Cutting Edge Clinical Trials
TRITON- TIMI 38:
Future Role of Prasugrel and Other New Anti-Platelet Agents in PCI

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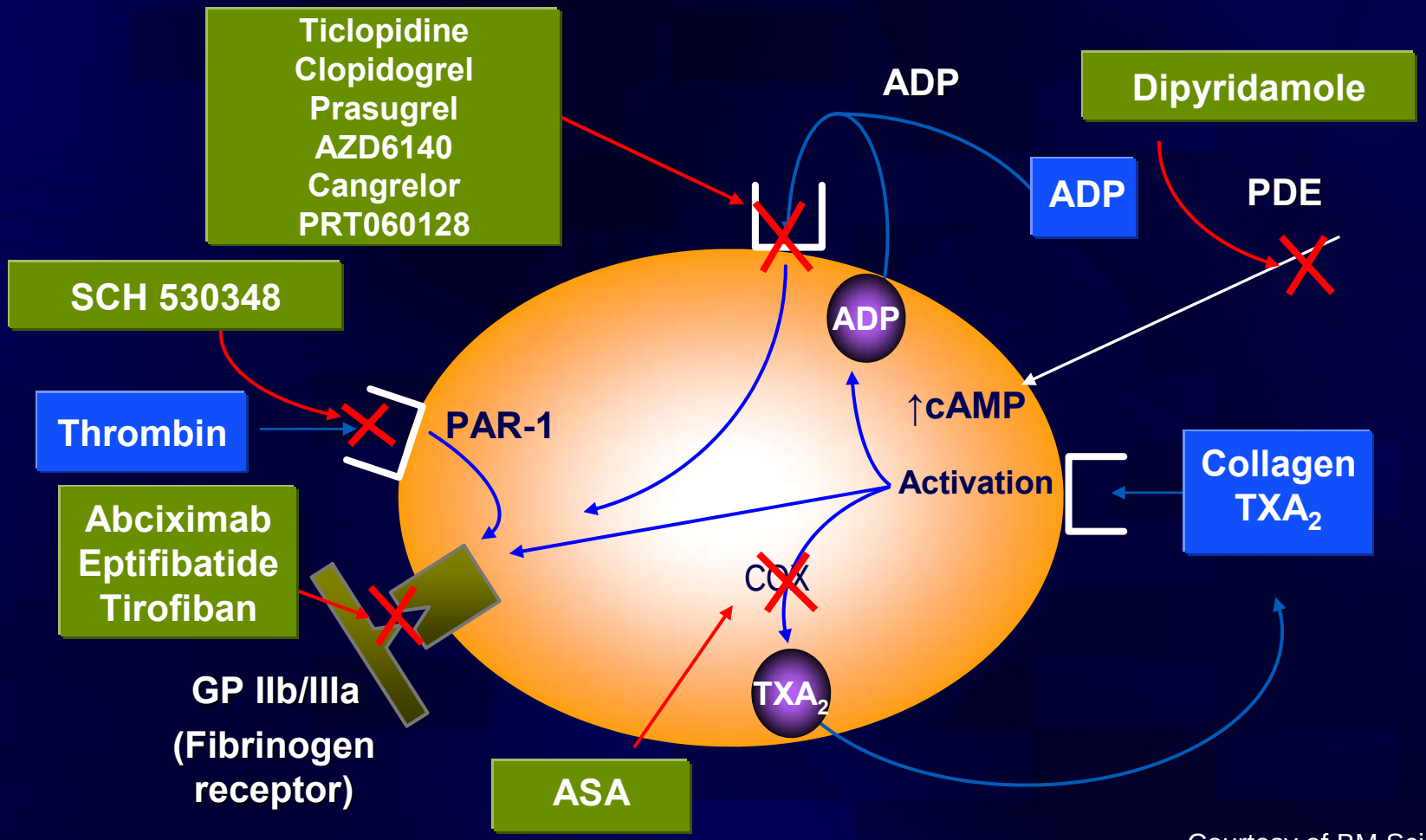
Targets for antiplatelet therapies

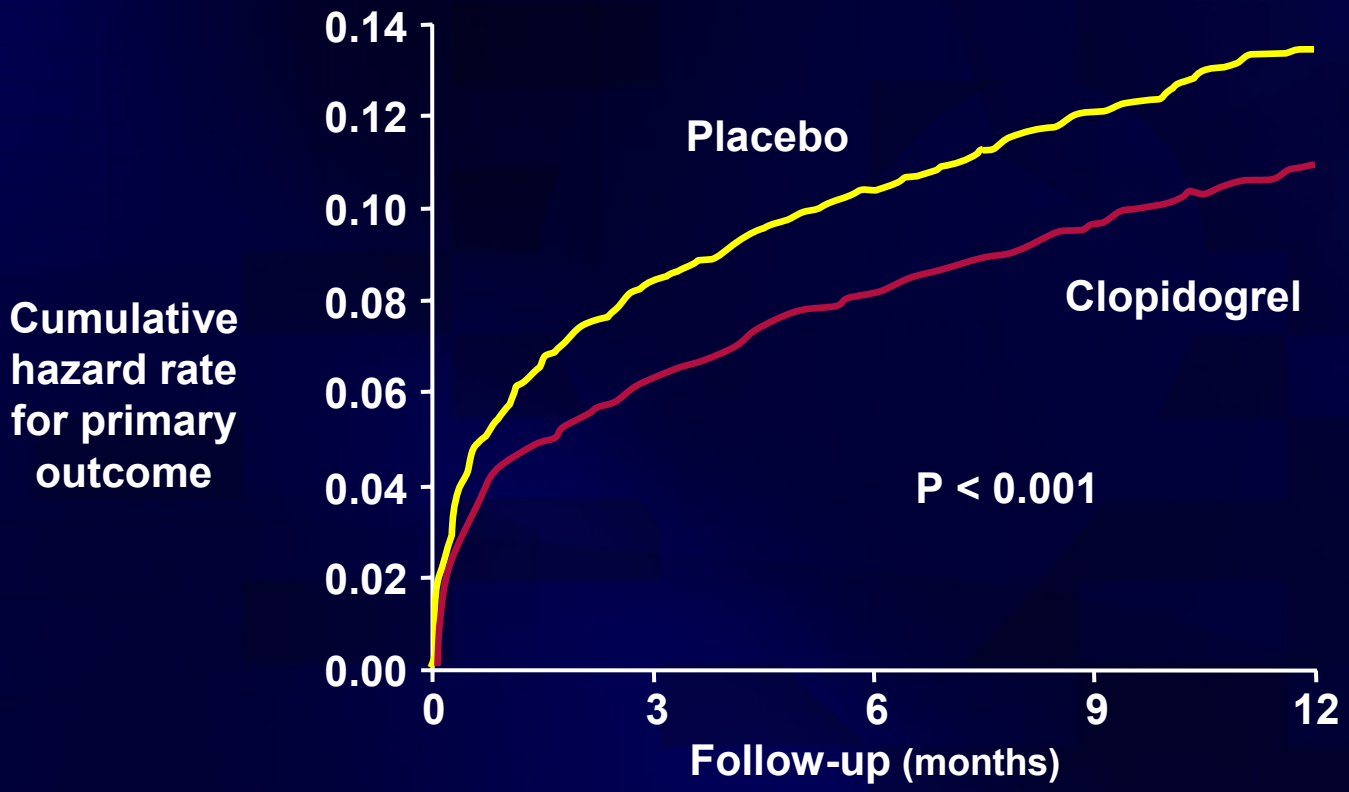


cAMP = cyclic adenosine monophosphate, COX = cyclooxygenase, PAR = protease-activated receptor, PDE = phosphodiesterase

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.

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.

Antiplatelet therapy: The changing landscape

- Wide variability in platelet response to clopidogrel
- New P2Y12 inhibitors: Potency vs bleeding risk
- New approaches to platelet inhibition beyond P2Y12 inhibition
- Implications of upstream direct thrombin inhibition
- Future role of GP IIb/IIIa inhibitors, given more potent oral agents and antithrombins

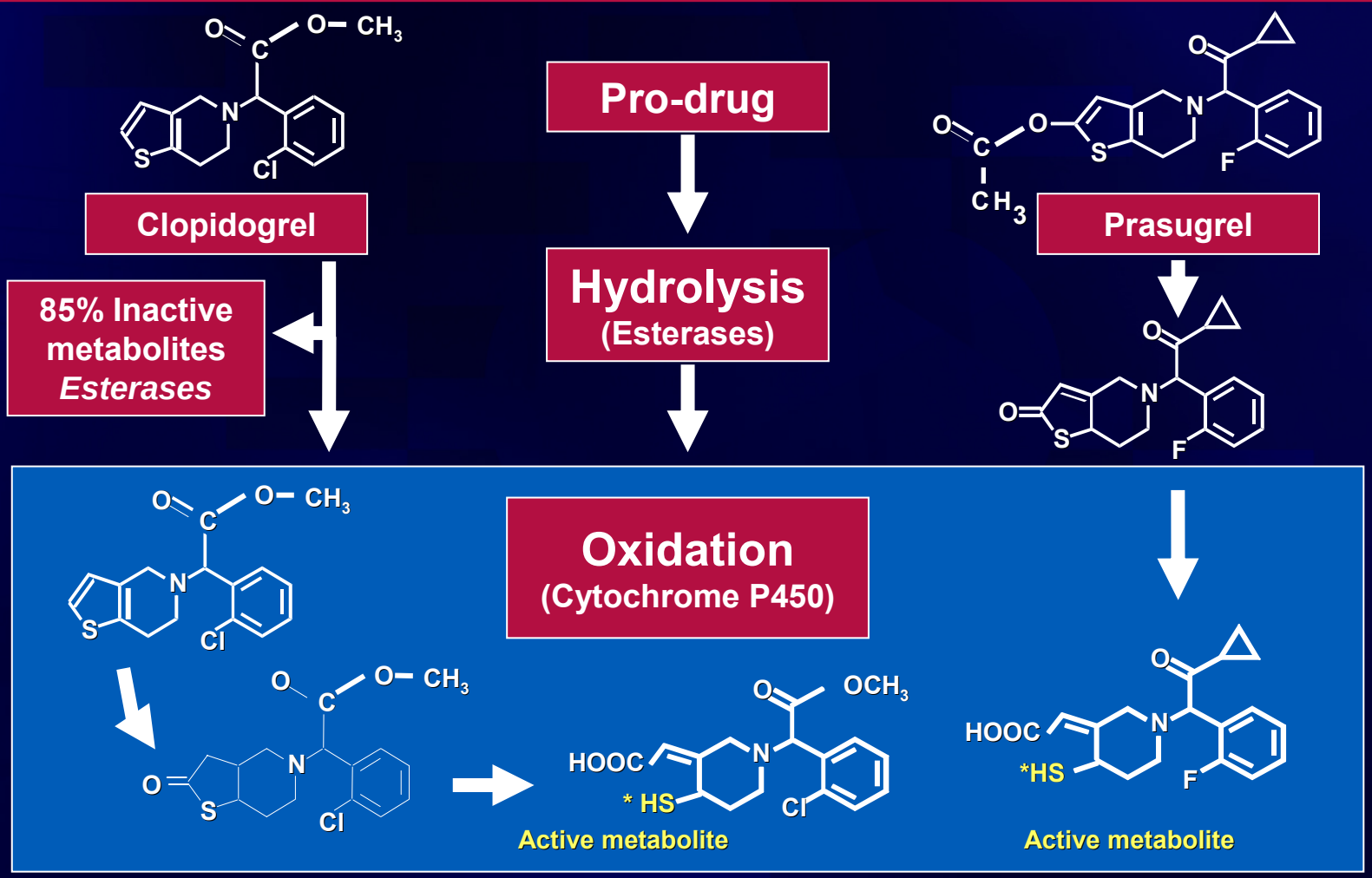
Prasugrel: Overview

- 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.

TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel

TRITON-TIMI 38

***Disclosure Statement*:**

The TRITON-TIMI 38 trial was supported by a research grant to the Brigham and Women's Hospital from Daiichi Sankyo Co. Ltd and Eli Lilly & Co.

