New Paradigms in Treatment of ACS/AMI

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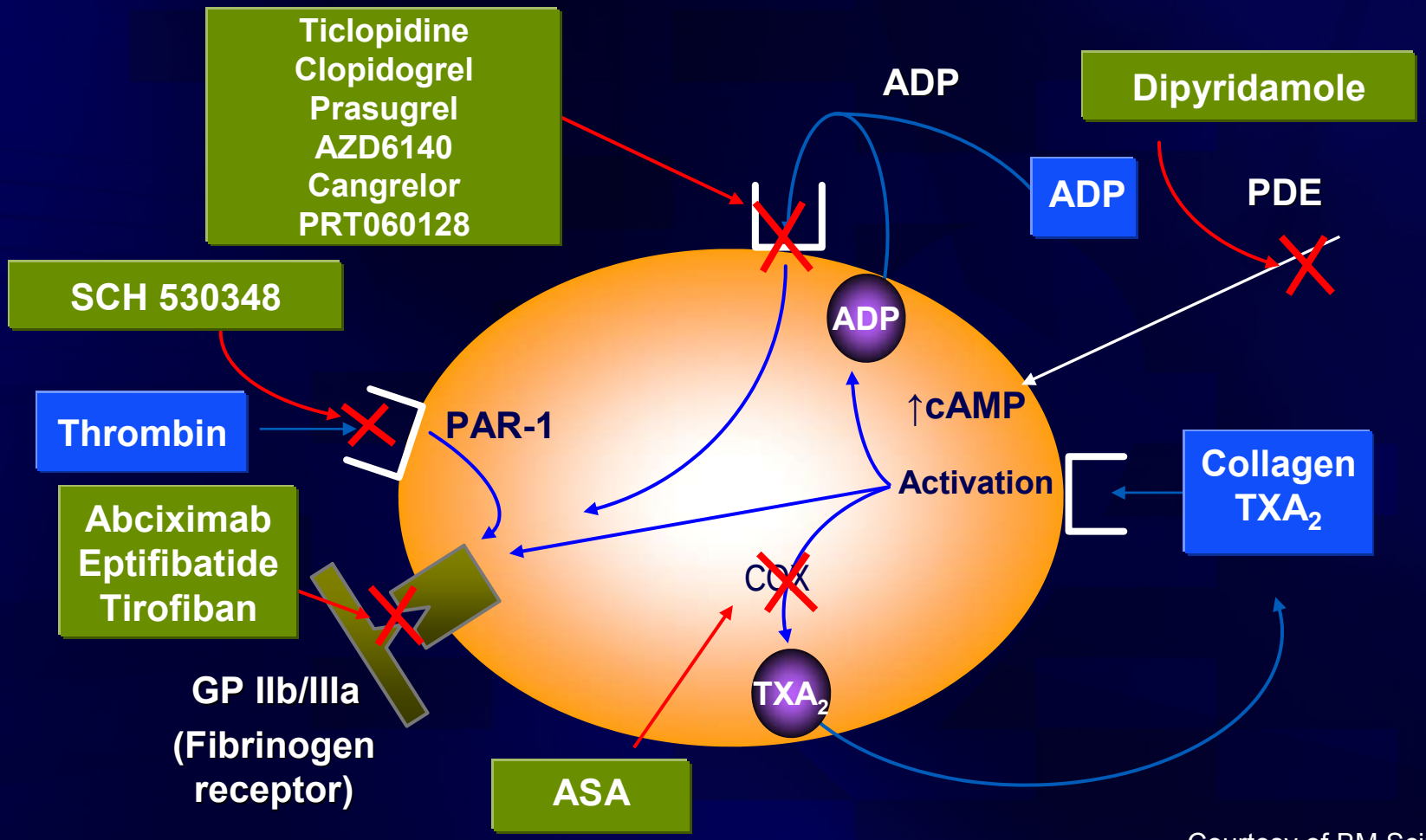
Targets for antiplatelet therapies

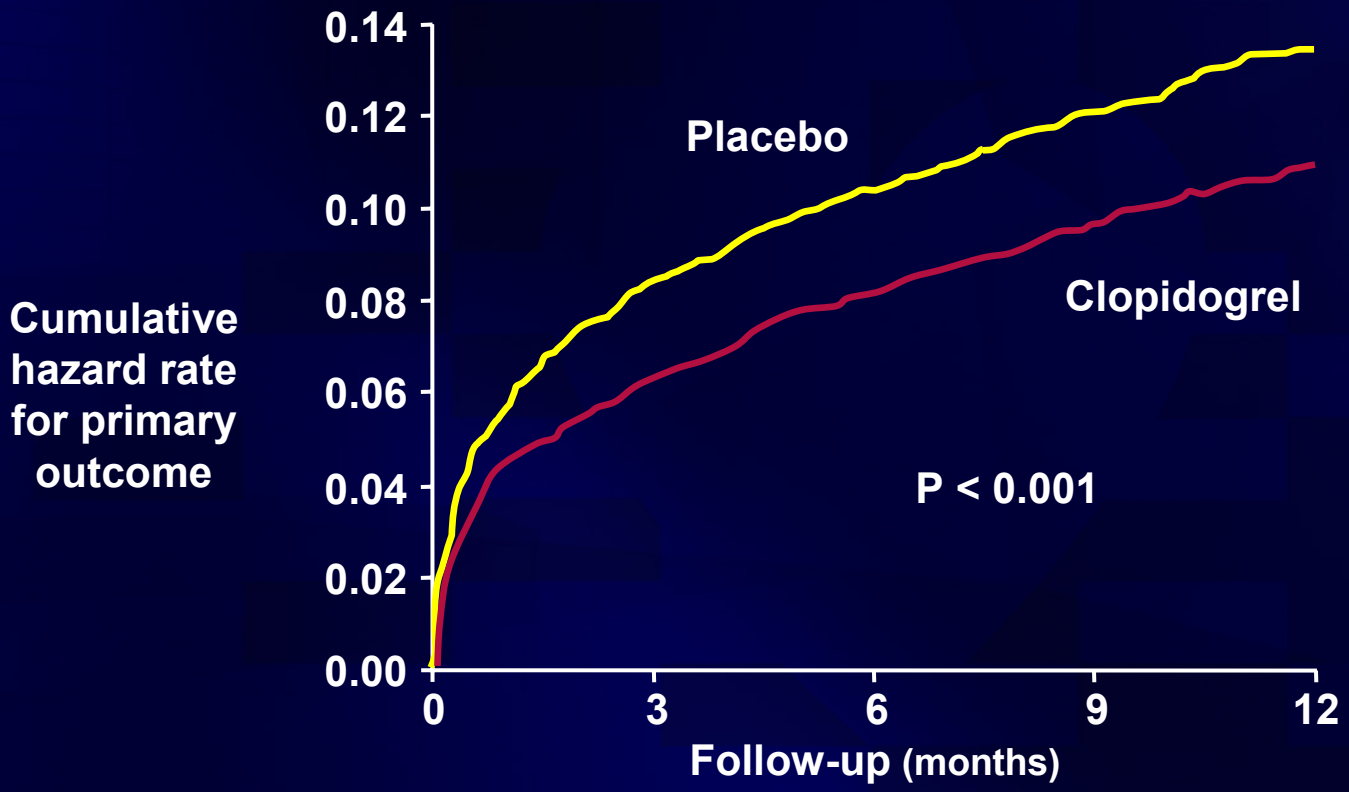


cAMP = cyclic adenosine monophosphate, COX = cyclooxygenase, PAR = protease-activated receptor, PDE = phosphodiesterase

Courtesy of BM Scirica, MD.
Adapted from Schafer AI.
Am J Med. 1996;101:199-209.

CURE: Patients continue to have recurrent CV events despite dual antiplatelet therapy

N = 12,562 with NSTE-ACS; all patients received ASA;
Primary outcome = CV death, MI, stroke

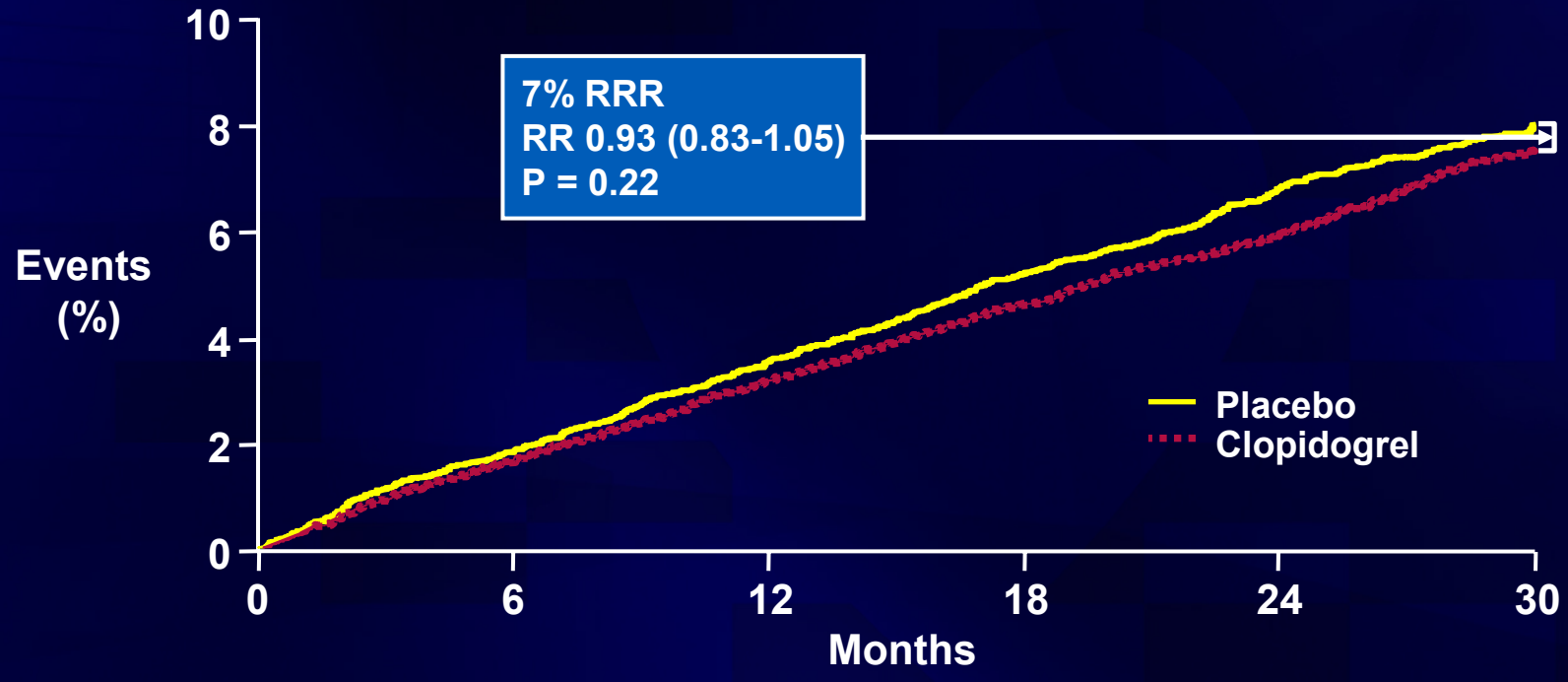


CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events

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

CHARISMA: Dual antiplatelet therapy not significantly better than ASA alone

N = 15,603 with either established vascular disease or multiple risk factors; all patients received ASA; primary outcome: MI, stroke, CV death

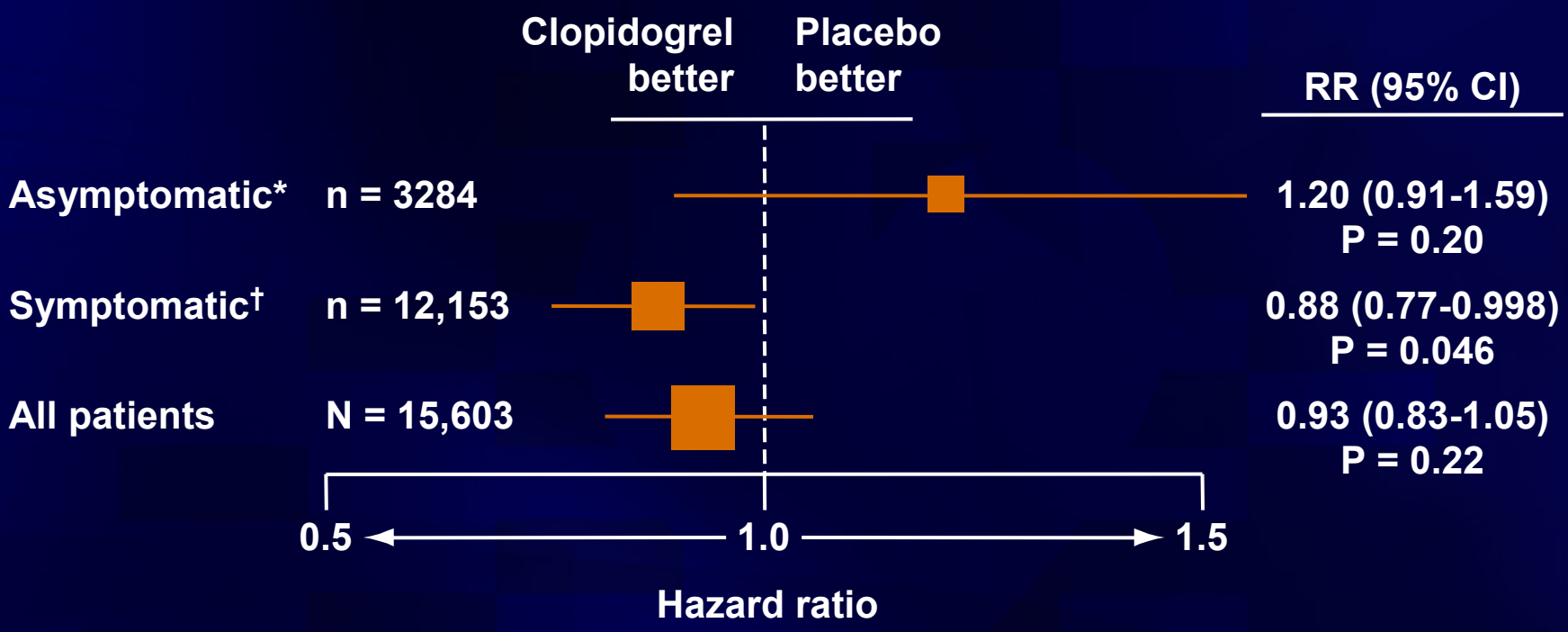


CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance

Bhatt DL et al. *N Engl J Med.* 2006;354:1706-17.

