STEMI and NSTEMI Pharmacology Confusion: How to Choose and Use Antithrombins (Unfractionated and Low Molecular Heparins, Bivalirudin, Fondaparinux) and Antiplatelet Agents (Aspirin, Clopidogrel and Prasugrel)

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Disclosures

- Gregg W. Stone
  - Research support from The Medicines Company

My Dilemma

How to Cover 25 Years of Data and >350 Randomized Trials in 20 minutes?

- **The Drugs**
  - *Antiplatelet agents*
    - Aspirin
    - Thienopyridines
    - GP IIb/IIIa inhibitors
  - *Antithrombins*
    - Unfractionated heparin
    - LMWH (enoxaparin)
    - Bivalirudin
    - Fondaparinux

- **The Settings**
  - *PCI in…*
    - ACS
    - AMI
      - Primary PCI
      - Rescue PCI
  - Acute use

    vs.

  - Chronic use

XXXXXXXX

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PCI Pharmacology

Aspirin

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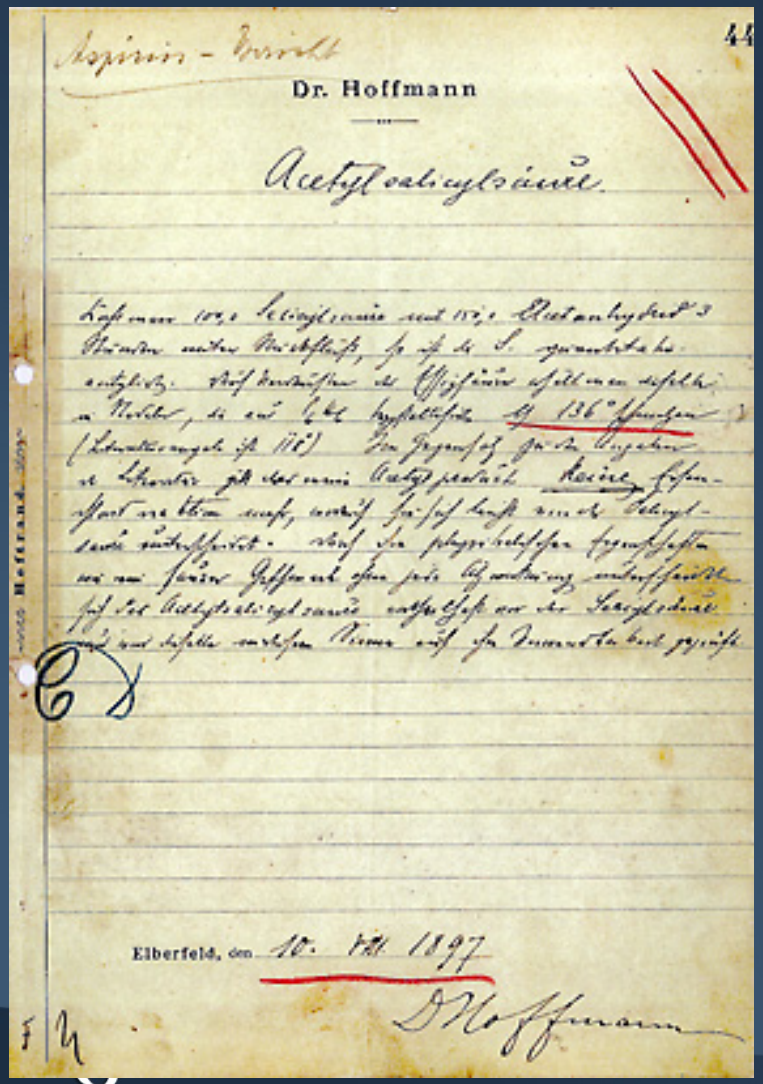
Aspirin

(From the German acetylspirsaure + chemical suffix – in)


Aspirin - Verfahren

Dr. Hoffmann

Acetylsalicylsäure

Elberfeld, den 10. VIII. 1897

First synthesized in pure form by Felix Hoffman of Friedr. Bayer & Co. in 1897.

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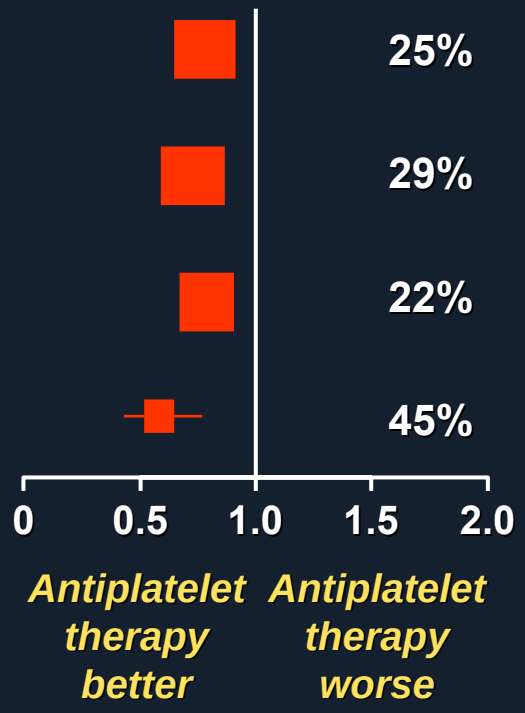
Aspirin in ACS (n=54,089)

Category of trial	N of trials	MI, Stroke, or Vascular Death: Anti-platelet	MI, Stroke, or Vascular Death: Adjusted controls	Odds ratio & CI (Antiplatelet: Control)	% odds reduction (SD)
Prior MI	11	1330/9677 (13.7%)	1693/9914 (17.1%)		25%
Acute MI	9	992/9388 (10.6%)	1348/9385 (14.4%)		29%
Prior Stroke/TIA	18	1076/5837 (18.4%)	1301/5870 (22.2%)		22%
Unstable Angina	7	182/1991 (9.1%)	285/2027 (14.1%)		45%



Antiplatelet Trialists' Collaboration. BMJ 1994;308:81–106

PCI Pharmacology

Thienopyridines

Ticlopidine (Ticlid)

Clopidogrel (Plavix)

300 mg pill also approved

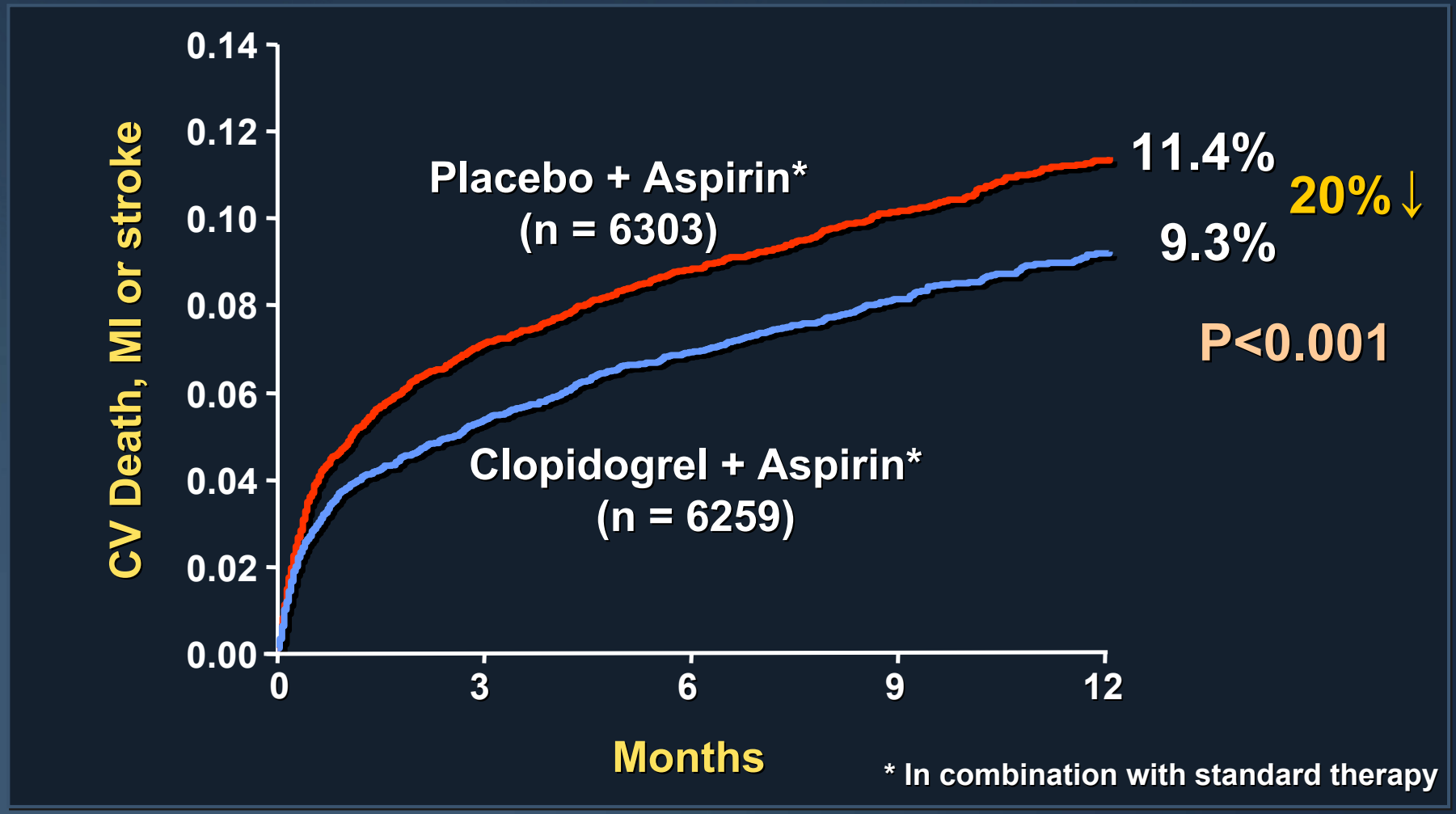
Prasugrel (Effient)

60 mg load
10 mg QD
Approved in EU

CURE

12,562 pts with ACS were treated with aspirin and randomized to clopidogrel vs. placebo and followed for up to 12 months

Primary endpoint = CV Death, MI, or Stroke



CURE Trial Investigators. N *Engl J Med* 2001;345:494–502.

CURE

12,562 pts with ACS were treated with aspirin and randomized to clopidogrel vs. placebo and followed for up to 12 months

Primary endpoint = CV Death, MI, or Stroke

	ASA + Clopidogrel	ASA + Placebo	P
CV death, MI, stroke	9.3%	11.4%	<0.001
CV death, MI, stroke, refractory ischemia	16.5%	18.8%	<0.001
- CV death	5.1%	5.5%	NS
- MI	5.2%	6.7%	<0.05
- Stroke	1.2%	1.4%	NS
- Refractory ischemia	8.7%	9.3%	NS
Non CV death	0.7%	0.7%	NS
Bleeding events, any	8.5%	5.0%	<0.001
- Major	3.7%	2.7%	0.001
- Minor	5.1%	2.4%	<0.001

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CURE Trial Investigators. N *Engl J Med* 2001;345:494–502

