Timing of Anti-Platelet Therapy for ACS (EARLY-ACS & ACUITY)

Mitchell W. Krucoff, MD, FACC

Professor, Medicine/Cardiology

Duke University Medical Center

Director, Cardiovascular Devices Unit

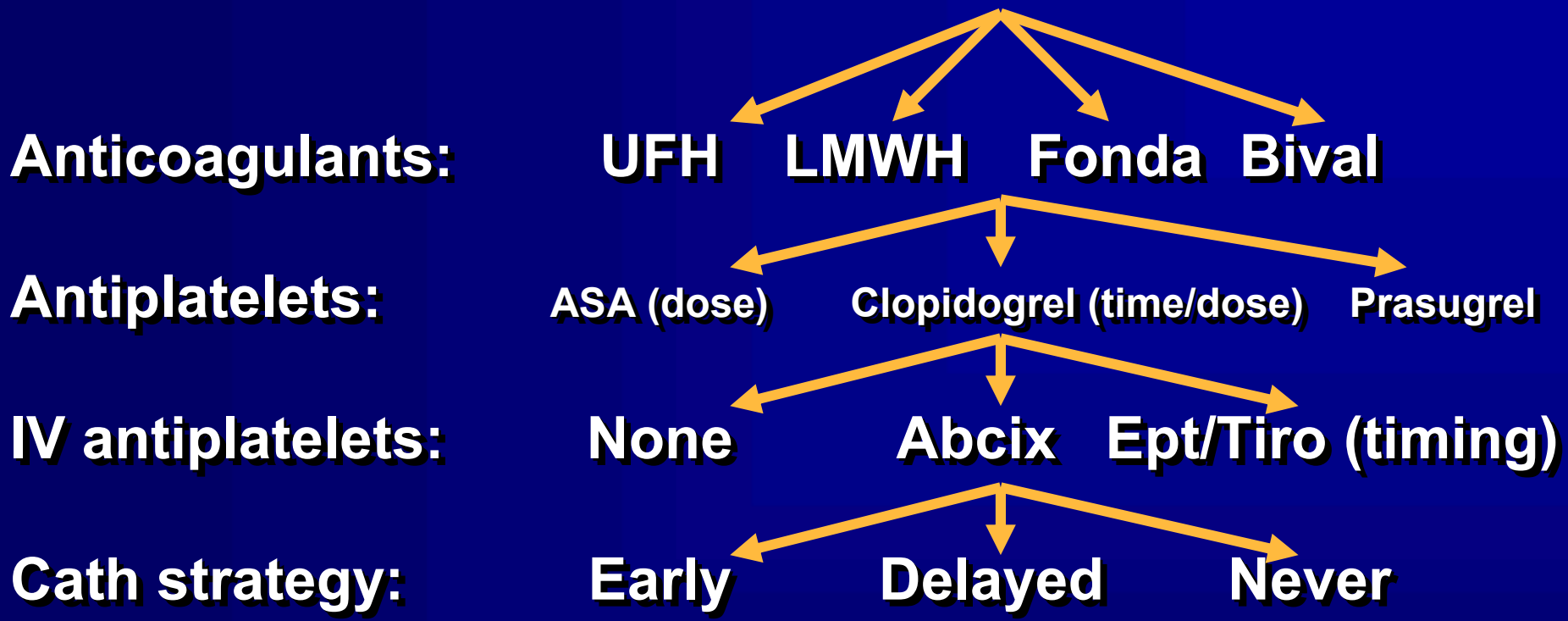
Duke Clinical Research Institute

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

With special thanks:

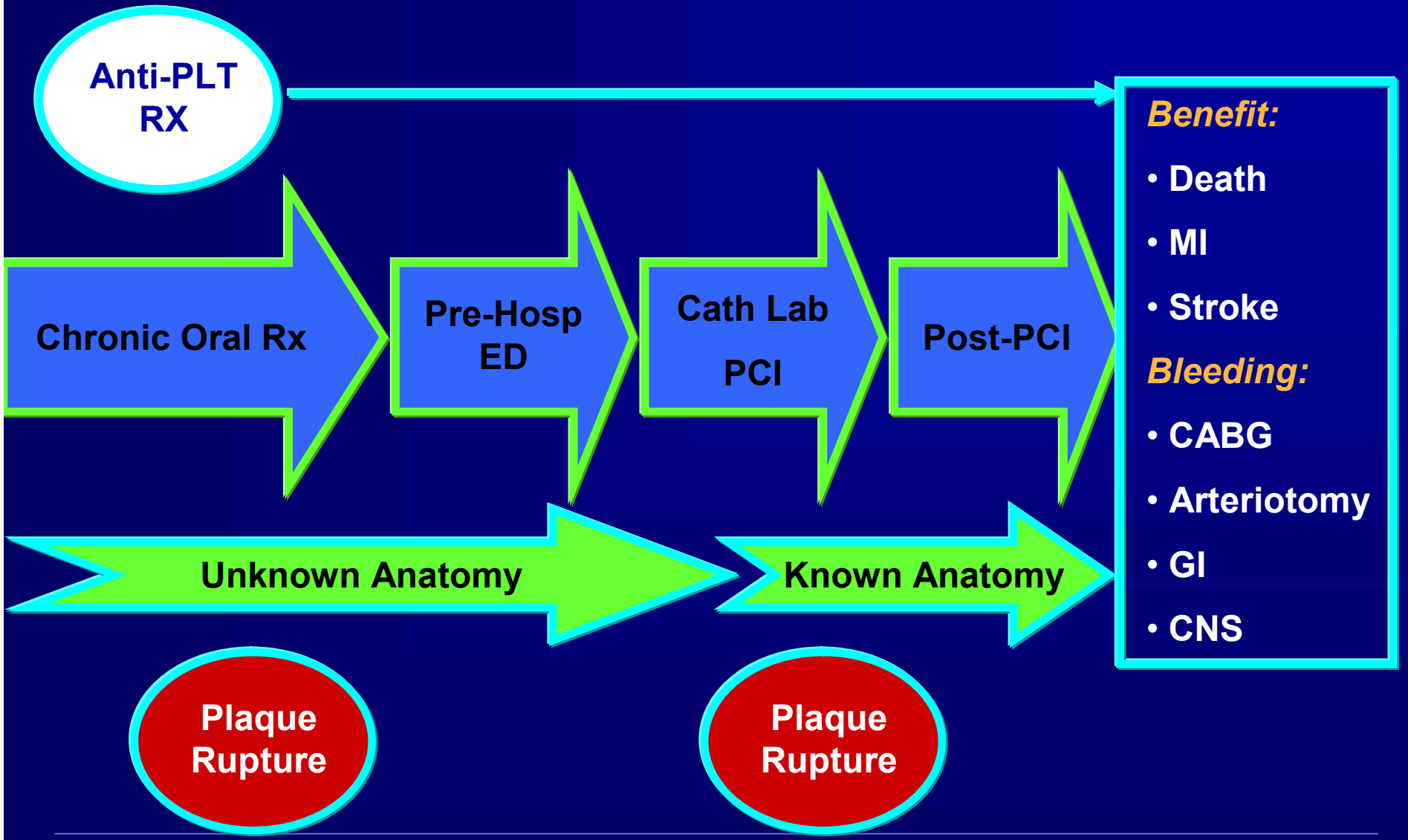
- Sunil Rao
- Kristin Newby
- George Dangas

Choices Impacting Anti-PLT Therapy



>100 Different Combinations!

When to start?



Delay of Invasive Therapy: Should We Prolong The "Upstream" Window?

Can we "passify" plaque & improve PCI & clinical outcomes?

