Direct Thrombin Inhibitors for PCI Pharmacology: Role of Bivalirudin in High-Risk PCI

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April 2007

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I. Background

II. REPLACE-2 Outcomes

III. ADEST Registry: High Risk Subgroups

IV. STENT Registry: High Risk Subgroup—Bivalirudin vs Heparin+GPIIbIIIa Agents

V. ACUITY PCI: High-Risk Subgroups

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ACC/AHA Class I Recommendations for Antithrombotic Therapy*

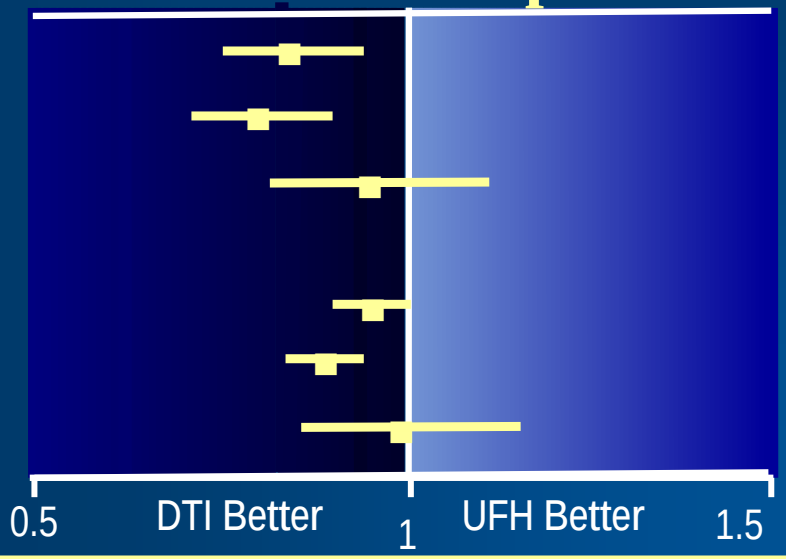
Possible ACS	Likely/Definite ACS	Definite ACS With Invasive Strategy (Catheterization/PCI) or High Risk (IIa)*
Aspirin	Aspirin + SQ LMWH* *or* IV Heparin Clopidogrel	Aspirin + IV Heparin + IV Platelet GP IIb/IIIa Antagonist Clopidogrel

* Class IIa: enoxaparin preferred over UFH unless CABG planned within 24 hours.

ACC, American College of Cardiology; AHA, American Heart association; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; SQLMWH, subcutaneous low molecular-weight heparin; IV, intravenous.

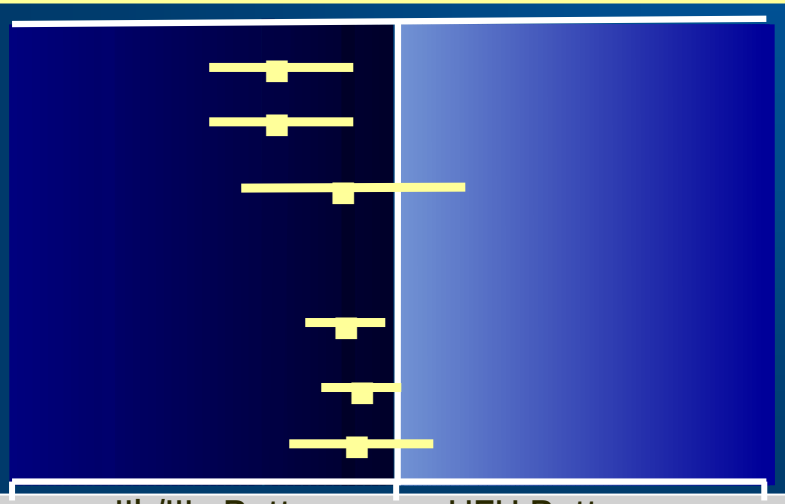
Braunwald E, et al. *J Am Coll Cardiol.* 2000;36:970-1062.

Direct Thrombin Inhibitors or GP IIb/IIIa Agents Versus Heparin Alone: ACS Meta-analyses



DTI vs UFH (end of Rx)	DTI	UFH	OR
Death/MI	4.3%	5.1%	0.85
MI	5.0%	5.8%	0.80
Death	7.4%	8.2%	0.95
DTI vs UFH (30 days)			
Death/MI	1.9%	2.0%	0.92
MI	2.2%	2.3%	0.88
Death	3.6%	3.7%	0.99

DTI Collab Group. *Lancet* 2002;359:294-302)



IIb/IIIa vs UFH (end of Rx)	IIb/IIIa	UFH	OR
Death/MI	5.7%	6.9%	0.84
MI	4.5%	5.6%	0.83
Death	1.2%	1.3%	0.93
IIb/IIIa vs UFH (30 days)			
Death/MI	10.8%	11.8%	0.91
MI	7.4%	8.1%	0.92
Death	3.4%	3.7%	0.91

Boersma *Lancet* 2002;359:189-98 (NSTE-ACS patients only)

