

Parenteral Anticoagulant Use in ACS: HORIZONS AMI, and SEPIA ACS Trial

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The Cardiovascular Research Foundation**



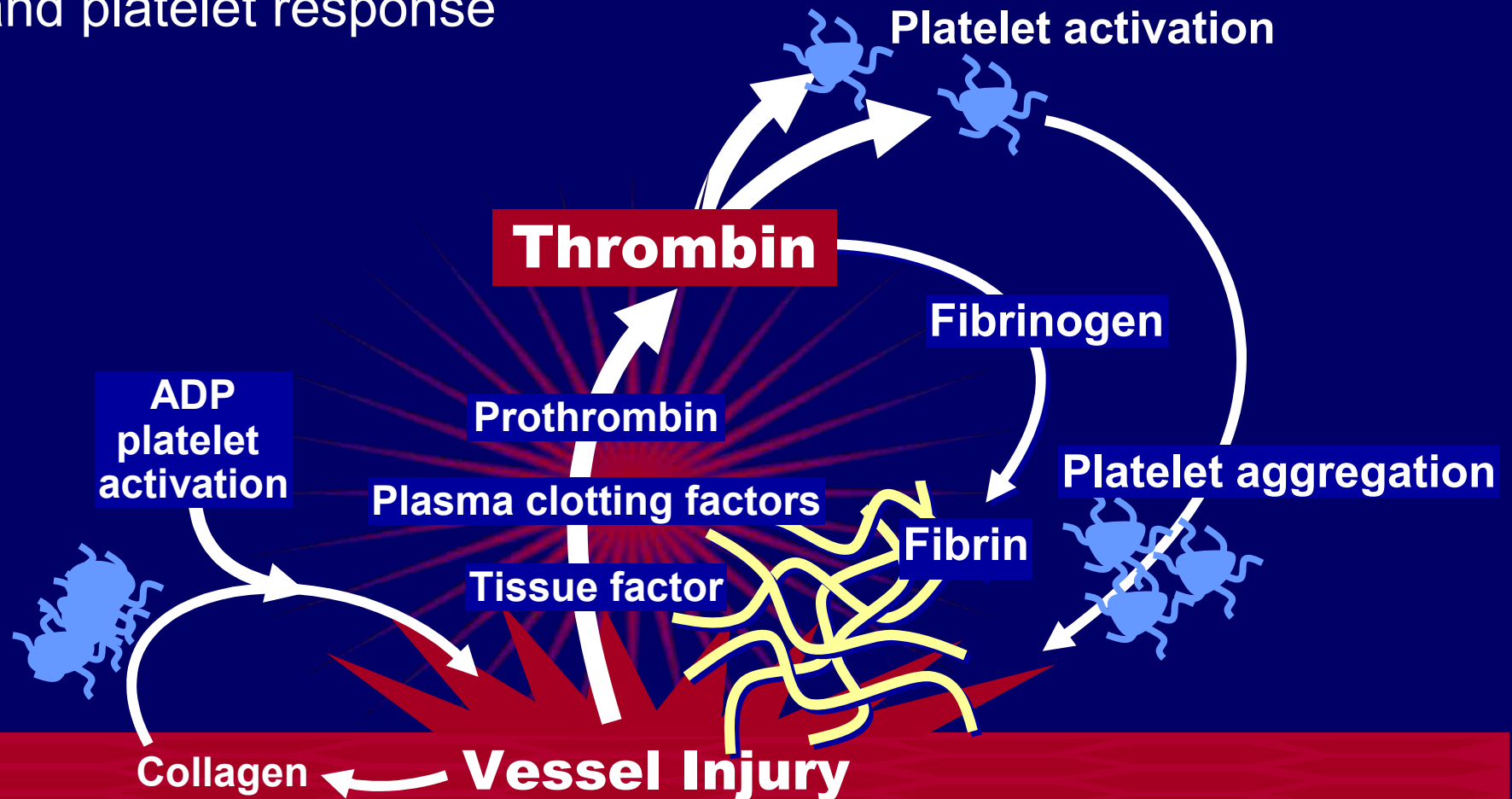
CARDIOVASCULAR RESEARCH
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MEDICAL CENTER

Why Direct Thrombin Inhibitors? The Critical Role of Thrombin

- Thrombin is a link between vessel injury, coagulation, and platelet response



ADP=adenosine diphosphate.

Coughlin SR. *Nature*. 2000;407:258-264. Monroe DM et al. *Arterioscler Thromb Vasc Biol*. 2002;22:1381-1389.

Bivalirudin

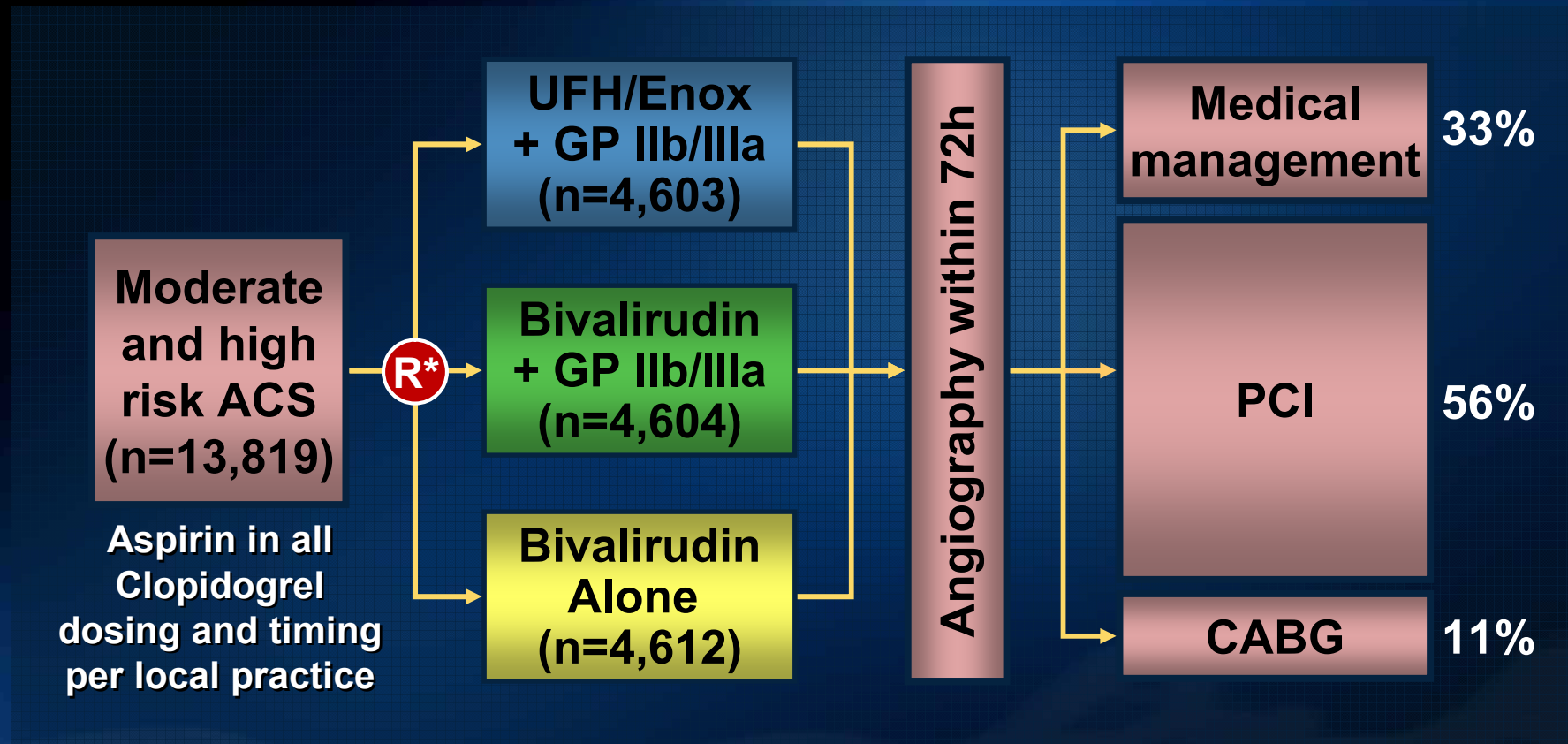
- **Highly specific direct thrombin inhibitor**
- **Synthetic peptide analog of hirudin**
- **20 amino acids MW = 2180 daltons, very low immunogenic potential**
- **No non-specific binding**
- **Reversible binding to thrombin**
- **Elimination by proteolytic and renal mechanisms**
 - Majority proteolytic
 - Clearance reduced ~20% in mild or moderate renal impairment
 - No active metabolites

FDA approval:

Patients undergoing PCI; patients with or at risk of HIT/TS

Study Design – First Randomization

Moderate and high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,819)



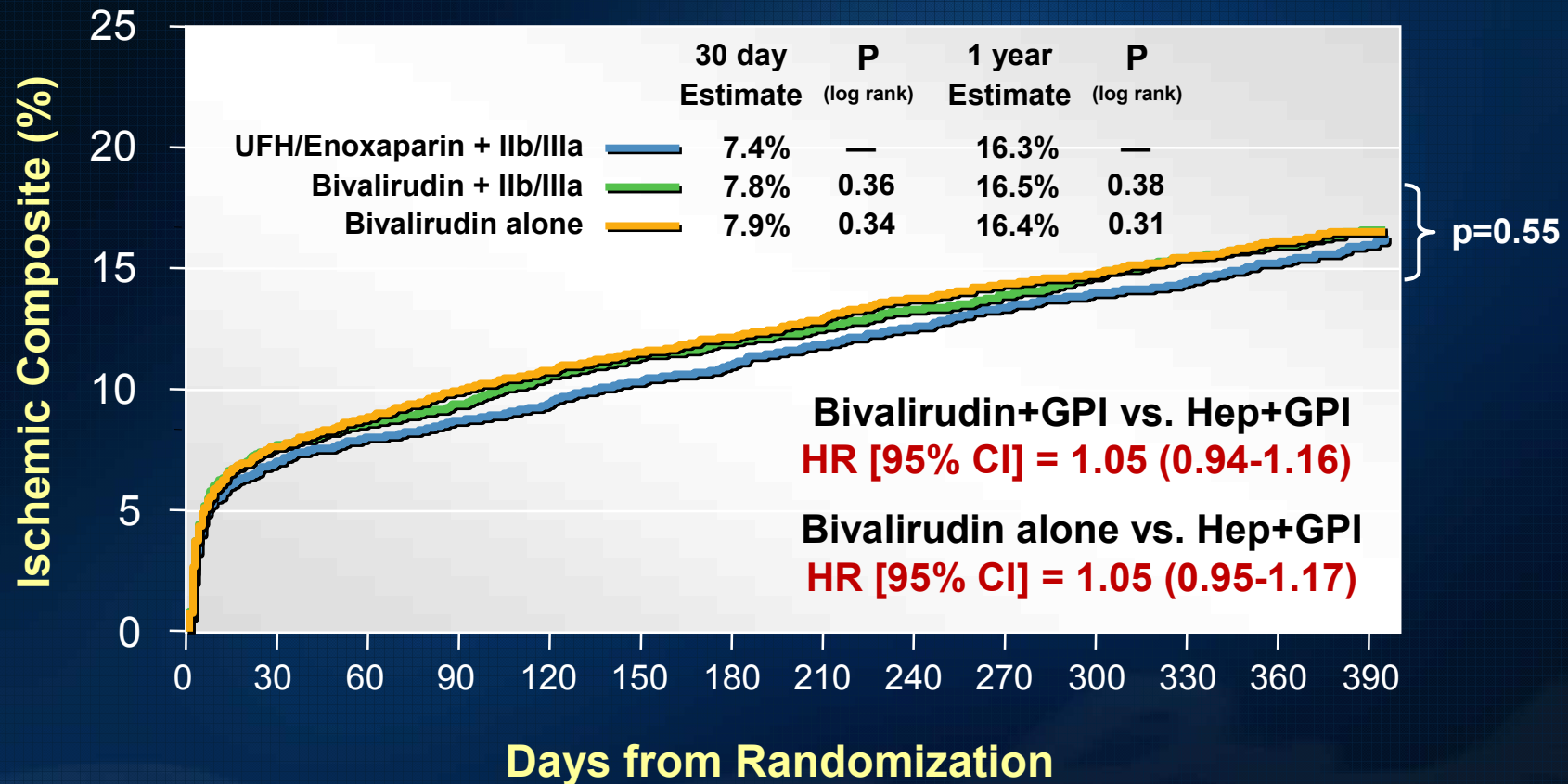
*Stratified by pre-angiography thienopyridine use or administration