TRITON TIMI-38

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

TRITON TIMI-38

Enrollment Criteria

- **Inclusion Criteria**

  Planned PCI for :

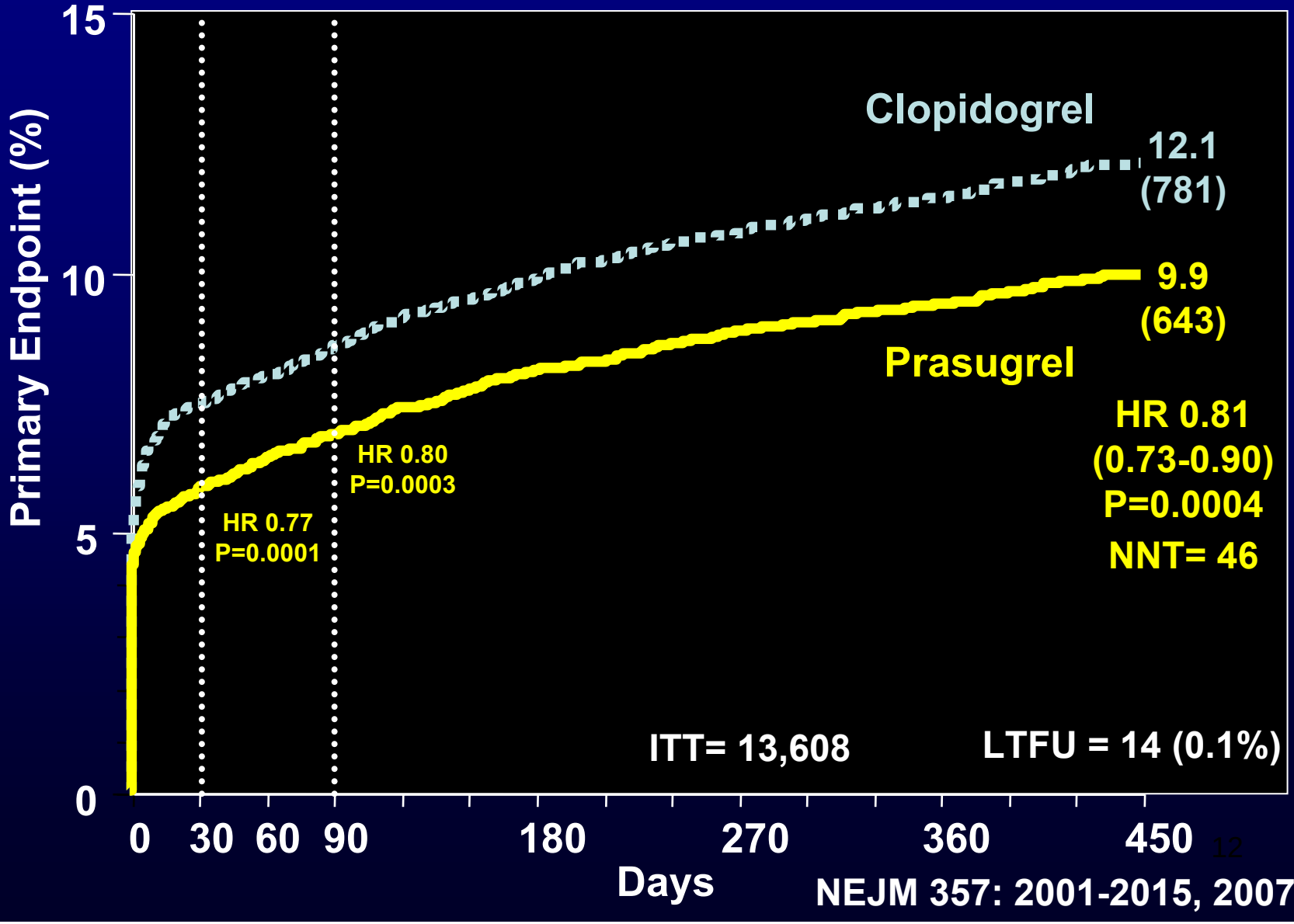
  Known Anatomy
  - **Mod-High Risk UA/NSTEMI (TRS ≥ 3)**
  - **STEMI: ≤ 14 days (ischemia or Rx strategy)**
  - **STEMI: Primary PCI**

- **Major Exclusion Criteria:**
  - **Severe comorbidity**
  - **Increased bleeding risk**
  - **Prior hemorrhagic stroke or any stroke ≤ 3 mos**
  - **Any thienopyridine within 5 days**
  - **No exclusion for advanced age or renal function**

NEJM 357: 2001-2015, 2007

TRITON TIMI-38

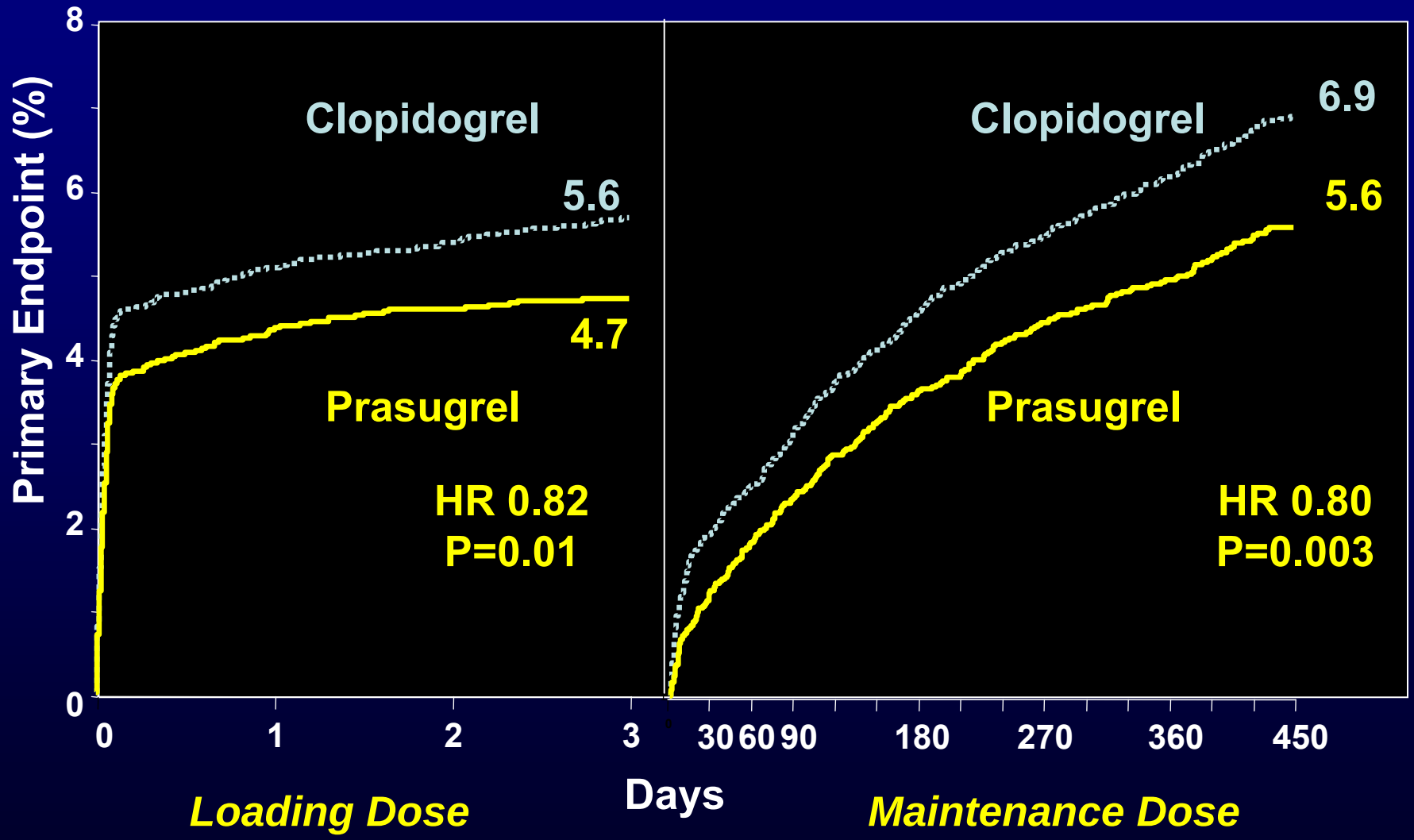
Primary Endpoint
CV Death,MI,Stroke



NEJM 357: 2001-2015, 2007

TRITON TIMI-38

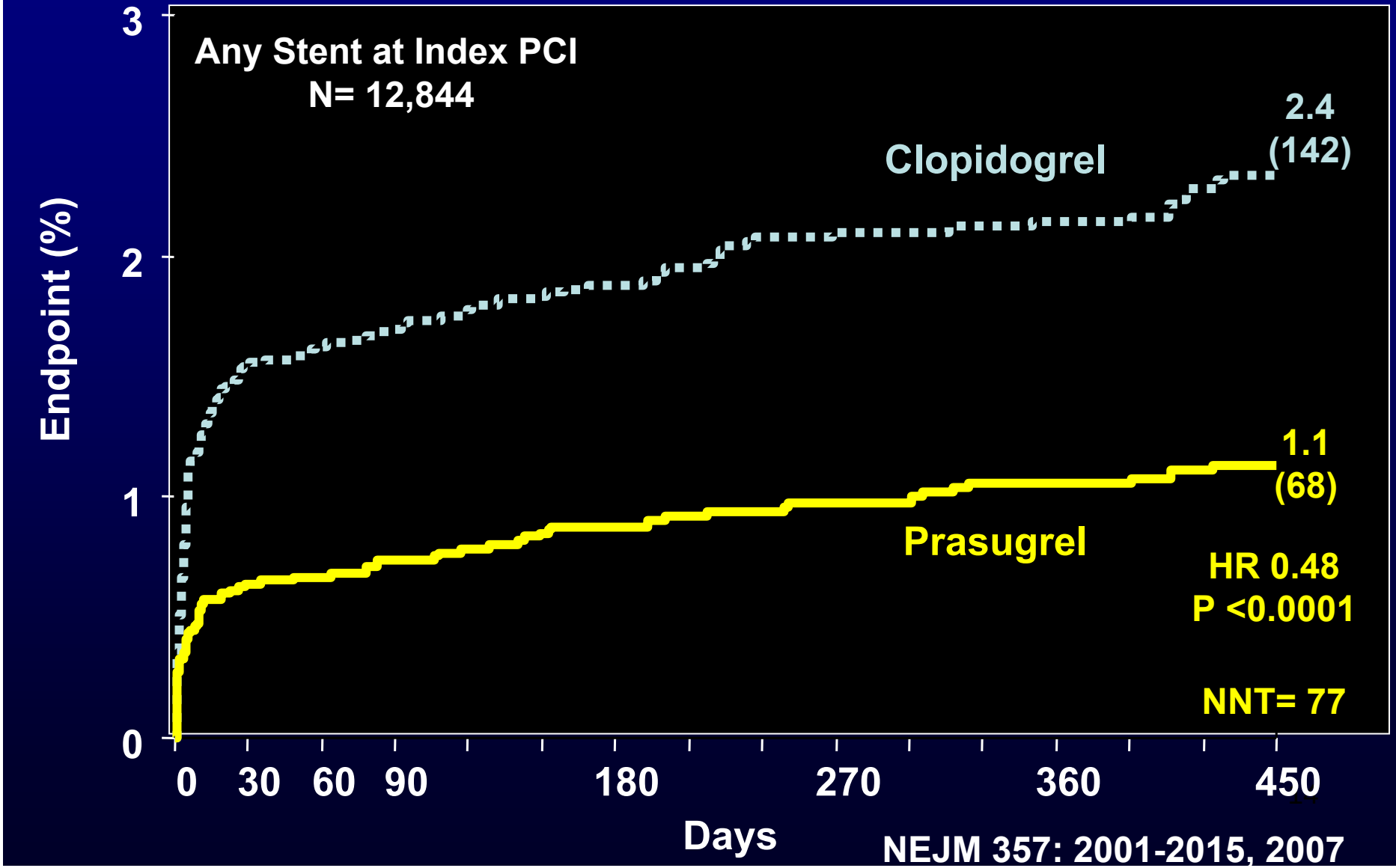
Timing of Benefit (Landmark Analysis)



