

Taking the Evidence-Based Approach to ACS Examination of New Trial Data

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Core Pharmacotherapy to Support an Invasive Strategy in ACS

Upstream and peri-procedural
Aspirin
Clopidogrel pre or post angio/PCI
Unfractionated heparin +
GP IIb/IIIa inhibitor (GPI) – upfront or PCI

The New Options

**Enoxaparin
(+ GPI)**

**Fondaparinux
(+ GPI)**

**Bivalirudin alone
(Provisional GPI)**

Trial: SYNERGY

OASIS-5

ACUITY

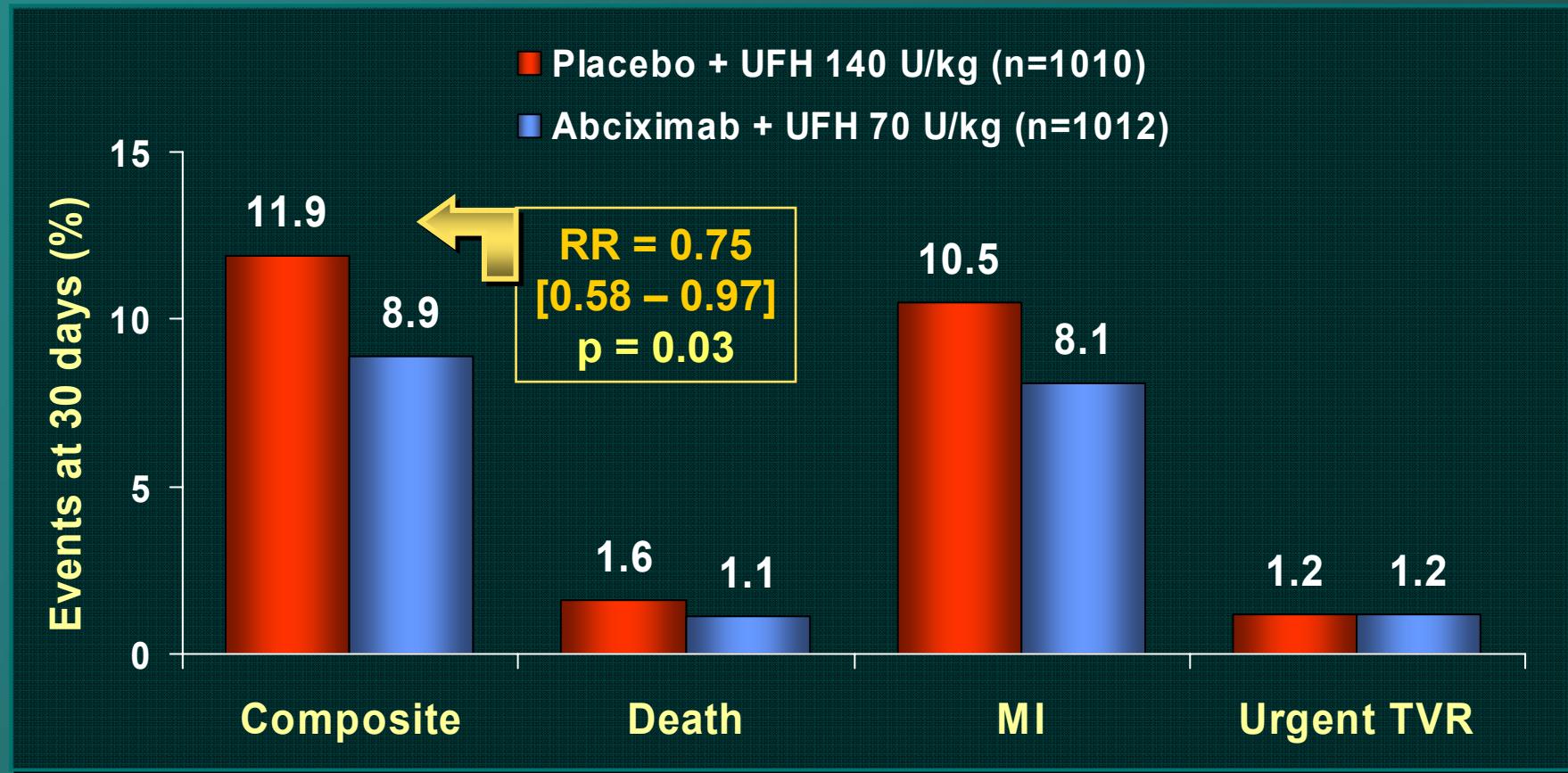


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CARDIOVASCULAR
RESEARCH FOUNDATION A red, stylized, flowing graphic element.

ISAR-REACT 2

Placebo-controlled randomized trial of abciximab in 2,022 ACS pts pre-loaded with 600 mg clopidogrel for ≥ 2 hrs
Inclusion: ACS with troponin +, ST changes, or new LBBB



Kastrati A et al. JAMA 2006;295:1531-8



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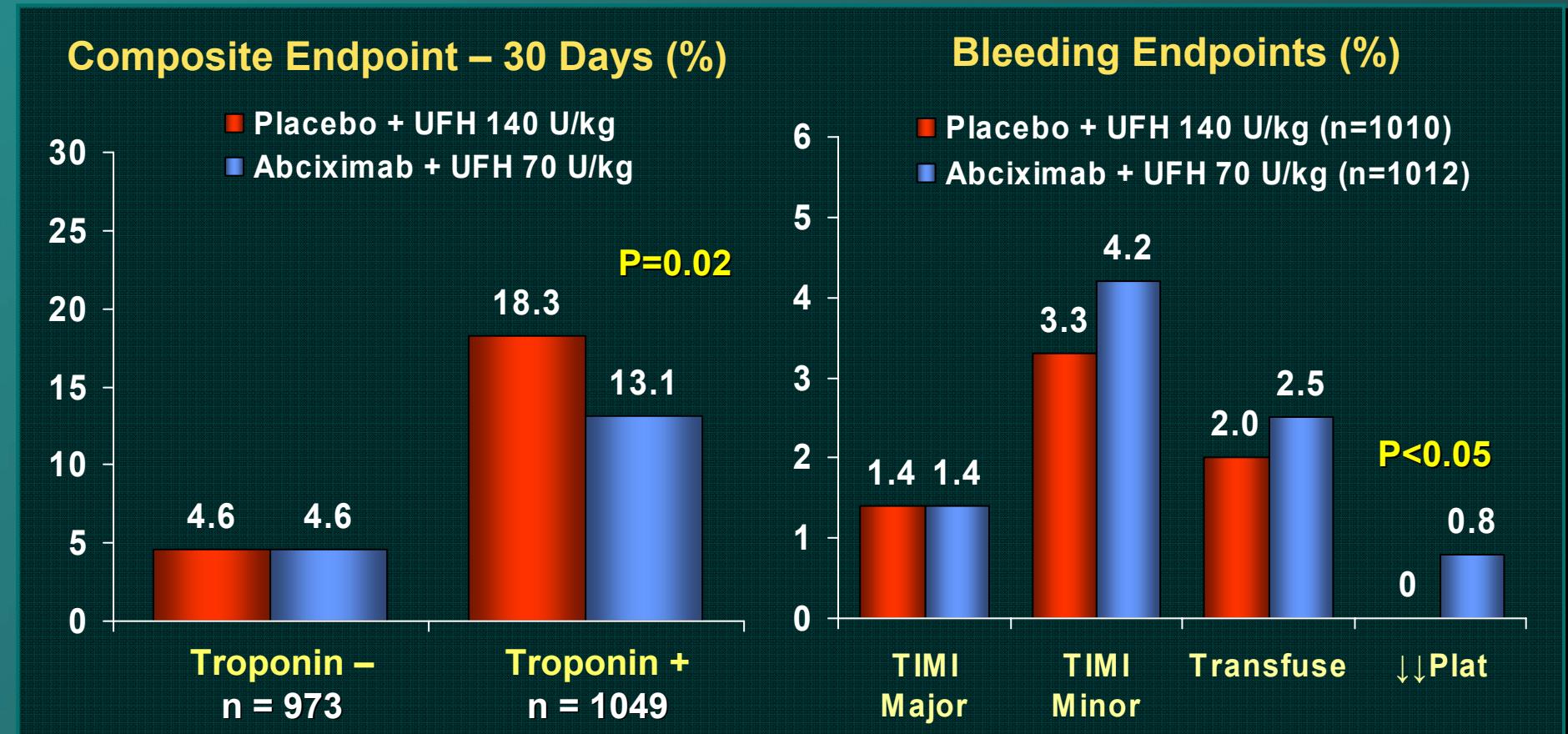
TCT 2006

