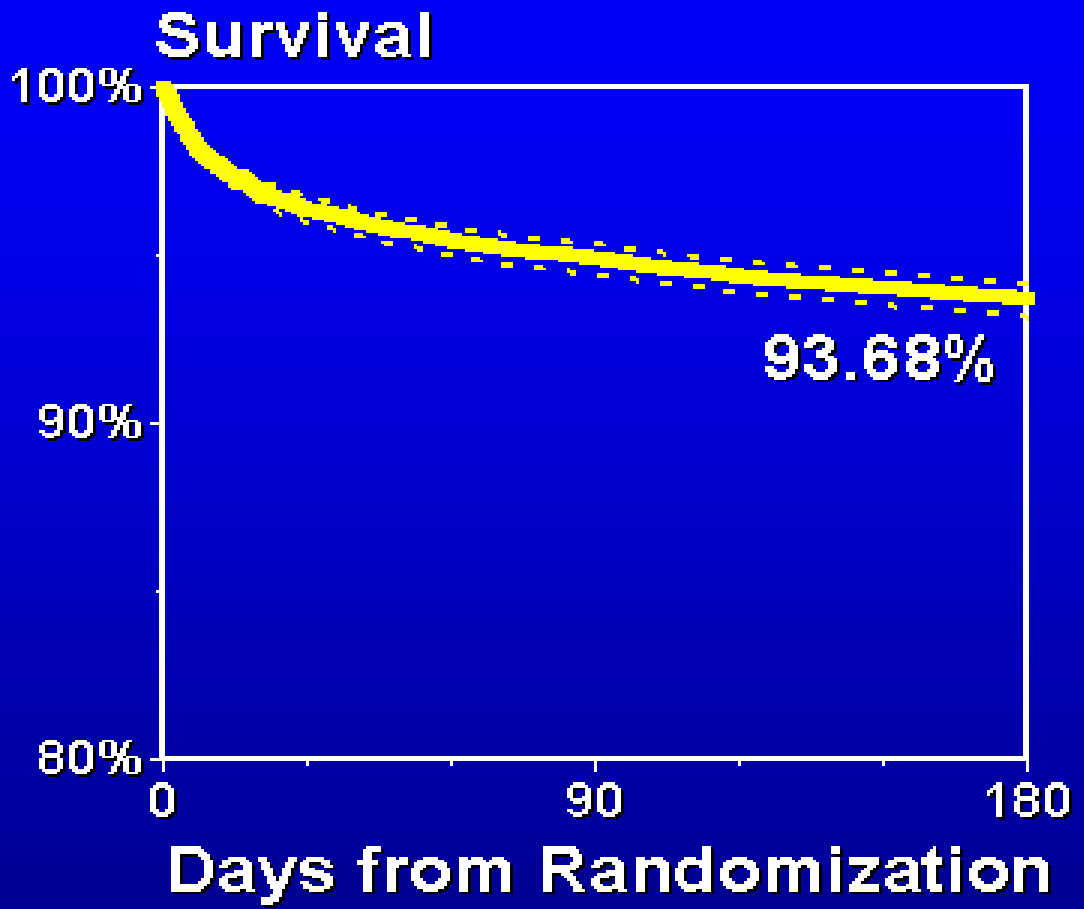
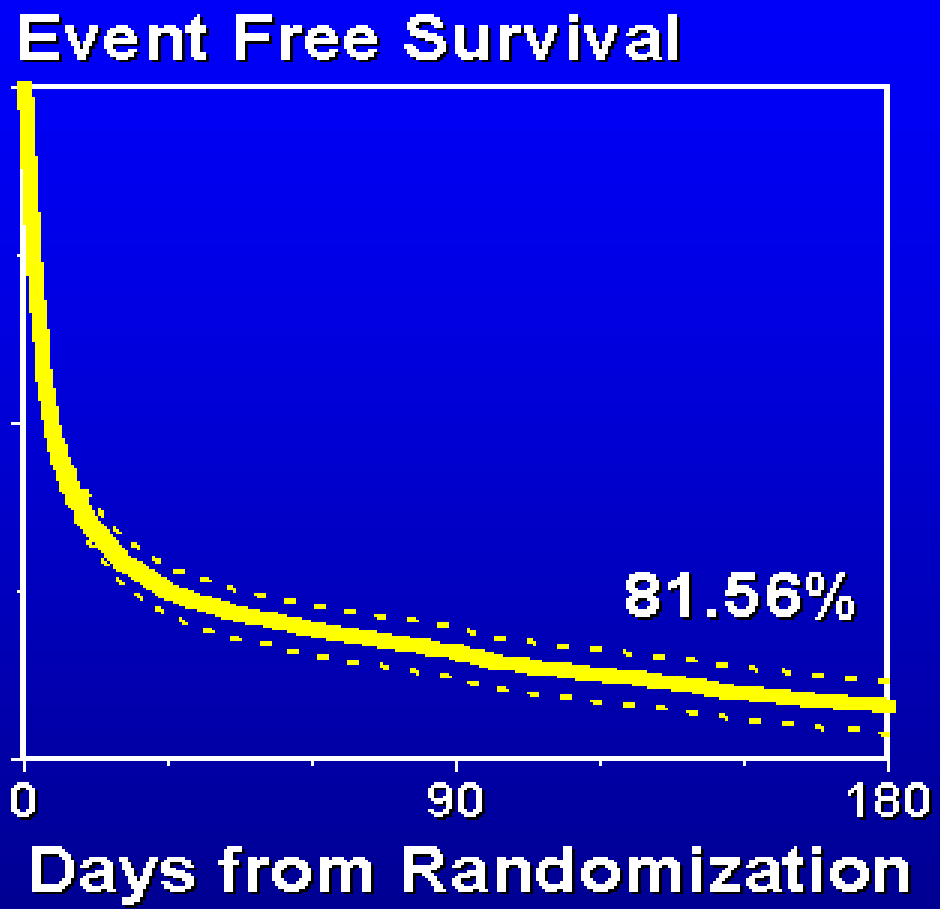
CURRENT MANAGEMENT OF ACUTE CORONORAY SYNDROMES

Timothy Jayasundera, M.D., F.A.C.C.
Director NYU Interventional Cardiology Network
Assistant Professor of Medicine
Leon H. Charney Division of Cardiology
NYU Langone Medical Center
New York, NY

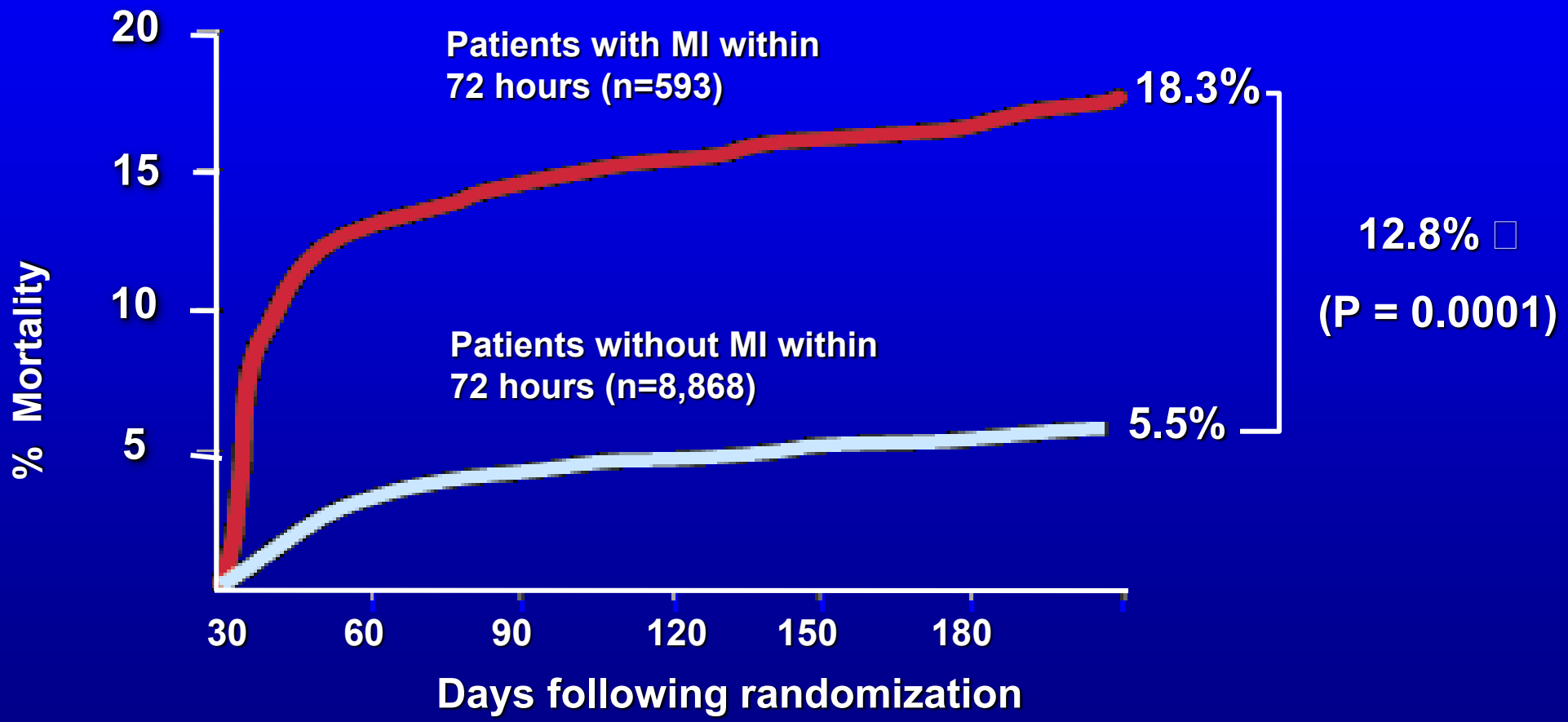
Prognosis in ACS





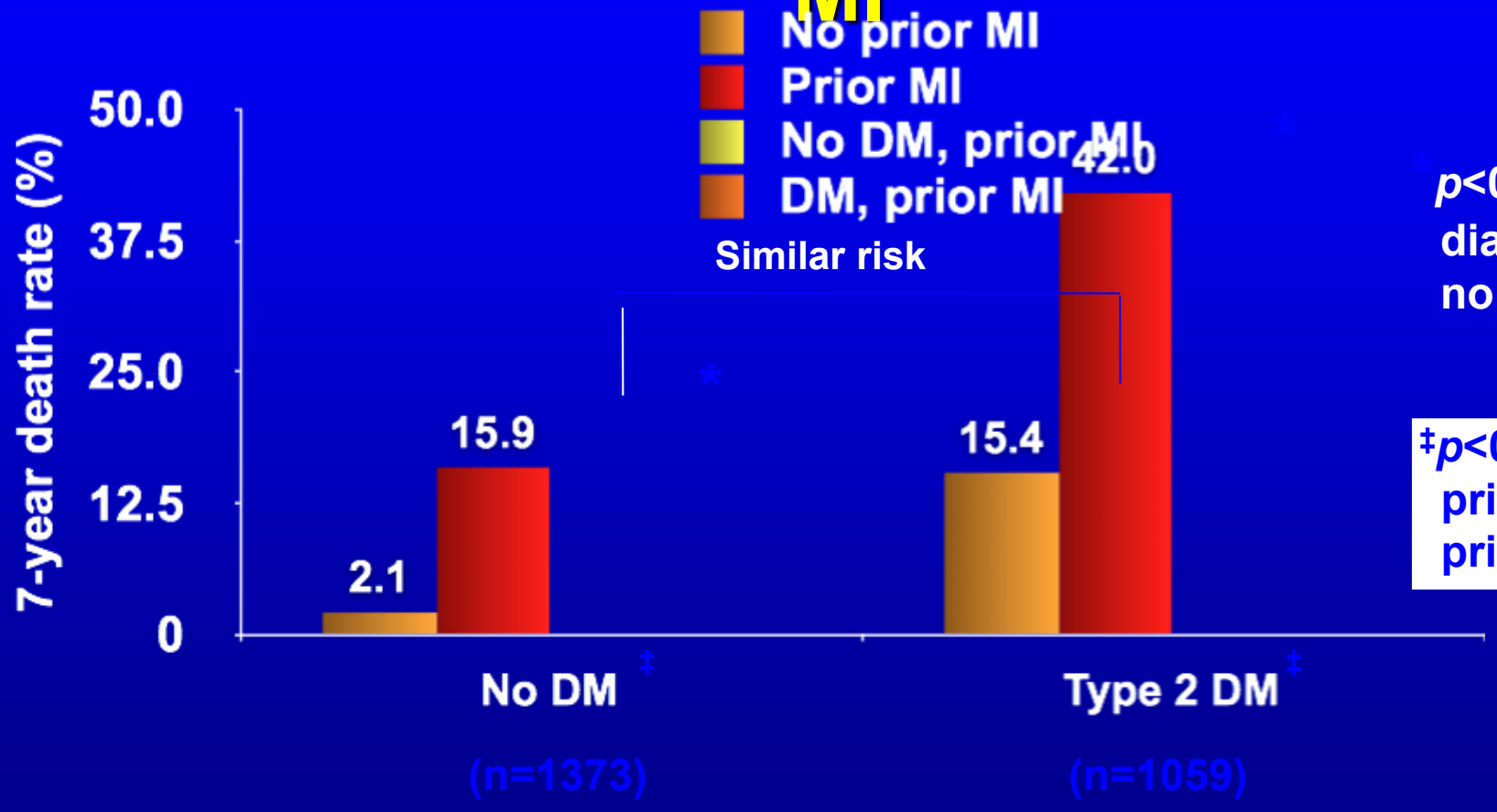
PURSUIT trial data

Mortality in Non-ST ACS Patients With Myocardial Infarction During Hospitalization



Fintel D, ACC, 2000

Patients with Diabetes Have Similar Risk of Death as Those Who Have Had a Prior MI

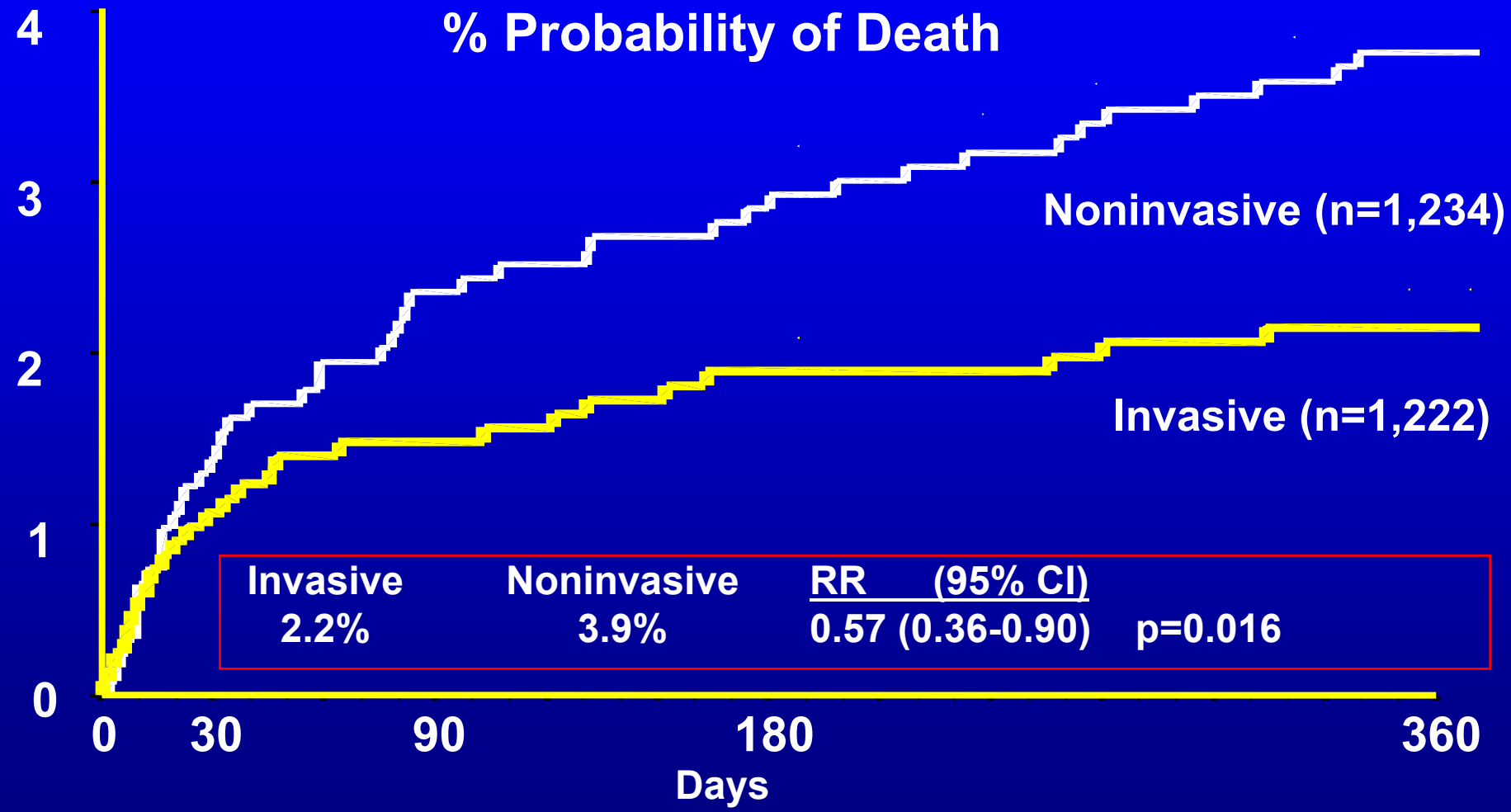


p<0.001 for diabetes vs no diabetes

‡*p*<0.001 for prior MI vs no prior MI

Haffner SM, et al. *N Engl J Med.* 1998;339:229-234.

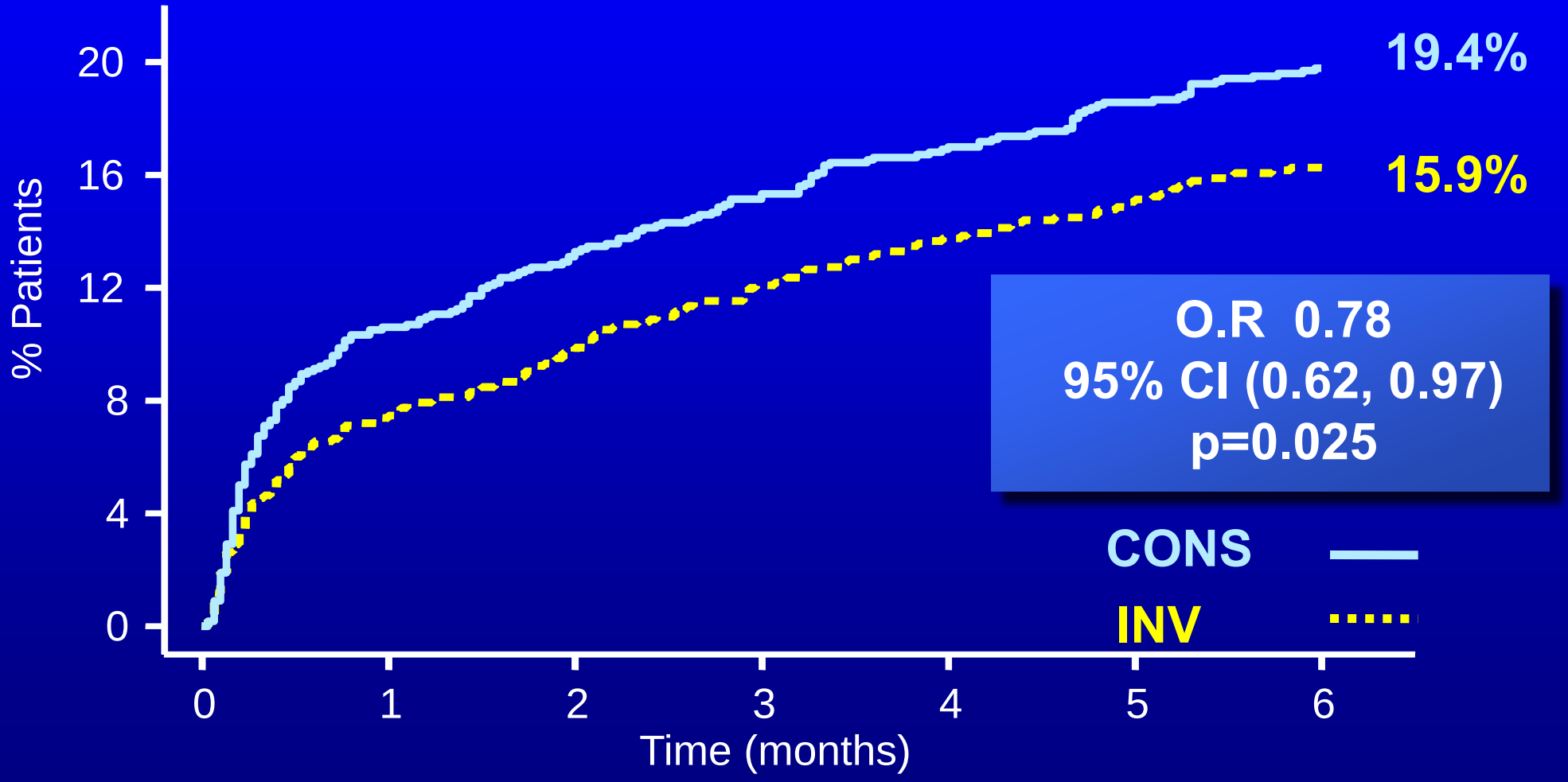
Management Strategies in High-Risk ACS: Early Invasive versus Conservative



The FRISC-II Trial. Wallentin L, et al. *Lancet.* 2000;356:9-16.

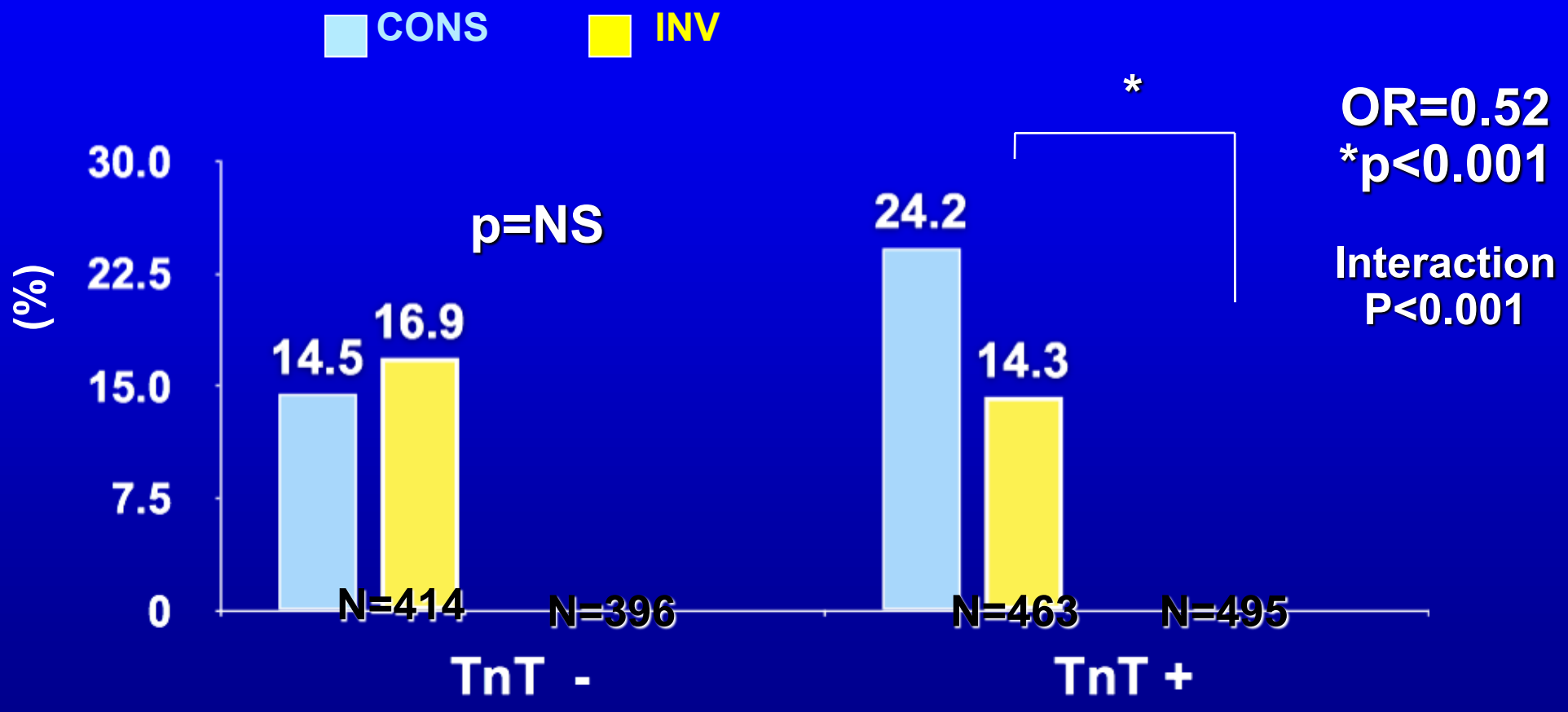
Tactics-TIMI 18 Primary Endpoint

Death, MI, Rehosp for ACS at 6 Months



Troponin T: 1ºEP at 6 months

Death, MI, Rehosp ACS at 6 Months



TnT cut point = 0.01 ng/ml *(54% of Pts TnT +)*

Troponin and Mortality TIMI 18

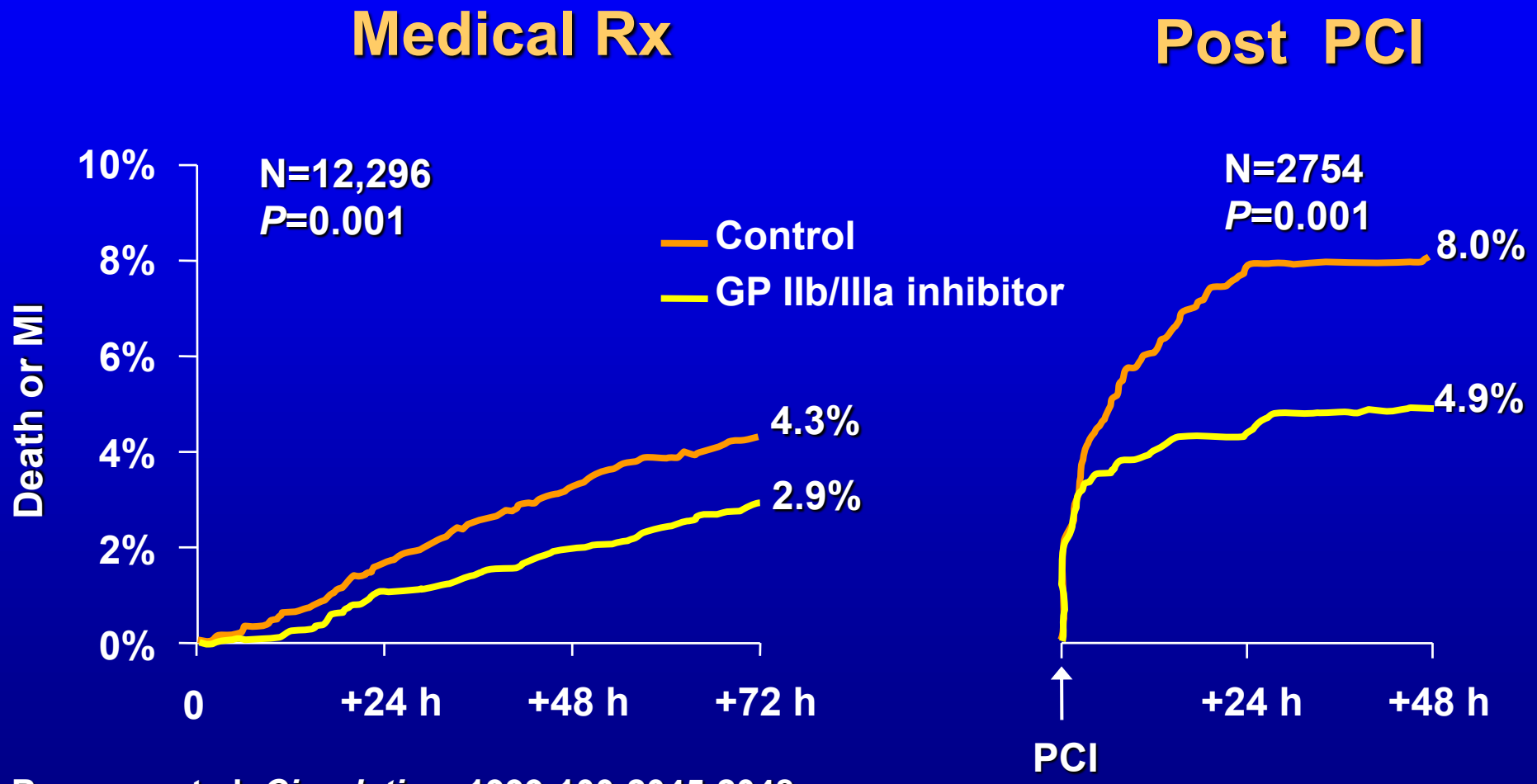
- Troponin
- Negative
- Positive
- Negative
- Positive

CAD	Mortality
Negative	0%
Negative	3.1%
Positive	5.8%
Positive	8.6%

- P=0.012

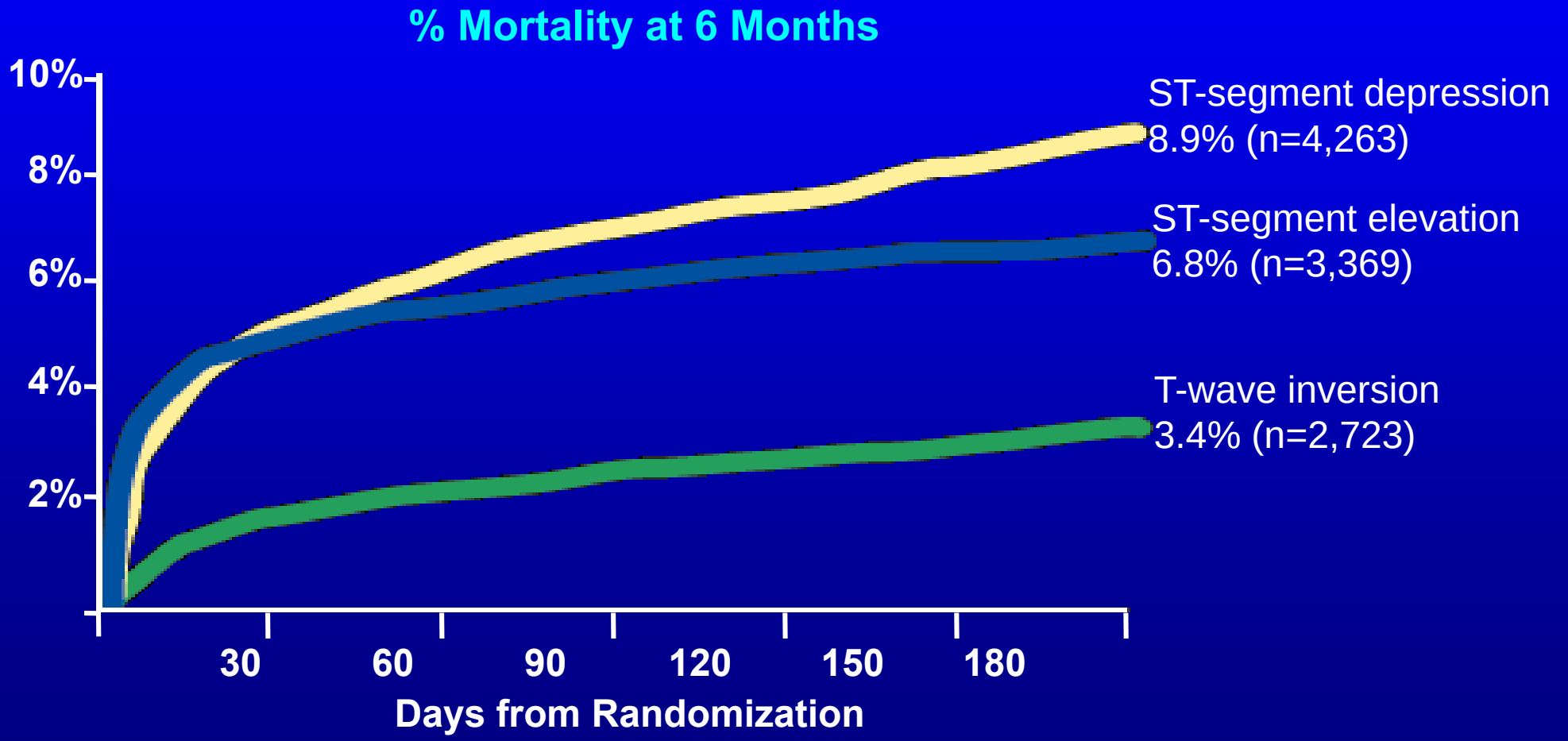
- JACC 2005

GP IIb/IIIa Inhibitor During Medical Rx and After PCI: CAPTURE, PURSUIT, PRISM-PLUS



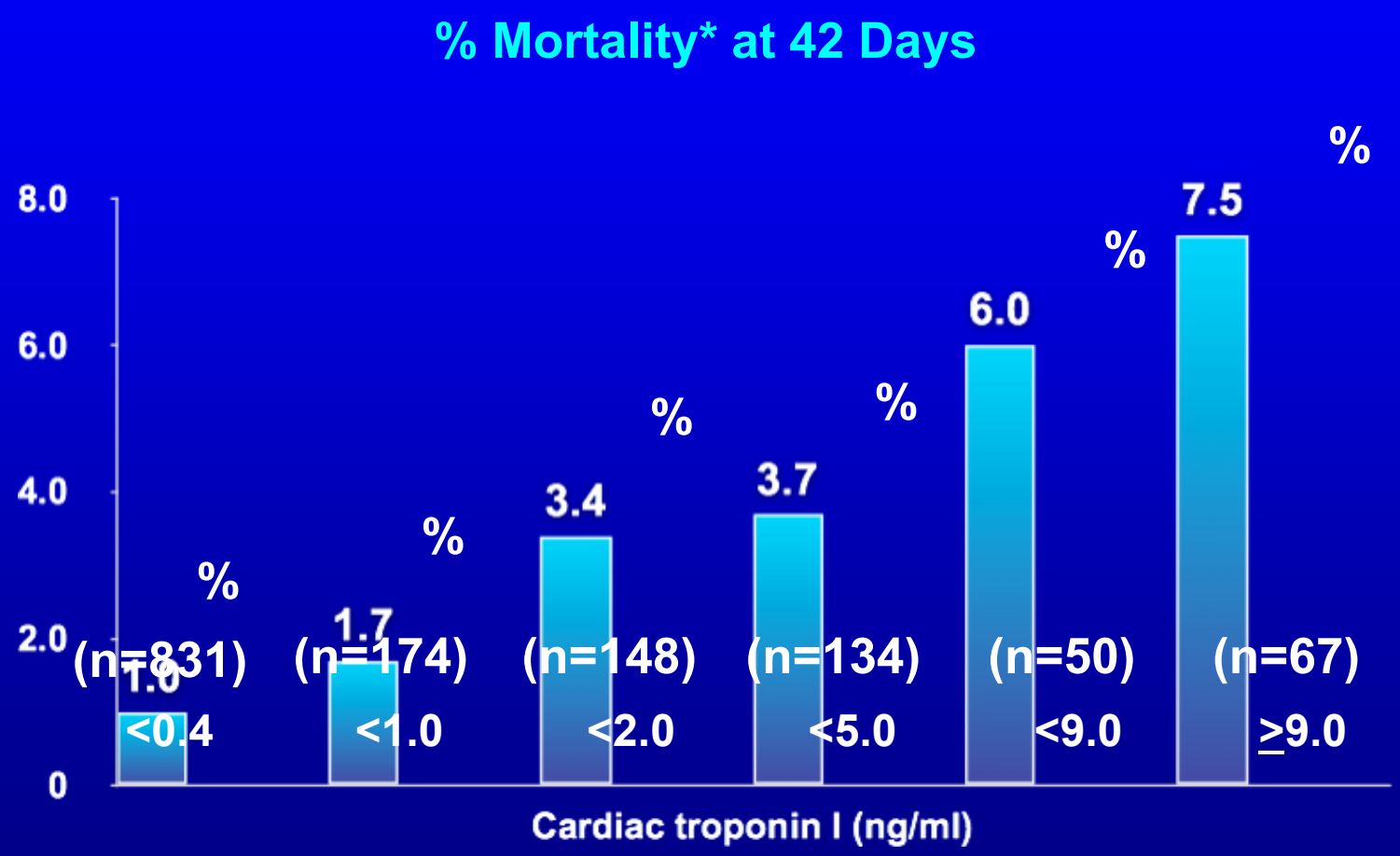
Boersma et al. *Circulation*. 1999;100:2045-2048.