NEJM 357: 2001-2015, 2007

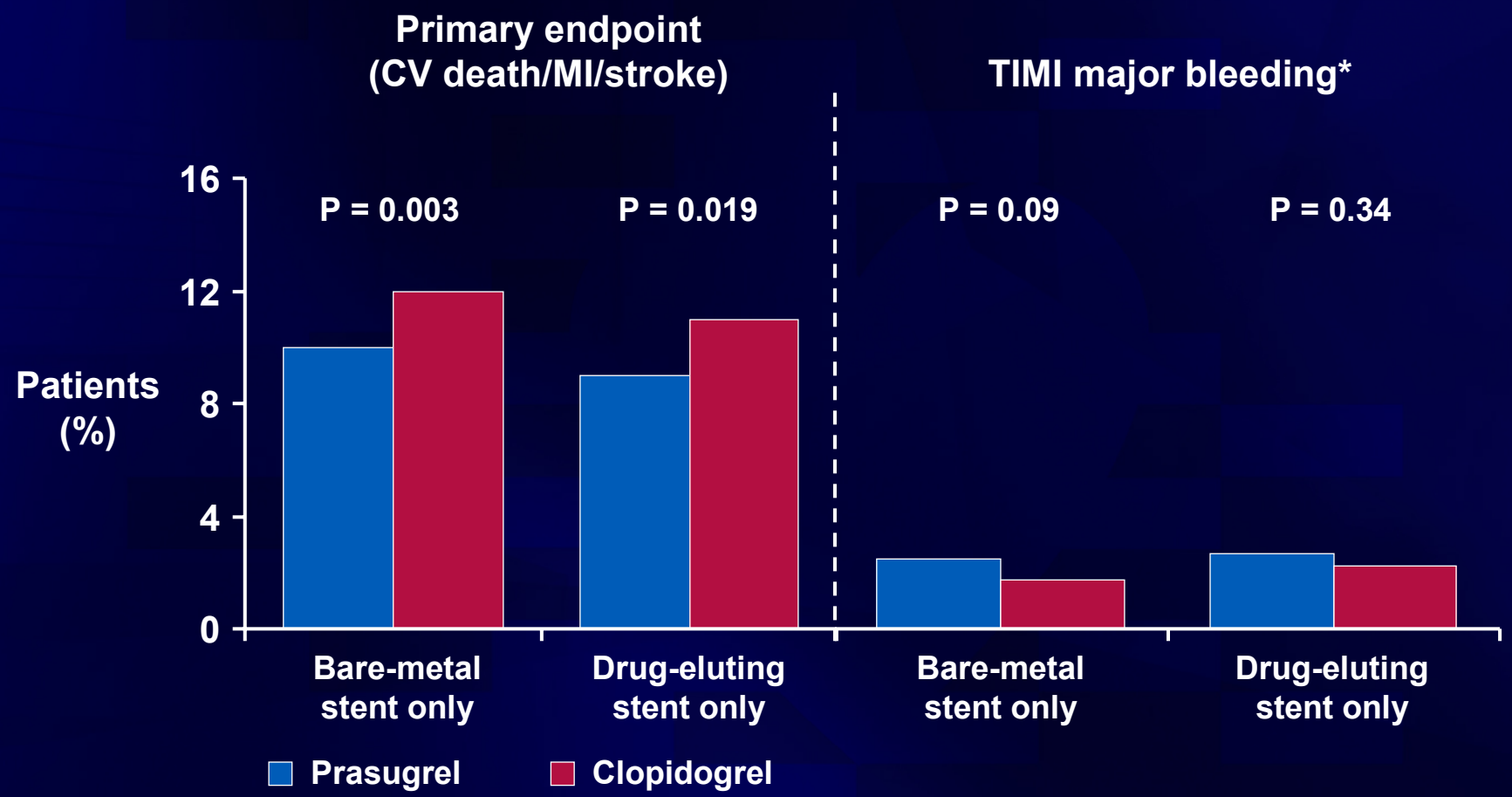
TRÎTON TIMI-38

Stent Thrombosis (ARC Definite + Probable)



NEJM 357: 2001-2015, 2007

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

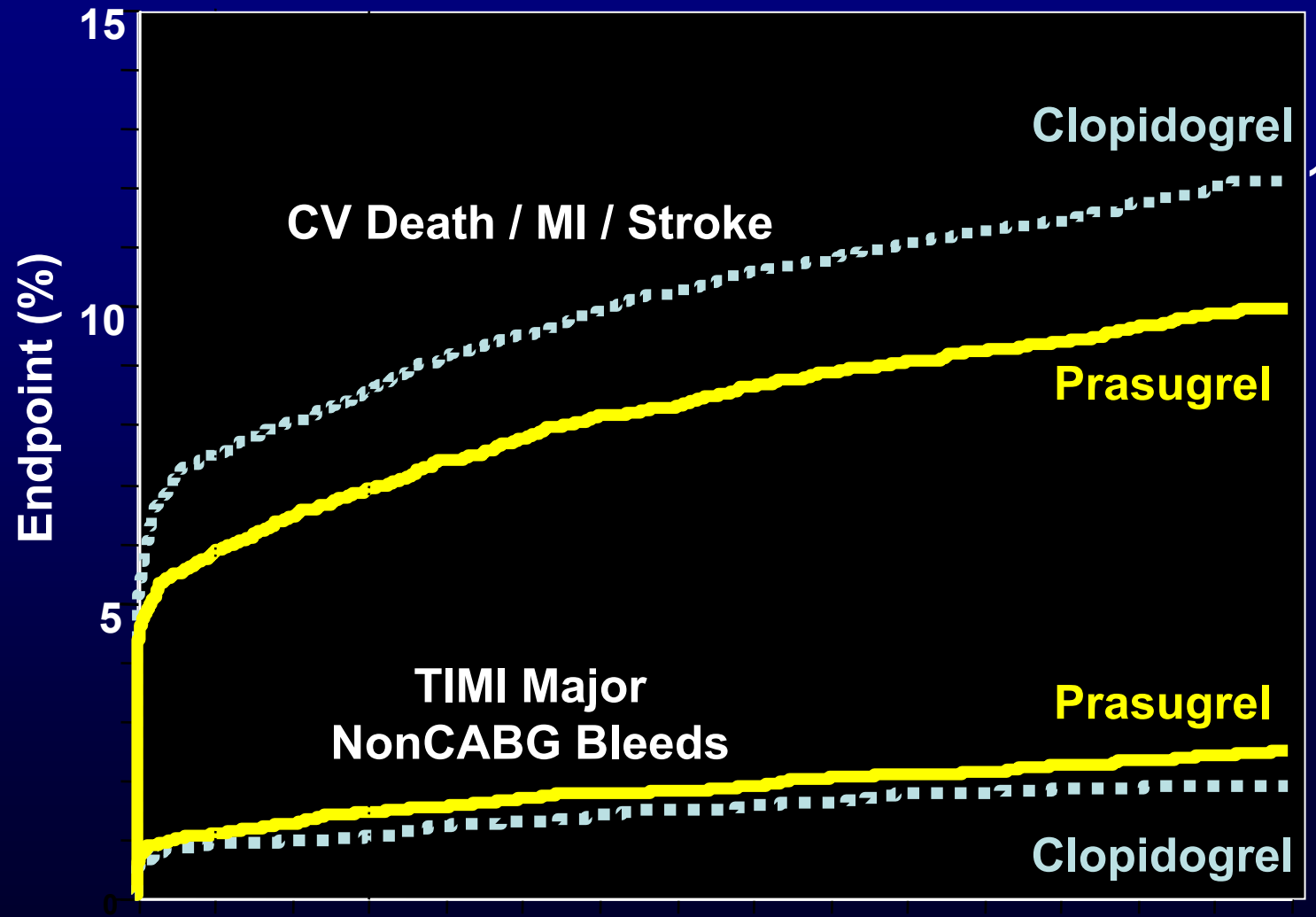


*Not related to coronary bypass surgery

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

TRITON TIMI-38

Balance of Efficacy and Safety



↓ 138 events

HR 0.81 (0.73-0.90) P=0.0004

NNT = 46

↑ 35 events

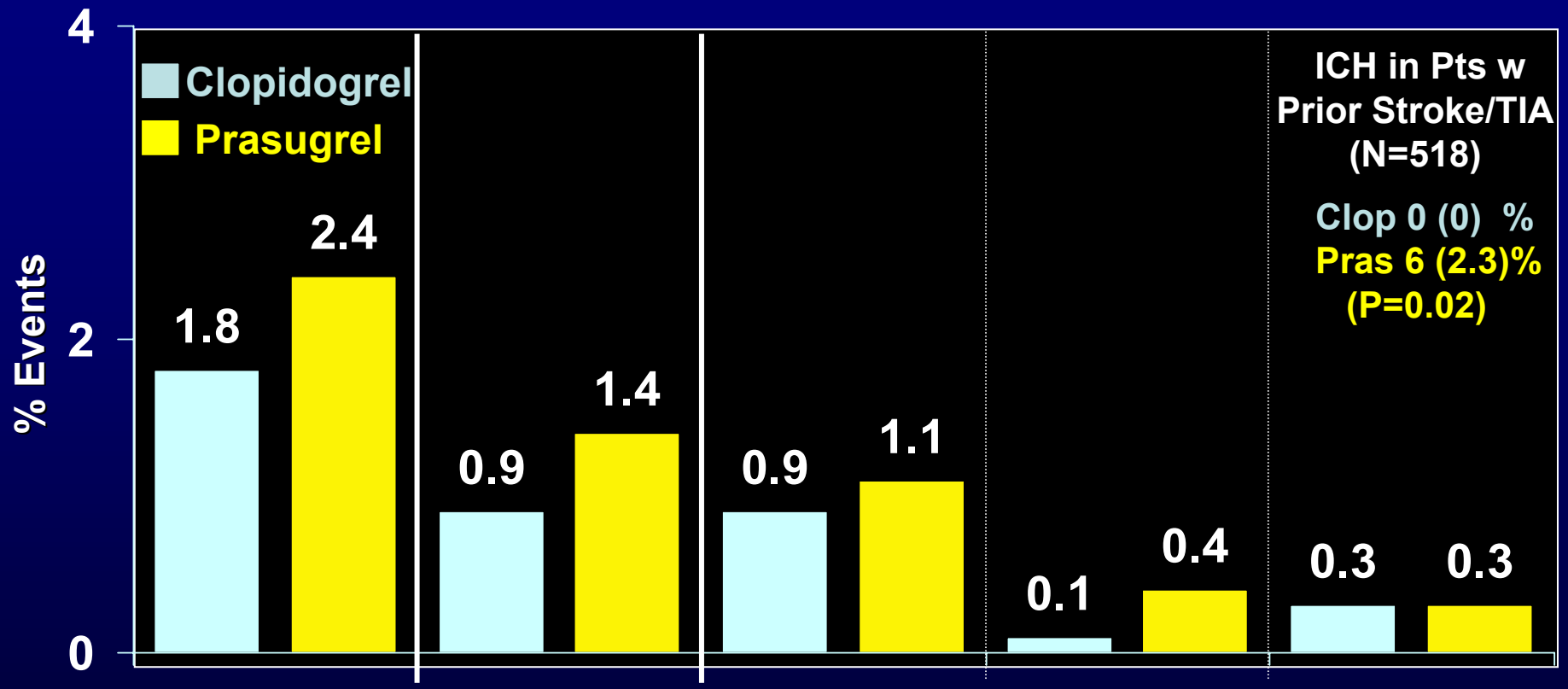
HR 1.32 (1.03-1.68) P=0.03

NNH = 167

NEJM 357: 2001-2015, 2007

TRITON TIMI-38

Bleeding Events
Safety Cohort
(N=13,457)



