ACUITY

ACUITY PCI

A Prospective Trial of Patients with ACS Undergoing PCI after Randomization to Heparin plus GP IIb/IIIa Inhibitors vs. Bivalirudin With or Without GP IIb/IIIa Inhibitors

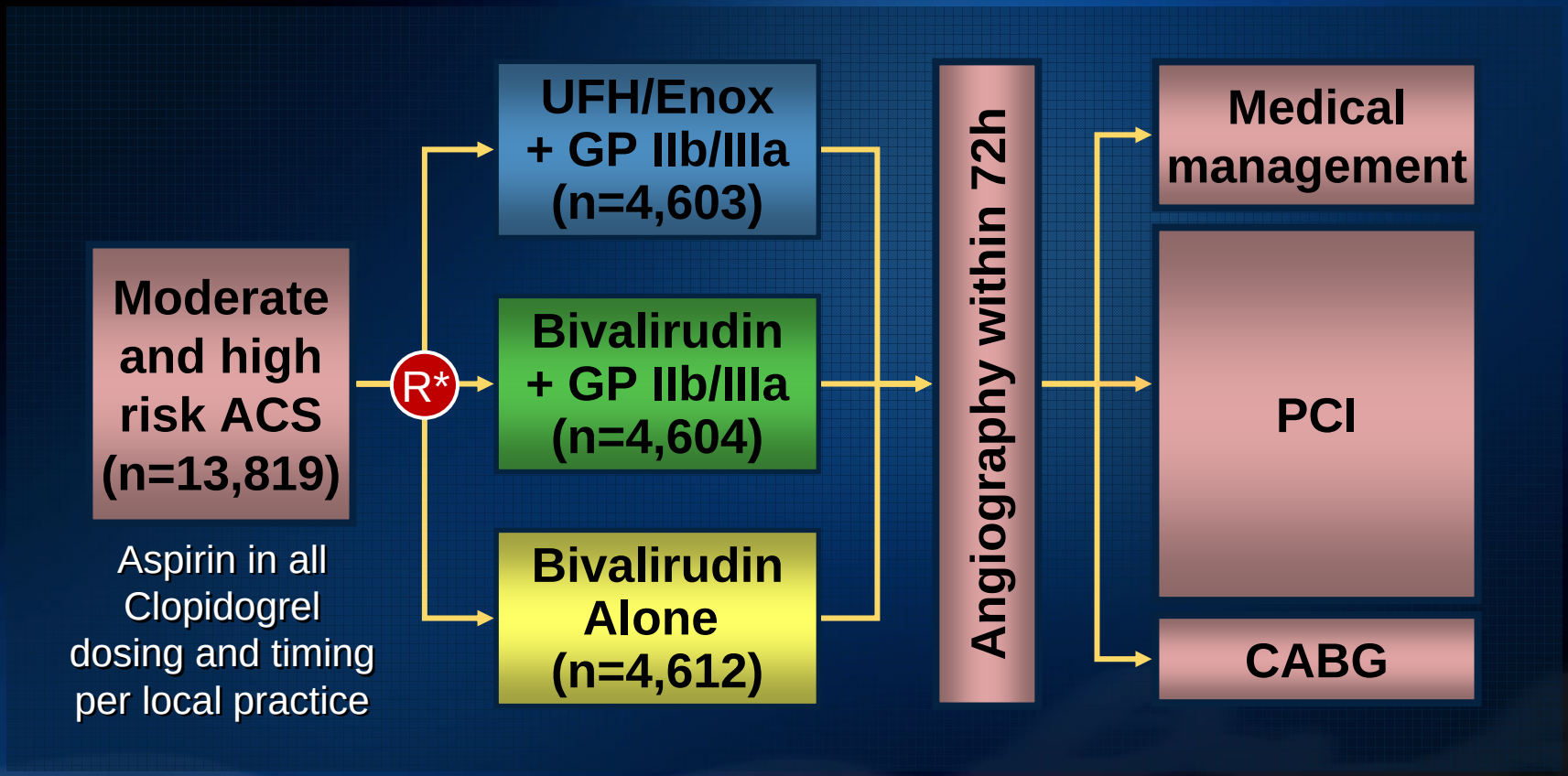
Gregg W. Stone MD

for the **ACUITY Investigators**

ACUITY PCI

Bivalirudin in ACS: The ACUITY Trial

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



*Stratified by pre-angiography thienopyridine use or administration

ACUITY

3 Primary Endpoints (at 30 Days)

1. Composite net clinical benefit =

2. Ischemic composite
or
3. Major bleeding

- **Death from any cause**
- **Myocardial infarction**
  - During medical Rx: Any biomarker elevation >ULN
  - Post PCI: CKMB >ULN with new Q waves or >3x ULN w/o Q waves
  - Post CABG: CKMB >5x ULN with new Q waves, >10x ULN w/o Q waves
- **Unplanned revascularization for ischemia**

ACUITY

3 Primary Endpoints (at 30 Days)

1. Composite net clinical benefit =

2. Ischemic composite

or

3. Major bleeding

- **Non CABG related bleeding**

- Intracranial bleeding or intraocular bleeding

- Retroperitoneal bleeding

-Access site bleed requiring intervention/surgery

- Hematoma ≥5 cm

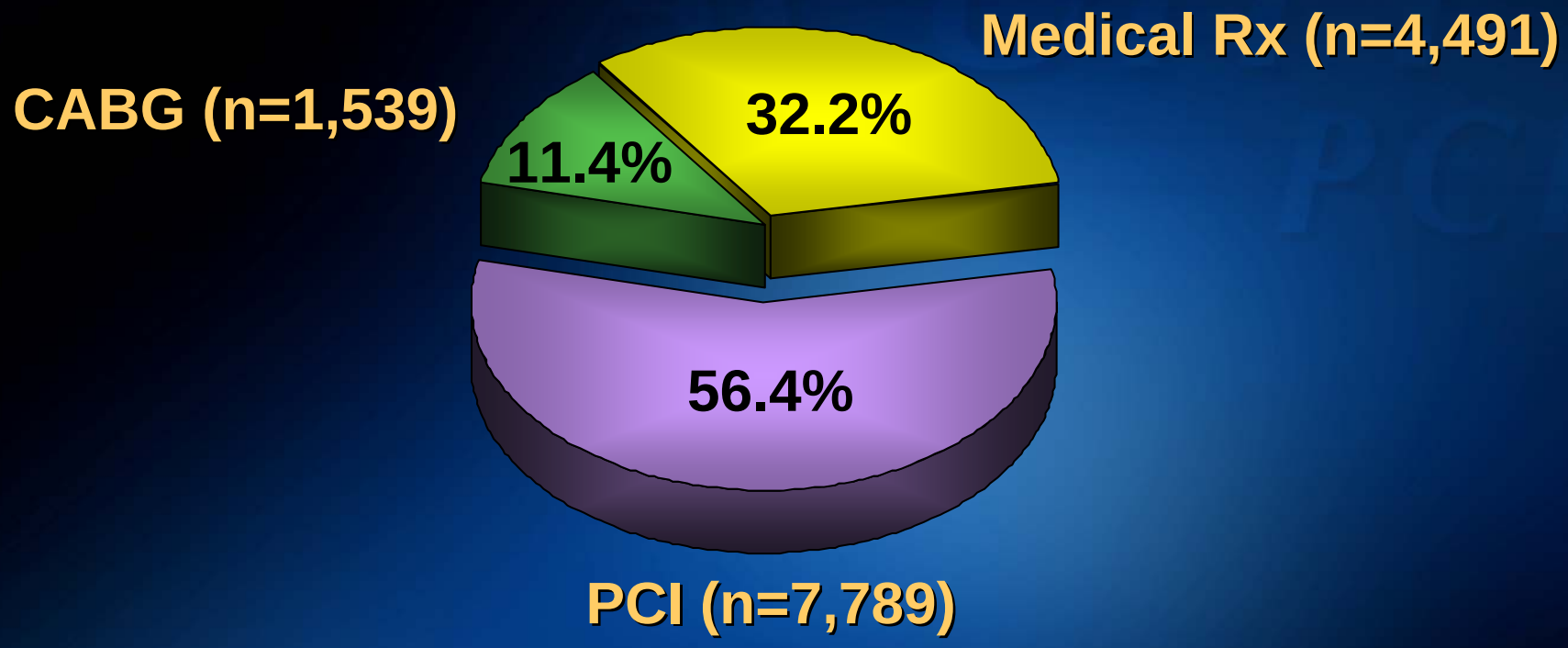
- Hgb ⇓≥3g/dL with an overt source or ⇓≥4g/dL w/o overt source

