

# Bivalirudin Versus Unfractionated Heparin in Biomarker Negative Patients With Stable and Unstable Angina Undergoing PCI

## ISAR-REACT 3

(Intracoronary Stenting and Antithrombotic Regimen-  
Rapid Early Action for Coronary Treatment 3)

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# Disclosures

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The company did not participate in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the presentation.

No other conflict of interest to disclose

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# Background

Bivalirudin has not been compared with unfractionated heparin during PCI in the modern era, or in patients who have received optimal pretreatment with clopidogrel.

# Prior RCTs Comparing Bivalirudin and Heparin

- **BAS (NEJM 1995)**
  - Control group: **UFH bolus of 175 U/kg + 18-24 hr infusion**
  - Different dose of bivalirudin than currently used as well
  - Balloon angioplasty only
  - No pretreatment with clopidogrel
  
- **REPLACE 2 (JAMA 2003)**
  - Control group: **UFH plus GPIIb/IIIa inhibitors**
  - Fictional comparator of UFH alone; no pts actually received it
  - Clopidogrel pretreatment in <85%; 300 mg load
  - Provisional IIb/IIIa inhibitors in 7.2% of bivalirudin pts

# Prior RCTs Comparing Bivalirudin and Heparin

- **REPLACE 1 (AJC 2004)**
  - Bivalirudin vs UFH; **GPIIb/IIIa inhibitors in 72%** in both groups
  - Open-label
  - Clopidogrel pretreatment in <60%, 300 mg
  
- **ACUITY and HORIZONS** – not relevant; compared bivalirudin with UFH and a **GPIIb/IIIa inhibitor** in high risk **ACS/STEMI** pts

## Aim

To compare bivalirudin alone to unfractionated heparin alone in biomarker negative pts undergoing PCI pretreated with clopidogrel 600 mg for  $\geq 2$  hours

## Hypothesis

Bivalirudin is superior to UFH for biomarker negative patients undergoing PCI after optimal pretreatment with clopidogrel

# Inclusion Criteria

- Patients older than 18 years of age undergoing PCI who were biomarker negative at study entry
- Clopidogrel loading  $\geq 2$  hrs prior to PCI

# Exclusion Criteria

- Acute coronary syndromes with positive biomarkers or ST-segment elevation on ECG
- Cardiogenic shock
- Active bleeding, bleeding diathesis
- Impaired renal function (creatinine  $>3$  mg/dl)

# Treatment Regimens

Clopidogrel 600 mg at least 2 hours before PCI  
Aspirin  $\geq$ 325 mg orally or intravenously

*Double-blind randomization; double-dummy administration*

## Bivalirudin group

- Bolus of 0.75 mg/kg
- Infusion of 1.75 mg/kg/hr

## UFH group

- Bolus of 140 U/kg
- Placebo Infusion

Clopidogrel 75-150 mg/day until discharge ( $\leq$ 3 days)  
75 mg/day for at least 6 months

Aspirin 80-325 mg/day indefinitely

# Primary (Quadruple) Endpoint at 30 Days

- Composite rate of:
  - Death
  - Myocardial infarction  
(defined as CK-MB  $\geq 2$ x upper limit normal)
  - Urgent target vessel revascularization
  - Major bleeding  
(according to the REPLACE-2 criteria, JAMA '03)
    - Intracranial, intraocular, or retroperitoneal bleeding, or
    - Clinically overt bleeding resulting in a decrease in Hb  $> 3$  g/dL, or
    - Any decrease in Hb  $> 4$  g/dL, or
    - Transfusion of  $\geq 2$  units of packed red blood cells or whole blood