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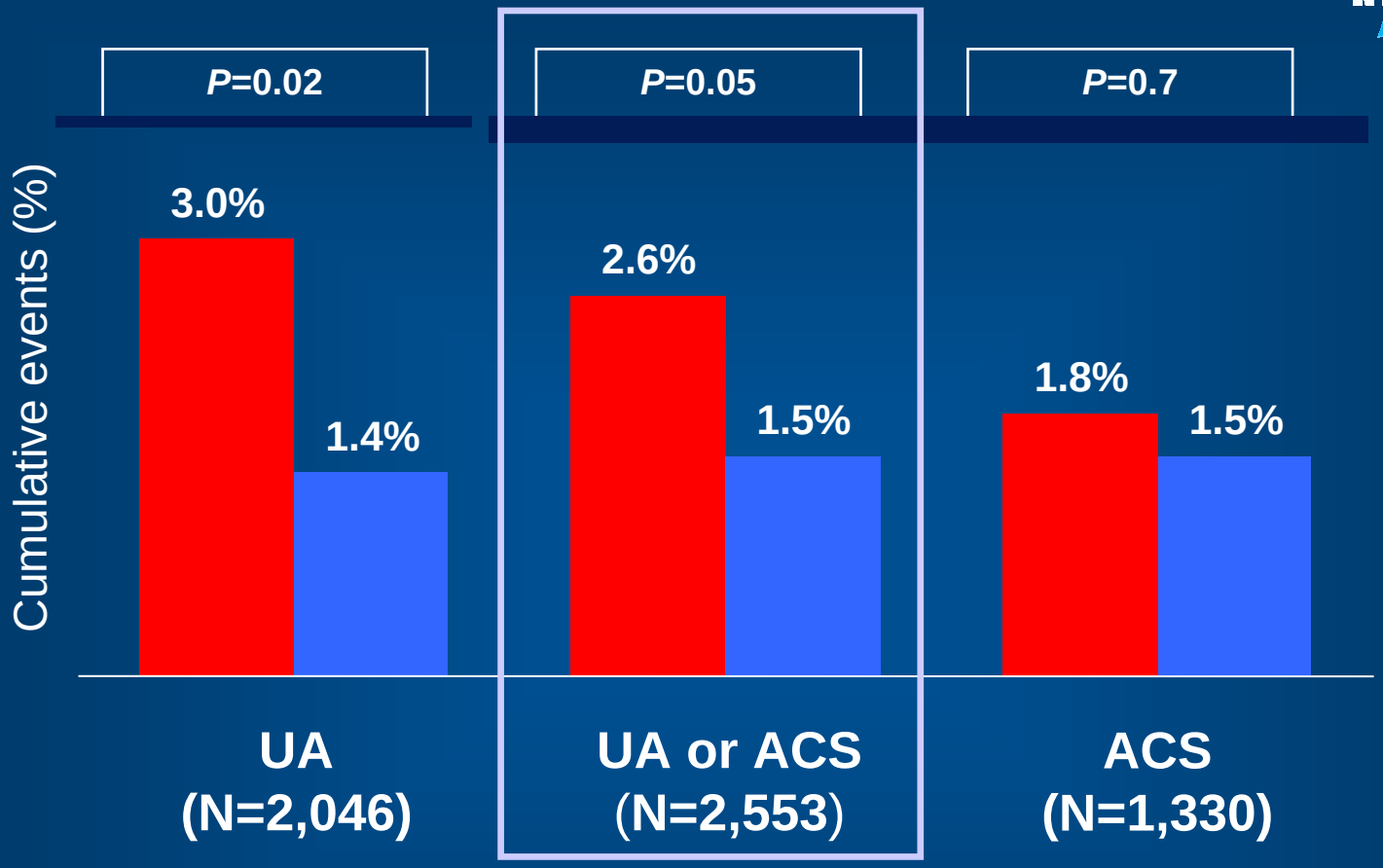
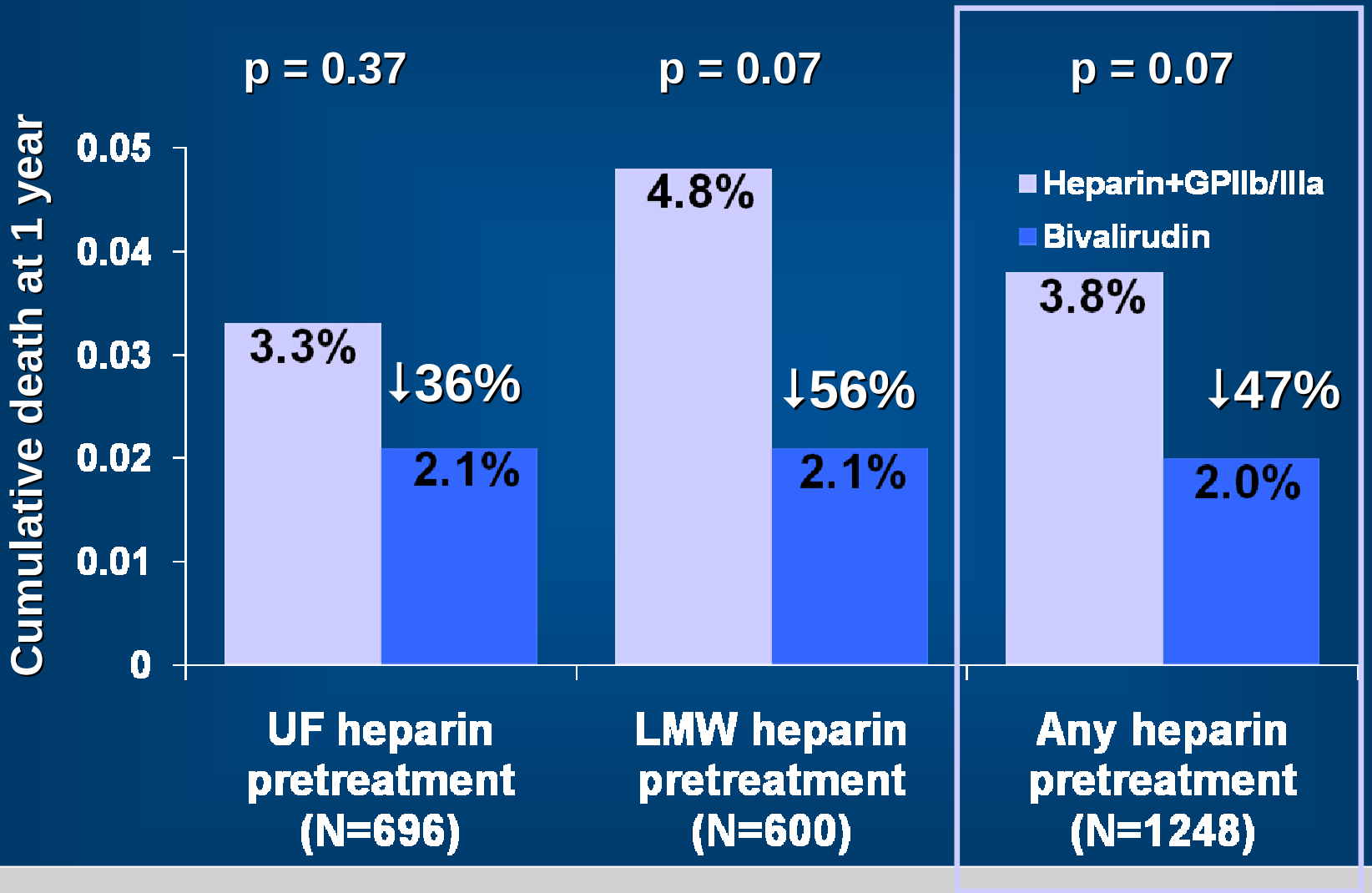
One-Year Mortality: ACS Subgroups



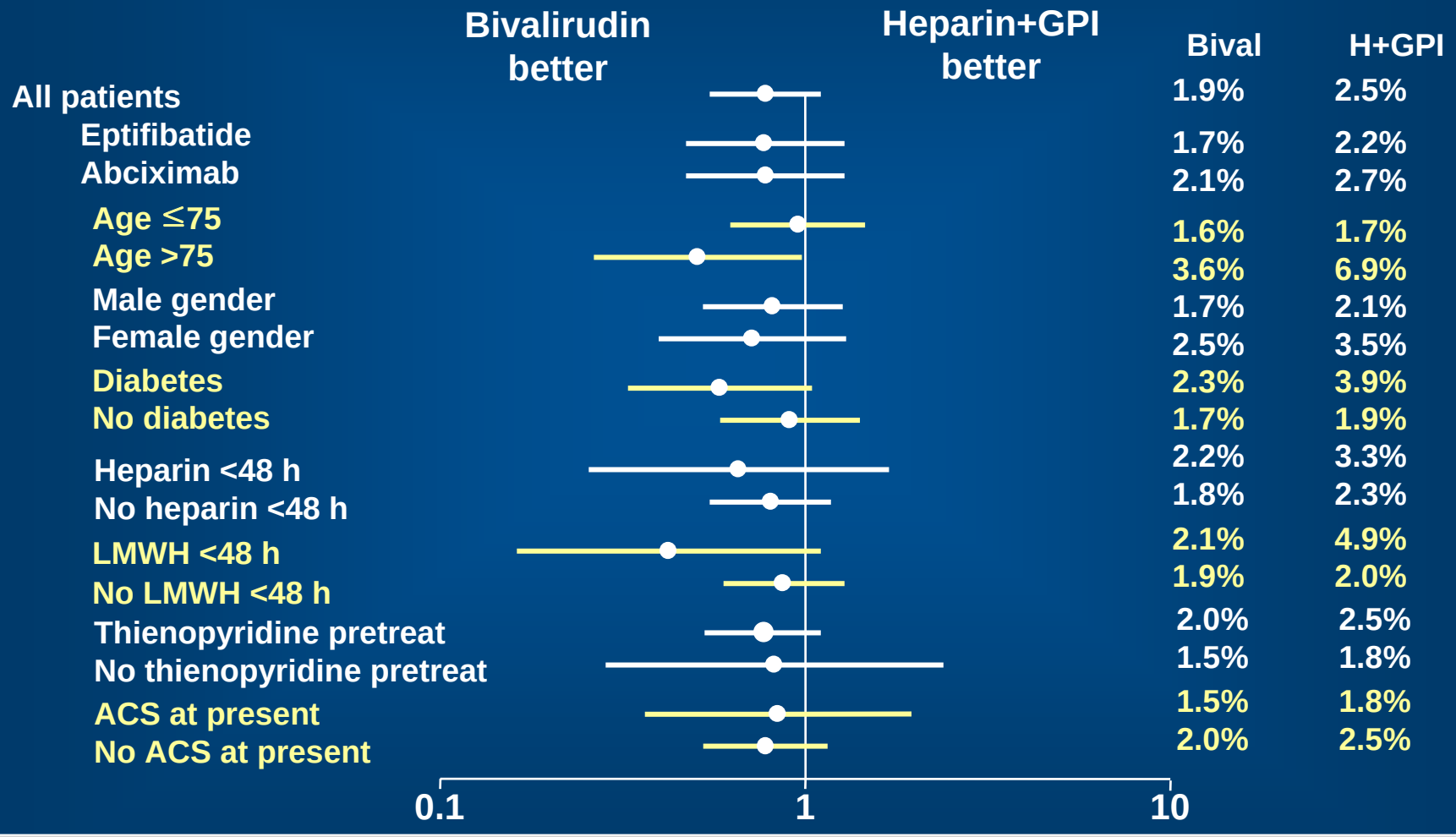
Lincoff AM et al. *JAMA*. 2004;292:696-703.
Stone GW. *J Invasive Cardiol.* 2004;16(suppl G):12-17.