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ISAR-REACT 2

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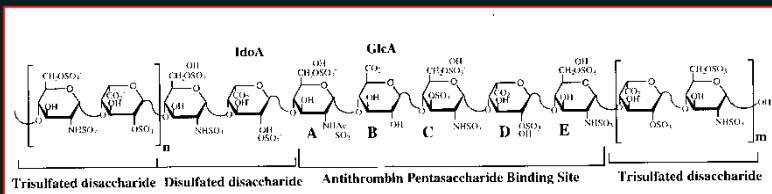
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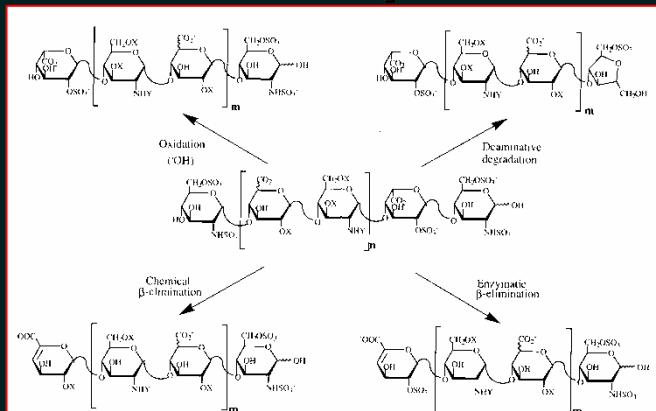
Anti-thrombin Alternatives for Patients with ACS and Those Undergoing PCI

Unfractionated heparin



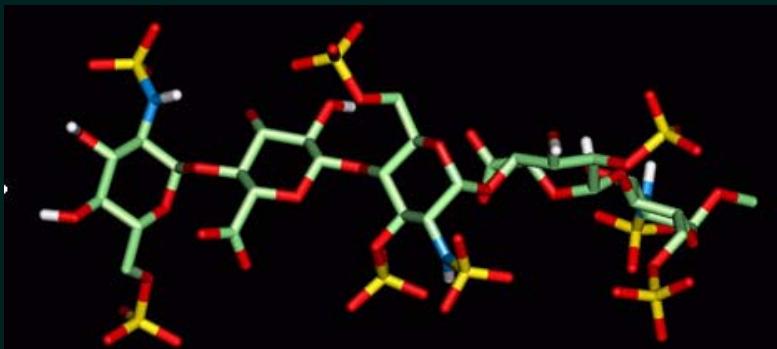
+ GP IIb/IIIa inhibitors

LMW heparin



+ GP IIb/IIIa inhibitors

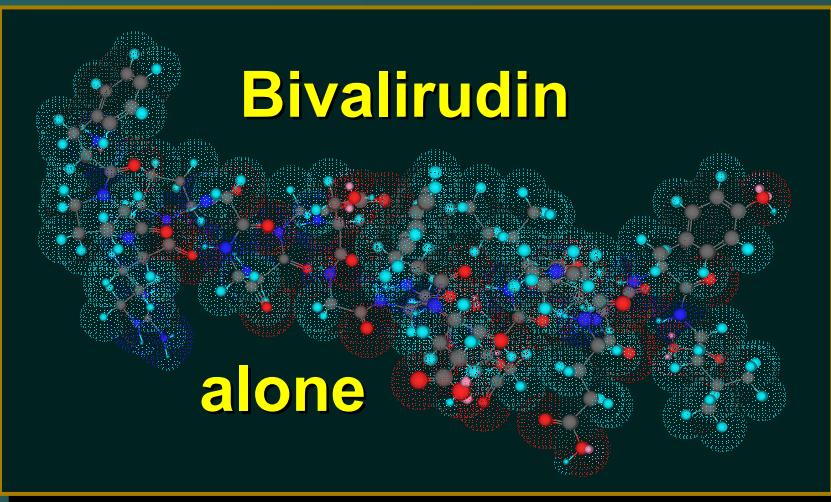
Fondaparinux



+ GP IIb/IIIa inhibitors

Bivalirudin

alone



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Overcoming Limitations of Heparins

Attribute	UFH	Enox	Fonda	Bivalirudin
Active moieties in substance	30-35%	40-60%	100%	100%
Action independent of AT	No	No	No	Yes
Non-specific binding	Yes	Partial	No	No
Variable PK-PD	Yes	Less	No	No
Inhibits fibrin-bound thrombin	No	No	No	Yes
Inhibits contact activation (catheter thrombosis)	Yes	Less	No	Yes
Activates/aggregates platelets	Yes	+/-	?	Inhibits
T _{0.5}	60-90'	270'	1032 hrs	25'
PF-4 complexing/risk of HIT	Yes	Reduced	Low	No