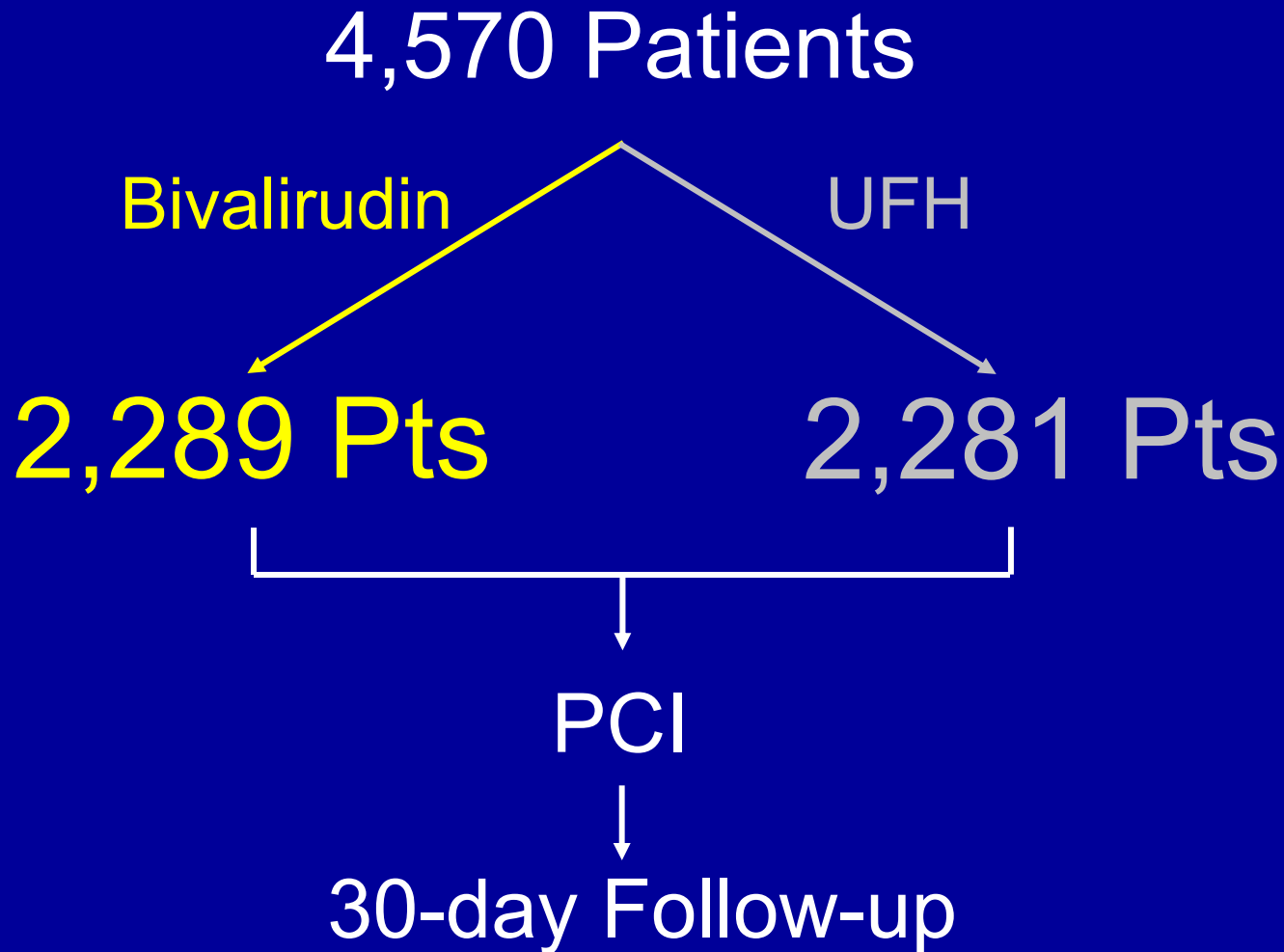
# Secondary (Triple) Endpoint at 30 Days

- Composite rate of:
  - Death
  - Myocardial infarction
  - Urgent target vessel revascularization

# Sample Size Calculation

- Assumed incidence of the 1<sup>o</sup> quadruple endpoint:
  - 8.0% in UFH group
  - 5.8% in bivalirudin group  
(a 27.5% reduction with bivalirudin)
- Power = 82%
- Two-sided  $\alpha$  level = 0.05
- Enrollment of 4500 patients required

