Antithrombotic Alternatives for Pts With ACS and PCI

Bivalirudin for the Best Overall Outcomes

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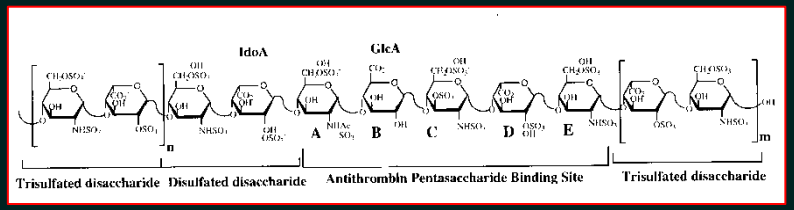
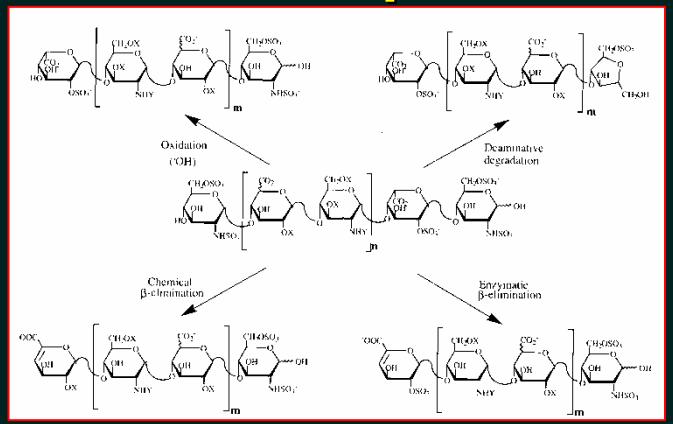
Anti-thrombin Alternatives for Patients with ACS and Those Undergoing PCI

Unfractionated heparin



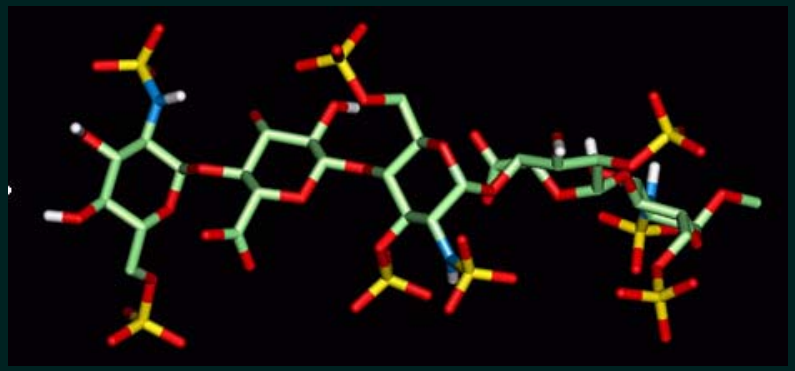
+ GP IIb/IIIa inhibitors

LMW heparin



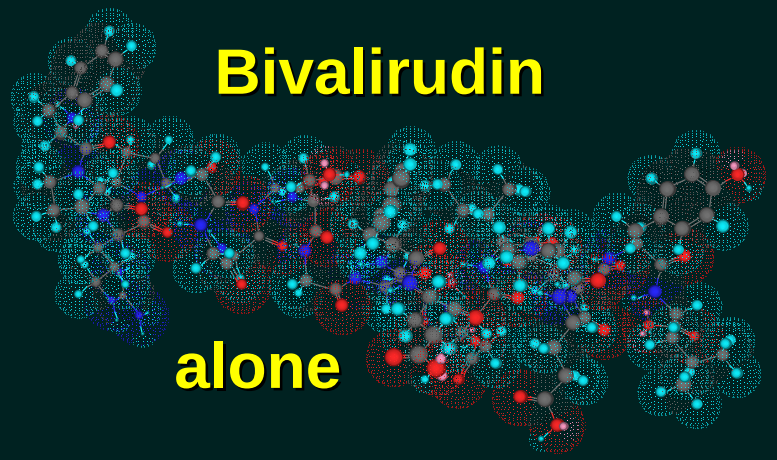
+ GP IIb/IIIa inhibitors

Fondaparinux



+ GP IIb/IIIa inhibitors

Bivalirudin



alone

GP IIb/IIIa Inhibitors: Chemical Structures

Abciximab

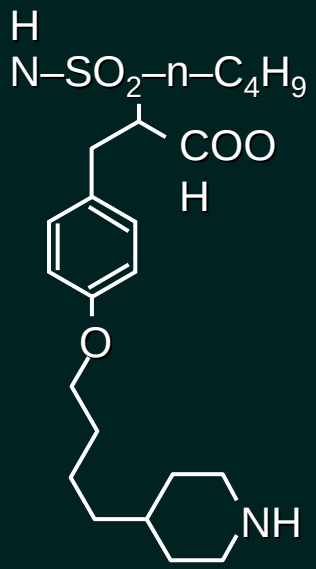
Chimeric Monoclonal Antibody

MW ≈ 50,000 D

Tirofiban

Nonpeptide Tyrosine Derivative

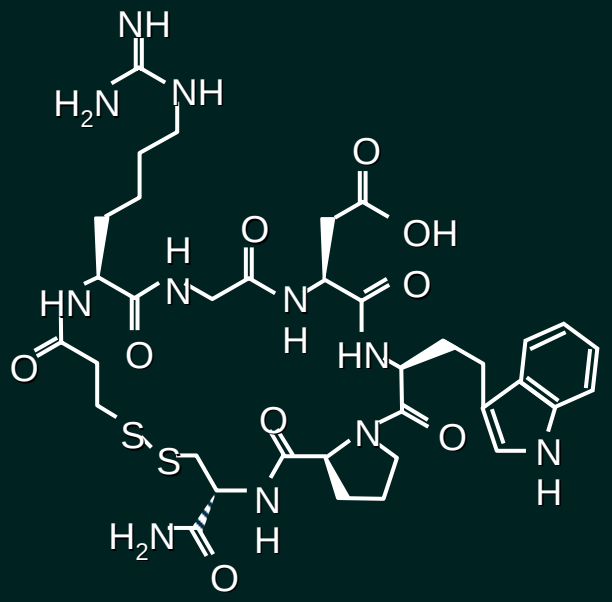
MW ≈ 500 D



Eptifibatide

Cyclic Heptapeptide

MW ≈ 800 D

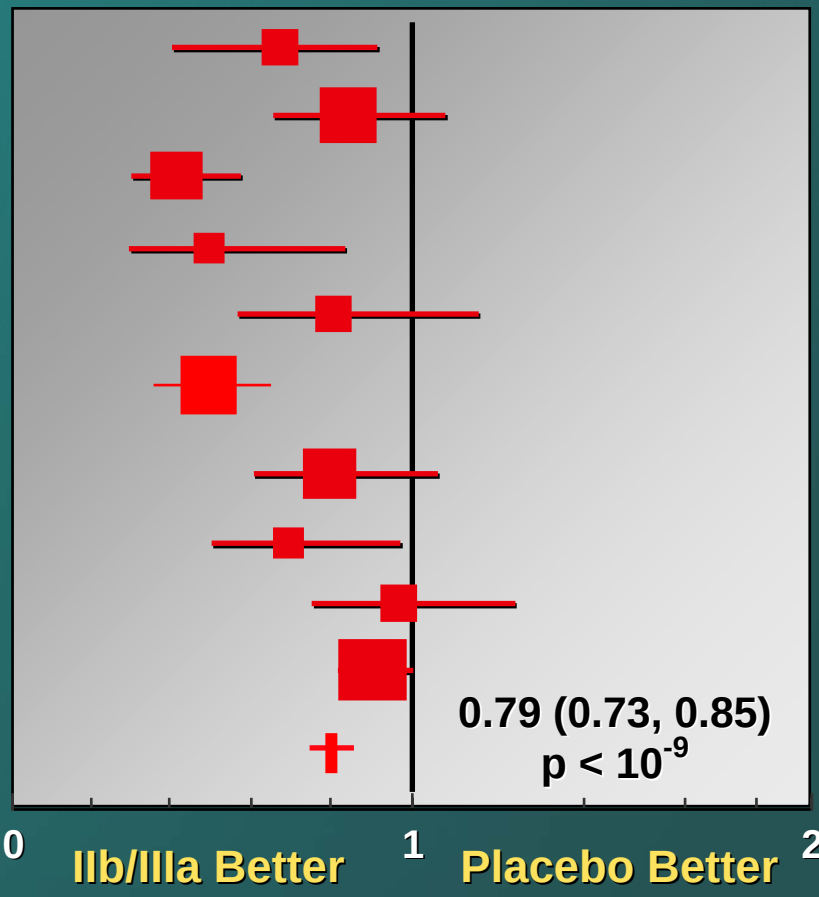


Slide from 1997

IIb/IIIa Inhibitors in PCI and ACS

Death/MI at 30 Days

Trial	N	Placebo	IIb/IIIa
EPIC	2,099	10.1%	7.0%
IMPACT-II	4,010	8.4%	7.1%
EPILOG	2,792	9.1%	4.0%
CAPTURE	1,265	9.0%	4.8%
RESTORE	2,139	6.3%	5.1%
EPISTENT	2,399	10.2%	5.2%
PRISM	3,231	7.0%	5.7%
PRISM PLUS	1,570	11.9%	8.7%
PARAGON	2,282	11.7%	11.3%
PURSUIT	10,948	15.7%	14.2%
Overall	30,336	11.1%	9.0%