ACUITY

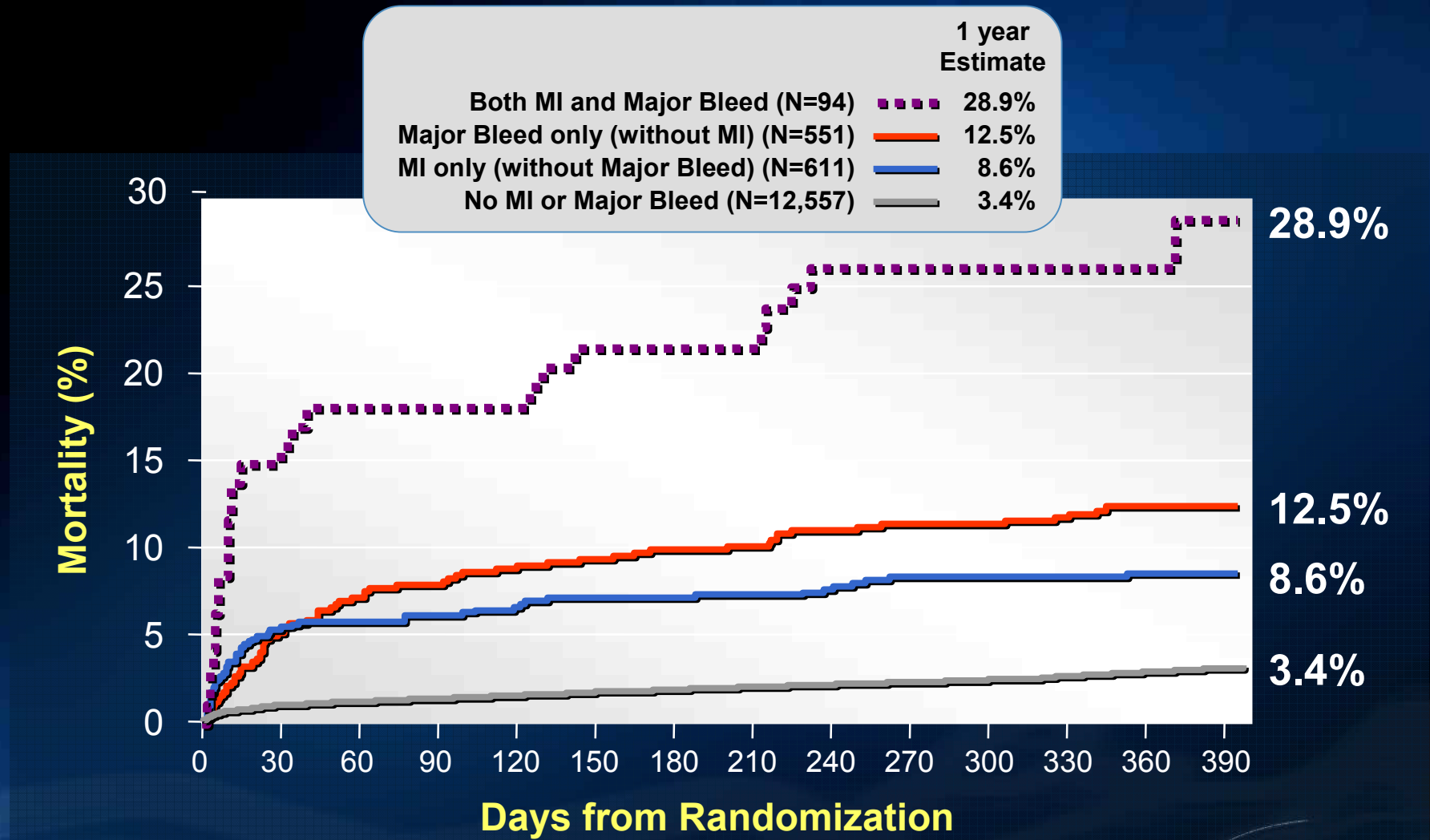
Ischemic Composite Endpoint

(Death, MI, unplanned revascularization for ischemia)

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



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



HORIZONSAMI

**Two-Year Follow-up from a Prospective,
Randomized Trial of Heparin Plus
Glycoprotein IIb/IIIa Inhibitors vs.
Bivalirudin and Paclitaxel-Eluting vs.
Bare-Metal Stents in STEMI**

Gregg W. Stone MD

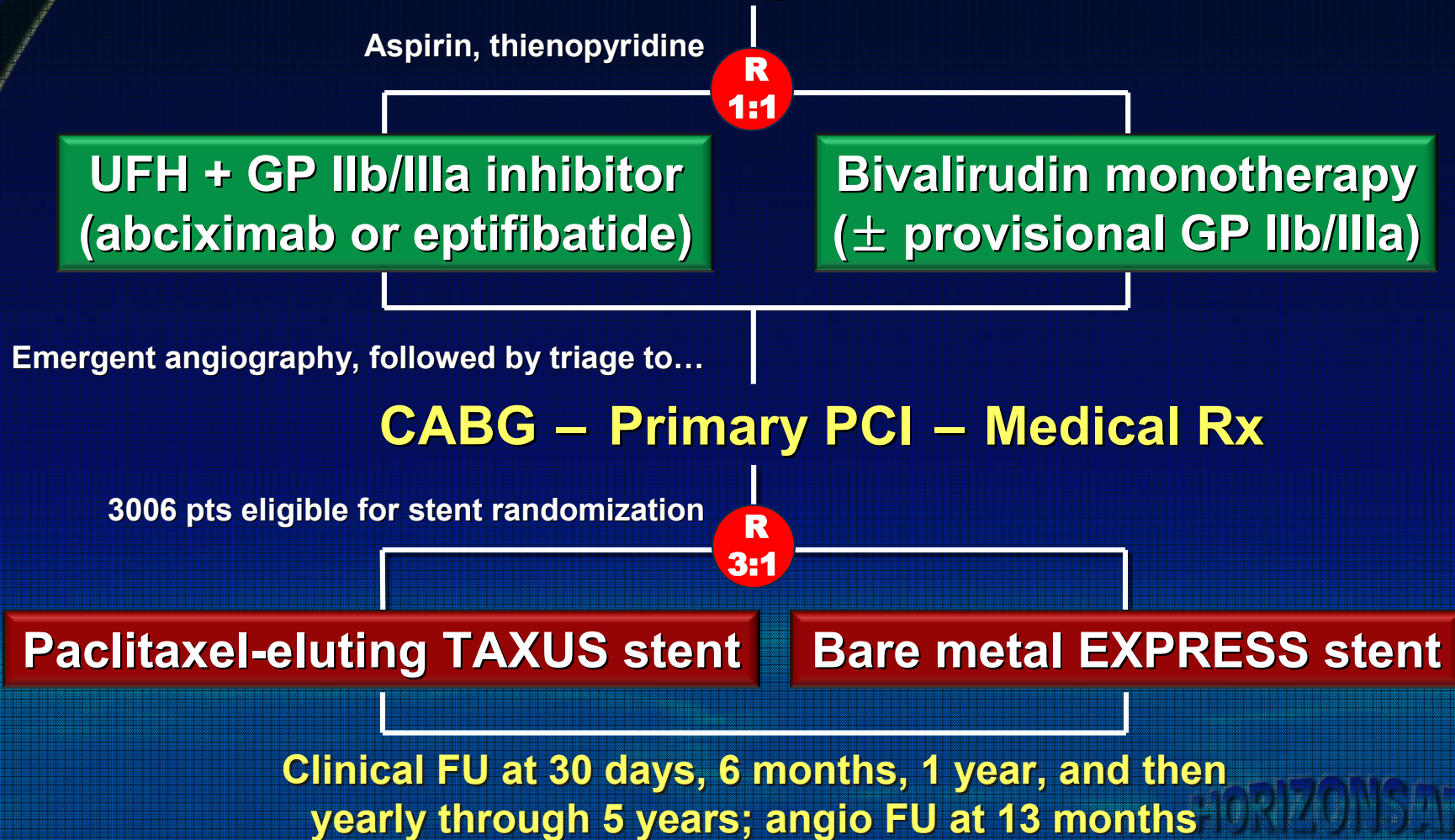
For the HORIZONS-AMI Investigators



HORIZONSAMI

Harmonizing Outcomes with Revascularization and Stents in AMI

3602 pts with STEMI with symptom onset ≤ 12 hours

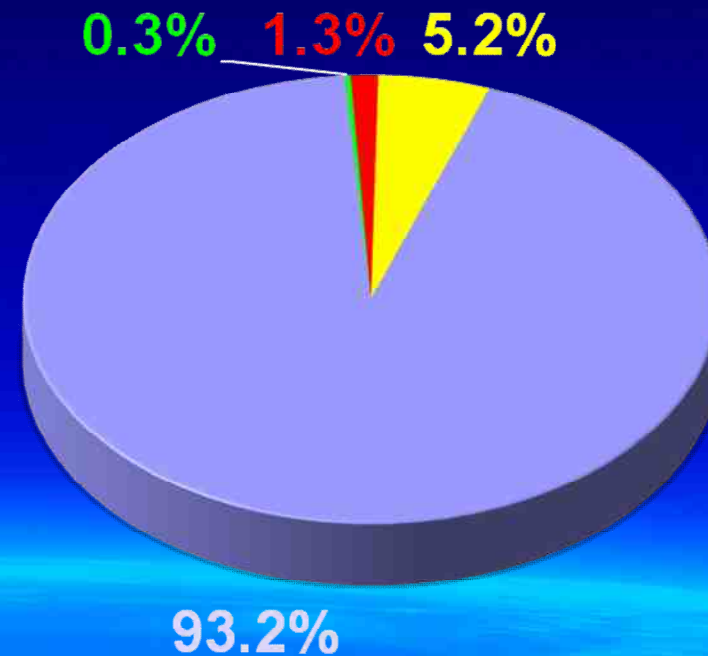
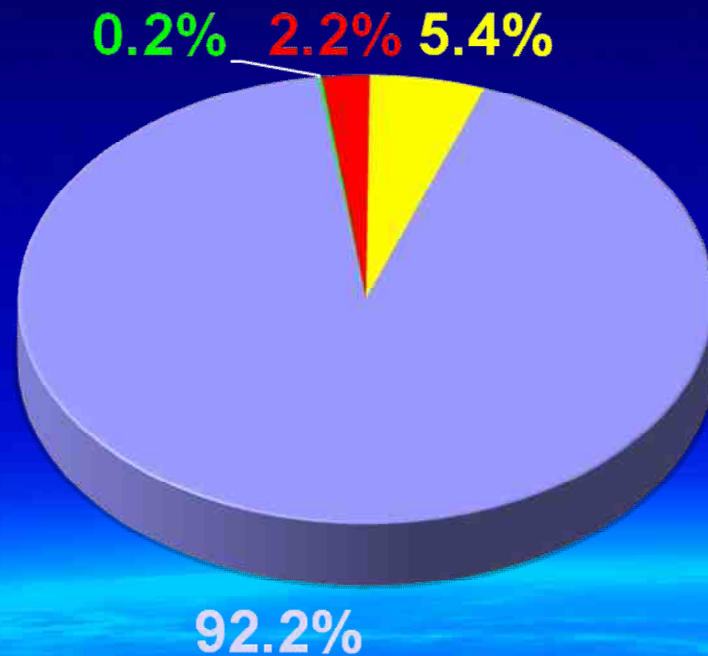


Primary Management Strategy*

UFH + GP IIb/IIIa Inhibitor N=1802

Bivalirudin Monotherapy N=1800

Primary PCI Deferred PCI CABG Medical Rx

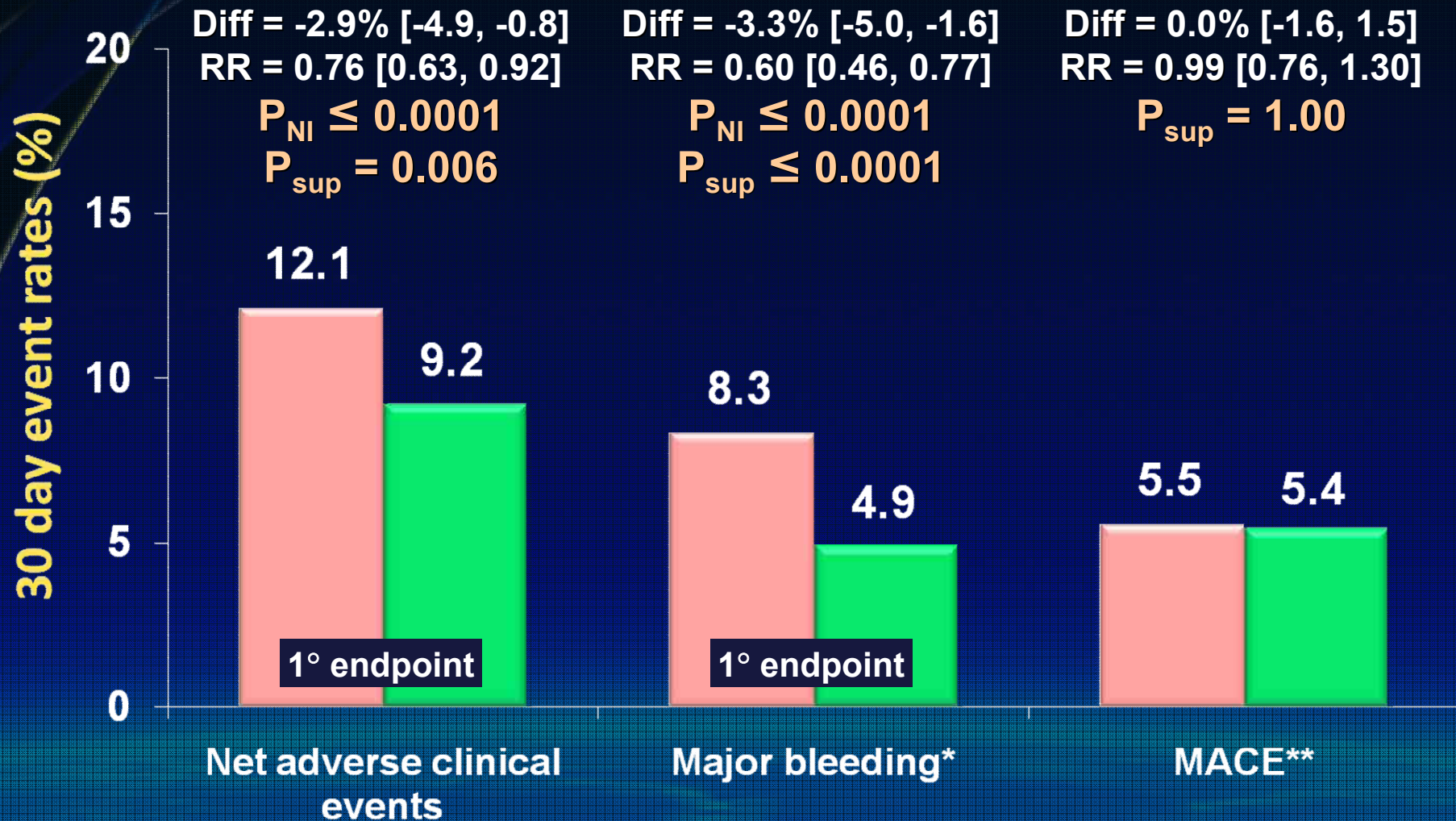


*Primary ITT analysis includes all pts regardless of treatment

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Primary Outcome Measures (ITT)