# Study Population



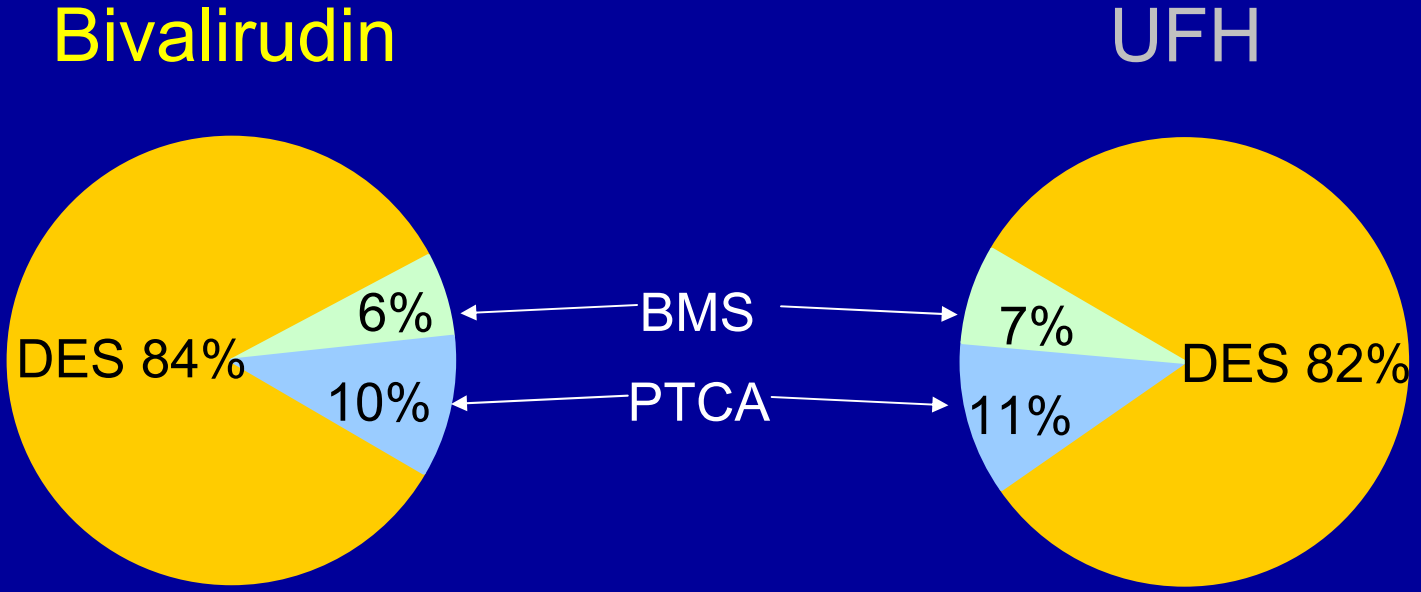
# Baseline Characteristics

	<u>Bivalirudin</u>	<u>UFH</u>
Age, yrs	67	67
Male	76	77
Body mass index, kg/m <sup>2</sup>	28	28
Diabetes, %	27	28
Hypertension, %	89	90
Current smoker, %	14	15
Hypercholesterolemia, %	81	79
History of MI, %	32	30
History of CABG, %	13	11
Unstable angina, %	18	18
Stable angina, %	82	82
Serum creatinine, mg/dl	1	1

# ISAR REACT 3 Angiographic Characteristics

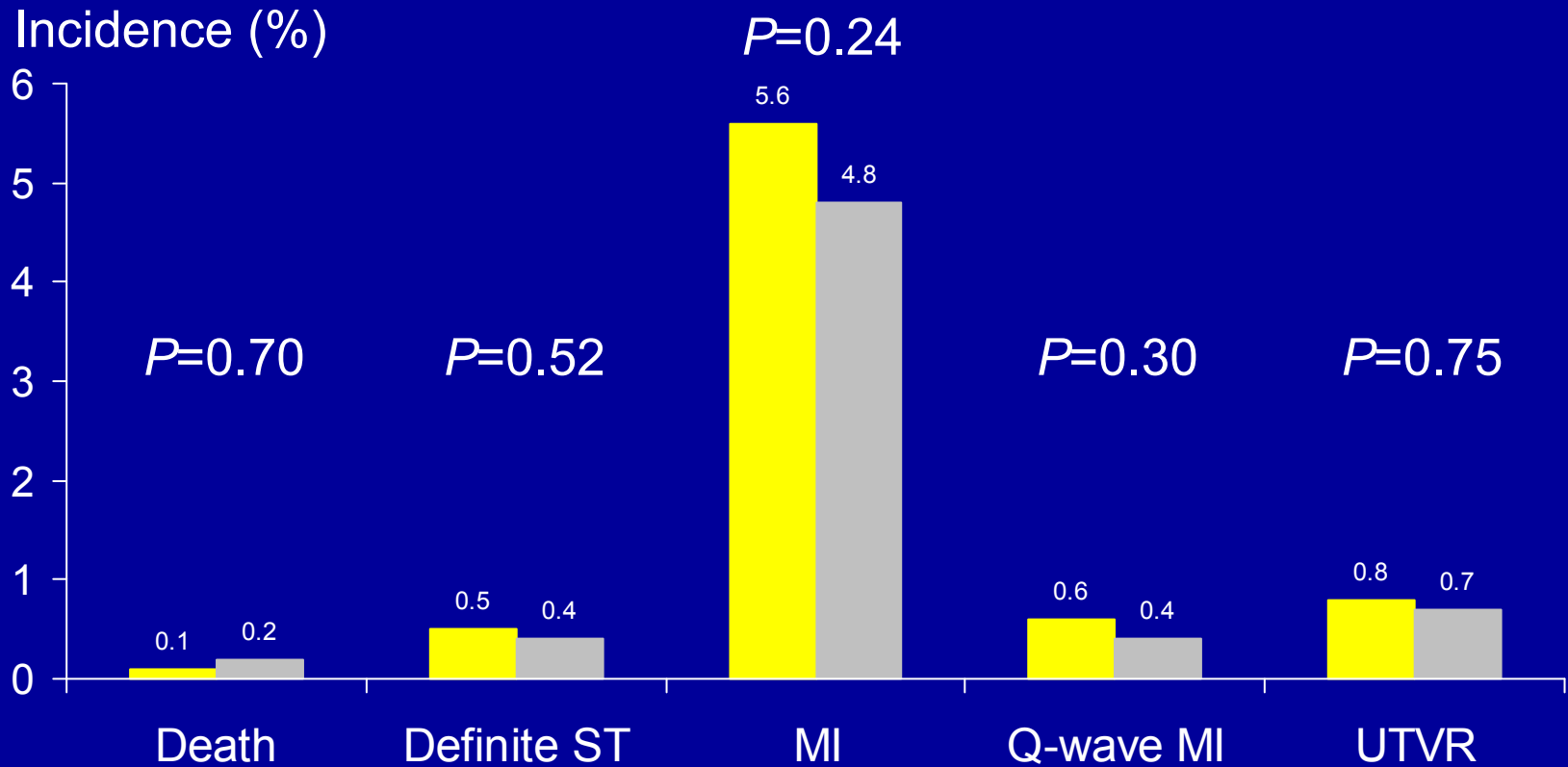
	<u>Bivalirudin</u>	<u>UFH</u>
Ejection fraction, %	58	58
Multivessel disease, %	80	80
Number of lesions/patient	2	2
Vessel treated, %		
left main	6	5
left anterior descending	39	37
circumflex	23	24
right coronary	30	32
bypass graft	2	2
B2/C lesion, %	64	64

