



XVII Jornadas **SOLACI** *6º Región Cono Sur*

**ANTIAGREGACIÓN PLAQUETARIA,
RESISTENCIA AL CLOPIDOGREL, NUEVAS
DROGAS**

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Elección de los antiagregantes plaquetarios en los SCA si ST
Debemos Cambiar nuestras practicas?

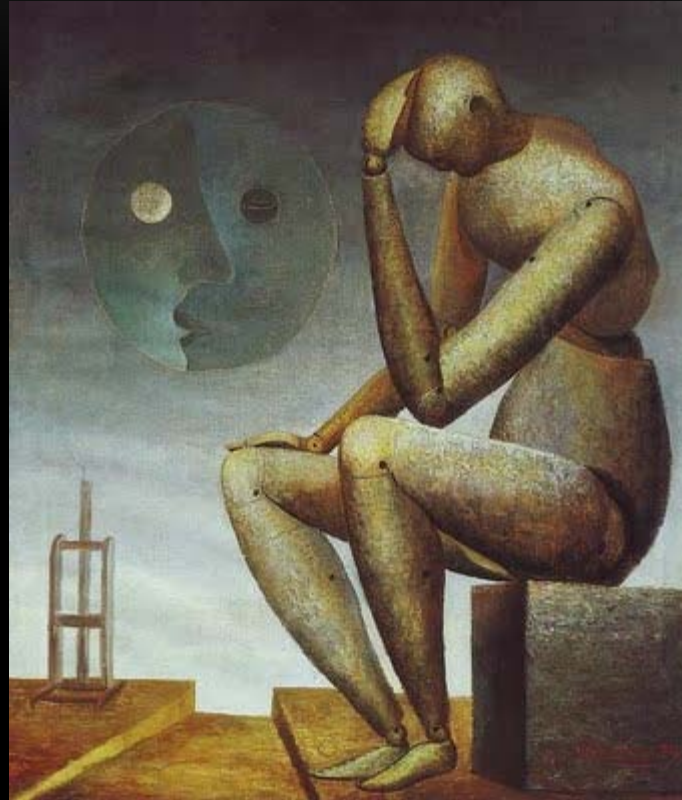
ANTIAGREGACIÓN PLAQUETARIA, RESISTENCIA AL CLOPIDOGREL, NUEVAS DROGAS

Antiagregantes y Stent. Que no sabemos?

Riesgo isquémico vs Hemorrágico

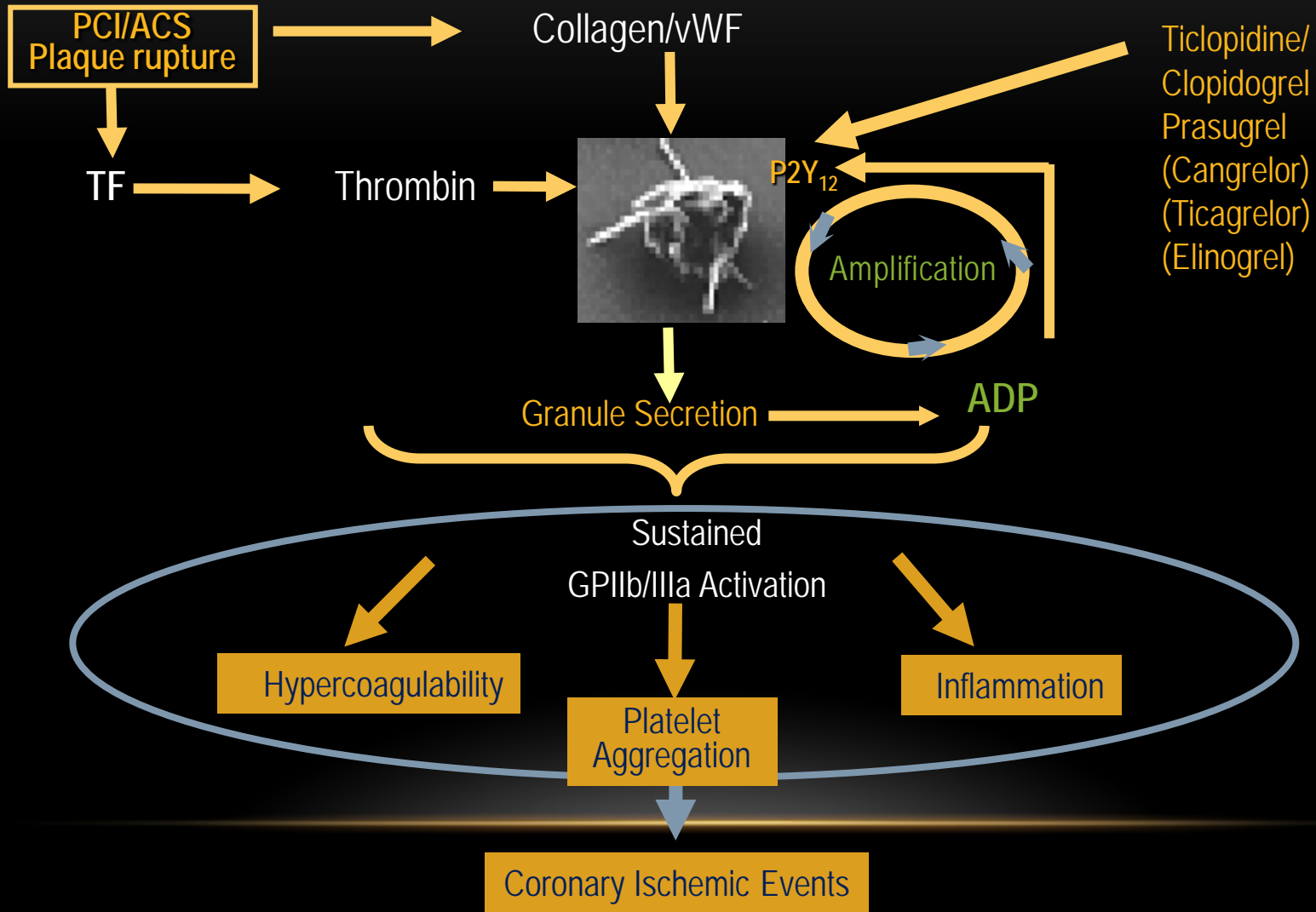
Doble antiagregación plaquetaria post ATC primaria

Que es lo que sabemos

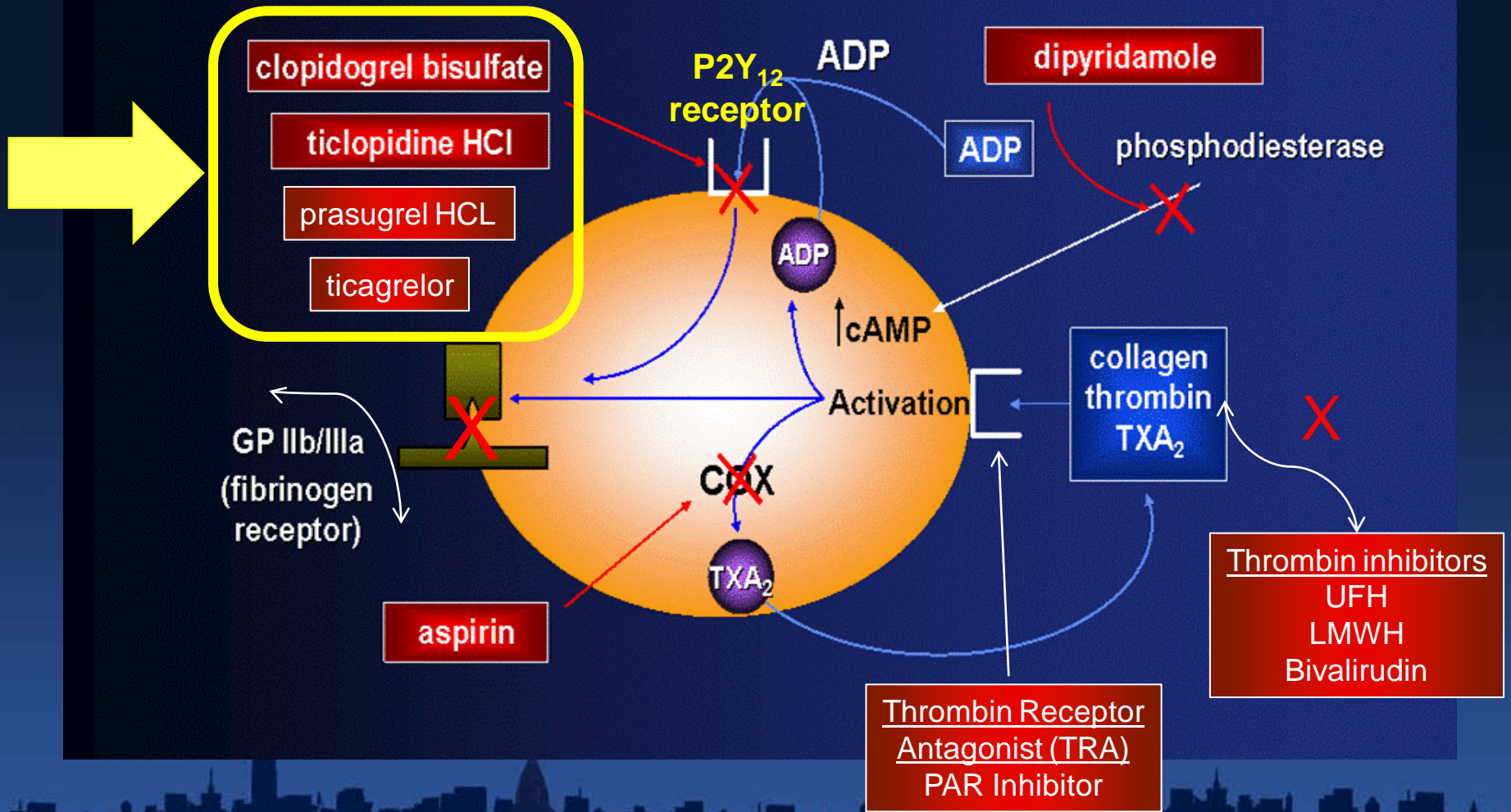


CORONARY ISCHEMIC/THROMBOTIC EVENTS-

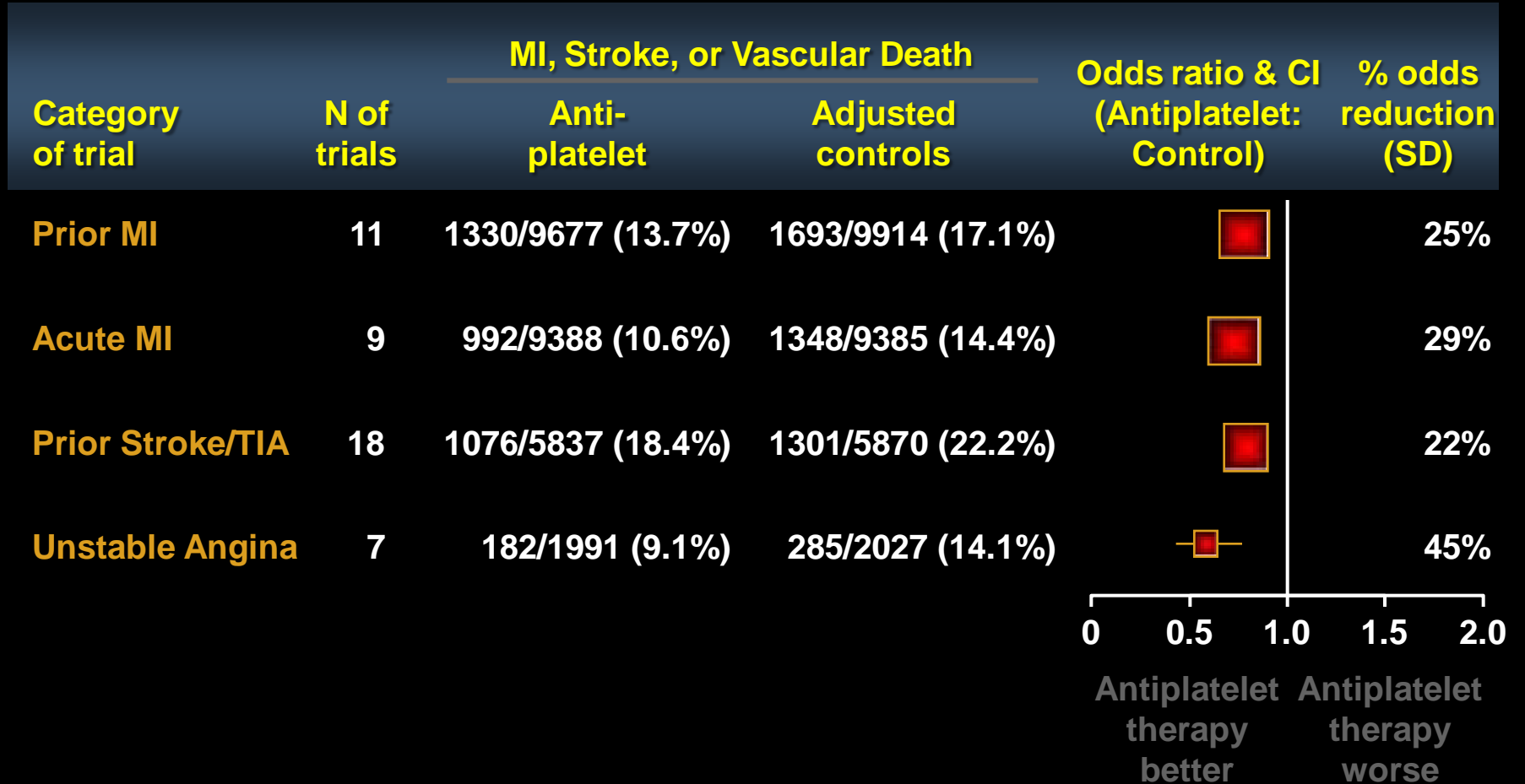
A "PLATELET-CENTRIC" PROBLEM!!!!