PURSUIT
Hemorrhagic Events (non CABG)

	Eptifibatide (N=4,679)	Placebo (N=4,696)	P value
TIMI minor	11.1%	4.7%	<0.001
TIMI major	3.0%	1.3%	<0.001
GUSTO mild	26.0%	10.4%	<0.001
GUSTO moderate	4.1%	1.7%	<0.001
GUSTO severe	1.1%	0.3%	<0.001

Limitations of heparins

Attribute	UFH	Enox	Impact
Active moieties in substance	30-35%	40-60%	Unpredictable
Action independent of AT	No	No	Unpredictable
Non-specific protease binding	Yes	Partial	Unpredictable
Variable PK-PD	Yes	Less	Unpredictable
Inhibits fibrin-bound thrombin	No	No	Need ↑ dose
Activates/aggregates platelets	Yes	+/-	Need IIb/IIIa
$T_{0.5}$ in minutes	60-90'	270'	↑ Bleeding
PF-4 complexing & risk of HIT	Yes	Reduced	Very bad

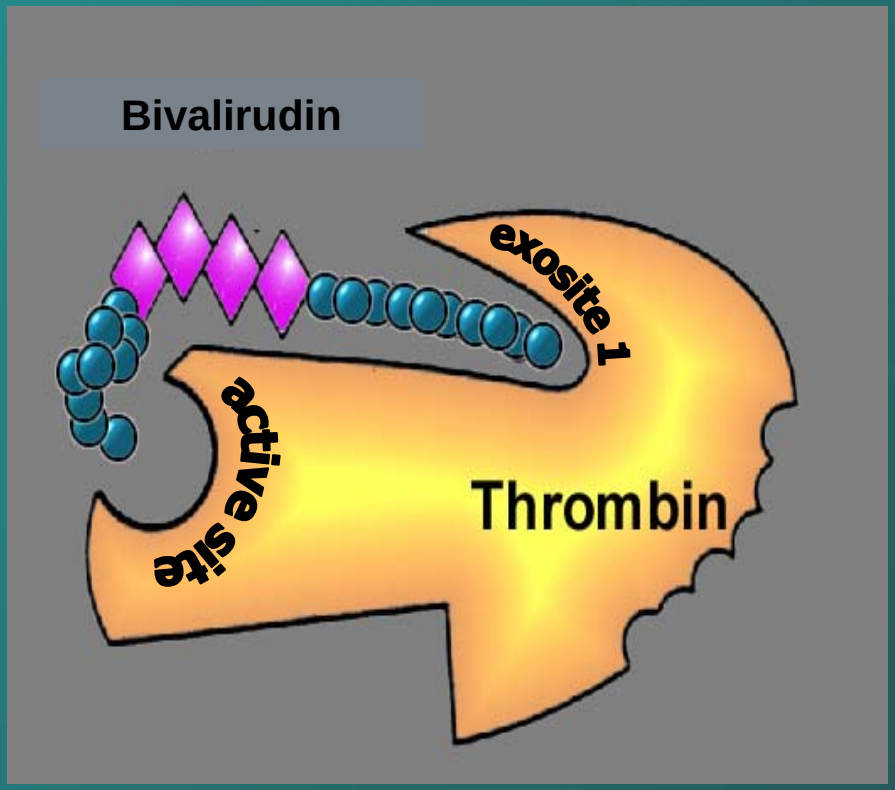
Limitations of Fondaparinux

- Has not been studied in PCI, or in ACS patients treated with an invasive strategy
  - In OASIS-5*, pts were maintained on study drug for mean 5.3 days, and only 63% underwent cath
- Catheter induced thrombus in ~1% of pts
  - Requires another antithrombin to prevent – not formally studied
- No readily available point of care test to monitor
- Long $t_{1/2}$ (15-18 hours)
  - Makes sheath management difficult
- Still requires a GP IIb/IIIa inhibitor to ↓ ischemia

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

Bivalirudin

Bivalent synthetic direct thrombin inhibitor



- **Specifically inhibits**
  - Fluid phase thrombin
  - Clot-bound thrombin
  - Thrombin-mediated platelet aggregation
- **Reversible**
- **$T_{0.5}$ 25 minutes**

Topol EJ: Textbook of Interventional Cardiology

Overcoming limitations of heparins

Attribute	UFH	Enox	Bivalirudin
Active moieties in substance	30-35%	40-60%	100%
Action independent of AT	No	No	Yes
Non-specific protease binding	Yes	Partial	No
Variable PK-PD	Yes	Less	No
Inhibits fibrin-bound thrombin	No	No	Yes
Activates/aggregates platelets	Yes	+/-	Inhibits
$T_{0.5}$ in minutes	60-90’	270’	25’
PF-4 complexing & risk of HIT	Yes	Reduced	No

Bivalirudin vs Heparin + GPIIb/IIIa During PCI

6,012 patients undergoing urgent or elective PCI

Randomization - double blind, triple dummy

Heparin
65 U/kg initial bolus

Planned GP IIb/IIIa
(abciximab or eptifibatide)

target ACT
≥ 225 sec

Bivalirudin
0.75 mg/kg initial bolus,
1.75 mg/kg-hr during PCI

Provisional GP IIb/IIIa
(abciximab or eptifibatide)

