New Strategies of Antiplatelet Therapy for ACS-PCI Patients

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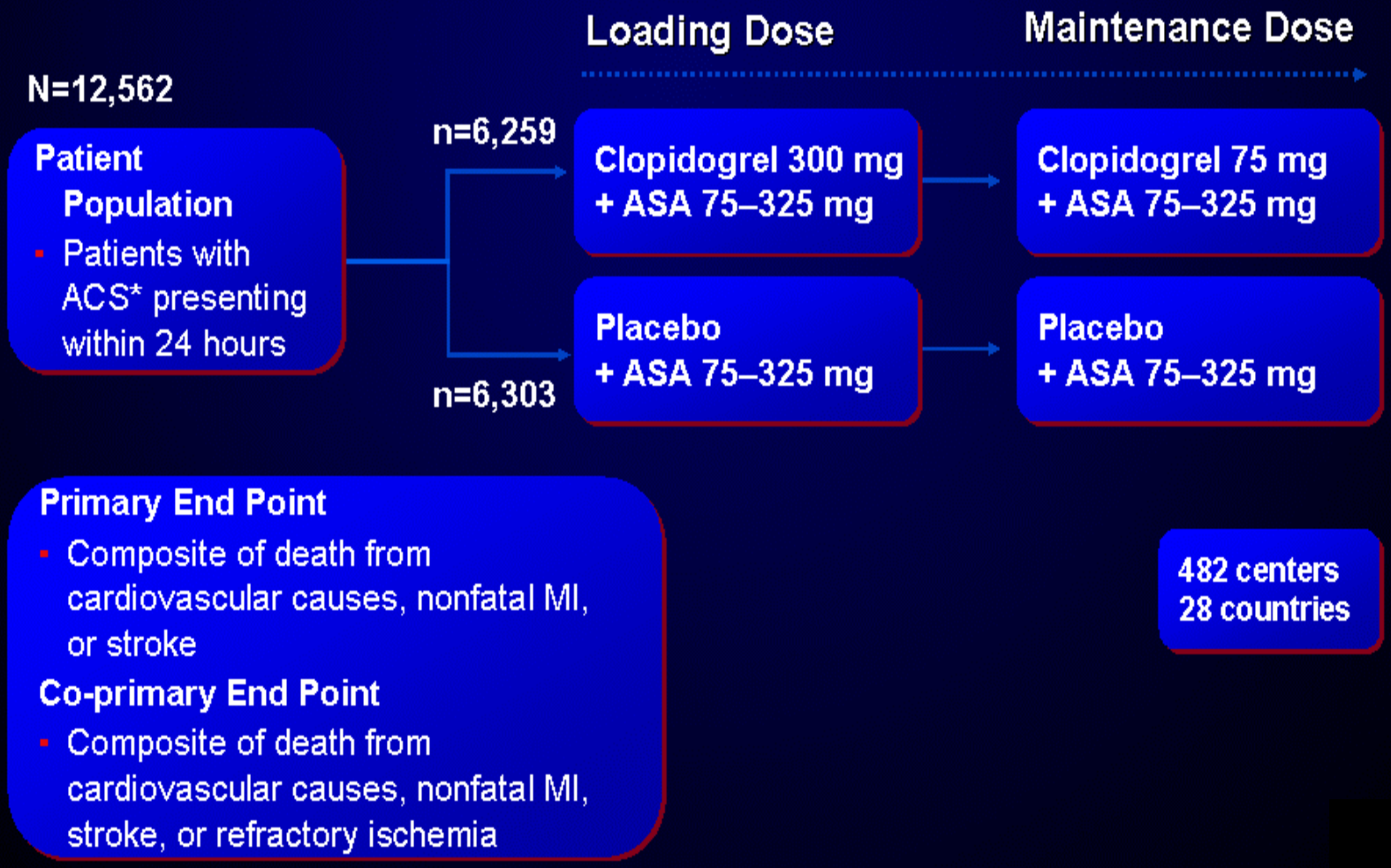
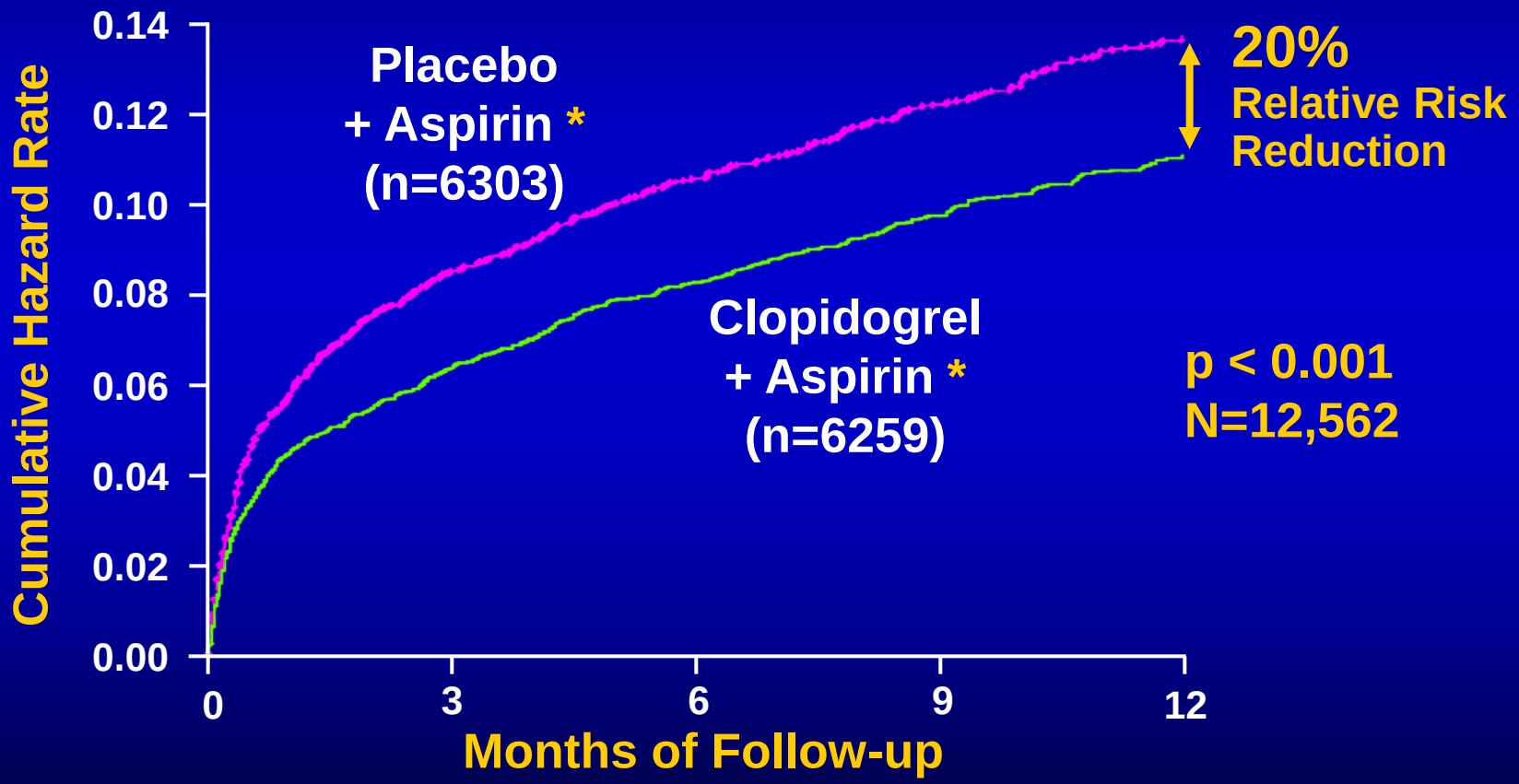
Clopidogrel in Unstable Angina to Prevent Recurrent Events



* UA/non–Q-wave MI (also known as non–ST-segment elevation myocardial infarction). CURE Trial Investigators. *N Engl J Med.* 2001;345:494-502.

CURE: Primary End Point

MI/Stroke/CV Death



* In addition to other standard therapies

Yusuf S: N Engl J Med 2001;345:494-502

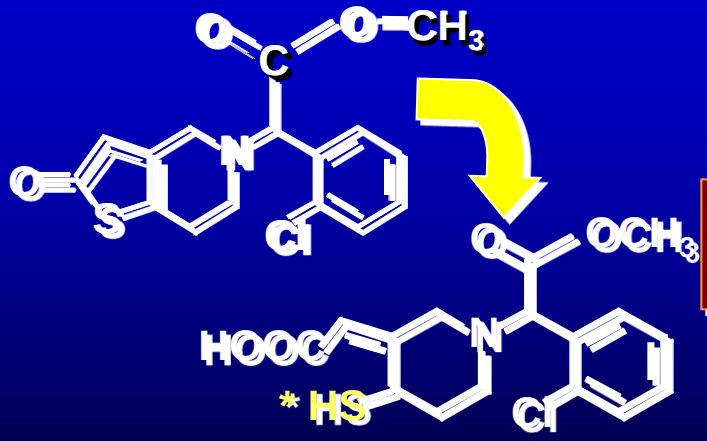
Limitations of Clopidogrel

- Slow onset of action
- Variable degree of platelet inhibition
- Variable clinical response
- Relatively long duration of effect
- Drug Interactions

Active Metabolite Formation

Clopidogrel

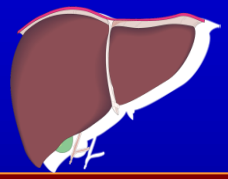
85% Inactive Metabolites
Esterases in blood



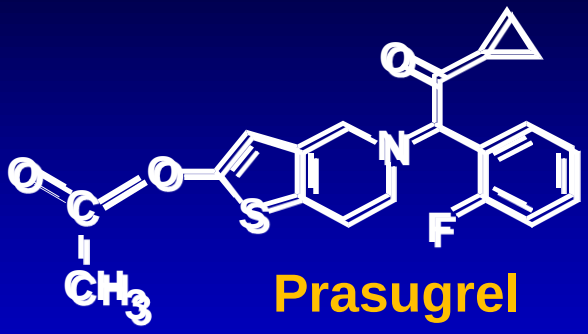
Active Metabolite

Pro-drug

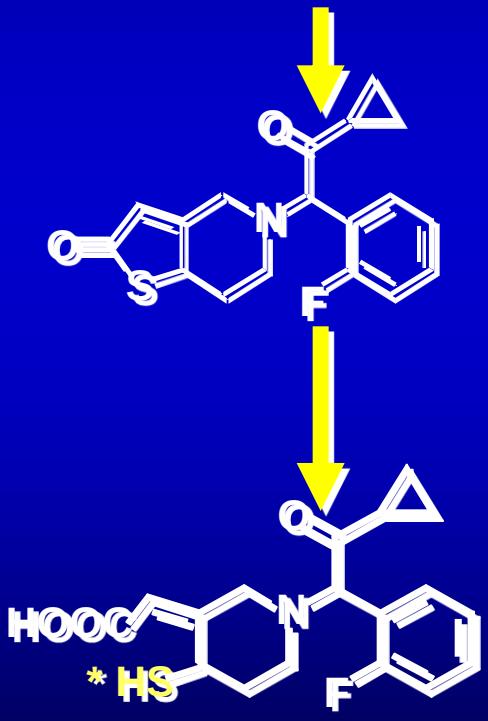
Pre-hepatic metabolism
Esterases in blood
(? Small Intestine)



Hepatic Metabolism
Cytochrome P450



Prasugrel

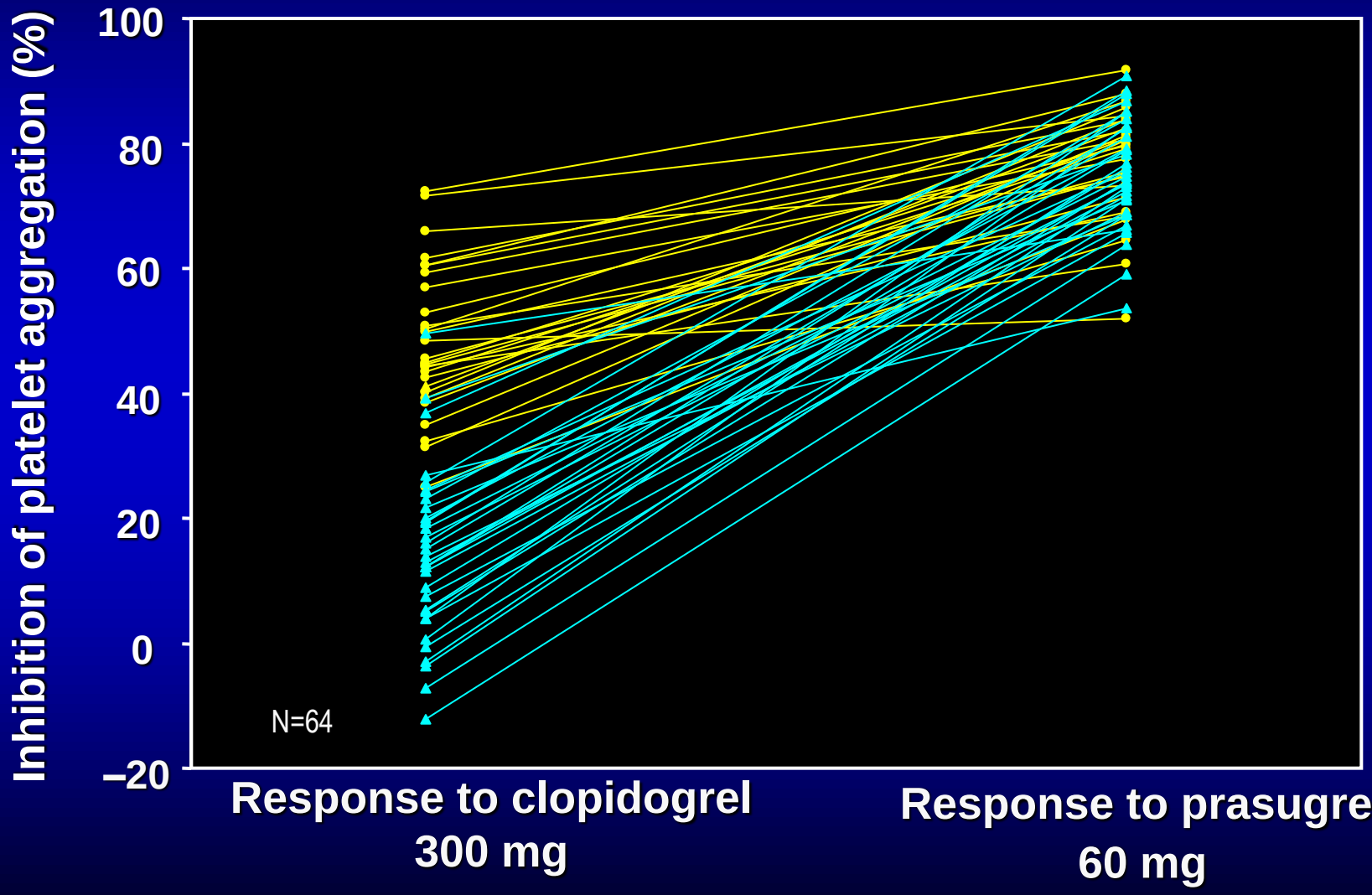


Active Metabolite

Sem Vasc Med 3:113, 2003

Sankyo Ann Report 51:1,1999

Healthy Volunteer Crossover Study
IPA (20 μM ADP) at 24 hours



Brandt J et al. AHJ 2006

Potential Mechanisms of Response Variability

Extrinsic Mechanisms

- Non-compliance
- Under-dosing
- Drug-drug interactions
- Absorption and/or metabolism
- Patient Factors (DM, ACS, etc…)

