Acute Coronary Syndromes:

Medical Management of UA/NSTEMI

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ACC/AHA Guideline for UA/NSTEMI

- Assess likelihood of CAD
- Risk stratification
- Target therapy: more aggressive treatment in higher-risk patients
- Anti-ischemic, antithrombotic therapy
- **Invasive** vs conservative strategy
- Discharge planning (risk factor modification and long-term medical therapy)

ACC/AHA, American College of Cardiology/American Heart Association; UA, unstable angina; NSTEMI, non–ST-segment elevation myocardial infarction.
Braunwald E, et al. *J Am Col. Cardiol.* 2000;36:970-1062.

Acute Management of UA/NSTEMI

Anti-Ischemic Therapy

- Oxygen, bed rest, ECG monitoring
- Nitroglycerin
- β-Blockers
- ACE inhibitors

Antithrombotic Therapy

Antiplatelet therapy

Anticoagulant therapy

UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; ECG, electrocardiogram; ACE, angiotensin-converting enzyme.

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

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.

Case Presentation: History and Exam

- 66세 여자
- 10-20분정도의 흉통을 수차례 호소, 응급실 내원,
- 과거력: 안정형협심증으로 NTG사용
  DM 8년, 경구하강제 사용
  고콜레스테롤 혈증 12년, statin사용
  40갑년의 흡연력
- 이학적 검사: 비만, 혈압150/94 mm Hg, 맥박78
- 검사
  심전도: 흉통시 1.5 mm ST depression (V2-5)
  Troponin I level: 2.1 ng/ml (nl <0.05 ng/ml)

Risk Stratification in UA/NSTEMI: TIMI Risk Score

Integrated risk predictor based on 7 variables:

1. Age ≥65 years
2. ≥3 risk factors for CAD
   - Diabetes
   - Family history of CAD
   - Hypertension
   - Hypercholesterolemia
   - Current smoker
3. ≥50% prior coronary stenosis
4. ST-segment deviation on EKG
5. At least 2 anginal events in prior 24 hours
6. Use of aspirin in prior 7 days
7. Elevated serum cardiac markers

This Patient Is High-Risk

Age ≥65 years

TIMI Score=5

≥3 risk factors for CAD
- Diabetes
- Hypertension
- Hypercholesterolemia
- Current smoker

ST-segment deviation

>2 anginal events in past 24 hours

Elevated troponin I(T)

Case Presentation: Plan of Action

A cardiologist is consulted and the patient is admitted at 10 pm

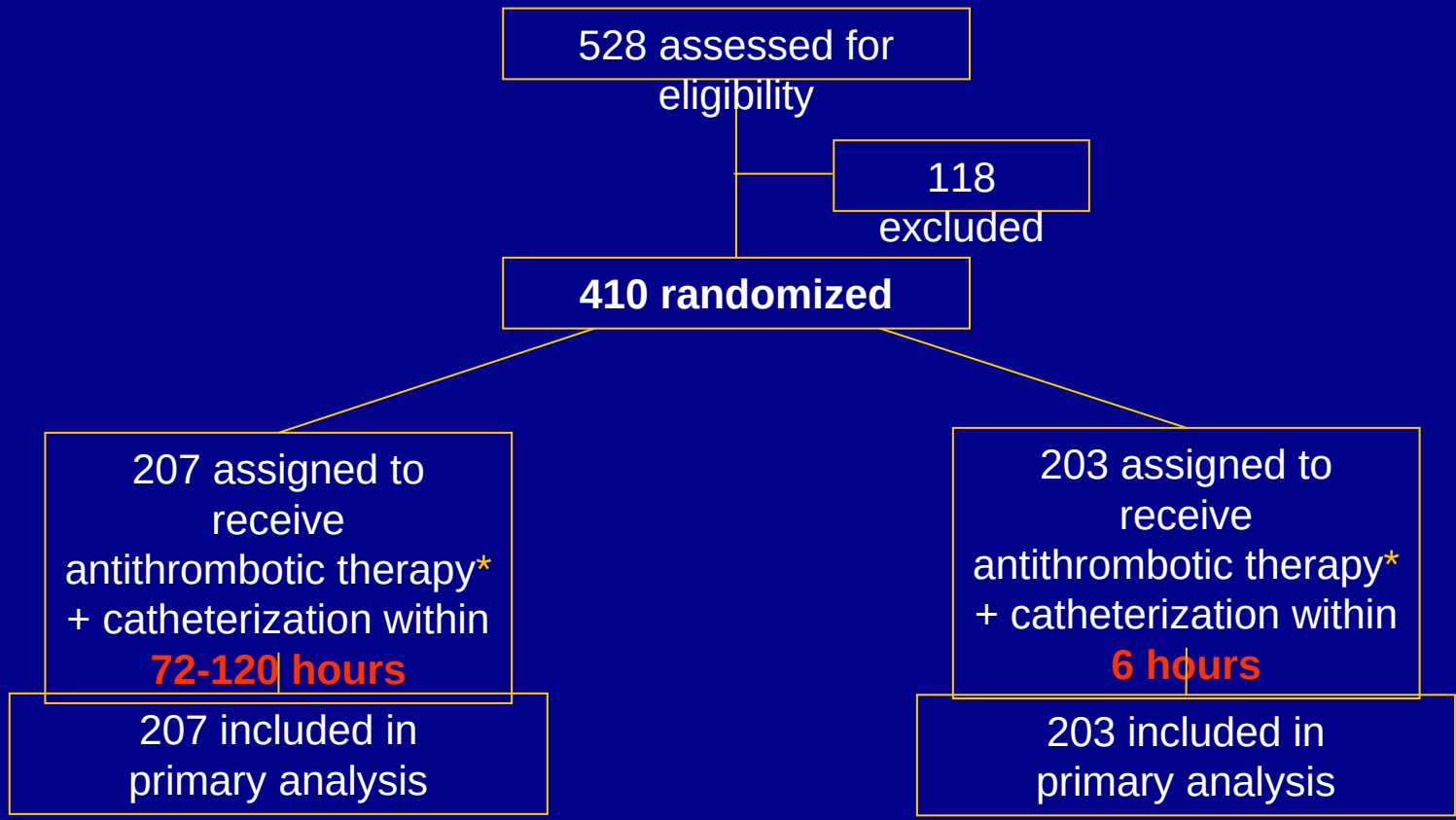
She is scheduled for an angiogram and possible PCI with stent insertion at 7 am the following morning

PCI=percutaneous coronary intervention.

How Would You Manage this Patient for the Next 9 Hours?

Intervention in 9 hours acceptible?

ISAR-COOL



*UFH 60 µ/kg bolus then infusion adjusted to PTT 60-85 seconds; aspirin 500 mg IV then 100 mg PO BID
clopidogrel 600 mg LD then 75 mg BID; tirofiban 100 µg/kg bolus then 0.10 µg/kg/min

PTT=partial thromboplastin time.

Adapted from Neumann FJ, et al. *JAMA*. 2003;290:1593-1599.

What "Early Intervention" Really Means

Study	Time to cath lab (hours)
PRISM-PLUS	mean 65
TACTICS-TIMI 18	mean 21*
SYNERGY	median 22
CRUSADE	median 26

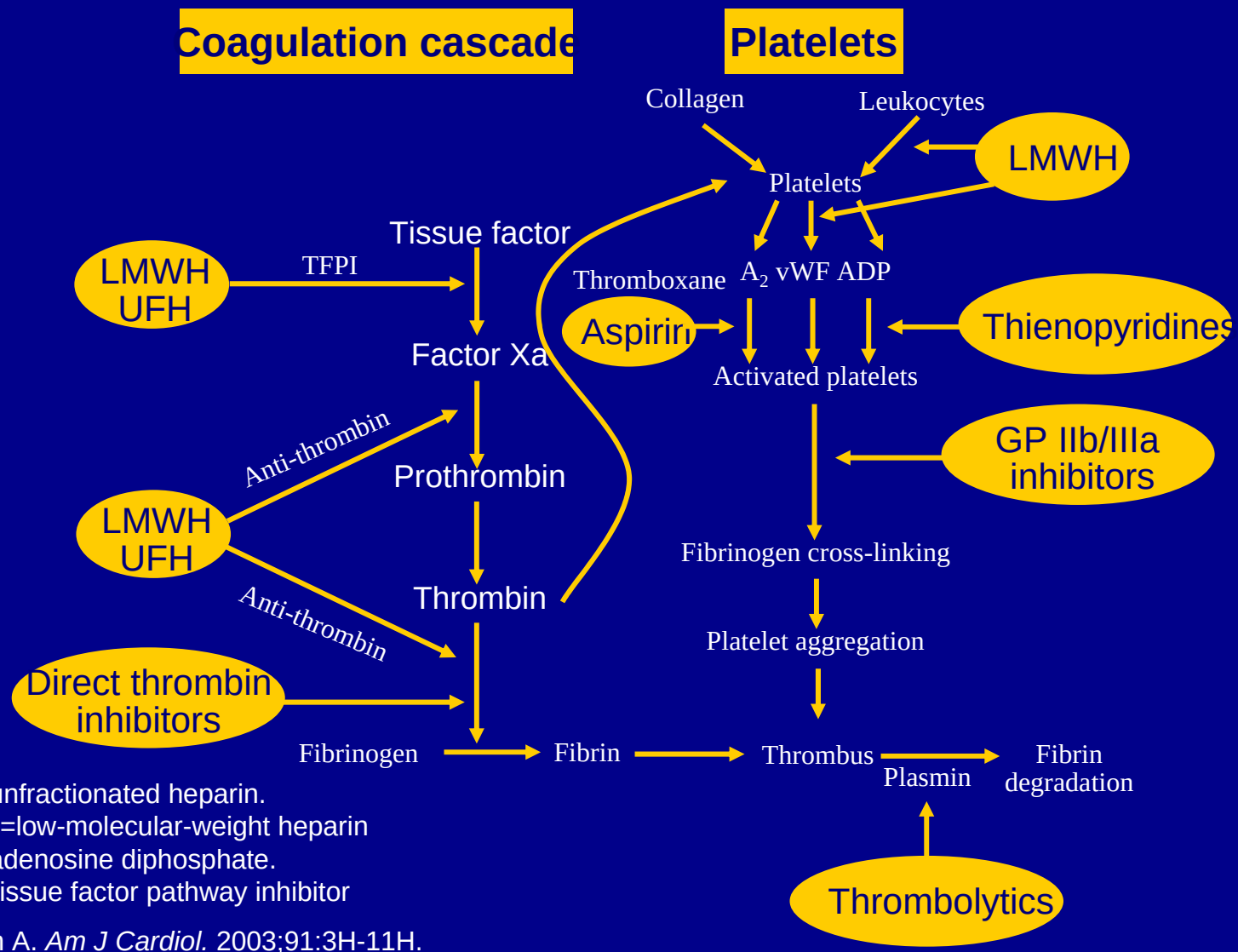
*In the early invasive group, scheduled 4-48 hours after randomization.

Zhao XQ, et al. *Circulation*. 1999;100:1609-1615.
Lakkis N, et al. *Crit Path Cardiol.* 2002;1:232-237.
Mahaffey KW. American College of Cardiology; March 7-10, 2004; New Orleans, LA.
CRUSADE Quality Improvement Initiative, Quarter 4 2003. Data on file at Duke Clinical Research Institute.

Antithrombotic Therapy Is Key to Maximizing Outcomes in UA/NSTEMI

- There is confusion as to which agents to use and whether they are safe when used in combination
- Therefore, it is important to address the **misperceptions** out the role of various antithrombotic agents in UA/NSTEMI management to improve patient outcomes

Rationale for Use: Pharmacologic Intervention in Thrombosis



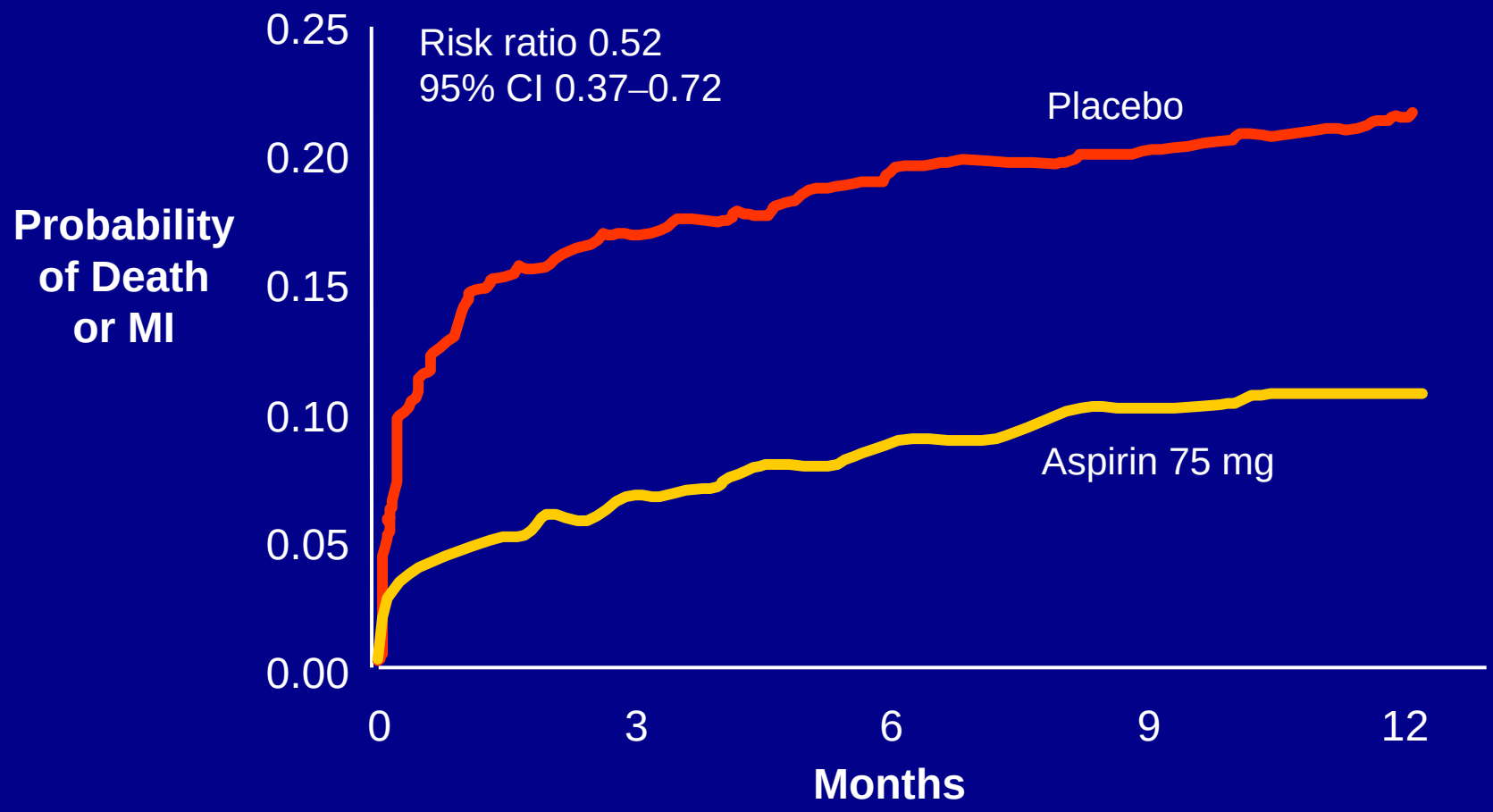
UFH=unfractionated heparin.
LMWH=low-molecular-weight heparin
ADP=adenosine diphosphate.
TFPI=tissue factor pathway inhibitor

Selwyn A. *Am J Cardiol.* 2003;91:3H-11H.

고정관념

Aspirin plus an Anti-thrombin Agent Provide Sufficient Anticoagulation for Patients with UA/NSTEMI

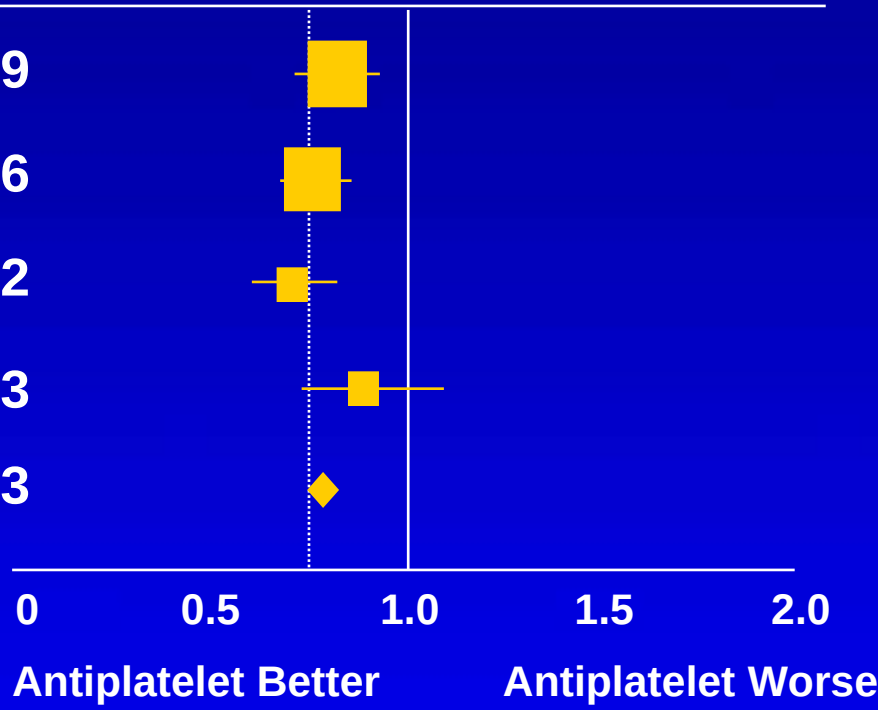
Aspirin in the Treatment of ACS



Wallentin LC, et al. *J Am Coll Cardiol.* 1991;18:1587-1593.

Indirect Comparisons of ASA Doses on Vascular Events in High-Risk Patients

Aspirin Dose	No. of Trials	OR* (%)
500-1500 mg	34	19
160-325 mg	19	26
75-150 mg	12	32
<75 mg	3	13
Any aspirin	65	23



* Odds reduction.
Treatment effect *P*<.0001.
ASA, acetylsalicylic acid.
Adapted with permission from BMJ Publishing Group. Antithrombotic Trialists' Collaboration. *BMJ.* 2002;324:71-86.

Aspirin Resistance: Possible Mechanisms

Clinical Factors
- Failure to prescribe
- Non-compliance
- Non-absorption
- Interaction with ibuprofen

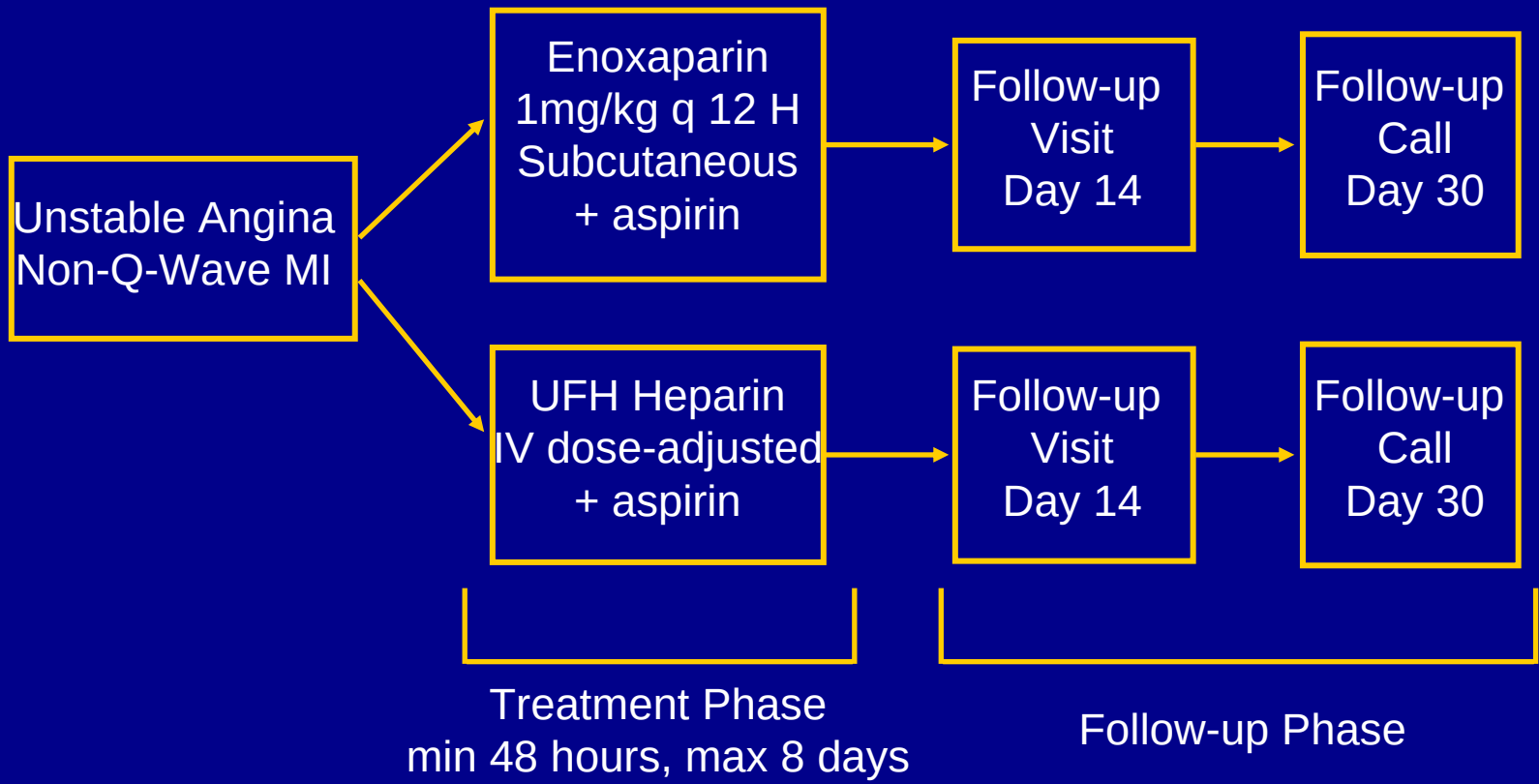
Cellular Factors
- Insufficient suppression of COX-1
- Erythrocyte induced platelet activation
- Increased norepinephrine
- Generation of 8-iso-PGF2a

Aspirin Resistance

General Polymorphisms
- COX-1
- GP IIb/IIIa receptor
- Collagen receptor
- vWF receptor

Bhatt DL. *J Am Coll Cardiol.* 2004;43:1127-1129.

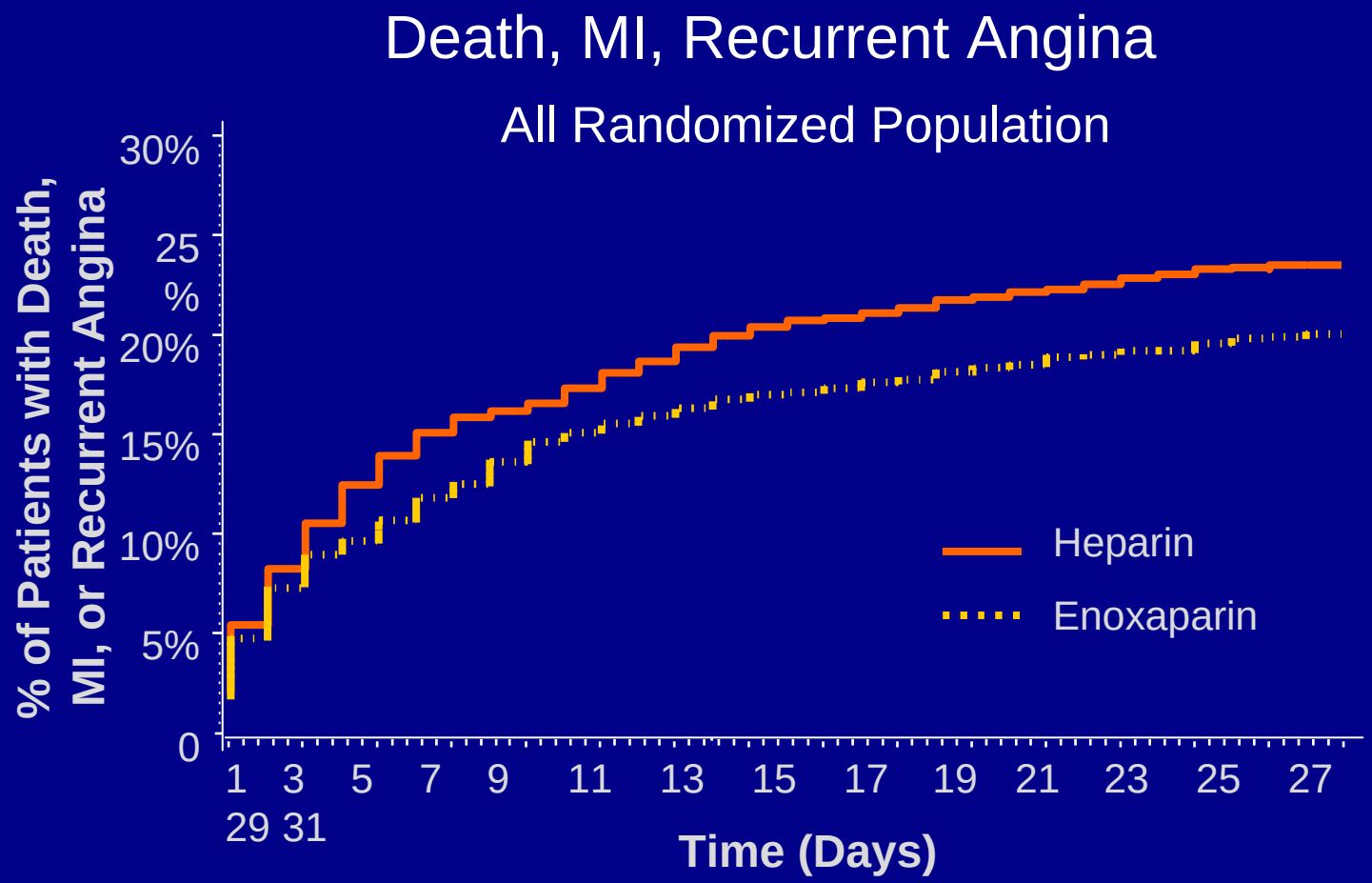
Low Molecular Heparin
ESSENCE: Study Design



MI=myocardial infarction.