Antiplatelet Therapies: Mechanisms of Action



ANTI-PLATELET THERAPY IN ACS

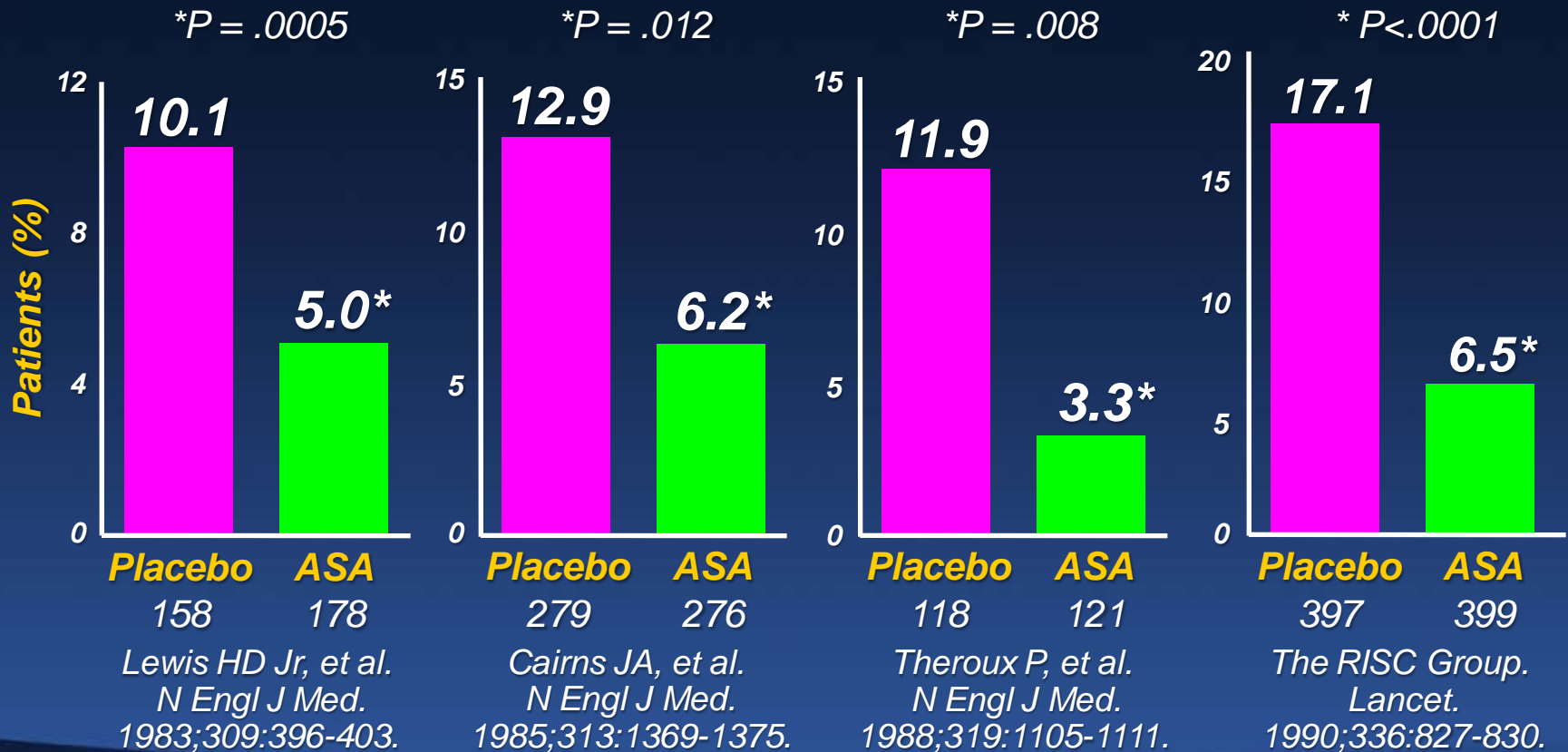


65 aspirin trials

Antiplatelet Trialists' Collaboration.
 BMJ 1994;308:81-106

Aspirin in UA/Non-ST-elevation MI

Death or MI





ASA Dose Comparison Primary Outcome and Bleeding

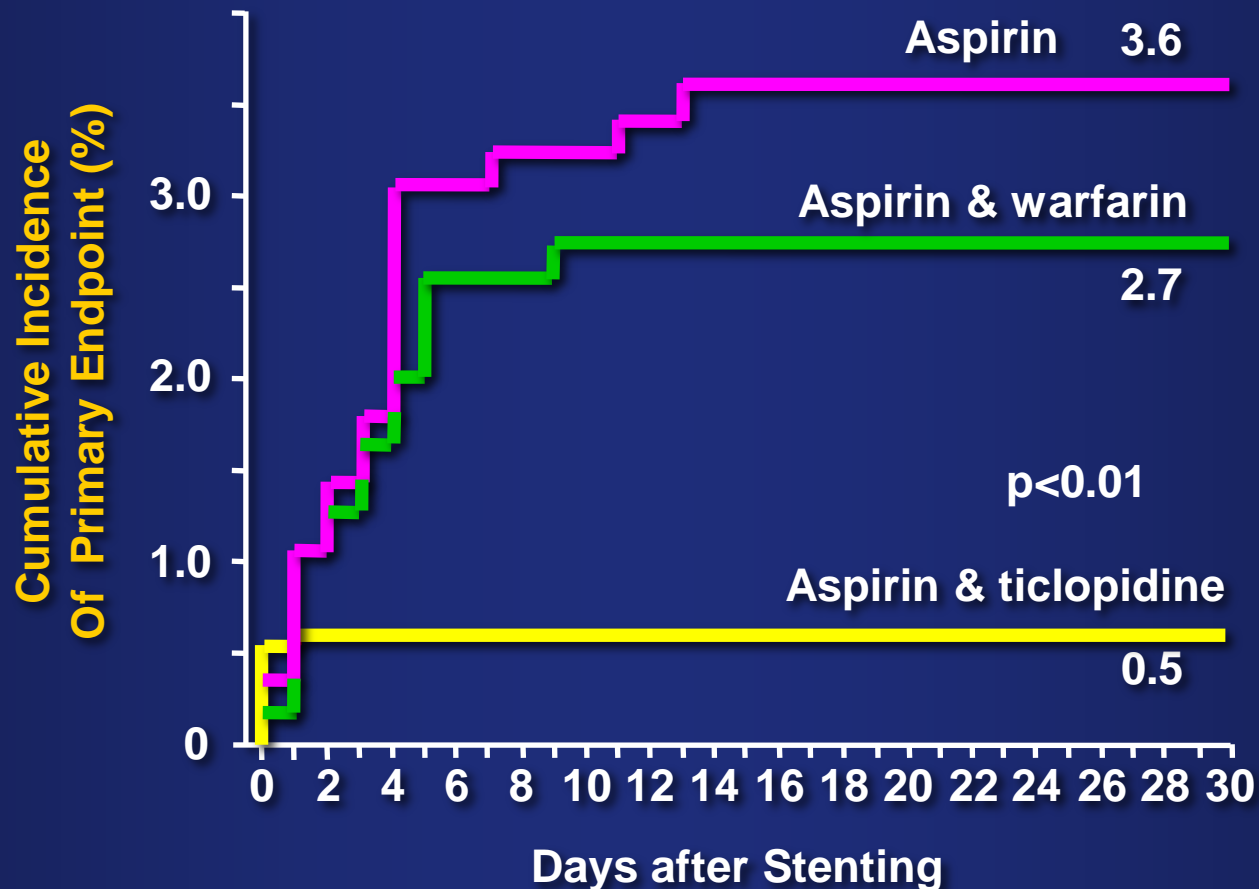
	ASA 75-100 mg	ASA 300-325 mg	HR	95% CI	P
CV Death/MI/Stroke					
PCI (2N=17,232)	4.2	4.1	0.98	0.84-1.13	0.76
No PCI (2N=7855)	4.7	4.4	0.92	0.75-1.14	0.44
Overall (2N=25,087)	4.4	4.2	0.96	0.85-1.08	0.47
Stent Thrombosis	2.1	1.9	0.91	0.73-1.12	0.37
TIMI Major Bleed	1.03	0.97	0.94	0.73-1.21	0.71
CURRENT Major Bleed	2.3	2.3	0.99	0.84-1.17	0.90
CURRENT Severe Bleed	1.7	1.7	1.00	0.83-1.21	1.00

GI Bleeds: 30 (0.24%) v 47 (0.38%), P=0.051

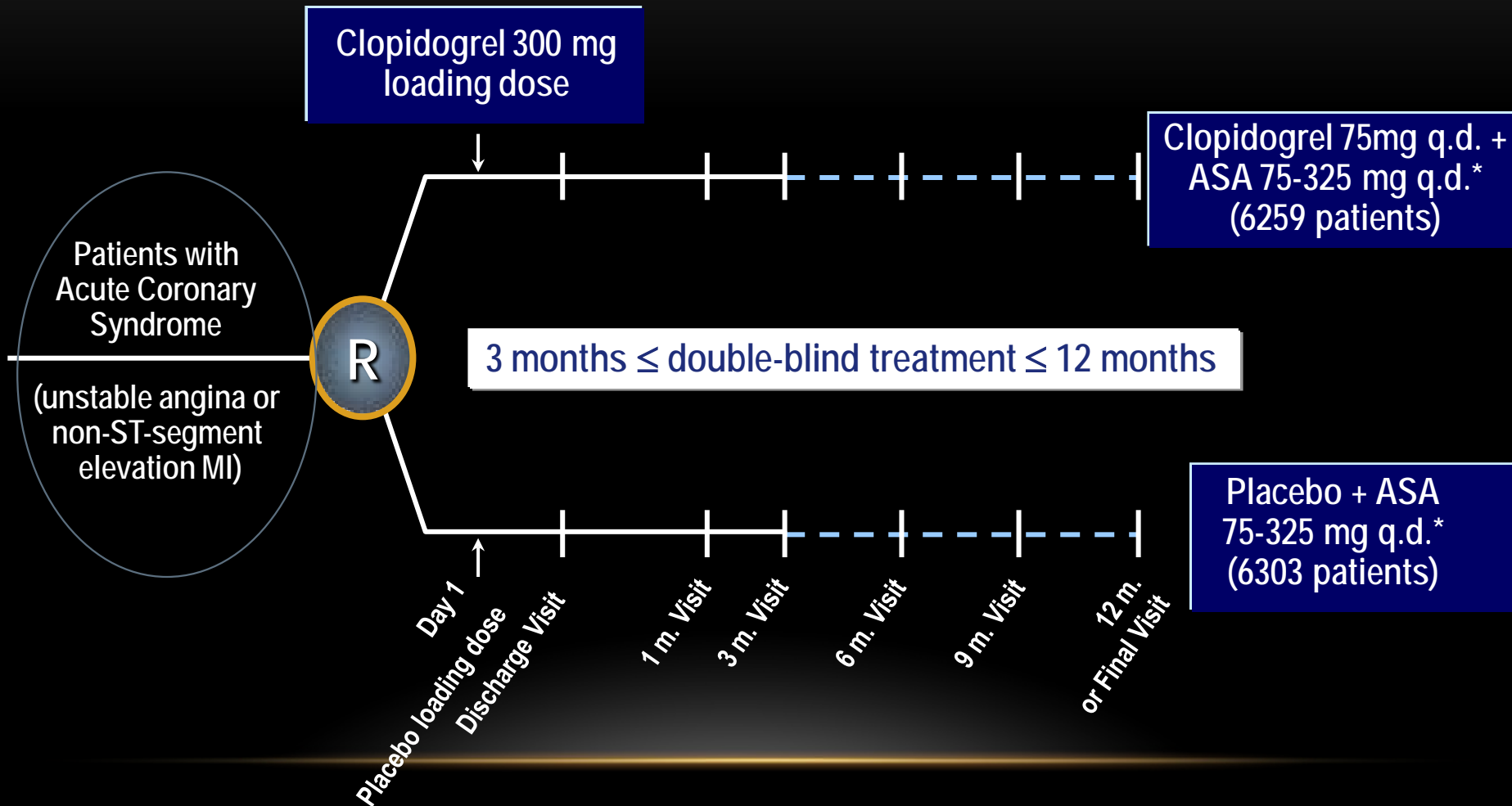
No other significant differences between ASA dose groups

STARS: DAPT with Aspirin and a Thienopyridine Reduces Thrombotic Events after PCI