Intrinsic Mechanisms

- P2Y12 receptor affinity (ADP or Drug) or number
- Variable response to agonist:
  - Release
  - GP IIb/IIIa receptor activation

Wiviott and Antman Circ 2004

Clopidogrel Black Box Warning

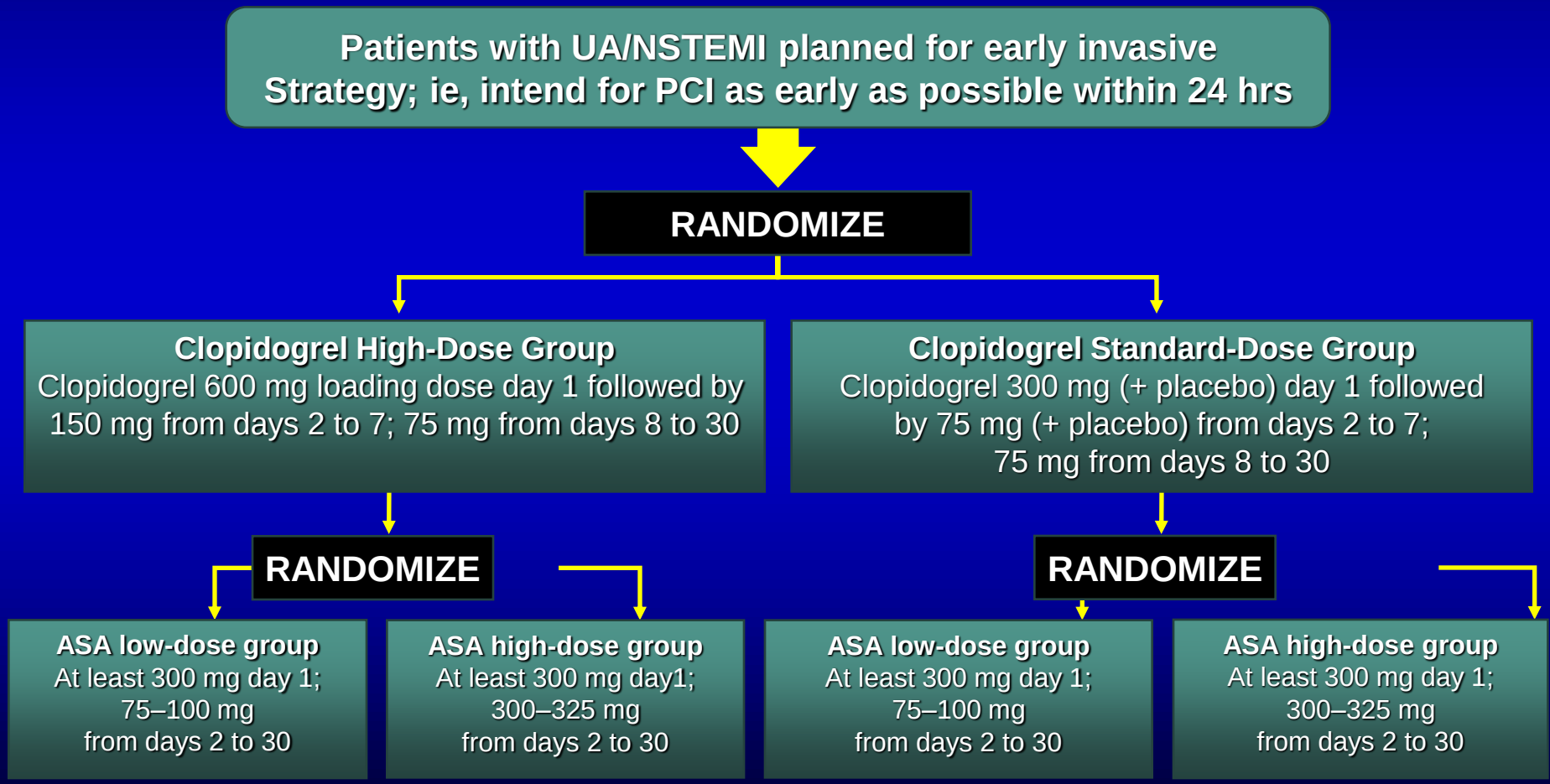
March 12, 2010

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1)]*. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy *[see Clinical Pharmacology (12.5)]*. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers *[see Dosage and Administration (2.3)]*.

CURRENT/OASIS 7

Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS

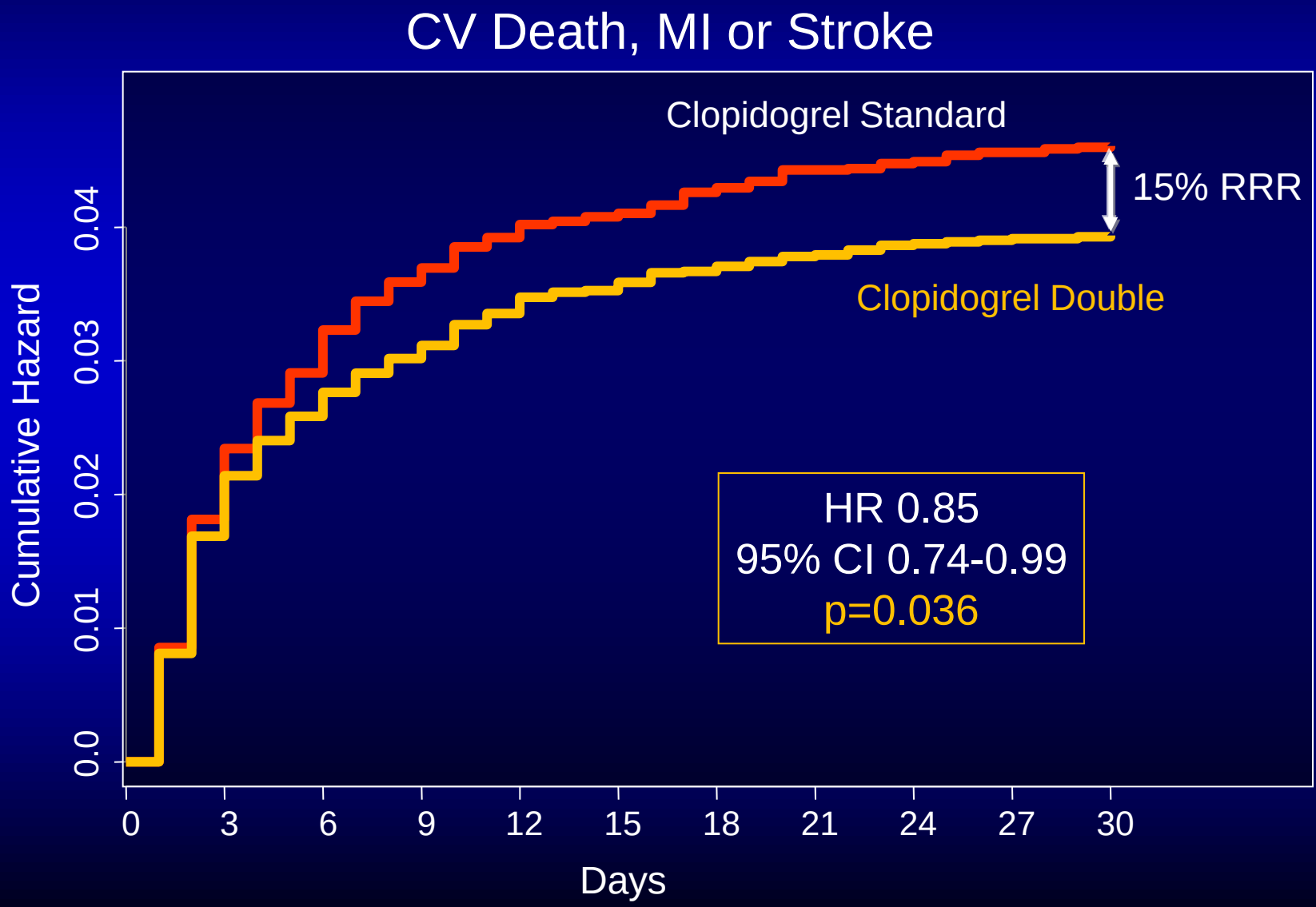


PCI: Percutaneous coronary intervention
UA/NSTEMI: Unstable angina/non-ST-segment elevation myocardial infarction