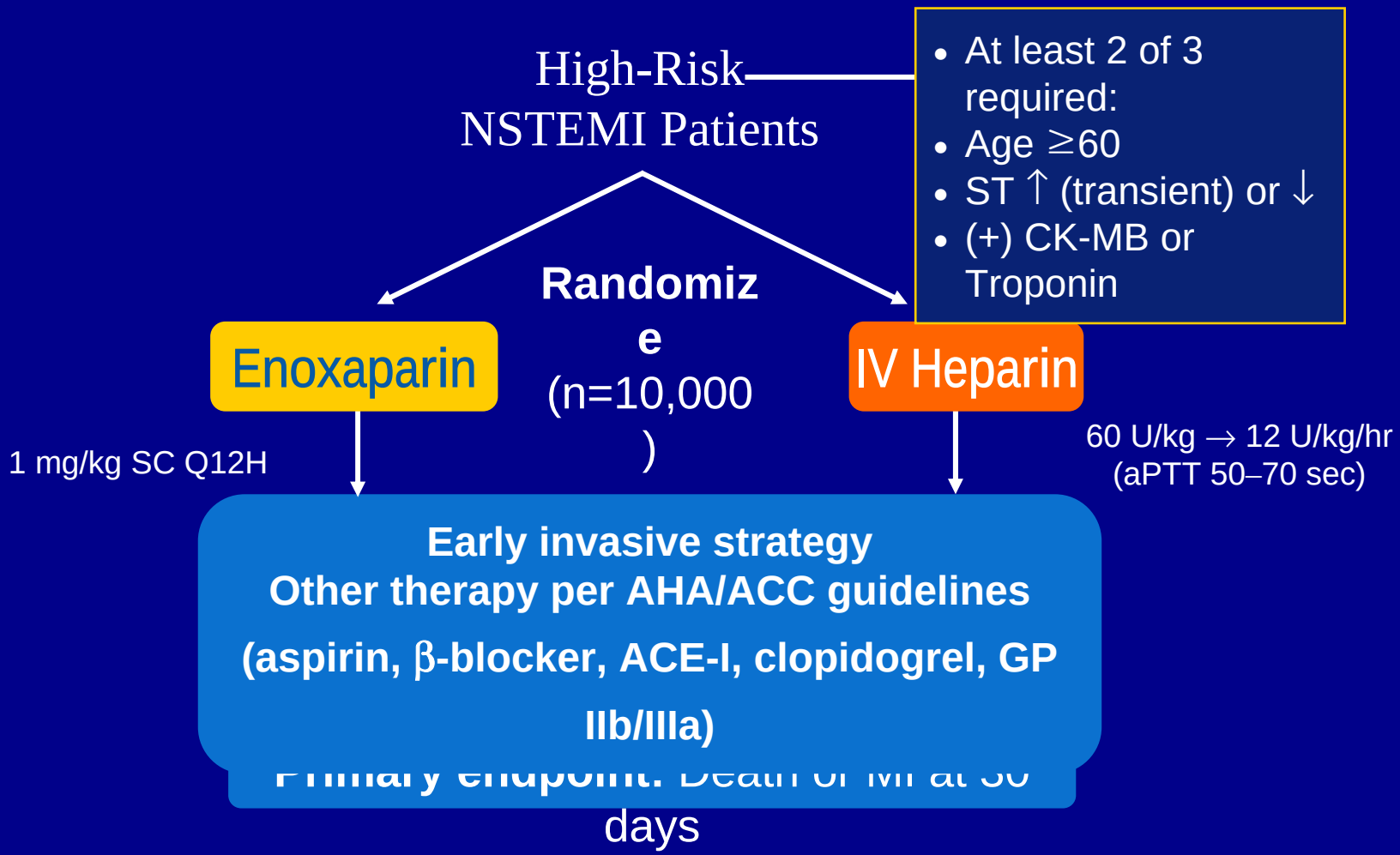
Cohen M, et al. *Am J Cardiol.* 1998;82:19L-24L.

ESSENCE: First 30 Days, Enoxaparin Is Superior to UFH



Cohen M, et al. *Am J Cardiol.* 1998;82:19L-24L.

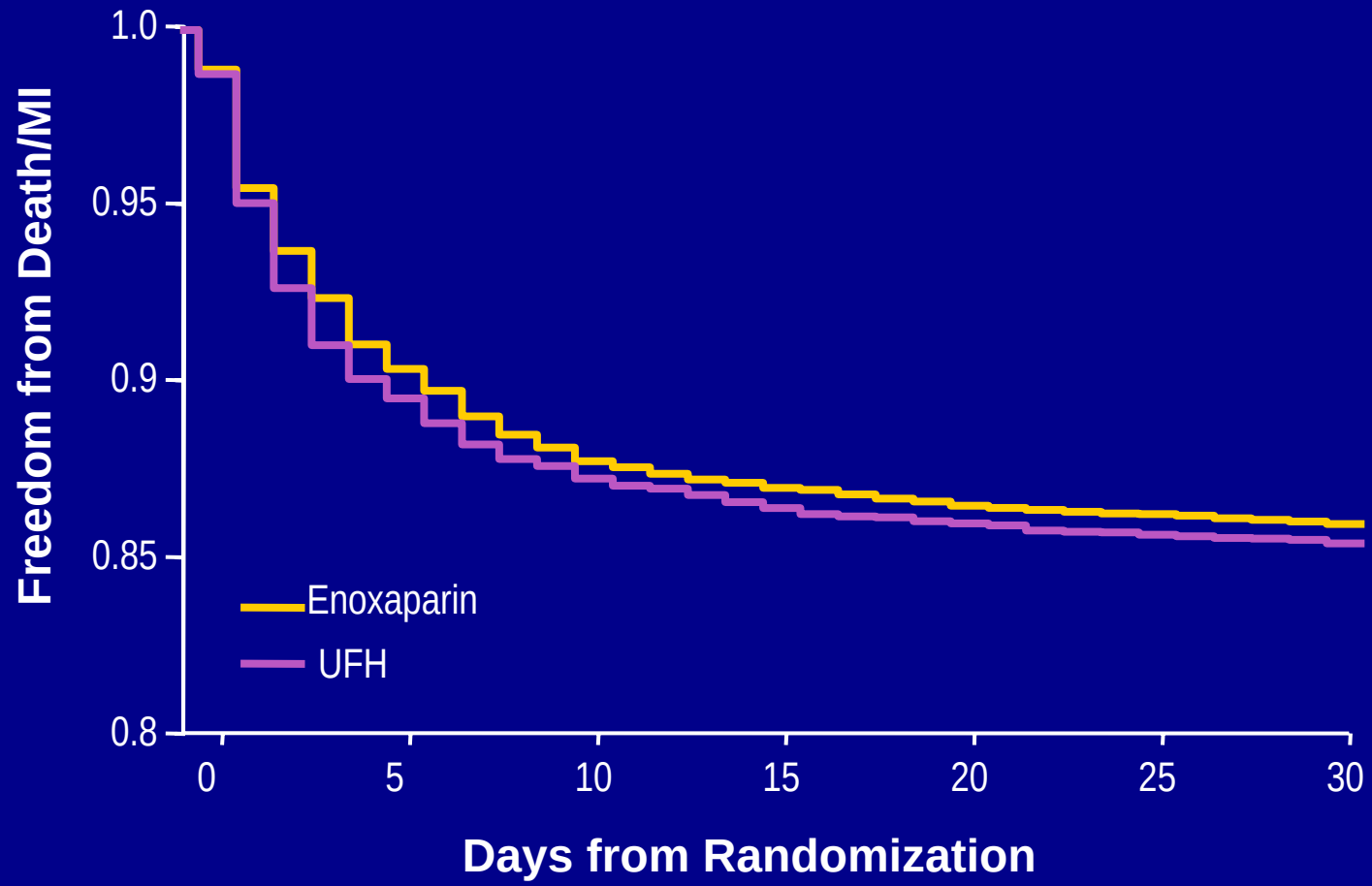
SYNERGY: Enoxaparin with Early Invasive Strategy in High-Risk UA/NSTEMI Patients



ACE-I=angiotensin-converting enzyme inhibitor.

SYNERGY Trial Investigators. *JAMA*. 2004;292:45-54.

SYNERGY: Enoxaparin and UFH Had Similar Reductions in 30-day Endpoint



SYNERGY Trial Investigators. *JAMA*. 2004;292:45-54.

Summary

- ESSENCE and SYNERGY prove that enoxaparin is a viable alternative to upstream use of UFH in high-risk patients with UA/NSTEMI
- Benefits of LMWHs:
  - Do not require continuous infusion
  - Do not require monitoring of aPTT
  - No effects on increasing surface GP IIb/IIIa receptors
- ESSENCE: No GP IIb/IIIa inhibitors were used and most patients did not undergo early catheterization
- **SYNERGY did not show that enoxaparin can be used instead of in antiplatelet agent, but rather that it can be used as a complementary agent**
  - More than half of patients received GP IIb/IIIa inhibitors
  - Almost all patients underwent early catheterization
- SYNERGY showed **increased bleeding** with enoxaparin
- High-risk patients did **not have an improved effect** with LMWH

aPTT=activated partial prothromboplastin time.

Direct antithrombin

REPLACE-2: Bivalirudin versus Heparin + GP IIb/IIIa During PCI

N=6010 Patients: Urgent or Elective PCI

Randomization

Heparin
65 U/kg initial bolus

Planned GP IIb/IIIa

Target ACT ≥225 sec

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

Provisional GP IIb/IIIa

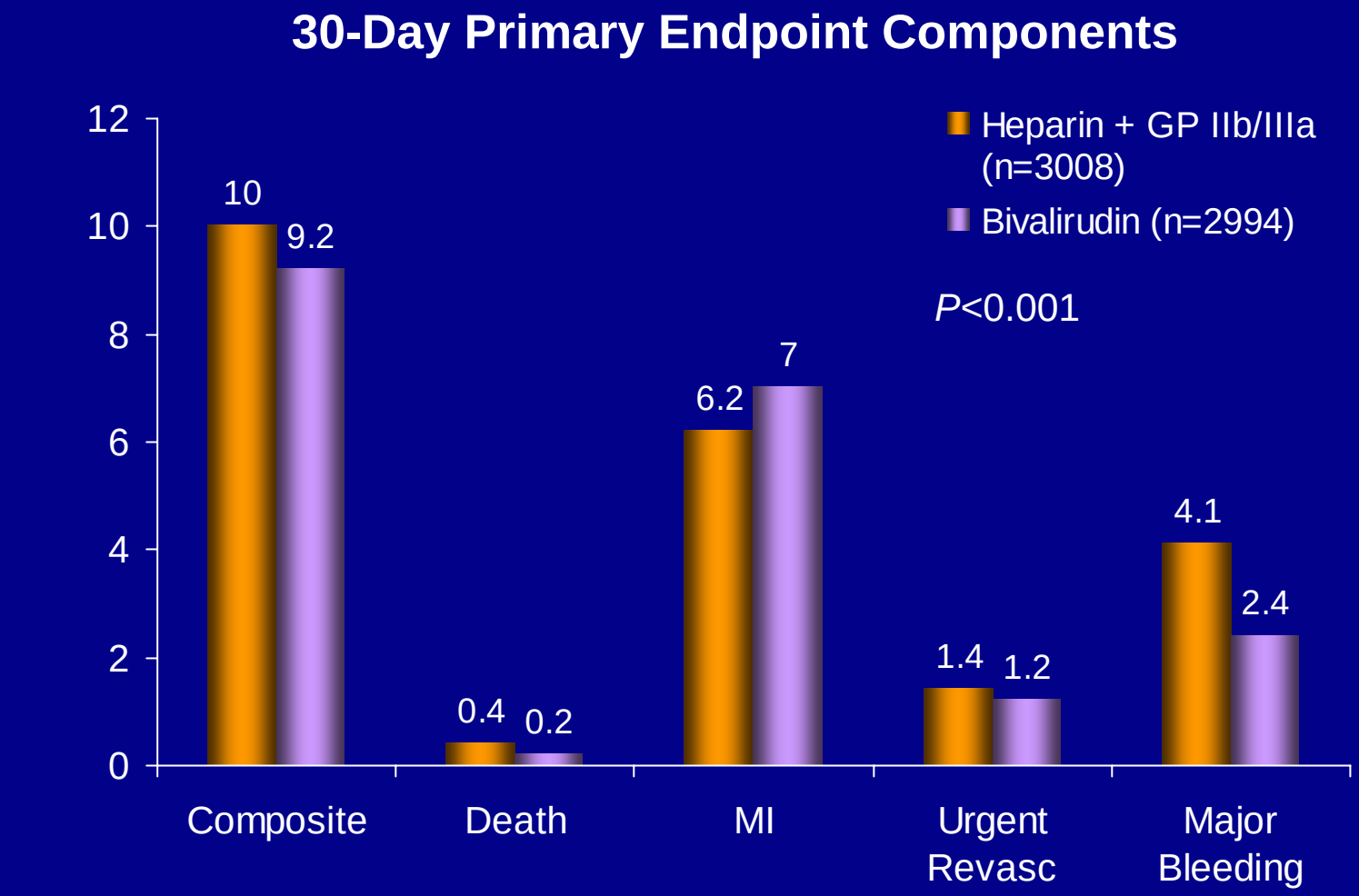
Abciximab: 0.25 mg/kg bolus, 0.125 µg/kg-min (max 10 µg/min) x 12 hou
Eptifibatide: 180 µg/kg double bolus, 2.0 µg/kg-min x 18–24 hours

Quadruple Endpoint at 30 Days

ACT=activated clotting time.

Lincoff AM, et al. *JAMA*. 2003;289:853-863.

REPLACE 2: At 30 Days, Bivalirudin Was Non-inferior to Heparin + GP IIb/IIIa Inhibitor Regimen



Lincoff AM, et al. *JAMA*. 2003;289:853-863.

REPLACE-2: Study Conclusion

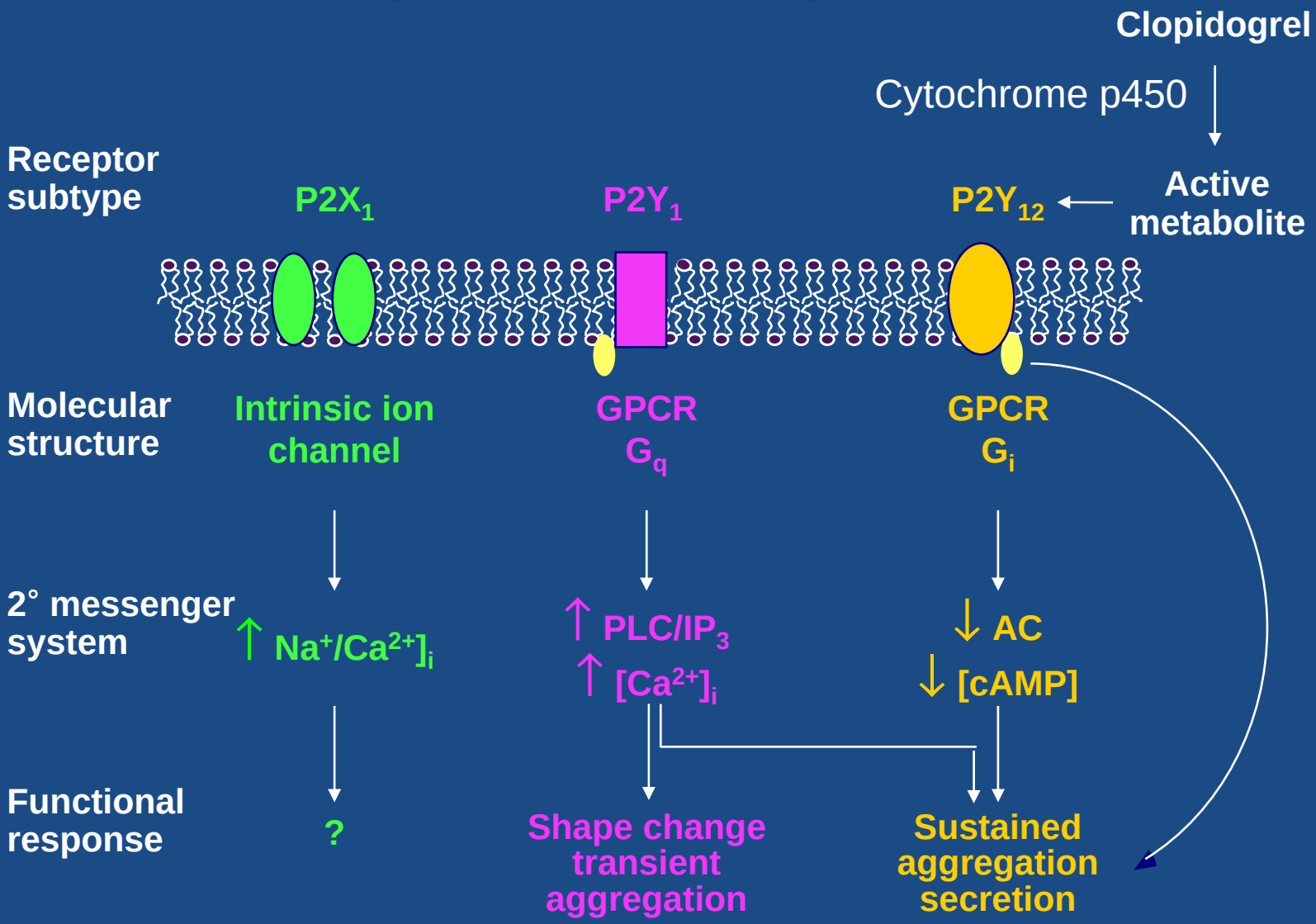
- Compared with UFH:
  - Bivalirudin reduces rate of death, MI, or revascularization with concurrent reduction in bleeding
  - Bivalirudin plus planned or rescue abciximab appears safe and at least as effective as UFH plus a GP IIb/IIIa inhibitor in patients undergoing PCI
  - Bivalirudin with provisional GP IIb/IIIa blockade is not inferior to UFH plus planned GP IIb/IIIa blockade during PCI

Lincoff AM, et al. *Am J Cardiol.* 2004;93(9):1092-1096.
Lincoff AM, et al. *Am Heart J.* 2002;143:847-853.

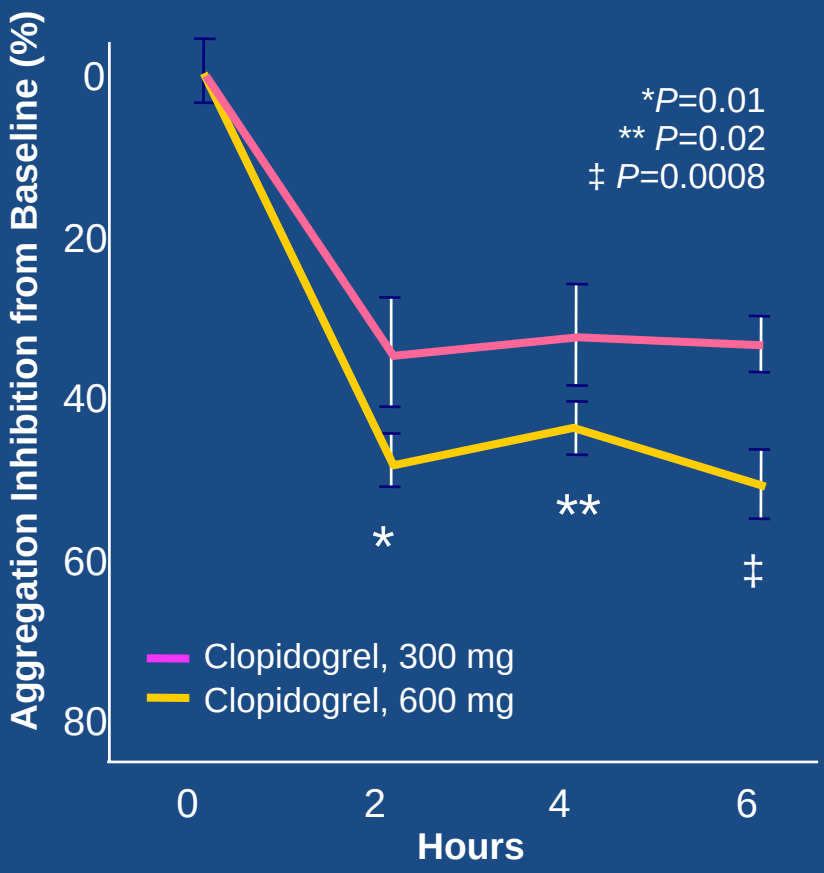
Direct Thrombin Inhibitors: Role in UA/NSTEMI

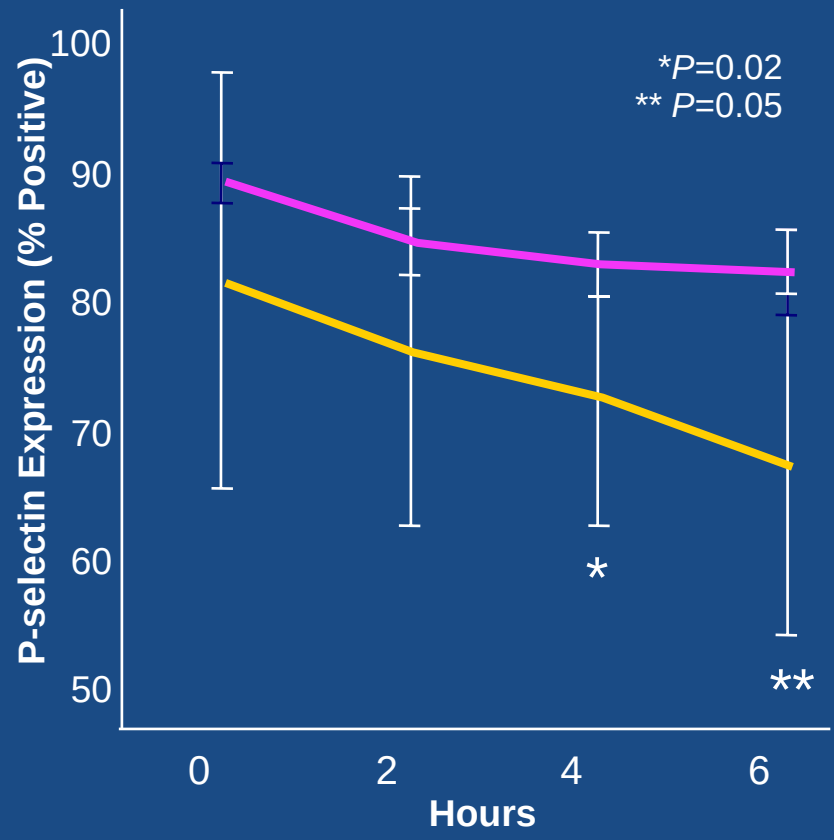
- Direct thrombin inhibitors, such as bivalirudin, are effective alternatives to UFH in PCI
- In REPLACE-2, patients were not stratified by risk; therefore, it is difficult to apply these data to high-risk populations
- No data currently exist on the efficacy of bivalirudin as primary treatment in patients with UA/NSTEMI
- Patients with acute MI and unstable ischemic syndromes were not included in REPLACE-2; thus, the results of this trial should not be interpreted to suggest that GP IIb/IIIa blockade should be supplanted in these patients

ADP Receptor Subtypes



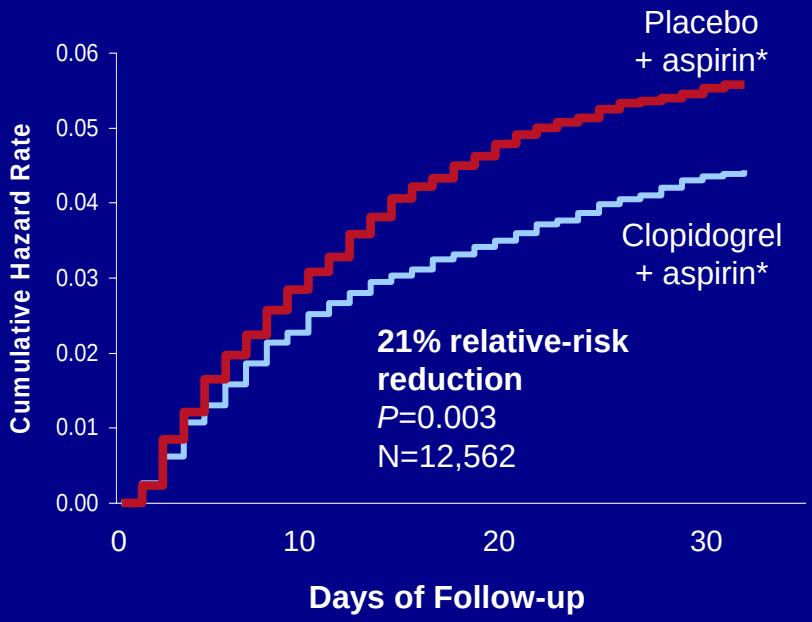
Clopidogrel Dose Effect

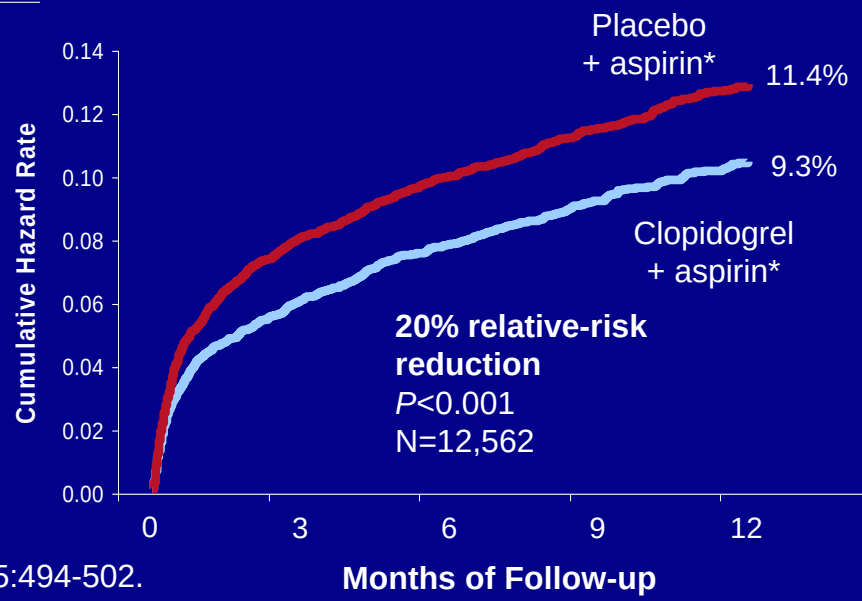




Zidar F, et al. *J Am Coll Cardiol.* 2004;43(5, suppl A);Abstract 1100-1159.