Primary Endpoint: Death, MI, TLR or thrombosis at 30 days



CURE STUDY DESIGN



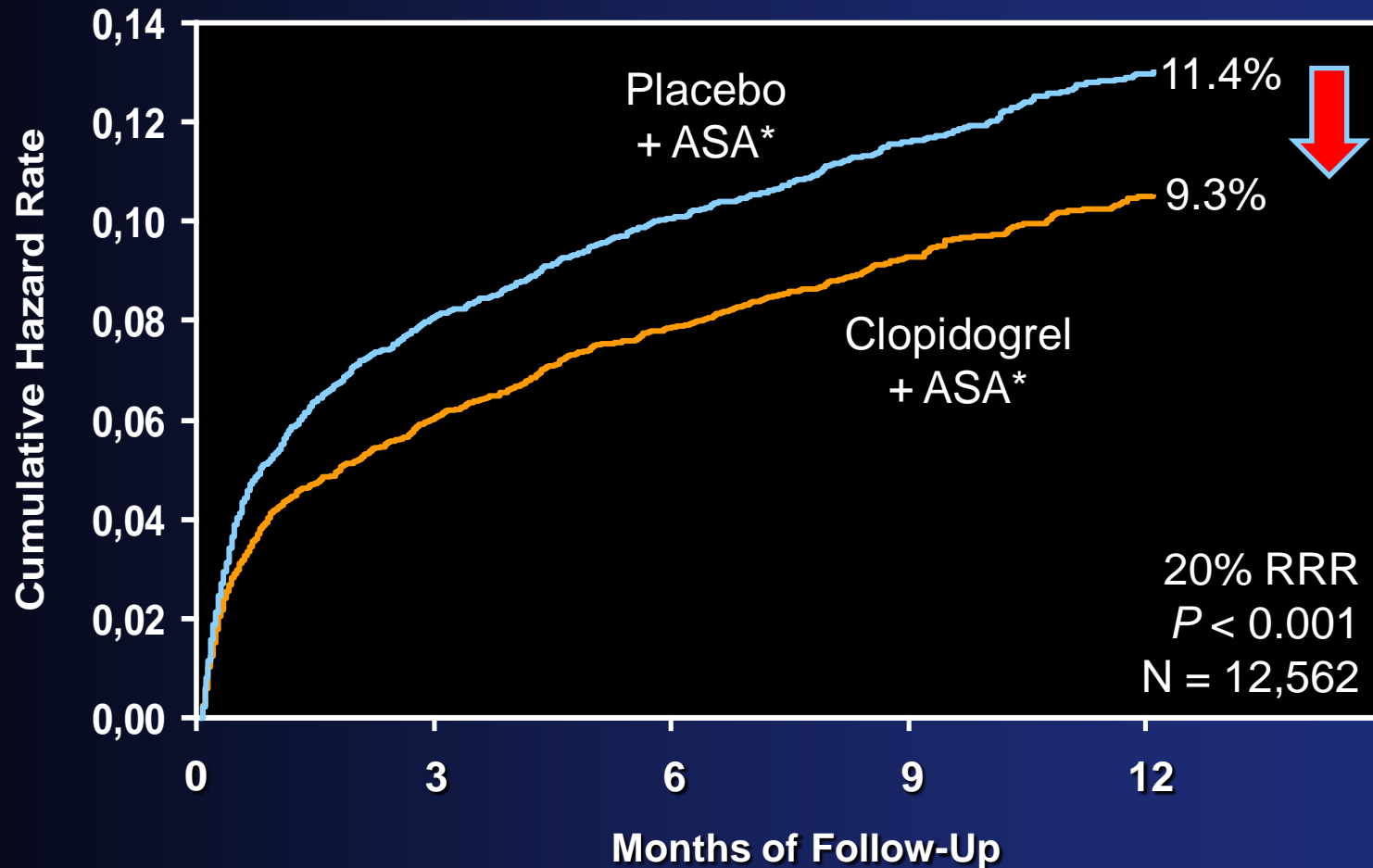
R = Randomization

* In combination with other standard therapy

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

CURE

Primary End Point - MI/Stroke/CV Death

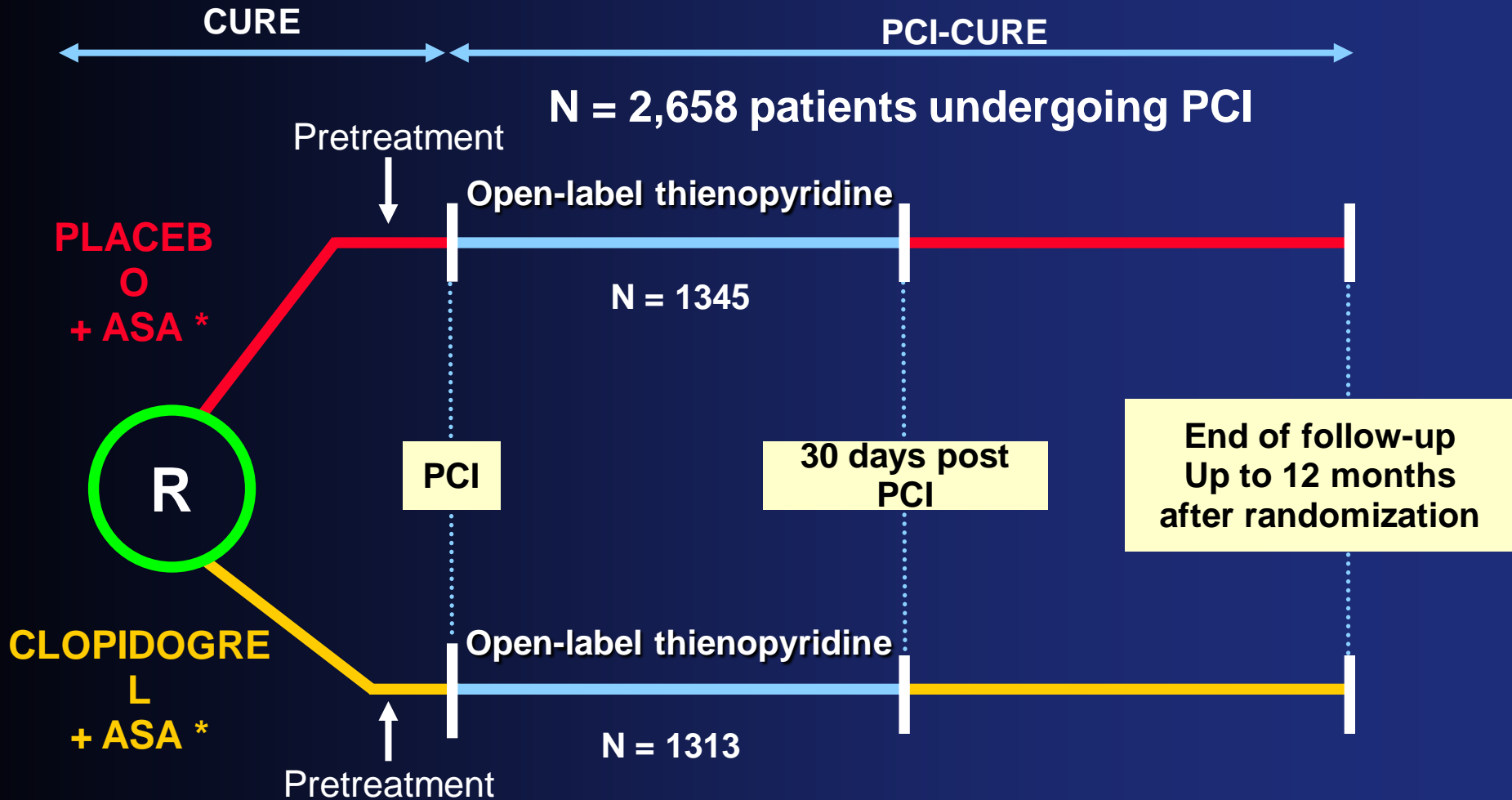


* In combination with standard therapy

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

PCI-CURE

Study Design



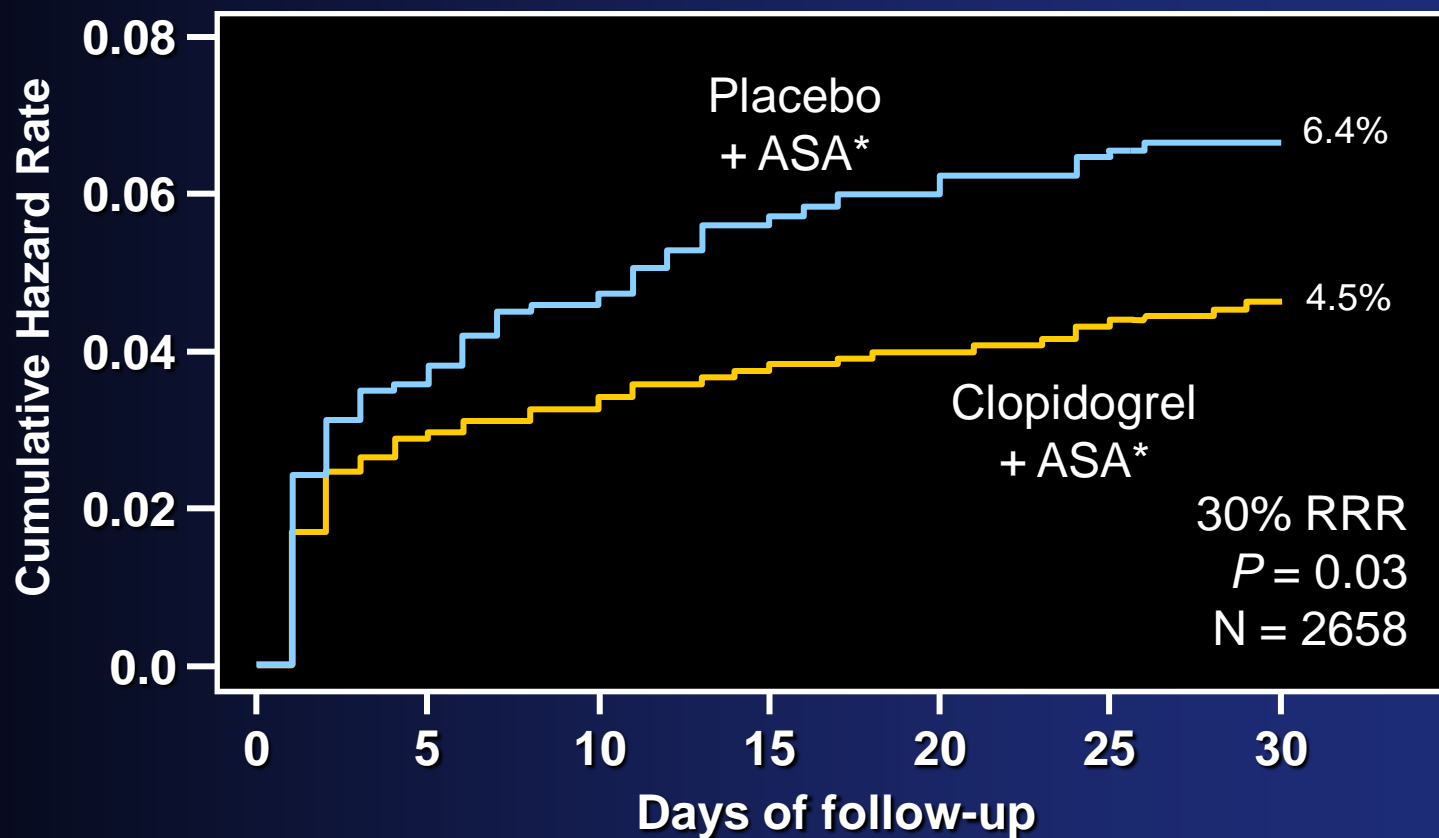
* In combination with standard therapy

Mehta, SR. et al for the CURE Trial Investigators. *N Engl J Med.* 2001;345:494-502.

PCI-CURE

30 Day Results

Composite of cardiovascular death, MI, or urgent revascularization

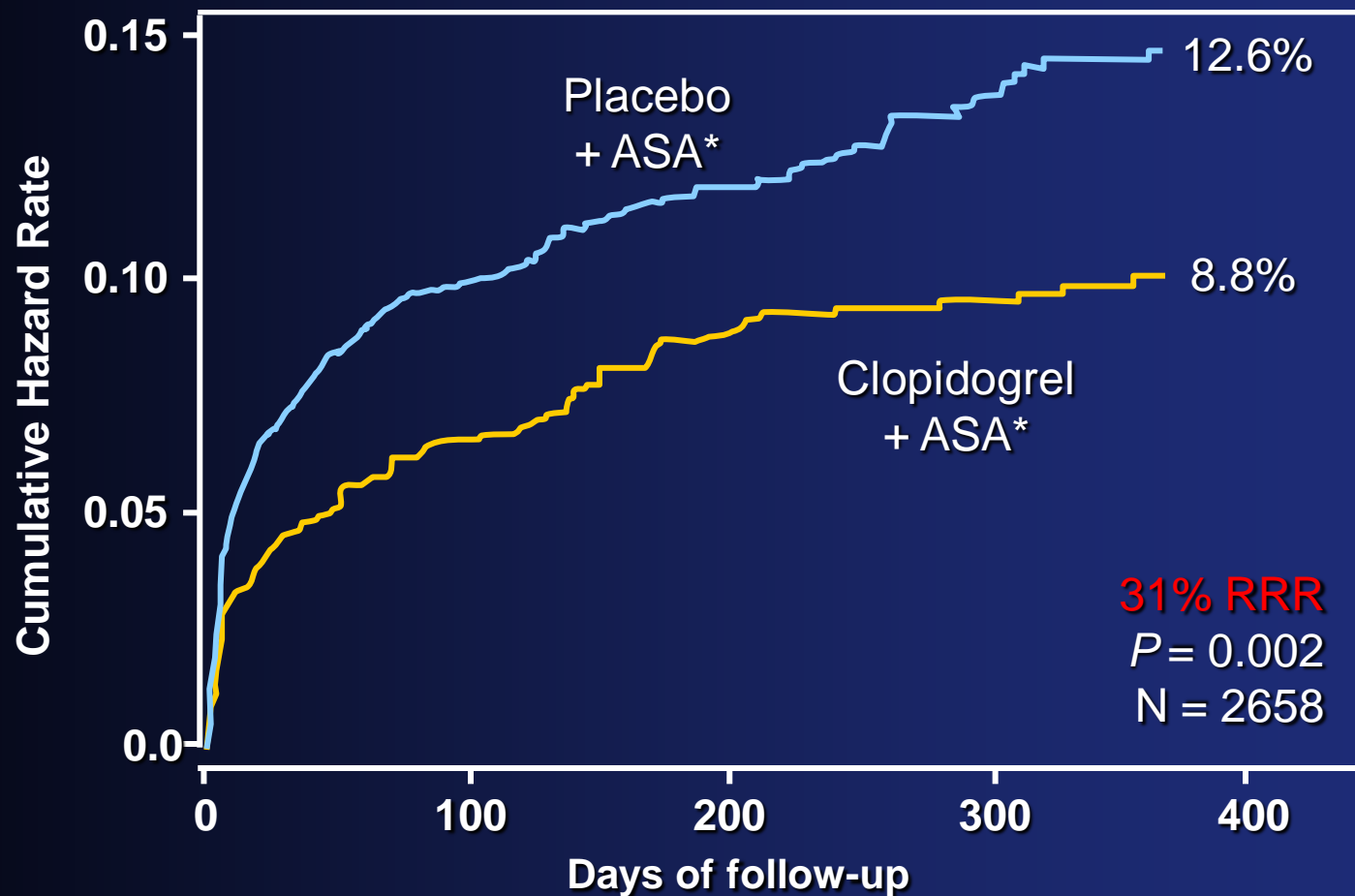


* In combination with standard therapy

Mehta, SR. et al for the CURE Trial Investigators. *Lancet*. August 2001;21:2033-41.

Overall Long-Term Results

Composite of cardiovascular death or MI from randomization to end of follow-up

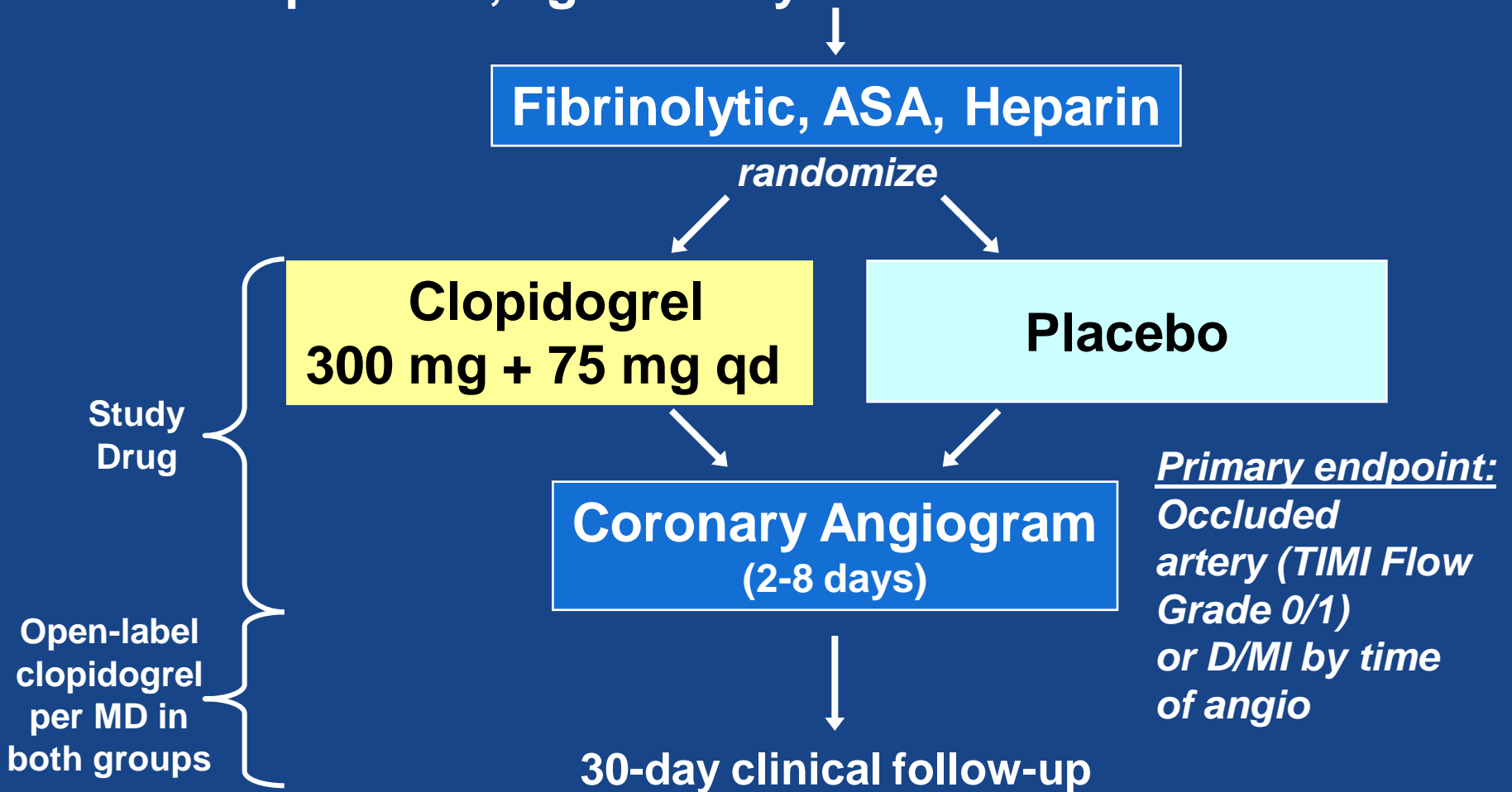


* In combination with standard therapy

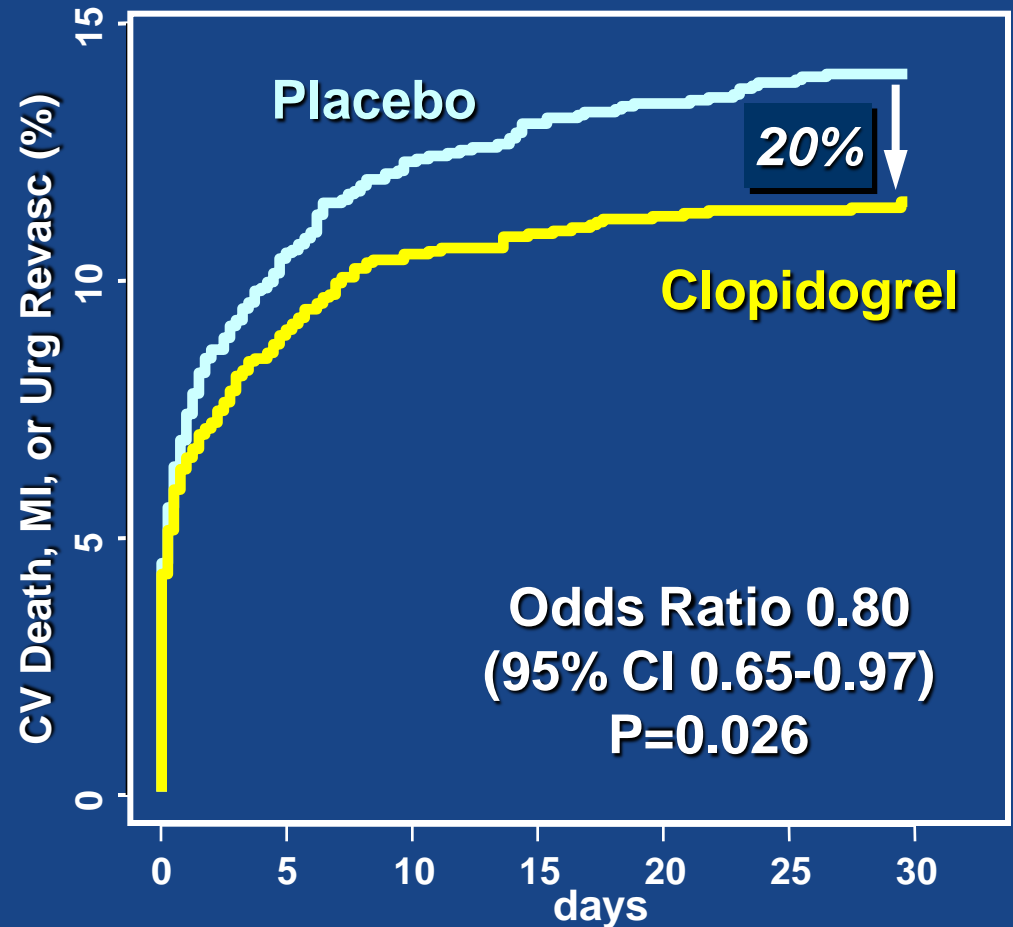
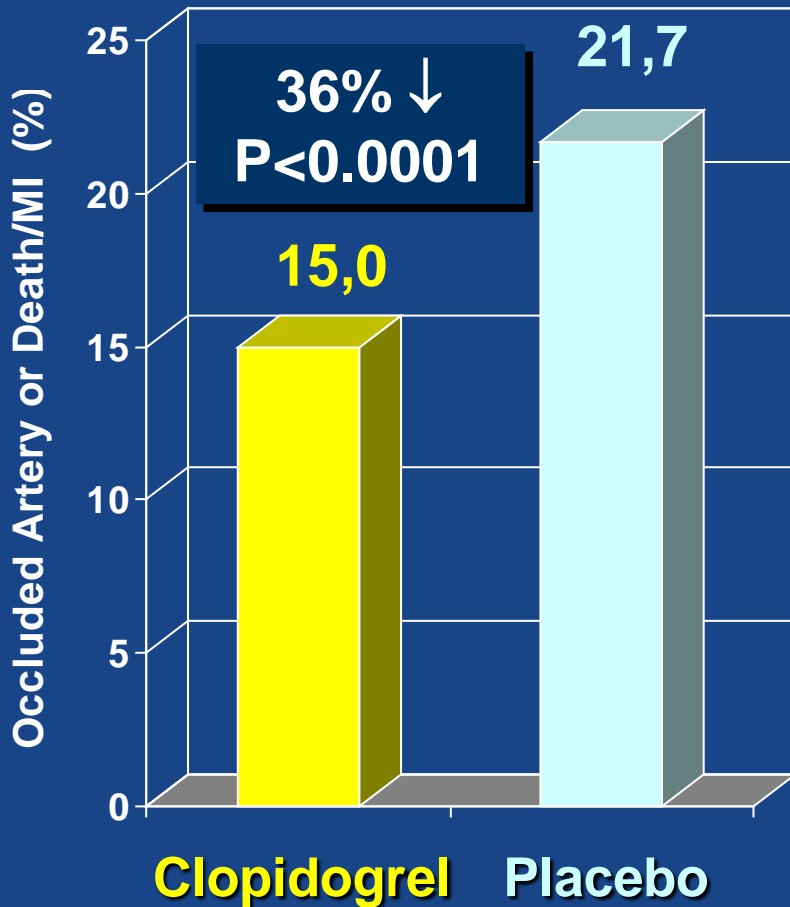
Mehta, SR. et al for the CURE Trial Investigators. *Lancet*. August 2001.

