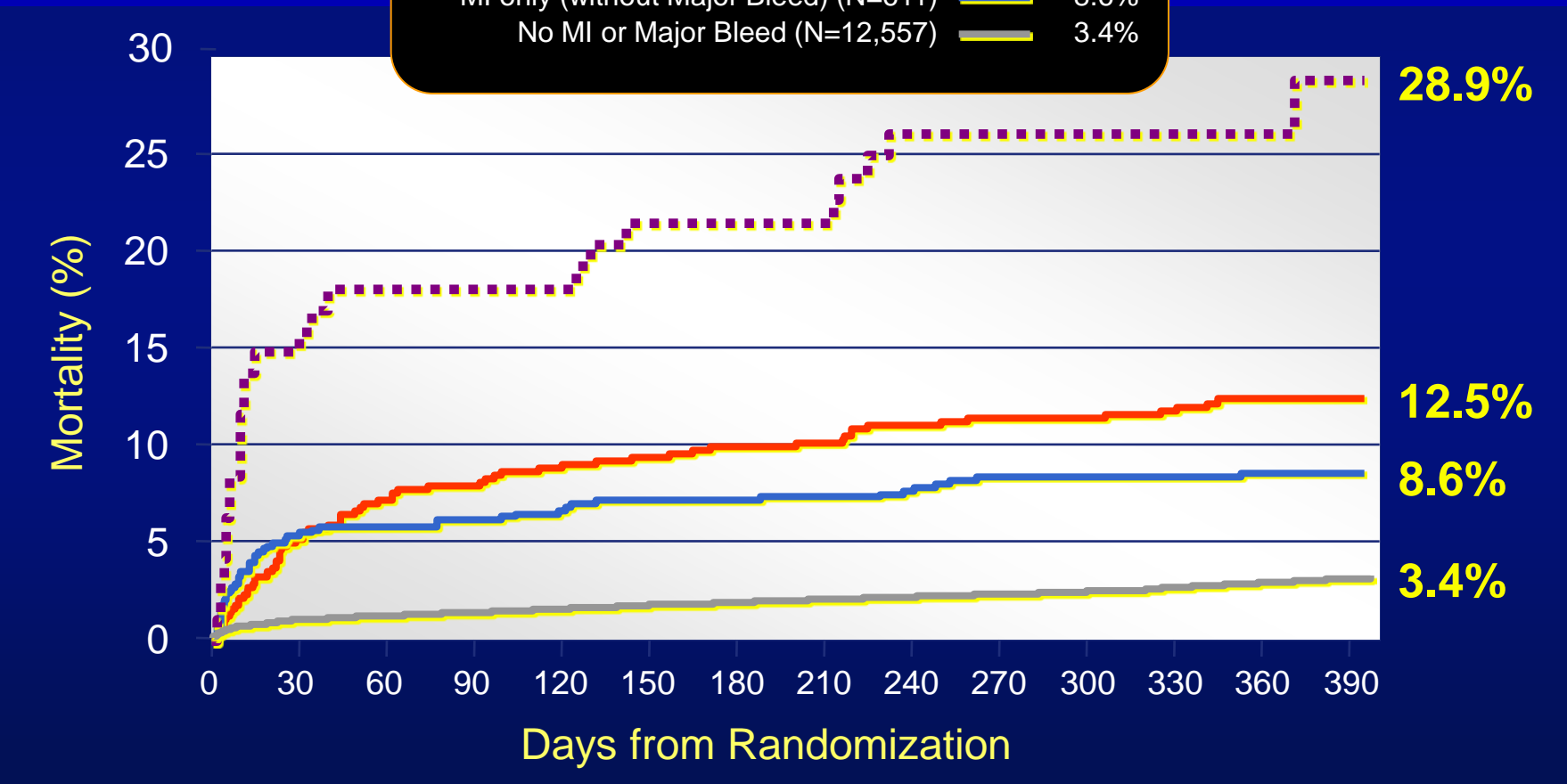
Antithrombotic Treatment during PCI



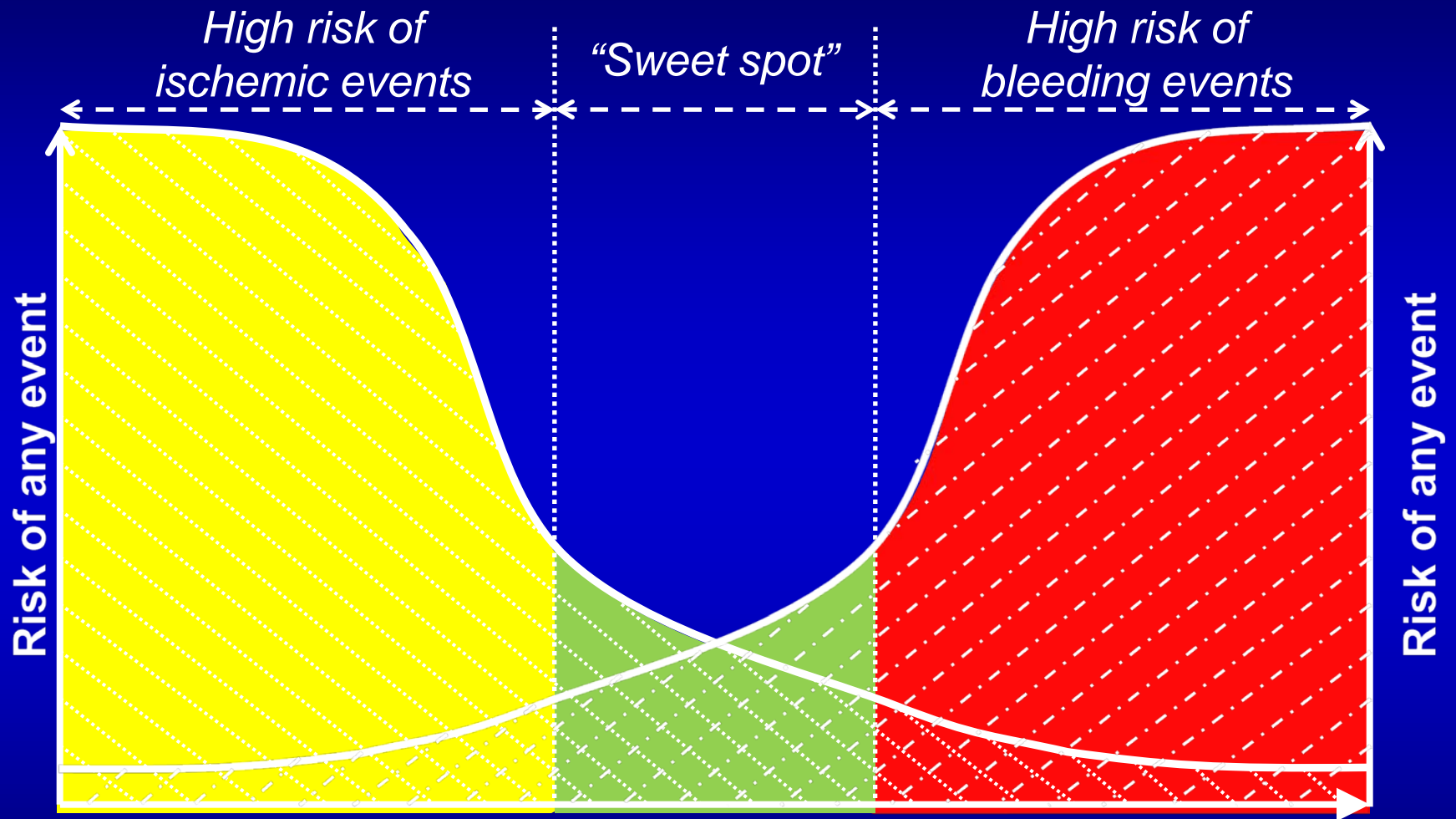
Impact of MI and Major Bleeding (non-CABG) in the First 30 Days on Risk of Death Over 1 Year. ACUITY Trial

1 year Estimate

Both MI and Major Bleed (N=94)	28.9%
Major Bleed only (without MI) (N=551)	12.5%
MI only (without Major Bleed) (N=611)	8.6%
No MI or Major Bleed (N=12,557)	3.4%



Balancing Safety and Efficacy



— Inhibition of platelet aggregation +

■ Ischemic risk

■ Bleeding risk

Current Controversies

Bivalirudin vs Heparin

Limitations of Heparin

- **Unable to bind thrombin inside the clot**
- **Needs a co-factor, Antithrombin III**
- **Induces platelets activation**

