

# Is it Time to Rethink Interventional Pharmacology in the Era of Radial PCI?

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# Disclosure Statement of Financial Interest

**I, Jeffrey W. Moses, have nothing to disclose.**

# First Question

- When did it become OK to once again use heparin only during primary PCI in STEMI?



# Heparin: A Disgusting Product

- Combine 5,000 lbs. intestines, 200 gallons water, 10 gallons chloroform, and 5 gallons toluene. Hold at 90°F for 17 hours.
- Add 30 gallons acetic acid, 35 gallons ammonia, sodium hydroxide to adjust pH, and 235 gallons water. Bring to a boil; then filter.
- Add 200 gallons hot water to filtrate and allow to stand overnight, then skim off the fat.
- Keep pancreatic extract at 100°F for three days, then bring to boil.
- Filter solids and assay for heparin content.

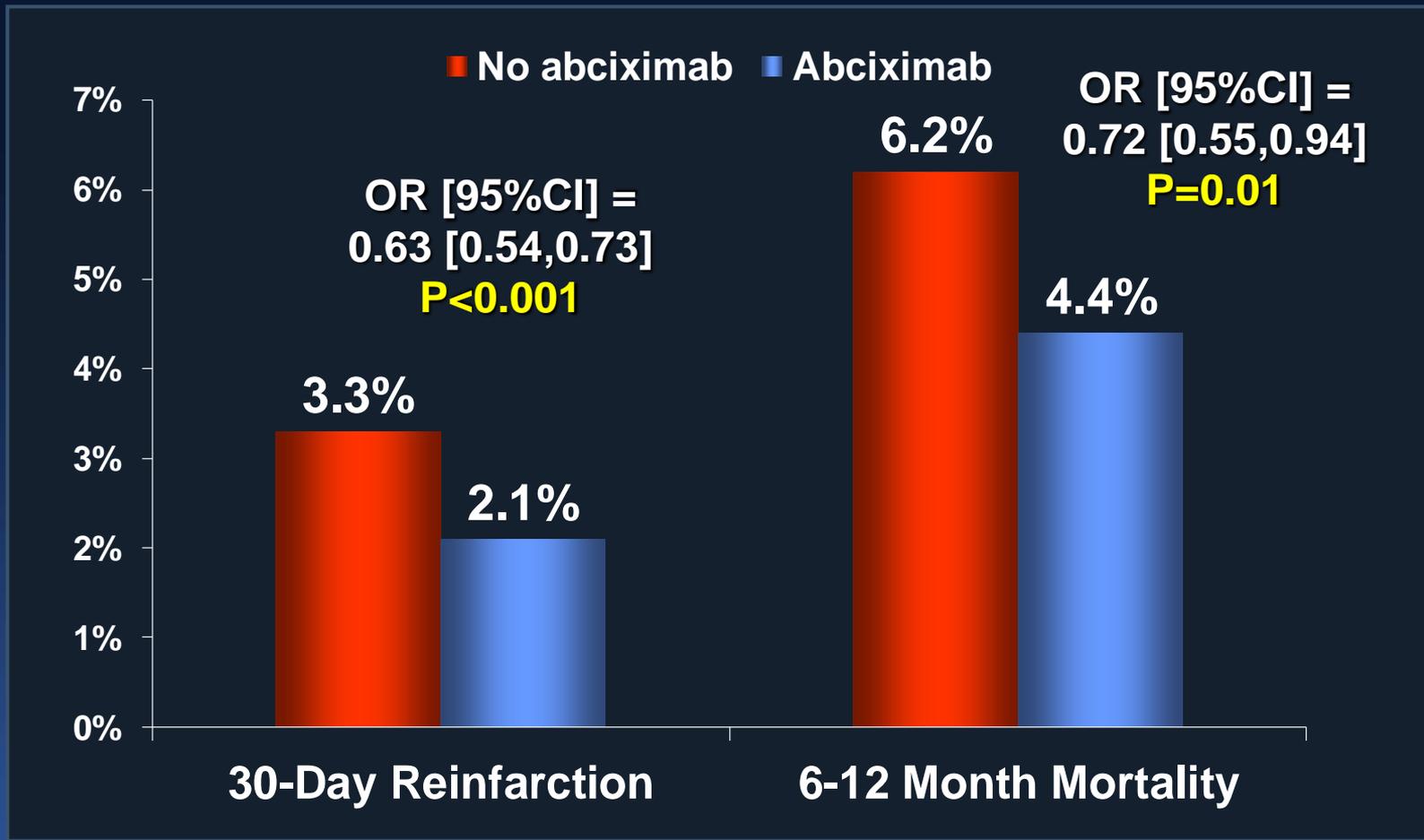


# Limitations of Heparins

Attribute	UFH	Enox	Impact
Active moieties in substance	30-35%	40-60%	Unpredictable
Action independent of AT	No	No	Unpredictable
Non-specific protease binding	Yes	Partial	Unpredictable
Variable PK-PD	Yes	Less	Unpredictable
Inhibits fibrin-bound thrombin	No	No	Need ↑ dose
Activates/aggregates platelets	Yes	+/-	Need IIb/IIIa
T <sub>0.5</sub> in minutes	60-90'	270'	↑ Bleeding
PF-4 complexing & risk of HIT	Yes	Reduced	Very bad

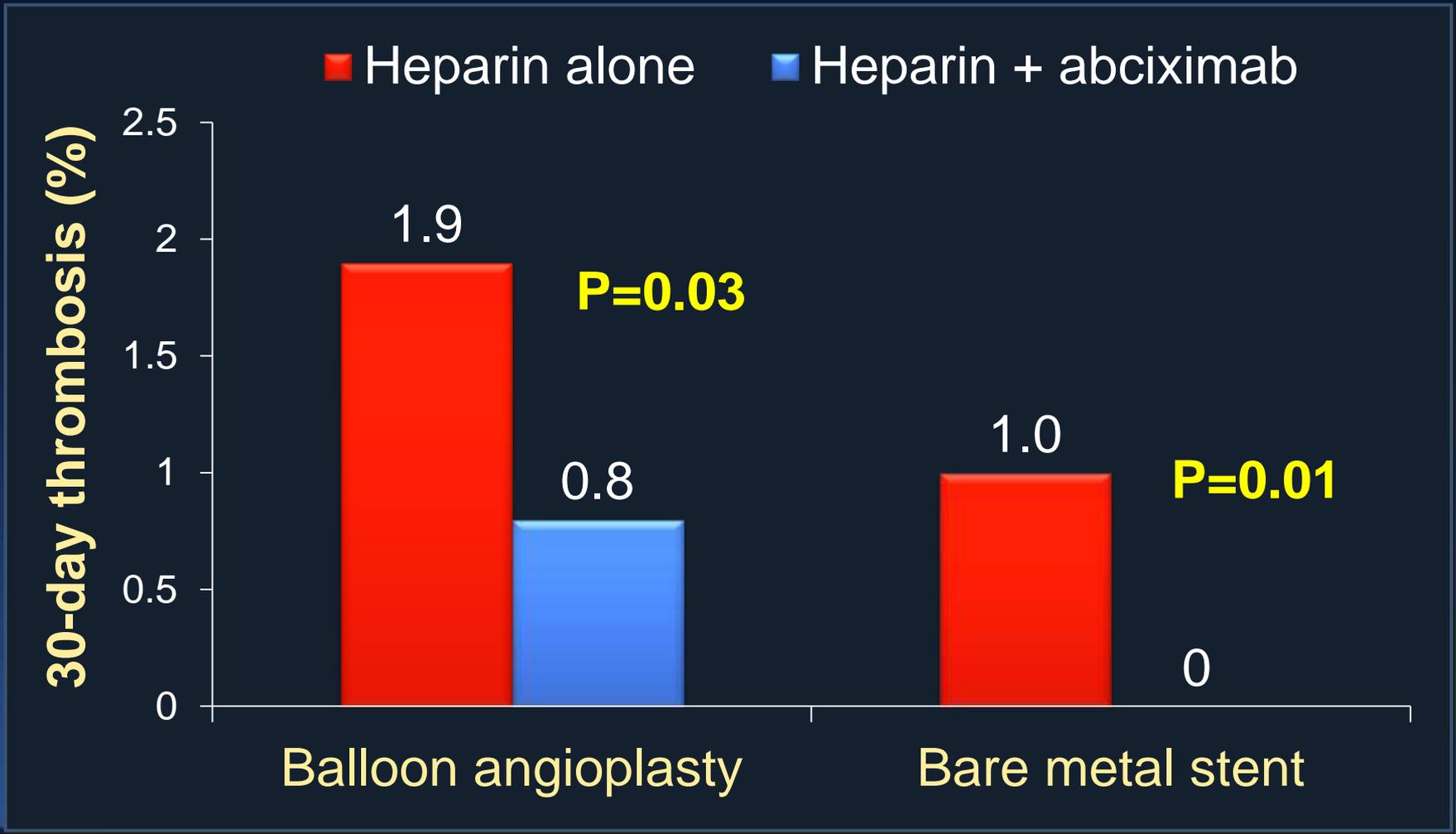
# Meta-analysis: UFH ± Abciximab in Primary PCI

8 RCTs, 3,949 pts with STEMI w/i 12° undergoing primary (7) or rescue (1) PCI randomized to UFH + abciximab vs. UFH alone



# CADILLAC (n=2,082)

## Subacute thrombosis: Impact of abciximab



# HORIZONS-AMI + EUROMAX

## Pooled 30-day results

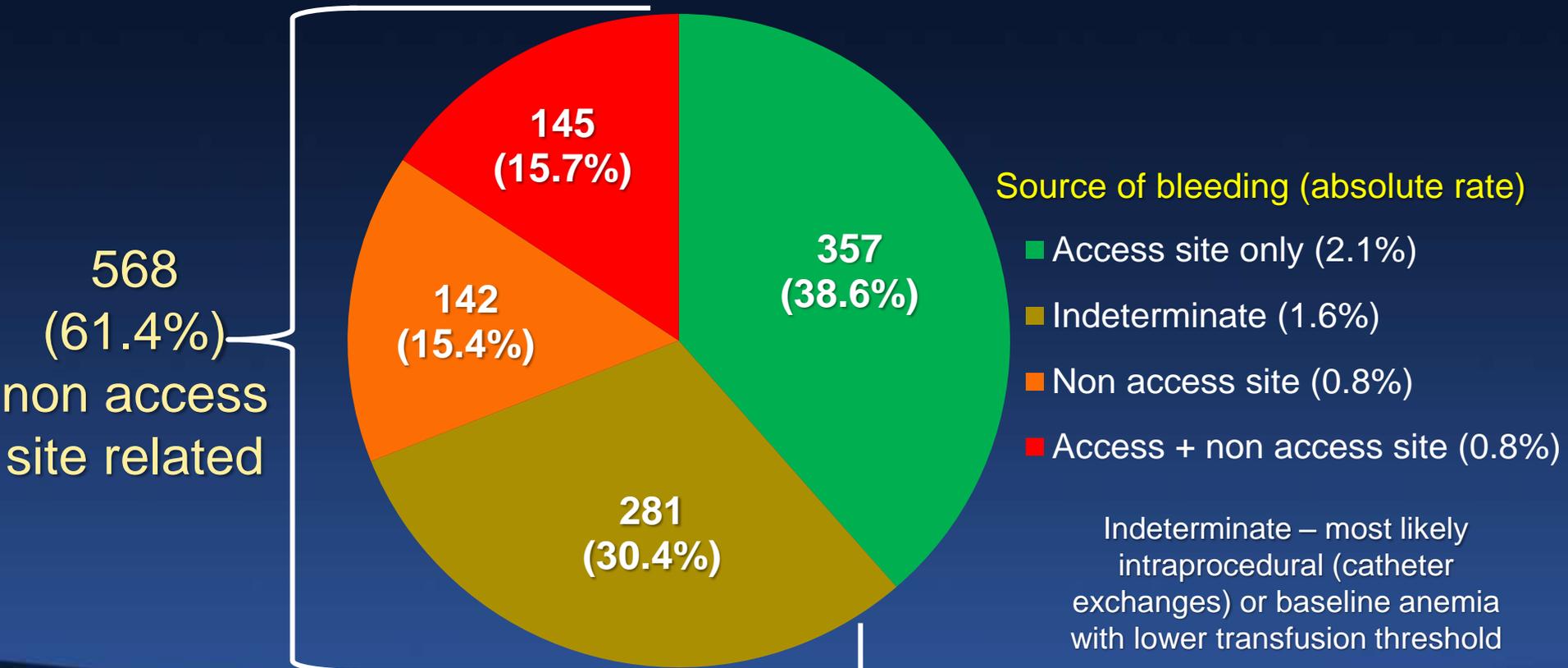
	Heparin ± GPI (N=2911)	Bivalirudin (N=2889)	Relative risk (95% CI)	P Value
Death	90 (3.1%)	69 (2.4%)	0.77 (0.57-1.05)	0.10
Cardiac	85 (2.9%)	59 (2.0%)	0.70 (0.50-0.97)	<b>0.03</b>
Non-cardiac	5 (0.2%)	10 (0.4%)	2.01 (0.69-5.88)	0.19
Reinfarction	42 (1.4%)	53 (1.8%)	1.27 (0.85-1.90)	0.24
Stent thrombosis (ARC)	40 (1.4%)	60 (2.1%)	1.51 (1.01-2.24)	<b>0.04</b>
Acute	6 (0.2%)	36 (1.2%)	6.04 (2.55-14.31)	<b>&lt;0.0001</b>
Sub-acute	34 (1.2%)	25 (0.9%)	0.74 (0.44-1.23)	0.24
MACE (death, MI, IDR, or stroke)	161 (5.5%)	163 (5.6%)	1.02 (0.83-1.26)	0.85
Protocol major bleeding	226 (7.8%)	120 (4.2%)	0.53 (0.43-0.66)	<b>&lt;0.0001</b>
Blood transfusion	110 (3.8%)	62 (2.1%)	0.57 (0.42-0.77)	<b>0.0002</b>
Acquired thrombocytopenia	77 (2.9%)	37 (1.4%)	0.48 (0.33-0.71)	<b>0.0002</b>
NACE (MACE or major bleeding)	346 (11.9%)	253 (8.8%)	0.74 (0.63-0.86)	<b>&lt;0.0001</b>