Clopidogrel in STEMI

Double-blind, randomized, placebo-controlled trial in 3491 patients, age 18-75 yrs with STEMI < 12 hours

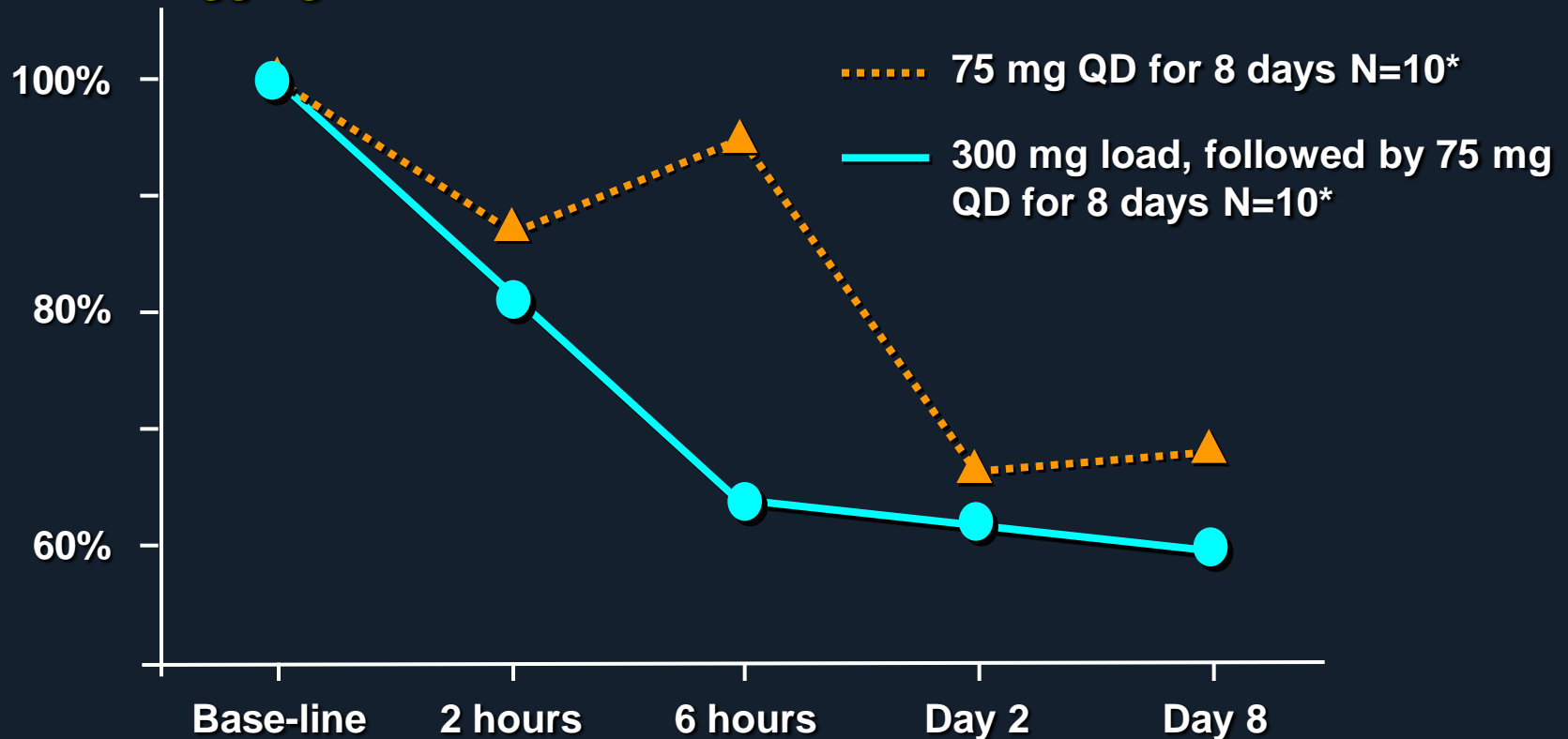


Clopidogrel in STEMI



Pharmacodynamics of Clopidogrel: Loading Dose of 300 mg vs. 75 mg QD

**% inhibition of 5 μ M ADP-
induced aggregation**

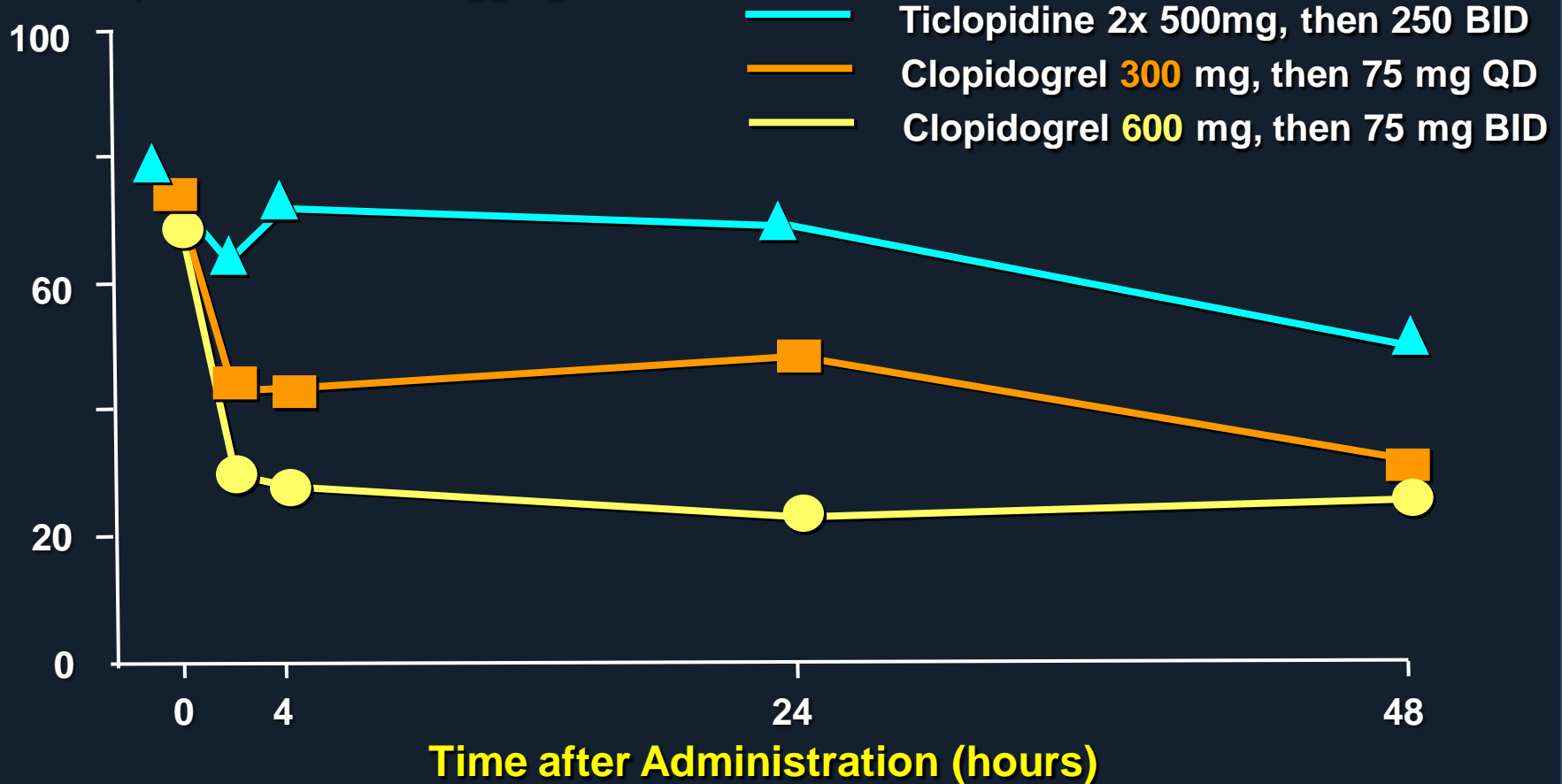


* All patients with stable arterial disease

Helft G. Arterioscler Thromb Vasc Biol 2000;20:2316-21

Clopidogrel LD: Is Higher Dosage Better?

% of 20 μ M ADP-induced aggregation



Study Design, Flow and Compliance

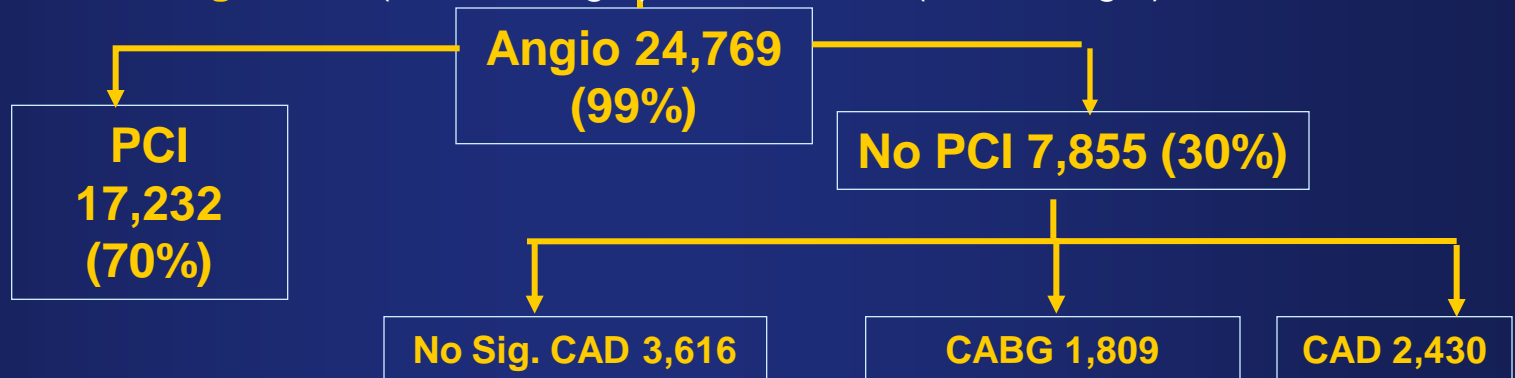
25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

- ✓ Planned Early (<24 h) Invasive Management with **intended PCI**
- ✓ Ischemic ECG Δ (80.8%) or \uparrow cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):

CLOPIDOGREL: Double-dose (600 mg then 150 mg/d x 7d then 75 mg/d) **vs Standard dose** (300 mg then 75 mg/d)

ASA: High Dose (300-325 mg/d) **vs Low dose** (75-100 mg/d)



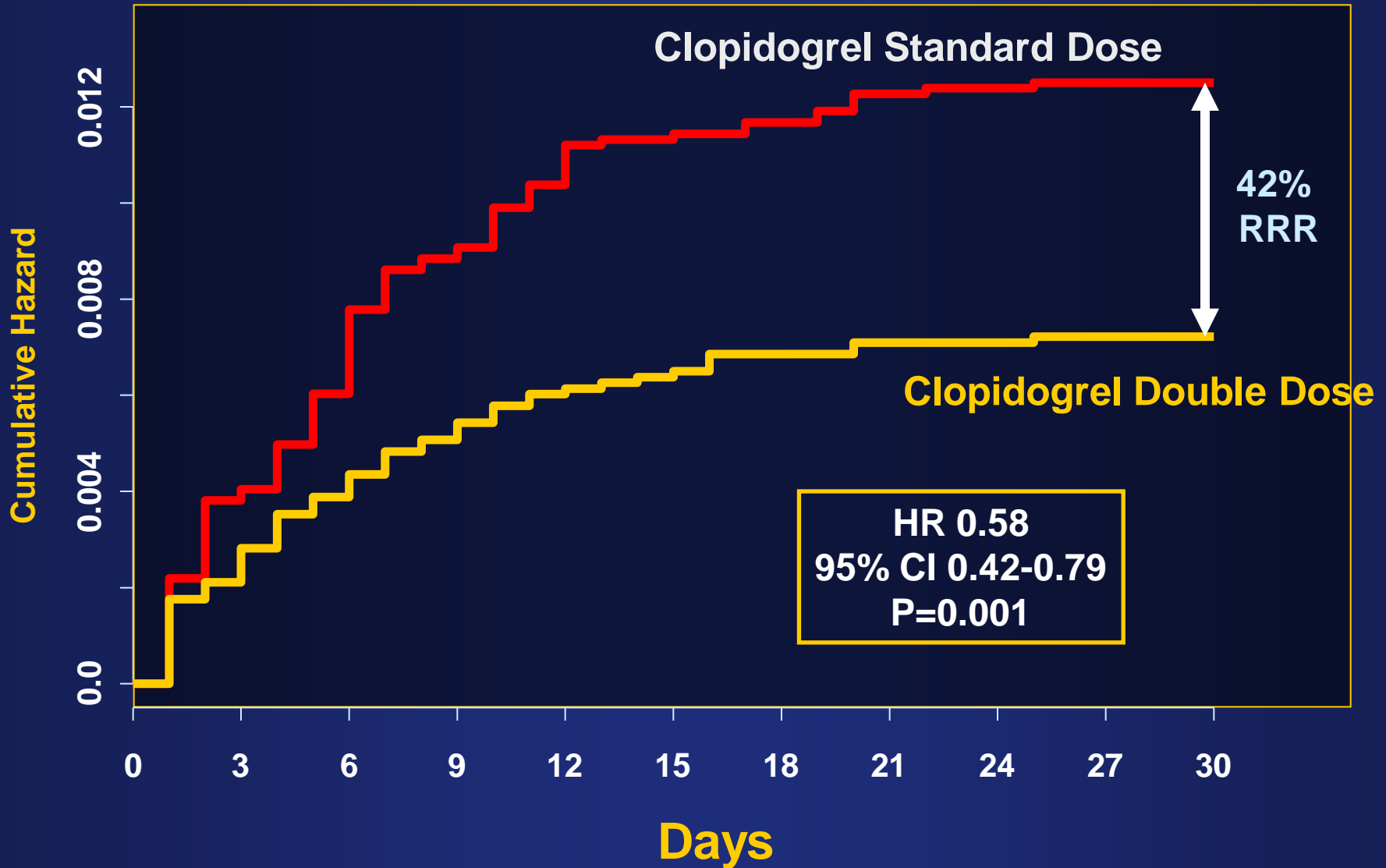
Efficacy Outcomes: CV Death, MI or stroke at day 30

Stent Thrombosis at day 30

Safety Outcomes: Bleeding (CURRENT defined Major/Severe and TIMI Major)

Key Subgroup: PCI v No PCI

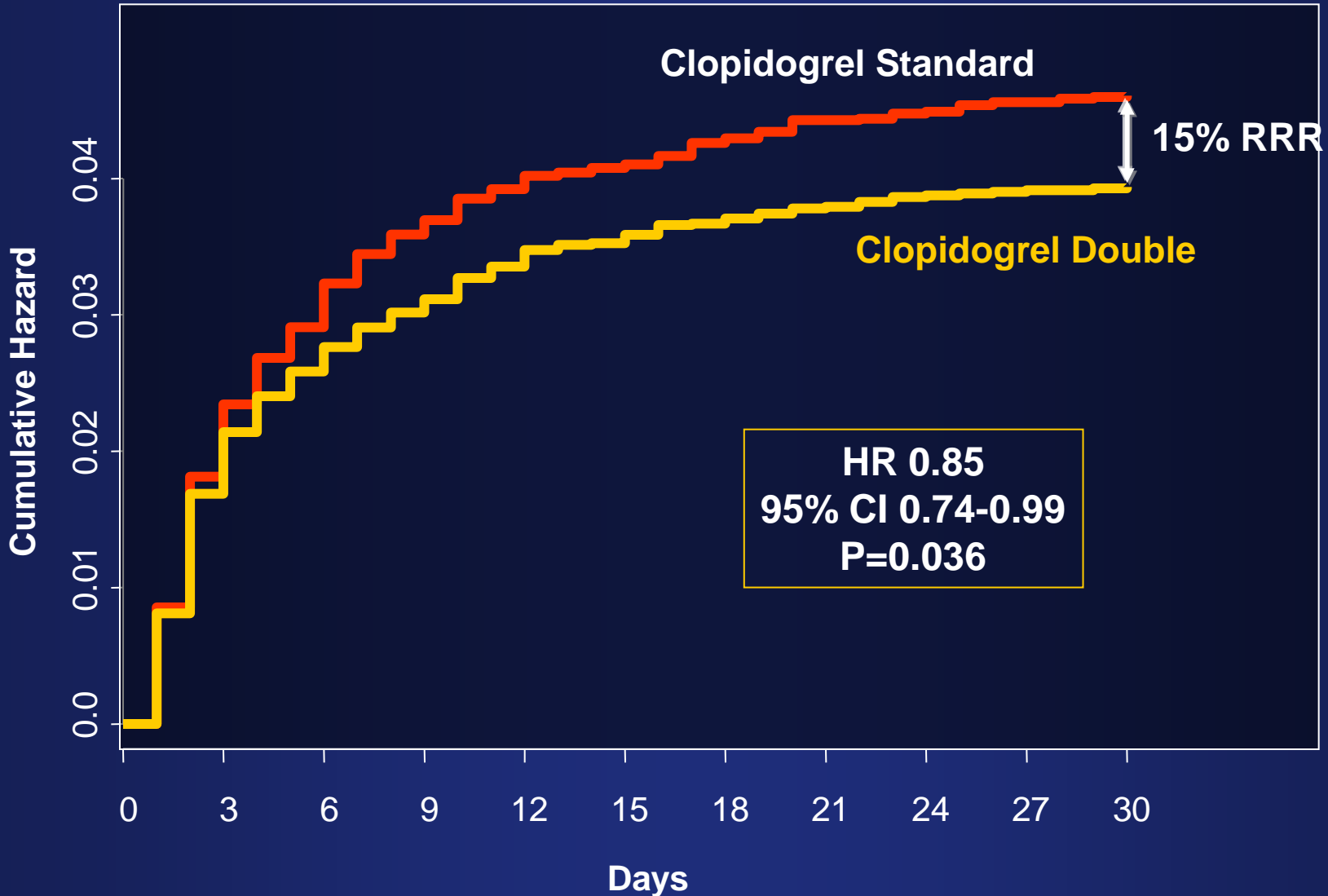
Clopidogrel: Double vs Standard Dose Definite Stent Thrombosis (Angio confirmed)