Bivalirudin in PCI

Elective PCI
ISAR REACT 3
2289 pts
Similar Ischemia
Bleeding 33%

Elective or Urgent PCI
REPLACE 2
6202 pts
Similar Ischemia
Bleeding 41%

NoSTEMI
BAT
4312 pts
Similar Ischemia
Bleeding 48%

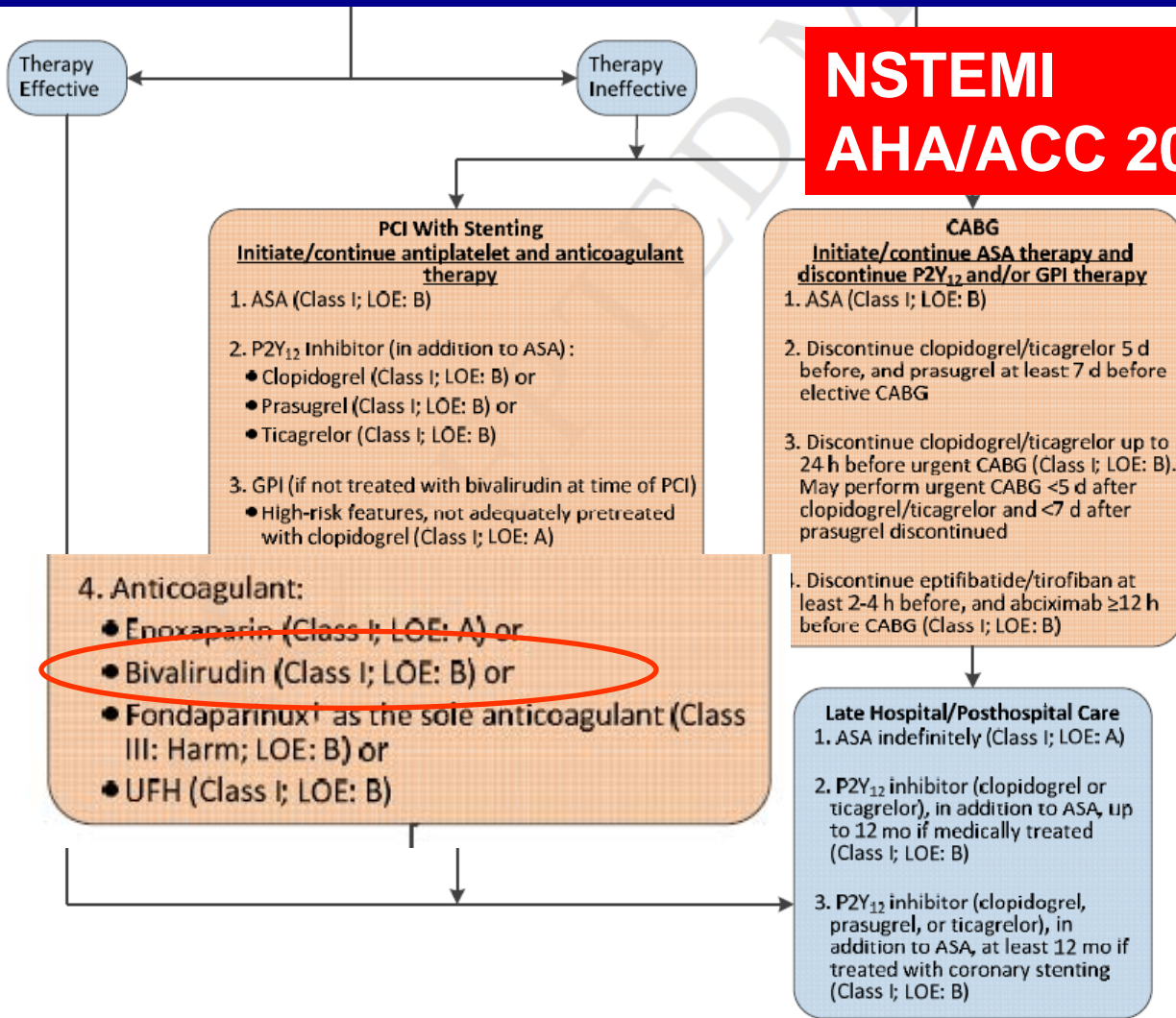
21,575 Patients

NoSTEMI
ACUITY
5170 pts
Similar Ischemia
Bleeding 62%

STEMI
HORIZONS
3602 pts
Similar Ischemia
Mortality 1% Absolute
Bleeding 41%

Current Controversies Bivalirudin vs Heparin

NSTEMI AHA/ACC 2014 GPG



Current Controversies Bivalirudin vs Heparin

**STEMI
AHA/ACC 2012 GPG**



**In Patients with STEMI
Bivalirudin is the preferred IV
anticoagulant agent**

**Mainly based on Mortality benefit
from HORIZON-AMI**



*Helping Cardiovascular Professionals
Learn. Advance. Heal.*



Bivalirudin vs Heparin in STEMI

Issues with HORIZONS AMI

- **A 4000U Bolus of heparin was used in almost 40% of patients**
- **Concern of increased ischemic event (AST)**
- **Concerns about even higher increased ischemic event in those without bolus of heparin**

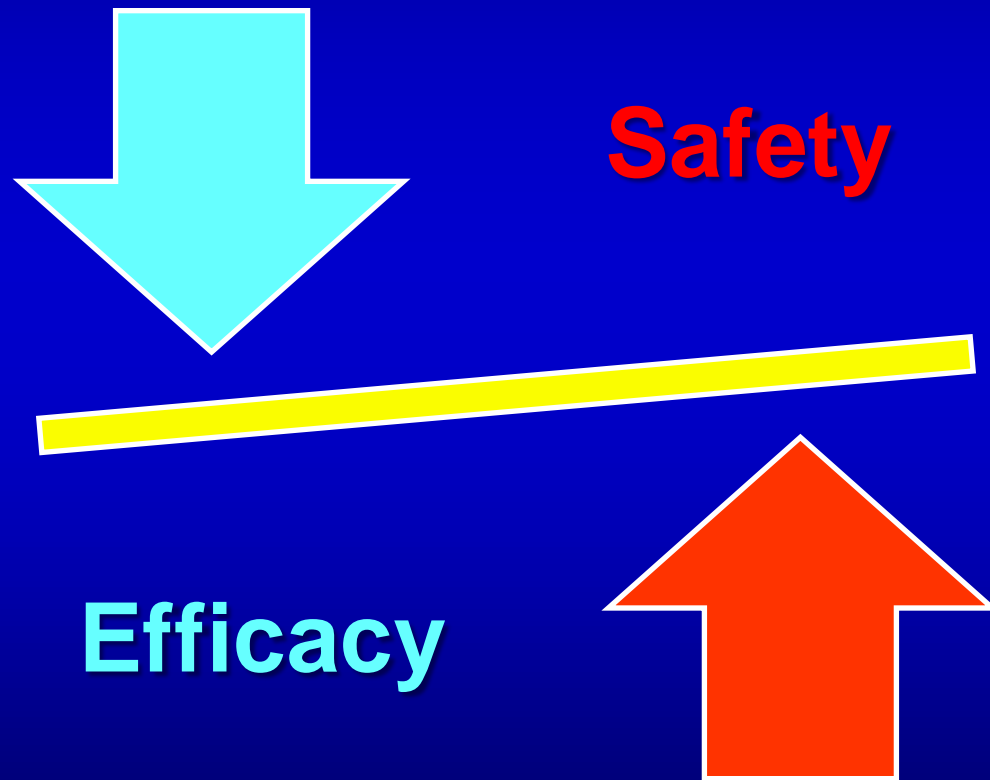


Bivalirudin vs Heparin in STEMI

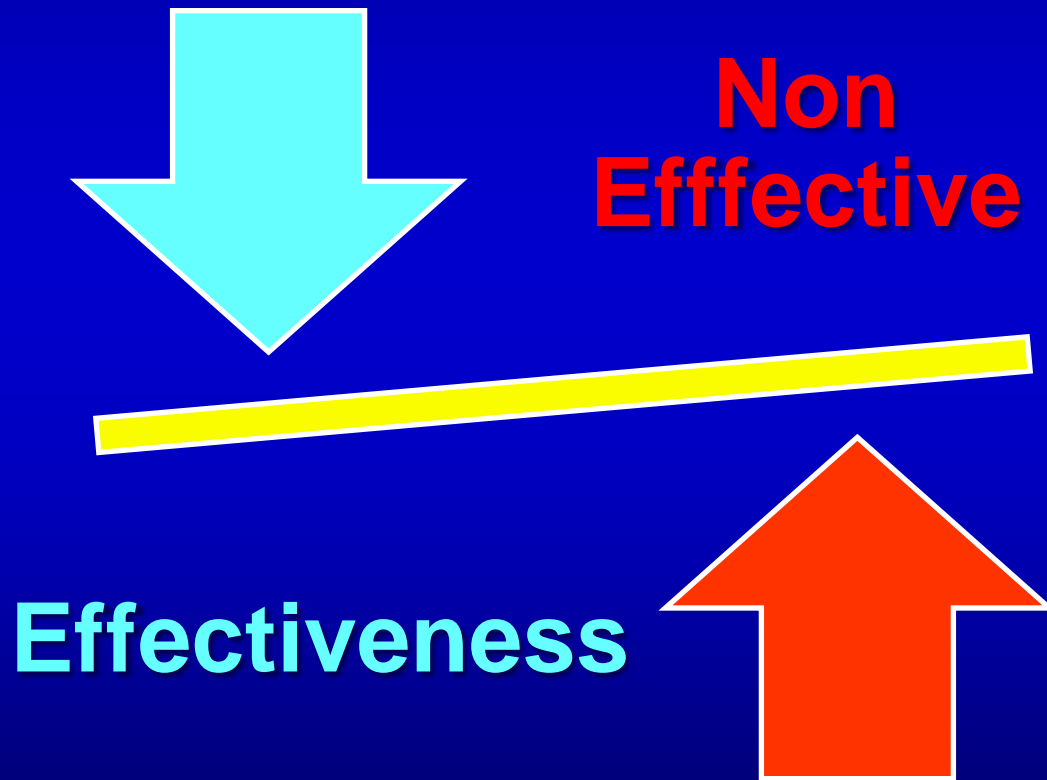
Issues with HORIZONS AMI

- **A 4000U Bolus of heparin was used in almost 40% of patients**
- **Concern of increased ischemic event (AST)**
- **Concerns about even higher increased ischemic event in those without bolus of heparin**
- **Concerns regarding increase bleeding event related to GPI**
- **Not head to head comparison with Heparin monotherapy**
- **Performed before the incorporation of new P2Y12 inhibitors**
- **Very low utilization of radial approach**

Antithrombotic Treatment during PCI



Antithrombotic Treatment during PCI



HORIZON-AMI
Heparin Bolus in Bivalirudin arm
Major ischemic events

Patients with Bolus CI:0.85 (0.60–1.14)

Patients without bolus CI:1.39 (0.85–2.28)

P Interaction 0.08

Current Controversies

Bivalirudin vs Heparin in STEMI

Recent Studies (6,200 pts)

	EROMAX	BRIGHT	HEAT PPCI
N Center	65	82	1
N patients	2,198	2,194	1,812
- Bivalirudin	1,089	735	905
- Heparin	460	729	907
- Heparin + GPI	649	730	--
- Heparin bolus	60 IU/kg	100 IU/kg	70 IU/kg
- Bival Infusion	4.5 hrs	4.0 hrs	No
- GPI Bail out	7.9% vs 25%	4.4% vs 5.6%	13.5% vs 15.5%
- New P2Y12	59%	0	89%
- Radial	47%	79%	81%

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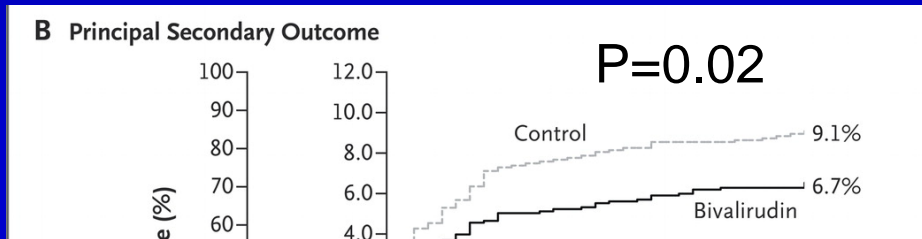
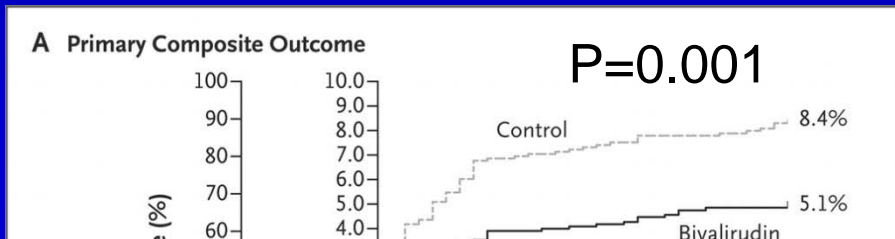
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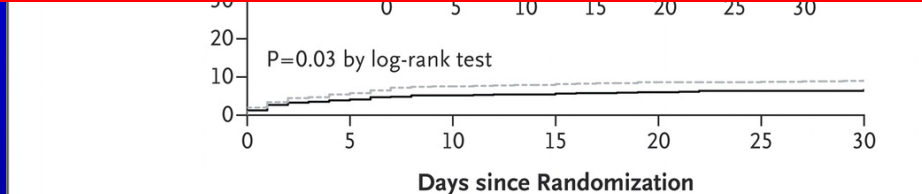
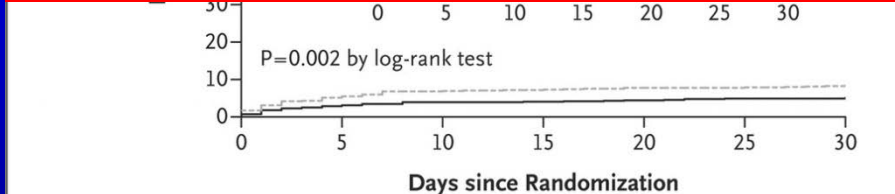
EUROMAX Trial: Bivalirudin vs Heparin in STEMI patients