ST-Segment Depression Predicts Higher Risk of Mortality in ACS



The GUSTO-IIb Trial. Savonitto S, et al. *JAMA.* 1999;281:707-713.

Troponin Levels Predict the Risk of Mortality in ACS



*Unadjusted

Antman EM, et al. *N Engl J Med.* 1996;335:1342-1349.

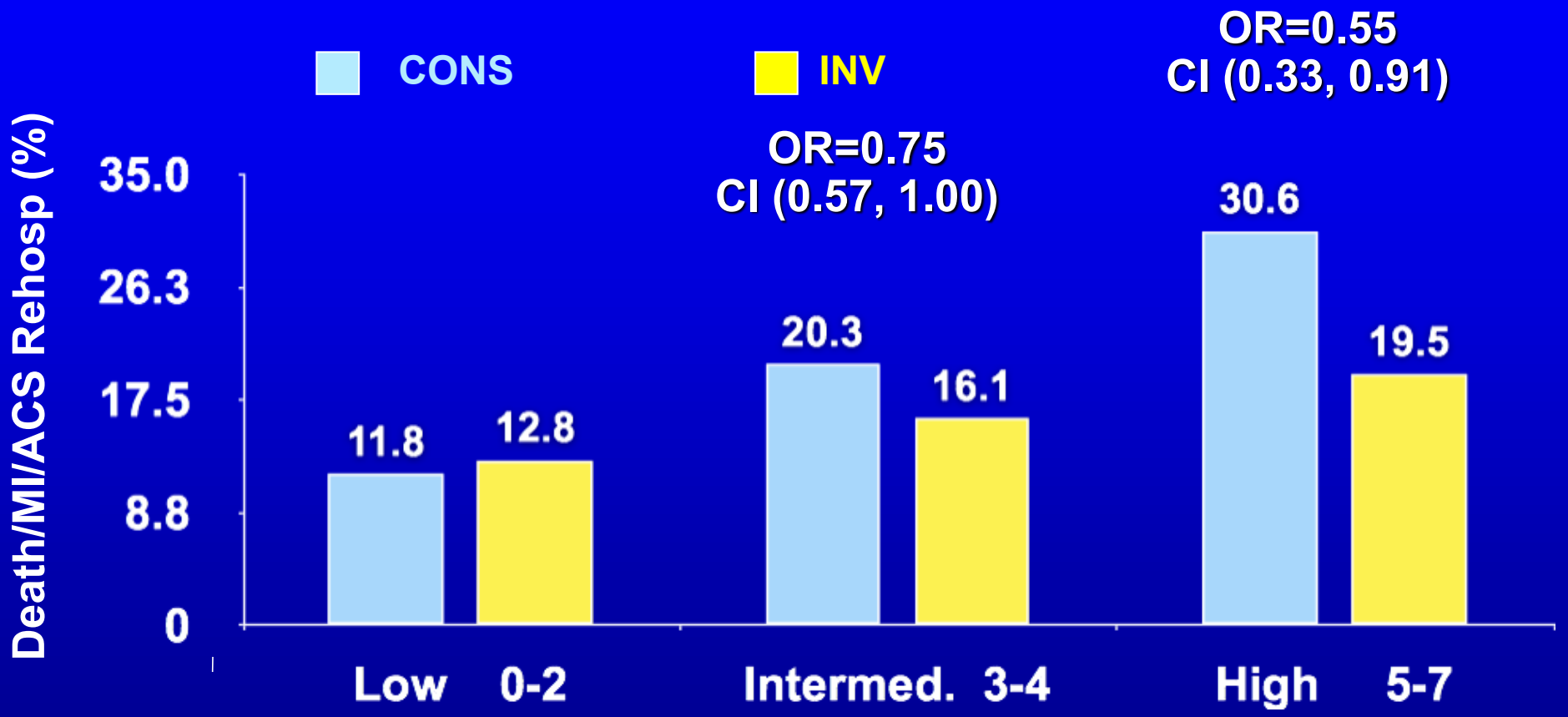
TIMI risk score: Suggested method for estimating early risk

Prognostic variables

- Age >65 years
- >3 coronary risk factors
- Prior angiographic coronary obstruction
- ST-segment deviation at presentation
- >2 angina events within 24 hours
- Use of aspirin within 7 days
- Elevated cardiac markers

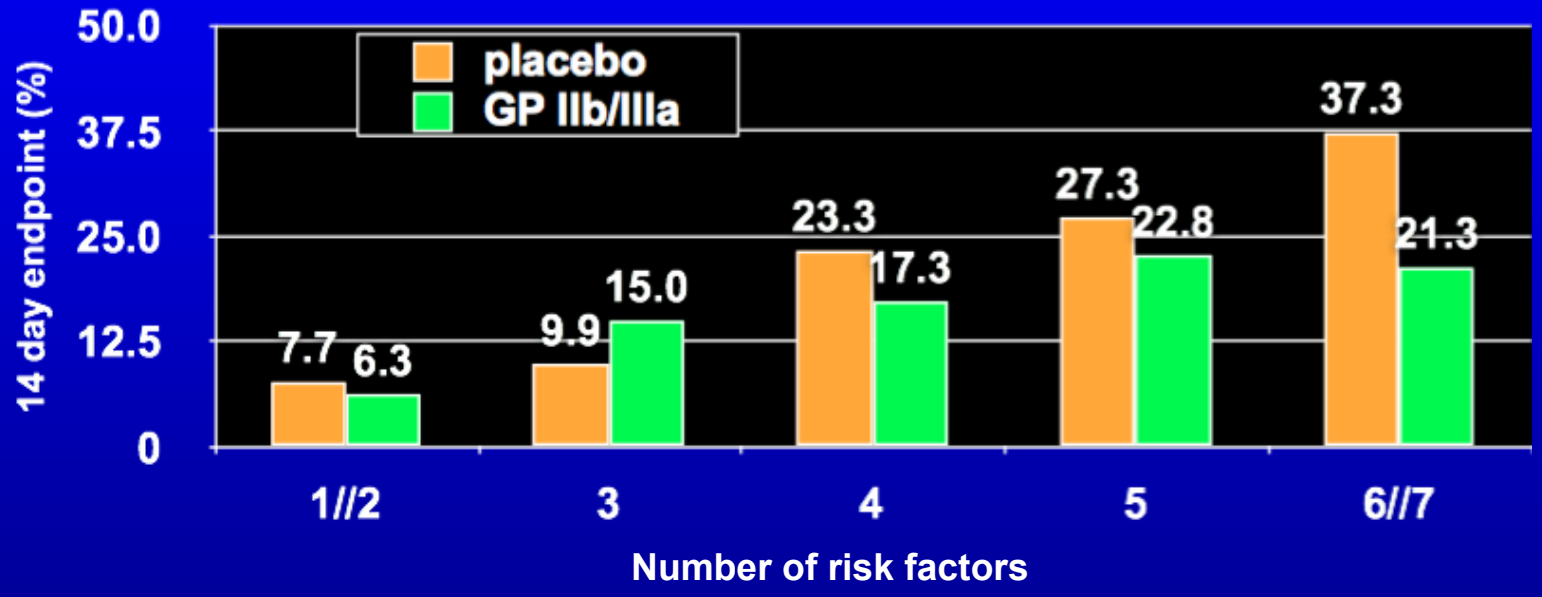
Antman EM, et al. *JAMA*. 2000;284:835-842.

TIMI UA Risk Score: 1°EP at 6 mos



% of Pts: 25% 60% 15%

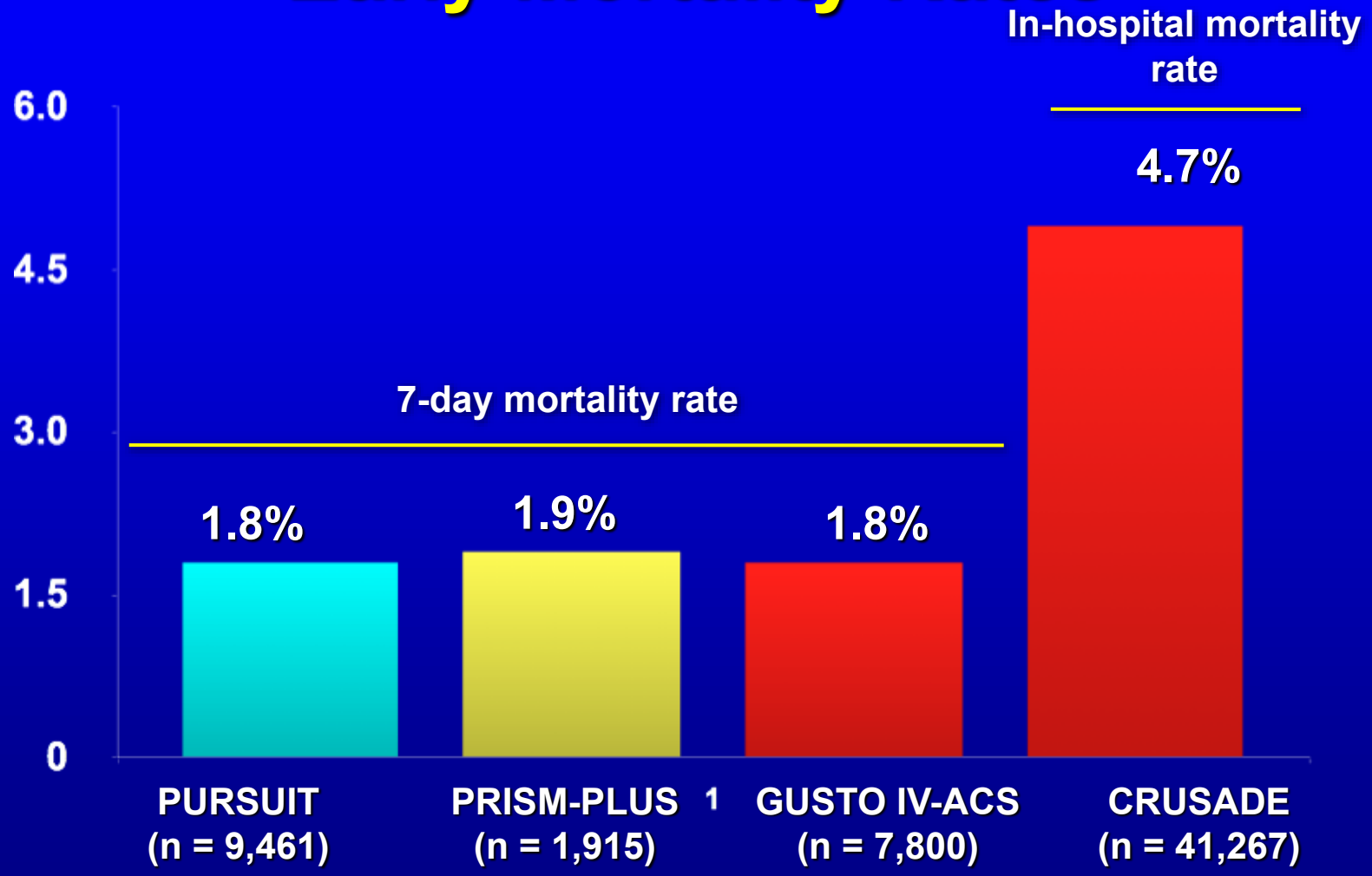
USING THE TIMI RISK SCORE TO PREDICT BENEFIT OF GP IIb-IIIa THERAPY



NNT	72	NA	17	22	6.2

Morow DA,Eur *HeartJ* 2002;23:223-229

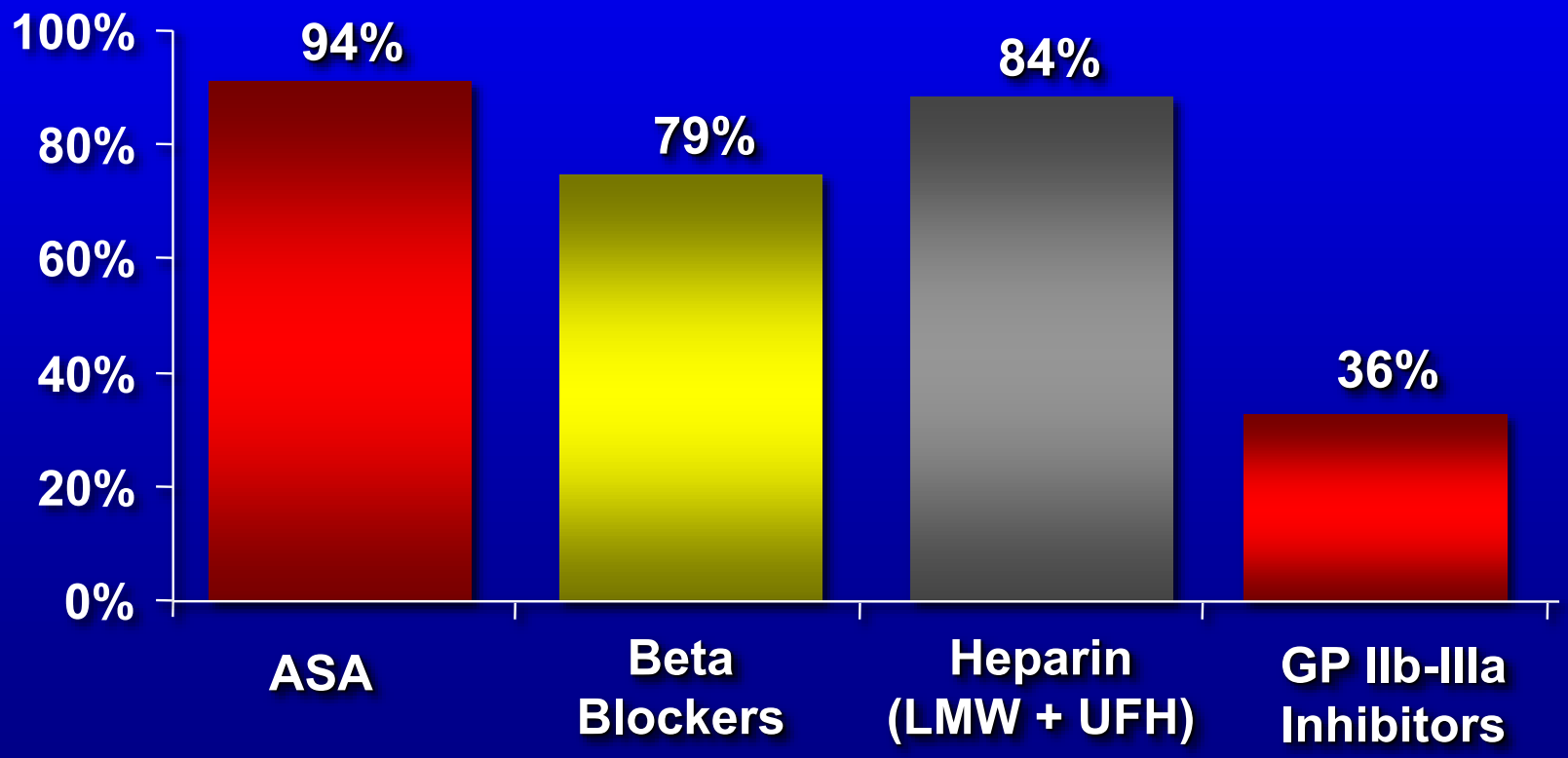
CRUSADE vs. ACS Clinical Trials: Early Mortality Rates



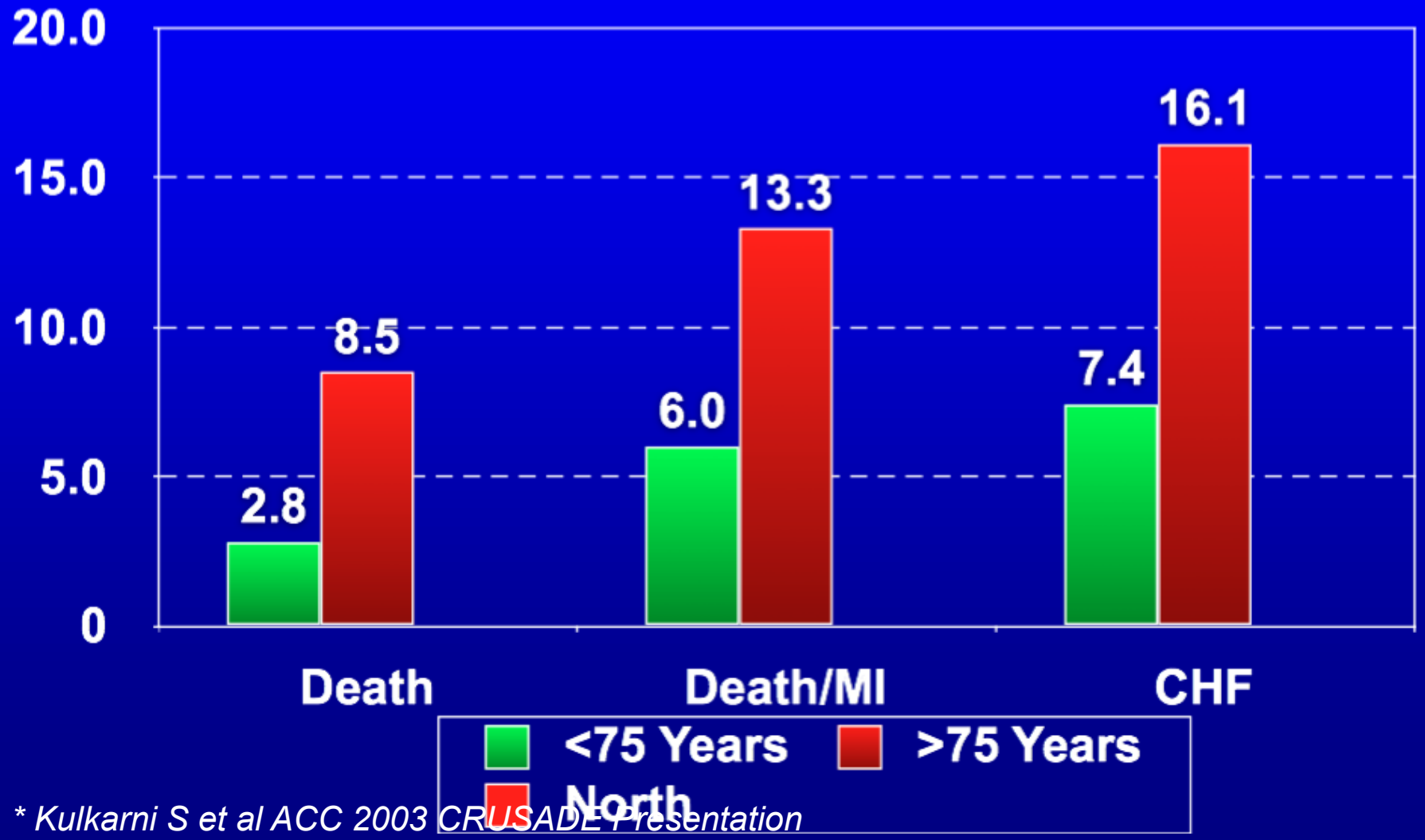
NEJM, 1998
Lancet, 2001

Acute Medication Use

(within 1st 24 hours)



Risk of ACS in Elderly*

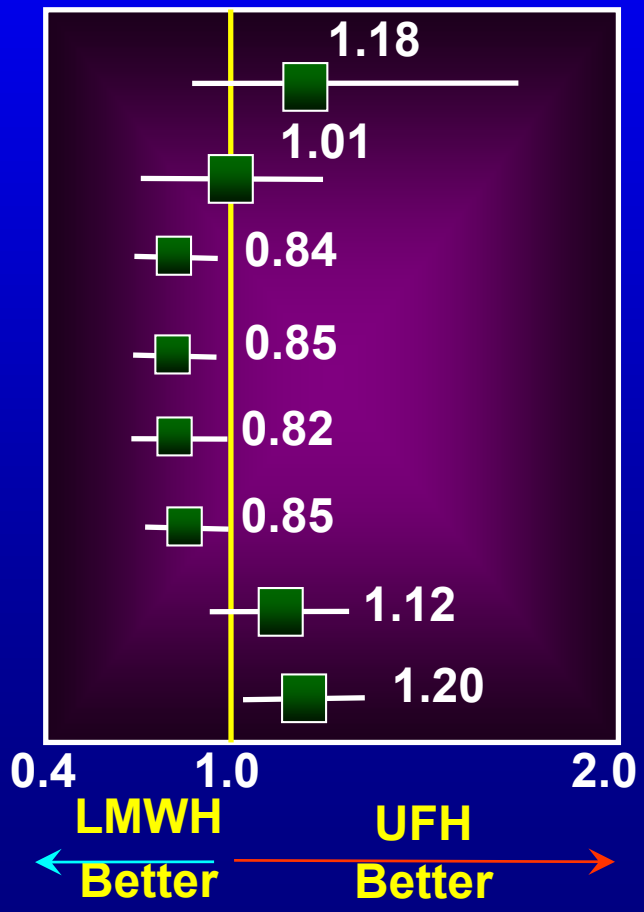


** Kulkarni S et al ACC 2003 CRUSADE Presentation*

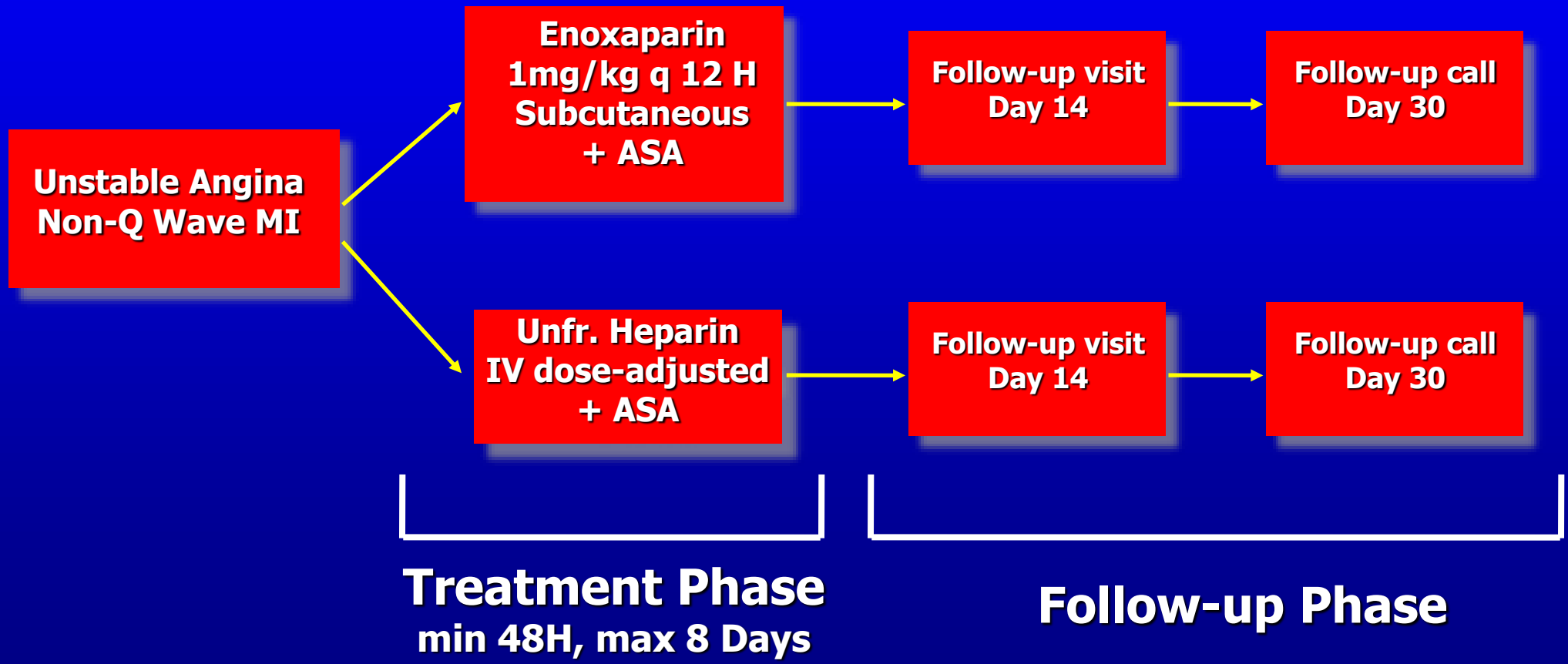
LMWH vs. UFH Trials in Acute Coronary Syndrome

Death / MI / Refractory Ischemia Endpoint

Trial (LMWH)	N	Timing of Endpoint	Relative risk & 95% CI	Event Rate (%) LMWH	UFH	P value
FRIC	1482	Day 1-6	1.18	9.3	7.6	0.247
(Dalteparin)		Day 6-45	1.01	12.3	12.3	0.99
ESSENCE	3171	Day 14	0.84	16.6	19.8	0.019
(Enoxaparin)		Day 30	0.85	19.8	23.3	0.017
TIMI-11B	3910	Day 14	0.82	14.2	16.7	0.032
(Enoxaparin)		Day 43	0.85	17.3	19.7	0.048
FRAXIS	2357	Day 14	1.12	20.0	18.1	0.243
(Nadroparin)		Day 90	1.20	26.2	22.2	0.025



ESSENCE: Enoxaparin in Unstable Angina and NQMI

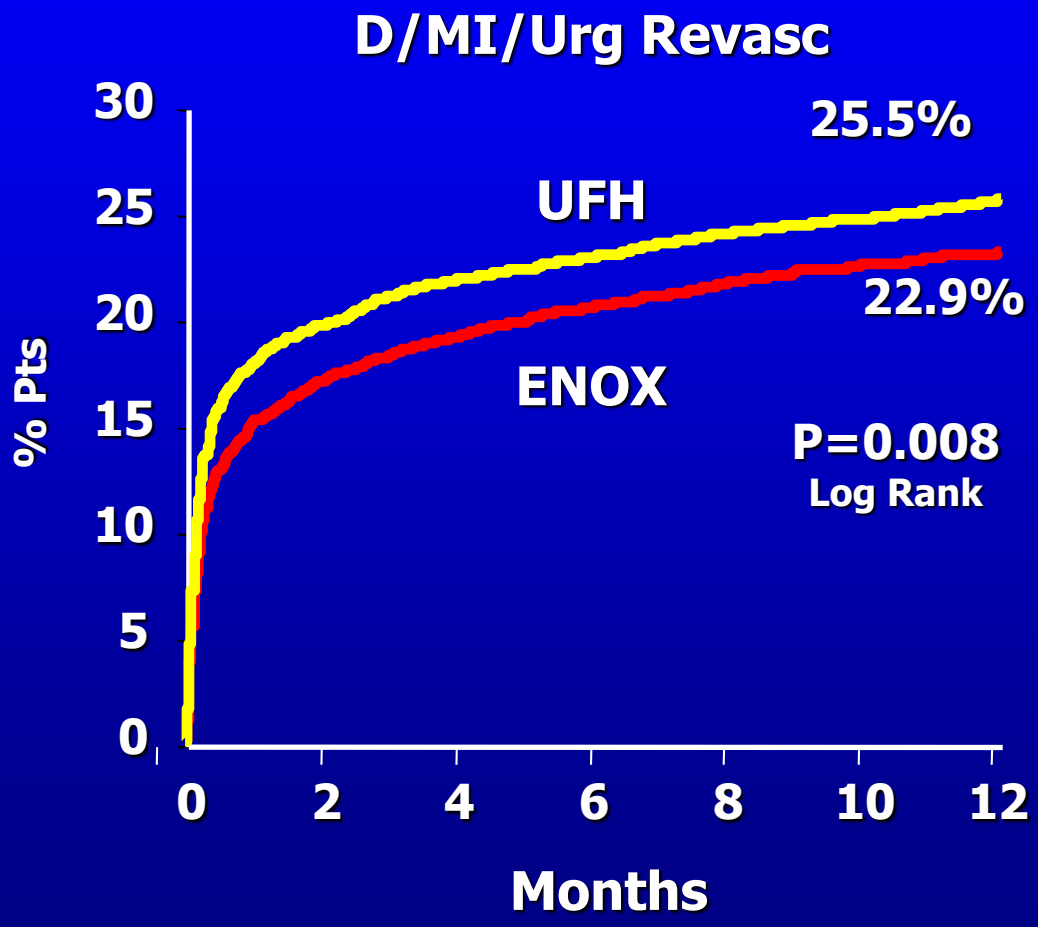


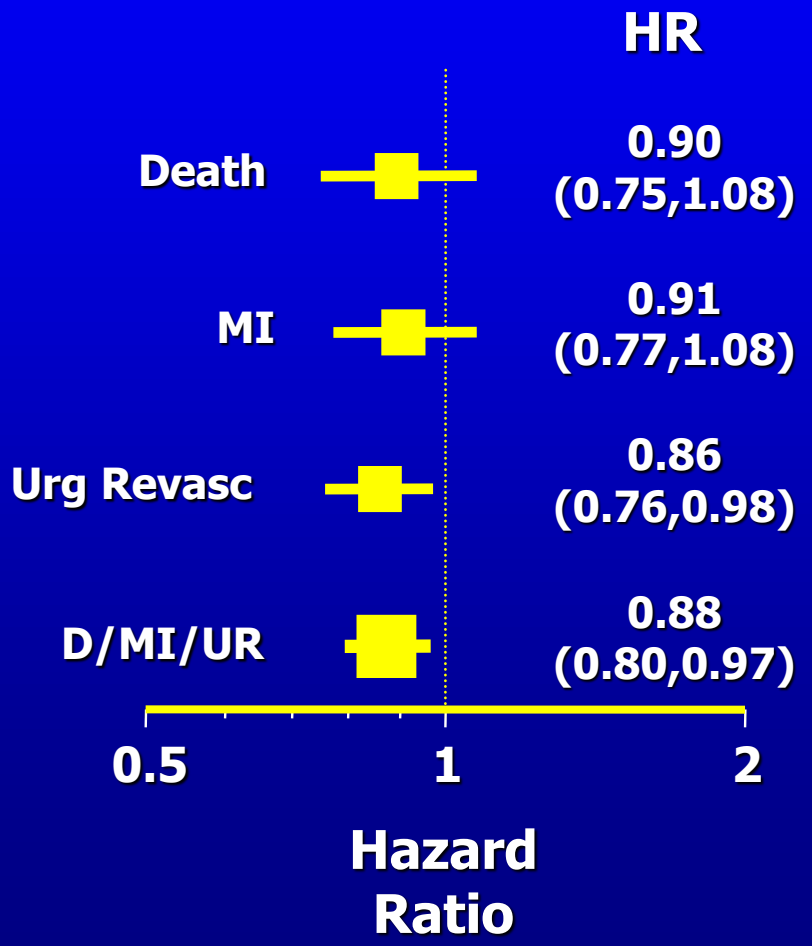
ESSENCE Results

Endpoints	UFH n=1564	Enoxaparin n=1607	p value
14 days			
Death, MI, recurrent angina	19.8%	16.6%	0.019
30 days			
Death, MI, recurrent angina	23.3%	19.8%	0.016
Revascularization	32.2%	27.0%	0.001
Major bleeding	7.0%	6.5%	
Any bleeding	14.2%	18.4%	0.001

Cohen M et al. NEJM 1997;337:447-452.