EARLY ACS Study Design

2 of 3 high-risk criteria:
1. Age ≥ 60 years
2. + CKMB or TnT/I
3. ST ↓ or transient ST ↑

(Or age 50-59, h/o CVD and + CKMB or TnT/I)

High-risk NSTE ACS
n = 10,500

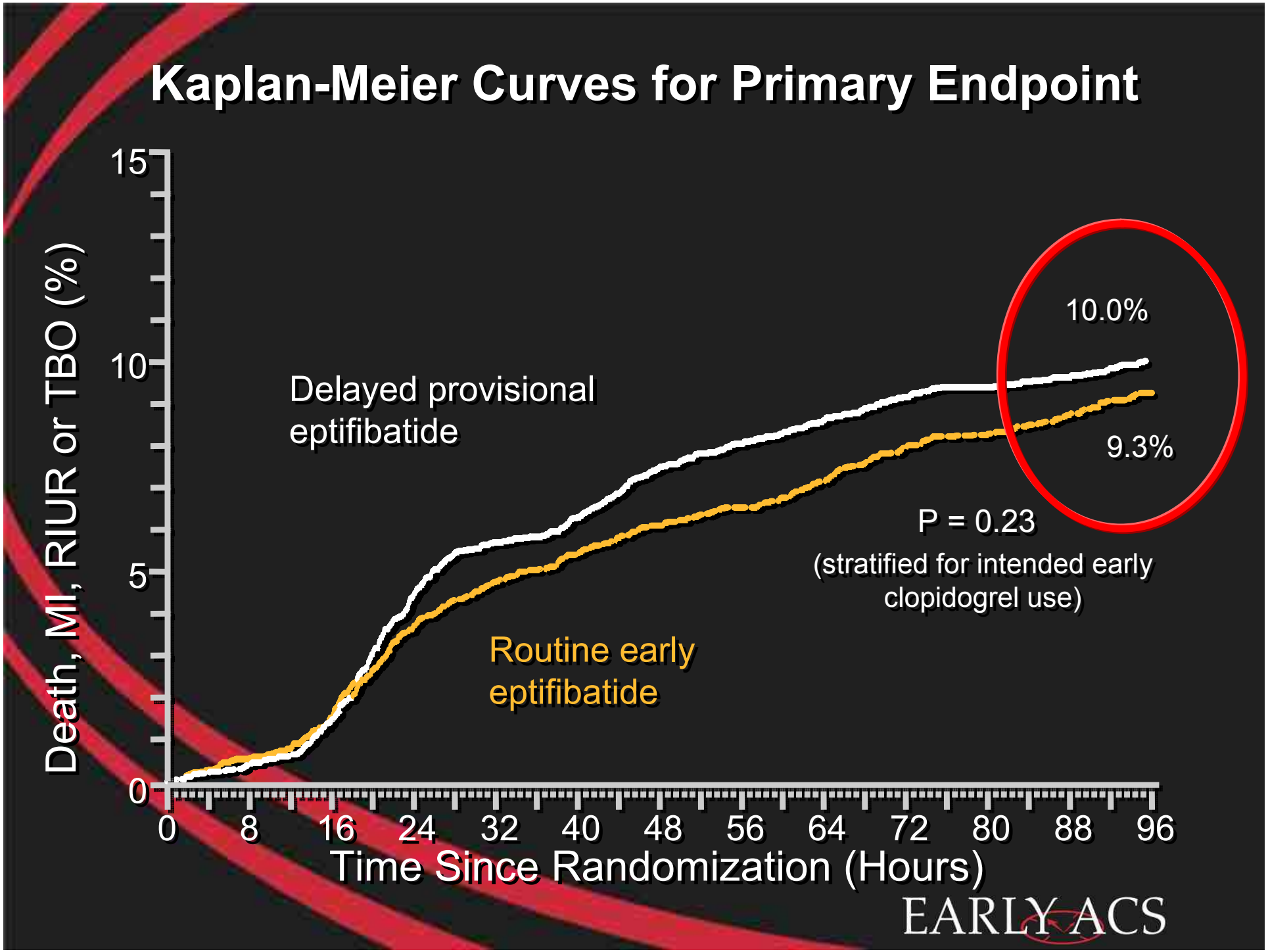
Routine, early eptifibatide
(180/2/180)

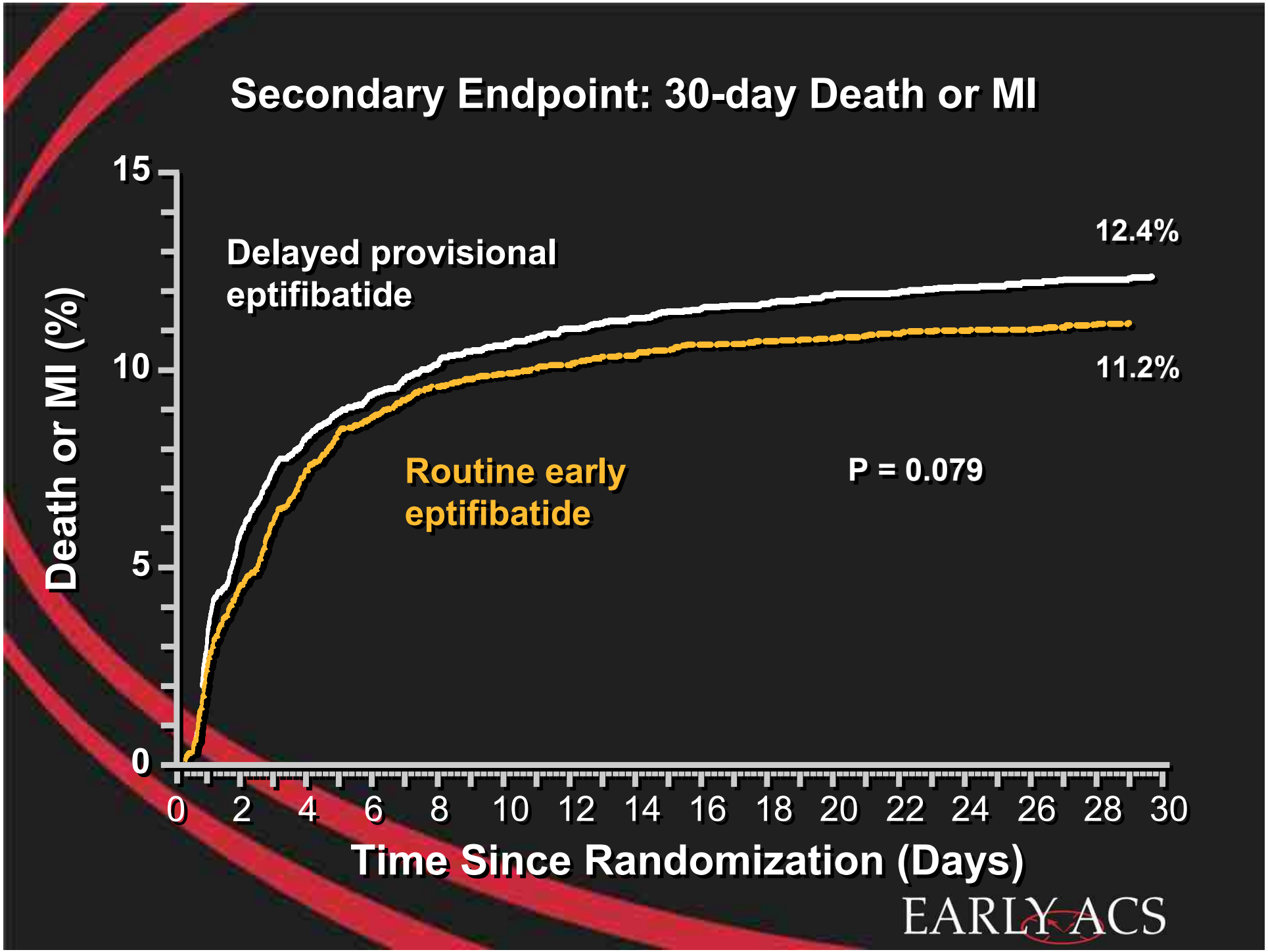
Placebo / delayed provisional eptifibatide pre-PCI

Randomize within 12 hours of presentation

Invasive strategy: 12 to 96 hours after randomization

Safety Endpoints at 120 hrs: Bleeding (GUSTO and TIMI scales), Transfusions, Stroke, Non-hemorrhagic SAEs


Kaplan-Meier Curves for Primary Endpoint
Death, MI, RIUR or TBO (%)
15
10
5
0
Delayed provisional eptifibatide
Routine early eptifibatide
10.0%
9.3%
P = 0.23
(stratified for intended early clopidogrel use)
0
8
16
24
32
40
48
56
64
72
80
88
96
Time Since Randomization (Hours)
EARLY ACS


Secondary Endpoint: 30-day Death or MI
Death or MI (%)
15
10
5
0
Delayed provisional eptifibatide
12.4%
Routine early eptifibatide
11.2%
P = 0.079
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Time Since Randomization (Days)
EARLY ACS

Secondary Endpoint: Bleeding

	Routine Early Eptifibatide (n=4686)	Delayed Provisional Eptifibatide (n=4643)	OR (95% CI)	P
Bleeding (all patients, %)				
TIMI major	2.6	1.8	1.42 (1.07-1.89)	0.015
GUSTO moderate or severe	7.6	5.1	1.52 (1.28-1.80)	<0.001
PRBC transfusion	8.6	6.7	1.31 (1.12-1.53)	0.001