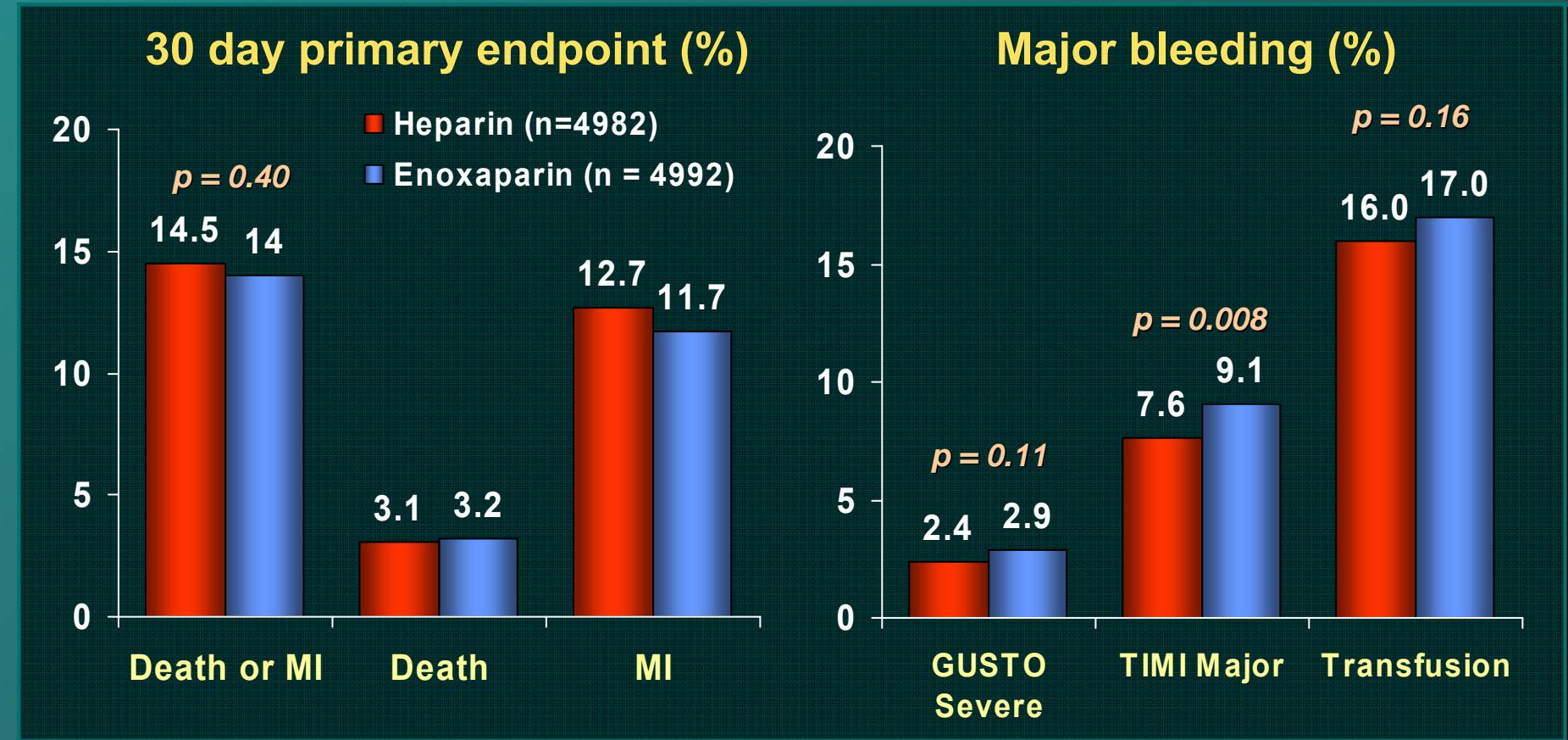


SYNERGY Trial

Enoxaparin vs. Heparin in 10,027 High Risk ACS Pts

Inclusion: 2/3 age ≥ 60 , EKGΔ or troponin/CKMB+ (85%)

Early invasive strategy (92% cath, 46% PCI, 19% CABG)



SYNERGY Investigators. JAMA 2004;292:45-54



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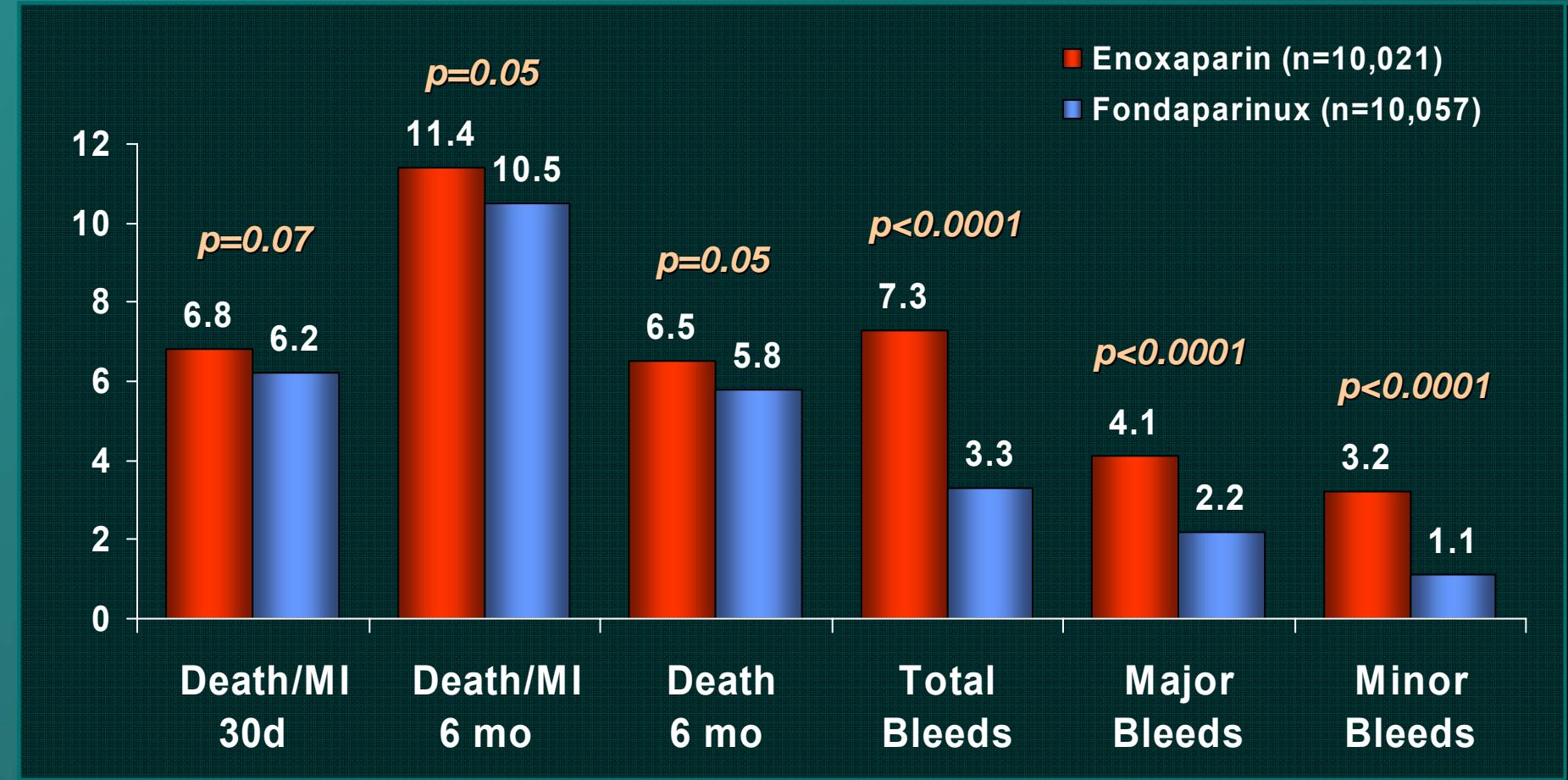
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OASIS-5