Clopidogrel: Double vs Standard Dose

Primary Outcome: PCI Patients

CV Death, MI or Stroke





Antiplatelet Drug Resistance / Response Variability: *An Emerging Clinical Problem*

Journal of the American College of Cardiology
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EDITORIAL COMMENT

Aspirin Resistance: **More Than Just a Laboratory Curiosity***

Deepak L. Bhatt, MD, FACC, FSCAI, FESC
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Journal of the American College of Cardiology
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EDITORIAL COMMENT

Platelet Function Assessment to Predict Outcomes After Coronary Interventions **Hype or Hope?***

Fernando Alfonso, MD, PhD, FESC,†
Dominick J. Angiolillo, MD, PhD, FACC‡
Madrid, Spain; and Jacksonville, Florida

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

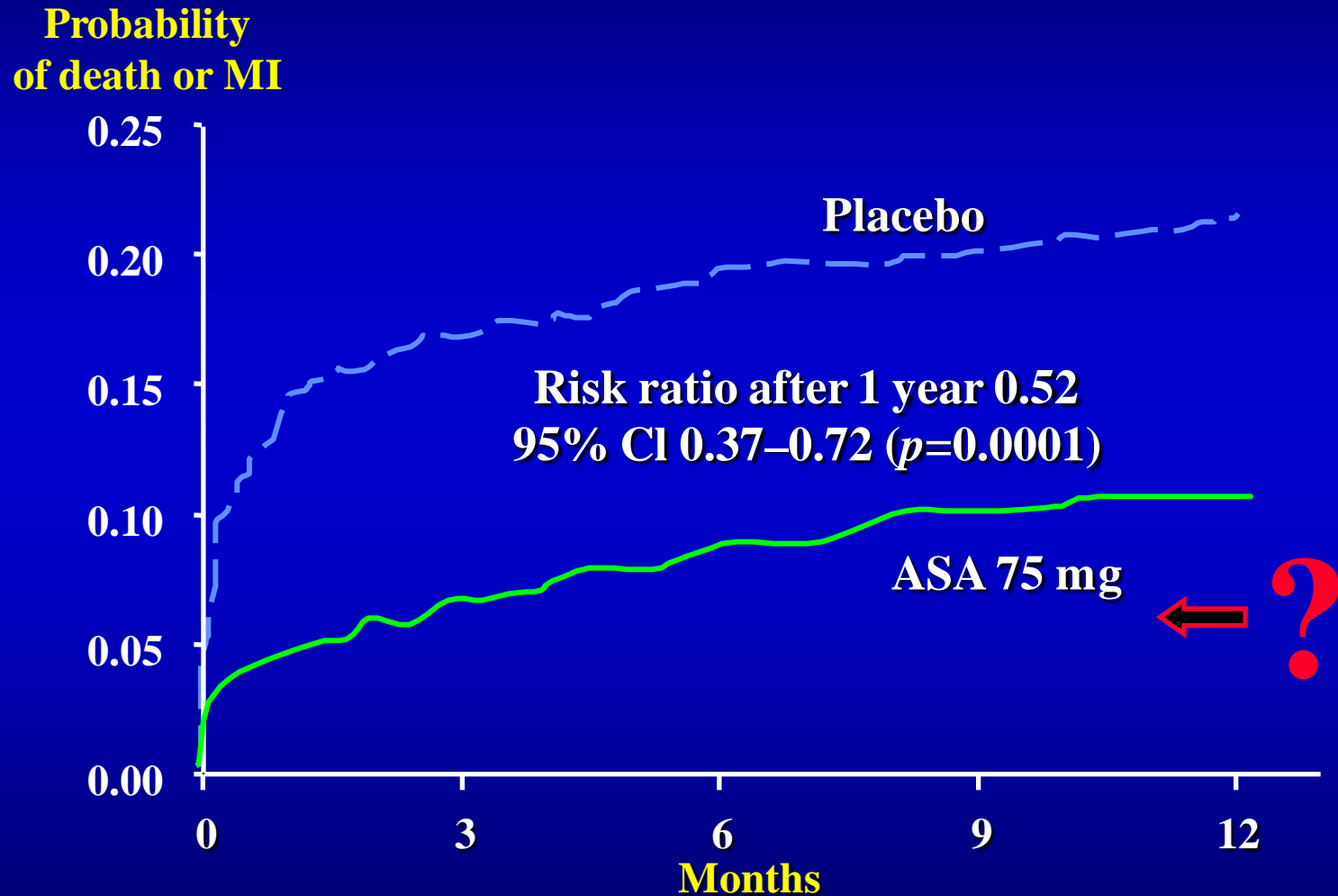
American Heart
Association® 
Learn and Live™

Clopidogrel Response Variability and Future Therapies

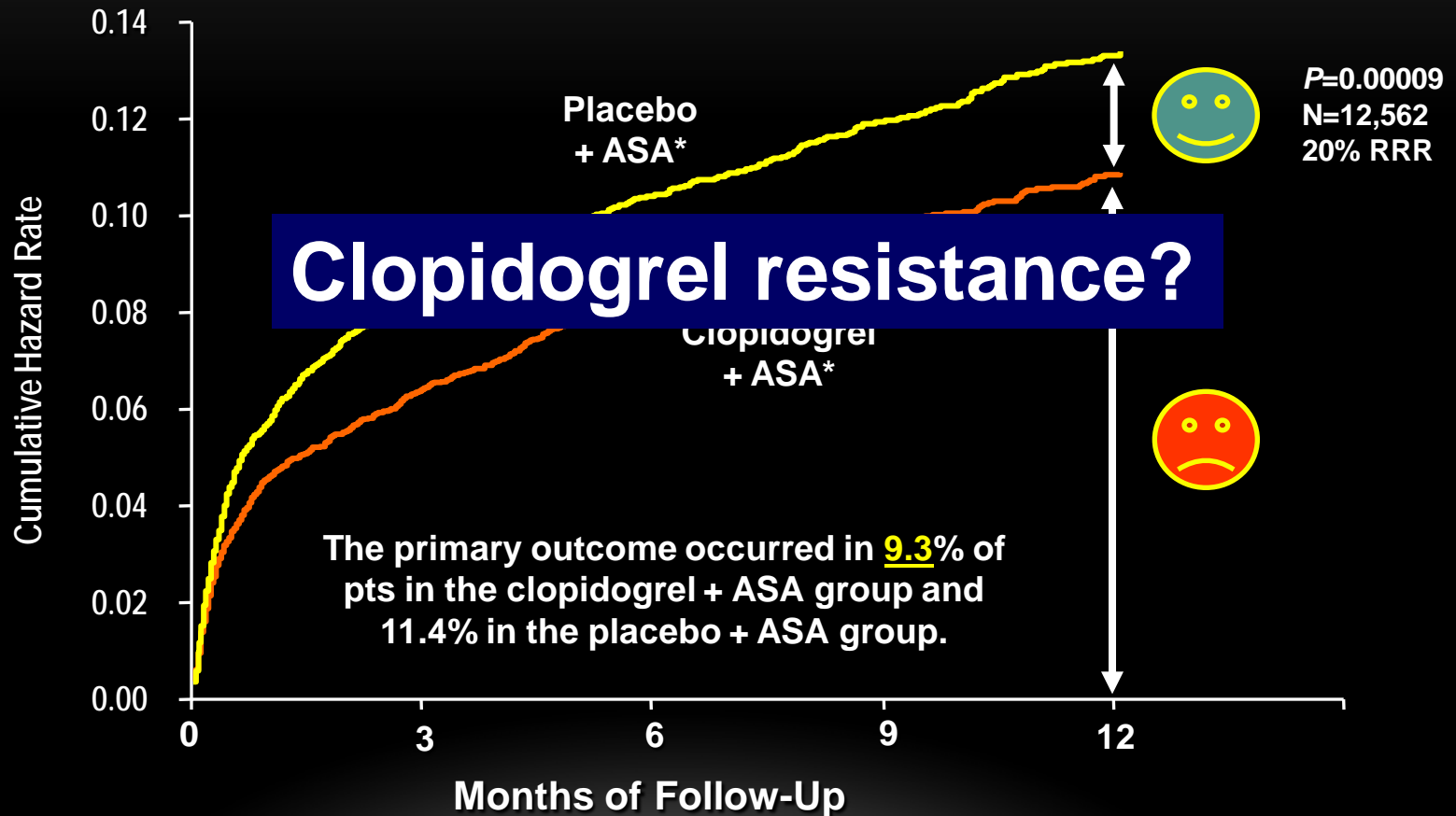
Clopidogrel: Does One Size Fit All?

Michelle O'Donoghue, MD; Stephen D. Wiviott, MD

Long-term Efficacy of ASA in Reducing Death or MI in Patients with Unstable Angina



PRIMARY ENDPOINT—MI/STROKE/CV DEATH

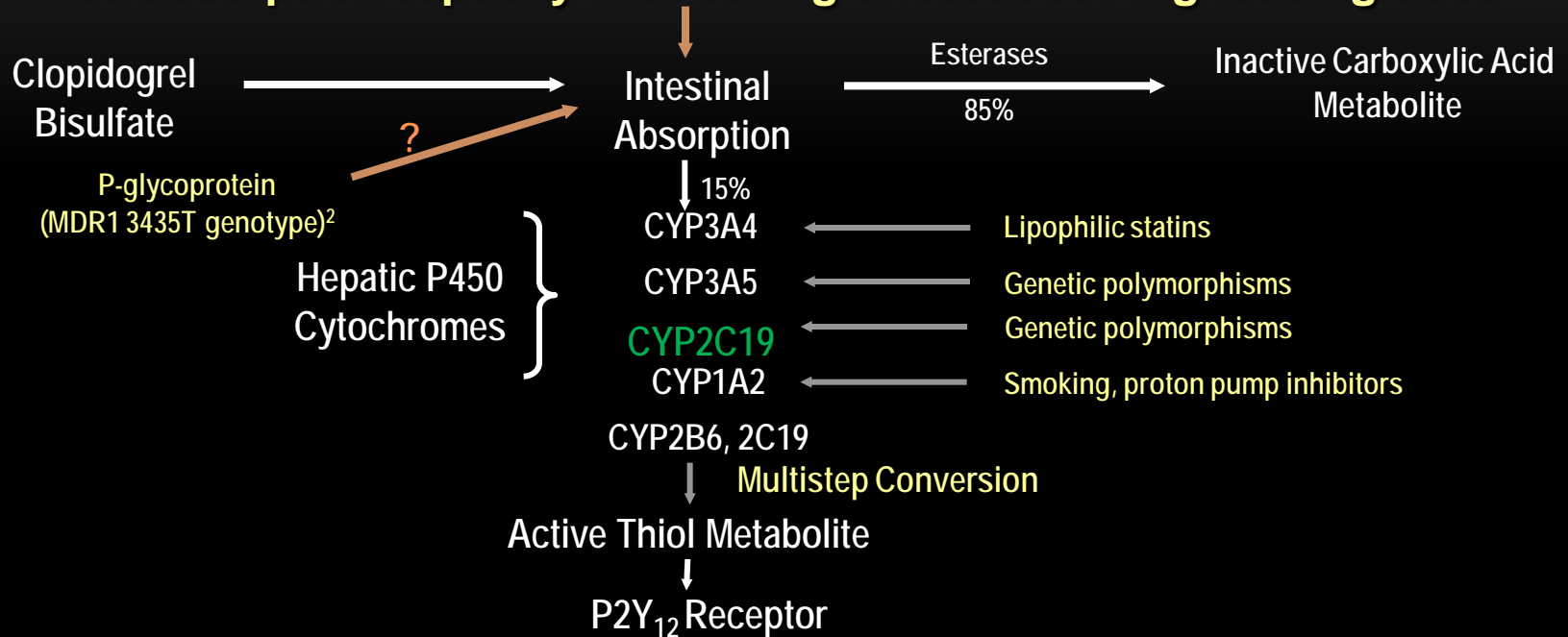


*Other standard therapies were used as appropriate.

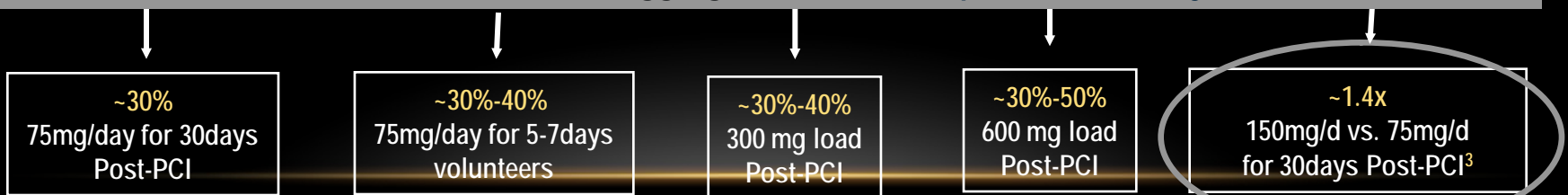
Yusuf S et al. *N Engl J Med.* 2001;345:494-502.

MECHANISM OF CLOPIDOGREL RESPONSE VARIABILITY

Limited absorption capacity with ceiling effect at 600 mg loading dose



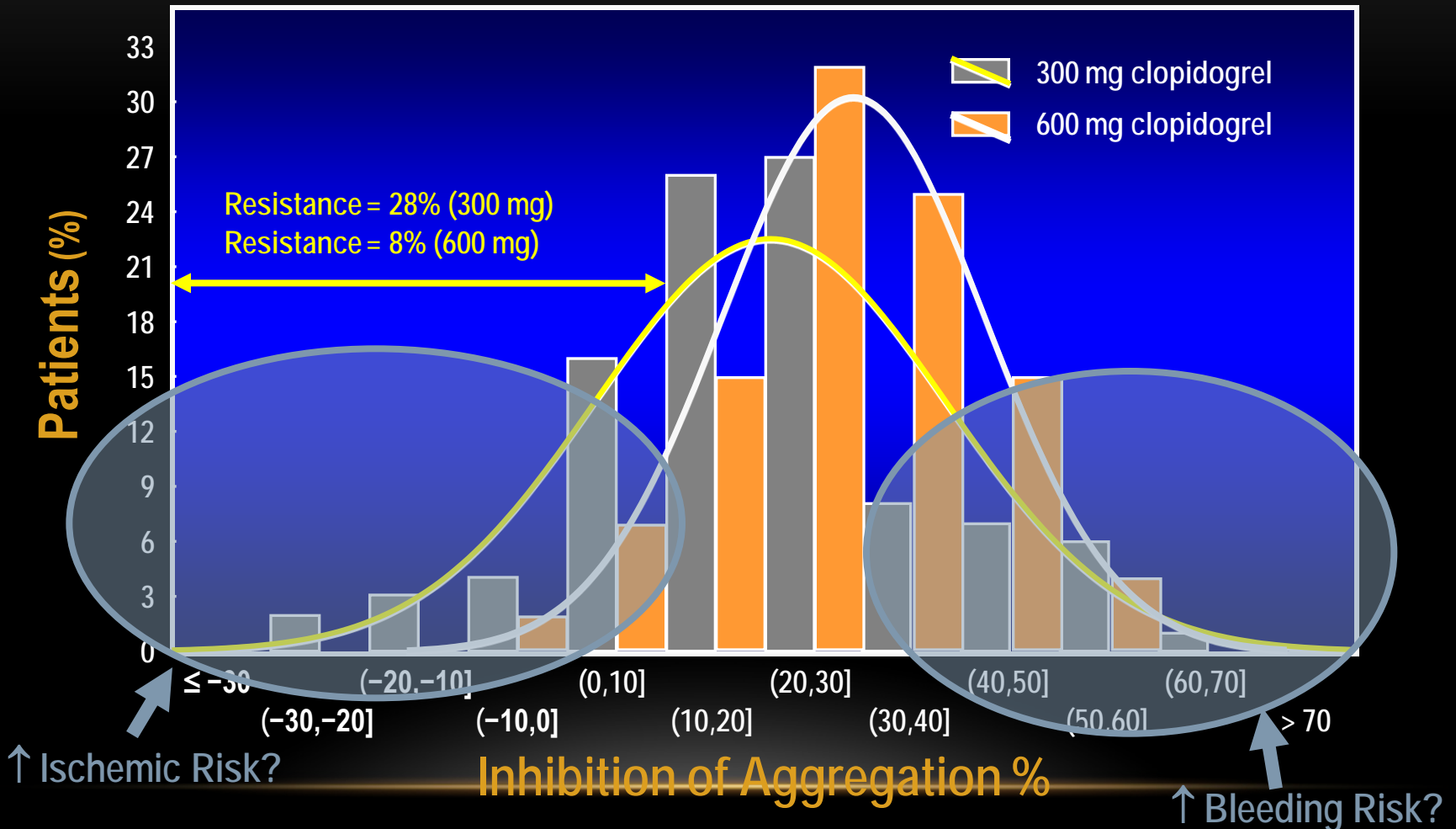
Inhibition of Platelet Aggregation (Wide Response Variability)¹



1. Gurbel PA et al. *Thromb Res.* 2007;120:311-321.
2. Taubert et al. *Clin Pharmacol.* 2006;80:486-501.
3. von Beckerth et al. *Eur Heart J.* 2007;28:1814-1819.