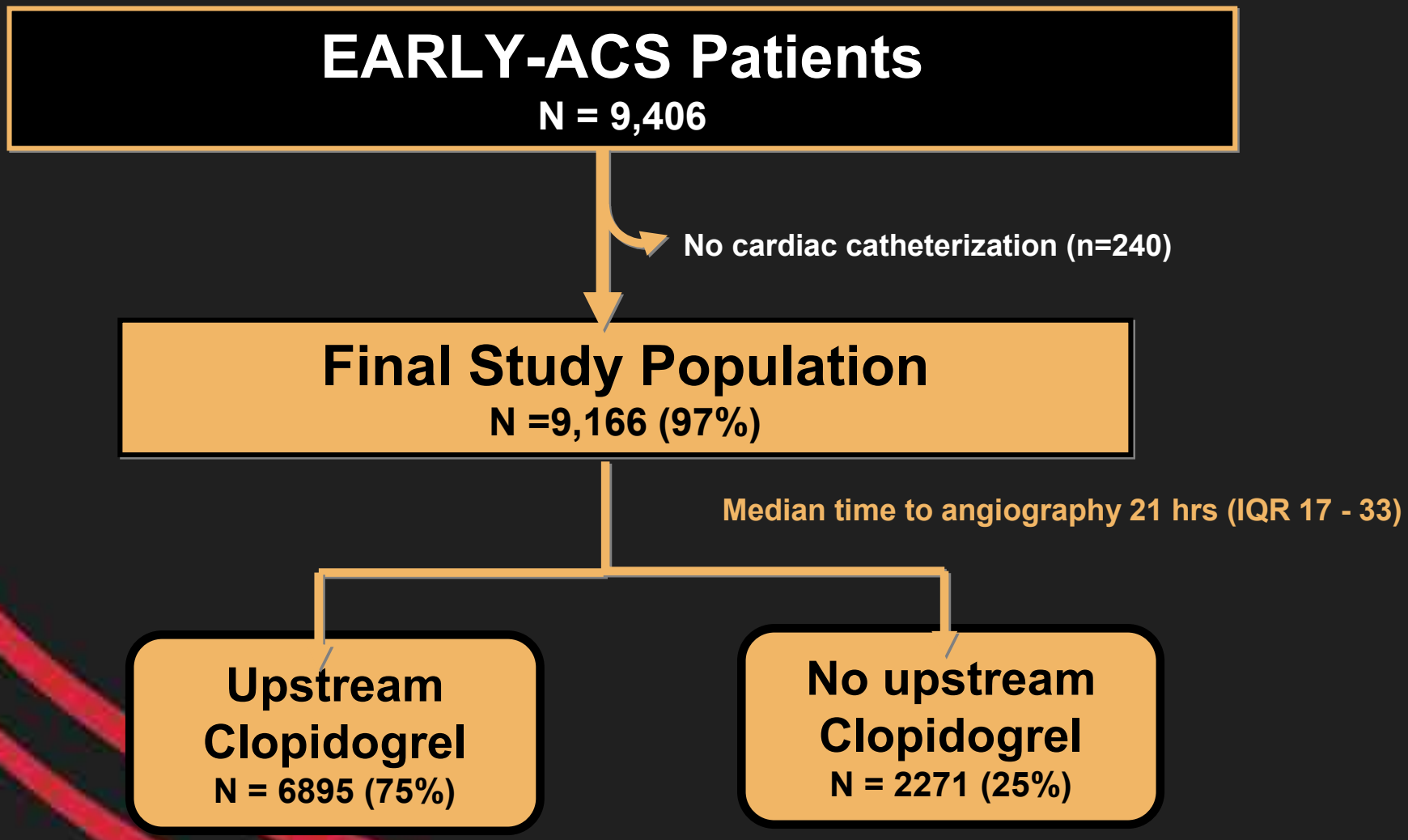
EARLY ACS

“Upstream” Clopidogrel Use in EARLY-ACS

- Clopidogrel use and timing were determined by treating physician
- Randomization in the EARLY-ACS Trial was stratified by declared intent for upstream clopidogrel use
- Does addition of early thienopyridine to early eptifibatide “passify” ACS lesions?