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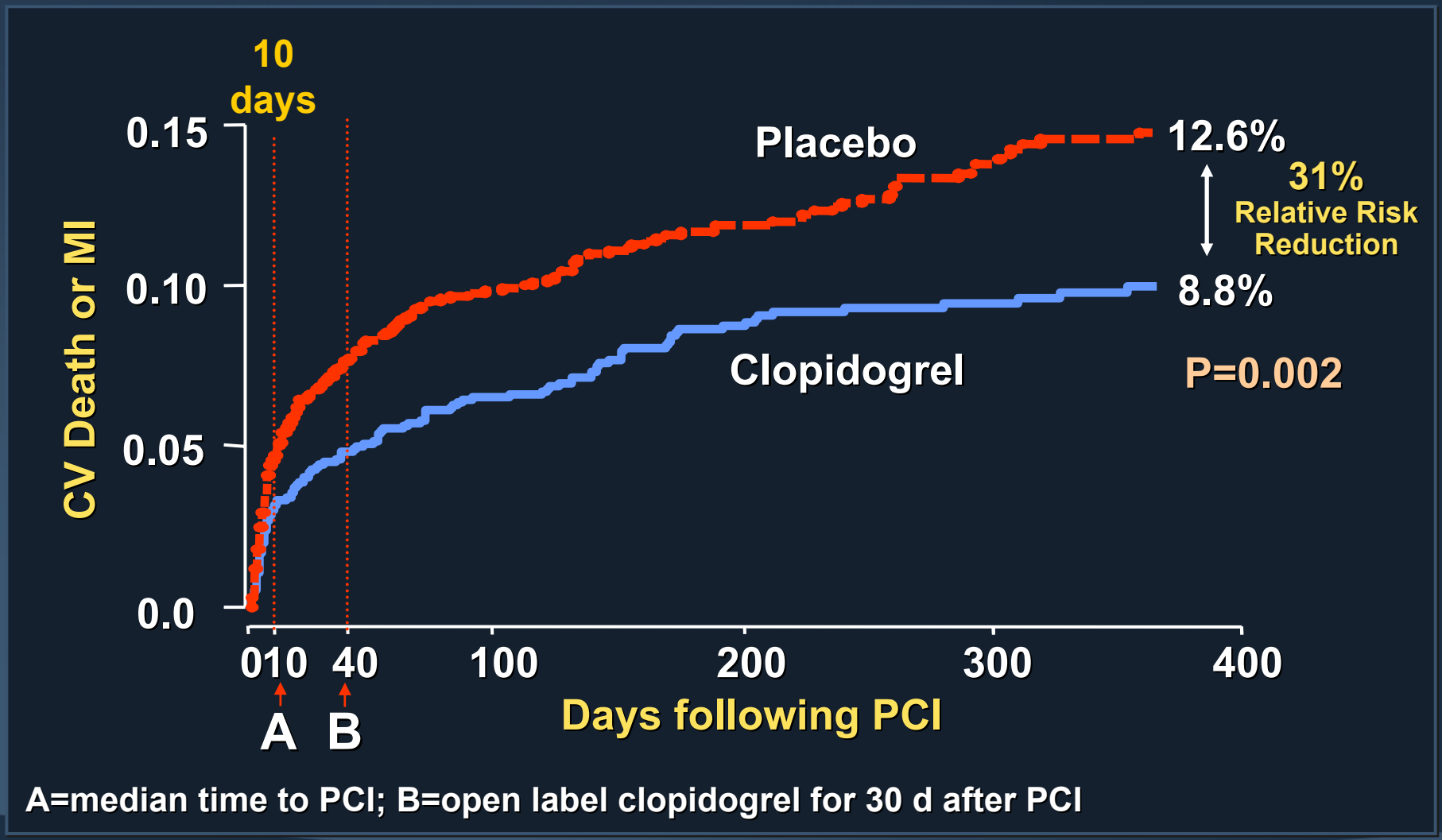
PCI-CURE

PCI was performed in 2658 pts (21%): *1 Yr CV Death or MI*



A=median time to PCI; B=open label clopidogrel for 30 d after PCI

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Mehta, SR et al. *Lancet* 2001;21:2033–41

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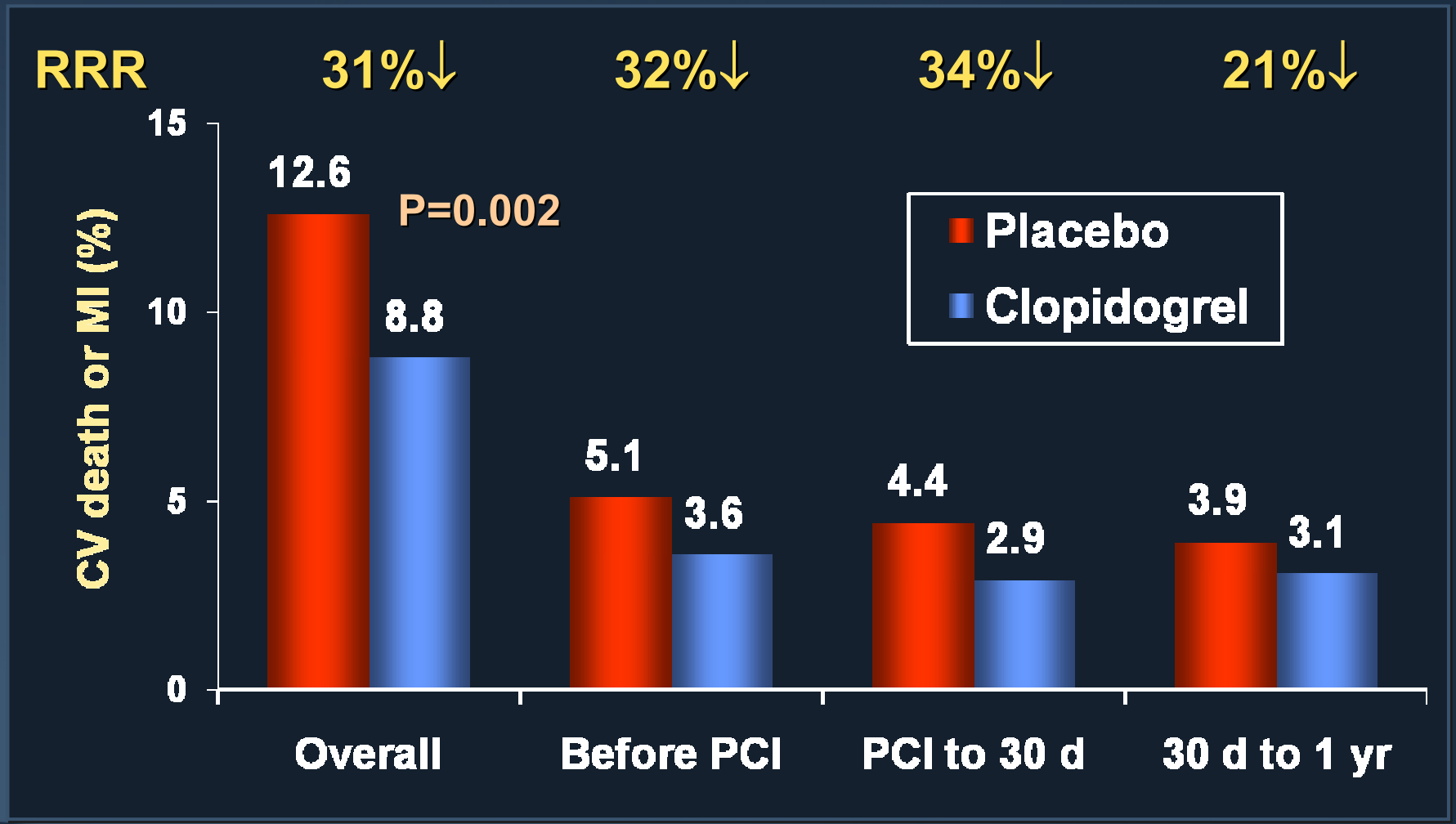
PCI-CURE

CV Death or MI at Various Intervals



Mehta, SR et al. *Lancet* 2001;21:2033–41

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Clopidogrel Pretreatment

Prior to Elective CABG

	Clopidogrel (n=59)	No Clopidogrel (n=165)	P-value
CT output 1st 24º	1224	840	0.001
Transfusions any	85%	61%	0.001
- RBC any	79%	58%	0.004
- RBC mean U	2.51	1.74	0.036
- Platelet any	51%	18%	0.001
- Plat mean U	0.86	0.24	0.001
Reop for bleed	6.8%	0.6%	0.02
Extubate <8º	54%	76%	0.002
LOS ≤5 days	34%	47%	0.09

CARDIOVASCULAR RESEARCH FOUNDATION

Hongo RH, et al. *JACC* 2002;40:231–7.

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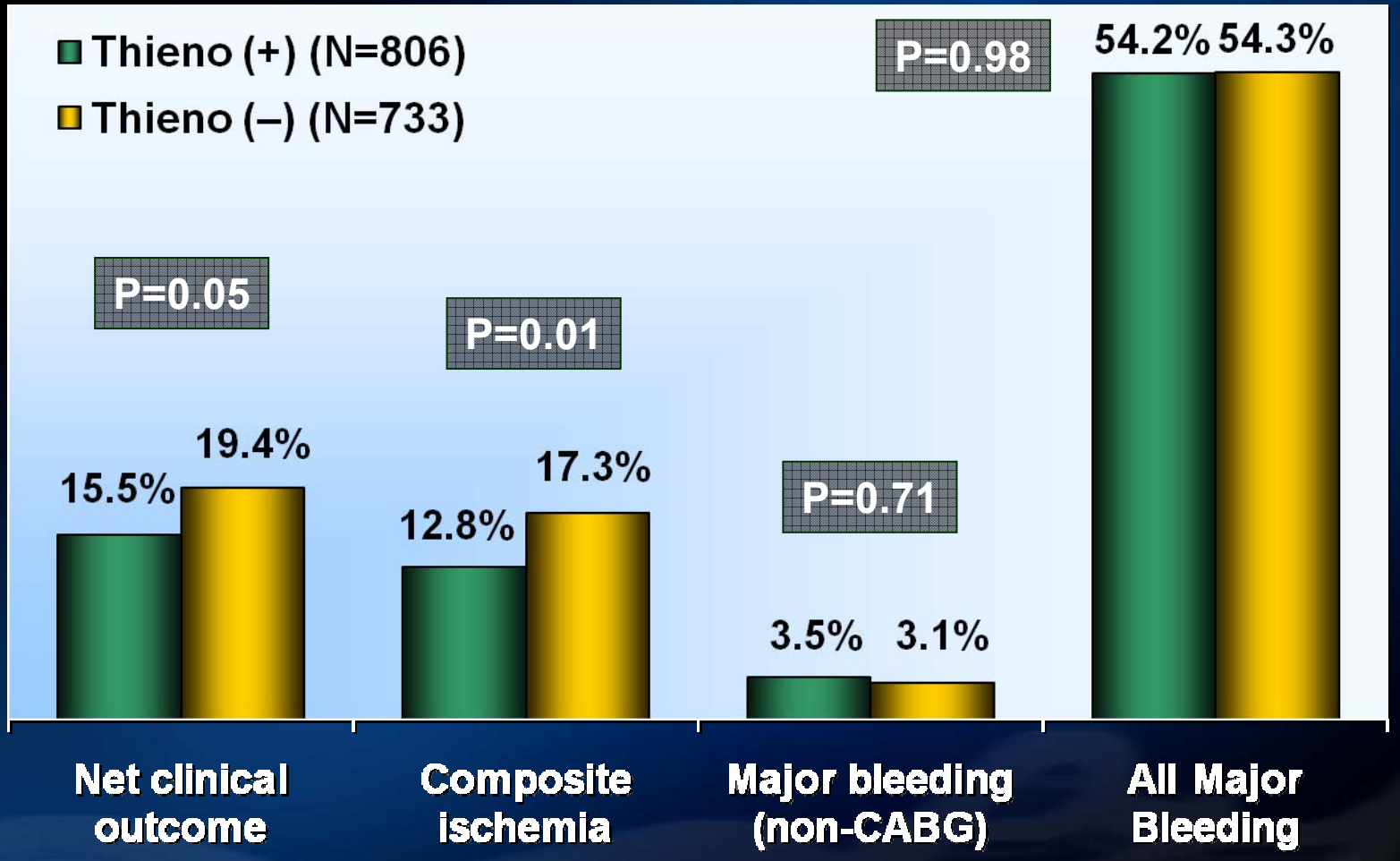
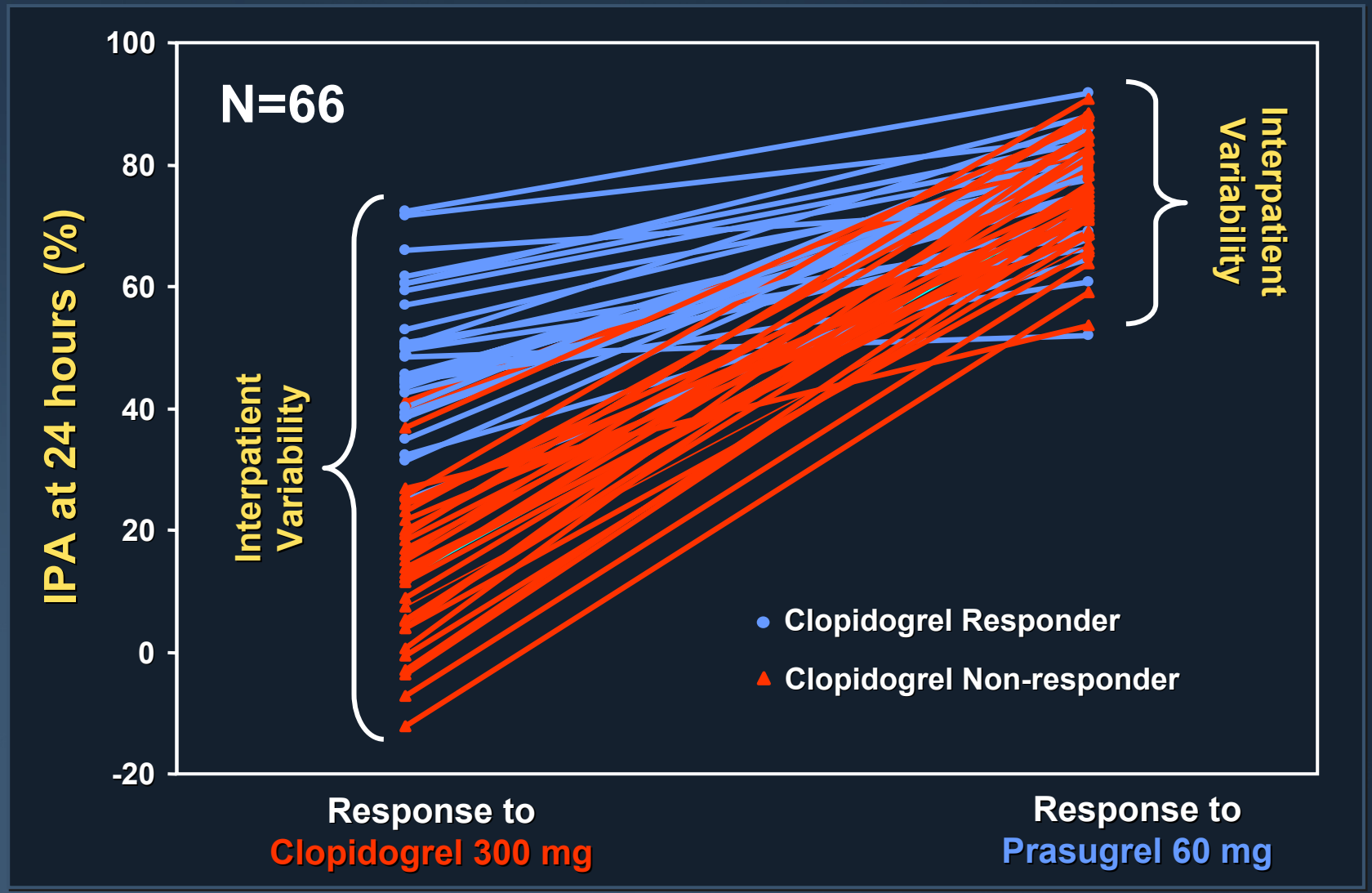
ACUITY: Impact of Thienopyridine Exposure Prior to CABG (n=1,539 pts)