TIMI 11B-ESSENCE
Meta-Analysis 1 Yr Follow-up





The INTERACT Study

720 patients UA/NSTEMI

- Chest pain > 10 min within 24 hr
- 0.5 mm ST Segment depression/ transient elevation
- Positive cardiac markers (CK-MB or troponin)

180/2.0 dose eptifibatide

Treatment Group A
UFH 70 IU/kg bolus/0.15 U/kg-hr
(aPTT 50-70 sec)
(n = 360)

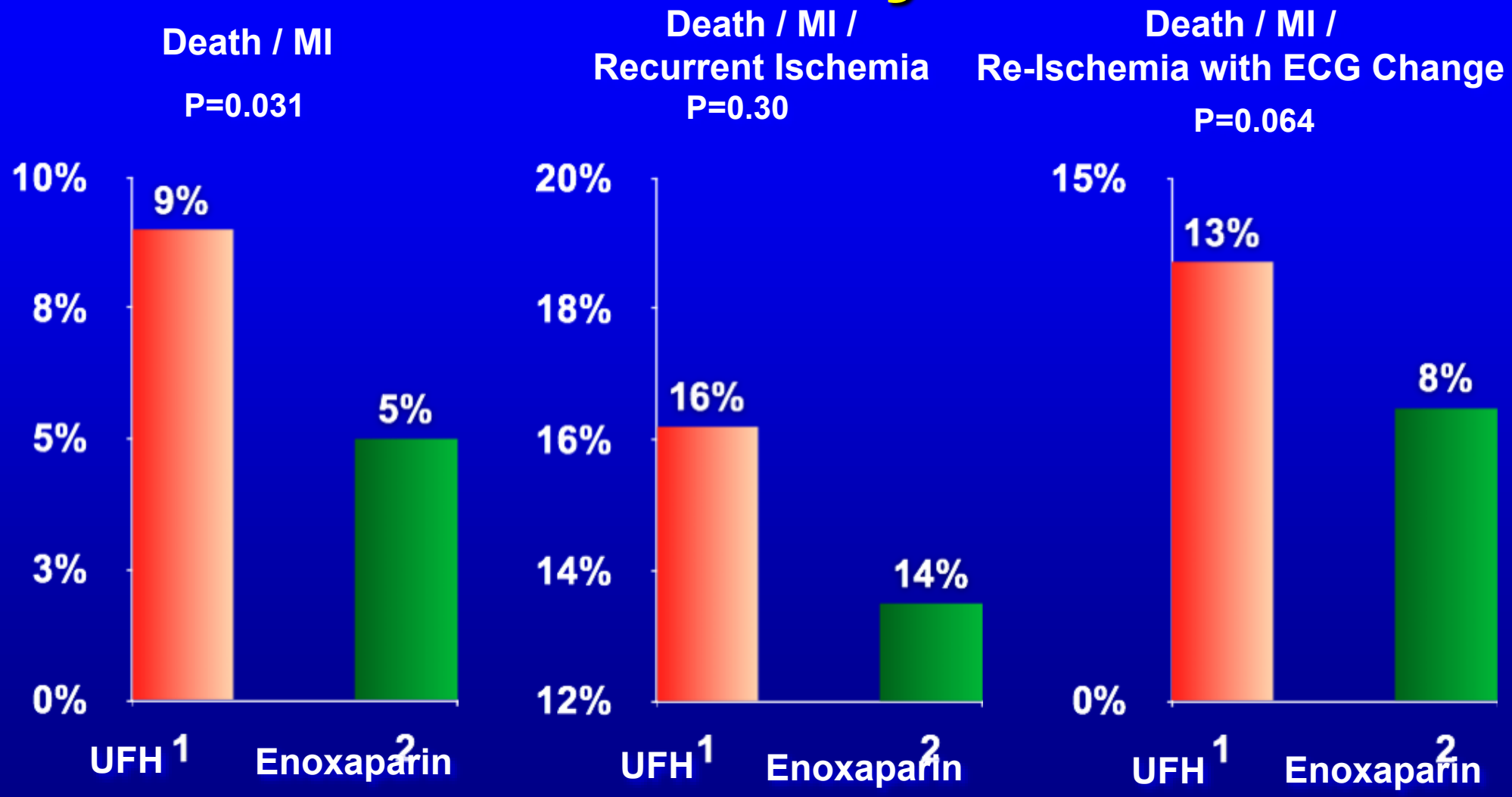
Treatment Group B
1.0 mg/kg q12 enoxaparin
(n = 360)

Endpoints:

- Primary - Major/Minor TIMI Bleeding
- Secondary - D/MI/recurrent ischemia
  - ST segment monitoring

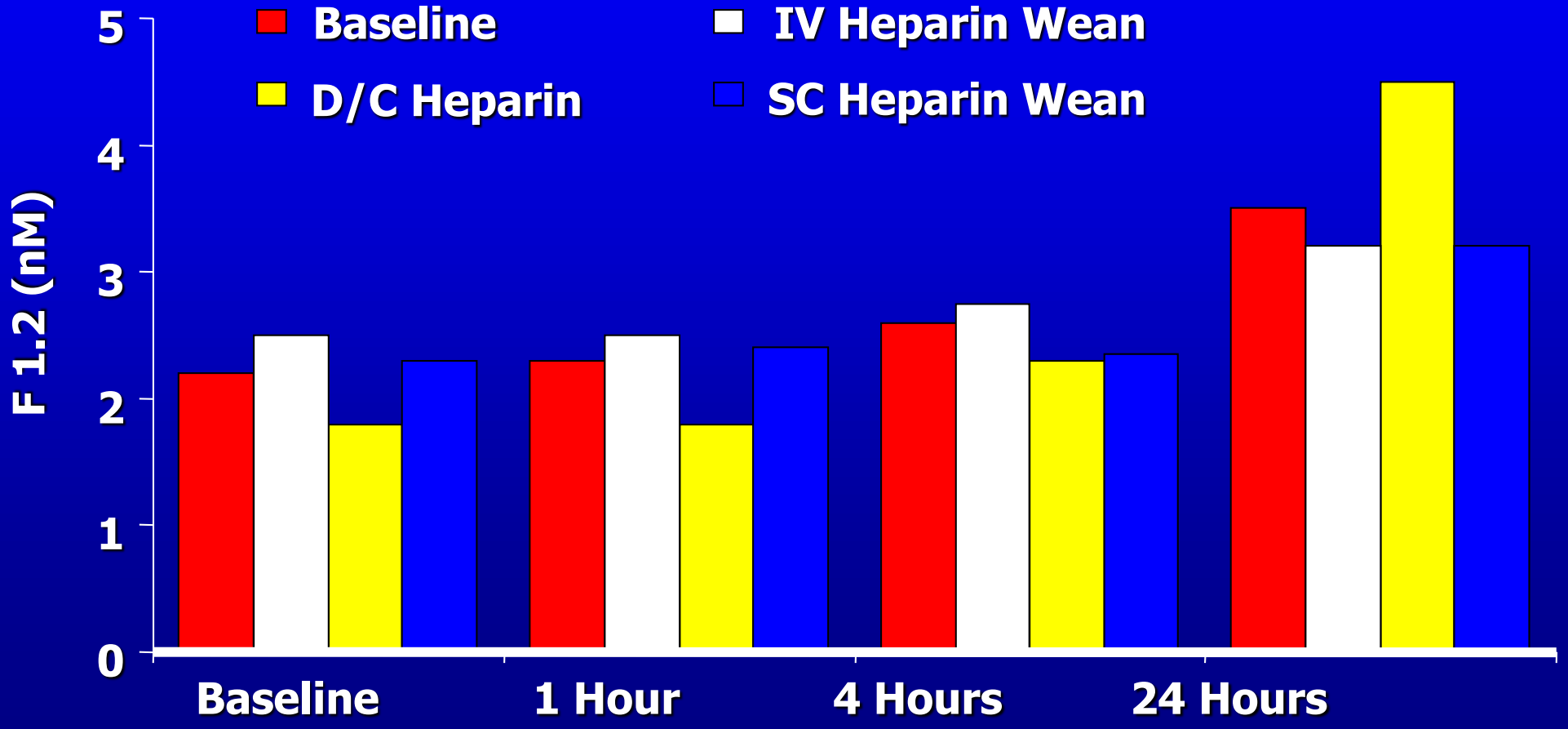
Goodman et al, ACC 2002

INTERACT: 30 Day Events



Goodman et al, ACC 2002

Thrombin Generation Follows Heparin Discontinuation in Patients with Acute Coronary Syndromes



Becker RC. JACC 1999;34:1020

Study Design

High-Risk ACS Patients

At least 2 of 3 required:

- Age ε 60
- ST □ (transient) or □
- (+) CK-MB or Troponin

Randomize
(n = 10,000)

Enoxaparin

1 mg/kg SC Q12H

IV Heparin

60 U/kg □ 12 U/kg/hr (aPTT 50-70 sec)

Early invasive strategy
Other therapy per AHA/ACC Guidelines
(ASA, ®-blocker, ACE, clopidogrel, GP IIb/IIIa)

Primary endpoint: Death or MI at 30 days

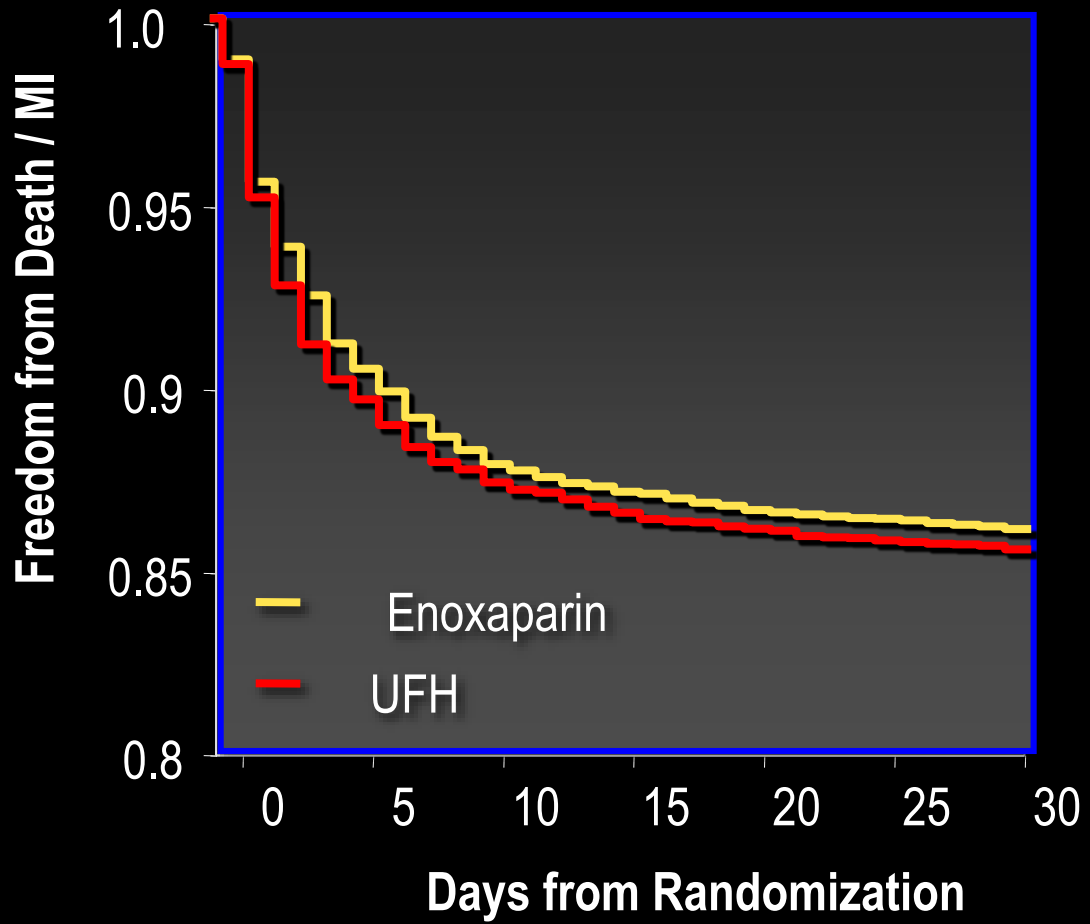
SYNERGY

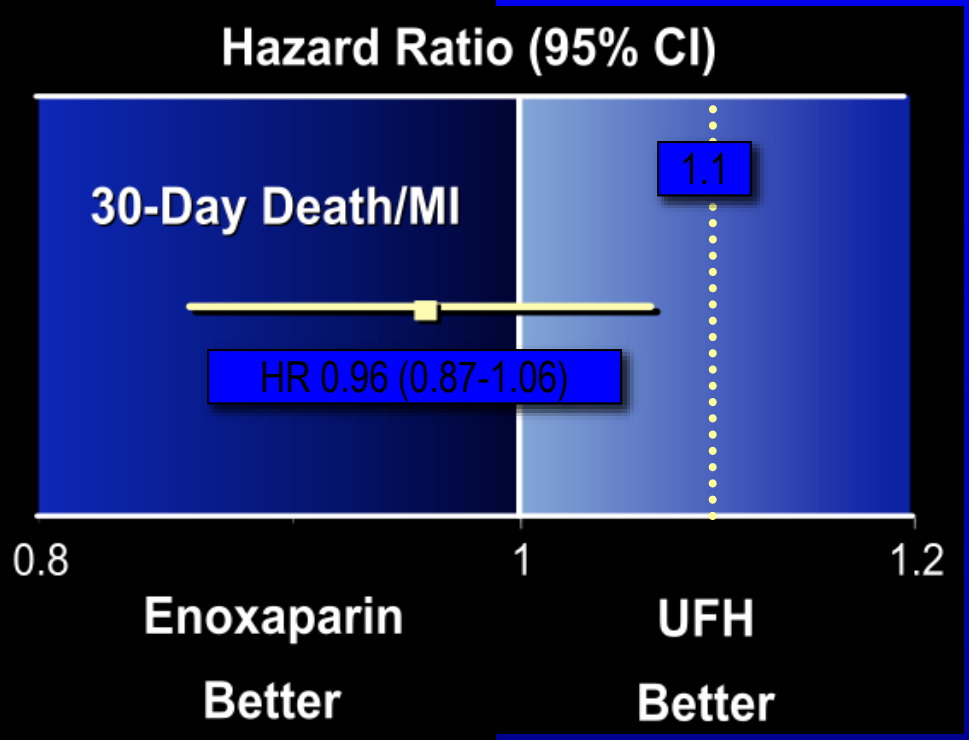
Primary Results (30 Days)

	Enoxaparin (n = 4993)	UFH (n = 4985)	Unadjusted P-value
Death and MI (%)	14.0	14.5	0.396
Death (%)	3.2	3.1	0.705
MI (%)	11.7	12.7	0.135

SYNERGY

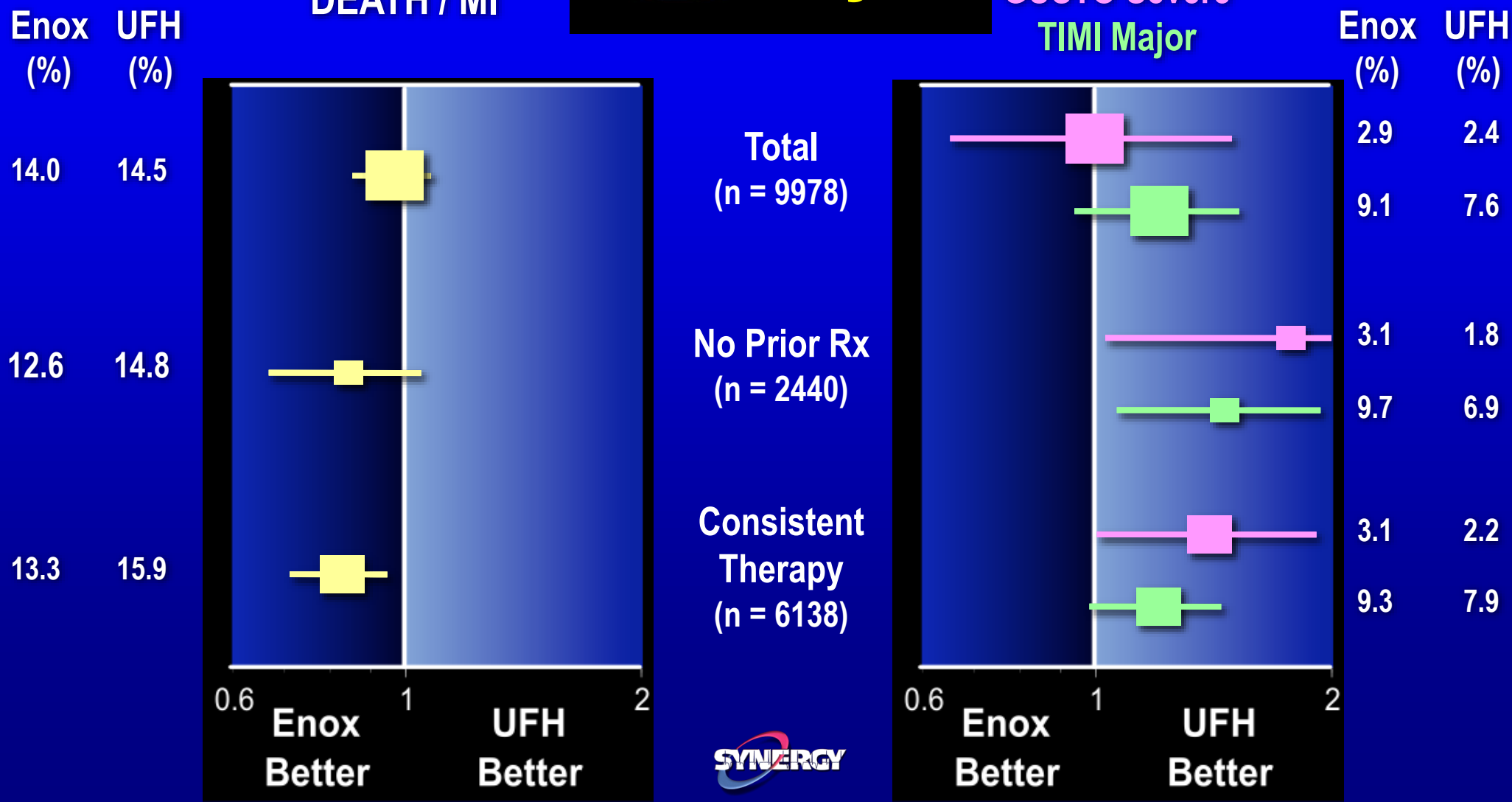
Death and MI at 30 Days



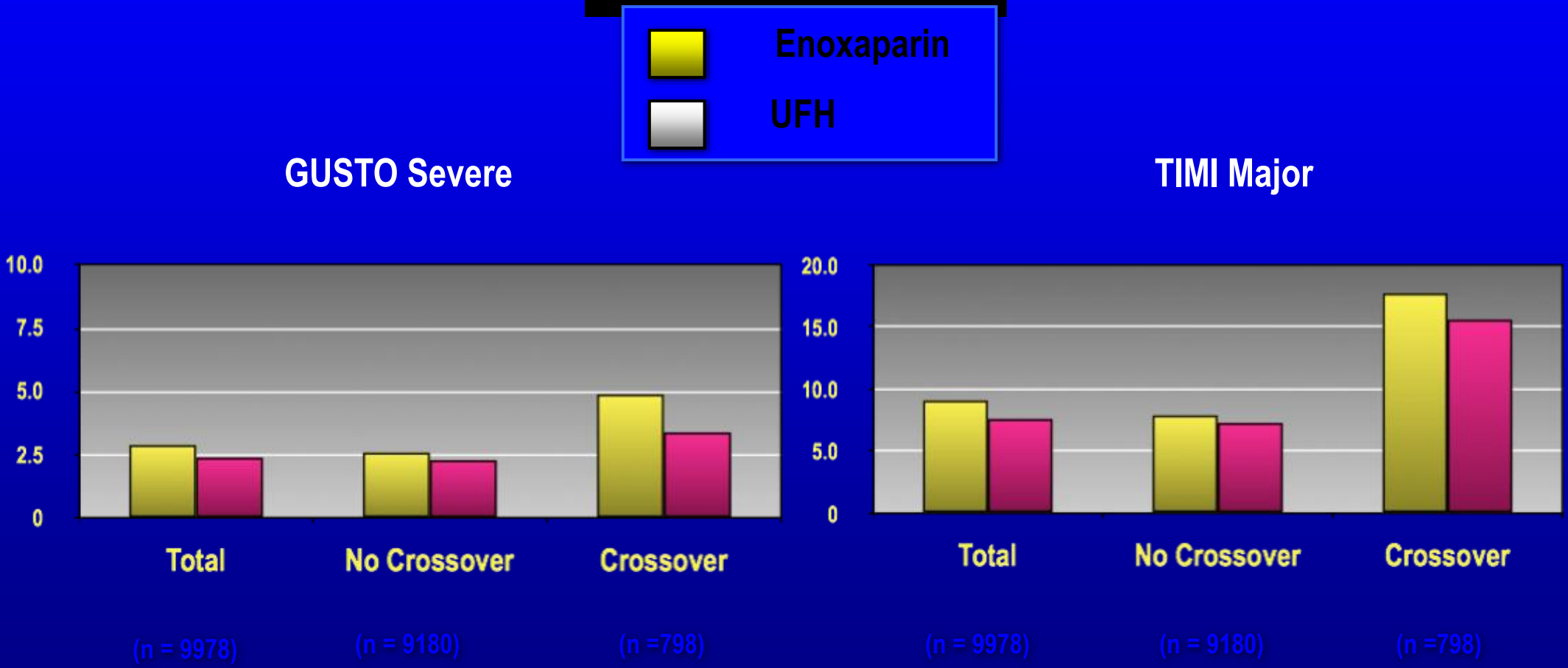


SYNERGY

Prior Antithrombin Therapy: Efficacy and Safety

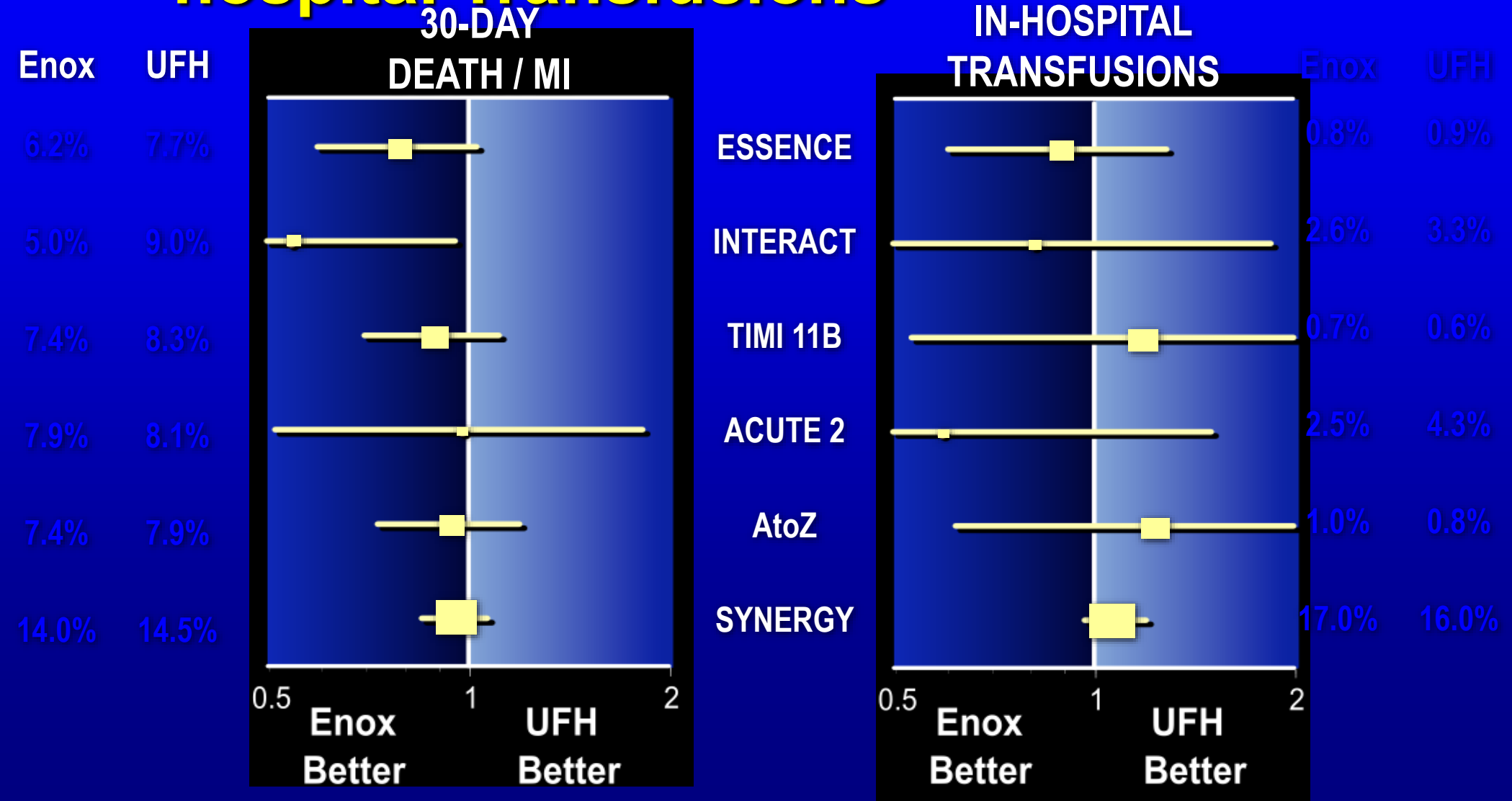


Crossovers: Relation to Bleeding

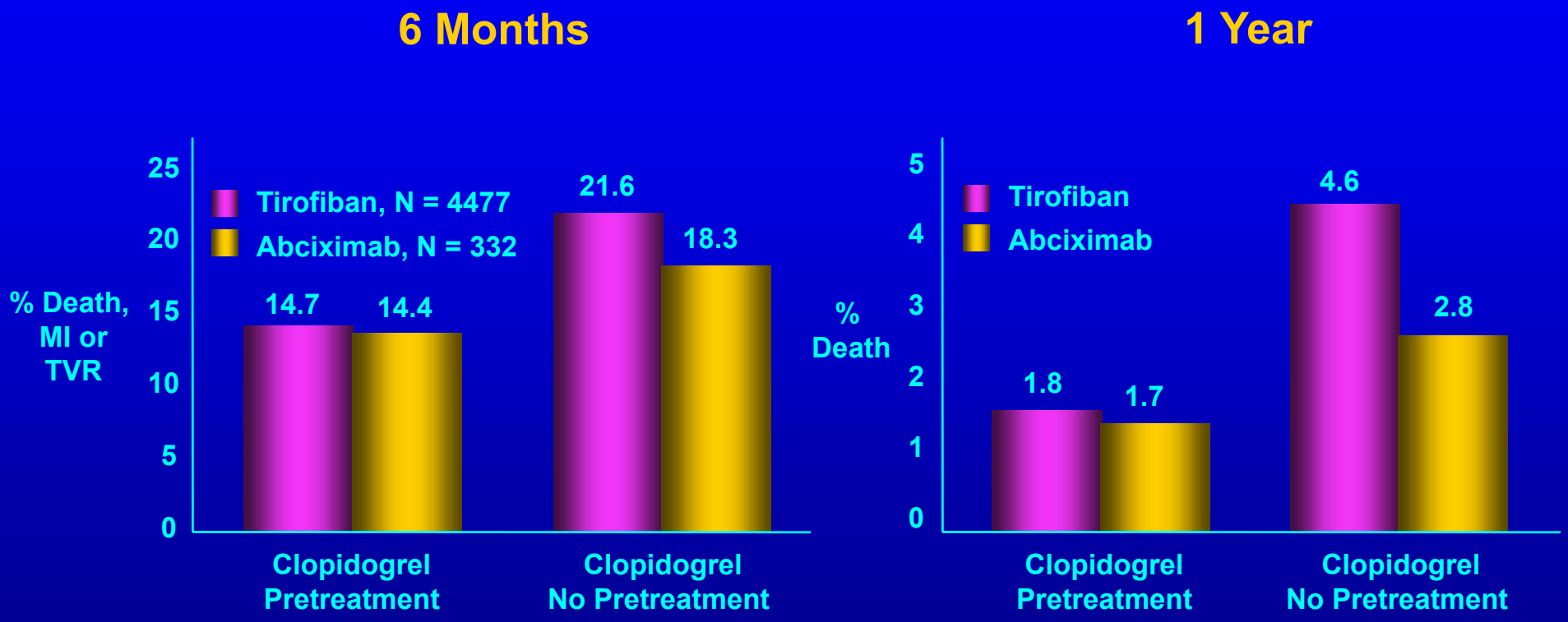


SYNERGY

Systematic Overview: 30-Day Death/MI and In-hospital Transfusions

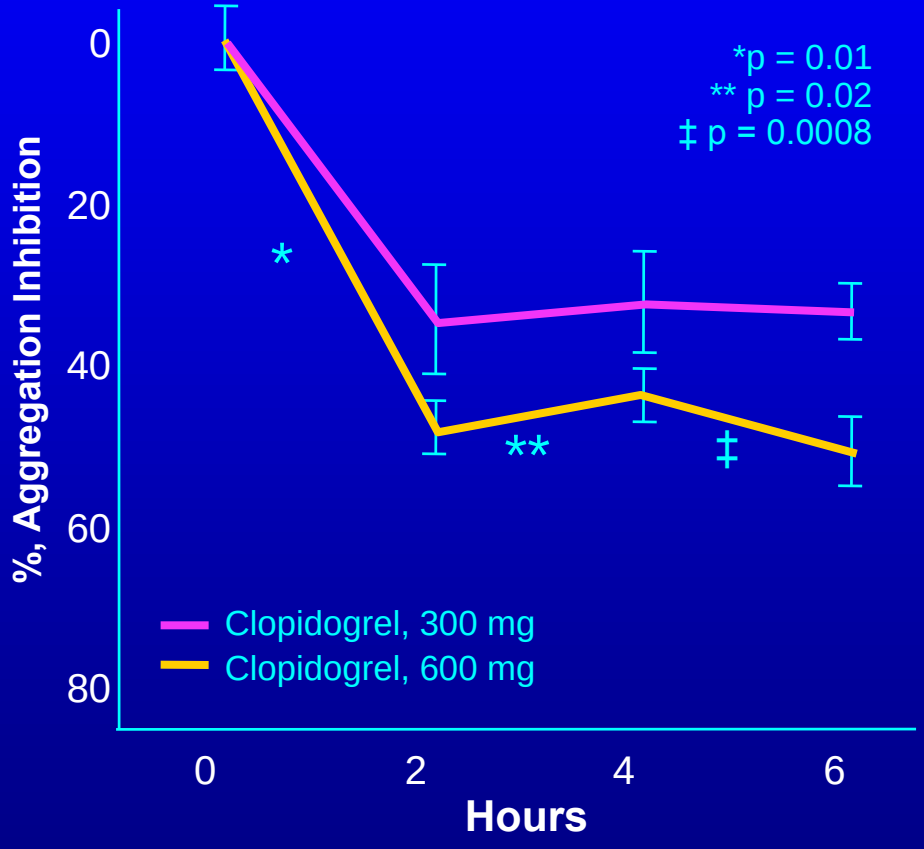


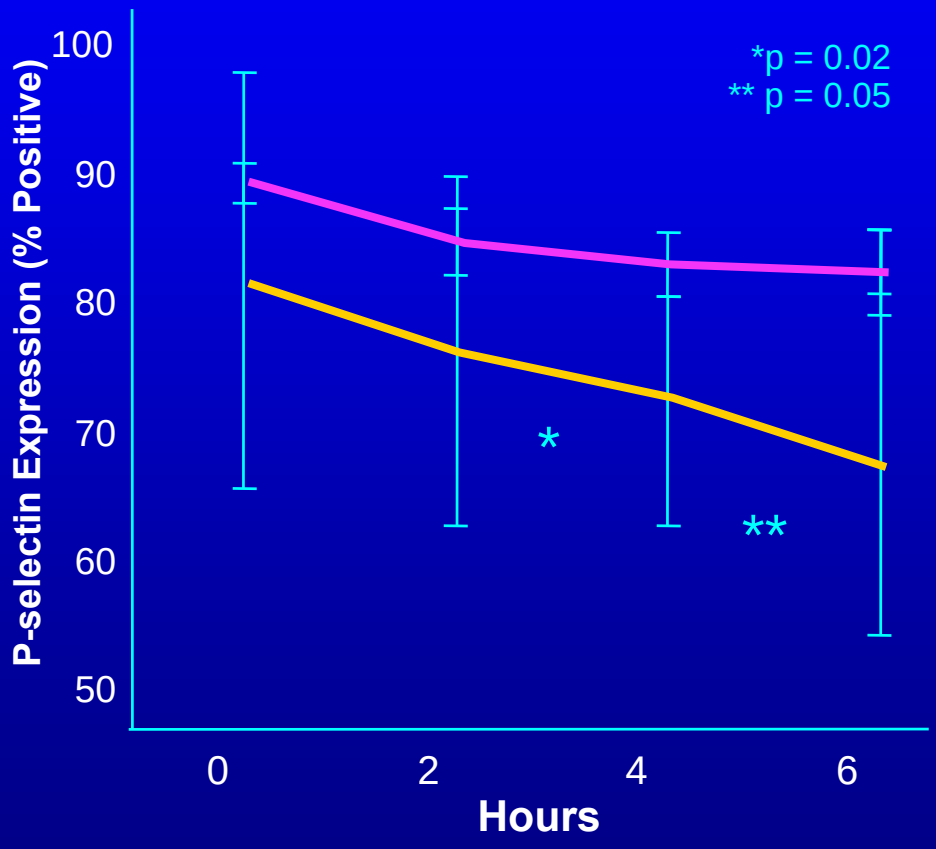
TARGET: Clopidogrel Pre-PCI



Chan A, et al. *J Am Coll Cardiol.* 2003;42:1188-95.