One year mortality: Prior Heparin



REPLACE-2

1-Year Mortality: Subgroup Analysis



	Bival	H+GPI
All patients	1.9%	2.5%
Eptifibatide	1.7%	2.2%
Abciximab	2.1%	2.7%
Age ≤75	1.6%	1.7%
Age >75	3.6%	6.9%
Male gender	1.7%	2.1%
Female gender	2.5%	3.5%
Diabetes	2.3%	3.9%
No diabetes	1.7%	1.9%
Heparin <48 h	2.2%	3.3%
No heparin <48 h	1.8%	2.3%
LMWH <48 h	2.1%	4.9%
No LMWH <48 h	1.9%	2.0%
Thienopyridine pretreat	2.0%	2.5%
No thienopyridine pretreat	1.5%	1.8%
ACS at present	1.5%	1.8%
No ACS at present	2.0%	2.5%

Odds ratio ±95% CI for death at 12 months

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Bivalirudin and DES: ADEST Registry

Table 3
Major adverse events in patients with high-risk features

High-Risk Patient Subgroup	In-hospital Events	Out-of-hospital Events	Cumulative to 30 Days
Diabetes mellitus	(n = 359)	(n = 341)	(n = 341)
MACE	4.7%	2.9%	7.9%
Stent thrombosis	0.3%	0%	0.3%
Major bleeding	0.8%	NA	0.8%
Minor bleeding	3.3%	NA	3.3%
Multivessel PCI	(n = 206)	(n = 199)	(n = 199)
MACE	6.8%	1.5%	8.0%
Stent thrombosis	1%	0.5%	1.5%
Major bleeding	0%	NA	0%
Minor bleeding	6.3%	NA	6.3%
Multilesion PCI	(n = 469)	(n = 450)	(n = 450)
MACE	7.0%	2.0	8.9%
Stent thrombosis	0.4%	0.4%	0.9%
Major bleeding	0.6%	NA	0.6%
Minor bleeding	4.1%	NA	4.1%
Saphenous venous graft PCI	(n = 110)	(n = 103)	(n = 103)
MACE	6.4%	1.9%	8.7%
Stent thrombosis	1.8%	0%	1.8%
Major bleeding	0.9%	NA	0.9%
Minor bleeding	2.7%	NA	2.7%
Chronic renal insufficiency	(n = 70)	(n = 67)	(n = 67)
MACE	8.6%	3.0%	11.9%
Stent thrombosis	0%	0%	0%
Major bleeding	1.4%	NA	1.4%
Minor bleeding	4.3%	NA	4.3%

Dangas, AJC 2005; 96:659-663

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Comparative Clinical Outcomes of Bivalirudin Versus Heparin Plus GPIIb/IIIa Agents in High-Risk Percutaneous Coronary Intervention (PCI): Results from the Strategic Transcatheter Evaluation of New Therapies (STENT) Group

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McLeod Regional Medical Center, Florence, SC
LeBauer Cardiovascular Research Foundation /
Moses Cone Hospital, Greensboro, NC
Sisters of Charity Providence Hospitals, Columbia, SC

STENT Group Data Coordinating Center:

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High Risk Patient-Level Characteristics Evaluated in Association with In-Hospital MACE (n=8107 procedures)

	W/O Factor % MACE	W/Factor % MACE	P-value
Age > 75	2.3	4.7	<0.0001
MI < 7 days	2.0	4.0	<0.0001
3 Vessel Disease	2.3	4.7	<0.0001
EF < 40	2.3	6.2	<0.0001
CHF (Hx or Acute)	2.4	5.7	<0.0001
Diabetes	2.8	2.5	0.4018
Hx of CABG	2.7	2.8	0.8999
Hx of MI	2.6	3.2	0.1451
Angina < 24 hours	2.7	3.2	0.4096

High Risk Lesion-Level Characteristics Evaluated in Association with In-Hospital MACE (n=8107 procedures)

	W/O Factor % MACE	W/Factor % MACE	P-value
Lesion > 20mm	2.2	4.8	<0.0001
Calcium	2.2	4.2	<0.0001
Thrombus Grade > 1	2.0	5.7	<0.0001
SVG	2.7	3.5	0.2257
Left Main	2.7	5.6	0.0900
Vessel Diameter <= 2.5mm	2.5	3.2	0.0729
Bifurcation	2.7	3.0	0.6472
Ostial	2.7	2.6	0.8596
CTO	2.7	2.6	0.9471

Volume of High Risk Procedures by Anti-Coagulation Therapy (n=8107 procedures)

	Low Risk	High Risk	Total
Bivalirudin Alone	243 (27%)	662 (73%)	905
GPIIbIIIa + Heparin	969 (21%)	3743 (79%)	4712
Other Therapy Groups	688 (28%)	1802 (72%)	2490
Total	1900 (23%)	6207 (77%)	8107

Adverse Outcomes: Definitions

BLEED-1

TIMI Major or TIMI Minor in-hospital

BLEED-2

TIMI Major or Decline in Hemoglobin $\geq$ 4 g/dL in hospital

MACE at 90 Days

Death, Myocardial Infarction, or Target Vessel Revascularization within 90 days of procedure

Unadjusted Associations with In-Hospital Bleeding Outcomes Comparing Bivalirudin Alone (BIV) to GPIIbIIIa + Heparin (GP/Hep) among High Risk Patients (n=4405)

	BIV (n=662)	GP/Hep (n=3743)	P-value
BLEED-1	**16 (2.4%)**	**123 (3.3%)**	**0.2383**
TIMI Major	6 (0.9%)	46 (1.2%)	0.4787
TIMI Minor	10 (1.5%)	77 (2.1%)	0.3515
BLEED-2	**9 (1.4%)**	**178 (4.8%)**	**<0.0001**
↓ Hg≥4g/dL	7 (1.1%)	174 (4.7%)	<0.0001

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Adjusted Associations with In-Hospital Bleeding Outcomes Comparing Bivalirudin Alone (BIV) to GPIIbIIIa + Heparin (GP/Hep) among High Risk Patients (n=4405)