Variability of Response to Clopidogrel

5 μ M ADP-induced Aggregation at 24 h



Gurbel et al. *Circulation*. 2003;107:2908-2913.

Gurbel et al. *J Am Coll Cardiol*. 2005;45:1392-1396.

Clinical Relevance of Clopidogrel Non-responsiveness

Post-Stent Ischemic Events and Periprocedural Infarction

	N	Functional Parameter	Clinical Relevance
Matezky et al. Circulation 2004	60	↑ platelet aggregation (4 th quartile)	Post-primary PCI ischemic events (6 months)
Gurbel et al. JACC 2005	192	↑ periprocedural platelet aggregation	Post-PCI ischemic events (6 months)
Gurbel et al. Circulation 2005	120	↑ periprocedural platelet aggregation	Myonecrosis and inflammation marker release
Cuisset et al. J Thromb Haemost 2006	106	↑ platelet aggregation	Post-PCI ischemic events (30 days)
Lev et al. JACC 2006	120	↑ clopidogrel/aspirin-resistant patients	Post PCI-myonecrosis
Cuisset et al. JACC 2006	292	↑ platelet aggregation	Post-PCI ischemic events (30 days)
Hocholzer et al. JACC 2006	802	↑ platelet aggregation (3 rd & 4 th quartiles)	Post-PCI ischemic events (30 days)
Geisler et al. Eur Heart J 2006	379	↓ platelet inhibition	Post-PCI ischemic events (3 months)
Bliden et al. JACC 2007	100	↑ platelet aggregation	Post-PCI ischemic events (12 months)
Angiolillo et al. JACC 2007	173	↑ platelet aggregation (4 th quartile)	Ischemic events (24 months)

adapted from Angiolillo DJ et al. *Am J Cardiovasc Drugs*. 2007.

Platelet function testing: Common testing devices

Light transmittance aggregometry (LTA)

Historical standard
Aggregation based, platelet rich plasma (PRP)
ADP peak platelet aggregation
Central laboratory, trained technicians
Time consuming



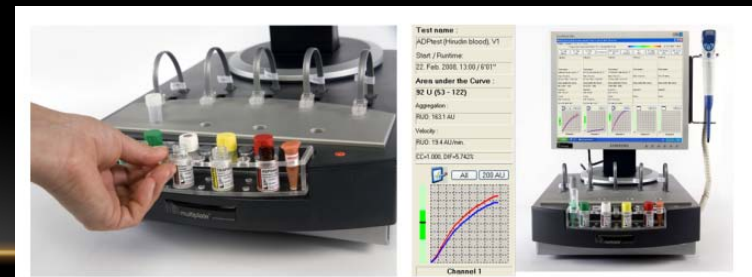
VerifyNow[®] P2Y12 assay

Aggregation based, whole blood
Bedside test. fully automated



Multiplate[®] (MULTIple PLATElet) function analyzer

Aggregation based, whole blood
Bedside test. fully automated
Sensitive for aspirin, ADP receptor inhibitor,
GP IIb/IIIa antagonists



GRAVITAS: Patient flow

5429 patients screened with VerifyNow P2Y12
12-24 hours post-PCI

2214 (41%) with high residual
platelet reactivity
(PRU \geq 230)

3215 (59%) without high
residual platelet reactivity
(PRU $<$ 230)

Clopidogrel
High Dose
N=1109

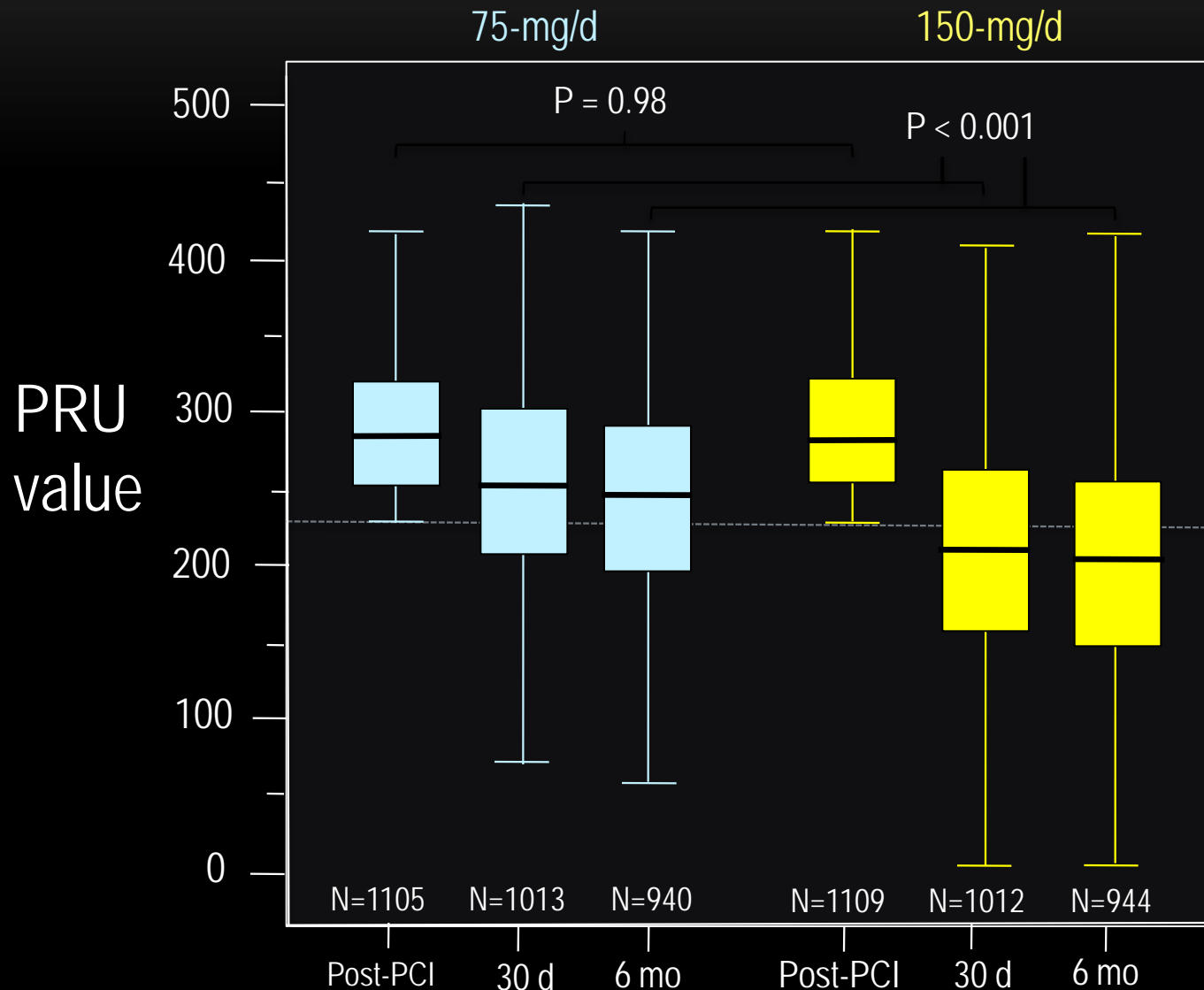
Clopidogrel
Standard Dose
N=1105

High-Dose Clopidogrel†
clopidogrel 600-mg, then
clopidogrel 150-mg daily X 6 months

Standard-Dose Clopidogrel†
clopidogrel 600-mg, then
clopidogrel 75-mg daily X 6 months

GRAVITAS:

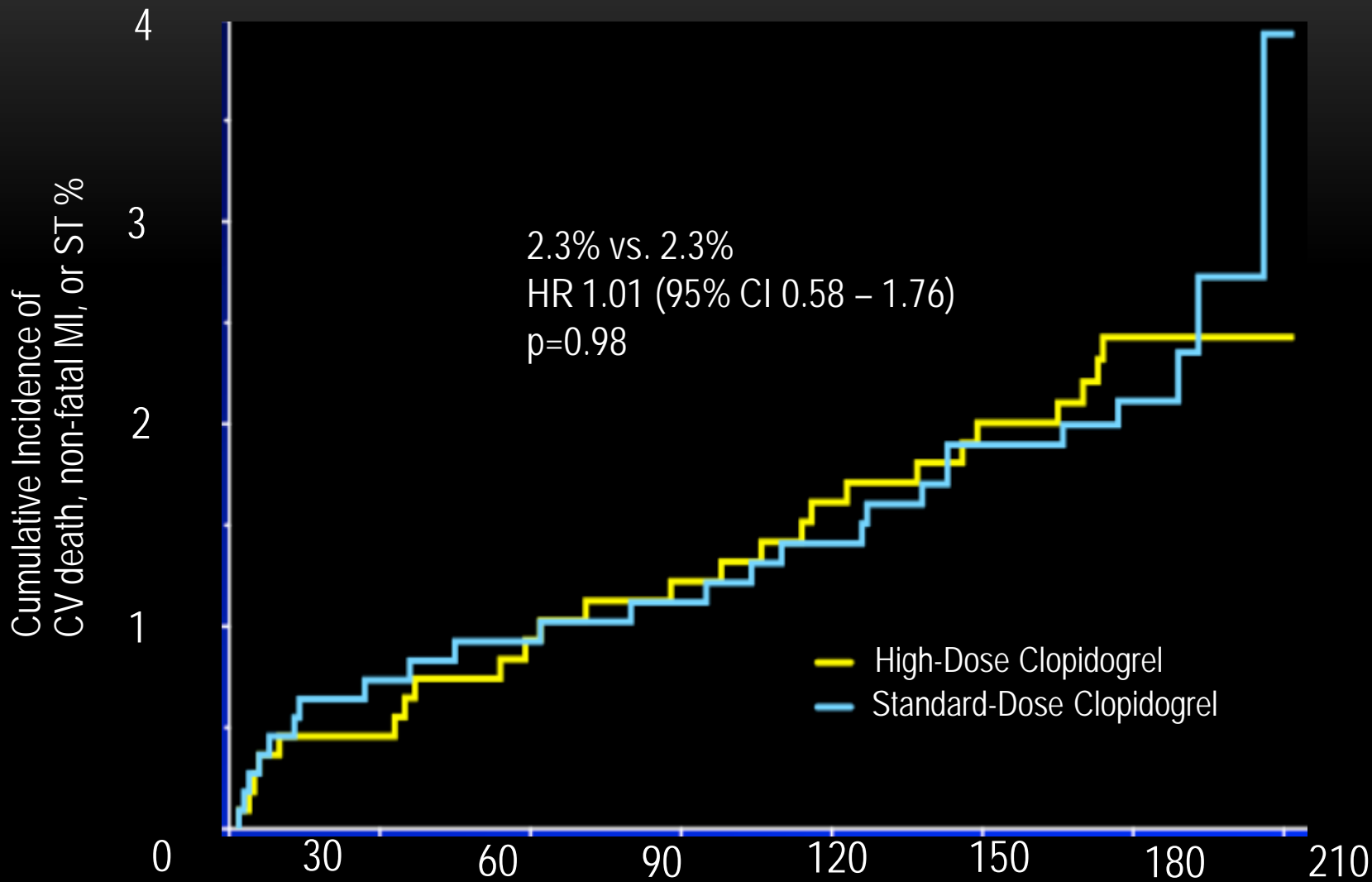
Pharmacodynamics: Effect of SD vs HD clopidogrel



PRU ≥ 230 at 30 days	
Clopidogrel 75mg/d	Clopidogrel 150mg/d
62%	40%
p < 0.001	

ITT population

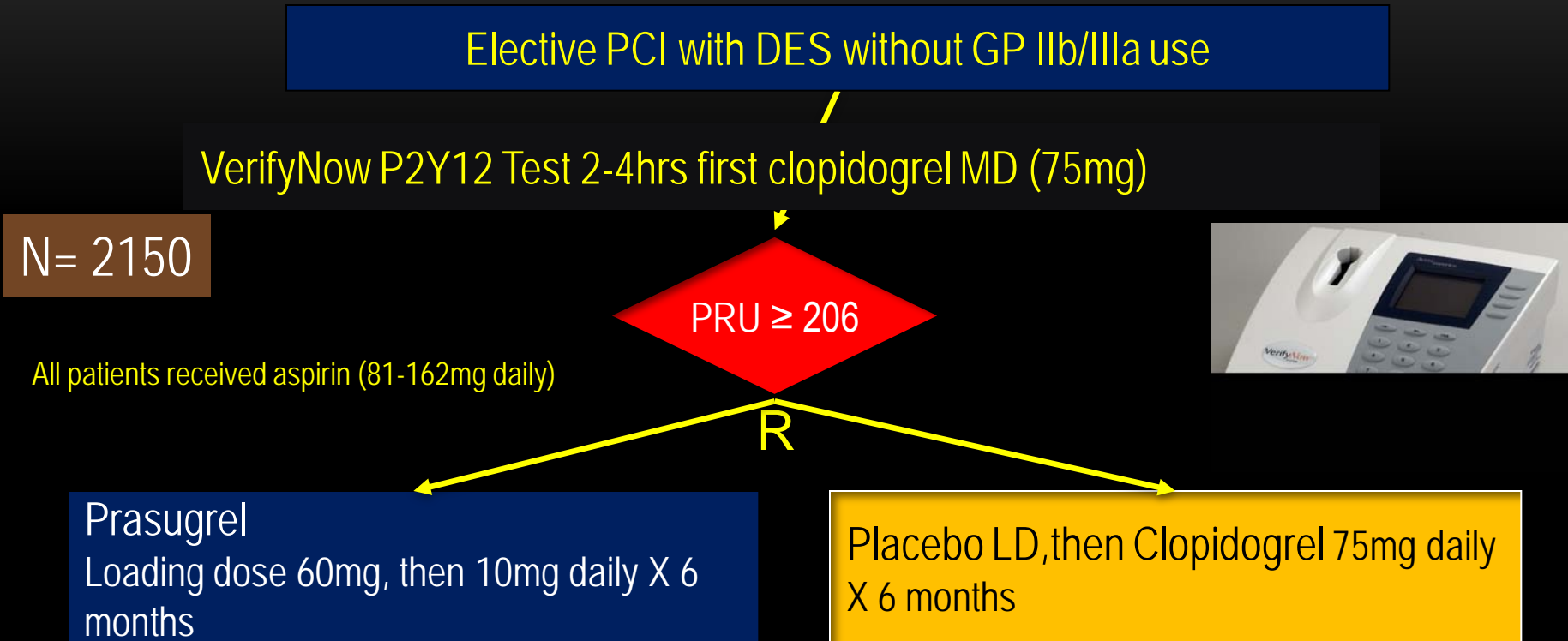
GRAVITAS Trial: Primary Endpoint: CV Death, MI, Stent Thrombosis



No. at Risk	30	60	90	120	150	180	210
High Dose Clopidogrel	1109	1007	1056	998	1029	747	1017
Standard Dose Clopidogrel	1105	1015	1057	1005	1028	773	1020