**Death
> Bleeding**

**Death/MI/
> Bleeding**



No Difference in TIMI > bleeding



No. at Risk

Bivalirudin	1089	1038	1024	1020	1007	988	791
Control	1109	1024	1003	998	984	958	765

No. at Risk

Bivalirudin	1089	1027	1010	1005	990	971	779
Control	1109	1020	996	990	975	949	760

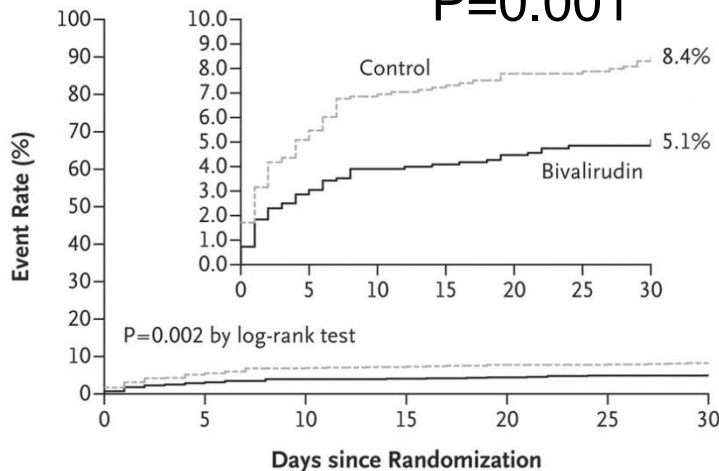
Death 32 (2.9) vs 34 (3.1) 0.96 (0.60–1.54) 0.86
MACE was 6.0% Bivalirudin vs 5.5% in Heparin p:0.56

EUROMAX Trial: Bivalirudin vs Heparin in STEMI patients

**Death
> Bleeding**

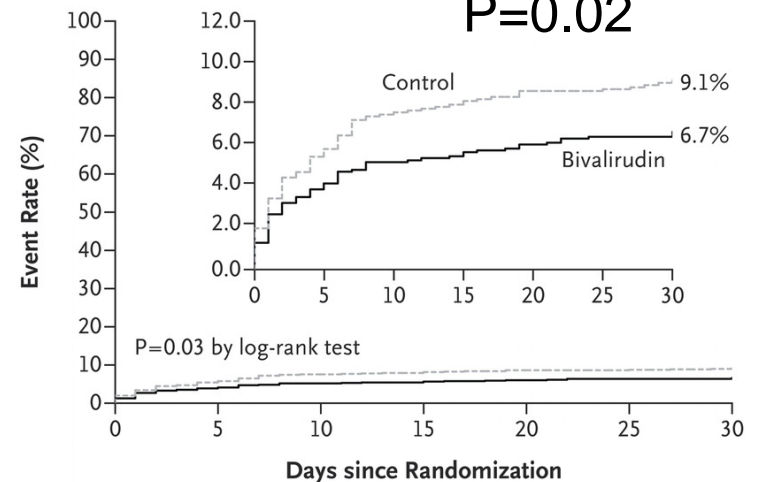
**Death/MI/
> Bleeding**

A Primary Composite Outcome



No. at Risk	0	5	10	15	20	25	30
Bivalirudin	1089	1038	1024	1020	1007	988	791
Control	1109	1024	1003	998	984	958	765

B Principal Secondary Outcome



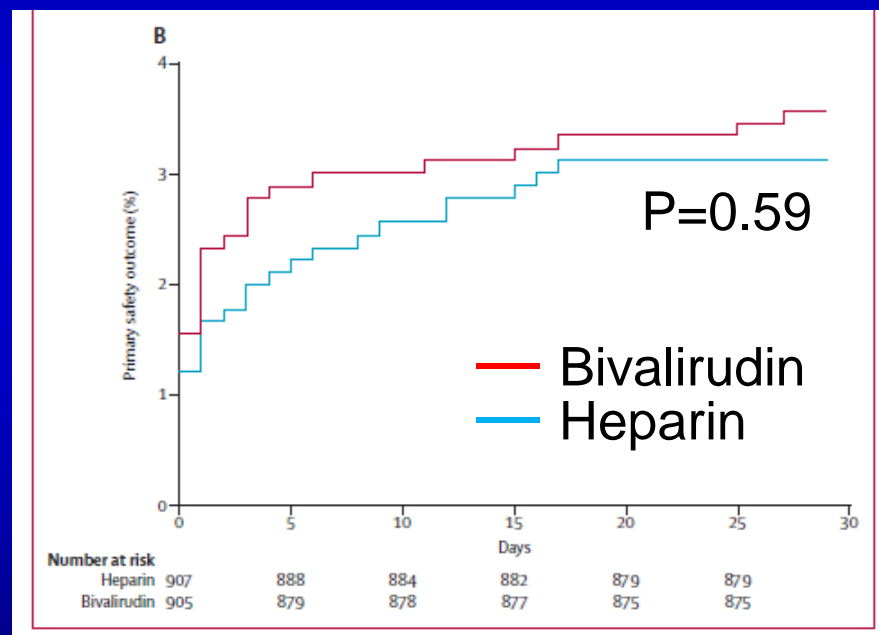
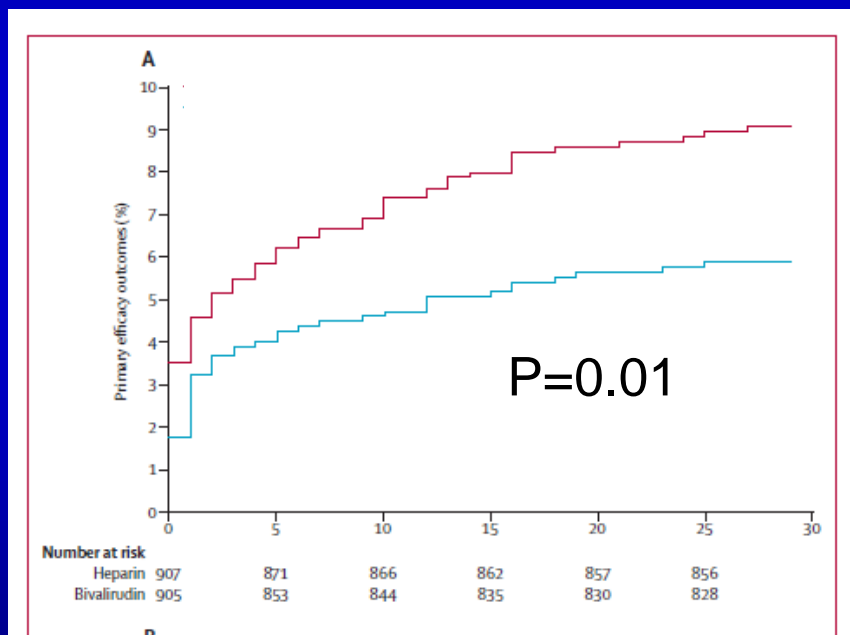
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Bivalirudin	1089	1027	1010	1005	990	971	779
Control	1109	1020	996	990	975	949	760