- Blood product transfusion

- Reoperation for bleeding

ACUITY

Management Strategy (N=13,819)



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

Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Baseline Characteristics – PCI pts

	Heparin + IIb/IIIa (N=2561)	Bivalirudin + IIb/IIIa (N=2609)	Bivalirudin alone (N=2619)
Age (median [range], yrs)	63 [25-91]	62 [21-95]	63 [30-92]
Male	72.6%	73.6%	73.3%
Weight (median [IQR], kg)	84 [73,96]	84 [74,96]	84 [75,95]
Diabetes	27.5%	27.3%	27.5%
- Insulin requiring	8.0%	8.0%	8.6%
Hypertension	65.3%	64.8%	65.4%
Hyperlipidemia	55.0%	55.2%	54.9%
Current smoker	30.1%	30.6%	30.4%
Prior MI	29.7%	29.1%	30.5%
Prior PCI	38.2%	37.5%	39.3%
Prior CABG	17.3%	17.3%	17.9%
Renal insufficiency*	19.0%	18.4%	17.8%

* creatinine clearance <60 mL/min

ACUITY PCI

Baseline High Risk Features – PCI pts

	Heparin + IIb/IIIa (N=2561)	Bivalirudin + IIb/IIIa (N=2609)	Bivalirudin alone (N=2619)
Cardiac biomarker ⇑ (MB or trop)	65.1%	63.7%	66.4%
- Troponin ⇑	64.8%	62.6%	66.2%
ST-segment Δ ≥1mm	35.4%	36.7%	35.3%
Cardiac biomarker ⇑ or ST-segments Δ	76.8%	75.3%	77.0%
TIMI Risk Score			
0-2*	16.7%	15.3%	16.0%
3-4	52.1%	54.6%	53.2%
5-7	31.2%	30.0%	30.8%

* 84.0% had +biomarkers or baseline STΔ

97% of all pts had +biomarkers or baseline STΔ, or were TIMI Int/High risk

ACUITY PCI

Antiplatelet Medications – PCI pts

	Heparin + IIb/IIIa (N=2561)	Bivalirudin + IIb/IIIa (N=2609)	Bivalirudin alone (N=2619)
Aspirin use or administration pre-angiography or PCI			
- Yes	98.0%	97.7%	98.0%
Thienopyridine use or administration pre PCI			
- Yes	68.0%	67.7%	69.0%
- Clopidogrel	67.5%	67.4%	68.7%
- Ticlopidine	1.0%	0.7%	0.7%

Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Procedural Characteristics – PCI pts

	Heparin + IIb/IIIa (N=2561)	Bivalirudin + IIb/IIIa (N=2609)	Bivalirudin alone (N=2619)
Attempted lesions per pt	1.50 ± 0.83	1.49 ± 0.82	1.51 ± 1.93
- 1	65.2%	64.7%	66.3%
- 2	24.4%	25.3%	23.2%
- ≥3	10.4%	10.0%	10.6%
Attempted vessels per pt	1.18 ± 0.44	1.18 ± 0.43	1.18 ± 0.42
- ≥2	16.3%	16.9%	16.0%
Target Vessel			
- Left main	1.7%	1.5%	1.5%
- LAD	41.2%	44.0%	43.5%
- LCX	34.7%	34.4%	35.7%
- RCA	38.4%	36.7%	35.4%
- Bypass graft conduit	7.2%	7.5%	7.0%