Clopidogrel: Double vs Standard Dose

CURRENT

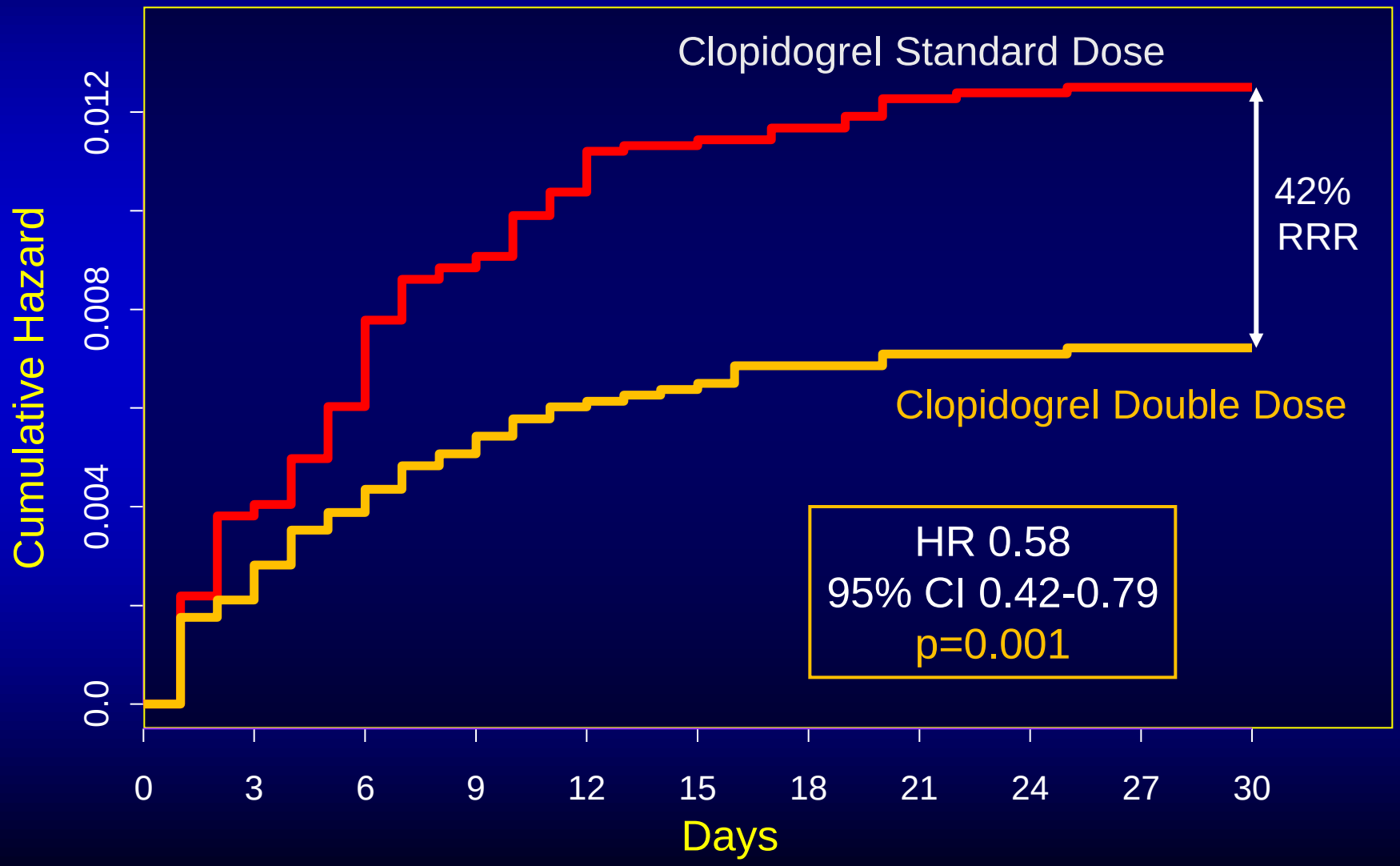
Primary Outcome: PCI Patients



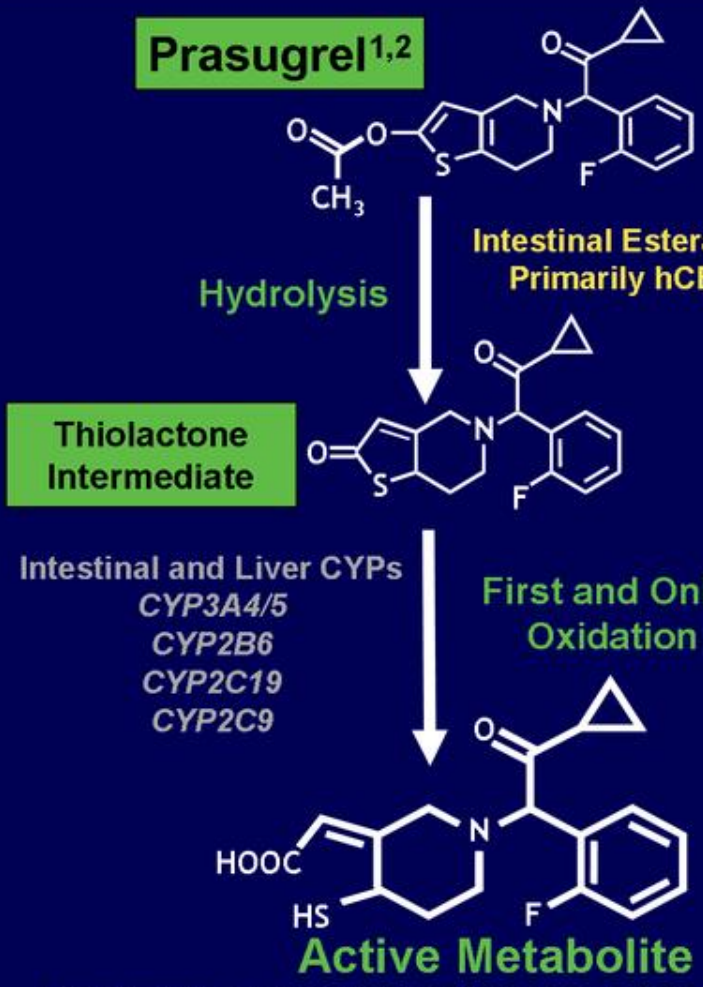
Clopidogrel: Double vs Standard Dose

CURRENT

Stent Thrombosis (Angio confirmed)



Active Metabolite Formation: Prasugrel



- In healthy subjects, there was no relevant effect of genetic variation in *CYP2B6*, *CYP2C9*, *CYP2C19*, or *CYP3A5* on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation[3]

Any difference in the pharmacokinetics of prasugrel compared with other antiplatelet agents has not been correlated to clinical outcomes.

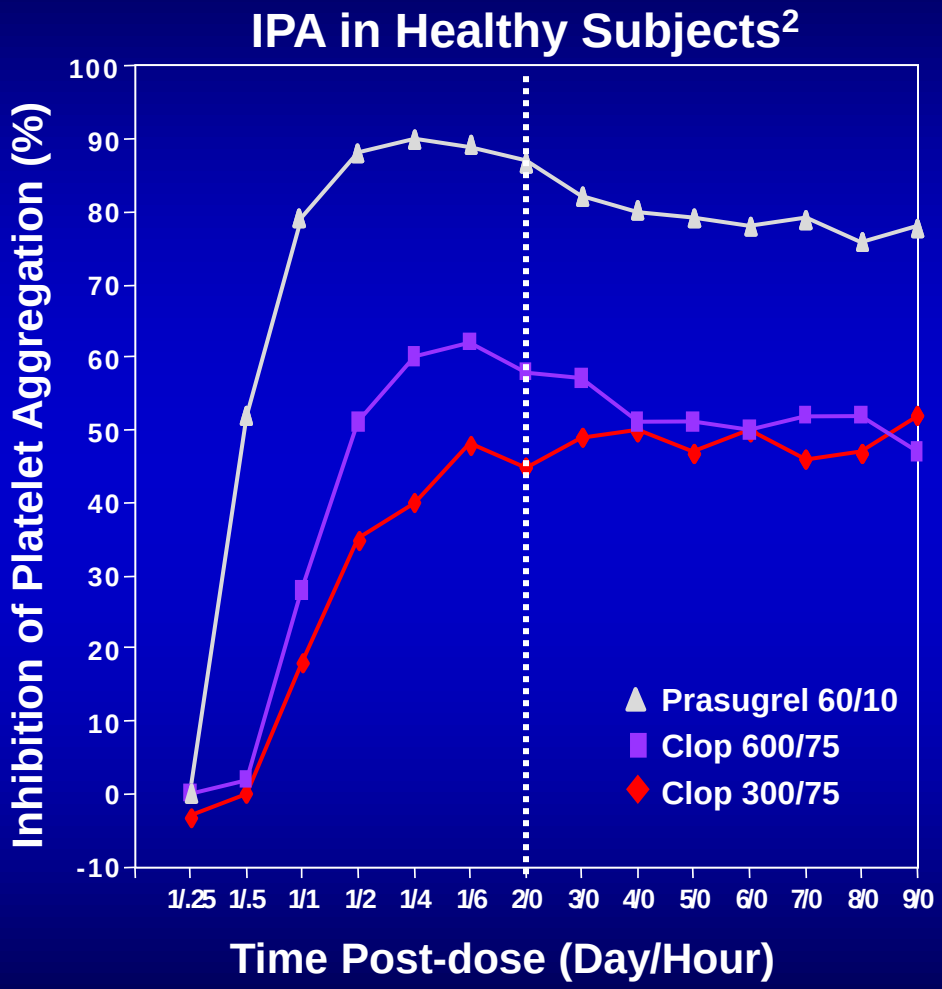
1. Rehmel et al. *Drug Metab Dispos.* 2006;34:600-607.
2. Williams et al. *Drug Metab Dispos.* 2008;36:1227-1232.
3. Effient Full Prescribing Information.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

Prasugrel†: More Effective Platelet Inhibition

Prasugrel vs Clopidogrel[1]

- More potent
- More rapid in onset
- More consistent IPA
- Less frequent poor IPA response
- More efficient generation of active metabolite



IPA = inhibition of platelet aggregation.

†For a complete listing of adverse events with prasugrel, refer to the 64th edition of the Physician Desk Reference.

1 Wiviott SD, et al. *Am Heart J.* 2006;152:627-635.

2 Payne CD, et al. *Am J Cardiol*. 2006;98:S8.

TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN With Prasugrel (TRITON)-TIMI 38

ACS (UA/NSTEMI or STEMI) and Planned PCI
N=13,608

Randomized
Double-blind

Prasugrel	Clopidogrel
60-mg LD/10-mg MD + Aspirin	300-mg LD/75-mg MD + Aspirin

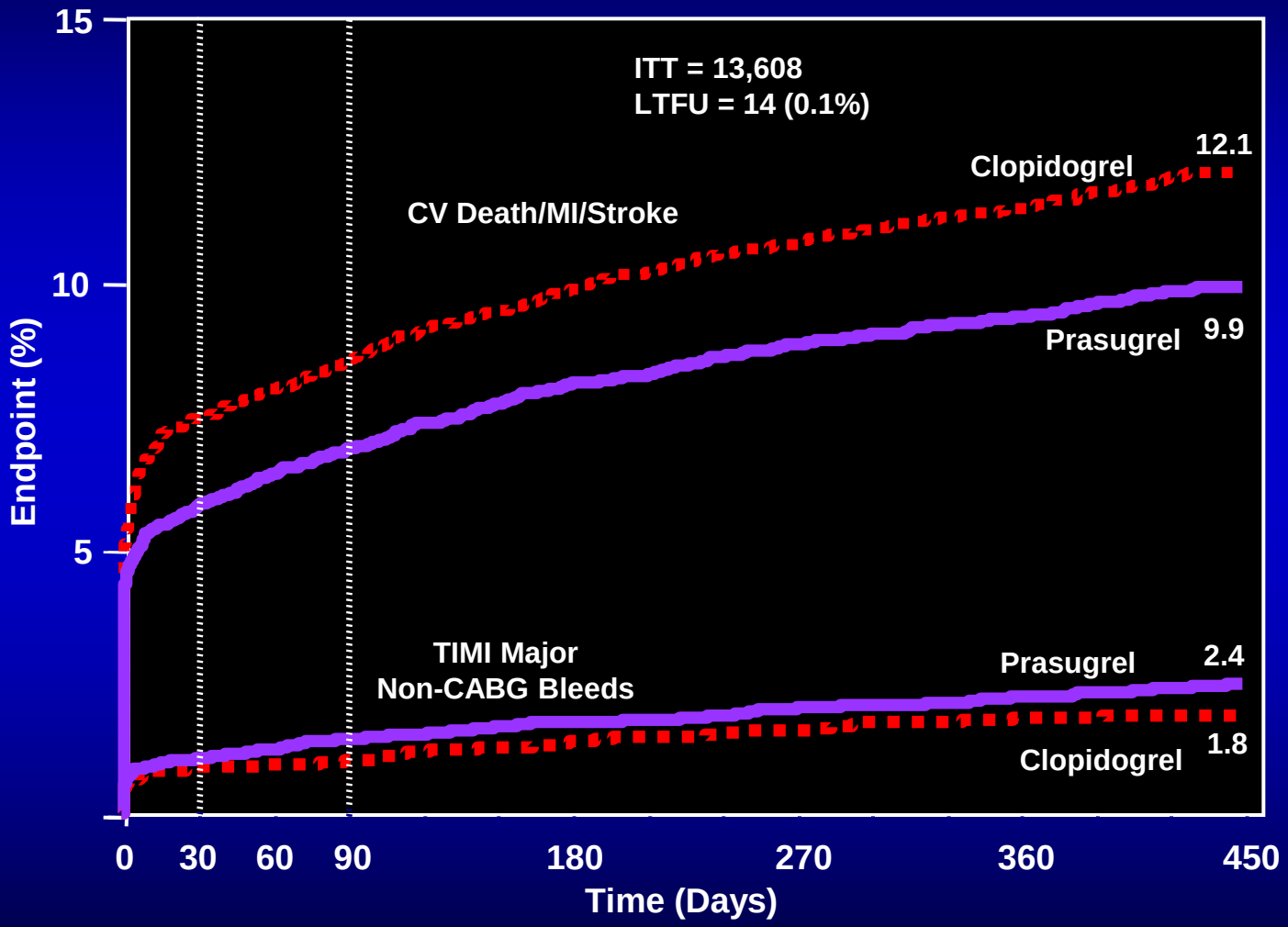
Median duration of follow up = 14.5 months

- Primary efficacy endpoint:
  - Composite CV death, nonfatal MI, or nonfatal stroke
- Safety endpoints:
  - TIMI major or minor bleeding

Administration of the clopidogrel LD in TRITON-TIMI 38 was delayed relative to the placebo-controlled trials that supported its approval for ACS.

Wiviott et al. *N Engl J Med*. 2007;357:2001-2015.

TRITON-TIMI 38: Balance of Efficacy and Safety



~10% Recurrent Ischemic Events

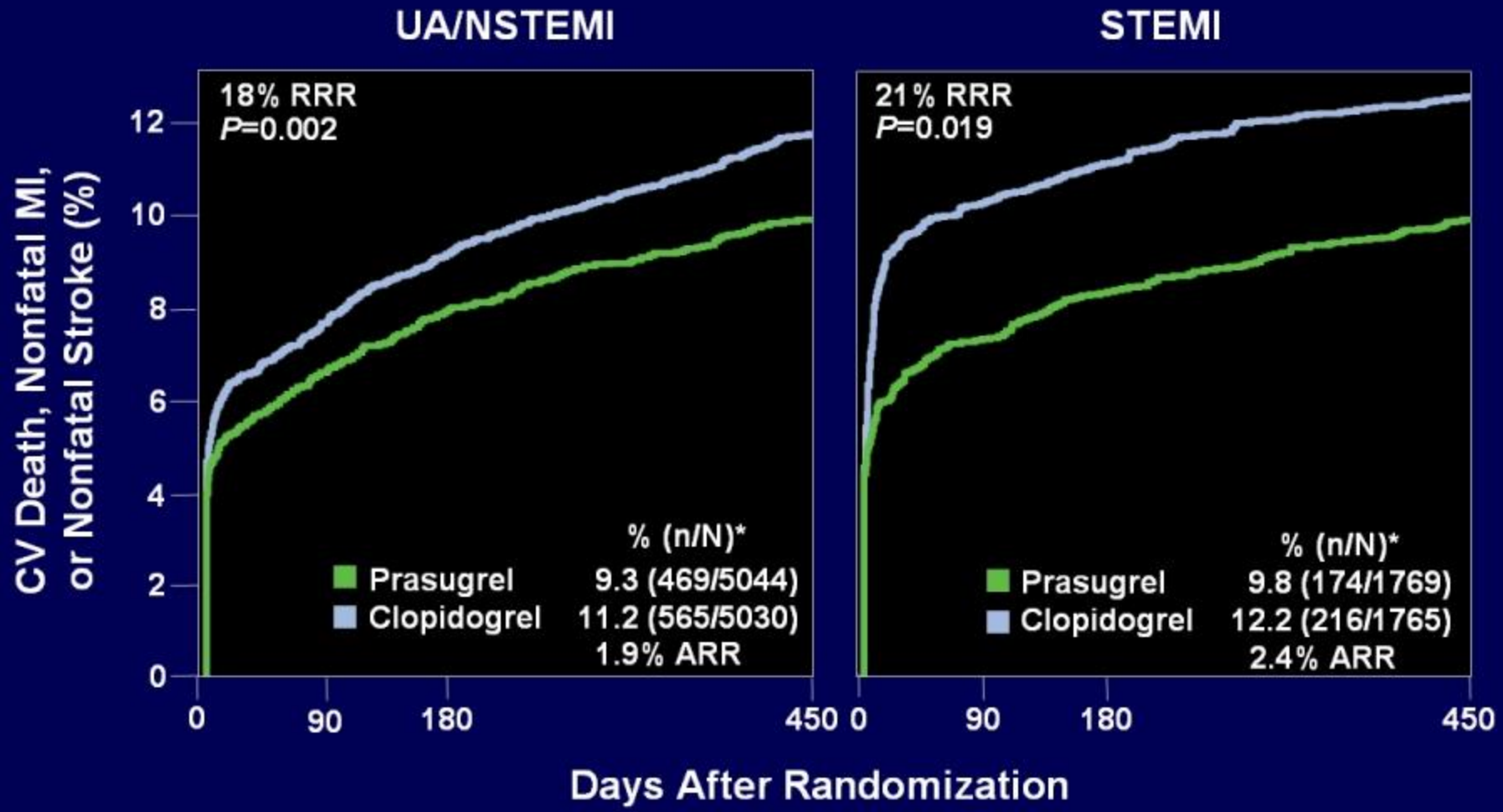
↓ 138 events
HR=0.81
(CI=0.73-0.90)
P=.0004
NNT=46

↑ 35 events
HR=1.32
(1.03-1.68)
P=.03
NNH=167

LTFU = lost to follow up. NNH = number needed to harm.