abciximab: 0.25 mg/kg bolus, 0.125 μg/kg-min (max 10 μg/min) x 12 hrs

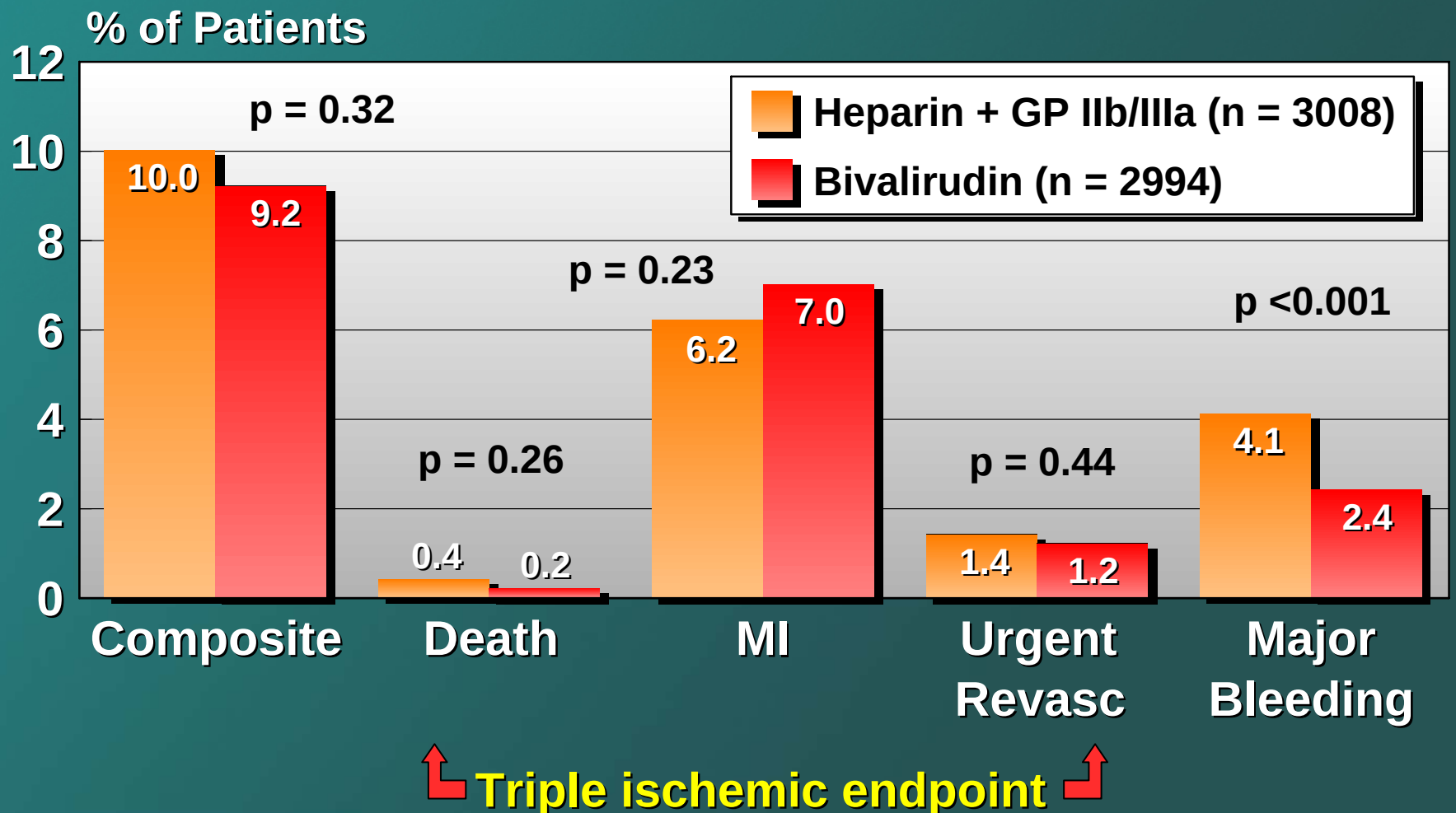
eptifibatide: 180 μg/kg double bolus, 2.0 μg/kg-min x 18-24 hrs

• **Primary "Quadruple Endpoint" at 30 Days** •

Lincoff AM et al. JAMA 2003;289:853-63

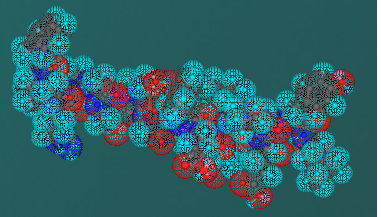
30 Day Primary Endpoint

6,012 patients undergoing PCI



Lincoff AM et al. JAMA 2003;289:853-63

Bleeding Complications

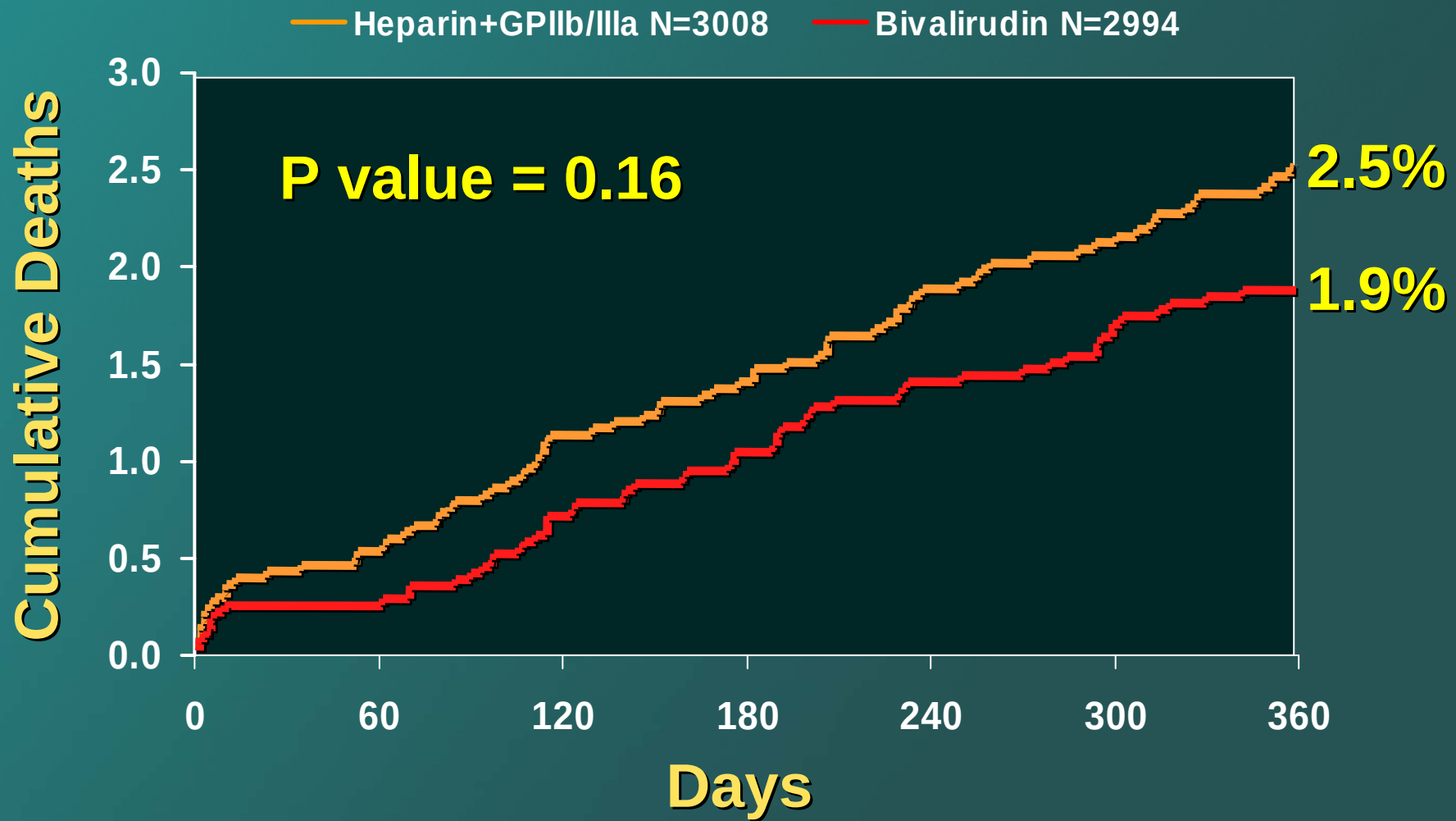


	Bivalirudin N = 2994	Heparin + GP IIb/IIIa N = 3008	P-value
Major bleeding	2.4	4.1	< 0.001
Minor bleeding	13.4	25.7	<0.001
Large hematoma	0.8	2.5	<0.001
Retroperitoneal hemorrhage	0.2	0.5	0.06
Major organ bleeding	0.5	1.5	<0.001
Intracranial hemorrhage	0	0.1	1.00
Thrombocytopenia (<100K)	0.7	1.7	<0.001
Transfusion	1.7	2.5	0.02