ACUITY PCI

Stone GW, et al. Lancet 2007;369:907-19

Device Use – PCI pts

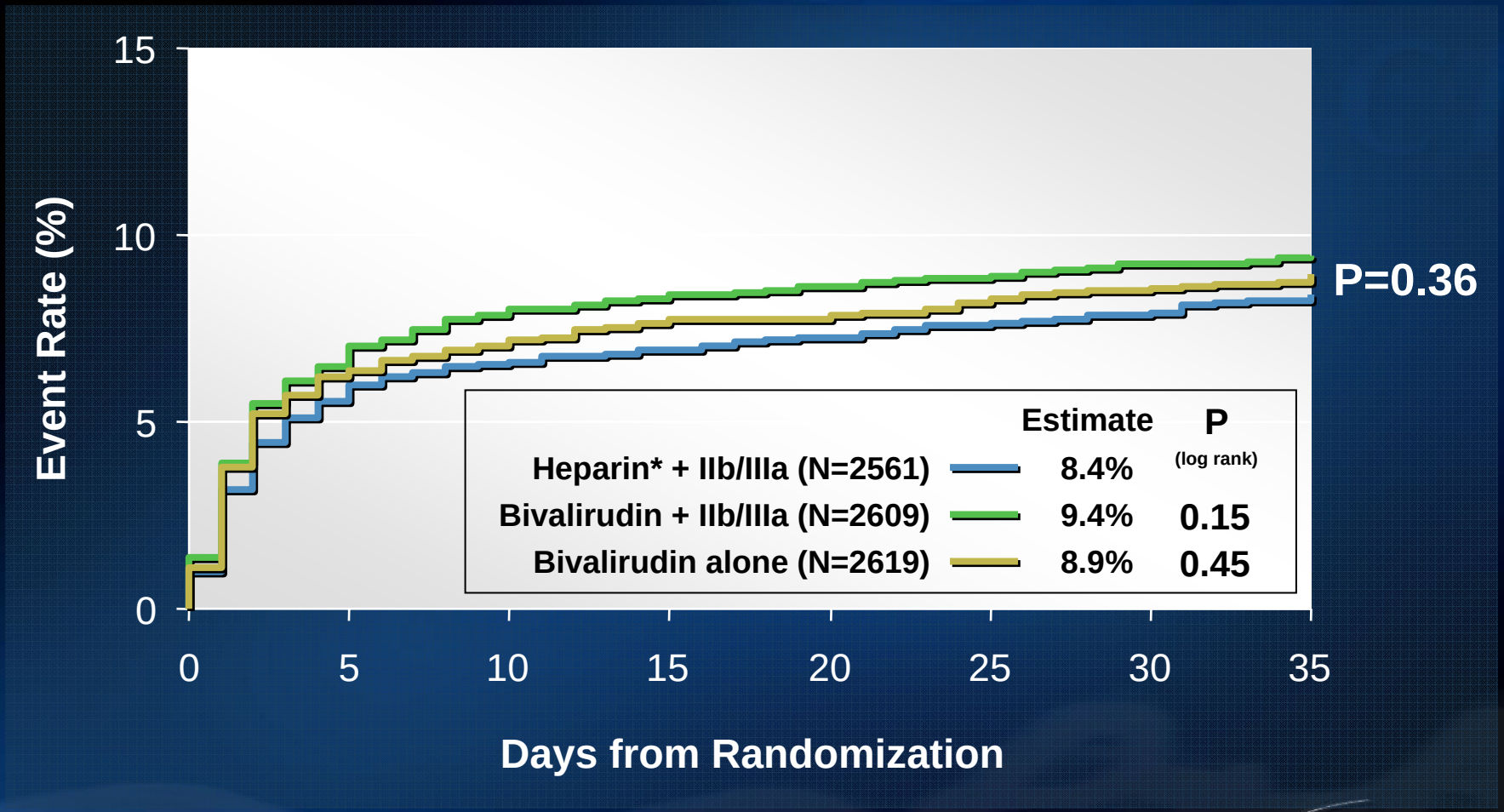
	Heparin + IIb/IIIa (N=2561)	Bivalirudin + IIb/IIIa (N=2609)	Bivalirudin alone (N=2619)
Stent implanted	92.7%	93.1%	92.7%
Drug-eluting stents	60.9%	59.7%	59.6%
- ≥1 Cypher implanted	26.5%	25.8%	24.8%
- ≥1 Taxus implanted	31.3%	30.4%	31.1%
- ≥1 other DES implanted	5.4%	5.1%	5.6%
Non-drug-eluting stent	36.2%	37.6%	37.7%
Thrombectomy	1.7%	1.5%	1.8%
Distal Protection	1.3%	1.7%	1.3%
Atherectomy	0.7%	0.6%	0.5%
Cutting Balloon	2.9%	3.2%	2.9%

Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Composite Ischemia – PCI pts

Heparin* + IIb/IIIa vs. Bivalirudin + IIb/IIIa vs. Bivalirudin Alone



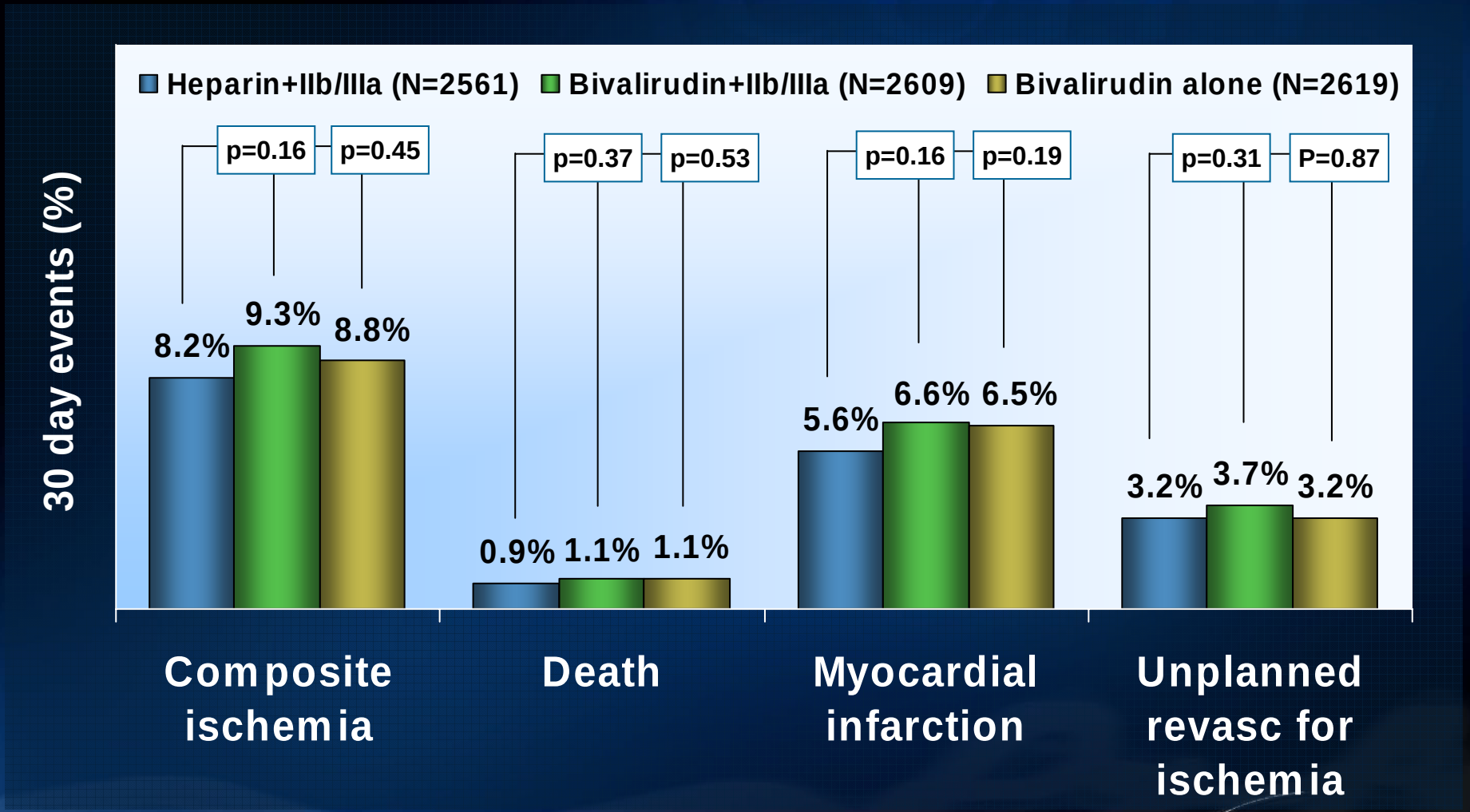
*Heparin=unfractionated or enoxaparin

Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Components of Ischemia – PCI pts