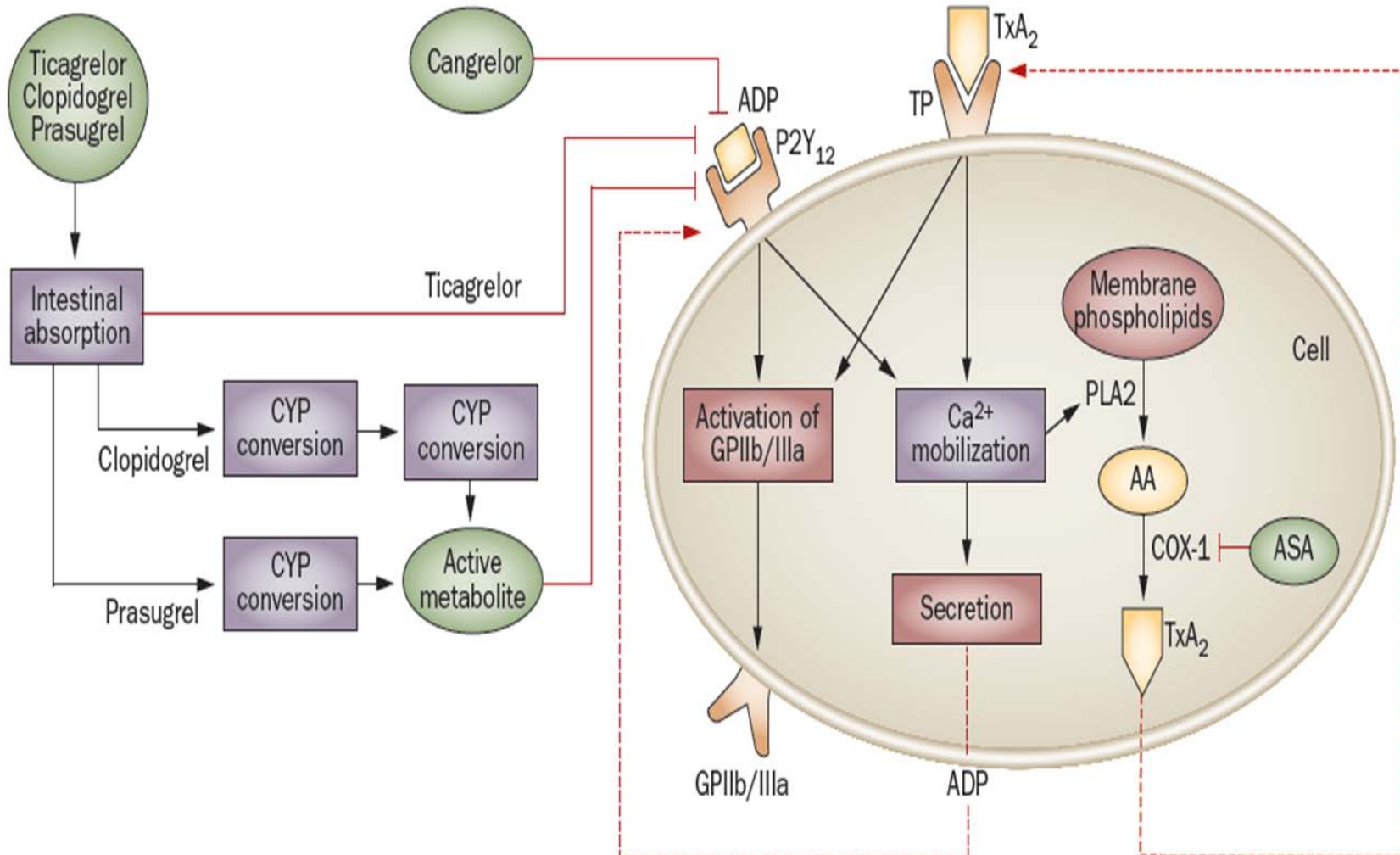
Observed event rates are listed; P value by log rank test.

TRIGGER PCI Trial: Study Design



Primary Efficacy Endpoint: CV Death, Non-Fatal MI at 6 mo
Key Safety Endpoint: Moderate or Severe Bleeding at 6 mo
Pharmacodynamics: Repeat VerifyNow P2Y12 at 3 and 6 months

Trial was halted after 432 pts enrolled because of <2% event rate (projected 7%) in 250 pts reaching 6M mark



TRITON-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

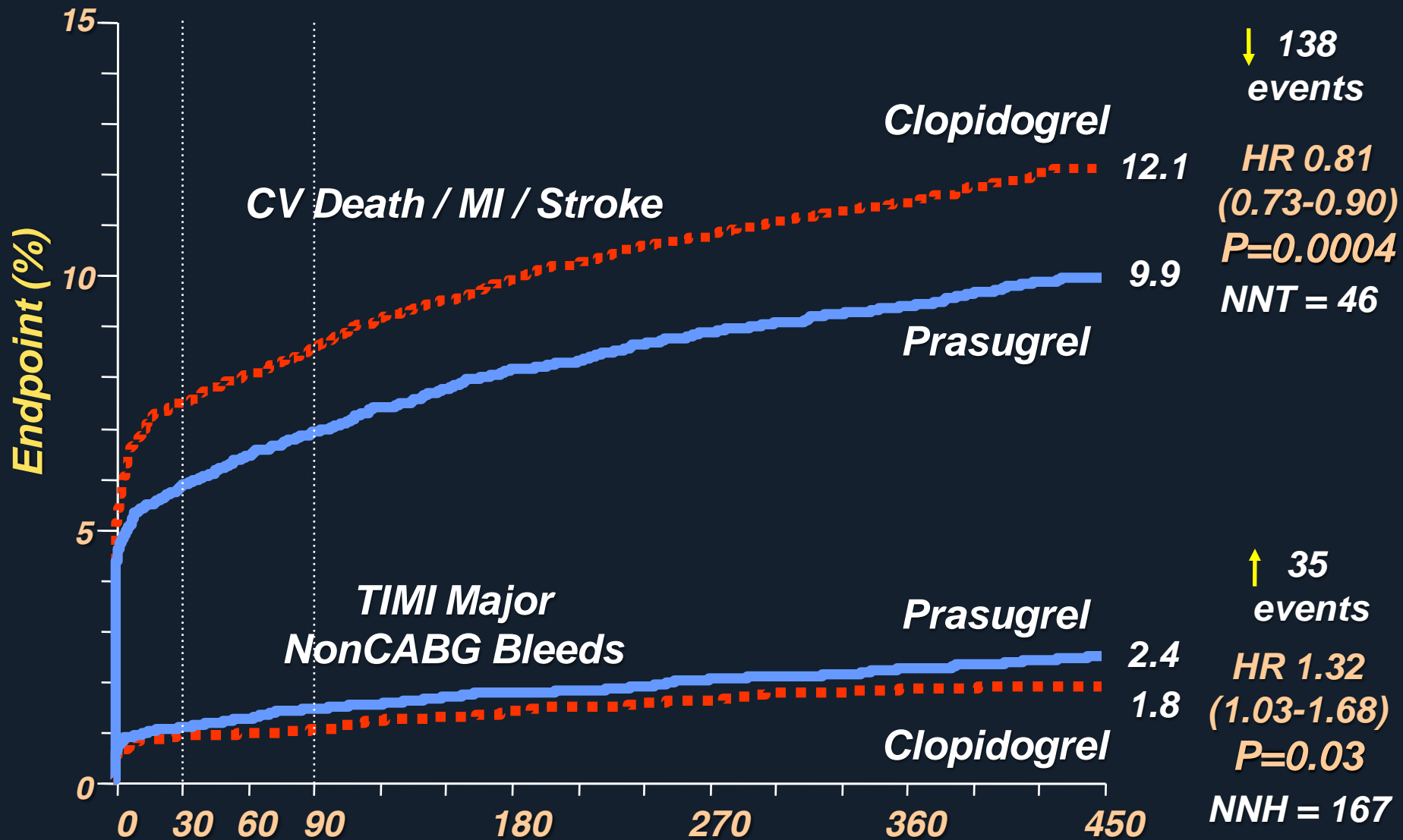
1° endpoint: CV death, MI, Stroke

2° endpoints: CV death, MI, Stroke, Rehosp-Rec Isch, CV death, MI, UTVR
Stent Thrombosis (ARC definite/prob.)

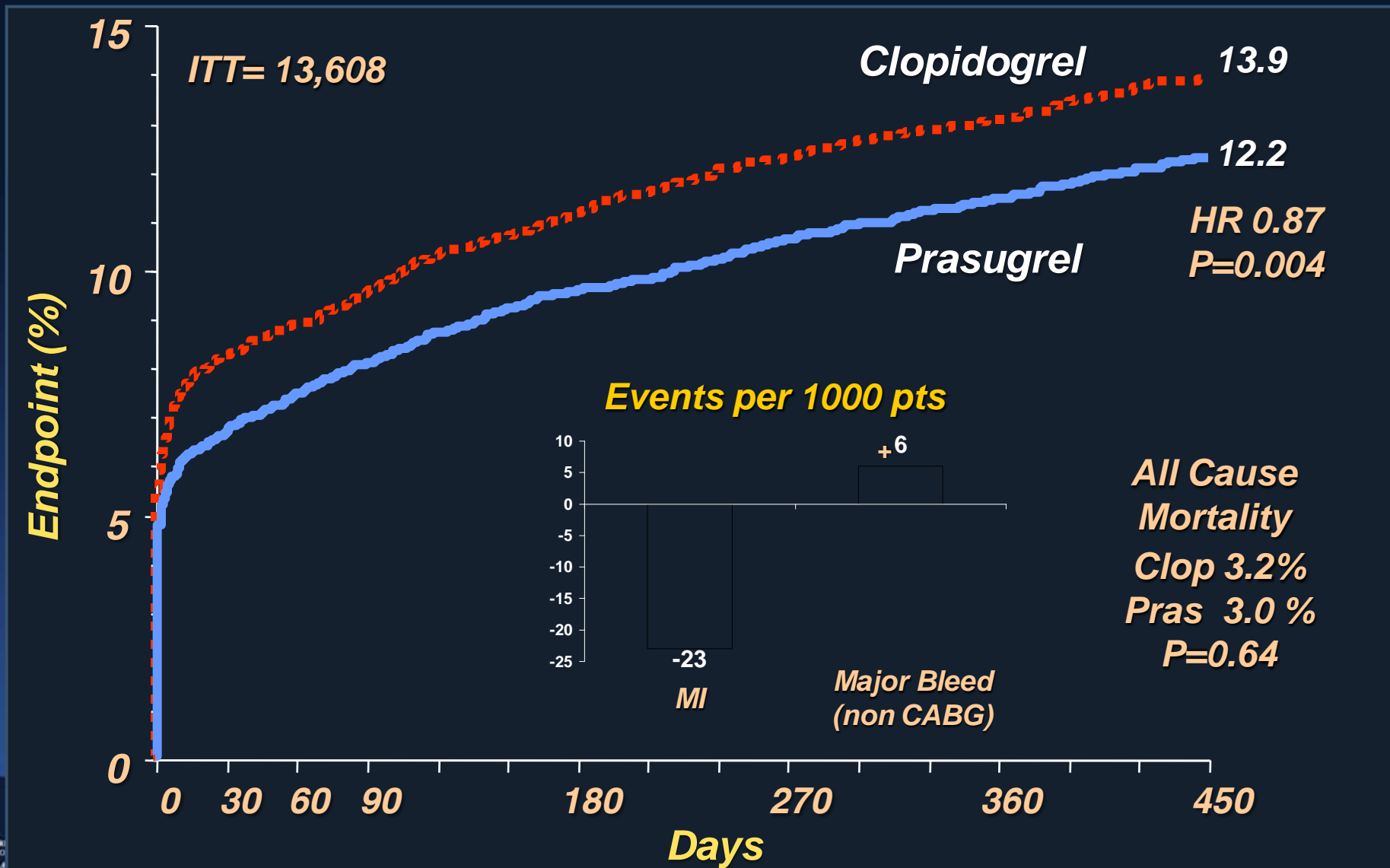
Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Key Substudies: Pharmacokinetic, Genomic

Balance of Efficacy and Safety



Net Clinical Benefit: Death, MI, Stroke, Major Bleed (non CABG)



Prasugrel: Summary of Boxed Warning

- ***Contraindications:*** Clinical hx of Stroke/TIA
- ***Generally not recommended*** for age ≥ 75 yrs, except in high risk situations (prior MI, DM) where the ischemic benefit appears to be greater
- ***Greater risk of bleeding*** in patients weighing <60 kg, can consider MD adjustment (5mg)

**NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)**

Clopidogrel

**If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)**

Ticagrelor

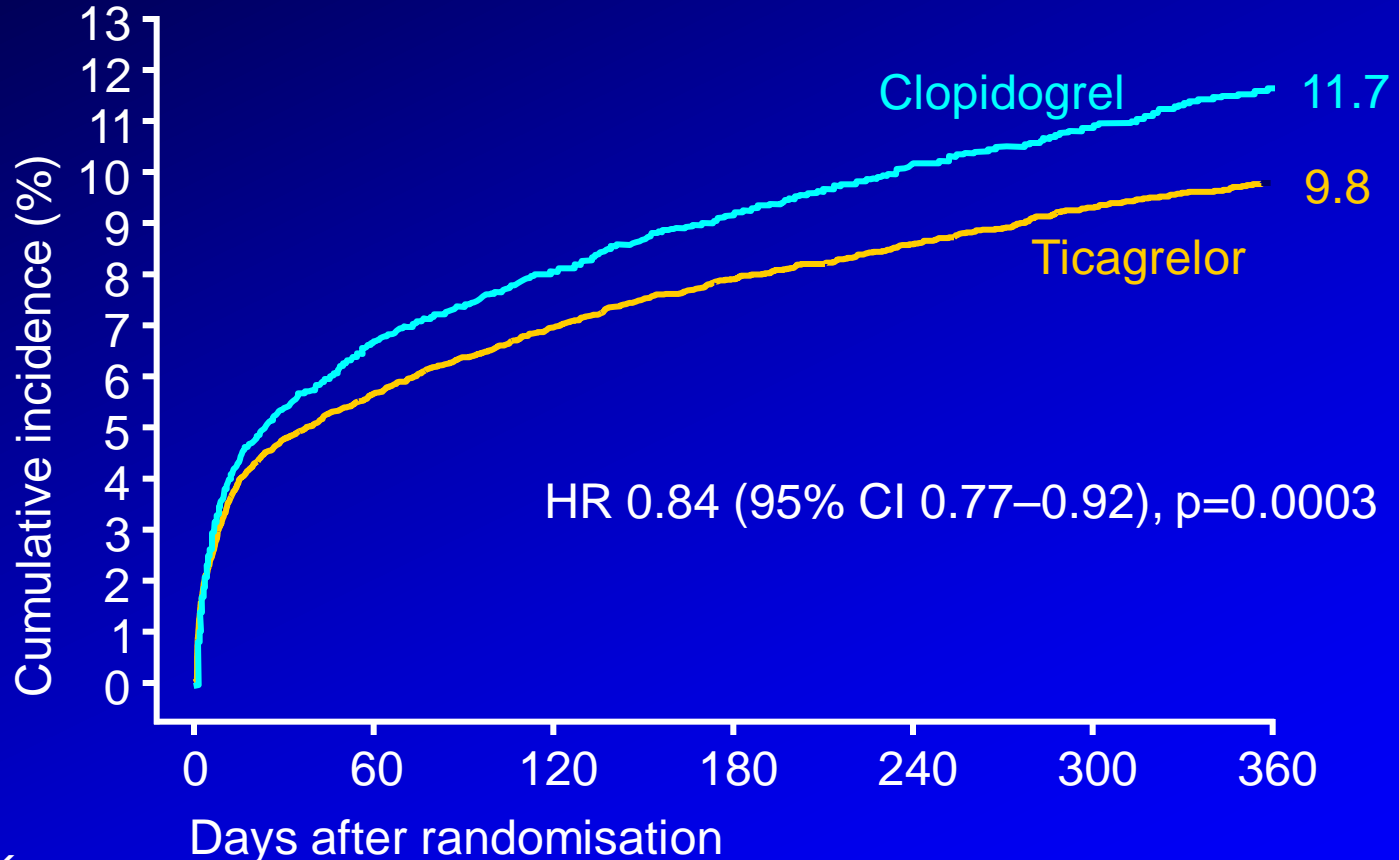
**180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)**

6–12-month exposure

**Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding**

PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack

PLATO: KM estimate of time to first primary efficacy event (CV death, MI or stroke)