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

# Impact of Access and Non-Access Site Bleeding after PCI

17,393 pts underwent PCI in REPLACE-2, ACUITY and HORIZONS

**925 pts (5.3%) had TIMI major or minor bleeding within 30 days**

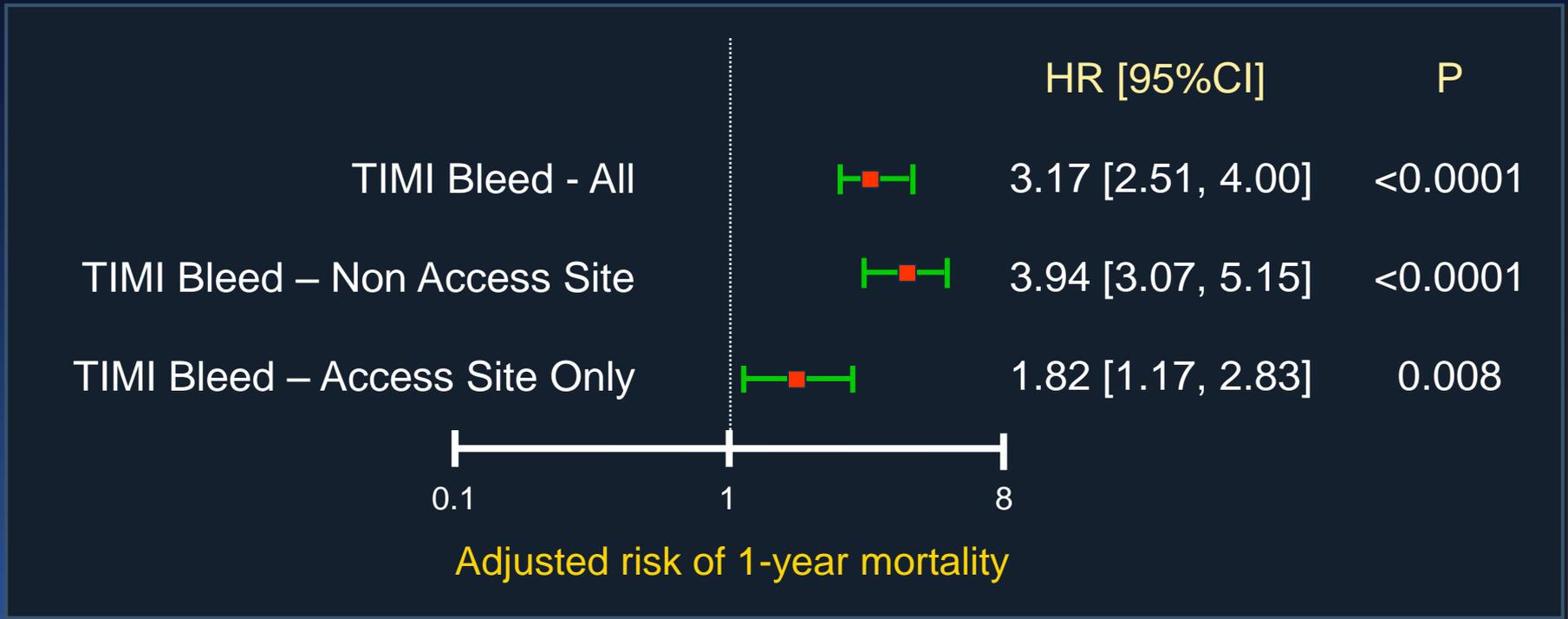


# Impact of Access and Non-Access Site Bleeding after PCI

17,393 pts underwent PCI in REPLACE-2, ACUITY and HORIZONS

925 pts (5.3%) had TIMI major or minor bleeding within 30 days

**Time-updated multivariable risk of death within 1-year**



# Second Question

- What are the results of randomized trials of bivalirudin vs. heparin (+ provisional GPI) during primary PCI in STEMI?

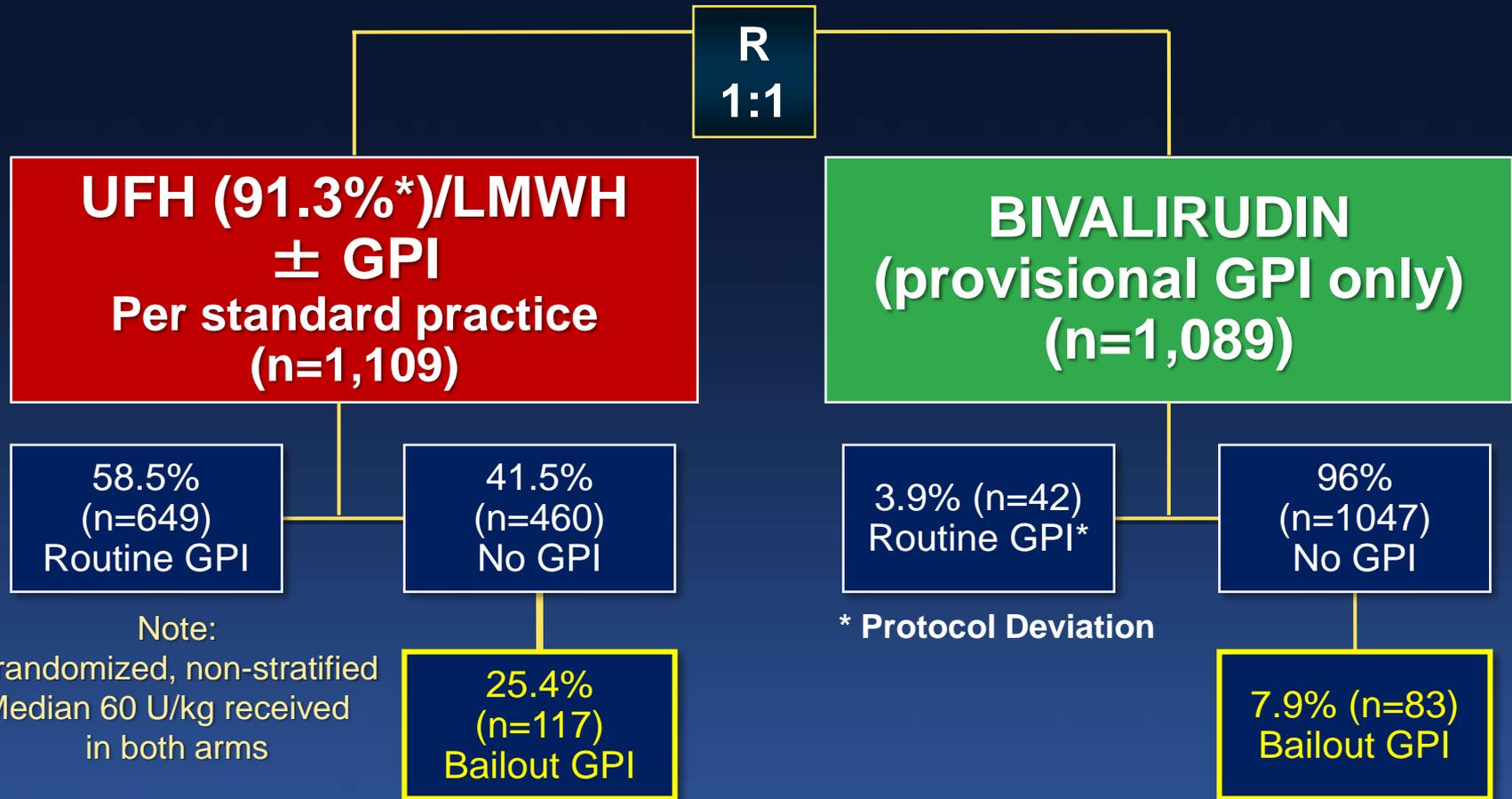


# Bivalirudin vs. Heparin Monotherapy During Primary PCI in STEMI: **Three major RCTs**

	EUROMAX	BRIGHT	HEAT PPCI
N centers	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 mono bolus	60 IU/kg	100 IU/kg	70 IU/kg
Bival infusion	Low or high dose Median 4 hrs	High dose Median 3 hrs	No
GPI bailout, Biv vs. Hep	7.9% vs. 25.4%	4.4% vs. 5.6%	13.5% vs. 15.5%
Prasugrel/ticagrelor	59%	0%	89%
Radial	47%	79%	81%

# EUROMAX: Treatment According to Routine GPI Use

**N = 2,198**

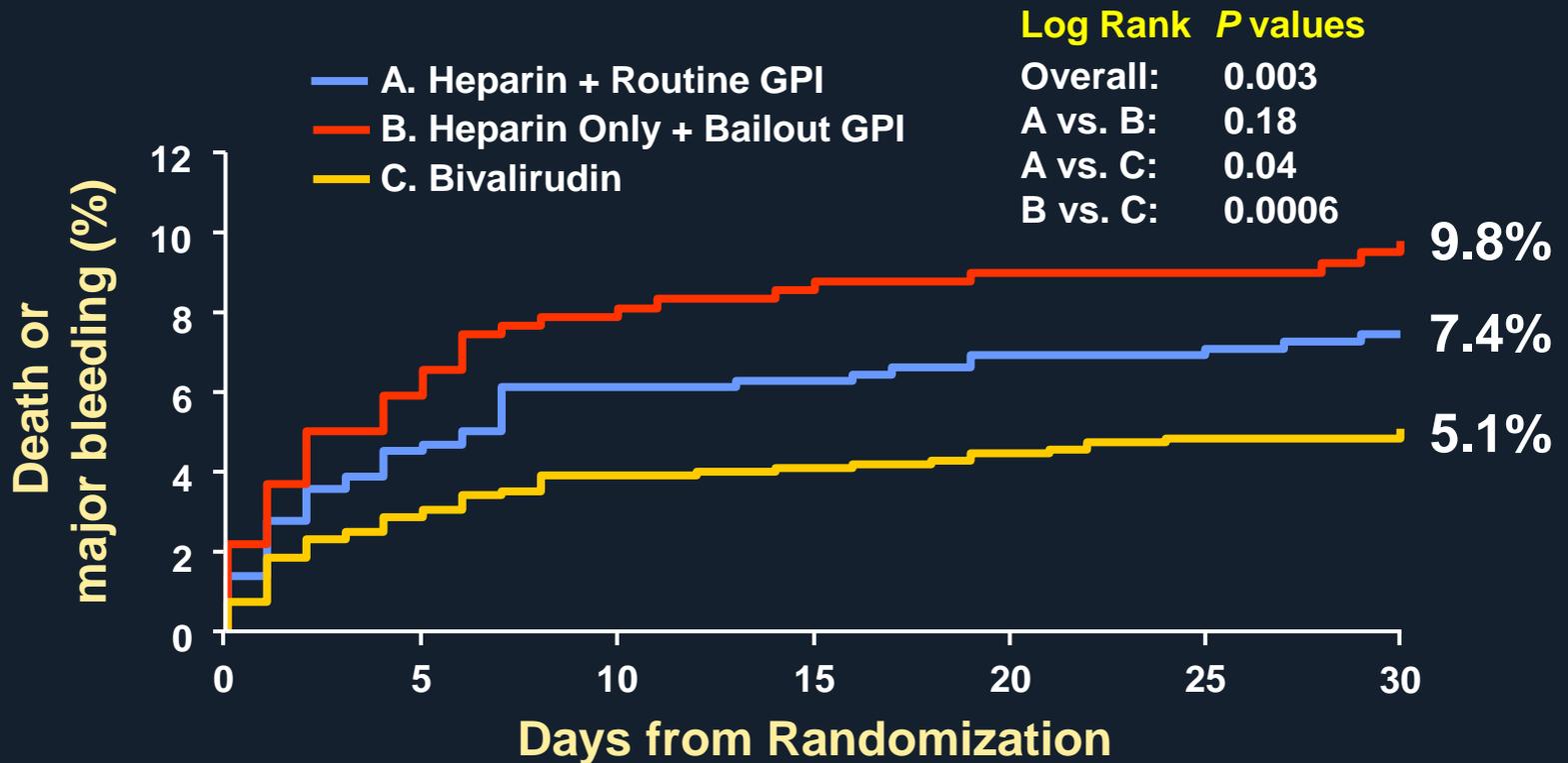


Note:

Non-randomized, non-stratified

\* Median 60 U/kg received  
in both arms

# EUROMAX: Primary Endpoint Death or Major Bleeding

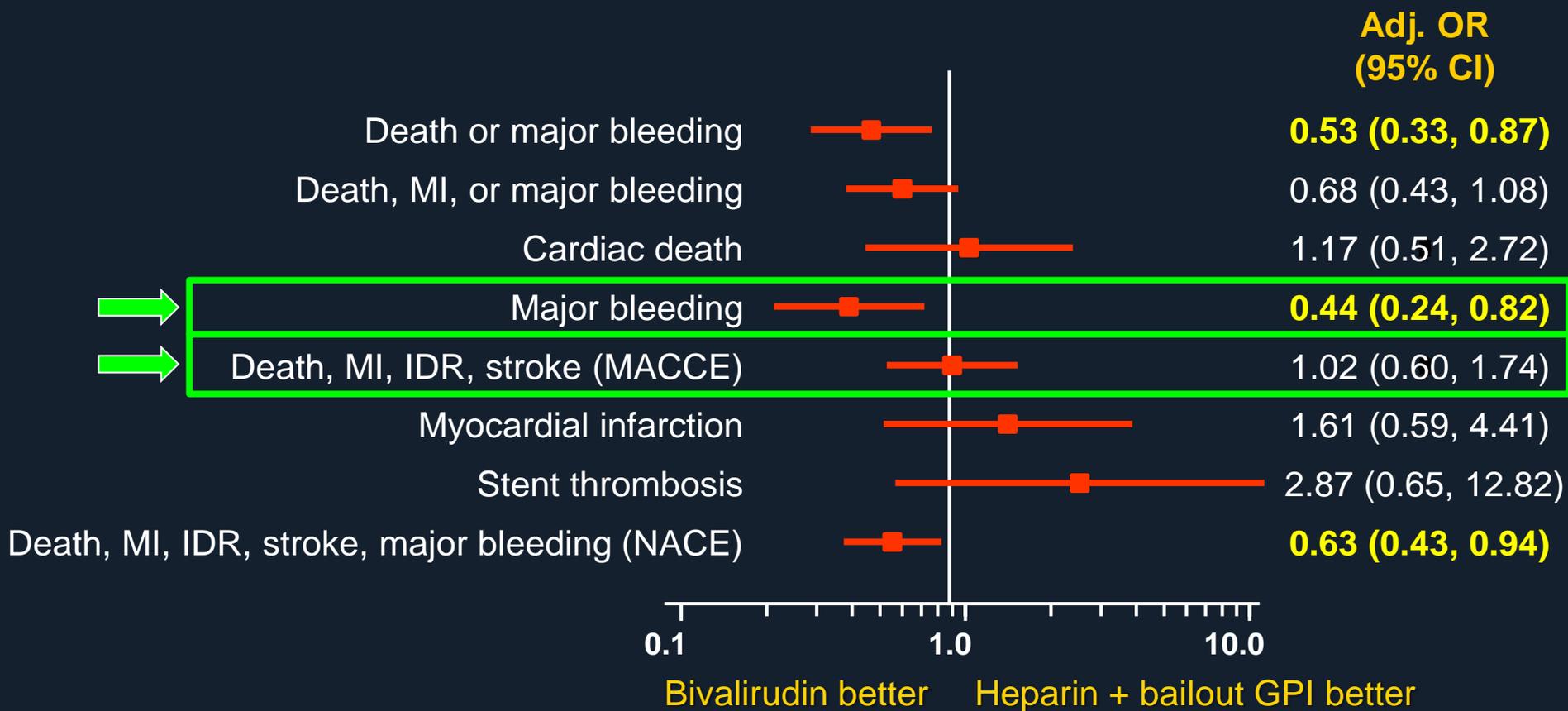


Patients at risk:

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

# EUROMAX: Bivalirudin vs. Heparin + b/o GPI

## Multivariable Analysis



# EuroMax

A prolonged high-dose bivalirudin infusion may safely reduce acute stent thrombosis

	<b>Heparin ± GPI</b> (n=1109)	<b>Bivalirudin + 0.25 mg/kg/hr infusion*</b> (n=670)‡	<b>Bivalirudin + 1.75 mg/kg/hr infusion*</b> (n=244)§
Acute ST	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

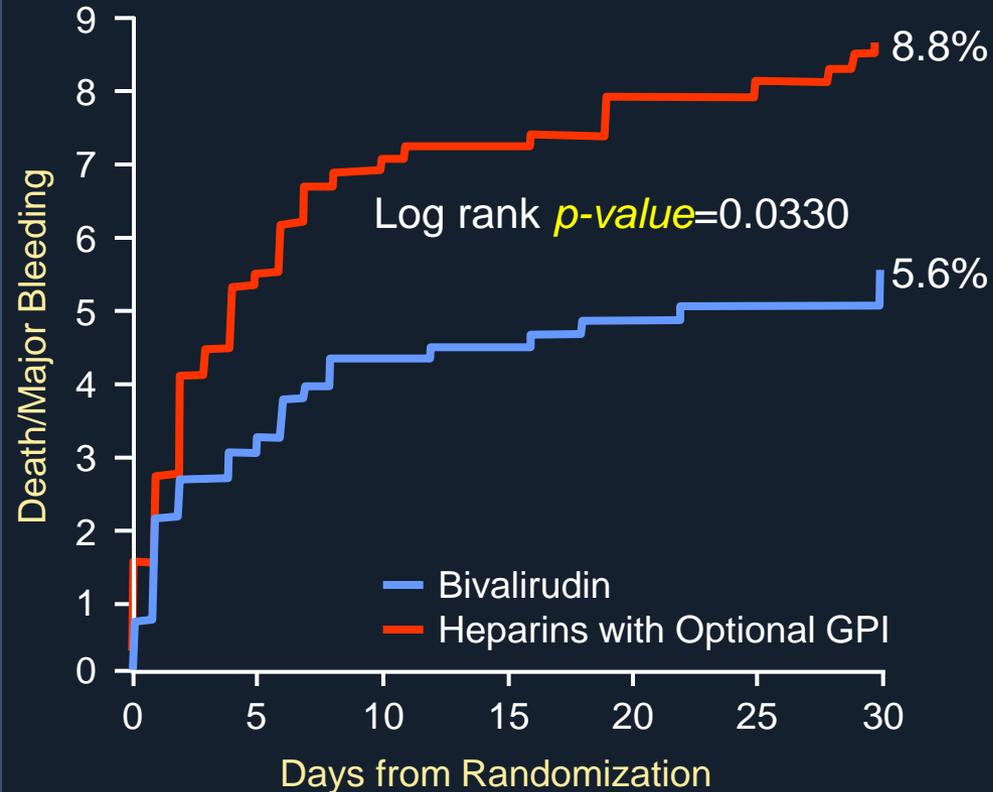
\* Median [95%CI] infusion duration was 4.5 [4.2, 4.9] hours

‡ 659 of these received at least 2 hours infusion post-PCI

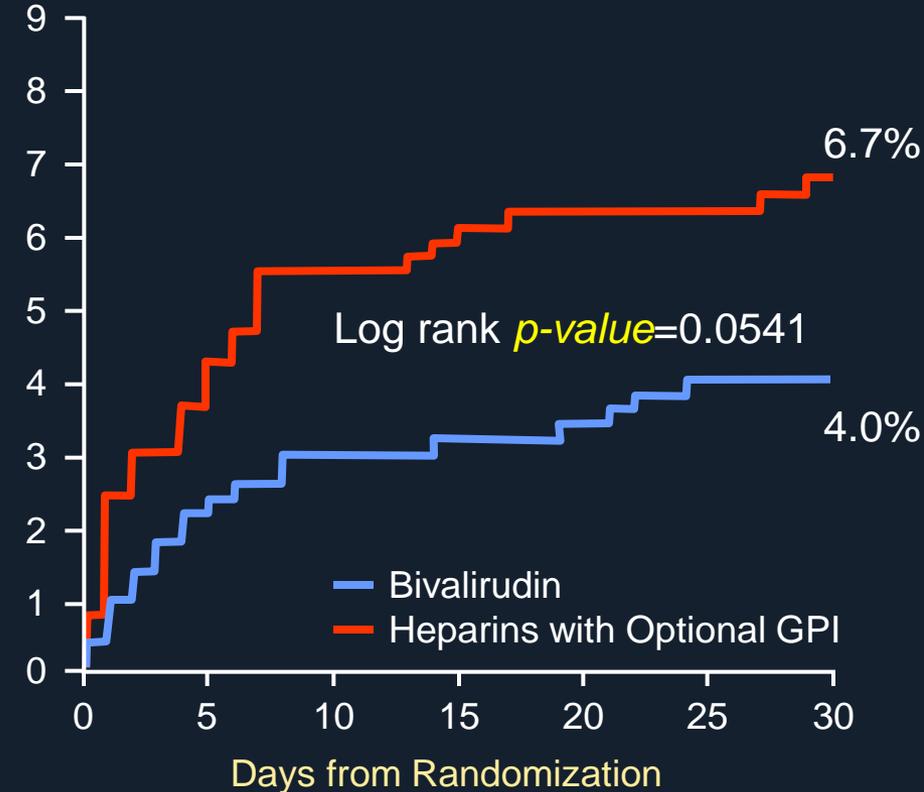
§ 191 of these received at least 2 hours infusion post-PCI

# EUROMAX: Bivalirudin vs. Heparin

## Radial

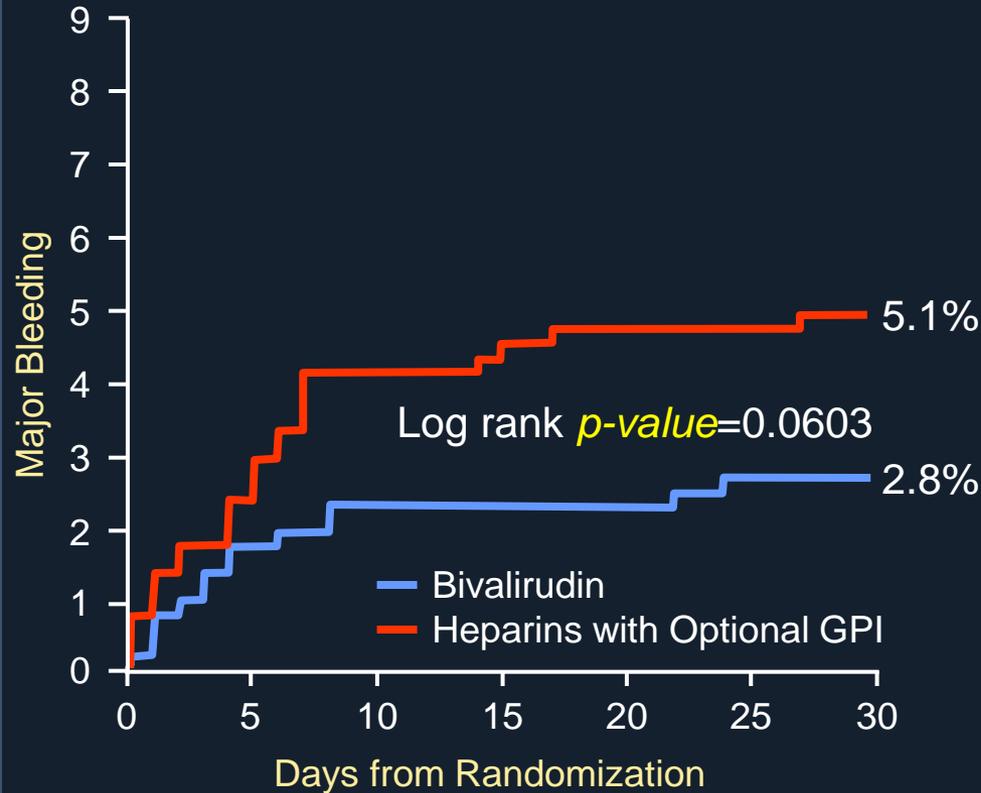


## Femoral

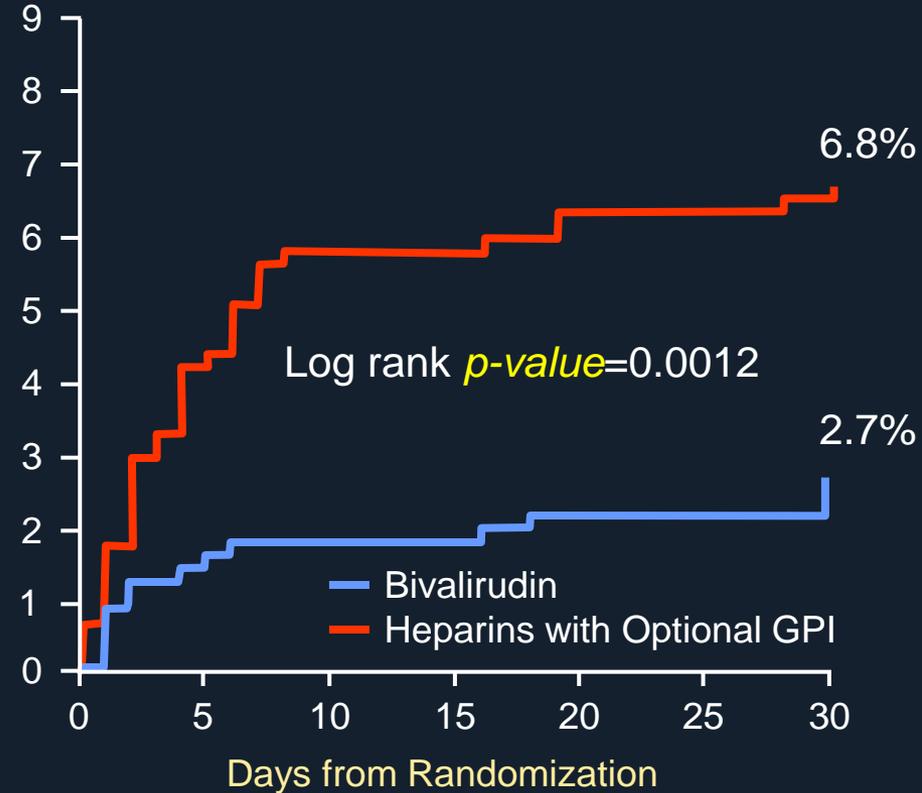


# EUROMAX: Bivalirudin vs. Heparin

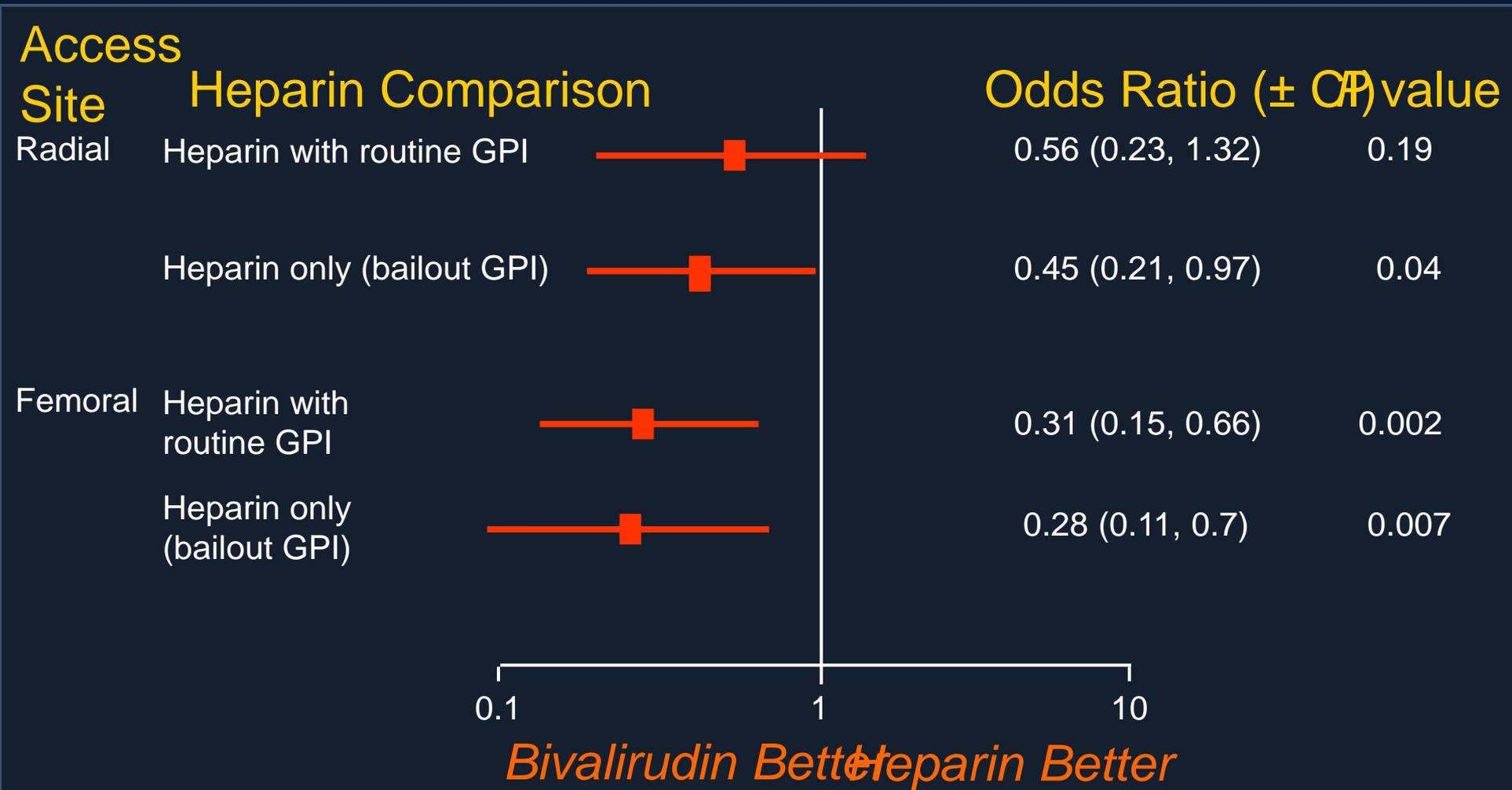
## Radial



## Femoral



# EUROMAX: Bleeding



# BRIGHT: Study flow



2,194 pts with AMI randomized at 82 centers in China

Aspirin and clopidogrel ↓

**Randomization (1:1:1)**

86.2 % STEMI  
13.8% NSTEMI  
79% radial

## **Bivalirudin alone**

N=735

Biv 0.75 mg/kg bolus + 1.75 mg/kg/h infusion (0.3 mg/kg bolus if ACT < 225s). Bailout GPI permitted. Biv infusion (1.75 mg/kg/h) continued for at least 30 min post PCI (**median 3h**).

**4.4% bailout tirofiban.**

## **UFH alone**

N=729

Heparin 100 U/kg bolus + additional dose if ACT < 200 s. Bailout GPI permitted.

ACT goal = 250-300.

**5.6% bailout tirofiban.**

## **UFH + Tirofiban**

N=730

Heparin 60U/kg bolus .  
Tirofiban 10µg/kg bolus +  
0.15 µg/kg/min infusion  
for 18-36 h.

ACT goal = 200-250.

**Follow-up at 30 days, 6 months and 1 year**

**Primary endpoint:** NACE, including MACCE (all-cause death, reMI, TVR or stroke) and bleeding events at 30 days.

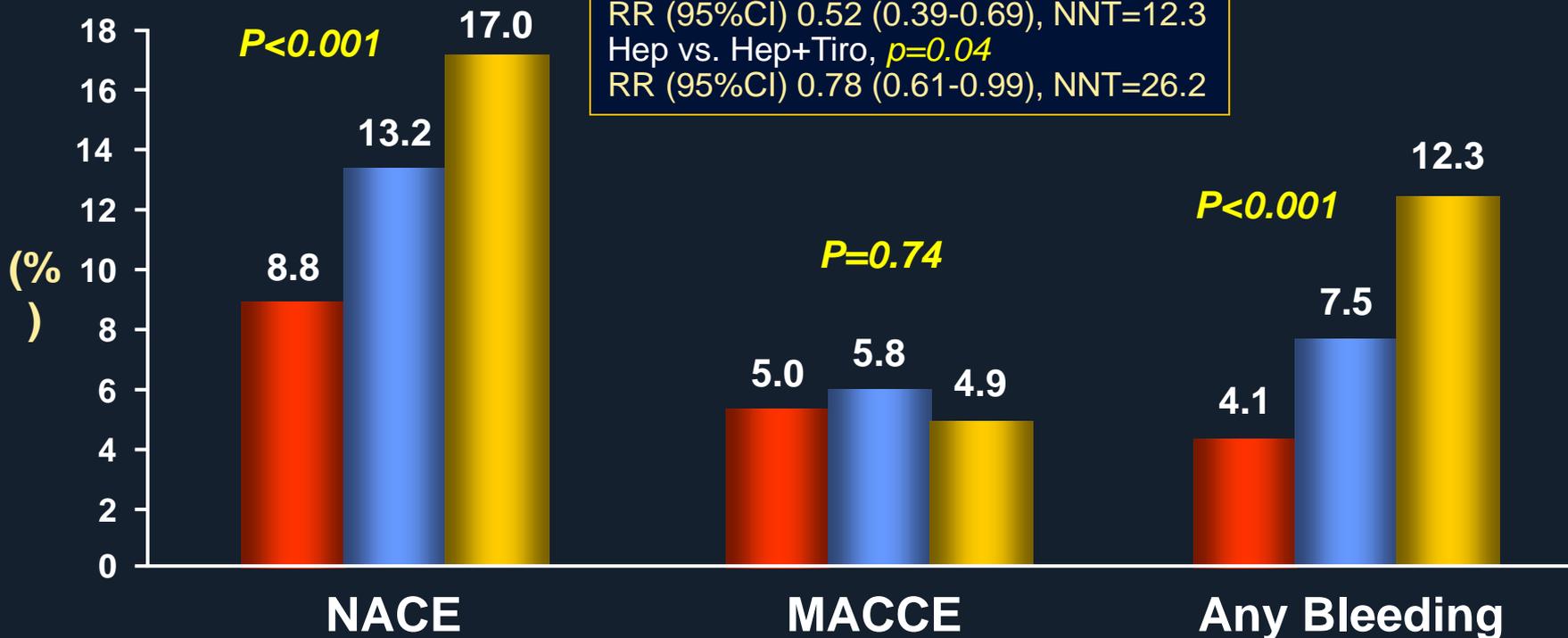
# BRIGHT: Primary and Major Secondary Endpoint Events at 30 Days



■ Bivalirudin (n=735) ■ Heparin (n=729) ■ Heparin + Tirofiban (n=730)

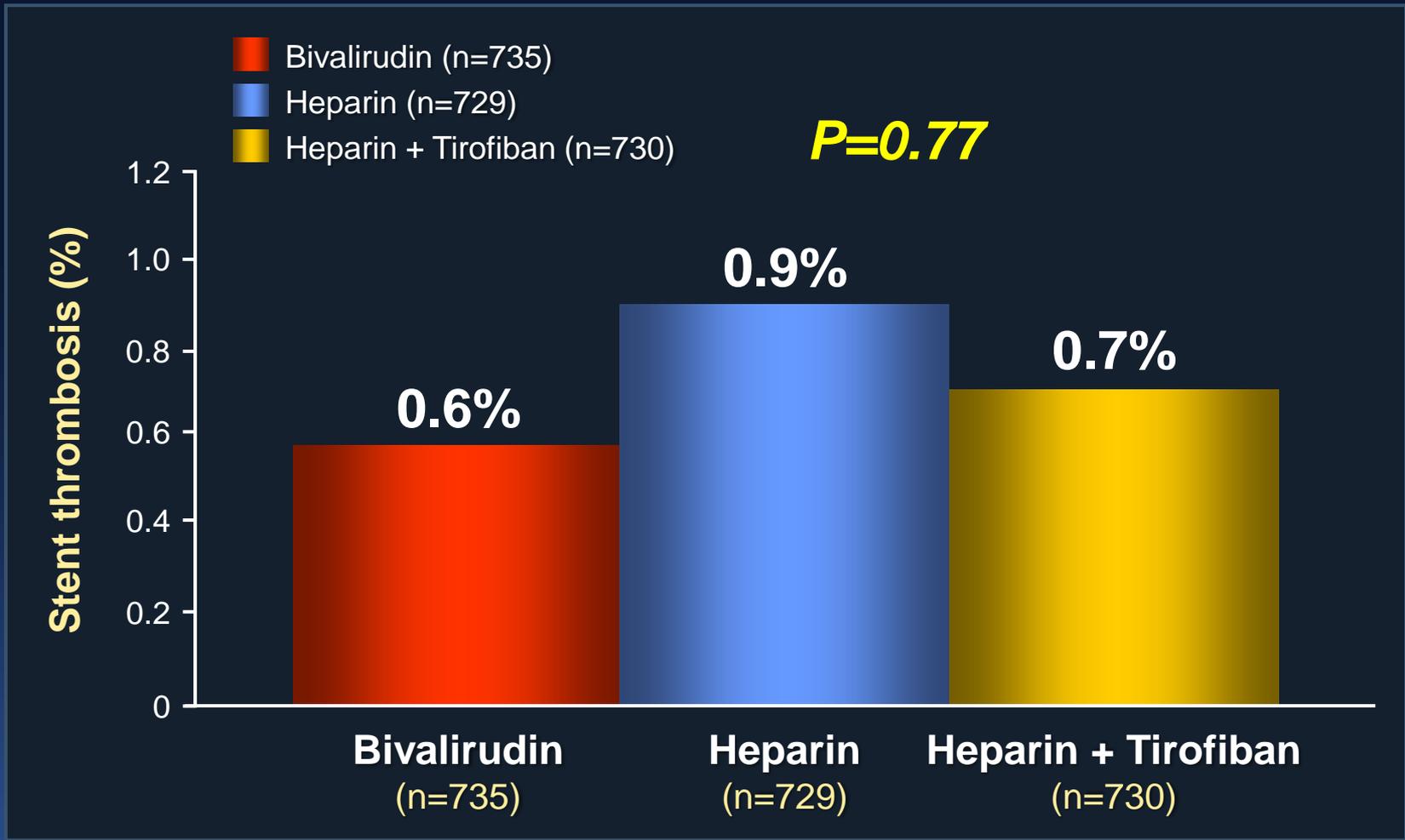
## Primary endpoint

Biv vs. Hep,  $p=0.009$   
RR (95%CI) 0.67 (0.50-0.90), NNT=23.1  
Biv vs. Hep+Tiro,  $p<0.001$   
RR (95%CI) 0.52 (0.39-0.69), NNT=12.3  
Hep vs. Hep+Tiro,  $p=0.04$   
RR (95%CI) 0.78 (0.61-0.99), NNT=26.2





# BRIGT: Stent Thrombosis at 30 Days



# BRIGHT: Ischemic Events at 30 Days



Event	Bivalirudin (N=735)	Heparin (N=729)	Heparin + Tirofiban (N=730)	P
NACE	65 (8.8)	96 (13.2)	124 (17.0)	<0.001
MACCE	37 (5.0)	42 (5.8)	36 (4.9)	0.74
Death	13 (1.8)	13 (1.8)	15 (2.1)	0.90
Cardiac	12 (1.7)	13 (1.8)	15 (2.1)	0.81
Non-cardiac	1 (0.1)	0 (0)	0 (0)	0.37
Reinfarction	7 (1.0)	9 (1.2)	6 (0.8)	0.72
Ischemia-driven TVR	12 (1.6)	13 (1.8)	9 (1.2)	0.68
Stroke	5 (0.7)	7 (1.0)	6 (0.8)	0.84
Stent thrombosis, def/prob*	4 (0.6)	6 (0.9)	5 (0.7)	0.77
Definite	3 (0.4)	5 (0.7)	4 (0.6)	0.72
Probable	1 (0.1)	1 (0.1)	1 (0.1)	1.00
Acute (<24 hrs)	2 (0.3)	2 (0.3)	2 (0.3)	1.00
Subacute (1-30 days)	2 (0.3)	4 (0.6)	3 (0.4)	0.66

\* Patients who received stent implantation

# HEAT PPCI: Design and enrollment

1917 STEMI pts scheduled for emergency angiography at a single center between Feb 2012–Nov 2013\*

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

1829 eligible for recruitment were randomized 1:1

Assigned to Heparin\* (n=914)

\*70 U/kg

Assigned to Heparin\* (n=907)

Assigned to Bivalirudin (n=915)

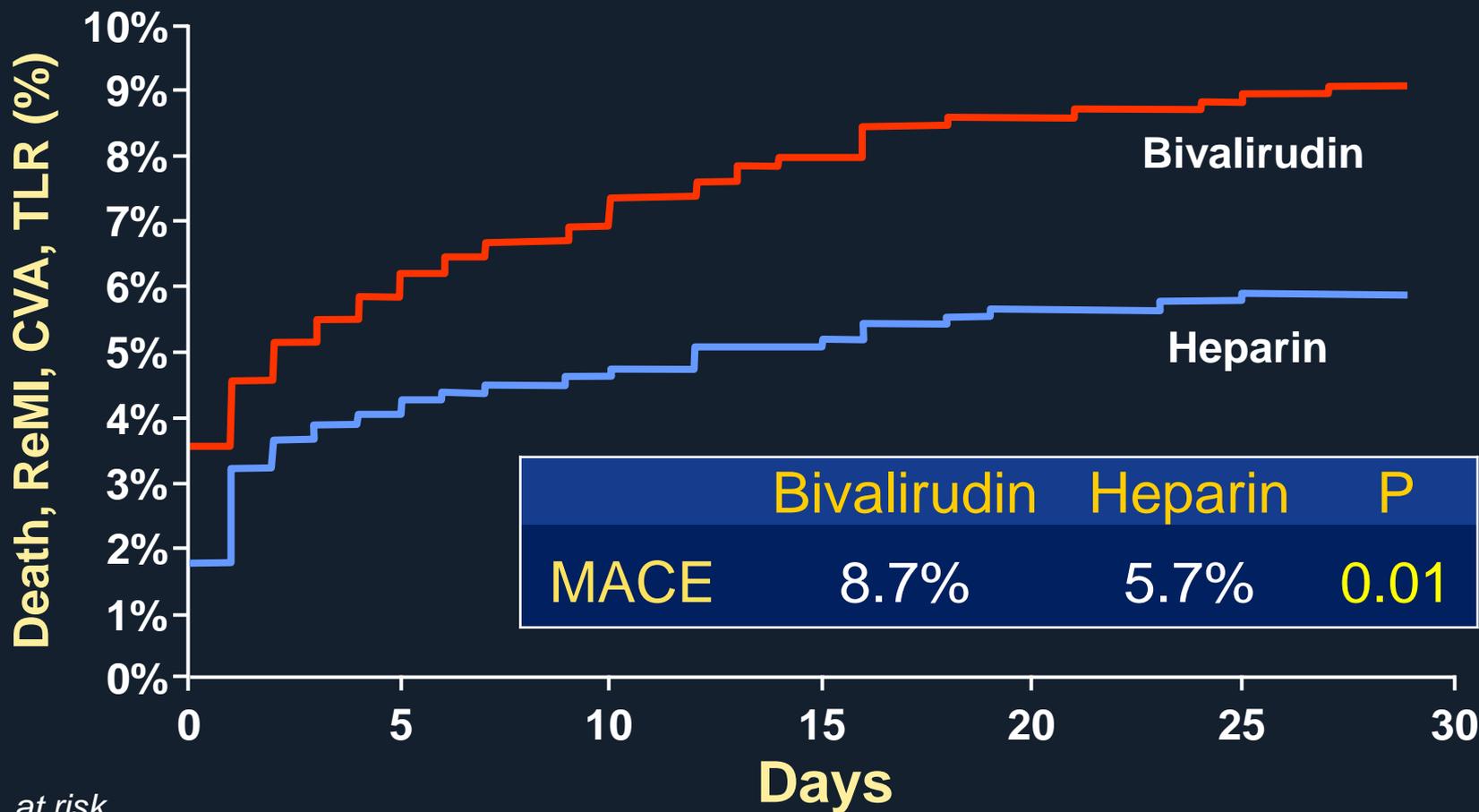
Assigned to Bivalirudin (n=905)

## Exclusion Criteria

- Active bleeding at presentation
- Factors precluding oral DAPT
- Intolerance or contraindication to trial medications
- Previous enrolment in this trial

17 (1%) refused post procedure consent and were withdrawn

# HEAT PPCI: 30-Day MACE



<u>No. at risk</u>						
Heparin	907	871	866	862	857	856
Bivalirudin	905	853	844	835	830	828

# HEAT PPCI: MACE Outcomes

	Bivalirudin (n=905)	Heparin (n=907)
Any MACE	79 (8.7%)	52 (5.7%)
- Death	46 (5.1%)	39 (4.3%)
- CVA	15 (1.6%)	11 (1.2%)
- Reinfarction	24 (2.7%)	8 (0.9%)
- TLR	24 (2.7%)	6 (0.7%)