	Adjusted* OR (GP/Hep vs BIV)	95% CI	P-value
BLEED -1	1.0	(0.6, 1.7)	0.9580
BLEED-2	2.7	(1.4, 5.3)	0.0057

*Additional factors in each model:

Bleed-1 (mi<7 days, calcium, and thrombus grade>1)

Bleed-2 (age, mi<7days, and thrombus grade> 1)

Unadjusted Associations with MACE at 90 days Comparing Bivalirudin Alone (BIV) to GPIIbIIIa + Heparin (GP/Hep) among High Risk Patients with Completed 90 Day Follow-Up (n=3355)

	BIV (n=595)	GP/Hep (n=2760)	P-value
MACE @ 90 Days	40 (6.7%)	170 (6.2%)	0.6069
Death	19 (3.2%)	82 (3.0%)	0.7735
MI	15 (2.5%)	62 (2.3%)	0.6849
TVR	13 (2.2%)	46 (1.7%)	0.3831

Adjusted Association with MACE at 90 Days Comparing Bivalirudin Alone (BIV) to GPIIbIIIa + Heparin (GP/Hep) among High Risk Patients (n=3355)

	Adjusted* OR (GP/Hep vs BIV)	95% CI	P-value
MACE @ 90 Days	0.9	(0.6, 1.3)	0.4437

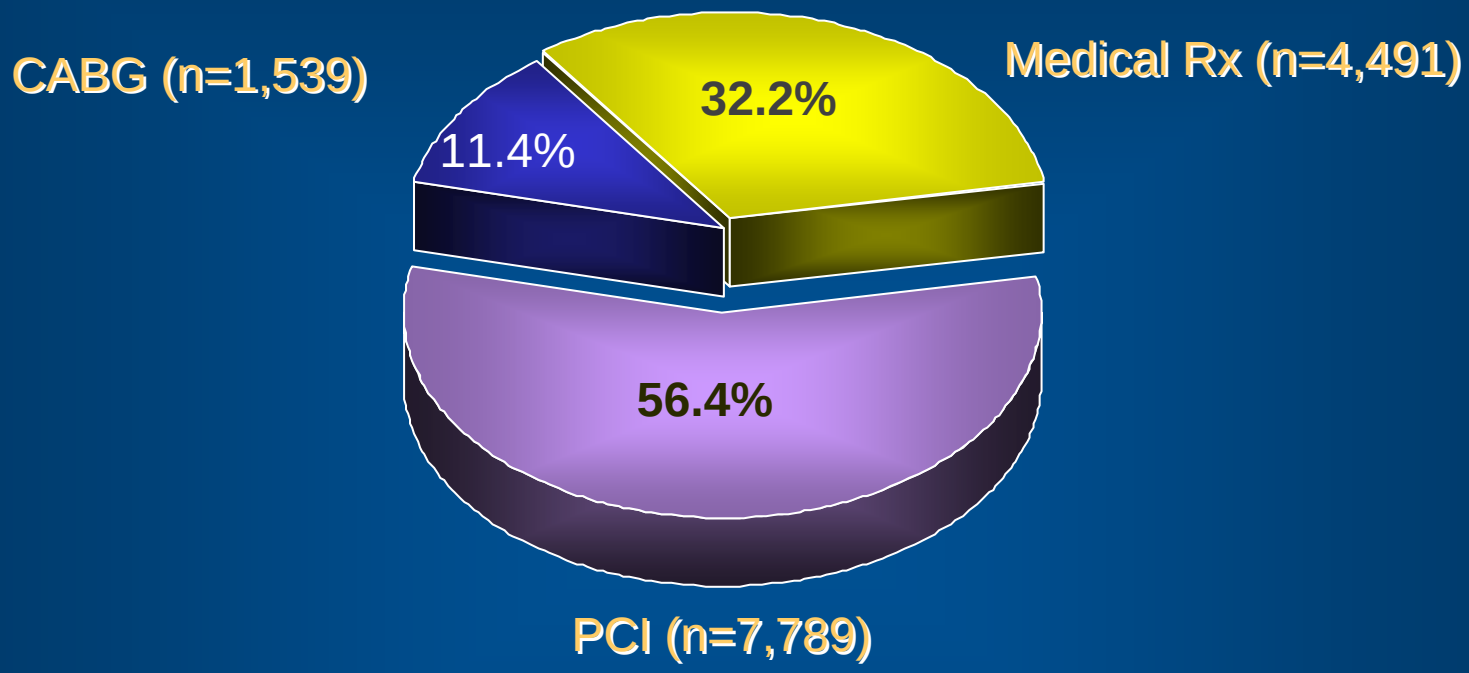
*Additional factors in model:

age, mi<7days, chf, lesion length>20mm, and thrombus grade > 1

ACUITY PCI Sub-study

- Examine the outcomes of bivalirudin ± GPIIb/IIIa inhibitors compared to heparin (unfractionated or enoxaparin) + GPIIb/IIIa inhibitors in pts with moderate and high risk ACS undergoing PCI
  - 3 primary clinical endpoints at 30 days
  - Angiographic outcomes from a large independent blinded core lab analysis
  - Specific subgroups and analyses of interest:
    - **Troponin positive pts**
    - **Impact of pre-PCI thienopyridine use**
    - **"ISAR-REACT-2 like" cohort**
    - **Angiographic thrombus**

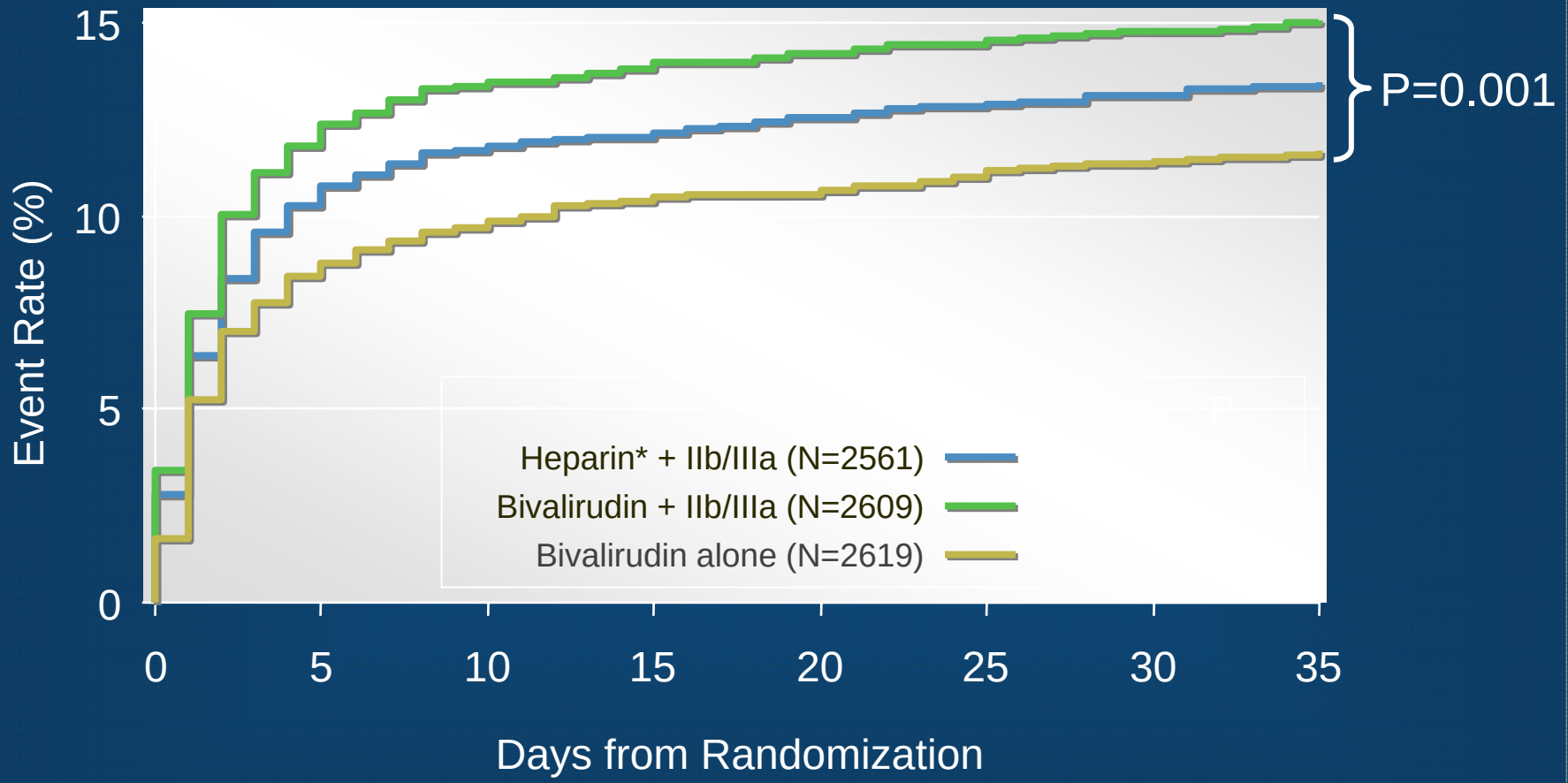
ACUITY PCI: Management Strategy (N=13,819)