ARD 0.6%
HR 1.32
P=0.03
NNH=167

ARD 0.5%
HR 1.52
P=0.01

ARD 0.2%
P=0.23

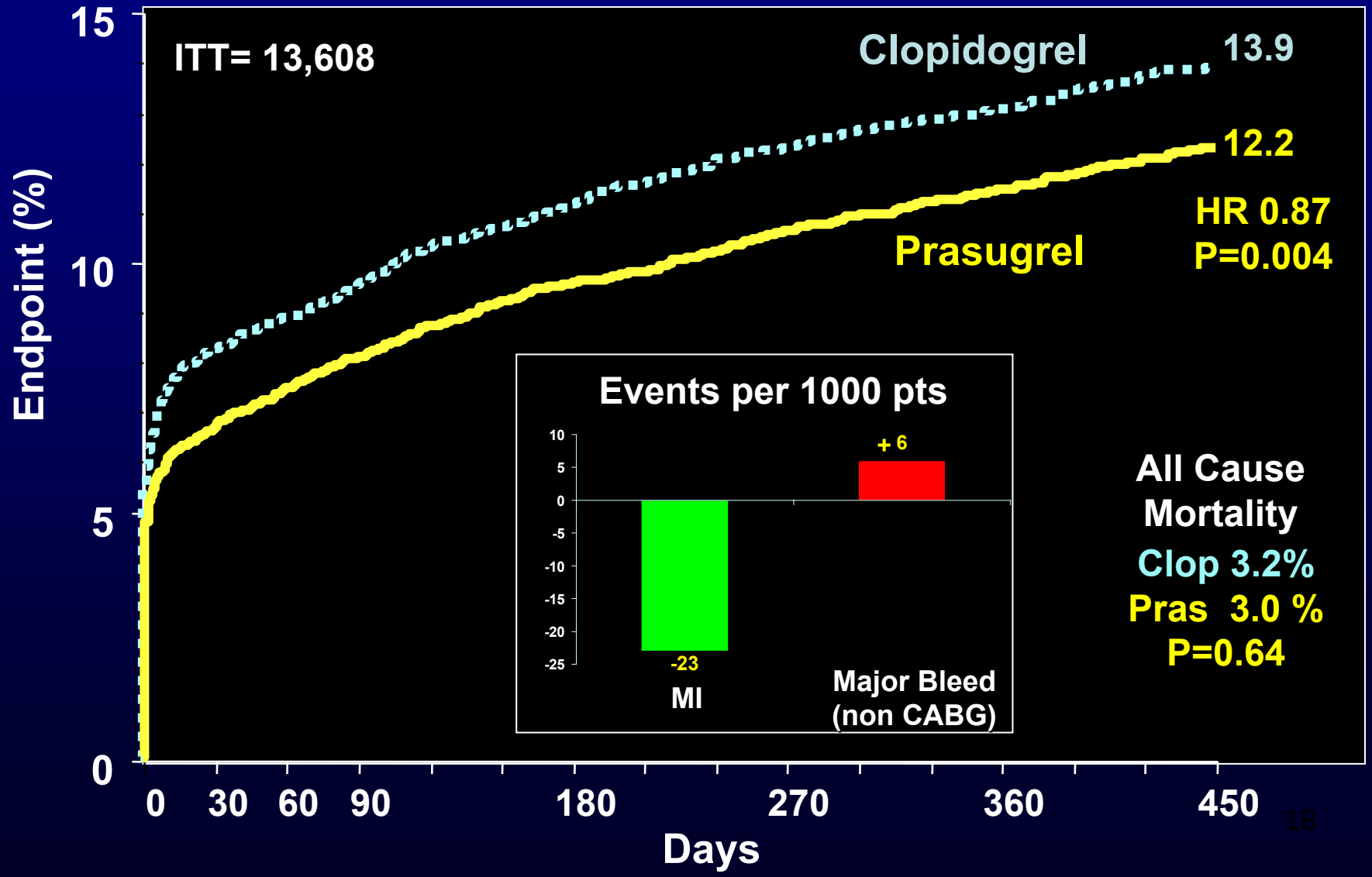
ARD 0.3%
P=0.002

ARD 0%
P=0.74

TRITON TIMI-38

Net Clinical Benefit

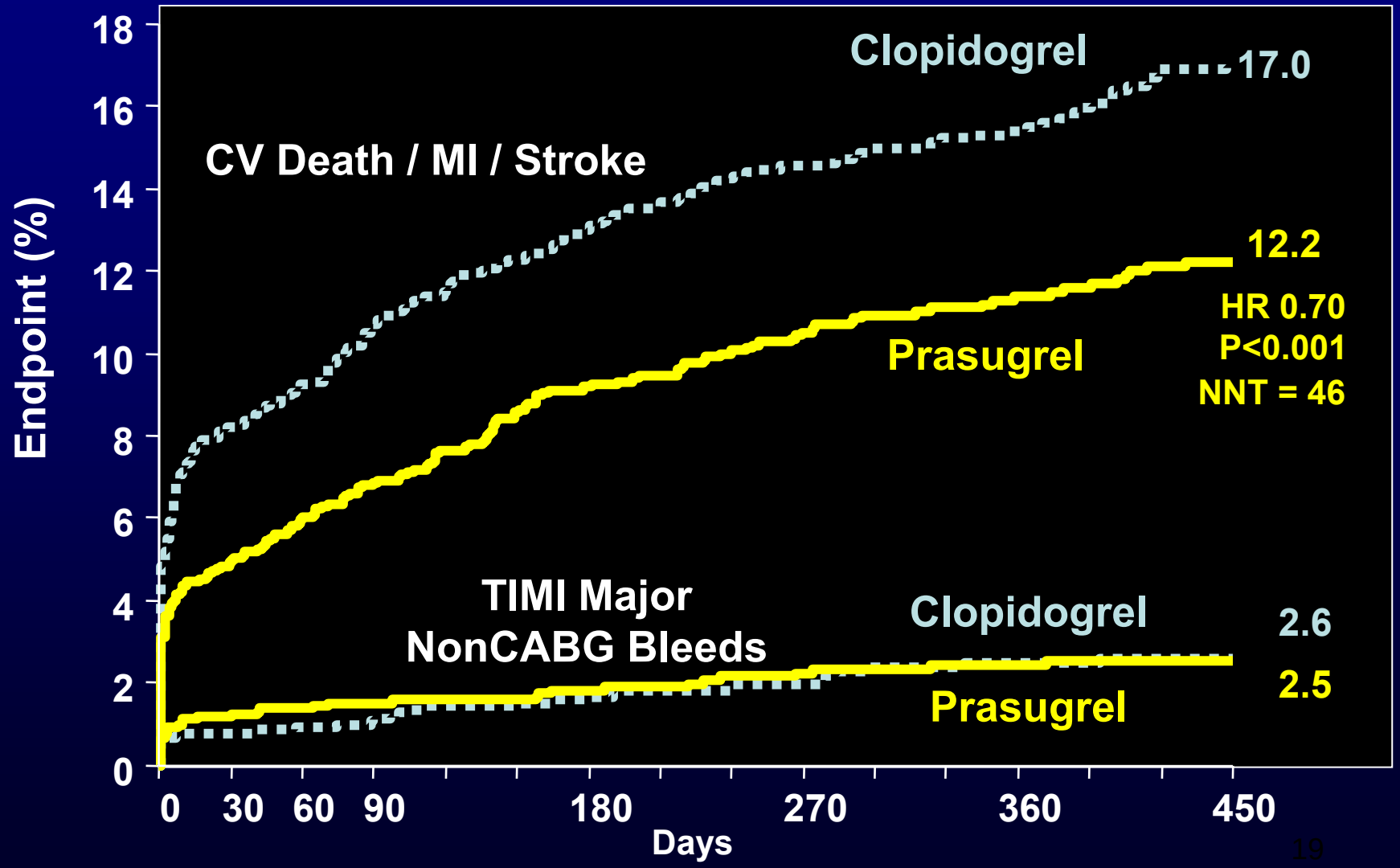
Death, MI, Stroke, Major Bleed (non CABG)