Wiviott SD, et al. *N Engl J Med*. 2007;357:2001-2015.

Primary Endpoint Events at End of Trial: UA/NSTEMI and STEMI Patients

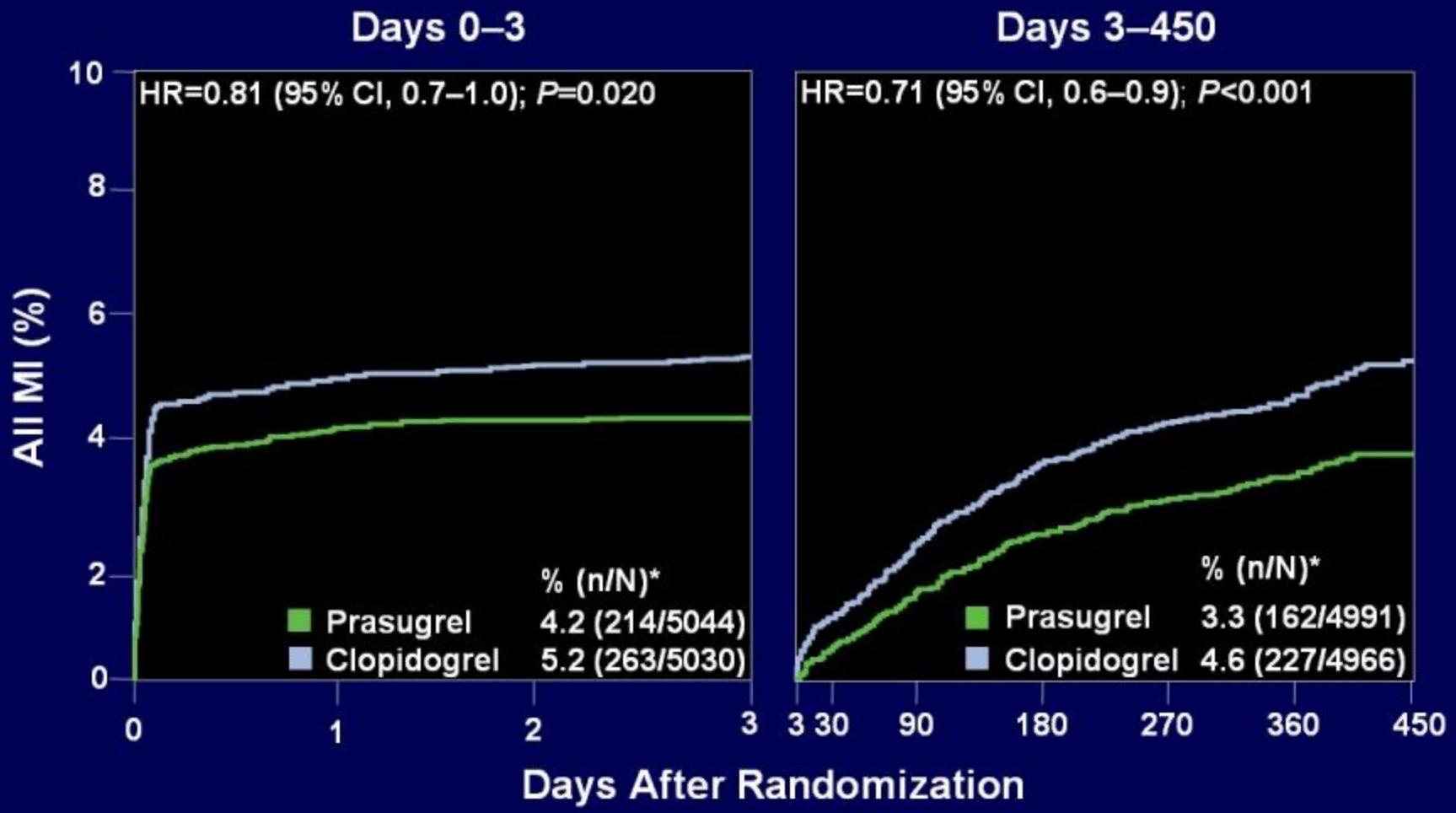


*Observed data.

1. Effient Full Prescribing Information.
2. Data on file: #EFF20091204a. DSI/Lilly.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

All MI at 0–3 Days and Day 3 to End of Trial in UA/NSTEMI Population

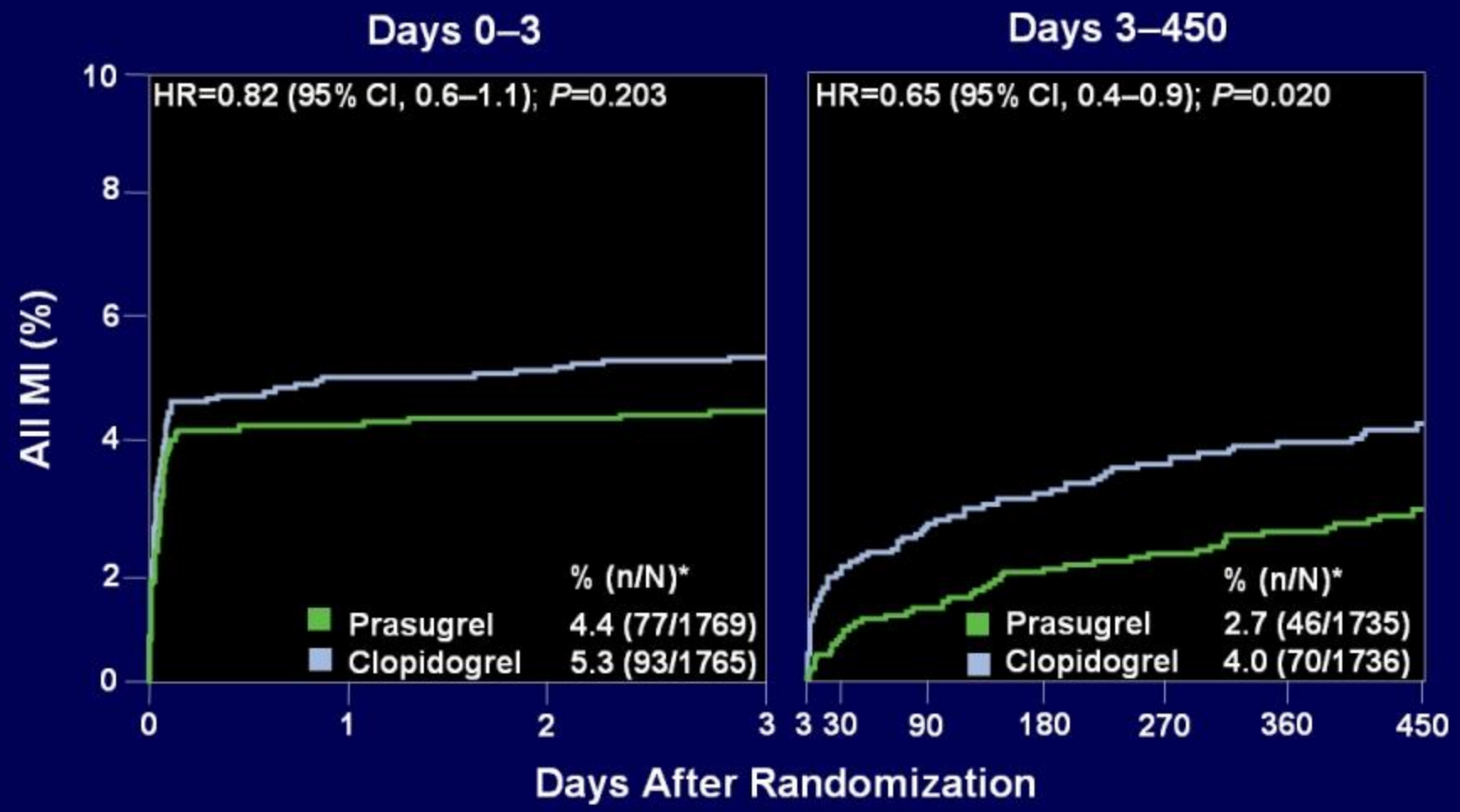


*Observed data.

Data on File: #EFF20091207d. DSI/Lilly.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

All MI at 0–3 Days and Day 3 to End of Trial in STEMI Population

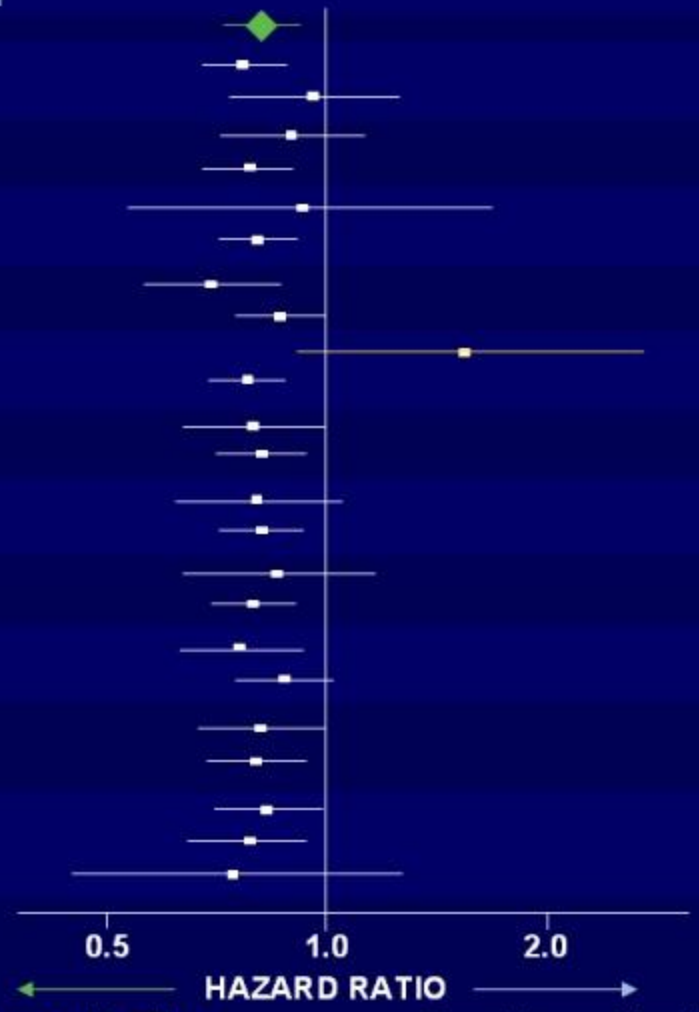


Data on File: #EFF20091207d. DSI/Lilly.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

Primary Endpoint Events Across Subpopulations in UA/NSTEMI Patients

Baseline Characteristics		N	Percent Events	
			Prasugrel	Clopidogrel
OVERALL		**10,074**	**9.9**	**12.1**
Age	<75 years	8672	8.2	10.5
	≥75 years	1402	15.8	16.2
Gender	Female	2724	10.3	11.4
	Male	7350	8.9	11.2
Body weight	<60 kg	503	9.2	9.8
	≥60 kg	9458	9.2	11.1
Diabetes mellitus	Yes	2472	10.8	15.0
	No	7602	8.8	10.0
Previous TIA/stroke	Yes	405	18.3	12.5
	No	9669	8.9	11.2
Previous MI	Yes	2075	12.9	15.8
	No	7999	8.3	10.1
Previous PCI	Yes	1597	12.0	14.8
	No	8477	8.8	10.6
Previous CABG	Yes	957	16.0	18.2
	No	9117	8.6	10.5
Time from symptom onset	≤24 hours	3902	8.3	10.8
	>24 hours	5976	10.1	11.5
GP IIb/IIIa inhibitor use	Yes	5183	9.9	11.9
	No	4891	8.7	10.5
Stent type	DES ≥1	5225	9.2	10.9
	BMS only	4362	9.2	11.6
	None	401	11.7	14.9