Lincoff AM et al. JAMA 2003;289:853-63

1-year Mortality

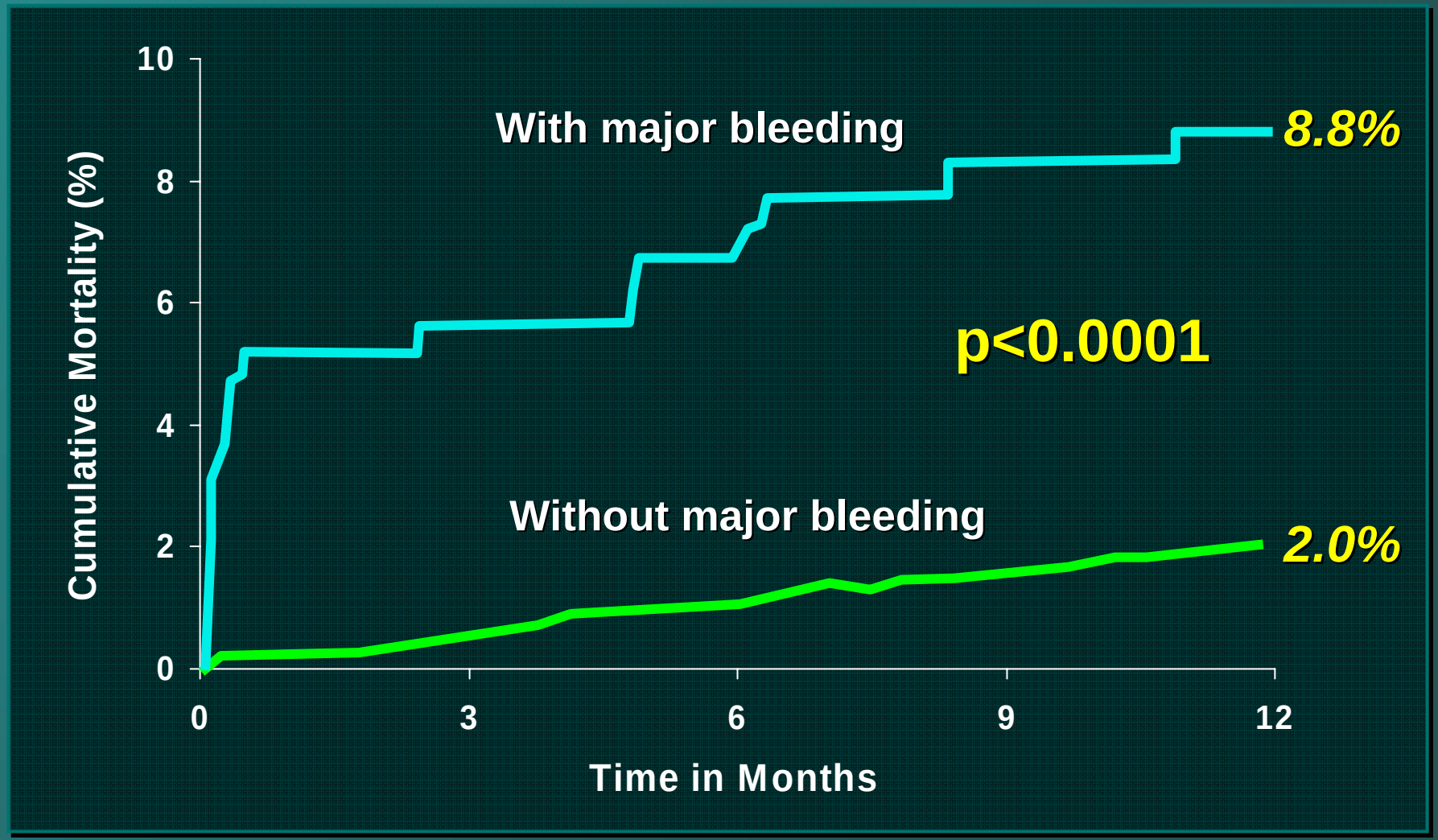
All 6,012 patients (ITT)



Lincoff AM et al. JAMA 2004;292:696-703

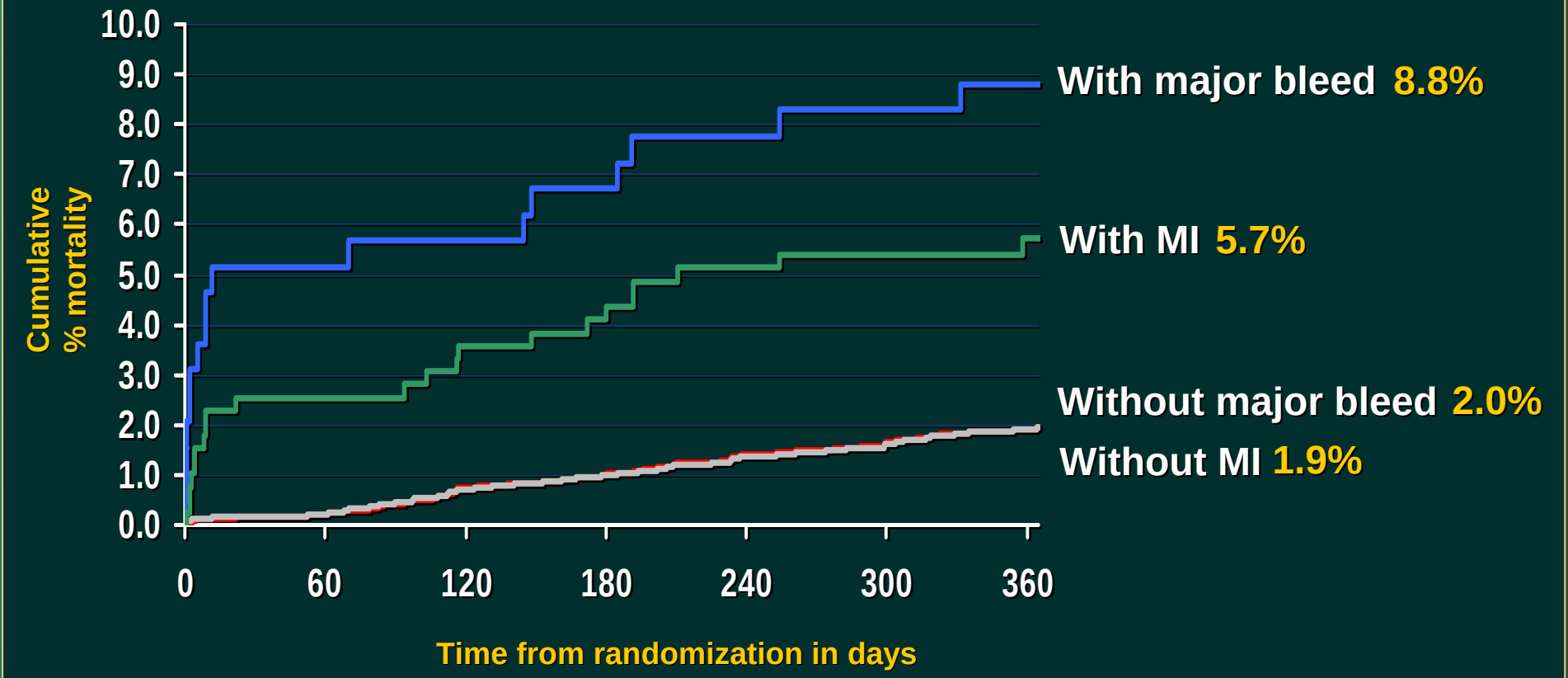
Impact of Major Bleed (all pts)