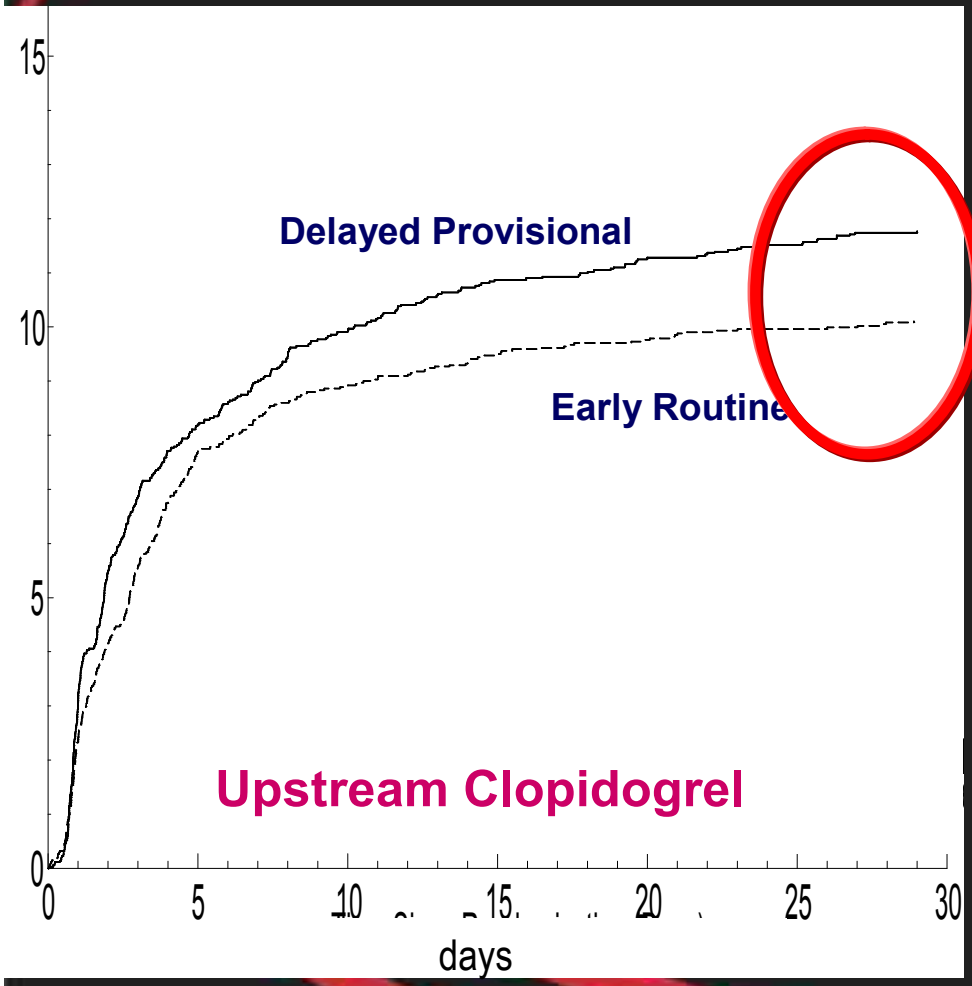
EARLY ACS

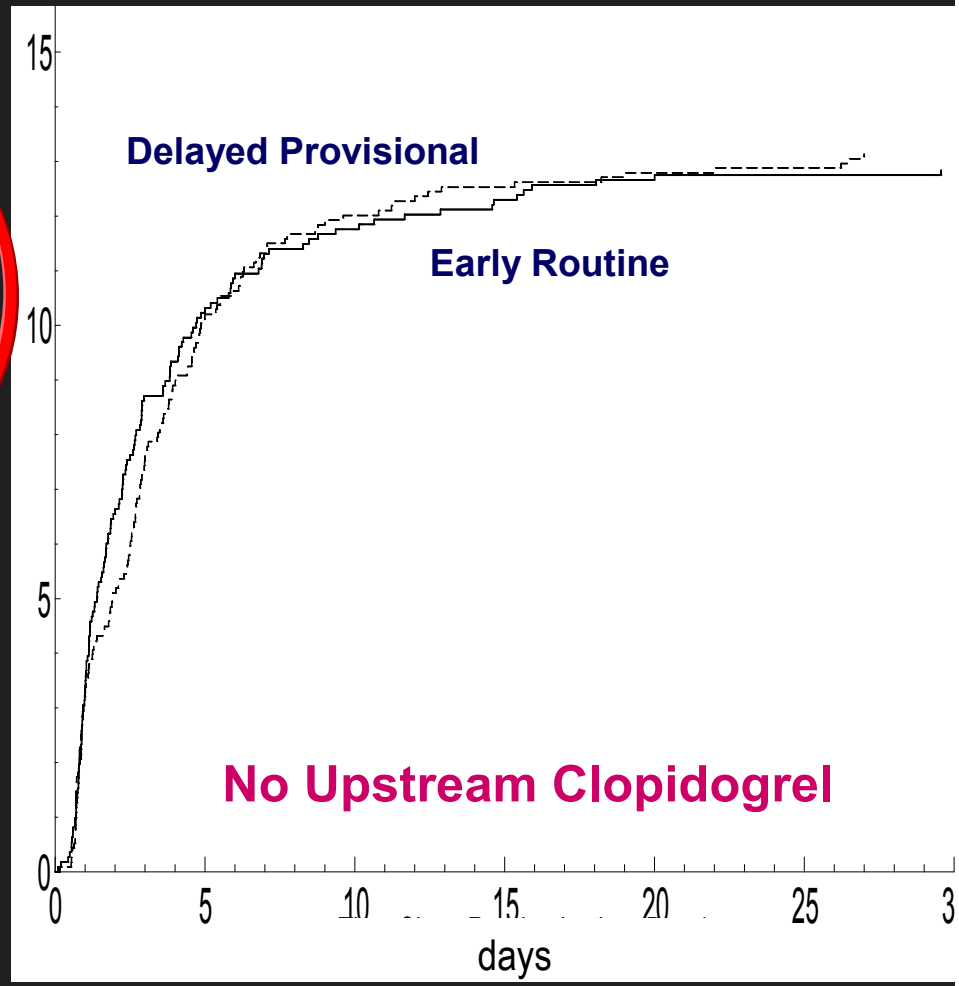
Study Population



EARLY ACS

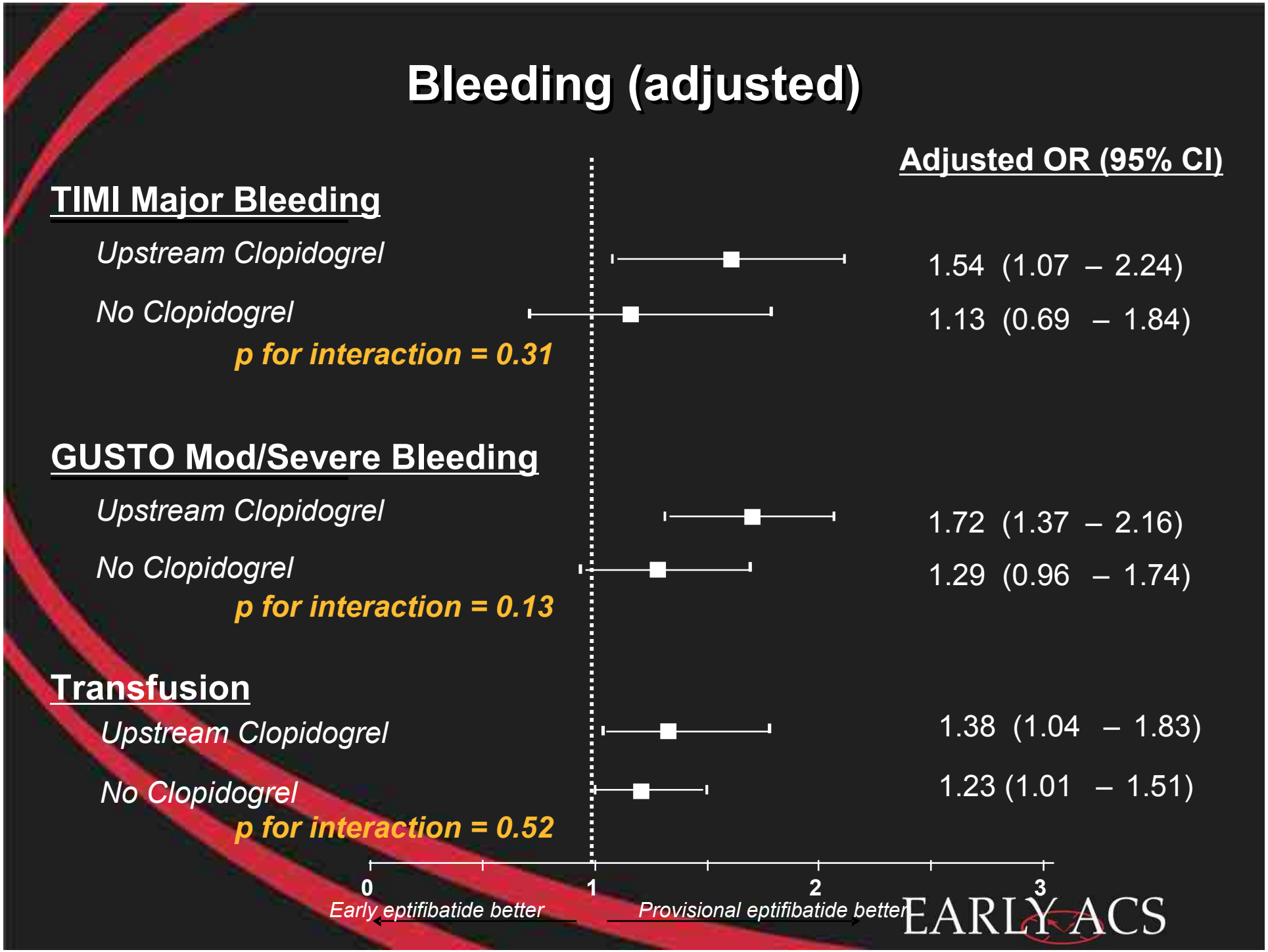
Death or MI at 30 days





EARLY ACS

Bleeding (adjusted)

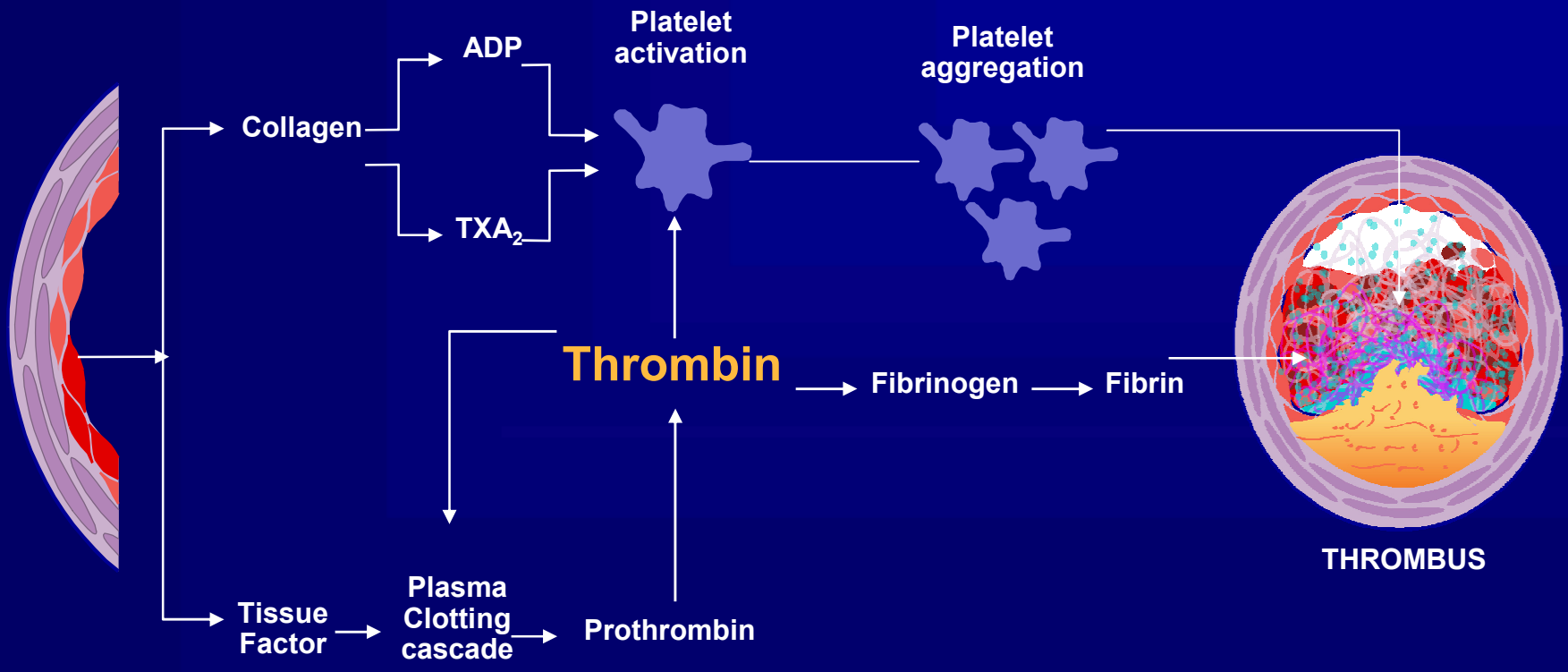


Can Need for "Upstream" Anti-Platelet Therapy Be Eliminated by Selective Anti-Thrombotics?