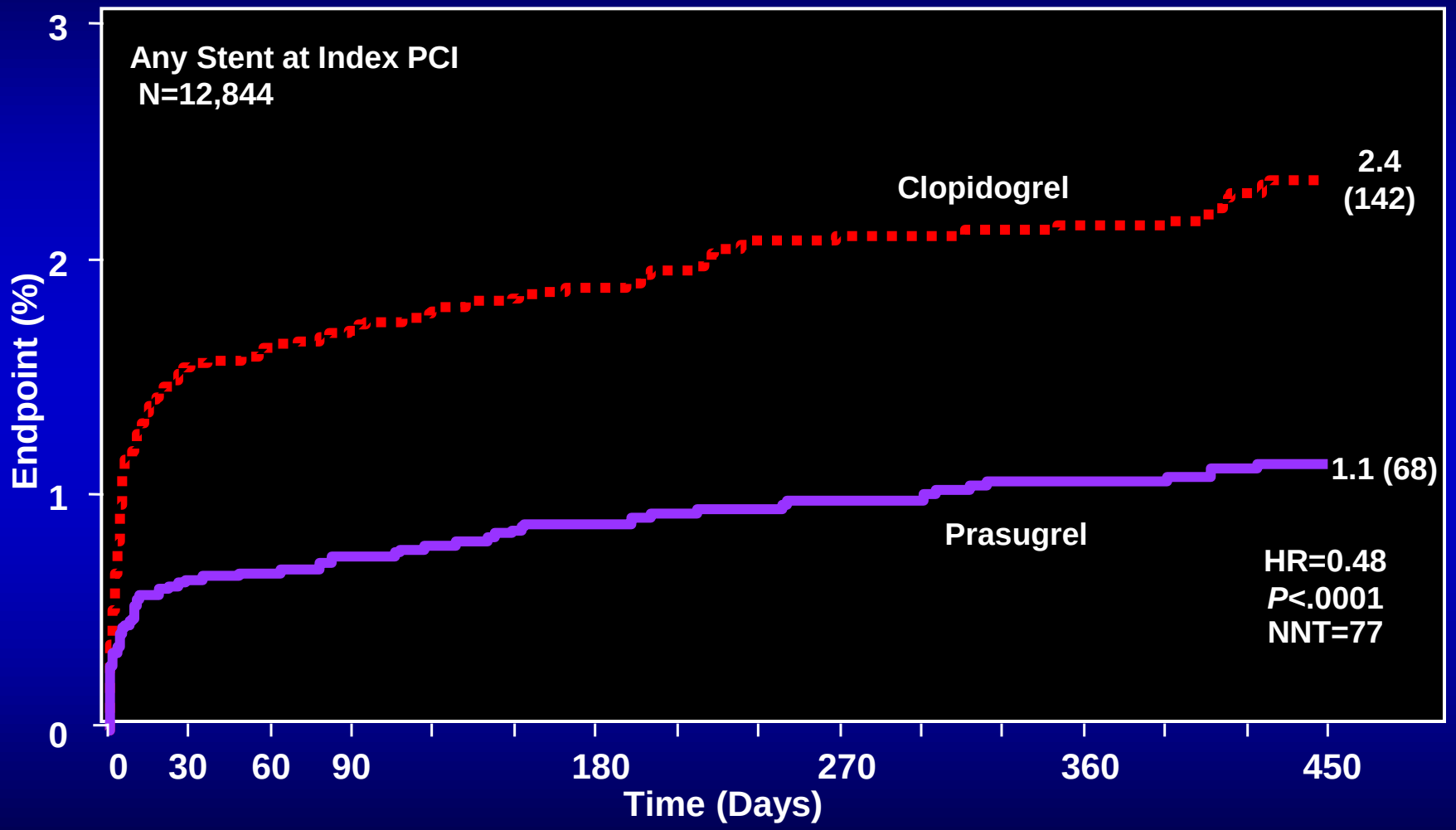


Based on Kaplan-Meier estimates.

Effient Full Prescribing Information.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

TRITON-TIMI 38: Stent Thrombosis (ARC Definite + Probable)



ARC = academic research consortium.

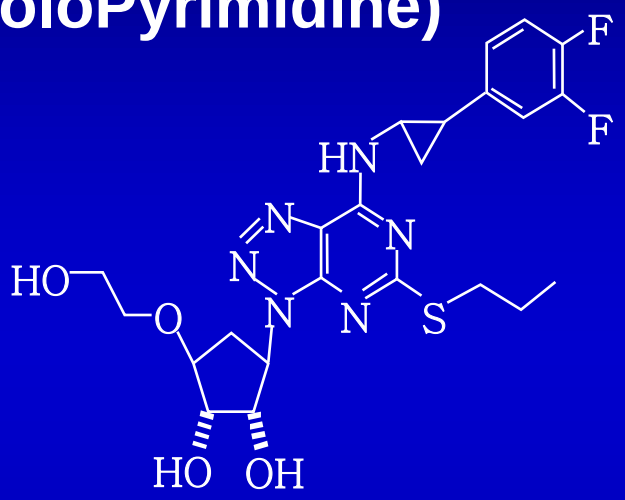
Wiviott SD, et al. *N Engl J Med*. 2007;357:2001-2015.

Appropriate Patient Selection

- Based on TRITON-TIMI 38 data, prasugrel appears to be most appropriate for use in patients with ACS managed with PCI who:
  - Have no history of TIA/stroke
  - Are <75 years of age
  - Weigh ≥60 kg (132 lb)

Ticagrelor (AZD6140)

- A **non-thienopyridine**, in the chemical class CPTP (CycloPentylTriazoloPyrimidine)



- First oral **reversible** ADP $P2Y_{12}$ receptor antagonist
- **Direct** acting via the $P2Y_{12}$ receptor - metabolism not required for activity
- **More potent** platelet inhibitor than clopidogrel

PLATO

Moderate- to high-risk ACS patients (UA/NSTEMI/STEMI, PCI, medically managed, or CABG)

(N=18,000)

ASA + Clopidogrel
300 mg ld/75 mg qd
600 mg ld allowed in PCI

ASA + AZD6140
180 mg ld/90 mg bid

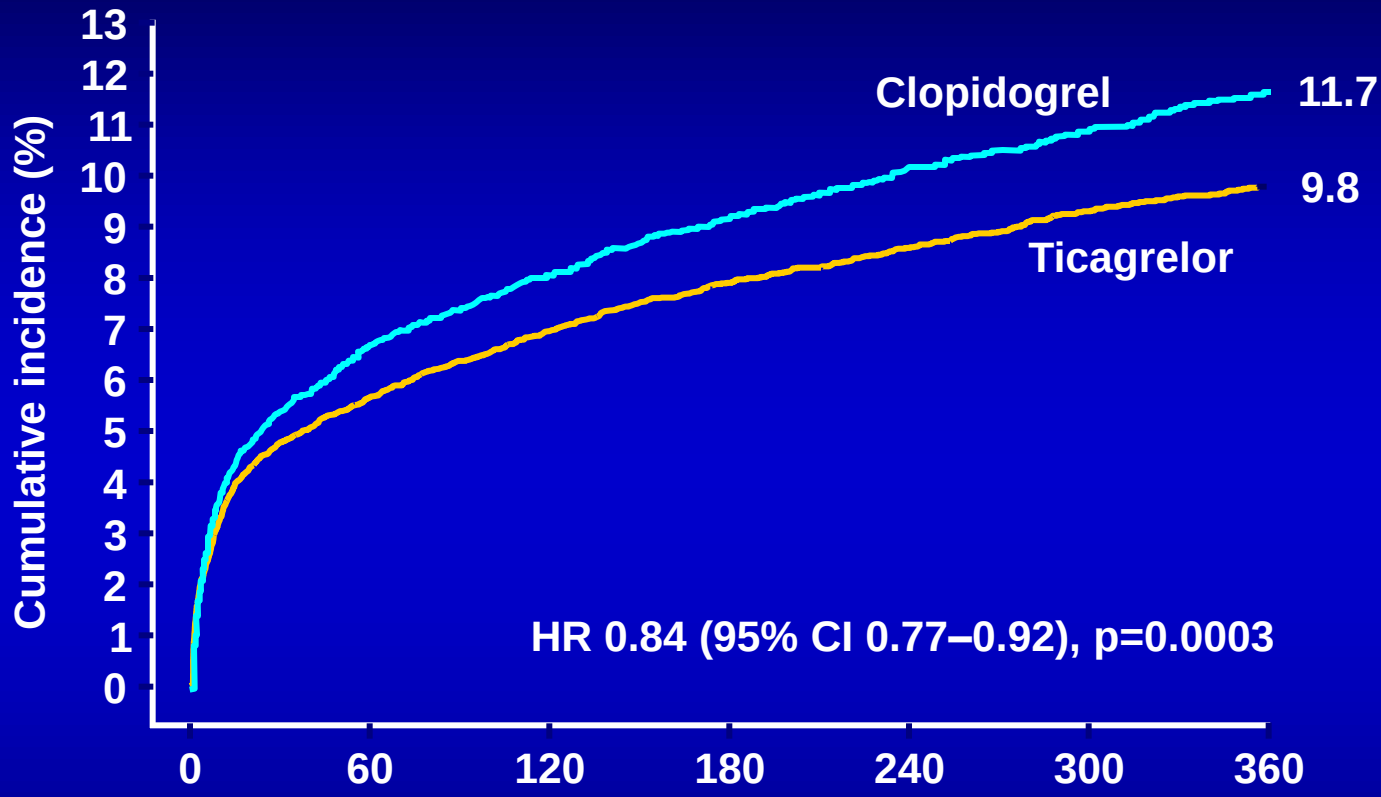
12-month maximum exposure
(Min = 6 mo, Max = 12 mo, Mean = 11 mo)

Primary endpoint:	**CVD/MI/stroke**
Secondary endpoint:	**CVD/MI/stroke/revascularization with PCI; CVD/MI/stroke, severe recurrent ischemia**

ASA = acetylsalicylic acid; bid = twice daily; CVD = cardiovascular disease; ld = loading dose; MI = myocardial infarction; NSTEMI = non-ST-segment elevation MI; qd = once daily; STEMI = ST-segment elevation MI; UA = unstable angina.

ClinicalTrials.gov Identifier: NCT00391872

K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)



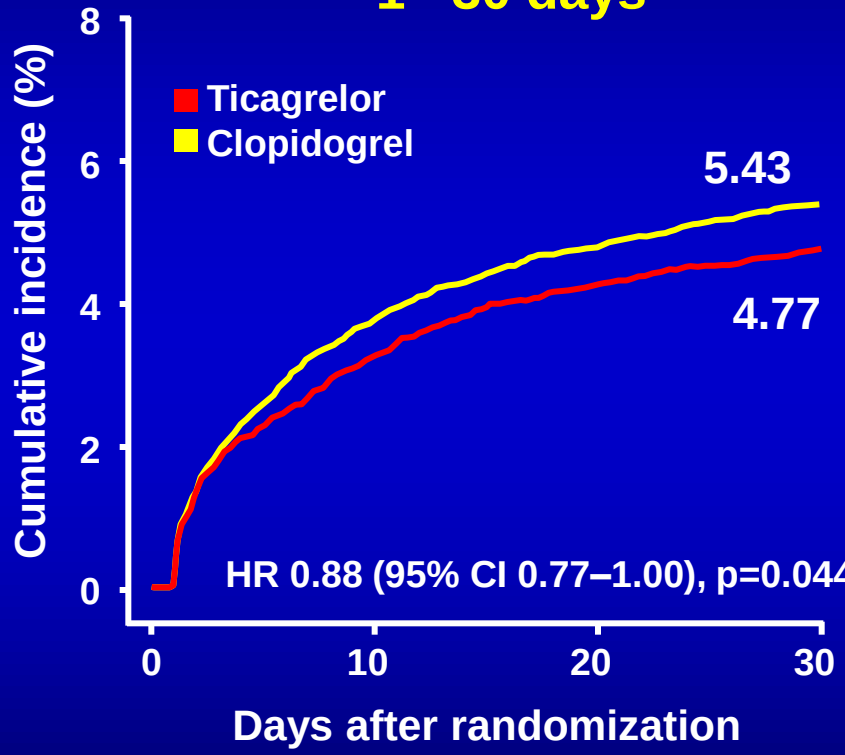
No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