1-Year Mortality



Impact of Major Bleed and MI

1-Year Mortality



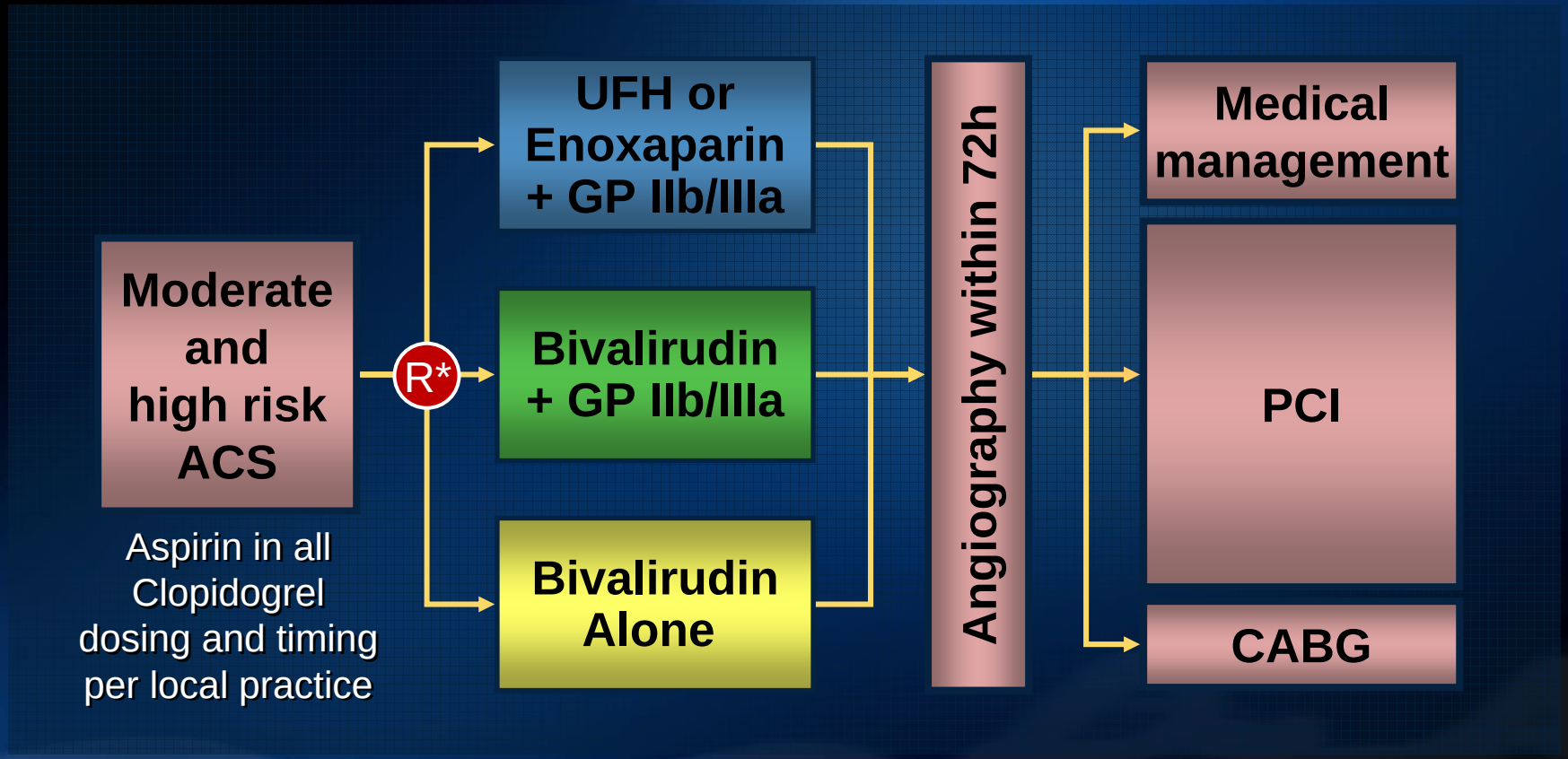
Predictors of 1-year mortality

Independent Variable	Groups	O.R.	(95% CI)	p-value
Creatinine clear.	<30 mL/min	7.21	(2.53-20.51)	
	30-60 mL/min	3.34	(1.92-5.78)	<0.0001
	60-90 mL/min	1.57	(0.96-2.57)	
CHF	Yes	4.38	(2.83-6.78)	<0.0001
Major Bleeding	**Yes**	**3.26**	**(1.78-5.96)**	**0.0001**
MI @30day	Yes	2.77	(1.62-4.75)	0.0002
Urg Revasc @30d	Yes	2.77	(1.15-6.71)	.024
Hx angina	Yes	2.18	(1.25-3.81)	0.006
Prior MI	Yes	1.81	(1.09-3.03)	0.023
Diabetes	Yes	1.64	(1.10-2.44)	0.015

Stone GW. J Inv Cardiol 2004;16(suppl G):12-17.

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

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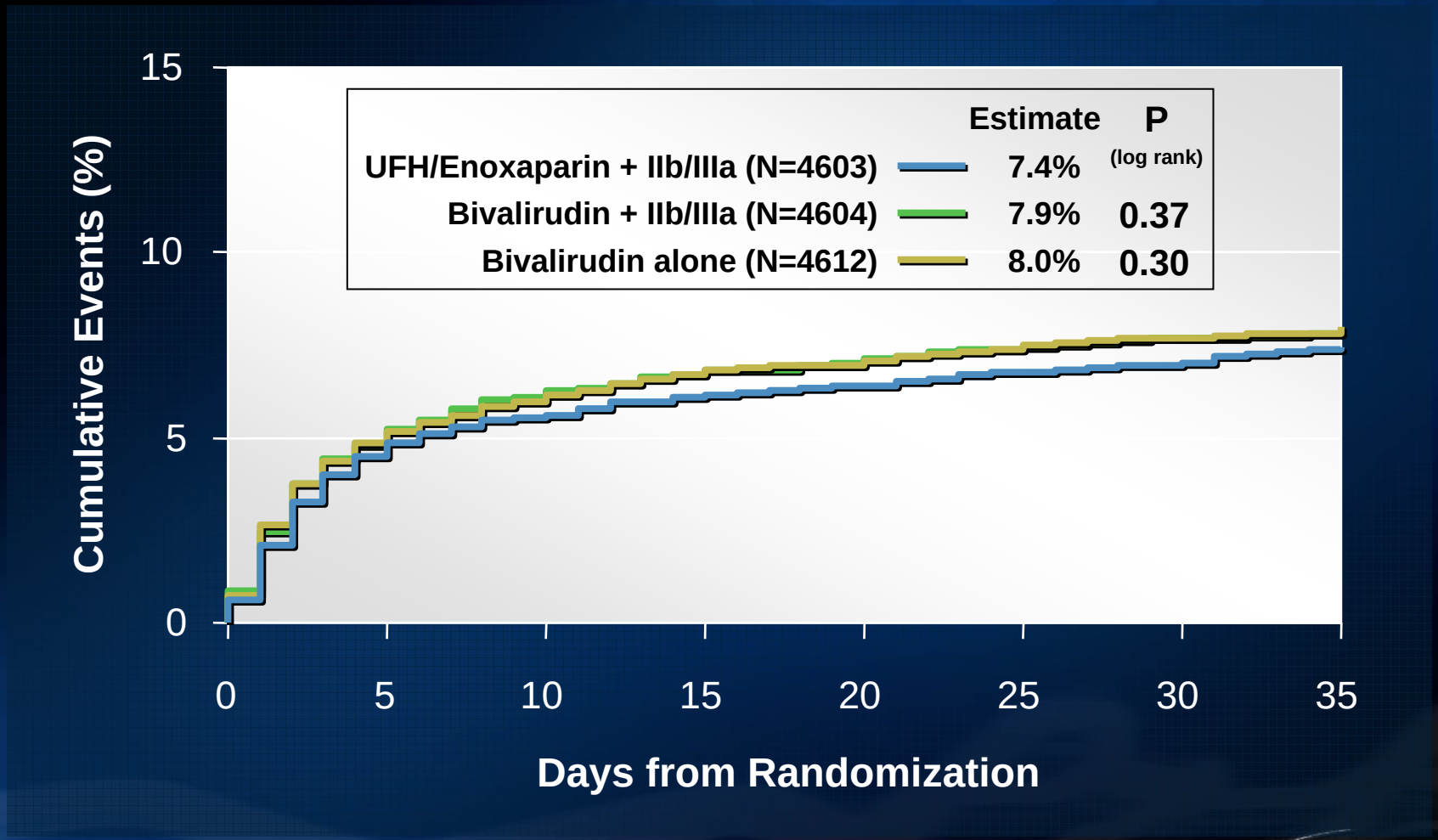
ACUITY Design. Stone GW et al. AHJ 2004;148:764–75