Heparin* + IIb/IIIa vs. Bivalirudin + IIb/IIIa vs. Bivalirudin Alone



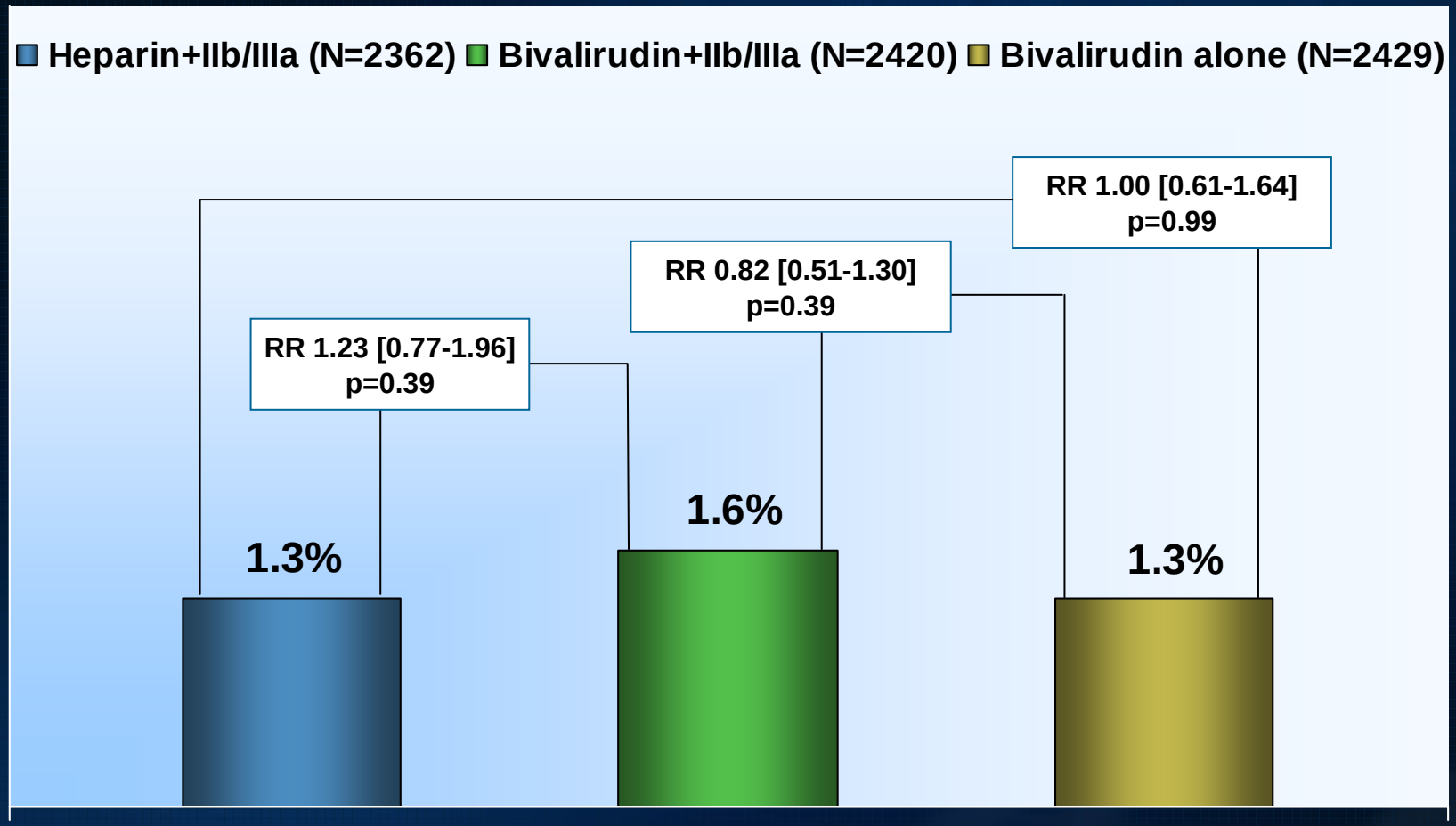
*Heparin=unfractionated or enoxaparin

Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Adjudicated Stent Thrombosis

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

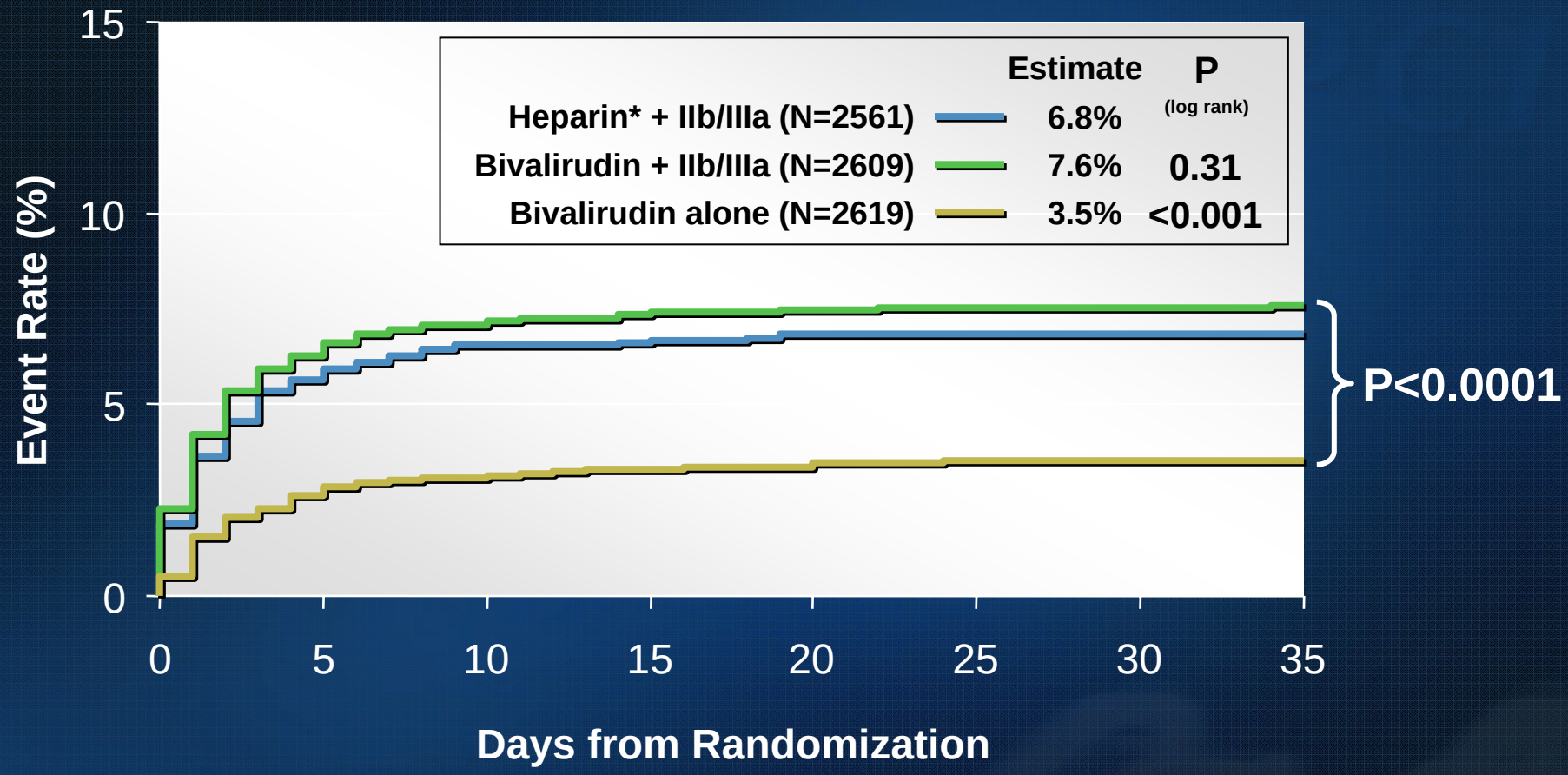


Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Major Bleeding (Non-CABG) – PCI pts