**ST was 1.5% Bivalirudin vs 0.5% in Heparin p:0.02
≤24 hr 12 (1.1) vs 2 (0.2) 6.11 (1.37–27.24) 0.007**

HEAT PPCI Trial: Bivalirudin vs Heparin Monotherapy in STEMI patients

**1ry End Point
D/MI/Stroke/UR**

**1ry Safety Major
Bleeding**



No mortality benefit

HEAT PPCI Trial: Bivalirudin vs Heparin Monotherapy in STEMI patients

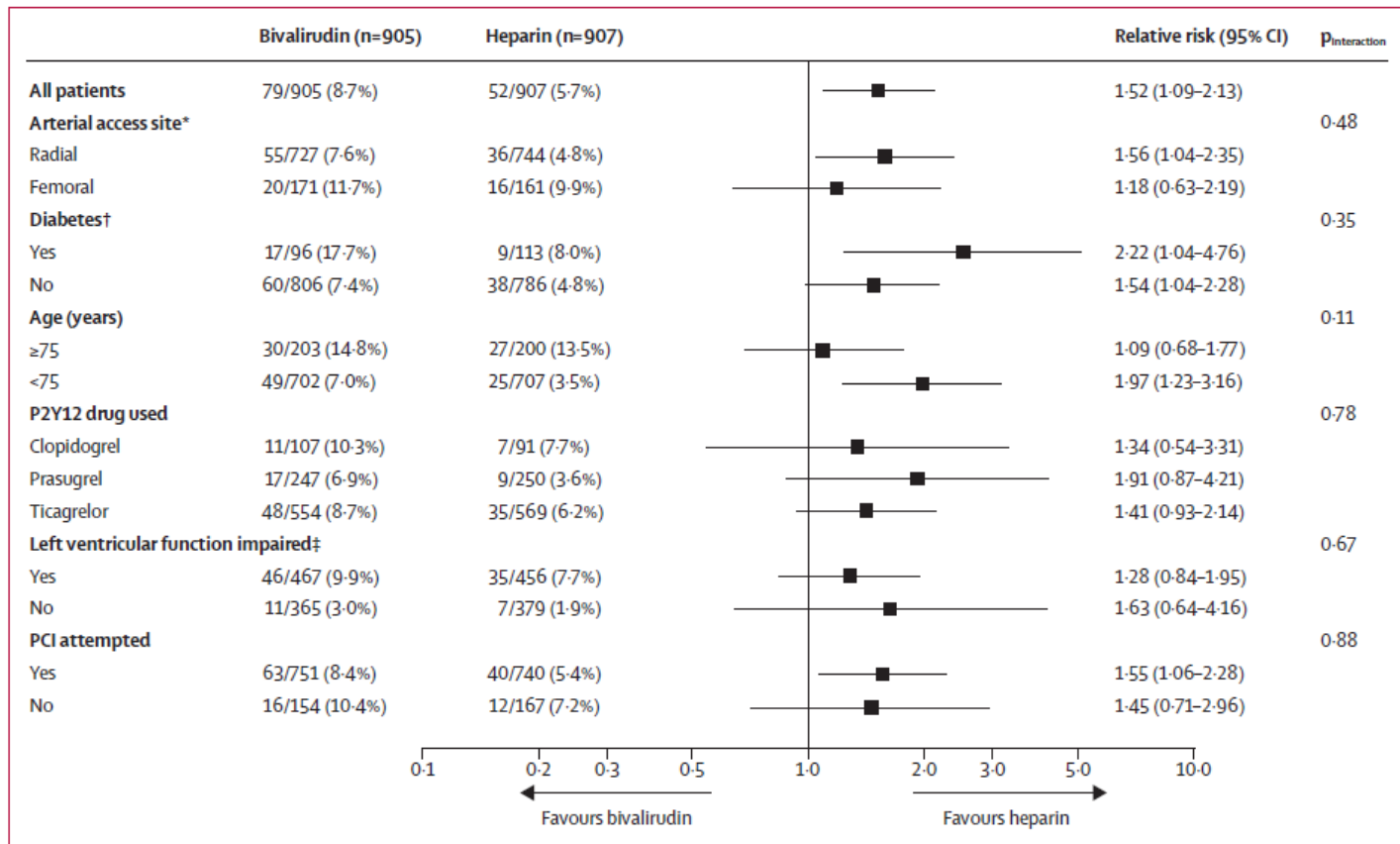


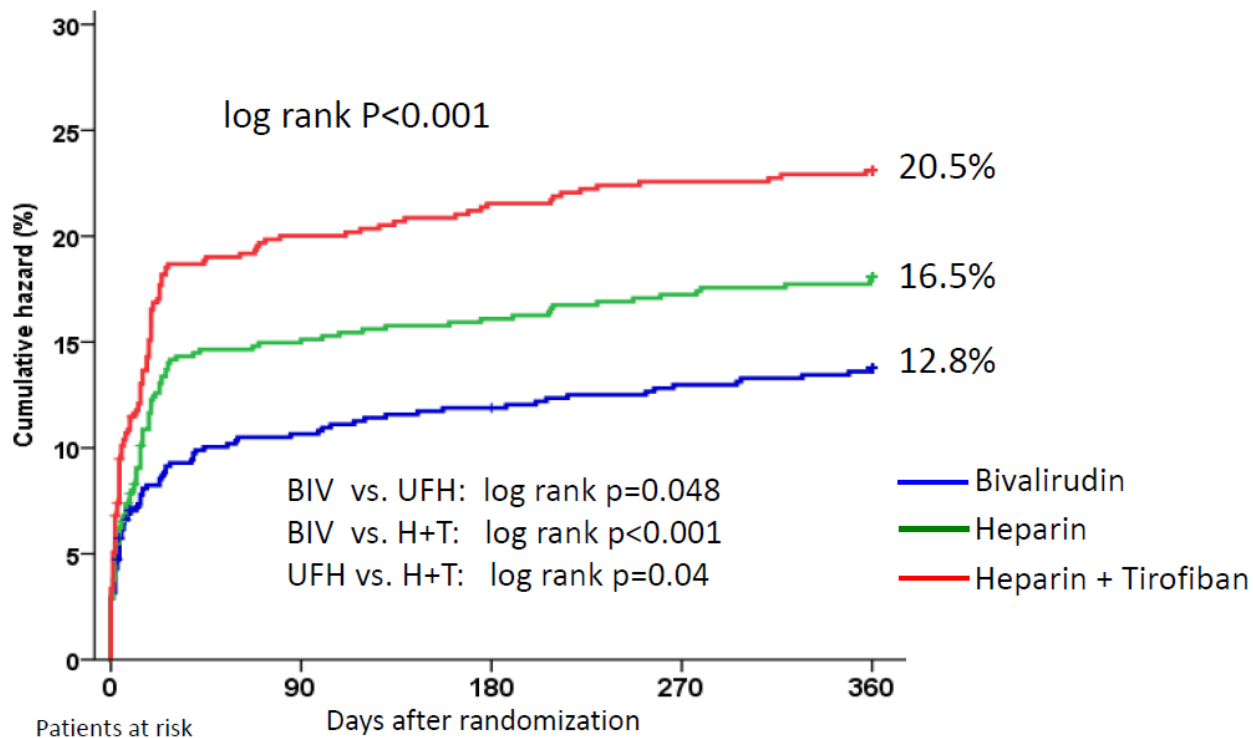
Figure 3: Subgroup analyses for primary composite outcome at 28 days

*Procedures completed exclusively via radial access (radial group) versus all other cases (femoral group). †Patients receiving oral hypoglycaemic or insulin therapy.

‡Left ventricular ejection fraction <55% in surviving patients after index event.

BRIGHT Trial Primary end Point

Time-to-Event Curves: NACE at 1 Year

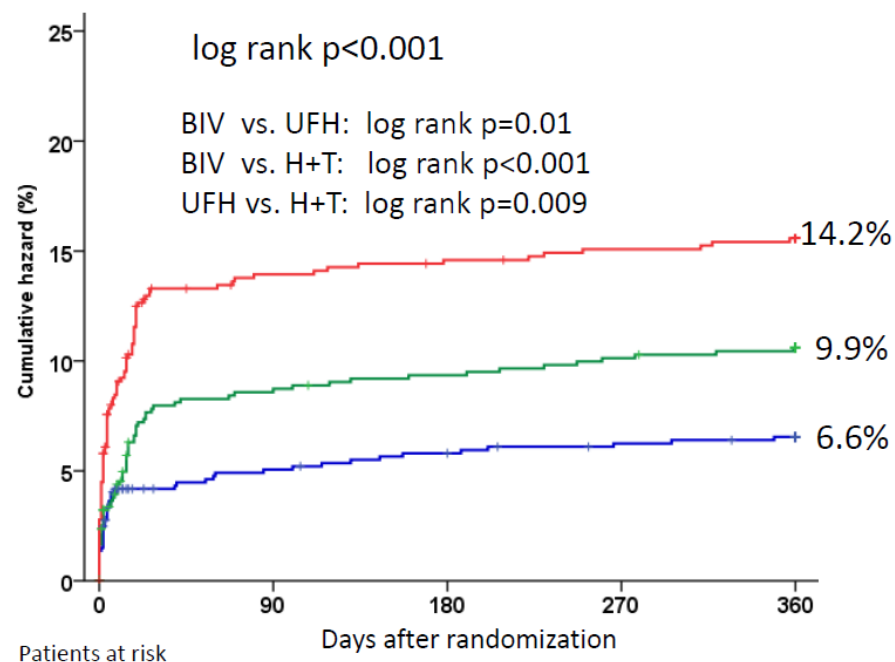
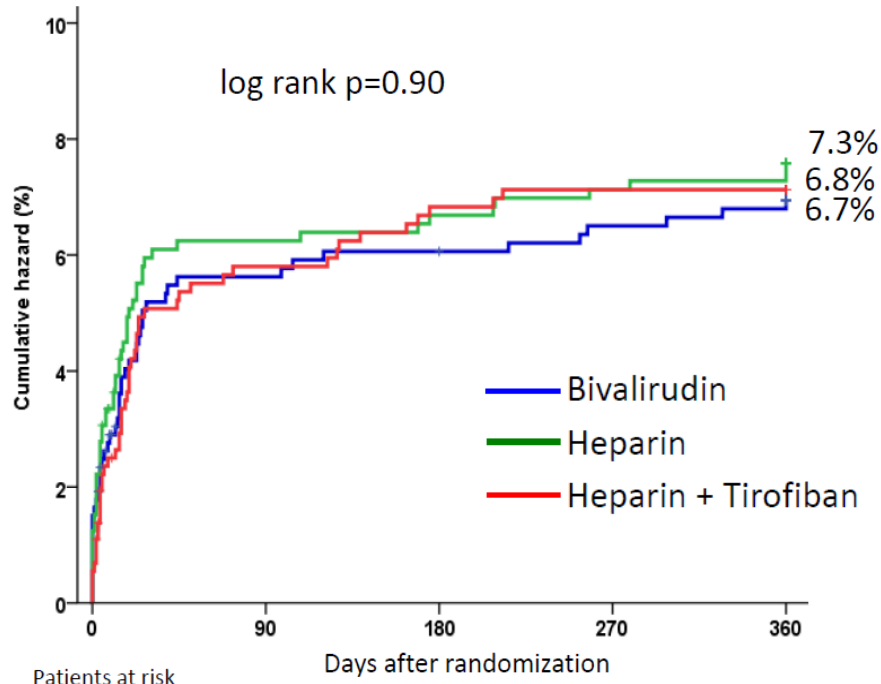


	0	90	180	270	360
Biv	735	654	646	638	634
UFH	729	623	616	609	605
H+T	730	594	585	579	576

BRIGHT Trial: 1 Year Events

MACE

> Bleeding



No mortality benefit

Presented at TCT 2014

Metanalysis: Bivalirudin vs Heparin

MACE

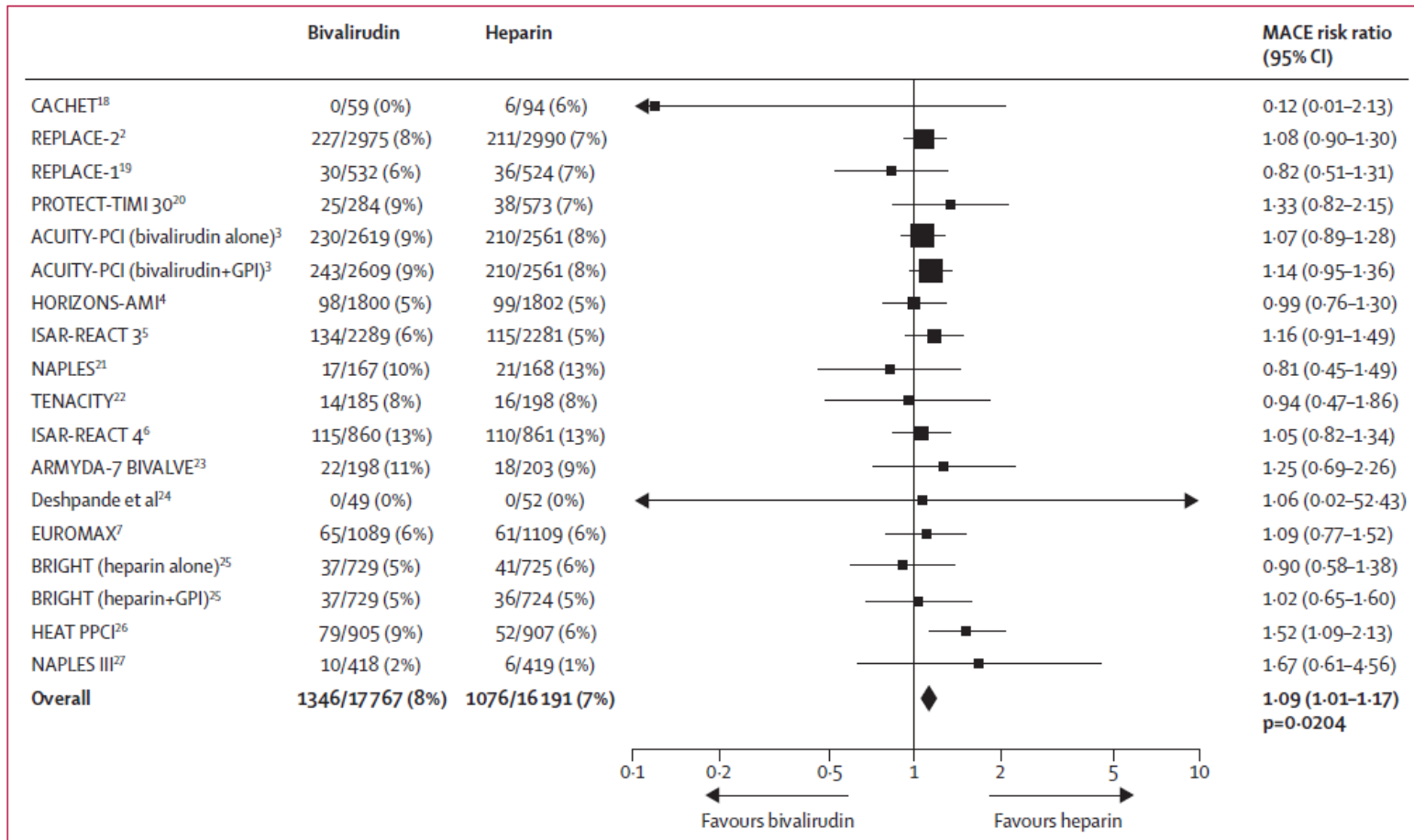


Figure 1: Major adverse cardiac events

There was no evidence of between-trial heterogeneity (Q statistic 12.1, df 17; p=0.79). GPI=glycoprotein IIb/IIIa inhibitor. MACE=major adverse cardiovascular events.