Heparin + IIb/IIIa	Bivalirudin + IIb/IIIa	Bivalirudin alone
N = 2,561	N = 2,609	N = 2,619

ACUITY PCI : Net Clinical Outcomes

Heparin + IIbIIIa vs Bivalirudin + IIbIIIa vs Bivalirudin Alone



*Heparin=unfractionated or enoxaparin

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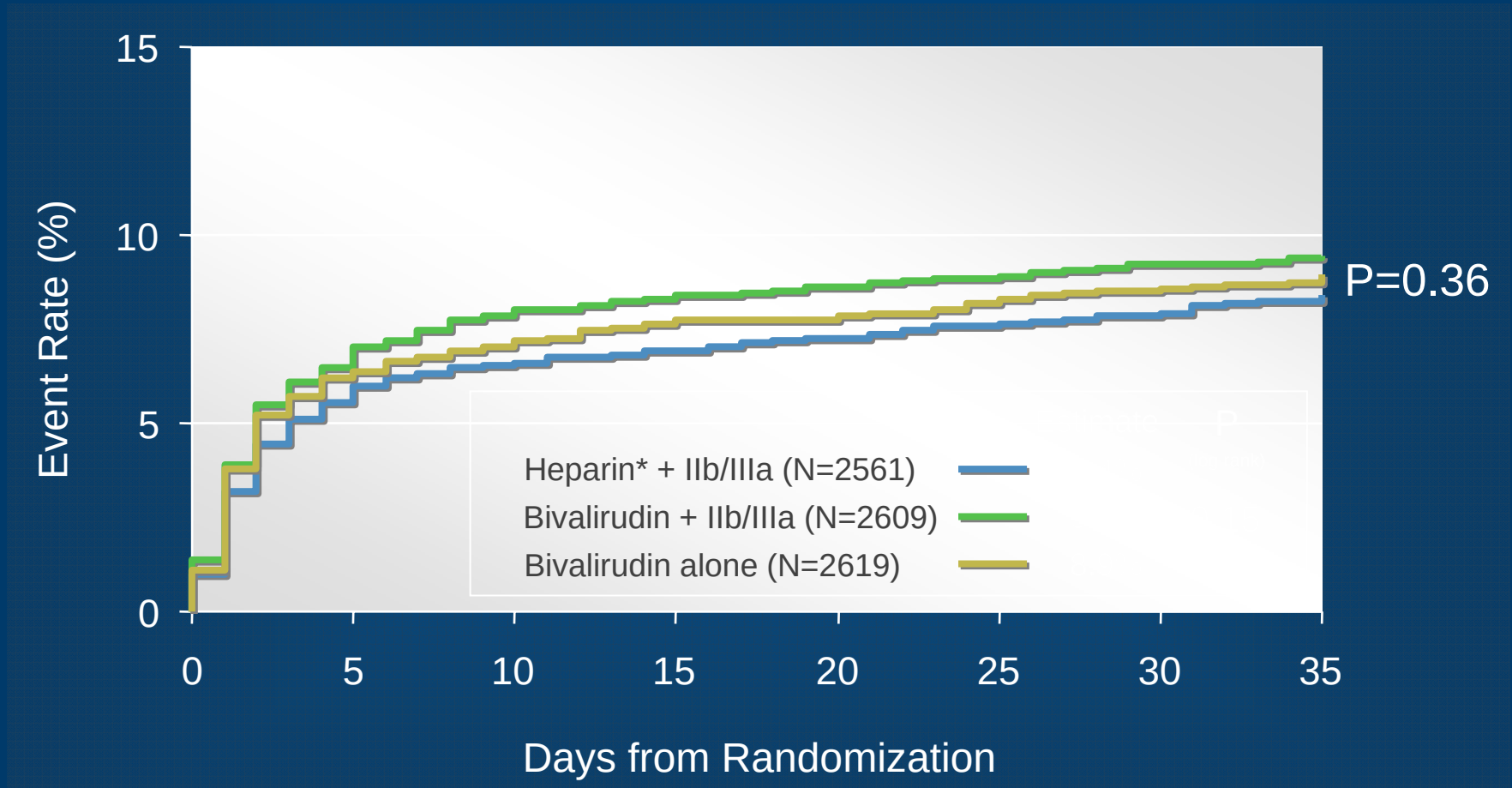
ACUITY PCI : Composite Ischemia

Heparin + IIbIIIa vs Bivalirudin + IIbIIIa vs Bivalirudin Alone



*Heparin=unfractionated or enoxaparin

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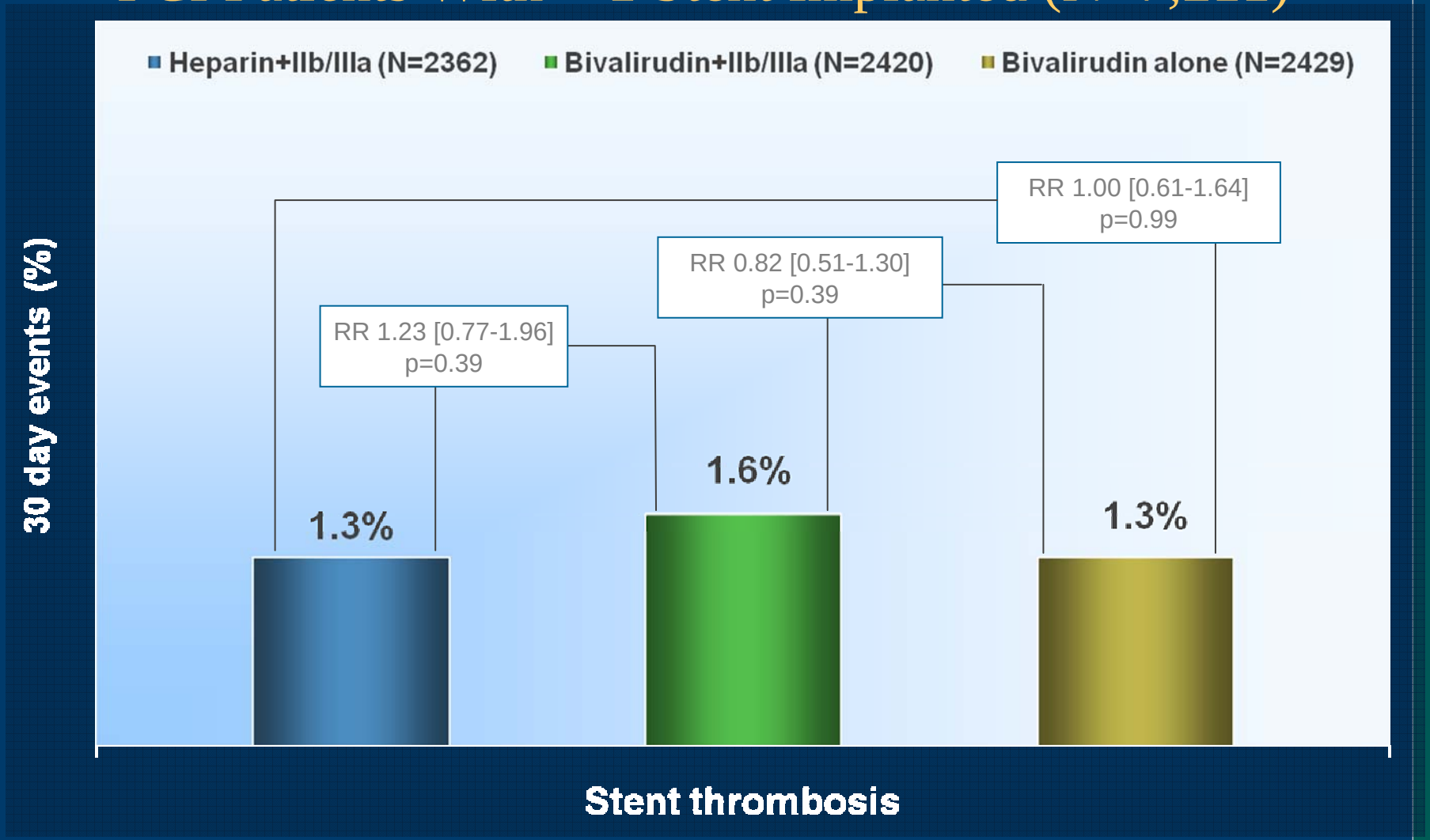
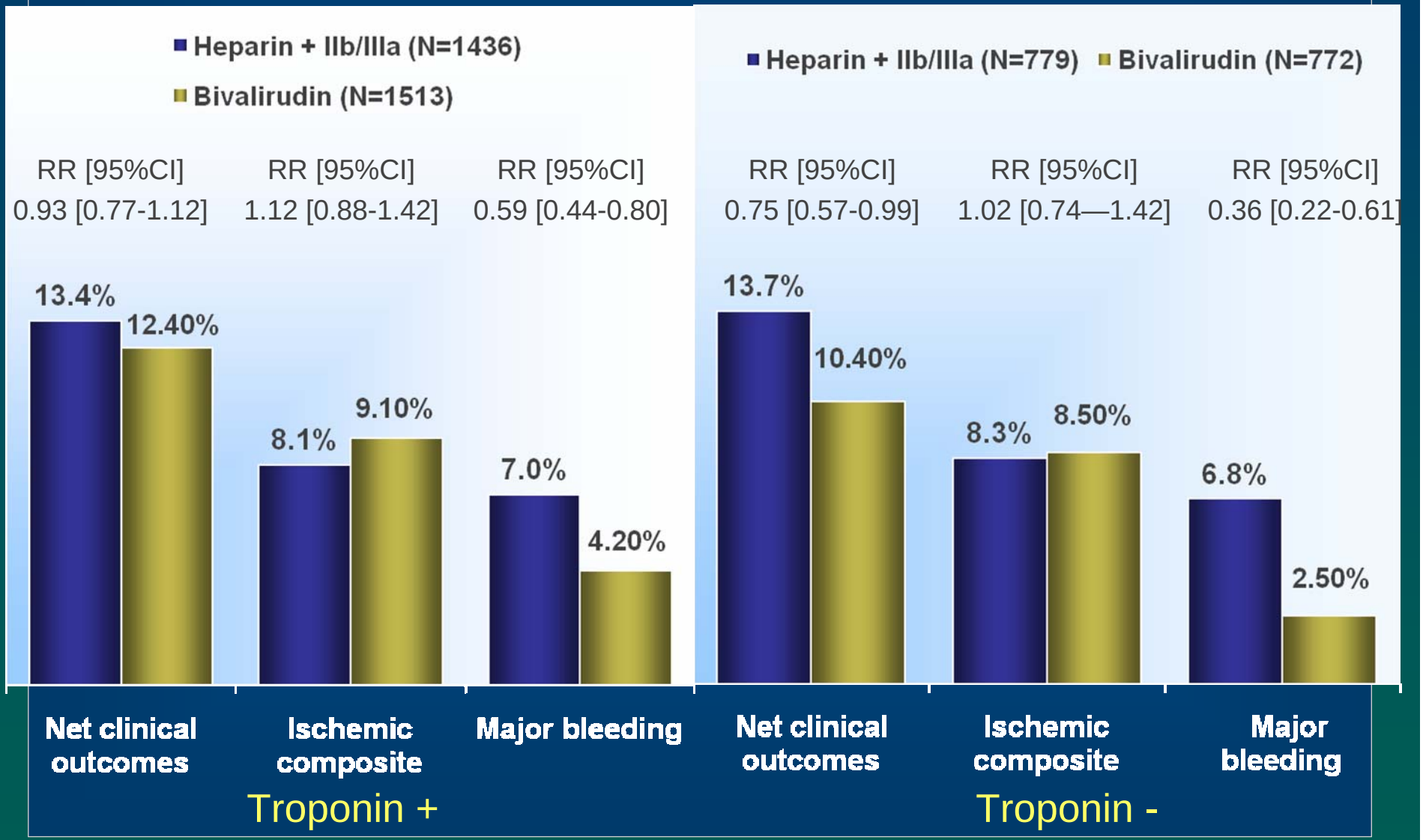
ACUITY PCI : Adjudicated Stent Thrombosis

PCI Patients With ≥1 Stent Implanted (N=7,211)