CHARISMA: Treatment effect by inclusion criteria

MI, stroke, CV death



*Multiple atherothrombotic risk factors
†Documented coronary, cerebrovascular, or peripheral arterial disease

Bhatt DL et al. *N Engl J Med.* 2006;354:1706-17.

CHARISMA: Safety endpoints by inclusion criteria

GUSTO criteria

	Event rate (%)		
	Clopidogrel + ASA	Placebo + ASA	P
Symptomatic			
Severe bleeding	1.6	1.4	0.39
Moderate bleeding	2.1	1.3	<0.001
Asymptomatic			
Severe bleeding	2.0	1.2	0.07
Moderate bleeding	2.2	1.4	0.08

GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries

Bhatt DL et al. *N Engl J Med.* 2006;354:1706-17.

P2Y12 antagonists

	Type	Activity	Binding	Dosing
Ticlopidine	Thienopyridine	Indirect*	Irreversible	PO
Clopidogrel	Thienopyridine	Indirect*	Irreversible	PO
Prasugrel	Thienopyridine	Indirect*	Irreversible	PO
AZD6140	Cyclopentyl-triazolopyrimidine	Direct	Reversible	PO
Cangrelor	ATP analog	Direct	Reversible	IV
PRT060128	N/A	Direct	Reversible	PO, IV

***Prodrug**
ATP = adenosine triphosphate

Adapted from Michelson AD. *Arterioscler Thromb Vasc Biol*. 2008;28:s33-s38.
Storey RF. *Eur Heart J Suppl*. 2008;10(Suppl D):D30-D37.

Limitations of current thienopyridines

- Slow onset requiring prolonged pretreatment for PCI efficacy
- Irreversibility and bleeding (especially related to CABG)
- Modest levels of platelet inhibition
- Variability of response

Michelson AD. *Arterioscler Thromb Vasc Biol*. 2008;28:s33-s38.

Platelet function testing: The beginning of personalized dosing with platelet inhibitors?

Selected examples shown (multiple tests available)

Test	Basis	Advantages	Disadvantages
Turbidometric aggregometry	Platelet aggregation	Historical gold standard	High sample volume Sample preparation Time consuming
Impedance aggregometry	Platelet aggregation	Whole blood assay	High sample volume Sample preparation Time consuming
VerifyNow®	Platelet aggregation	Simple, rapid Point-of-care (no pipetting required) Low sample volume Whole blood assay	Limited hematocrit & platelet count range
PFA-100®	In vitro cessation of high shear blood flow by platelet plug	Simple, rapid Point-of-care Low sample volume No sample prep Whole blood assay Shear	Dependent on VWF & hematocrit Requires pipetting Does not correlate well with clopidogrel therapy

Courtesy of JE Freedman, MD

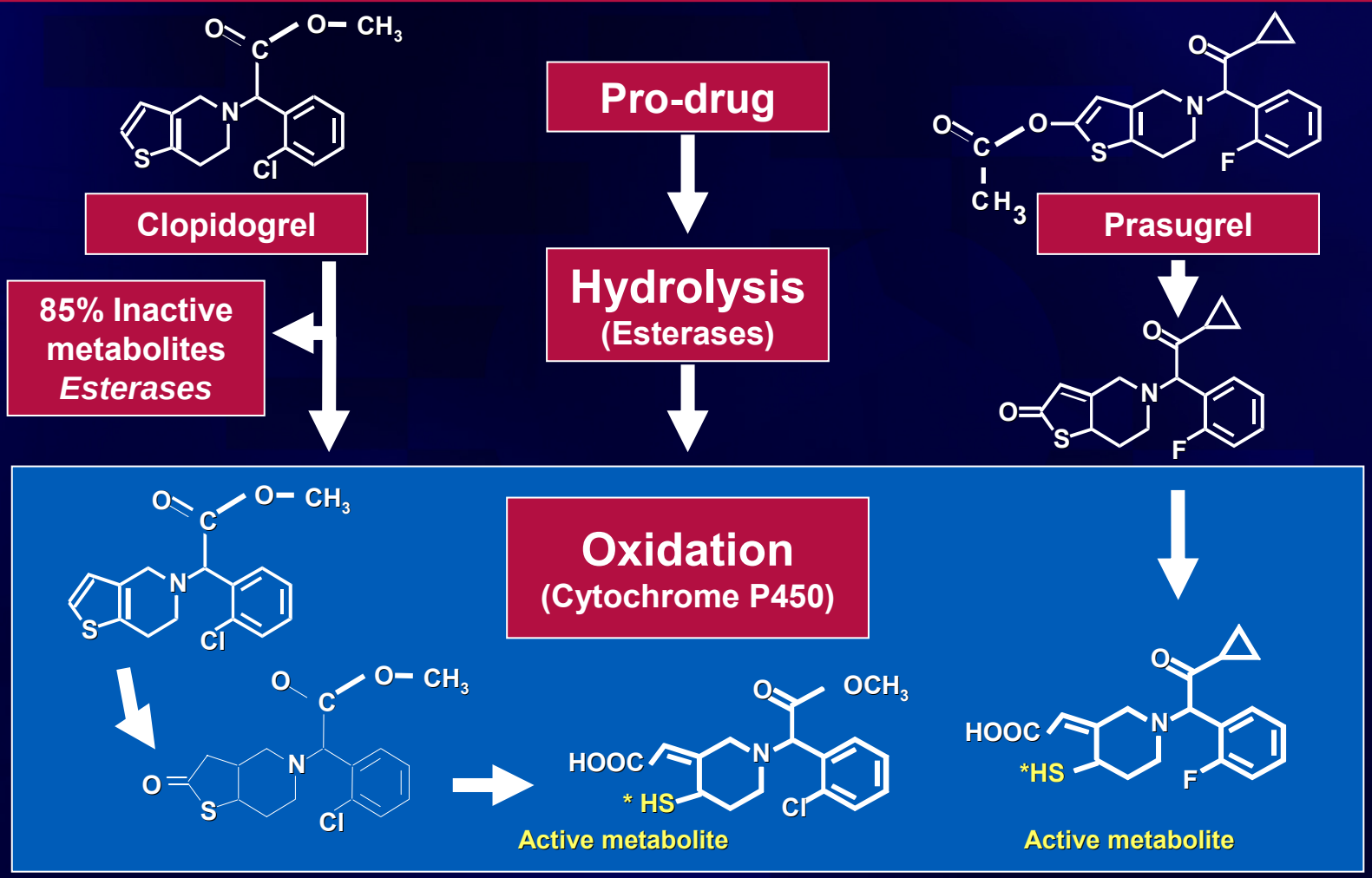
Prasugrel: Overview

- Thienopyridine, orally administered as prodrug (more efficiently metabolized vs clopidogrel), irreversible inhibition of P2Y12 receptor
- TRITON-TIMI 38: Prasugrel 60/10 mg vs clopidogrel 300/75 mg
  - Clinical events
  - Bleeding rates and high-risk indicators
- PRINCIPLE-TIMI 44: Platelet inhibition with prasugrel 60/10 mg vs clopidogrel 600/150 mg
- TRILOGY ACS: Ongoing clinical outcomes trial

PRINCIPLE-TIMI = Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction, TRITON = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel, TRILOGY ACS = Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes

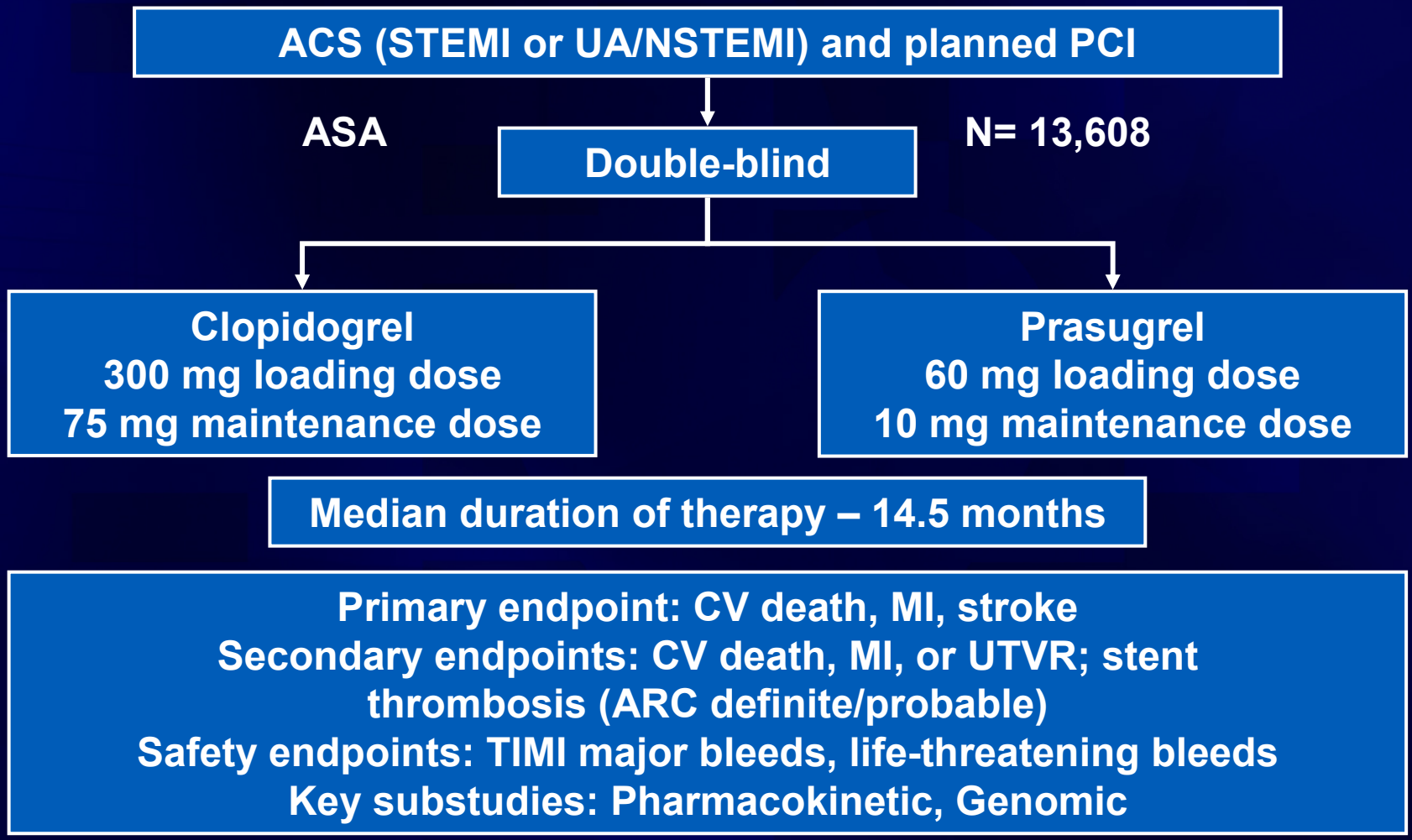
Michelson AD. *Arterioscler Thromb Vasc Biol*. 2008;28:s33-s38.

Clopidogrel response variability: Change the agent?



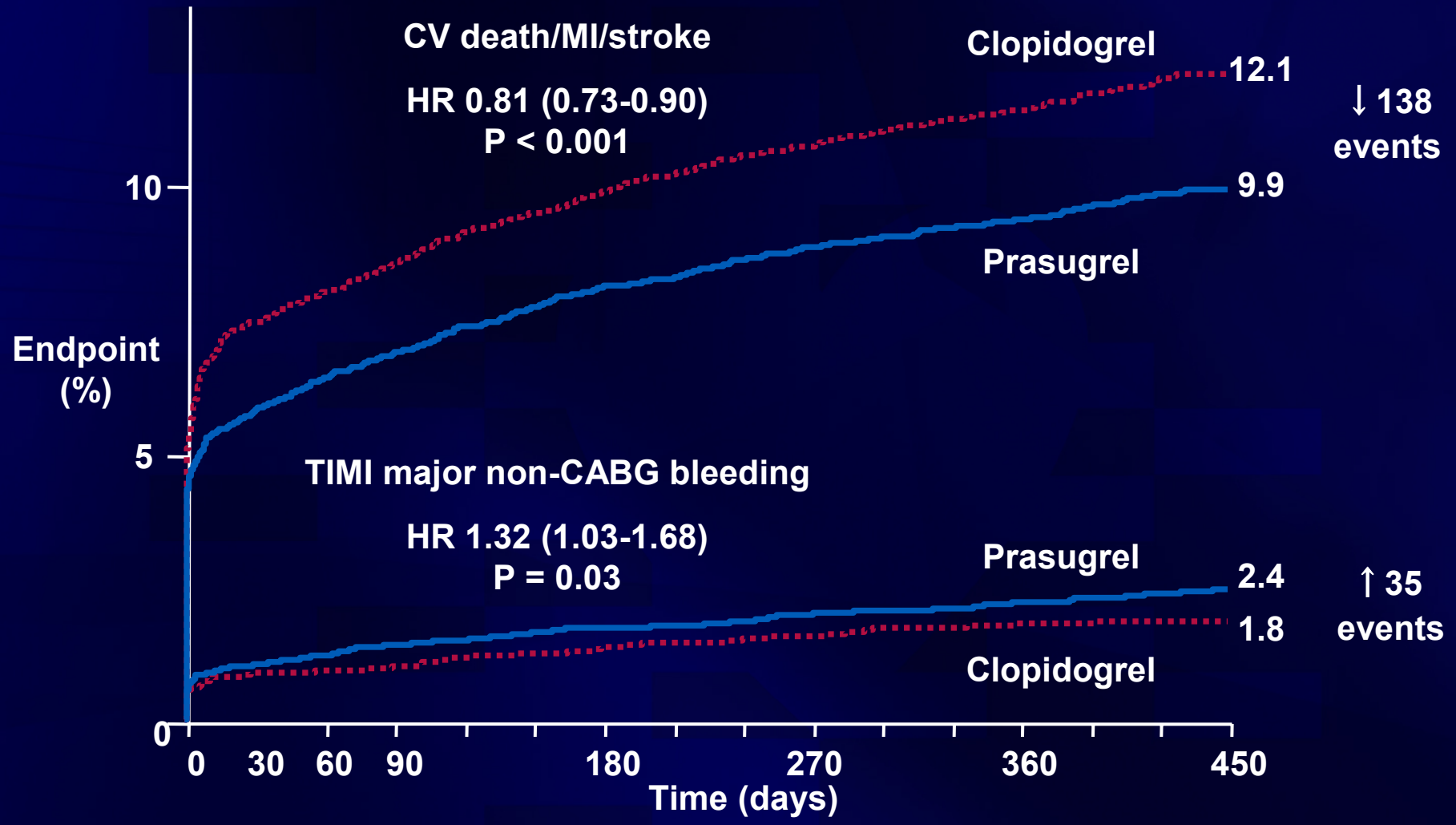
Herbert JM et al. *Sem Vasc Med.* 2003;3:113-22.

