

UFH Versus Bivalirudin in ACS: Which One Should I Use?

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Disclosures

- **None**

Large-scale Bivalirudin RCTs in ACS

NSTEACS RCTs

ACUITY (n=13,819)
ISAR-REACT 4 (n=1721) } multicenter

STEMI RCTs

HORIZONS-AMI (n=3602)
EUROMAX (n=2198)
BRIGHT (n=2194) } multicenter
HEAT PPCI (n=1812) ---single center

STEMI + NSTEMI RCTs

MATRIX (n=7213) ---multicenter

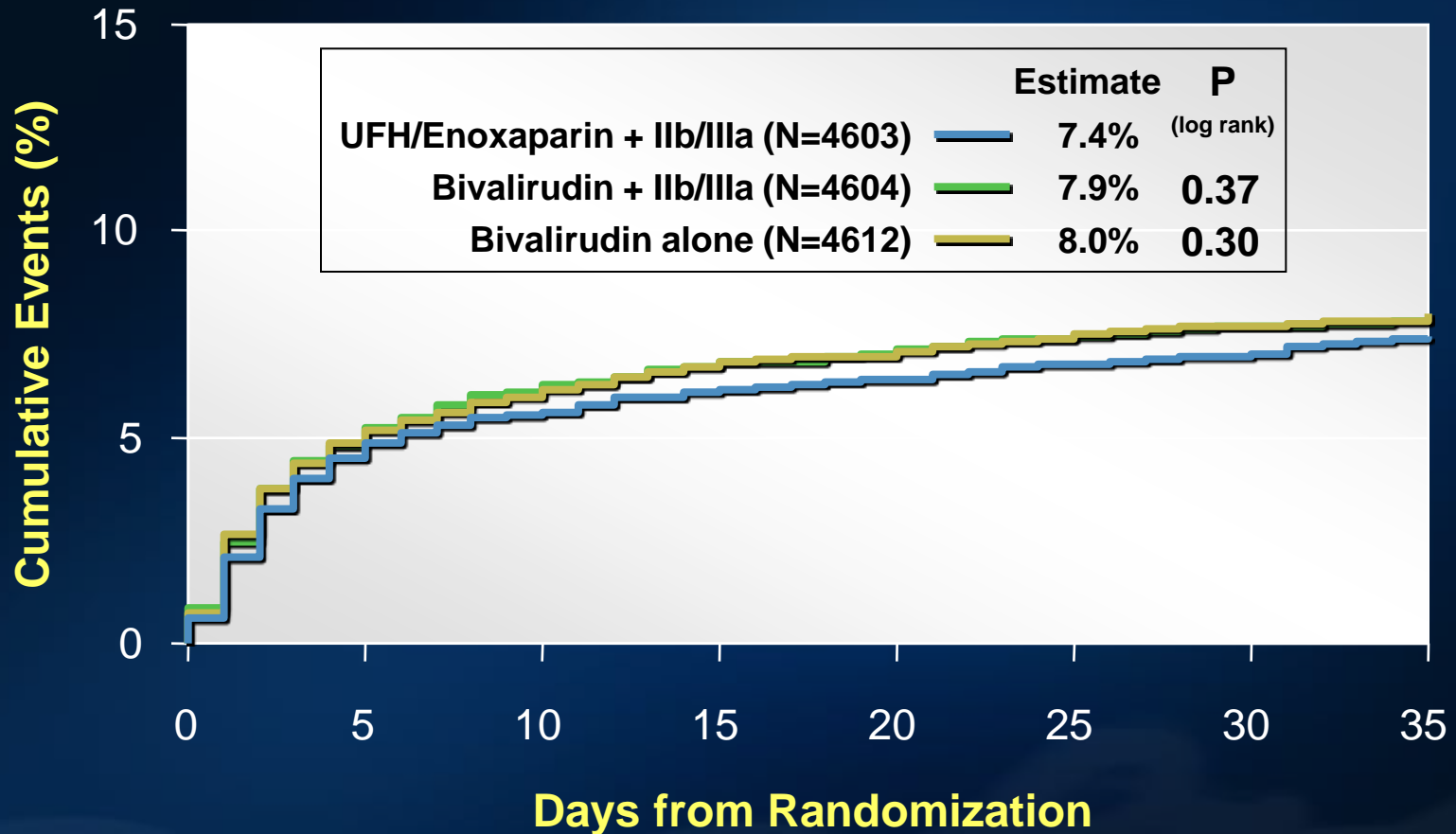
NSTEACS: Pathophysiology



Ruptured plaque with sub-occlusive thrombus

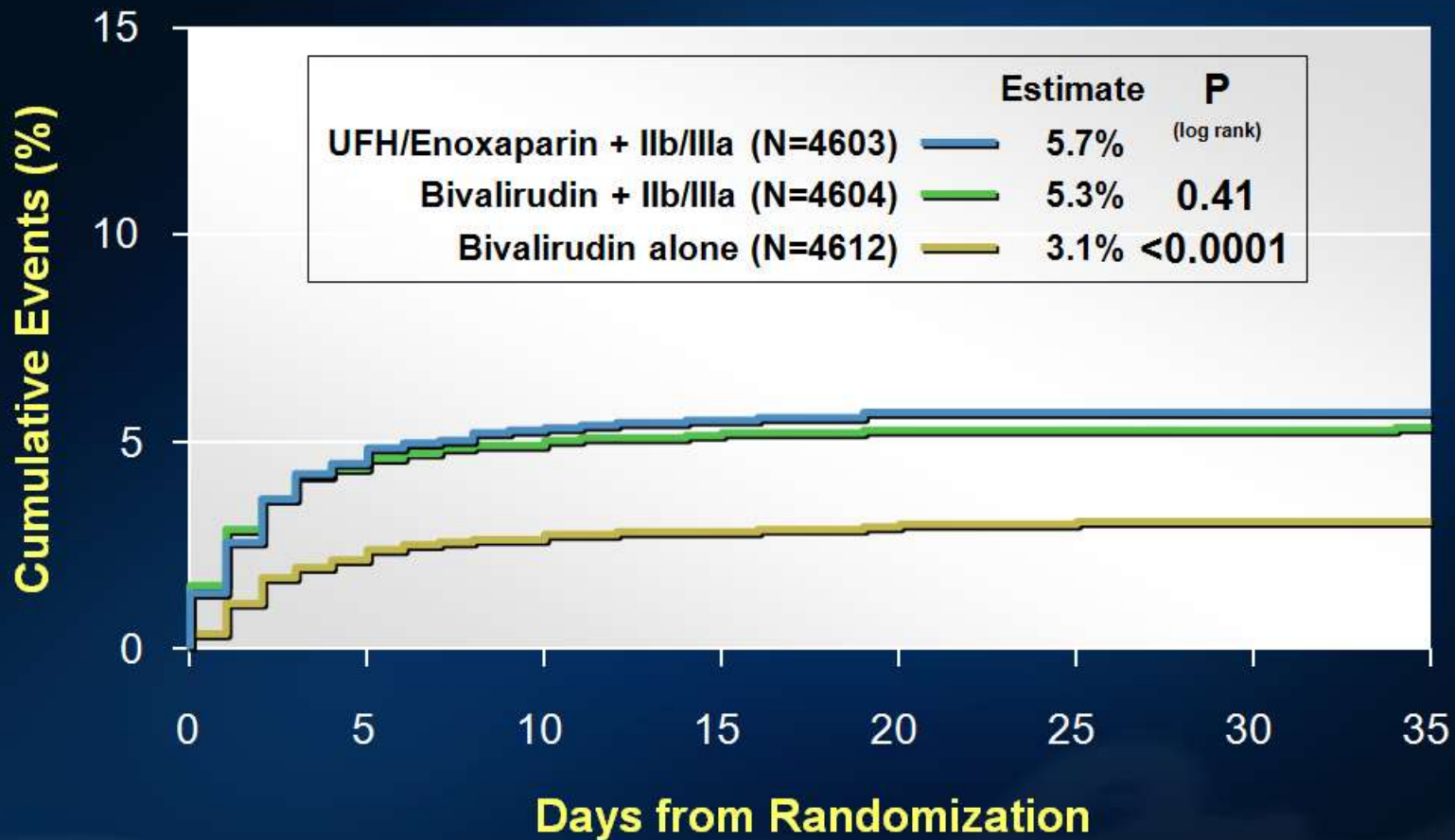
ACUITY: Ischemic MACE (n=13,819)