Can we "passify" thrombin signaling for better PCI & clinical outcomes?

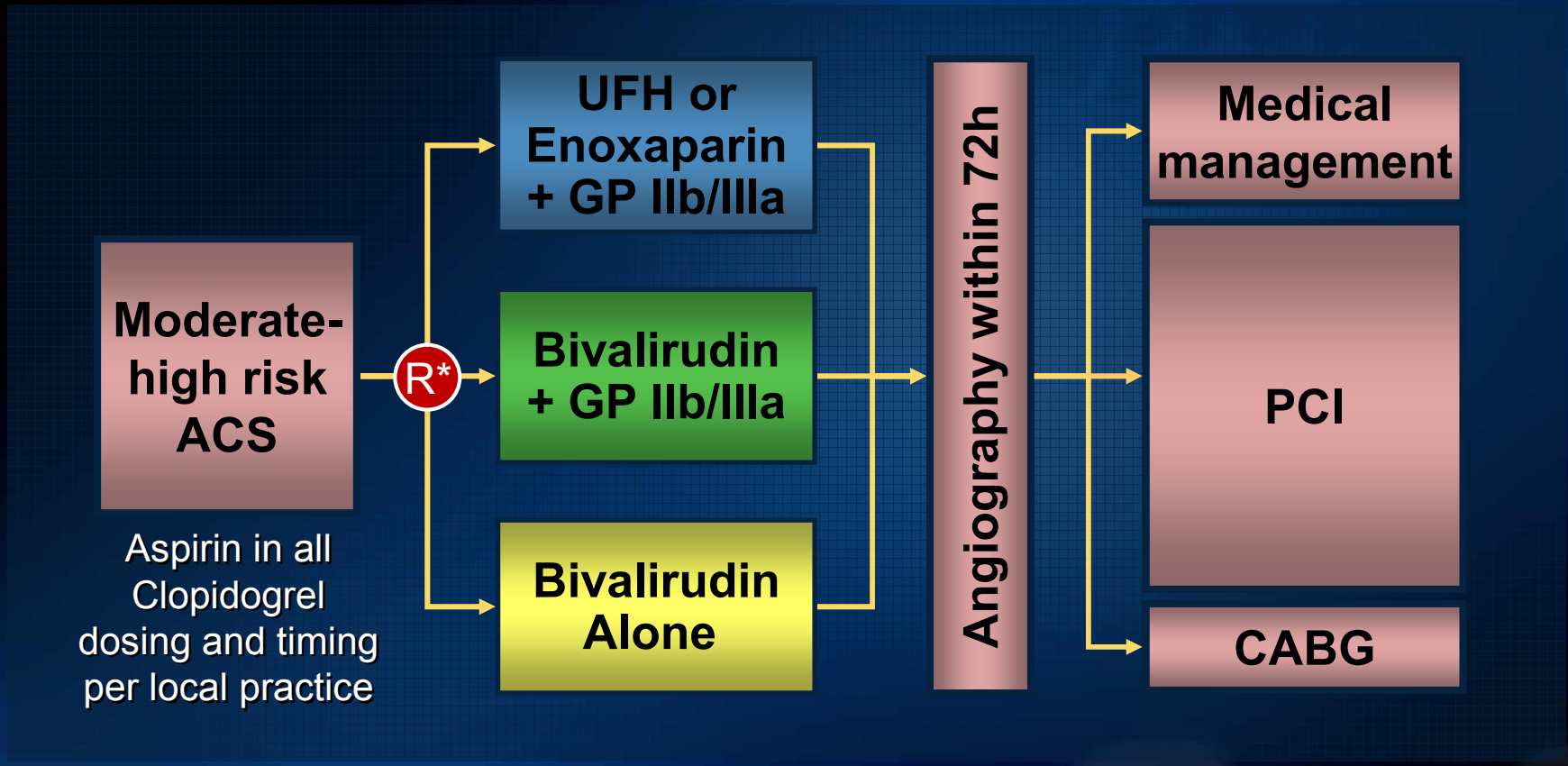
Thrombus formation

Thrombin plays a central role among tissue injury, coagulation, and platelet response.



ACUITY - Study design

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



Primary endpoint: "Net Clinical Composite"