Ebrahimi et al, In press

ACUITY

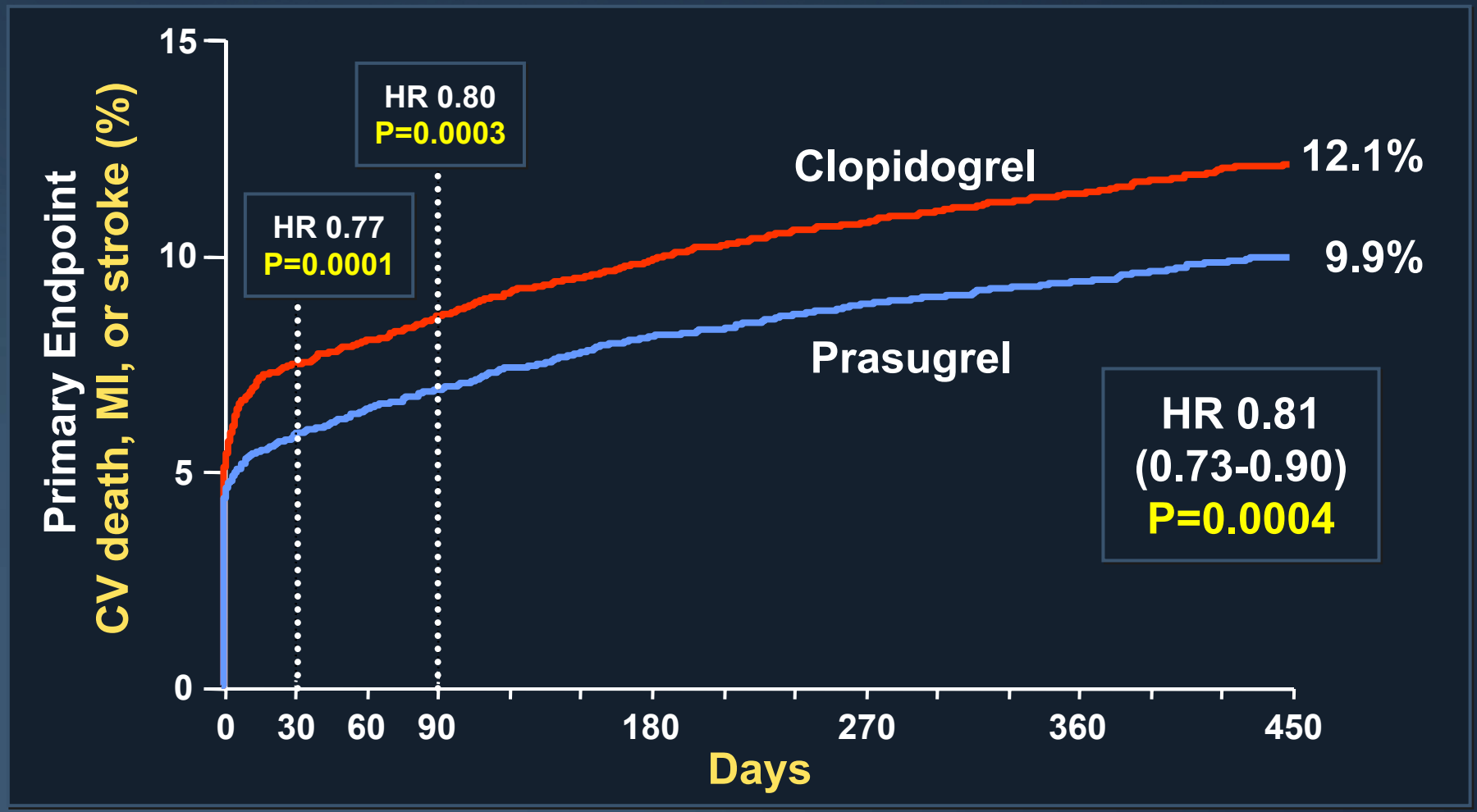
Healthy Volunteer Crossover Study



From Brandt JT et al. *AHJ* 2007;153:66.e9-66.e16

TRITON-TIMI-38

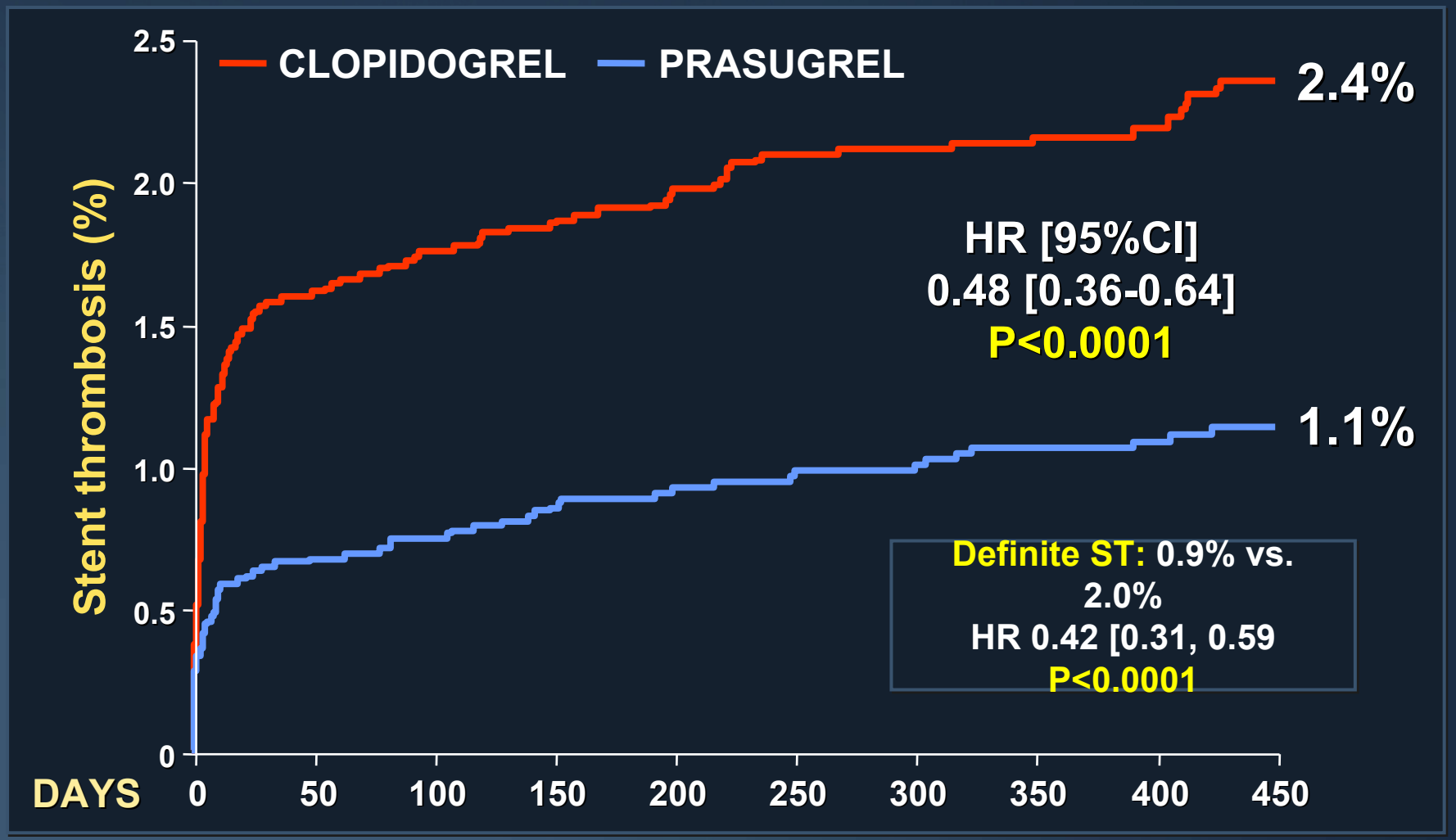
13,608 pts with ACS (unstable angina, NSTEMI, acute STEMI, or recent STEMI) undergoing PCI with known coronary anatomy (except for primary PCI pts) were treated with aspirin and randomized to clopidogrel 300 mg load + 75 mg qd vs. prasugrel 60 mg load + 10 mg qd and followed for 6-15 mos (median 12 mos)



Wiviott SD et al. NEJM 2007;357:2001-15

TRITON-TIMI-38

Definite or probable stent thrombosis in 12,844 pts receiving any stent



Wiviott SD et al. Lancet. 2008;371:1353-63

TRITON-TIMI-38

	Prasugrel (n=6813)	Clopidogrel (n=6795)	HR [95%CI]	P
CV death, MI, stroke	9.9%	12.1%	0.81 [0.73, 0.90]	<0.001
- CV death	2.1%	2.4%	0.89 [0.70, 1.12]	0.31
- Nonfatal MI	7.3%	9.5%	0.76 [0.67, 0.85]	<0.001
- Non fatal stroke	1.0%	1.0%	1.02 [0.71, 1.45]	0.93
Urgent TVR	2.5%	3.7%	0.66 [0.54, 0.81]	<0.001
Death, all-cause	3.0%	3.2%	0.95 [0.78, 1.16]	0.64
TIMI bleed, major or minor	5.0%	3.8%	1.31 [1.11, 1.56]	0.002
- Major, CABG related	13.4%	3.2%	4.73 [1.90, 11.82]	<0.001
- Major, non CABG related	2.4%	1.8%	1.32 [1.03, 1.68]	0.03
- Life-threatening	1.4%	0.9%	1.52 [1.08, 2.13]	0.01
- Fatal	0.4%	0.1%	4.19 [1.58, 11.11]	0.002
- Requiring transfusion	4.0%	3.0%	1.34 [1.11, 1.63]	<0.001