Fondaparinux vs Enoxaparin in ACS

20,078 Pts with Unstable Angina or NSTEMI within 48 hrs
70% troponin +



Yusuf S et al. NEJM 2006;354:1464-76



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OASIS 5: Select Features

	Enoxaparin (n=10,021)	Fondaparinux (n=10,057)
N days on drug	5.2 ± 2.3	5.4 ± 2.4
<u>In-hospital medications and procedures</u>		
Angiography	63.1%	63.5%
PCI	34.3%	34.3%
CABG	9.0%	9.6%
Clopidogrel/ticlopidine	67.2%	67.6%
GP IIb/IIIa	17.6%	18.6%
- During PCI	41.0%	41.7%
Unfractionated heparin	31.2%	22.0%





OASIS-5

Fondaparinux vs. Enoxaparin in ACS

Outcome in Pts Undergoing PCI Within First 8 Days (N = 6239)

	Enoxaparin (n = 3104)	Fondaparinux (n = 3135)
Unfractionated heparin	55.5	20.8
GP IIb/IIIa inhibitor	41.0	41.7
Thienopyridine	74.6	74.9
Acute closure, new thrombus, dissection or no reflow	5.2	6.0
Catheter-related thrombi (CEC)	0.4	0.9*
Death, MI or stroke (30 days)	7.3	7.4
Major bleeding	5.4	2.8

Yusuf S et al. NEJM 2006;354:1464-76

*P=0.008



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OASIS 6: Fondaparinux During Primary PCI

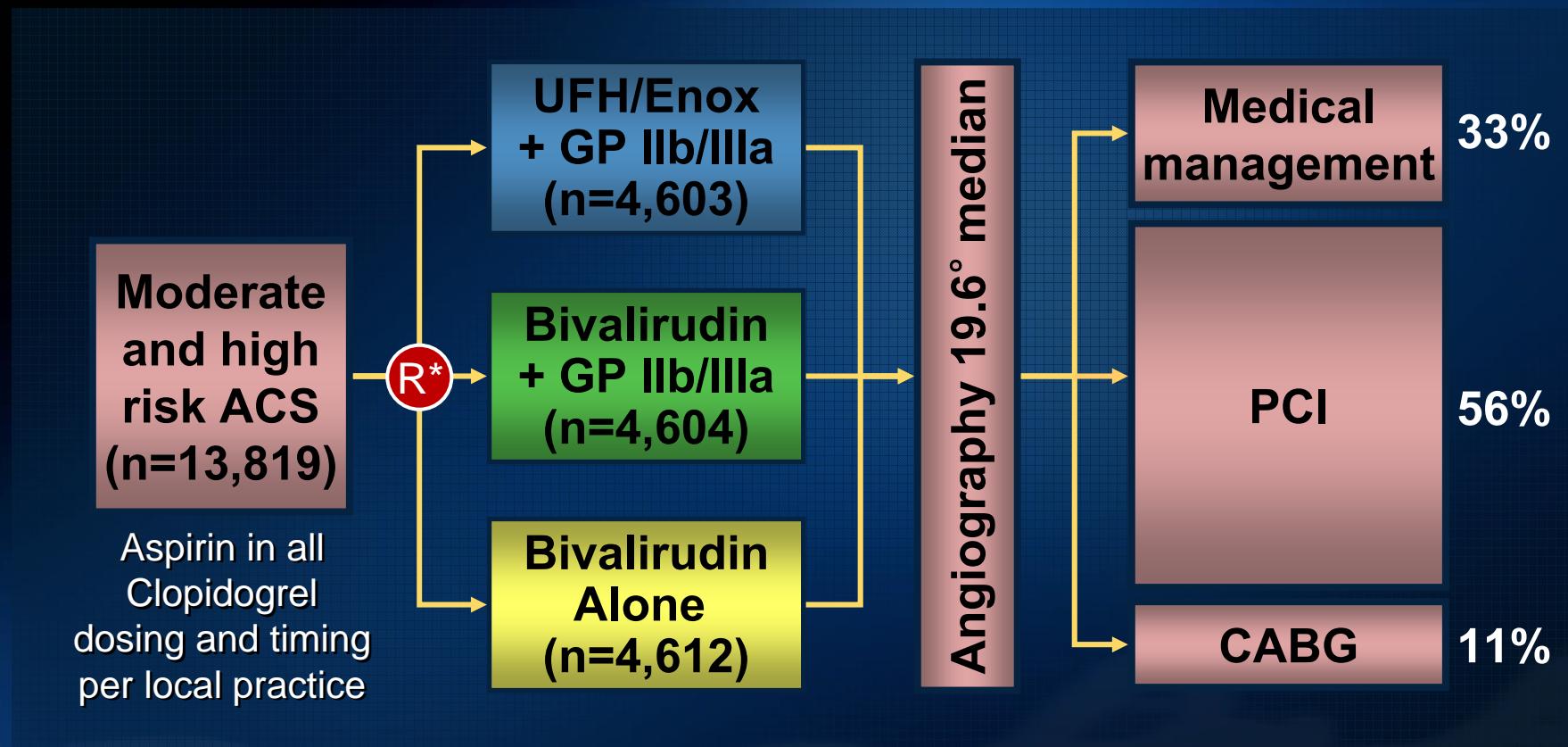
3,788 pts with STEMI undergoing primary PCI were randomized to UFH for 24-48 hrs vs. the factor Xa inhibitor fondaparinux 2.5 mg SQ QD for up to 8 days in a placebo-controlled double-blind trial

30 day events	UFH (n=1,898)	Fonda (n=1,890)	P value
Death or MI	4.9%	6.0%	0.13
Severe bleed	0.5%	0.8%	0.16
Catheter thrombus	0%	1.2%	<0.001
Coronary complications*	11.9%	14.3%	0.04

*Abrupt coronary closure, new angio thrombus, catheter thrombus, no reflow, dissection, or perforation