Clopidogrel Dose Effect





Zidar F, et al. *J Am Coll Cardiol.* 2004;43:5-suppl A;Abstract 1100-59.

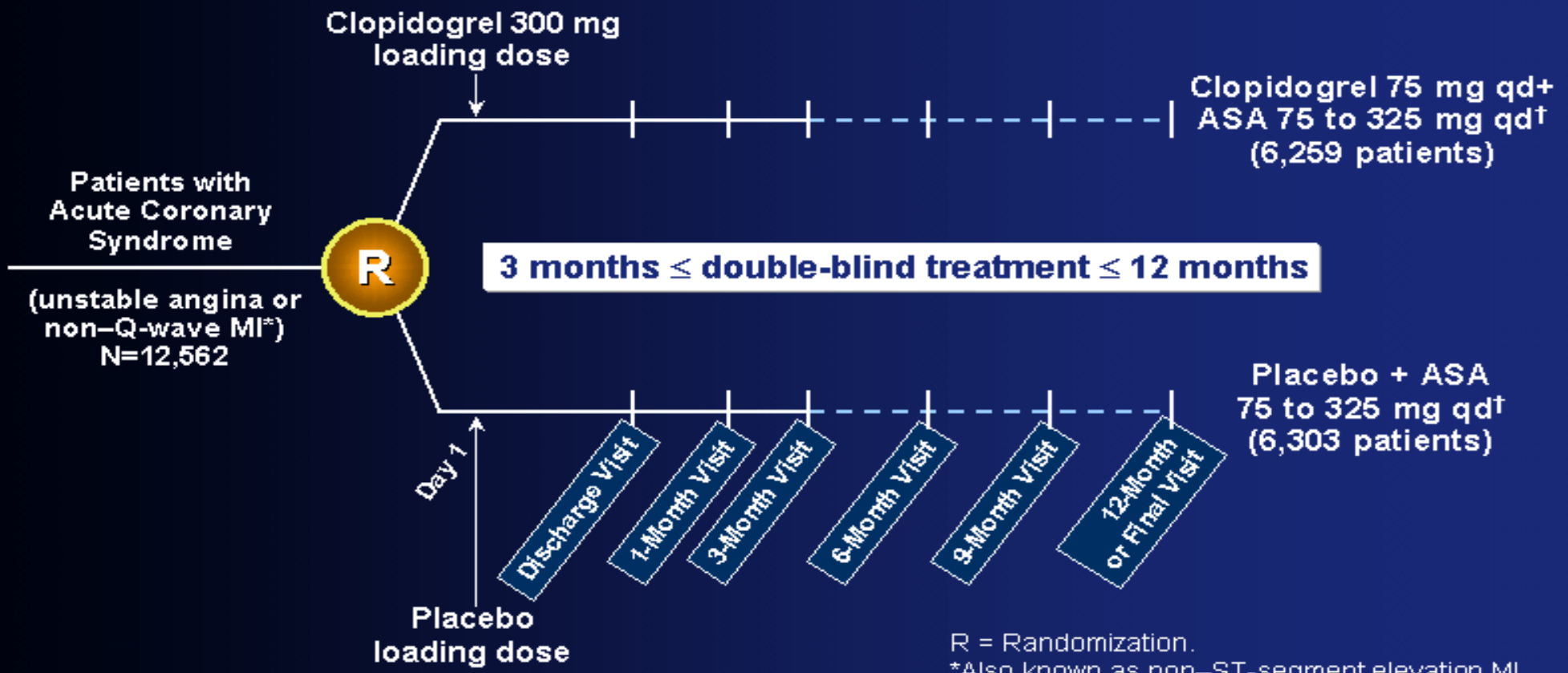
Oral Antiplatelet Agents

Mechanism of Action

Binds selectively and noncompetitively to the platelet ADP receptor (irreversible) manner, preventing activation of the glycoprotein IIb/IIIa receptor, which mediates the final common pathway of platelet aggregation

CURE Study

Study Design

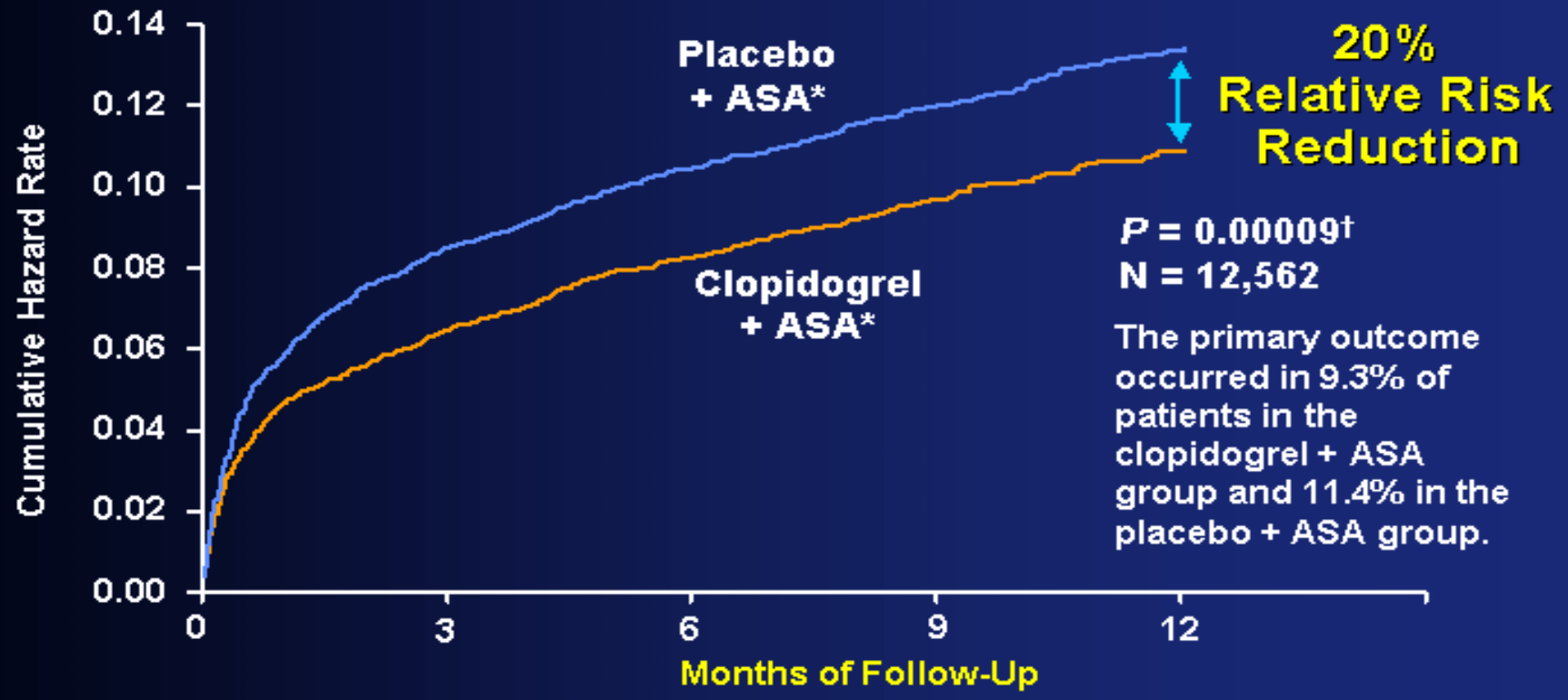


R = Randomization.
*Also known as non–ST-segment elevation MI (NSTEMI).
†In addition to other standard therapy.

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

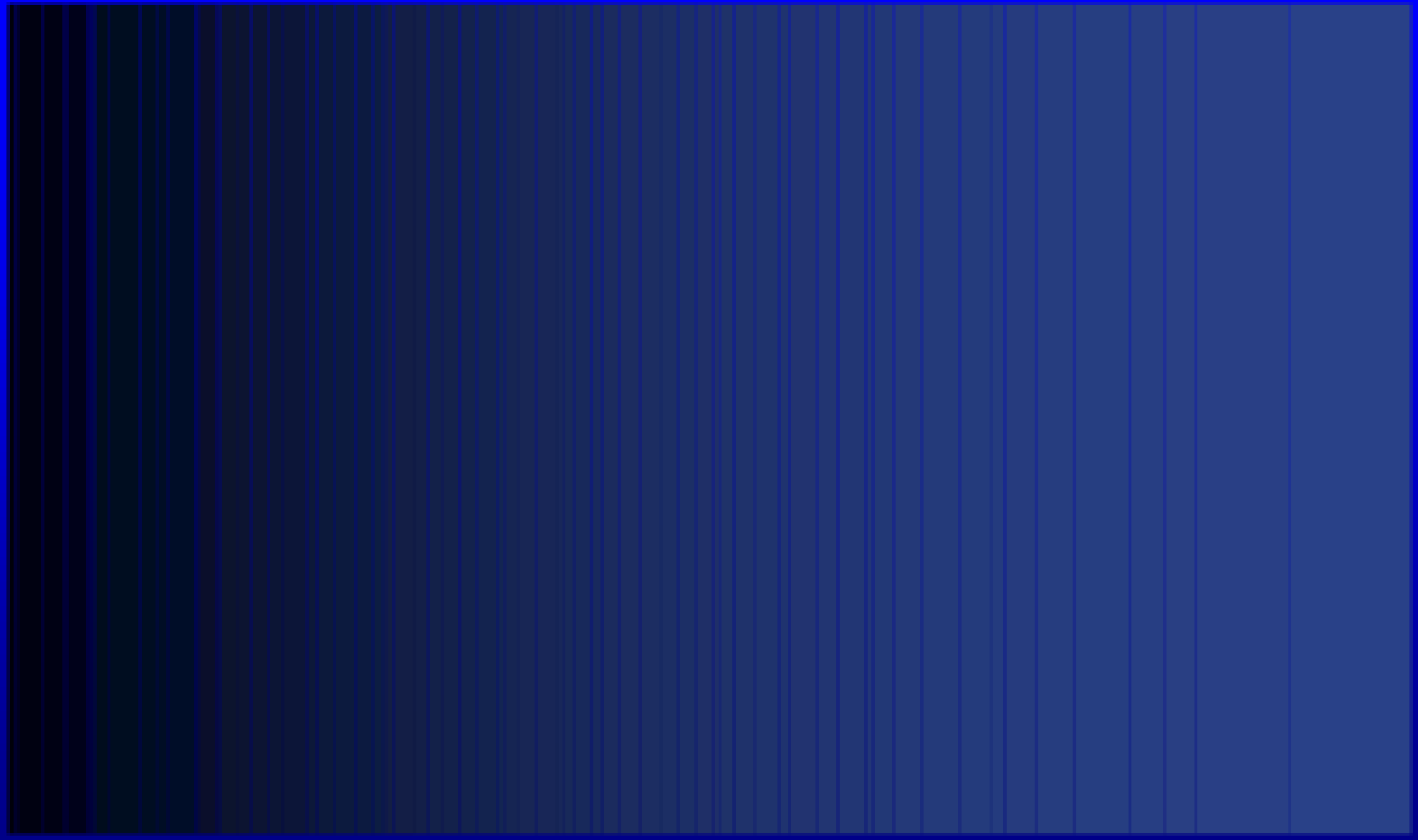
CURE Study

Primary End Point—MI/Stroke/CV Death



*Other standard therapies were used as appropriate.
†PLAVIX Prescribing Information.

Adapted with permission (2002) from the Massachusetts Medical Society. The CURE Trial Investigators. *N Engl J Med.* 2001;345:494-502.



ISAR-REACT Trial

2,159 low-risk patients undergoing elective stenting, excluding patients with:

- Acute coronary syndrome
- Acute MI with 14 days
- ST-segment depression
- Positive biomarkers
- Insulin-dependent diabetes
- Chronic total occlusions
- EF <=30%
- Thrombus presence
- Lesions in bypass grafts

Clopidogrel
(600 mg loading dose, 2 x 75 mg/d through discharge, 75 mg/d for 4 weeks)

Abciximab
(n = 1,079)

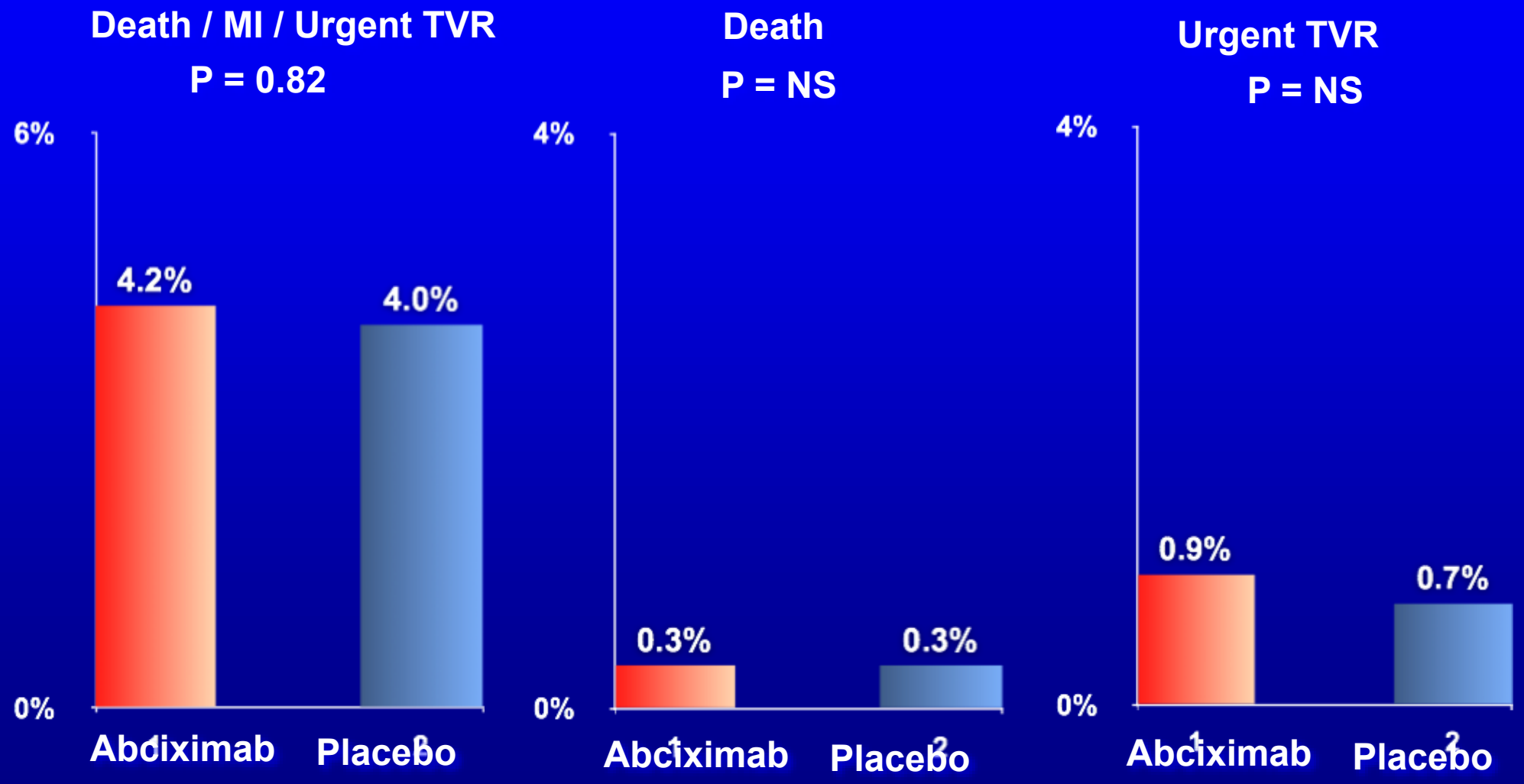
Placebo
(n = 1,080)

Endpoints:

- Primary – 30 day death / MI / urgent target vessel revascularization
- Secondary –30 day bleeding complications

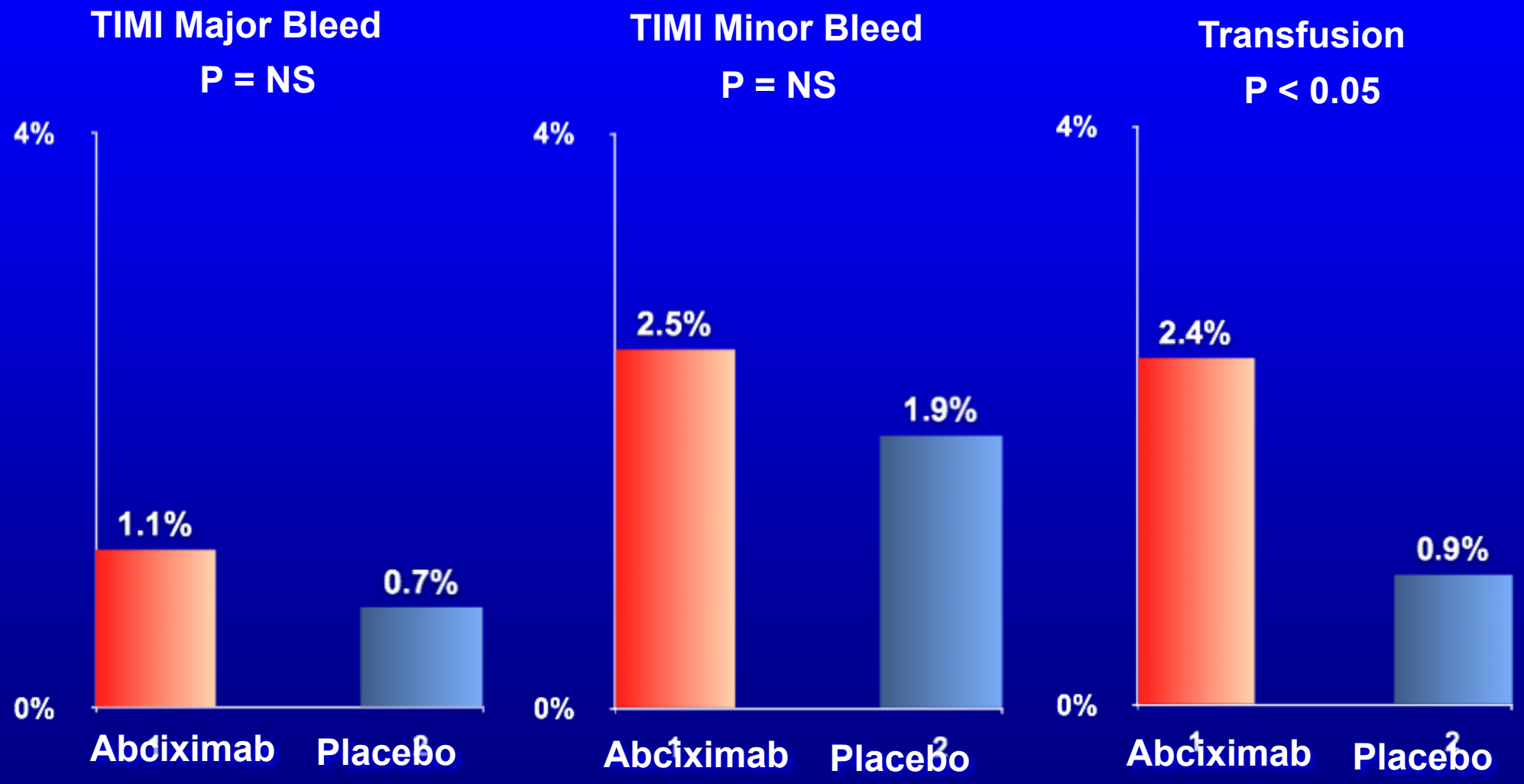
ACC 2003, Late Breaking Trials

ISAR-REACT Trial: 30 Day Endpoints



ACC 2003, Late Breaking Trials

ISAR-REACT Trial: Bleeding Results



ACC 2003, Late Breaking Trials

ISAR-REACT 2 Trial: Study Design

2022 patients with an episode of angina within the preceding 48 hours and an elevated troponin T level or new ST-segment depression of ≥0.1 mV or transient (<20 minutes) ST-segment elevation of ≥0.1 mV or new or presumed new bundle-branch block; significant angiographic lesions in a native coronary vessel or venous bypass graft amenable to and requiring a PCI

Placebo Controlled. Randomized. Blinded.

24% female, mean age 66 years, mean follow-up 30 days

Pre-treatment with high dose (600mg) clopidogrel at least 2 hours pre-procedure

Abciximab
(usual bolus or infusion dose)
n=1012

Placebo
n=1010

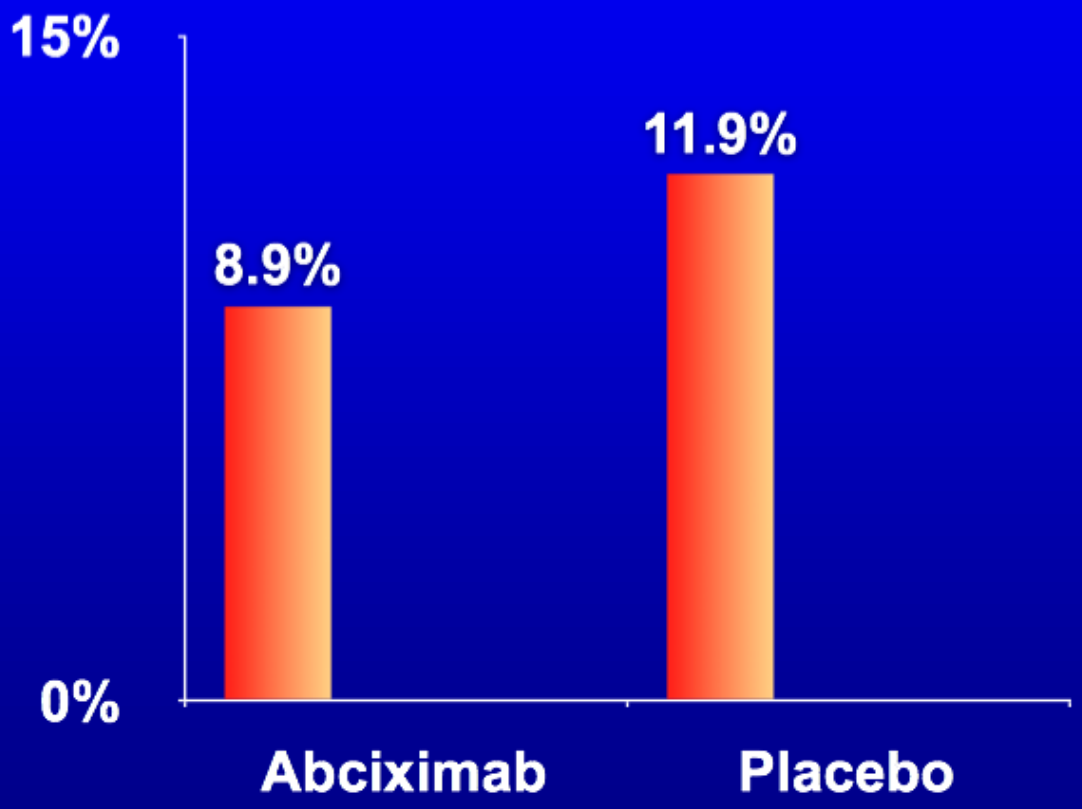
- Primary Endpoint: Composite of death, MI, and urgent target vessel revascularization (TVR) due to myocardial ischemia within 30 days
- Secondary Endpoint: In-hospital major and minor bleeding

Presented at ACC 2006

ISAR-REACT 2 Trial: Primary Composite Endpoint

Composite of death, MI, or urgent TVR due to Myocardial Ischemia within 30 days (%)

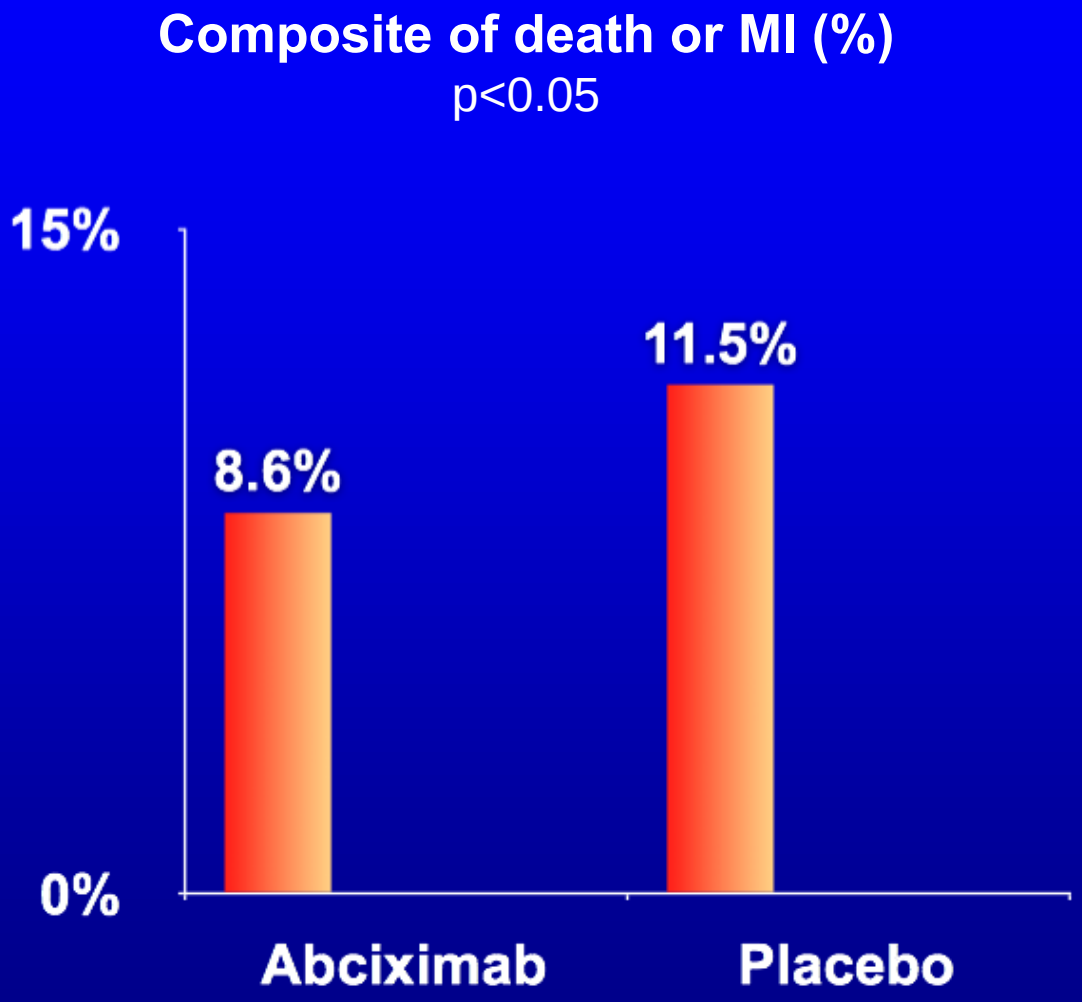
p=0.03



- **The primary composite endpoint occurred less frequently in the abciximab group compared to placebo (8.9% vs 11.9%; relative risk [RR] 0.75 p=0.03)**

Presented at ACC 2006

ISAR-REACT 2 Trial: Death or MI

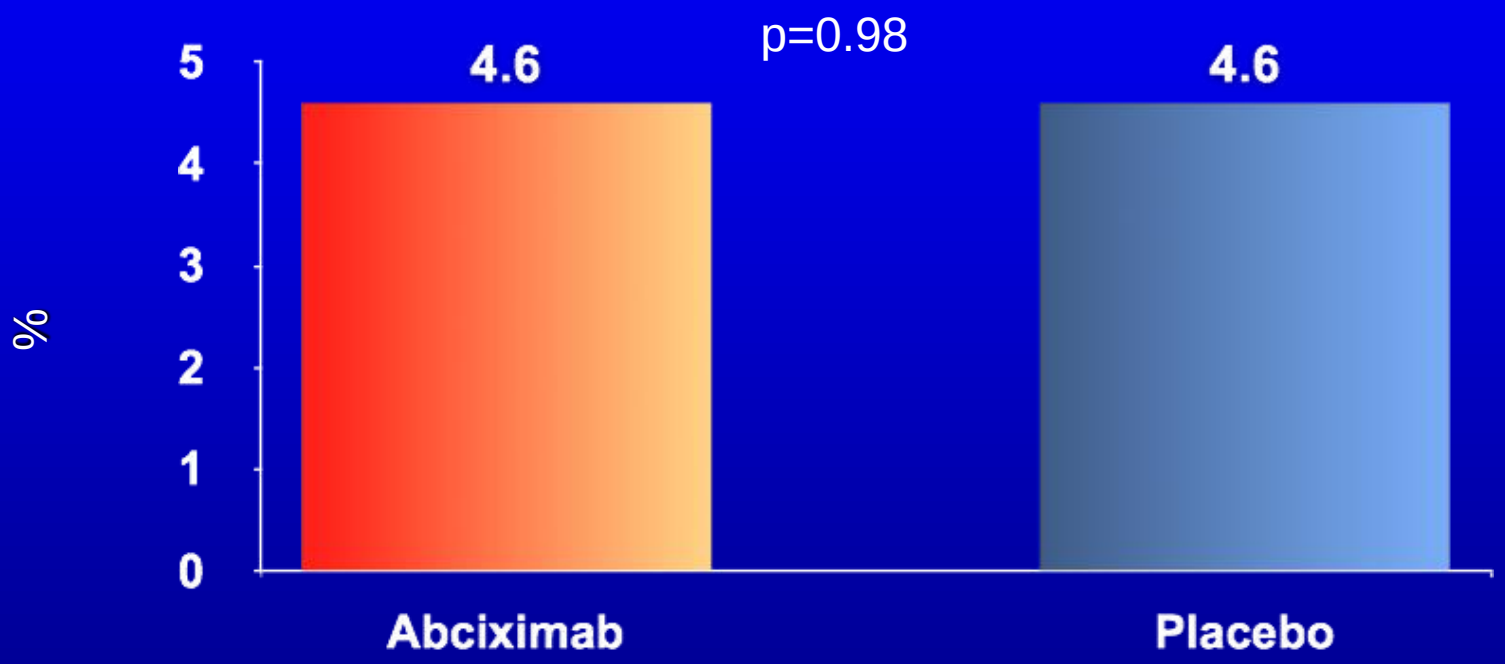


- The composite endpoint of death or MI was also significantly reduced in the abciximab group compared to placebo (8.6% vs 11.5%; RR 0.75; p<0.05)

Presented at ACC 2006

ISAR-REACT 2 Trial: Primary Endpoint (subgroup)