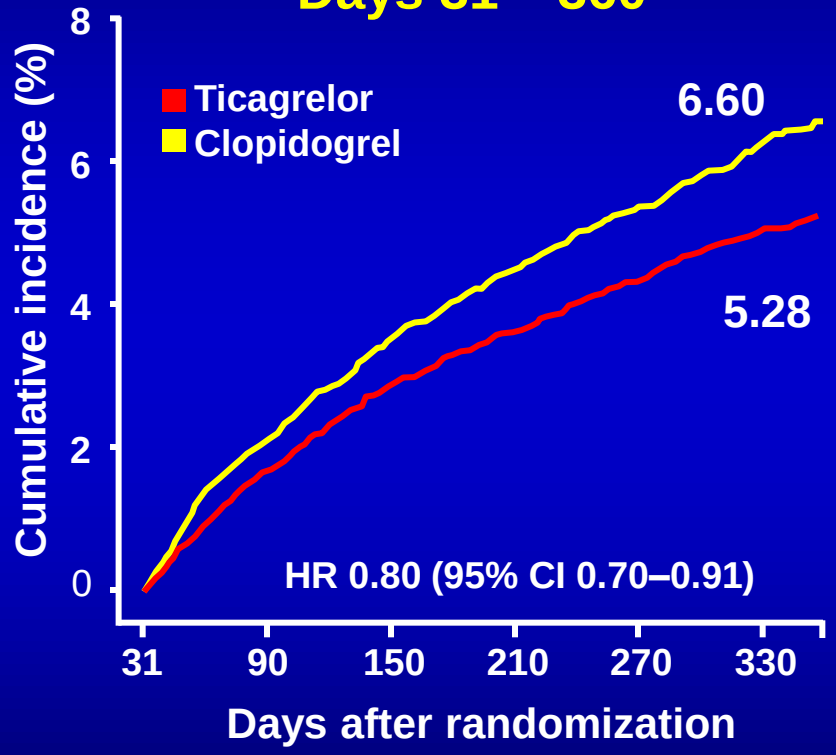
Wallentin L et al. *NEJM* Aug 30, 2009

PLATO: Early and Late Effects

Landmark Analysis: 1st 30 days



Landmark Analysis: Days 31 – 360*



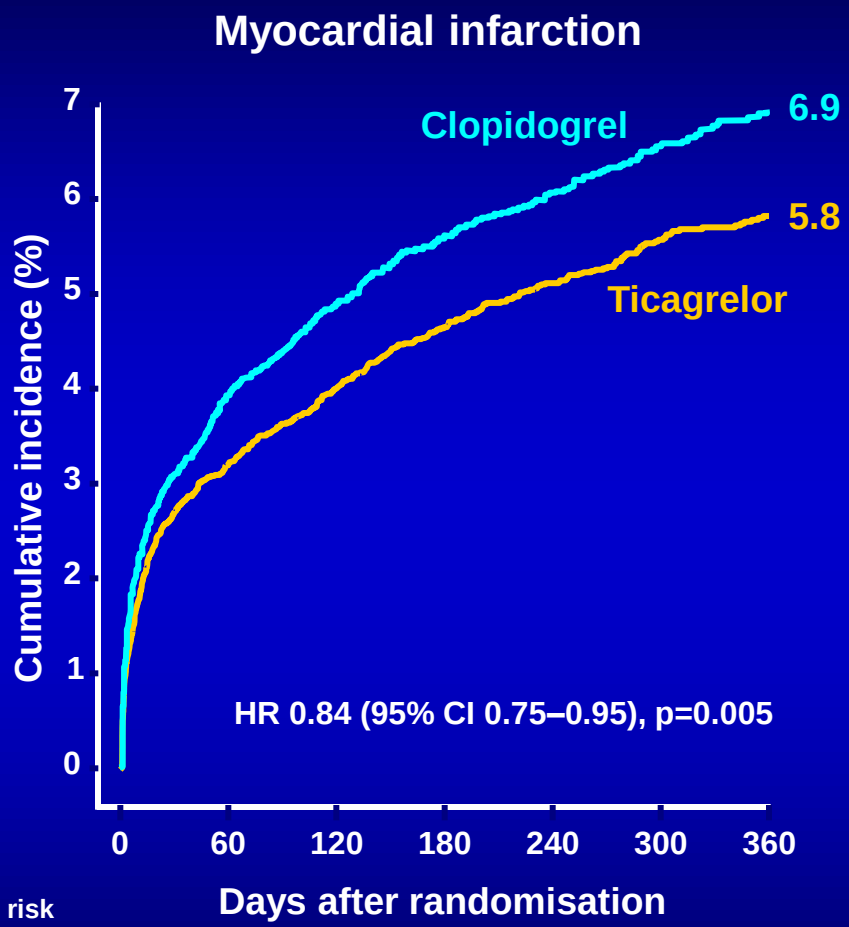
No. at risk

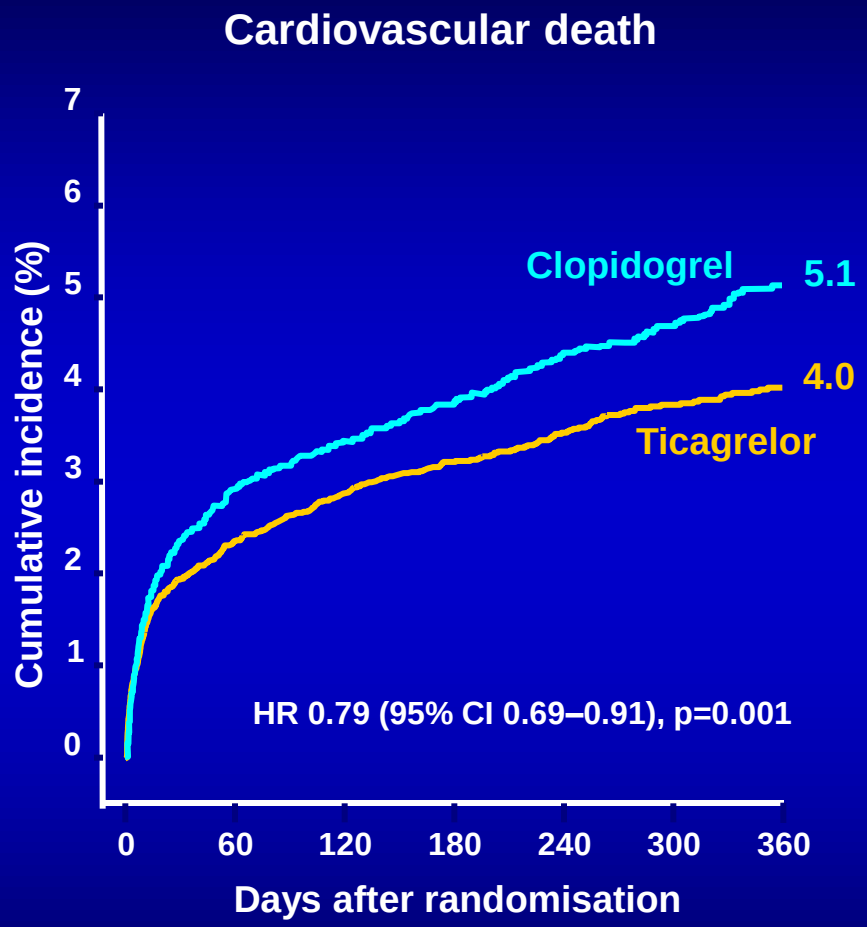
Ticagrelor	9333	8942	8827	8763	8673	8543	8397	7028	6480	4822
Clopidogrel	9291	8875	8763	8688	8688	8437	8286	6945	6379	4751

*Excludes patients with any primary event during the first 30 days

Wallentin L et al. *NEJM* Aug 30, 2009

Secondary efficacy endpoints over time





No. at risk

Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

9,333	8,294	8,822	8,626	7119	5,482	4,419
9,291	8,865	8,780	8,589	7079	5,441	4,364

Wallentin L et al. *NEJM* Aug 30, 2009

Stent thrombosis

	Ticagrelor (n=6,732)	Clopidogrel (n=6,676)	HR for ticagrelor (95% CI)	p value*
Stent thrombosis, %				
Definite	**1.0**	**1.6**	**0.62 (0.45–0.85)**	**0.003**
Probable or definite	**1.7**	**2.3**	**0.72 (0.56–0.93)**	**0.01**
Possible, probable, or definite	**2.2**	**3.1**	**0.72 (0.58–0.90)**	**0.003**

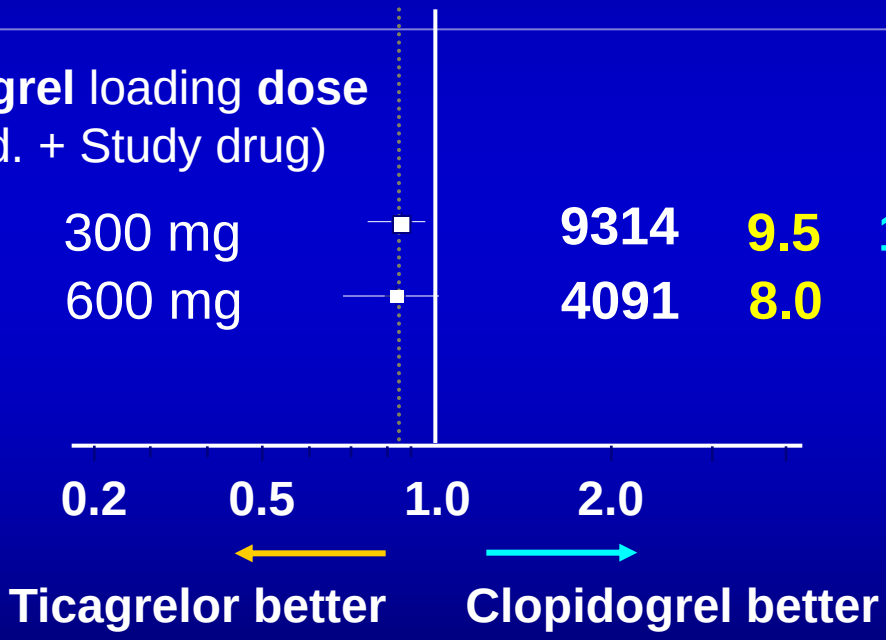
¶ Evaluated in patients with any stent during the study

Time-at-risk is calculated from the date of first stent insertion in the study or date of randomization

* By univariate Cox model

Cannon CP et al. *Lancet 2010*

Primary efficacy endpoint by clopidogrel loading dose

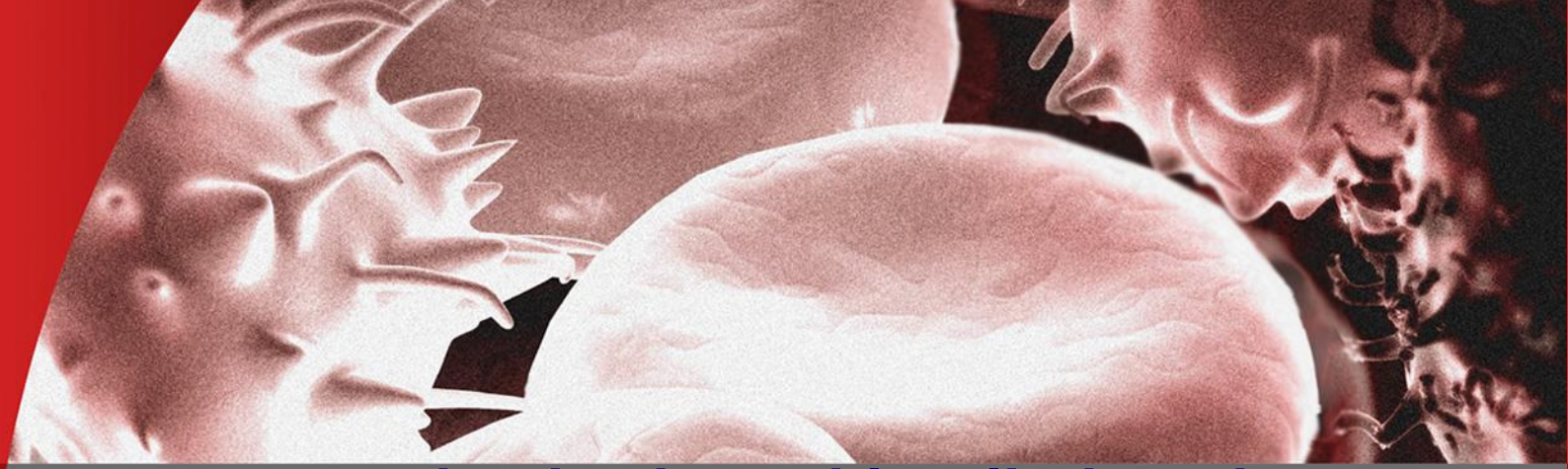


Characteristic	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)	p value (Interaction)
Clopidogrel loading **dose** (Pre-rand. + Study drug)					0.917
300 mg	9314	9.5	11.2	0.85 (0.74, 0.96)	
600 mg	4091	8.0	9.5	0.83 (0.67, 1.03)	

Cannon CP et al. *Lancet 2010*

Other Findings

	Ticagrelor	Clopidogrel	p value
Dyspnoea, %			
Any	13.8	7.8	<0.001
With discontinuation of study treatment	0.9	0.1	<0.001
Ventricular pauses ≥3 seconds, 1 week %	5.8	3.6	0.01
% increase in creatinine from baseline			
At 1 month	10 ± 22	8 ± 21	<0.001
At 12 months	11 ± 22	9 ± 22	<0.001
% increase in uric acid from baseline			
At 1 month	14 ± 46	7 ± 44	<0.001
At 12 months	15 ± 52	7 ± 31	<0.001



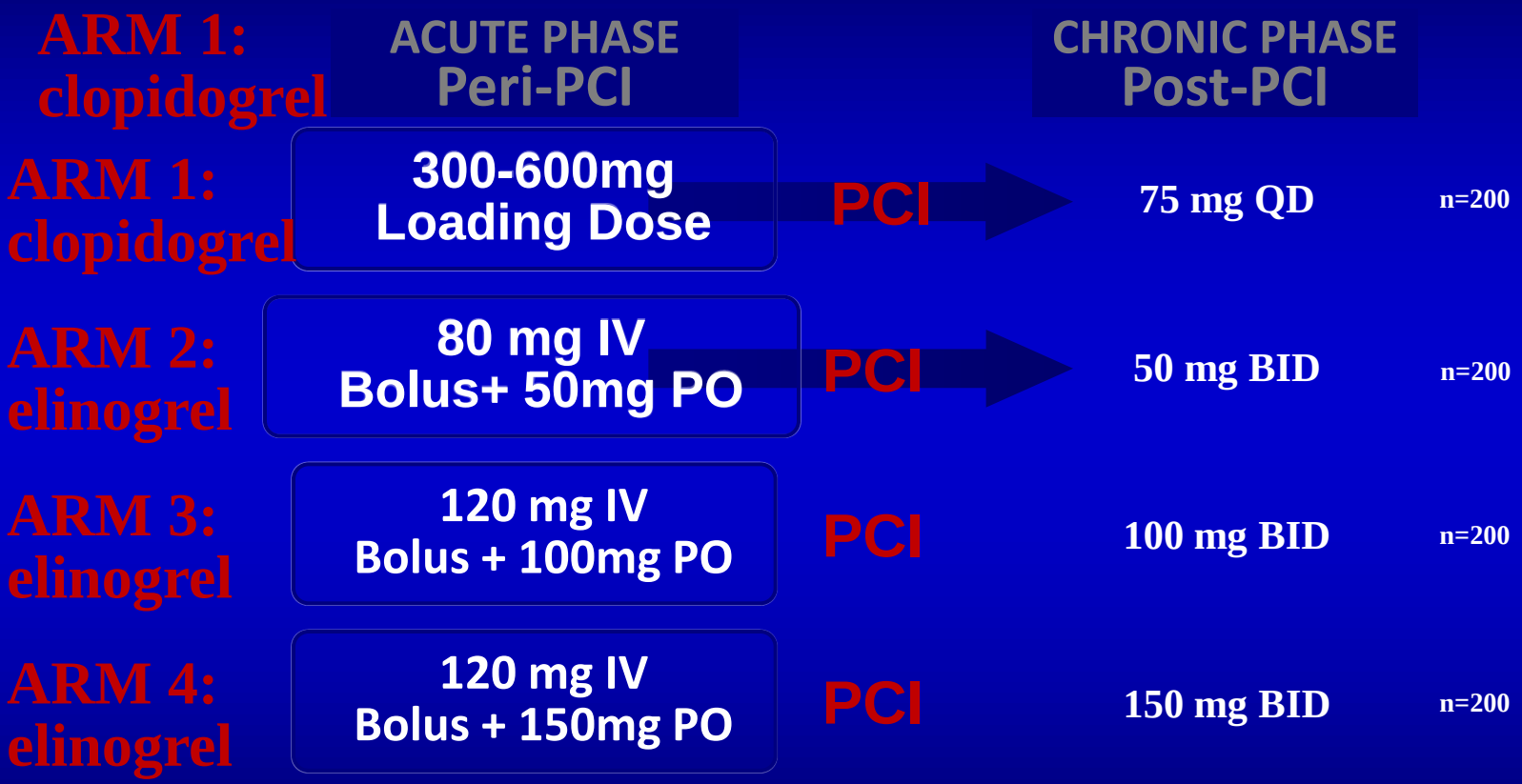
A Randomized, Double-Blind, Active Controlled Trial to Evaluate Intravenous and Oral PRT060128 (elinogrel), a Selective and Reversible $P2Y_{12}$ Receptor Inhibitor, vs. Clopidogrel, as a Novel Antiplatelet Therapy in Patients Undergoing Non-urgent Percutaneous Coronary Interventions (INNOVATE-PCI)