■ Heparin + GPIIb/IIIa inhibitor (N=1802) ■ Bivalirudin monotherapy (N=1800)



*Not related to CABG

**MACE = All cause death, reinfarction, ischemic TVR or stroke

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30 Day Bleeding Endpoints

	UFH + GP IIb/IIIa (N=1802)	Bivalirudin (N=1800)	P Value
Protocol Major, non CABG*	8.3%	4.9%	<0.0001
Protocol Major, All	10.8%	6.8%	<0.0001
Protocol Minor	15.4%	8.6%	<0.0001
Blood transfusion	3.5%	2.1%	0.01
TIMI Major	5.0%	3.1%	0.003
TIMI Minor	4.6%	2.8%	0.008
TIMI Major or Minor	9.6%	5.9%	<0.0001
GUSTO LT** or Severe	0.6%	0.4%	0.65
GUSTO Moderate	5.0%	3.1%	0.003
GUSTO LT - Sev - Mod	5.6%	3.5%	0.003

*Primary endpoint; **Life threatening

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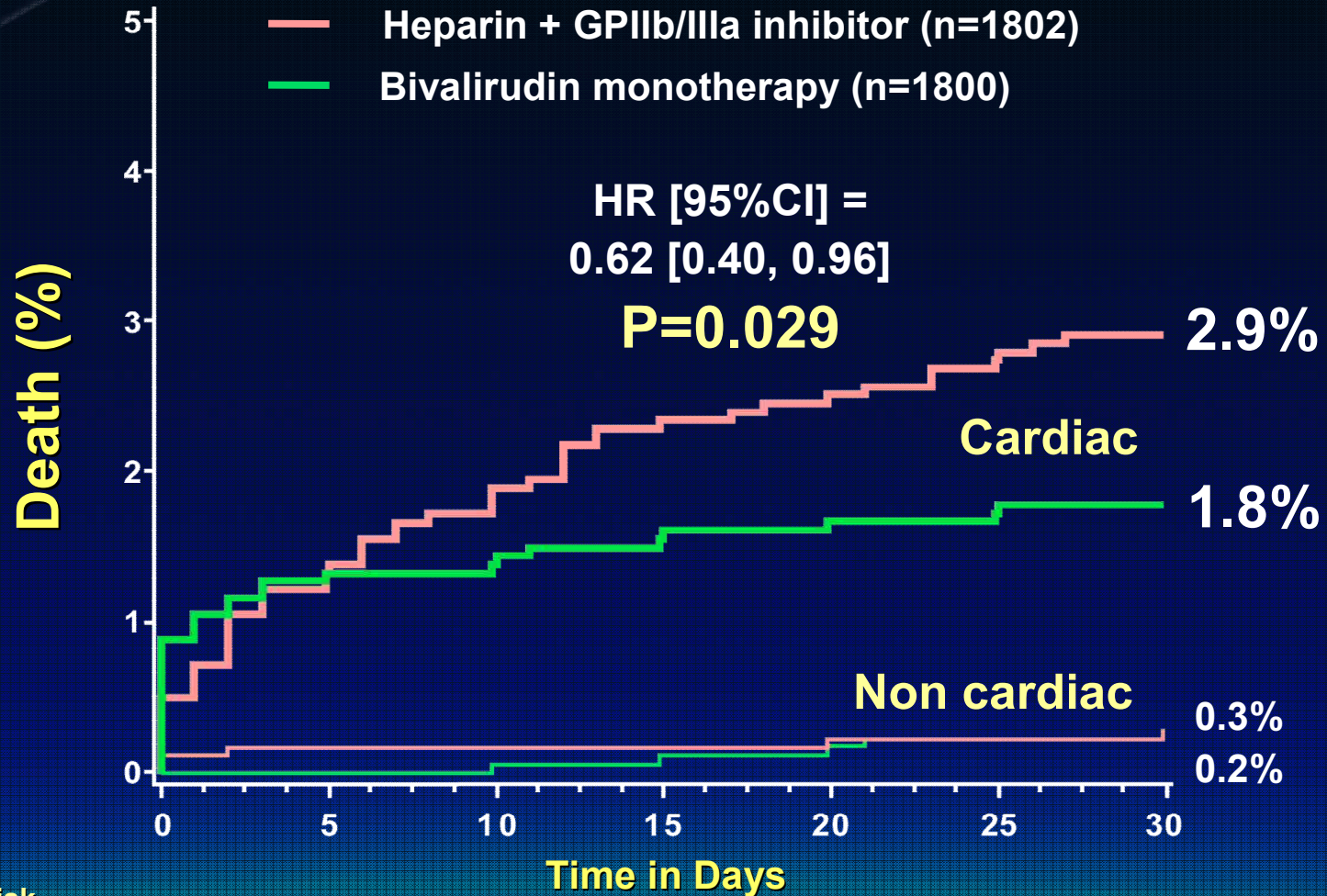
30 Day Stent Thrombosis (N=3,124)

	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

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30 Day Mortality: Cardiac and Non Cardiac

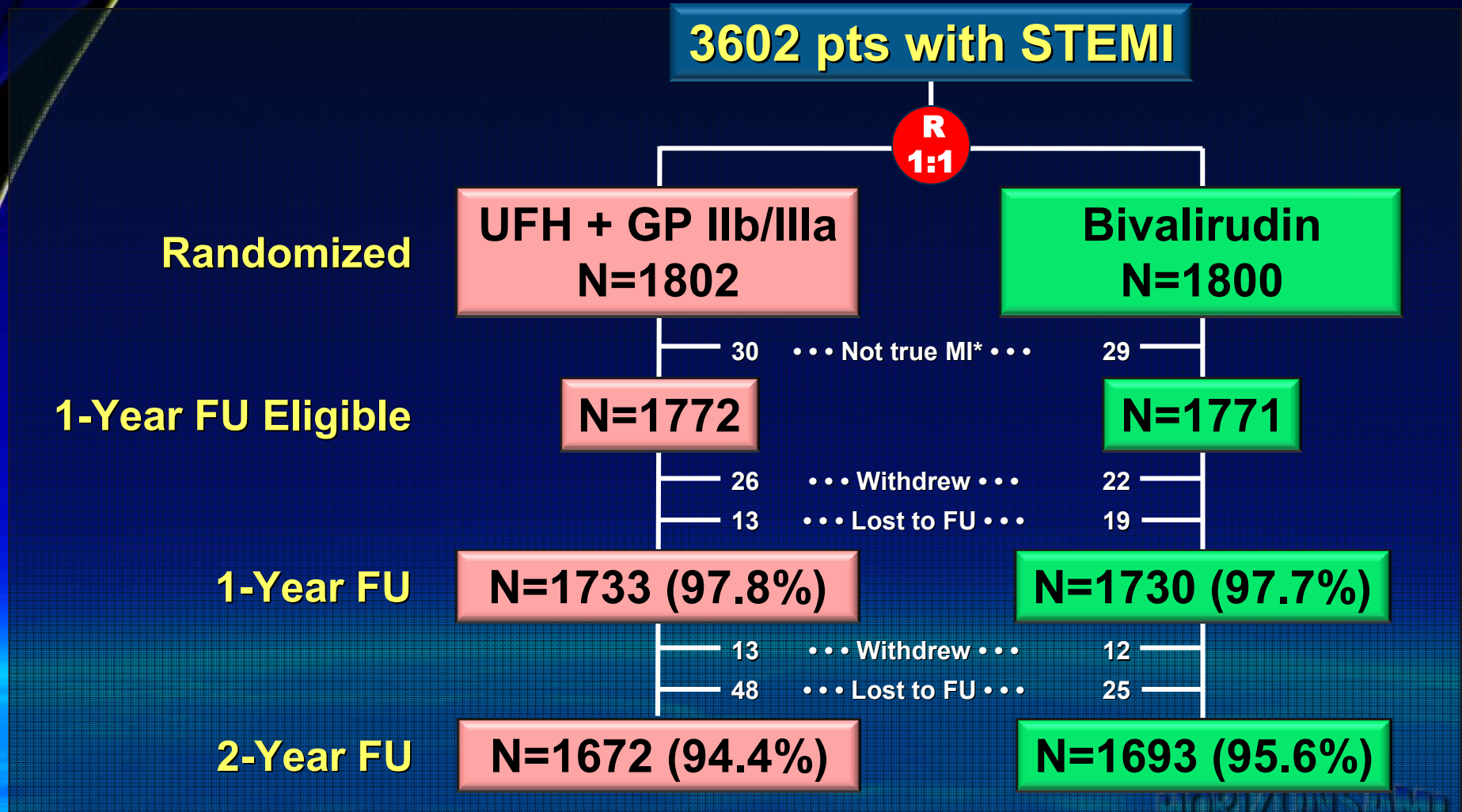


Number at risk

Bivalirudin	1800	1758	1751	1746
	1742	1729	1666	
Heparin + GPIIb/IIIa	1802	1764	1748	1736
	1728	1707	1630	

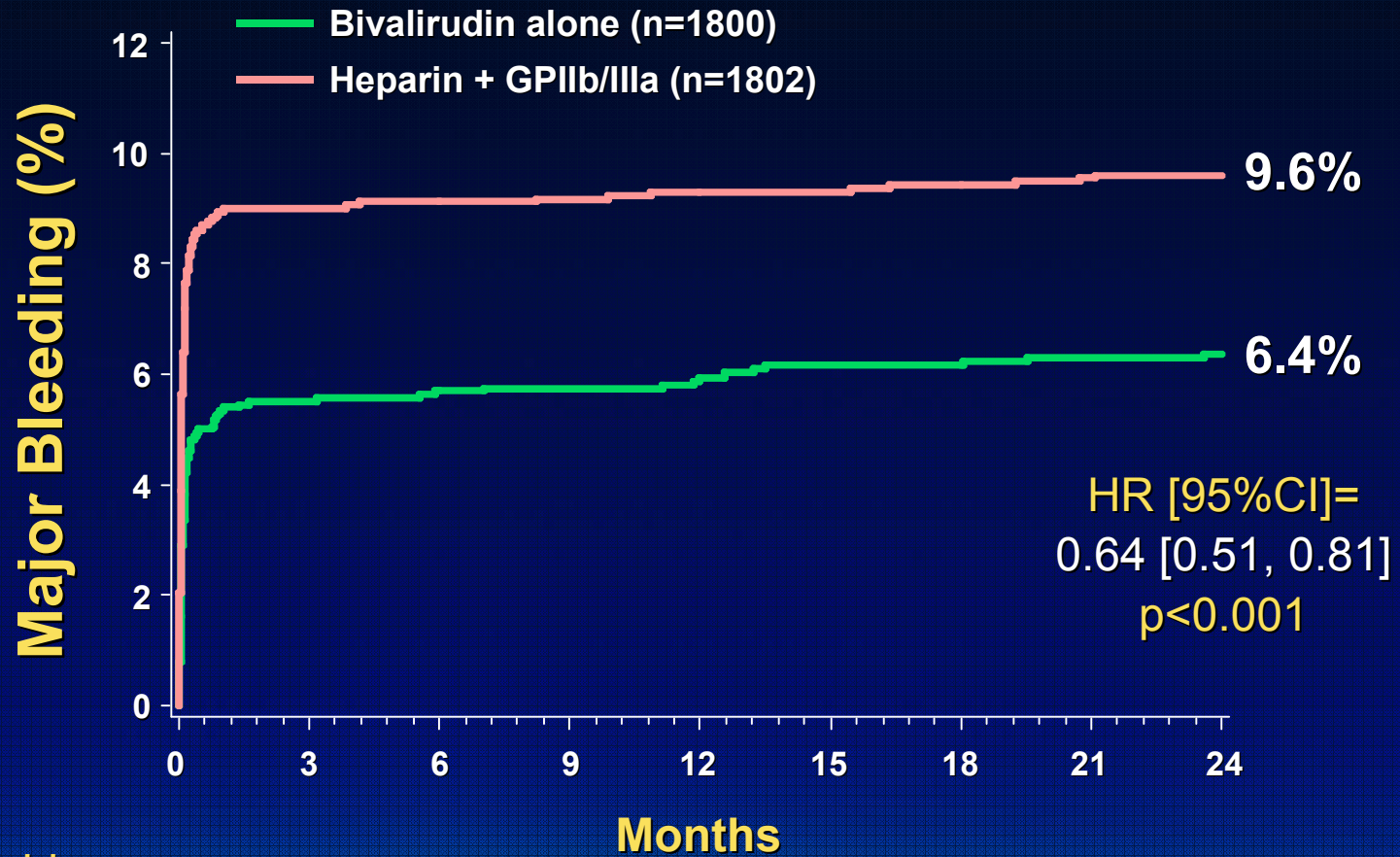
HORIZONSAMI

Harmonizing Outcomes with Revascularization and Stents in AMI



* Biomarkers WNL and no DS >50% by core lab determination (30 day FU only)