TRITON TIMI-38

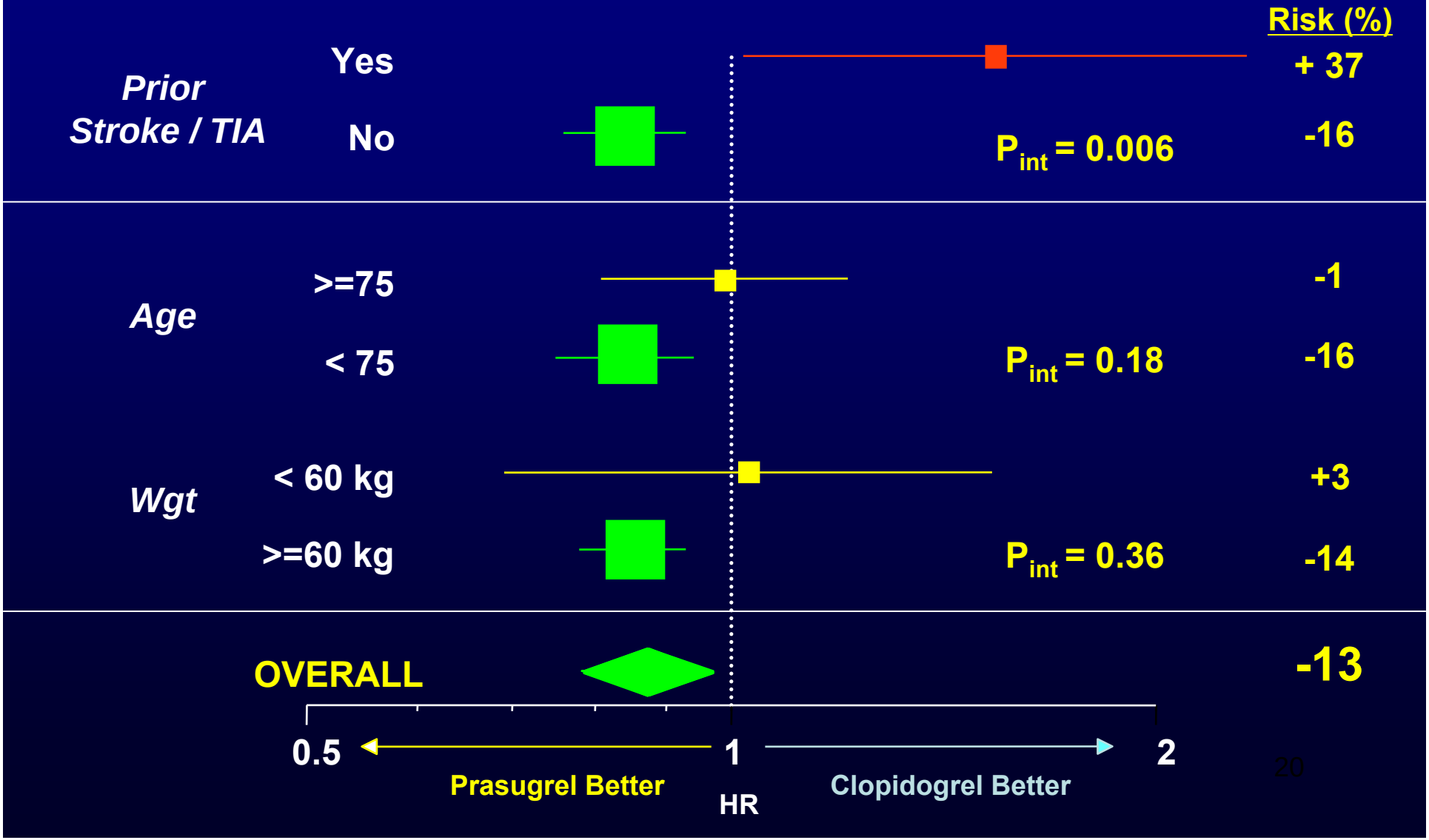
Diabetic Subgroup

N=3146



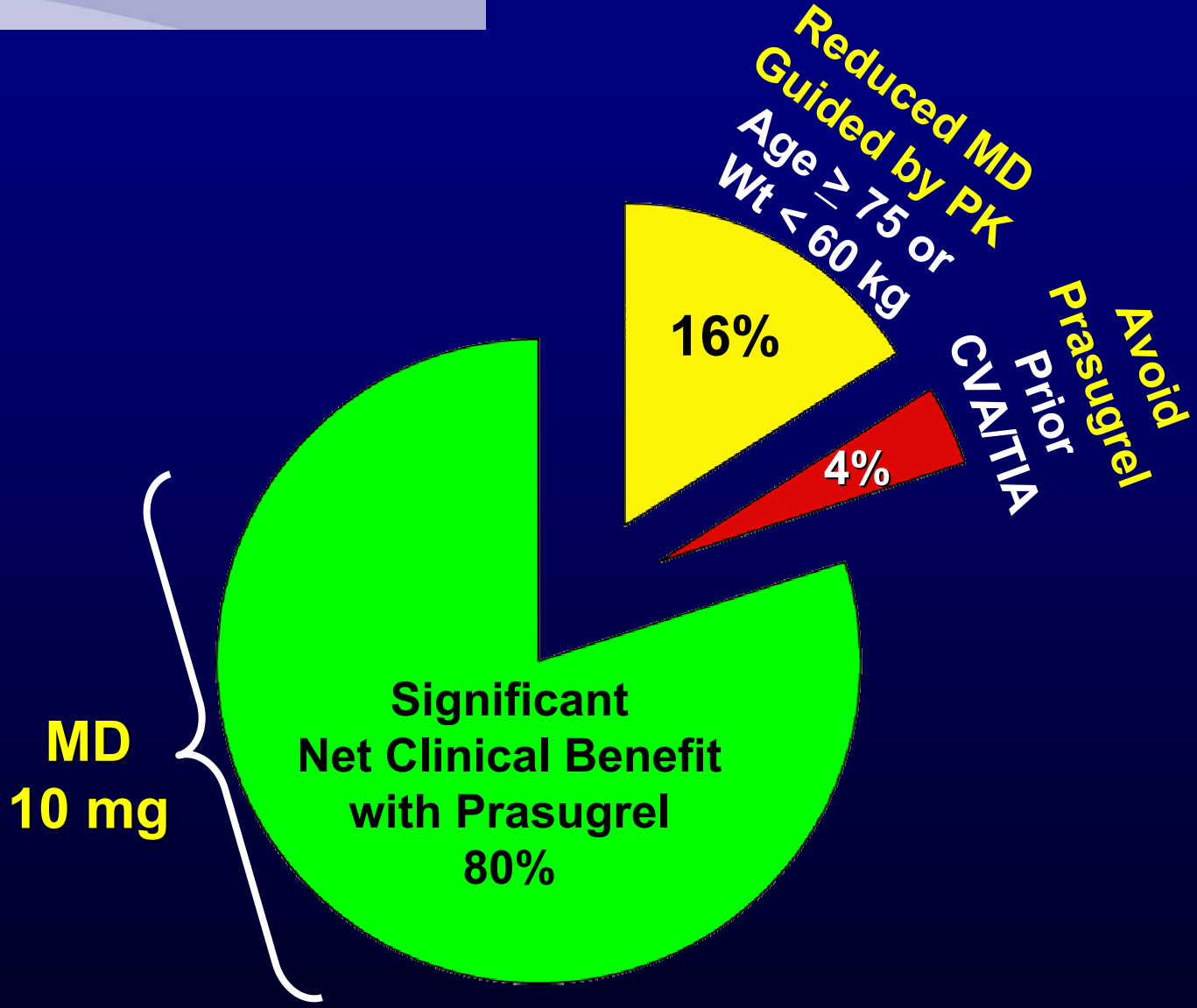
TRITON TIMI-38

Net Clinical Benefit
Bleeding Risk Subgroups
Post-hoc analysis



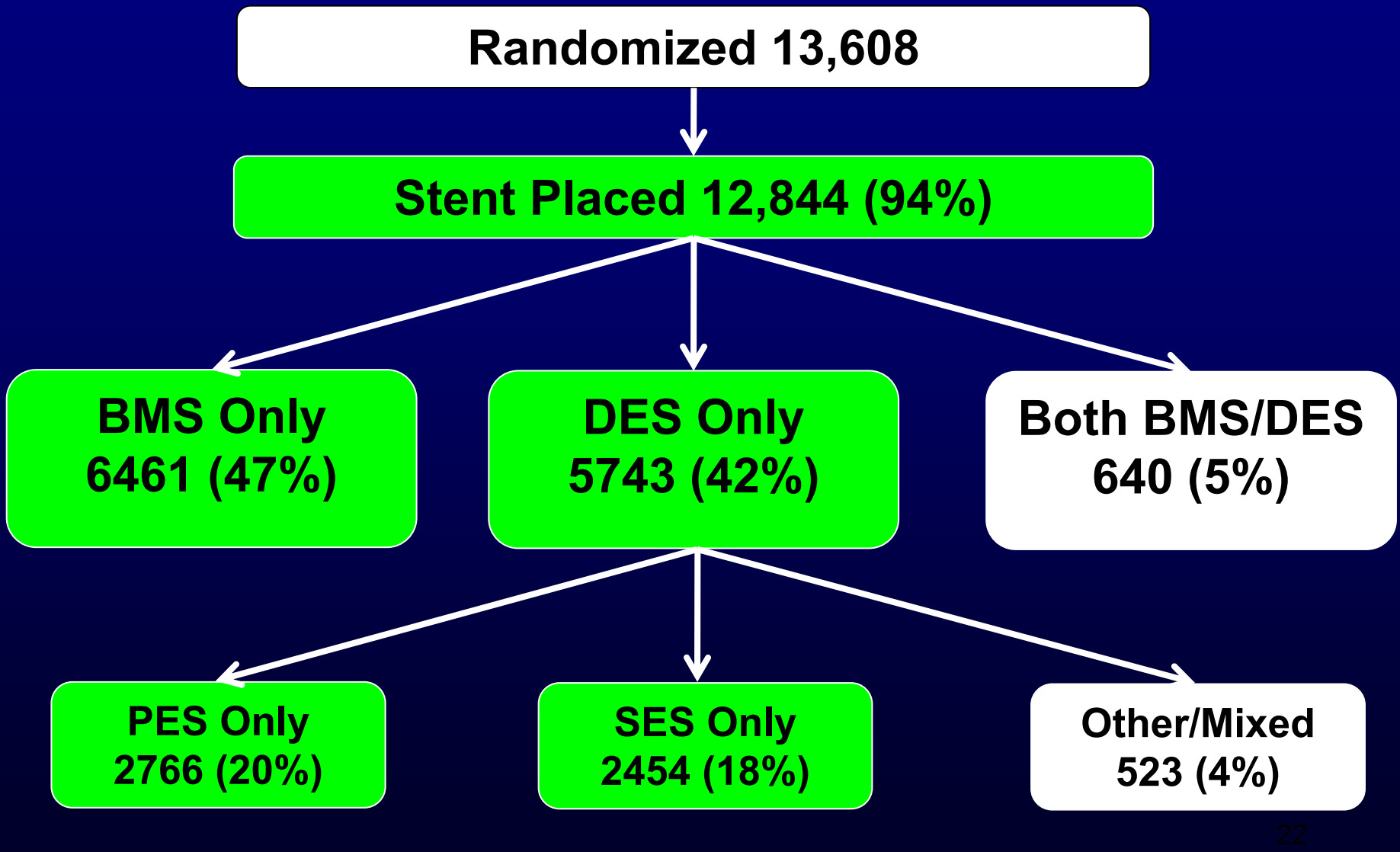
TRITON TIMI-38

Bleeding Risk Subgroups
Therapeutic Considerations



TRÎTON TIMI-38
STENT ANALYSIS

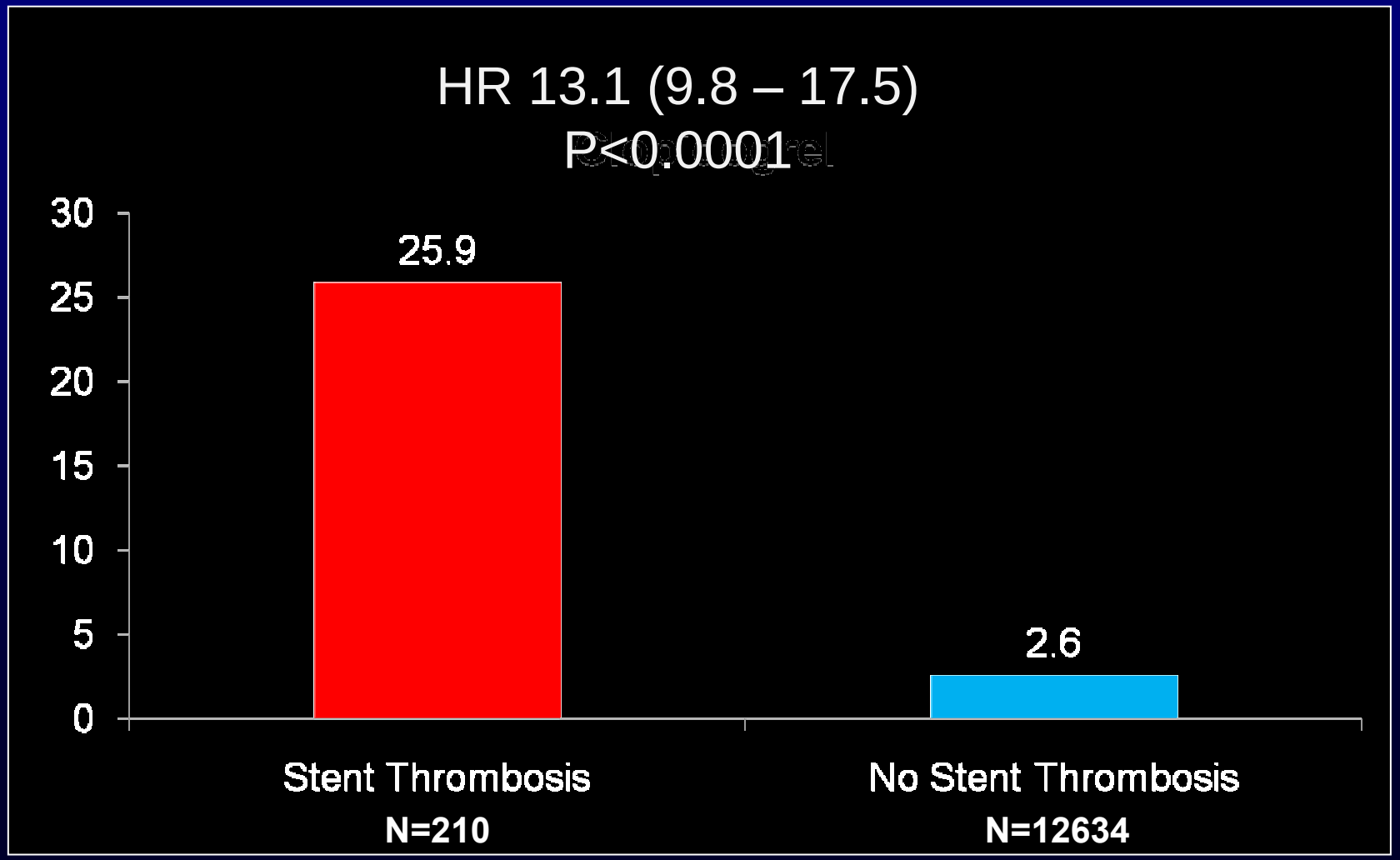
Patient Population



TRÎTON TIMI·38
STENT ANALYSIS

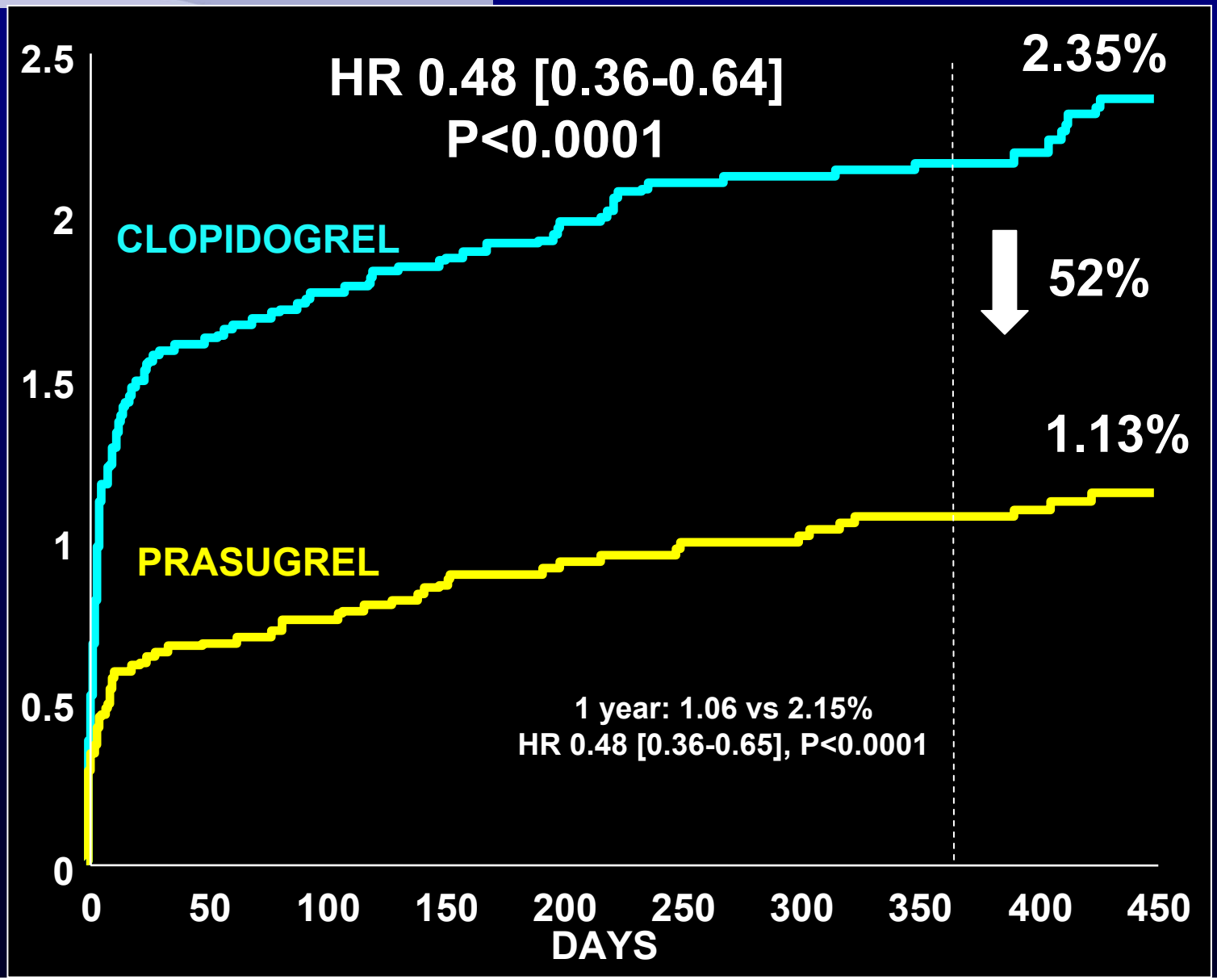
Death Following ST

Mortality During Follow up (%) Post-Stent Thrombosis



TRITON TIMI-38
STENT ANALYSIS

Definite/Probable ST: Any Stent (N=12844)



TRITON TIMI-38
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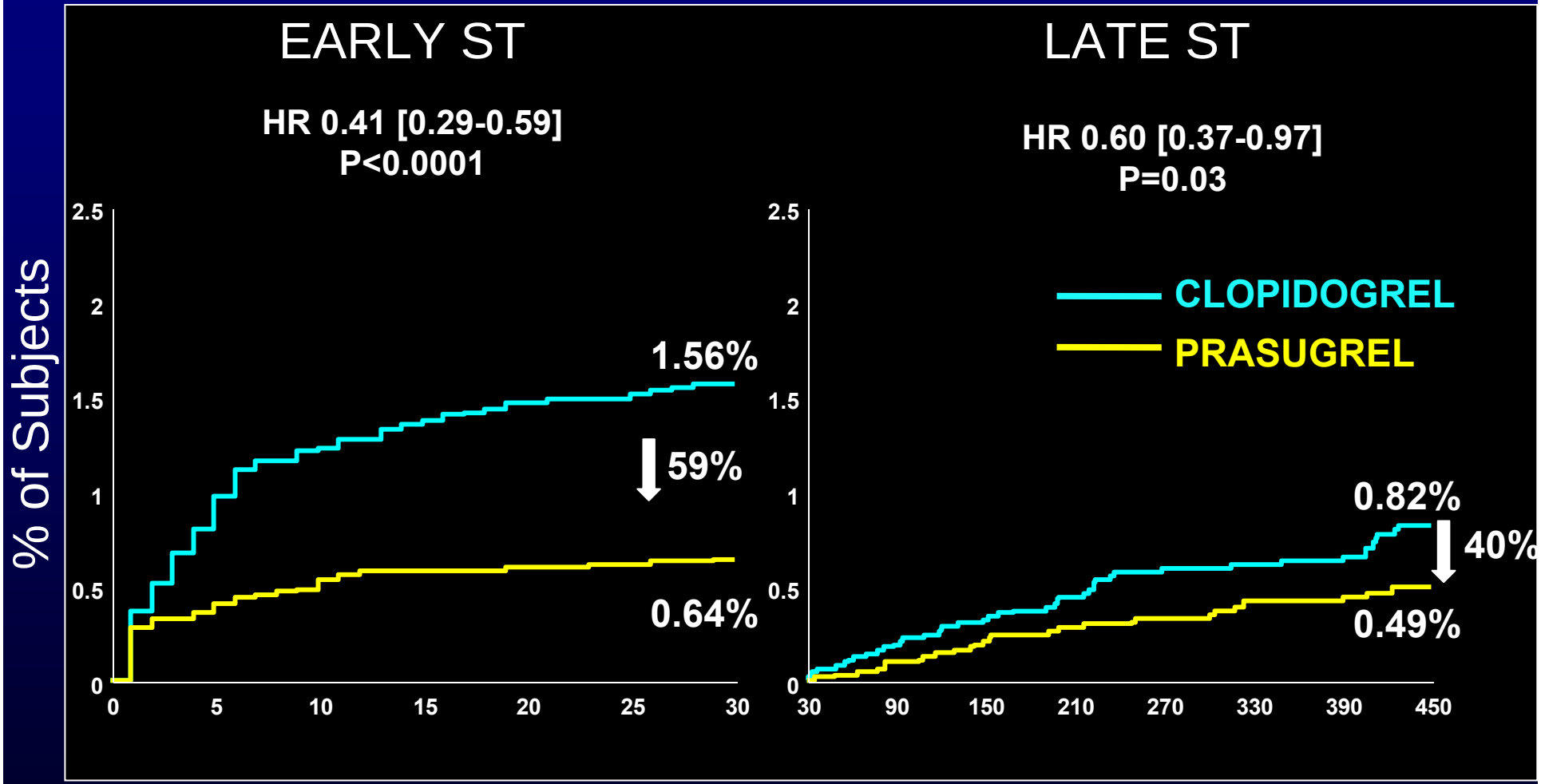
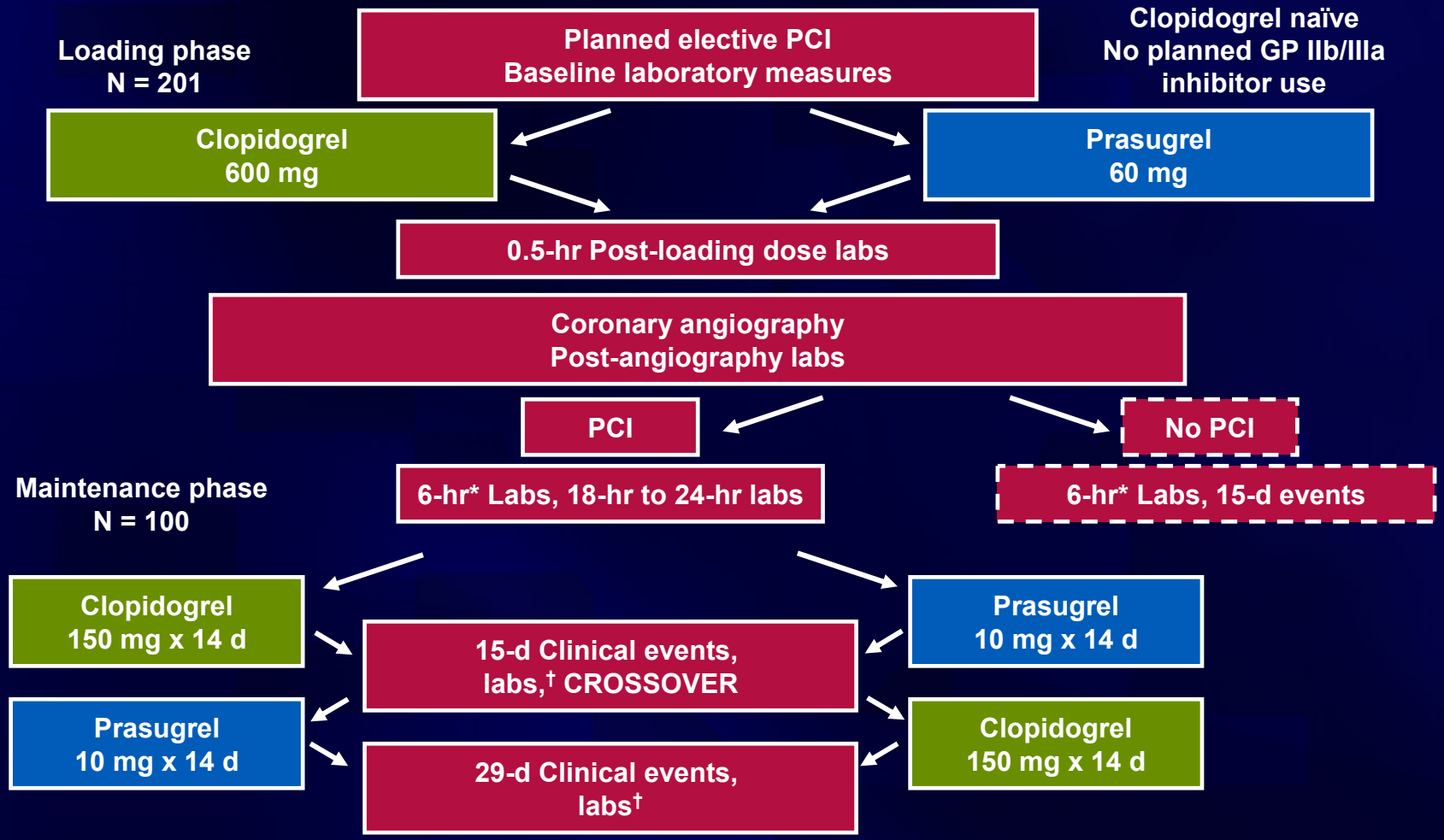


PRINCIPLE-TIMI 44: Study design

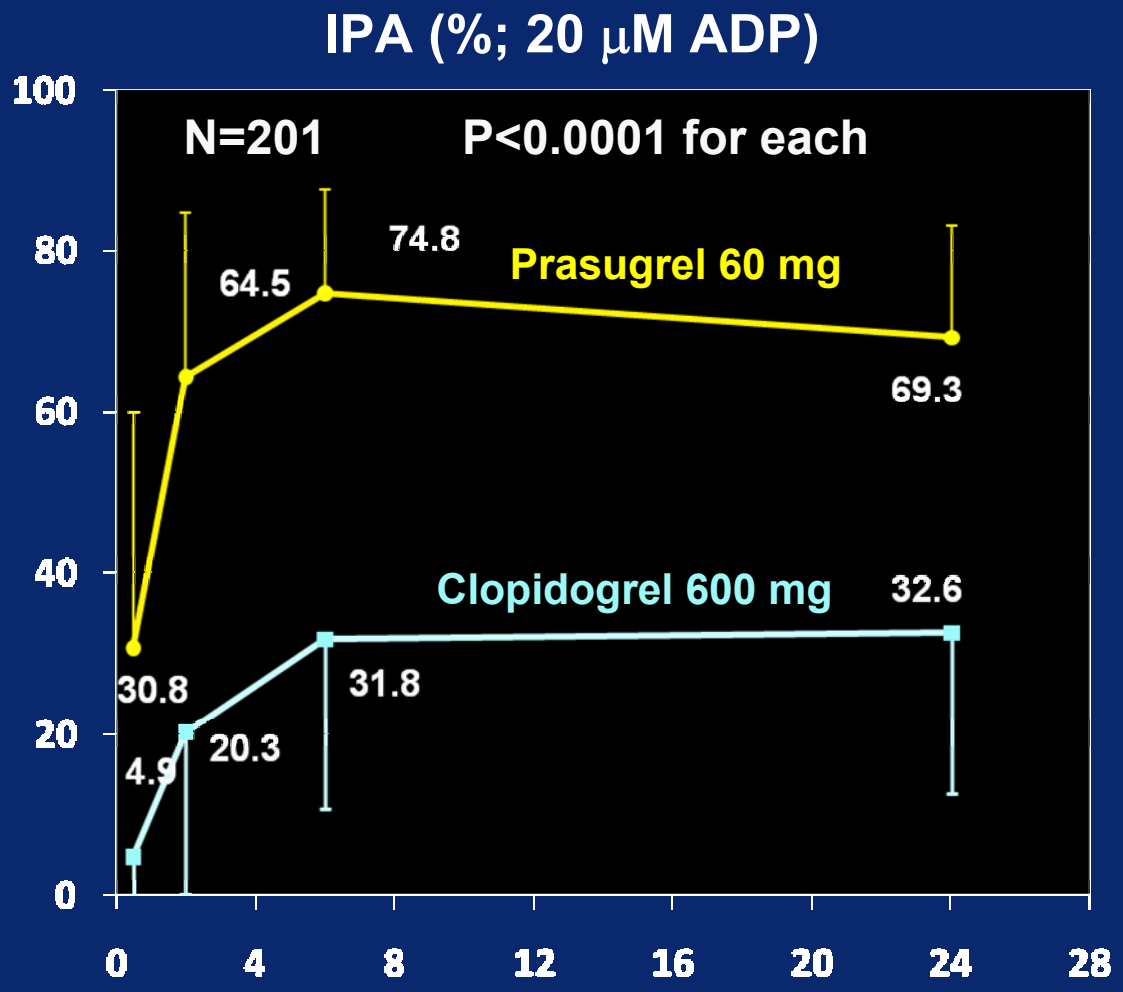


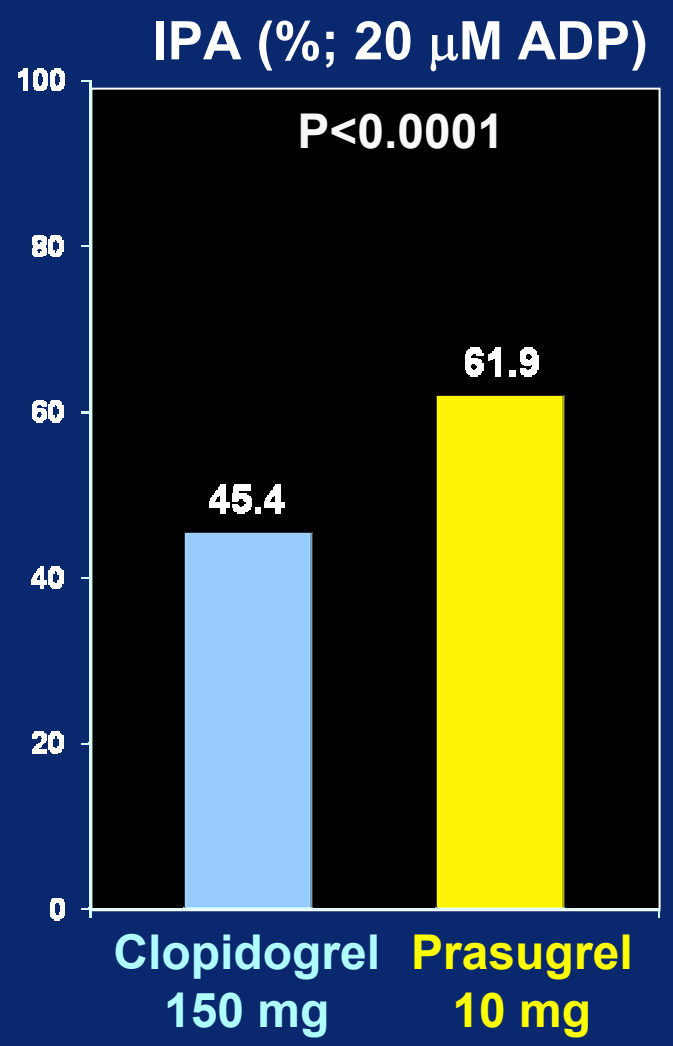
1º Endpoints: *Loading = 6-hr inhibition of platelet aggregation (IPA); †Maintenance = 14-d and 29-d IPA

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

PRINCIPLE TIMI 44

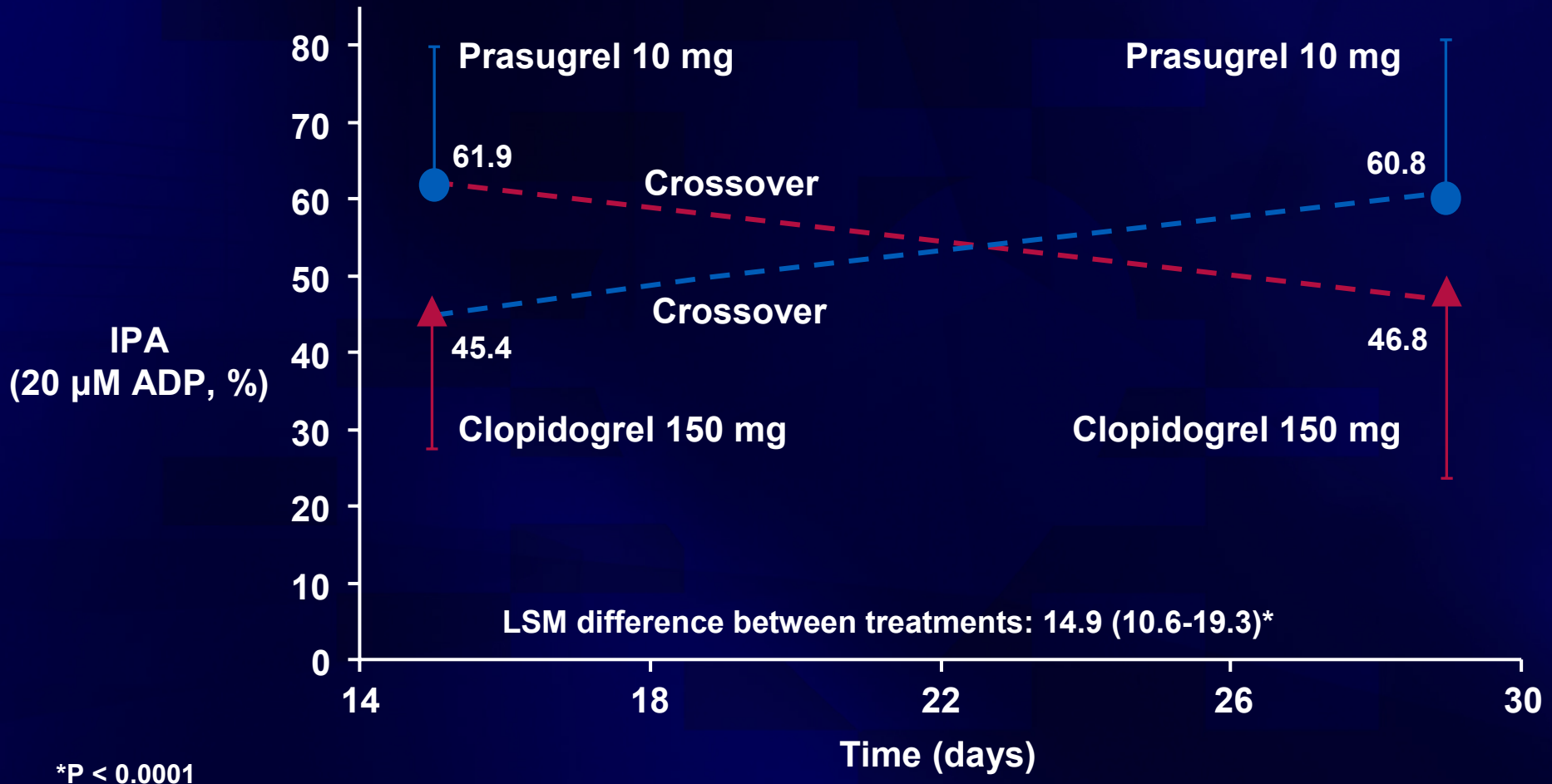
Comparison with Higher Dose Clopidogrel





Wiviott et al Circ 2007 (In Press)

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

Conclusions

Higher IPA to Support PCI

Prasugrel 60 mg LD/10mg MD vs Clopidogrel 300 mg LD/ 75 mg MD

Efficacy

1. A significant reduction in:
   - *CV Death/MI/Stroke* 19%
   - Stent Thrombosis 52%
   - uTVR 34%
   - MI 24%
2. An early and sustained benefit
3. Across ACS spectrum

Safety

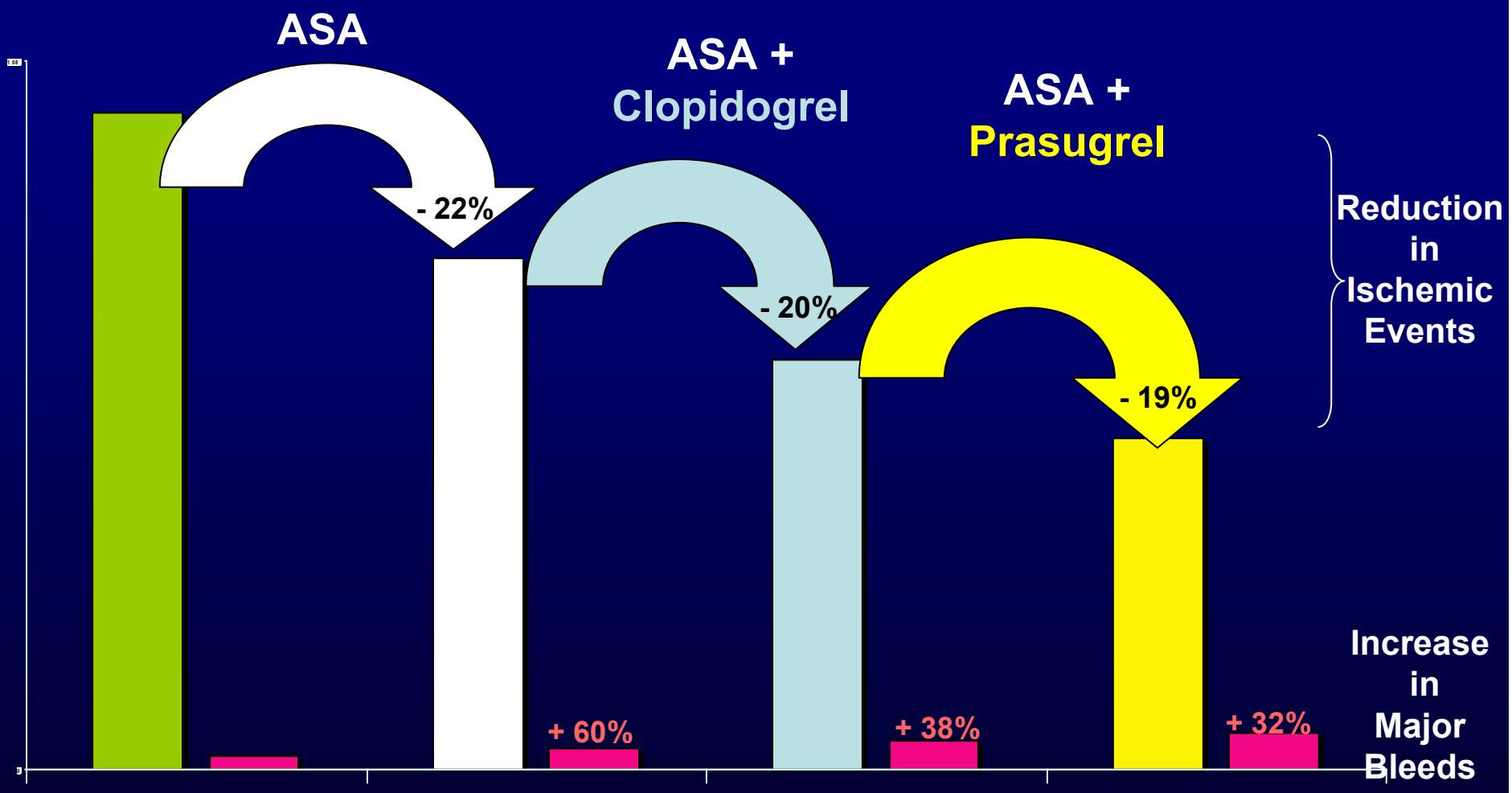
Significant increase in serious bleeding (32% increase)

Avoid in pts with prior CVA/TIA

Net clinical benefit significantly favored Prasugrel

Optimization of Prasugrel maintenance dosing in a minority of patients may help improve the benefit : risk balance

Antiplatelet Therapy in ACS



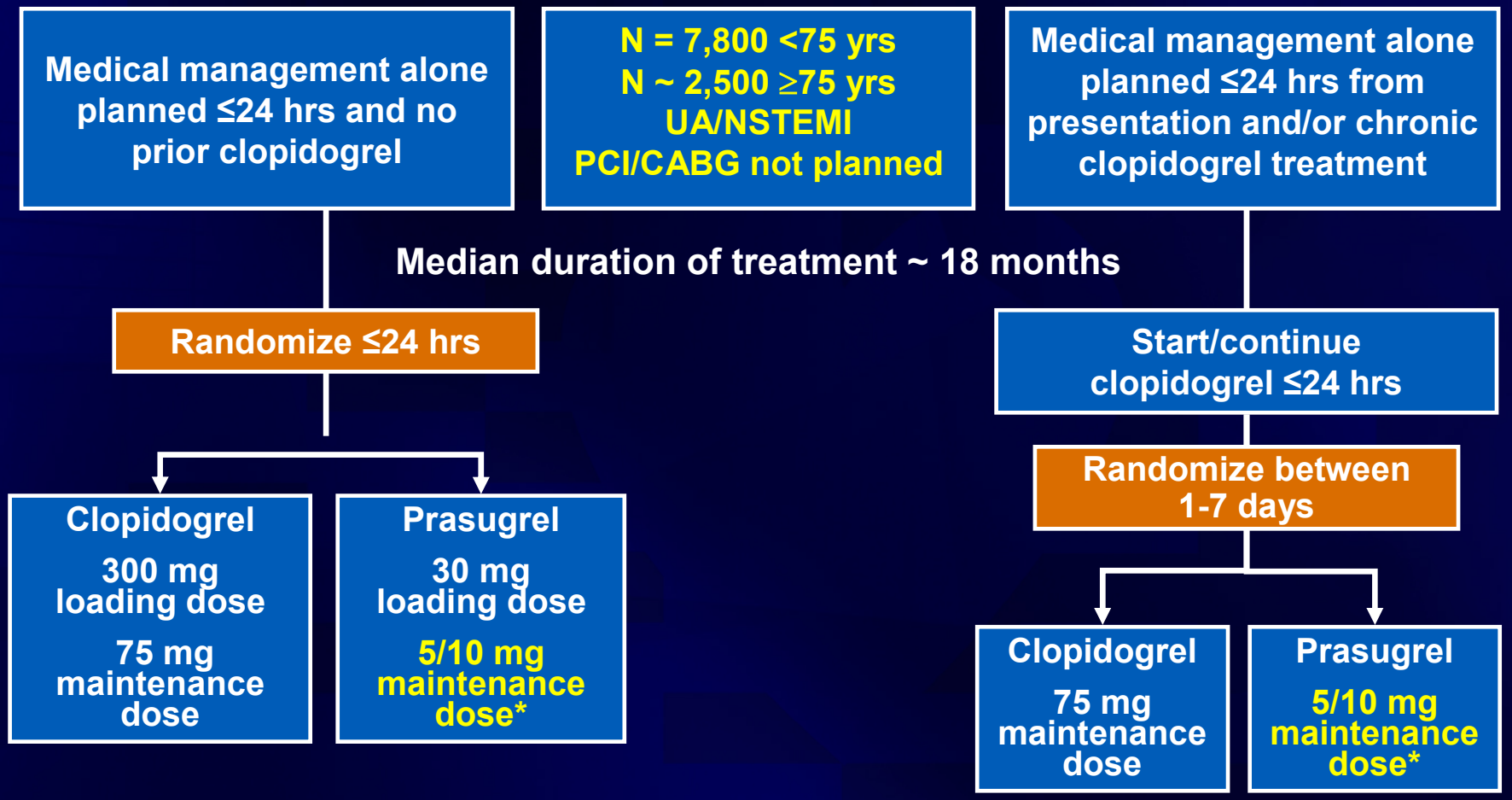
TRITON-TIMI 38, PRINCIPLE-TIMI 44: Conclusions

- 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

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?

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.

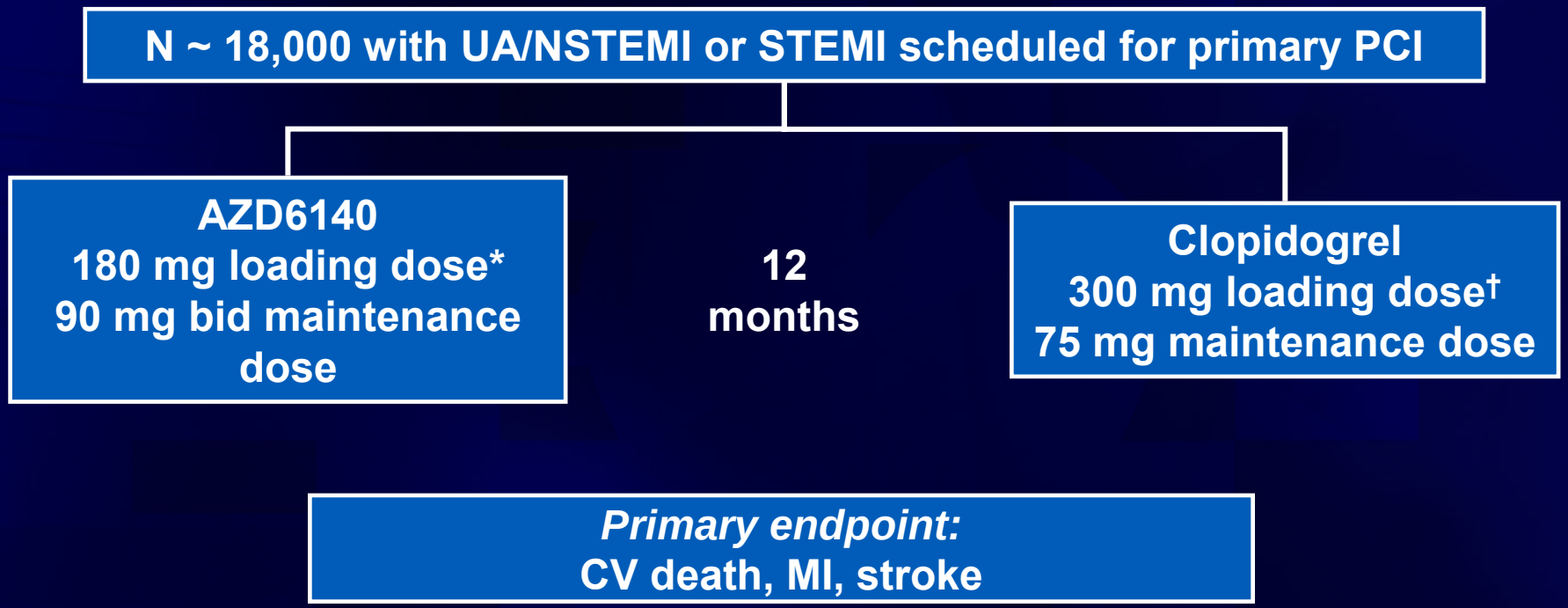
AZD6140: Overview

- Oral, direct-acting cyclopentyltriazolopyrimidine, reversible inhibition of P2Y12 receptor
- DISPERSE-2: Dose optimization and safety study
- Potency in clopidogrel pretreated patients
- PLATO: Ongoing clinical outcomes trial vs clopidogrel

DISPERSE = Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in Non-ST-Elevation Myocardial Infarction, PLATO = Platelet Inhibition and Patient Outcomes

Cannon CP et al. *J Am Coll Cardiol.* 2007;50:1844-51.
Michelson AD. *Arterioscler Thromb Vasc Biol*. 2008;28:s33-s38.

PLATO: Study design



*Additional 90 mg allowed pre-PCI
†In clopidogrel-naïve patients (no loading dose if pretreated); Additional 300 mg allowed in either clopidogrel group pre-PCI

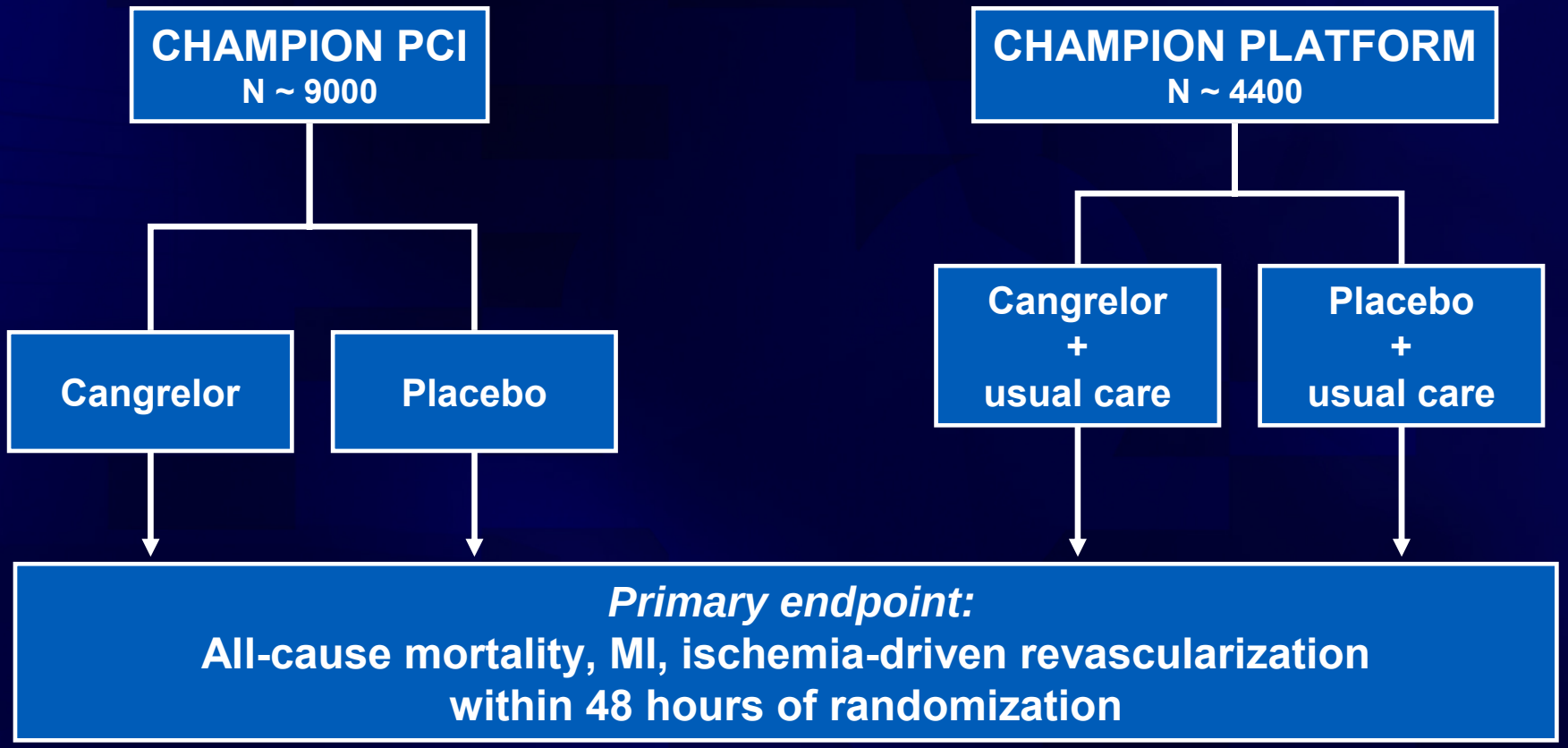
Storey RF. *Eur Heart J Suppl.* 2008;10(suppl D):D30-D37.

Cangrelor: Overview

- Intravenous, direct-acting ATP analog, reversible inhibitor of P2Y12 receptor, plasma half-life 2.6-3.3 minutes
- Dose-finding study
- CHAMPION: Placebo-controlled, ongoing clinical outcomes trial program

Angiolillo DJ and Capranzano P. *Am Heart J*. 2008;156:S10-S15.

Cangrelor: Ongoing clinical trials



Storey RF. *Eur Heart J Suppl.* 2008;10(suppl D):D30-D37.
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

ACC/AHA guidelines for UA/NSTEMI: Dosing of oral antiplatelet therapy

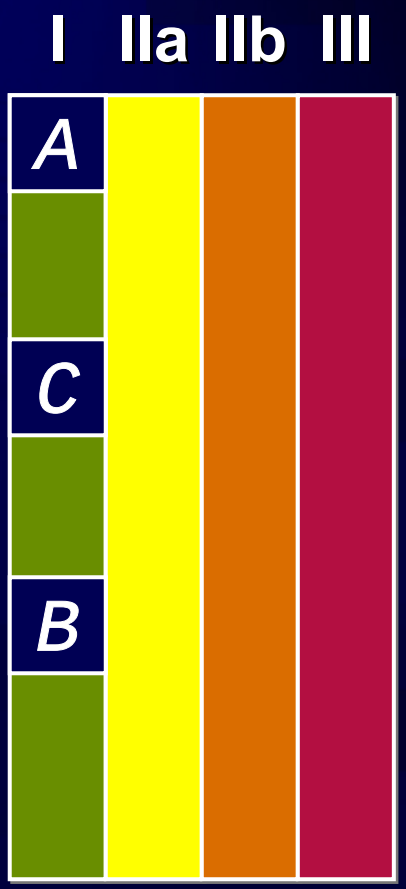
Drug	Initial Med Tx	During PCI		After PCI	Discharge
		Rec'd initial medical treatment	No initial medical treatment		
Aspirin	162-325 mg nonenteric formulation	No additional treatment	162-325 mg nonenteric formulation	BMS: 162-325 mg ≥1 mo, SES: 3 mo, PES: 6 mo; then ASA 75-162 mg indefinitely	BMS: 162-325 mg ≥1 mo, SES: 3 mo, PES: 6 mo; then ASA 75-162 mg indefinitely
Clopidogrel	Loading dose: 300-600 mg Maintenance dose: 75 mg	Second loading dose 300 mg may be given	Loading dose: 300-600 mg	BMS: 75 mg ≥1 mo and ideally up to 1 yr; DES: 75 mg ≥1 yr*	BMS: 75 mg ≥1 mo and ideally up to 1 yr; DES: 75 mg ≥1 yr*
Ticlopidine	Loading dose: 500 mg Maintenance dose: 250 mg bid	No additional treatment	Loading dose: 500 mg	Maintenance dose: 250 mg bid (duration same as clopidogrel)	Maintenance dose: 250 mg bid (duration same as clopidogrel)

*In patients who are not at high risk of bleeding; BMS = bare-metal stent, DES = drug-eluting stent, PES = paclitaxel-eluting stent, SES = sirolimus-eluting stent

Anderson JL et al. *Circulation*. 2007;116:803-77.

ACC/AHA/SCAI 2007 focused update for PCI: Oral antiplatelet therapy

ASA for all patients



Patients already taking daily long-term ASA should take 75 mg-325 mg before PCI is performed

Patients not already taking daily ASA should be given 300 mg-325 mg ≥2 hours and preferably 24 hours before PCI is performed

After PCI, in patients without allergy or increased risk of bleeding, ASA 162 mg-325 mg daily should be given for ≥1 month (BMS), 3 months (SES), 6 months (PES), after which daily long-term ASA use should be continued indefinitely at a dose of 75 mg-162 mg

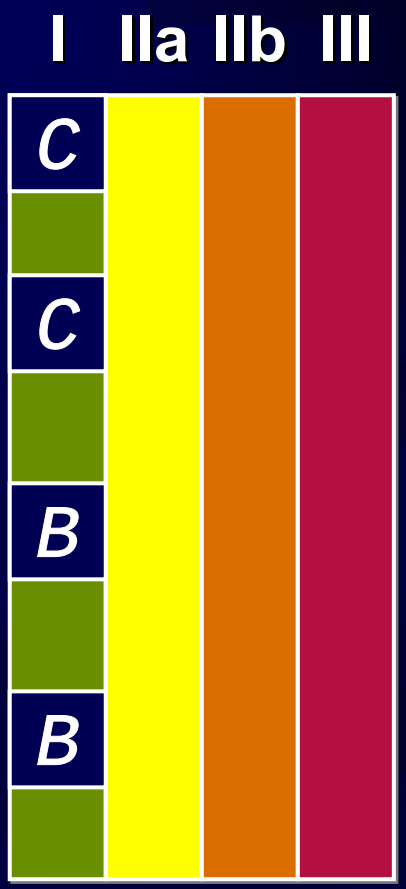
MODIFIED

SCAI = Society for Cardiovascular Angiography and Interventions

King SB III et al. *J Am Coll Cardiol*. 2008;51:172-209.

ACC/AHA/SCAI 2007 focused update for PCI: Oral antiplatelet therapy, cont'd

ASA for all patients



A loading dose of clopidogrel, generally 600 mg, should be administered before or when PCI is performed — MODIFIED

In patients undergoing PCI within 12-24 hours of receiving fibrinolytic therapy, a clopidogrel oral loading dose of 300 mg may be considered — MODIFIED

For all post-PCI stented patients receiving a DES, clopidogrel 75 mg daily should be given for ≥12 months if not at high risk of bleeding — MODIFIED

For post-PCI patients receiving BMS, clopidogrel should be given for ≥1 month and ideally up to 12 months (unless at increased risk of bleeding; then it should be given for ≥2 weeks) — MODIFIED

King SB III et al. *J Am Coll Cardiol*. 2008;51:172-209.