TRITON-TIMI 38: Study design



Wiviott SD et al. *N Engl J Med.* 2007;357:2001-15.

TRITON-TIMI 38: Treatment effects on primary efficacy and key safety endpoints

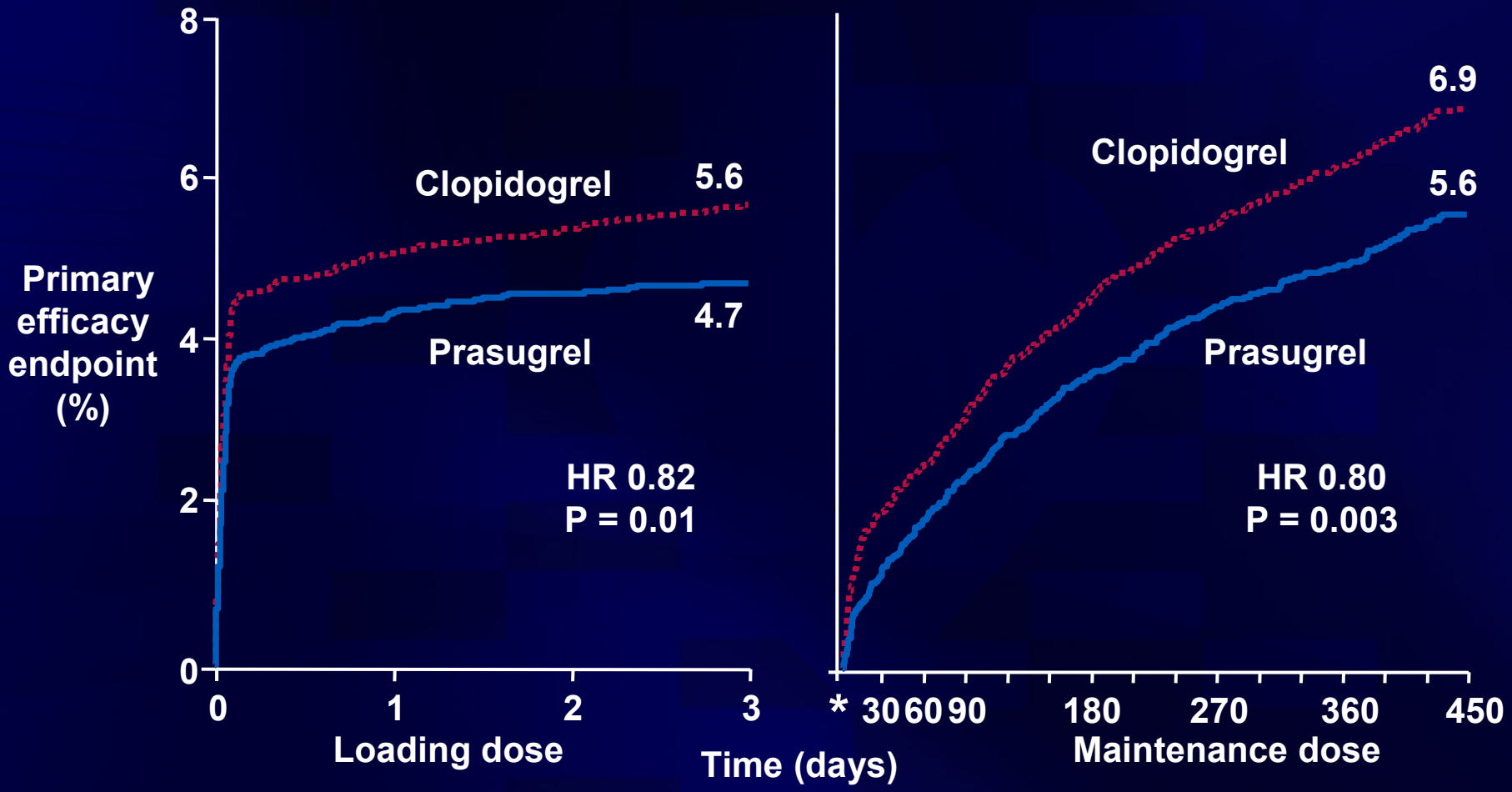


HR = hazard ratio

Wiviott SD et al. *N Engl J Med.* 2007;357:2001-15.

TRITON-TIMI 38: Timing of benefit

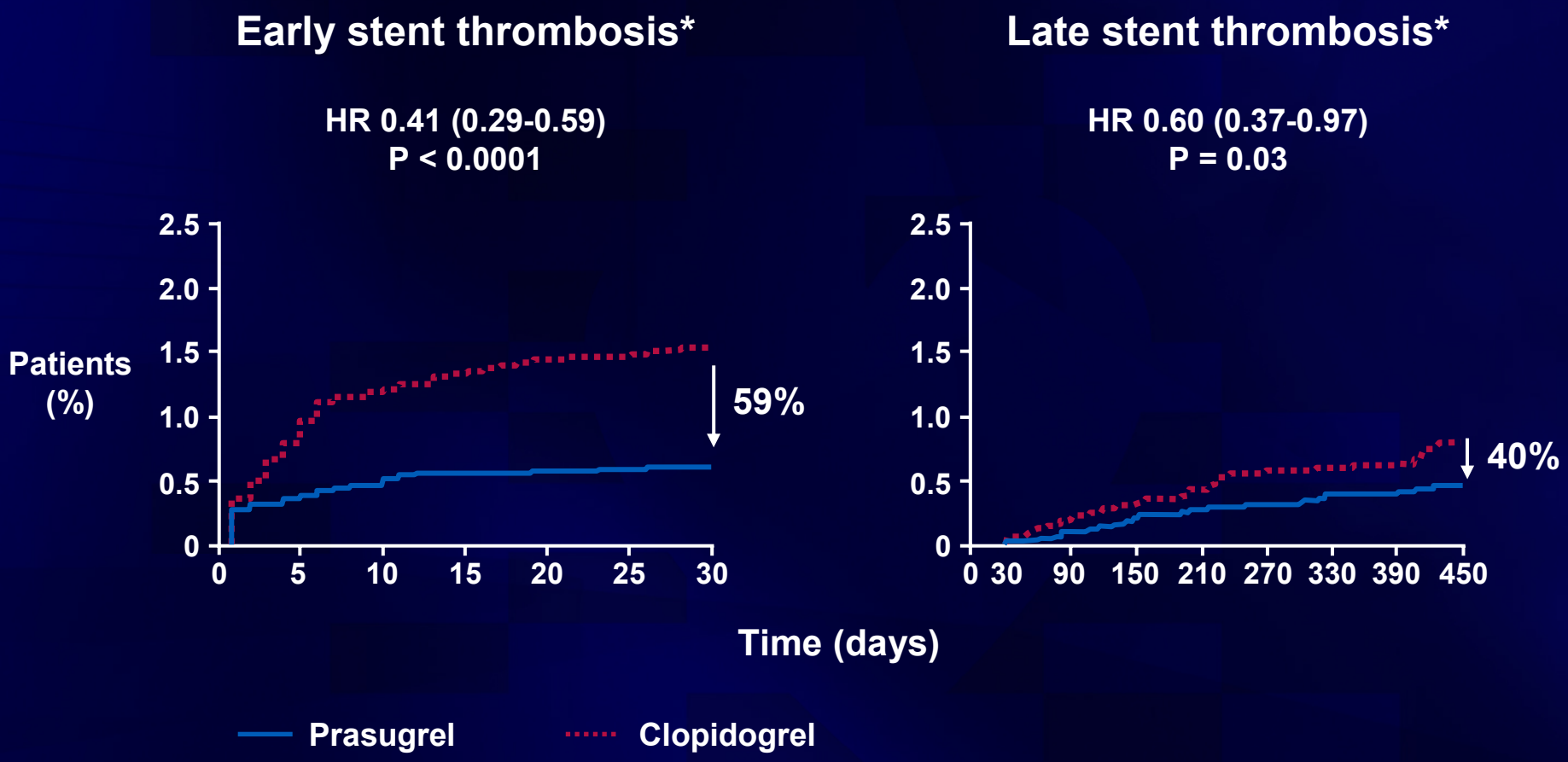
Landmark analysis



*All endpoints occurring before day 3 censored

Wiviott SD et al. *N Engl J Med.* 2007;357:2001-15.

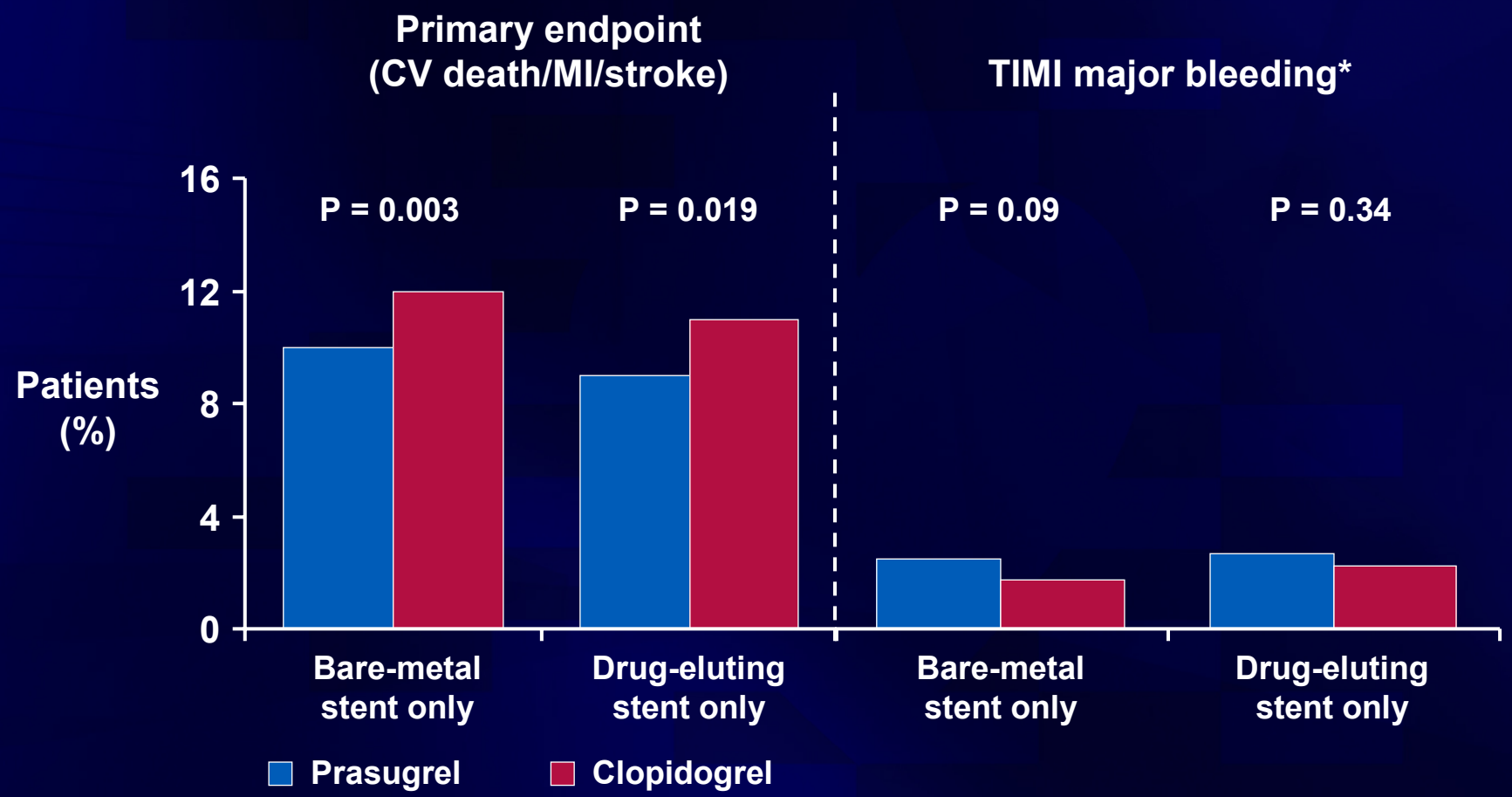
TRITON-TIMI 38: Stent thrombosis for all patients receiving at least one intracoronary stent



*Definite or probable using Academic Research Consortium designation

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

TRITON-TIMI 38: Clinical events for prasugrel vs clopidogrel stratified by stent type

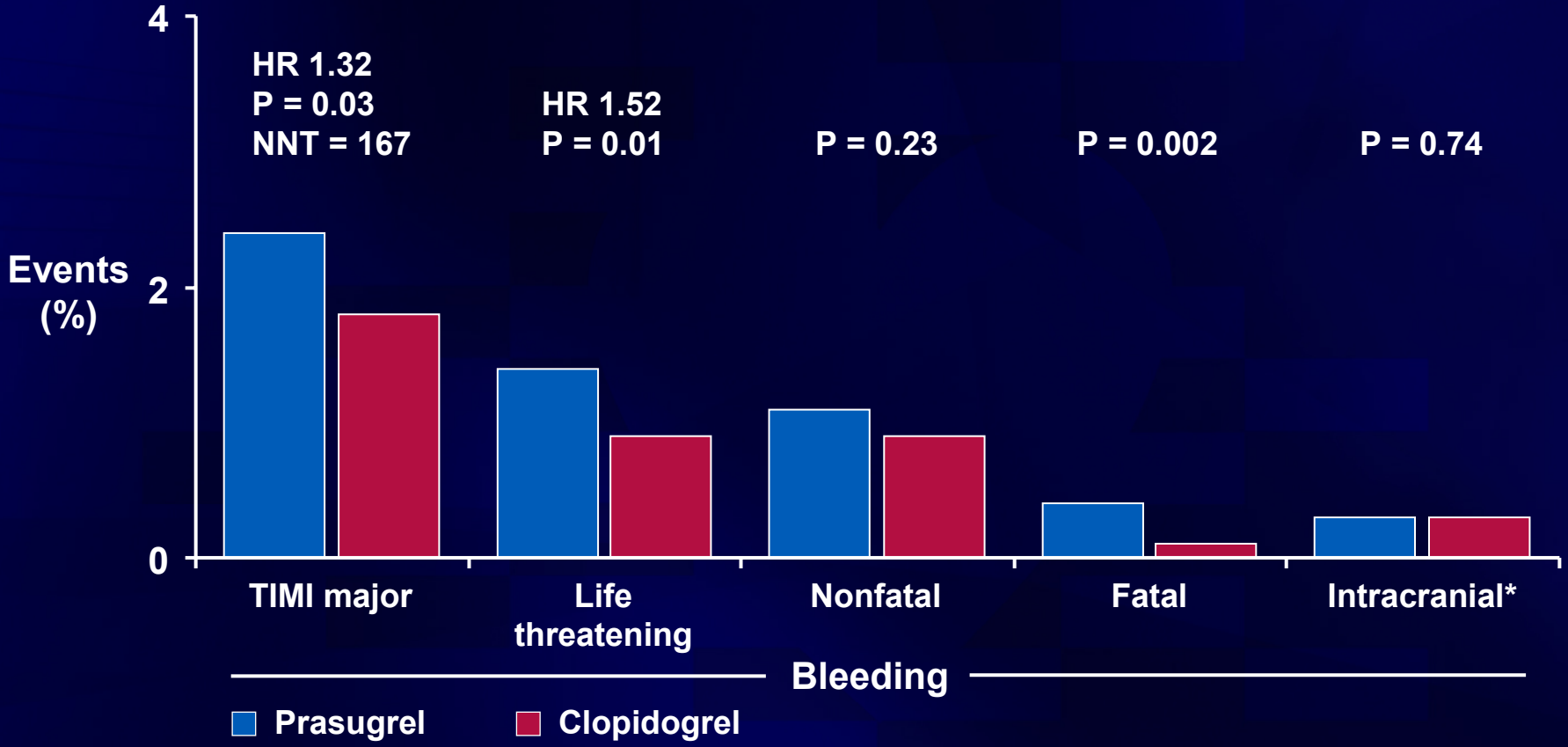


*Not related to coronary bypass surgery

Wiviott SD et al. *Lancet*. 2008;371:1353-63.
Wiviott SD et al. Presented at SCAI-ACC 2008.