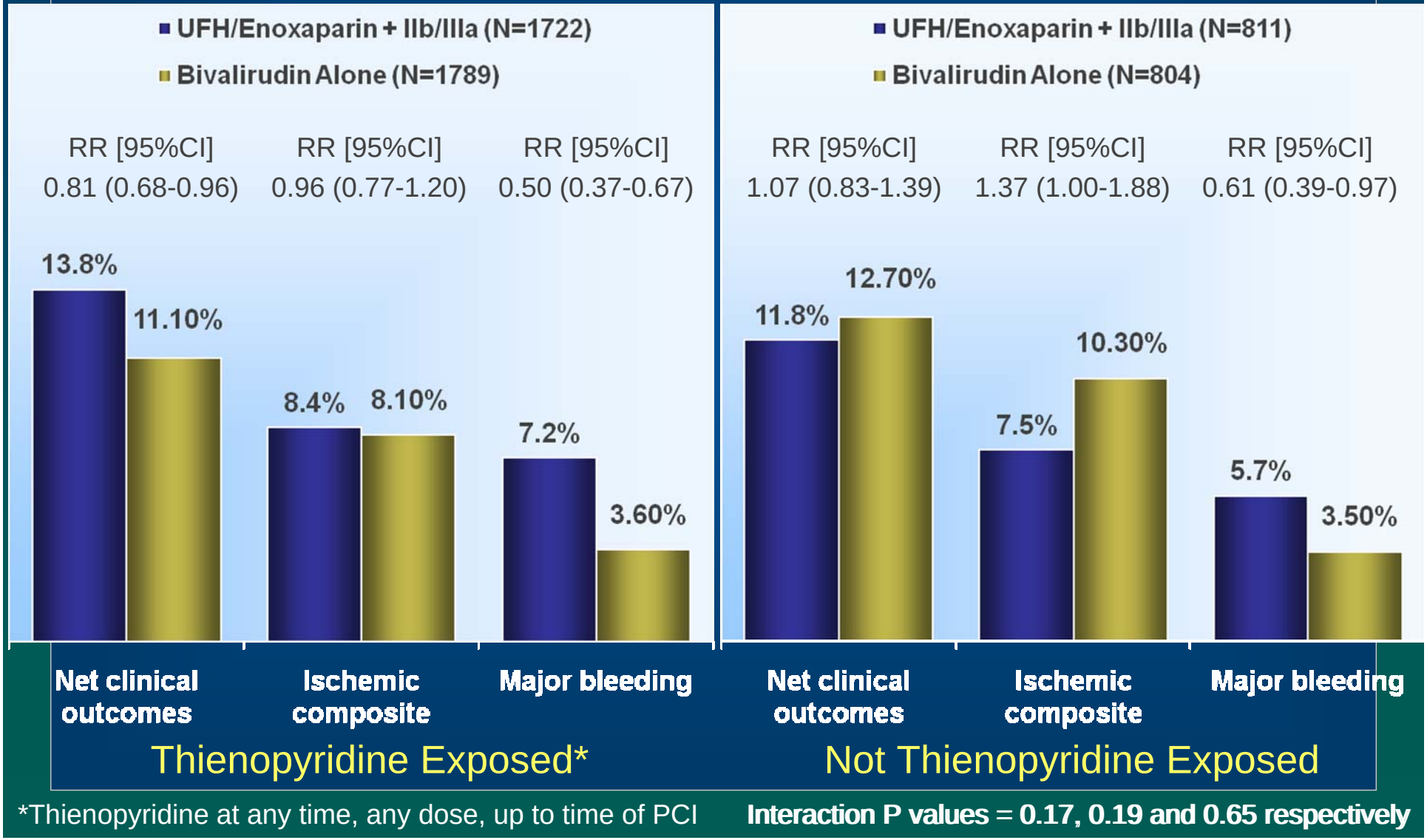


ACUITY PCI : Impact of Baseline Troponins



Interaction P values = 0.46, 0.86 and 0.28 respectively

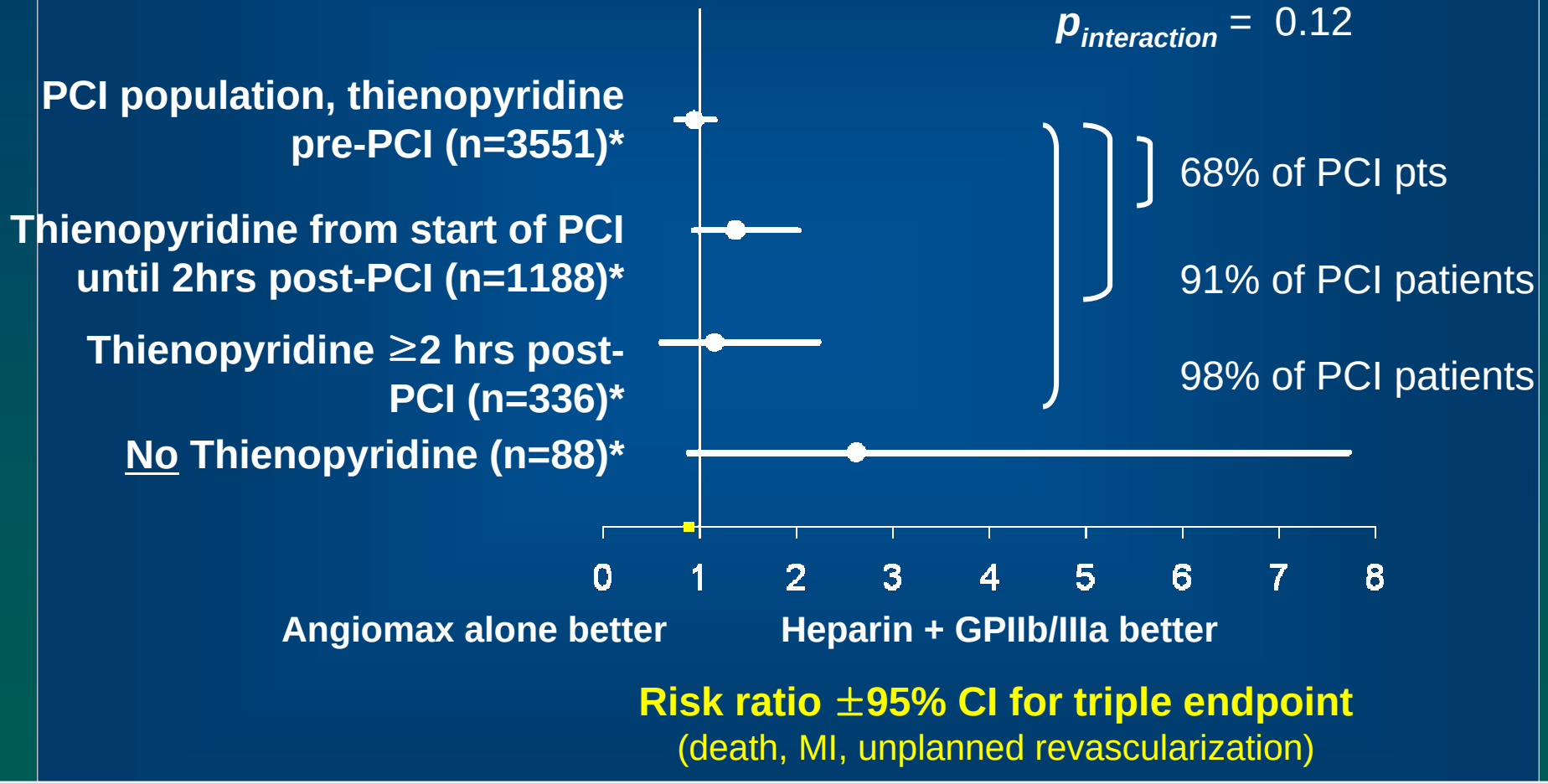
ACUITY PCI : Influence of Thienopyridines 30 Day Primary Endpoint Adverse Events