Metanalysis: Bivalirudin vs Heparin Ischemic Events

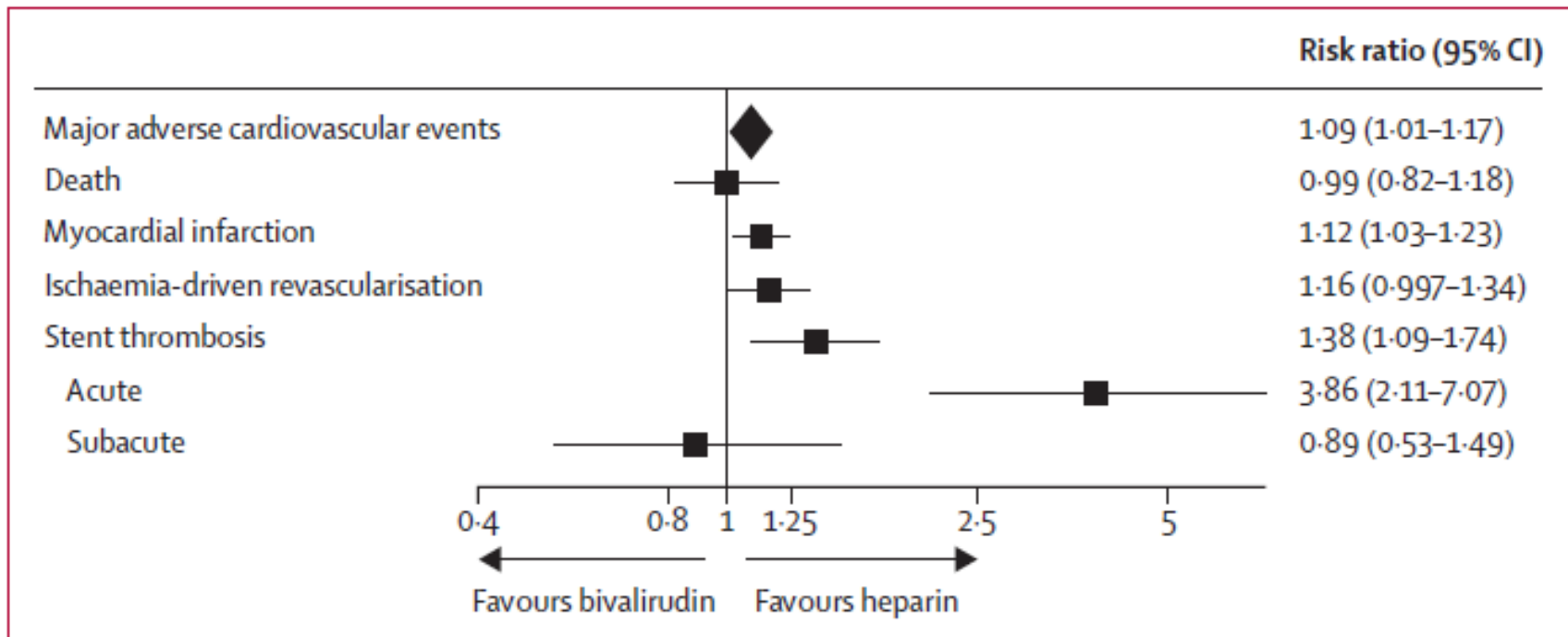


Figure 2: Major adverse cardiovascular events and individual cardiovascular events

Metanalysis: Bivalirudin vs Heparin Stent Thrombosis

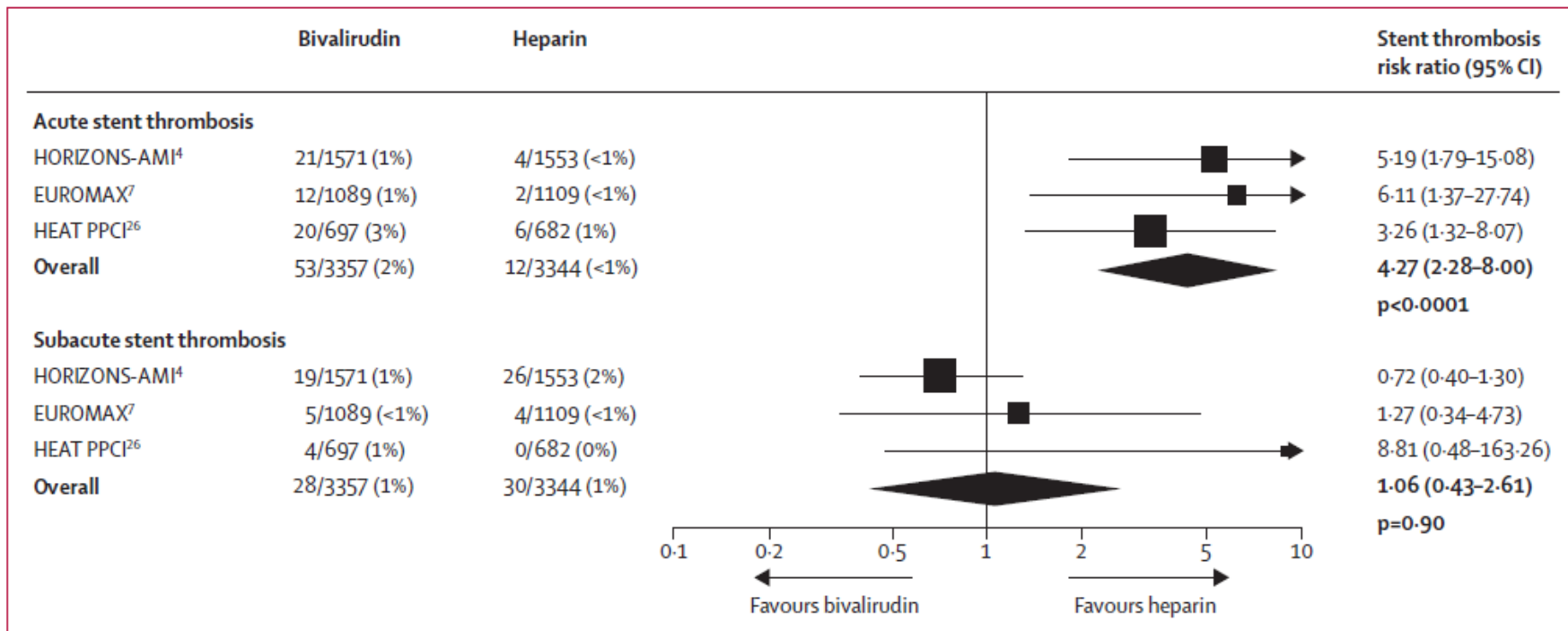


Figure 3: Acute and subacute stent thrombosis in trials with predominantly patients with ST-segment elevation myocardial infarction

There was no evidence of between-trial heterogeneity for acute stent thrombosis (Q statistic 0.7, df 2; p=0.71) or subacute stent thrombosis (Q statistic 3.1, df 2; p=0.21).

Metanalysis: Bivalirudin vs Heparin

Bleeding and GPI Utilization

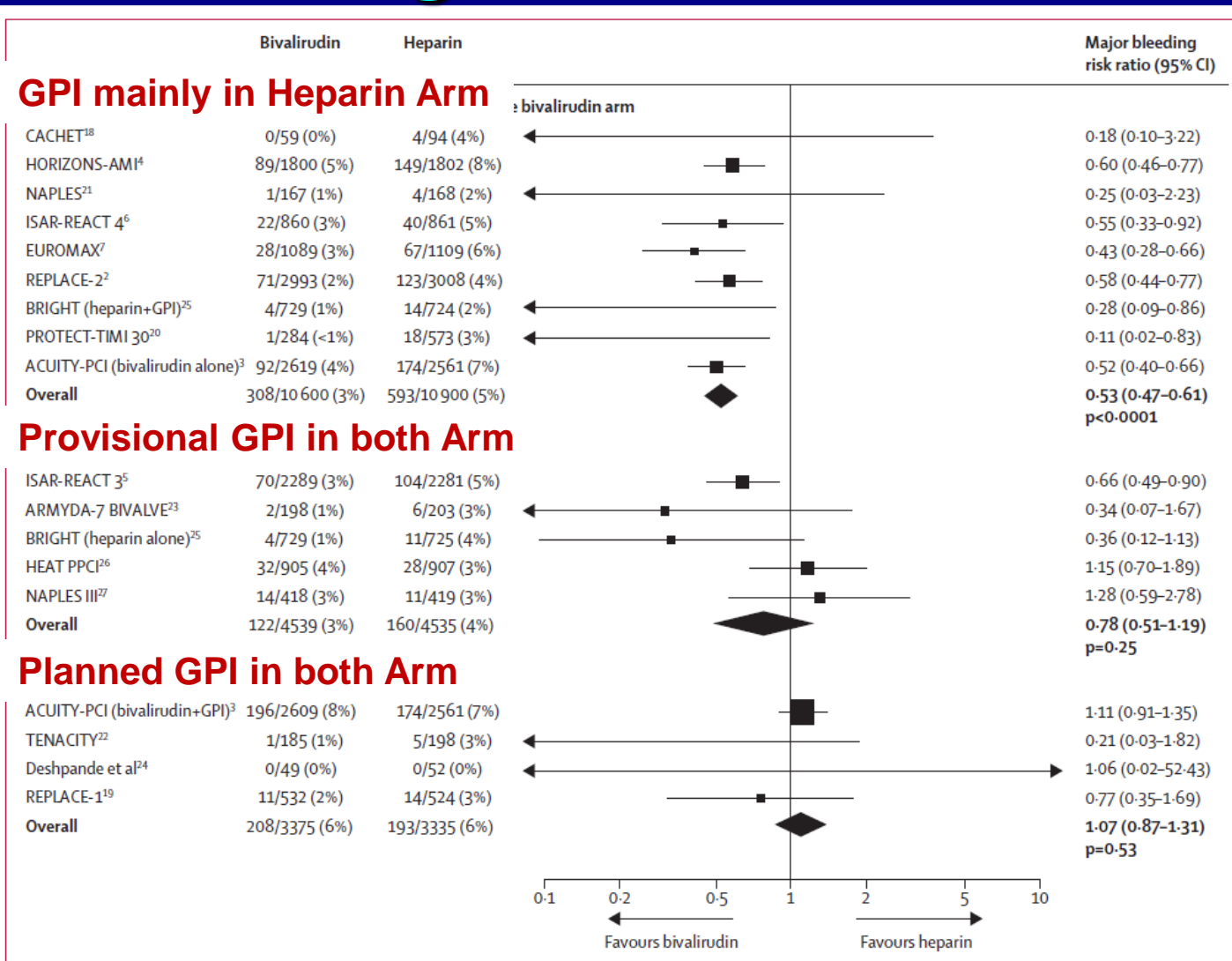
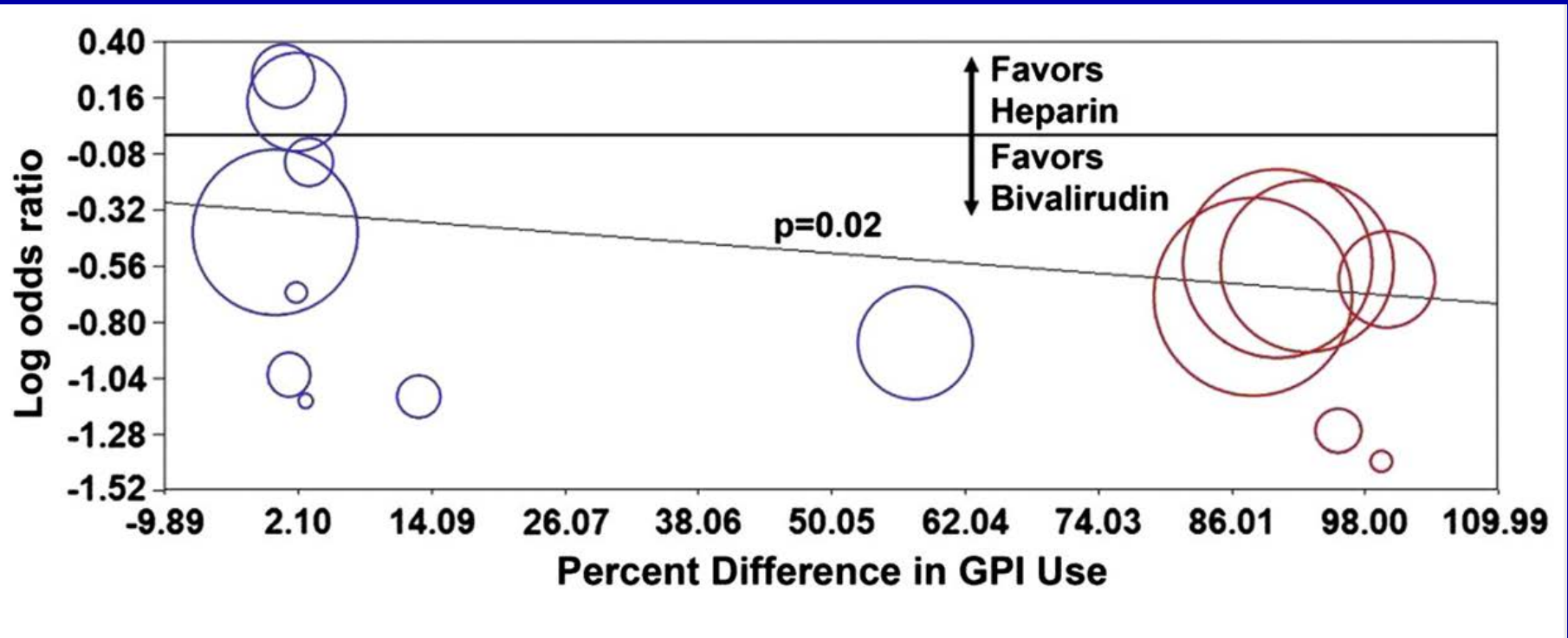