# Type of PCI



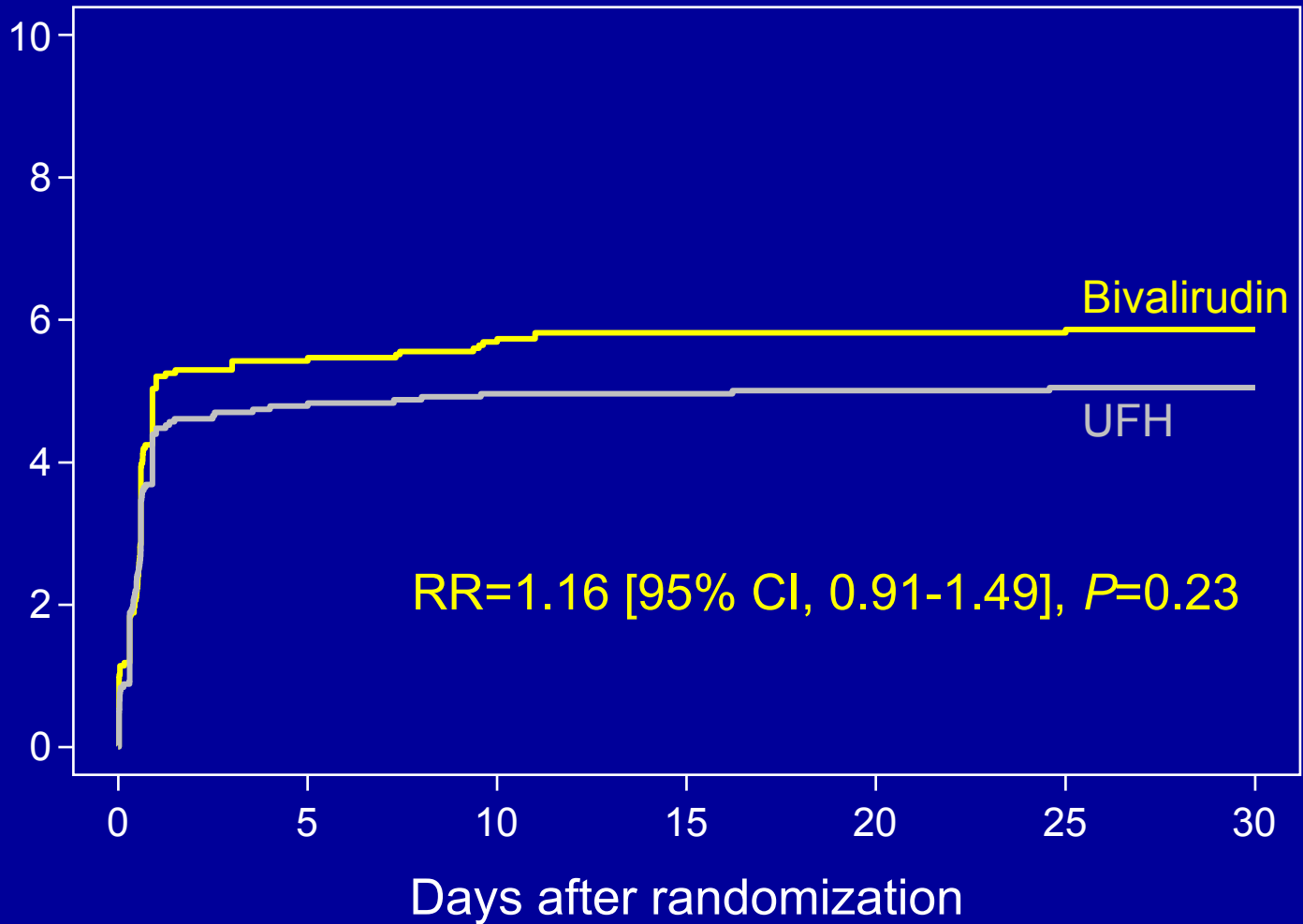
# Ischemic Events

 Bivalirudin  
 UFH

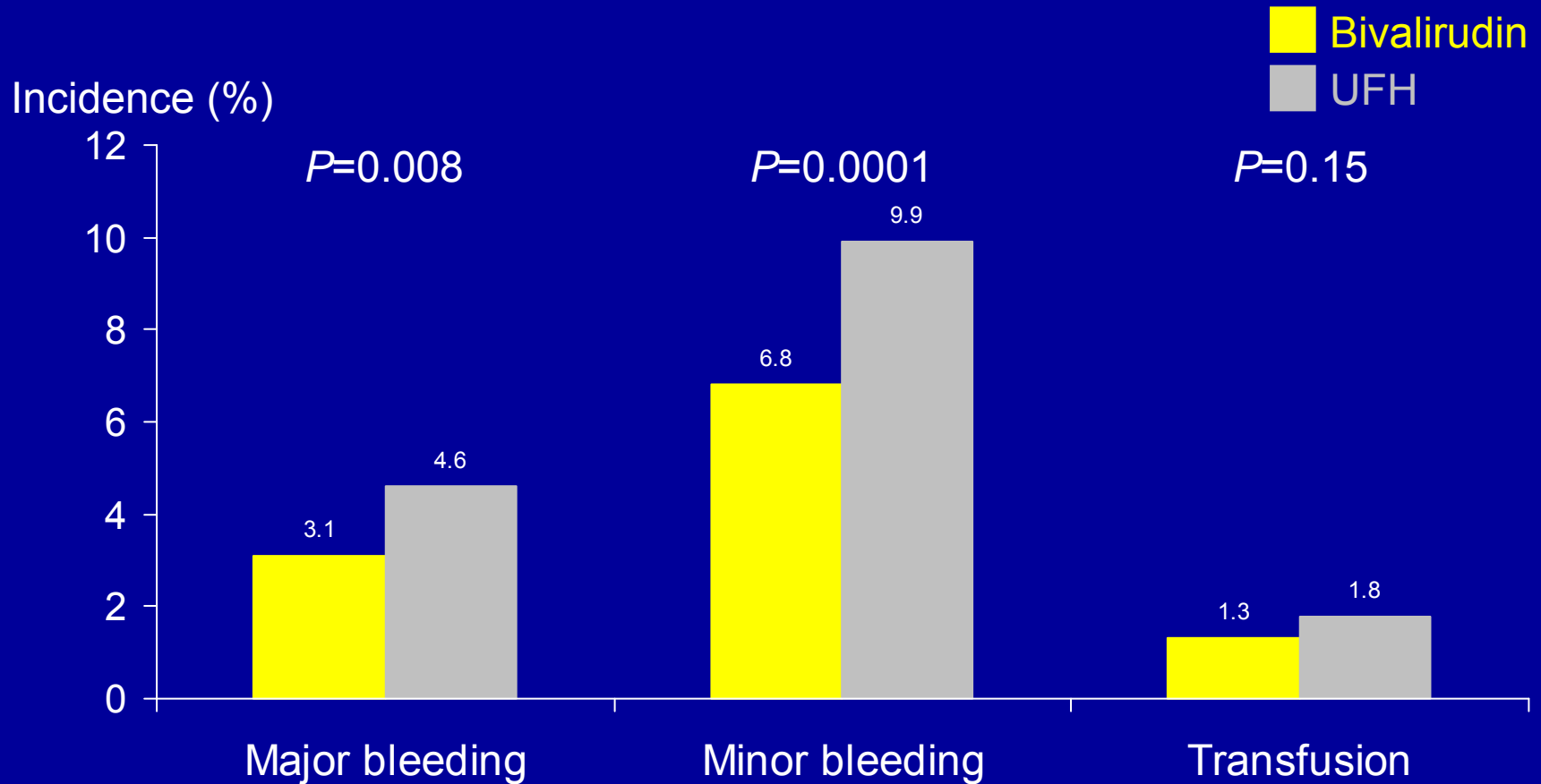