Two-Year Major Bleeding (non-CABG)*



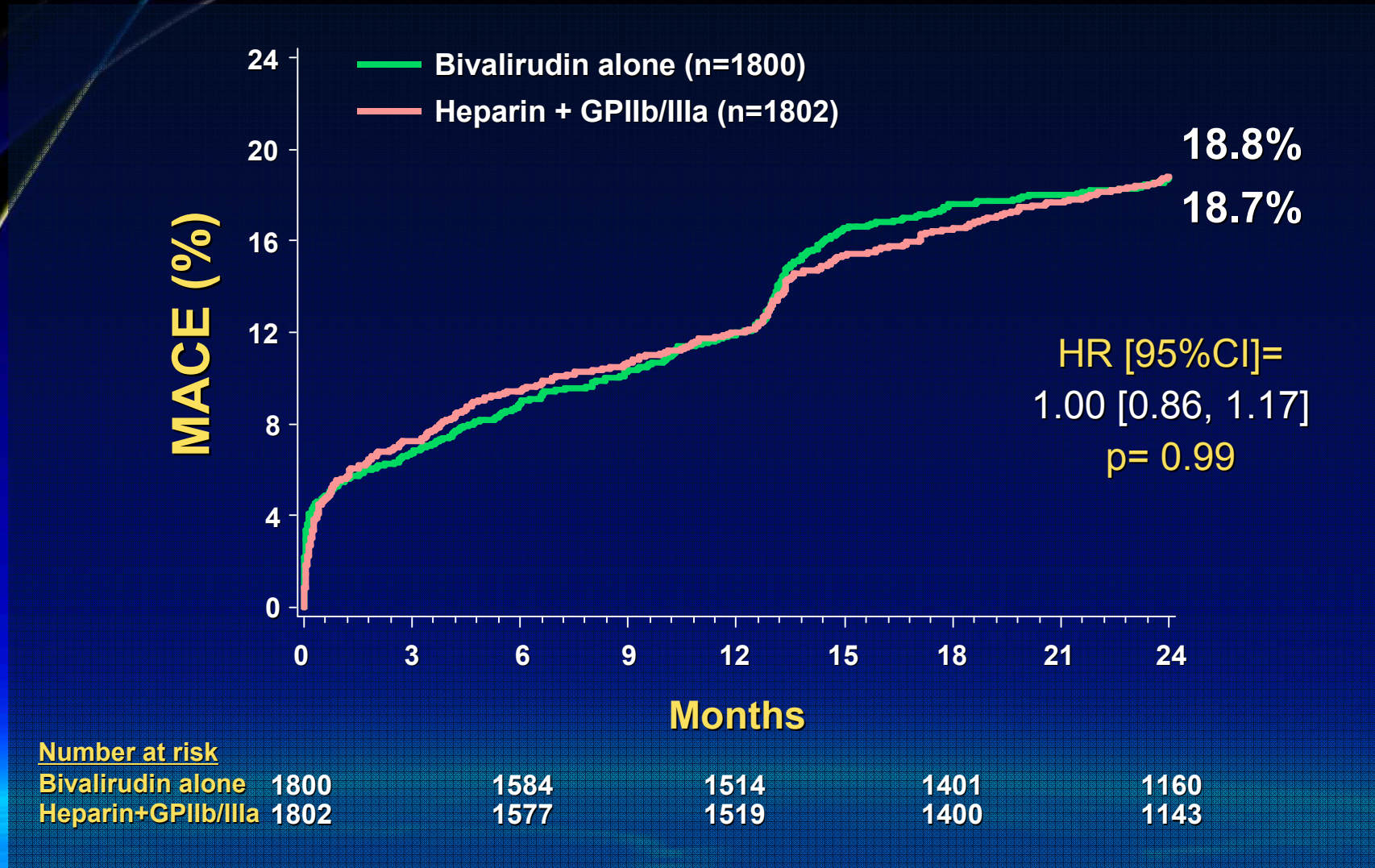
Number at risk

	0	3	6	9	12	15	18	21	24
Bivalirudin alone	1800	1603	1571	1540	1505	1453	1290		
Heparin+GPIIb/IIIa	1802	1535	1505	1453	1218				

*Intracranial intraocular, retroperitoneal, access site bleed requiring intervention/surgery, hematoma ≥ 5 cm, hgb $\downarrow \geq 3$ g/dL with or ≥ 4 g/dL w/o overt source; reoperation for bleeding; or blood product transfusion

HORIZONSAMI

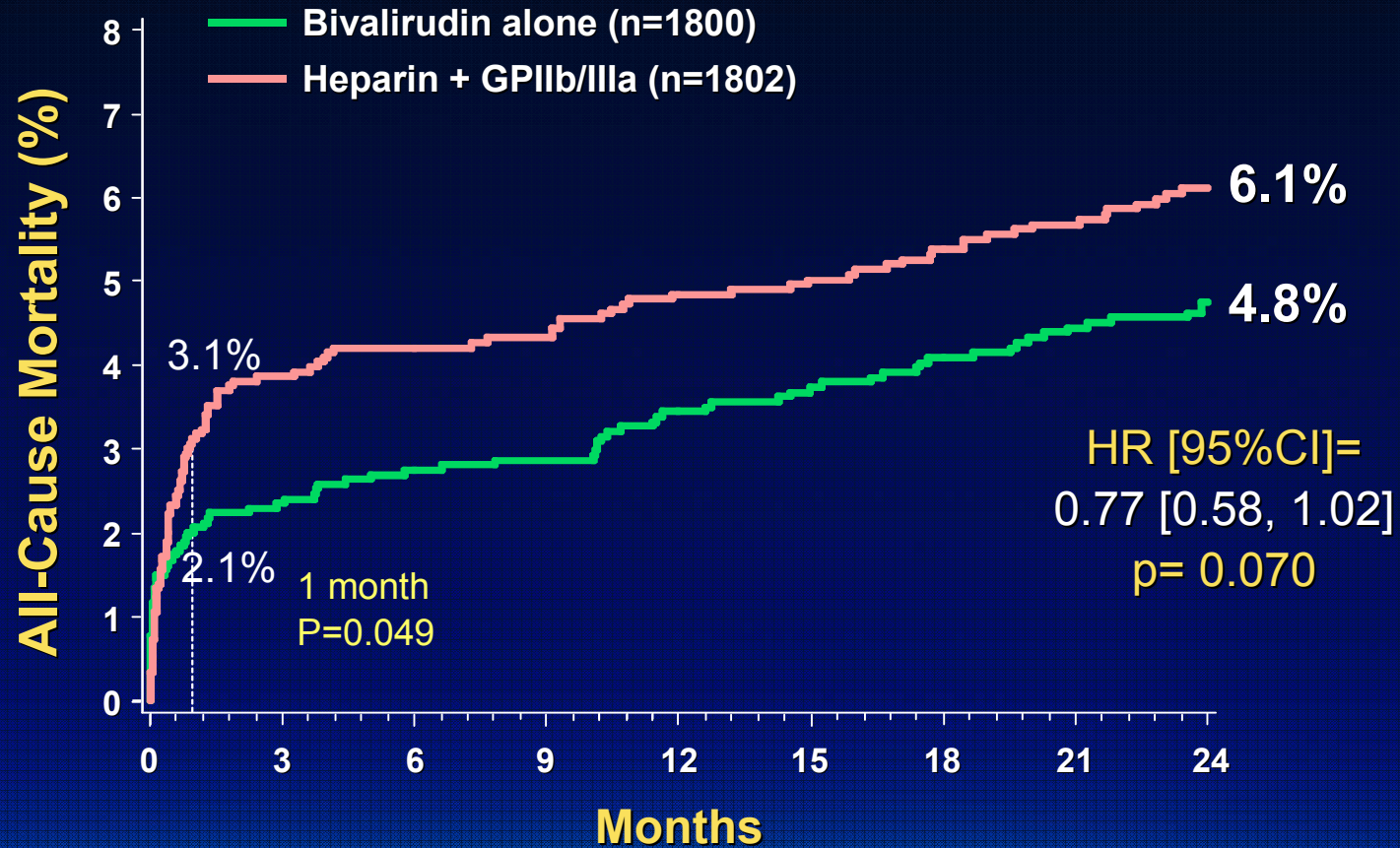
Two-Year Major Adverse CV Events*



*MACE = All cause death, reinfarction, ischemic TVR or stroke

HORIZONSAMI

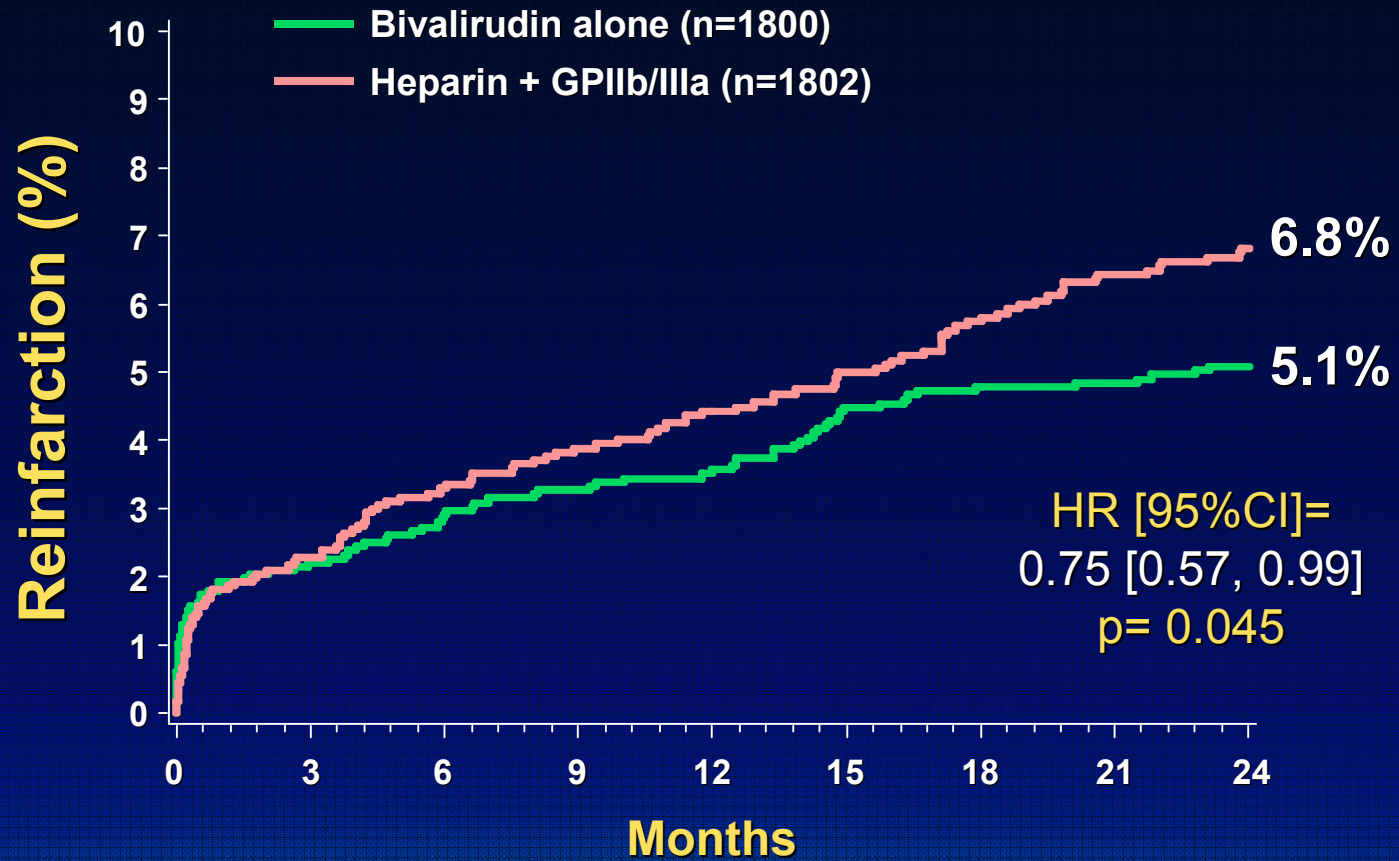
Two-Year All-Cause Mortality



Number at risk

Bivalirudin alone	1800	1690	1658	1626	1357
Heparin+GPIIb/IIIa	1802	1669	1637	1579	1324