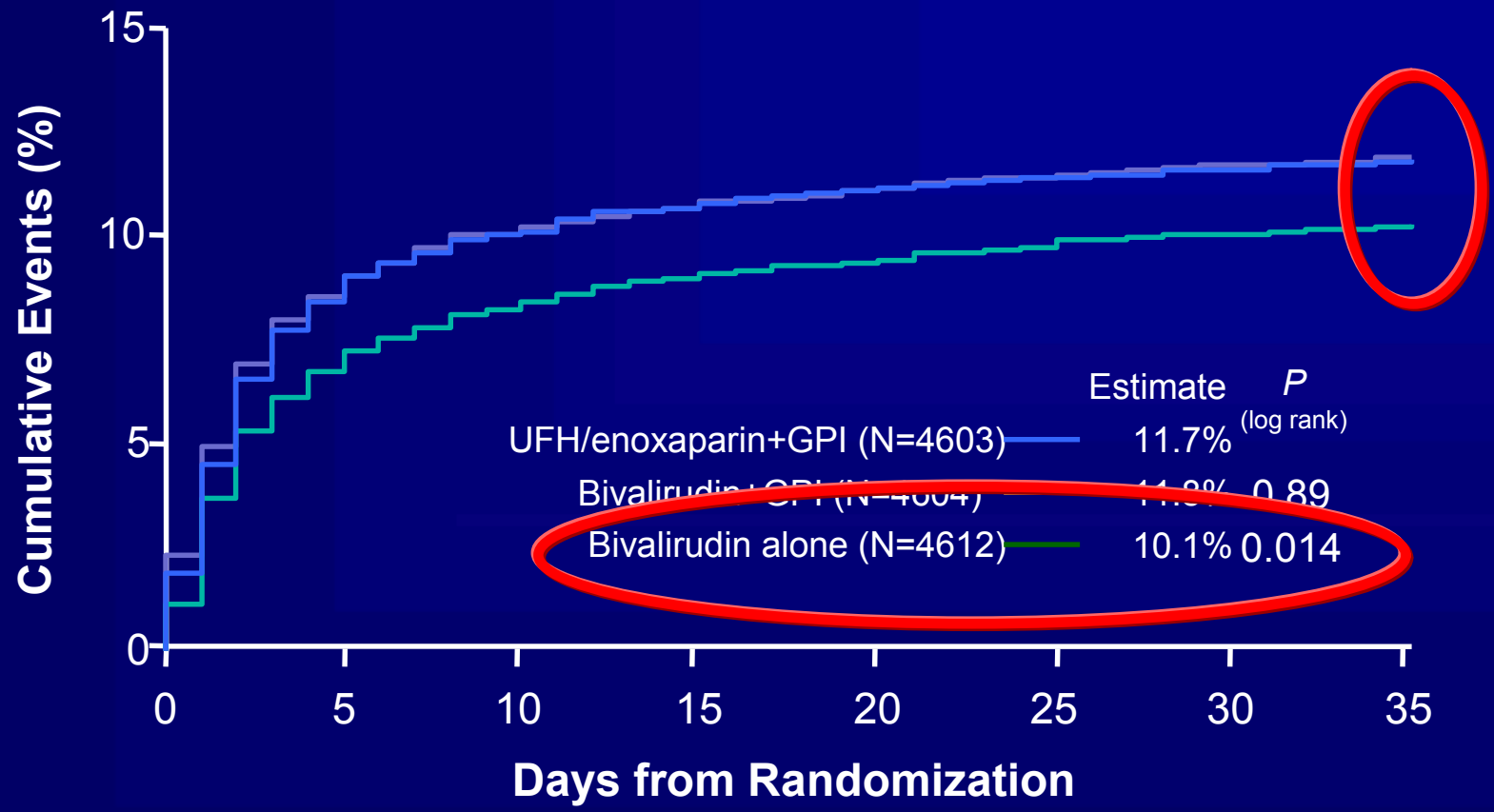
Death, MI, TVR, Bleeding

ACUITY TIMING

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

ACUITY: Net Clinical Outcome Composite Endpoint: Death, MI, TVR, Bleeding

UFH/enoxaparin+GPI vs bivalirudin+GPI vs bivalirudin alone

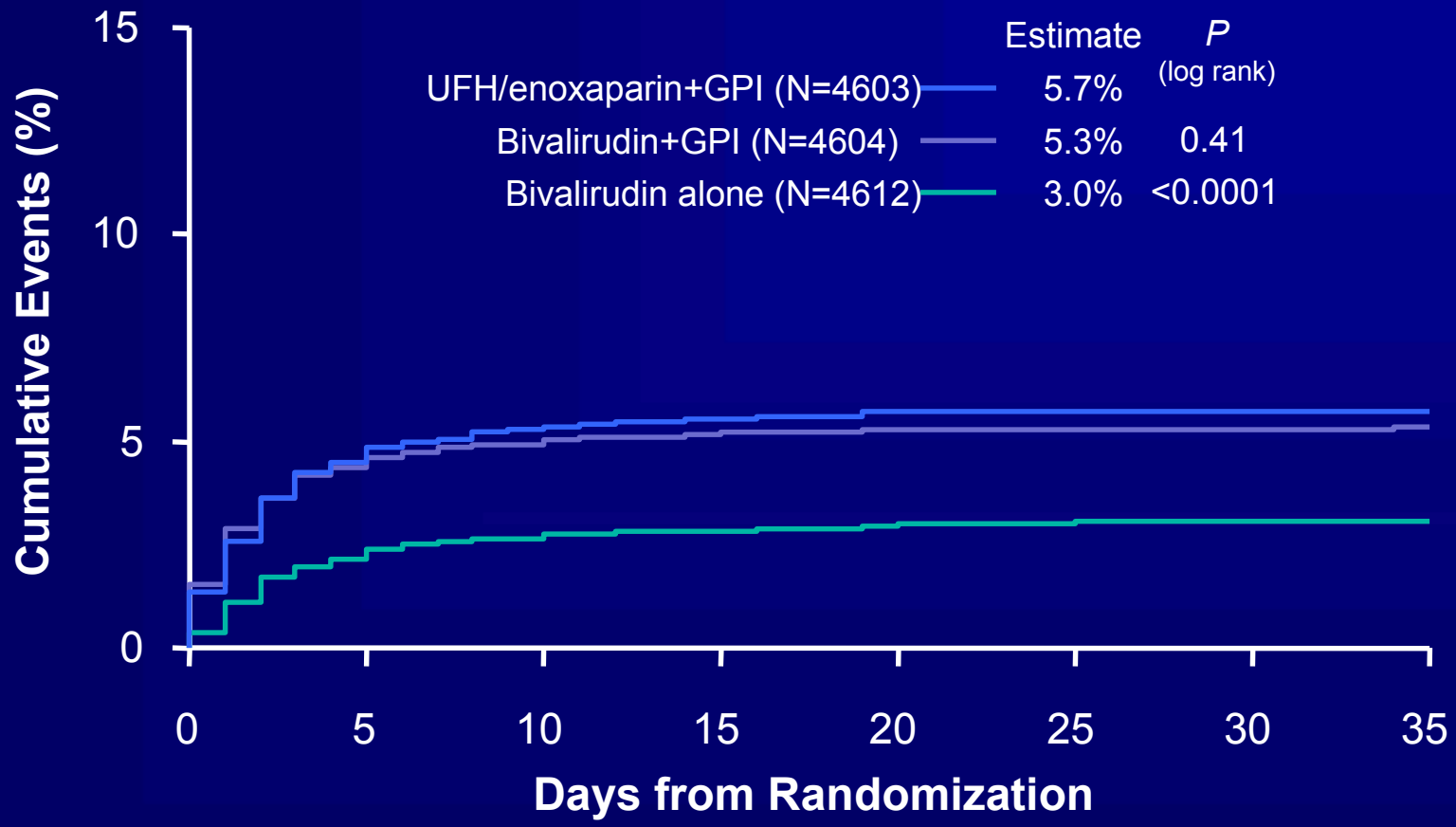


Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

UFH, unfractionated heparin; GPI, glycoprotein IIb/IIIa inhibitor.
Stone GW. *NEJM* 2007.

ACUITY: Major Bleeding Endpoint

UFH/enoxaparin+GPI vs bivalirudin+GPI vs bivalirudin alone

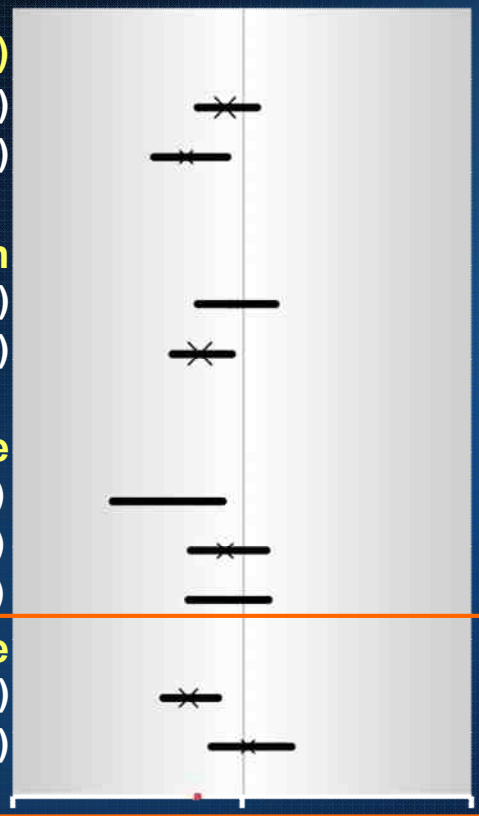


Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

UFH, unfractionated heparin; GPI, glycoprotein IIb/IIIa inhibitor.
Stone GW. *NEJM* 2007.

Net Clinical Outcome Composite

UFH/Enoxaparin + IIb/IIIa vs. Bivalirudin Alone



	Bival Alone	UFH/Enox + IIb/IIIa	RR (95% CI)	P	P_{int}
Biomarkers (CK/Trop)					
Elevated (n=5368)	12.2%	13.3%	0.92 (0.80-1.06)	0.23	0.35
Normal (n=3841)	7.1%	9.4%	0.75 (0.61-0.93)	0.01	
ST Deviation					
Yes (n=3197)	13.0%	13.7%	0.96 (0.80-1.14)	0.61	0.42
No (n=6008)	8.6%	10.6%	0.81 (0.69-0.95)	0.01	
TIMI Risk Score					
Low (0-2) (n=1291)	6.4%	10.2%	0.63 (0.43-0.91)	0.01	0.18
Intermed (3-4) (n=4407)	9.4%	10.2%	0.92 (0.77-1.10)	0.34	
High (5-7) (n=2449)	13.9%	15.2%	0.92 (0.76-1.11)	0.36	
Pre Thienopyridine					
Yes (n=5192)	9.2%	12.2%	0.76 (0.65-0.89)	<0.001	0.02
No (n=4023)	11.3%	11.1%	1.02 (0.86-1.21)	0.83	