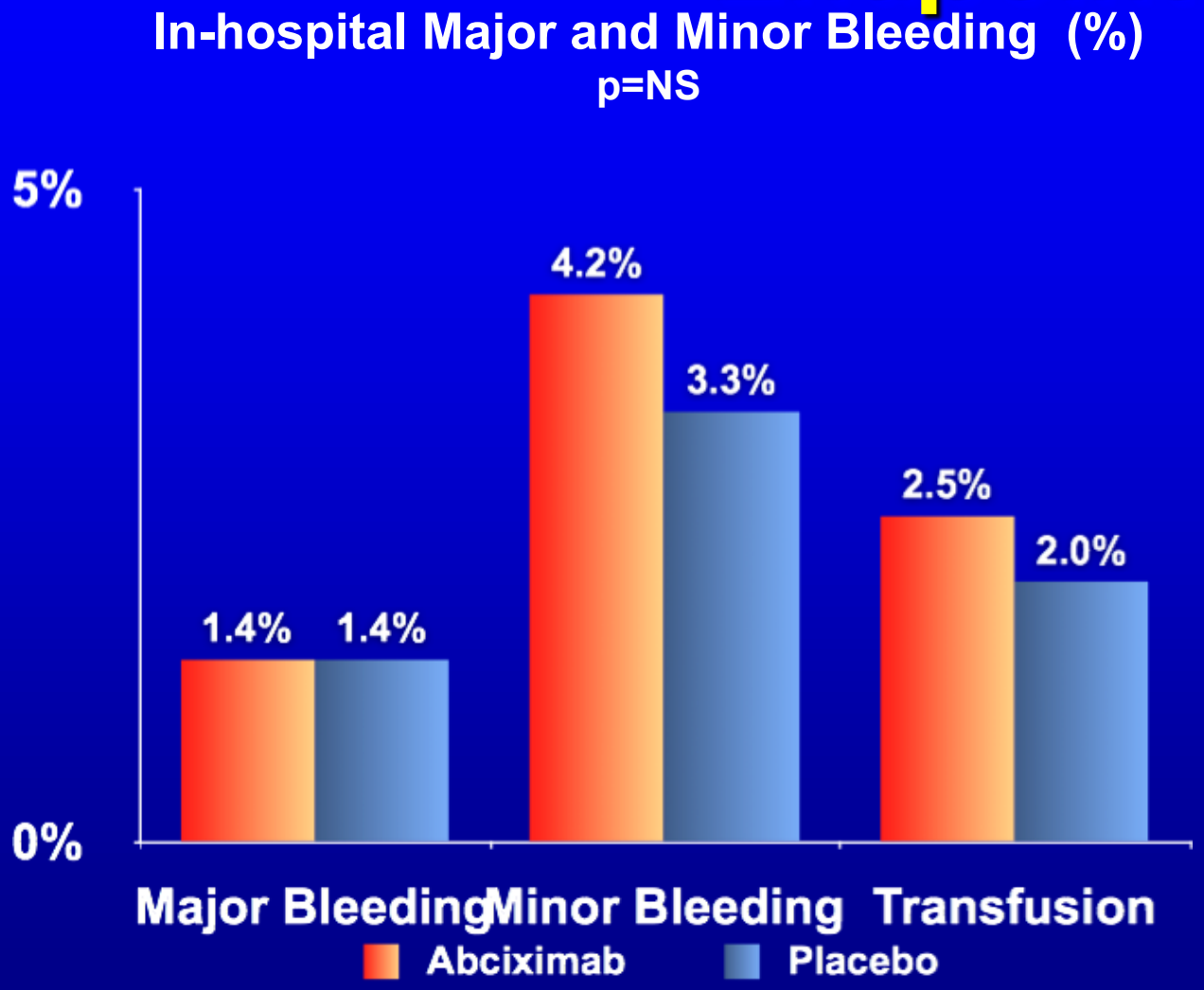
Primary endpoint in troponin negative patients (defined as <0.03µg/L, n=973)



- There was no difference seen in patients who were troponin negative at baseline (4.6% each; RR 0.99; p=0.98; interaction p=0.07)

Presented at ACC 2006

ISAR-REACT 2 Trial: Secondary Endpoint

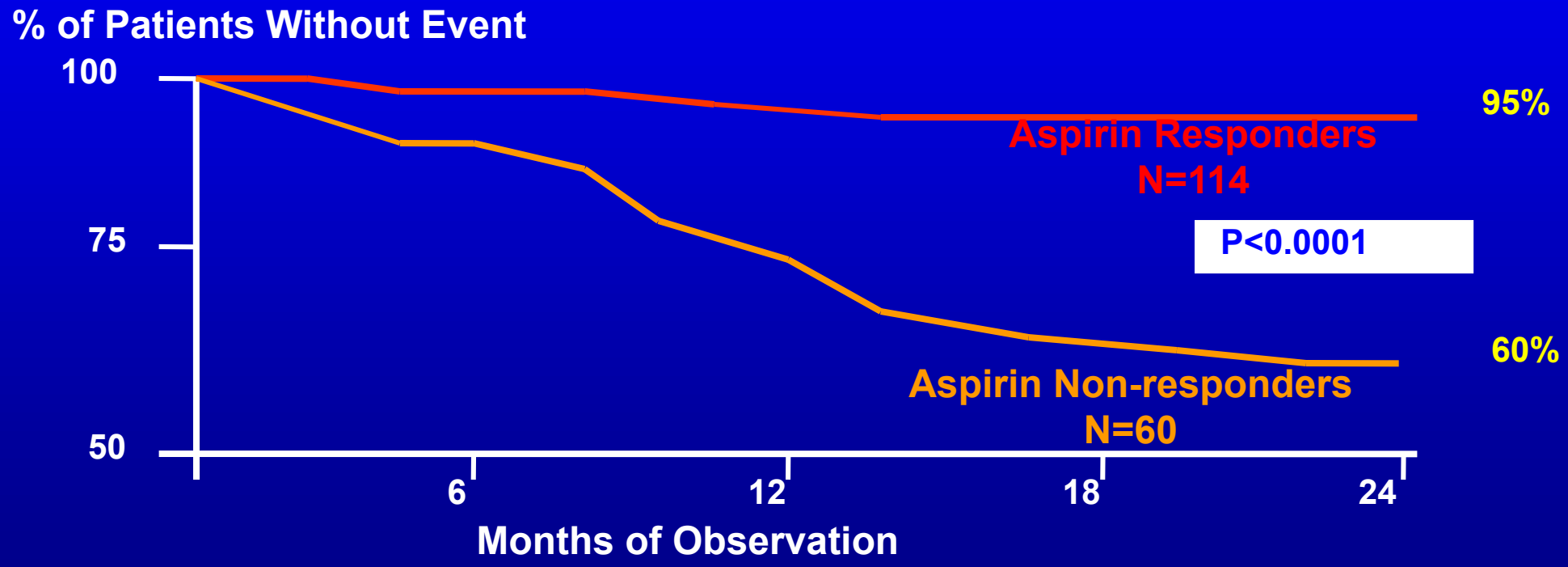


- There was no difference between the abciximab and placebo groups in in-hospital major and minor bleeding (p=NS for both).
- There was one intracranial bleed in each group.
- 2.5% of patients received transfusions in the abciximab group compared with 2.0% in the placebo group (RR 1.25)

Presented at ACC 2006

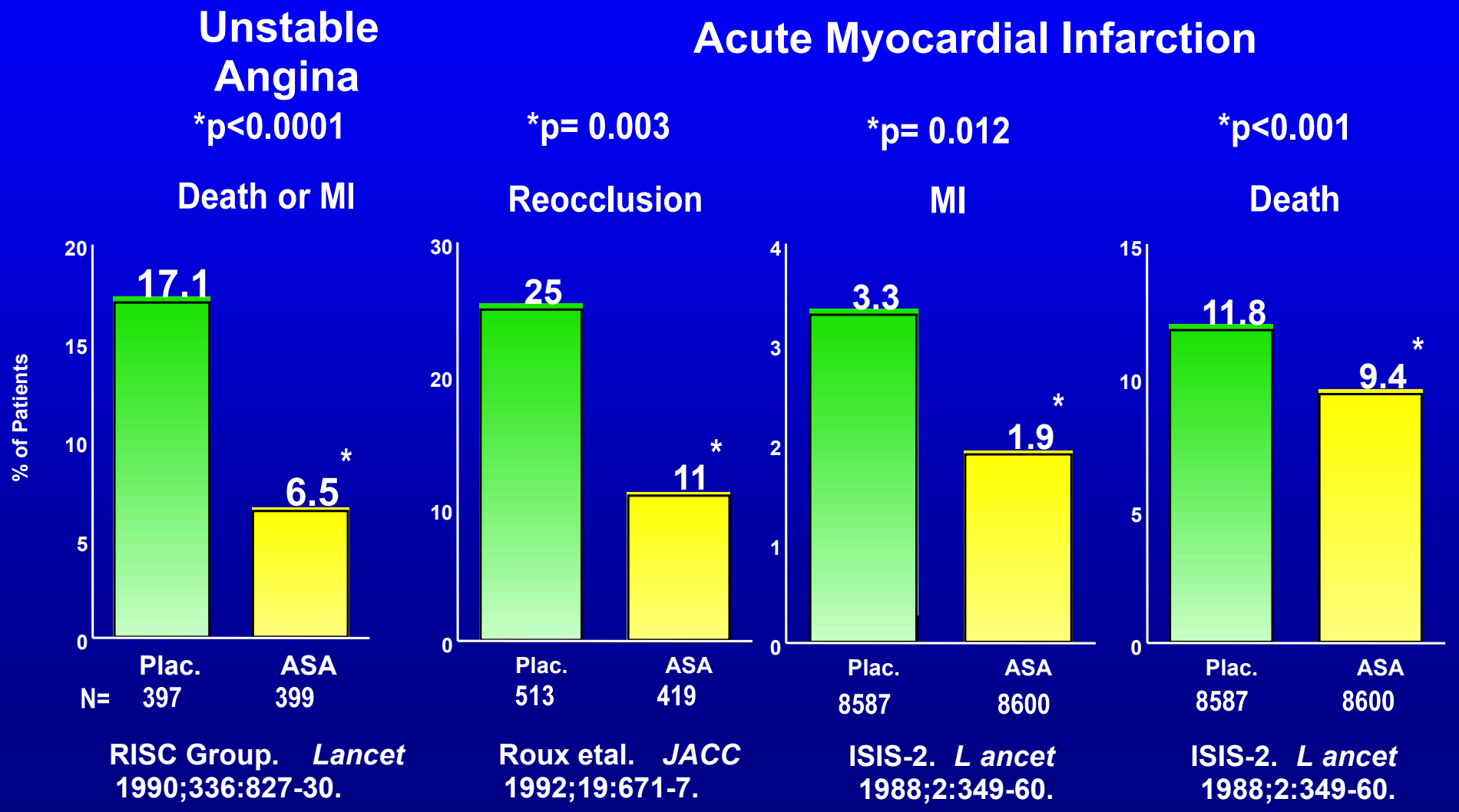
Aspirin Responsiveness and Clinical Outcome

181 patients, following CVA. Aspirin 500 mg TID.
Followed-up for 24 months.

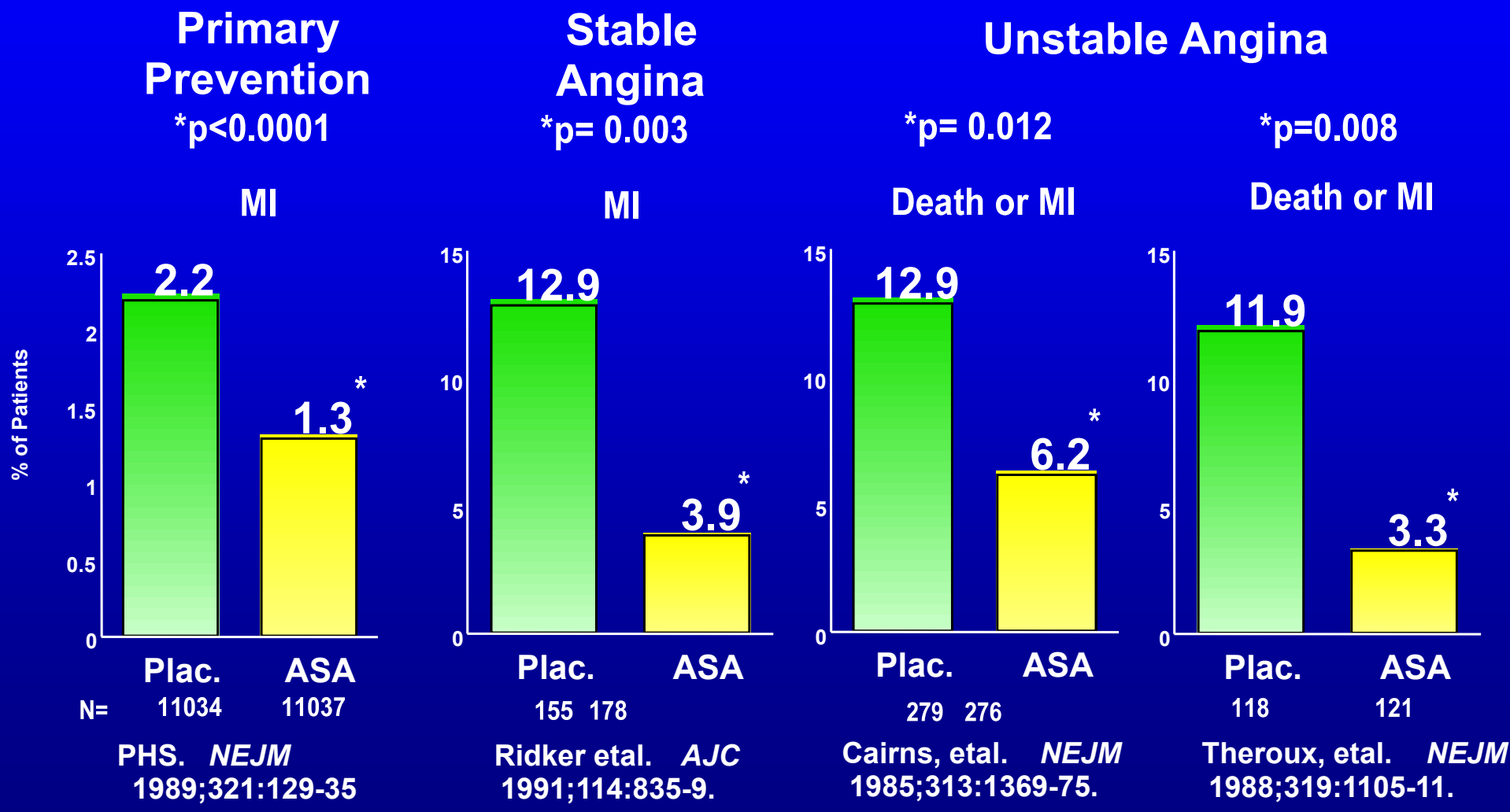


Grotemeyer, Thrombosis Research 1993;71:397

Aspirin in Acute Coronary Syndromes



Aspirin in Acute Coronary Syndromes

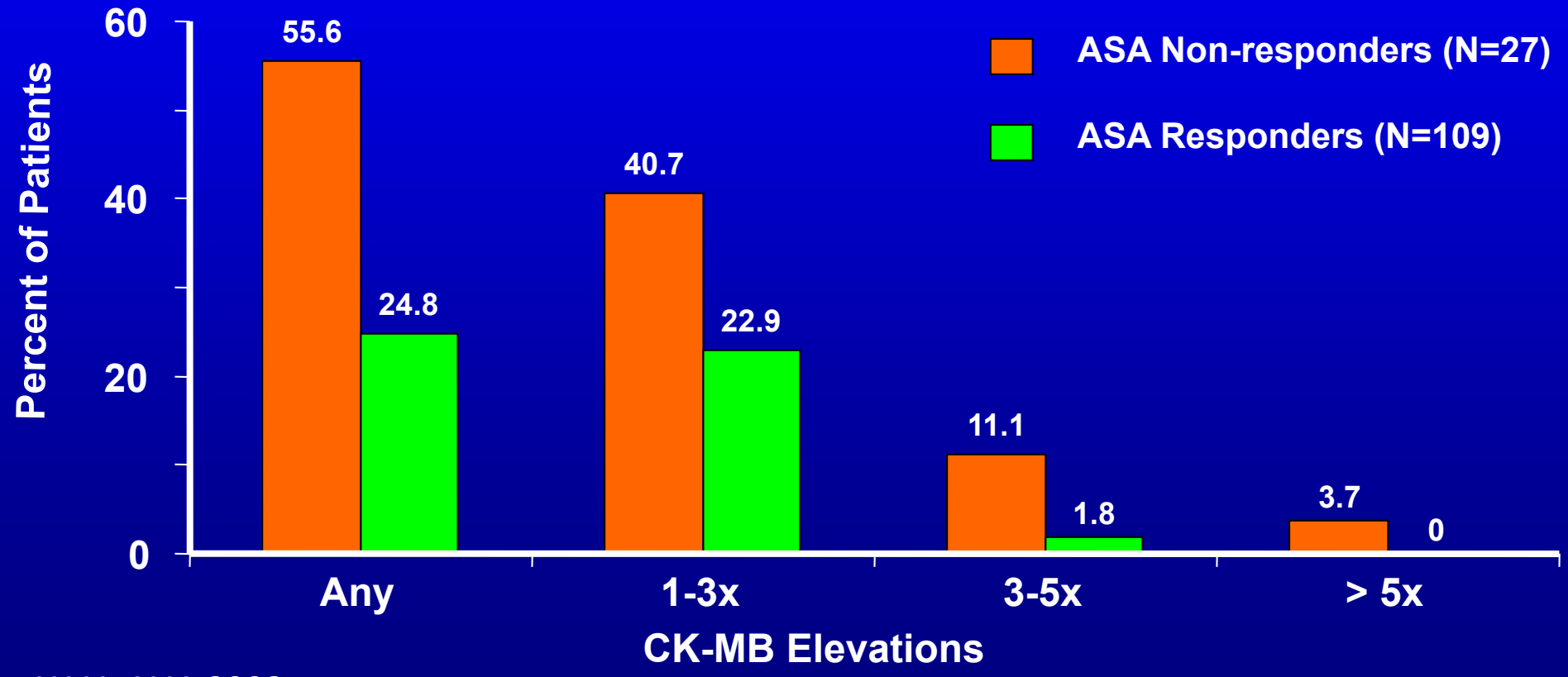


ASA resistance associated with increased CK and TnI post PCI

- 151 pts undergoing PCI
- 29 pts (19.2%) ASA resistant
- Clopidogrel 300 mg given >12 hrs prior

CK Elevations Post PCI

136 patients undergoing elective PCI. No GpIIb/IIIa, and 300mg clopidogrel >12 hours prior to PCI.



Chen W-H. AHA 2003

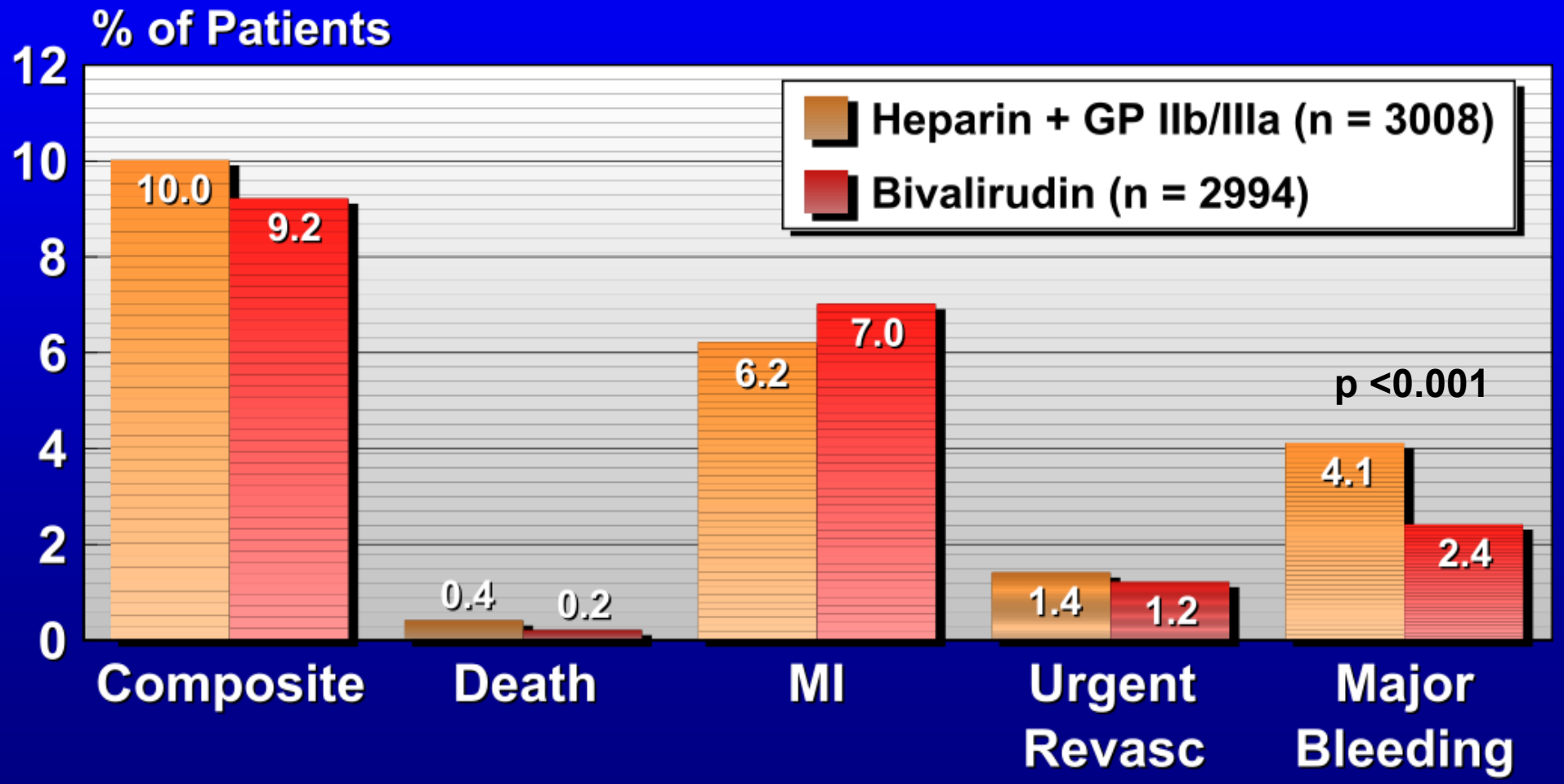
ASA resistance CK-MB and TnI

	ASA Resistant	ASA Sensitive	p
CK-MB	51.7%	24.6%	P=0.006
TnI	65.5%	38.5%	P=0.012

REPLACE-2

Quadruple Endpoint

30 Day Primary Endpoint Components



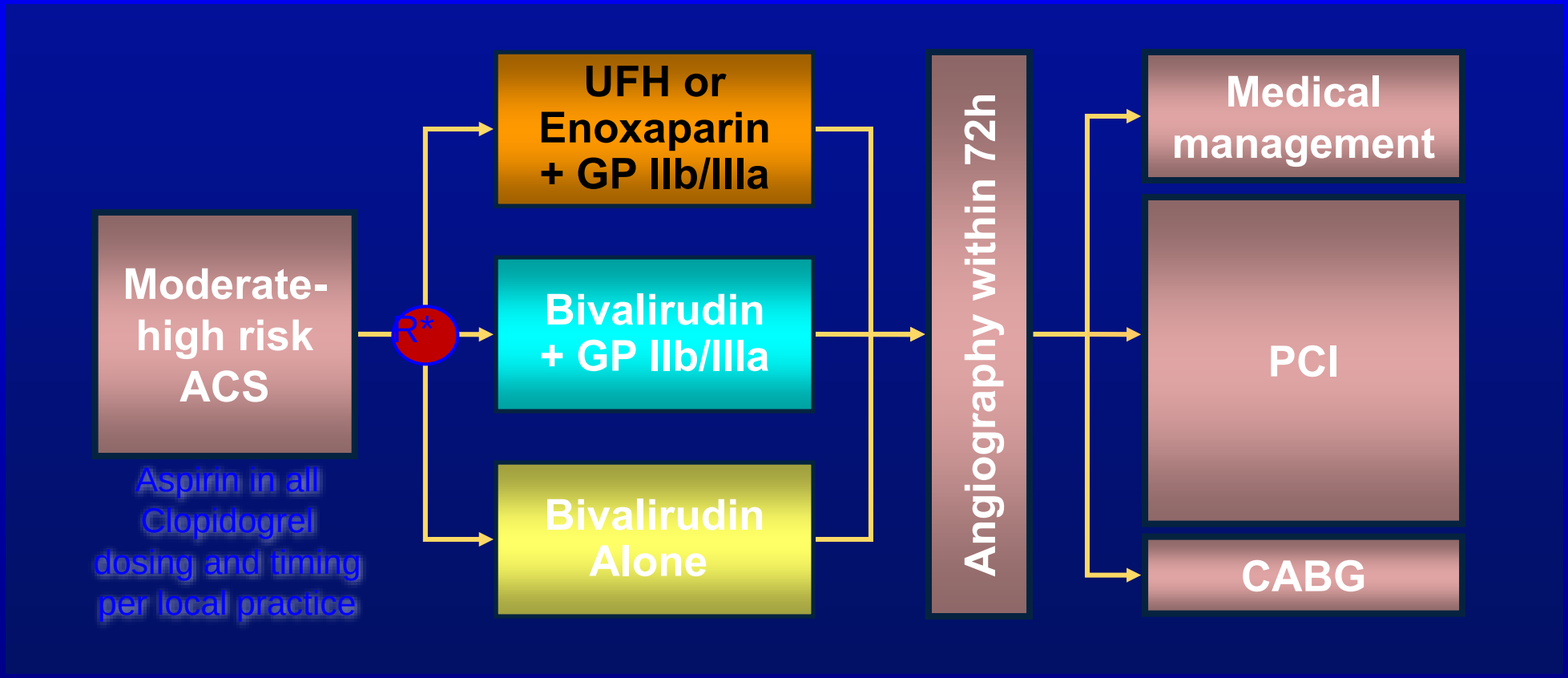
Bivalirudin as an Alternative to UFH/LMWH

- Advantages of the direct thrombin inhibitor bivalirudin
  - No requirement for anti-thrombin III
  - Effective on clot-bound thrombin
  - Inhibits thrombin-mediated platelet activation
  - No interactions with PF-4
  - Plasma half-life 25 minutes
  - No requirement for anticoagulant monitoring
- Clinical results with bivalirudin in PCI
  - Similar protection from ischemic events as UFH + GP IIb/IIIa inhibitors, with markedly reduced bleeding[1]
- Not previously tested in contemporary ACS patients

REPLACE 2. Lincoff AM et al. JAMA 2003;289:853-863

Study Design – First Randomization

Moderate-high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,800)

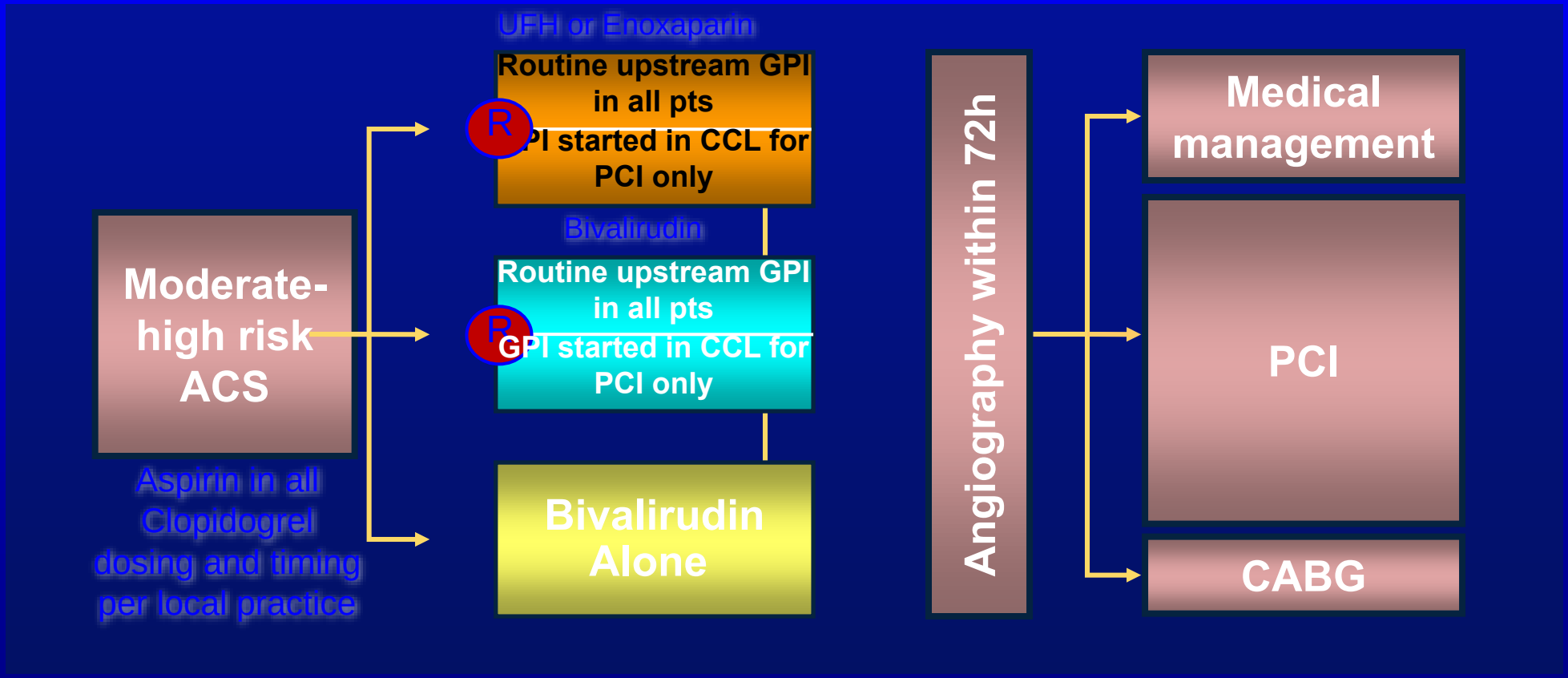


*Stratified by pre-angiography thienopyridine use or administration

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

Study Design – Second Randomization

Moderate-high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,800)



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

3 Primary Endpoints (at 30 Days)

1. Composite net clinical benefit =

or

2. Ischemic composite

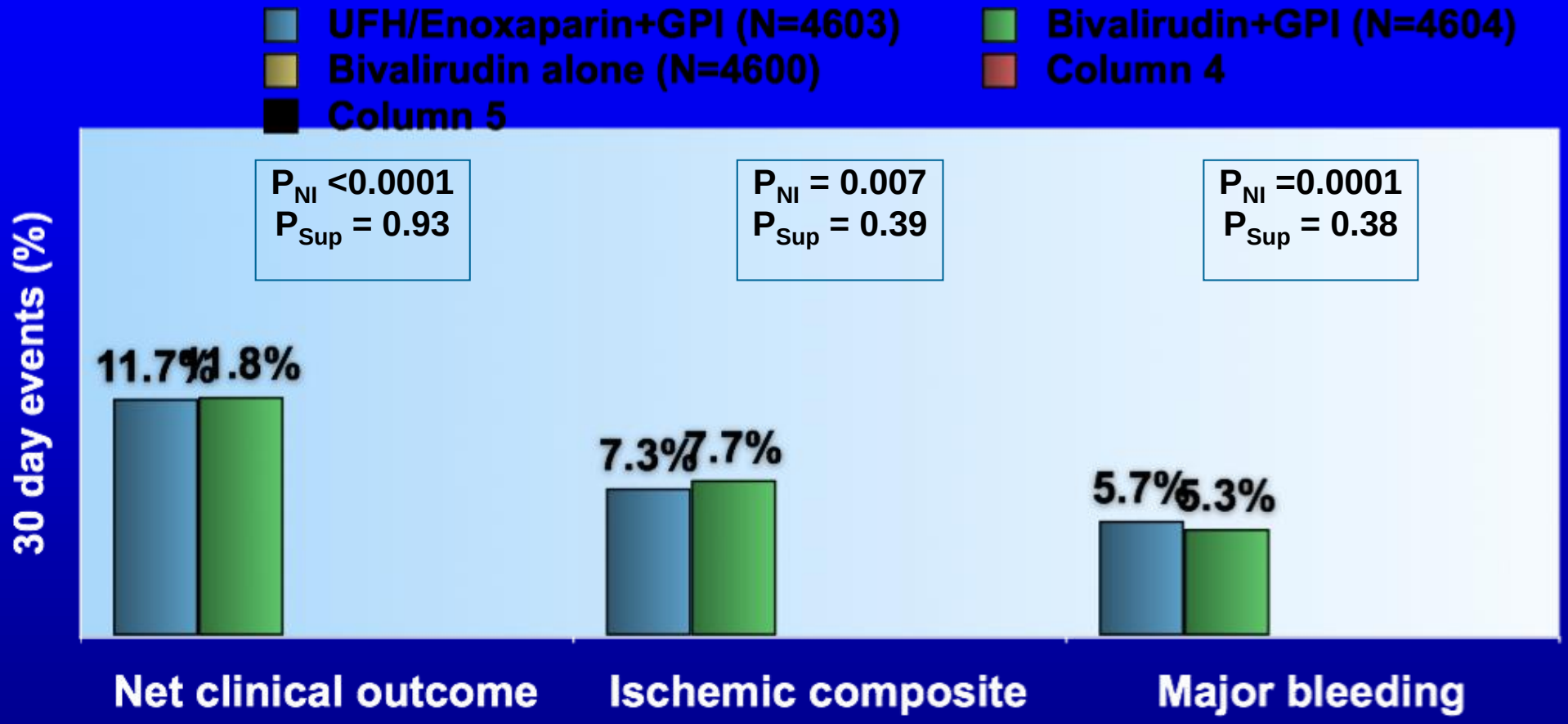
or

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

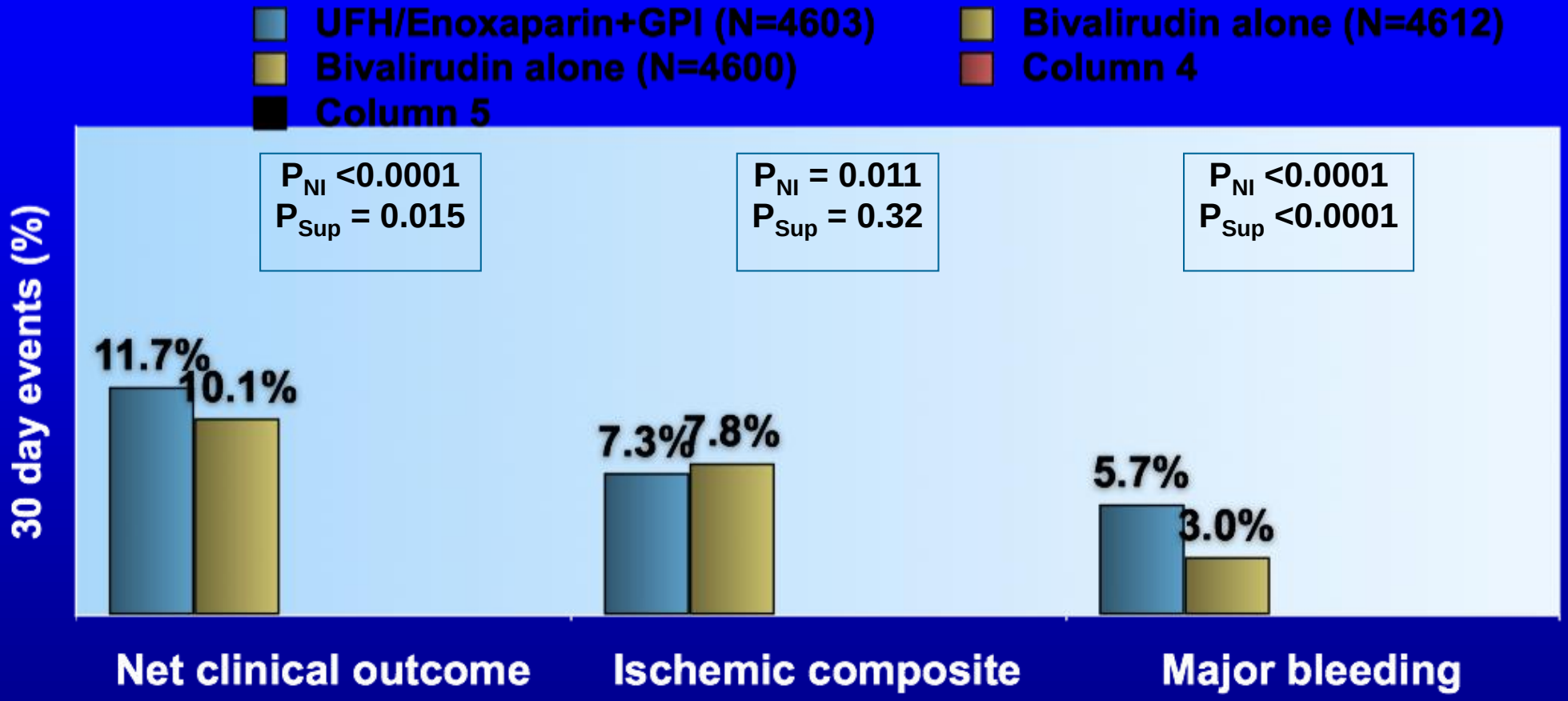
UFH/Enoxaparin + GPI vs. Bivalirudin + GPI