TRITON-TIMI 38: Bleeding events

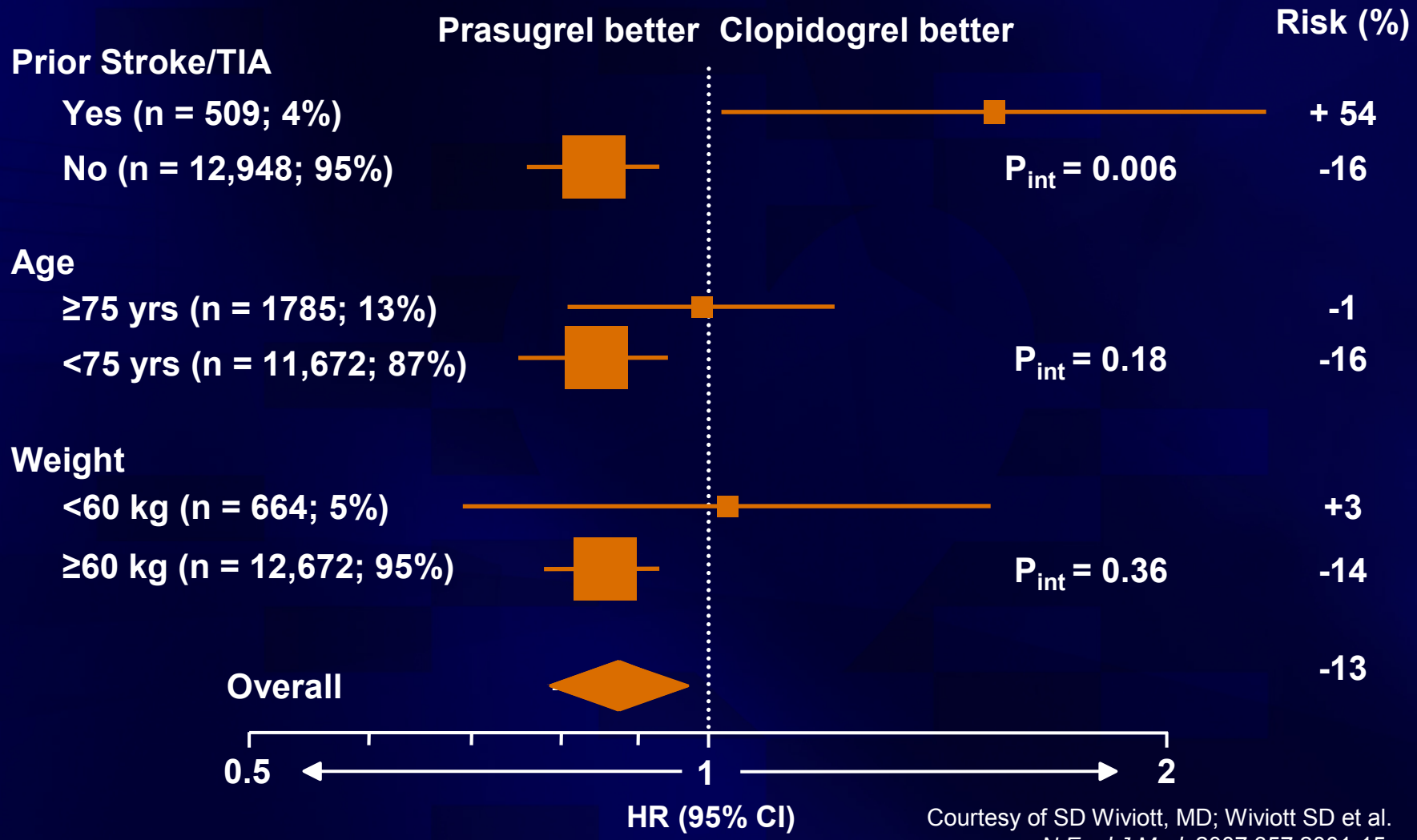
Safety cohort; n = 13,457



*P = 0.02 in patients with prior stroke/TIA (0% clopidogrel vs 2.3% prasugrel)
NNT = number needed to treat

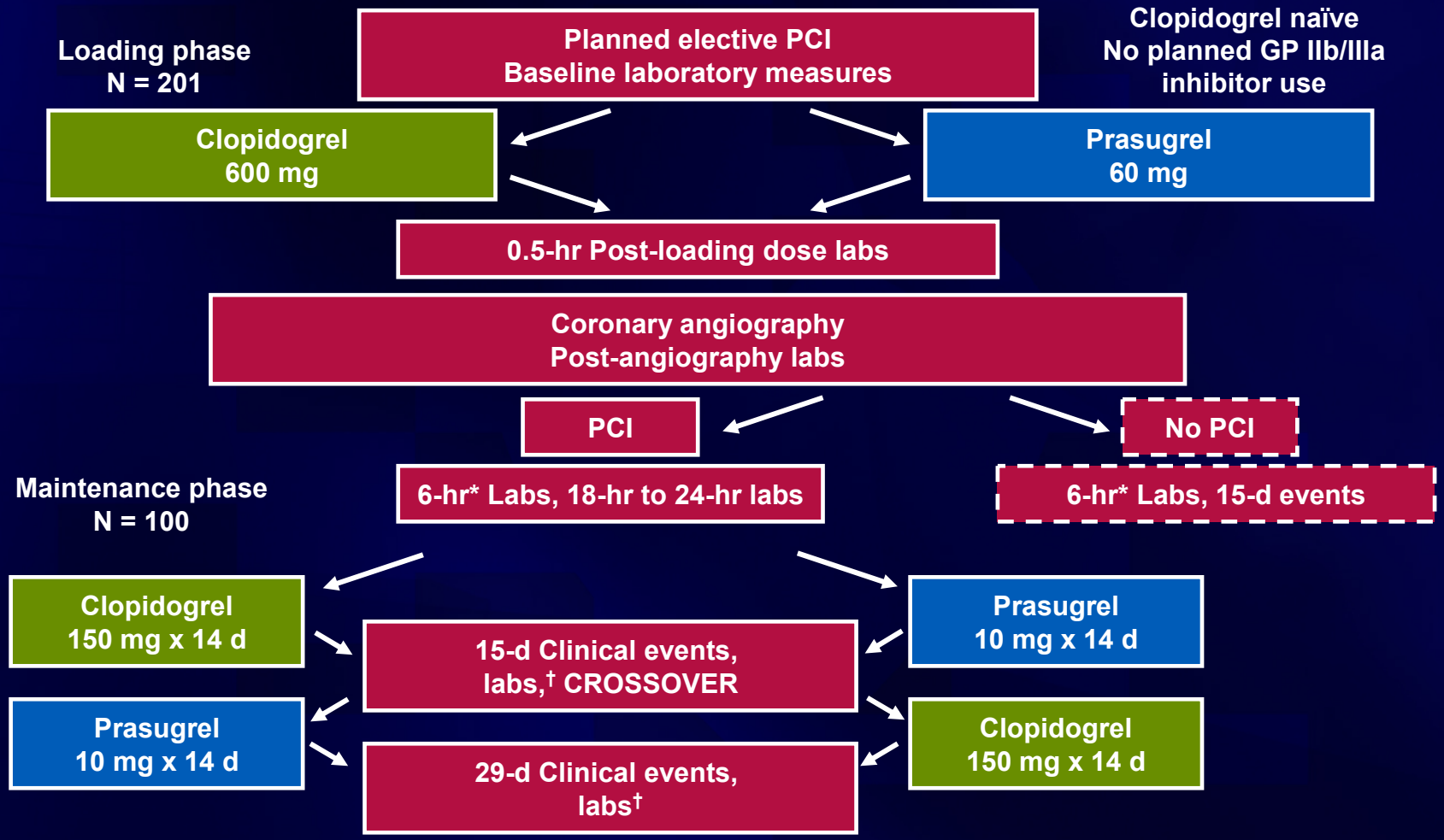
Wiviott SD et al. *N Engl J Med.* 2007;357:2001-15.

TRITON-TIMI 38 post hoc analysis: Net clinical benefit in subgroups at increased bleeding risk



Courtesy of SD Wiviott, MD; Wiviott SD et al. *N Engl J Med*. 2007;357:2001-15.

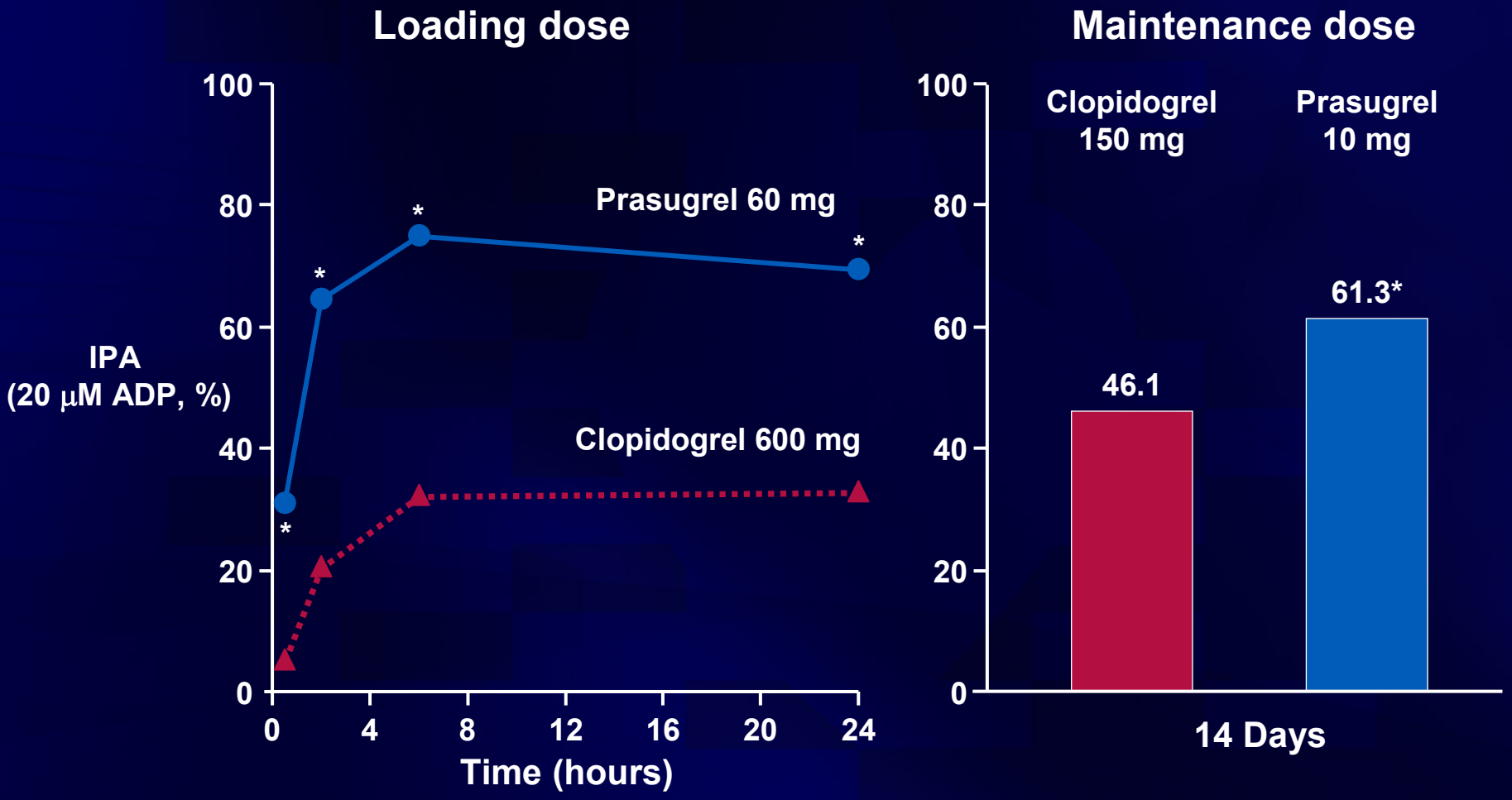
PRINCIPLE-TIMI 44: Study design



1º Endpoints: *Loading = 6-hr inhibition of platelet aggregation (IPA); †Maintenance = 14-d and 29-d IPA

Wiviott SD et al. *Circulation.* 2007;116:2923-32.

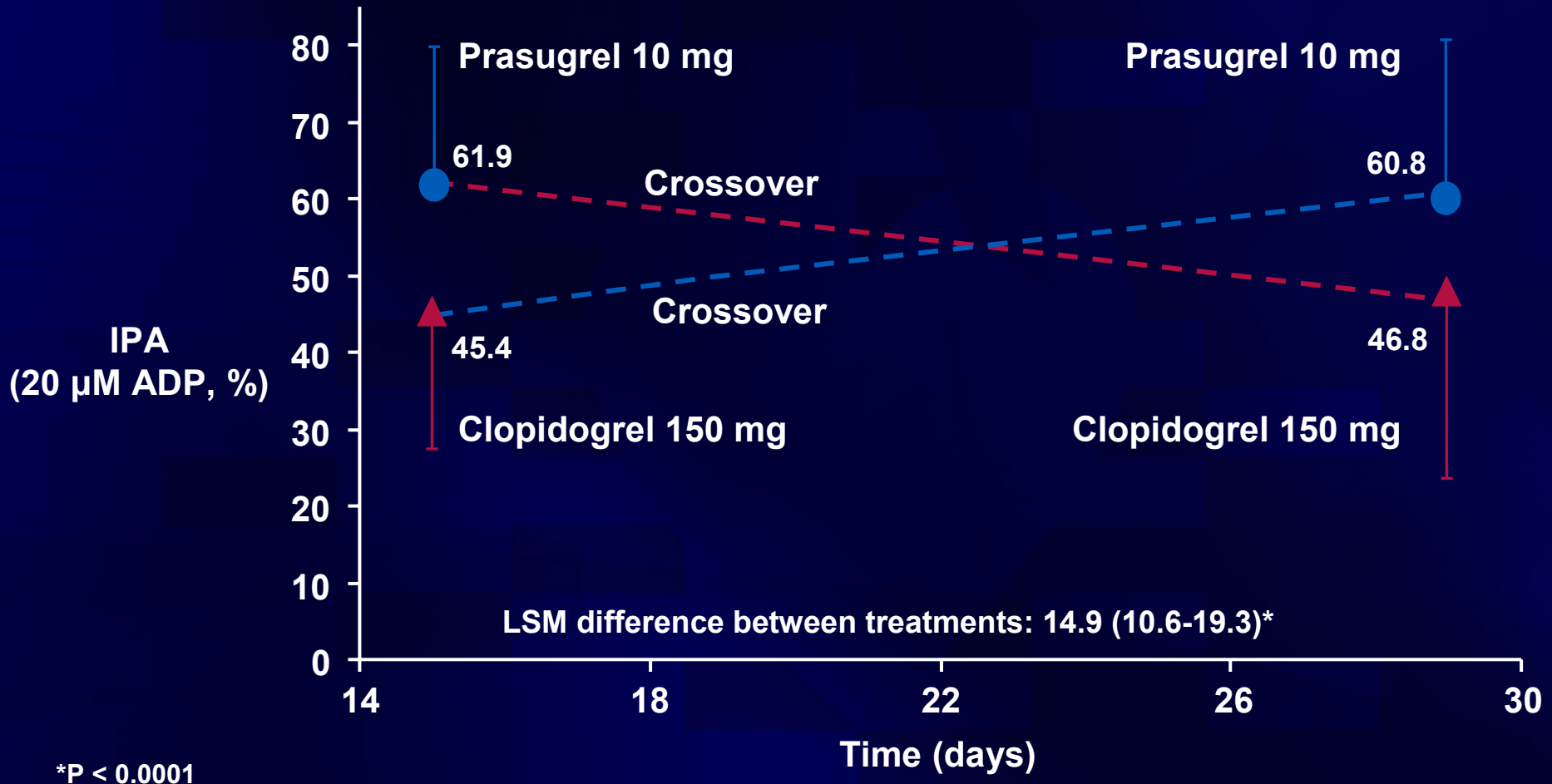
PRINCIPLE-TIMI 44: Inhibition of platelet aggregation with loading and maintenance doses



*P < 0.0001 vs clopidogrel
IPA = inhibition of platelet aggregation

Wiviott SD et al. *Circulation.* 2007;116:2923-32.

PRINCIPLE-TIMI 44 (crossover phase): Inhibition of platelet aggregation with maintenance dose



*P < 0.0001
LSM = least square mean
IPA = inhibition of platelet aggregation

Wiviott SD et al. *Circulation.* 2007;116:2923-32.

TRITON-TIMI 38, PRINCIPLE-TIMI 44: Conclusions

- In ACS patients undergoing PCI, a thienopyridine agent that achieves faster, more consistent, and greater levels of platelet inhibition than standard clopidogrel results in:
  - ↓Ischemic events, particularly MI and stent thrombosis
  - ↑Bleeding, including serious bleeding, particularly in specific patient subsets

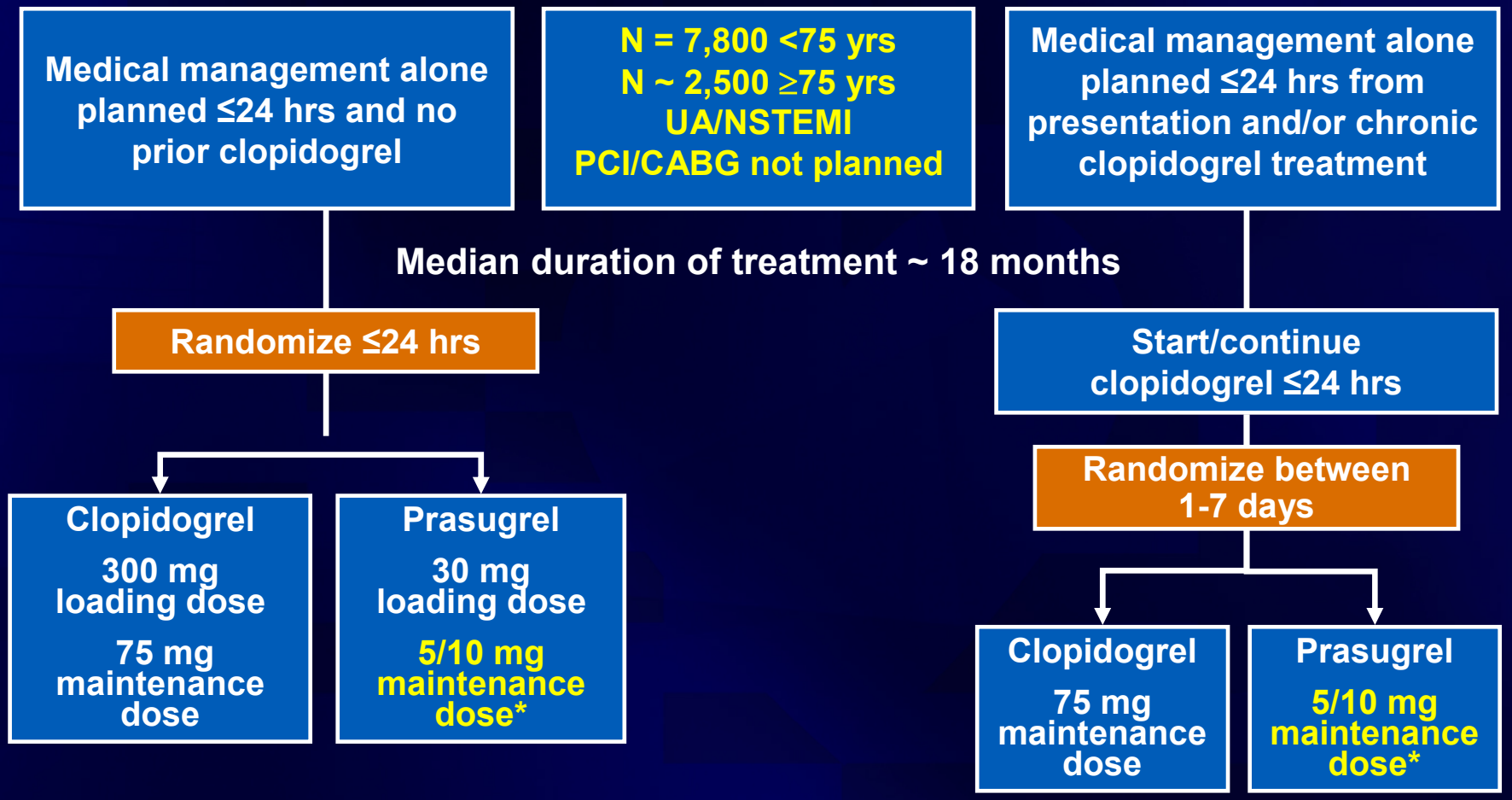
Courtesy of DA Morrow, MD and BM Scirica, MD.

TRITON-TIMI 38, PRINCIPLE-TIMI 44: Uncertainties

- What aspect(s) of prasugrel resulted in benefits?
  - Speed
  - Consistency
  - Potency
- Would this translate to other methods of inhibition?
  - P2Y12 signaling
  - Platelet activation, adhesion, and aggregation unrelated to P2Y12
- What are appropriate surrogate markers of platelet function?

Courtesy of DA Morrow, MD and BM Scirica, MD.

TRILOGY ACS: Study design



*5 mg maintenance dose of prasugrel for age ≥75 yrs or weight <60 kg

Courtesy of MT Roe, MD
NIH. www.clinicaltrials.gov.

Achieving optimal platelet inhibition in ACS: Summary

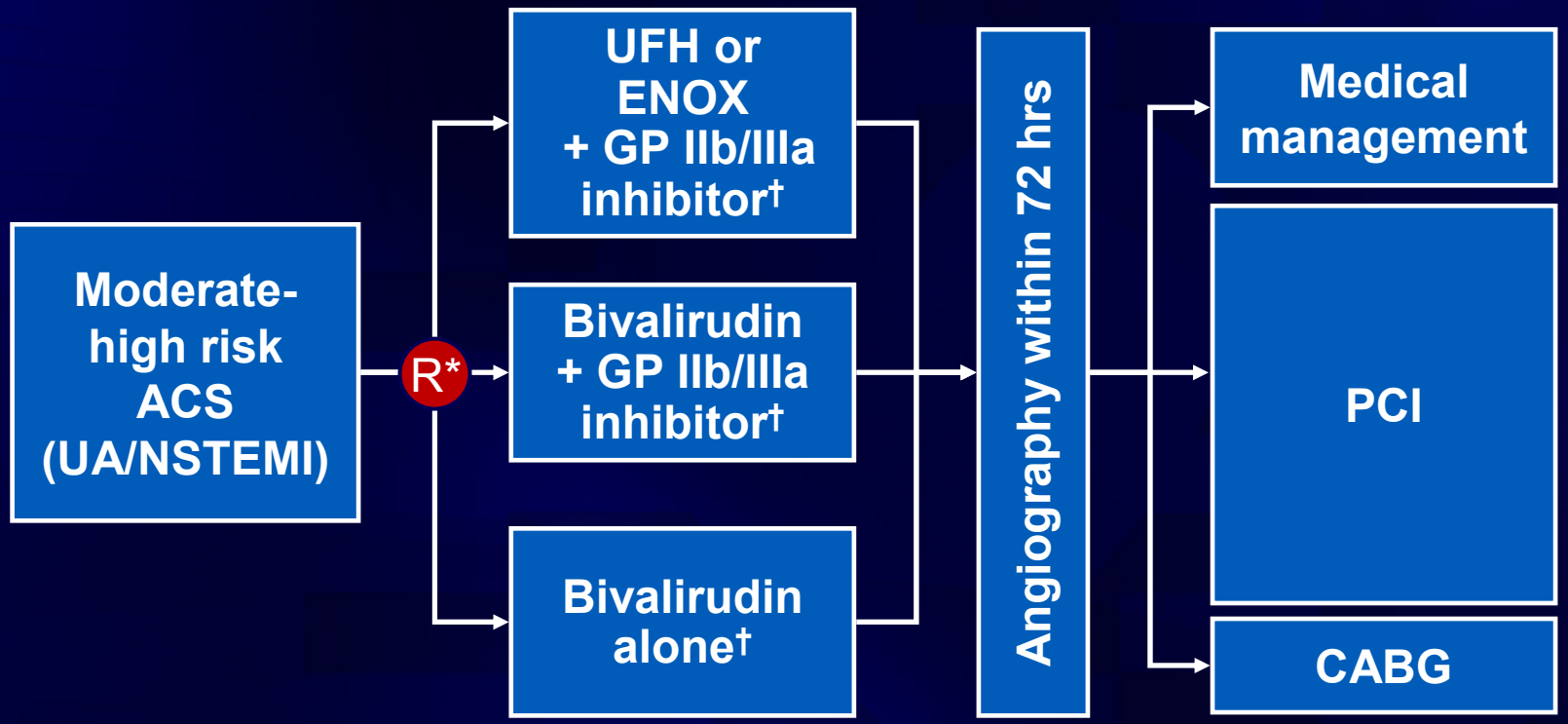
- TRITON-TIMI 38 demonstrated that higher and more consistent levels of platelet inhibition are associated with fewer ischemic events
- However, greater potency was associated with increased risk for bleeding in important, easily identifiable subgroups
  - Careful patient selection is critical to minimizing risk

Section overview

- Clinical trial update on thrombin receptor inhibitors
- Evolving role of direct thrombin inhibitors vs antithrombin plus GP IIb/IIIa inhibitors
- Guideline recommendations for antiplatelet therapy
  - UA/NSTEMI
  - STEMI
  - PCI

ACUITY: Study design—First randomization

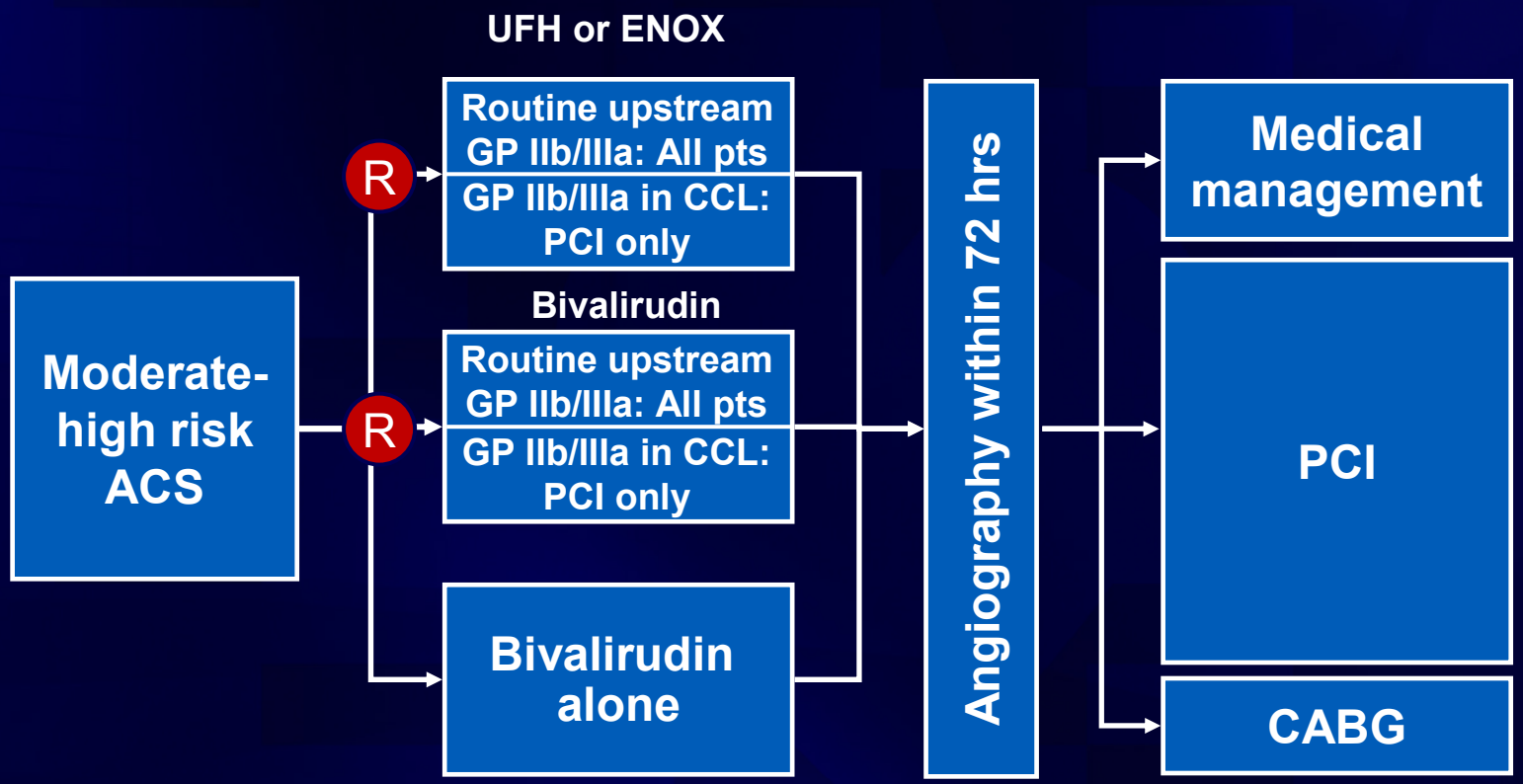
Acute Catheterization and Urgent Intervention Triage Strategy
N = 13,819 with ACS undergoing invasive strategy



*Stratified by pre-angiography use/intent to administer thienopyridine
†All patients receive ASA and clopidogrel; ENOX = enoxaparin, UFH = unfractionated heparin

Stone GW et al. *Am Heart J.* 2004;148:764-75.
Stone GW et al. *N Engl J Med*. 2006;355:2203-16.

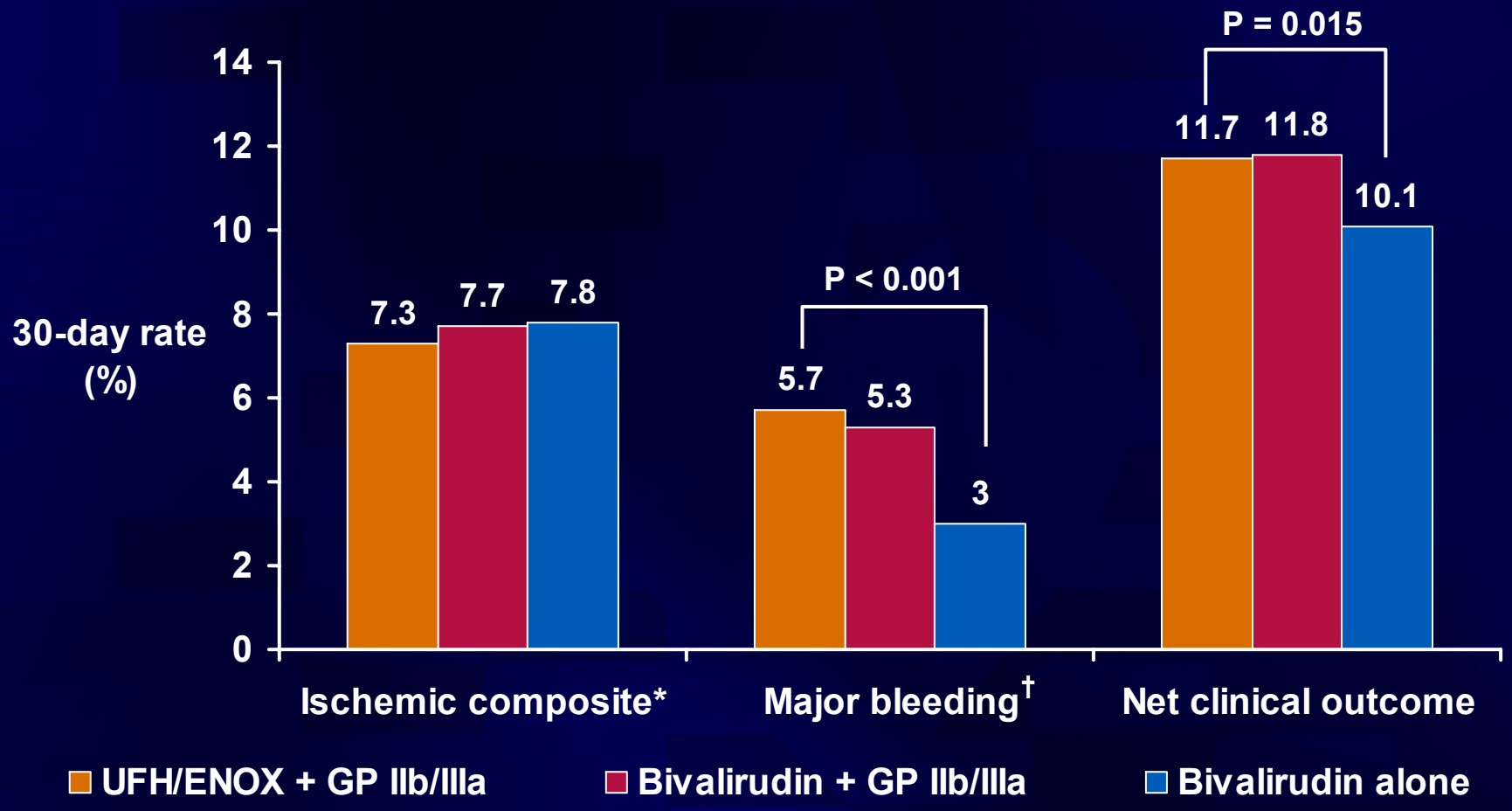
ACUITY: Study design—Second randomization



CCL = cardiac catheterization laboratory
GP IIb/IIIa = GP IIb/IIIa inhibitor, pts = patients

Stone GW et al. *Am Heart J.* 2004;148:764-75.
Stone GW et al. *N Engl J Med*. 2006;355:2203-16.

ACUITY: Treatment effects on primary outcomes—All patients

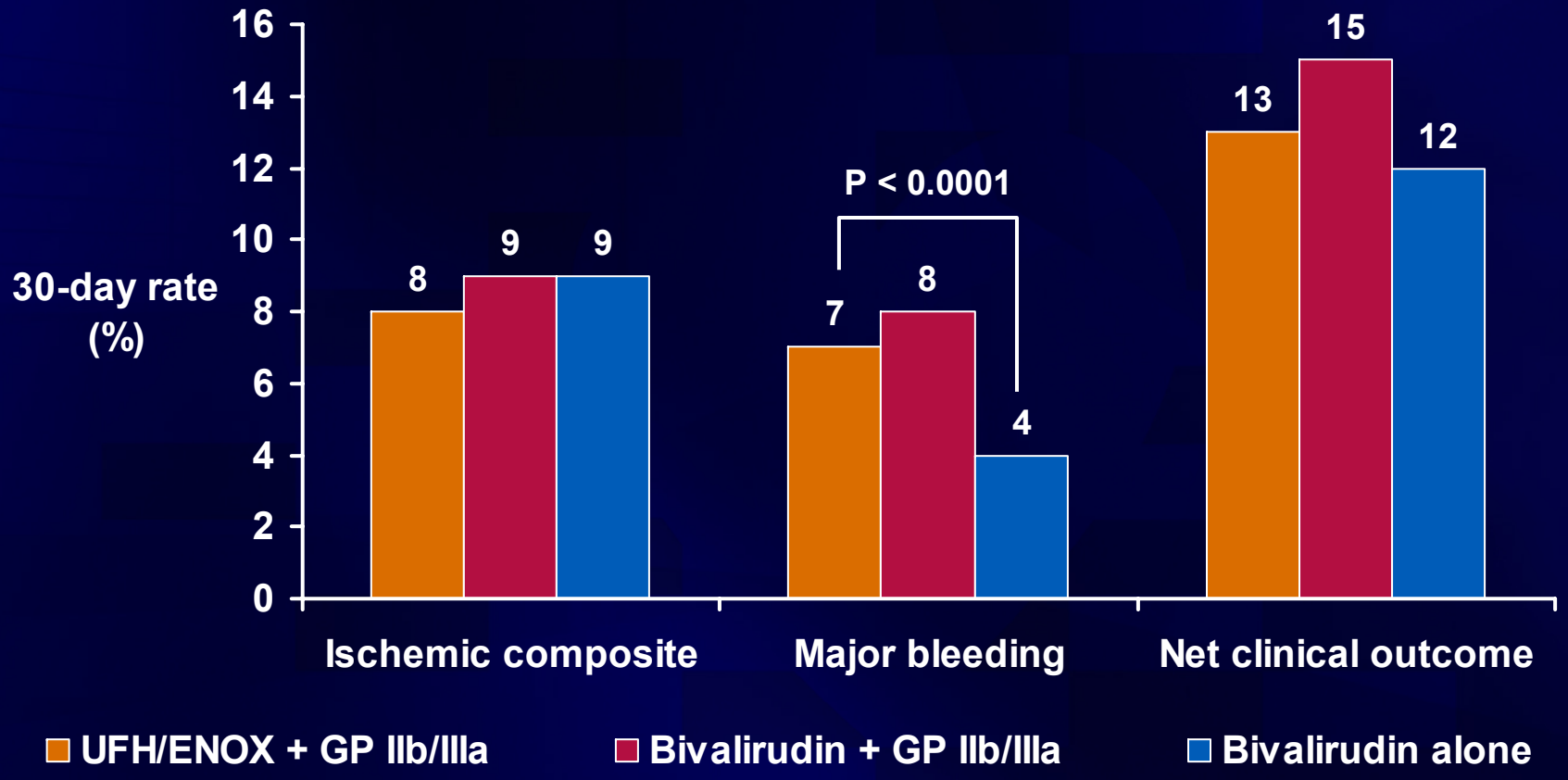


*Death, MI, unplanned revascularization for ischemia
†Non-CABG

Stone GW et al. *N Engl J Med.* 2006;355:2203-16.

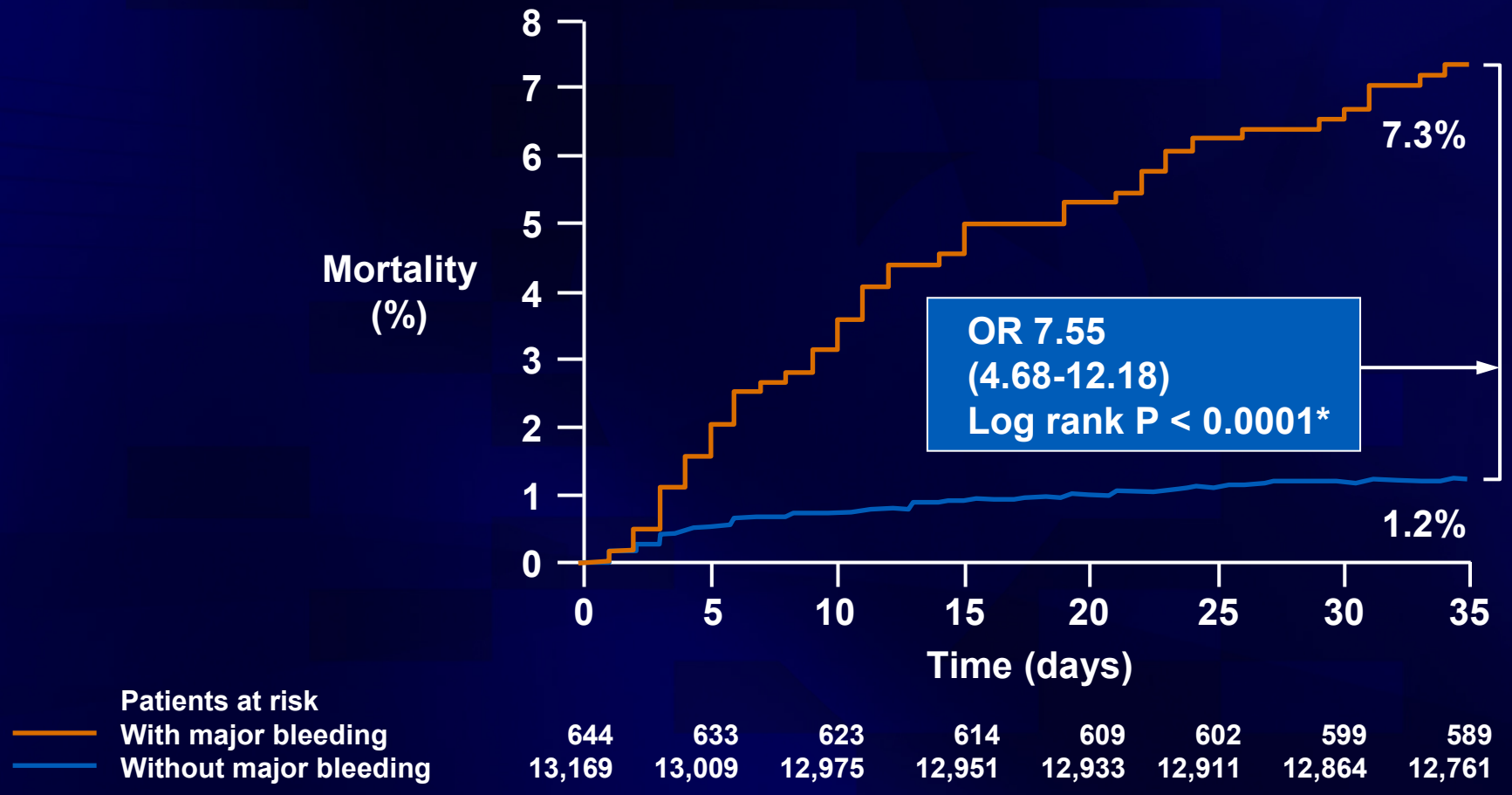
ACUITY: Treatment effects on primary outcomes—PCI subgroup

n = 7789 with ACS who underwent PCI



Stone GW et al. *Lancet.* 2007;369:907-19.

ACUITY: Major bleeding predicts mortality—All patients

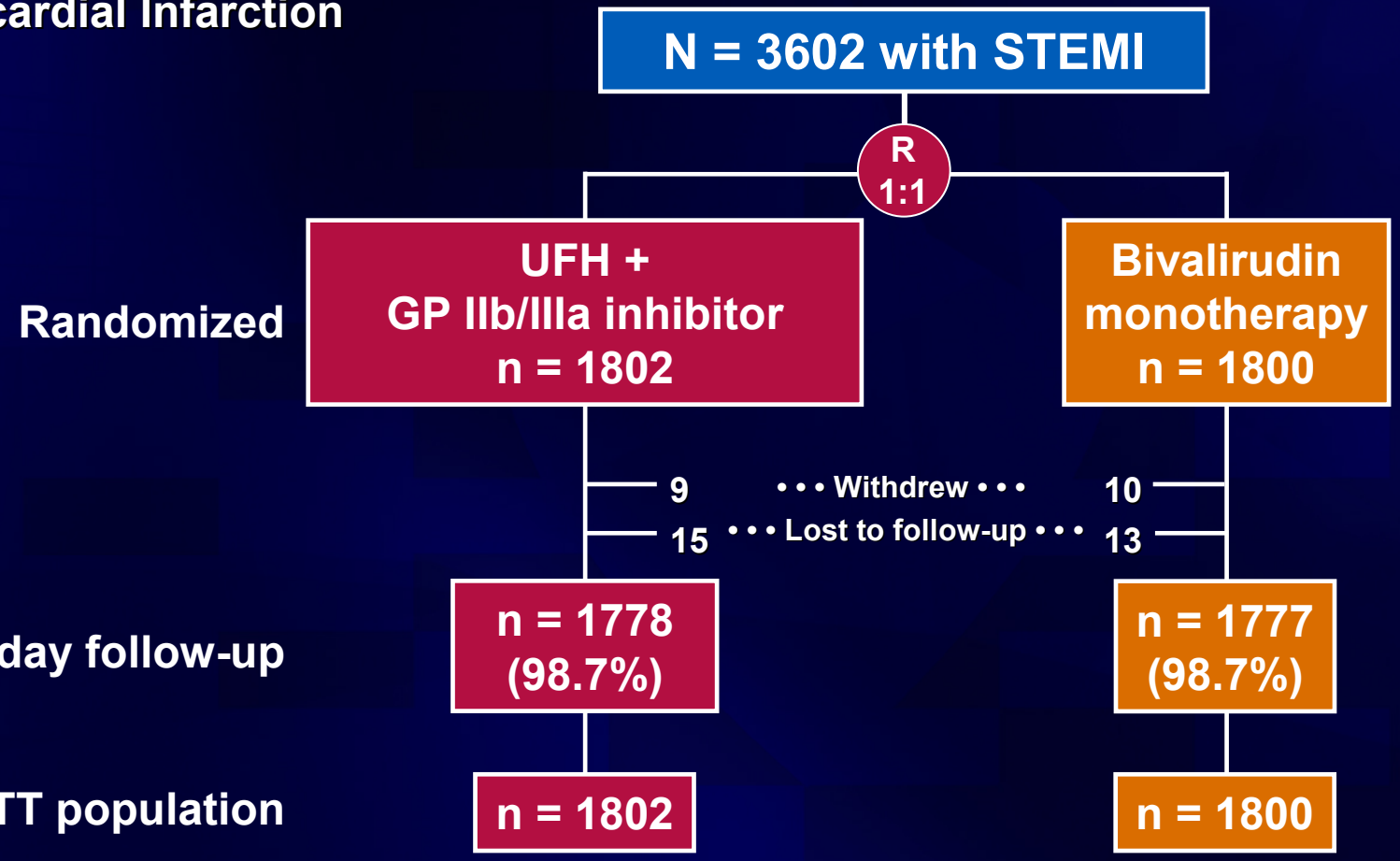


*Unadjusted

Manoukian SV et al. *J Am Coll Cardiol.* 2007;49:1362-8.

HORIZONS-AMI: Study design

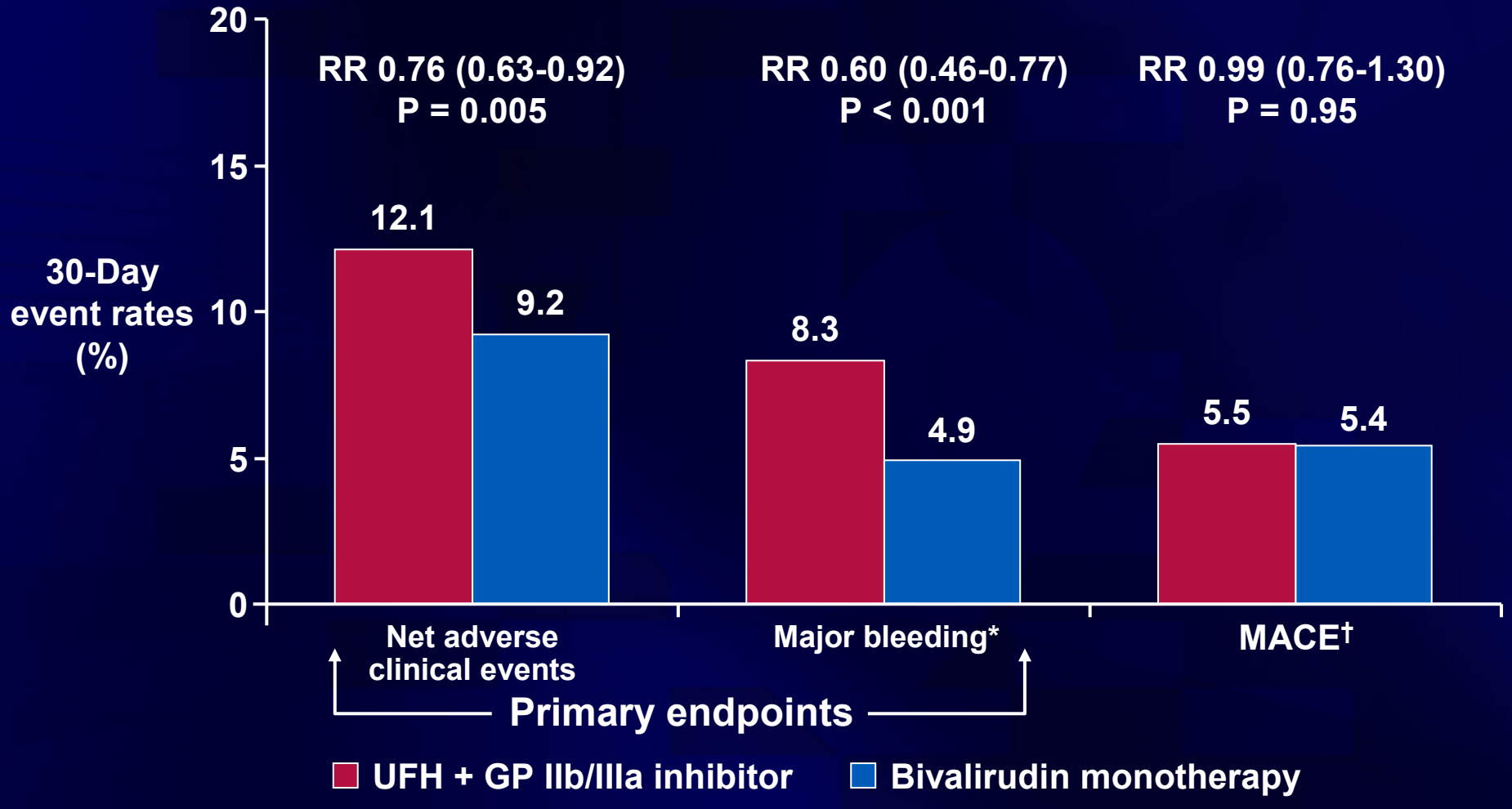
Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction



ITT = intention to treat

Courtesy of R Mehran, MD; Mehran R et al. *Am Heart J*. 2008;156:44-56.

HORIZONS-AMI: Treatment effects on primary outcome measures (ITT)



*Not related to CABG

†All cause death, reinfarction, ischemic TVR, or stroke

Stone GW et al. *N Engl J Med*. 2008;358:2218-30.

HORIZONSAMI

One Year Data and Outcomes from HORIZONS-AMI Trial

Presented by Roxana Mehran, MD at TCT 2008, October 15, 2008

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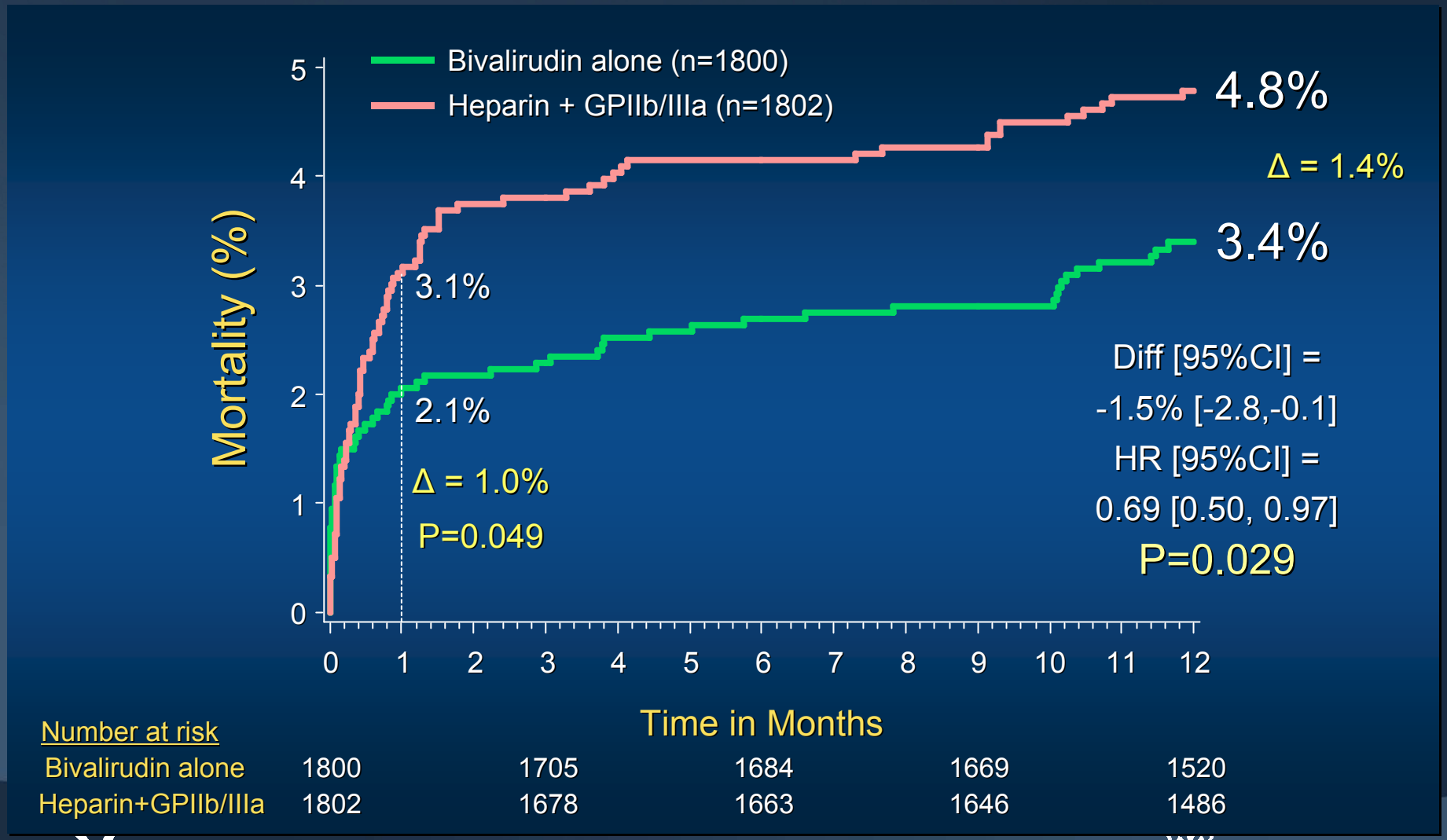
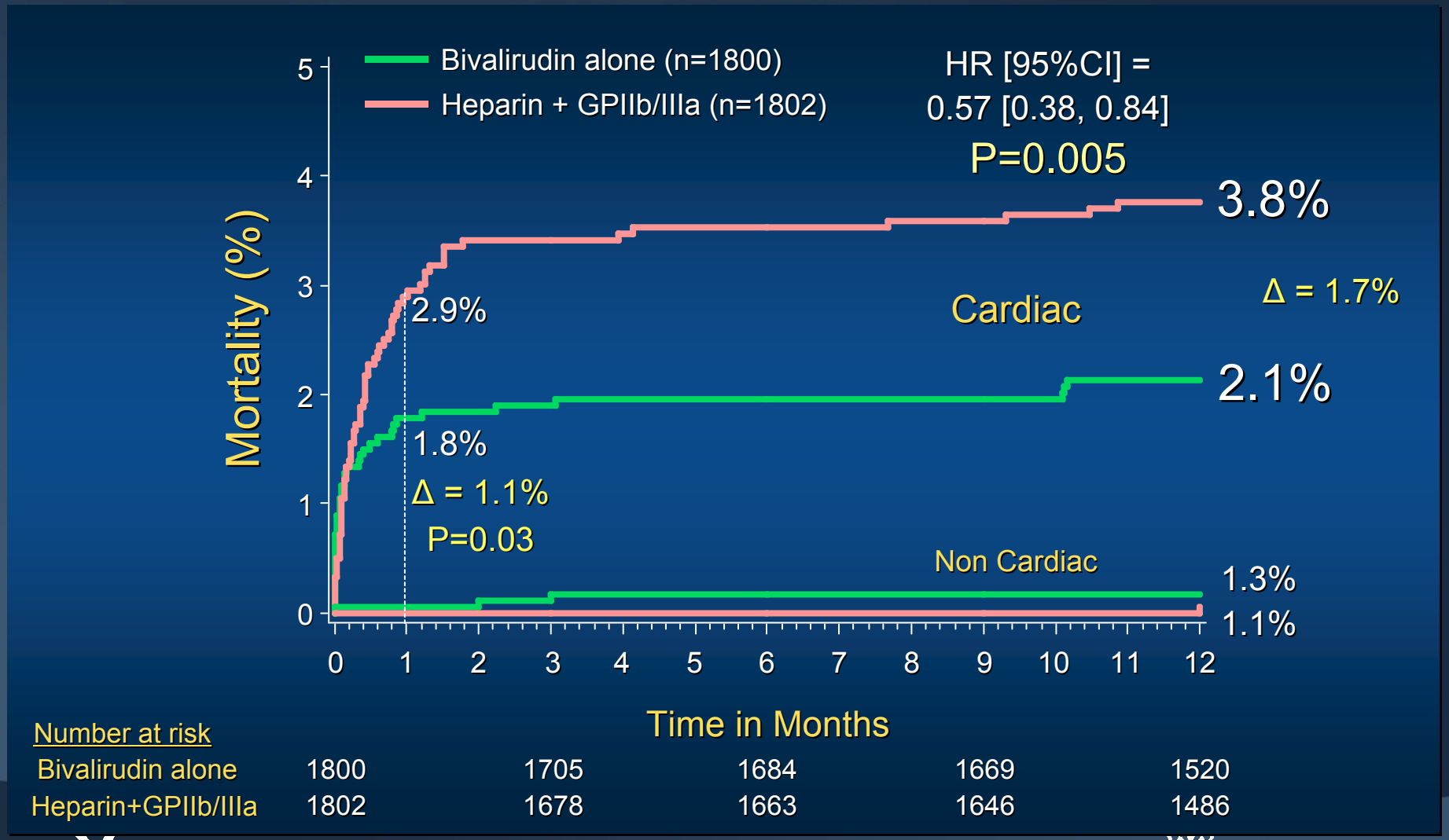
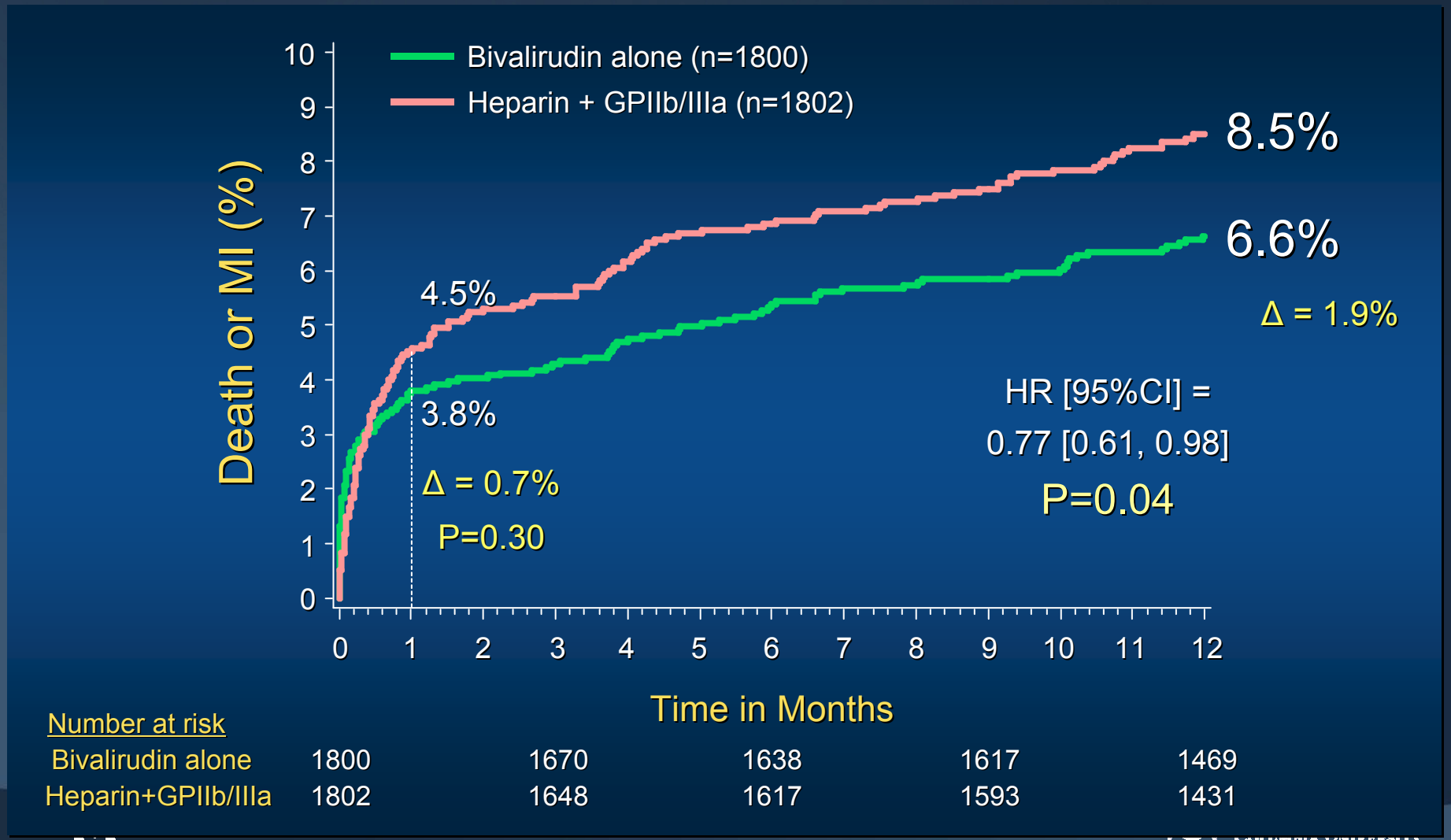
1-Year All-Cause Mortality



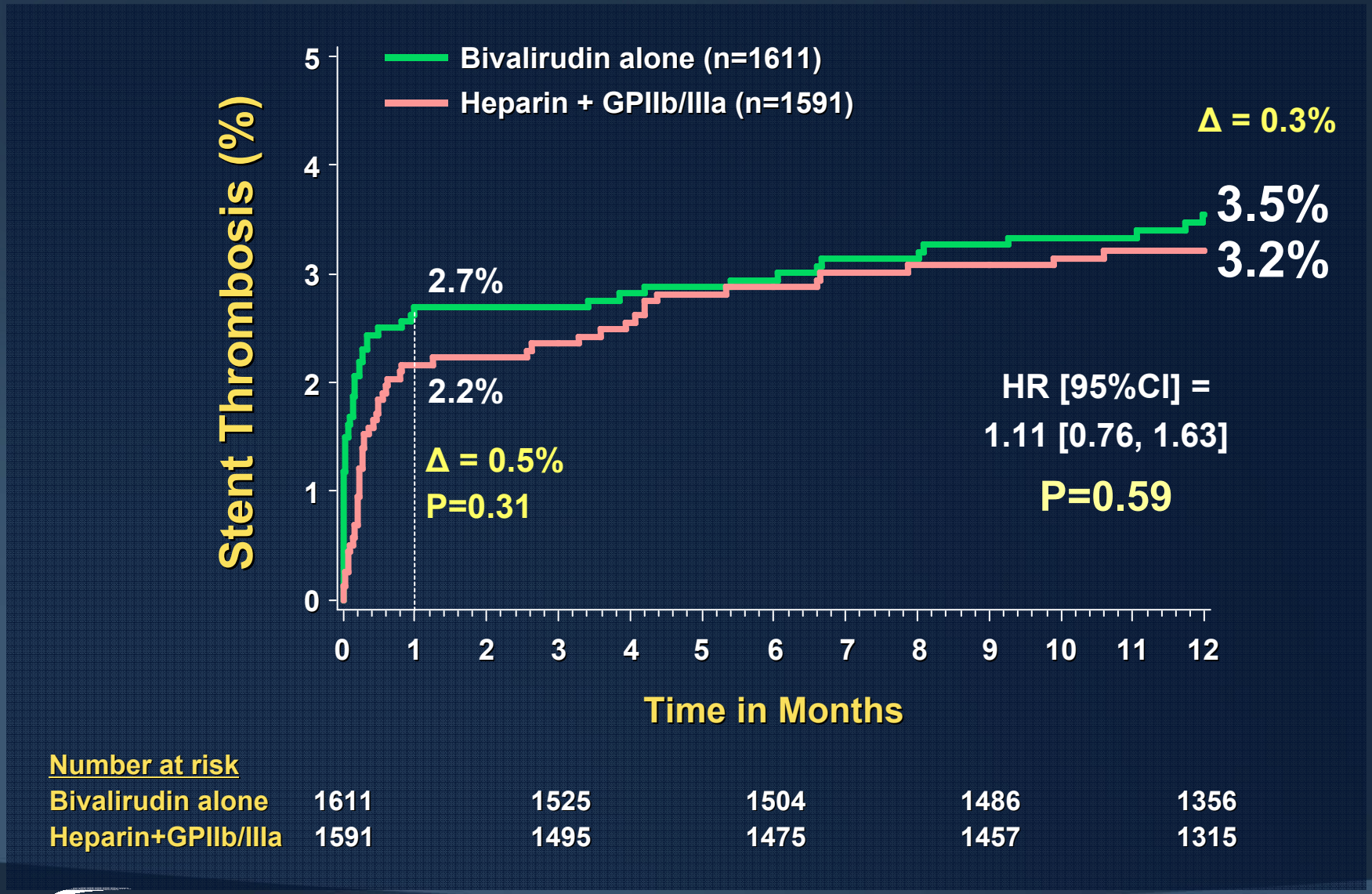
1-Year Mortality: Cardiac and Non Cardiac



1-Year Death or Reinfarction



1-Year Stent Thrombosis (ARC Definite/Probable)



Number at risk

Bivalirudin alone	1611	1525	1504	1486	1356
Heparin+GPIIb/IIIa	1591	1495	1475	1457	1315

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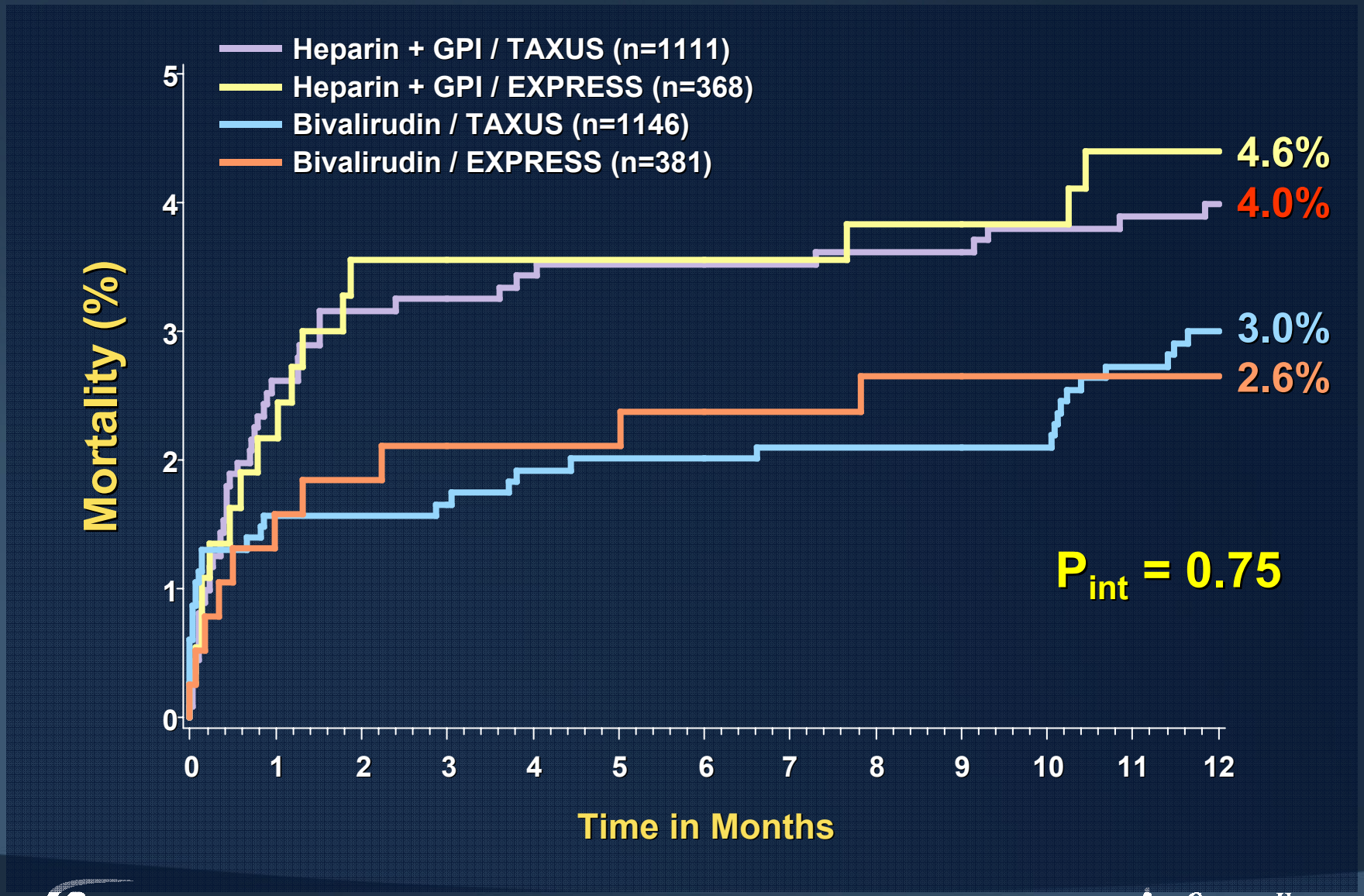
1-Year Mortality (All-Cause)



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Conclusions

HORIZONS-AMI

- In this large scale, prospective, randomized trial of patients with STEMI undergoing a primary PCI management strategy, bivalirudin monotherapy compared to UFH plus the routine use of GP IIb/IIIa inhibitors resulted in:
  - A significant 16% reduction in the 1-year rate of composite net adverse clinical events
  - A significant 39% reduction in the 1-year rate of major bleeding

Conclusions

- In this large scale, prospective, randomized trial of patients with STEMI undergoing a primary PCI management strategy, bivalirudin monotherapy compared to UFH plus the routine use of GP IIb/IIIa inhibitors resulted in:
  - Significant 31% and 43% reductions in the 1-year rates of all-cause and cardiac mortality (absolute 1.4% and 1.7% reductions), with non significantly different rates of reinfarction, stent thrombosis, stroke and TVR at 1-year

Clinical Implications

- HORIZONS has demonstrated that the prevention of hemorrhagic complications after primary PCI in STEMI results in improved early and late survival
  - Optimal drug selection and technique to minimize bleeding are essential to enhance outcomes for patients undergoing interventional therapies

Conclusions: ACS/STEMI

- Anti-platelet agents play and important role in ACS/AMI
- The newer, more potent agents such as Prasugrel have improved ischemic complications post ACS/STEMI
- However, bleeding complication is increased with these agents and has been identified in certain patient subgroups
- Judicious use of these agents is paramount to improving overall outcomes of patients with ACS/AMI