# Secondary (Triple) Endpoint Death, MI, UTVR

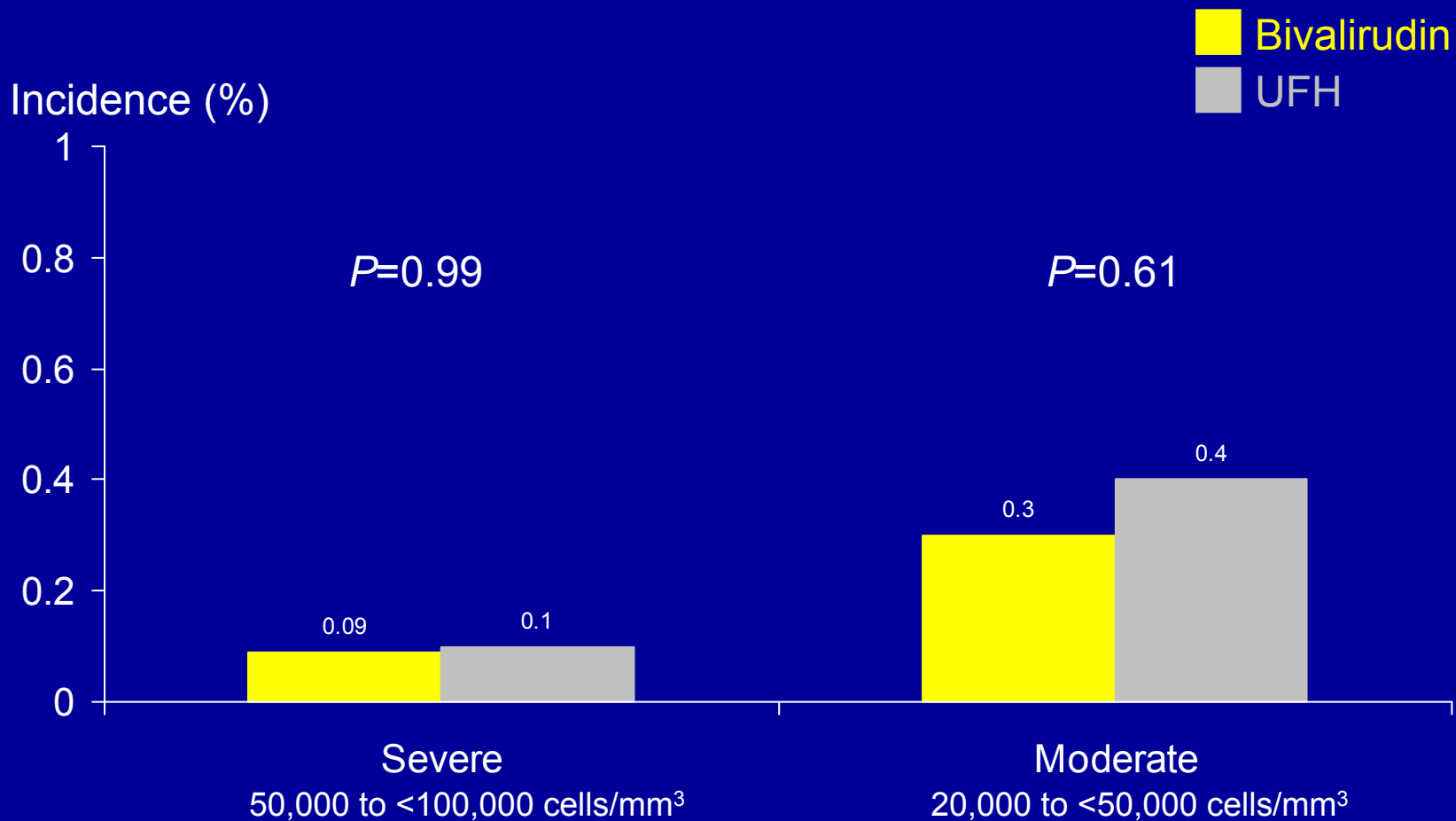
Cumulative incidence (%)