Figure 4: Major bleeding, stratified by use of glycoprotein IIb/IIIa inhibitors

Increasing Bleeding According to GPI Utilization



Current Controversies Bivalirudin vs Heparin

GPI Utilization

Not related to
ST

New P2Y12

Not related to
ST

Radial Access

Not related to
Bleeding

Prolong Infusion

Not related to
ST

Sabatine M. The Lancet 2014

Lipinski M, et al. Cardiovascular Revasc Medicine 2014;15:315-22

Current Controversies Bivalirudin vs Heparin

Reason for Increase bleeding

- *Systematic use of GPI*
- *Bolus of Heparin*

ISAR REACT 3 trial: increased RR of bleeding by 6.6% per each 10 u/Kg increase in UFH

- *Femoral access*

Current Controversies Bivalirudin vs Heparin

Maybe more personalized Tx

Increase bleeding risk (less aggressive)

- ***Older***
- ***CKD***
- ***Low body weight***
- ***Prior CVA***

Increased ischemic risk (more aggressive)

- ***Large MI***
- ***Large thrombus burden***
- ***Complex anatomy***
- ***Long or multiple stents***

ESC 2014 Guidelines

Recommendations for antithrombotic treatment in patients with STEMI undergoing primary PCI

Recommendations	Class ^a	Level ^b	Ref ^c
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	776,794
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	828
• Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication	I	B	823
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B	812
It is recommended to give P2Y ₁₂ inhibitors at the time of first medical contact.	I	B	777,846–848
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	271,834, 835,849
Anticoagulants			
Anticoagulation is recommended for all patients undergoing primary PCI.			
The anticoagulation is selected according to the clinical profile of the chosen agent.			
Unfractionated heparin: 70–100 U/kg i.v. bolus followed by i.v. infusion at 15–20 U/kg/h.	I	C	–
GP IIb/IIIa inhibitor.			
Bivalirudin 0.75 mg/kg i.v. bolus followed by i.v. infusion at 1.25 mg/kg/h.	IIa	A	80,841
Enoxaparin i.v. 0.5 mg/kg with or without GP IIb/IIIa inhibitor.	IIa	B	842–844,850

ASA = acetylsalicylic acid; GP = glycoprotein; i.v. = intravenous; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

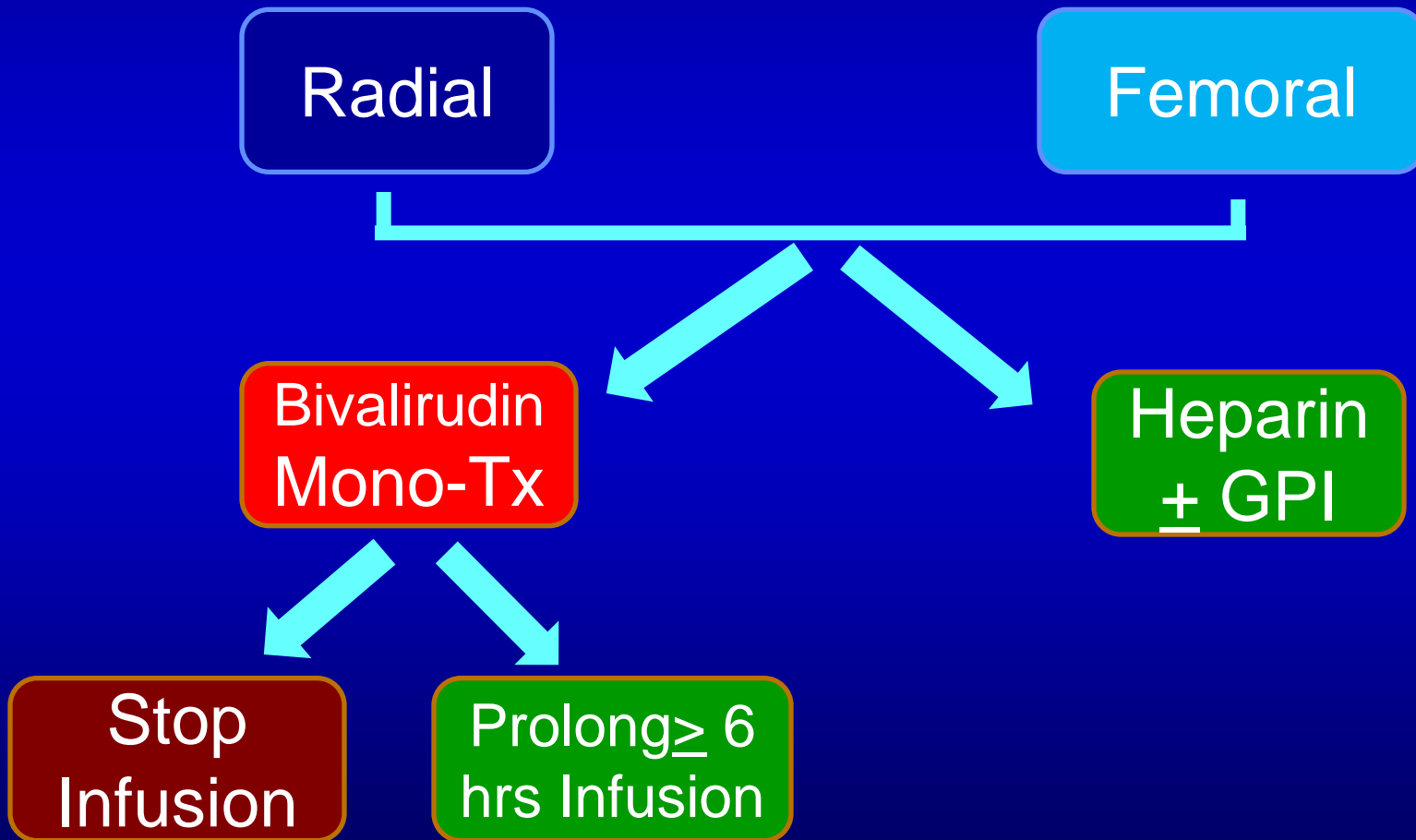
^aClass of recommendation.

^bLevel of evidence.

^cReferences.

MATRIX RCT

NSTEMI or STEMI with Invasive Management
Aspirin + P2Y12 Blocker



Ongoing Swedish RCT

REAL-SWEDEHEART

VALIDATE-SWEDEHEART

STEMI
N:3450

STEMI:3000
NSTEMI:3000

Radial
N:1725

Femoral
N:1725

Heparin
N:3000

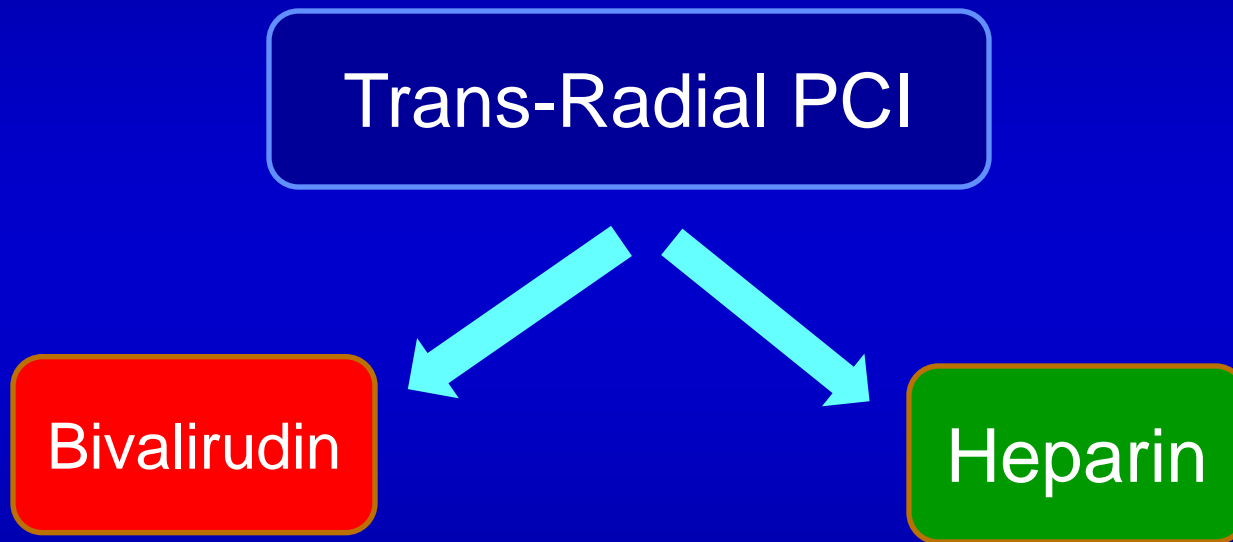
Bivalirudin
N:3000

Primary Outcome
Death at 180 days

Primary Outcome
Death/MI/>Bleeding at 180 days

EASY B2B RCT

Patients with high risk for Non-acute site bleeding: ≥ 2 risk factors. Age >70 . Female, CKD, recent GI/organ bleeding, anemia, DM, Prior GPI, TNK, oral anticoag