Wiviott SD et al. NEJM 2007;357:2001-15

PCI Pharmacology

Antithrombins I: Unfractionated Heparin and Enoxaparin

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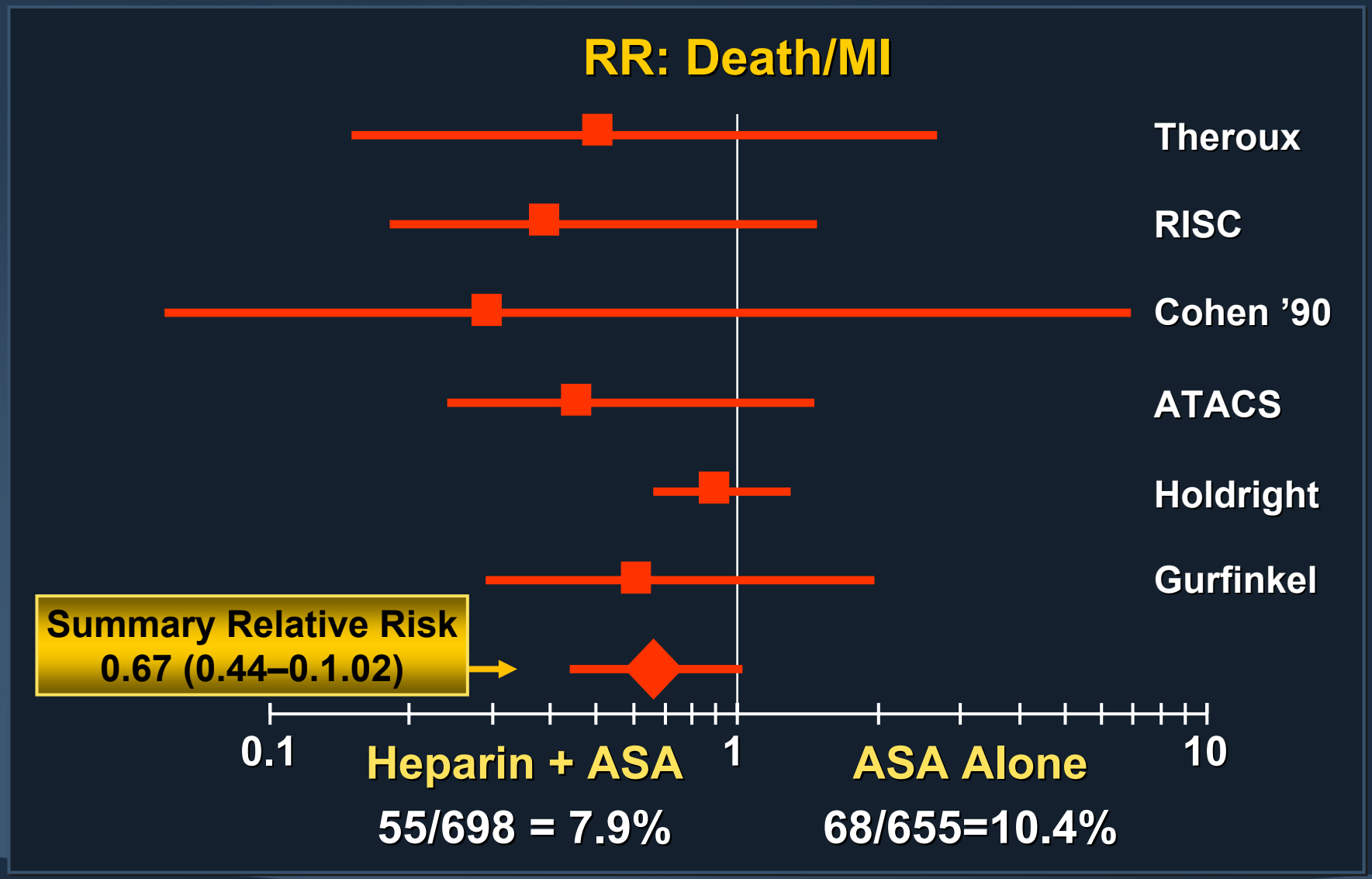
Unfractionated Heparin in ACS (N=1353)



Oler et al. *JAMA* 1996;276:811–6

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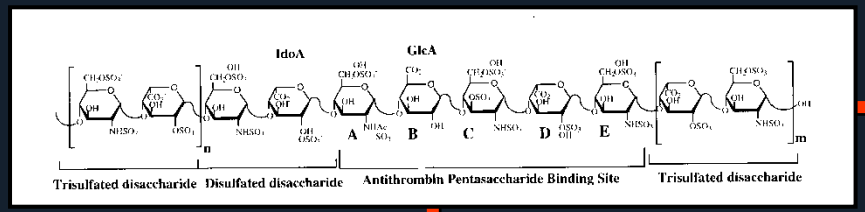
Antithrombin Choices for PCI, ACS and AMI

Unfractionated heparin



LMW Heparin

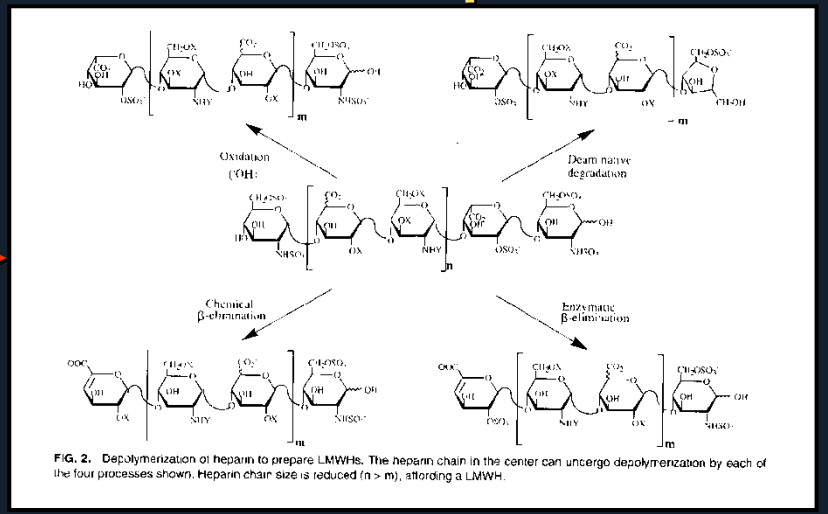
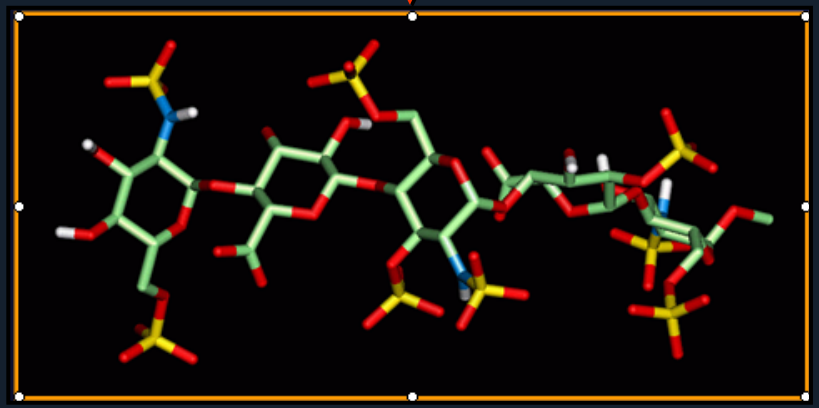


FIG. 2. Depolymerization of heparin to prepare LMWHs. The heparin chain in the center can undergo depolymerization by each of the four processes shown. Heparin chain size is reduced (n > m), affording a LMWH.



Fondaparinux

Bivalirudin

2/3 of :
- Age > 60
- (+) ST ↓
- (+) biomarkers

Invasive Management Strategy

High-risk ACS patients

n = 10,027
467 sites
12 countries

Enoxaparin 1 mg/kg SQ

UF heparin 60 U/kg

Per MD

Timing of cath
Clopidogrel use
GP IIb/IIIa Rx
Agent
Timing

Primary Endpoint:
Death / MI at 30 days

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Ferguson JJ et al. *JAMA*. 2004;292:45–54

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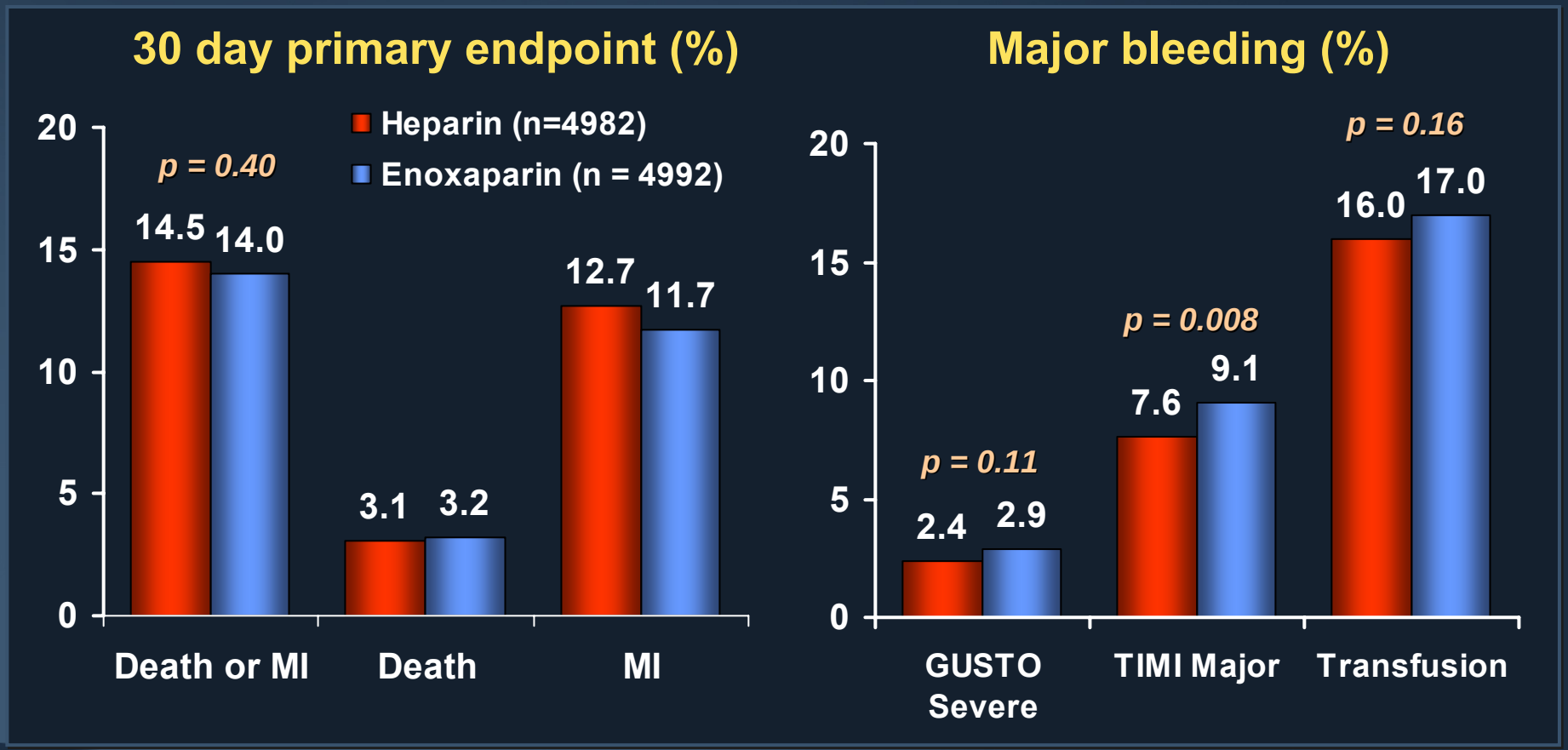
SYNERGY

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)