ADP receptor blocker
CURE: Clopidogrel Reduces MI/Stroke/CV Death in High-Risk UA/NSTEMI Patients

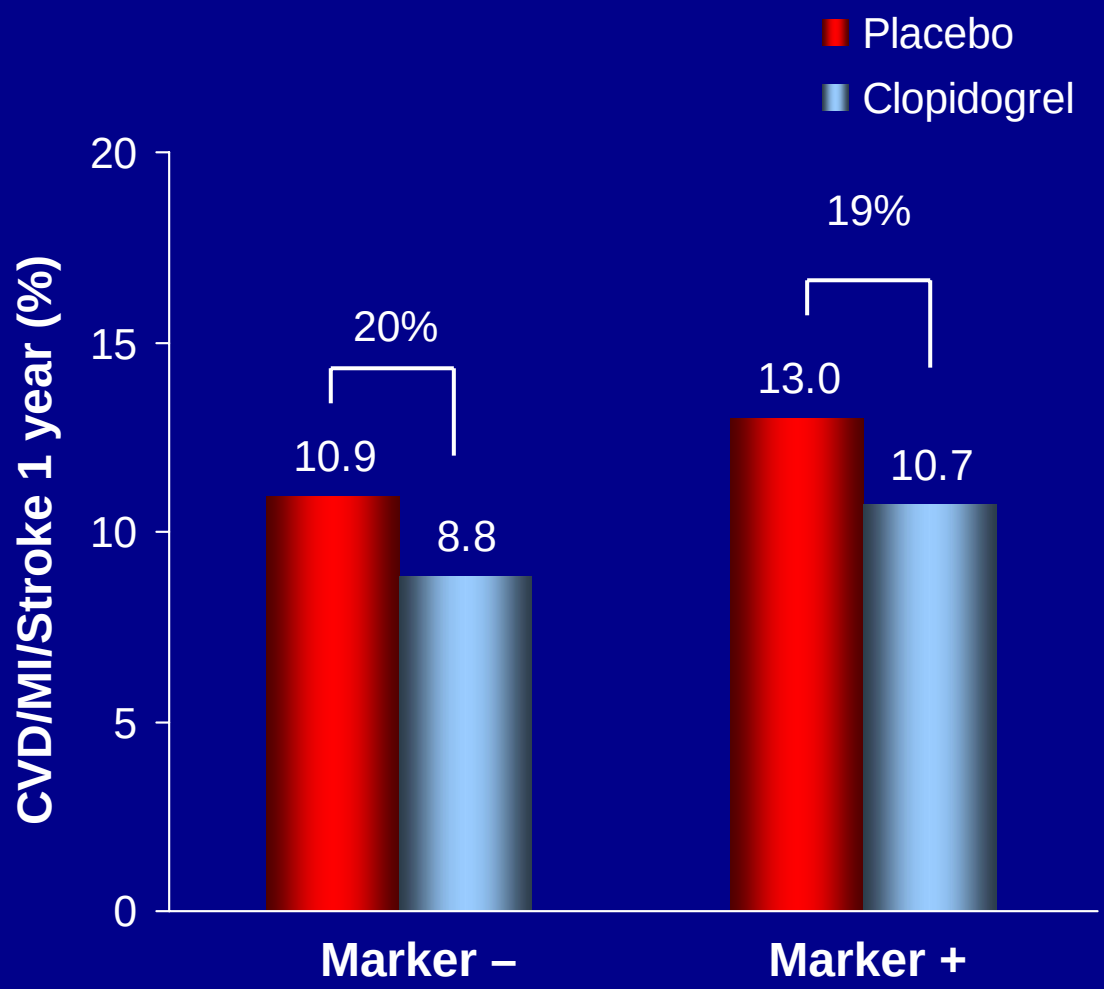




*In combination with standard therapy.
CV=cardiovascular.

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

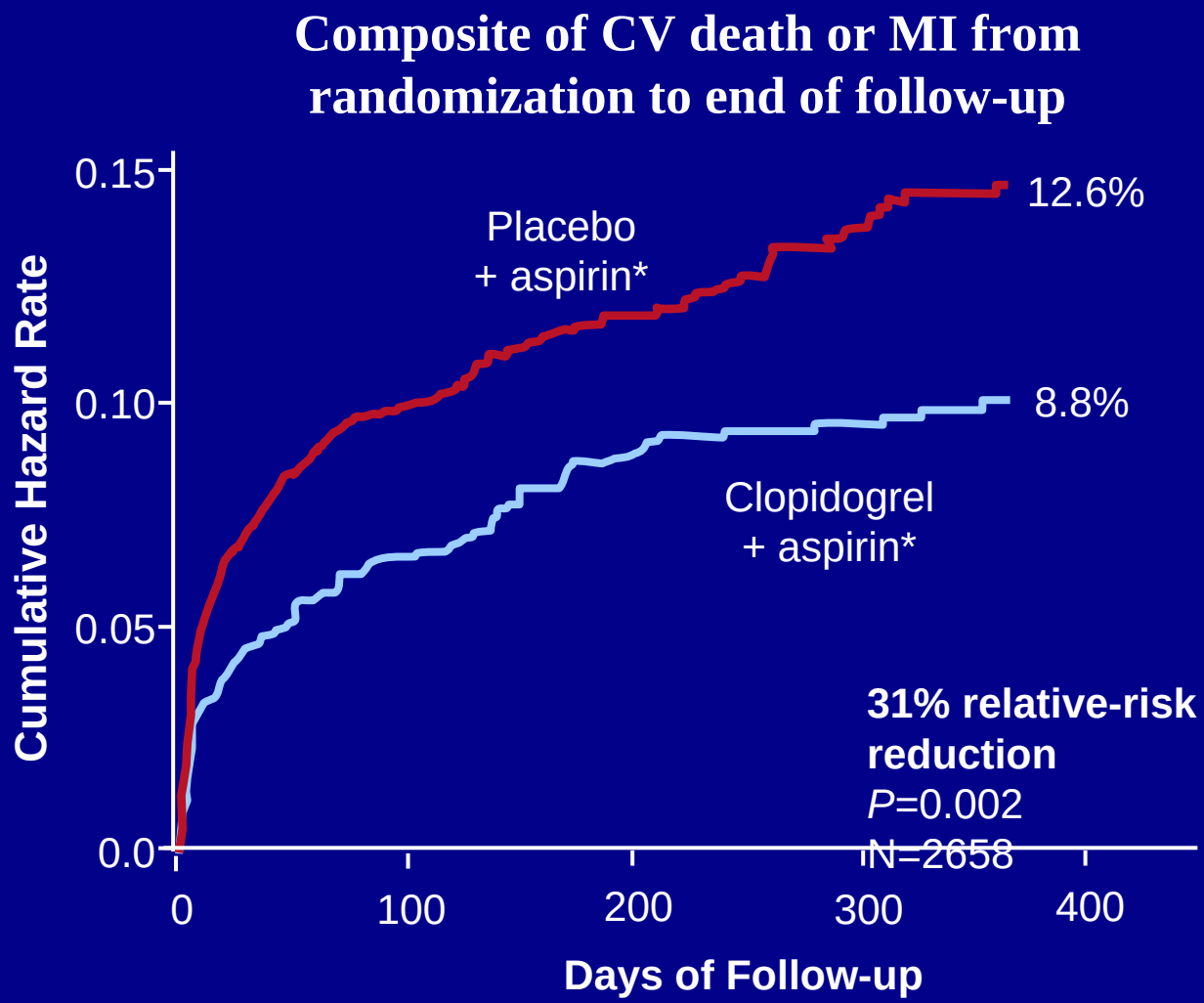
CURE: Benefit of Clopidogrel Not Affected by Cardiac Marker* Status



*Troponin, creatine kinase, MB isoenzyme.
CVD=cardiovascular death.

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

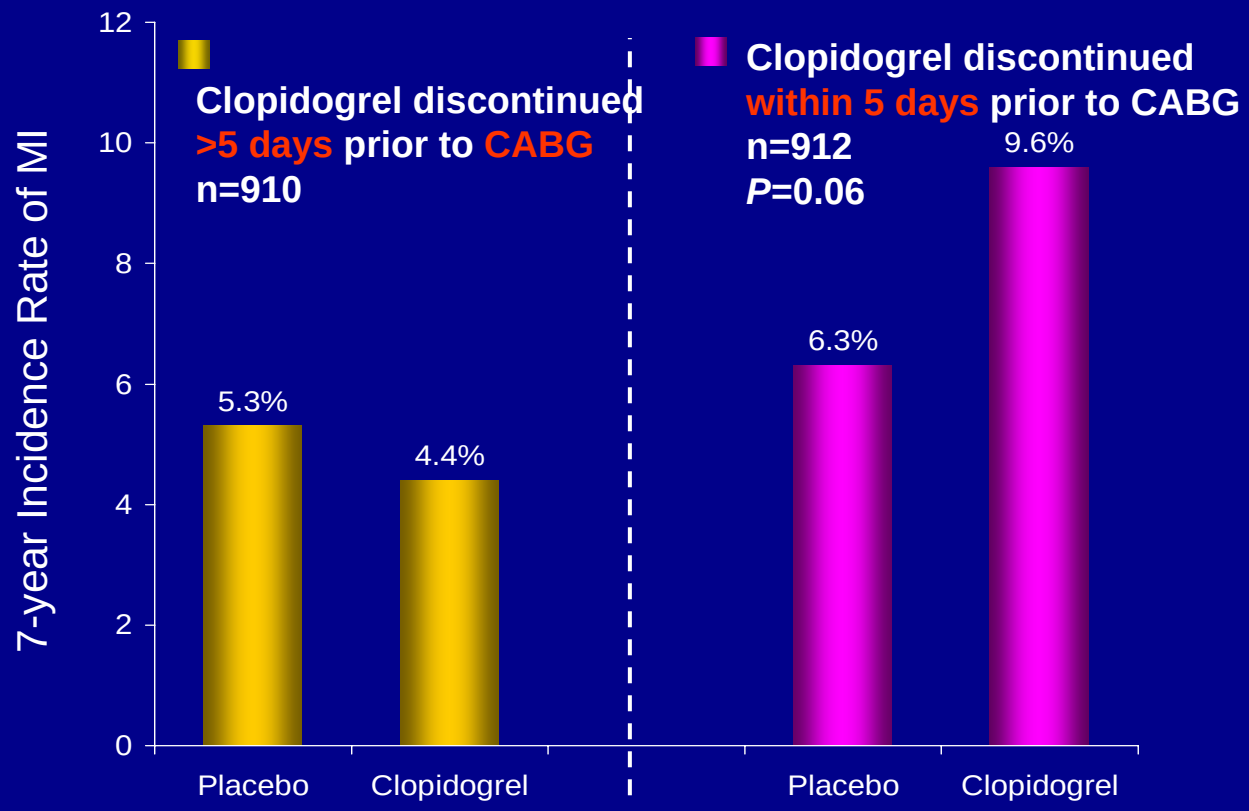
PCI-CURE: Overall Long-term Results



*In combination with standard therapy.

Mehta SR, et al. *Lancet.* 2001;358:527-533.

CURE: Time of Clopidogrel Discontinuation and Bleeding Risk



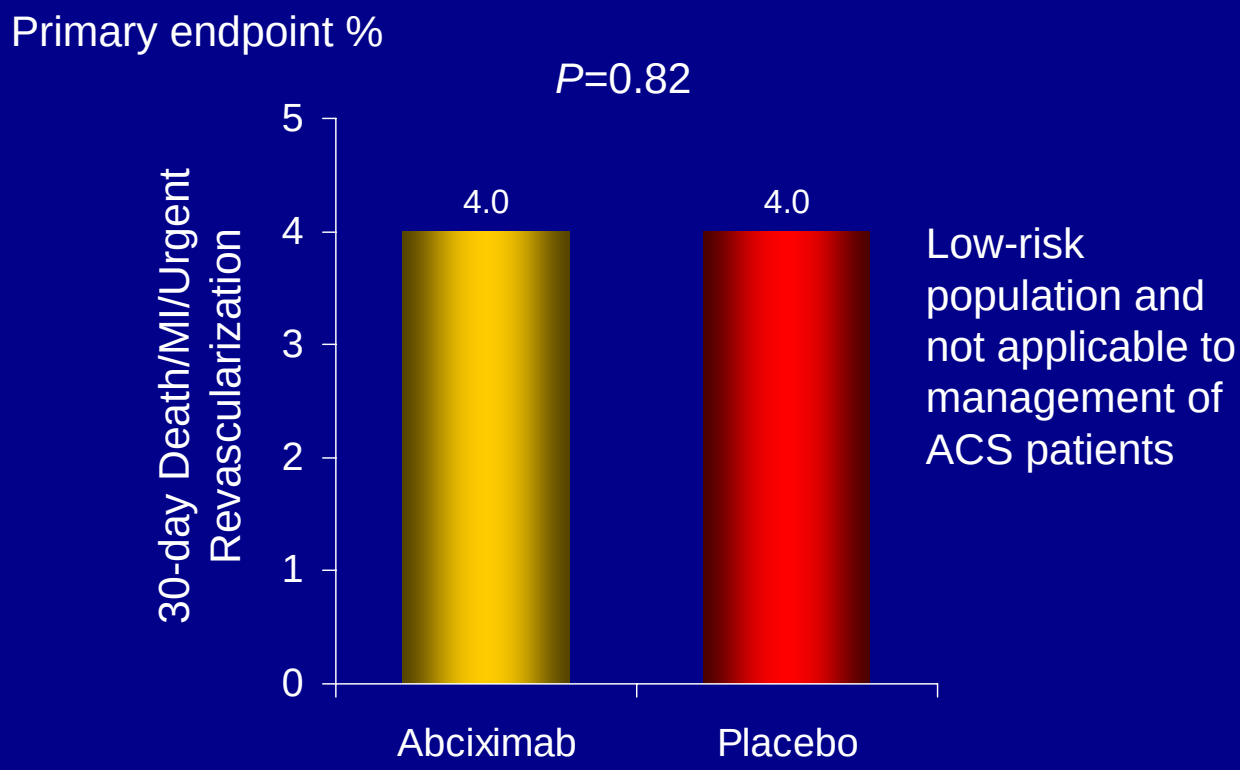
The CURE Trial Investigators. *N Engl J Med.* 2001;345:494-502.

고정관념

GP IIb/IIIa Inhibitor Therapy Does Not Provide Added Benefit to High-Risk Patients with UA/NSTEMI Treated with Clopidogrel

Clopidogrel+GPIIb/IIIa blocker

ISAR-REACT: Effect of Pre-treatment with Clopidogrel* in Low-risk Patients Undergoing Elective PCI



*Clopidogrel 600 mg.

Kastrati A, et al. *N Engl J Med*. 2004;350:232-238.

ISAR-Sweet results spur debate over abciximab's benefits in the setting of clopidogrel pretreatment

ISAR-SWEET end points

End point	Abciximab (%)	Placebo (%)	p
Death or MI	8.3	8.6	0.91
Death	4.8	5.1	0.86
MI	4.8	4.3	0.72
Revascularization	23.4	26.7	0.33

Mehilli J. American Heart Associatio
Sessions 2004. Nov 7-10, 2004; New Orleans, LA.

Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study

METHODS

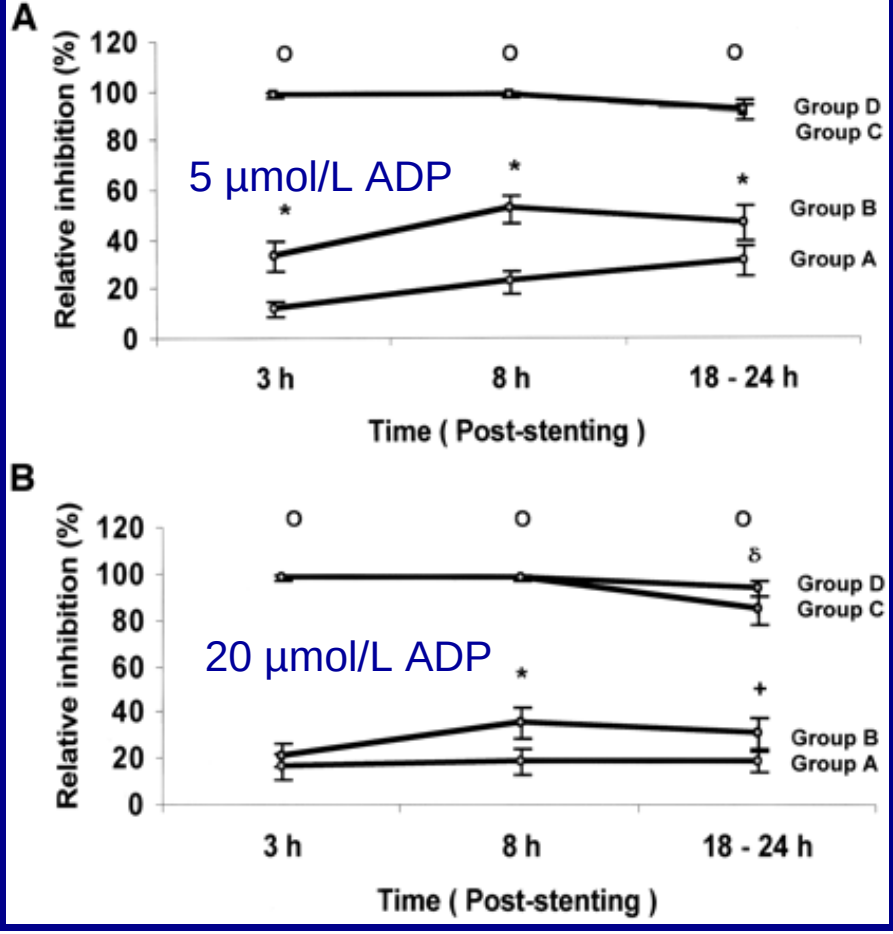
Patients undergoing elective stenting (n=120)

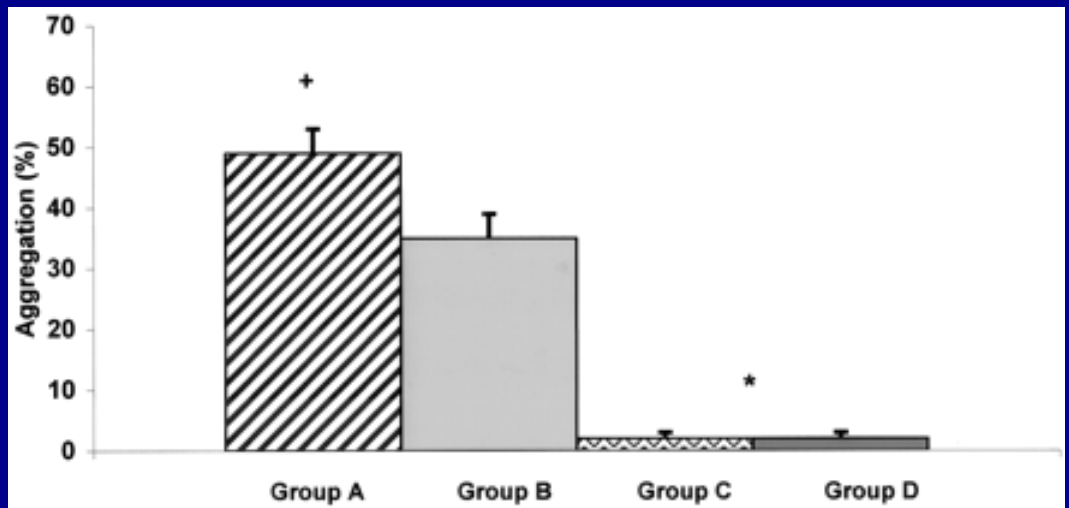
300 mg clopidogrel without eptifibatide (group A)

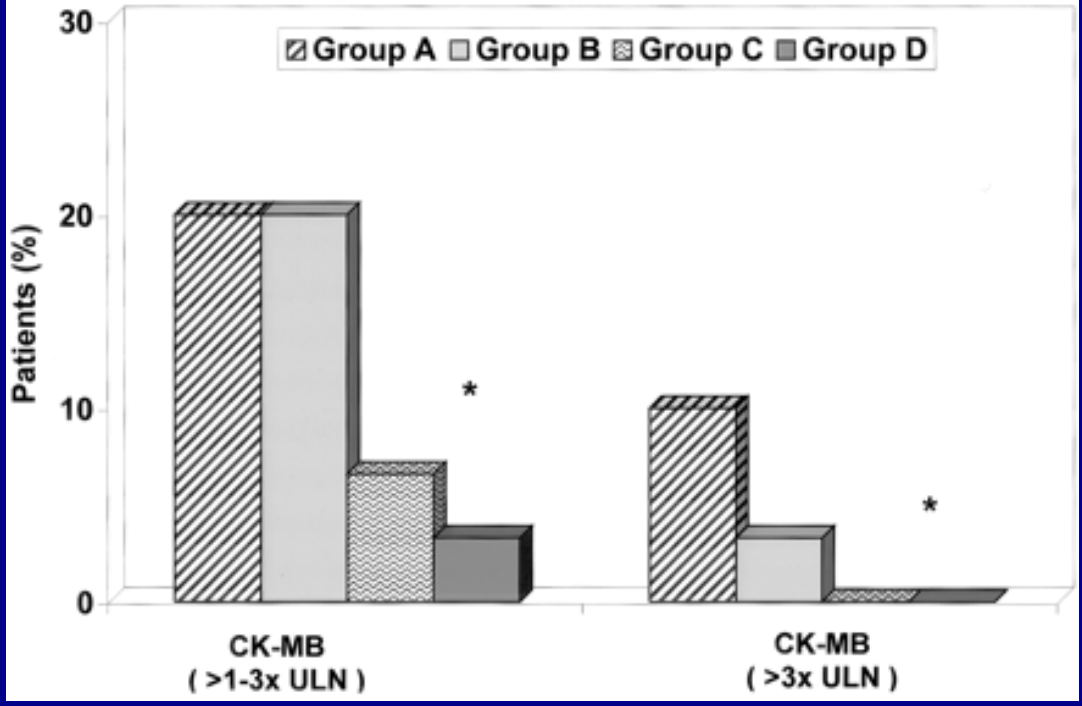
with eptifibatide (group B)

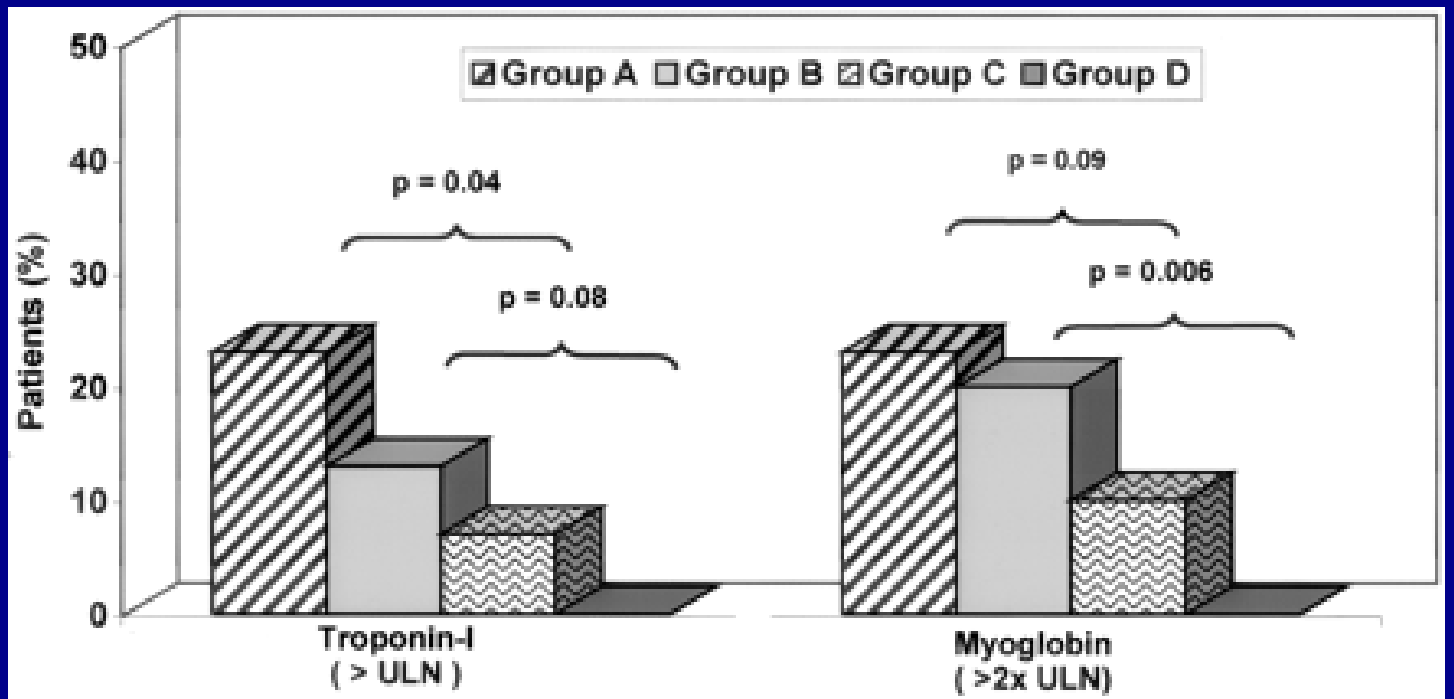
600 mg clopidogrel without eptifibatide (group C)