UFH/Enoxaparin + GPI vs. Bivalirudin + GPI vs. Bivalirudin Alone

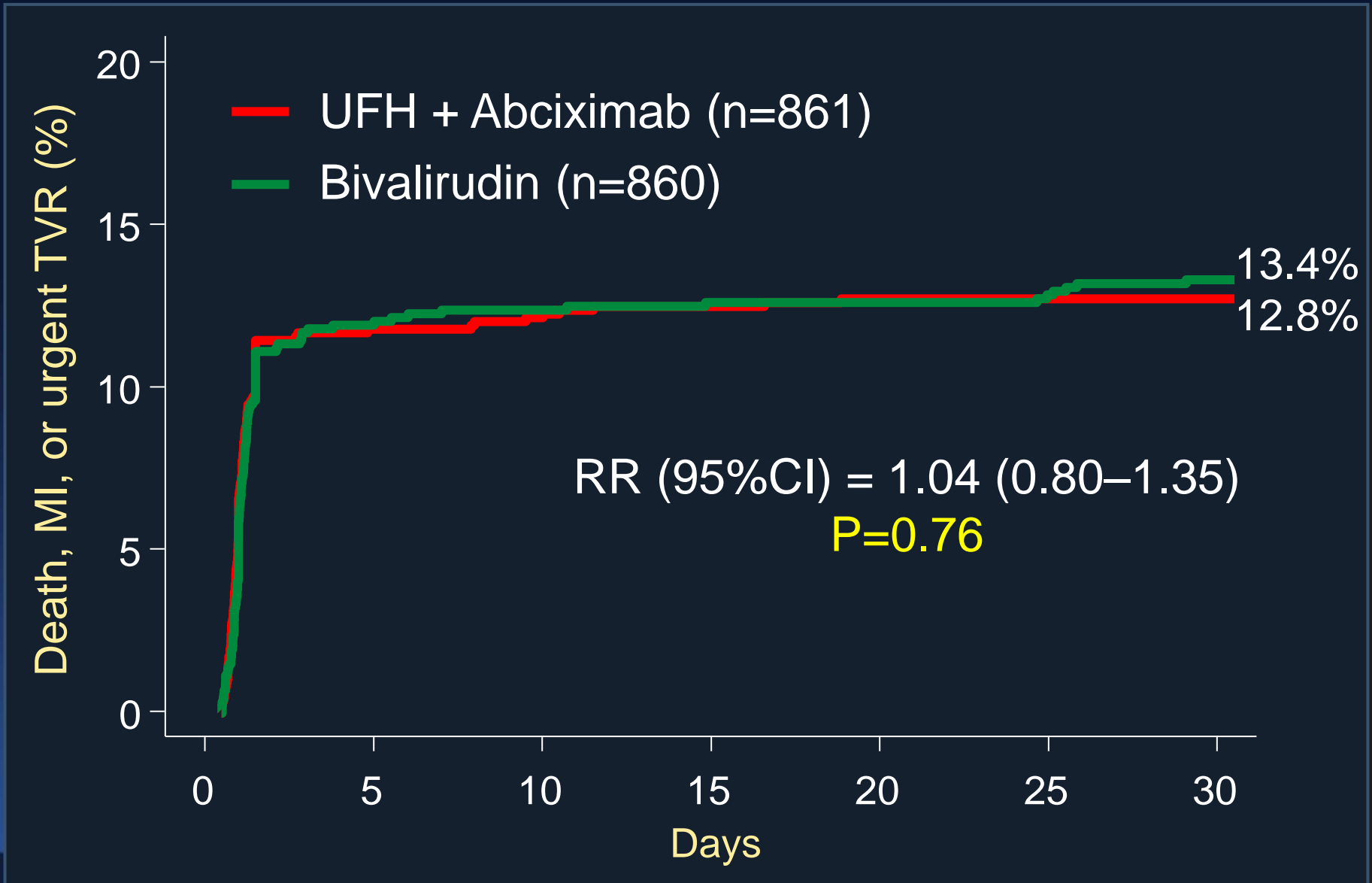


ACUITY: Major Bleeding (n=13,819)

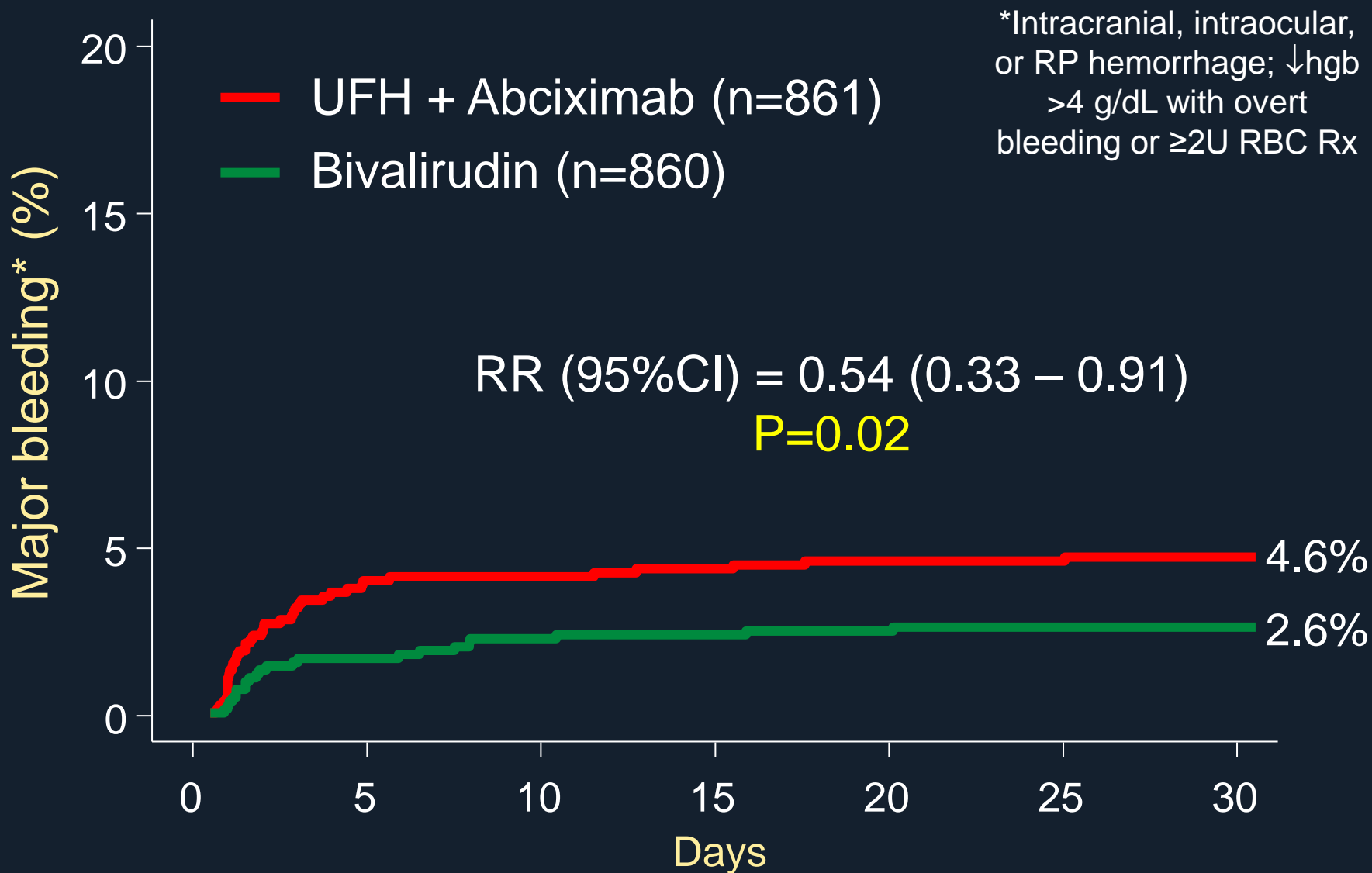
UFH/Enoxaparin + GPI vs. Bivalirudin + GPI vs. Bivalirudin Alone