Bivalirudin in ACS: ACUITY

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



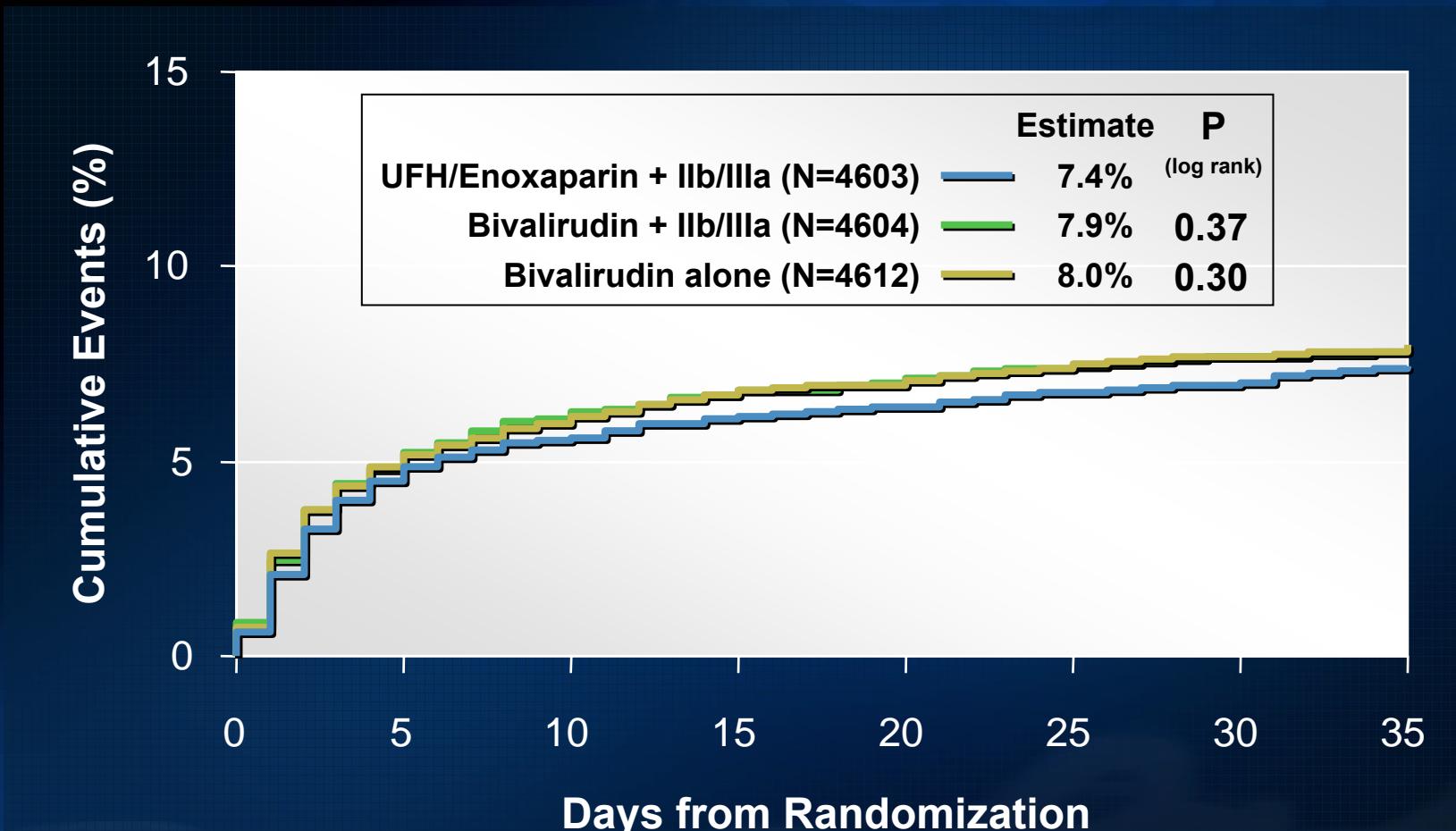
*Stratified by pre-angiography thienopyridine use or administration

Stone GW et al. NEJM 2006;355:2203-16

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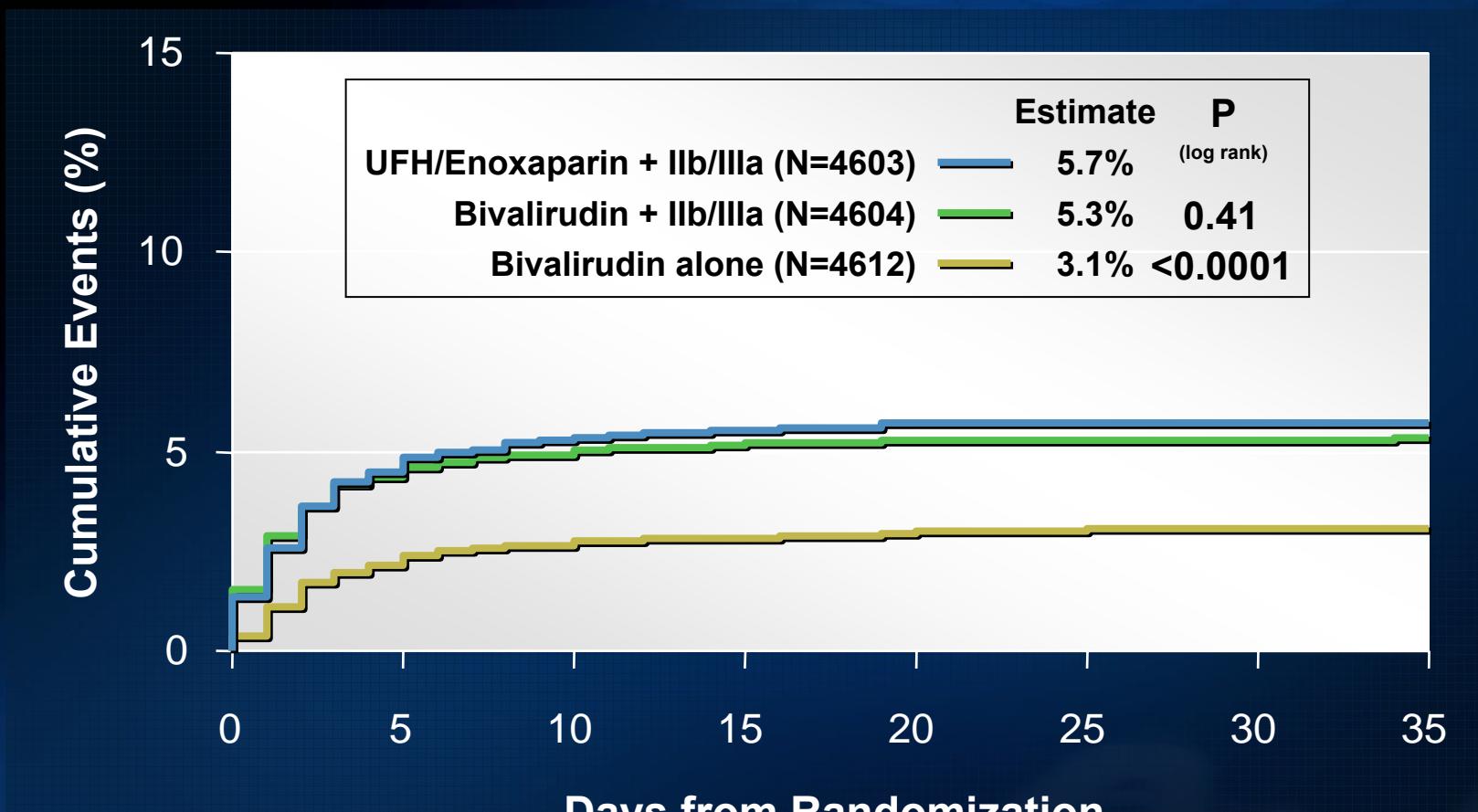
Ischemic Composite Endpoint