Primary Endpoint Measures (ITT)



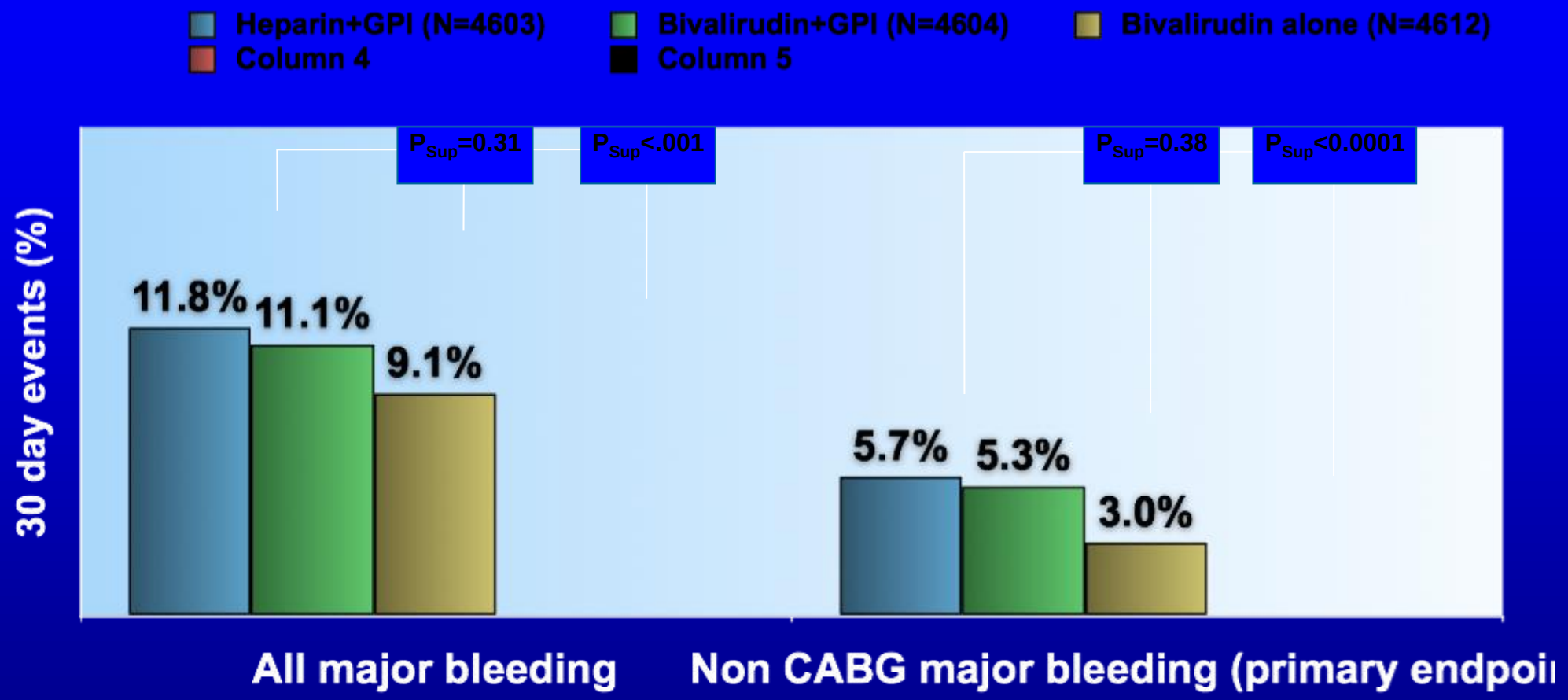
UFH/Enoxaparin + GPI vs. Bivalirudin Alone

Primary Endpoint Measures (ITT)



Major Bleeding Endpoints

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



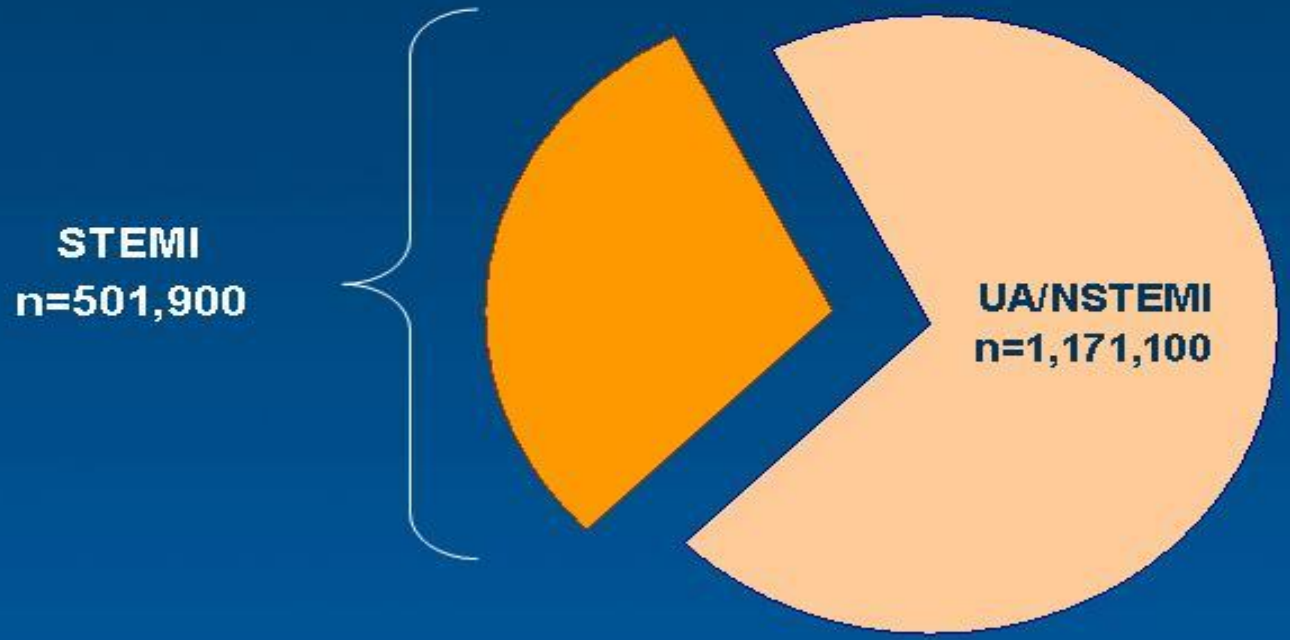
Conclusions: Primary Results

	UFH/Enox + GP IIb/IIIa	Bivalirudin + GP IIb/IIIa		Bivalirudin alone	
Observed Endpoint	Rate	Rate	P Value	Rate	P Value
Net clinical outcome	11.7%	11.8%	<0.001 NI	10.1%	0.015 Sup
Ischemic events	7.3%	7.7%	0.007 NI	7.8%	0.011 NI
Major bleeding	5.7%	5.3%	0.001 NI	3.0%	<0.001 Sup

NI = non-inferiority; Sup = superiority

The Place of STEMI in the ACS Management Spectrum

- Each year 501,900 ACS patients experience STEMI
- This accounts for about 30% of ACS



AHA. *Heart Disease and Stroke Statistics—2005 Update.* Available at: http://www.americanheart.org/downloadable/heart/1105390918119HDSStats2005Update.pdf. Accessed September 7, 2006.

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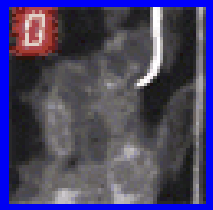
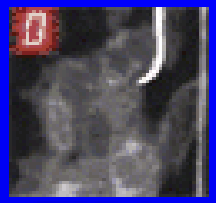
Restoration of "Normal" Epicardial Flow Yields Better Outcomes



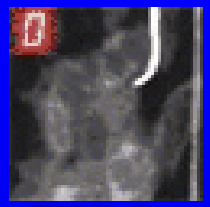
TIMI 0

Occlusion



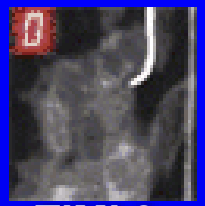
TIMI 1

Penetration



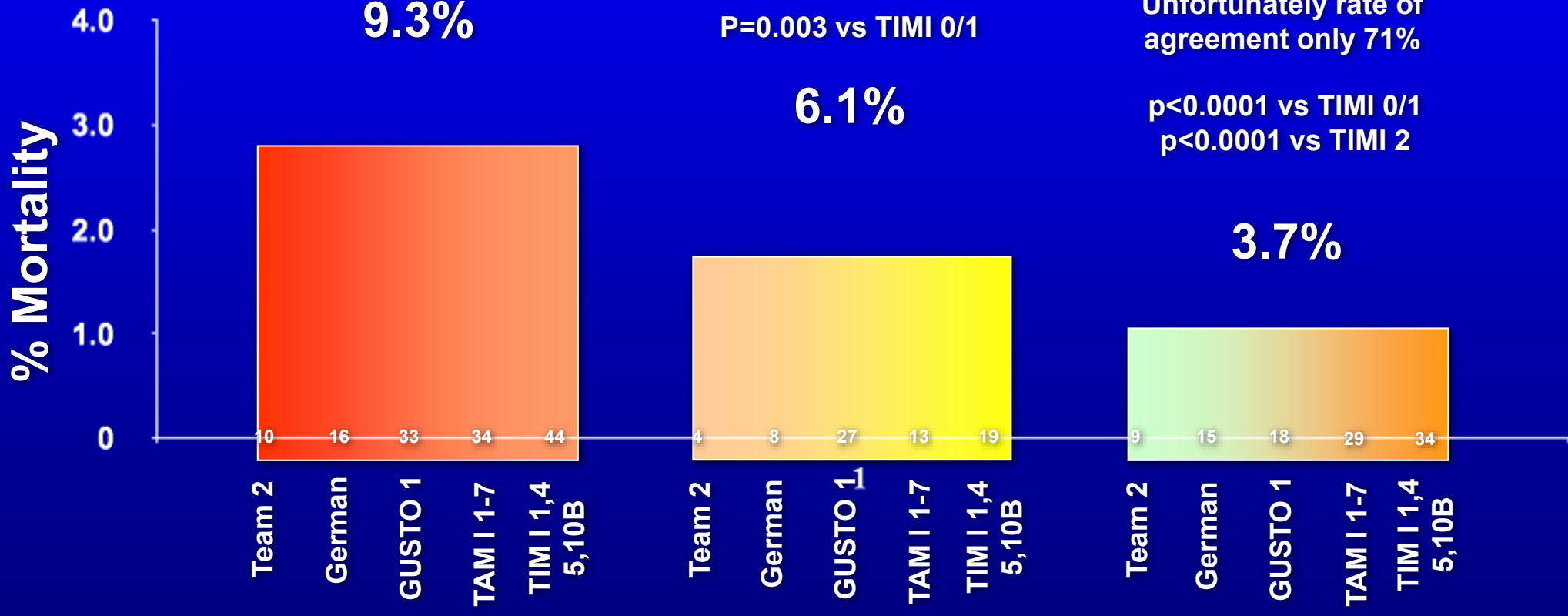
TIMI 2

Slow Flow



TIMI 3

Normal Flow



CM Gibson 2001 in Braunwald Heart Disease

ACC/AHA Guidelines and Antithrombins in STEMI

- In the management of STEMI patients, the ACC/AHA guidelines support the use of both UFH and LMWH as potential ancillary therapy to reperfusion therapy

Please see full prescribing information for enoxaparin, including boxed WARNING

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ACC/AHA Guidelines for STEMI
Antithrombotics

Class I

- IV UFH or LMWH should be used in patients after STEMI who are at high risk for systemic emboli (large or anterior MI, AF, previous embolus, known LV thrombus, or cardiogenic shock) (Level of Evidence: C)

Class IIa

- It is reasonable that STEMI patients not undergoing reperfusion therapy who do not have a contraindication to anticoagulation be treated with IV or SC UFH or with SC LMWH for at least 48 hours (Level of Evidence: C)
- In patients whose clinical condition necessitates prolonged bedrest and/or minimized activities, it is reasonable that treatment be continued until the patient is ambulatory (Level of Evidence: C)

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Antman EM et al. *J Am Coll Cardiol.* 2004;44:1-211.

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ACC/AHA Guidelines for STEMI
UFH as Ancillary Therapy to Reperfusion

Class I

- Patients undergoing percutaneous or surgical revascularization should be given UFH (Level of Evidence: C)
- IV UFH to patients undergoing reperfusion therapy with alteplase, reteplase, or tenecteplase (Level of Evidence: C)
- IV UFH for patients treated with nonselective fibrinolytic agents (SK, anistreplase, or urokinase) who are at high risk for systemic emboli (Level of Evidence: B)
- Platelet counts should be monitored daily in patients taking UFH (Level of Evidence: C)

Class IIb

- It may be reasonable to administer IV UFH to patients undergoing reperfusion therapy with streptokinase (Level of Evidence: B)

SK, streptokinase.
Antman EM et al. *J Am Coll Cardiol.* 2004;44:1-211.

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ACC/AHA Guidelines for STEMI
LMWH as Ancillary Therapy to Reperfusion

Class IIb

- **LMWH might be considered an acceptable alternative to UFH as ancillary therapy for patients less than 75 years of age who are receiving fibrinolytic therapy**, provided that significant renal dysfunction (serum creatinine greater than 2.5 mg/dL in men or 2.0 mg/dL in women) is not present (Level of Evidence: B)
- **Enoxaparin (30 mg IV bolus plus 1 mg/kg SC dose followed by 1 mg/kg subcutaneous injection every 12 hours until hospital discharge) with full-dose tenecteplase is the most comprehensively studied regimen in patients less than 75 years of age** (Level of Evidence: B)

Class III

- LMWH should not be used as an alternative to UFH as ancillary therapy in patients >75 years old who are receiving fibrinolytic therapy (Level of Evidence: B). LMWH should not be used as an alternative to UFH as ancillary therapy in patients <75 years old who are receiving fibrinolytic therapy but have significant renal dysfunction (SCr >2.5 mg/dL in men or 2.0 mg/dL in women) (Level of Evidence: B)

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Antman EM et al. *J Am Coll Cardiol.* 2004;44:1-211.

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Enoxaparin Dosing in STEMI Patients

STEMI DOSING FOR SPECIAL POPULATIONS	**STEMI dosing by patient population***	
	<75 years of age	**30 mg IV bolus** plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC every 12 hours†‡
	Elderly	
	≥75 years of age	**No initial IV bolus;** 0.75 mg/kg q12h SC†§
	Severe renal impairment (creatinine clearance <30 mL/min)	
	<75 years of age	**30 mg IV bolus** plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC once daily
	≥75 years of age	**No initial IV bolus;** 1 mg/kg SC once daily

- In ExTRACT-TIMI 25 the first SC dose was given within 15 minutes after the IV bolus dose

*All patients should receive oral ASA (aspirin) therapy as soon as they are identified as having STEMI and maintained with 75 to 325 mg once daily unless contraindicated.
†Enoxaparin was administered for a duration of 8 days or until hospital discharge, whichever came first.
‡Maximum 100 mg for the first 2 doses only.
§Maximum 75 mg for the first 2 doses only.

Please see full prescribing information for enoxaparin, including boxed WARNING

LOVENOX® (enoxaparin sodium injection) Prescribing Information. sanofi-aventis U.S. LLC. May 2007.

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Dosing for STEMI Patients

Thrombolytic therapy*	
When LOVENOX® (enoxaparin sodium injection) administered in conjunction with thrombolytic (fibrin-specific or non-fibrin specific)	Give LOVENOX® between 15 minutes before and 30 minutes after start of fibrinolytic therapy

Patients managed with PCI*

For patients managed with PCI, if the last LOVENOX® SC administration was given:

- <8 hours before balloon inflation: No additional dosing needed
- >8 hours before balloon inflation: Administer an IV bolus of 0.3 mg/kg of LOVENOX®

- In the pivotal clinical study (ExTRACT-TIMI 25), the LOVENOX® treatment duration was 8 days or until hospital discharge, whichever came first
- An optimal duration of treatment is not known, but it is likely to be longer than 8 days

*All patients should receive oral ASA (aspirin) therapy as soon as they are identified as having STEMI and maintained with 75 to 325 mg once daily unless contraindicated.

Please see full prescribing information for enoxaparin, including boxed WARNING

LOVENOX® (enoxaparin sodium injection) Prescribing Information. sanofi-aventis U.S. LLC. May 2007.

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ACC/AHA Guidelines: Management of STEMI Patients: Selecting Reperfusion Treatment

If presentation is <3 hours and there is no delay to an invasive strategy, there is no preference for either strategy

Fibrinolysis Generally Preferred

- Early presentation (≤3 hours from symptom onset and delay to invasive strategy)
- Invasive strategy not an option
  - Cath lab occupied or not available
  - Vascular access difficulties
  - No access to skilled PCI lab
- Delay to invasive strategy
  - Prolonged transport
  - Door-to-balloon >90 minutes
  - >1 hour vs fibrinolysis (fibrin-specific agent)

Invasive Strategy Generally Preferred

- Skilled PCI lab available with surgical backup
  - Door-to-balloon <90 minutes
- High risk from STEMI
  - Cardiogenic shock, Killip class ≥3
- Contraindications to fibrinolysis, including increased risk of bleeding and ICH
- Late presentation
  - >3 hours from symptom onset
- Diagnosis of STEMI is in doubt

ICH, intracerebral hemorrhage.
Killip class ≥3=pulmonary edema with rales involving >one third of the lung fields and systolic blood pressure of ≥90 mm Hg.
Antman EM et al. *J Am Coll Cardiol.* 2004;44:1-211.

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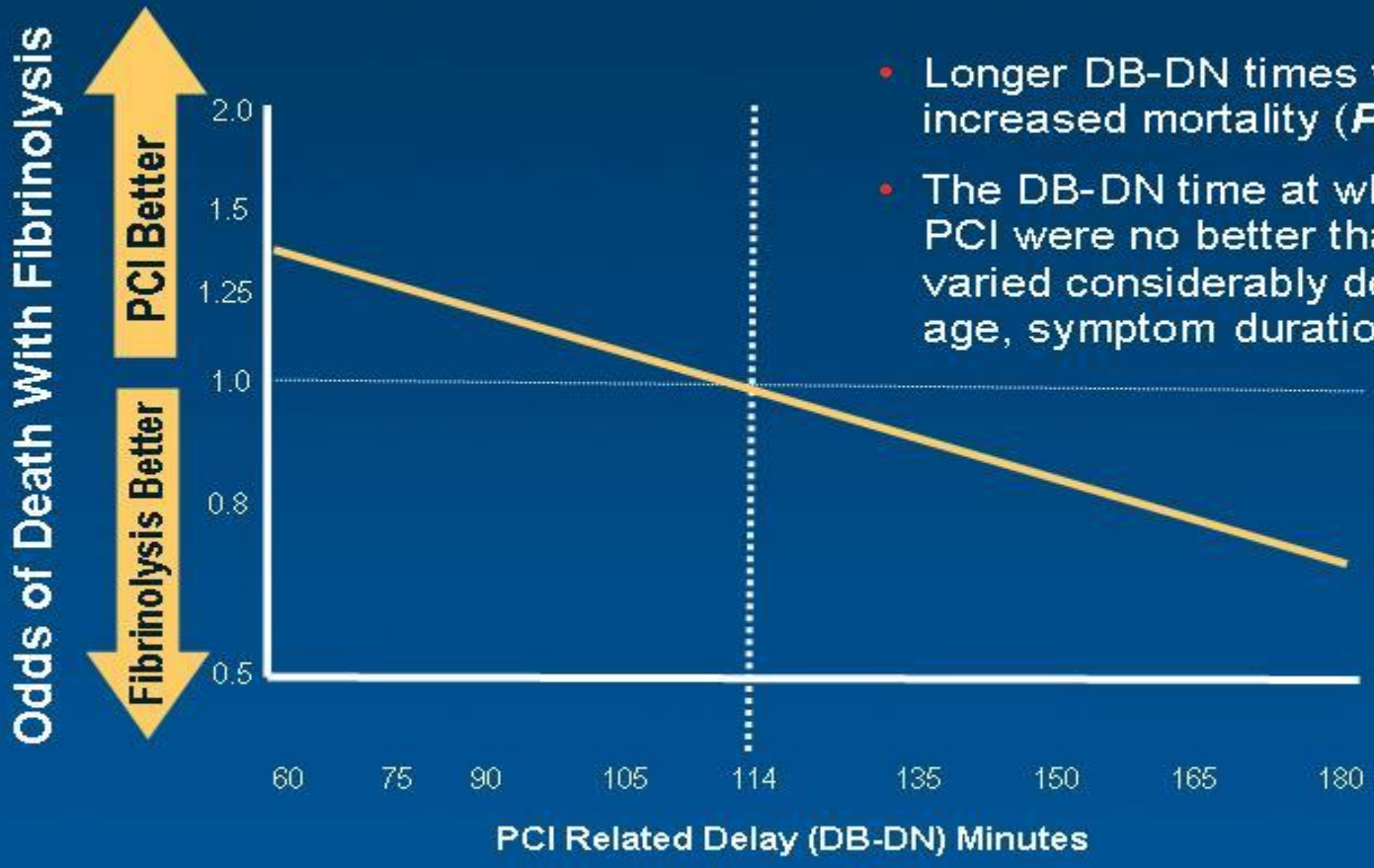
As Door-to-Balloon and Door-to-Needle Times Increase, the Mortality Advantage of PCI Over Fibrinolysis Declines



- Longer DB-DN times were associated with increased mortality (***P*<0.001**)
- The DB-DN time at which mortality rates with PCI were no better than that of fibrinolysis varied considerably depending on patient age, symptom duration, and infarct location

Data from 192,509 patients at 645 National Registry of Myocardial Infarction hospitals.

DB, door-to-balloon; DN, door-to-needle.

Pinto DS et al. *Circulation*. 2006;114:2019-2025.

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Door-to-Balloon Times Often Exceed 120 Minutes

CathPCI Registry™ data from ACC (voluntary enrollment)

PCI	Overall Mean	"Leading" Centers Mean (top 25%)	"Lagging" Centers Mean (bottom 25%)
Mean door-to-balloon time (DBT), minutes	143	92	144
Percentage of patients with DBT <90 min	51	64	37
Percentage of patients with DBT <120 min	73	85	66

- **Mean time to PCI based on Joint Commission Standardized Measures: 293 minutes**
- **Percentage of acute MI patients receiving PCI with 120 minutes of hospital arrival based on national Medicare and Medicaid data: 66%**

Rosamond W et al. *Circulation*. 2007;115:e69-e171.

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Thrombolysis Remains an Important Reperfusion Strategy Worldwide in STEMI Patients

	GRACE[1] (n=5476)	NRMI 3-4[2] (n=153,486)
Thrombolytic agent (%)	45.0	52.0*
Catheterization (%)	61.0	–
PCI	44.4	–
Primary PCI	–	48.0*
CABG (%)	5.0	–

*Of STEMI patients receiving early reperfusion therapy.

GRACE, Global Registry of Acute Coronary Events; NRMI, National Registry of Myocardial Infarction.

1. Goldberg RJ et al. *Am J Cardiol.* 2004;93:288-293.
2. Wiviott SD et al. *J Am Coll Cardiol.* 2004;44:783-789.

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AHA Multidisciplinary AMI Advisory Working Group, 2007

- Among patients who receive either PCI or fibrinolytic therapy in the United States, fewer than 50% are treated within the recommended time frames after arriving at the hospital
  - Fibrinolytic therapy is the mainstay of treatment due to its wide availability
  - Up to 30% of STEMI patients do not receive any reperfusion therapy despite availability and absence of contraindications
  - Up to 20% of patients with STEMI are not eligible for fibrinolytic therapy; yet 70% of these patients do not receive primary PCI, their only reperfusion option

"…these considerations… have fueled the concept of systems and centers of care for STEMI patients and the mounting enthusiasm for the potential benefits of regional STEMI networks."

Jacobs AK et al. *Circulation*. 2007;115:1-14 [EPub ahead of print].

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ExTRACT-TIMI 25 Protocol Design

STEMI < 6 h
Lytic eligible

ASA

Lytic choice by MD
(TNK, tPA, rPA, SK)

Double-blind, double-dummy

ENOX

< 75 y: 30 mg IV bolus
SC 1.0 mg / kg q 12 h (Hosp DC)

≥ 75 y: No bolus
SC 0.75 mg / kg q 12 h (Hosp DC)

CrCl ≤ 30: 1.0 mg / kg q 24 h

UFH

60 U / kg bolus (4000 U)
Inf 12 U / kg / h (1000 U / h)
Duration: at least 48 h
Cont'd at MD discretion

Day 30

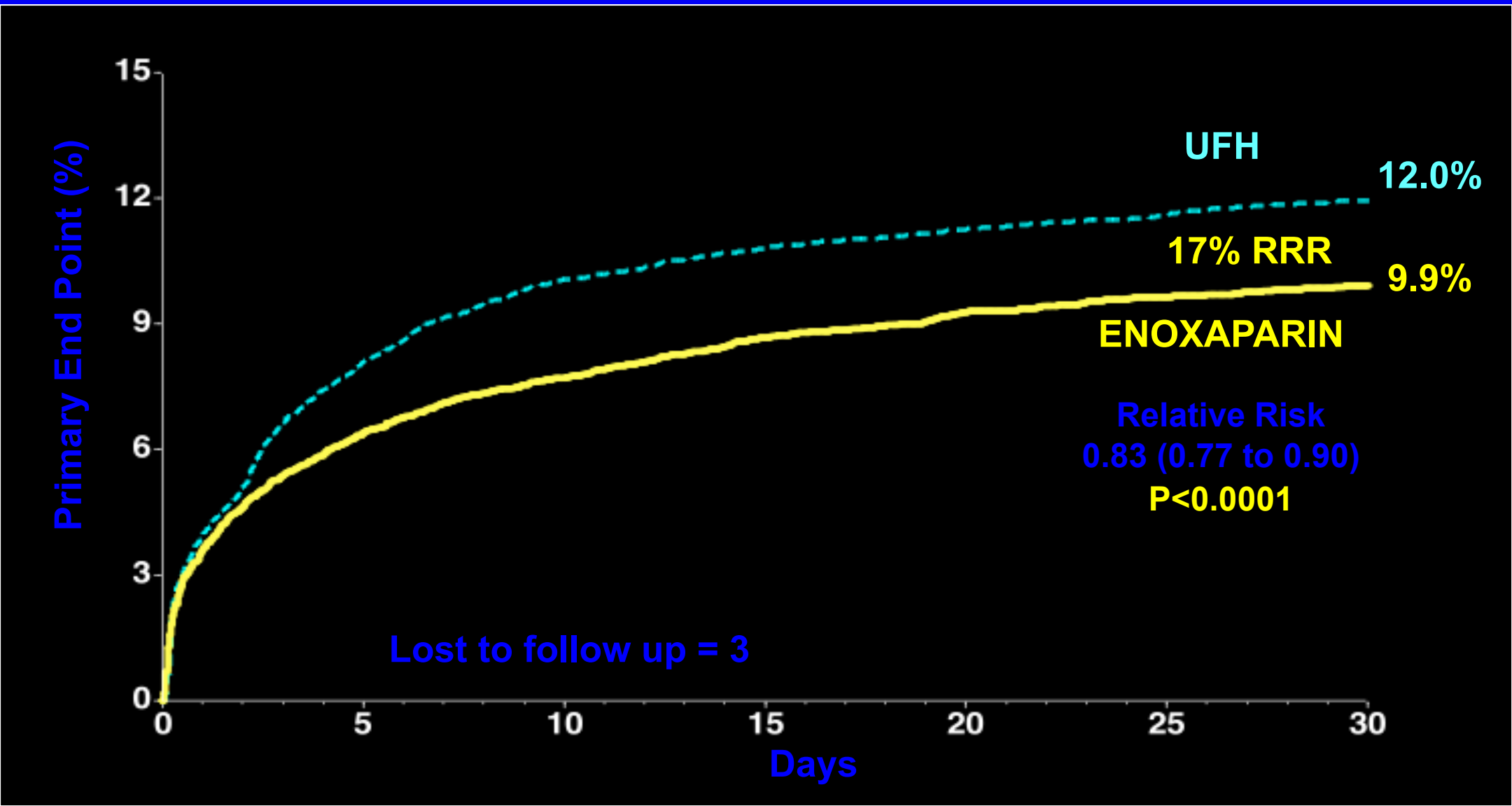
1° Efficacy Endpoint: Death or Nonfatal MI
1° Safety Endpoint: TIMI Major Hemorrhage

Medications
ITT N = 20,479

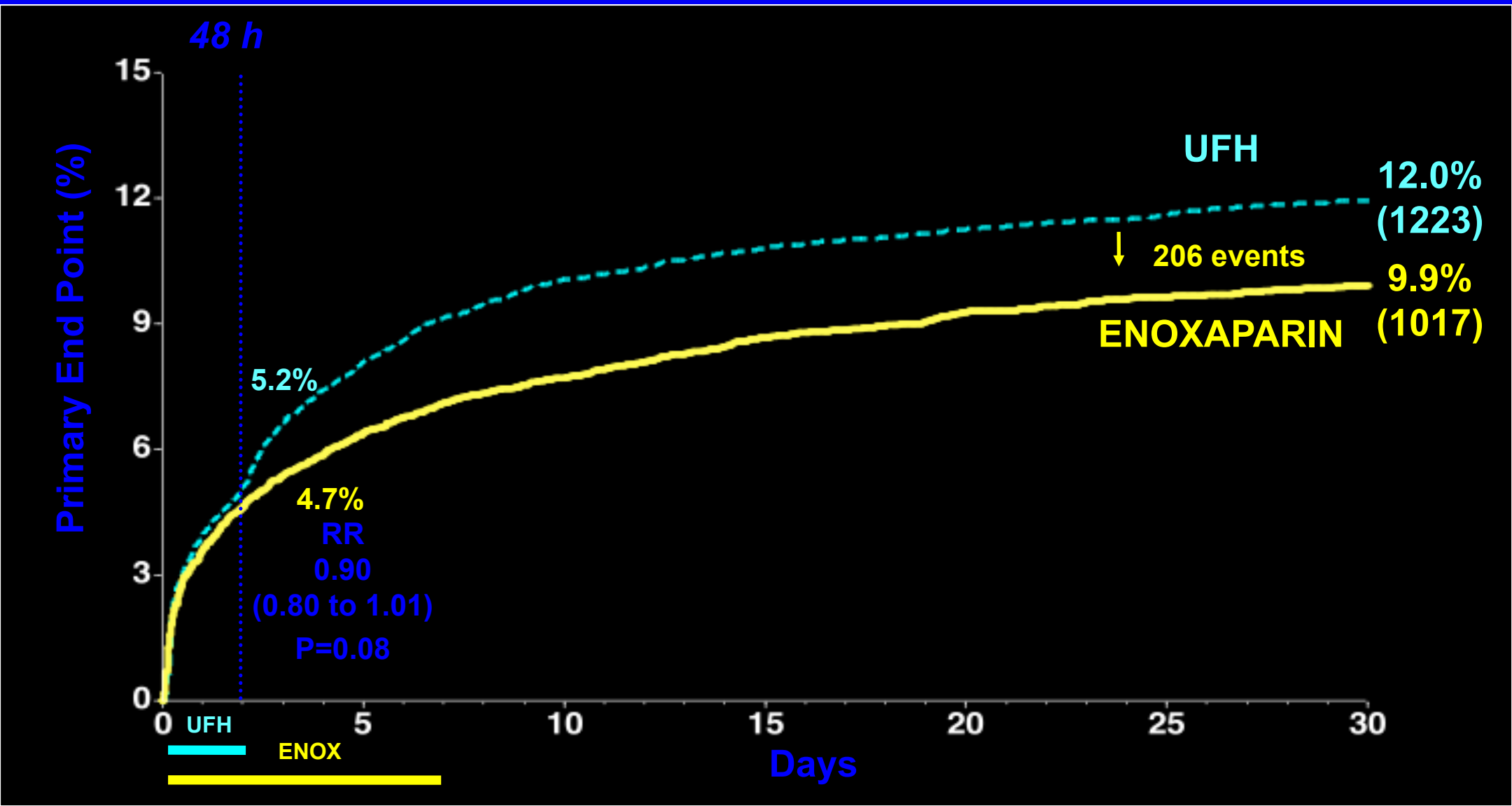
Fibrinolytic	
SK (%)	20
Fibrin-specific (%)	80
ASA (%)	95
Beta Blocker (%)	86
ACEI / ARB (%)	80
Statin (%)	70