ISAR-REACT 4: Ischemic MACE (n=1721)

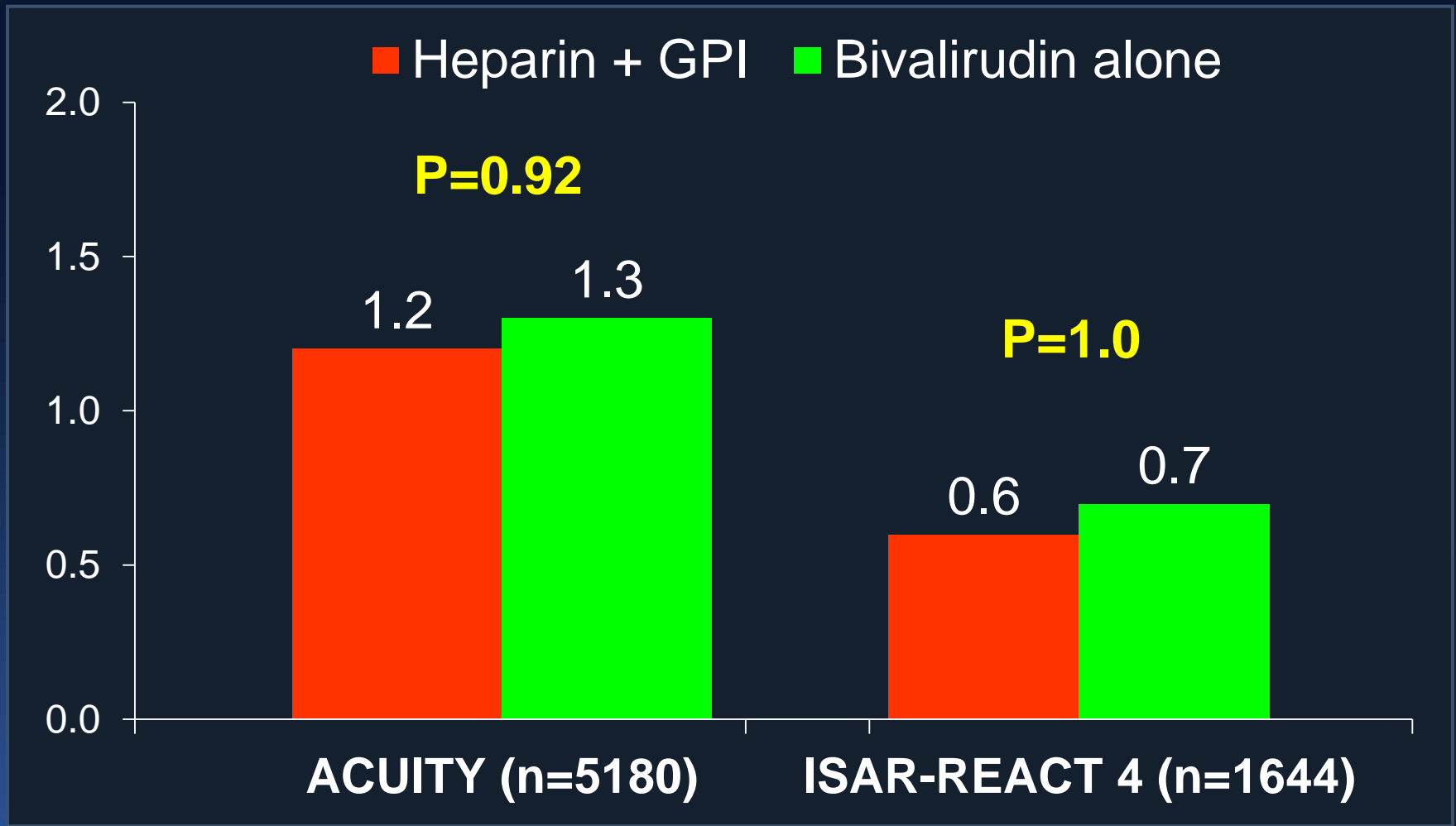


ISAR-REACT 4: Major bleeding (n=1721)