Bail out GPI permitted

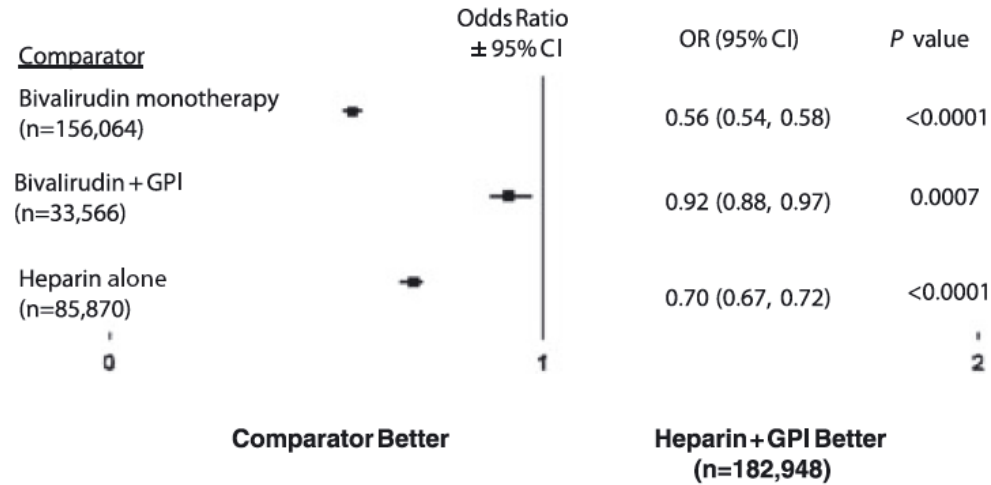
Primary end point: 30 days
Death/Urgent Revasc/ $>$ bleeding

THANK YOU

ESC 2014 Guidelines

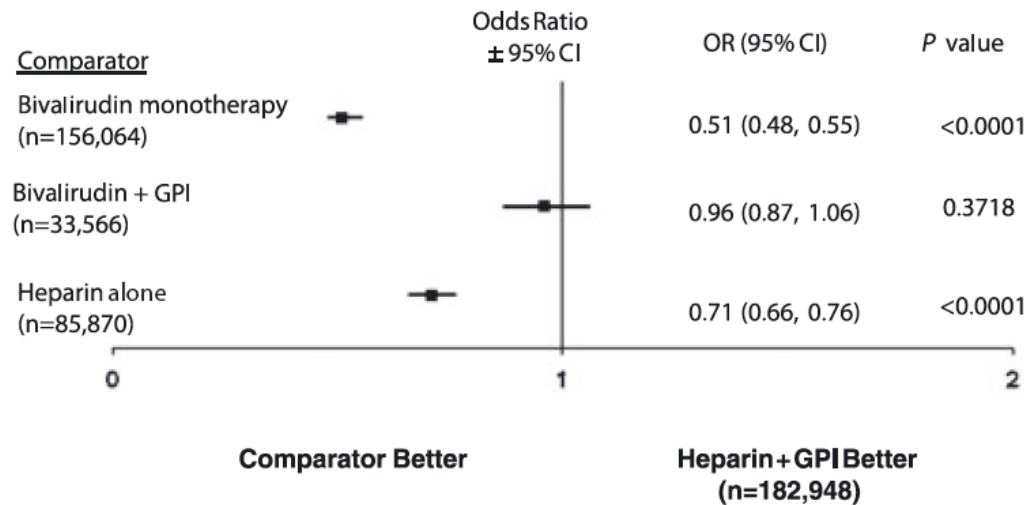
A)

Clinically Apparent Bleeding



B)

Clinically Apparent Bleeding Requiring Transfusion



ESC 2014 Guidelines

EDITORIAL VIEWPOINT

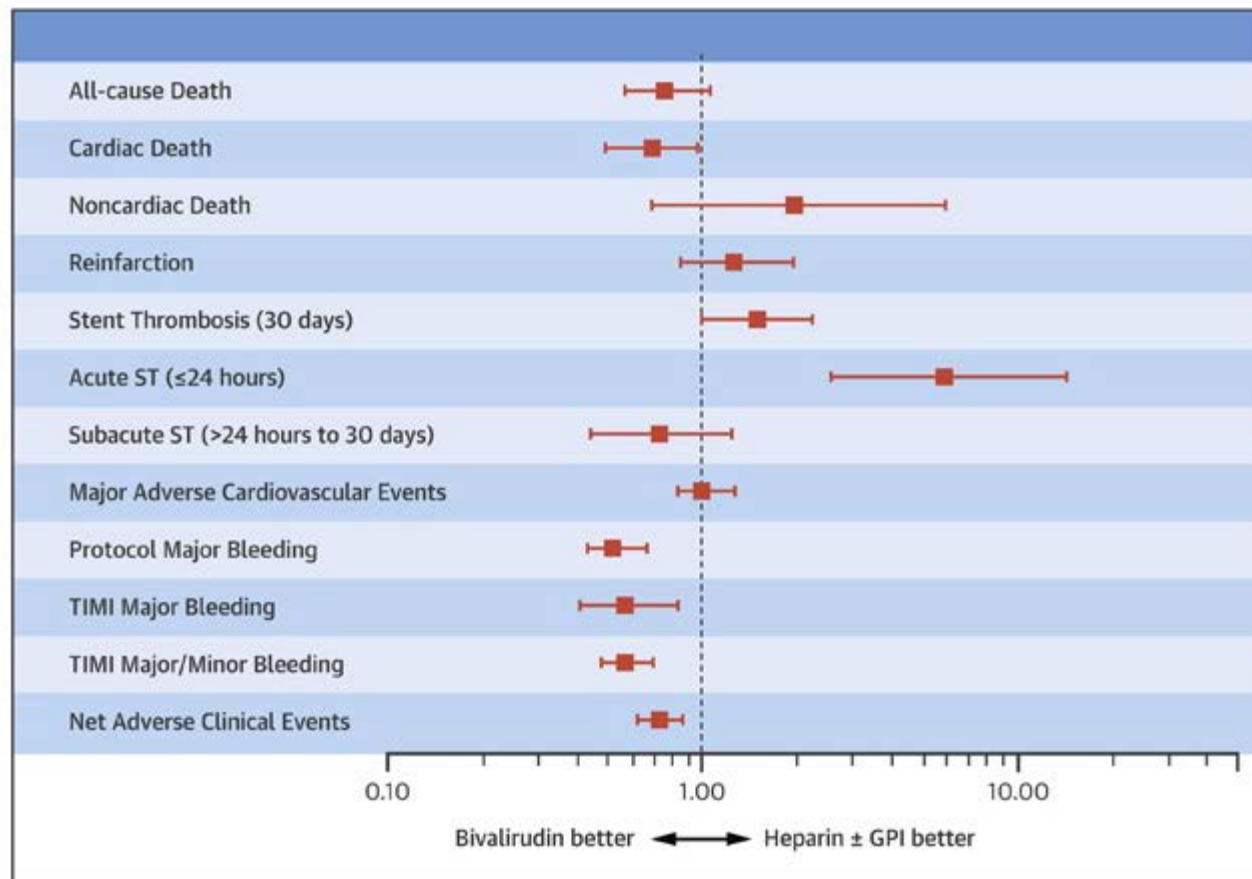
Choice of Optimal Anticoagulant to Support Primary PCI