# Bleeding Events

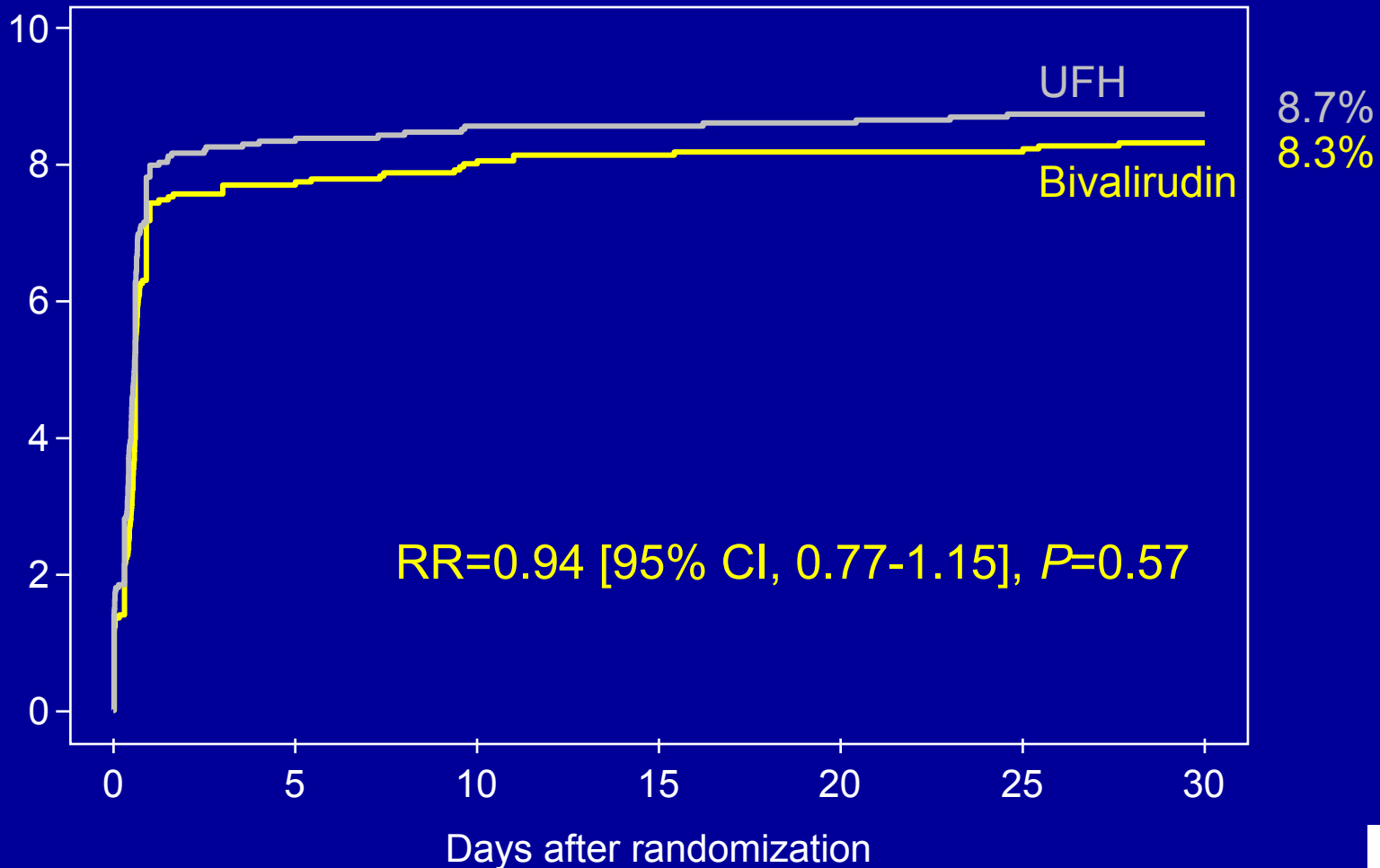


# Thrombocytopenia



# Primary (Quadruple) Endpoint