*Thienopyridine at any time, any dose, up to time of PCI

Interaction P values = 0.17, 0.19 and 0.65 respectively

ACUITY PCI: Thienopyridine Use and Relative Risk of Composite Ischemic Endpoint



*reflects patients in two study arms

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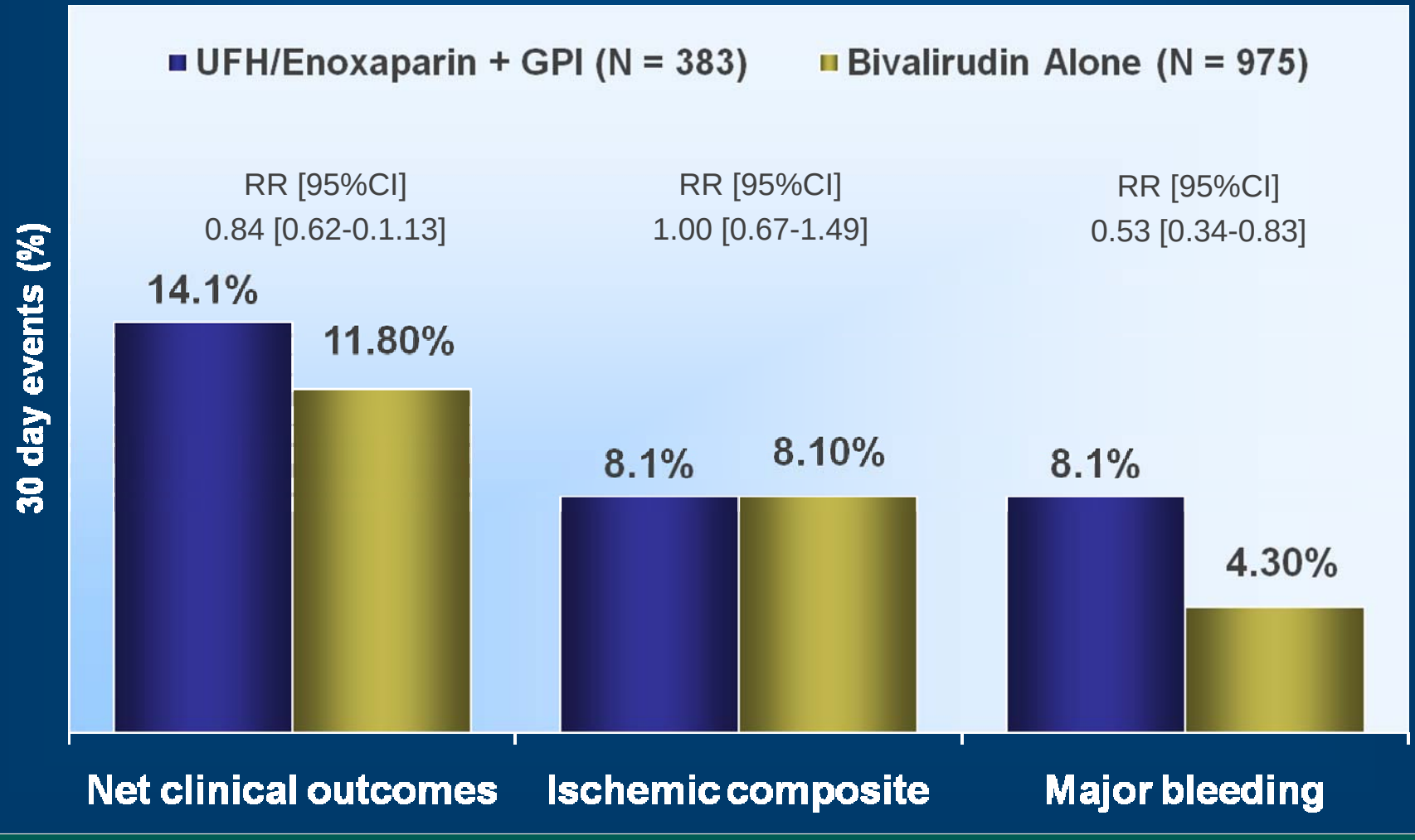
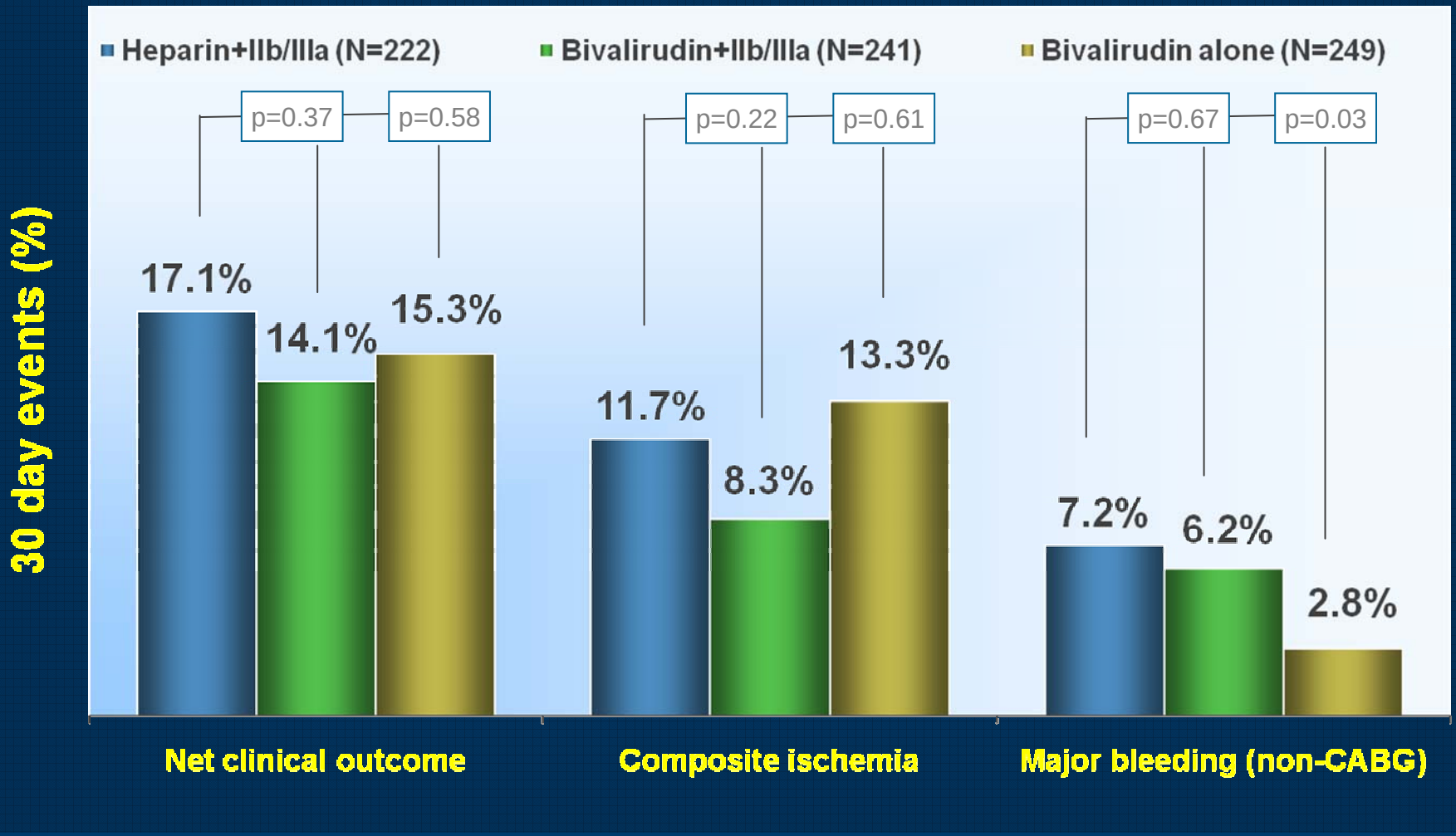
"ISAR-REACT-2 Like" Patients (N=1,358)

Troponin+ PCI pts, Thienopyridine use prior to PCI,
GPI started after angiography but before PCI



ACUITY PCI: Thrombotic Lesions

Patients with ≥1 PCI Thrombotic Lesion at Baseline (n=712)



*Heparin=unfractionated or enoxaparin

Conclusions and Clinical Implications

- In patients with moderate and high risk ACS undergoing PCI
  - Replacing upstream heparin with bivalirudin in pts treated with GP IIb/IIIa inhibitors provides similar clinical and angiographic outcomes
  - Replacing heparin and GP IIb/IIIa inhibitors with bivalirudin alone (with provisional IIb/IIIa inhibitor use in <10% of pts) results in similar rates of ischemia with markedly reduced hemorrhagic complications, thereby improving overall event-free survival