Heparin* + IIb/IIIa vs. Bivalirudin + IIb/IIIa vs. Bivalirudin Alone



*Heparin=unfractionated or enoxaparin

Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Major Bleeding (non-CABG) – PCI pts

	Heparin + IIb/IIIa (N=2561)	Bivalirudin + IIb/IIIa (N=2609)	Bivalirudin alone (N=2619)	P value*
Major bleeding	6.8%	7.5%	3.5%	<0.001
Intracranial	0% (1)	0% (1)	0% (1)	1.00
Retroperitoneal	0.7%	0.9%	0.2%	0.006
Access site	3.3%	3.6%	1.0%	<0.001
- req interv/surgery	0.6%	0.8%	0.3%	0.13
- hematoma ≥5 cm	2.9%	3.1%	0.8%	<0.001
Hgb ⇓ ≥3 g/dL with overt source	2.8%	2.9%	1.2%	<0.001
Hgb ⇓ ≥4 g/dL with no overt source	1.0%	1.1%	0.9%	0.82
Blood transfusion	3.0%	3.9%	1.7%	0.002
Reoperation for bleed	0% (1)	0.2% (5)	0.1% (3)	0.33

*P value for bivalirudin alone vs. heparin + IIb/IIIa inhibitor

ACUITY PCI

Bleeding Endpoints – PCI pts

	Heparin + IIb/IIIa (N=2561)	Bivalirudin + IIb/IIIa (N=2609)	Bivalirudin alone (N=2619)	P Value
ACUITY Scale				
- Major Bleed, all	7.3%	8.0%	4.2%	<0.001
- Major, non-CABG	6.8%	7.5%	3.5%	<0.001
- Minor, non-CABG	26.0%	28.4%	14.9%	<0.001
TIMI Scale				
- Any	7.8%	8.5%	4.5%	<0.001
- Major	2.3%	2.4%	0.8%	<0.001
- Minor	7.5%	8.2%	4.2%	<0.001
Transfusions, non-CABG	3.0%	3.9%	1.7%	0.002

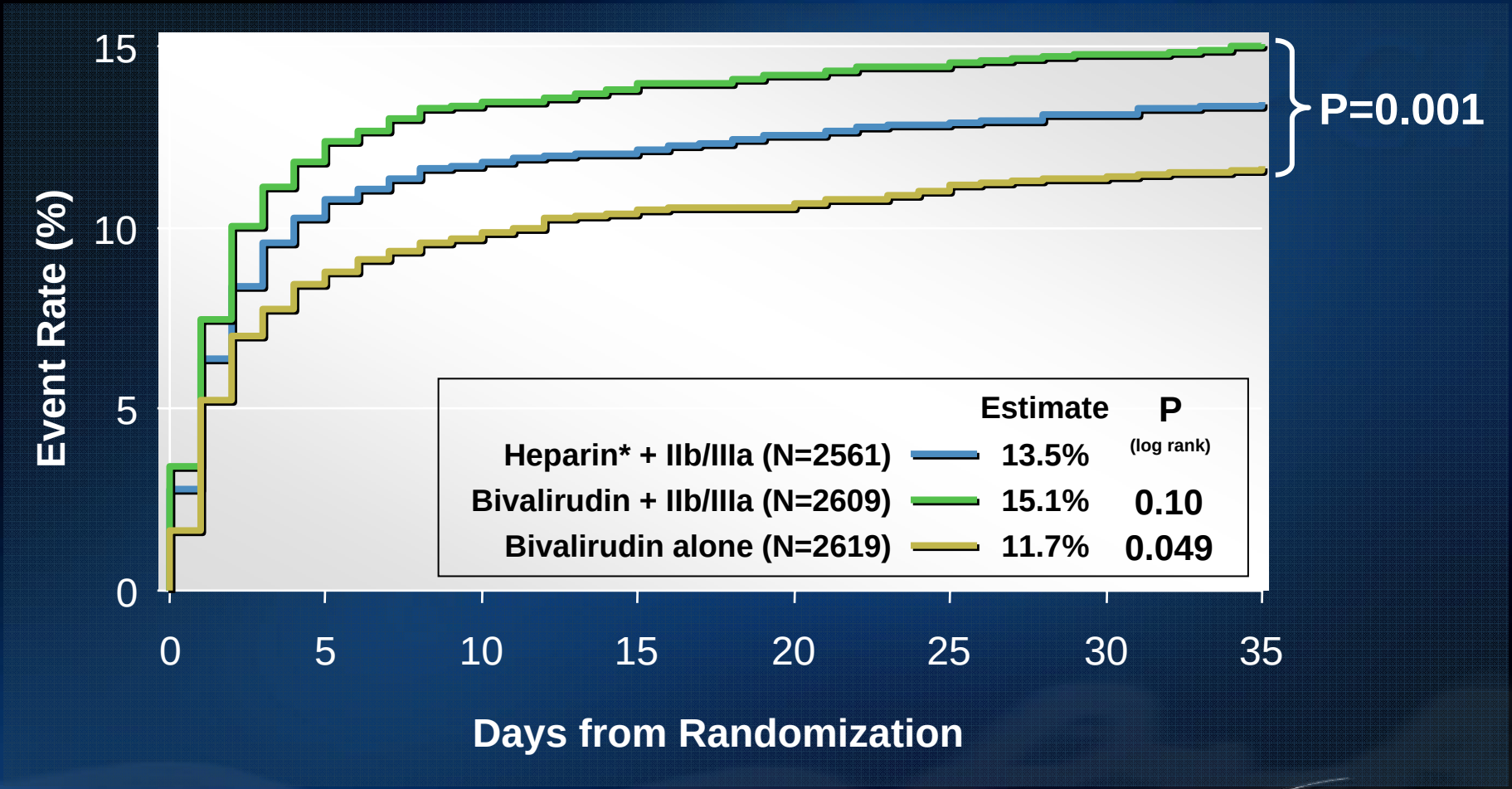
*P value for bivalirudin alone vs. heparin + IIb/IIIa inhibitor

Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Net Clinical Outcomes – PCI pts