# HEAT PPCI: Stent Thrombosis

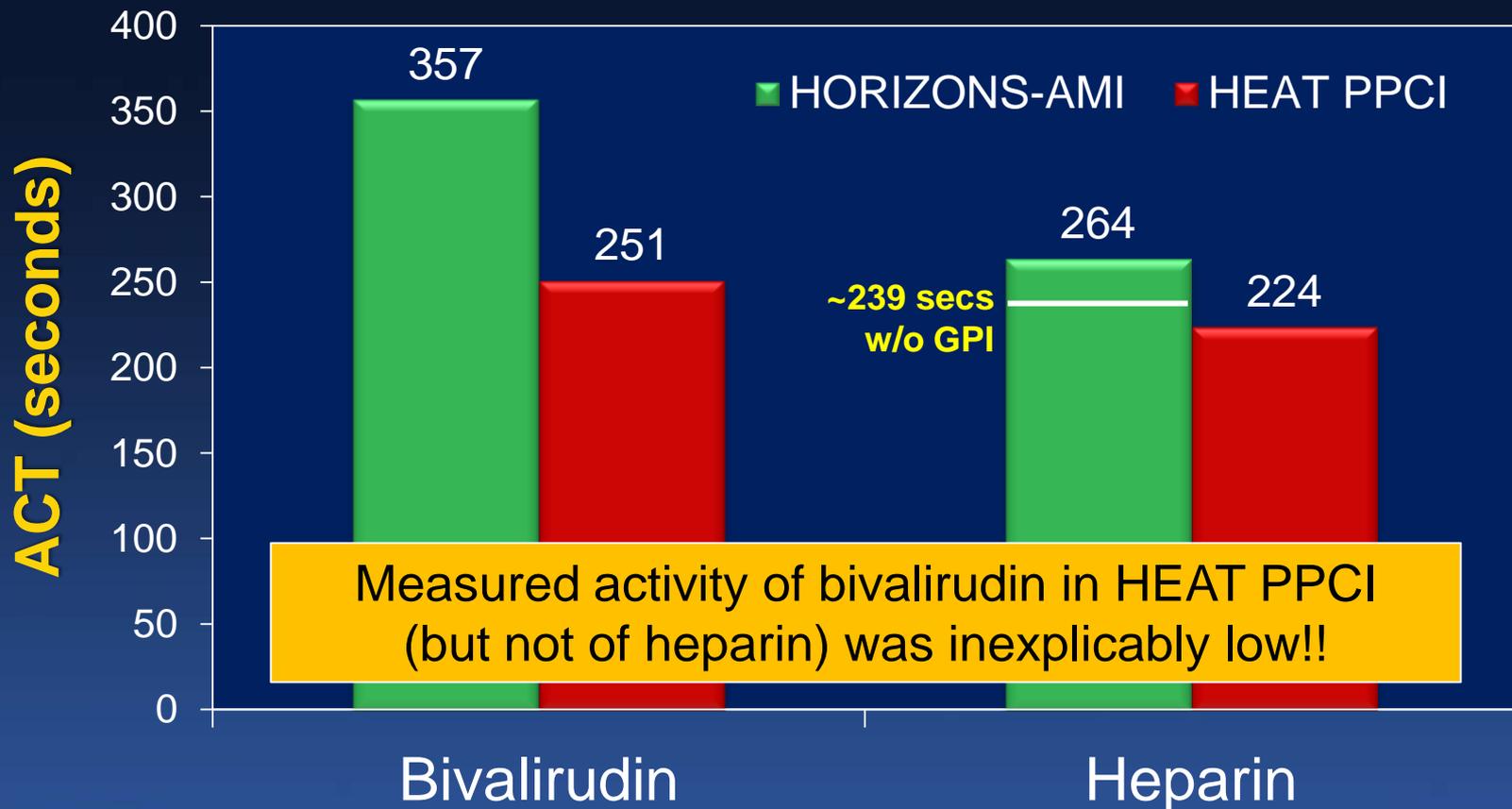
ARC definite or probable stent thrombosis

	Bivalirudin (n=905)	Heparin (n=907)
Definite or probable	24 (3.4%)	6 (0.9%)
- Definite	23 (3.3%)	5 (0.7%)
- Probable	1 (0.1%)	1 (0.1%)
- Acute	20 (2.9%)	6 (0.9%)
- Subacute	4 (0.6%)	0 (0%)

2-3x higher than in other trials

Why were the rates of acute stent thrombosis higher in HEAT PPCI than in any other bivalirudin STEMI trial?

## Median activated clotting time post bolus



# HEAT PPCI: ACT\* and GPI bailout Bivalirudin arm (n=915)

	N	Measure
ACT 5-15 mins after bolus	806 (88%)	251 [229, 285] sec
ACT end-procedure	771 (84%)	246 [229, 270] sec
Bivalirudin rebolus anytime**	12.7%	<div style="border: 2px solid red; padding: 5px;">                     ~25% &lt;229 seconds; rebolus rate should have been ~25%                 </div>
GPI bailout	13.5%	

\*Actalyke XL MAX-ACT system

\*\*By protocol, rebolus for ACT <225 seconds

# HEAT PPCI: Safety Outcomes

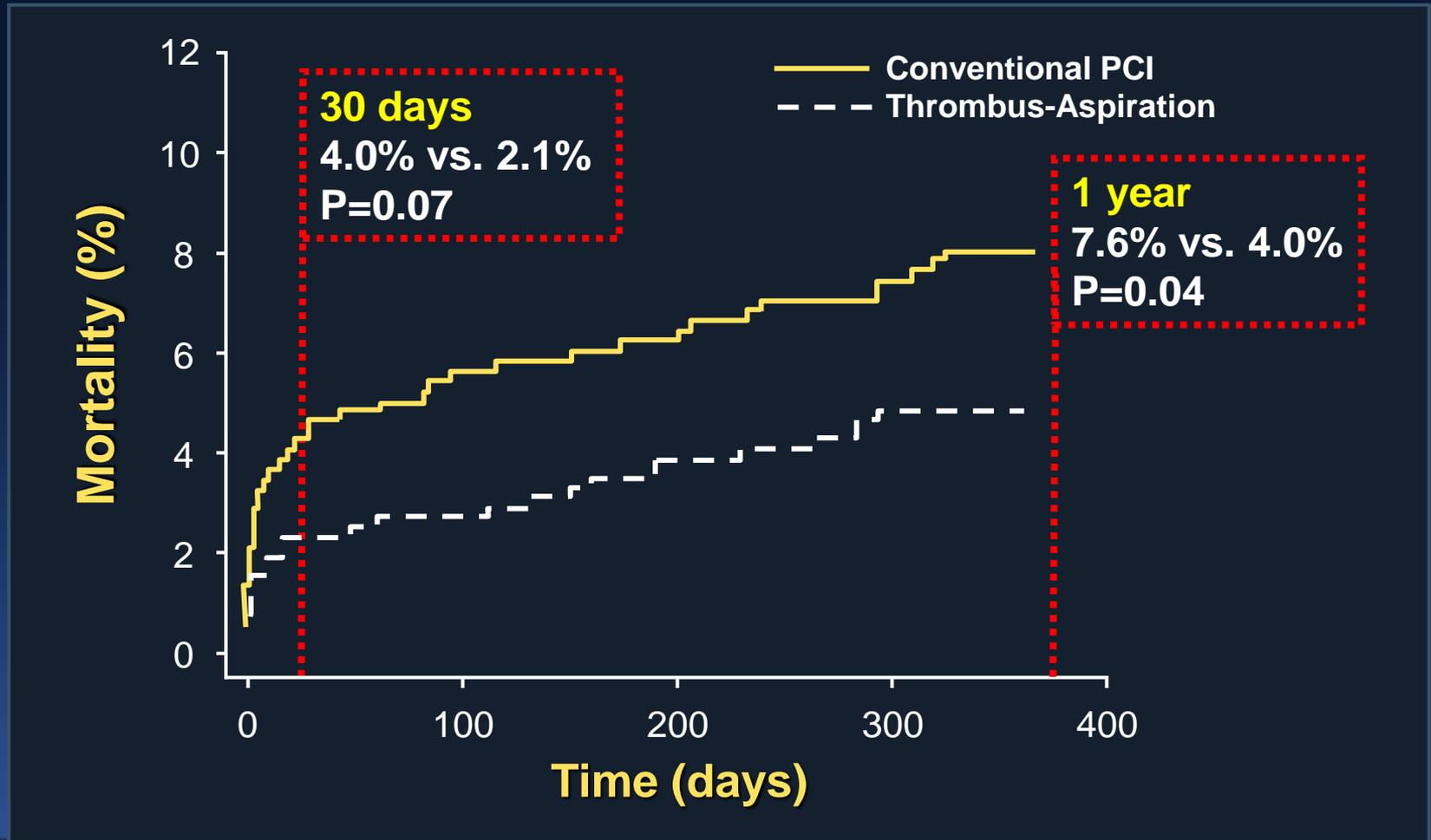
	Bivalirudin (n=905)	Heparin (n=907)	P
BARC 2-5	115 (12.7%)	126 (13.9%)	0.54
- BARC 3-5	32 (3.5%)	28 (3.1%)	0.59
- BARC 2	83 (9.2%)	98 (10.8%)	0.25
Thrombocytopenia (moderate/severe)	6 (0.8%)	6 (0.8%)	0.99

# The Bottom Line

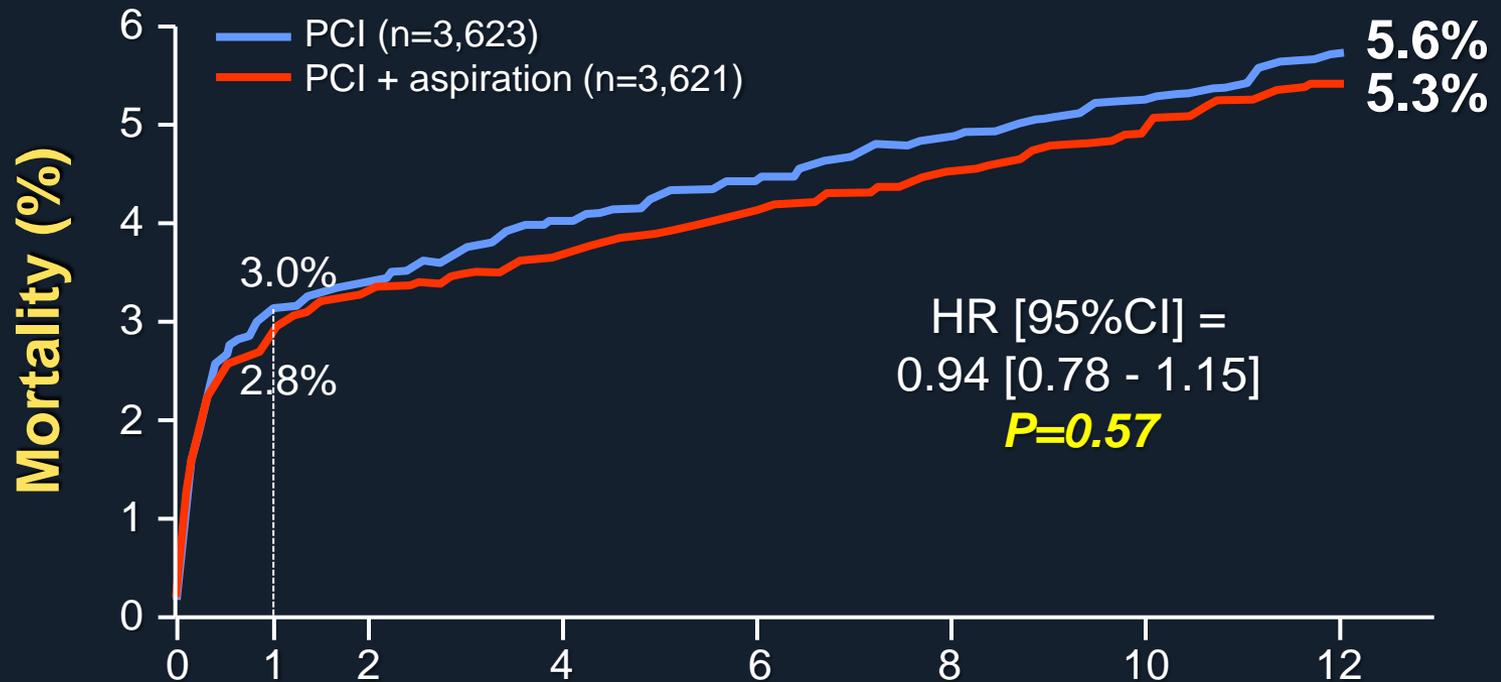
**I don't know exactly why bivalirudin  
“didn't work” at the Liverpool Heart  
and Chest Hospital, but it didn't!**

The results from any single center trial must be interpreted very cautiously, especially when it disagrees with the outcomes from multicenter trials

# **TAPAS:** 1,071 pts with STEMI undergoing primary PCI at a single center randomized to manual aspiration vs. control



# TASTE 7,244 pts with STEMI undergoing primary PCI at 31 centers randomized to manual aspiration vs. control



### No. at risk

	0	1	2	4	6	8	10	12
PCI + asp	3621	3500	3485	3470	3456	3440	3425	3425
PCI	3623	3503	3481	3466	3450	3435	3420	3420

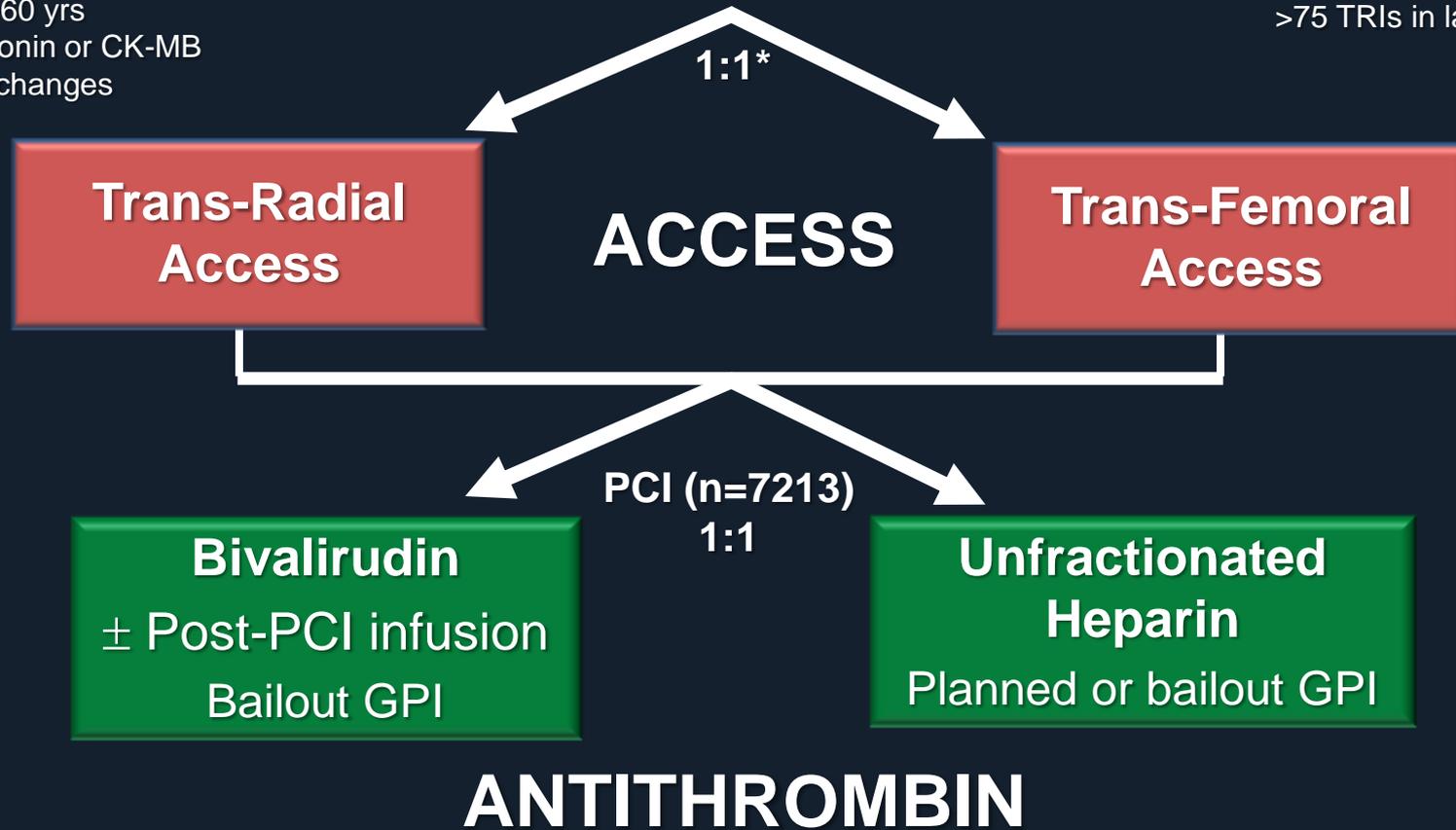
# MATRIX: Trial Design

## NSTEACS or STEMI with Invasive Management (n=8404)

+  $\geq 2$  high-risk criteria:  
 Age >60 yrs  
 $\uparrow$  Troponin or CK-MB  
 ECG changes