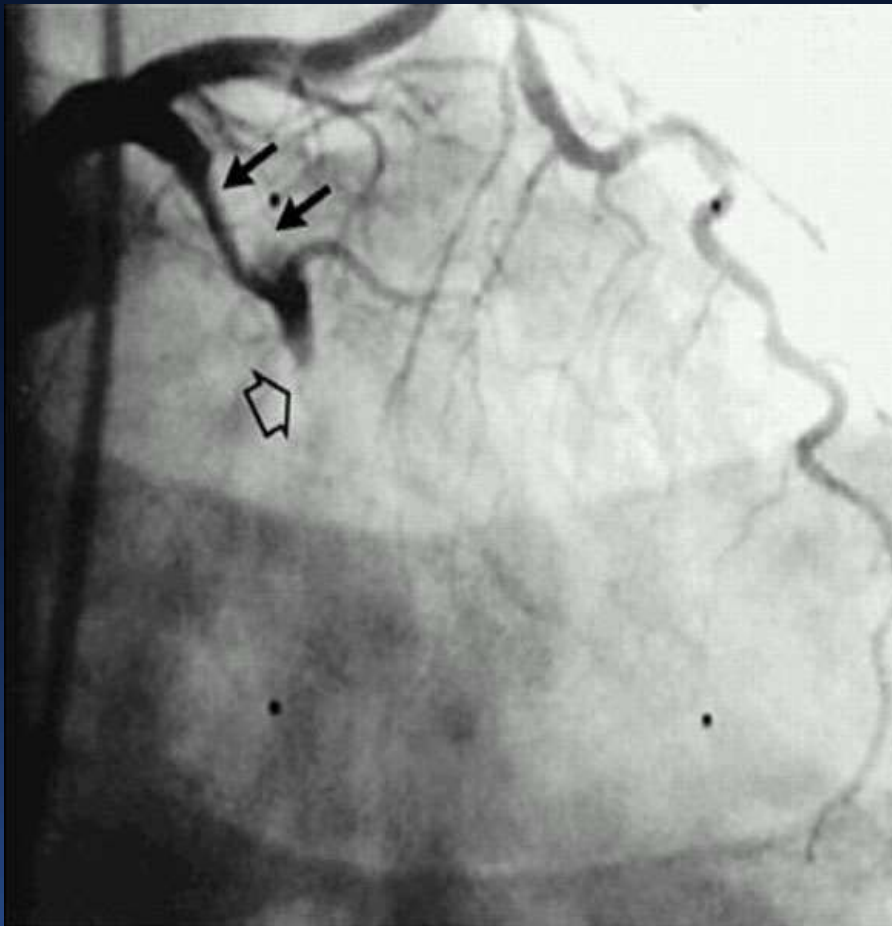


30-day Stent Thrombosis in NSTEACS

Bivalirudin (no infusion) vs. Heparin + GPI



STEMI: Pathophysiology



Ruptured plaque with occlusive thrombus

HORIZONS-AMI + EUROMAX

Pooled 30-day results (n=5800)

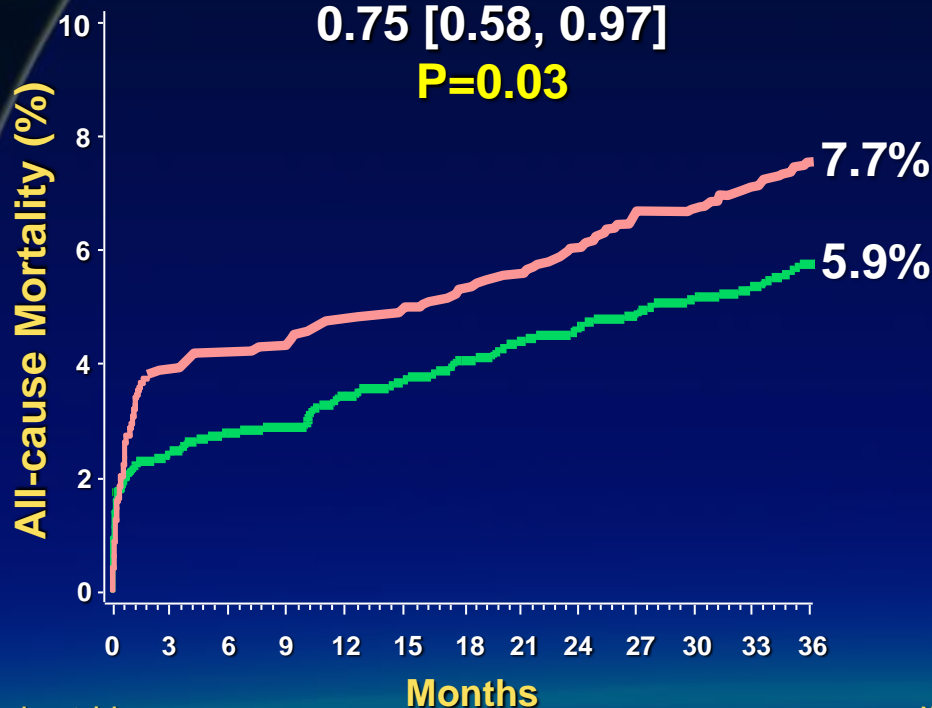
	Heparin ± GPI (N=2911)	Bivalirudin (N=2889)	P Value	Δ/1000 pts Biv v Hep
Death	90 (3.1%)	69 (2.4%)	0.10	
Cardiac	85 (2.9%)	59 (2.0%)	0.03	-9
Non-cardiac	5 (0.2%)	10 (0.4%)	0.19	
Reinfarction	42 (1.4%)	53 (1.8%)	0.24	
Ischemia-driven revascularization	69 (2.4%)	52 (1.8%)	0.11	
MACE (death, MI, IDR, or stroke)	161 (5.5%)	163 (5.6%)	0.85	
Stent thrombosis (ARC)	40 (1.4%)	60 (2.1%)	0.04	+7
Acute	6 (0.2%)	36 (1.2%)	<0.0001	+10
Sub-acute	34 (1.2%)	25 (0.9%)	0.24	
Protocol major bleeding	226 (7.8%)	120 (4.2%)	<0.0001	-36
Blood transfusion	110 (3.8%)	62 (2.1%)	0.0002	-17
Acquired thrombocytopenia	77 (2.9%)	37 (1.4%)	0.0002	-15
NACE (MACE, ST, or major bleeding)	346 (11.9%)	253 (8.8%)	<0.0001	-31

HORIZONS-AMI

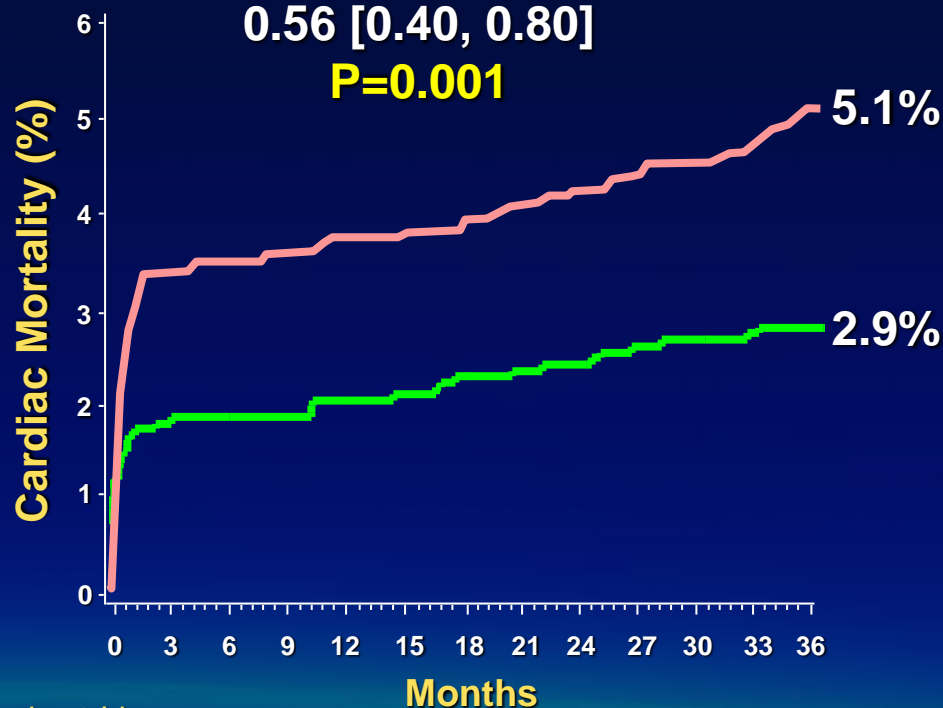
3-Year All-cause and Cardiac Mortality

— Heparin + GPIIb/IIIa (n=1802) — Bivalirudin alone (n=1800)

3-yr HR [95%CI] =
0.75 [0.58, 0.97]
P=0.03



3-yr HR [95%CI] =
0.56 [0.40, 0.80]
P=0.001



Number at risk

Months	0	3	6	9	12	15	18	21	24	27	30	33	36
Bival	1800	1689	1660	1633	1611	1574	1574	1574	1574	1574	1574	1574	1574
H + GPI	1802	1670	1643	1593	1568	1525	1525	1525	1525	1525	1525	1525	1525

Number at risk

Months	0	3	6	9	12	15	18	21	24	27	30	33	36
Bival	1800	1689	1660	1633	1611	1574	1574	1574	1574	1574	1574	1574	1574
H + GPI	1802	1670	1643	1593	1568	1525	1525	1525	1525	1525	1525	1525	1525

HEAT PPCI: Stent Thrombosis

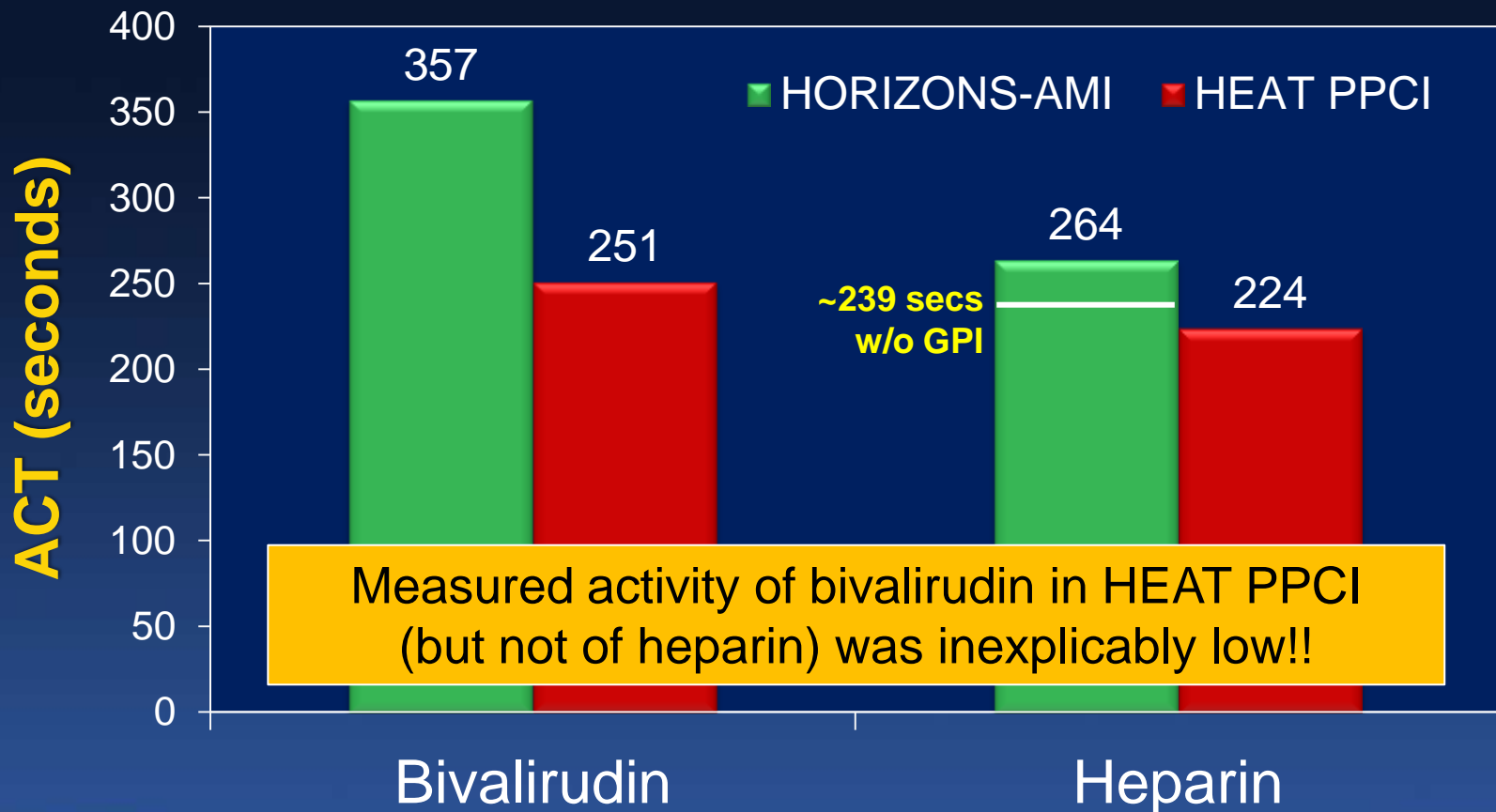
ARC definite or probable stent thrombosis

	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 – no post-PCI infusion

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



Why we should be wary of single-center trials

Rinaldo Bellomo, MD, FRACP, FJFICM; Stephen J. Warrillow, MBBS, FRACP, FJFICM;
Michael C. Reade, MBBS, MPH, DPhil, FANZCA, FJFICM

1. Limited external validity
2. Implausible effect size
3. Unequal allocation of resources
4. Lack of blinding
5. Numerous examples where single-center trials were “reversed” by multiple multicenter trials

“What works in one location may not in others due differences in baseline risk, intercurrent care, opportunity cost, and the fidelity with which the intervention can be delivered.”

“Single-center studies are valuable hypothesis-generating investigations. However, the evidence shows that....they have typically not been confirmed by larger multicenter studies....the history of this field argues that two beneficial RCTs are necessary with at least one being a confirmatory trial. Accordingly, we should be very careful in taking single-center trials as a demonstration of a biological truth and should avoid giving them undue weight or value.practice guidelines should rarely, if ever, be based on evidence from single-center trials.”

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.

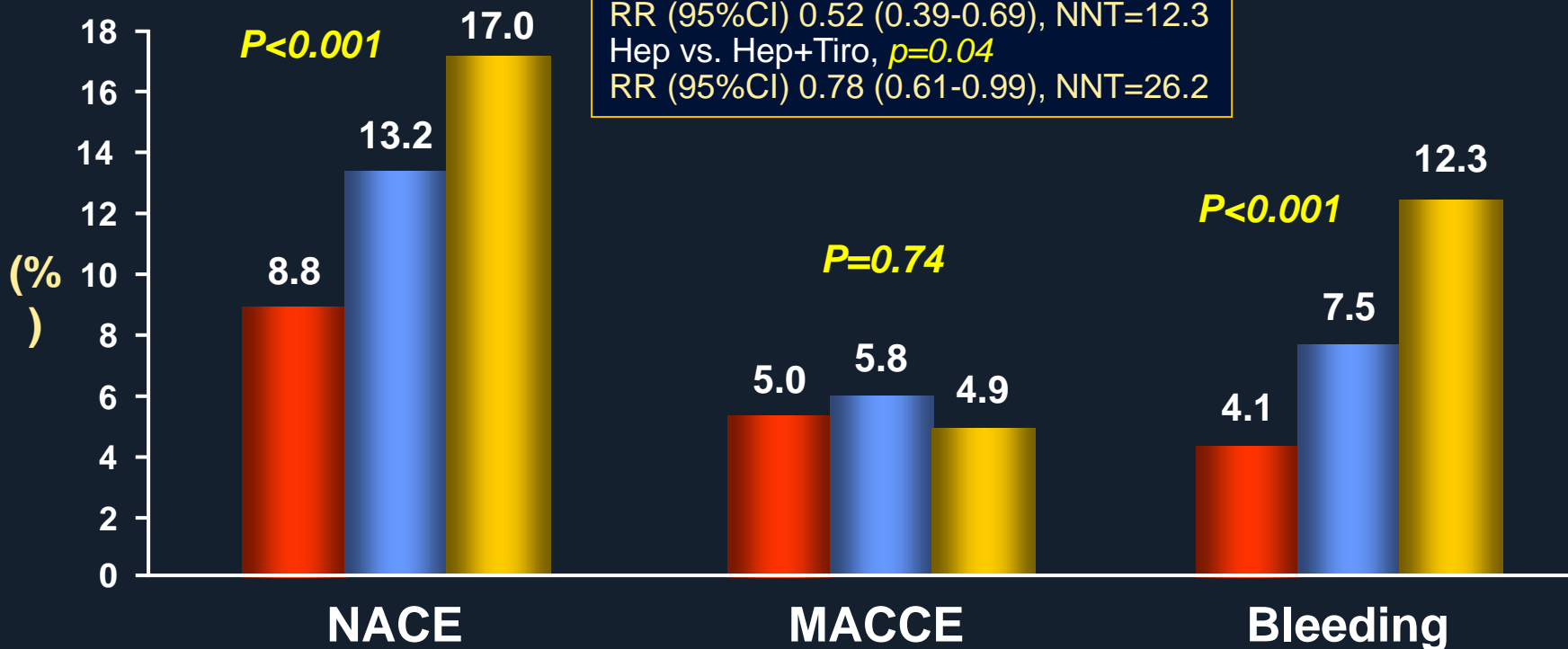
BRIGHT: Primary and Major Secondary Endpoint Events at 30 Days



■ 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



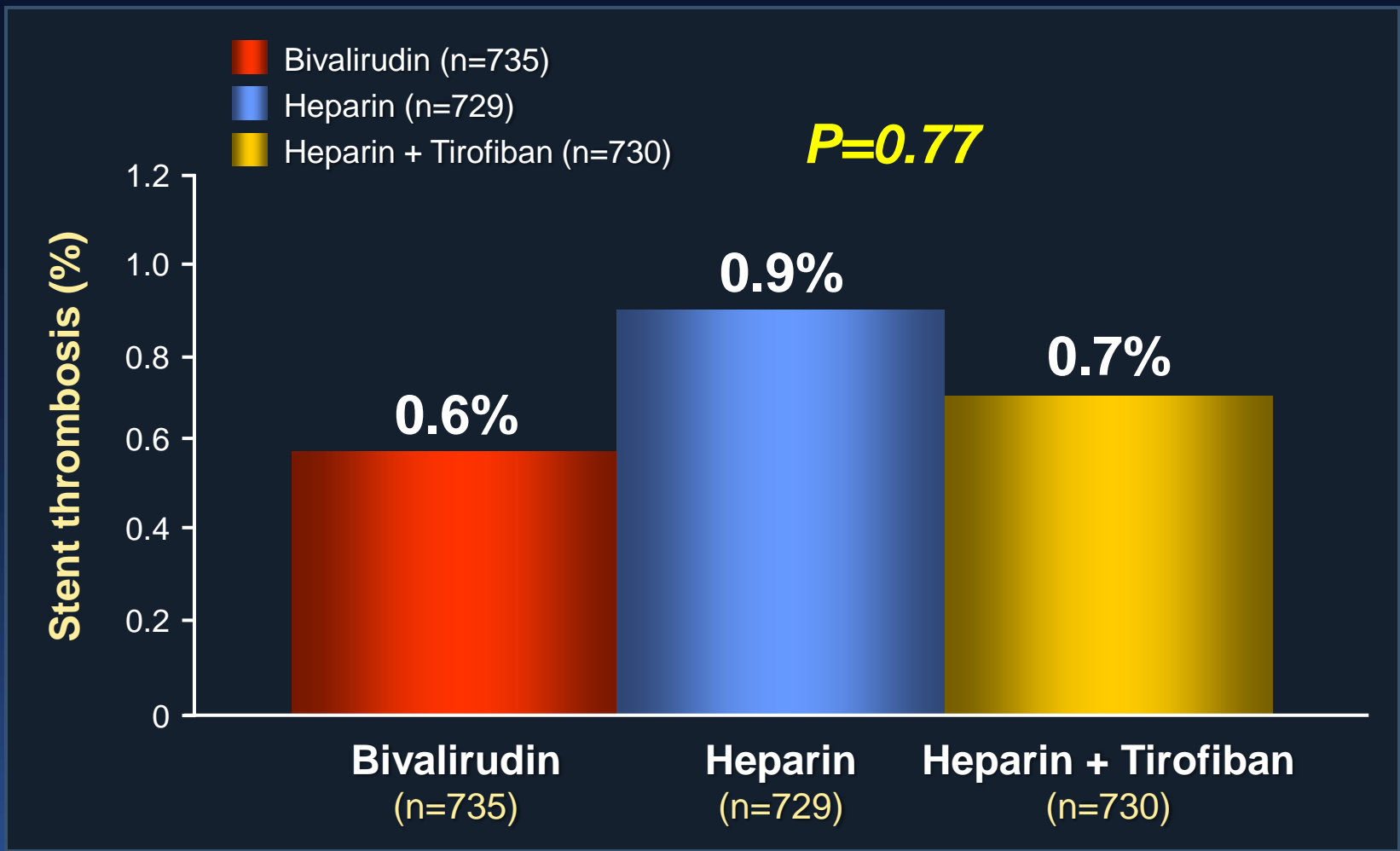
BRIGHT: 30-day BARC 2-5 Bleeding



	Bivalirudin (n=735)	Heparin (n=729)	Heparin + tirofiban (n=730)	P value
Access site	2 (0.3%)	8 (1.1%)	12 (1.6%)	0.03
Radial	1 (0.1%)	3 (0.4%)	3 (0.4%)	
Femoral	1 (0.1%)	5 (0.7%)	9 (1.2%)	
Non-access site	7 (1.0%)	18 (2.5%)	25 (3.4%)	0.005
Intracranial	0	0	0	
Gastrointestinal	4 (0.5%)	10 (1.4%)	14 (1.9%)	
Other	3 (0.4%)	8 (1.1%)	11 (1.5%)	