Ischemic Composite Endpoint

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



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

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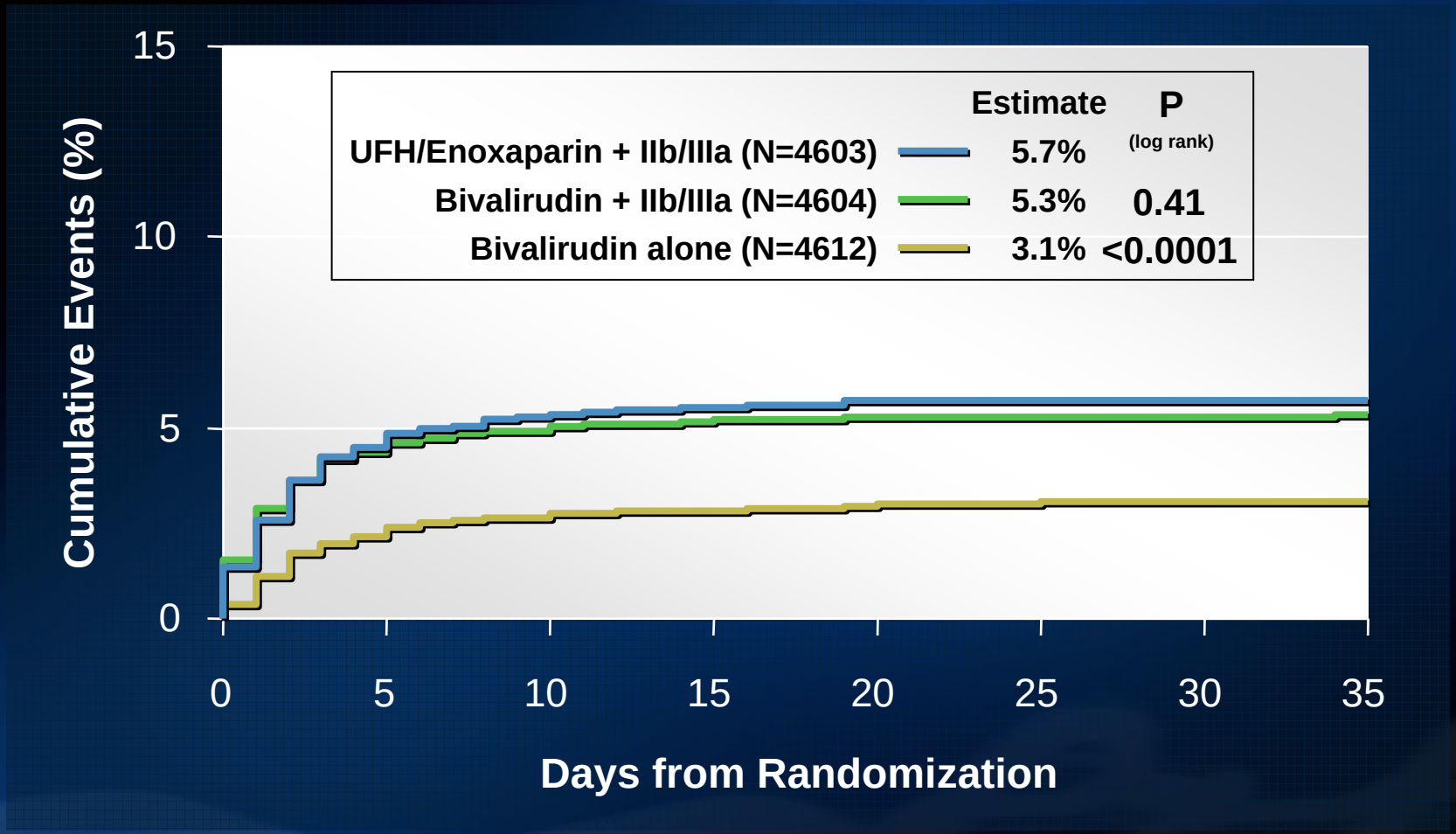
Major Bleeding Endpoint

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



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

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Major Bleeding (Primary Endpoint)

	UFH/Enoxaparin + GP IIb/IIIa (N=4,603)	Bivalirudin + GP IIb/IIIa (N=4,604)	Bivalirudin alone (N=4,612)	P value*
Any major bleeding	5.7%	5.3%	3.0%	<0.001
• Intracranial	0.07%	0.04%	0.07%	1.00
• Retroperitoneal	0.5%	0.6%	0.2%	0.002
• Access site	2.6%	2.6%	0.8%	<0.001
- req interv/surgery	0.3%	0.5%	0.2%	0.10
- hematoma ≥5 cm	2.2%	2.2%	0.7%	<0.001
• Hgb ⇓ ≥3 g/dL with overt source	2.2%	1.8%	1.0%	<0.001
• Hgb ⇓ ≥4 g/dL with no overt source	0.8%	0.7%	0.7%	0.47
• Blood transfusion	2.7%	2.6%	1.6%	<0.001
• Reoperation for bleed	0.04%	0.1%	0.1%	0.69

*P value for Bivalirudin alone vs. UFH/Enox + GP IIb/IIIa inhibitor

ACUITY

Bleeding Endpoints

	UFH/Enoxaparin + GP IIb/IIIa (N=4,603)	Bivalirudin + GP IIb/IIIa (N=4,604)	Bivalirudin alone (N=4,612)	P Value
ACUITY Scale				
- Major Bleed, all	11.8%	11.1%	9.1%	<0.001
- Major, non-CABG	5.7%	5.3%	3.0%	<0.001
- Minor, non-CABG	21.6%	21.7%	12.8%	<0.001
TIMI Scale				
- Any	6.6%	6.5%	4.0%	<0.001
- Major	1.9%	1.7%	0.9%	<0.001
- Minor	6.4%	6.1%	3.7%	<0.001
Blood transfusion	2.7%	2.6%	1.6%	<0.001
Thrombocytopenia	11.1%	10.8%	9.9%	0.06

*P value for Bivalirudin alone vs. UFH/Enox + GP IIb/IIIa inhibitor

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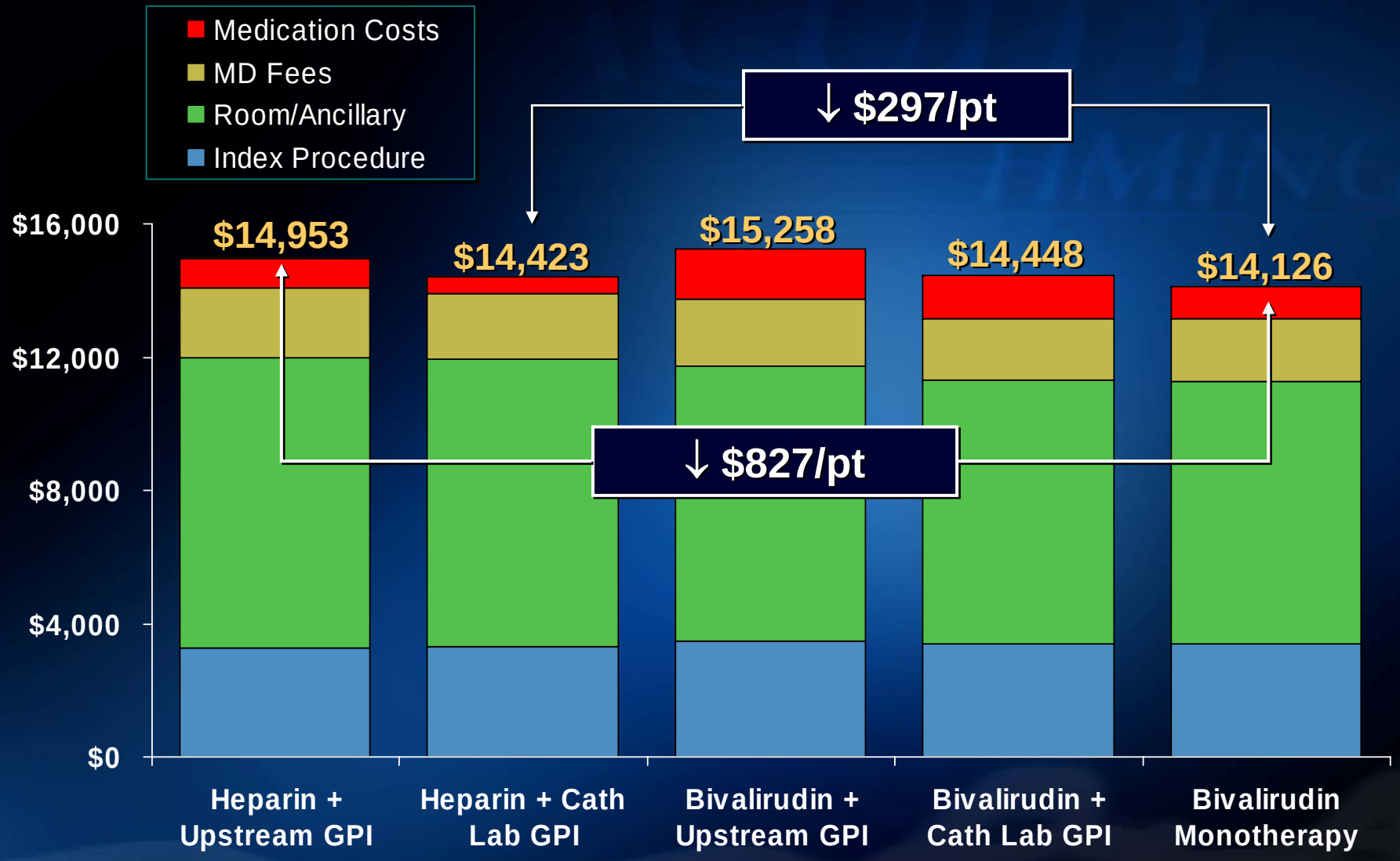
Mean Initial Hospitalization Costs