Aspirin + P2Y12 receptor inhibitor

At 78 EU centers with  
 >75 TRIs in last year



\* Stratified by STEMI vs. NSTEMI and P2Y12 type

PI: M. Valgimigli



# MATRIX antithrombin: Baseline Characteristics

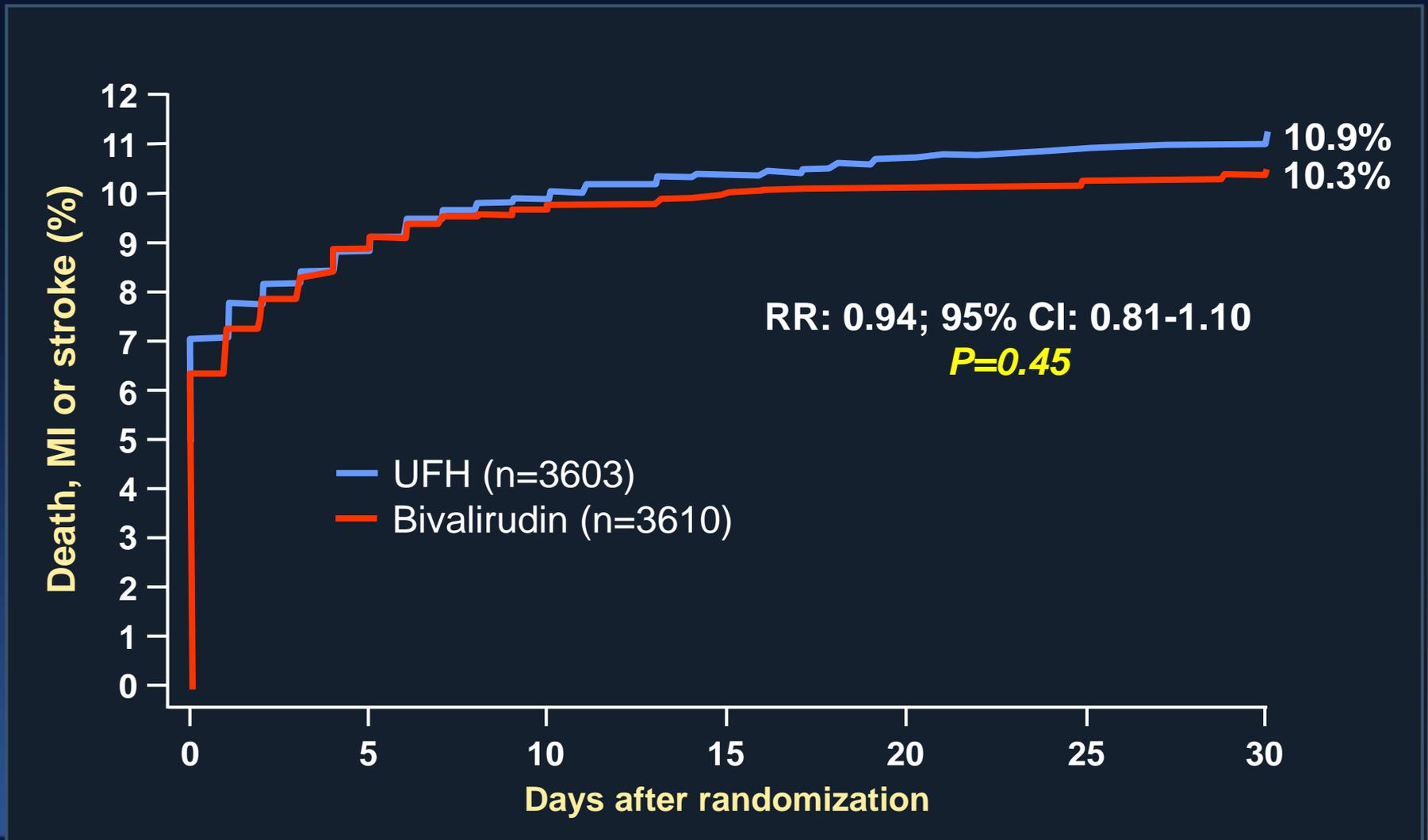
	Bivalirudin (N=3,610)	UFH (N=3,603)
Age (years)	65.4 ± 11.9	65.4 ± 11.9
Male (%)	75.7	76.7
BMI (kg/m <sup>2</sup> )	27.2 ± 4.2	27.0 ± 4.1
Previous stroke (%)	5.0	5.1
PAD (%)	8.2	7.9
Killip > 1 (%)	9.3	10.1
STEMI (%)	55.7	40.0
NSTEMI (%)	39.7	55.5
Pre-lab P2Y <sub>12</sub> inhibitor (%)	83.4	81.4
Clopidogrel	47.0	44.8
Ticagrelor or prasugrel	36.4	36.6
Pre-lab anticoagulation (%)	56.7	57.5
Enoxaparin (%)	15.0	15.3
Fondaparinux (%)	9.4	9.4
UFH (%)	32.3	32.8

# MATRIX antithrombin: Procedural Characteristics

Index Procedure	Bivalirudin (N=3,610)*	UFH (N=3,603)
PCI attempted (%)	94.2	94.6
CABG (%)	0.7	0.5
Medical Tx (%)	5.1	4.8
Medications in the lab (%)		
Clopidogrel	6.7	8.0
Ticagrelor or prasugrel	19.7	19.2
Gp IIb/IIIa inhibitor	4.6	25.8
Giant thrombus	2.2	-
Sustained no reflow	1.0	-
Other reasons	1.0	-
Treated vessel - LAD	50.7	49.2
Multivessel PCI (%)	14.1	14.4
Total stent length (mm)	31.7 ± 20	32.1 ± 20

\* 47.7% received prolonged infusion post-PCI of which 36% received 1.75 mg/kg/hr

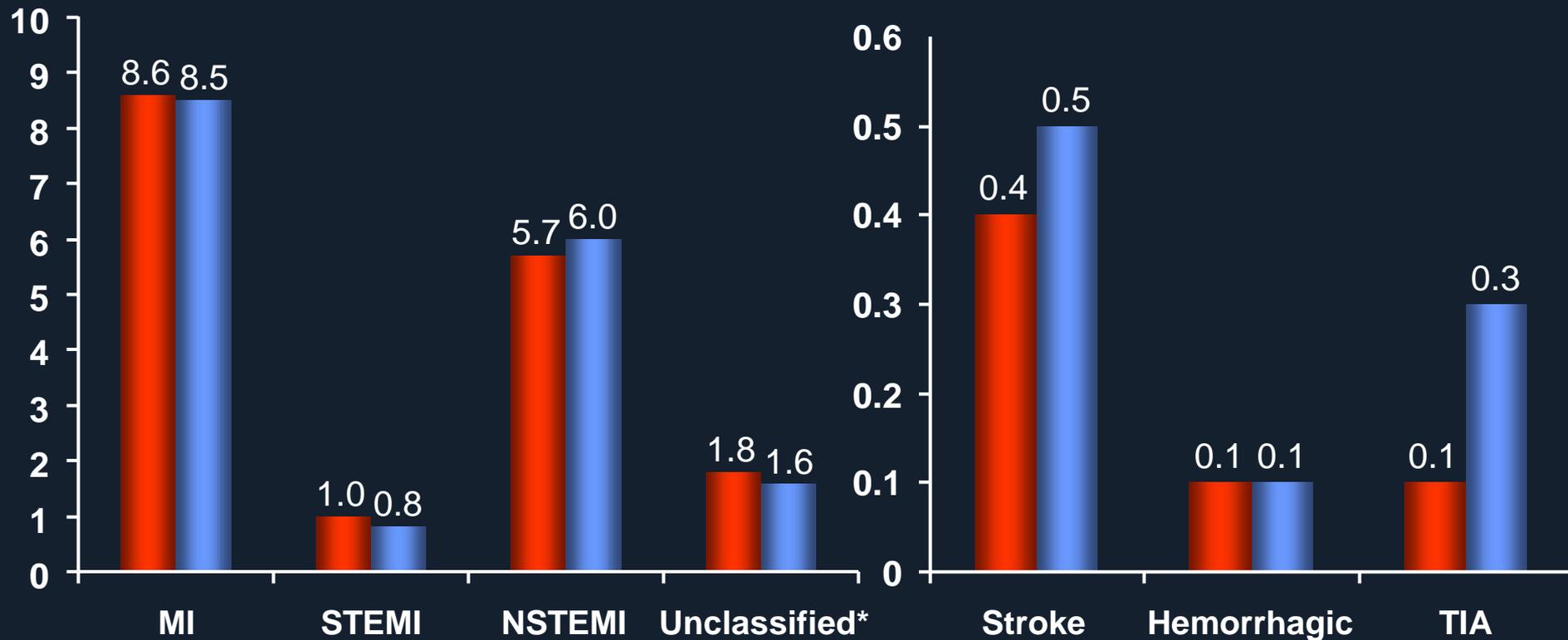
# MATRIX antithrombin: Primary EP - MACE



# MATRIX antithrombin: MI and Stroke

■ Bivalirudin (n=3610) ■ UFH (n=3603)

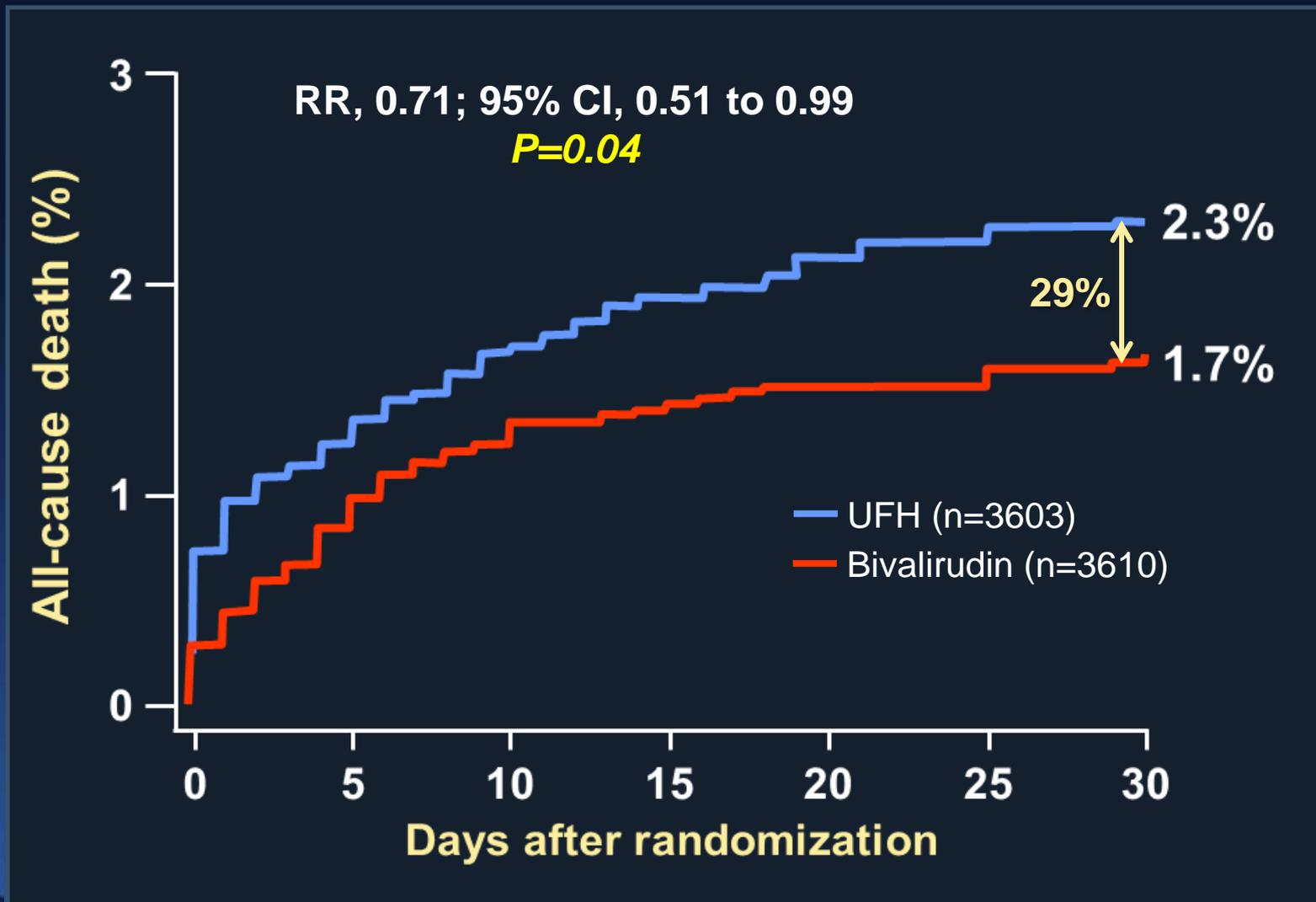
**All P=NS**



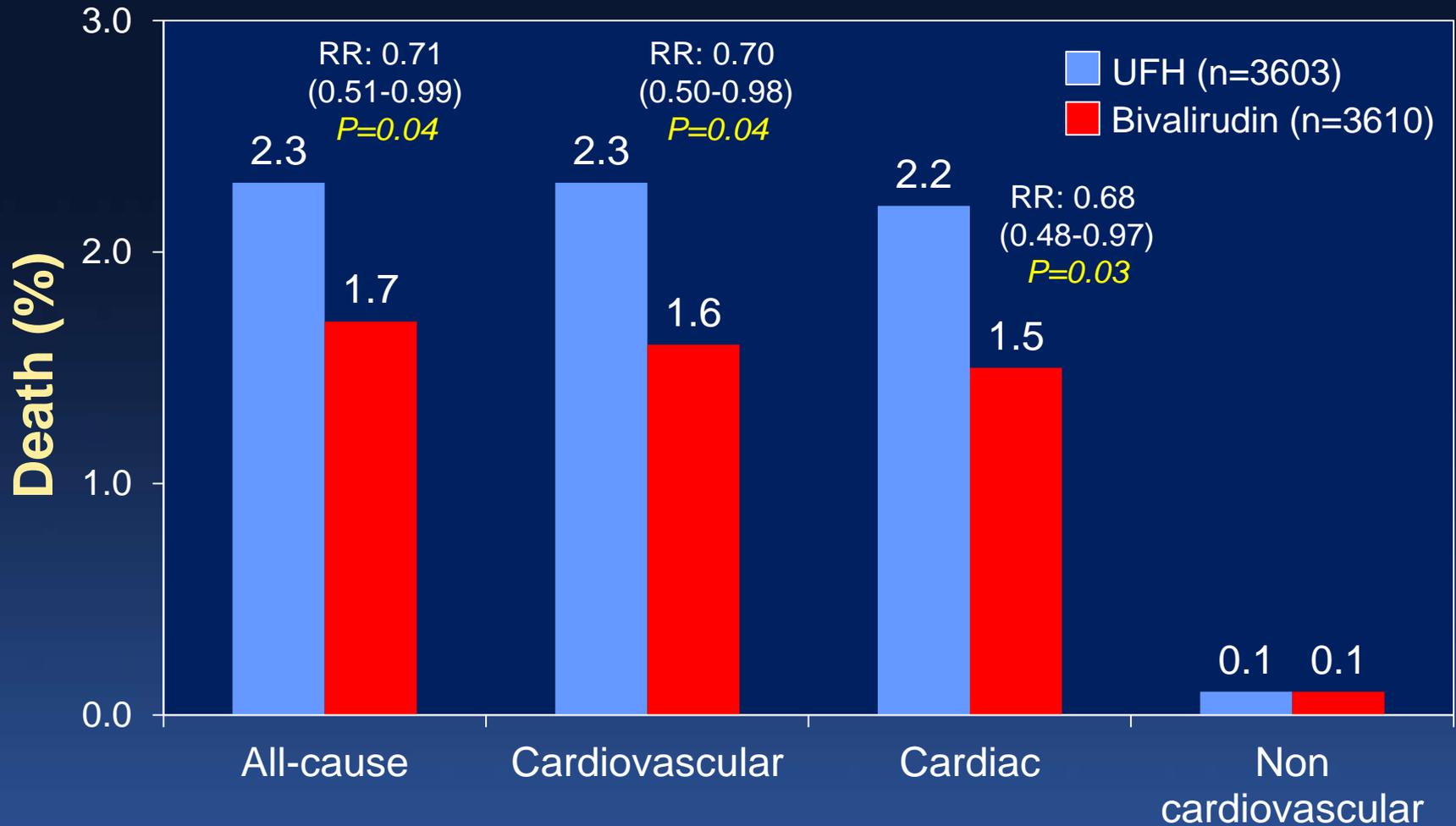
\*LBBB, paced rhythm, or unavailability of interpretable ECG



# MATRIX antithrombin: All-cause Mortality



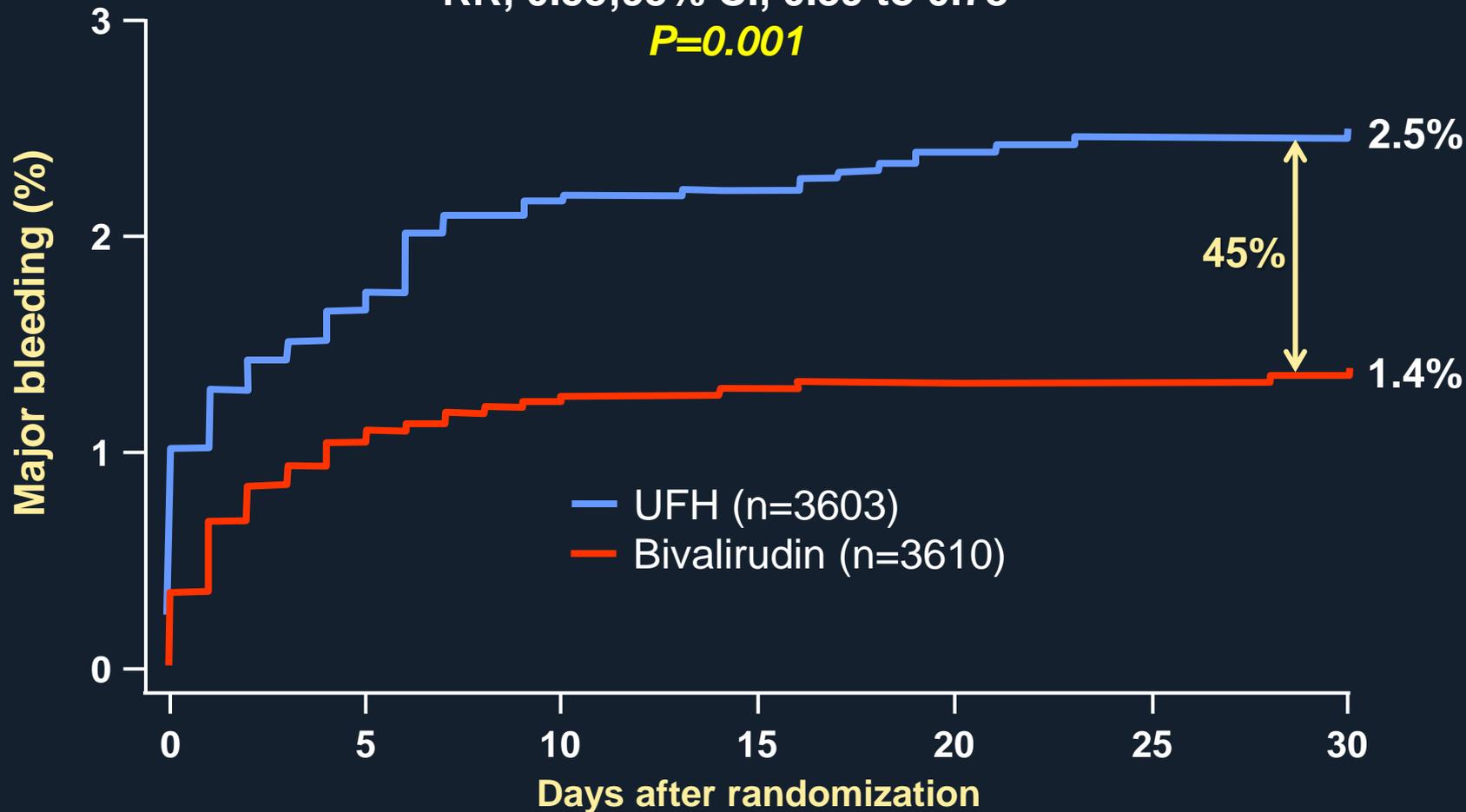
# MATRIX antithrombin: Mortality



# MATRIX antithrombin: BARC 3 or 5 Bleeding

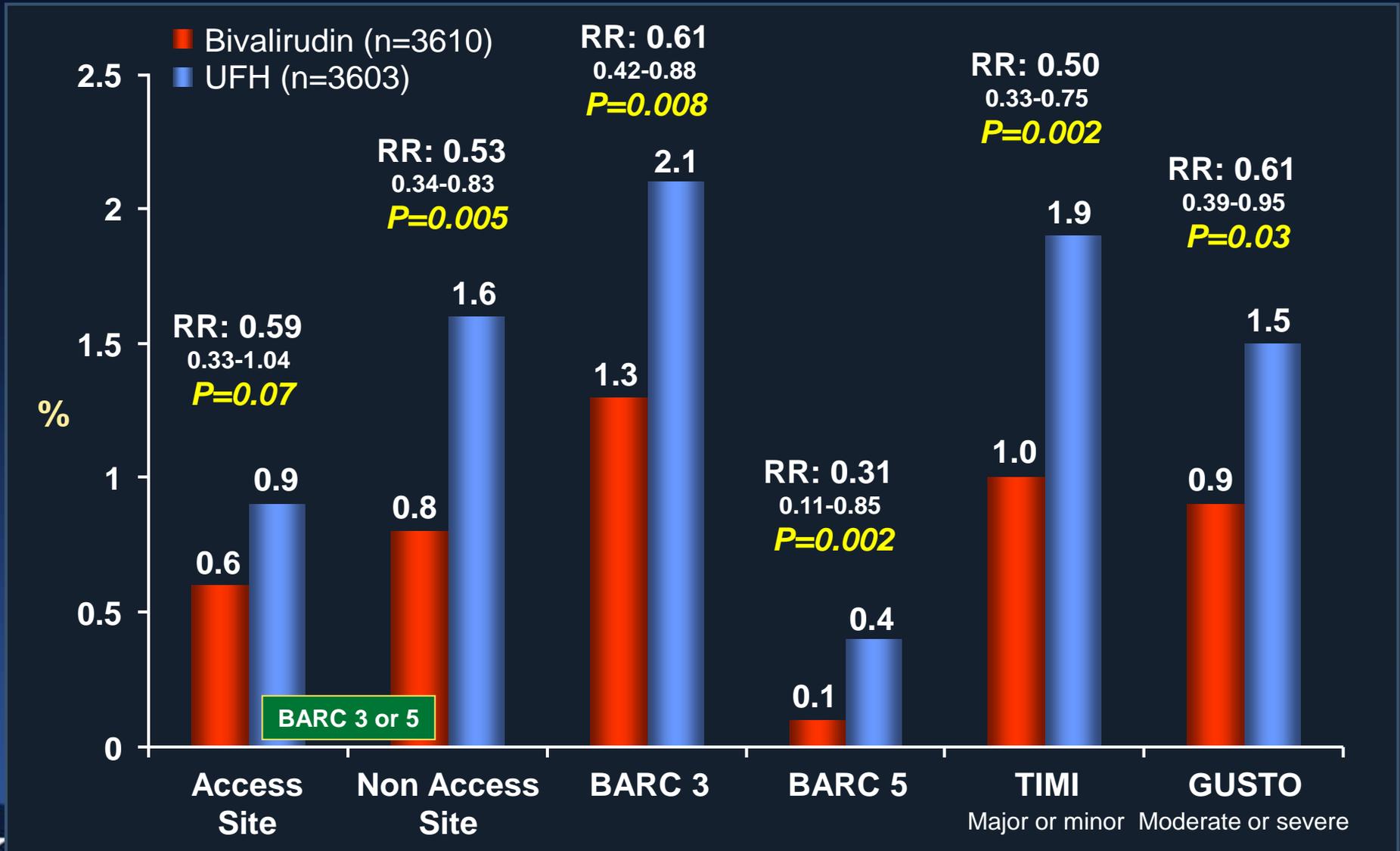
RR, 0.55;95% CI, 0.39 to 0.78

*P=0.001*

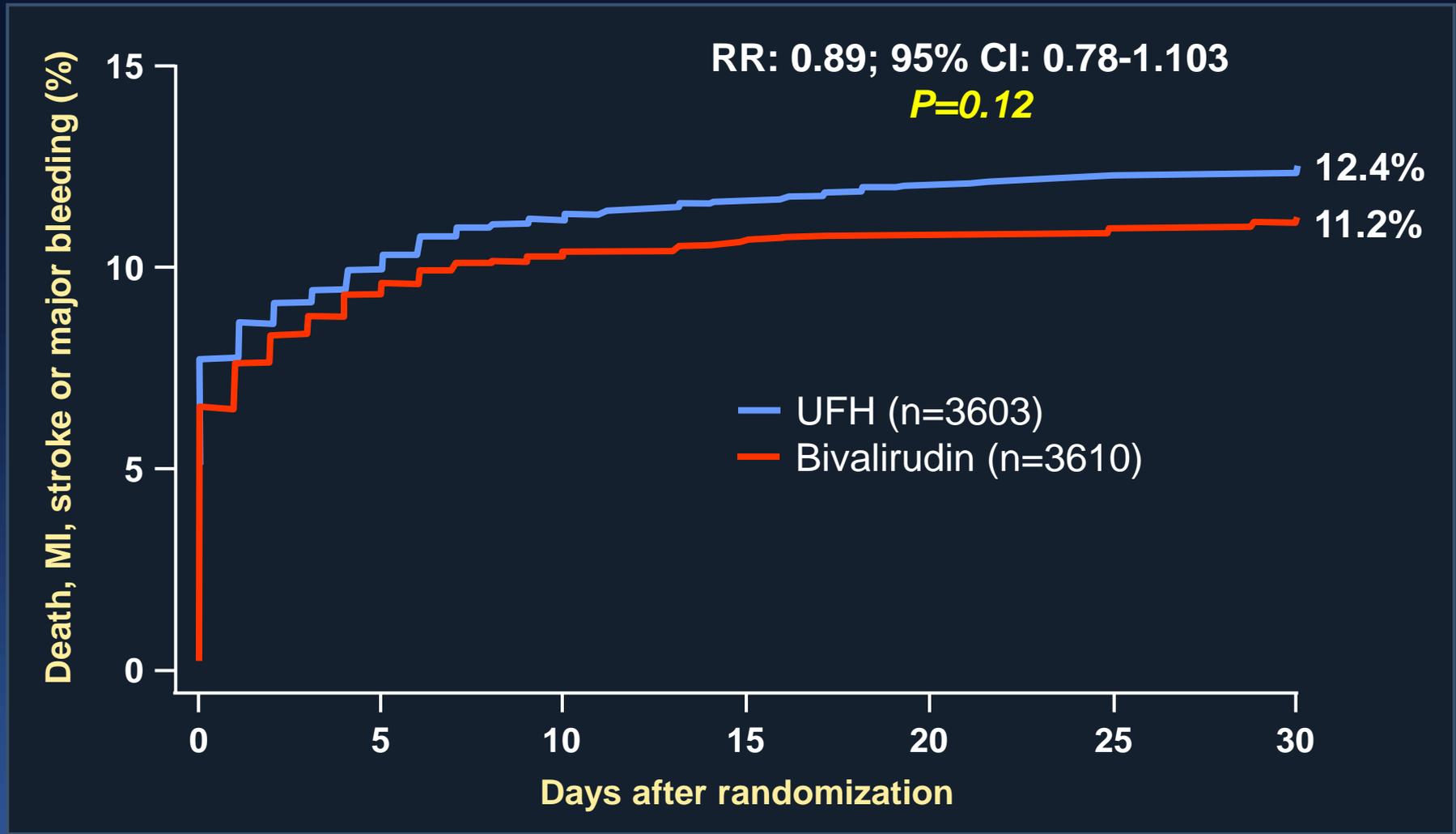




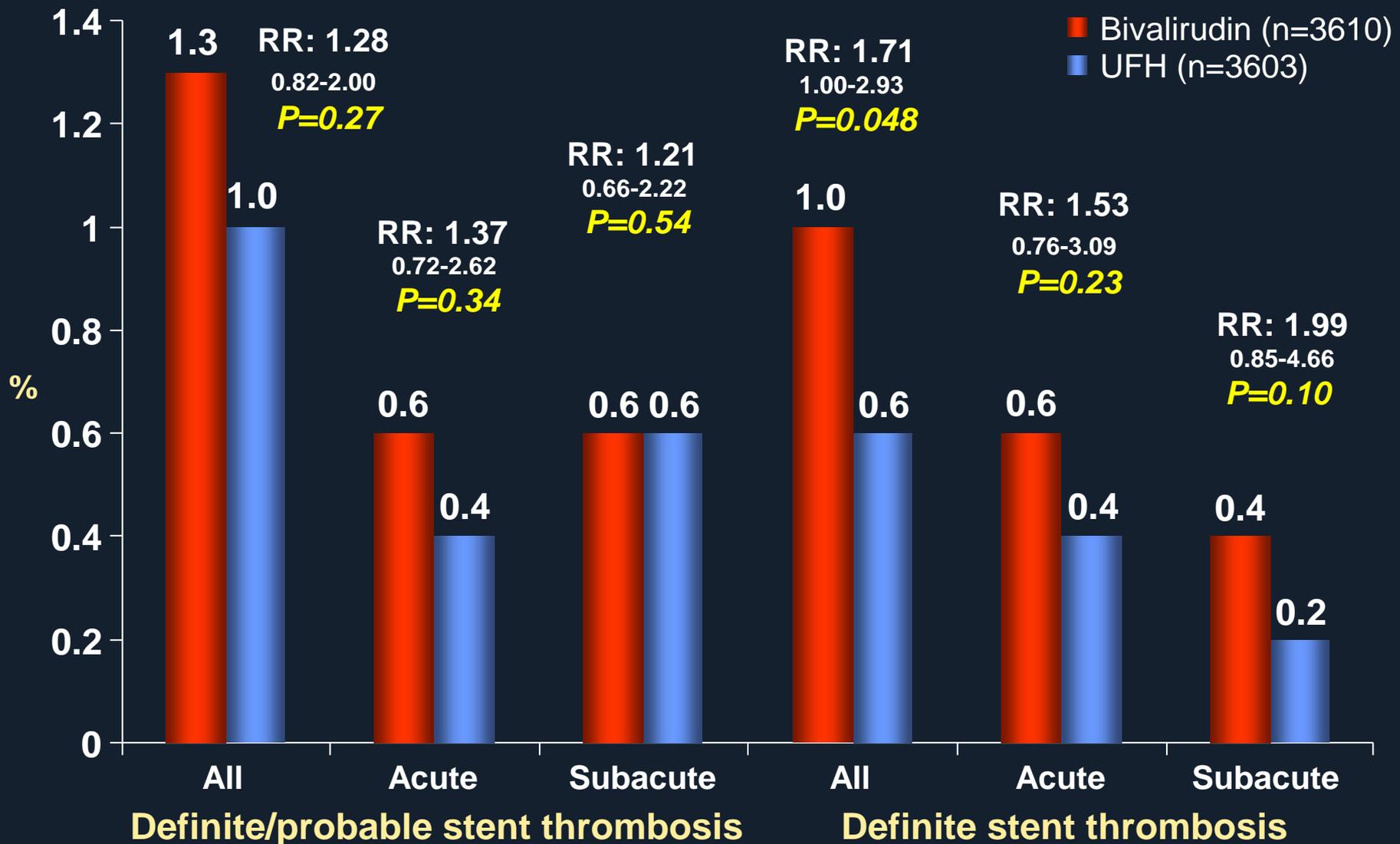
# MATRIX antithrombin: Bleeding Endpoints