BRIGT: Stent Thrombosis at 30 Days



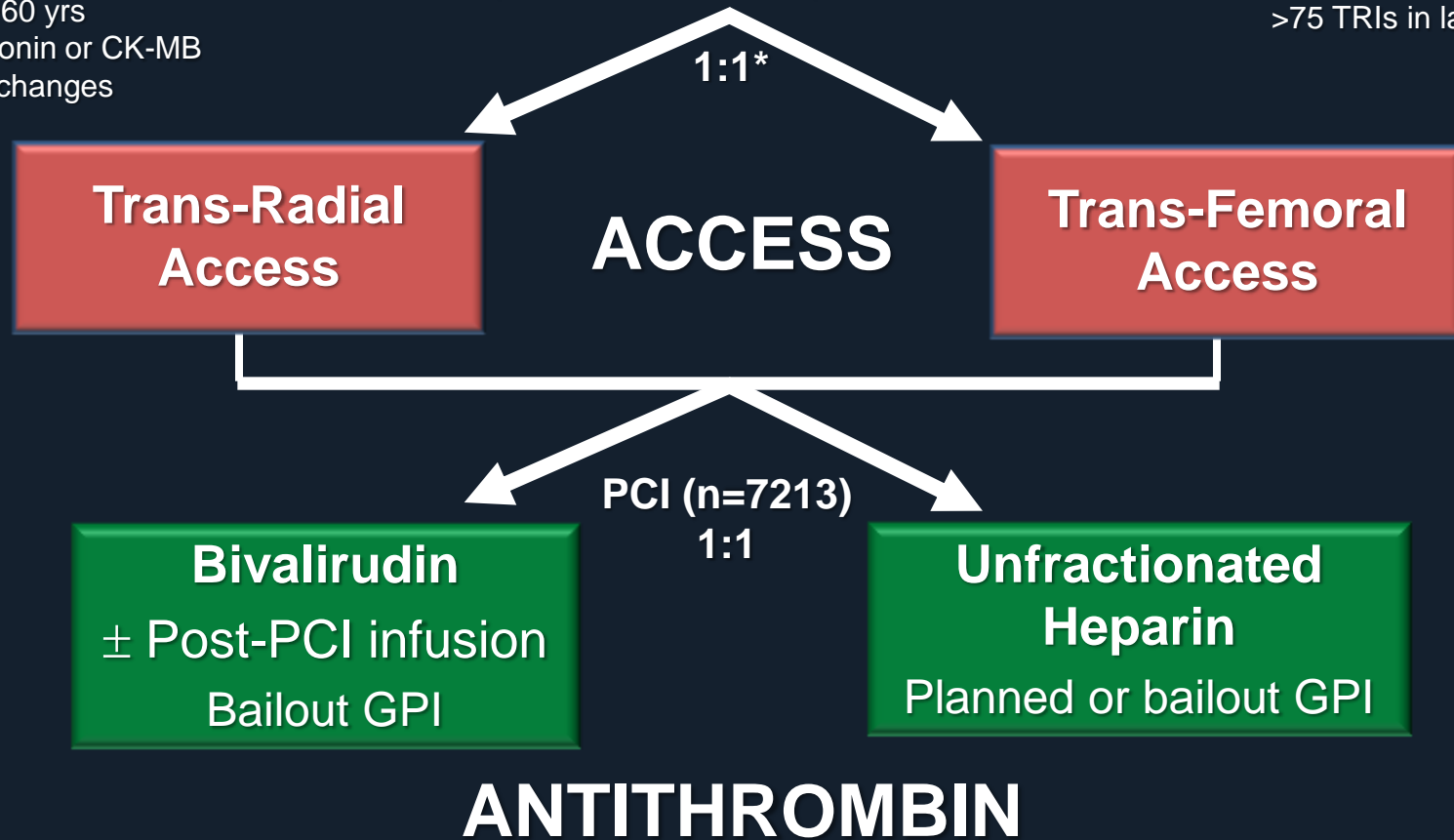
MATRIX: Trial Design

NSTEACS or STEMI with Invasive Management (n=8404)