ALL P = NS

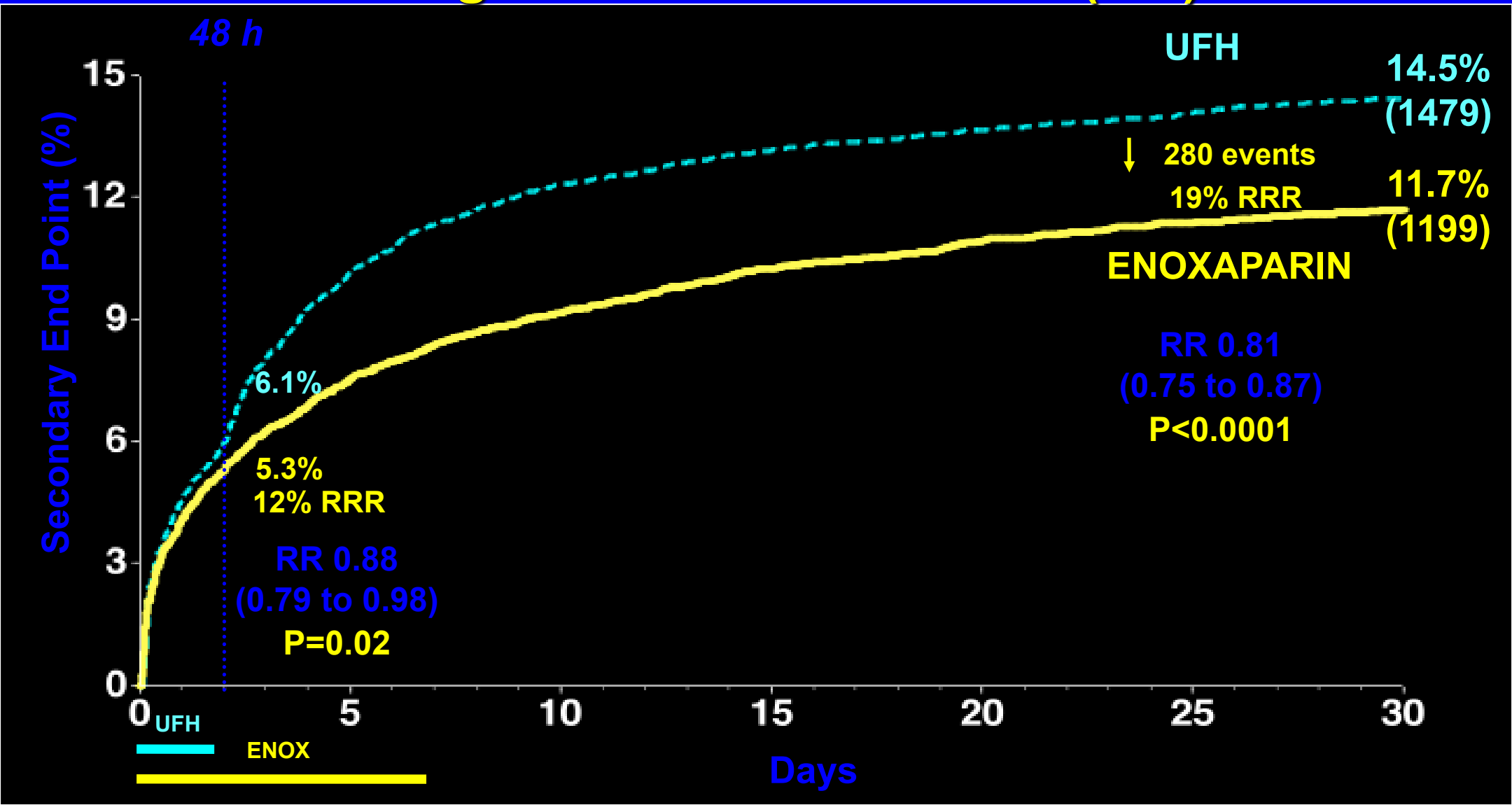
Primary End Point (ITT)
Death or Nonfatal MI



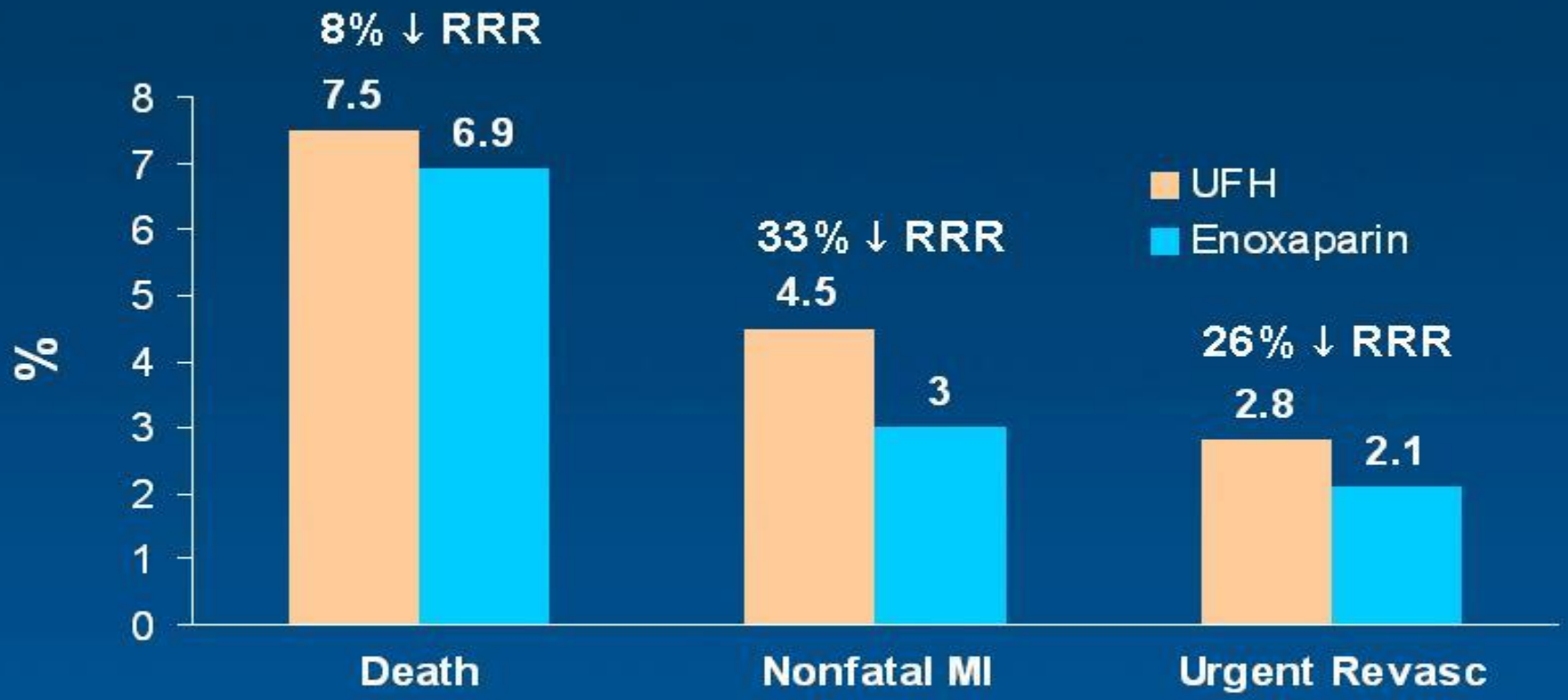
Treatment Benefit over Time (ITT)
Death or Nonfatal MI



Major Secondary End Point Death or Nonfatal MI or Urgent Revascularization (ITT)



ExTRACT-TIMI 25:
Outcomes at 30 Days (ITT)



	Death	Nonfatal MI	Urgent Revasc
RR	0.92	0.67	0.74
***P* value**	**0.11**	**<0.001**	**<0.001**

Please see full prescribing information for enoxaparin, including boxed WARNING

Antman EM et al. *N Engl J Med.* 2006;354:1477-1488.

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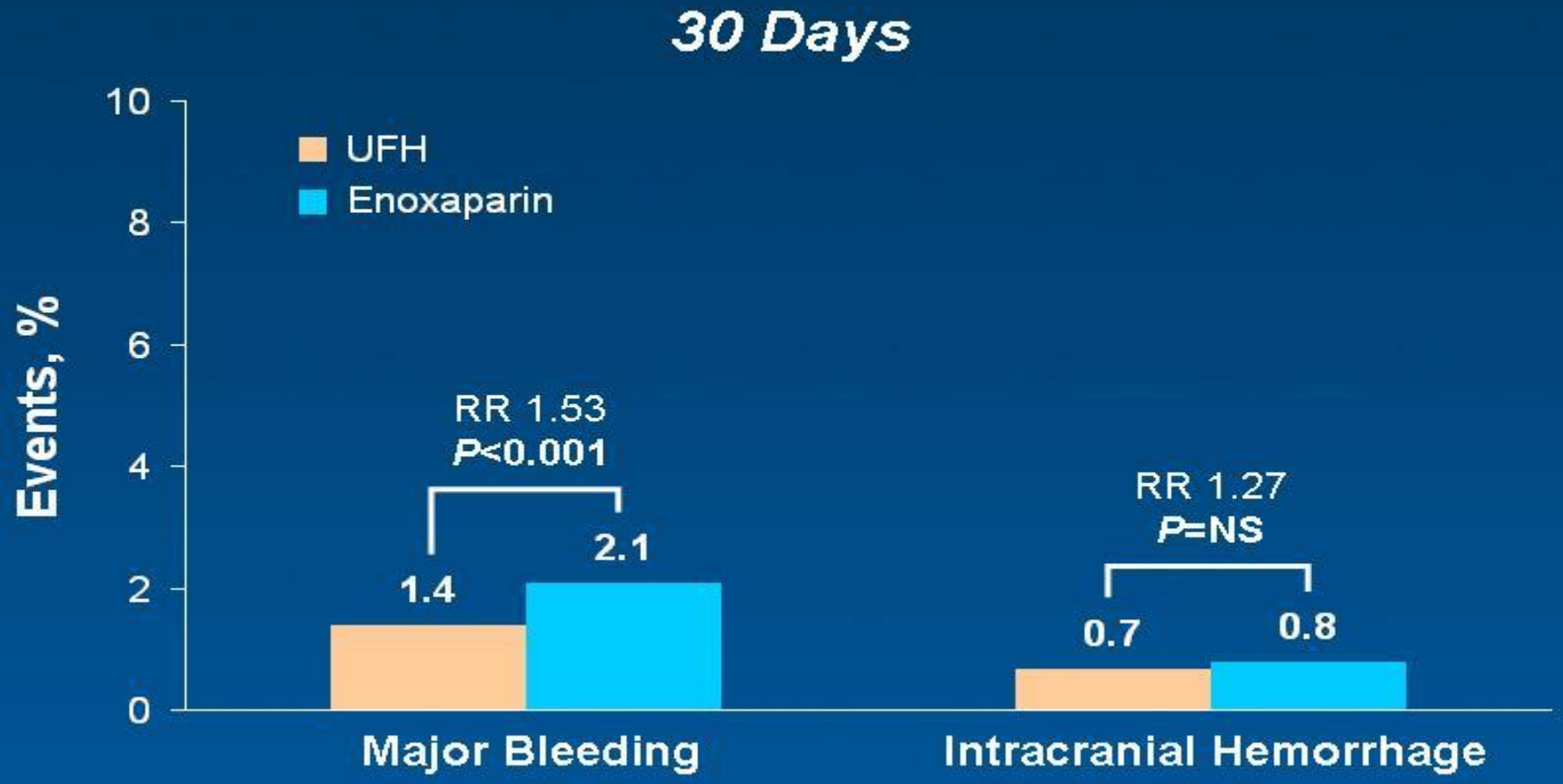
ExTRACT-TIMI 25:
Bleeding Endpoints (TIMI)



Please see full prescribing information for enoxaparin, including boxed WARNING

Antman EM et al. *N Engl J Med.* 2006;354:1477-1488.

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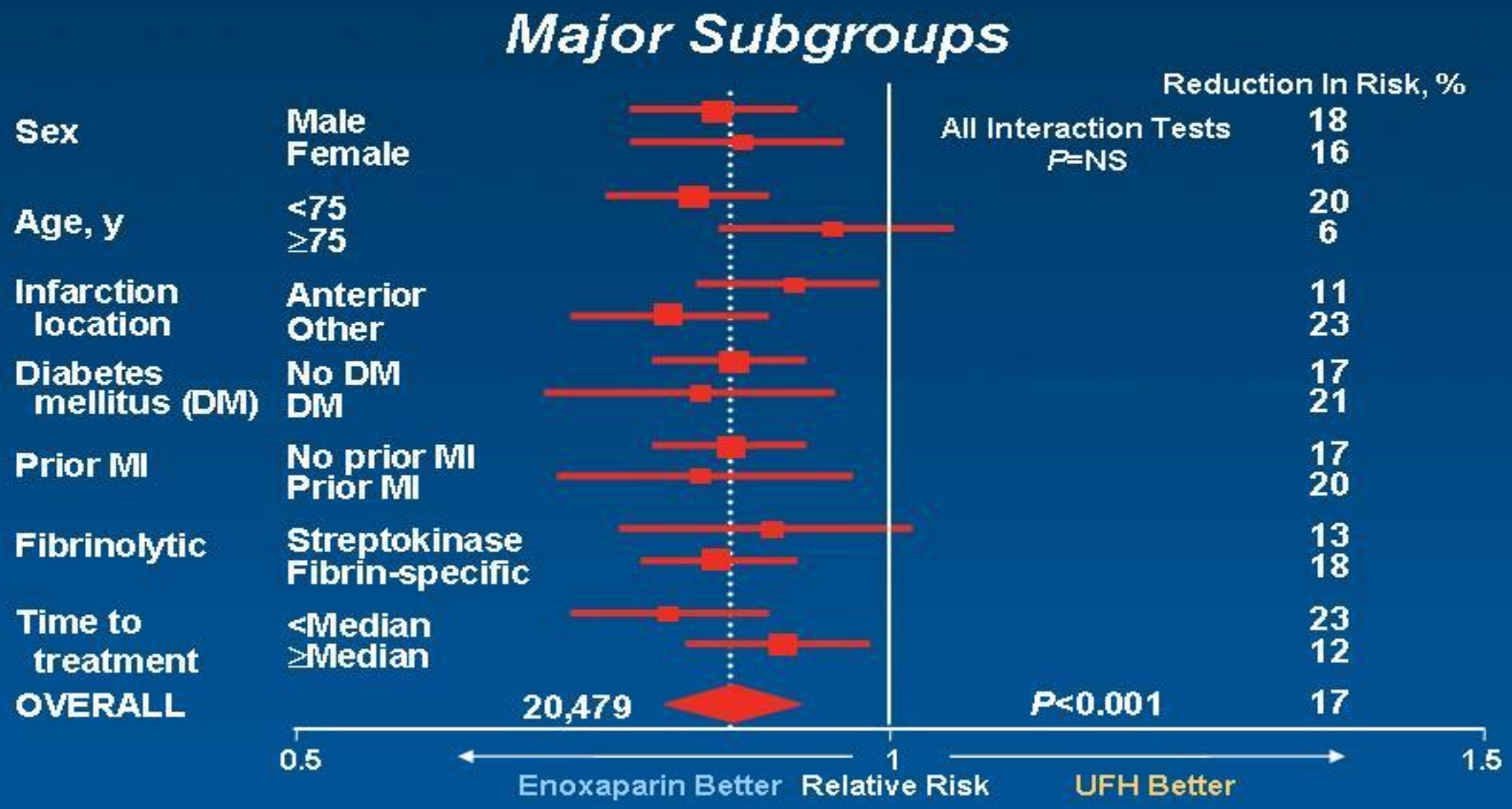
ExTRACT-TIMI 25:
Primary Endpoint in Various Subgroups – Day 30



Please see full prescribing information for enoxaparin, including boxed WARNING

Antman EM et al. *N Engl J Med.* 2006;354:1477-1488.

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ExTRACT-TIMI 25:
Efficacy Results for Patients ≥75 Years Old

Day 30

	UFH, % (n=1291)	Enoxaparin, % (n=1241)	RR, %
Death or nonfatal MI	26.3	24.8	6
Death/nonfatal MI/ urgent revascularization	28.4	26.0	8
Death/nonfatal MI/ major bleed	27.3	25.8	6

Efficacy analyses based on intent-to-treat cohort, prespecified to include all patients randomized for whom follow-up information was available.

Please see full prescribing information for enoxaparin, including boxed WARNING

White HD et al. *Eur Heart J.* 2007. [EPub in advance of print].

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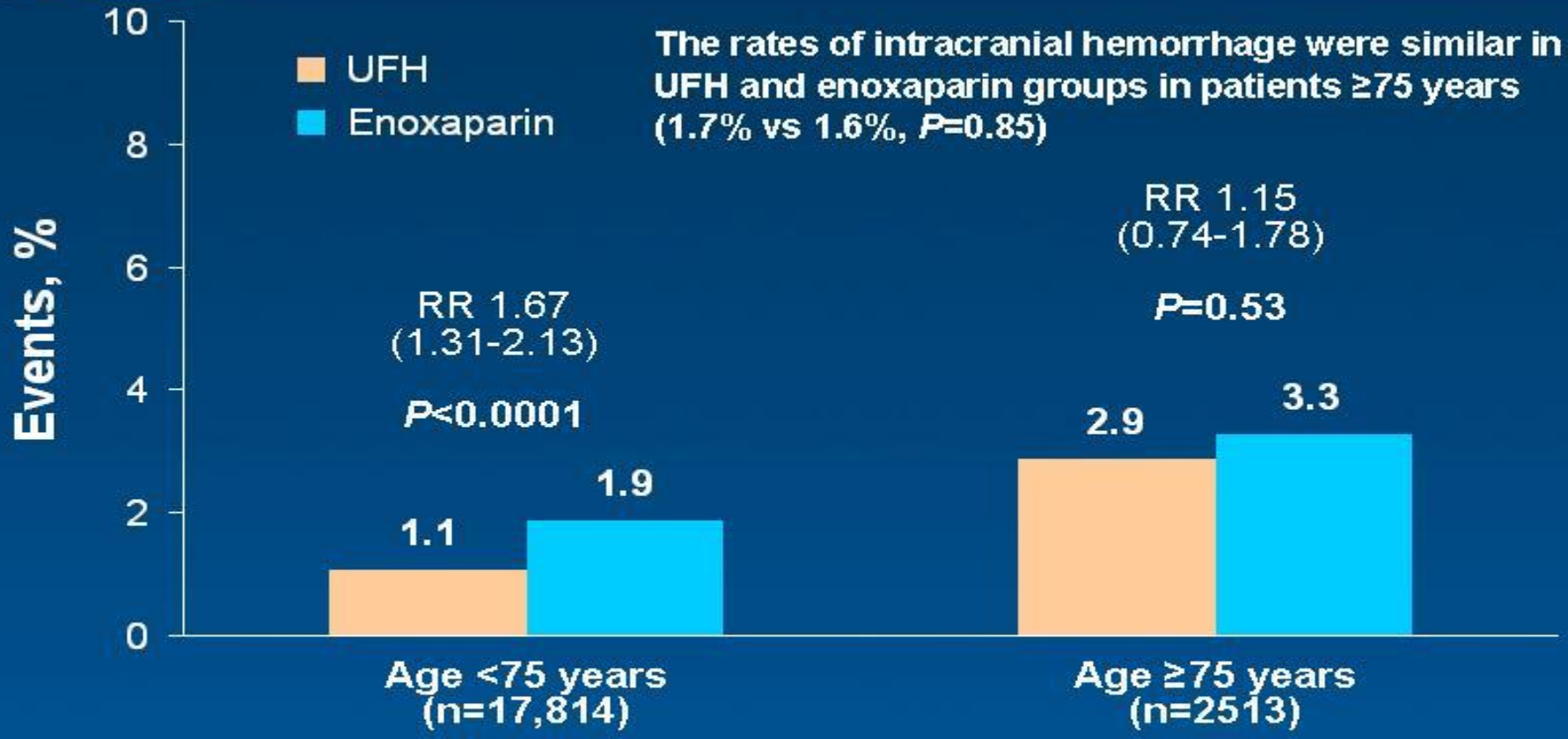
ExTRACT-TIMI 25:
Major Bleeding at 30 Days, Elderly and Younger Patients



Safety analyses were performed according to the treatment actually received.

Please see full prescribing information for enoxaparin, including boxed WARNING

White HD et al. *Eur Heart J.* 2007. [EPub in advance of print].

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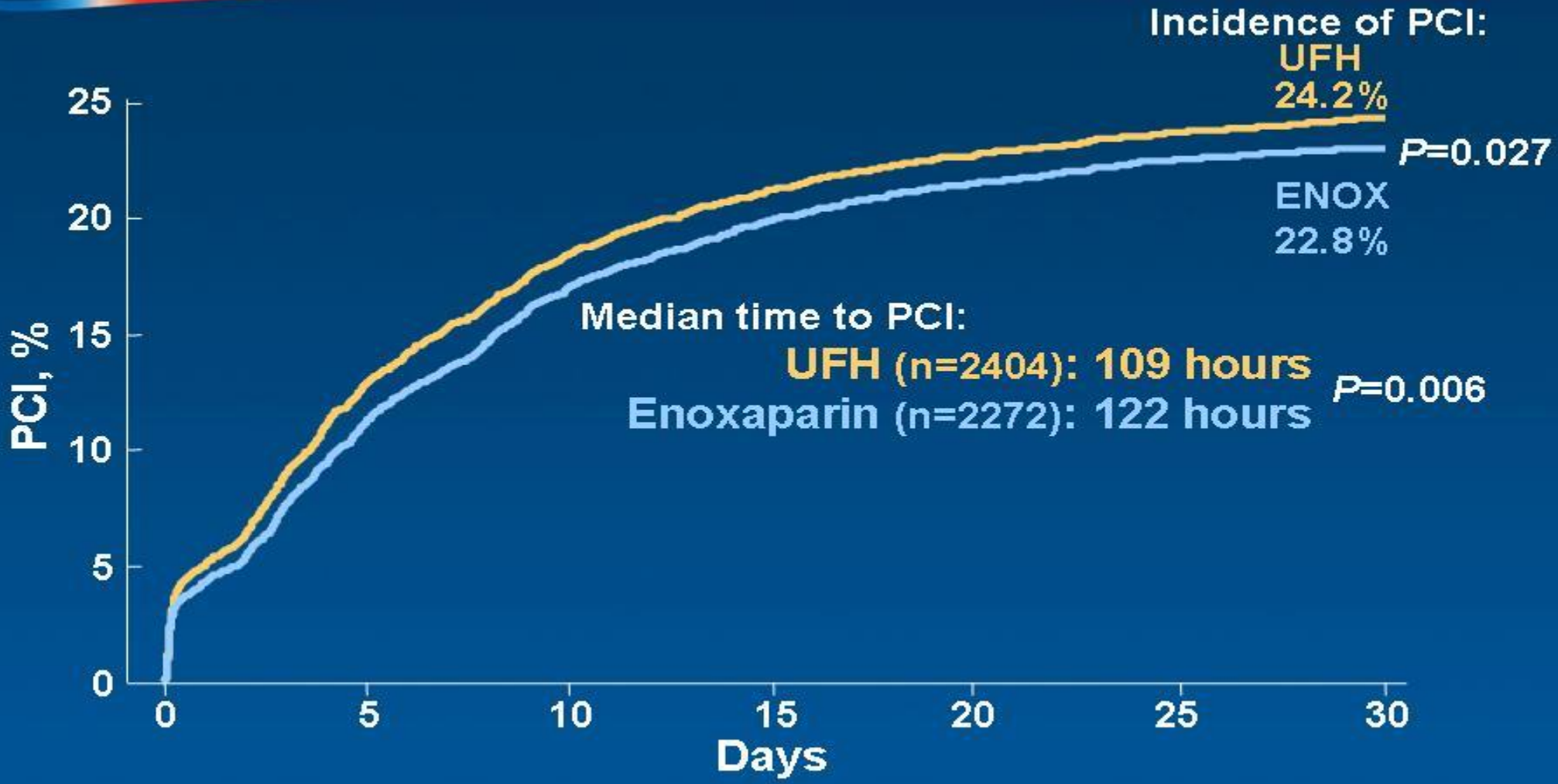
PCI ExTRACT-TIMI 25:
Incidence and Timing of PCI



Please see full prescribing information for enoxaparin, including boxed WARNING

Gibson CM et al. *J Am Coll Cardiol.* 2007;49:2238-2246.

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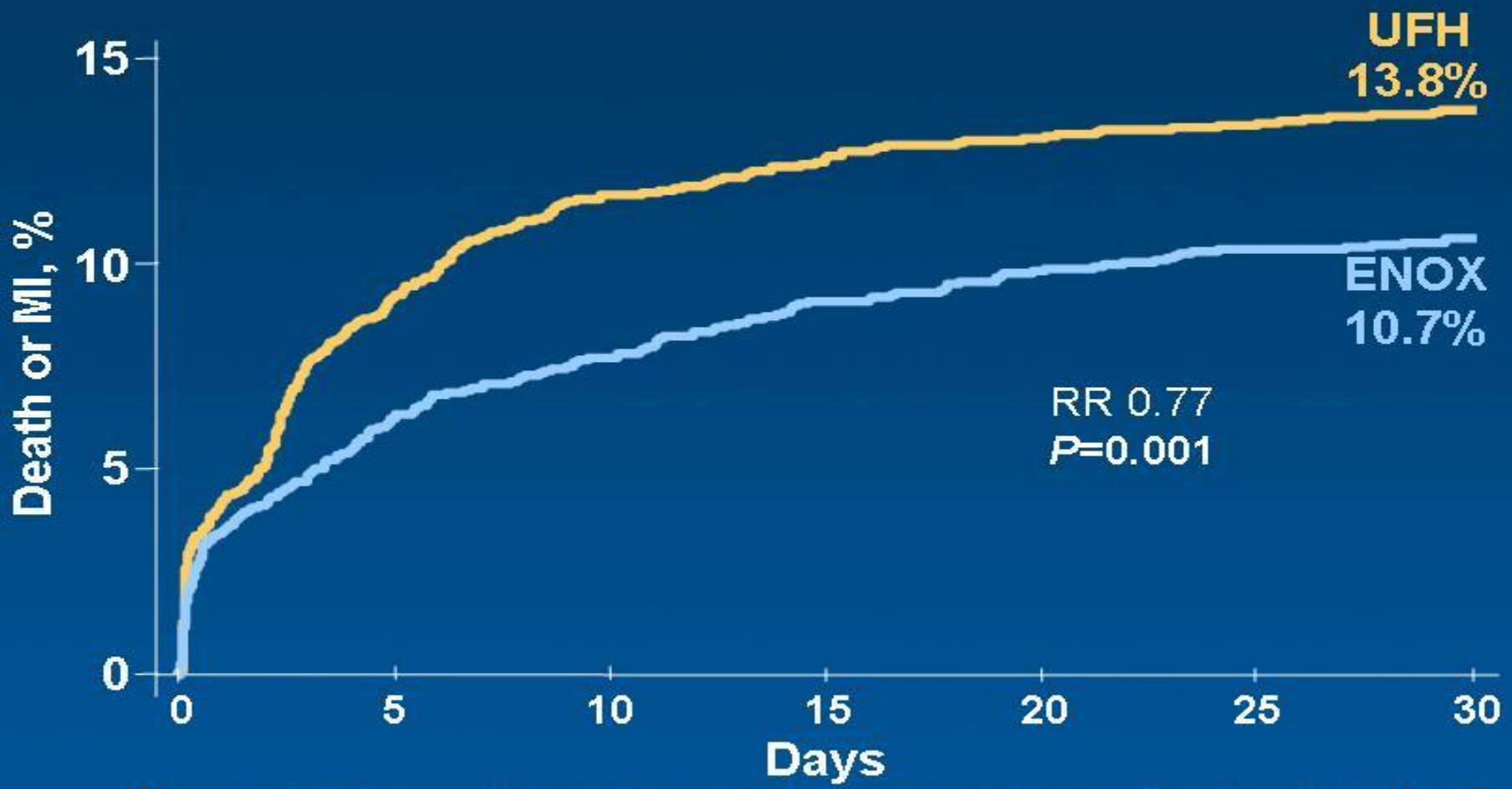
PCI ExTRACT-TIMI 25:
Death or Nonfatal MI by 30 Days



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Gibson CM et al. *J Am Coll Cardiol.* 2007;49:2238-2246.