INNOVATE PCI

Properties of Elinogrel

- The only reversible and competitive $P2Y_{12}$ receptor antagonist
- Direct-acting: no metabolic activation required
- Available for intravenous and oral administration, enabling acute and chronic use
- Immediate and near maximal platelet inhibition achieved with IV
- Duration of action
  - Half-life: 12 hours
- No major CYP metabolism – low potential for drug-drug interactions (including PPIs)
- Balanced clearance: 50% renal; 50% hepatic (10% metabolized to pharmacologically inactive metabolite)

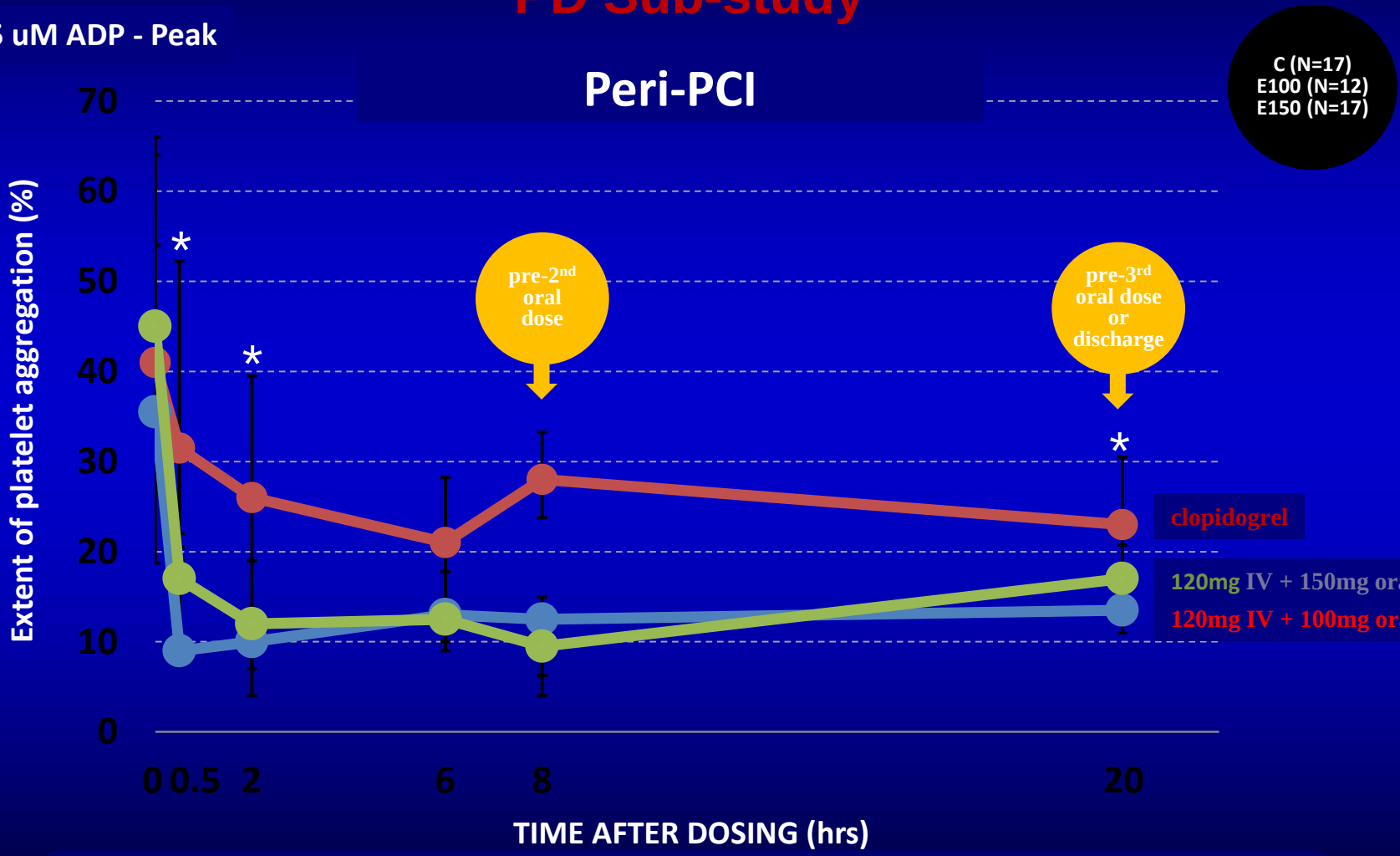
Treatment Schema



- April 8, 2009 (116 pts enrolled): The DSMC recommended discontinuation of the 50 mg BID dose and increasing IV bolus dose to 120 mg as per protocol
- April 16, 2009: Chronic phase extended from 60 days to 120 days of treatment

Pharmacodynamic Effect of Elinogrel vs. Clopidogrel

PD Sub-study



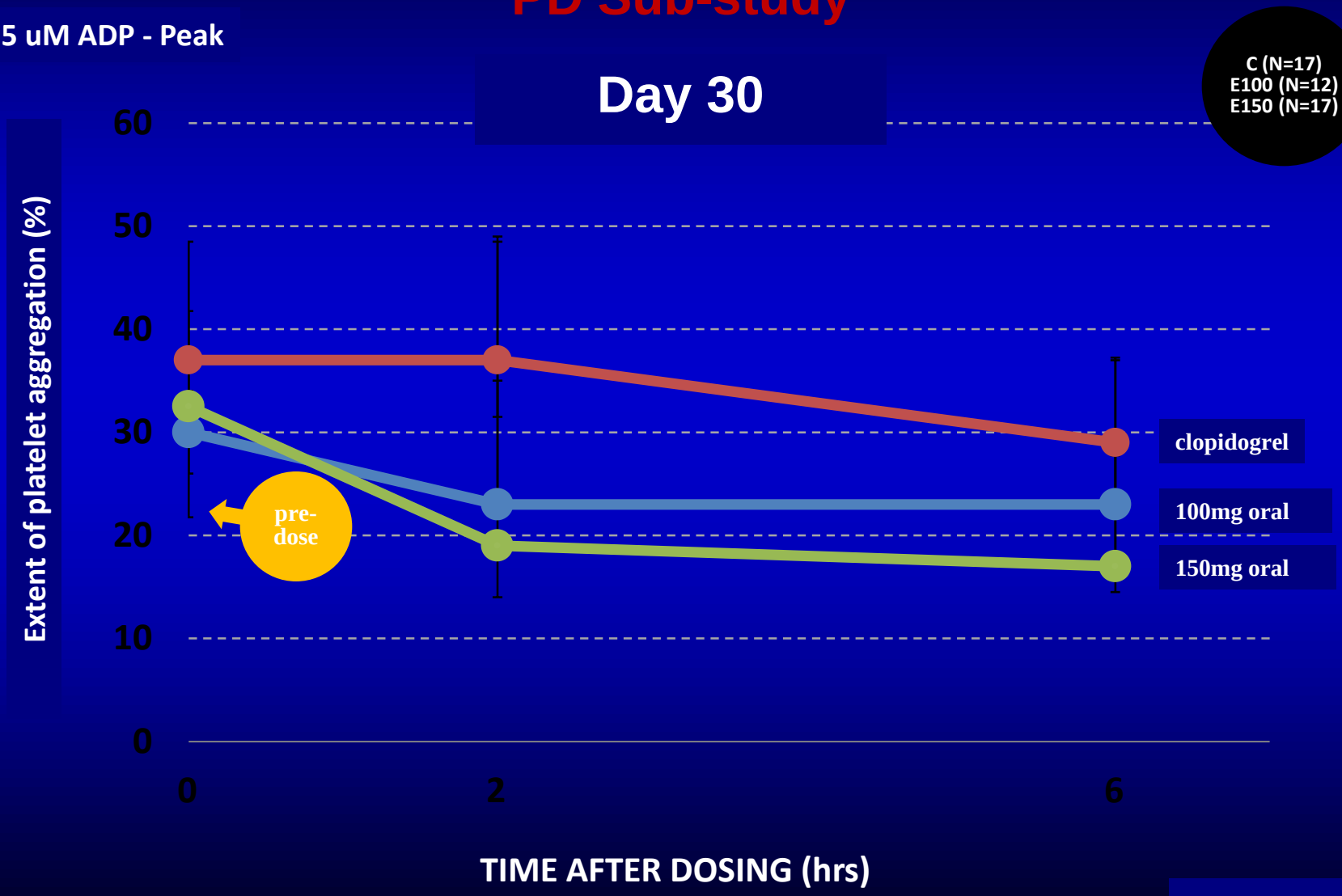
74% of pts represented above were on maintenance clopidogrel