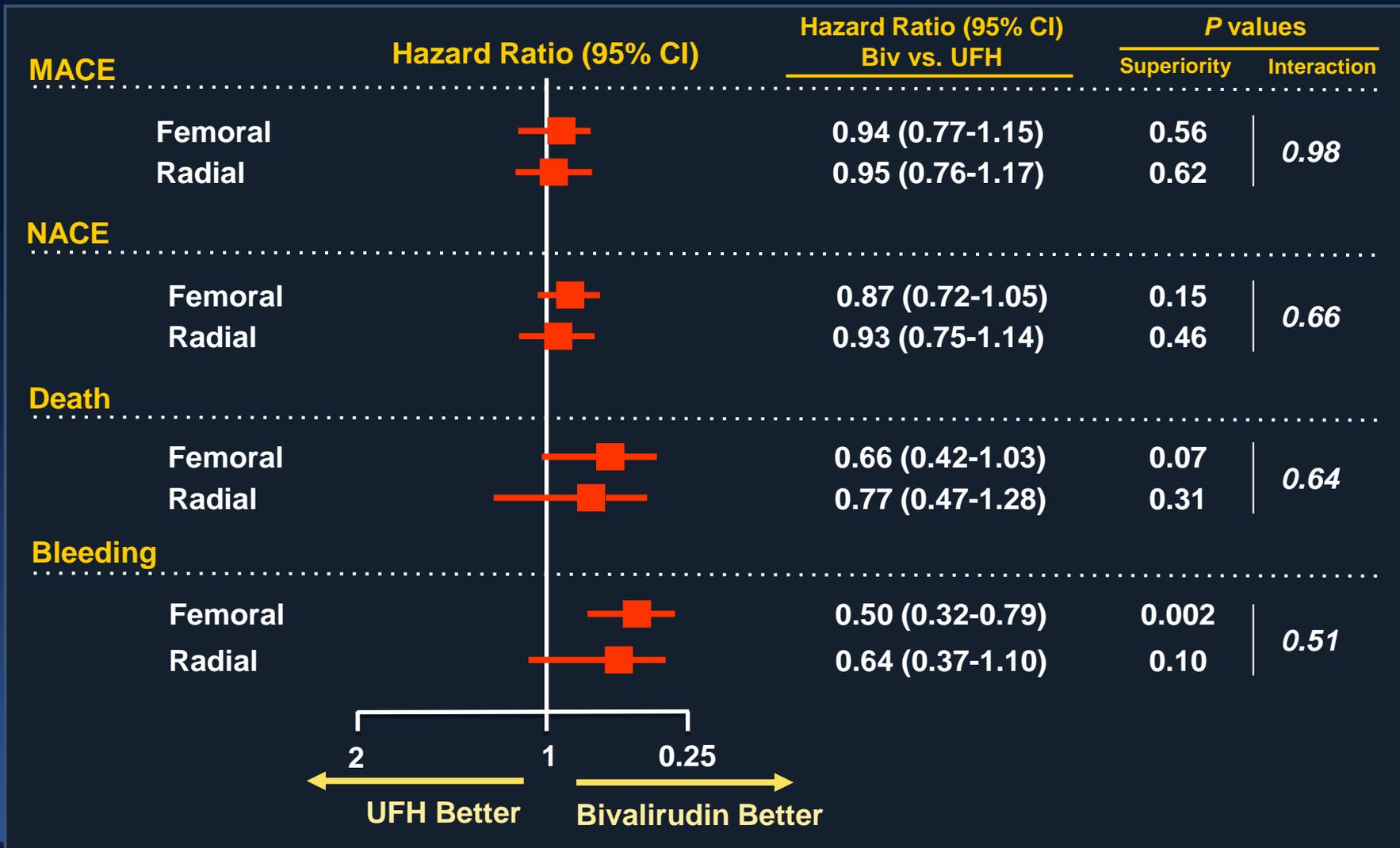
# MATRIX antithrombin: Primary EP - NACE



# MATRIX antithrombin: Stent Thrombosis



# MATRIX antithrombin: Access Site Subgroup Analysis



# MATRIX: What reduces bleeding more?

## Radial Access or Bivalirudin?

■ Bivalirudin (n=3,610)

■ Heparin (n=3,603)

■ Radial (n=4,197)

■ Femoral (n=4,207)



# Third Question

- What does the “real world” say?

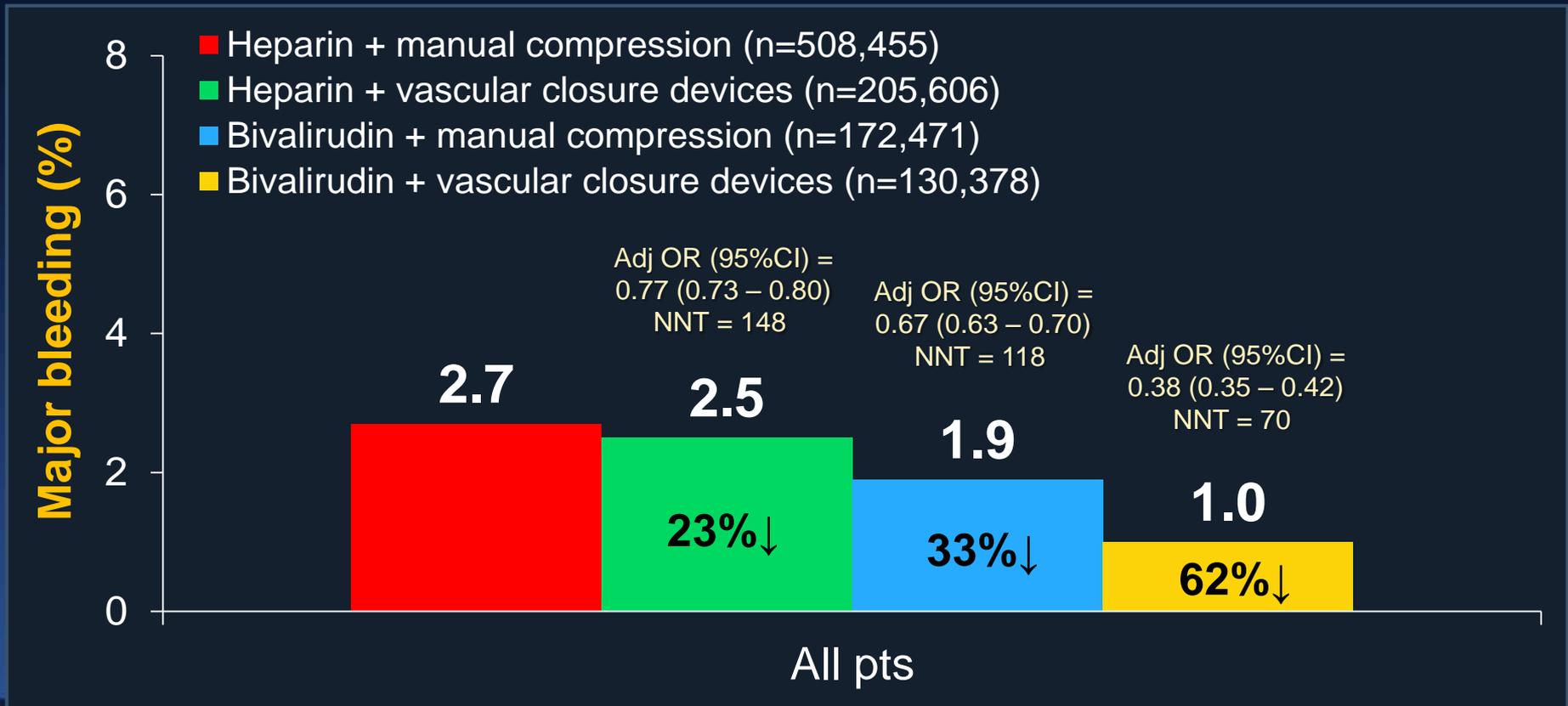


# Impact of Bleeding Avoidance Strategies

NCDR CathPCI Registry 2004-2008: PCI in 1,522,935 pts

Manual compression alone, closure devices, bivalirudin, or both were used in 35%, 24%, 23%, and 18% of pts, respectively.

## Propensity-adjusted major bleeding

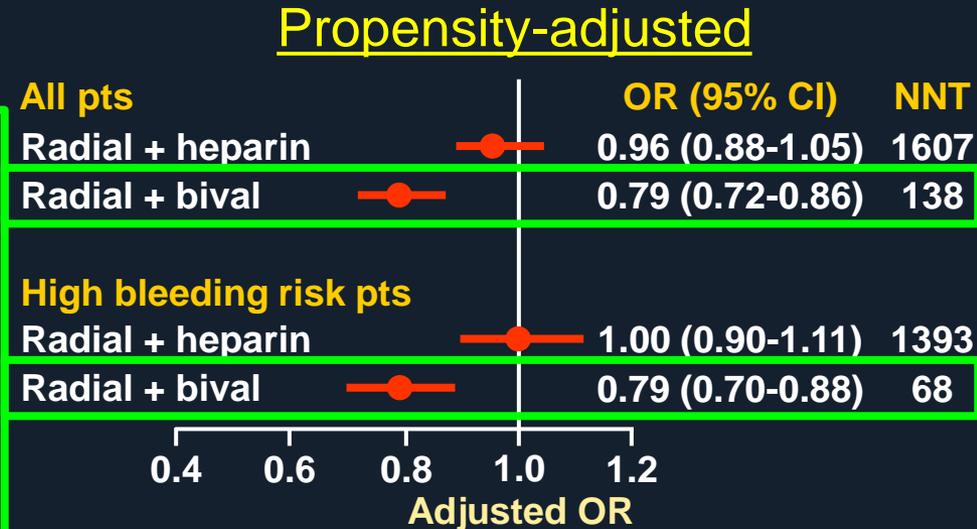
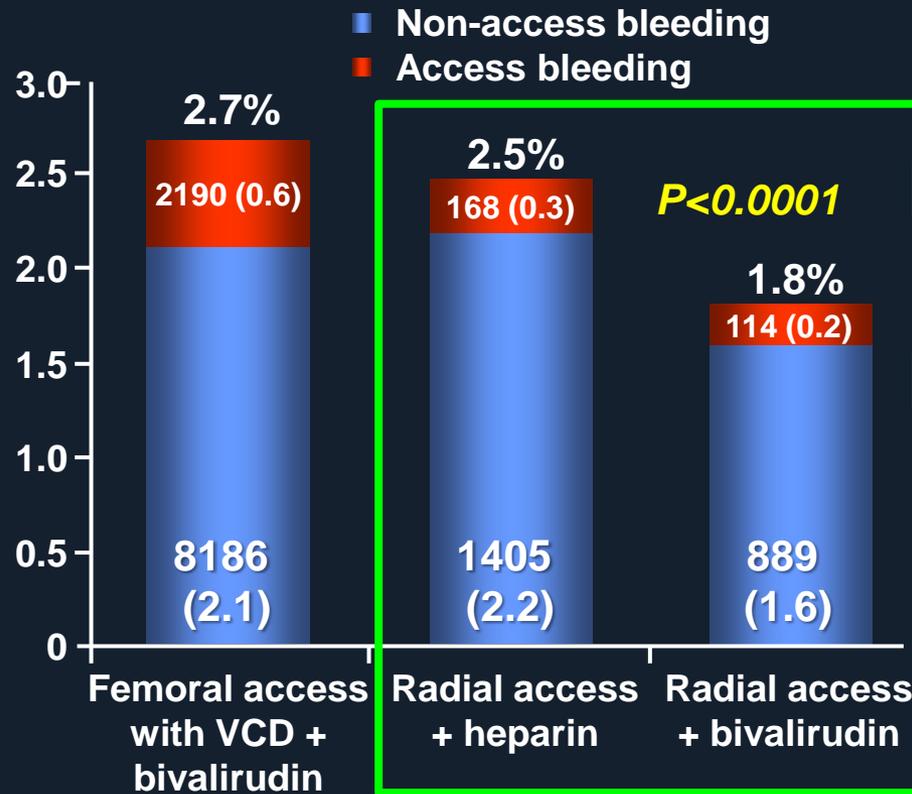


# Impact of Bivalirudin in Radial Procedures

NCDR CathPCI Registry 2009-2012: **PCI in 501,017 pts**

Femoral access with closure devices, radial access with heparin, and radial access with bivalirudin were used in 76%, 13%, 11%, and 18% of pts.

## Major bleeding:



Radial access/bivalirudin combination was used less frequently in pts at highest risk for bleeding

# Conclusions: Bivalirudin vs. Heparin for Primary PCI Even with Radial !

- Compared to heparin alone, heparin + GPI reduces death, reinfarction and recurrent ischemia, at the cost of increased bleeding and thrombocytopenia
- Compared to heparin alone or heparin + GPI, bivalirudin reduces bleeding and thrombocytopenia, and may reduce cardiac mortality at the cost of a 1% increase in acute stent thrombosis
  - The increase in acute stent thrombosis with bivalirudin is mitigated by a 3-4 hour post-PCI bivalirudin infusion (PCI dose)