Out With the New, In With the Old*

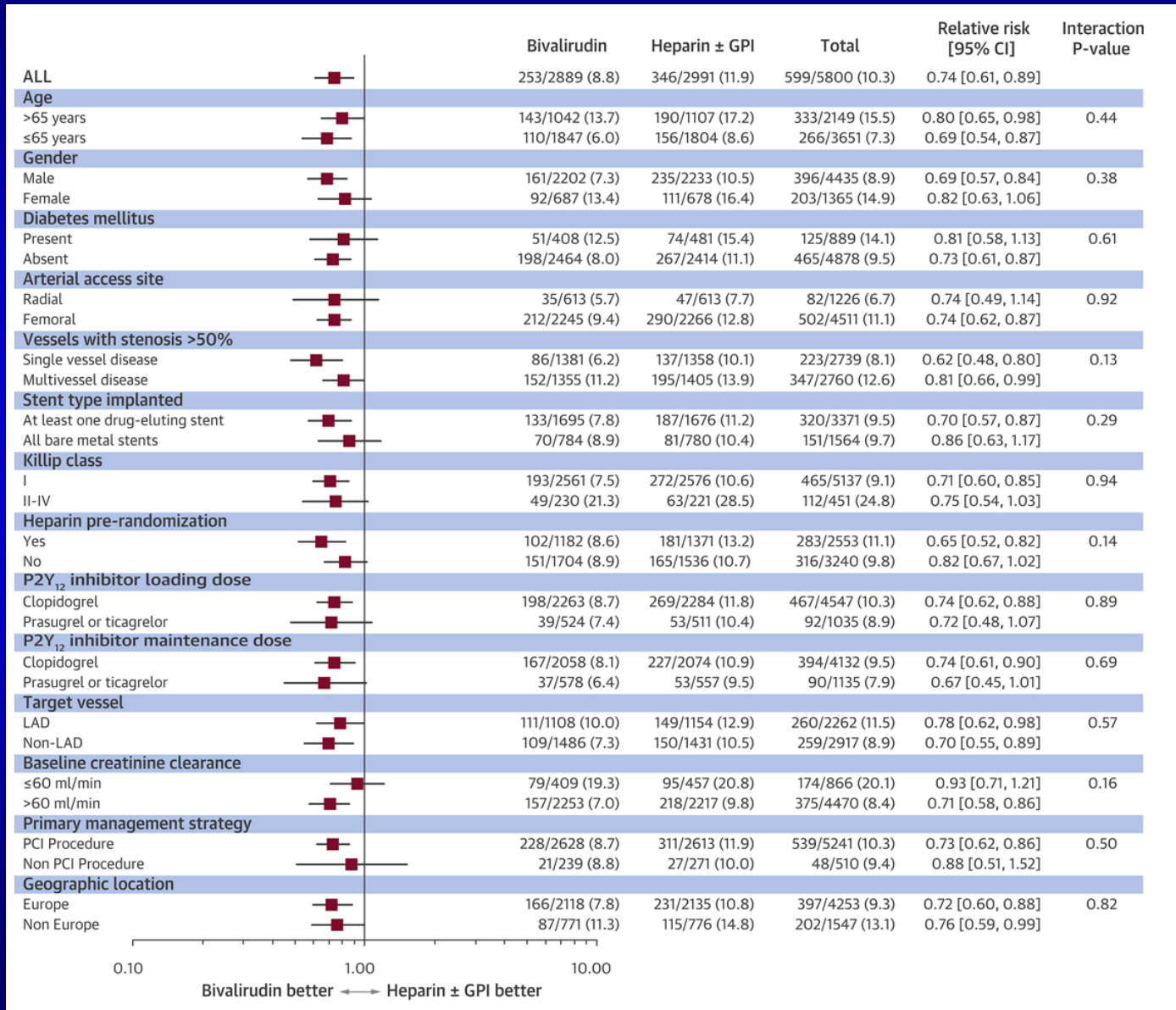
Sanjay Kaul, MD



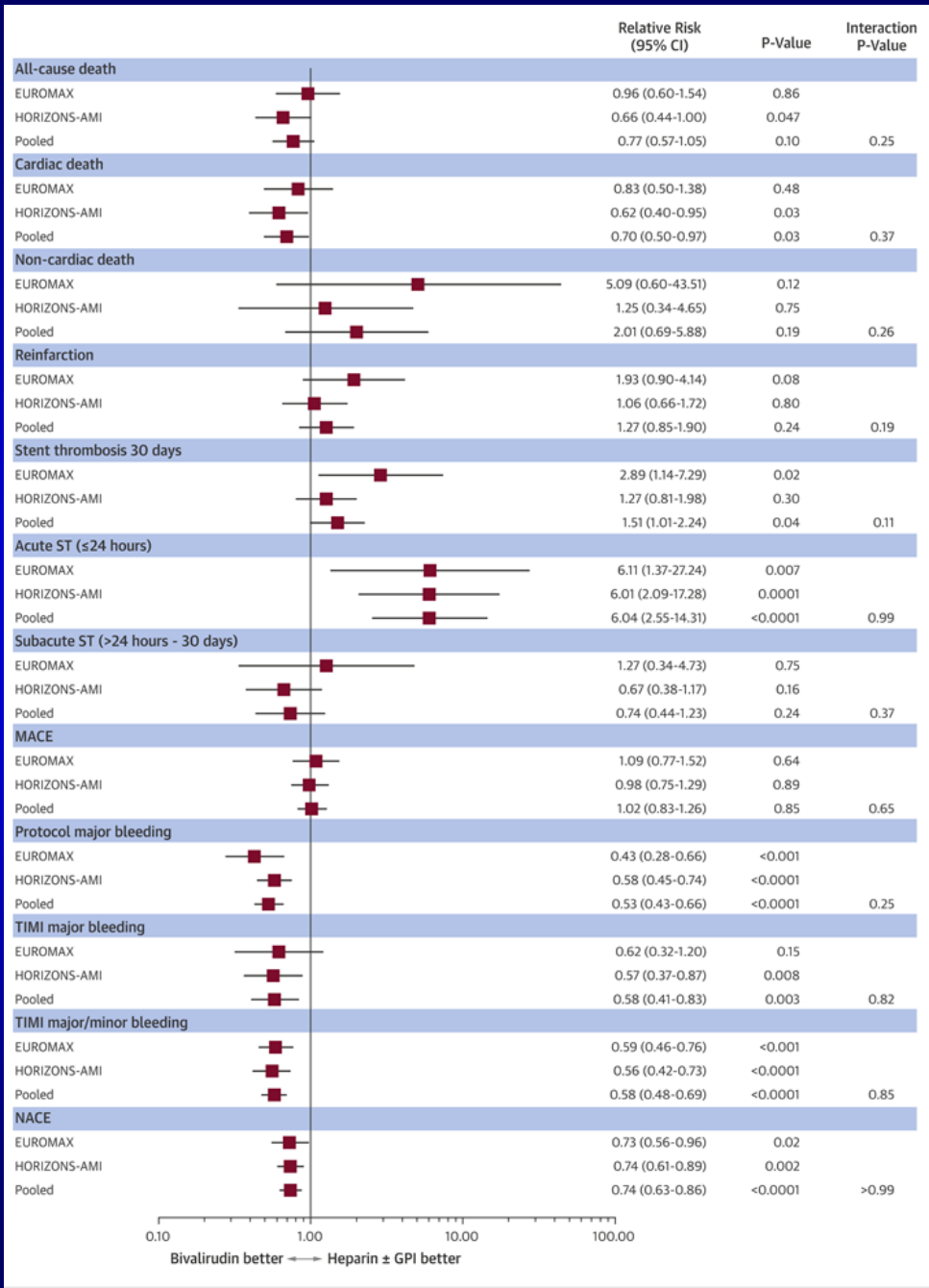
ESC 2014 Guidelines



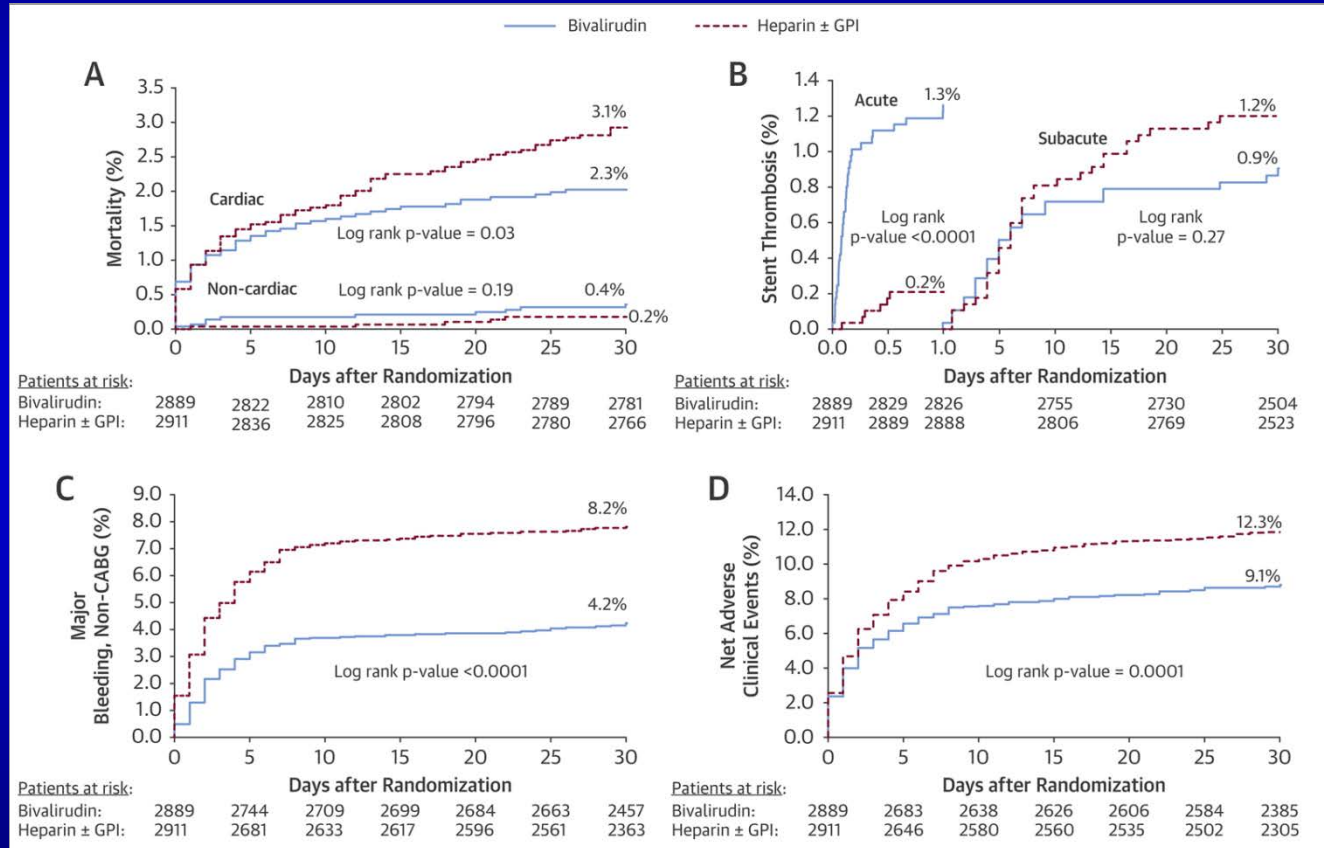
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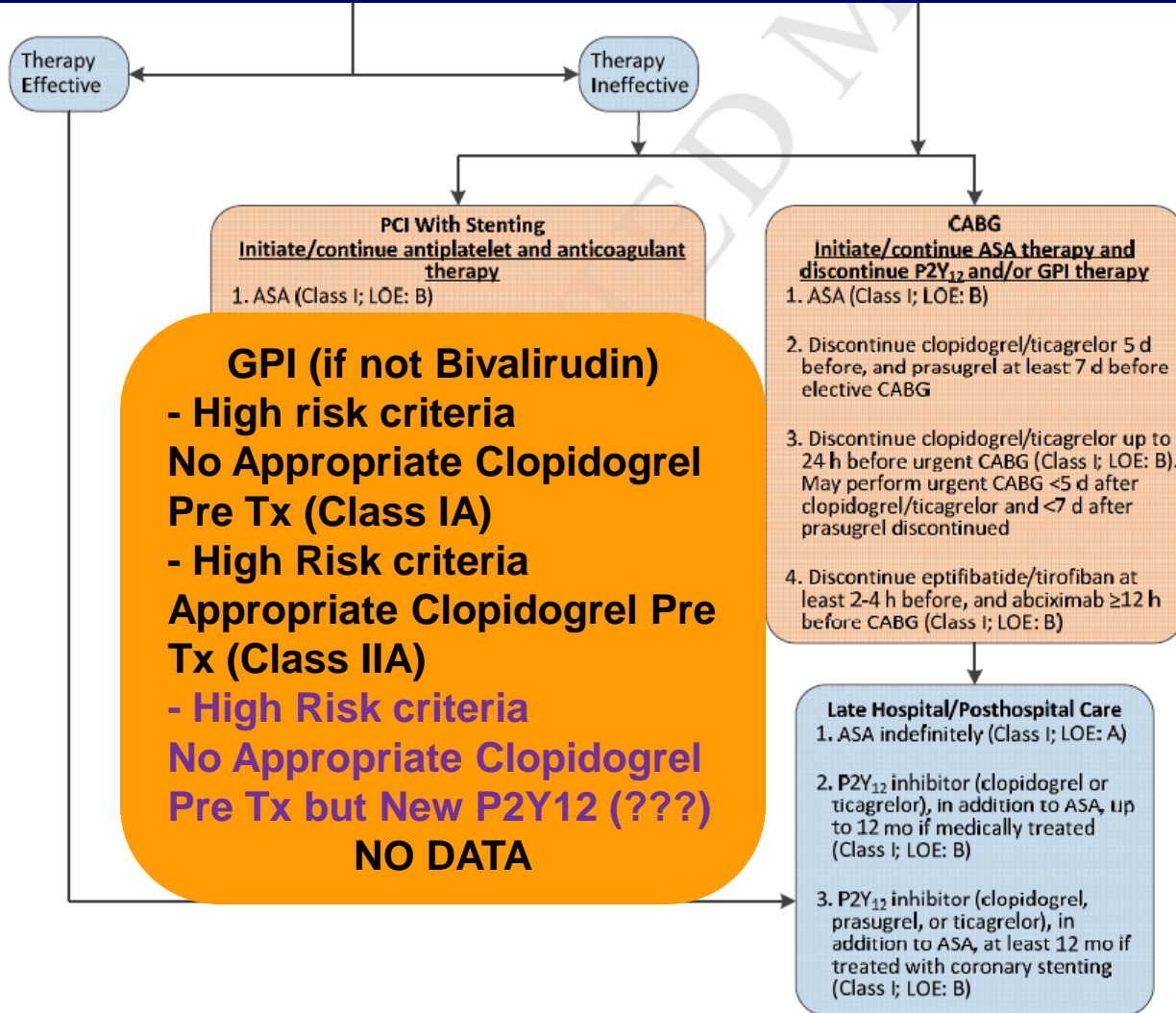


Guidelines



ESC 2014 Guidelines





MUCHAS GRACIAS