Heparin* + IIb/IIIa vs. Bivalirudin + IIb/IIIa vs. Bivalirudin Alone



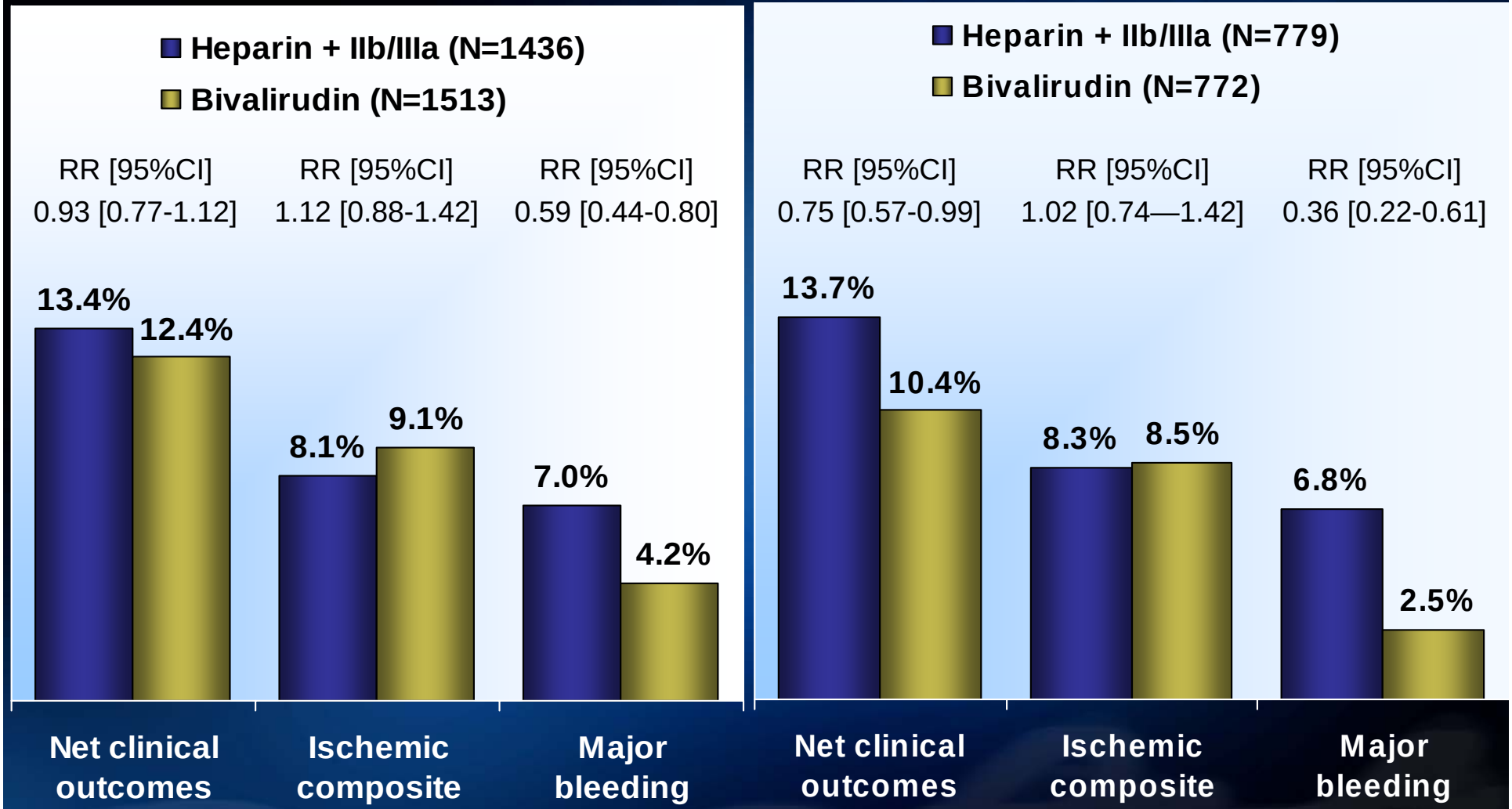
*Heparin=unfractionated or enoxaparin

Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Impact of Baseline Troponins – PCI pts

UFH/Enoxaparin + IIb/IIIa vs. Bivalirudin Alone

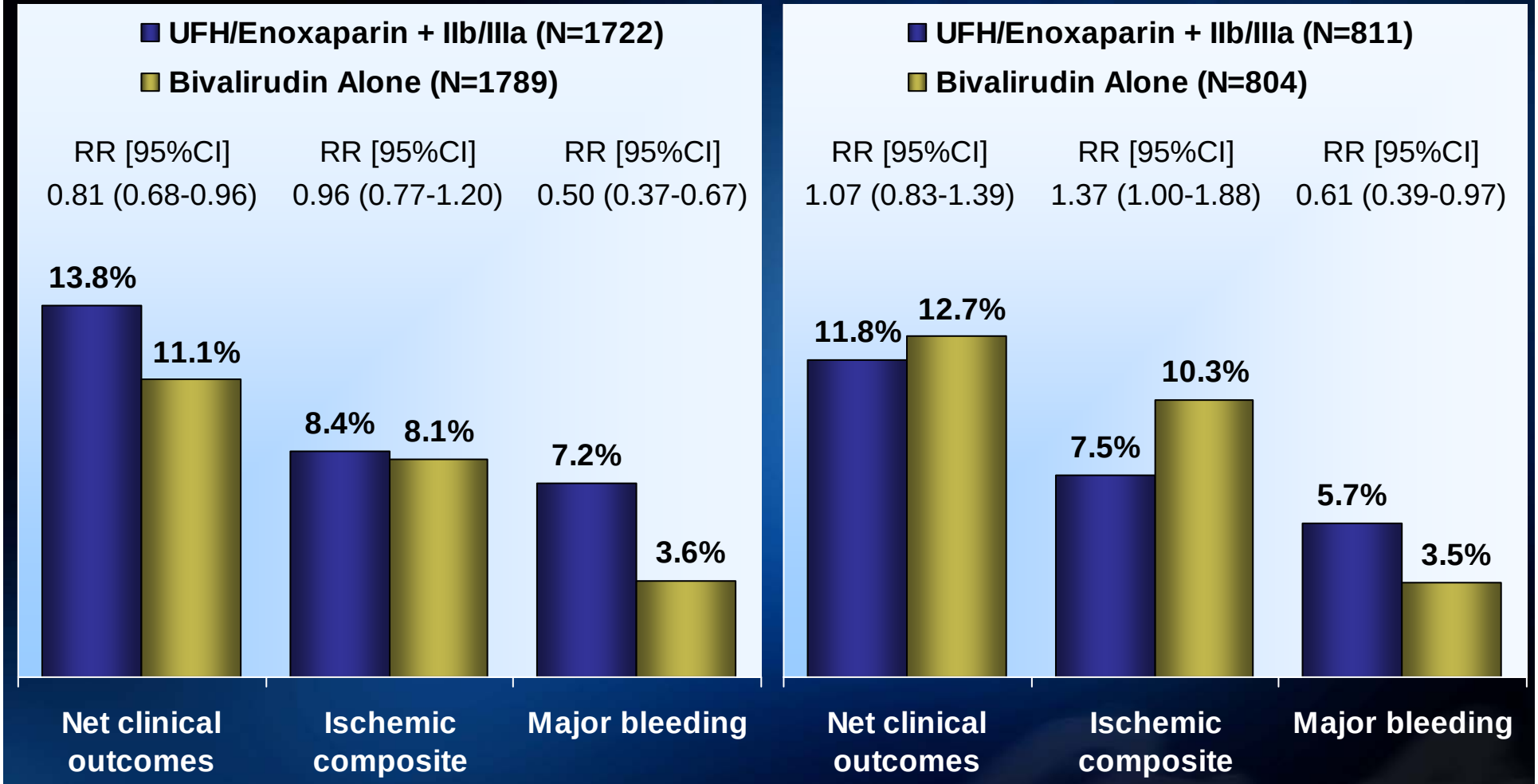


Interaction P values = 0.46, 0.86 and 0.28 respectively

ACUITY PCI

Influence of Thienopyridine Exposure – PCI pts

30 Day Primary Endpoint Adverse Events



Thienopyridine Exposed (anytime before PCI)