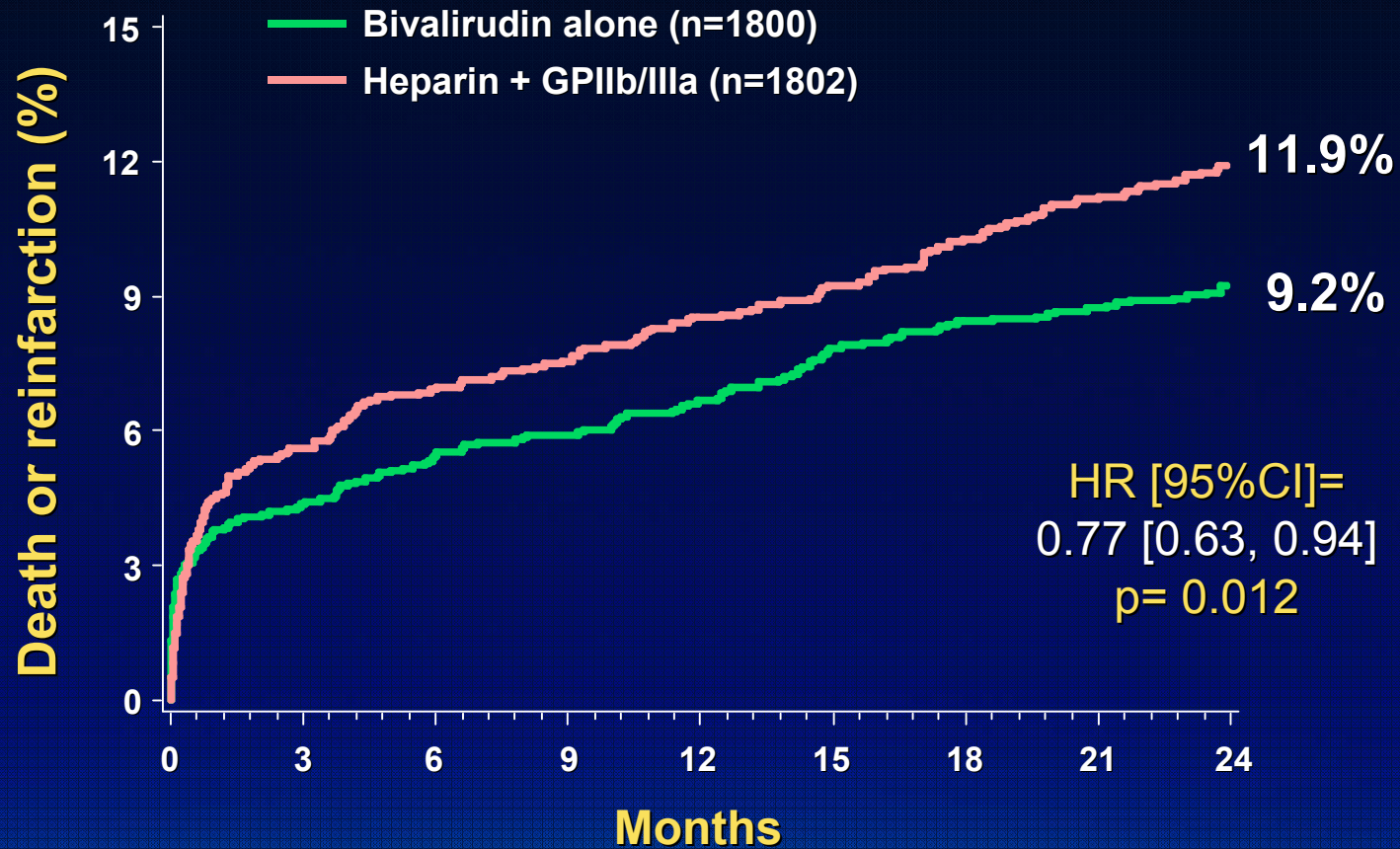
Two-Year Reinfarction



Number at risk

Bivalirudin alone	1800	1644	1603	1553	1296
Heparin+GPIIb/IIIa	1802	1622	1577	1501	1245

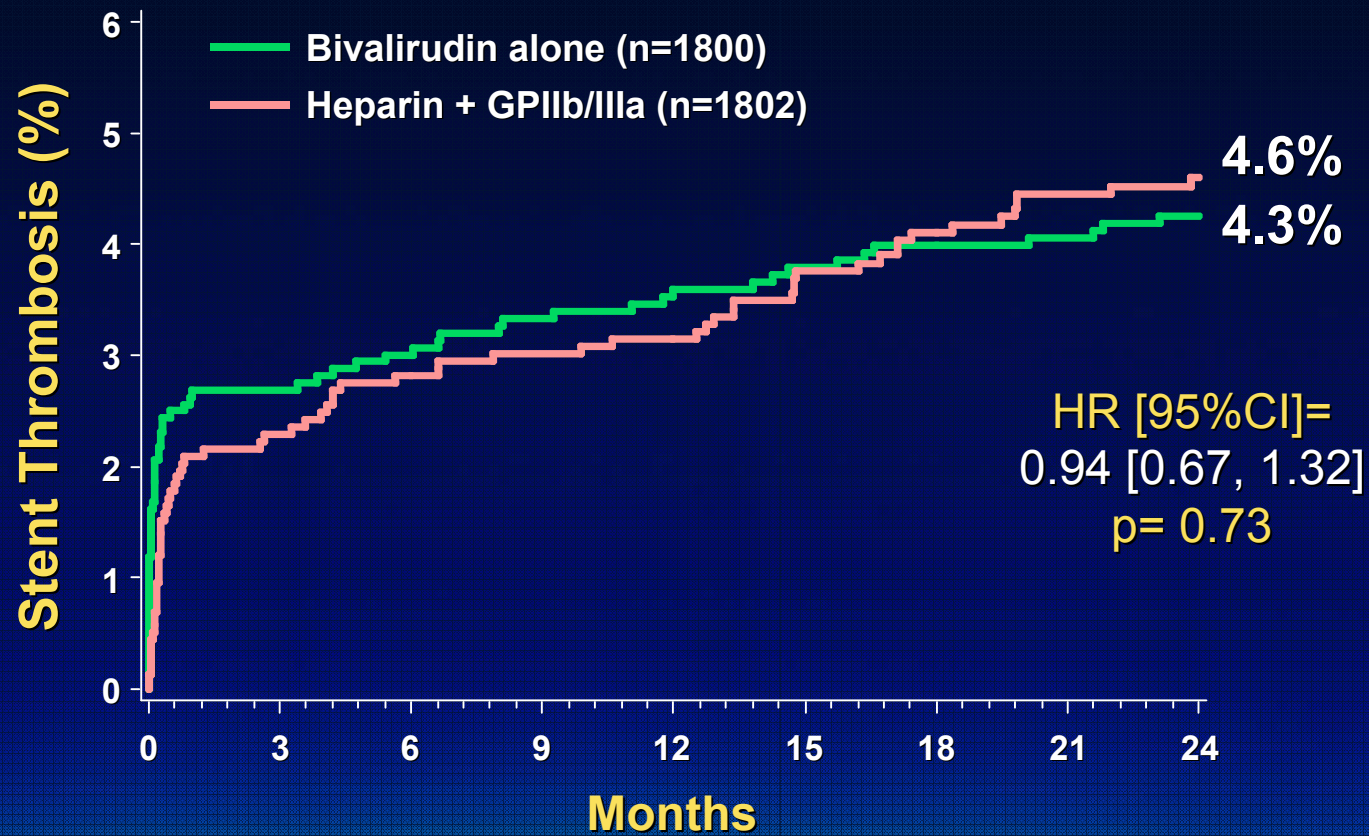
Two-Year Death or Reinfarction



Number at risk

Bivalirudin alone	1800	1644	1603	1553	1296
Heparin+GPIIb/IIIa	1802	1622	1577	1501	1245

2-Year Stent Thrombosis (ARC Definite/Probable)



Number at risk

	0	3	6	9	12	15	18	21	24
Bivalirudin alone	1611	1509	1475	1444	1444	1444	1444	1204	1204
Heparin+GPIIb/IIIa	1591	1482	1449	1449	1386	1386	1386	1153	1153

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2-Year Stent Thrombosis* (N=3,202)

	UFH + GPI (N=1591)	Bivalirudin (N=1611)	P Value
ARC definite or probable, ≤24 hours	0.3%	1.5%	<0.001
- definite, ≤24 hours	0.2%	1.5%	<0.001
- probable, ≤24 hours	0.1%	0.0%	0.32
ARC definite or probable, >24h – 2y	4.4%	2.9%	0.03
- definite, >24 hours – 2 year	3.6%	2.6%	0.11
- probable, >24 hours – 2 year	0.8%	0.3%	0.08
ARC definite or probable, ≤2 years	4.6%	4.3%	0.73
- definite, ≤2-year	3.8%	3.9%	0.71
- probable, ≤2-year	0.8%	0.3%	0.05

*All Kaplan-Meier estimates; all CEC adjudicated

HORIZONSAMI

THE LANCET

Articles

Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42): a randomised, double-blind, active-controlled, phase 2 trial

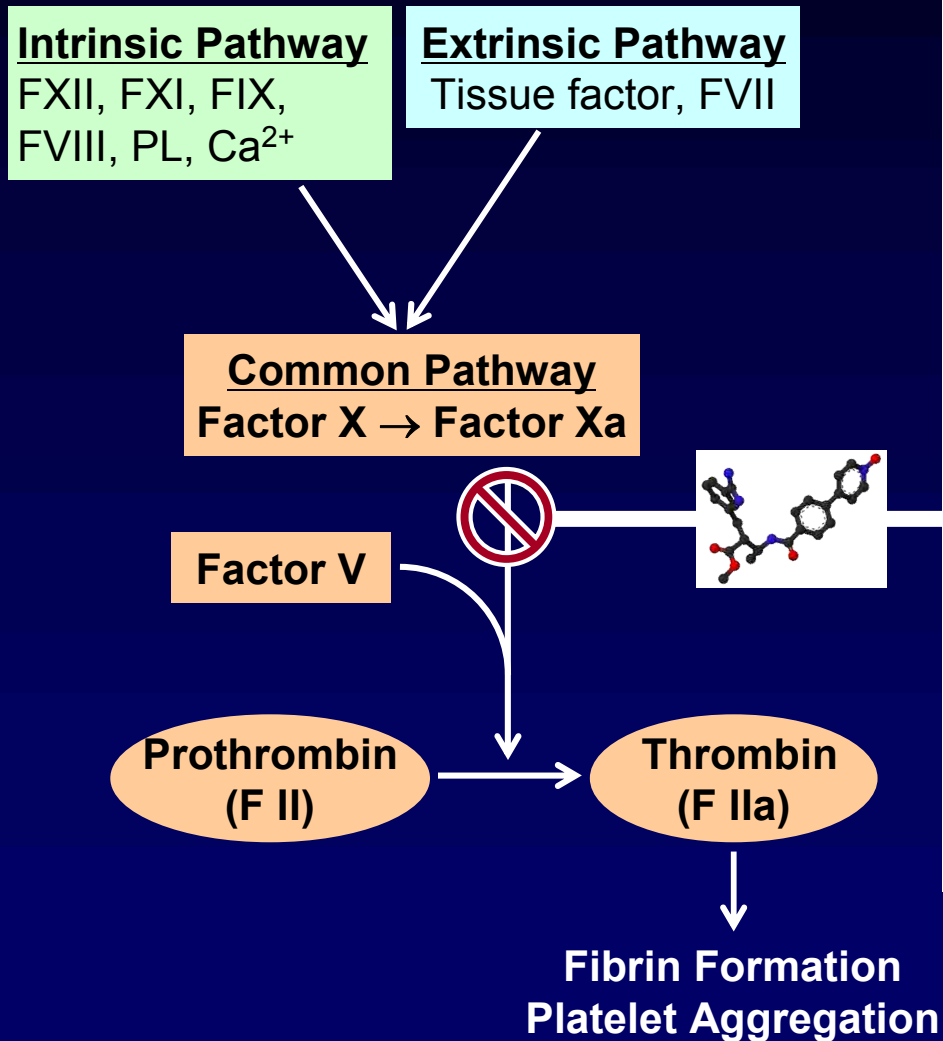


Marc S Sabatine, Elliott M Antman, Petr Widimsky, Iftikhar O Ebrahim, Robert G Kiss, André Saaiman, Rostislav Polasek, Charles F Contant, Carolyn H McCabe, Eugene Braunwald