Ferguson JJ et al. *JAMA*. 2004;292:45–54

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PCI Pharmacology

Antithrombins II:
Fondaparinux

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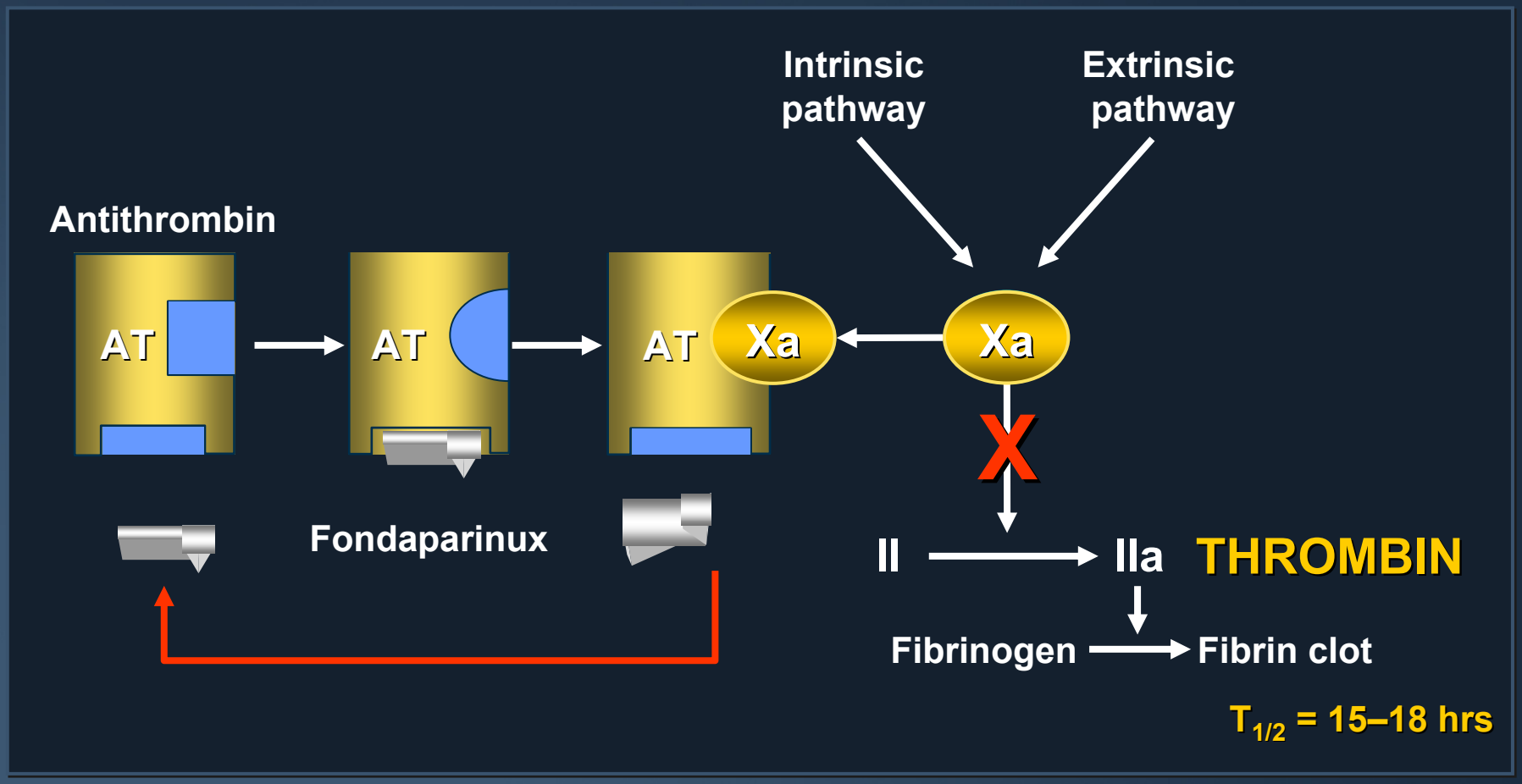
Fondaparinux: An Indirect Synthetic Factor Xa Inhibitor – Activates ATIII

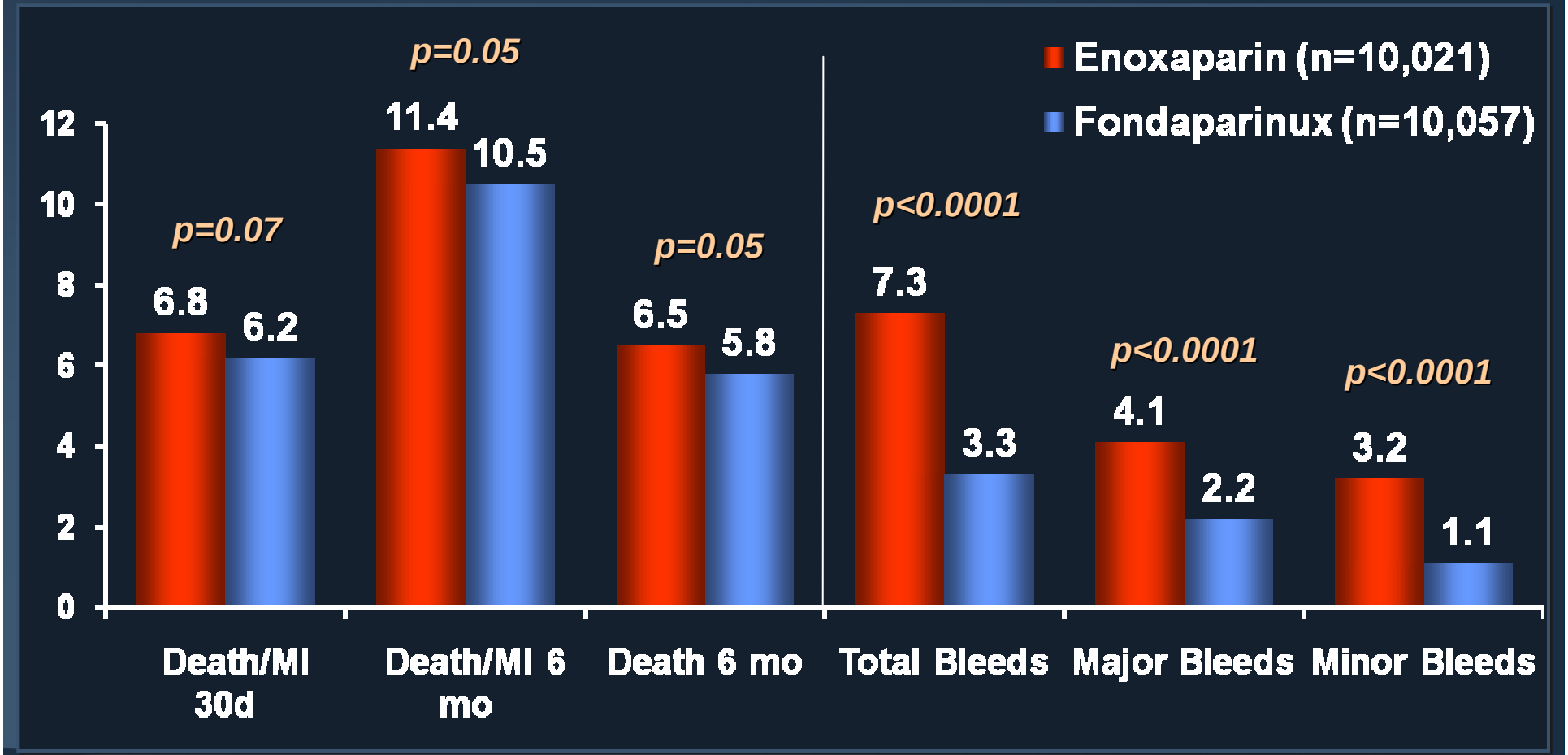


Adapted from Turpie AGG et al. *NEJM* 2001;344:619.

OASIS-5

Fondaparinux vs Enoxaparin in ACS

20,078 pts with unstable angina or NSTEMI; 70% troponin +



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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
Hospital meds and procedures		
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%

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

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**	P=0.008	**0.9**
Death, MI or stroke (30 days)	7.3		7.4
Major bleeding	5.4		2.8

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

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OASIS 6: Fondaparinux During Primary PCI

3,788 pts with STEMI undergoing primary PCI were randomized to UFH for 4-48 hrs vs. 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
Catheter thrombus	0%	1.2%	<0.001
Coronary complications*	11.9%	14.3%	0.04
Death or MI	4.9%	6.0%	0.13
Severe bleed	0.5%	0.8%	0.16

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

Yusuf S et al. *JAMA* 2006;295:1519–30

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PCI Pharmacology

Antithrombins III:
Bivalirudin

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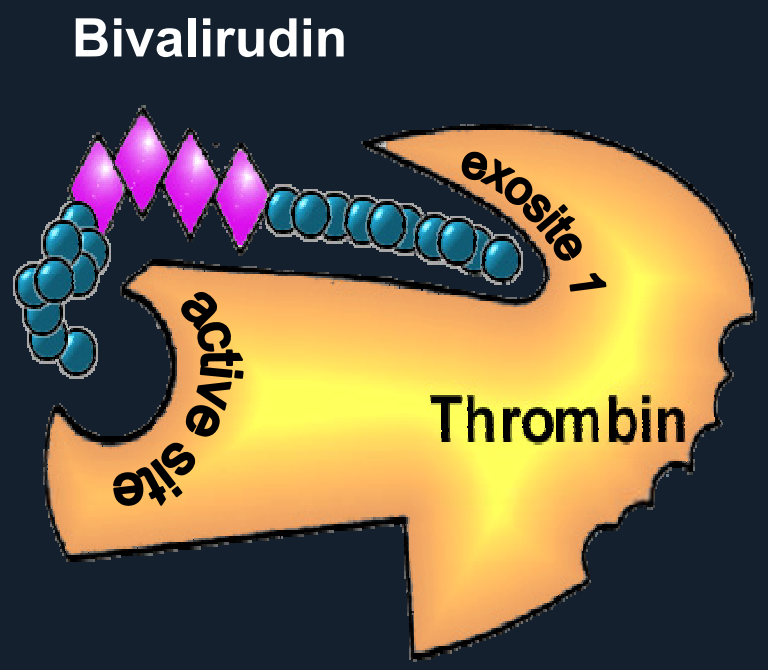
Bivalirudin

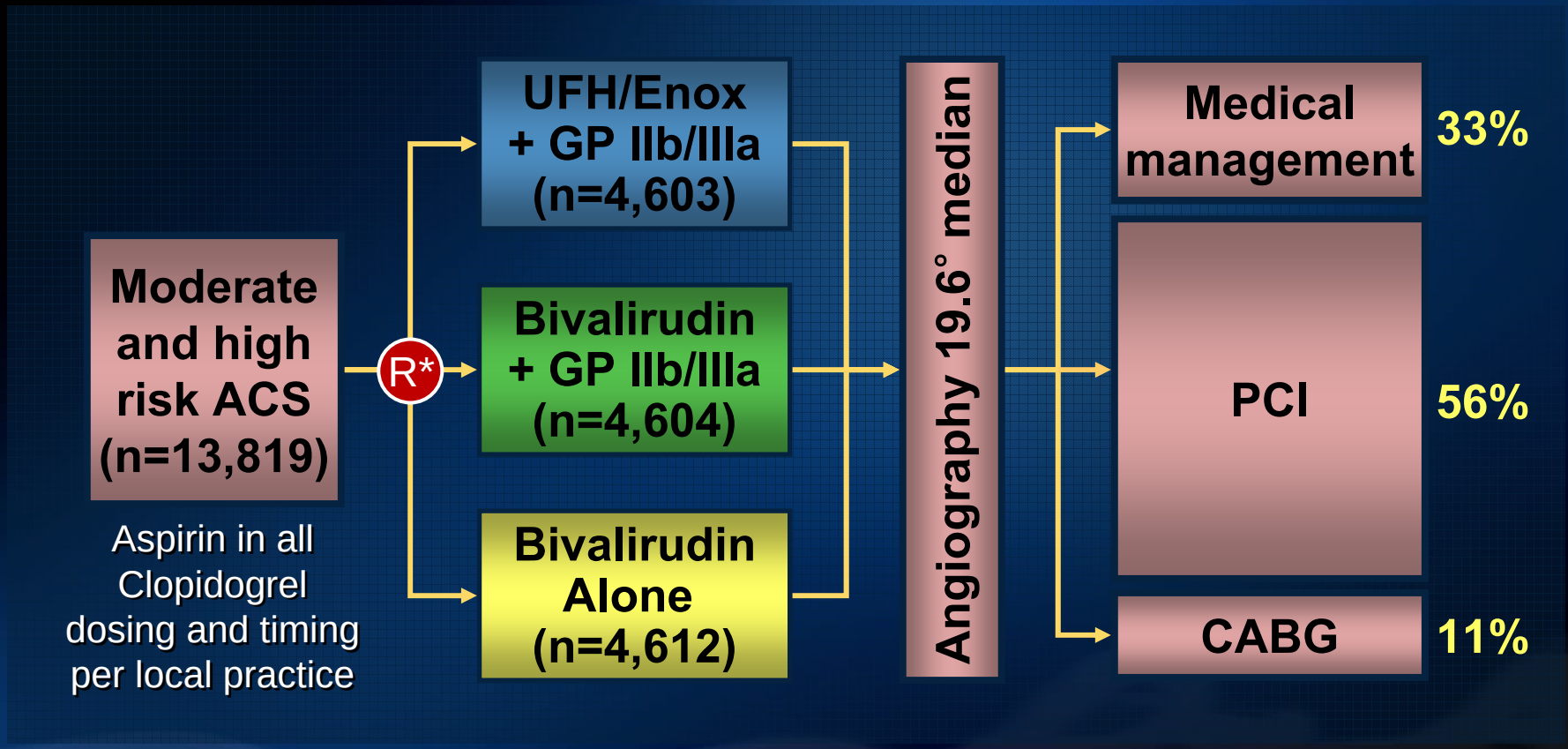
Bivalent Synthetic Direct Thrombin Inhibitor



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

ACUITY: First Randomization

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



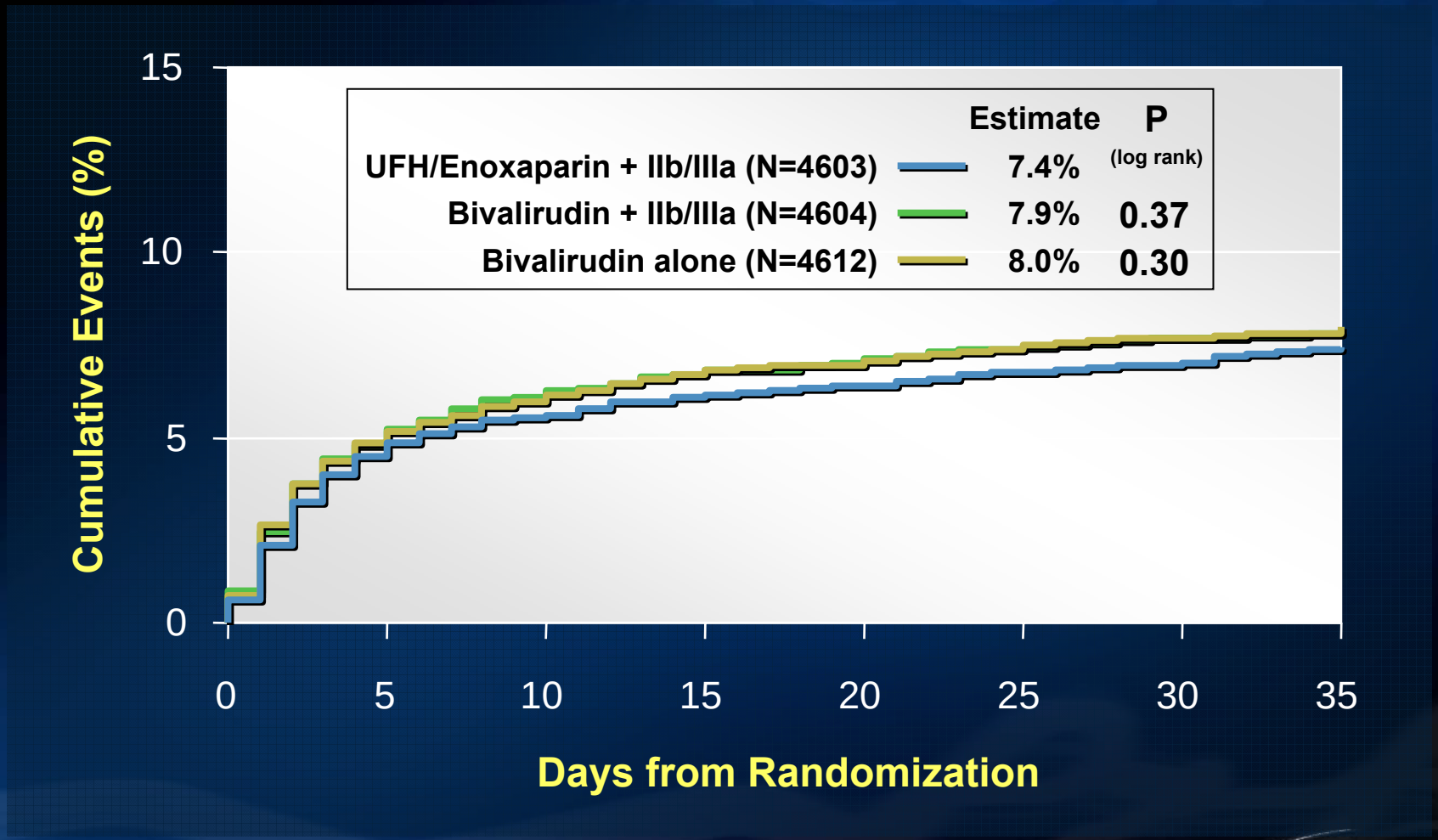
*Stratified by pre-angiography thienopyridine use or administration

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

ACUITY

Ischemic Composite Endpoint

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

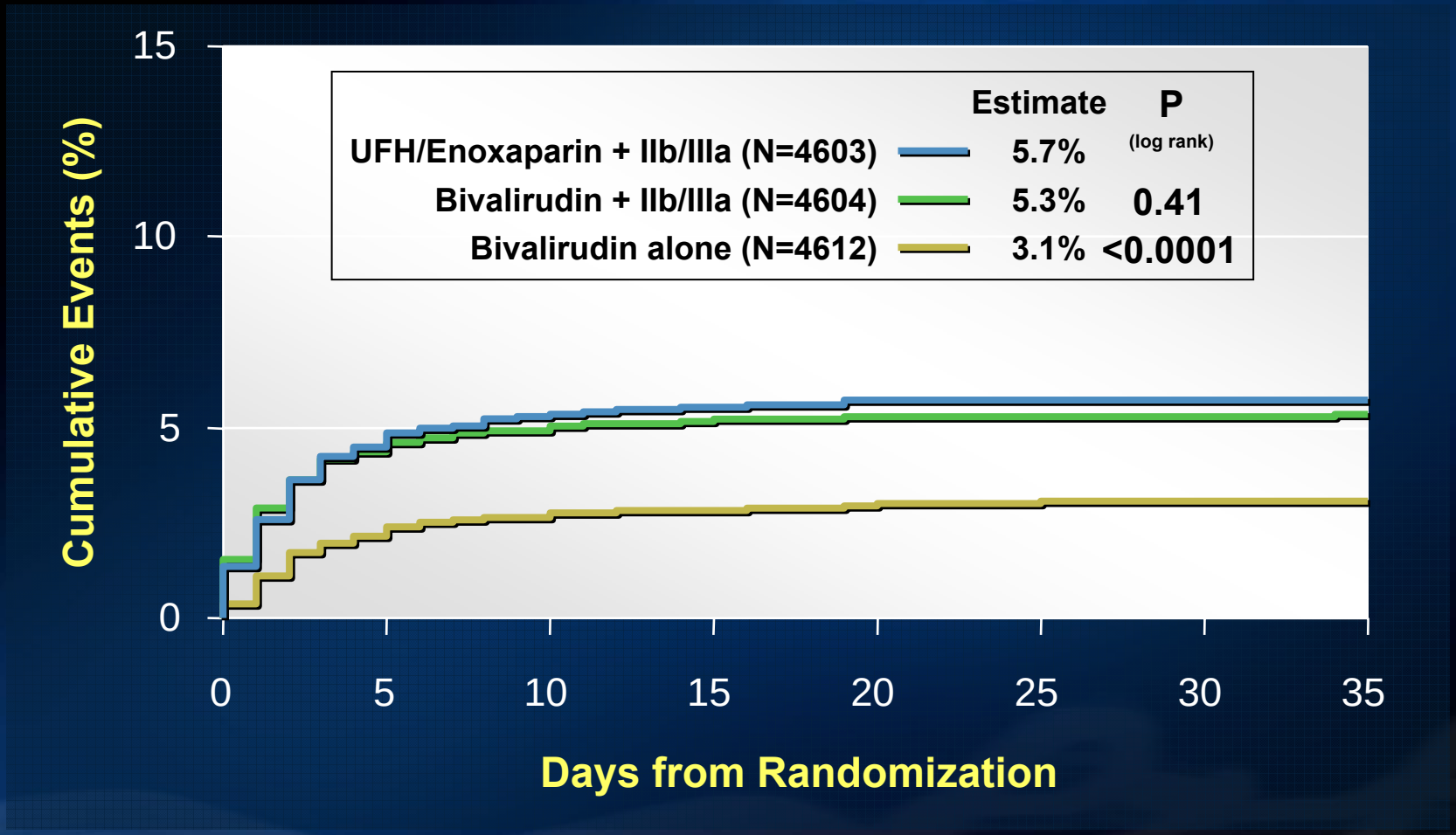


Stone GW et al. NEJM 2006;355:2203-16

ACUITY

Major Bleeding Endpoint

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



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

ACUITY

Bleeding Endpoints

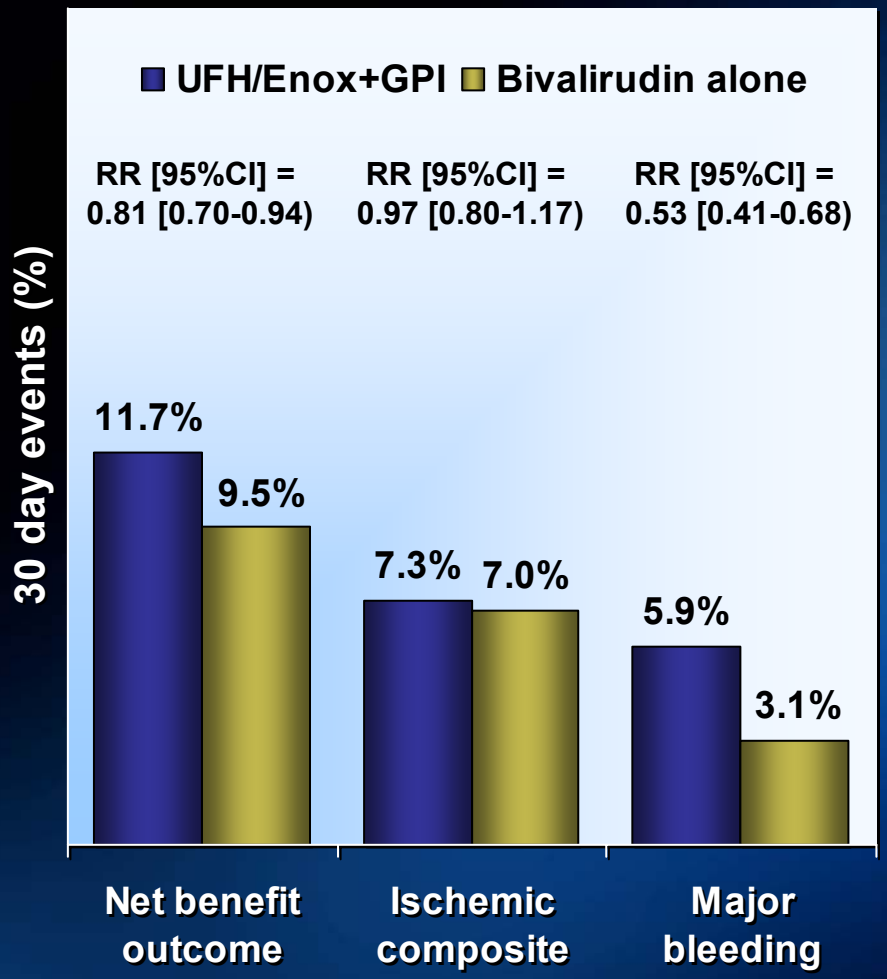
	UFH/Enoxaparin + GP IIb/IIIa (N=4,603)	Bivalirudin + GP IIb/IIIa (N=4,604)	Bivalirudin alone (N=4,612)	P Value
ACUITY Scale				
- Major Bleed, all	11.8%	11.1%	9.1%	<0.001
- Major, non-CABG	5.7%	5.3%	3.0%	<0.001
- Minor, non-CABG	21.6%	21.7%	12.8%	<0.001
TIMI Scale				
- Any	6.6%	6.5%	4.0%	<0.001
- Major	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%	0.01*