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



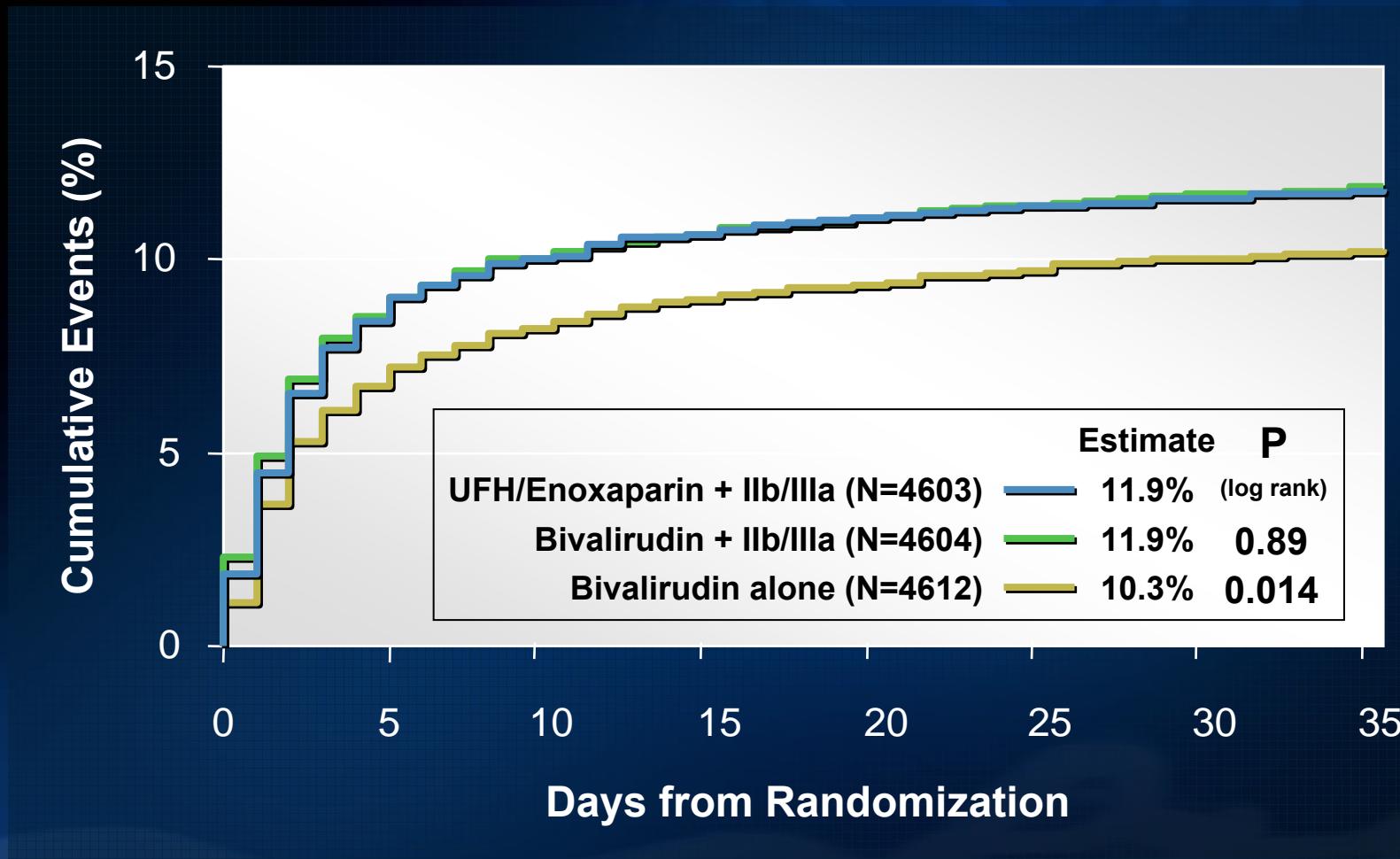
Major Bleeding Endpoint

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



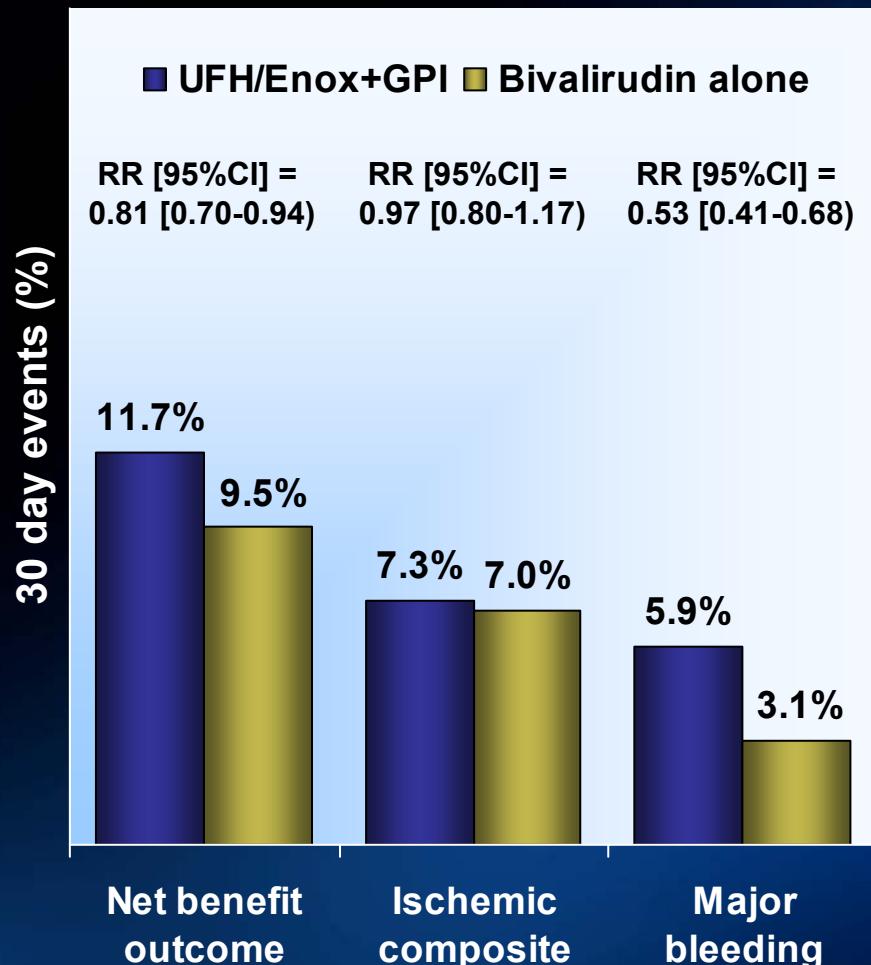
Net Clinical Outcome Composite Endpoint

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

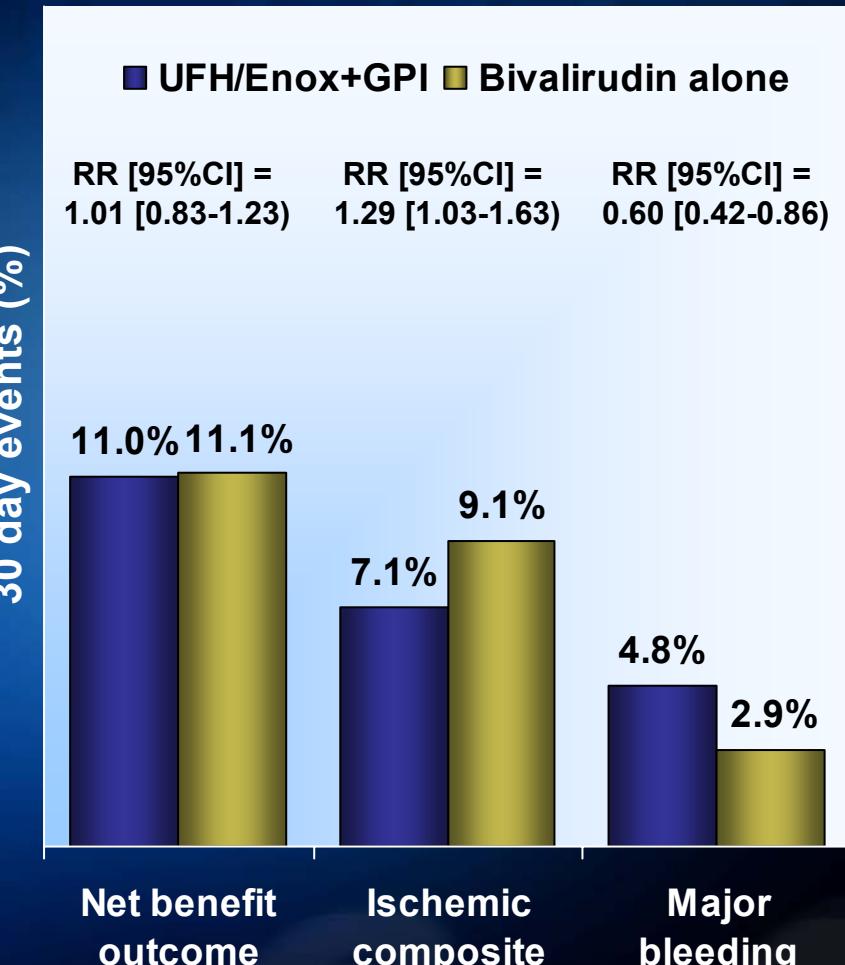


Impact of Thienopyridine Pre-Administration

UFH/Enoxaparin + GPI vs. Bivalirudin Alone