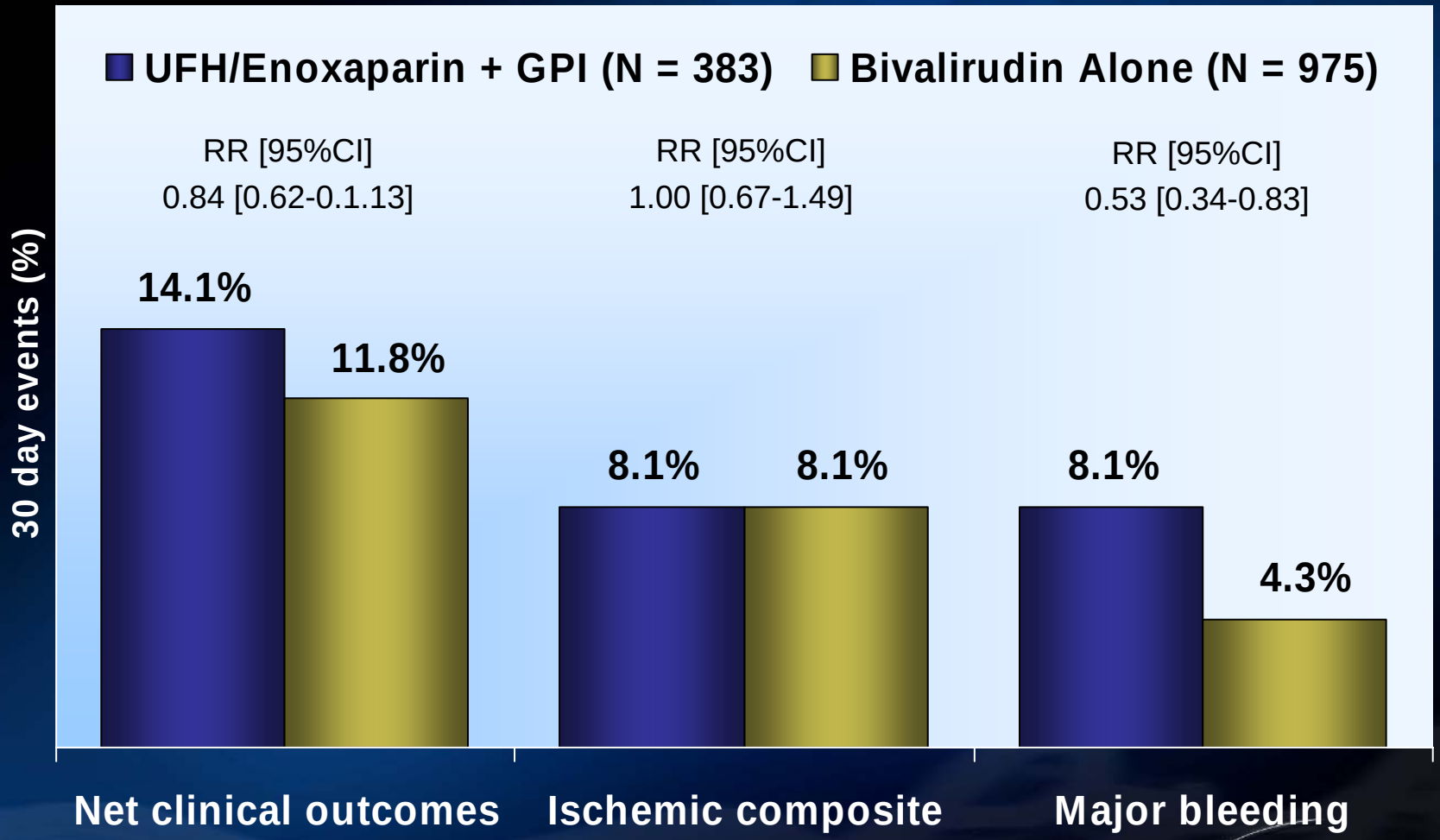
Not Thienopyridine Exposed

Interaction P values = 0.17, 0.19 and 0.65 respectively

ACUITY PCI

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

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

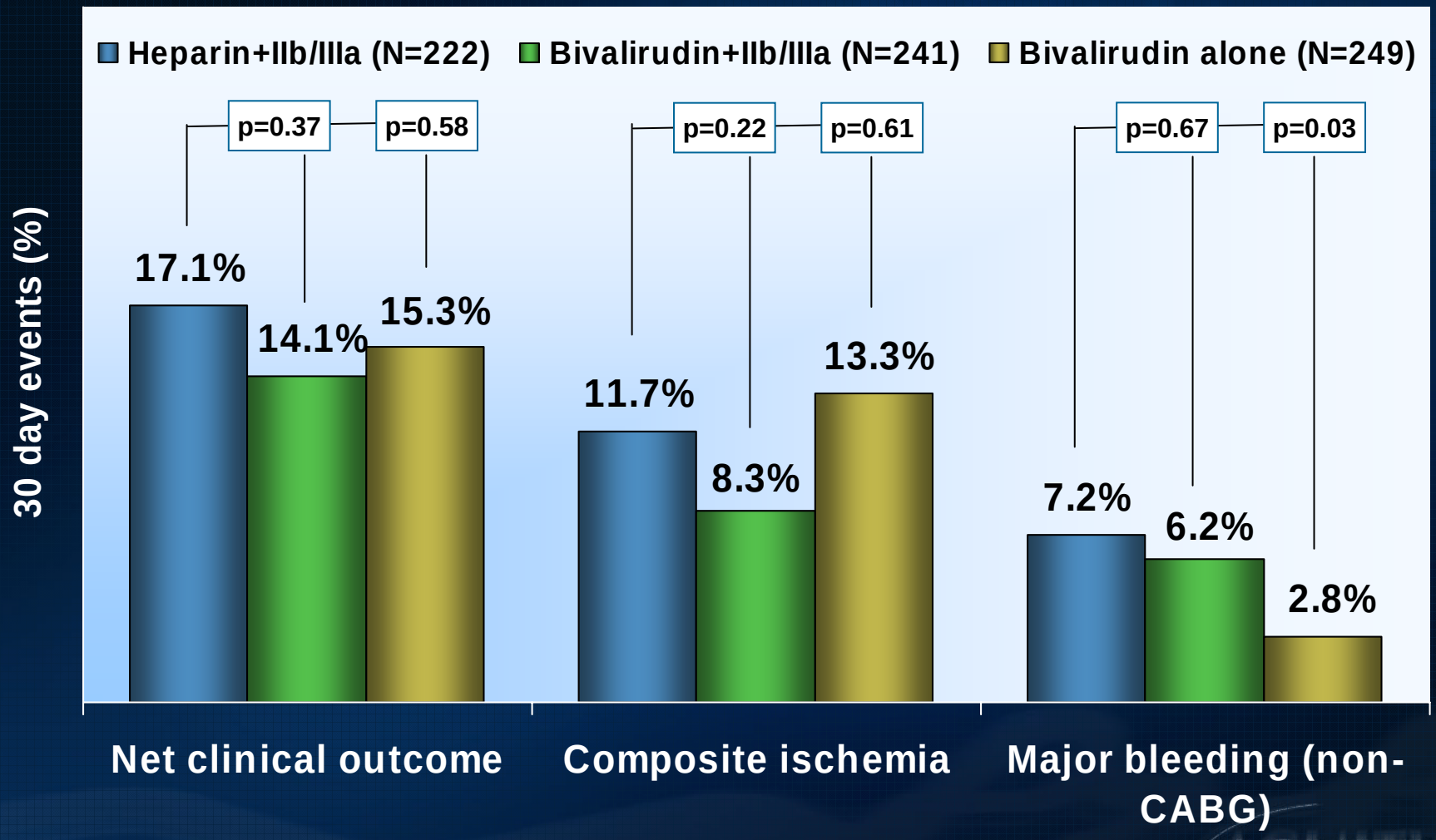


Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Primary Endpoint Measures

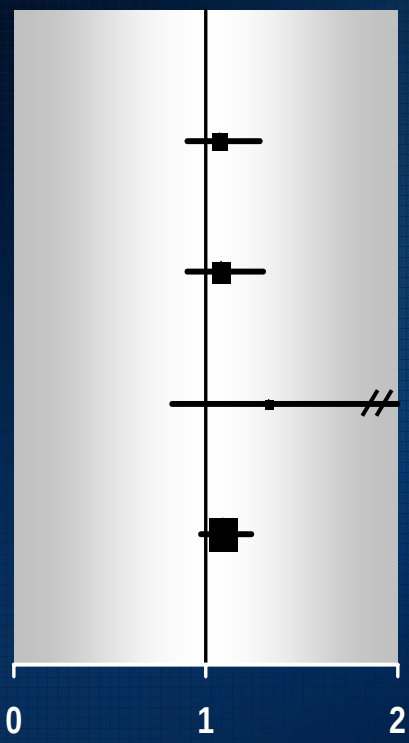
Patients with ≥1 PCI Thrombotic Lesion at Baseline (n=712)



ACUITY PCI

*Heparin=unfractionated or enoxaparin

Meta-Analysis of Contemporary PCI Trials
Composite Ischemia



Trial	Risk ratio ±95% CI	Bival alone	UFH/Enox + IIb/IIIa	RR (95% CI)	p value
ACUITY-PCI* (n=5180)		8.8%	8.2%	1.07 (0.90-1.28)	
REPLACE-2* (n=5965)		7.6%	7.0%	1.08 (0.90-1.30)	
PROTECT-TIMI-30** (n=857)		8.8%	6.6%	1.33 (0.82-2.15)	
Total (n=12,002)		**8.2%**	**7.5%**	**1.09 (0.97-1.24)**	**0.15**

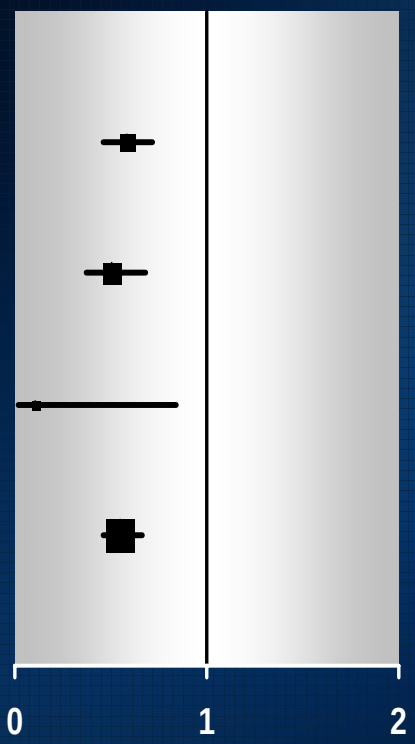
Bivalirudin alone better — UFH/Enox + IIb/IIIa better

*Acuity-PCI/Replace-2 (30 day event rates: Death/MI/Unplanned Revasc)