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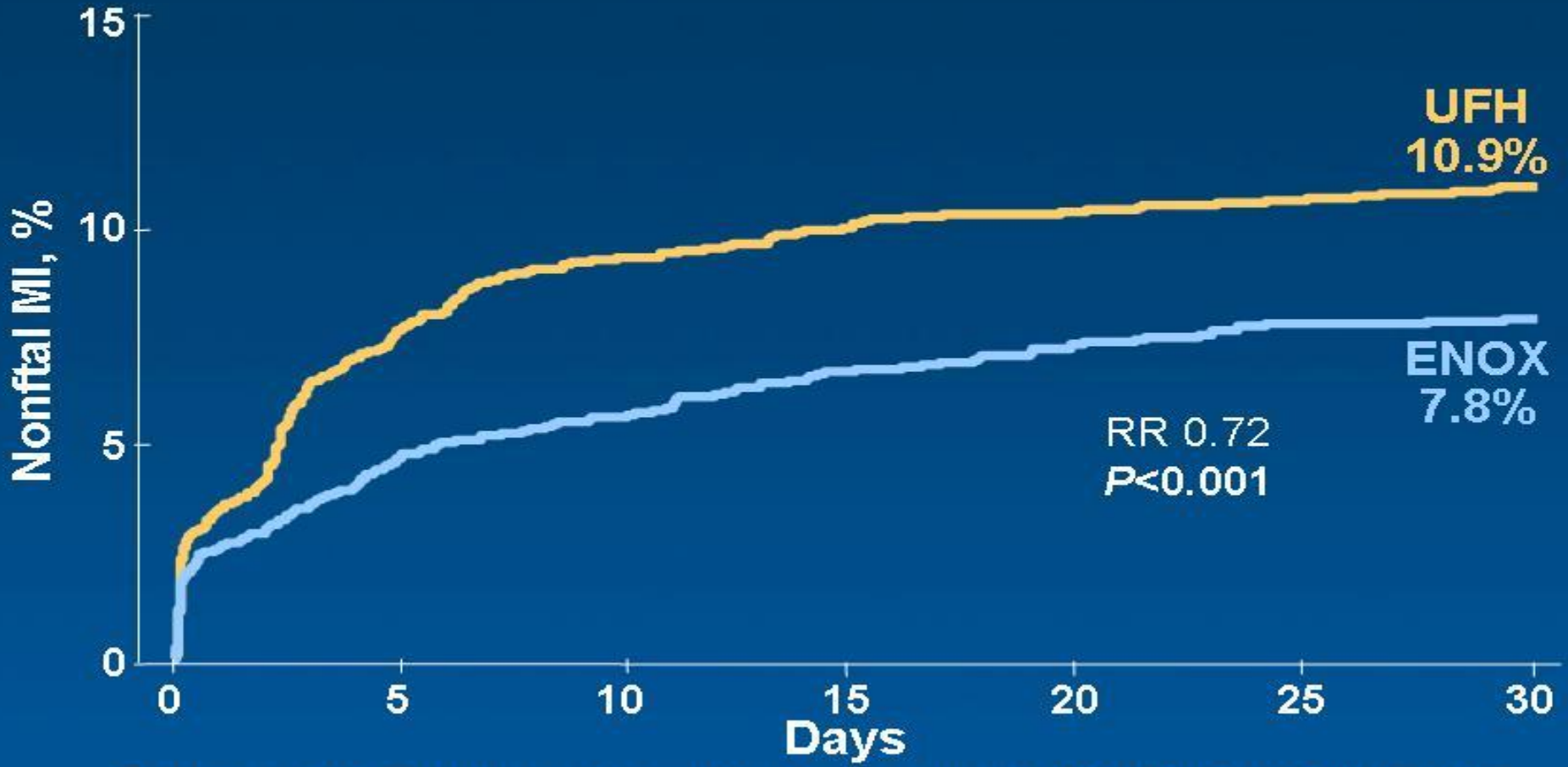
PCI ExTRACT-TIMI 25:
Nonfatal MI by 30 Days

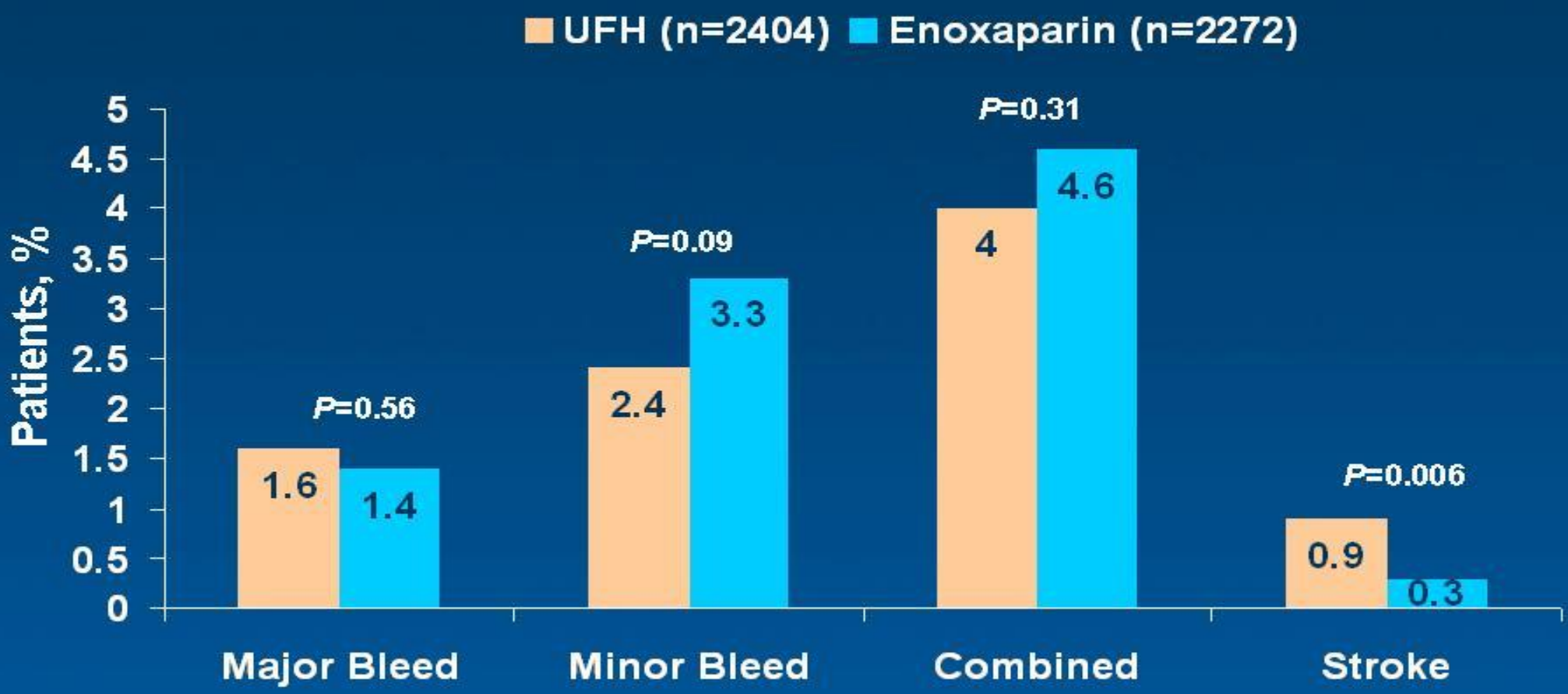


Please see full prescribing information for enoxaparin, including boxed WARNING

Gibson CM et al. *J Am Coll Cardiol.* 2007;49:2238-2246.

sanofi aventis

PCI ExTRACT-TIMI 25: Safety



Please see full prescribing information for enoxaparin, including boxed WARNING

Gibson CM et al. *J Am Coll Cardiol.* 2007;49:2238-2246.

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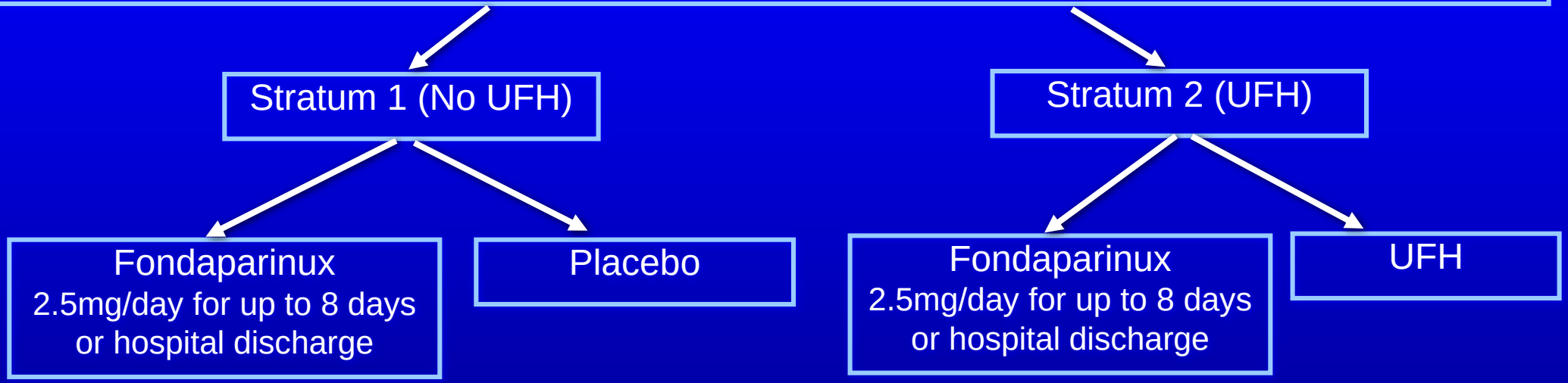
OASIS – 6

12,092 patients presenting with STEMI within 24 hours of symptom onset (shortened to 12 hours of symptom onset midway through trial)

Randomized. Blinded. Factorial.

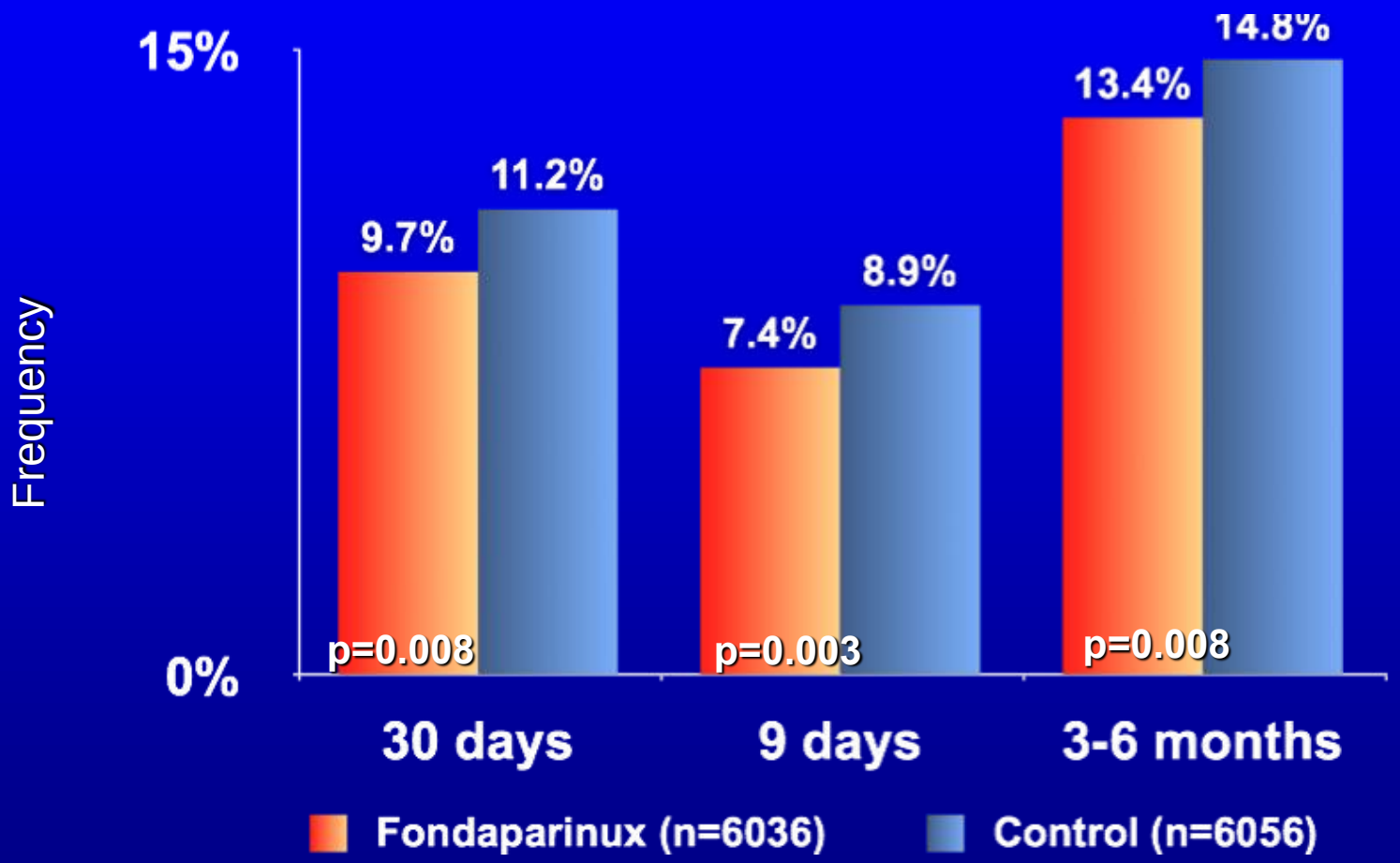
28% female, mean age 62 years, mean follow-up 3-6 months



- Primary Endpoint: Composite of death or reinfarction at 30 days
- Secondary Endpoint: Composite of death or reinfarction at 9 days and at final follow-up

Presented at ACC 2006

OASIS – 6 Trial: Primary Endpoint

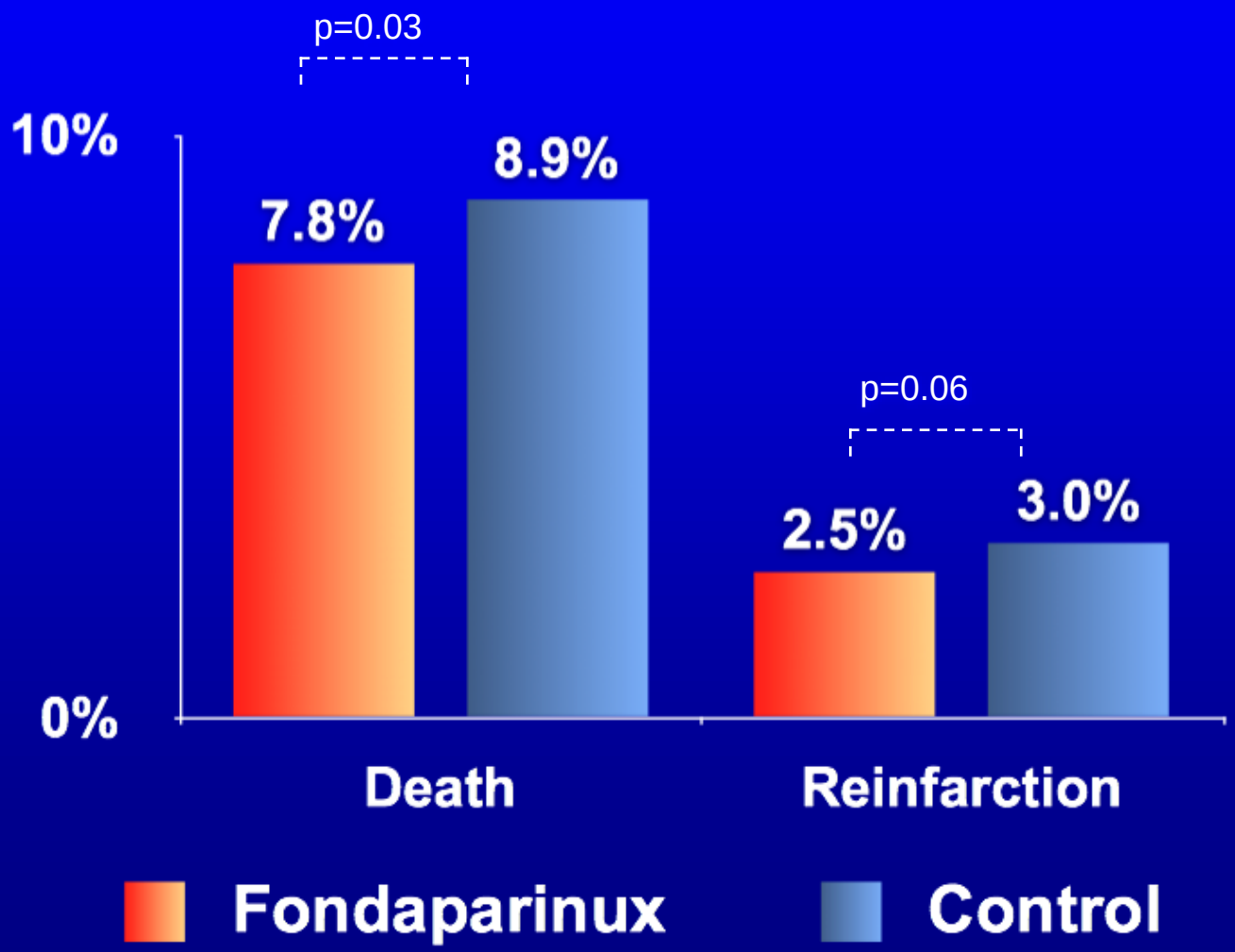


- The primary endpoint was lower in the fondaparinux group compared with the control group (9.7% vs.11.2%, HR 0.86, p=0.008)
- The results were similar at 9 days (HR 0.83, p=0.003) and at study end (HR 0.88, p=0.008)

Presented at ACC 2006

OASIS – 6 Trial: Primary Composite Endpoint

Components of Primary Composite Endpoint (%)



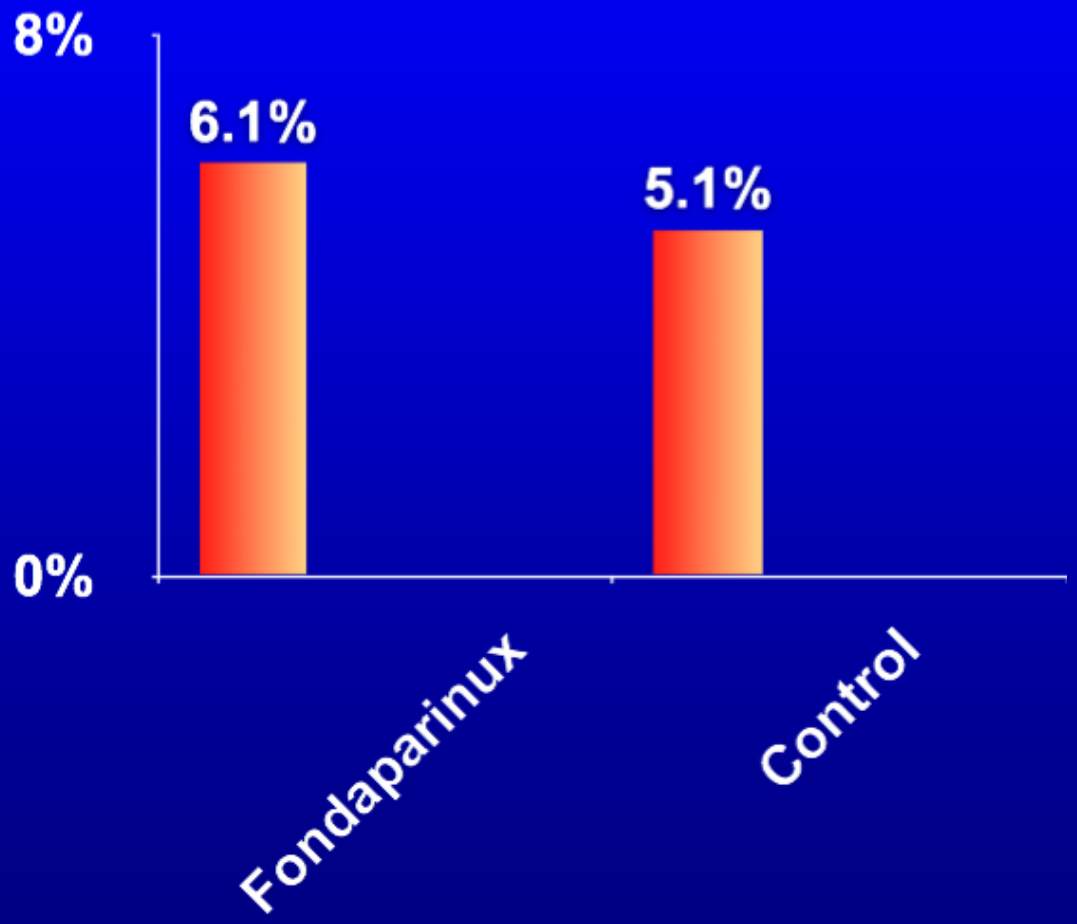
- Among the components of the composite at 30 days, mortality was lower in the fondaparinux group compared to the control group (7.8% vs. 8.9%, HR 0.87, p=0.03).
- Reinfarction was also lower in the fondaparinux group compared to the control group (2.5% vs. 3.0% HR 0.81, p=0.06).

Presented at ACC 2006

OASIS - 6 Trial: PCI Substudy at 30 Days

Primary Endpoint of Death or MI in PCI Cohort (%)

p=0.19



- There was no difference in the primary endpoint for patients who were managed with primary PCI (6.1% vs 5.1%, p=0.19).
- Guiding catheter thrombosis in the primary PCI cohort occurred more often with fondaparinux compared with control (n=22 vs. n=0, p<0.001)

Presented at ACC 2006

Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

N= 13,600

Double-blind

CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

Median duration of therapy - 12 months

1º endpoint: CV death, MI, Stroke

2º endpoints: CV death, MI, Stroke, Rehosp-Rec Isch

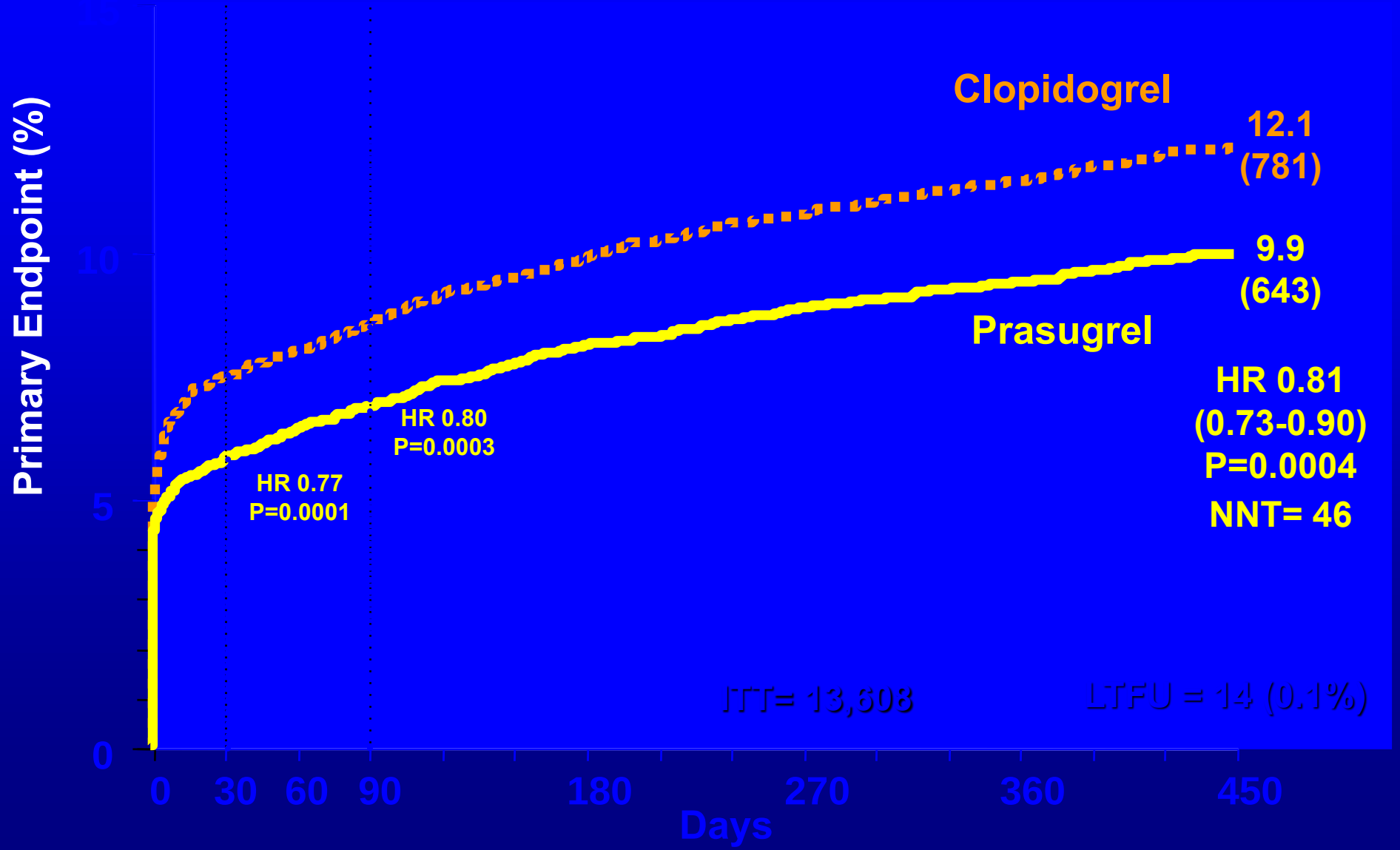
CV death, MI, UTVR

Stent Thrombosis (ARC definite/prob.)

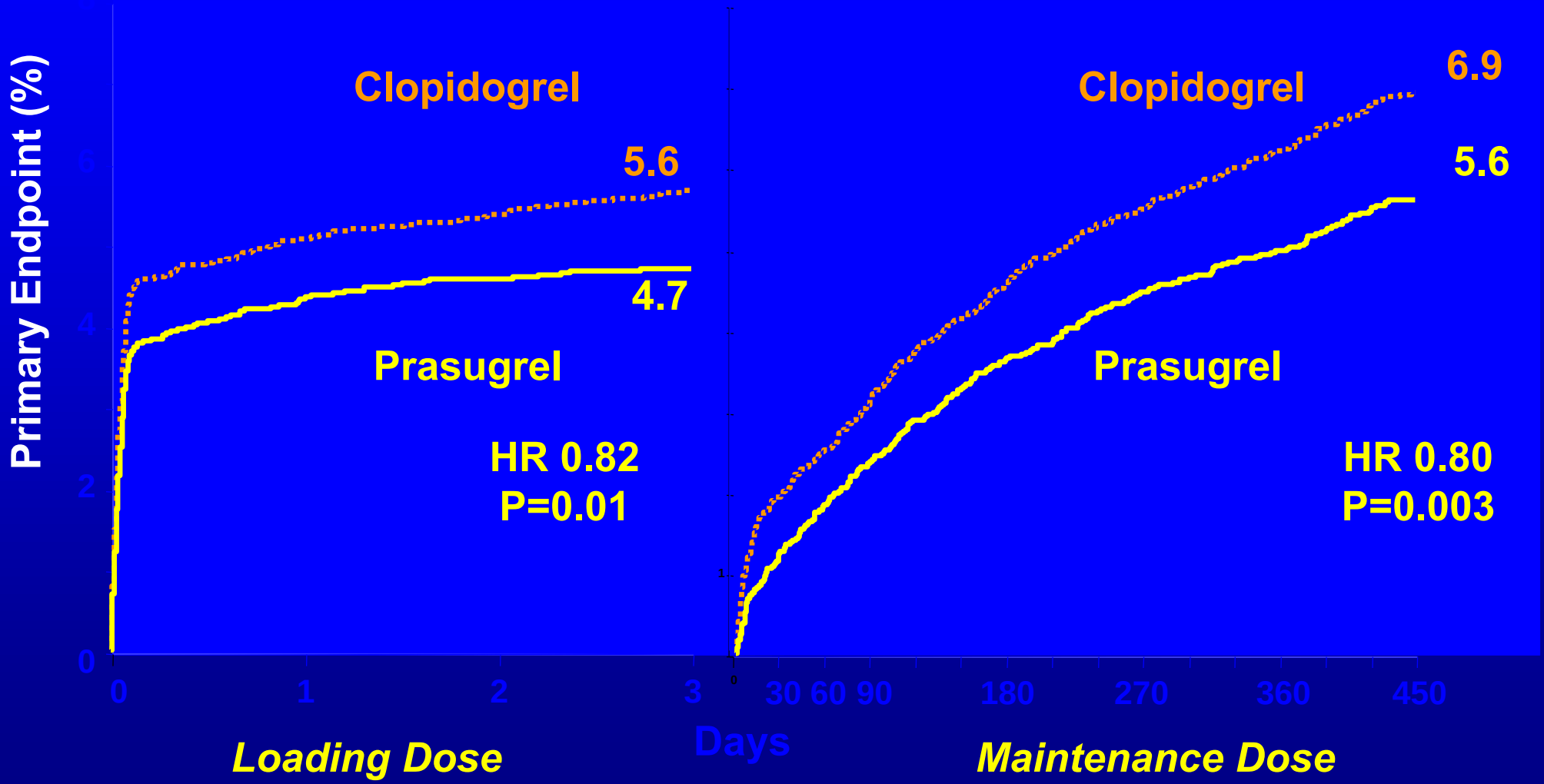
Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Key Substudies: Pharmacokinetic, Genomic

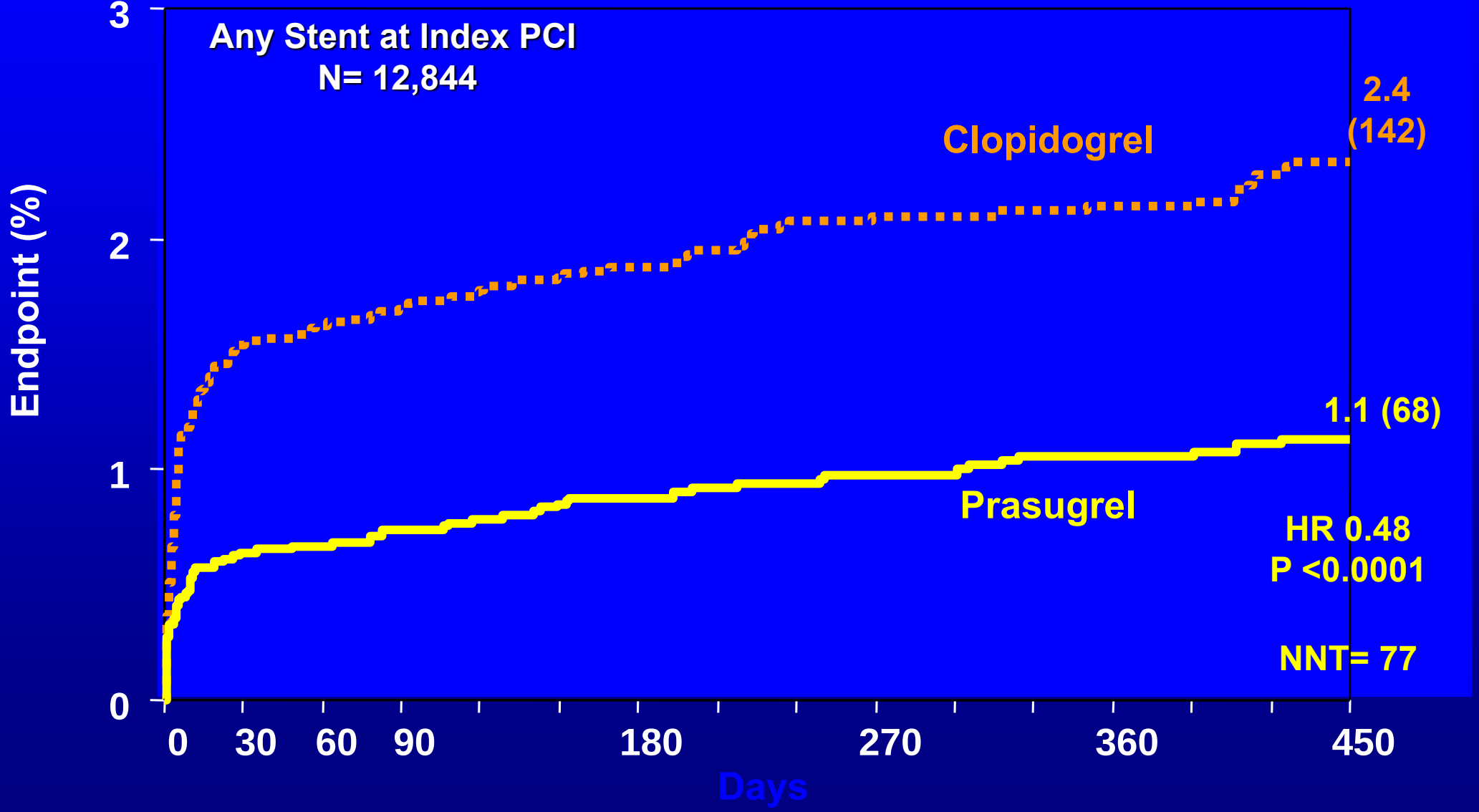
Primary Endpoint
CV Death,MI,Stroke



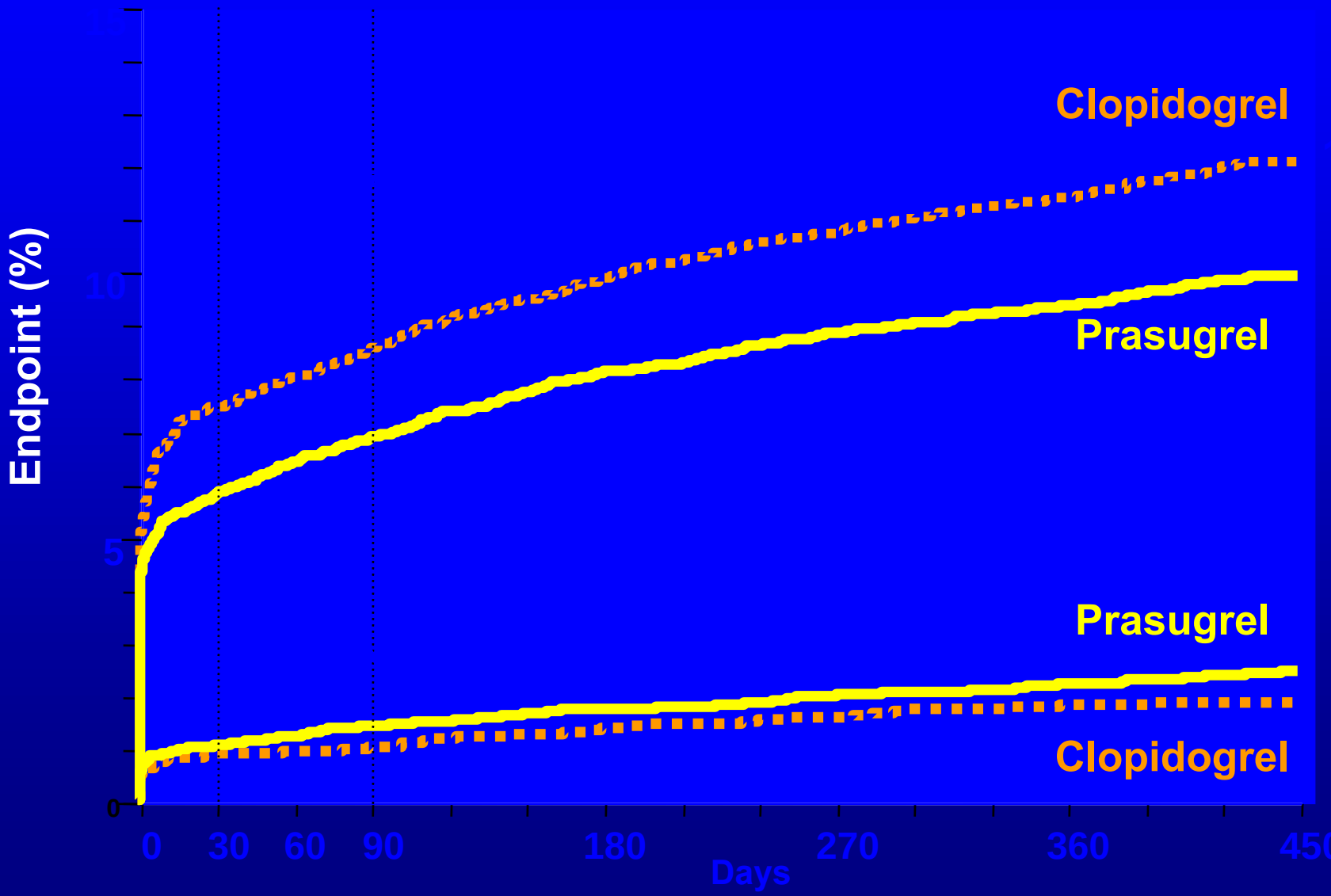
Timing of Benefit (Landmark Analysis)



Stent Thrombosis (ARC Definite + Probable)



Balance of Efficacy and Safety



↓ 138 events

HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

↑ 35 events

HR 1.32
(1.03-1.68)
P=0.03

NNH = 167