**Thienopyridine
pre angio/interv (n=5,753)**

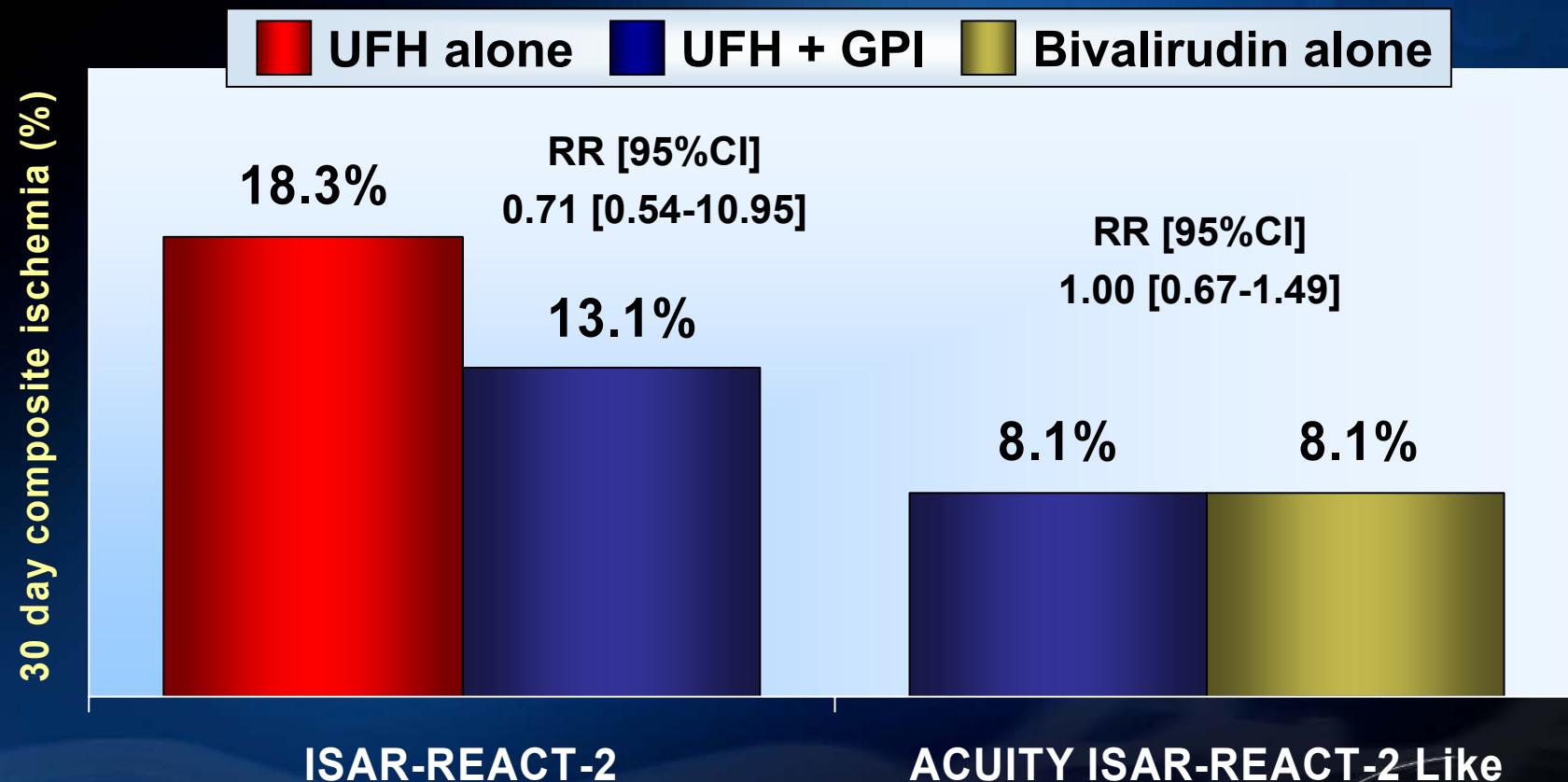


**No thienopyridine
pre angio/interv (n=3,304)**

Net benefit $P_{int}=0.08$; Ischemic composite $P_{int}=0.054$; Major bleed $P_{int}=0.53$

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Composite Ischemia: ISAR-REACT-2 Pts (N=2,022) **vs.**
ACUITY “ISAR-REACT-2 Like” Pts (N=1,358)
*Troponin+ PCI pts, thienopyridine prior to PCI,
GPI started after angiography but before PCI*