**Protect-TIMI 30 (48 hour event rate: Death/MI)

Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Meta-Analysis of Contemporary PCI Trials
TIMI Major or Minor Bleeding



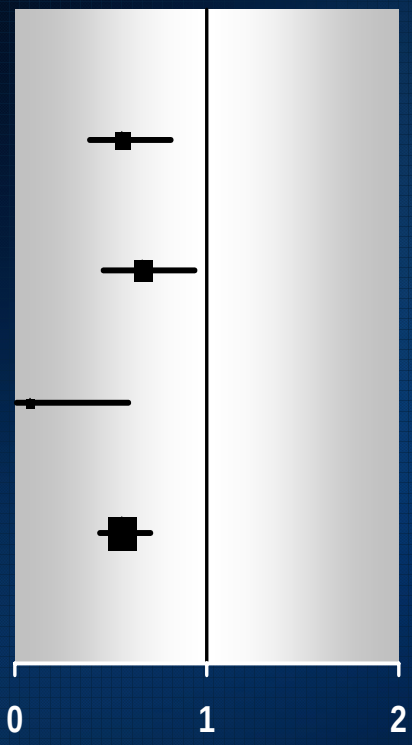
Trial	Risk ratio ±95% CI	Bival alone	UFH/Enox + IIb/IIIa	RR (95% CI)	p value
ACUITY-PCI (n=5180)		4.5%	7.8%	0.58 (0.46-0.72)	
REPLACE-2 (n=6001)		1.9%	3.9%	0.50 (0.37-0.68)	
PROTECT-TIMI-30 (n=839)		0.4%	3.0%	0.11 (0.02-0.84)	
Total (n=12,038)		**3.0%**	**5.5%**	**0.55 (0.46-0.66)**	**<0.0001**

Bivalirudin alone better UFH/Enox + IIb/IIIa better

Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

Meta-Analysis of Contemporary PCI Trials
Blood Transfusion (non-CABG)



Trial	Risk ratio ±95% CI	Bival alone	UFH/Enox + IIb/IIIa	RR (95% CI)	p value
ACUITY-PCI (n=5180)		1.7%	3.0%	0.56 (0.39-0.81)	
REPLACE-2 (n=6001)		1.7%	2.5%	0.66 (0.46-0.94)	
PROTECT-TIMI-30 (n=857)		0.4%	4.4%	0.08 (0.01-0.59)	
Total (n=12,038)		**1.6%**	**2.9%**	**0.56 (0.44-0.71)**	**<0.0001**

Bivalirudin alone better UFH/Enox + IIb/IIIa better

Stone GW, et al. Lancet 2007;369:907-19

ACUITY PCI

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

ACUITY PCI