Death, MI, UTVR, Major Bleeding

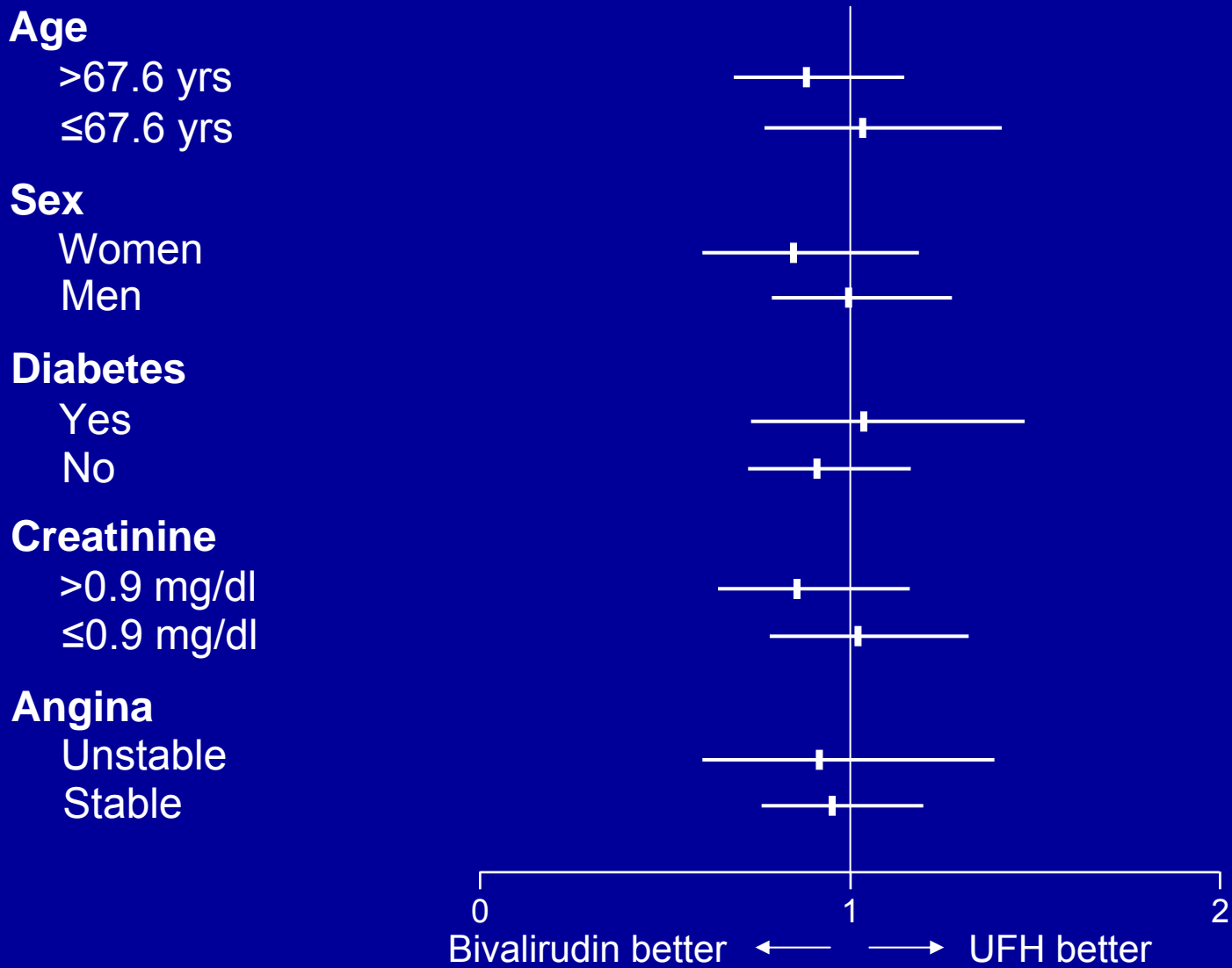
Cumulative incidence (%)