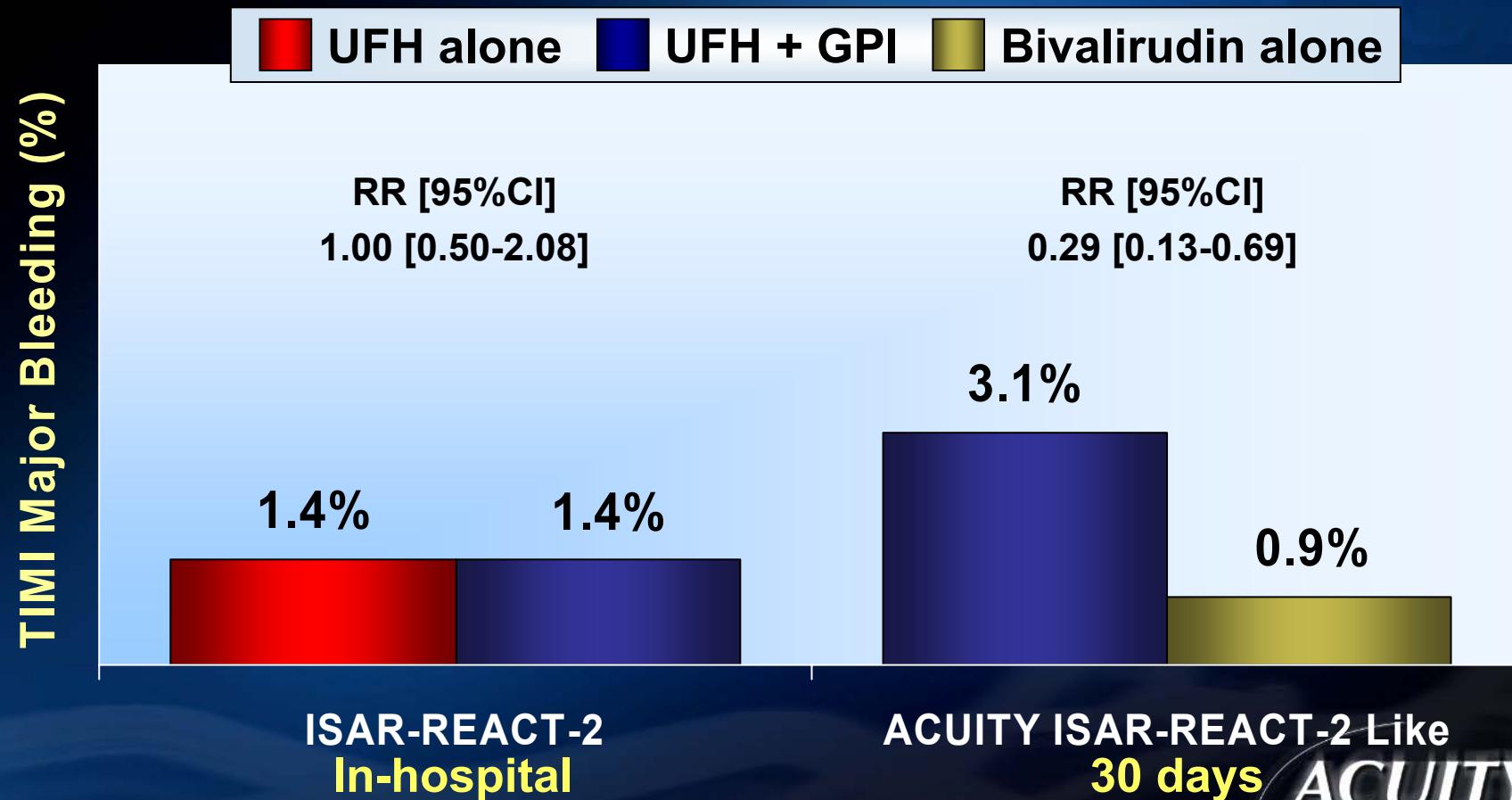


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PCI

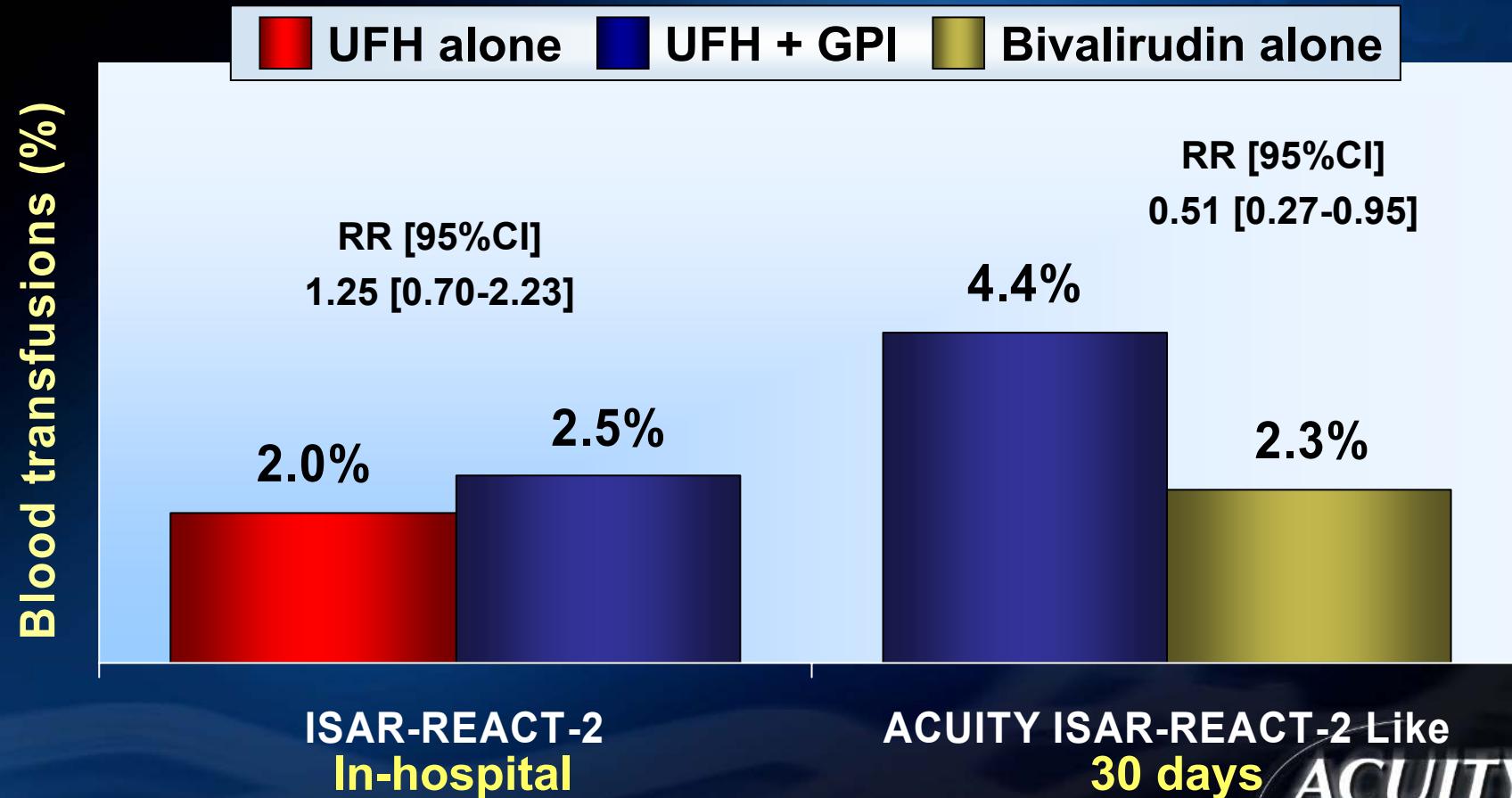
TIMI Major Bleeding: ISAR-REACT-2 Pts (N=2,022) vs.

ACUITY “ISAR-REACT-2 Like” Pts (N=1,358)

*Troponin+ PCI pts, thienopyridine prior to PCI,
GPI started after angiography but before PCI*



Blood transfusions: ISAR-REACT-2 Pts (N=2,022) vs.
ACUITY “ISAR-REACT-2 Like” Pts (N=1,358)
*Troponin+ PCI pts, thienopyridine prior to PCI,
GPI started after angiography but before PCI*



Core Pharmacotherapy to Support an Invasive Strategy in ACS: Paradigm Shift