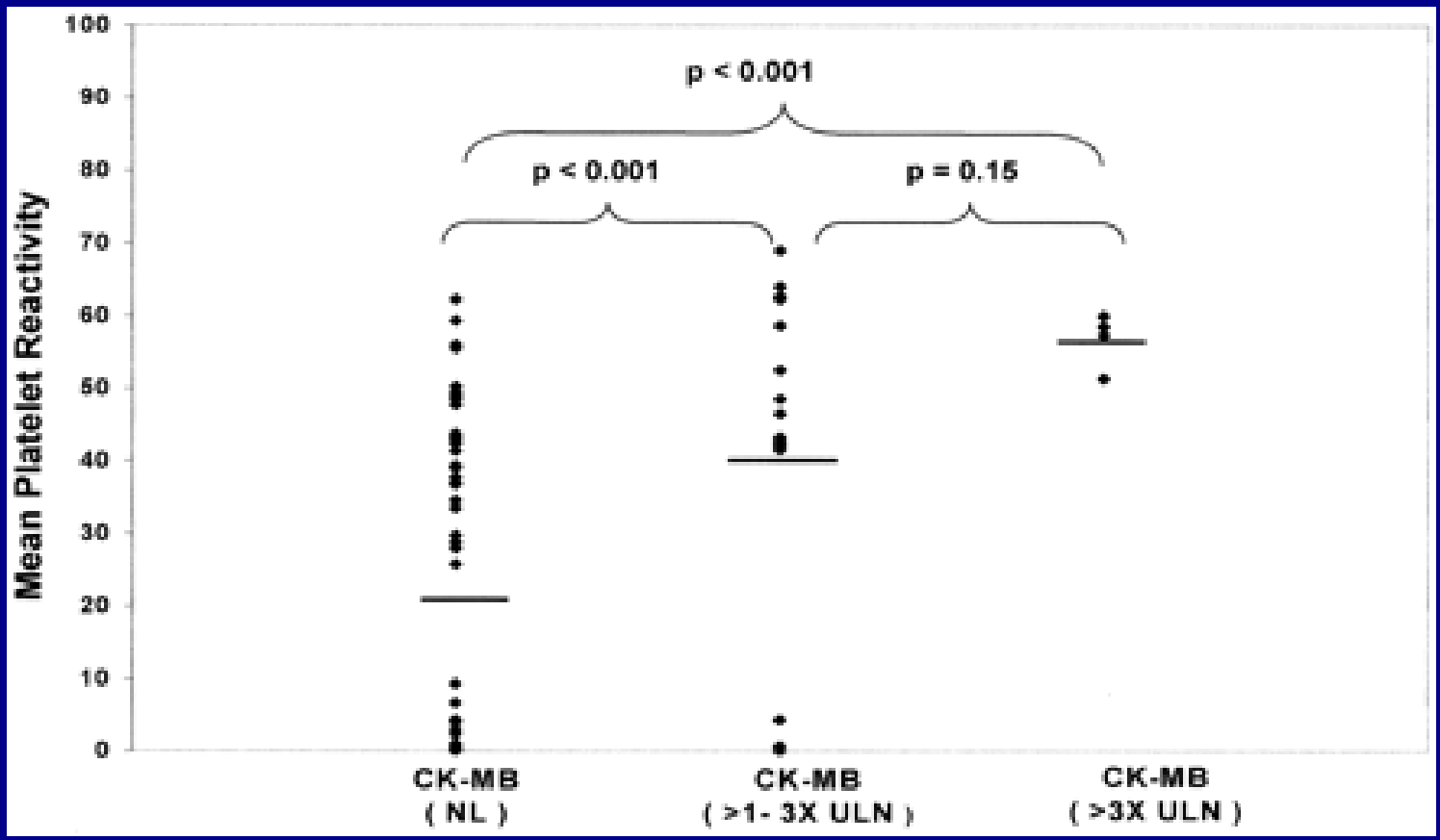
with eptifibatide (group D)


A
Relative inhibition (%)
120
100
80
60
40
20
0
5 µmol/L ADP
Group D
Group C
Group B
Group A
3 h
8 h
18 - 24 h
Time (Post-stenting)
B
Relative inhibition (%)
120
100
80
60
40
20
0
20 µmol/L ADP
Group D
Group C
Group B
Group A
3 h
8 h
18 - 24 h
Time (Post-stenting)


Aggregation (%)
70
60
50
40
30
20
10
0
Group A
Group B
Group C
Group D


Group A
Group B
Group C
Group D
30
20
10
0
Patients (%)
*
*
CK-MB
(>1-3x ULN)
CK-MB
(>3x ULN)


Group A
Group B
Group C
Group D
50
40
30
20
10
0
Patients (%)
p = 0.04
p = 0.08
p = 0.09
p = 0.006
Troponin-I
(> ULN)
Myoglobin
(>2x ULN)


Mean Platelet Reactivity
100
90
80
70
60
50
40
30
20
10
0
p < 0.001
p < 0.001
p = 0.15
CK-MB
(NL)
CK-MB
(>1- 3X ULN)
CK-MB
(>3X ULN)

RESULTS

In elective stenting without clopidogrel pretreatment, use of a GPIIb/IIIa inhibitor produces superior platelet inhibition and lower myocardial necrosis compared with high-dose (600 mg) or standard-dose (300 mg) clopidogrel loading alone. In the absence of a GPIIb/IIIa inhibitor, 600 mg clopidogrel provides better platelet inhibition than the standard 300-mg dose. These results require confirmation in a large-scale clinical trial.

Clinical Implications

Our data support a future larger clinical study to investigate whether 600 mg should become the new standard loading strategy for this drug in elective coronary stenting.

Focus on Clopidogrel: Role in UA/NSTEMI Therapy

- CURE study demonstrated significant reductions in ischemic complications when clopidrogrel was added to aspirin
  - Associated with consistent 20% reduction across risk subgroups
- Associated with higher risk of bleeding than aspirin
- Studies clarifying **combined use** of GP IIb/IIIa inhibitors and clopidogrel in upstream setting are **lacking**
- Pretreatment with clopidogrel in GP IIb/IIIa interventional studies appear favorable, suggesting additive benefit
  - However, it is important to recognize that patients in ISAR-REACT were not high-risk and underwent elective PCI
- **Benefits of clopidogrel and GP IIb/IIIa inhibitors appear complementary**

The CURE Trial Investigators. *N Engl J Med.* 345:494-502.
Januzzi JL, et al. *Am Heart J.* 2003;146:764-774.
Avlies RJ, Bhatt DL. *J Thromb Thrombolysis.* 2002;13:177-182.

Clopidogrel Summary

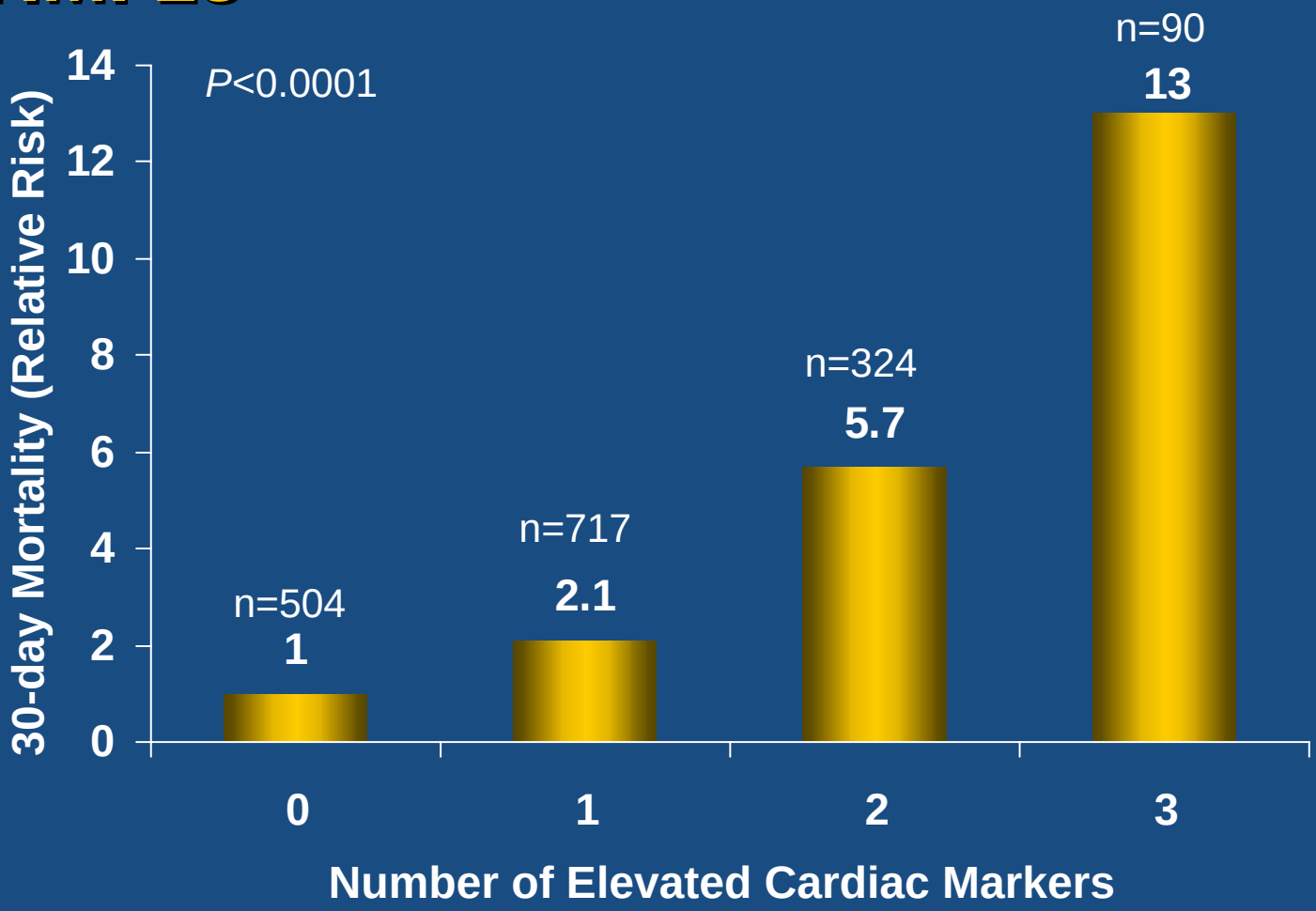
- Clopidogrel has been shown to be more effective at reducing events than aspirin alone in patients with UA/NSTEMI
- Relative-risk reduction with clopidogrel in UA/NSTEMI is 20% alone vs. 44% with the addition of GP IIb/IIIa inhibitors
- Clopidogrel is an effective part of the UA/NSTEMI treatment strategy
- Clopidogrel is long-acting, therefore consideration should be taken when using it prior to catheterization, due to potential bleeding risk

The CURE Trial Investigators. *N Engl J Med.* 345:494-502.
Januzzi JL, et al. *Am Heart J.* 2003;146:764-774.
Avlies RJ, Bhatt DL. *J Thromb Thrombolysis.* 2002;13:177-182.

고정관념

The Beneficial Effects of GP IIb/IIIa Inhibitors Are Related Only to Large-vessel Thrombus Resolution

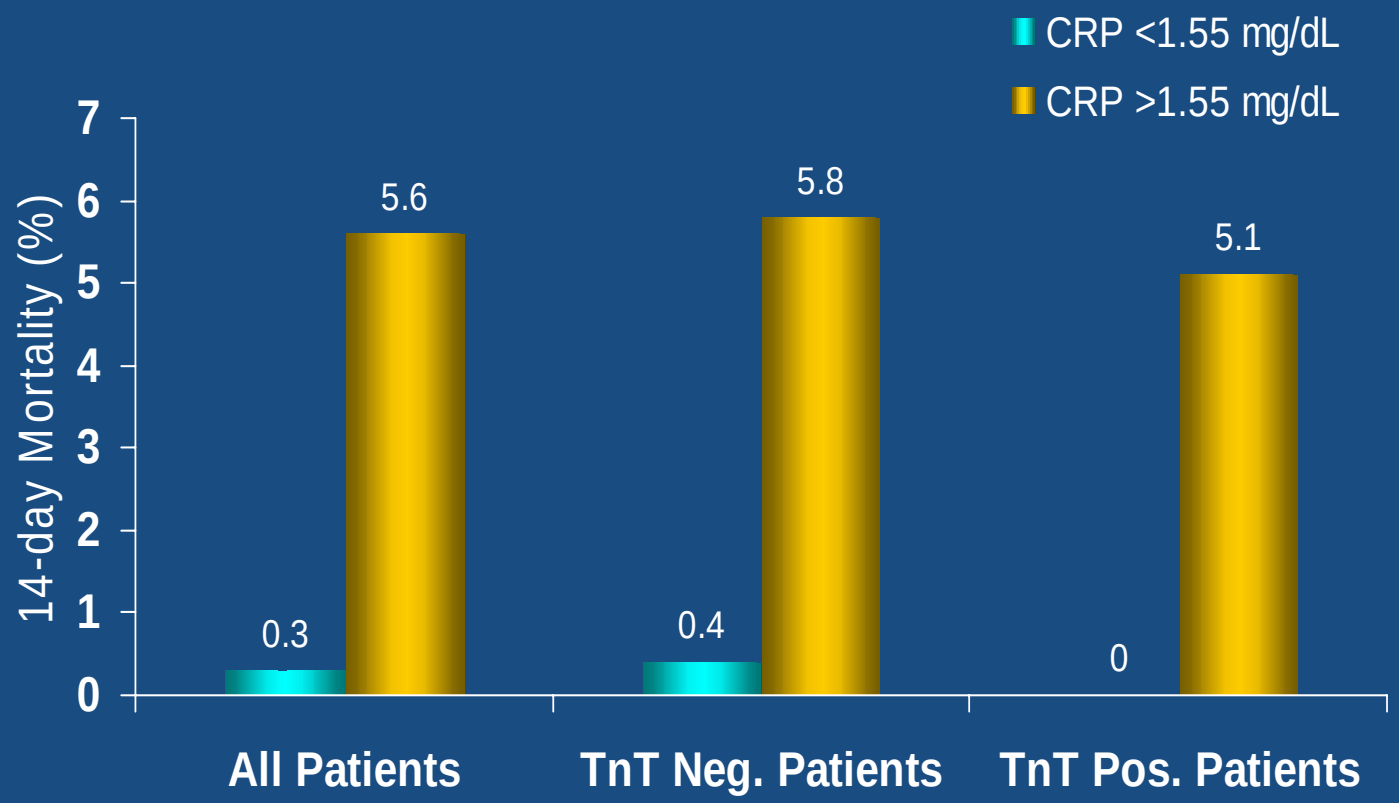
Mortality Increases with Number of Elevated Cardiac Markers*: TACTICS-TIMI 18



*Cardiac biomarkers=troponin I, C-reactive protein (CRP), brain natriuretic peptide (BNP).

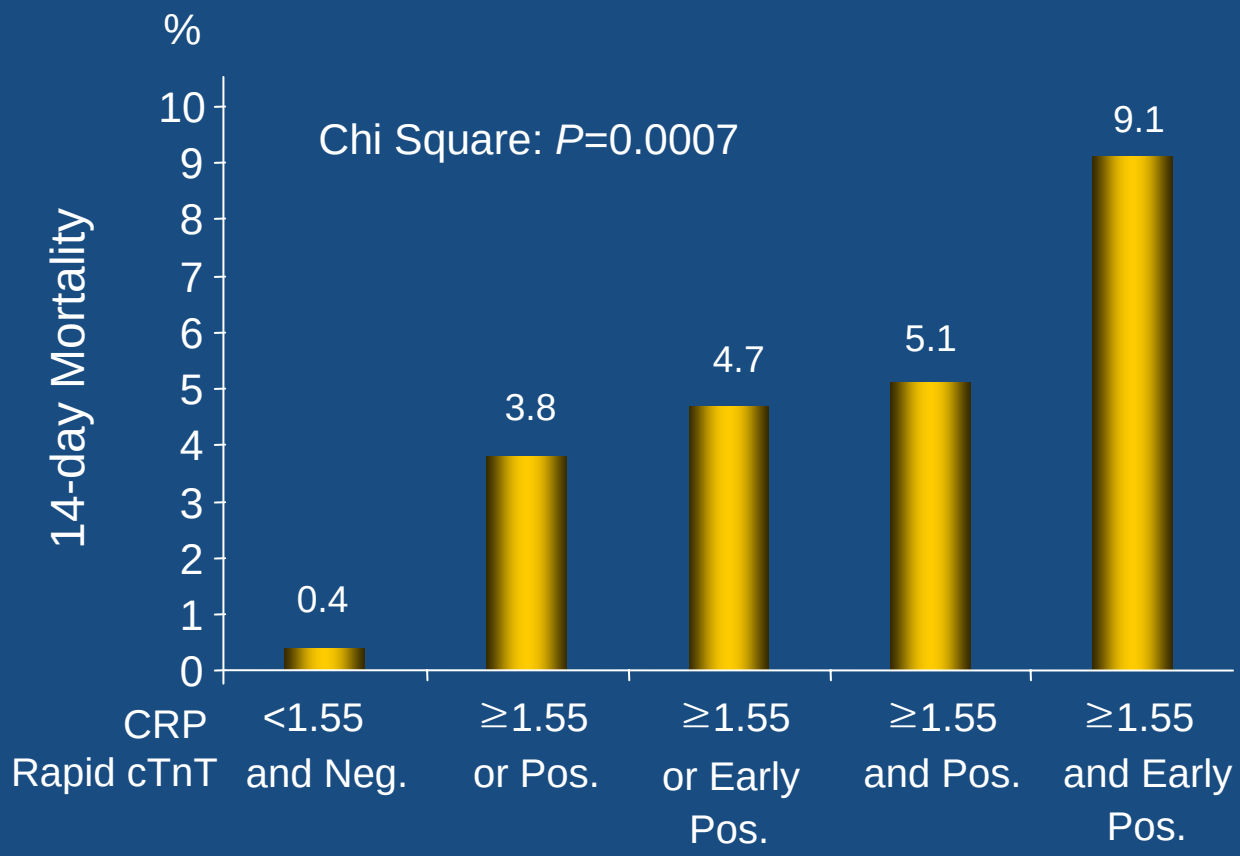
Sabatine M, et al. *Circulation.* 2002;105:1760-1763.

Mortality Increased in Patients with High CRP Concentrations: TIMI-11A Substudy



Morrow D, et al. *J Am Coll Cardiol.* 1998;31:1460-1465.

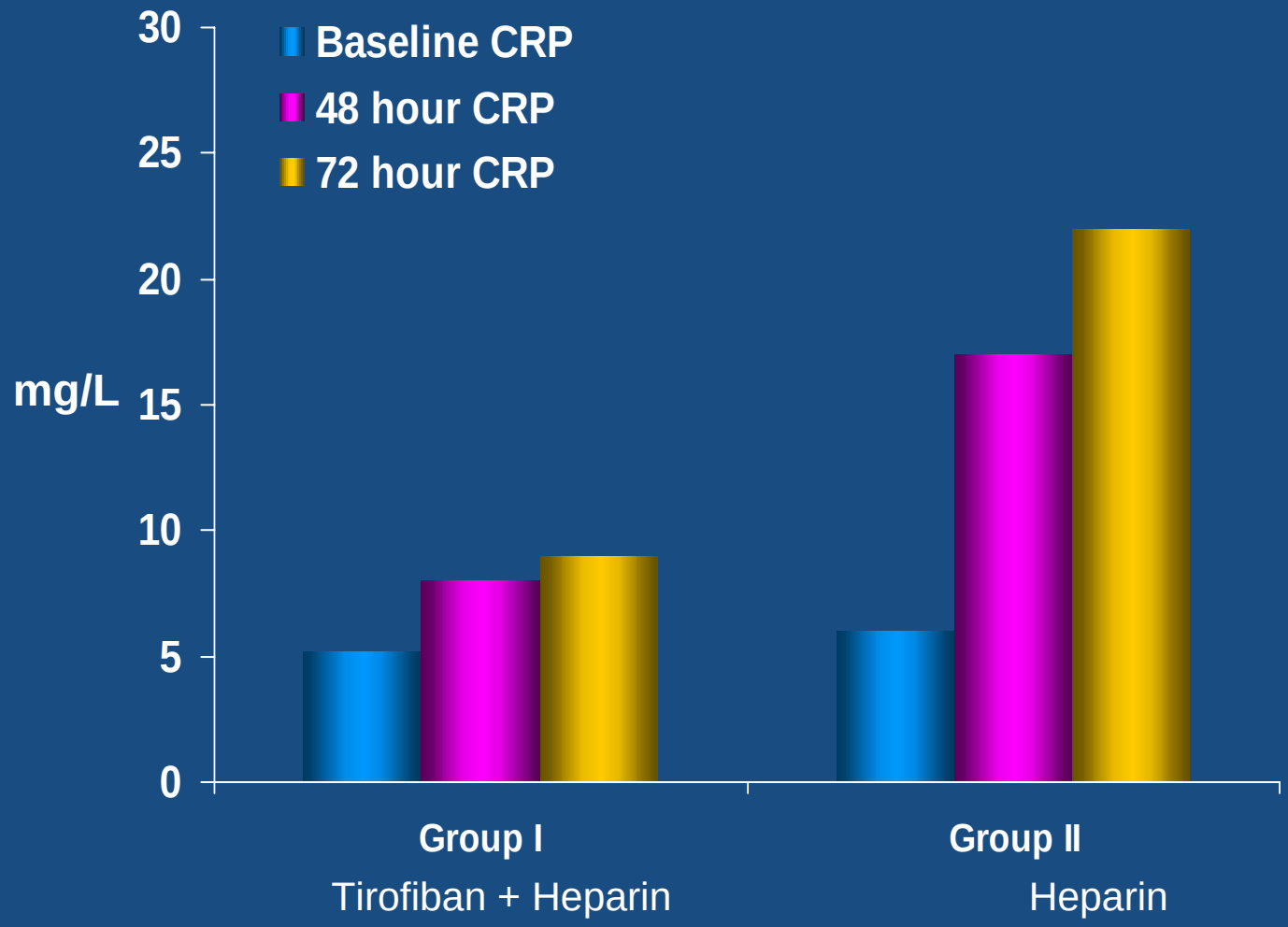
Risk Stratification by CRP (mg/dl) and Rapid Assay Status Expressed as 14-day Mortality by CRP and Rapid Troponin T Result



cTnT=cardiac troponin T.

Morrow D, et al. *J Am Coll Cardiol.* 1998;31:1460-465.

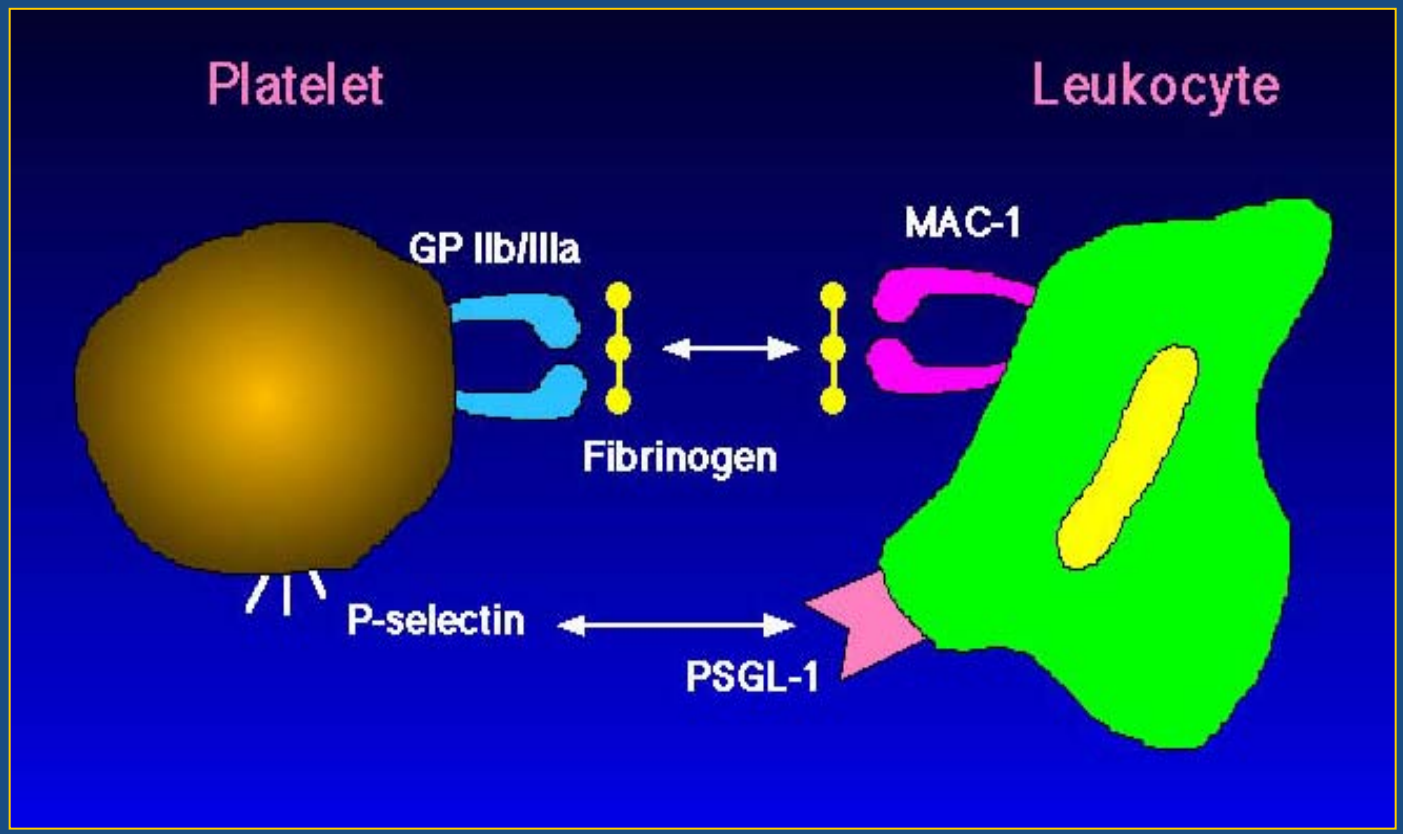
1.CRP Levels and Tirofiban Therapy



Ercan E, et al. *Am Heart J.* 2004;147:e1.

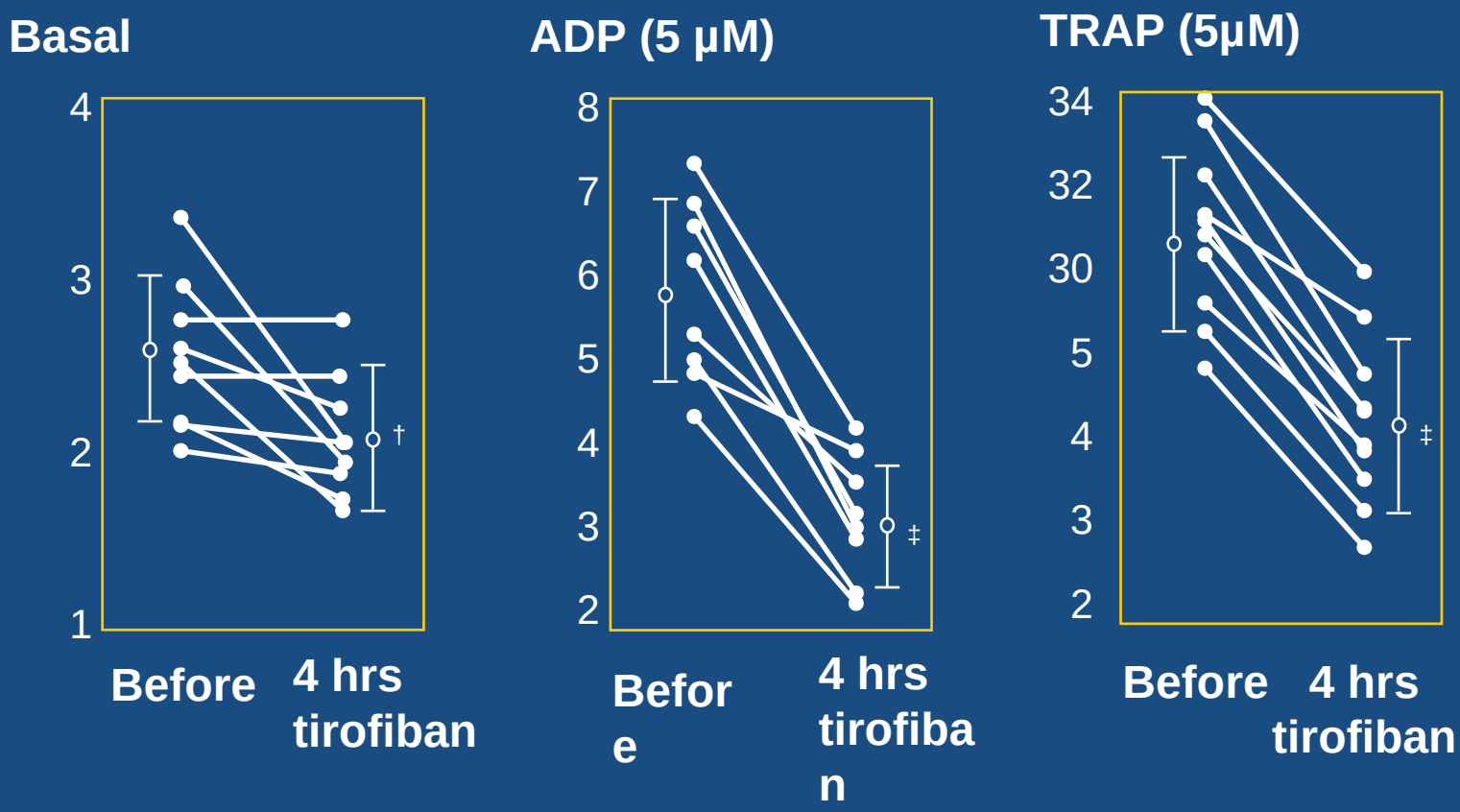
2. Plaque Passivation with GP IIb/IIIa Receptor Blockade

Mechanisms for Platelet-leukocyte Interaction



Prevention of Platelet-leukocyte Interaction with Tirofiban

Binding Density of Platelets in Coaggregates

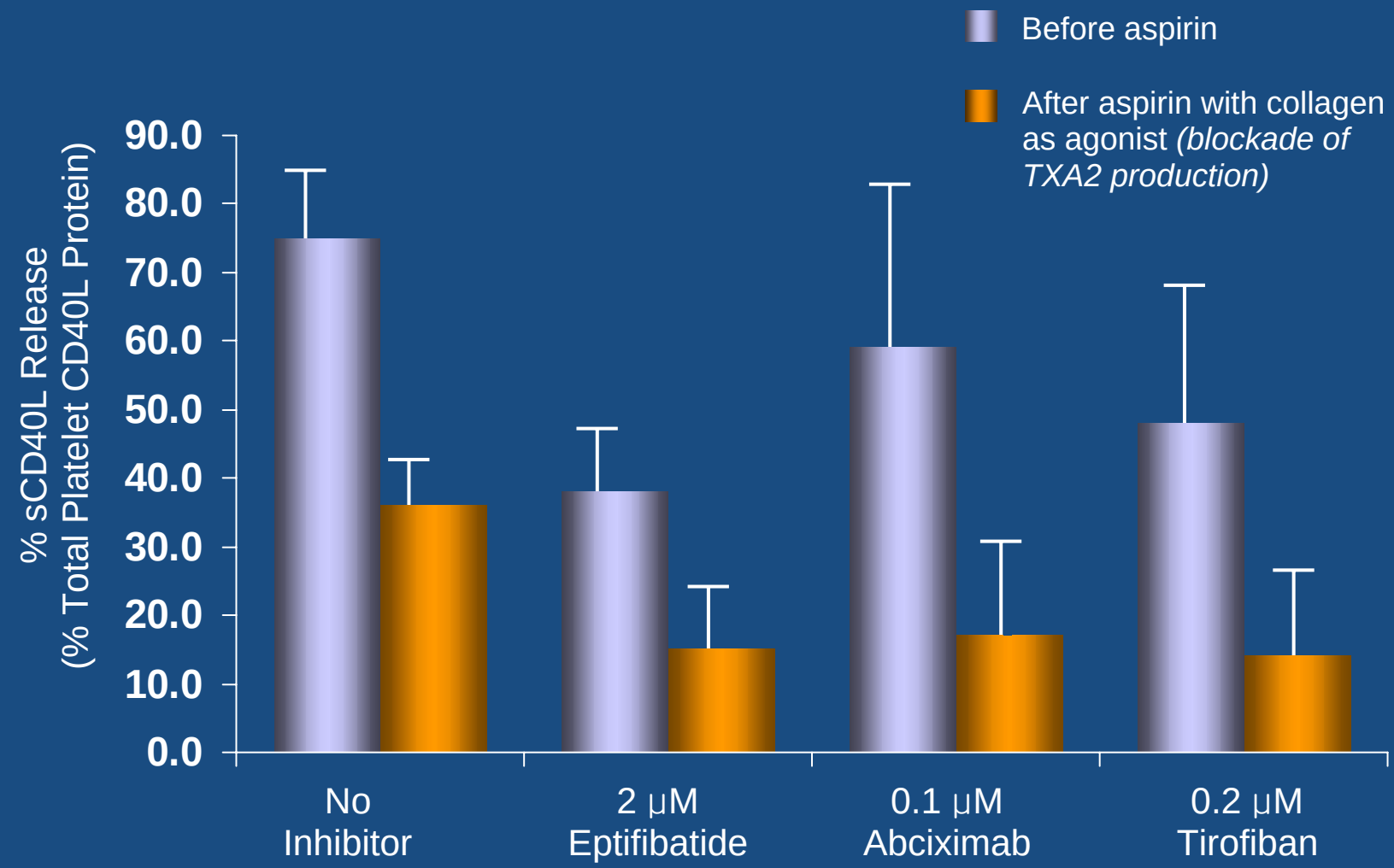


† P<0.05 vs before

‡ P<0.01 vs before

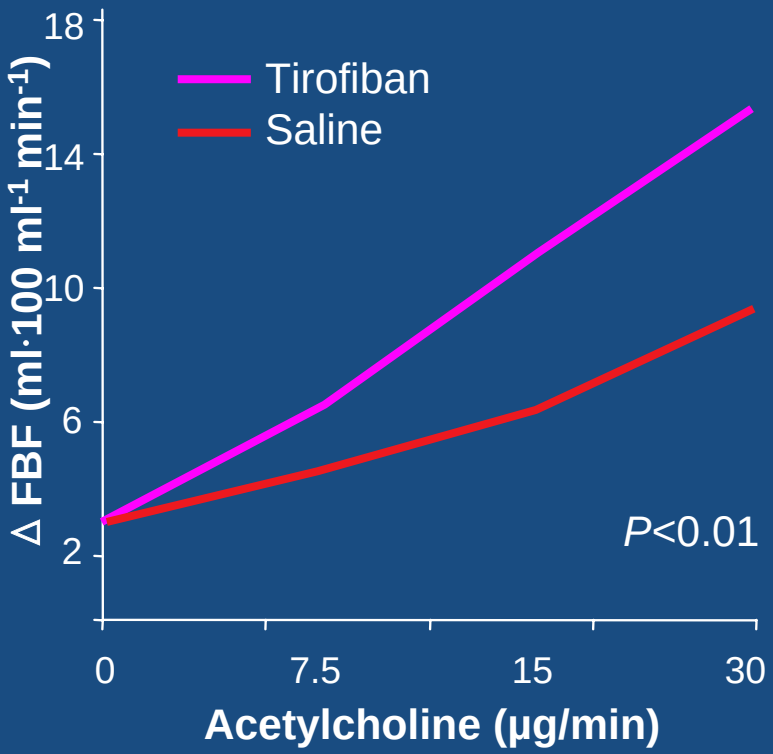
Xiao Z, et al. *Thromb Haemost.* 1999;81:281-285.

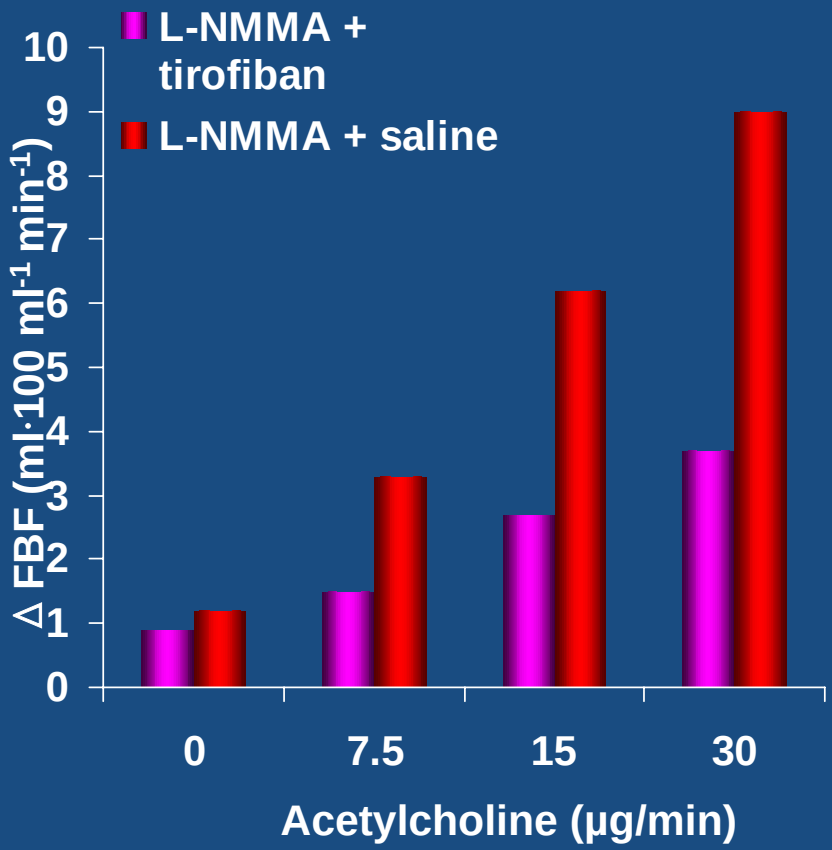
GP IIb/IIIa Antagonists Inhibit Inflammation through Blockade of sCD40L



Nannizzi-Alaimo L, et al. *Circulation*. 2003;107:1123-1128.

3.GP IIb/IIIa Inhibitors Improve Vascular Nitric Oxide Bioavailability

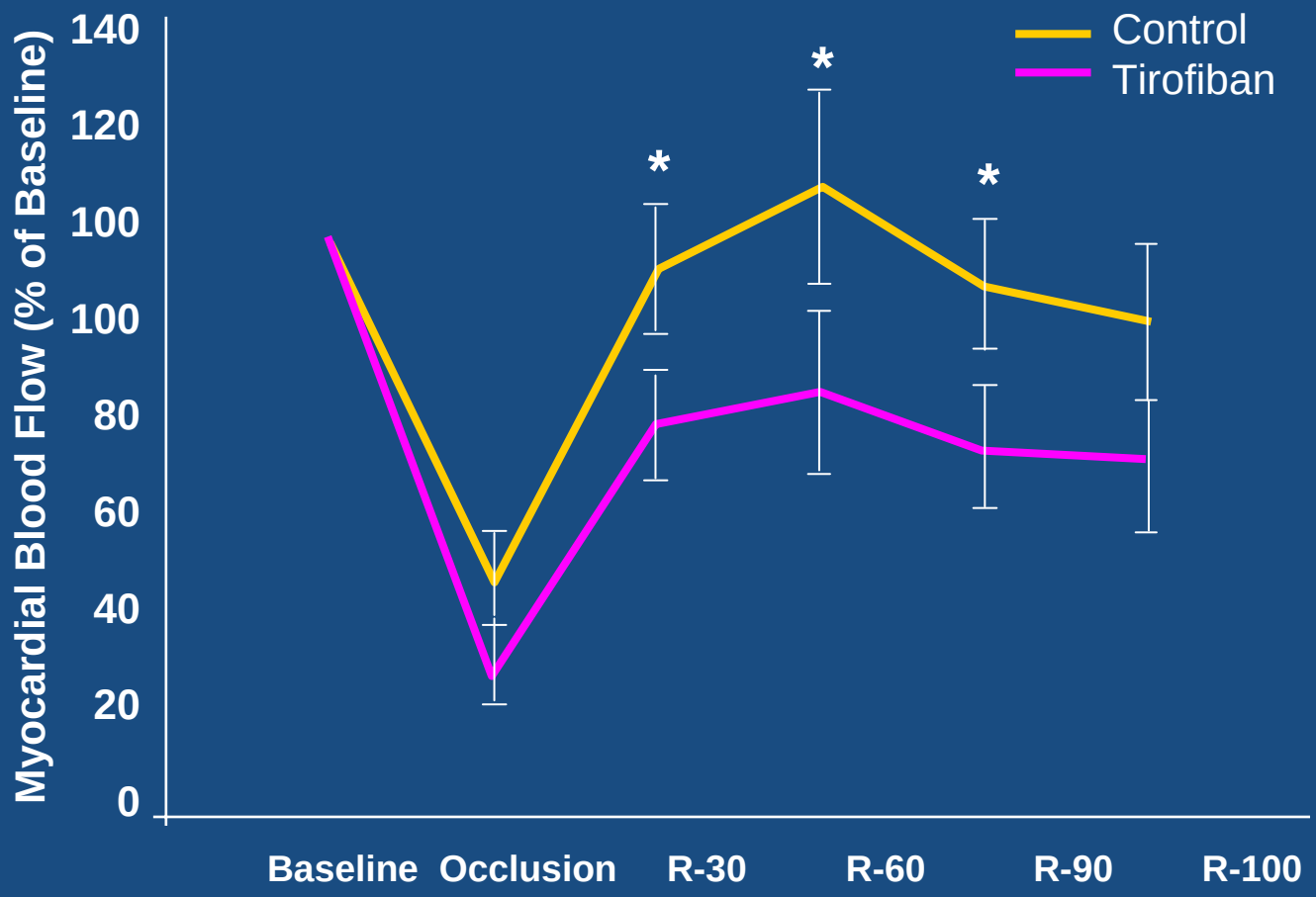




FBF=forearm blood flow.
L-NMMA=NG-monomethyl-L-arginine.

Heitzer T, et al. *Circulation*. 2003;108:536-541.

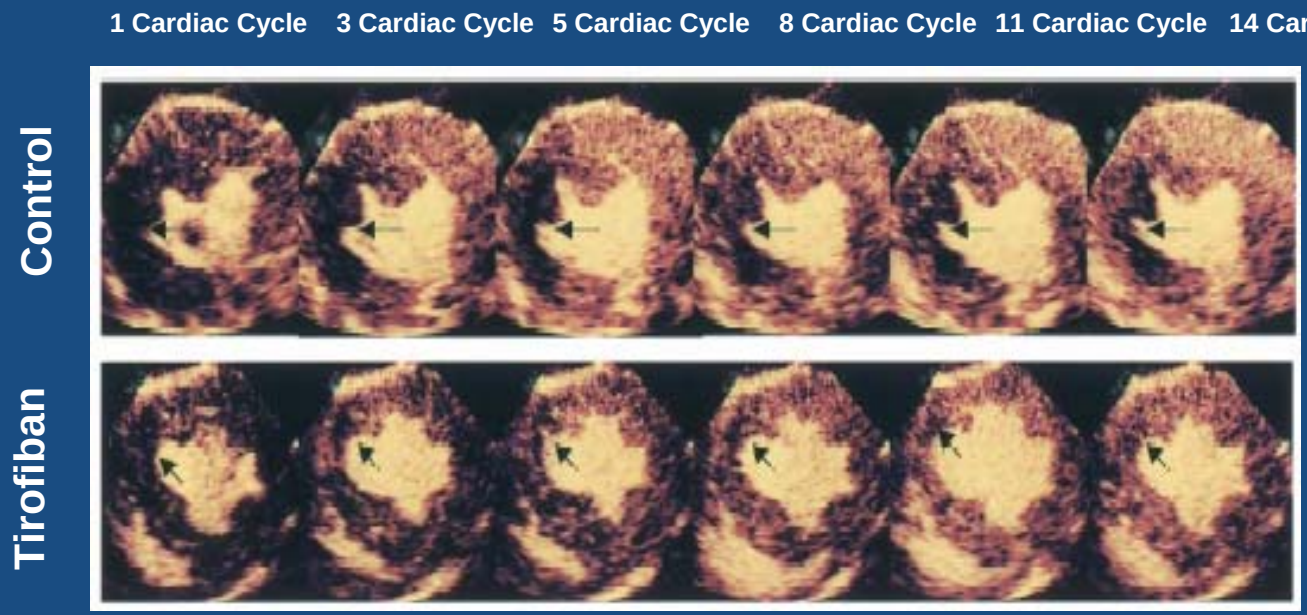
4.Tirofiban Increases Microvascular Blood Flow after revascularization*



*Study completed in canine model.

Kunichika H, et al. *J Am Coll Cardiol.* 2004;43(2):276-283.

GP IIb/IIIa Inhibitors Increase Myocardial Blood Flow after Revascularization



Kunichika H et al. *J Am Coll Cardiol*. 2004;43(2):284-286.

Summary

- GP IIb/IIIa inhibitors have been shown to have effects in factors beyond platelet aggregation
- GP IIb/IIIa inhibitors improved myocardial perfusion as evidenced by improved TIMI perfusion grade
- These effects may potentially contribute to their efficacy

고정관념

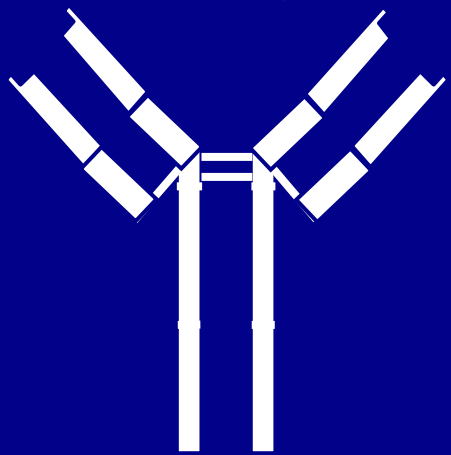
GP IIb/IIIa Inhibitors Only Provide Value when Initiated In the Cardiac Catheterization Laboratory

GP IIb/IIIa Inhibitors: Chemical Structures

Abciximab

Fab fragment of a chimeric monoclonal antibody

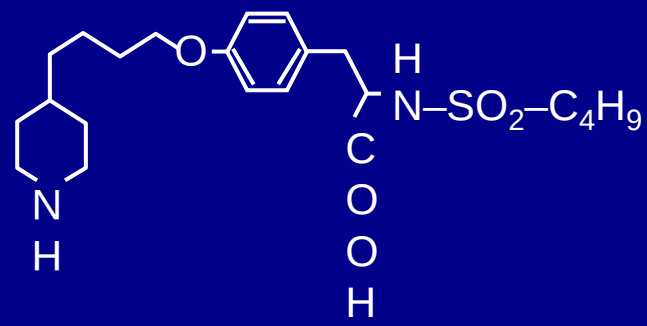
MW ≈ 50,000 D



Tirofiban

Nonpeptide tyrosine derivative

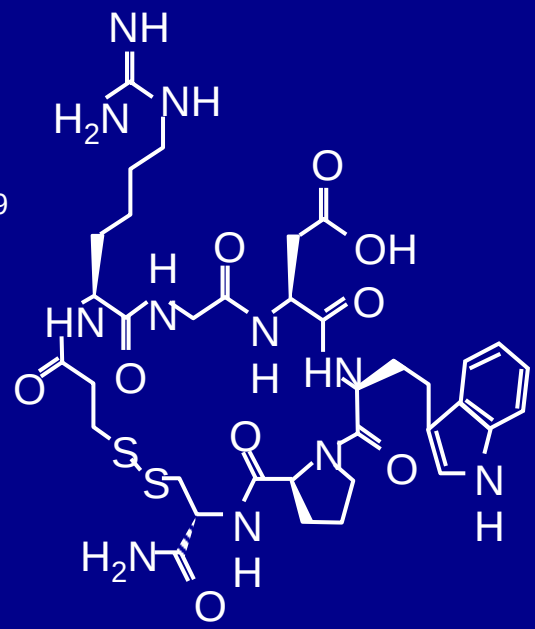
MW ≈ 500 D



Eptifibatide

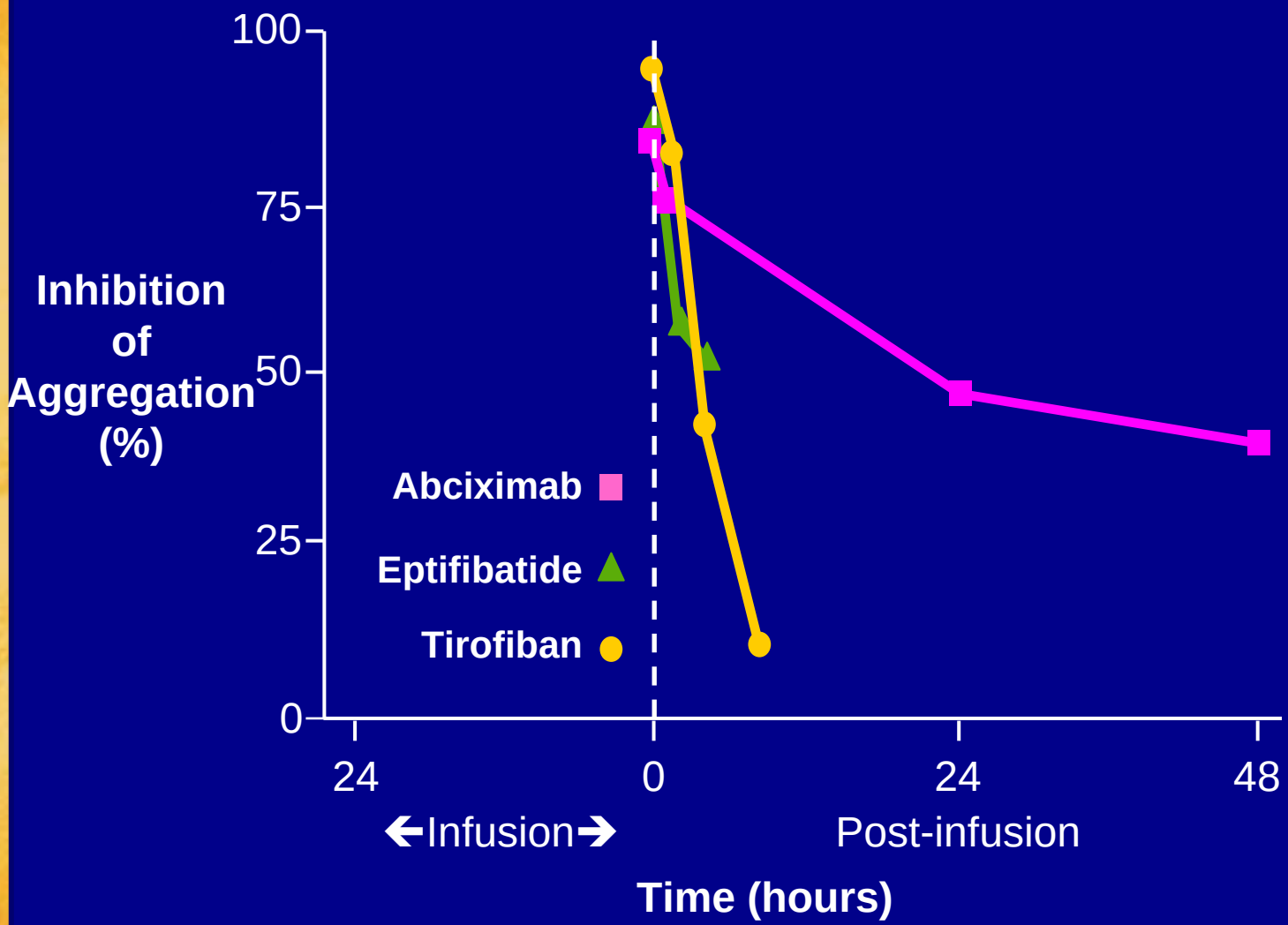
Cyclic heptapeptide

MW ≈ 800 D



Topol E, et al. *Lancet*. 1999;353:227-231.

Reversibility of GP IIb/IIIa Inhibition



Scarborough RM, et al. *Circulation*. 1999;100:437-444.

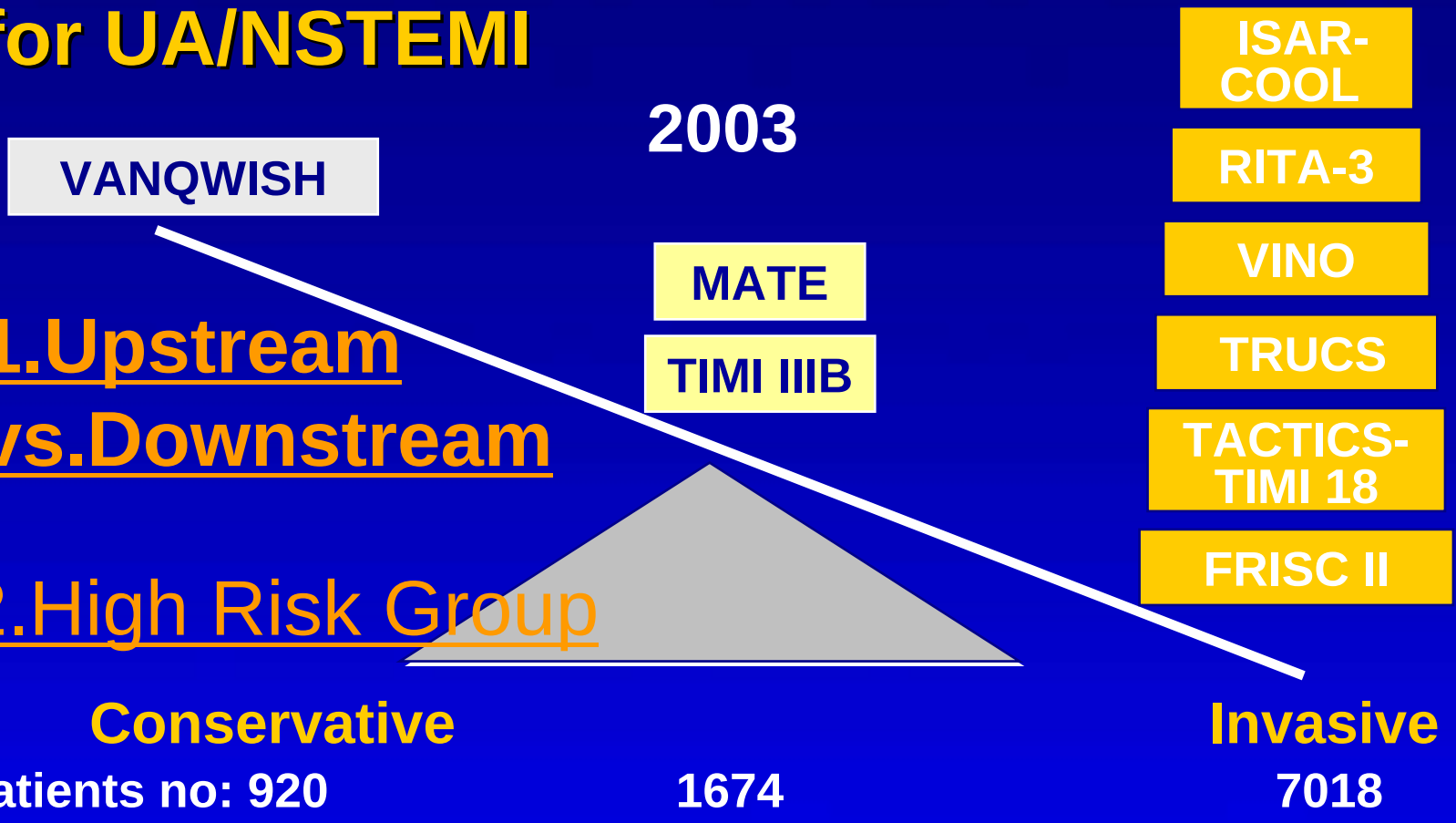
DOSE:
Higher Boluses of Tirofiban

- **Identify a tirofiban bolus that achieves inhibition of platelet aggregation (IPA) similar to that of abciximab—greater than 85% (mean 90%) through 60 minutes**
- **LTA induced by 20 μM ADP in PRP prepared from PPACK anticoagulated blood**
- **Study Population: Patients with ACS undergoing PCI**

  - **The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high- risk coronary angioplasty: the ADVANCE Trial.**
    HDB tirofiban (25 microg/kg/3 min,
    and infusion of 0.15 microg/kg/min for 24 to 48 h)

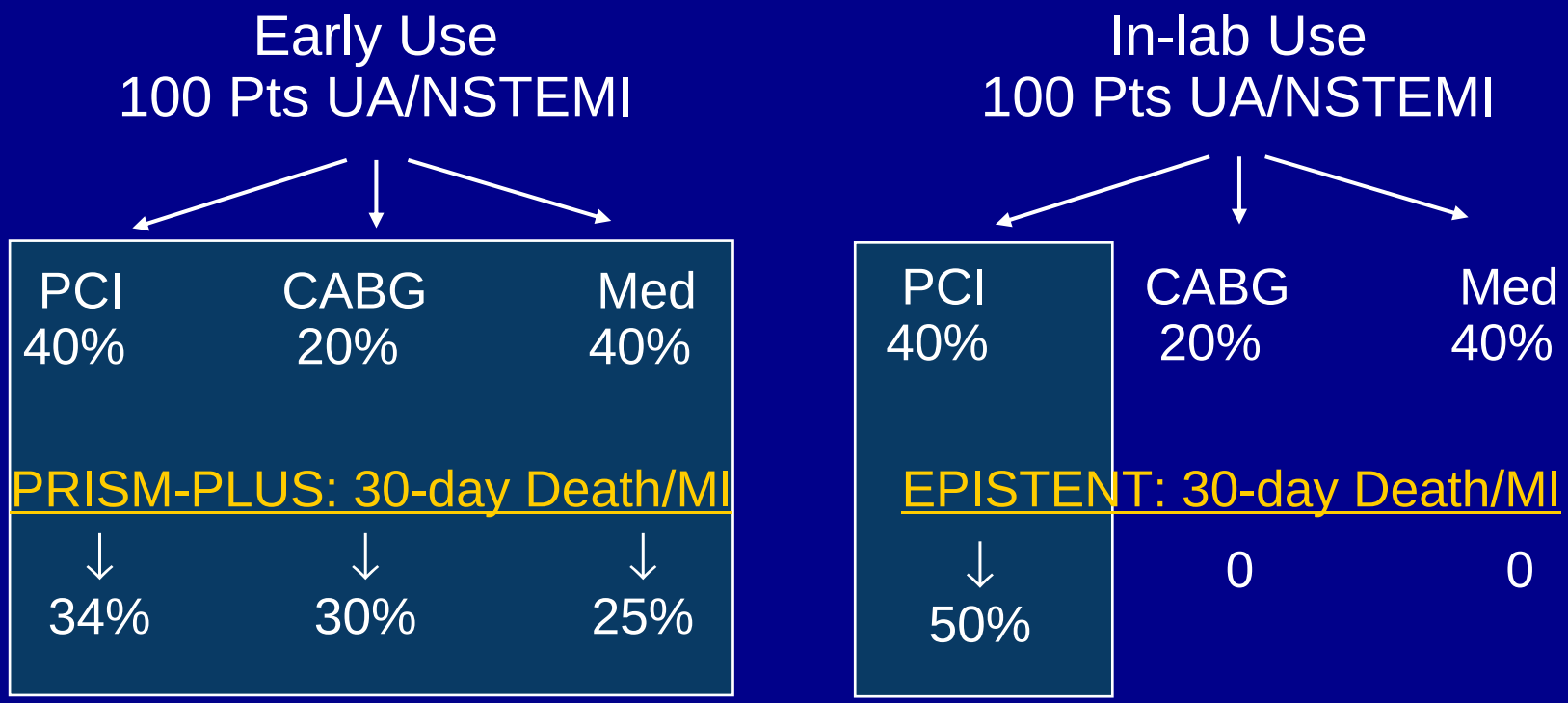
LTA=light transmission aggregation.
ADP=adenosine diphosphate.
PRP=platelet-rich plasma.
PPACK=D-phenylalanyl-L-prolyl-L-arginine chloromethylketone.

Invasive vs Conservative Strategy for UA/NSTEMI



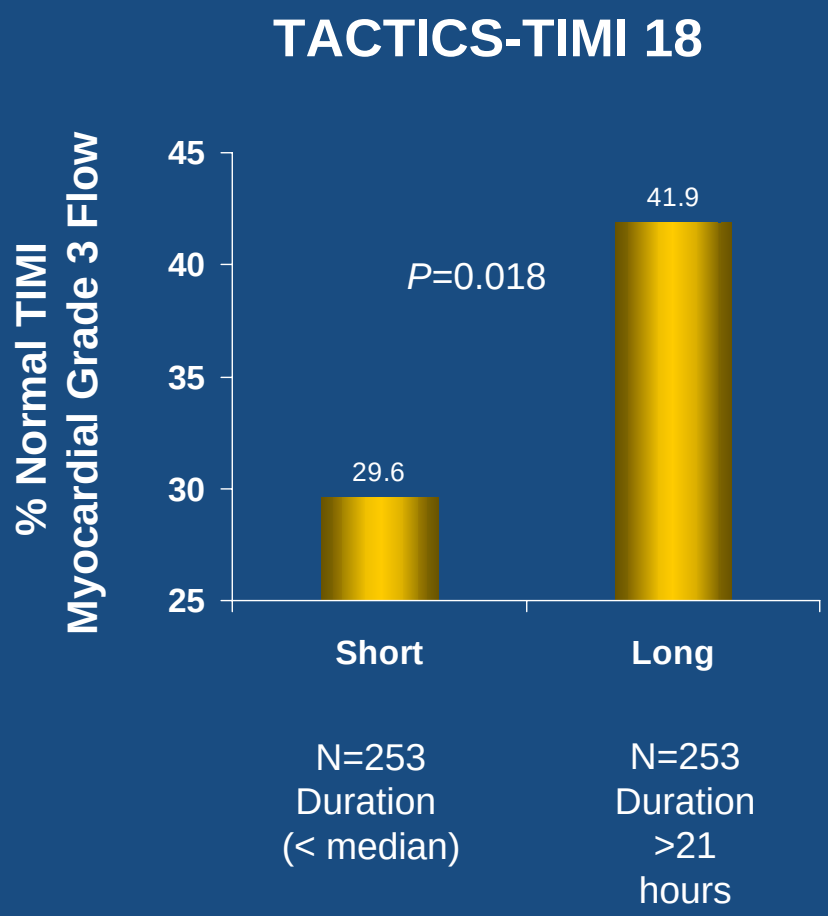
UA, unstable angina, NSTEMI, non–ST-segment myocardial infarction; ISAR, Intracoronary Stenting and Antithrombic Regimen Trial; RITA, Randomized Intervention Treatment of Angina; VANQWISH, Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital study; MATE, Medicine vs Angioplasty for Thrombolytic Exclusions trial; TACTICS-TIMI18, Treat Angina with Aggrestat® and Determine Cost of Therpay with Invasive or Conservative Strategy; FRISC, Fragmin during InStability in Coronary artery disease.

1.Upstream use:
Early Use of GP IIb/IIIa Inhibition Benefits all Strategies



= Benefit of GP IIb/IIIa inhibition

PCI-TACTICS: Duration of Pre-treatment



A longer duration of therapy was associated with improvements in:

↑ TIMI myocardial perfusion grade 3: Odds 52% (*P*=0.012)

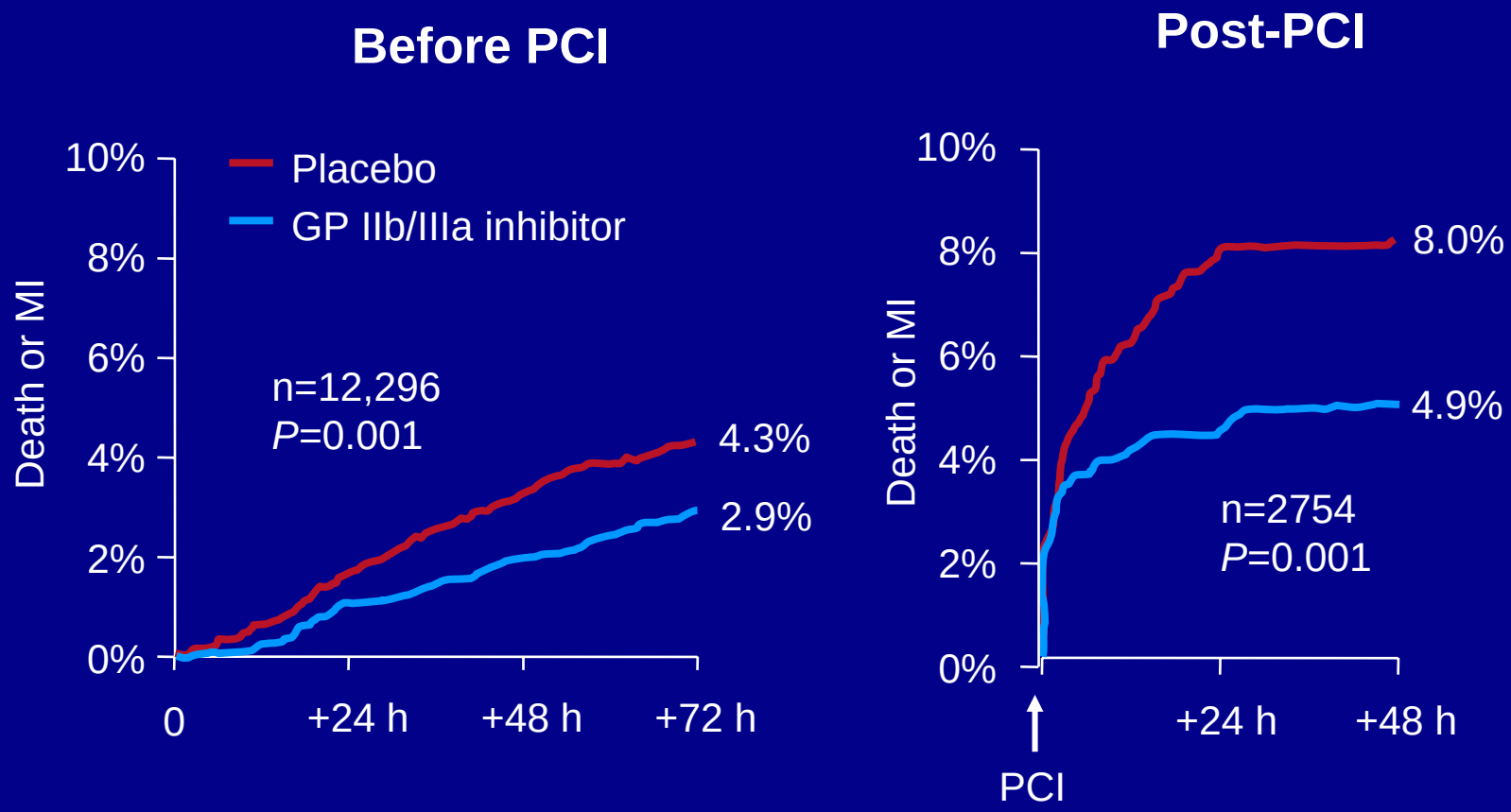
↑ TIMI epicardial flow grade 3: Odds 61% (*P*=0.054)

↑ Minimum diameter: *P*=0.032

*Adjusted for baseline TnT.

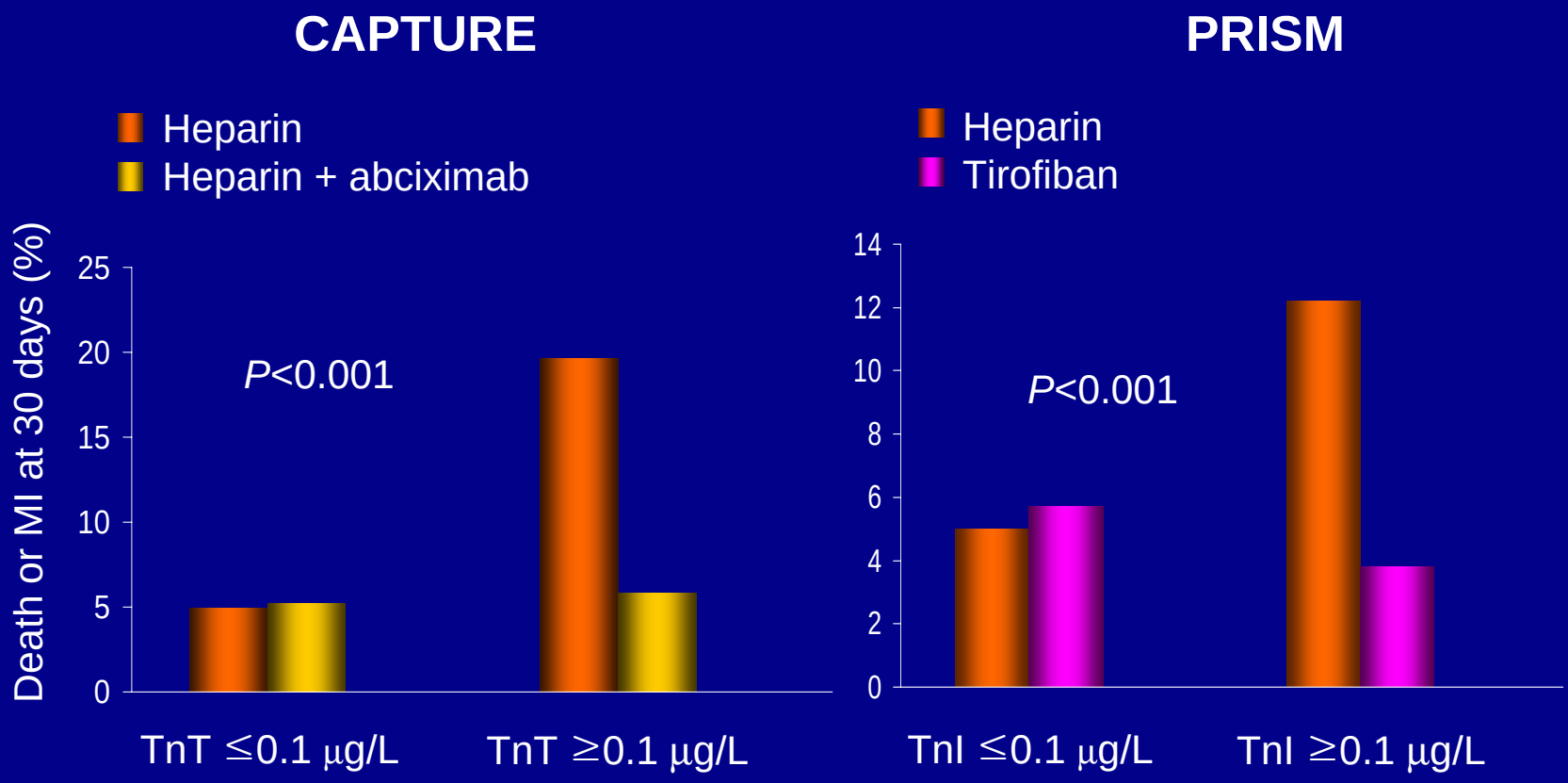
Gibson CM. Presented at: AHA Scientific Sessions; November 11-14, 2001; Anaheim, Ca.

Early and Continued Use of GP IIb/IIIa Inhibition Improves PCI Outcome: CAPTURE, PURSUIT, and PRISM-PLUS



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

2.High-risk group:
Benefit of GP IIb/IIIa Inhibitors in High-Risk Patients: Elevated Troponin Levels



TnT=troponin T.
TnI=troponin I.

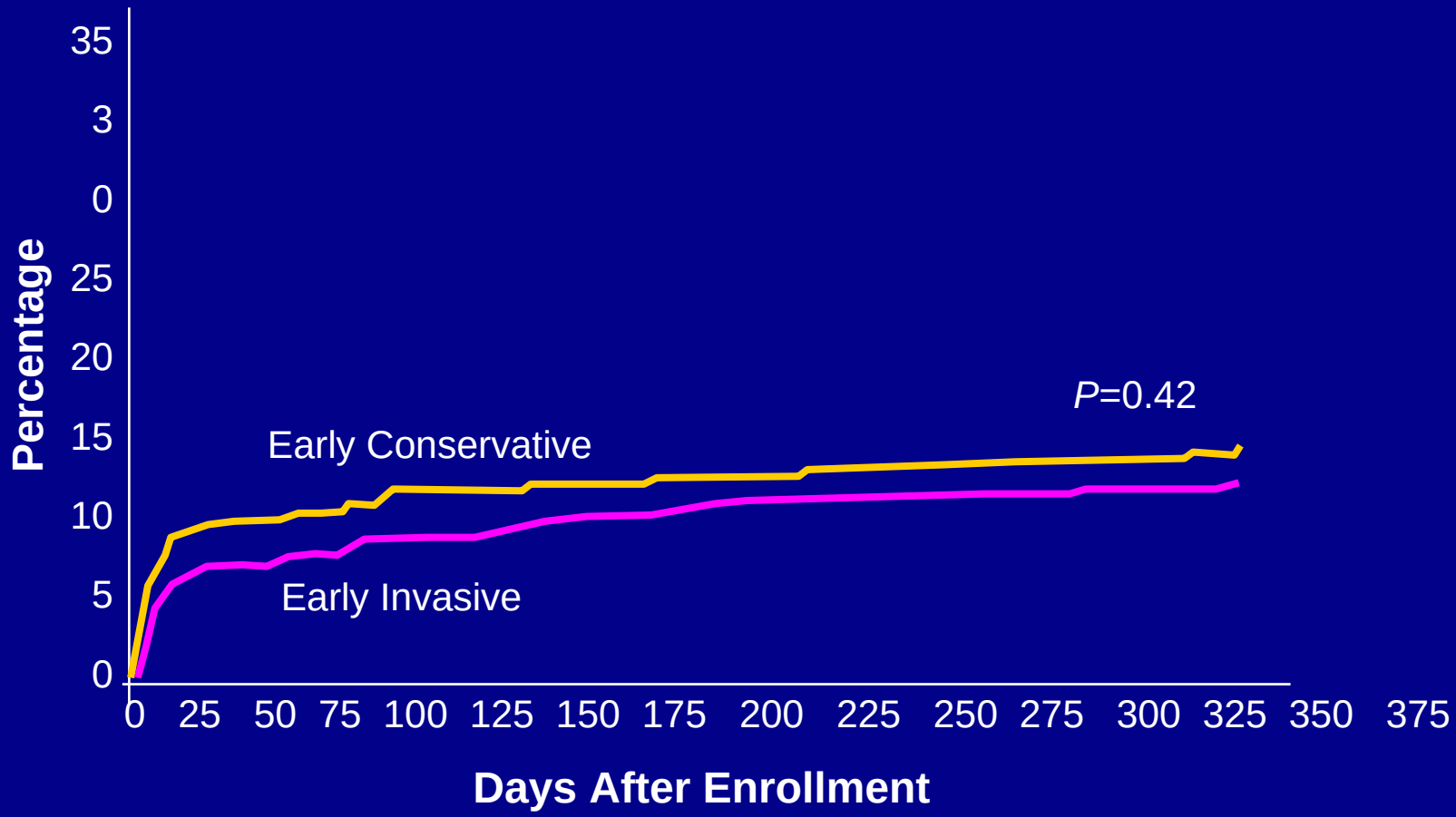
Hamm CW, et al. *N Engl J Med.* 1999;340:1623-1629.
Heeschen C, et al. *Lancet*. 1999;354:1757-1762.

Implications of Upstream Glycoprotein IIb/IIIa Inhibition and Coronary Artery Stenting in the Invasive Management of Unstable Angina/ Non-ST-elevation Myocardial Infarction: A Comparison of the TIMI IIIB and TACTICS-TIMI 18 Trials

Sabatine M, et al. *Circulation*. 2004;109:874-880.

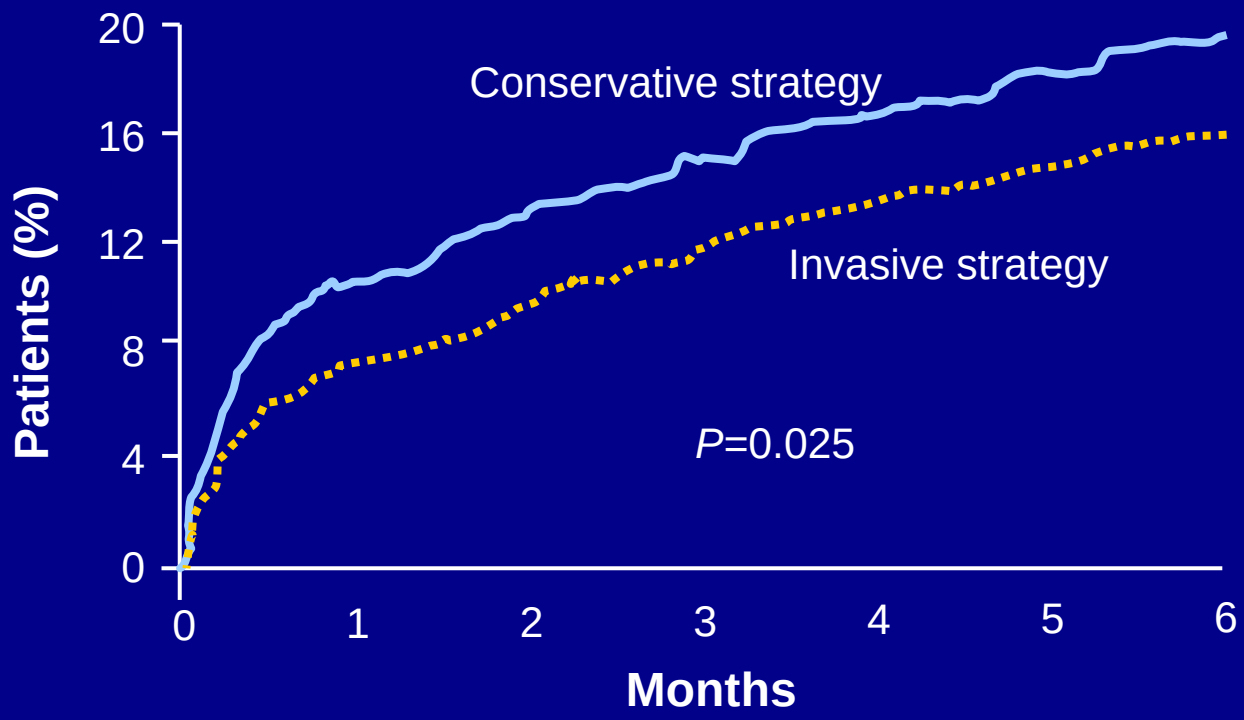
- Evaluates the efficacy of tirofiban and stents in lowering event rates of NSTEMI patients
- Evaluates an early invasive vs. conservative strategy for the treatment of NSTEMI patients

TIMI IIIB: 1-year Cumulative Rates of Death or MI



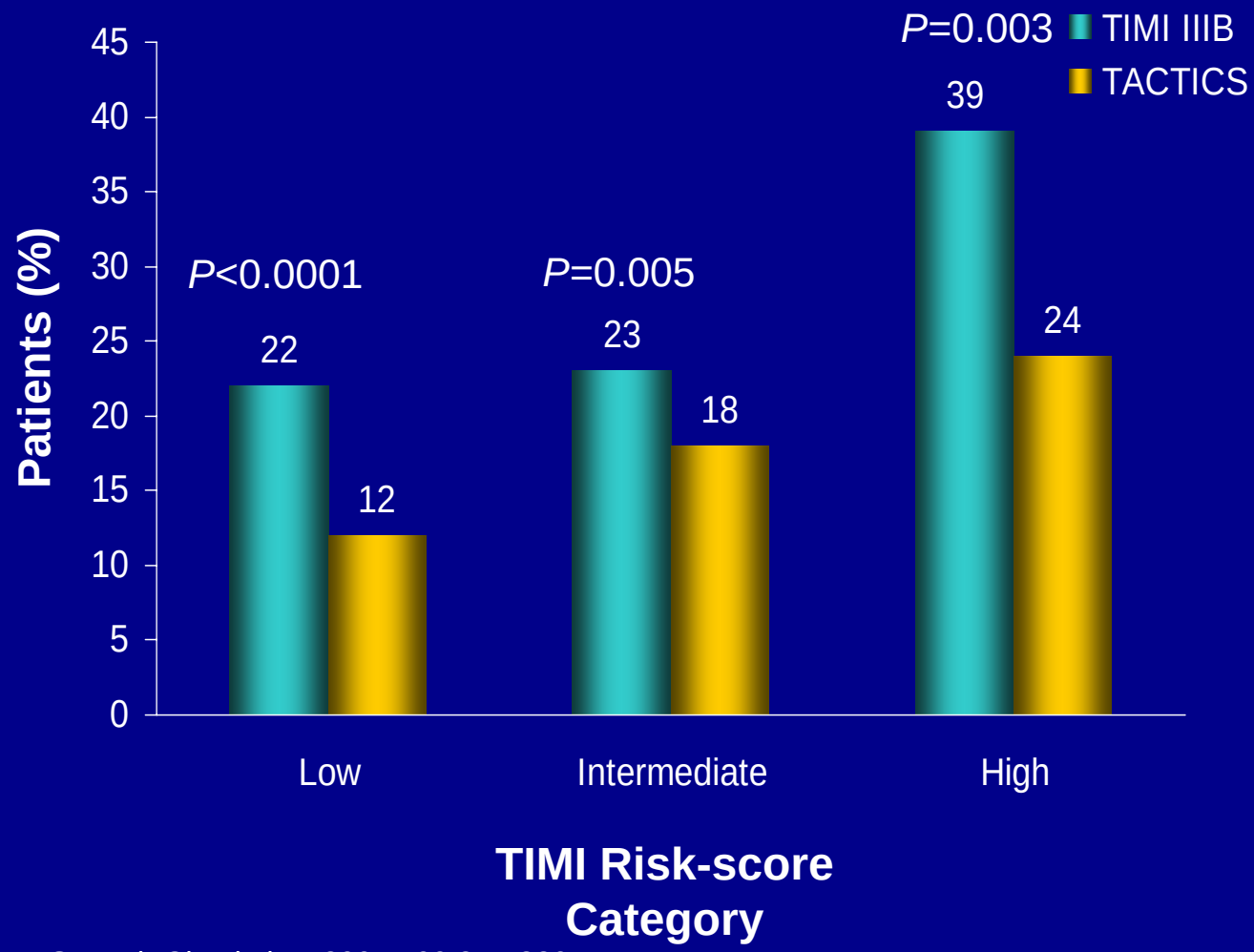
Anderson HV, et al. *J Am Coll Cardiol.* 1995;26:1643-1650.

TACTICS-TIMI 18: Cumulative Incidence of the Primary Endpoint of Death, Nonfatal MI, or Re-hospitalization



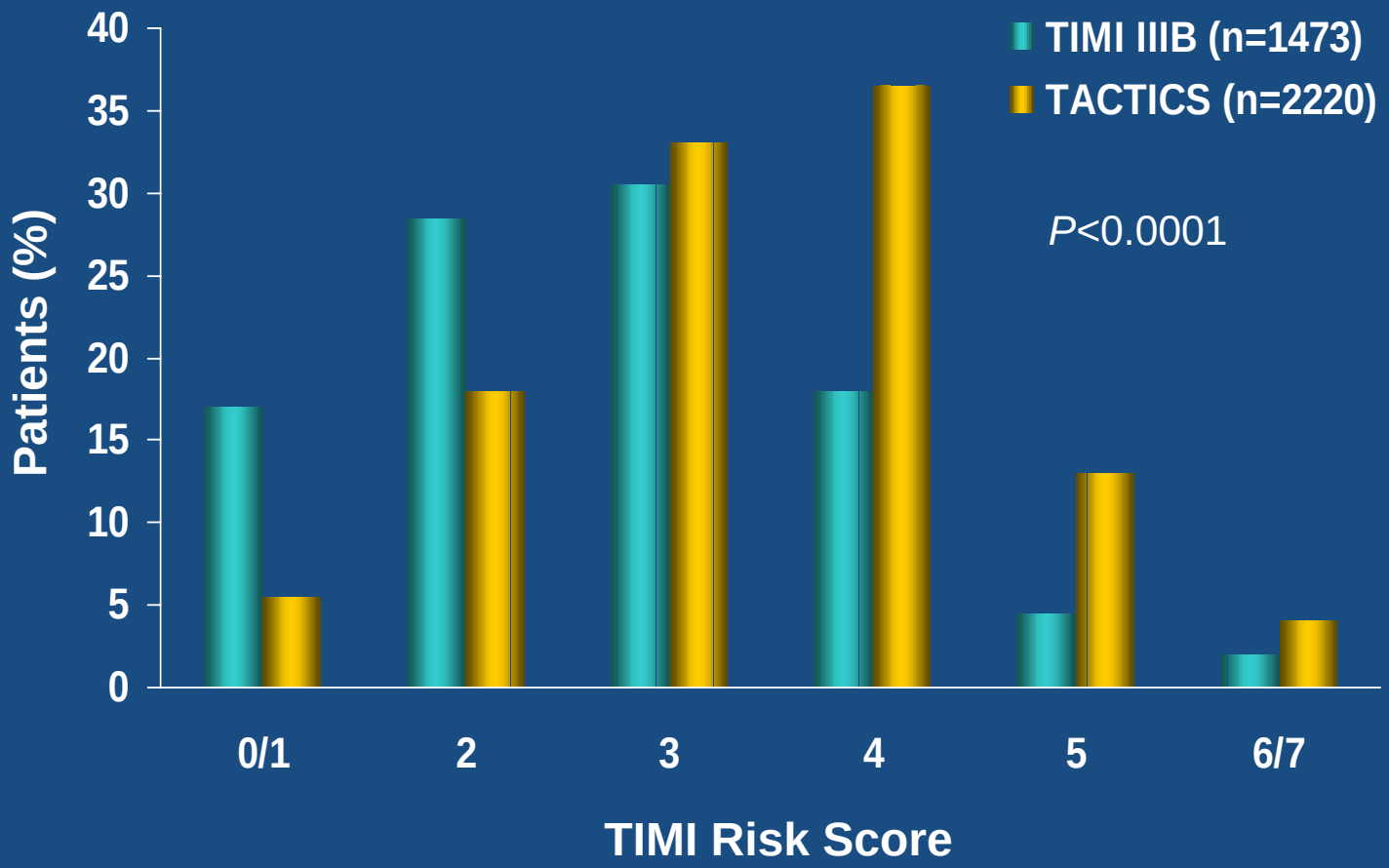
Cannon C, et al. *N Engl J Med.* 2001;344:1879-1887.

TIMI IIIB versus TACTICS-TIMI 18: Percent of Patients with Death/MI/ACS through 6 Months



Sabatine MS, et al. *Circulation*. 2004;109:874-880.

TIMI Risk-score Distribution Significantly Higher in TACTICS-TIMI 18



Sabatine MS, et al. *Circulation*. 2004;109:874-880.

TIMI IIIB versus TACTICS-TIMI 18: Subgroup Analyses of Death, MI, or Re-hospitalization for ACS

	Odds ratio (95% CI)		
Risk* Strategy	**Low**	**Intermediate**	**High**
Conservative	0.60 (0.38–0.95)	0.78 (0.57–1.06)	**0.59 (0.31–1.11)**
Invasive	0.43 (0.28–0.66)	0.67 (0.48–0.93)	**0.46 (0.23–0.90)**
Actual Revascularization Status			
Medical	0.53 (0.34–0.84)	0.61 (0.44–0.85)	**0.53 (0.24–1.18)**
PCI	0.44 (0.27–0.73)	0.94 (0.64–1.39)	**0.40 (0.19–0.83)**
CABG	0.32 (0.11–0.90)	0.57 (0.33–0.99)	**0.48 (0.17–1.33)**

*As defined by TIMI Risk Score.

Sabatine MS, et al. *Circulation*. 2004;109:874-880.

Conclusions: TIMI IIIB versus TACTICS-TIMI 18

- Benefits of an early invasive strategy were significantly greater with increasing baseline risk
- Differences in favor of TACTICS most likely reflect the use of GP IIb/IIIa inhibitors and coronary stents
- Findings support ACC/AHA guidelines, which recommend GP IIb/IIIa inhibition and early invasive approach in patients with high-risk UA/NSTEMI

Sabatine MS, et al. *Circulation*. 2004;109:874-880.

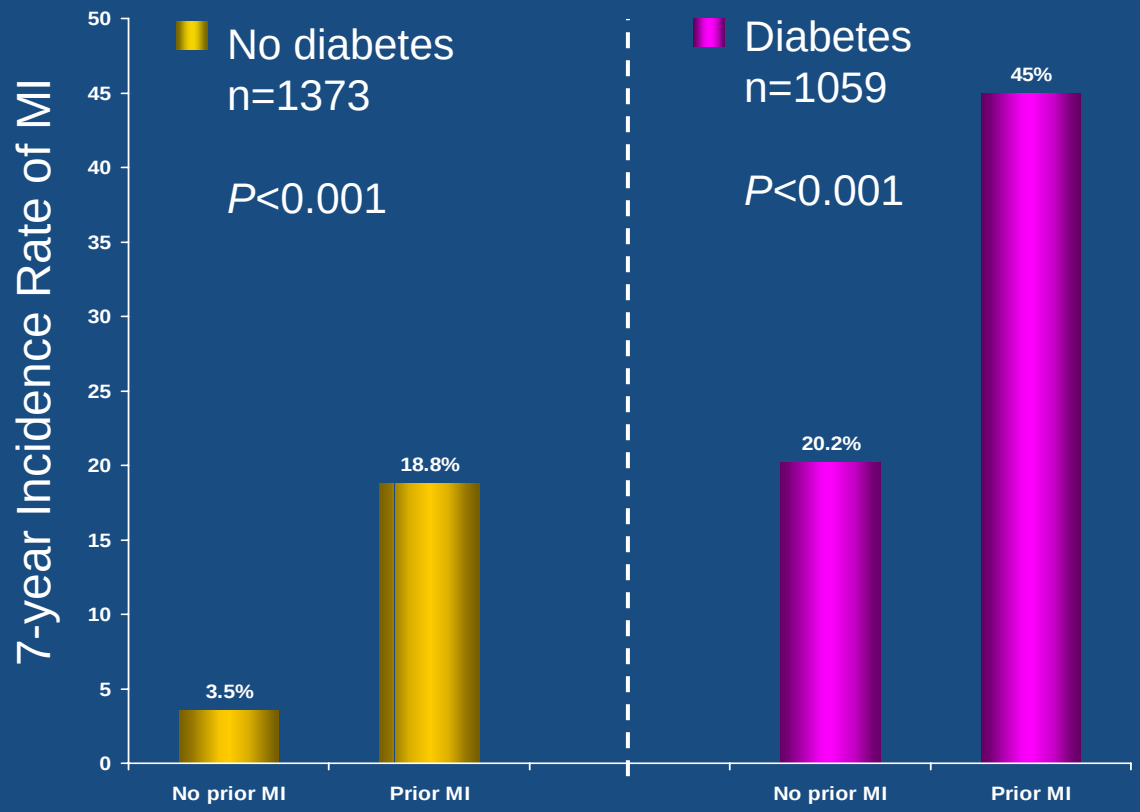
Summary

- Early use of GP IIb/IIIa inhibitors with early invasive strategy results in improved outcomes in UA/NSTEMI
- GP IIb/IIIa inhibitor therapy started early and continued throughout PCI has additive effects

고정관념

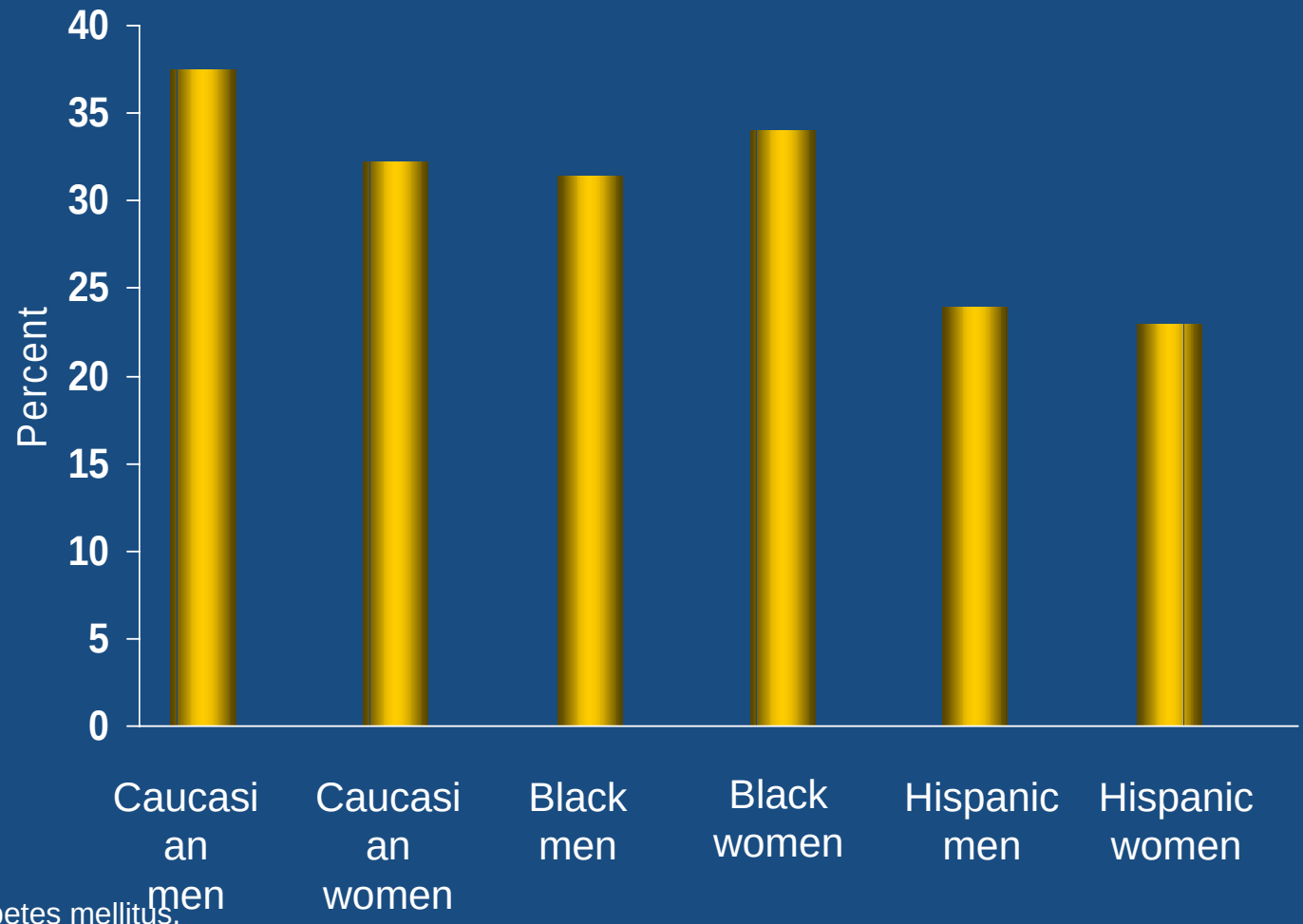
GP IIb/IIIa Inhibitors Produce Similar Outcomes in Patients with and without Diabetes

Increased Rates of MI in Type 2 Diabetes: 7-year Incidence of Fatal/Nonfatal MI



Haffner SM, et al. *N Engl J Med.* 1998;339(4):229-234.

Prevalence of CVD in Patients with DM (Age >35 Years)



DM=diabetes mellitus.

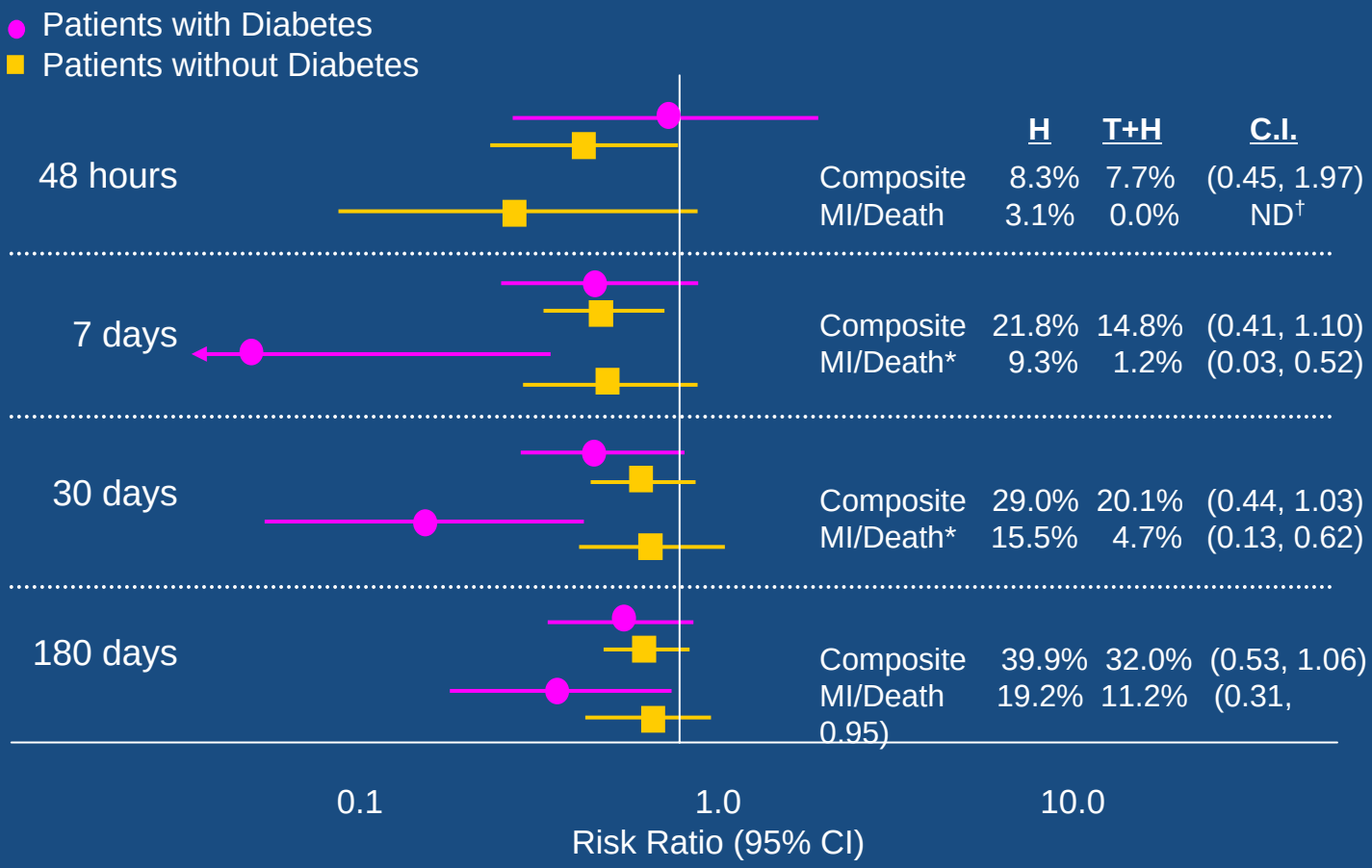
Heart Disease and Stroke Statistics – 2004 Update. Dallas, TX: American Heart Association.

The Diabetic Platelet

- Platelets are larger and more easily activated
- Higher density of GP IIb/IIIa receptors
- Glycation end products enhance platelet aggregation
- Increased inflammatory response
- Increased circulation of thrombogenic agents
- Impaired fibrinolysis is associated with diabetes

Glassman AB. *Ann Clin Lab Sci.* 1993;23:47-50.
Colwell JA, Nesto RW. *Diabetes Care.* 2003;26:2181-2188.

GP IIb/IIIa Inhibitors Are More Effective in Patients with Diabetes: PRISM-PLUS

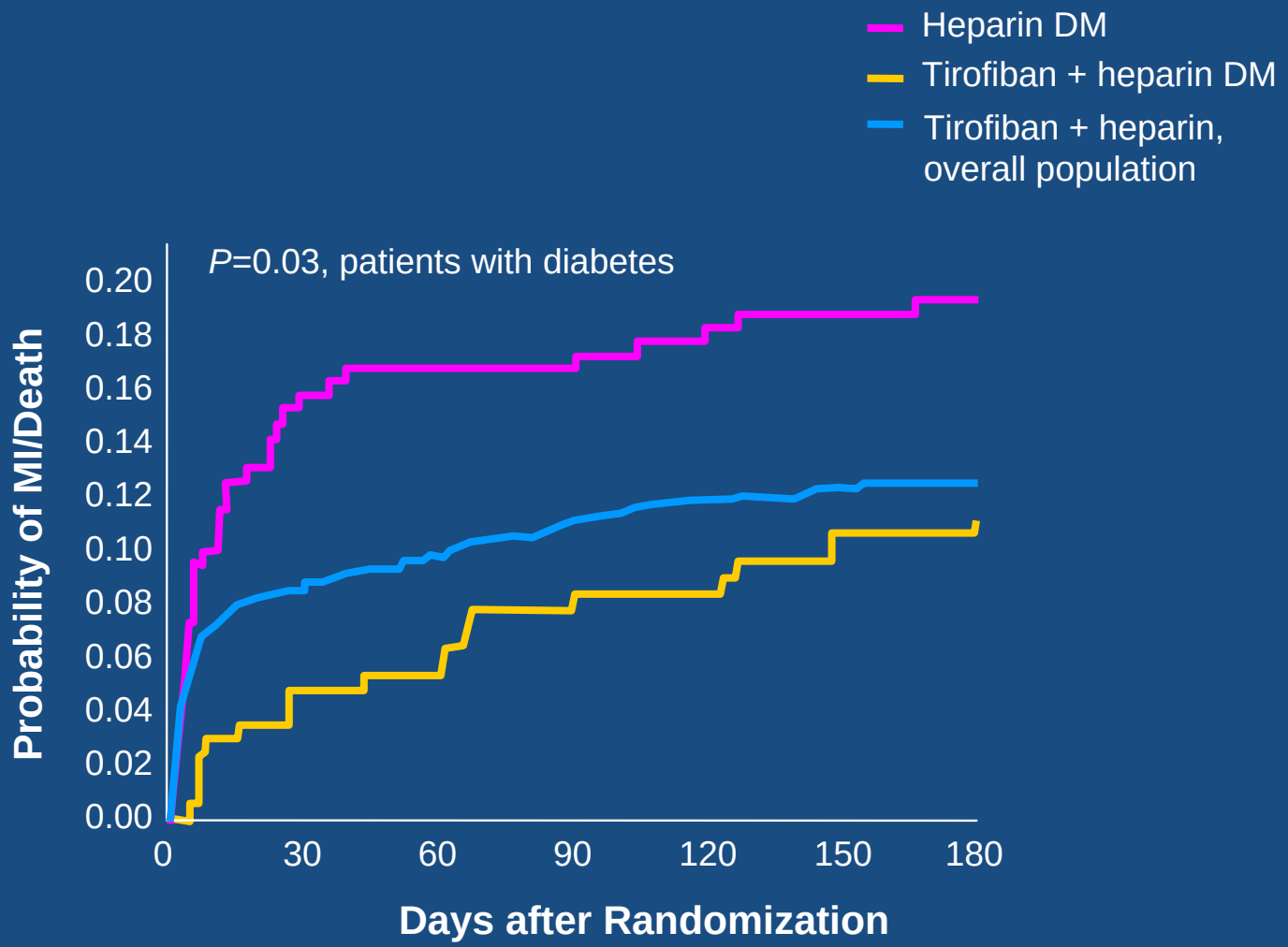


*Statistically significant ($P<0.05$) interactions were found between tirofiban therapy and diabetic status for these endpoints, suggesting that tirofiban was more efficacious among diabetic than among non-diabetic patients.

†Not defined.

Théroux P, et al. *Circulation*. 2000;102:2466-2472.

PRISM-PLUS: MI/Death in Patients with and without DM



Théroux P, et al. *Circulation.* 2000;102:2466-2472
PRISM-PLUS. *N Engl J Med*. 1998;338:1488-97.

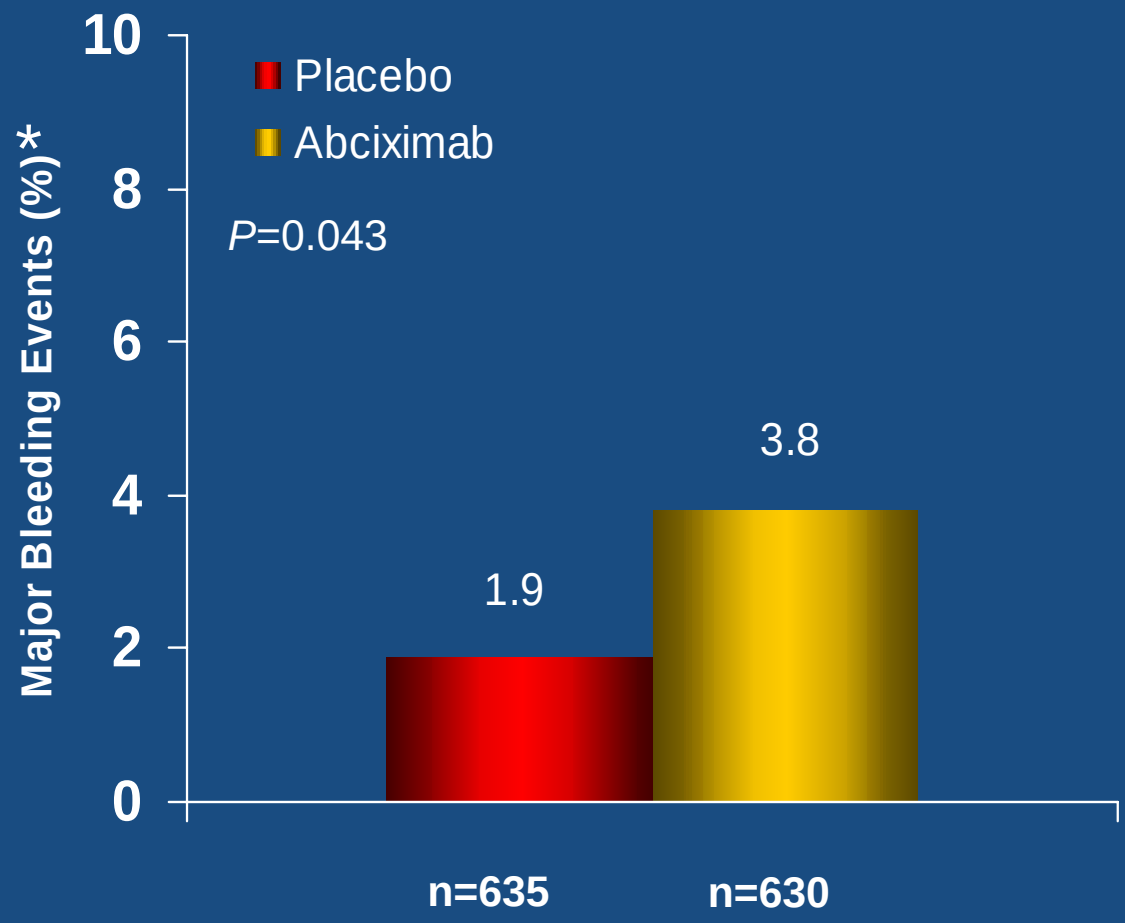
Summary

- Patients with diabetes experience increased cardiovascular morbidity and mortality compared to individuals without diabetes
- Multiple studies have demonstrated that GP IIb/IIIa inhibitors reduce the risk of future events in patients with diabetes

고정관념

The Use of GP IIb/IIIa Inhibitors Results in Excess Bleeding

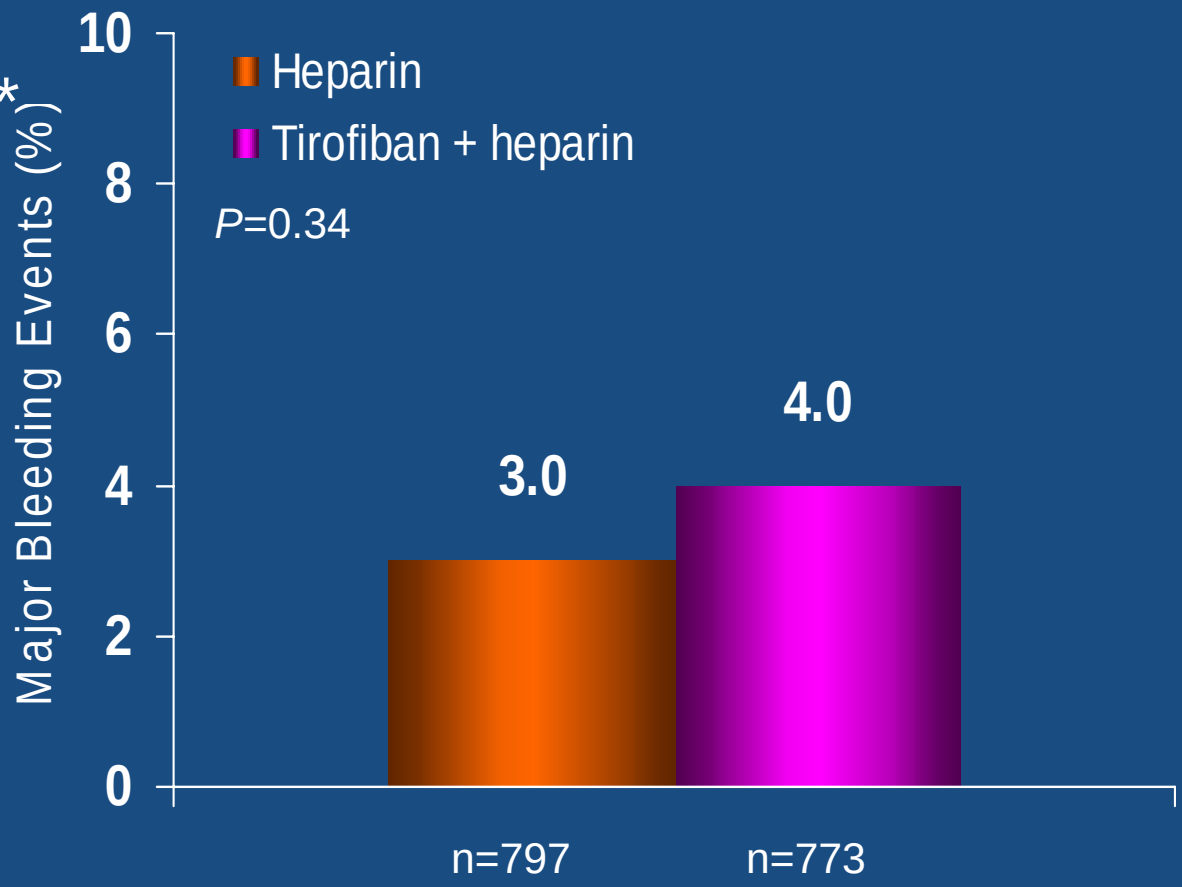
Focus on Safety: CAPTURE



*Major bleeds were defined as intracranial bleeding or episodes associated with a decrease in hemoglobin of more than 5g/L.

CAPTURE Investigators. *Lancet*. 1997;349:1429-1435.

Focus on Safety: PRISM-PLUS

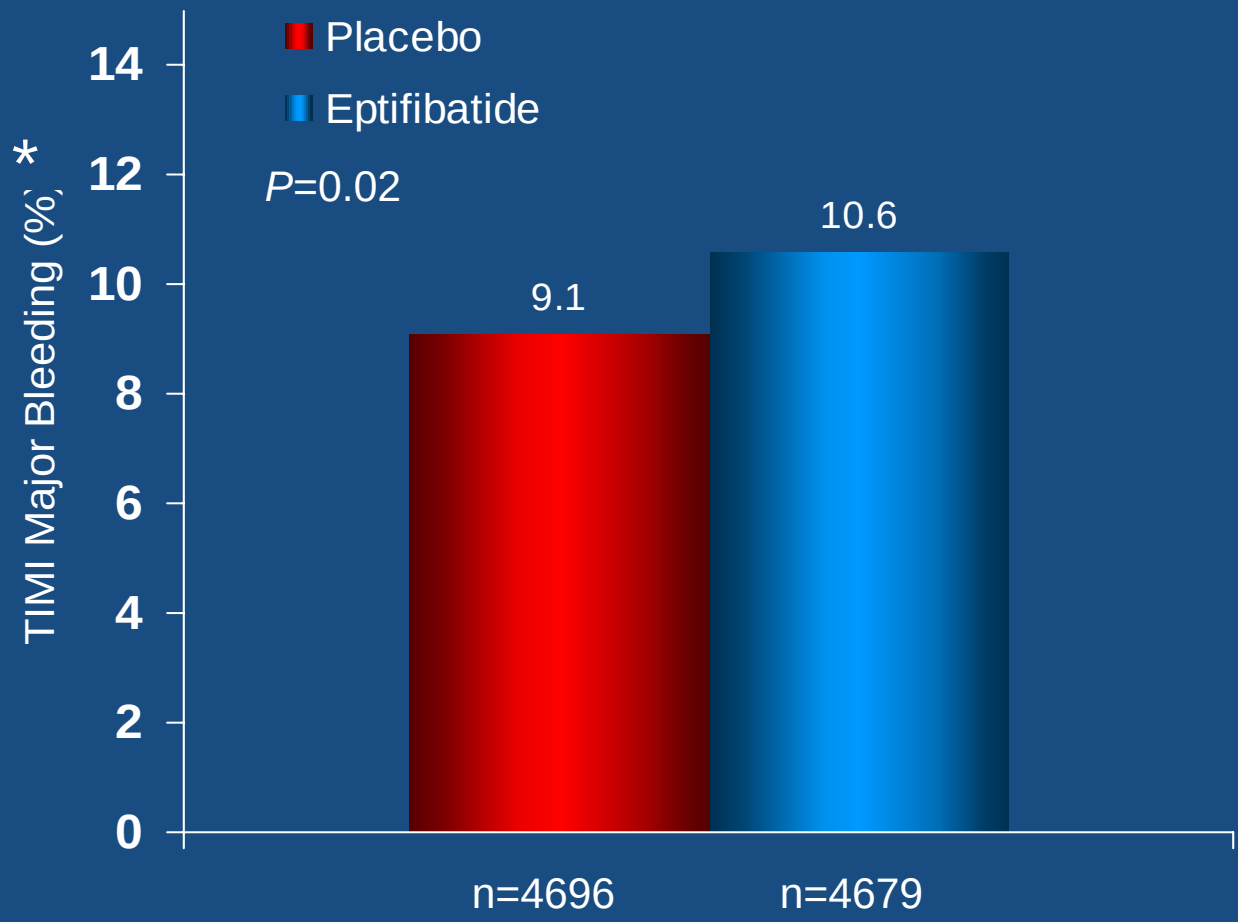


*Major bleeding was defined as a decrease in the blood hemoglobin level of more than 4.0 g/dL, the need for the transfusion of 2 or more units of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal hemorrhage, or any combination of these events.

PRISM-PLUS Study Investigators. *N Engl J Med.* 1998;338:1488-1497.

Focus on Safety: PURSUIT

All Patients

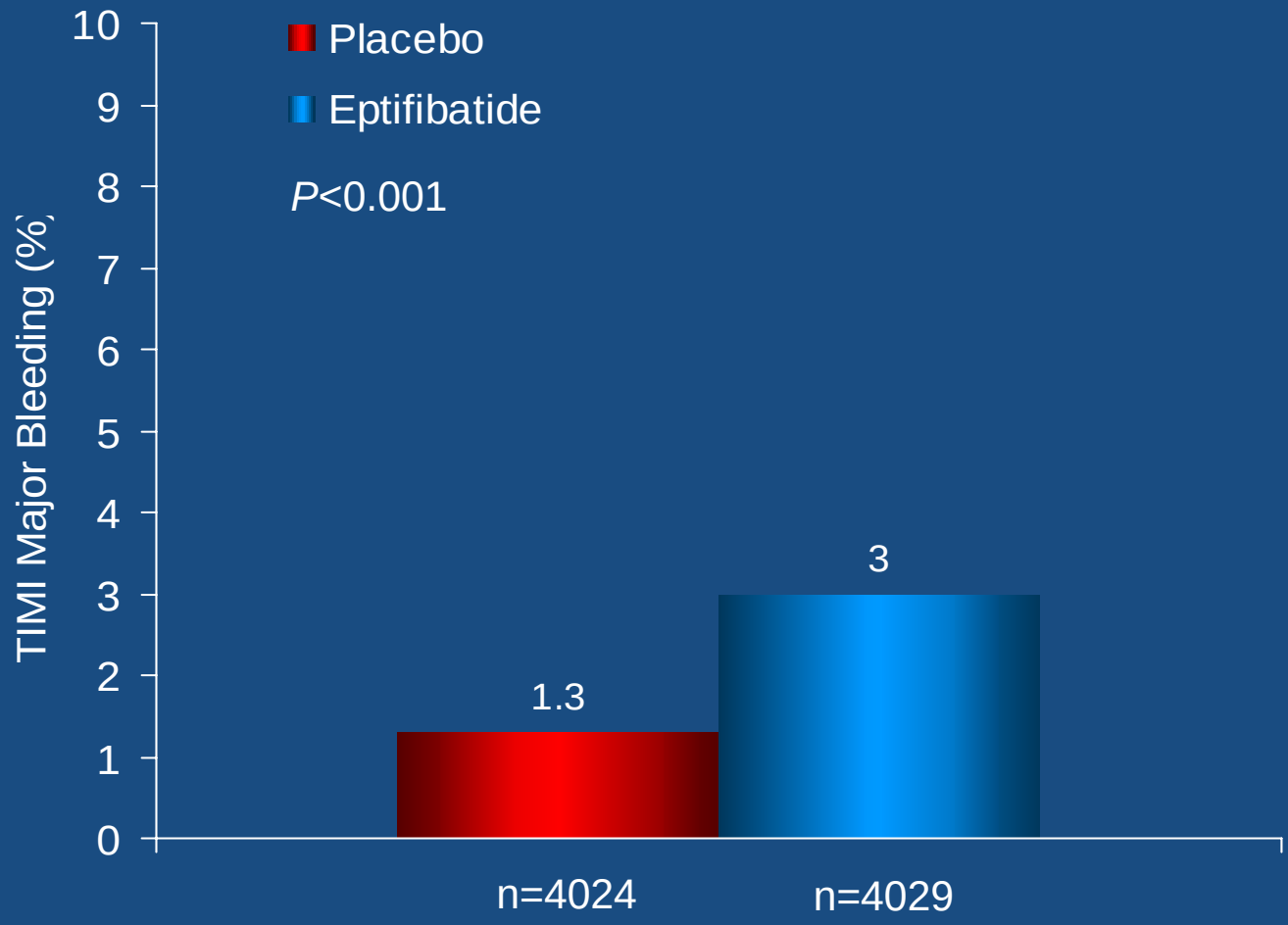


*Major bleeding was defined as intracranial hemorrhage or bleeding associated with a drop of 15 percentage points or more in the hematocrit or of 5 g/dL or more in the hemoglobin concentration.

PURSUIT Trial Investigators. *N Engl J Med.* 1998;339:436-443.

Focus on Safety: PURSUIT

Patients without CABG



PURSUIT Trial Investigators. *N Engl J Med.* 1998;339:436-443.

Summary

- Bleeding rates increase when more than one antithrombotic agent is used
- It does not appear that GP IIb/IIIa inhibitors dramatically increase bleeding
- Careful dosing of anti-thrombins is important in reducing bleeding complications
  - Avoid excessive heparin
- It is important to note that bleeding definitions were different in the various trials, therefore comparisons across trials cannot be done

고정관념

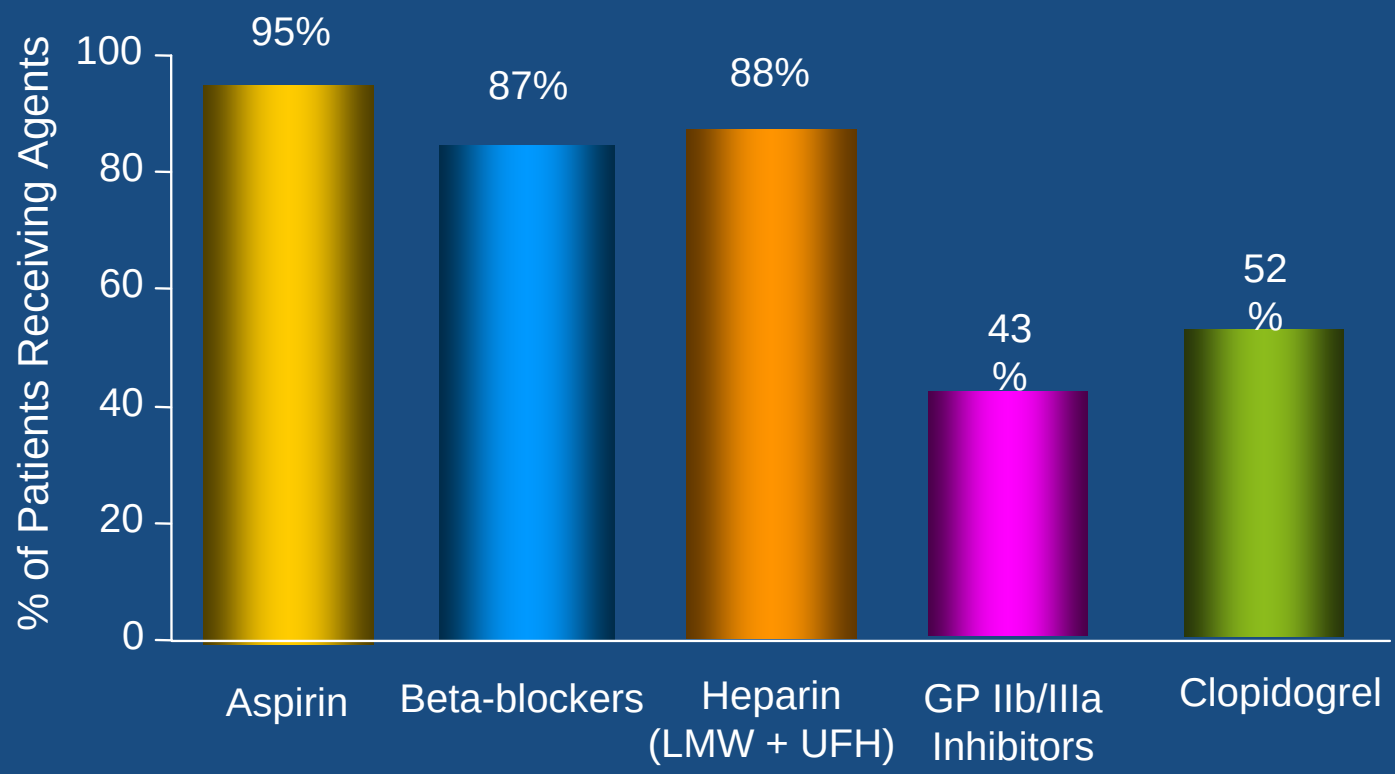
ACC/AHA Guidelines for UA/NSTEMI Management Are Universally Practiced

Only ≈30% of Eligible Patients Receive GP IIb/IIIa Inhibitors

	TIMI III Registry (1990–1993) (n=3647)	GUARANTEE (1995–1996) (n=2948)	GRACE (1999–2000) (n=2893)	CRUSADE (2001–2002) (n=18,937)
Type of patients	UA	UA	NSTEMI	UA/NSTEMI
Aspirin (%)	92	82	91	90
Beta-blockers (%)	45	52	78	76
Heparin (%)	60	67	61	53
GP IIb/IIIa inhibitors (%)	–	–	20	31
In-hospital mortality (%)	–	1.0	6.0	4.9

Roe MT, et al. *Am Heart J*. 2003;146(4):605-612.

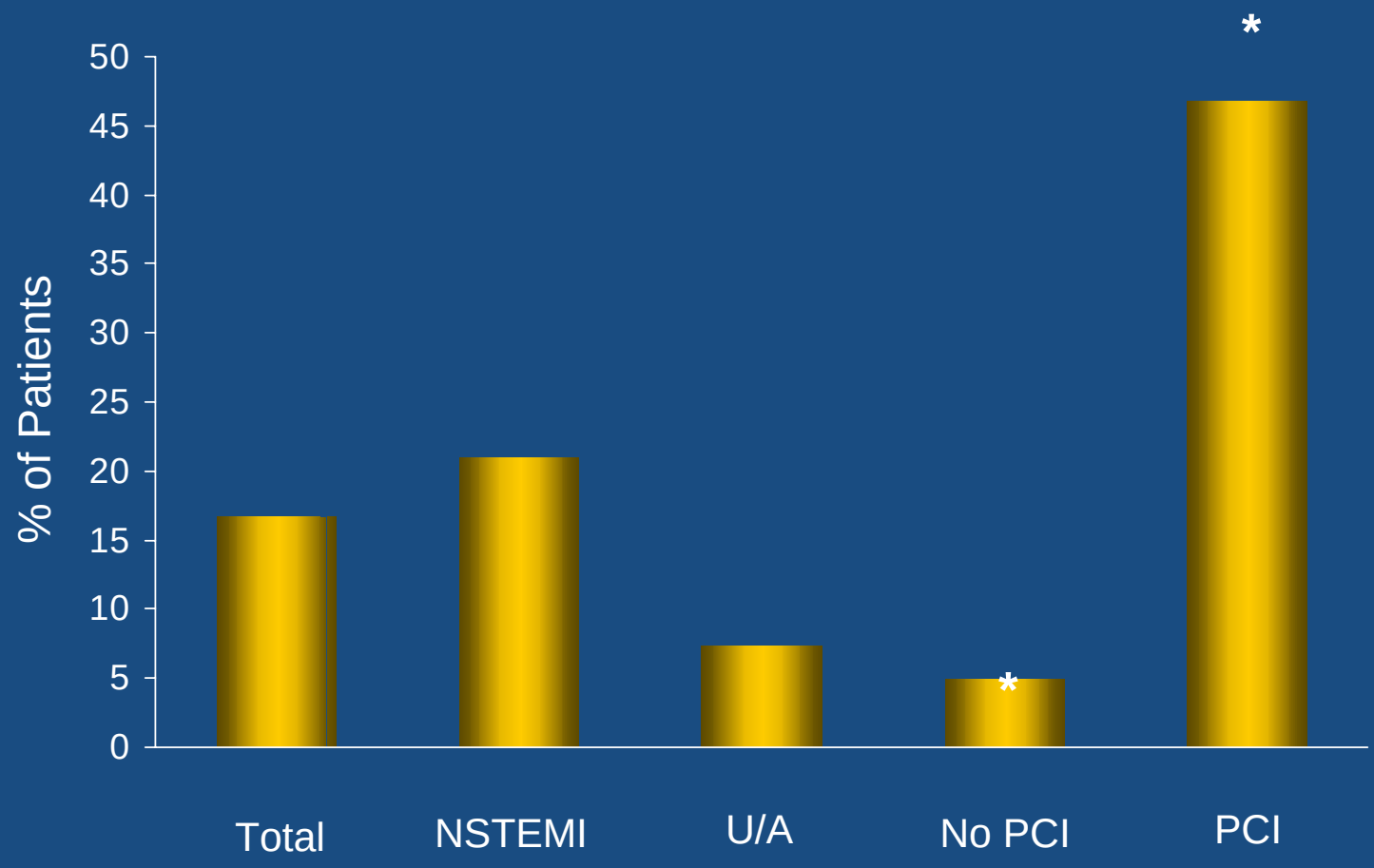
CRUSADE: Acute Medication Use* Lowest for GP IIb/IIIa Inhibitors



*Within first 24 hours.

CRUSADE Quality Improvement Initiative, Quarter 4, 2003.
Data on file at the Duke Clinical Research Institute.

GRACE: Use of GP IIb/IIIa Inhibitors by Syndrome and PCI Use



*Percent of patients treated with GP IIb/IIIa inhibitors who did or did not undergo PCI.

Budaj A, et al. *Am Heart J.* 2003;146:999-1006.

Potential Reasons for Under-use

- Lack of agreement that guidelines are applicable to daily practice
- Limited information of impact of guidelines on care
- Inherent difficulties in changing established practice patterns
- Lack of awareness of benefits in high-risk patients
- Safety concerns
- Reimbursement in Korea

Conclusions

- Aspirin plus an anti-thrombin agent does not provide sufficient anticoagulation for patients with UA/NSTEMI
- GP IIb/IIIa inhibitor therapy is useful in high-risk UA/NSTEMI patients receiving clopidogrel; however, clopidogrel and GP IIb/IIIa inhibitors have not been directly compared
- The benefits of GP IIb/IIIa inhibitors go beyond the direct effects on the platelet
- Early use of GP IIb/IIIa inhibitors is beneficial
- GP IIb/IIIa inhibitors appear to be more beneficial in patients with diabetes
- GP IIb/IIIa inhibitors are not associated with excessive bleeding

Case: Treatment (66세,여,NSTEMI)

- ACEI, beta blocker, insulin
- Aspirin 100mg
- Clopidogrel 300 mg loading, 75mg od
- Heparin infusion

  ESSENCE: No GP IIb/IIIa inhibitors were used and most patients did not undergo early catheterization

  SYNERGY showed **increased bleeding** with enoxaparin

  High-risk patients did **not have an improved effect** with LMWH
- Tirofiban infusion (high risk-group and DM)
- PCI with DES
- High-dose statin, exercise, diet