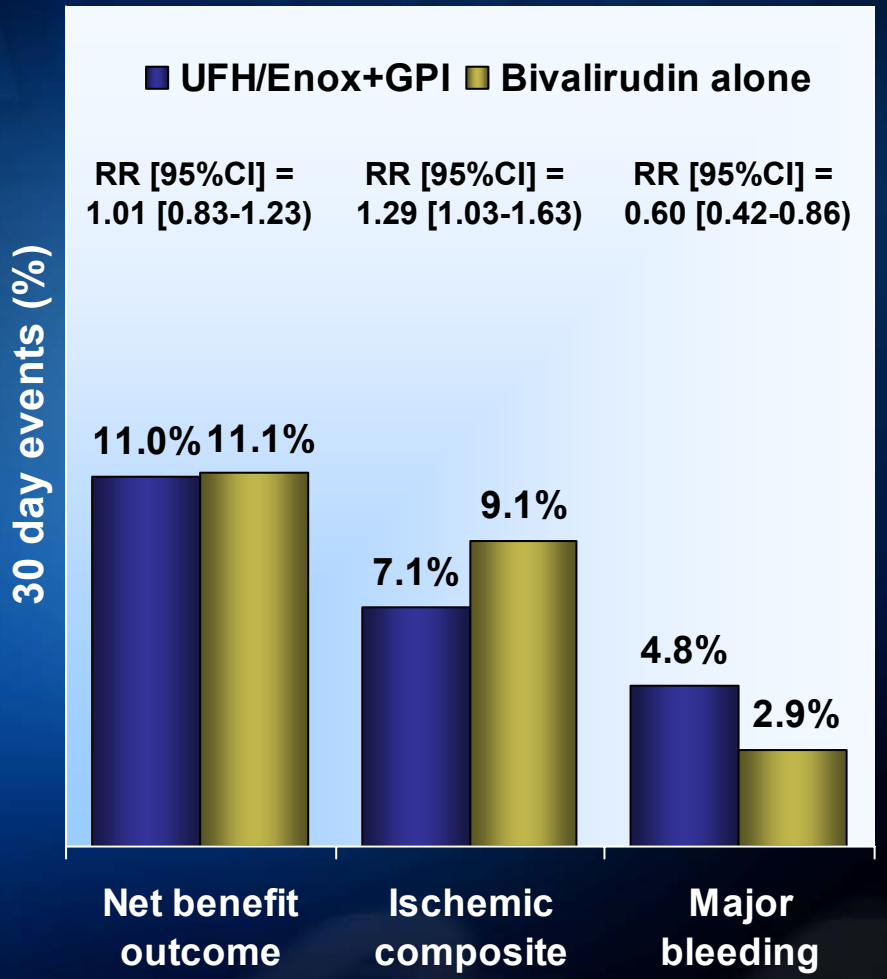
*P value for Bivalirudin alone vs. GP IIb/IIIa inhibitor based regimen

ACUITY

Impact of Thienopyridine Pre-Administration

UFH/Enoxaparin + GPI vs. Bivalirudin Alone





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

ACUITY

HORIZONS-AMI

Harmonizing Outcomes with Revascularization and Stents in AMI

3602 pts with STEMI with symptom onset ≤12 hours

Aspirin, thienopyridine

R 1:1

- **UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide)**
- **Bivalirudin monotherapy (± provisional GP IIb/IIIa)**

Emergent angiography, followed by triage to primary PCI, CABG or medical therapy

3006 pts eligible for stent randomization

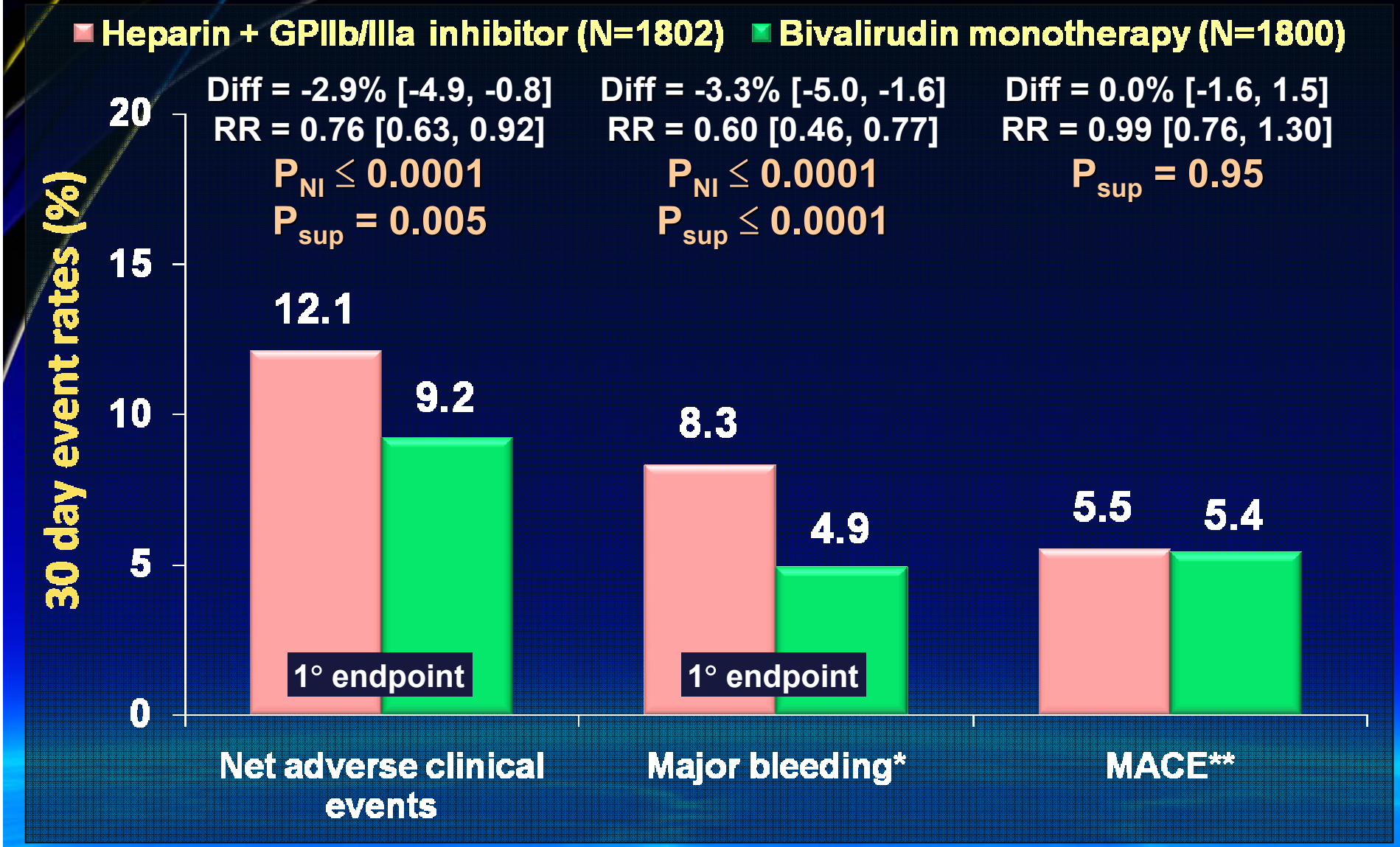
R 1:3

- **Bare metal EXPRESS stent**
- **Paclitaxel-eluting TAXUS stent**

Clinical FU at 30 days, 6 months, 1 year, and then yearly through 5 years

HORIZONS-AMI

Primary Outcome Measures (ITT)