* p<0.025 for both elinogrel vs. clopidogrel comparisons

Median, quartiles

Pharmacodynamic Effect of Elinogrel vs. Clopidogrel

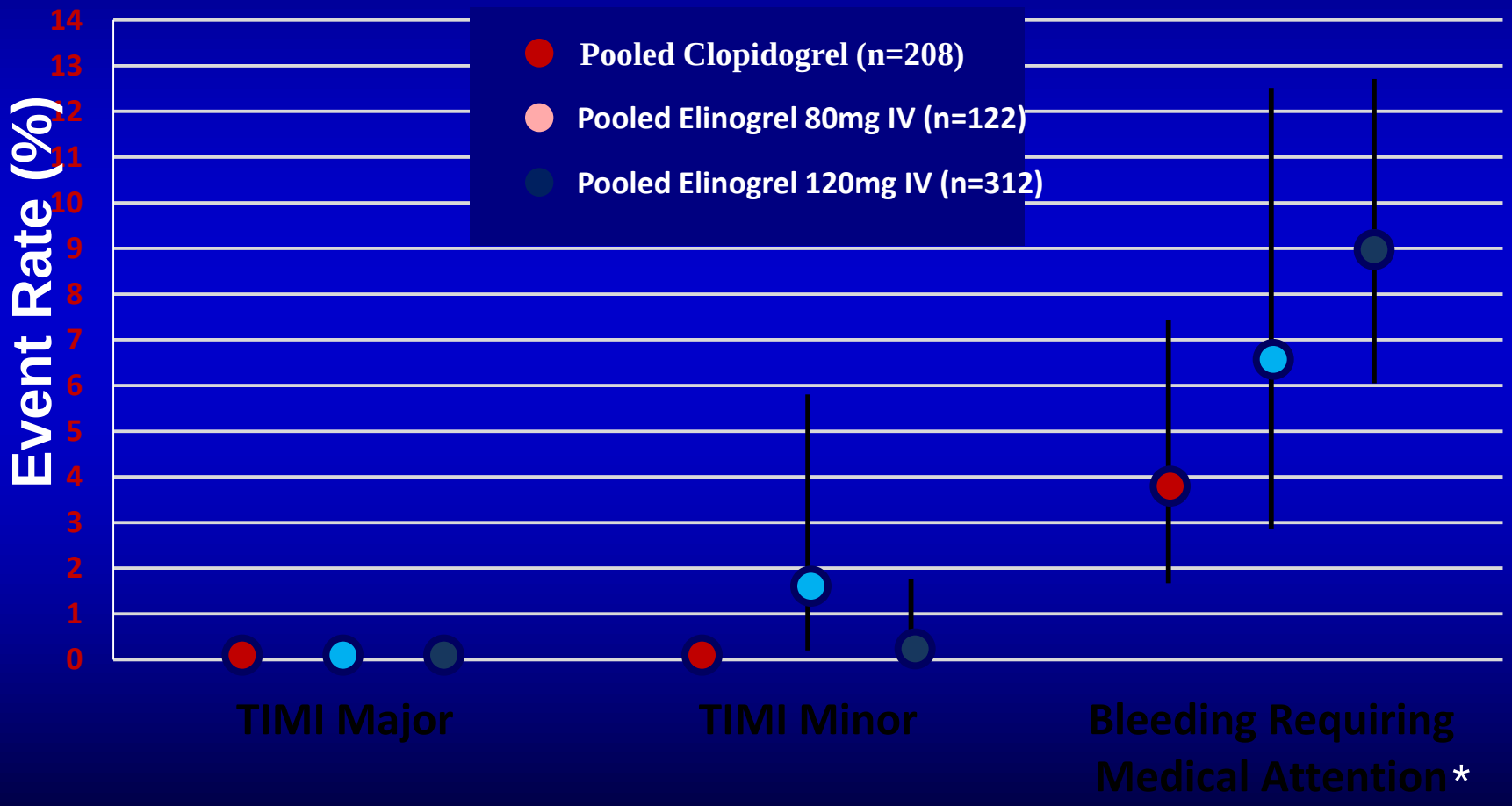
PD Sub-study



Median, quartiles

Bleeding at 24 hrs or d/c – TIMI Scale

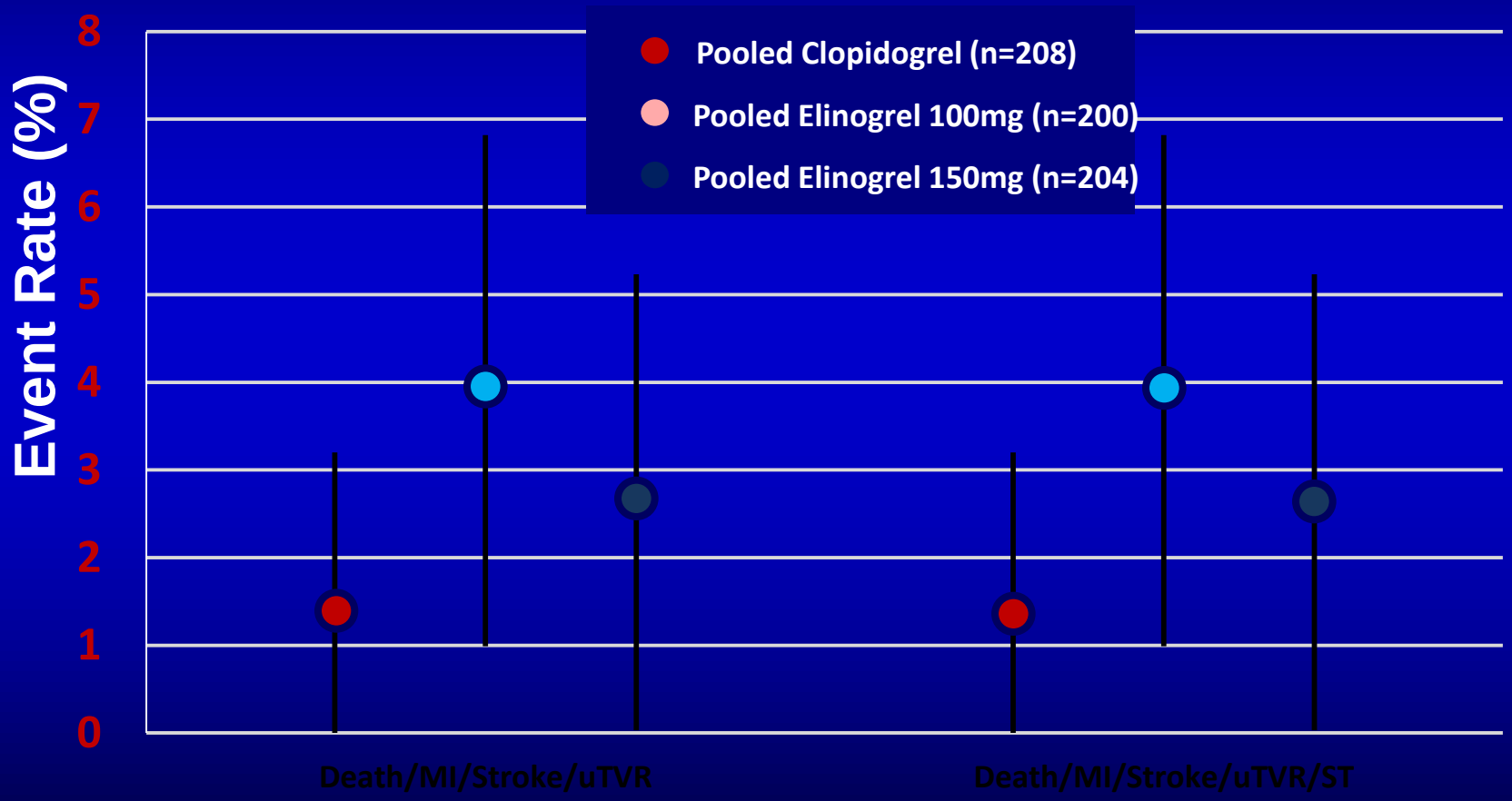
Rates and 95% confidence intervals



* Mainly at access site

Efficacy at 24h-120 Days

Rates and 95% confidence intervals



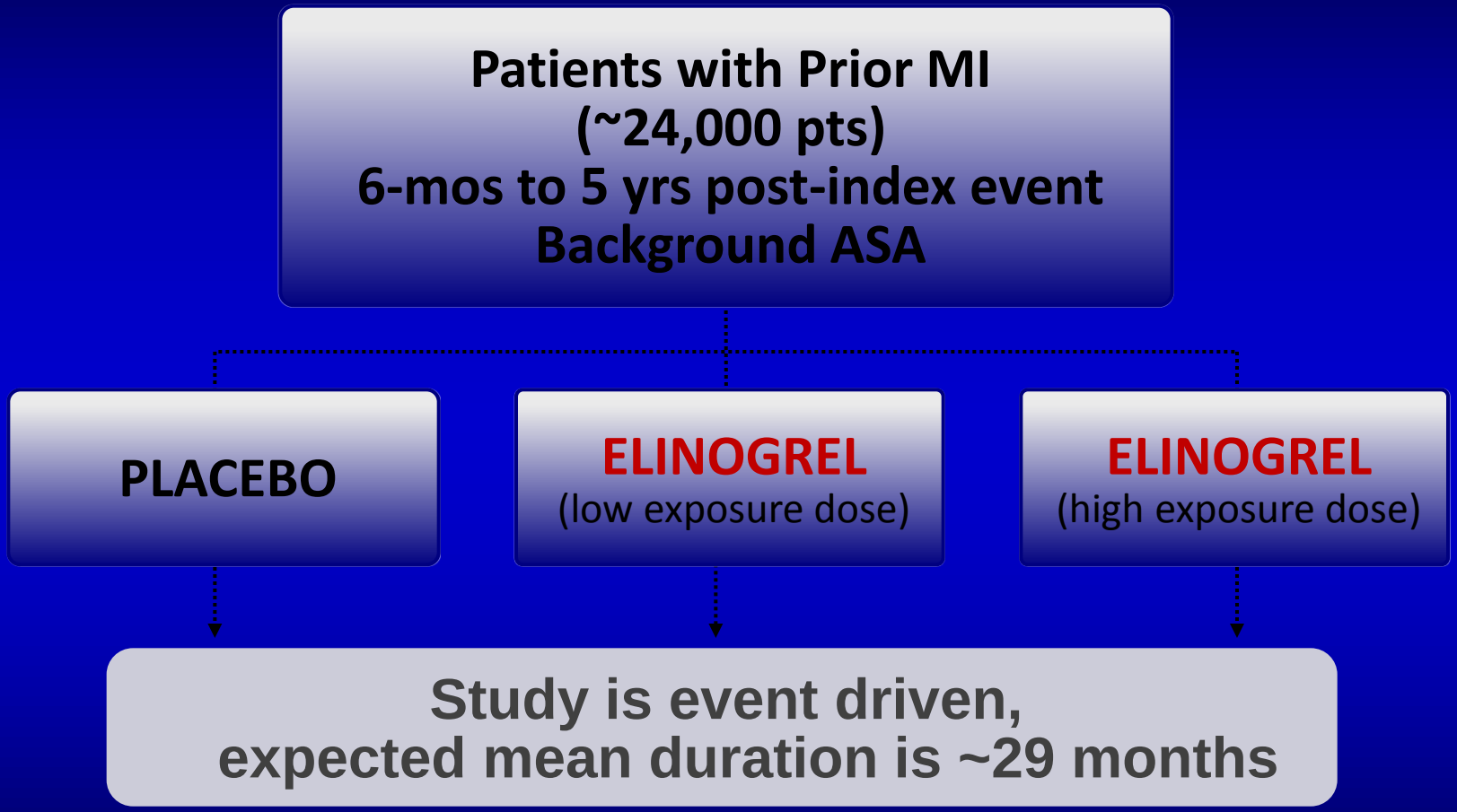
Adverse Events

	Clopidogrel N=208	Pooled elinogrel 100 mg N=201	Pooled elinogrel 150 mg N=207
Any SAE	11.1%	14.9%	12.6%
Drug d/c due to AE or SAE	7.2%	7.5%	10.1%
Dyspnea*	4.3%	15.4%	12.1%
Bradycardia	0.5%	1.0%	0.5%
Syncope	0.5%	1.5%	0.5%
ALT/AST > 3x^	1.0%	4.0%	4.8%
ALT/AST > 5x	0.5%	2.0%	3.4%

*** Dyspnea was generally mild, transient, and infrequently led to discontinuation**

^ Most cases occurred within first 60 days and were asymptomatic; All cases resolved, even when treatment was continued; No Hy's Law cases.

Phase 3 Chronic CHD Trial – Sponsored by Novartis



PRIMARY EFFICACY ENDPOINT:
CV Death, MI, Stroke

Conclusions

- IV and oral elinogrel result in greater and more rapid antiplatelet effect than clopidogrel during both the acute and chronic phase of therapy
- No excess TIMI major or minor bleeding at both the 24-hr and 120-day timepoints
- Dose-dependent trend of increase in less severe bleeds (Bleeding Requiring Medical Attention), mostly occurring at the vascular access site in the peri-procedural period
- No significant differences in efficacy at 24 hrs or 120 days (trial not powered for efficacy)

TRA Background

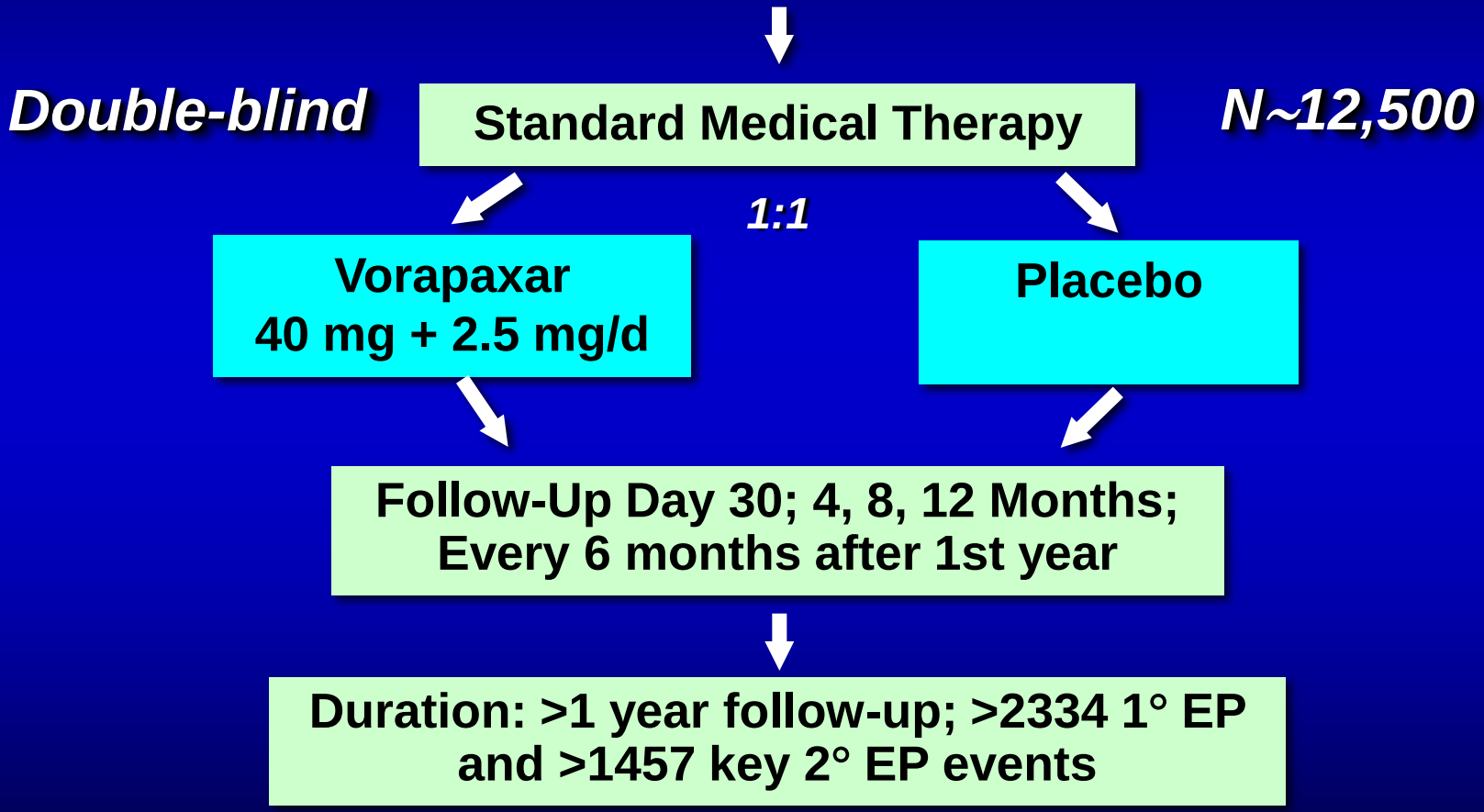
- Vorapaxar is an oral, potent, selective thrombin receptor antagonist (TRA) being developed for the prevention and treatment of atherothrombosis.
- Preclinical and early clinical studies have demonstrated vorapaxar to have antithrombotic properties, with no increase in bleeding time or clotting times (aPTT, PT, ACT).

Galbulimima baccata

- Himbacine derivative
- Bark of the Australian Magnolia
- Found in the tropical zones of eastern Malaysia, New Guinea, northern Australia and the Solomon Islands.

TRA•CER Study Design

Patients with high-risk Non-ST-Segment Elevation Acute Coronary Syndrome ≤24h of symptoms



1° EP:CV Death/MI/stroke/hosp for RI/urgent coronary revasc.
2° EP: CV Death/MI/stroke

Thrombin Receptor Antagonism

TRA Development
~37,500 patients

Vorapaxar | **Placebo** | **Vorapaxar** | **Placebo**

F/U: 30 Days, 4, 8, 12 months and 6 months thereafter
F/U 1 yr minimum

Primary EP: Composite of CV Death, MI, Stroke, RI with Rehosp, Urgent Revascularization

Primary EP: Composite of CV Death, MI, Stroke and Urgent Revascularization

Thank you!