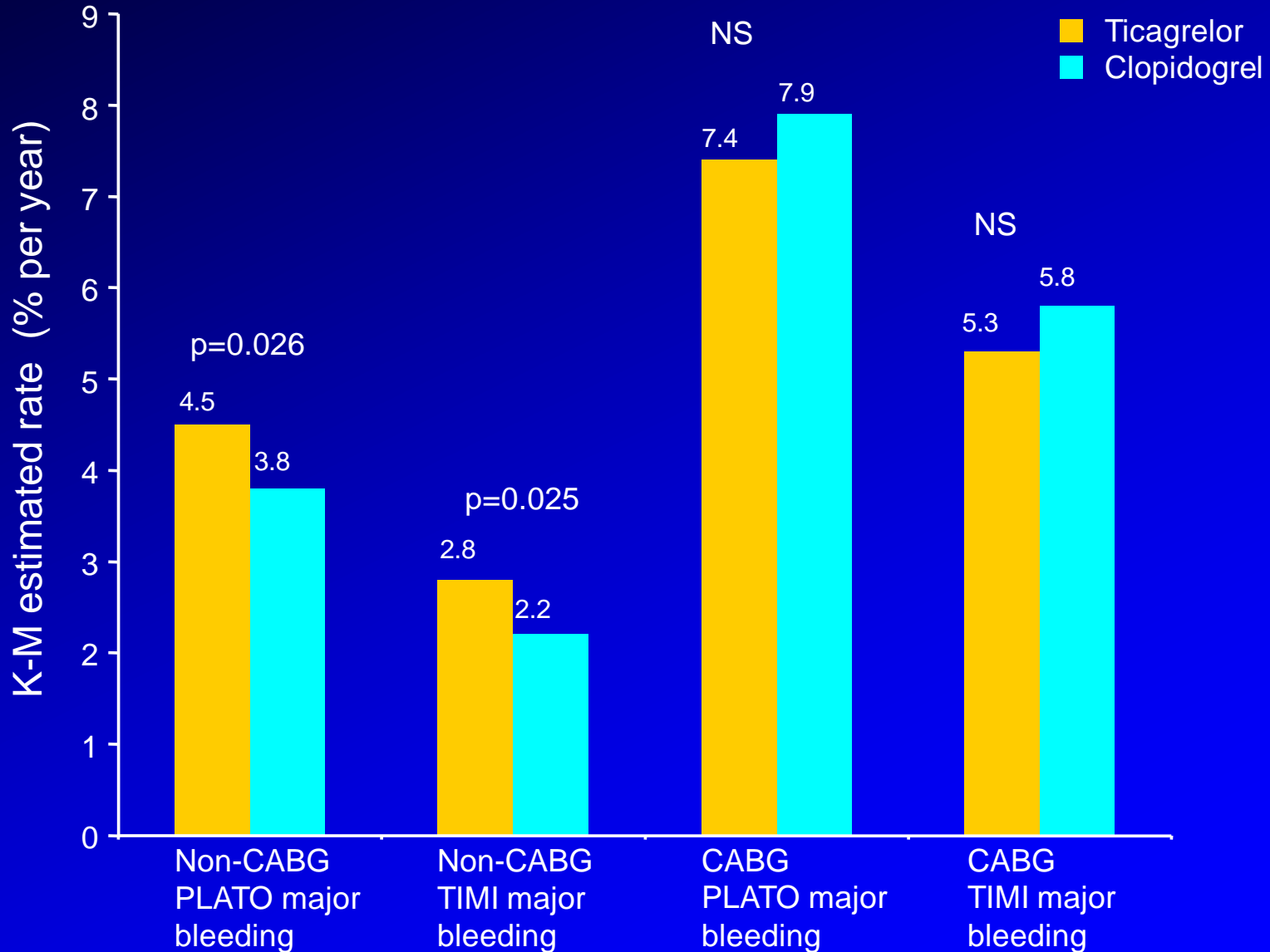


No. at risk

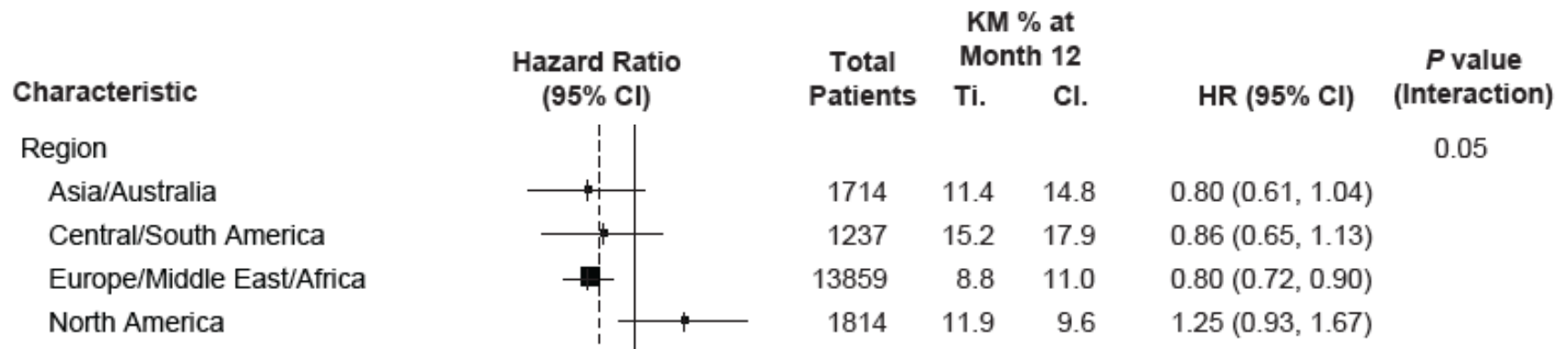
Ticagrelor 9,333 8,628 8,460 8,219 6,743 5,161 4,147

Clopidogrel 9,291 8,521 8,362 8,124 6,743 5,096 4,047

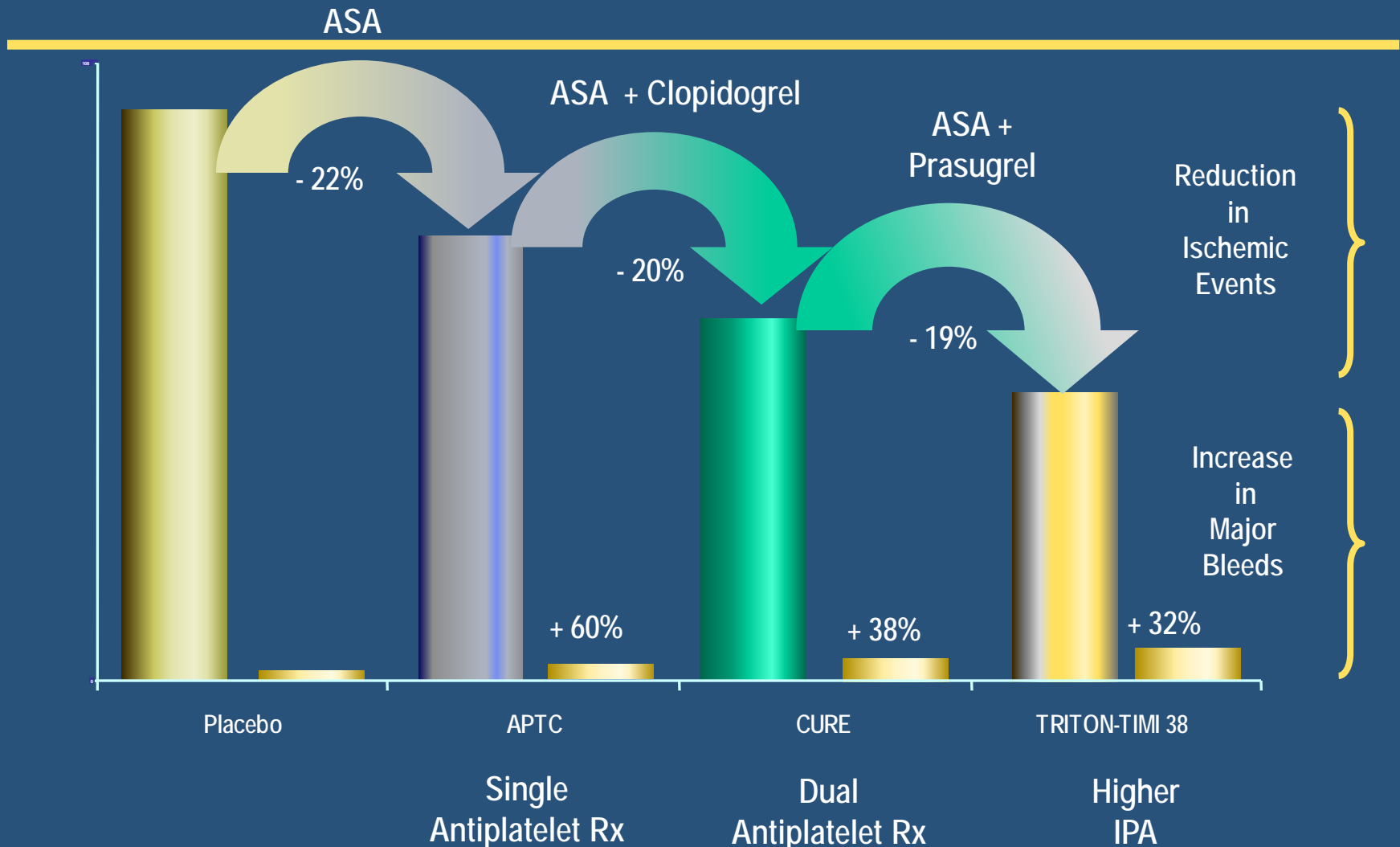
PLATO: Non-CABG and CABG-related major bleeding



PLATO: Association Between Ischemic Benefit With Ticagrelor And Geographic Region



Evolution of Antiplatelet Therapy in ACS

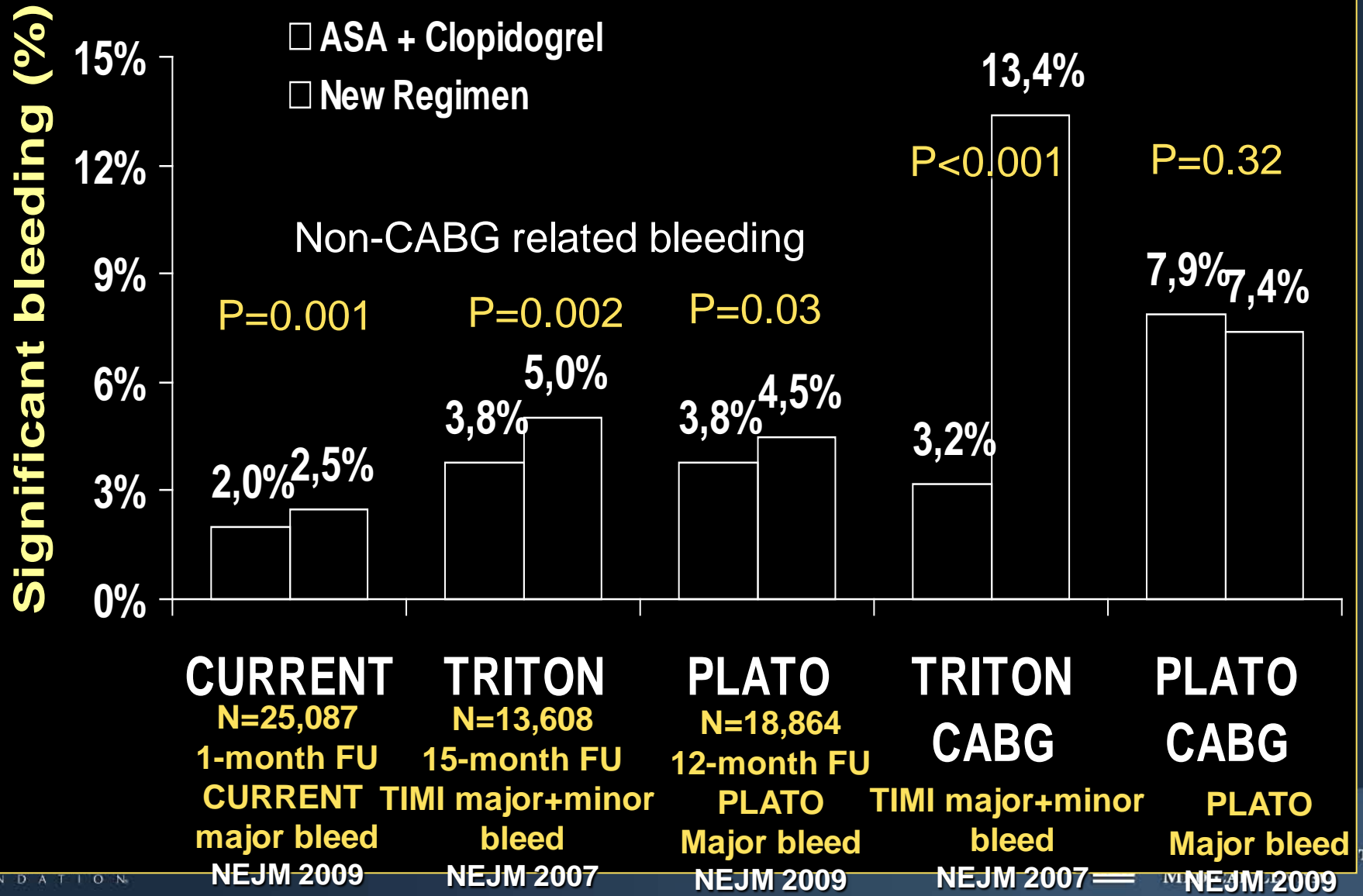


APTC. *BMJ*. 1994;308:81-106.

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

Safety of New DAPT Regimens

3 Active Controlled Trials (vs Standard Clop)



RIESGO GLOBAL
Evidencia Científica
INDUSTRIA

PCI

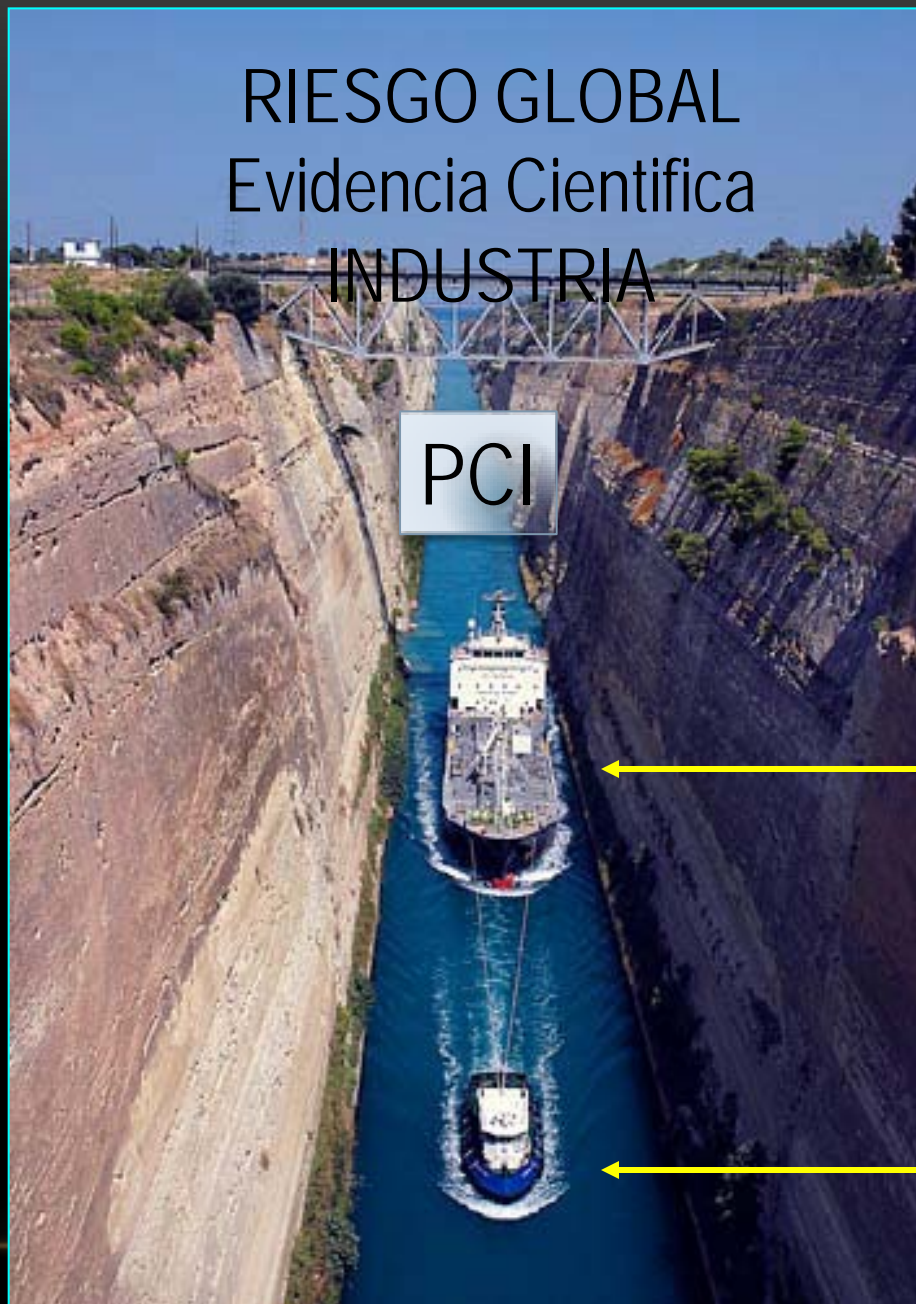
ISQUEMIA

HEMORRAGIA

Paciente

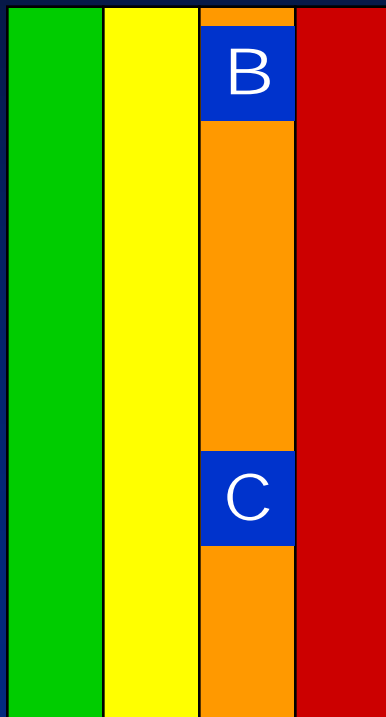
Cardiologo

Resultado
Final



Recommendations for Additional Management of Antiplatelet and Anticoagulant Therapy *New Recommendation*

I IIa IIb III



Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on thienopyridine therapy may be considered if results of testing may alter management

Genotyping for a CYP2C19 loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on clopidogrel therapy might be considered if results of testing may alter management

Class IIb: Benefit \geq Risk; **Treatment may be considered**

Additional studies w/broad objectives needed; additional registry data would be helpful.