p<0.001 for overall comparison

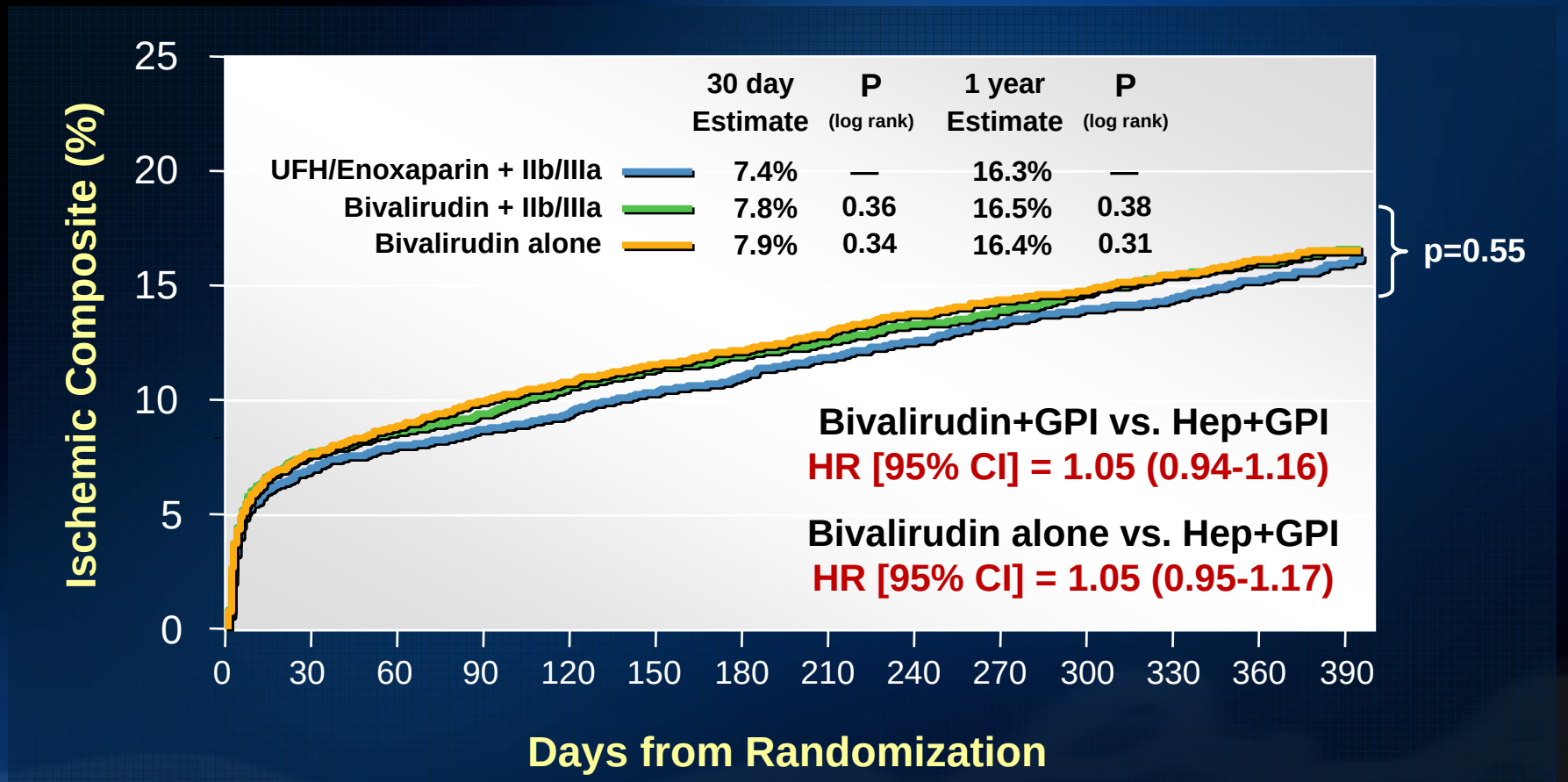
Cohen DJ. TCT2006

ACUITY TIMING

Ischemic Composite Endpoint

(Death, MI, unplanned revascularization for ischemia)

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



Stone GW et al. ACC 2007

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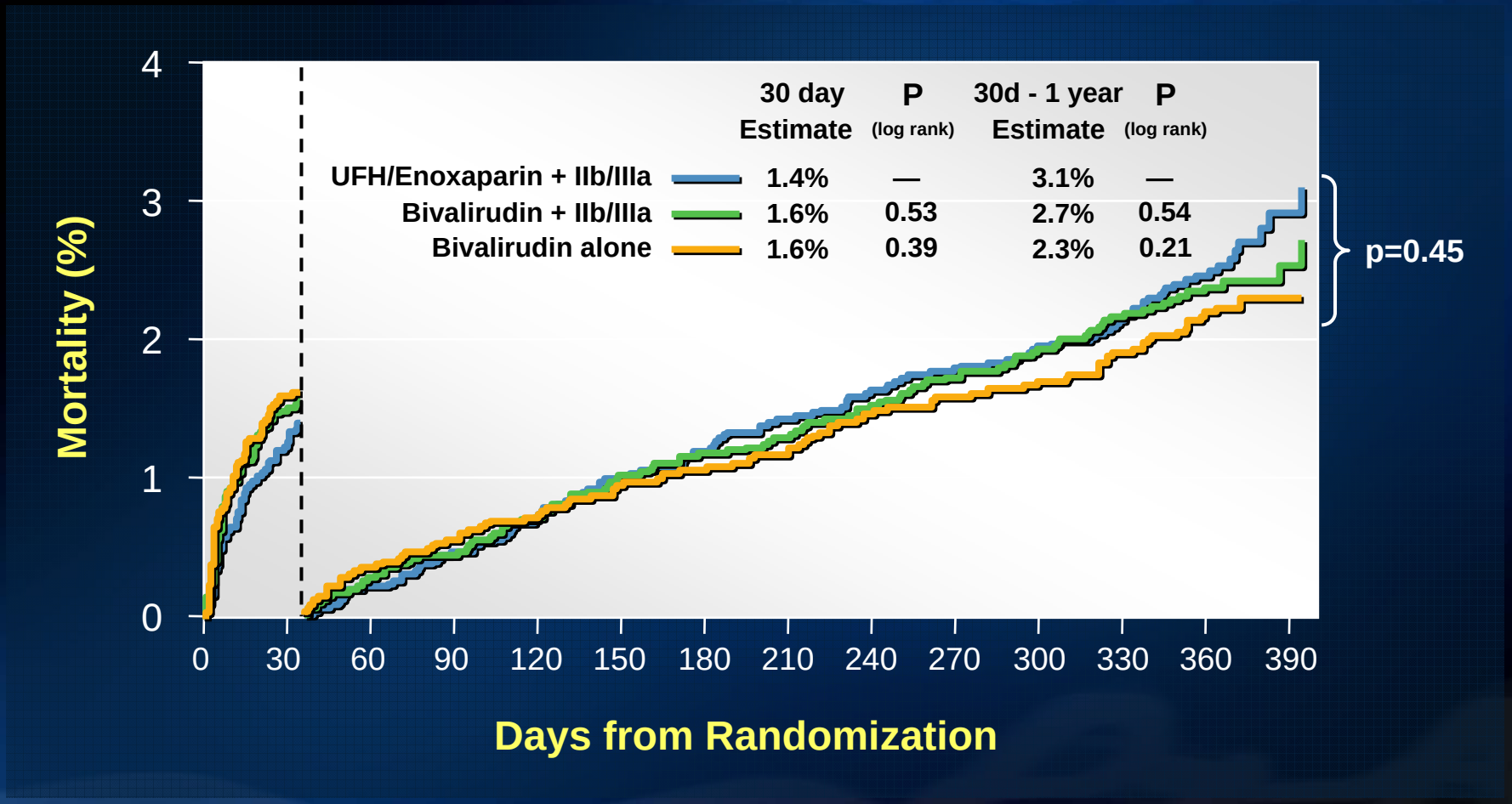
Early and Late Mortality
Landmark analysis