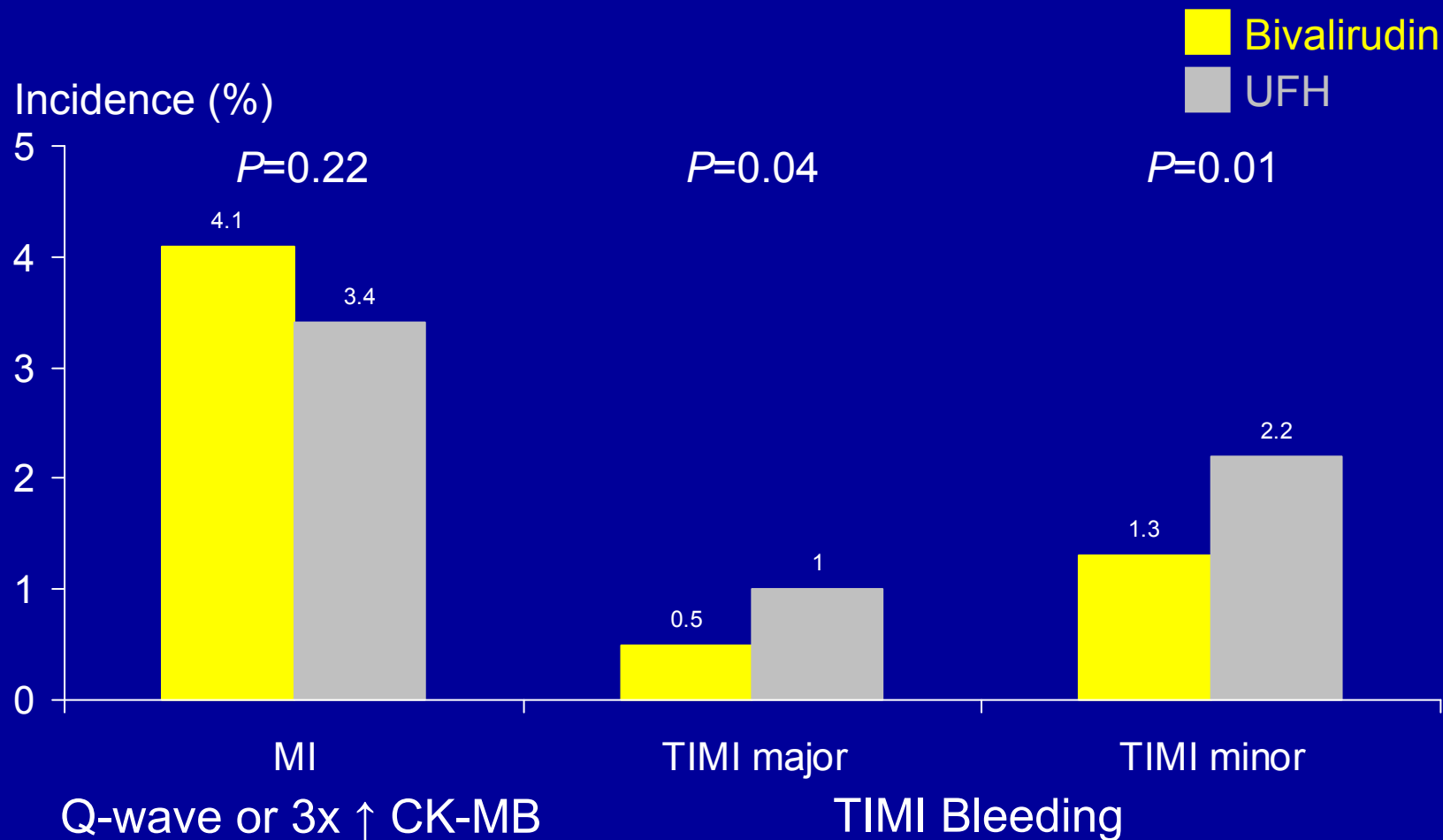
# Prespecified Subgroup Analyses

## Primary (Quadruple) Endpoint

Relative Risk (95% Confidence Intervals)



# Rates of MI and Bleeding Using Alternative Definitions



# Limitations

- The total dose of UFH (140 U/kg bolus without ACT guidance and with no additional doses) might be higher than that used in other recent PCI trials in the USA; whether and to what degree this affected outcome cannot be determined
- The results ought not be generalized to pts not pretreated with clopidogrel

# Conclusion

In biomarker negative patients with stable and unstable angina undergoing PCI pretreated with clopidogrel 600 mg for  $\geq 2$  hours, bivalirudin does not improve “net clinical benefit” – the quadruple endpoint – at 30 days compared to UFH, although it significantly reduces bleeding