Available at www.thelancet.com

Presentation slides available at www.timi.org

Coagulation Cascade



OTAMIXABAN

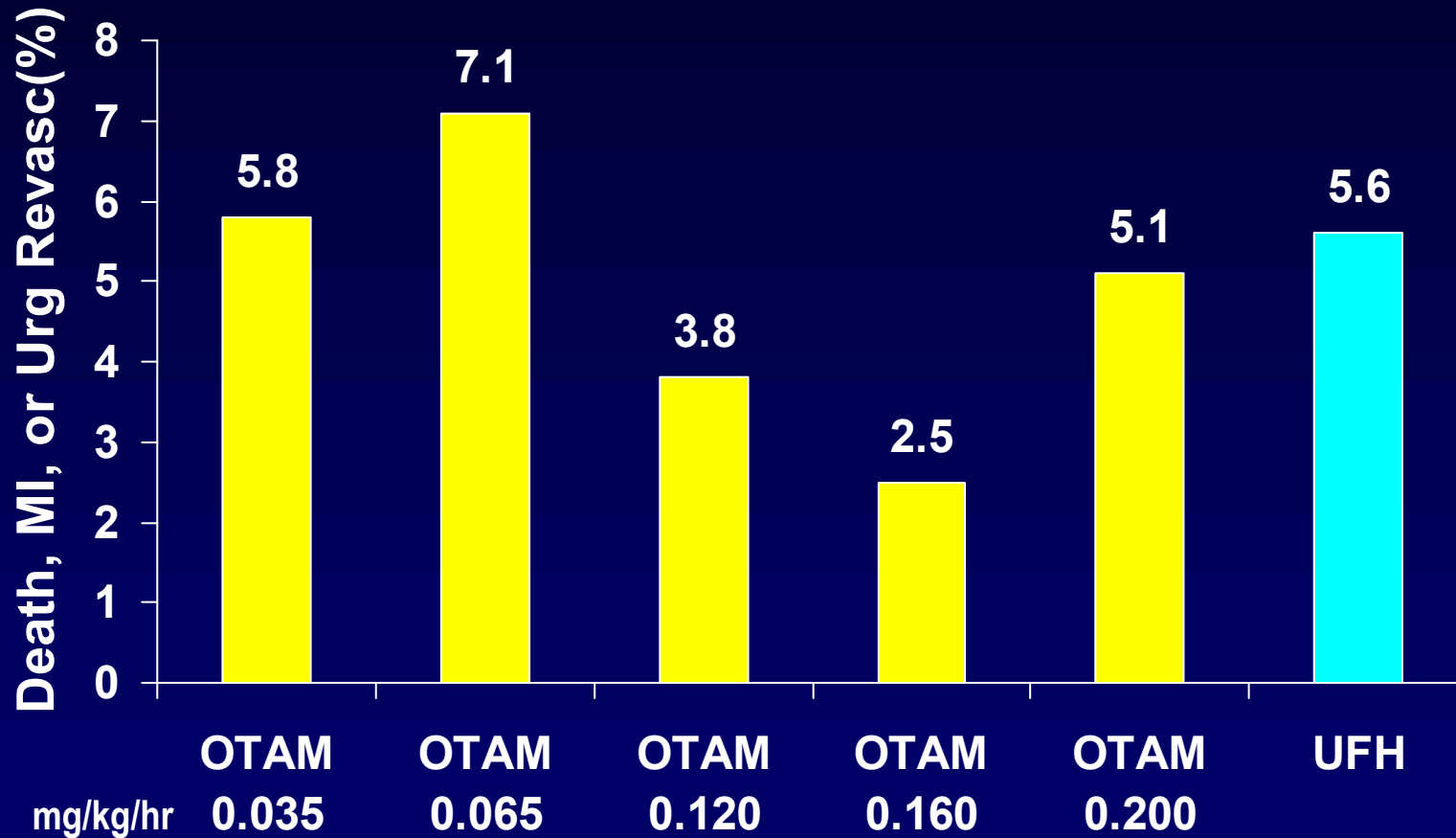
- **Specific, Direct, IV, Factor Xa Inhib**
 - Proximal inhib of coag cascade
- **Small molecule**
 - Inhibits clot-bound factor Xa, which is inaccessible to large molecule & indirect inhibitors
- **Favorable PK/PD profile**
 - Short-acting (half-life 30 min)
 - Wt-based bolus & infusion
 - No need for monitoring
 - No significant renal elimination

SEPIA-PCI

Clinical Efficacy Composite

947 patients undergoing non-urgent PCI

Greater reduction in thrombin generation w/ OTAM vs. UFH





Study Design: Phase II, Dose-Ranging



Mod-to-High Risk NSTEMI ACS (ST deviation or \oplus biomarker)
w/ Planned Early Invasive Strategy

Aspirin + Clopidogrel at or before randomization

R *double-blind*

Blinded bail-out eptifibatide if rec. ischemia or thrombotic complic. during PCI



Coronary angiography \pm PCI within 3 days

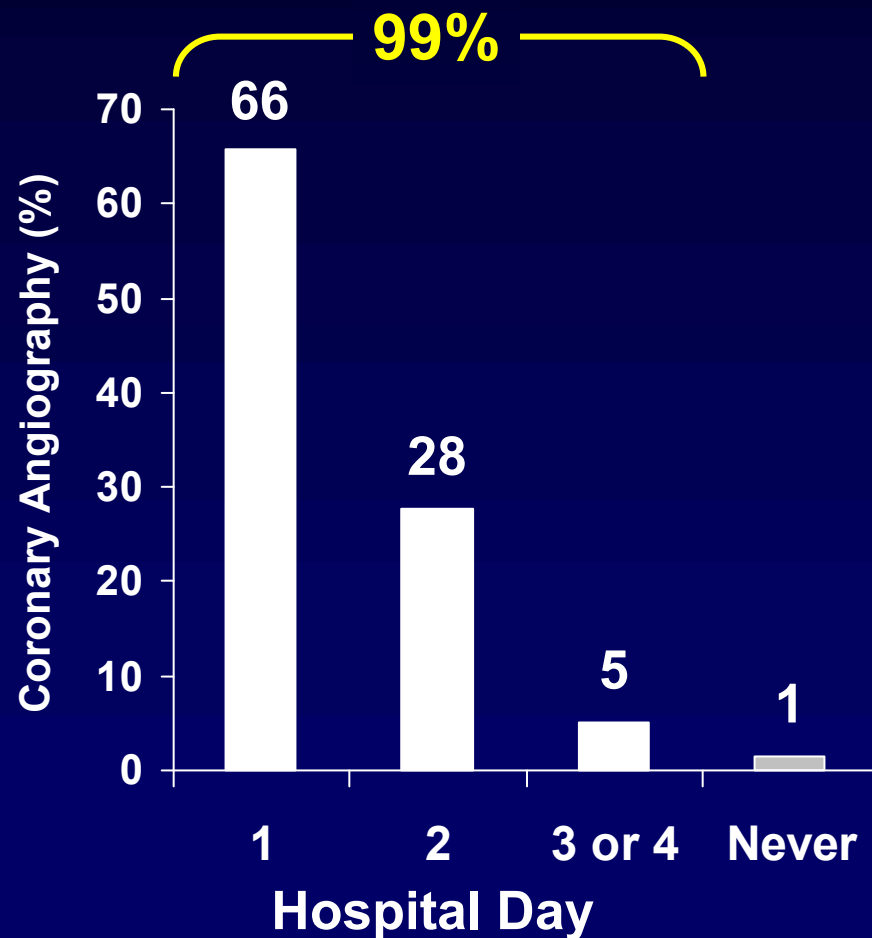
OTAM / UFH until end of PCI (or longer if indic)
Eptifibatide until 18-24 h after end of PCI