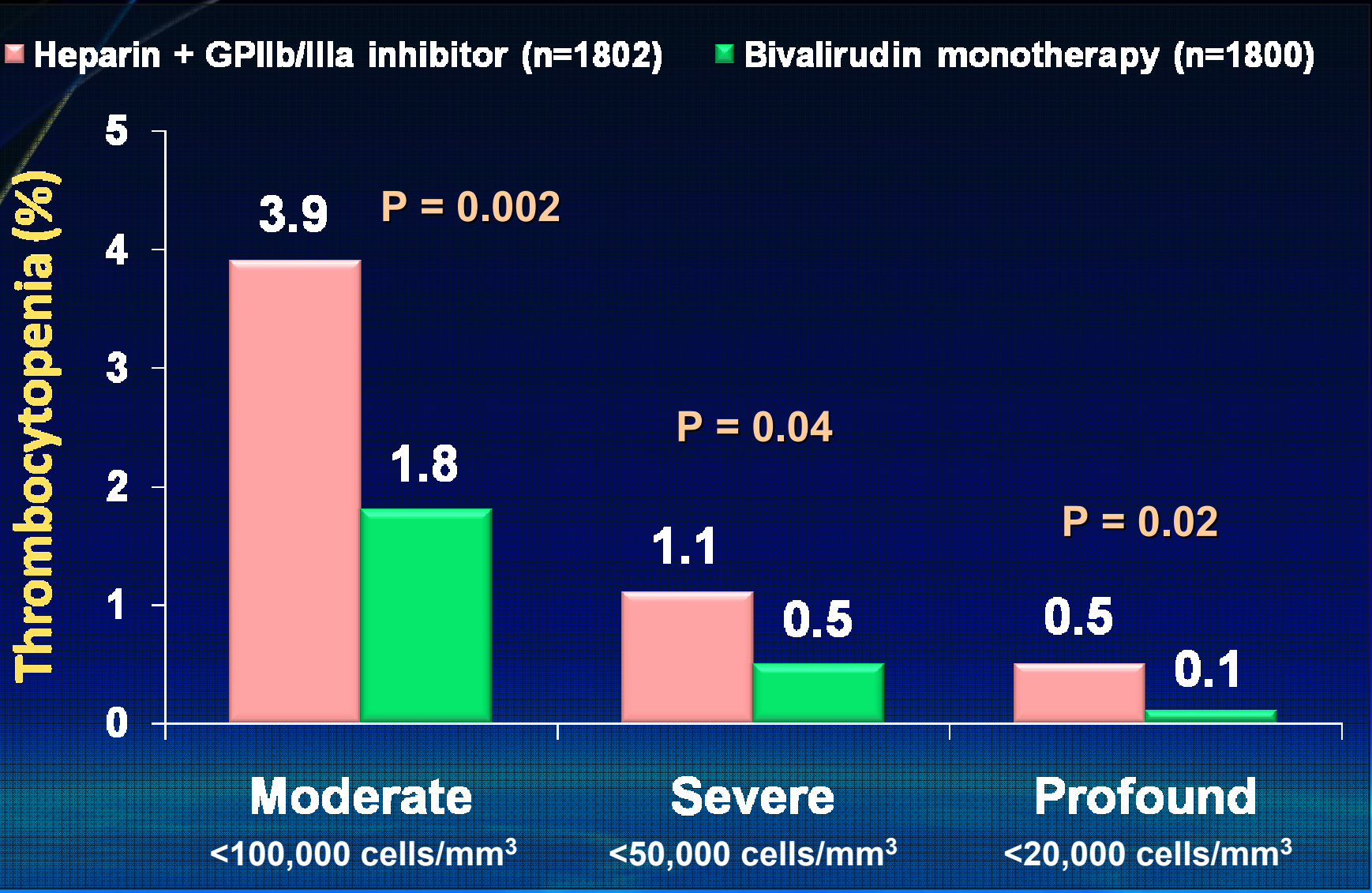


*Not related to CABG
**MACE; Death, reMI, iTVR , or stroke

Stone GW et al. NEJM 2008;358:2218-30

HORIZONS AMI

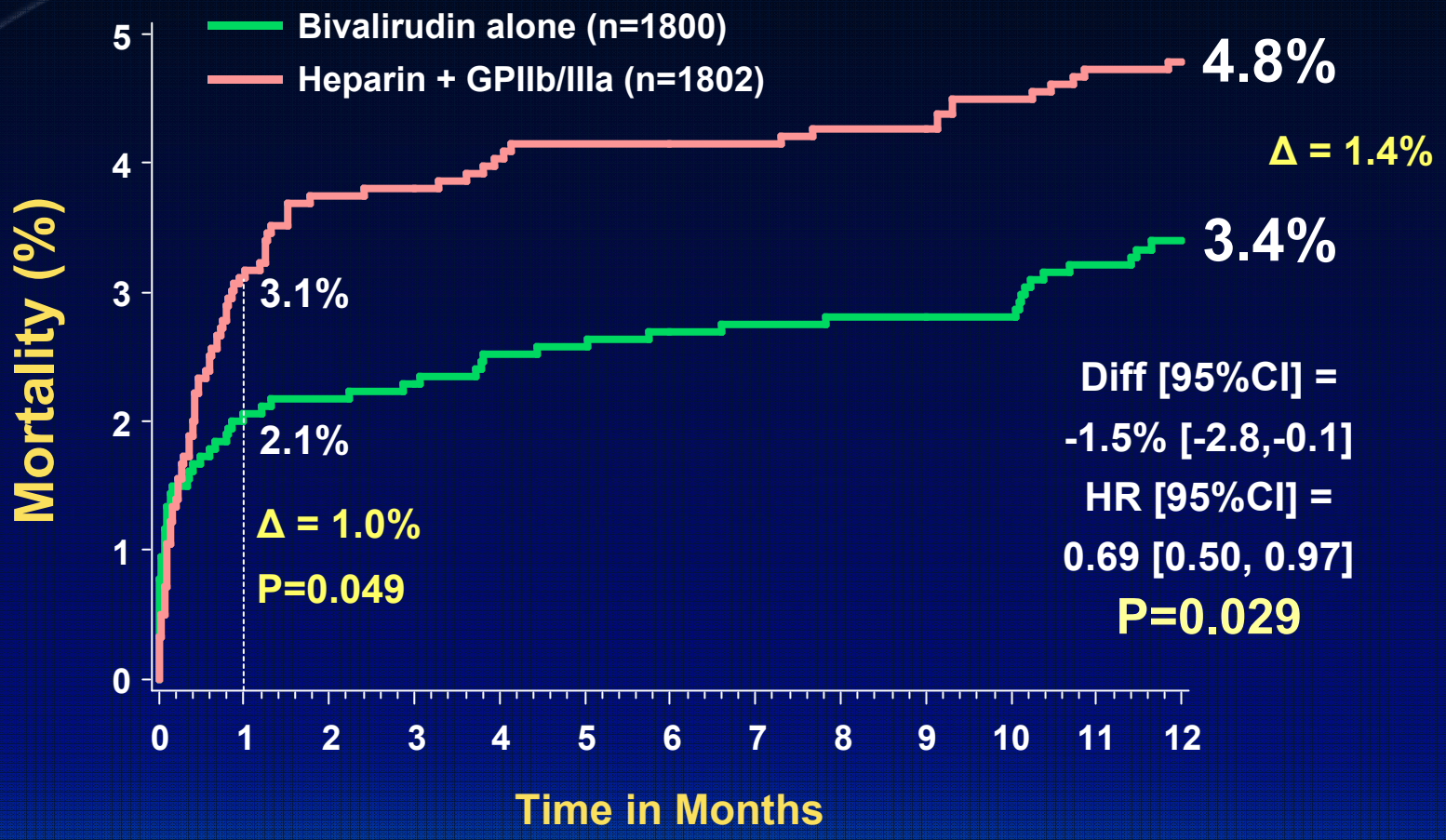
Thrombocytopenia



Stone GW et al. NEJM 2008;358:2218-30

HORIZONS-AMI

1-Year All-Cause Mortality

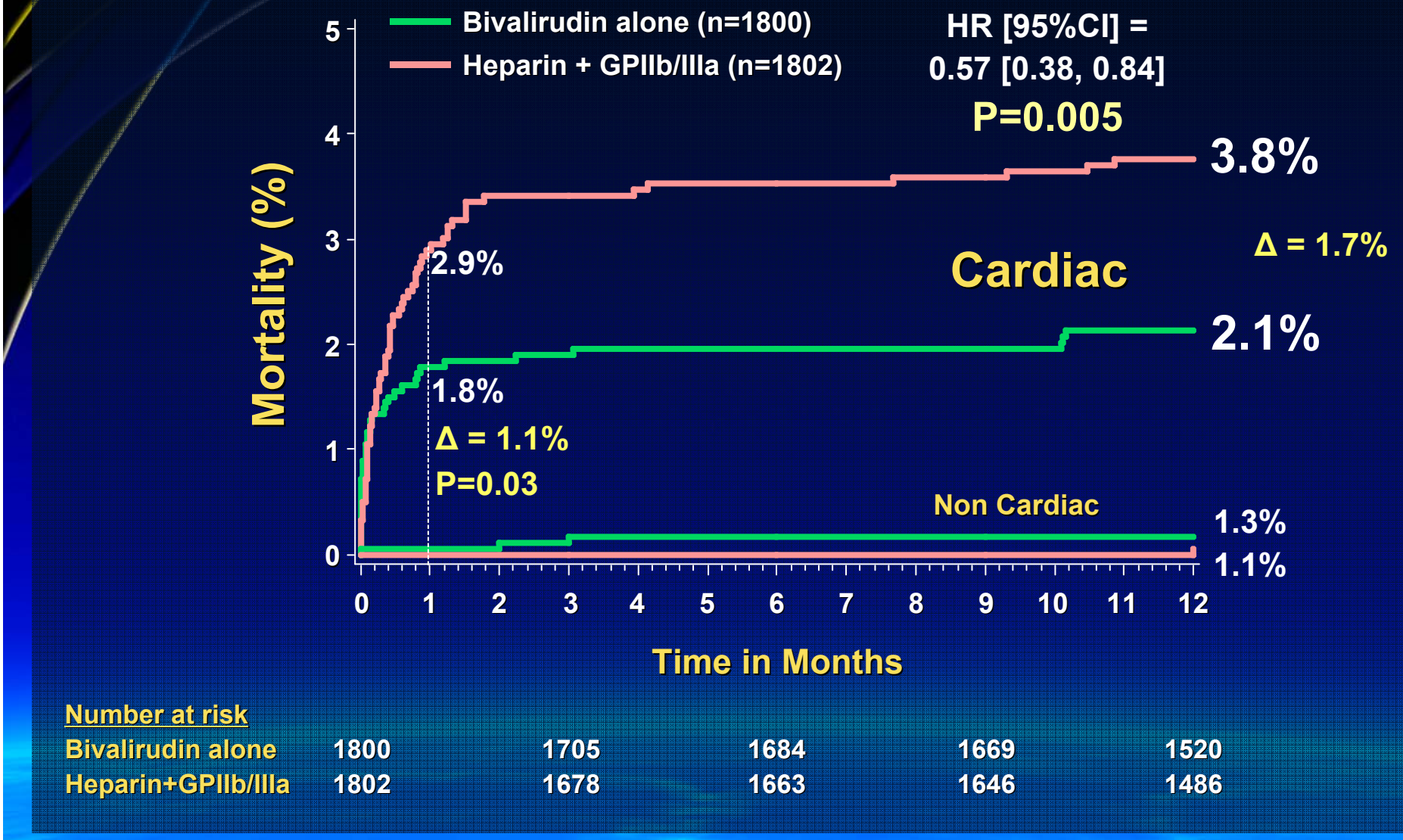


Number at risk					
Bivalirudin alone	1800	1705	1684	1669	1520
Heparin+GPIIb/IIIa	1802	1678	1663	1646	1486

Mehran R. TCT 2008

HORIZONSAMI

1-Year Mortality: Cardiac and Non Cardiac



Number at risk

Bivalirudin alone	1800	1705	1684	1669	1520
Heparin+GPIIb/IIIa	1802	1678	1663	1646	1486

Mehran R. TCT 2008

HORIZONS-AMI

Core Pharmacotherapy to Support Primary PCI in STEMI

Ambulance or emergency room

Aspirin 324 mg chewed
Clopidogrel* 600 mg load
Bivalirudin 0.75 mg/kg IV
or UFH 2500-5000 U IV

↓

Immediate angiography followed by PCI if appropriate (~90%)

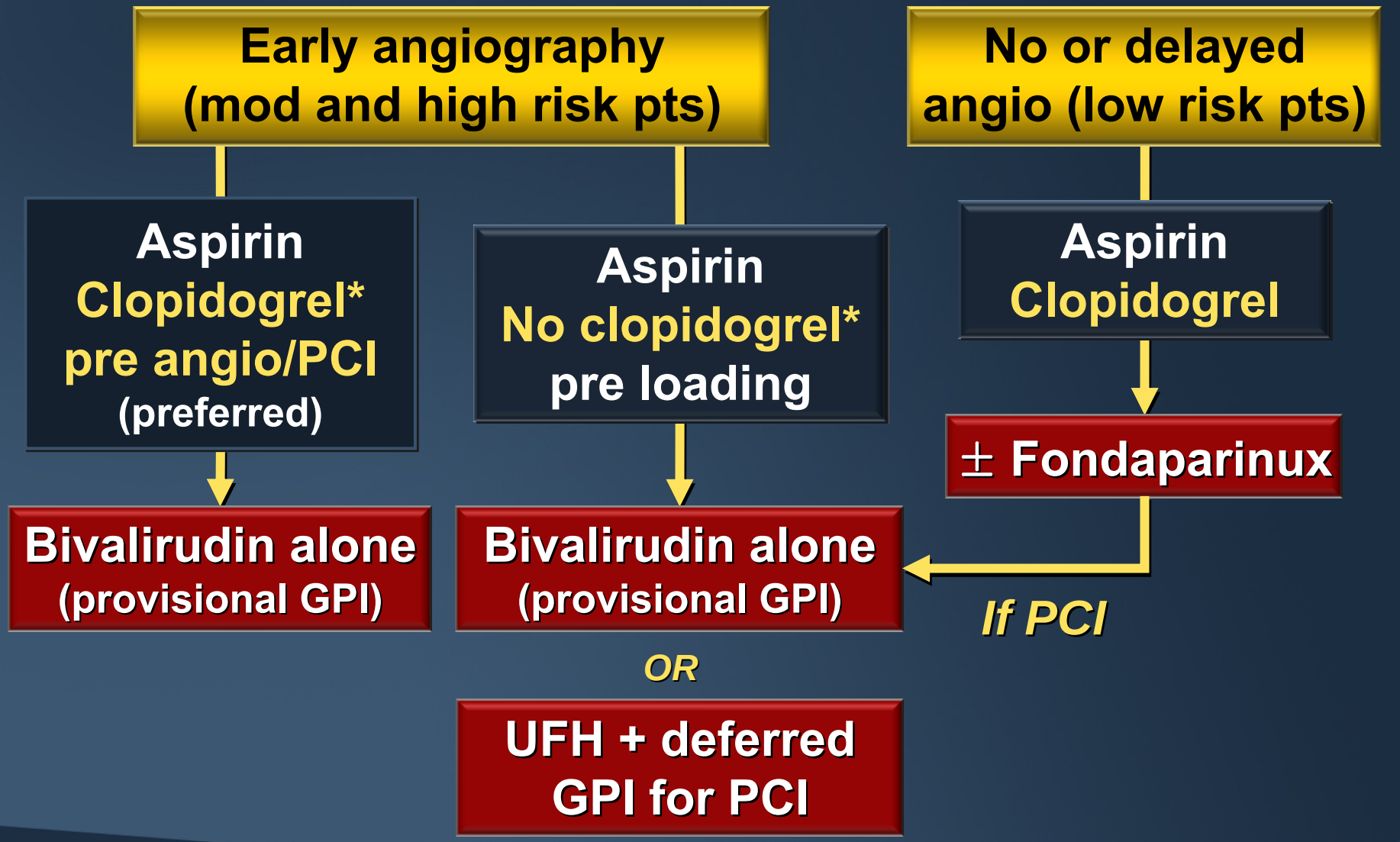
↓

Cath lab

Bivalirudin 0.75 mg/kg IV
+ 1.75 mg/kg/hr; d/c post PCI

*Consider prasugrel 60 mg in pts with low/mod bleeding risk

Core Pharmacotherapy in NSTEMI



*Consider prasugrel 60 mg in pts with low/mod bleeding risk

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