+ ≥ 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

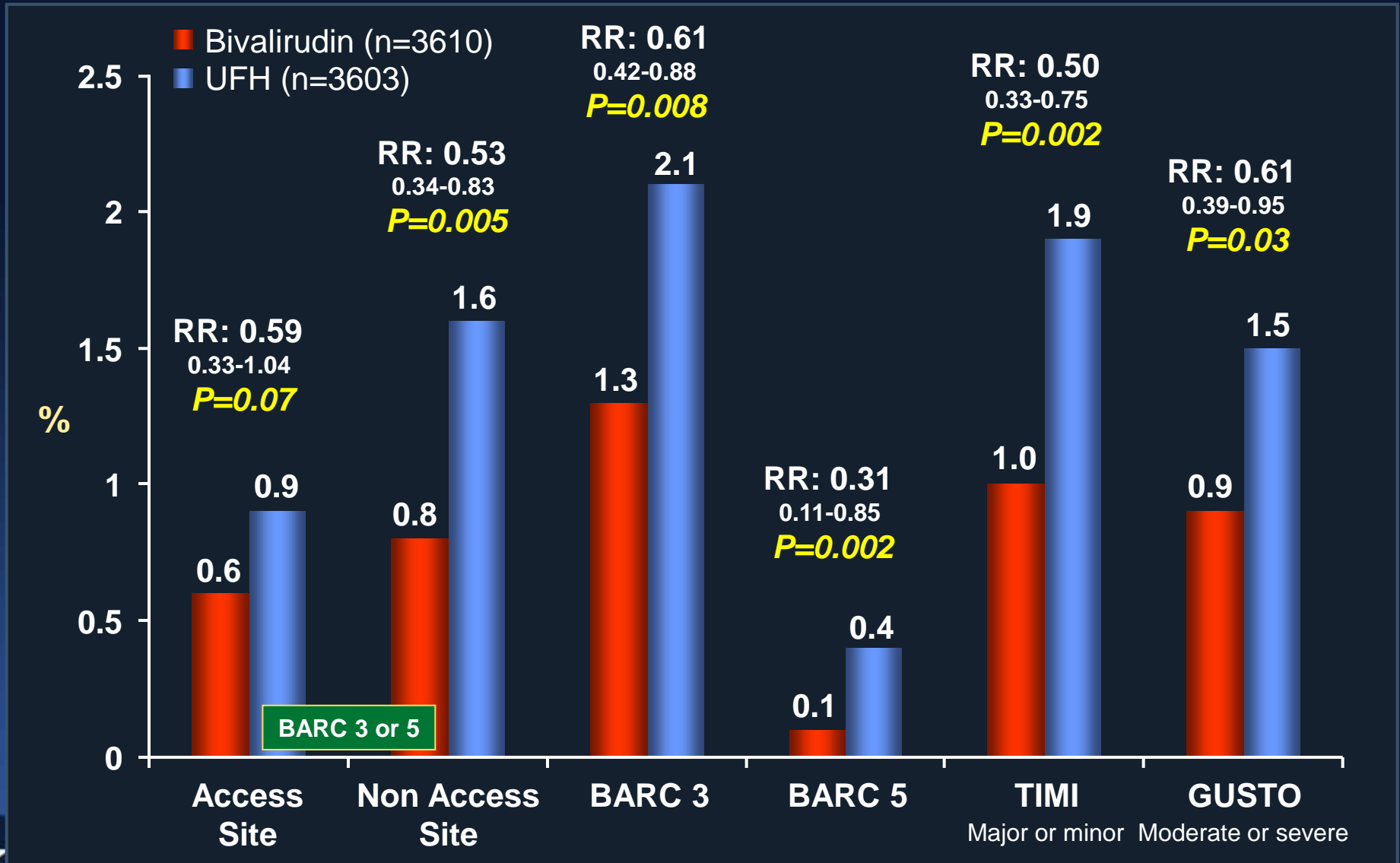


* Stratified by STEMI vs. NSTEACS and P2Y12 type

PI: M. Valgimigli

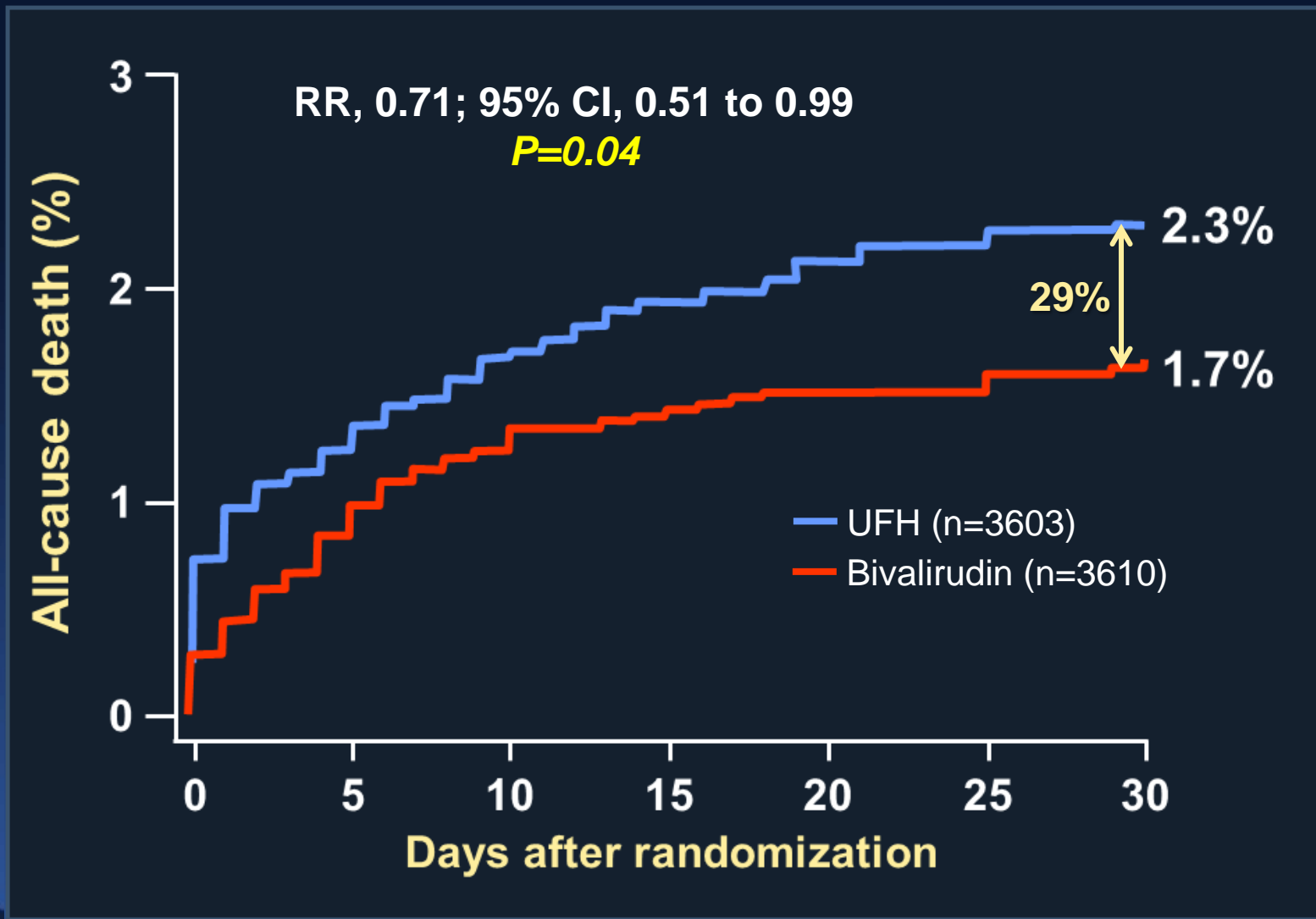


MATRIX antithrombin: Bleeding Endpoints

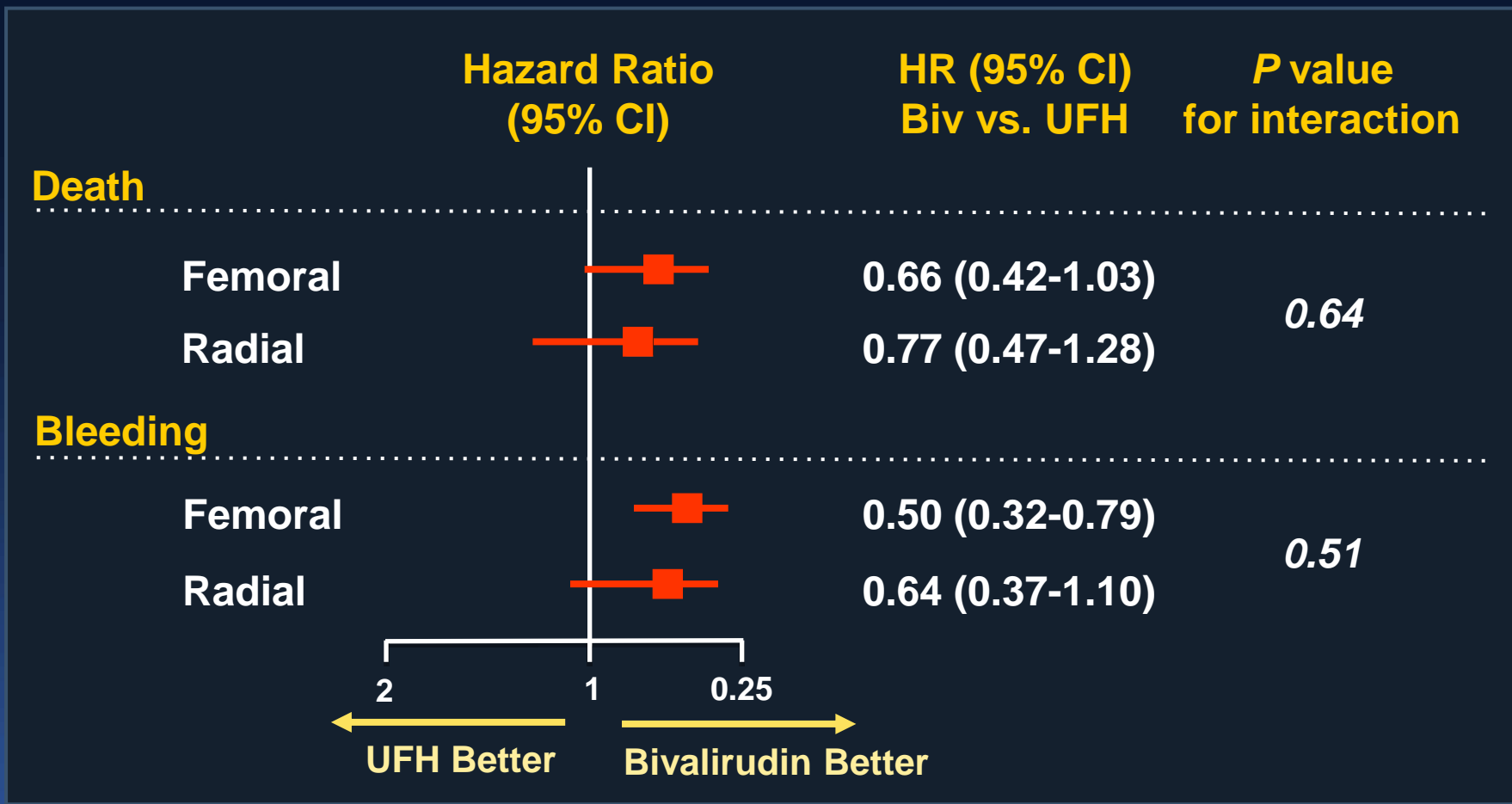




MATRIX antithrombin: All-cause Mortality



MATRIX antithrombin: Access Site Subgroup Analysis



Conclusions: Bivalirudin vs. Heparin for in ACS

- **NSTEACS:** Compared to heparin + GPI in NSTEACS, bivalirudin (with no post procedural infusion) reduces bleeding and thrombocytopenia, with similar rates of stent thrombosis, MI, and MACE
- **STEMI:** Compared to heparin alone or heparin + GPI in STEMI, bivalirudin reduces cardiac mortality, bleeding and thrombocytopenia, with similar rates of MI and MACE, and similar rates of stent thrombosis with a 3-hour post-procedural PCI-dose infusion
- **Bivalirudin has the best benefit-risk profile in ACS!**