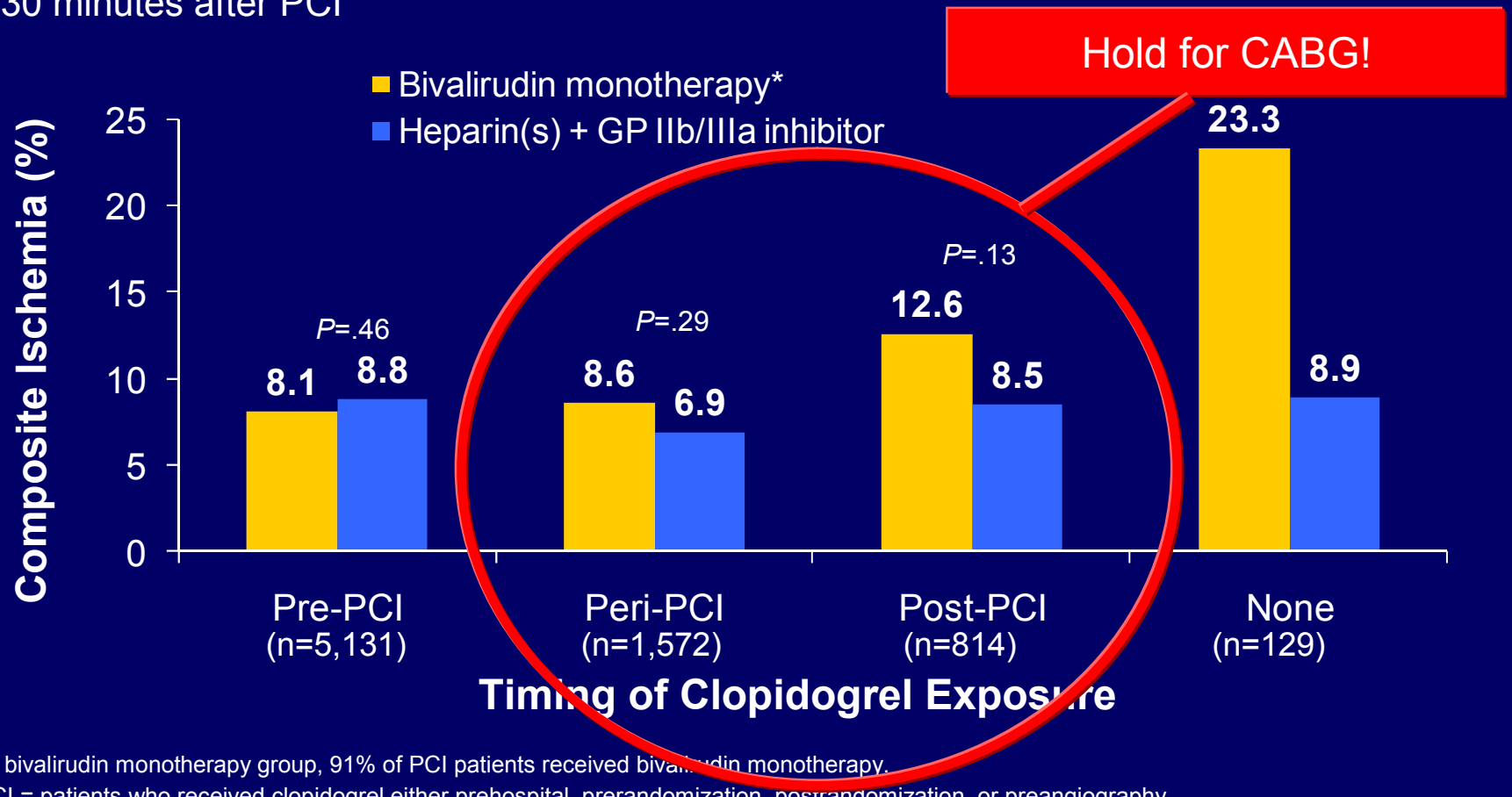
ACUITY TIMING

Stone GW. *NEJM* 2007

Clopidogrel Timing and Incidence of 30-Day Composite Ischemic Outcome

ACUITY PCI Subgroup

- Similar rates of composite ischemia were demonstrated with bivalirudin monotherapy vs heparin + GP IIb/IIIa inhibitor when clopidogrel was administered either before or within 30 minutes after PCI



*In the bivalirudin monotherapy group, 91% of PCI patients received bivalirudin monotherapy.
Pre-PCI = patients who received clopidogrel either prehospital, prerandomization, postrandomization, or preangiography.
Peri-PCI= patients who received clopidogrel after angiography and within 30 minutes after PCI procedure.
Post-PCI = patients who received clopidogrel any time >30 minutes after PCI within the index hospitalization.
None= patients who had no documentation of receiving clopidogrel at any time before or after the PCI procedure.

Lincoff AM et al. *JACC Cardiovasc Interv*. 2008;1:639-648.

Routine Upstream Initiation vs Deferred Selective Use of Glycoprotein IIb/IIIa Inhibitors in Acute Coronary Syndromes

The ACUITY Timing Trial

Gregg W. Stone, MD
Michel E. Bertrand, MD
Jeffrey W. Moses, MD
E. Magnus Ohman, MD
A. Michael Lincoff, MD
James H. Ware, PhD
Stuart J. Pocock, PhD
Brent T. McLaurin, MD
David A. Cox, MD
M. Zubair Jafar, MD
Harish Chandna, MD
Franz Hartmann, MD
Franz Leisch, MD

Context In patients with moderate- and high-risk acute coronary syndromes (ACS) who undergo an early, invasive treatment strategy, current guidelines recommend administration of platelet glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibitors, either upstream to all patients prior to angiography or deferred for selective use in the catheterization laboratory just prior to angioplasty. The preferred approach is undetermined.

Objective To determine the optimal strategy for the use of Gp IIb/IIIa inhibitors in patients with moderate- and high-risk ACS undergoing an early, invasive treatment strategy.

Design Prospective, randomized, open-label trial with 30-day clinical follow-up.

Setting Four hundred fifty academic and community-based institutions in 17 countries.

Patients A total of 9207 patients with moderate- and high-risk ACS undergoing an invasive treatment strategy.

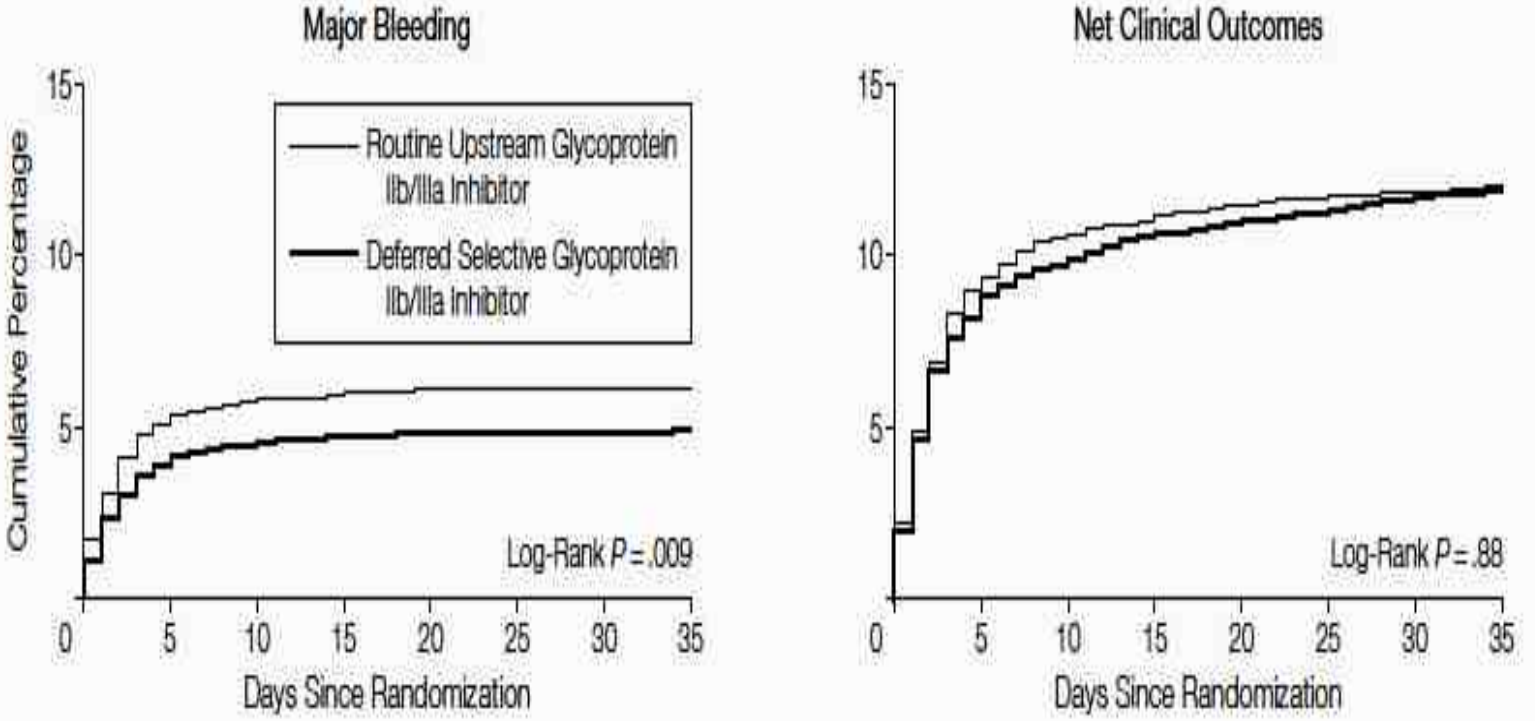
Interventions Patients were randomly assigned to receive either routine upstream (n=4605) or deferred selective (n=4602) Gp IIb/IIIa inhibitor administration, respectively.