Stone GW et al. ACC 2007

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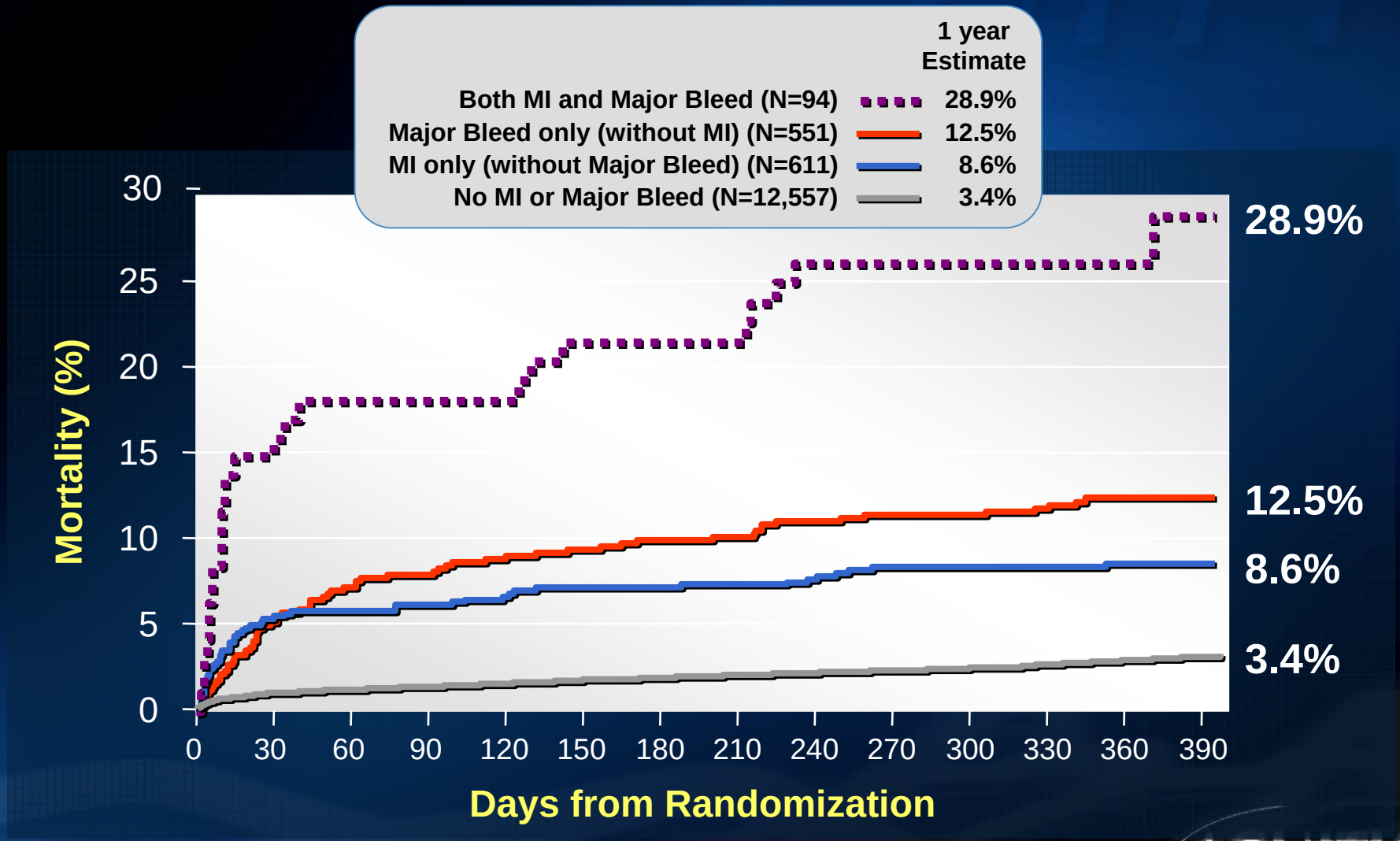
Impact of MI and Major Bleeding (non-CABG) in the First 30 Days on Risk of Death Over 1 Year



Stone GW et al. ACC 2007

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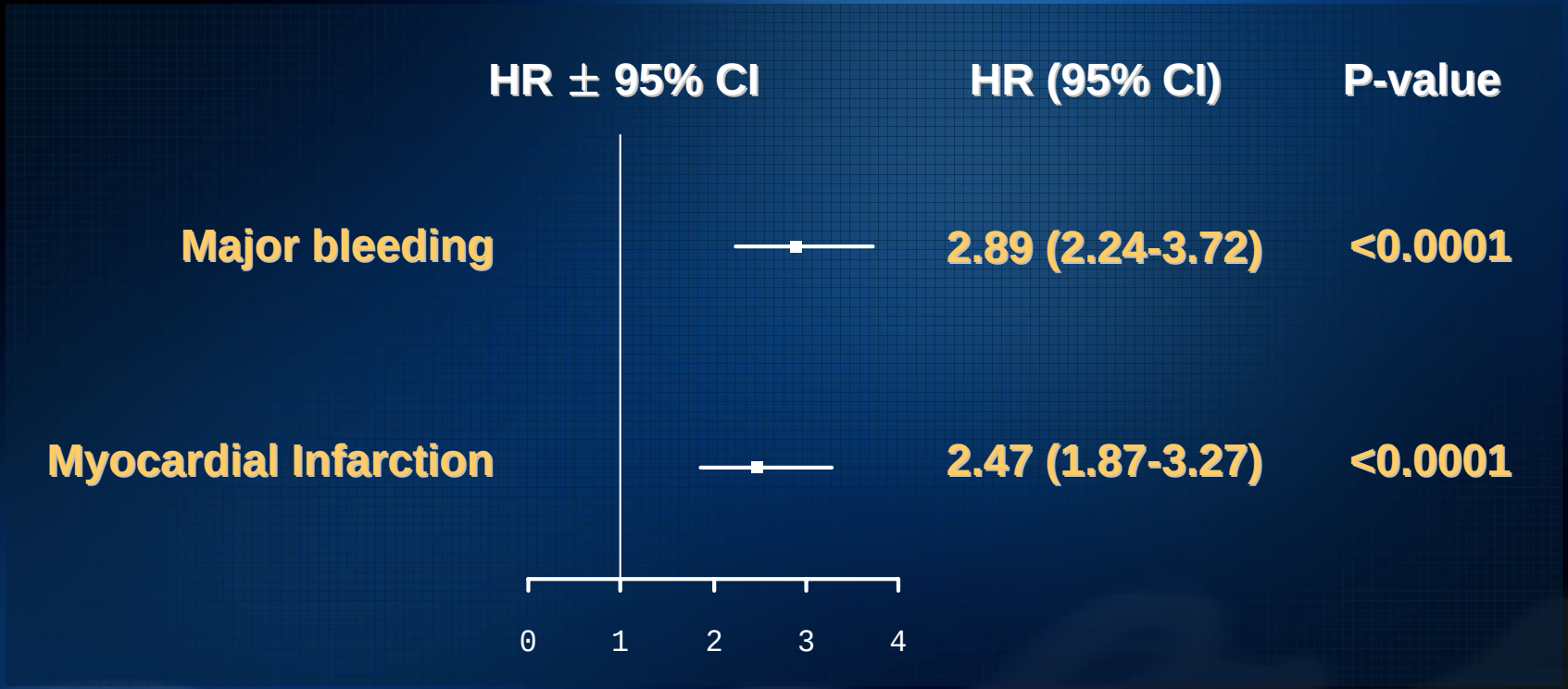
Influence of Major Bleeding and MI in the First 30 Days on Risk of Death Over 1 Year

Cox model adjusted for baseline predictors, with non-CABG major bleeding and MI as time-updated covariates



Stone GW et al. ACC 2007

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The Case for Bivalirudin Alone in ACS and PCI

- The simplest regimen by far
  - No GP IIb/IIIa inhibitors (except provisional use)
  - IV infusion discontinued after cath (ACS and PCI)
  - Monitoring of aPTT and ACT possible but not necessary
- Provides similar protection from ischemic complications as heparin (UFH or enoxaparin) + GP IIb/IIIa inhibitors with markedly less bleeding, and is cost-effective

ACUITY