1° EP: Death, MI, Urgent Revasc, Bail-out IIb/IIIa thru 7 d

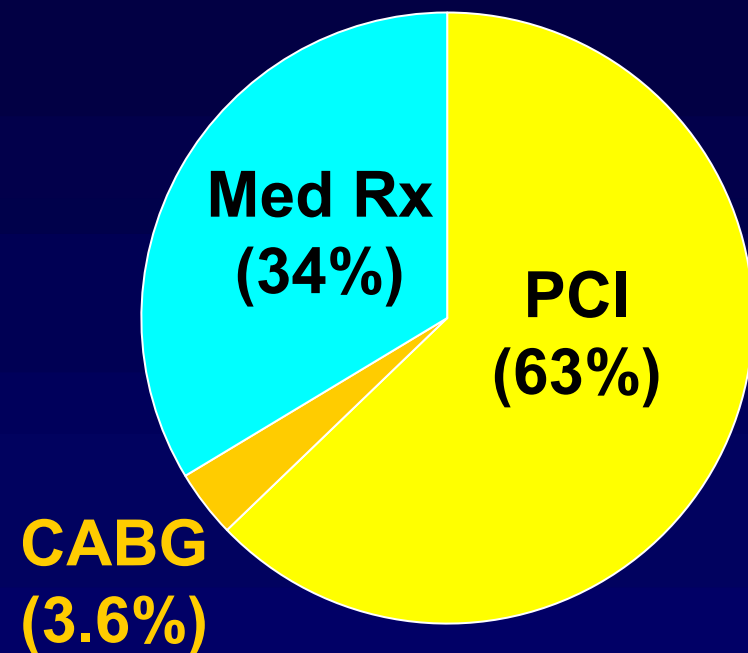
Follow-up at Day 30, Day 90, Day 180



Cardiac Procedures



Coronary Treatment



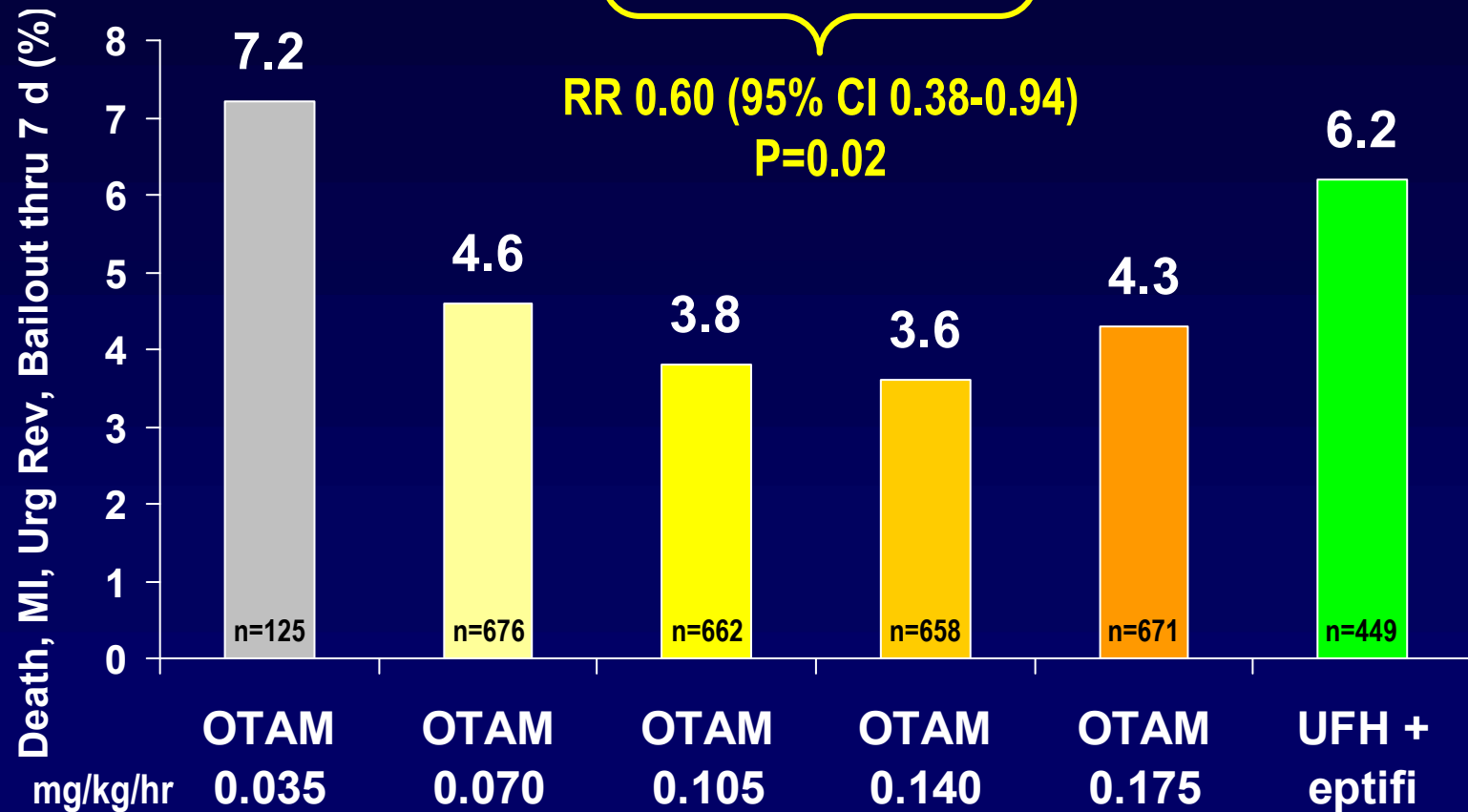


Primary Efficacy Endpoint

Death, MI, Urg Revasc, or Bailout GP IIb/IIIa



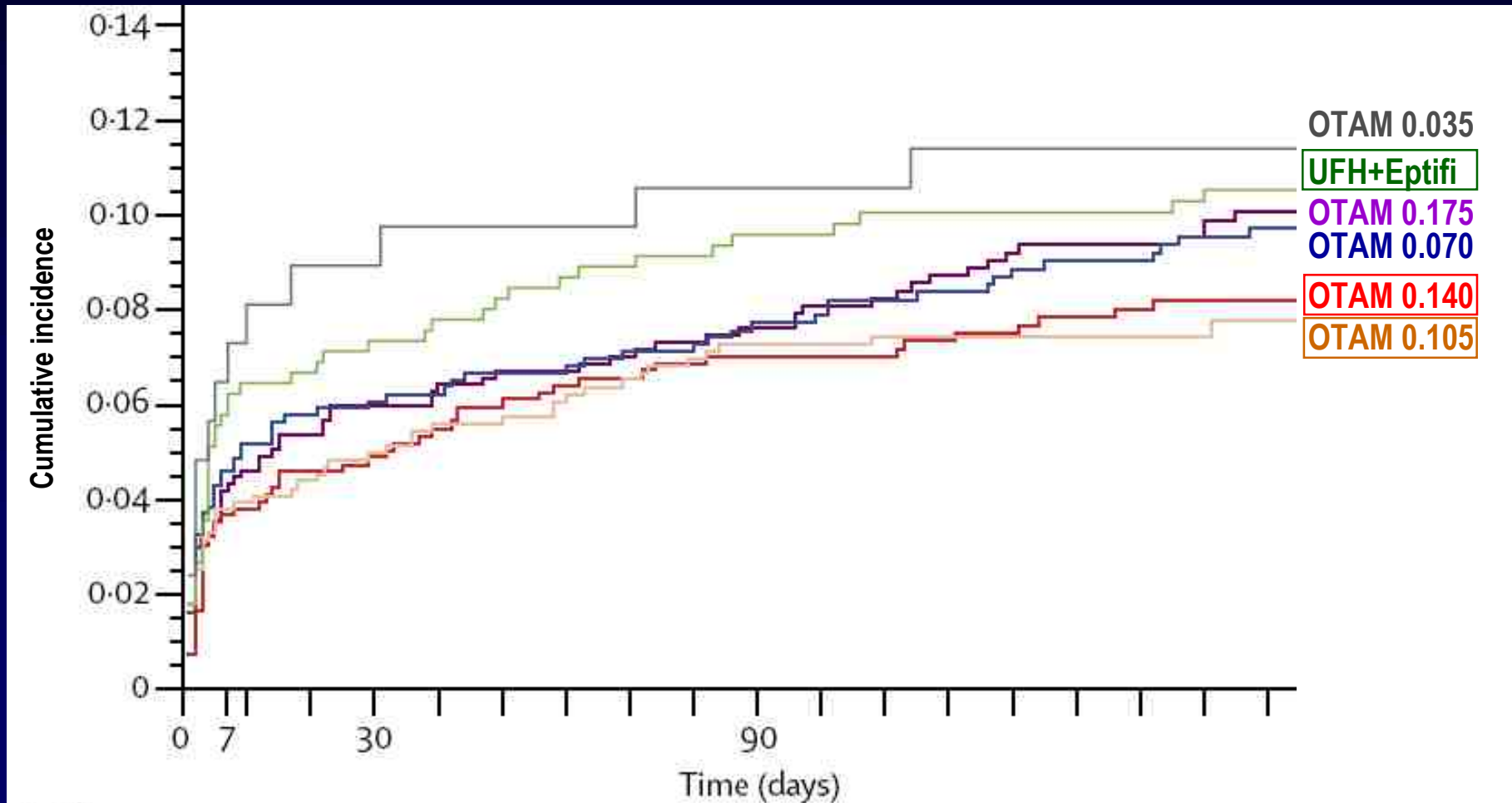
RR vs UFH 1.16 0.74 0.61 0.58 0.69
(95% CI) (0.56-2.38) (0.45-1.21) (0.36-1.02) (0.34-0.996) (0.42-1.15)



P=0.34 for trend across OTAM Dose Arms



Primary Endpoint over 180 Days

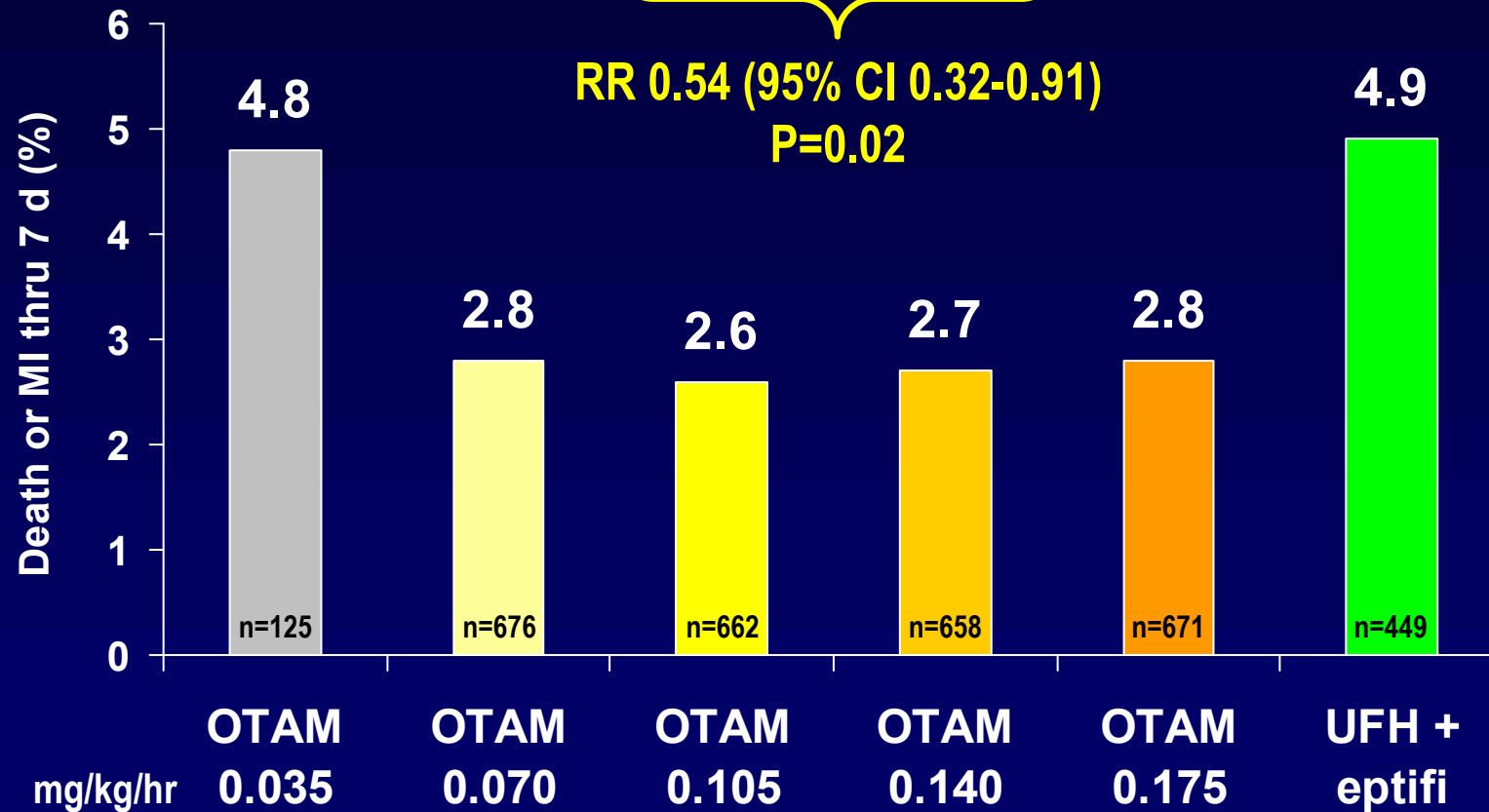




Death or MI



RR vs UFH 0.98 0.57 0.52 0.56 0.58
(95% CI) (0.41-2.36) (0.31-1.05) (0.28-0.98) (0.30-1.03) (0.32-1.06)





Thrombotic Complications



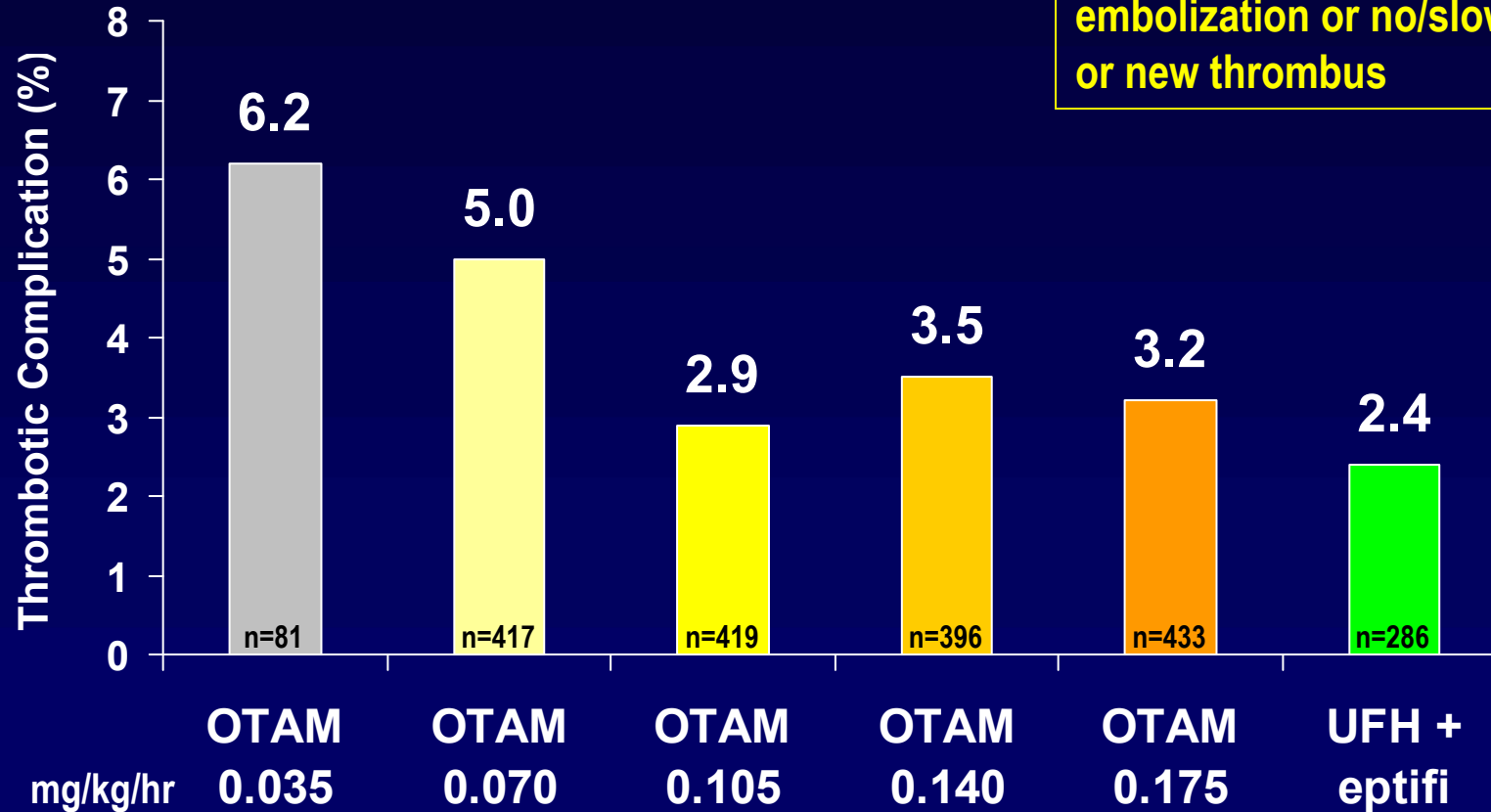
PCI Subset, *n*=2032 (63%)

RR vs UFH
(95% CI)

2.52
(0.82-7.74)

2.06
(0.89-4.78)

Defined as: abrupt or side branch closure, distal embolization or no/slow reflow, or new thrombus



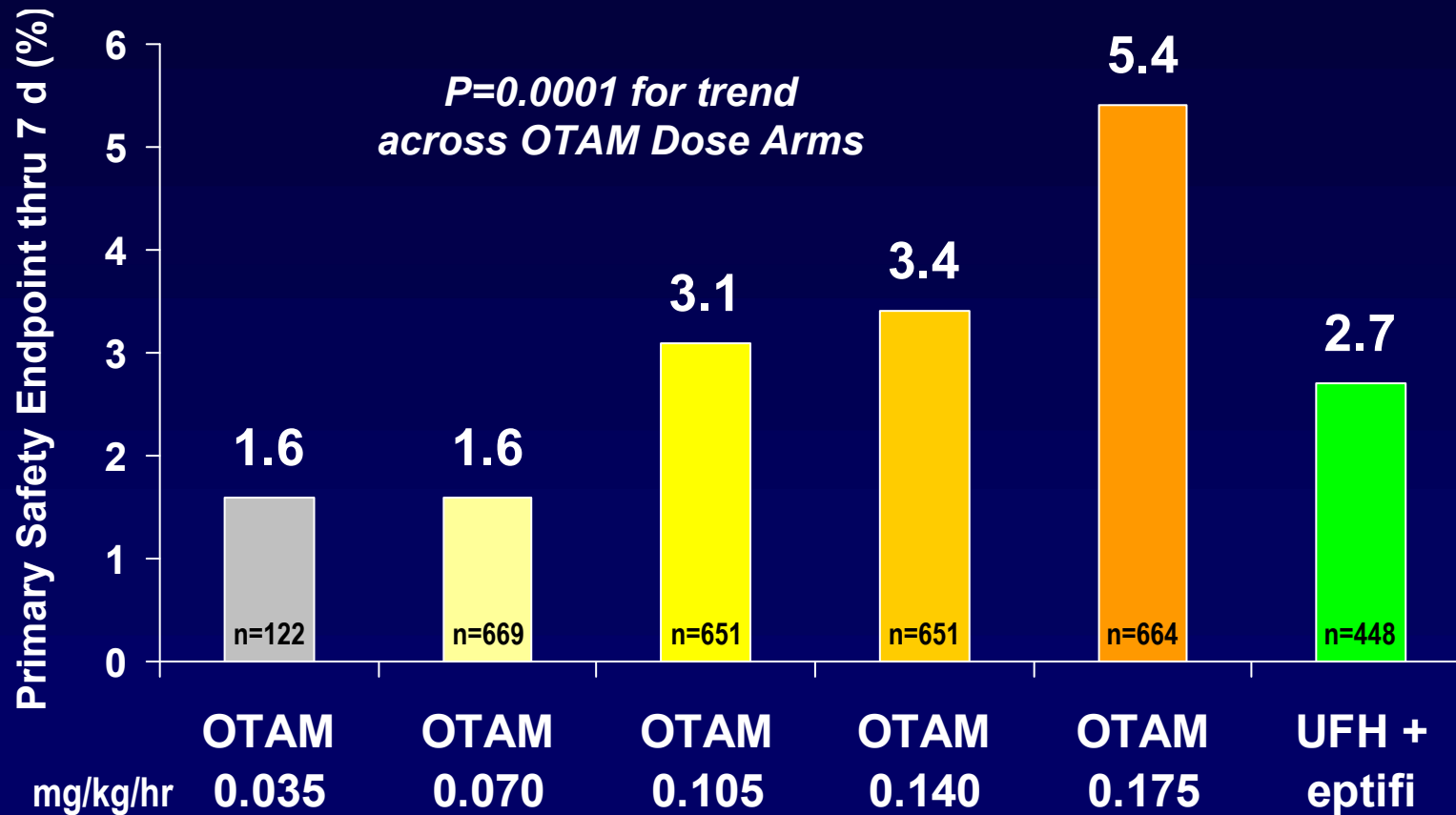


Primary Safety Endpoint

TIMI Major or Minor Bleed unrelated to CABG
(defined as bleed with \downarrow in Hgb of ≥ 3 g/dL or ICH)



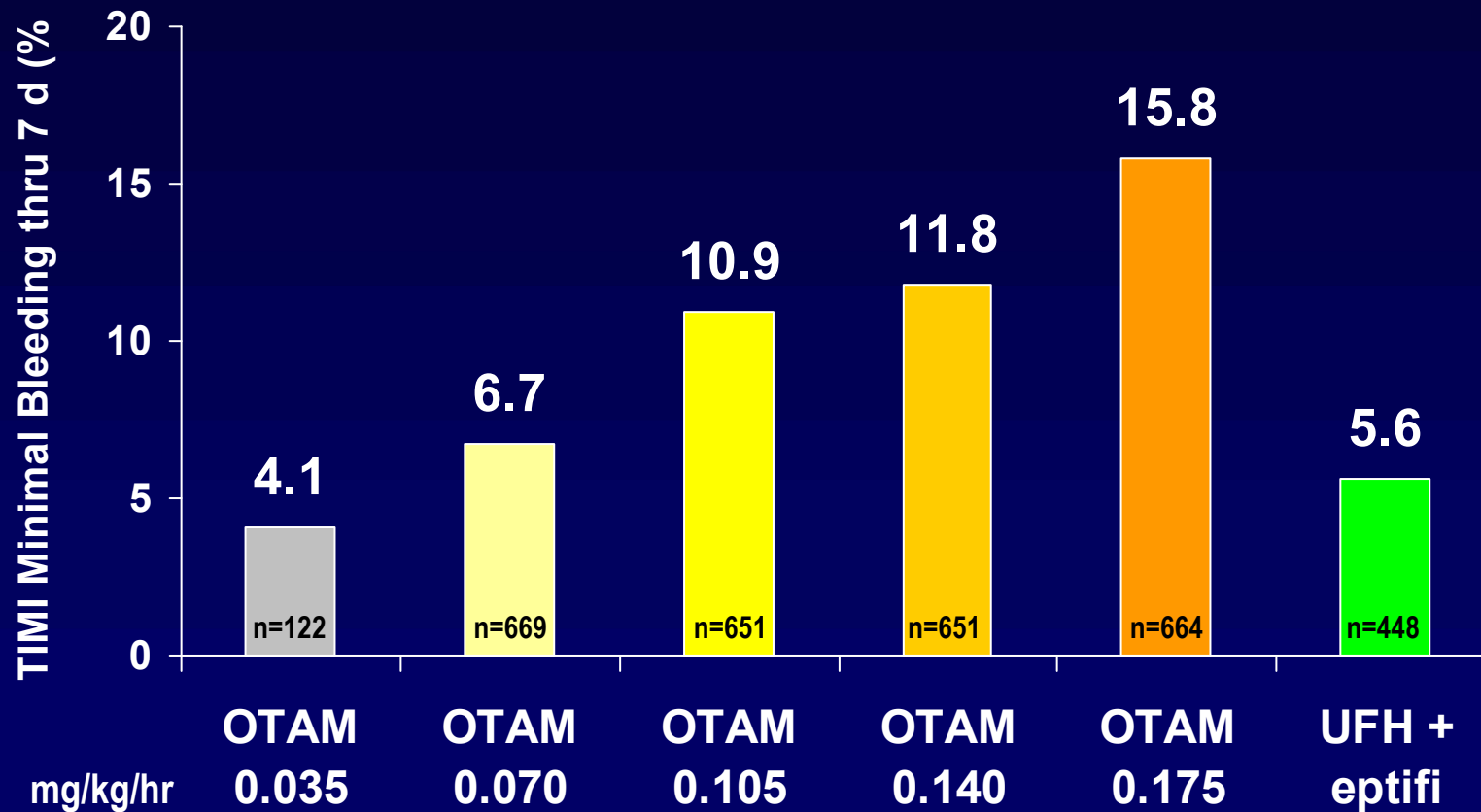
RR vs UFH 0.61 0.61 1.15 1.26 2.02
(95% CI) (0.14-2.70) (0.27-1.38) (0.57-2.32) (0.63-2.52) (1.07-3.85)



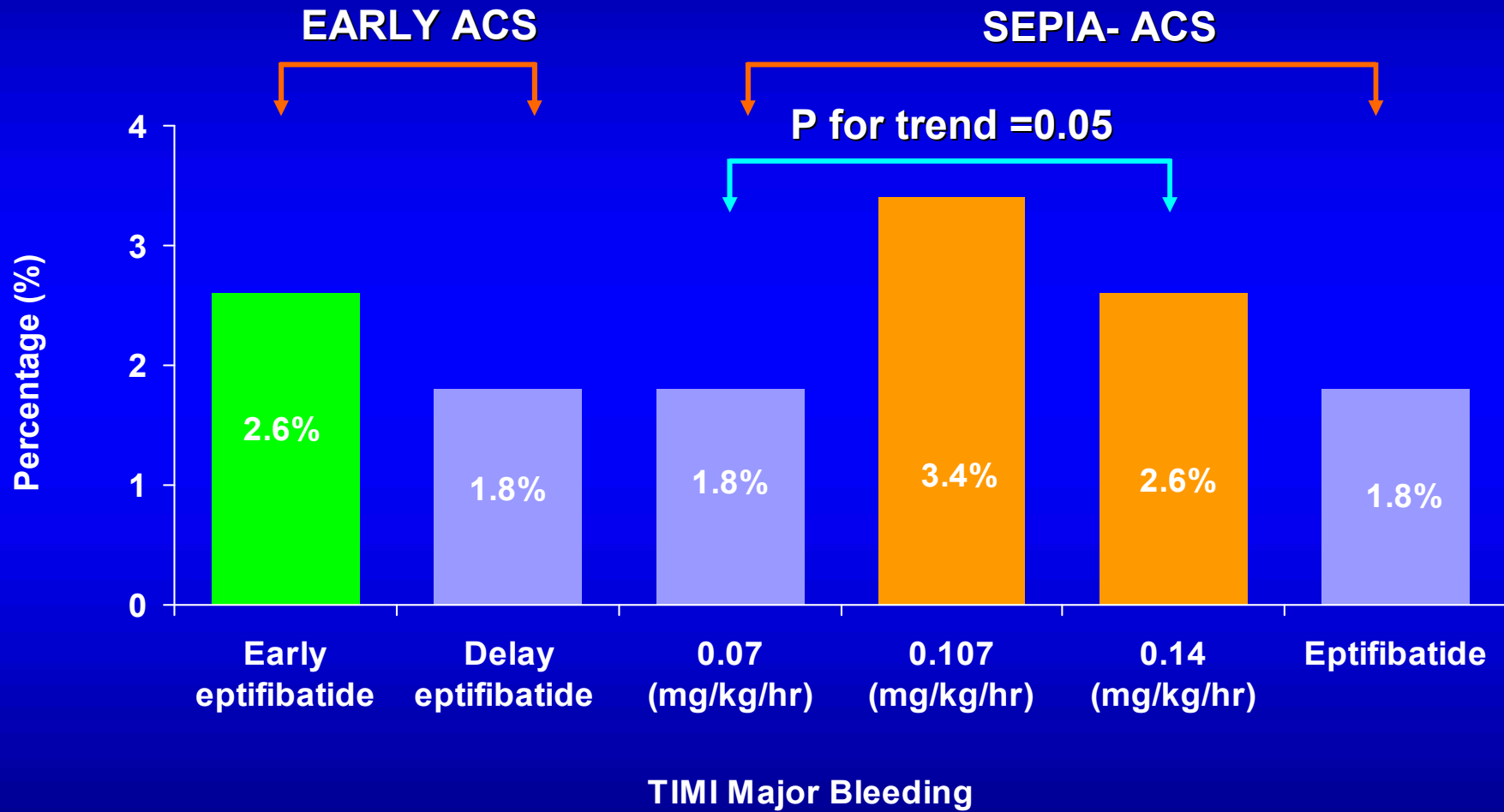


TIMI Minimal Bleeding

(defined as any overt bleed with ↓ in Hgb of <3 g/dL)

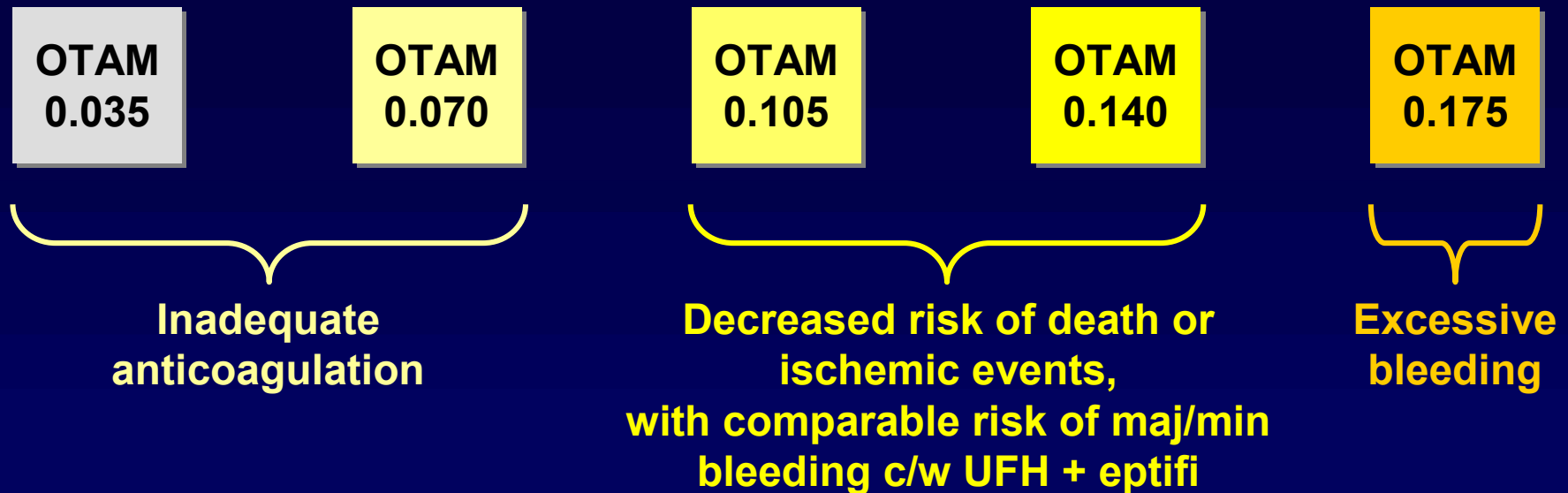


TIMI major bleeding





Conclusions



Otamixaban 0.105-0.140 mg/kg/h appears to be best range for further study as a replacement for UFH + GP IIb/IIIa