Main Outcome Measures The primary outcome was assessment of noninferiority of deferred Gp IIb/IIIa inhibitor use compared with upstream administration for the prevention of composite ischemic events (death, myocardial infarction, or un-

JAMA. 2007;297:591-602

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

Figure 3. Time-to-Event Curves of Routine Upstream and Deferred Selective Glycoprotein IIb/IIIa Inhibitor Administration for Major Bleeding and Net Clinical Outcomes

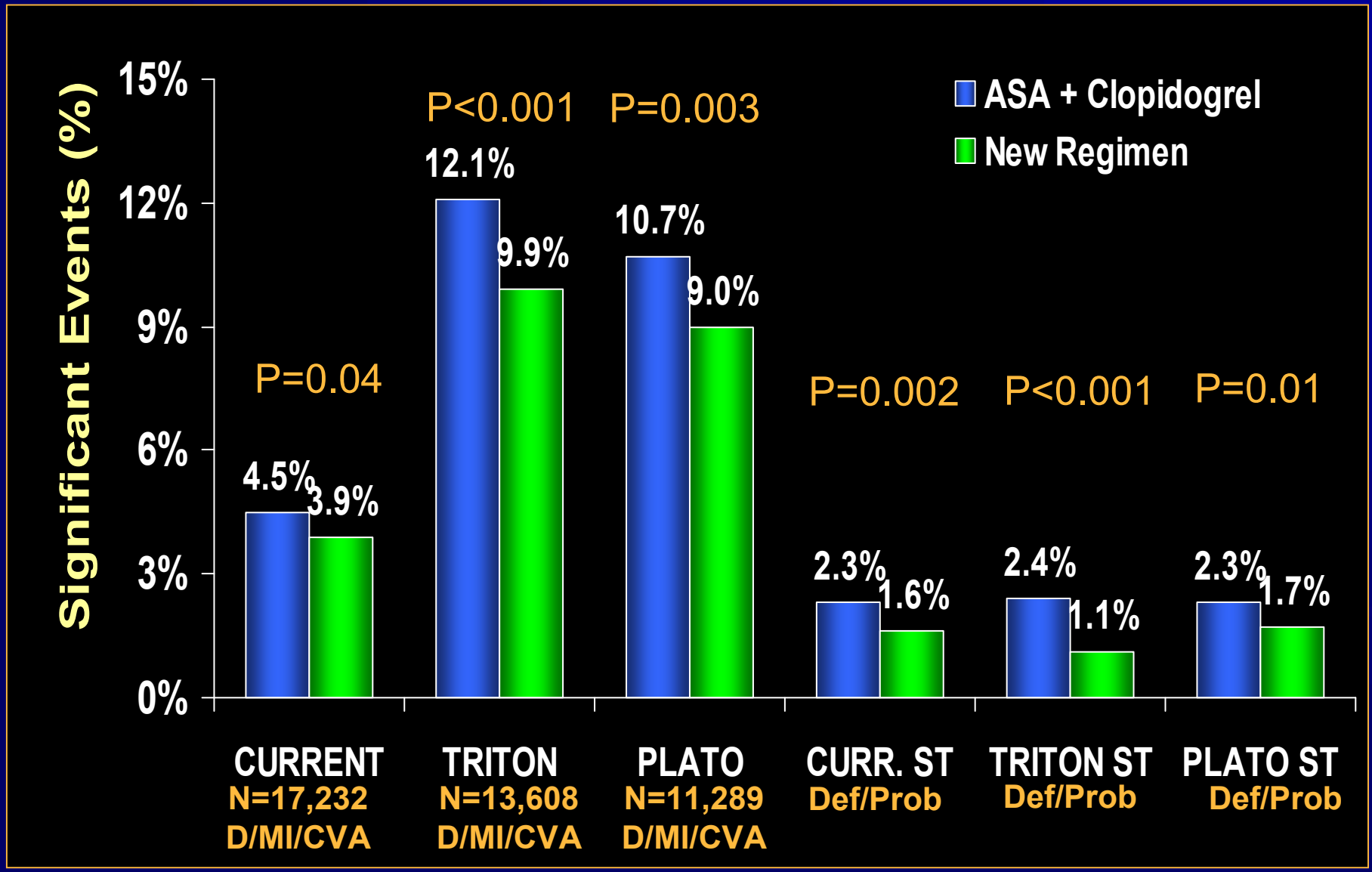


No. at Risk								
Routine Upstream Glycoprotein IIb/IIIa Inhibitor	4605	4304	4257	4238	4225	4191	3685	2563
Deferred Selective Glycoprotein IIb/IIIa Inhibitor	4602	4361	4311	4286	4269	4239	3805	2637

Routine Upstream Glycoprotein IIb/IIIa Inhibitor	4605	4149	4071	4043	4018	3983	3500	2424
Deferred Selective Glycoprotein IIb/IIIa Inhibitor	4602	4181	4104	4064	4042	4005	3579	2465

Optimal Dosing, Duration, & New Novel Agents

ACS+PCI: 3 RCTs vs. Std Clopidogrel



Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

- TRITON—NEJM 2007
- PLATO—NEJM 2009
- CURRENT—ESC 2009

Initial Invasive Strategy: Antiplatelet, Anticoagulant Therapy

- Aspirin
- Initiate anticoagulant therapy as soon as possible after presentation (I, A). Regimens with established efficacy:
  - Enoxaparin or UFH (I, A)
  - Bivalirudin or fondaparinux (I, B)
- Prior to angiography, initiate one (I, A) or both (IIa, B)
  - Clopidogrel
  - IV GP IIb/IIIa inhibitor

  Use both if:
    - Delay to angiography
    - High-risk features
    - Early recurrent ischemic syndromes

Changes coming?

- **Bivalirudin + later thienopyridine?**
- **Prasugrel ?**

Anderson JL, et al. *J Am Coll Cardiol.* 2007;50(7):e1-e157.

Optimal Use of Anti-PLT Therapies: Conclusions

1. Cath should not be delayed to “passify” lesions with IIbIIIa therapy (EARLY-ACS, ACUITY)
2. Combined/prolonged thienopyridine and eptifibatide might provide benefit, but clearly with added bleeding (EARLY-ACS)
3. Specific thrombin inhibitors may obviate the need for “upstream” platelet inhibition, but are not sufficient as solo therapy (ACUITY)
4. Reduced arteriotomy site bleeding through trans-radial approach might improve “net” clinical benefit

Shifting the Balance of Potency and Bleeding Risk for Anti-Coagulant and Anti-Platelet Agents Through Radial Arteriotomy:

An Obligatory Drug-Device Safety Interaction Cardiac Safety Critical Path Thinktank/Incubator

23-June, 2010
Washington D.C.
FDA Headquarters

With intellectual and program planning support from the (alphabetical) Academic Research Consortium (ARC), the American College of Cardiology (ACC), the Cardiac Safety Research Consortium (CSRC), the Duke Clinical Research Institute (DCRI), the Society of Coronary Angiography and Intervention (SCAI) and the United States Food and Drug Administration (FDA).

- Cleveland Clinic
- Columbia University
- Duke University
- Harvard
- Johns Hopkins
- Washington Heart Ctr
- U.S. FDA
- AHRQ
- NIH
- ACC
- SCAI
- SOLACI
- ESC

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

www.cardiac-safety.org

Timing of Anti-Platelet Therapy for ACS (EARLY-ACS & ACUITY)

Mitchell W. Krucoff, MD, FACC

Professor, Medicine/Cardiology

Duke University Medical Center

Director, Cardiovascular Devices Unit

Duke Clinical Research Institute

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER