

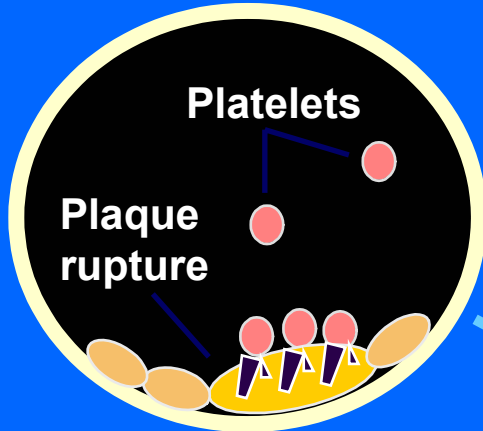
Thienopyridines after CLARITY-PCI. An Update for STEMI

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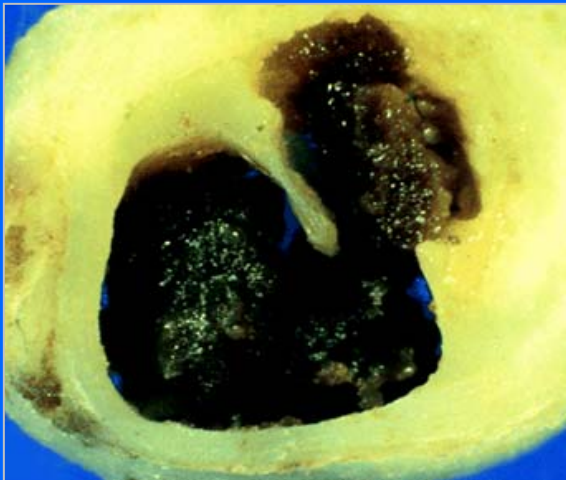
Fundamental Role of Platelets in ACS

Importance of Antiplatelet Therapy

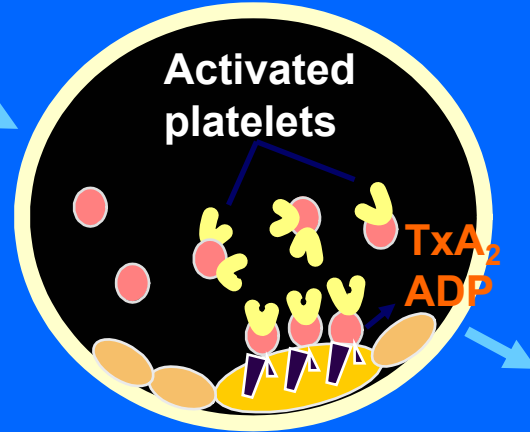
1 Adhesion



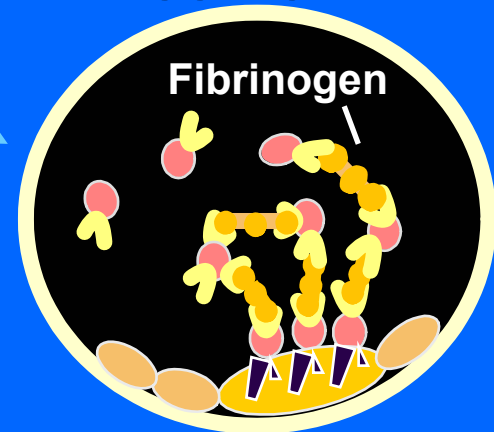
STEMI-occlusive thrombus



2 Activation



3 Aggregation

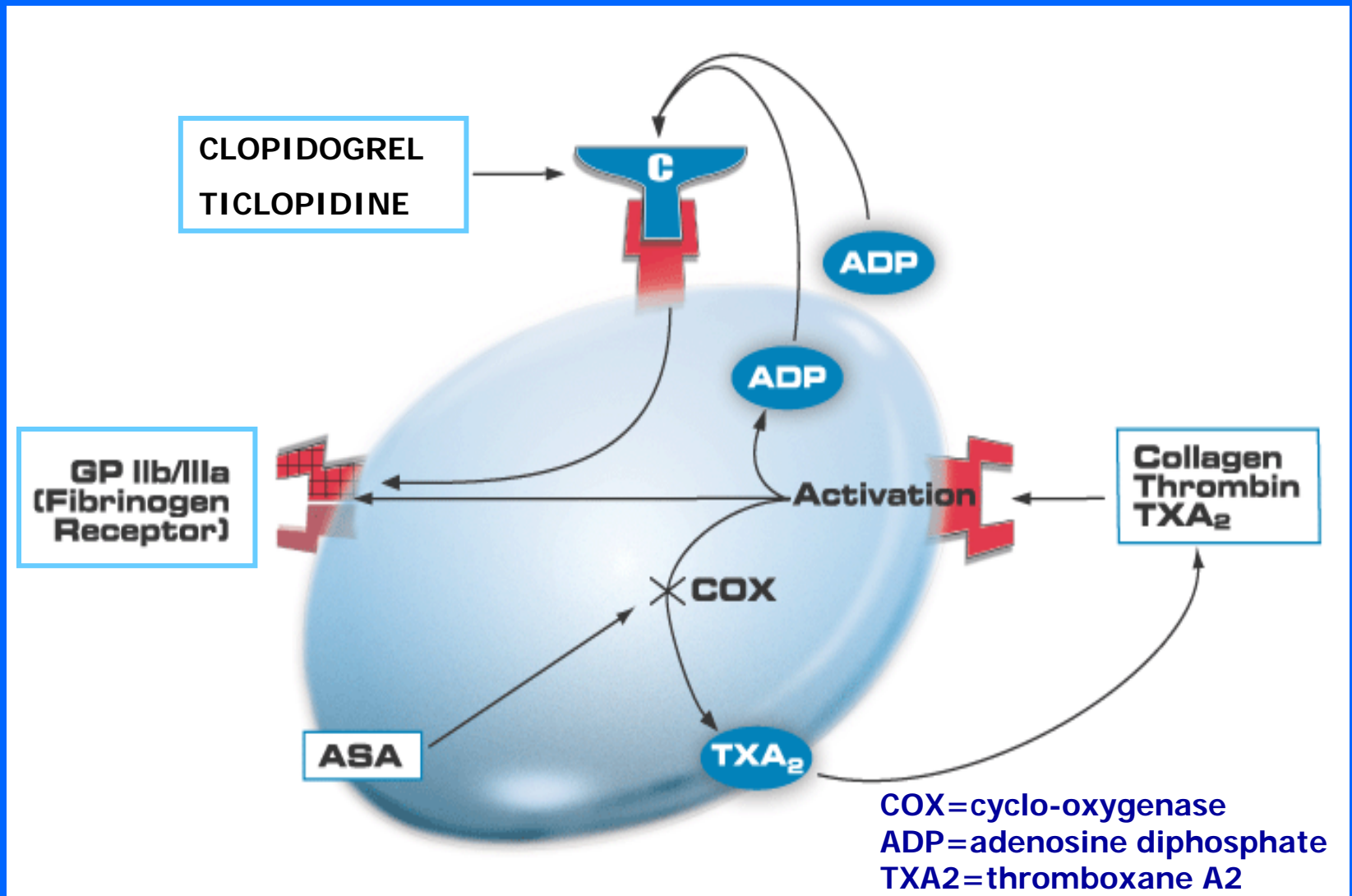


1. Cannon CP et al. *Heart Disease: A Textbook of Cardiovascular Medicine*. 6th ed. Philadelphia, PA: WB Saunders, 2001: 1232–1263.

2. Antman EM. In: Califf RM, ed. *Atlas of Heart Diseases*, VIII. Philadelphia, PA: Current Medicine, 1996.

Antiplatelet Therapy is a Cornerstone in Pharmacologic Facilitation in STEMI Patients Undergoing PCI (and Fibrinolysis)

Antiplatelet Drugs: Mechanism of Action



Thienopyridine Issues in STEMI Patients

- Current guidelines
- Clopidogrel vs Ticlopidine
- Early trials
- Insights from CLARITY, CLARITY-PCI and COMMIT
- Safety profile of Clopidogrel
- Remaining problems:
 - ✓ Loading dose: 300-600 mg ? Or more?
 - ✓ Clopidogrel resistance

Background

GUIDELINES

Clopidogrel as adjunctive medication for PCI, ESC 2005

Table 8 Recommendations for clopidogrel as adjunctive medication for PCI

Indication	Initiation and duration	Classes of recommendations and levels of evidence	Randomized studies for levels A or B
Pre-treatment of planned PCI in stable CAD	Loading dose of 300 mg at least 6 h before PCI, ideally the day before	I C	—
Pre-treatment for primary PCI in STEMI or immediate PCI in NSTEMI-ACS or ad hoc PCI in stable CAD	Loading dose of 600 mg, immediately after first medical contact, if clinically justifiable	I C	ARMYDA-2
After all bare metal stent procedures	3–4 weeks	I A	CLASSICS TOPPS Bad Krozingen
After vascular brachytherapy	12 months	I C	—
After drug-eluting stents	6–12 months	I C	—
After NSTEMI-ACS	Prolonged for 9–12 months	I B	After STEMI? CURE

Guidelines for Percutaneous Coronary Interventions. Eur Heart J 2005; 26: 804-47

Thienopyridines (AHA/ACC/SCAI)

❑ Loading dose of Clopidogrel should be administered before PCI is performed

class I, level of evidence A

❑ An oral loading dose of 300 mg at least 6 hours before the PCI

class I, level of evidence B

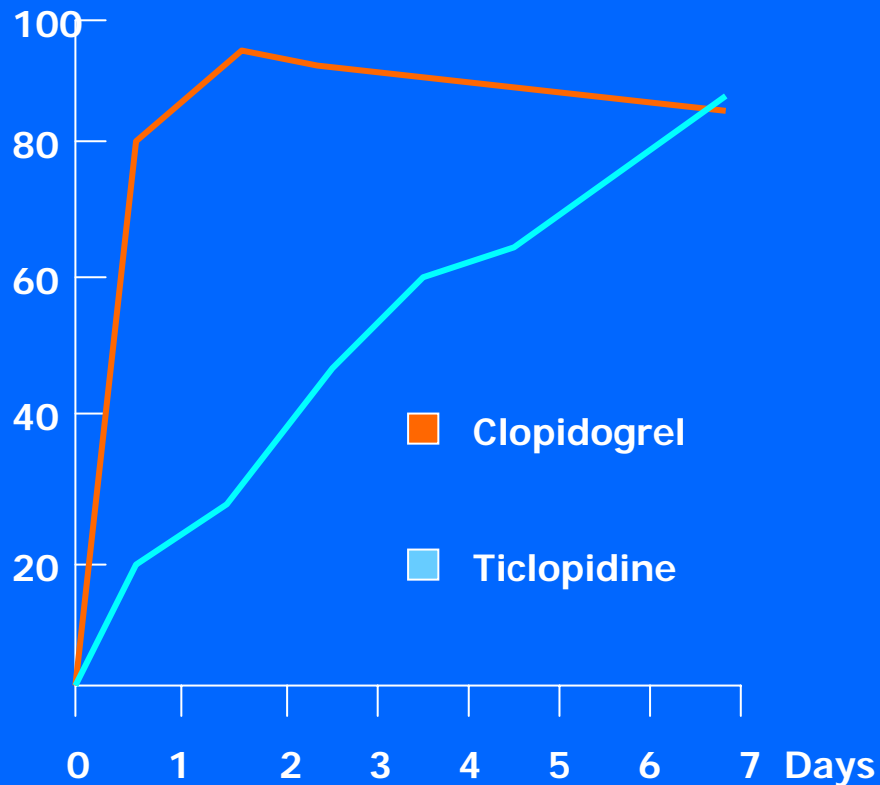
❑ When loading dose of Clopidogrel is administered, a regimen of greater than 300 mg is reasonable to achieve higher levels of antiplatelet activity more rapidly, but the efficacy and safety compared to 300 mg are less well established

class IIa, level of evidence C

Clopidogrel vs Ticlopidine

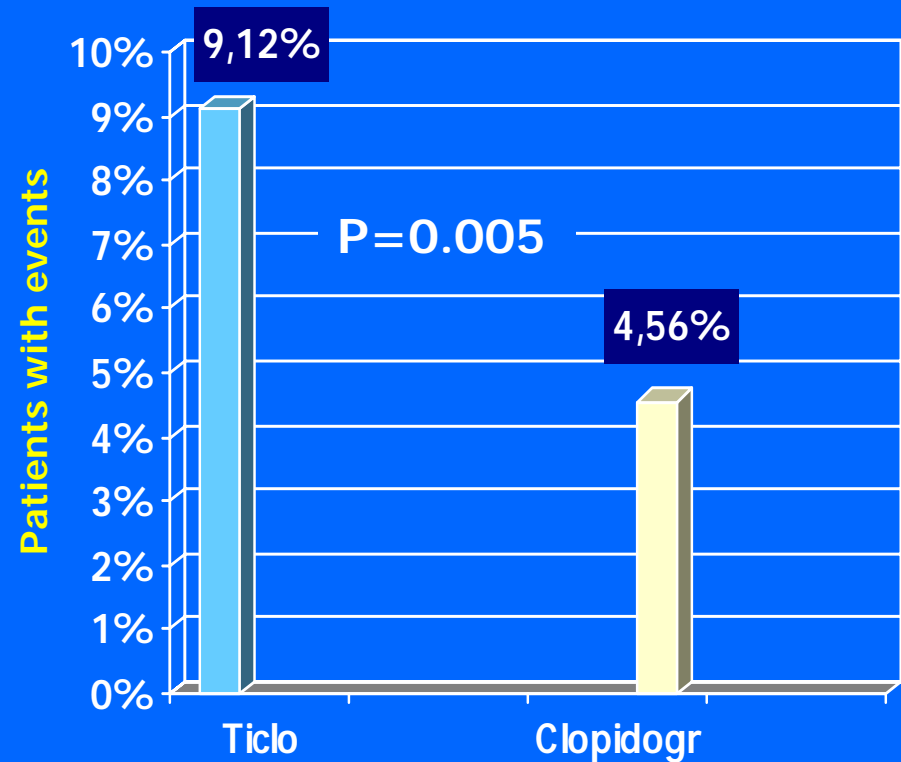
Clopidogrel vs Ticlopidine

% of inhibition of ADP-induced platelet aggregation



Bachman Eur Heart J 1996

CLASSICS: Safety Profile of Clopidogrel vs Ticlopidine at 28 Days



Bertrand ME et al., Circulation 2000; 102: 624-29

CLOPIDOGREL Early Trials (CURE-PCI, CREDO)

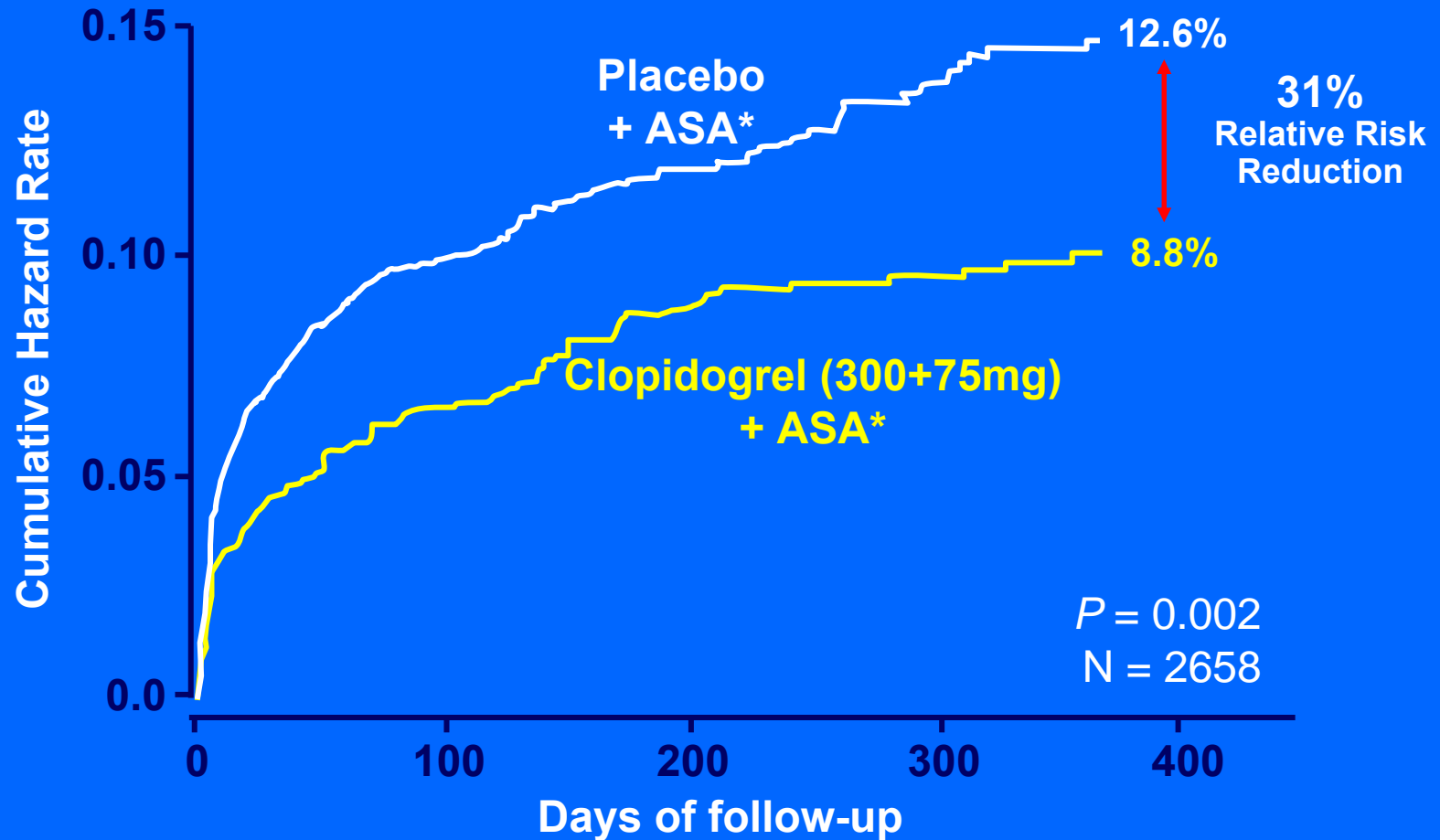
- Pretreatment**

- Timing of Loading Dose**

PCI-CURE: Overall Long-Term Results

NSTE-ACS, n=2.658

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



* In addition to other standard therapies.

Mehta et al for the CURE Investigators. *Lancet*. 2001;358:527-533.

Objectives

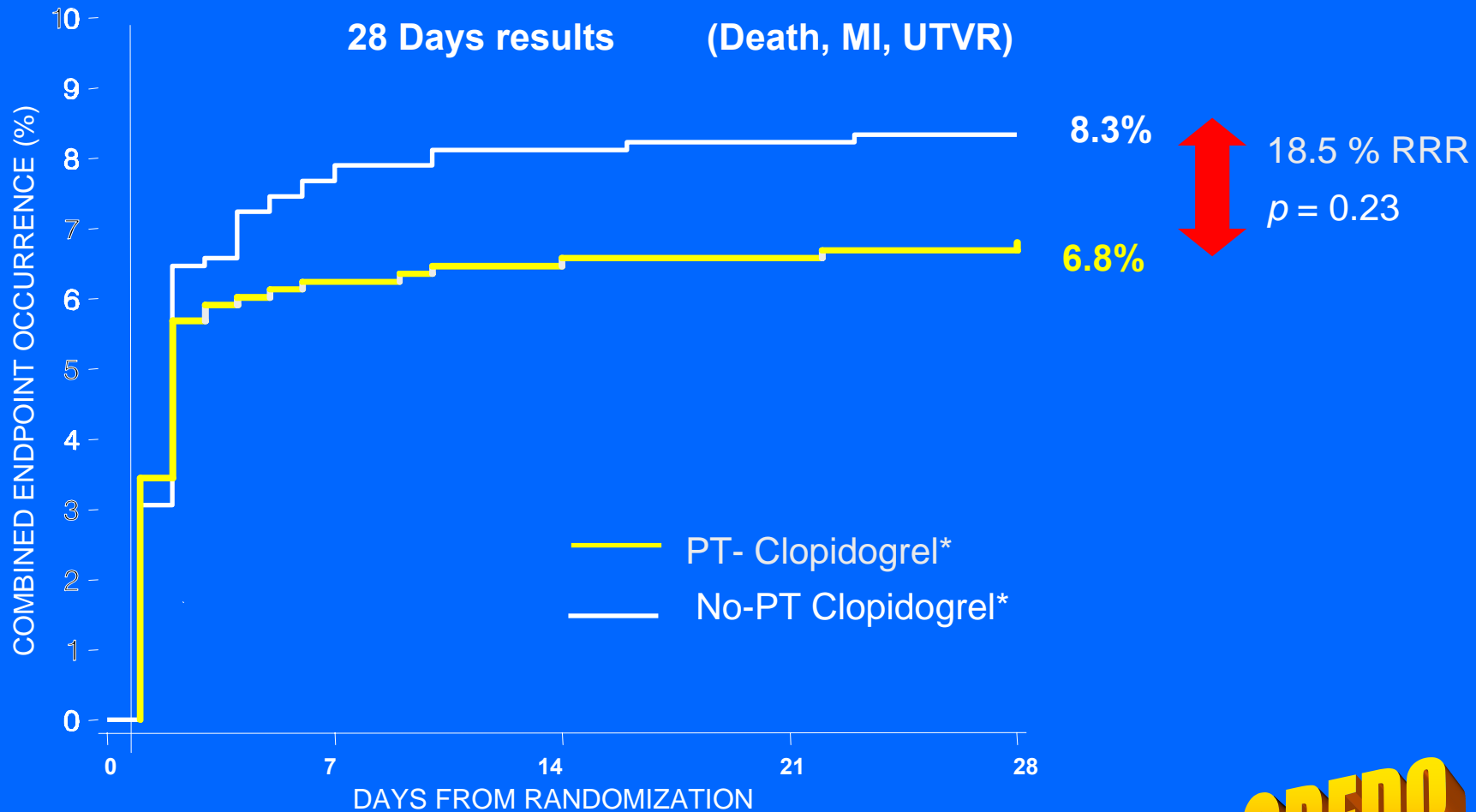
Objectives

- To evaluate the long term efficacy of prolonged (1 year) therapy with clopidogrel 75mg vs placebo in patients on top of standard therapy (including ASA)
- To evaluate the effect of pretreatment with a clopidogrel 300 mg loading dose on the composite of death (all-cause), MI (Q- or non-Q-wave), or UTVR at Day 28, in patients who underwent elective PCI
- To evaluate the safety of clopidogrel, specifically the frequency of major bleeding events and early discontinuation of study drug

UTVR= Urgent Target Vessel Revascularization



Early Effects of Pretreatment with Clopidogrel: Per - Protocol



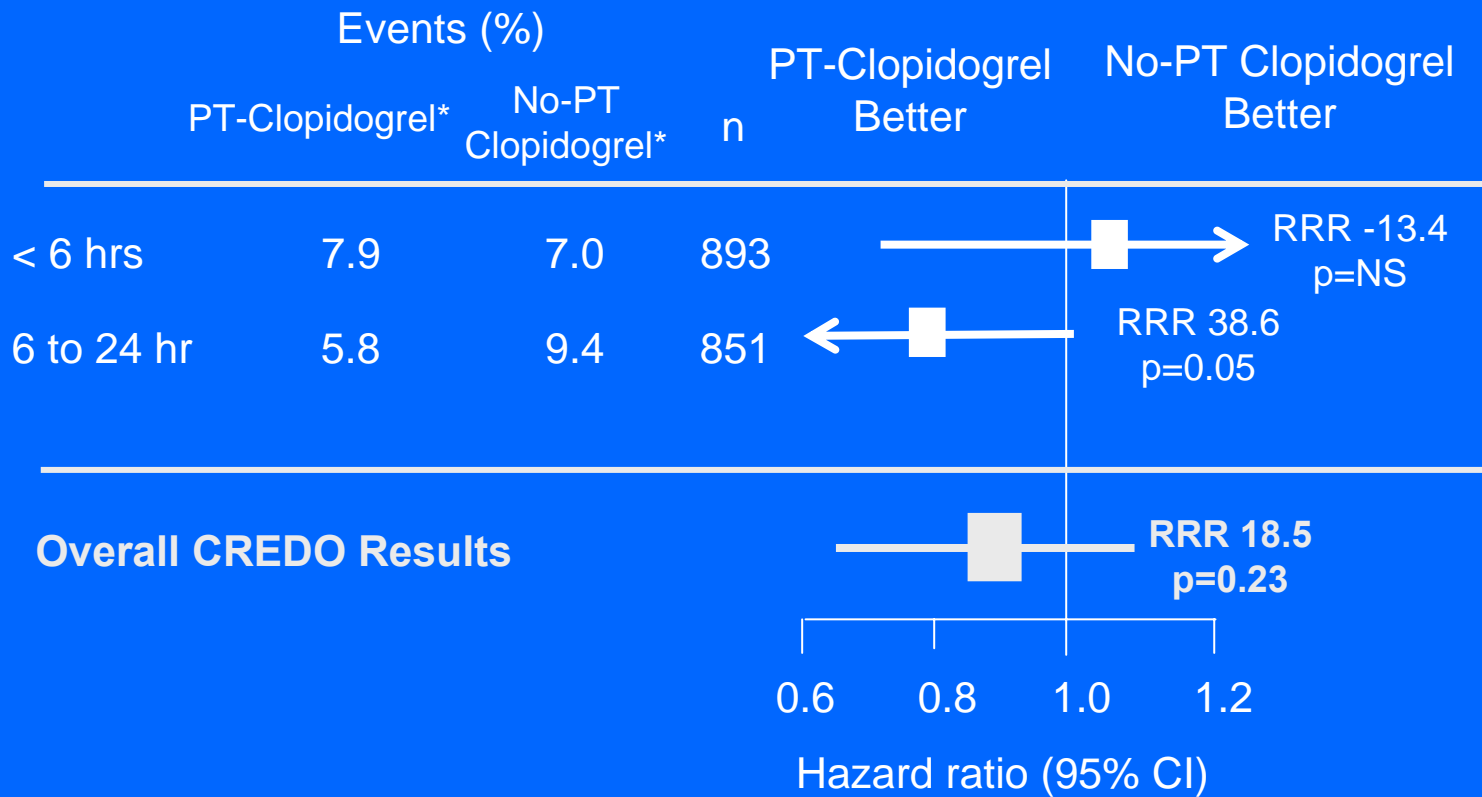
*From PCI to 28 days, on top of standard therapy including ASA (325mg from randomization to Day 28)

PT= Pretreatment

UTVR: Urgent Target Vessel Revascularization



Timing of Loading Dose - 28 Days

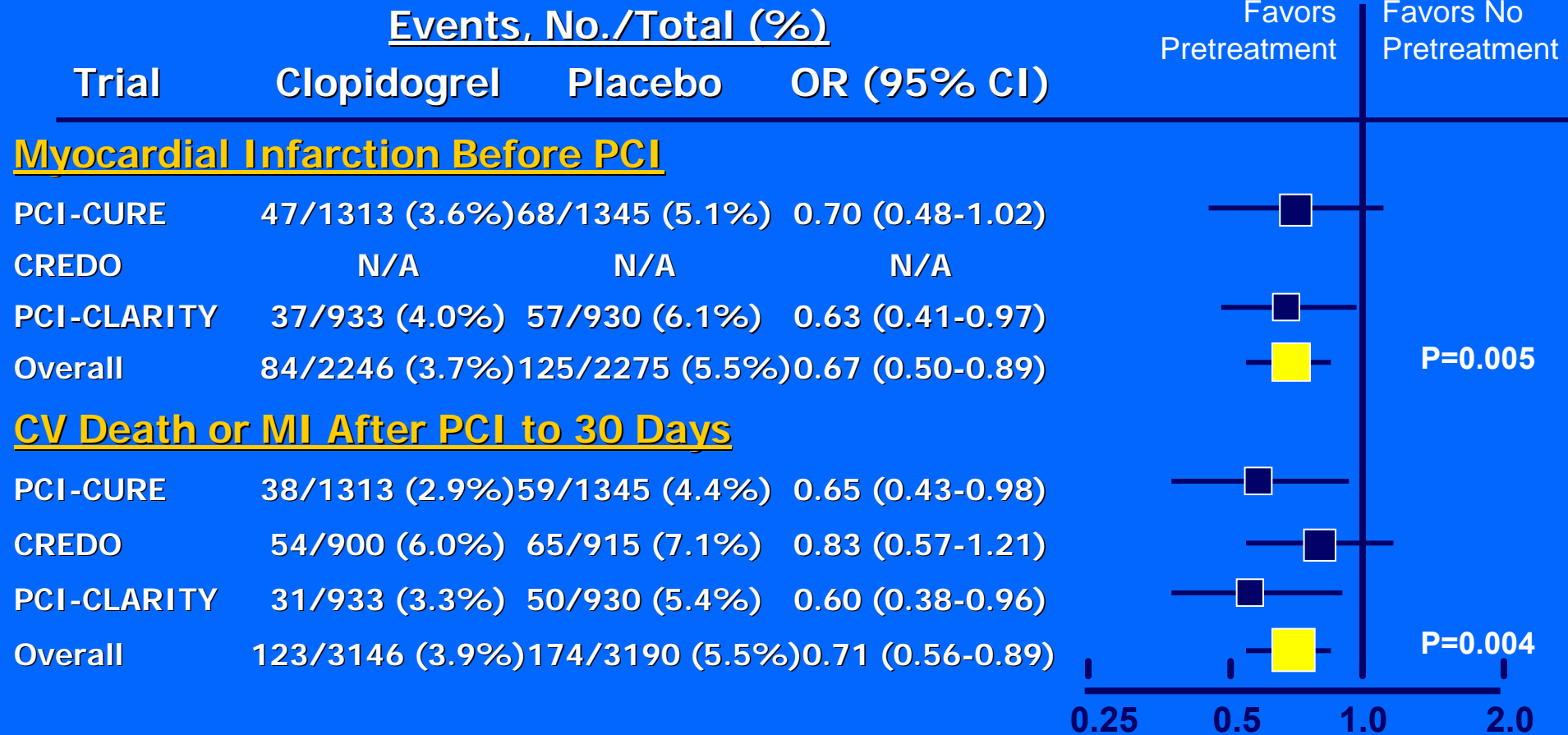


* On top of standard therapy including ASA, PT= Pretreatment



Meta-Analysis of Clopidogrel Pretreatment in PCI

Earlier is Better



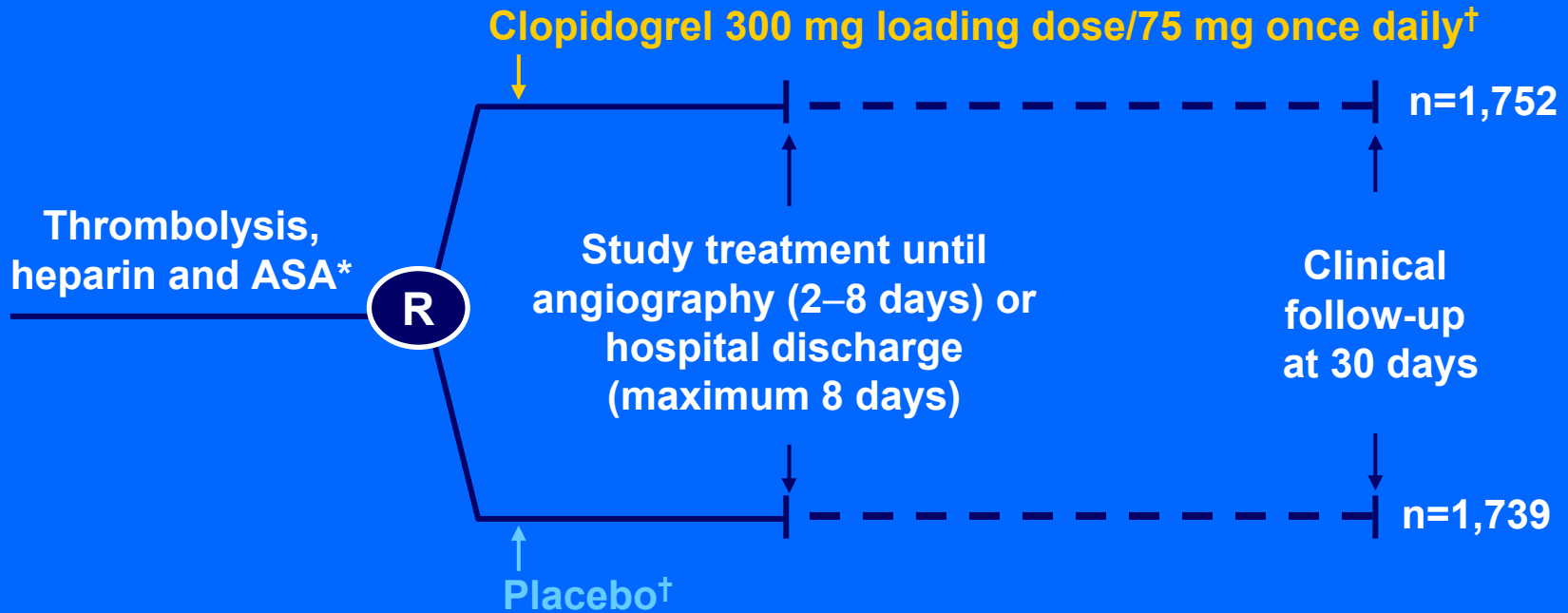
CLARITY, CLARITY-PCI & COMMIT

Hypothesis

- The addition of clopidogrel to standard fibrinolytic regimens that include aspirin would:
 - Improve infarct-related artery patency
 - Decrease ischemic complications

Study Design

Double-blind, randomized, placebo-controlled trial in patients aged 18–75 years with STEMI ≤ 12 hours



Primary endpoint: occluded artery (Thrombolysis In Myocardial Infarction [TIMI] flow grade [TFG] 0/1) on the angiogram or death/MI by time of angiography

*ASA=150–325 mg (if no ASA within prior 24 hours) as loading dose. Patients received heparin if they received a fibrin specific thrombolytic

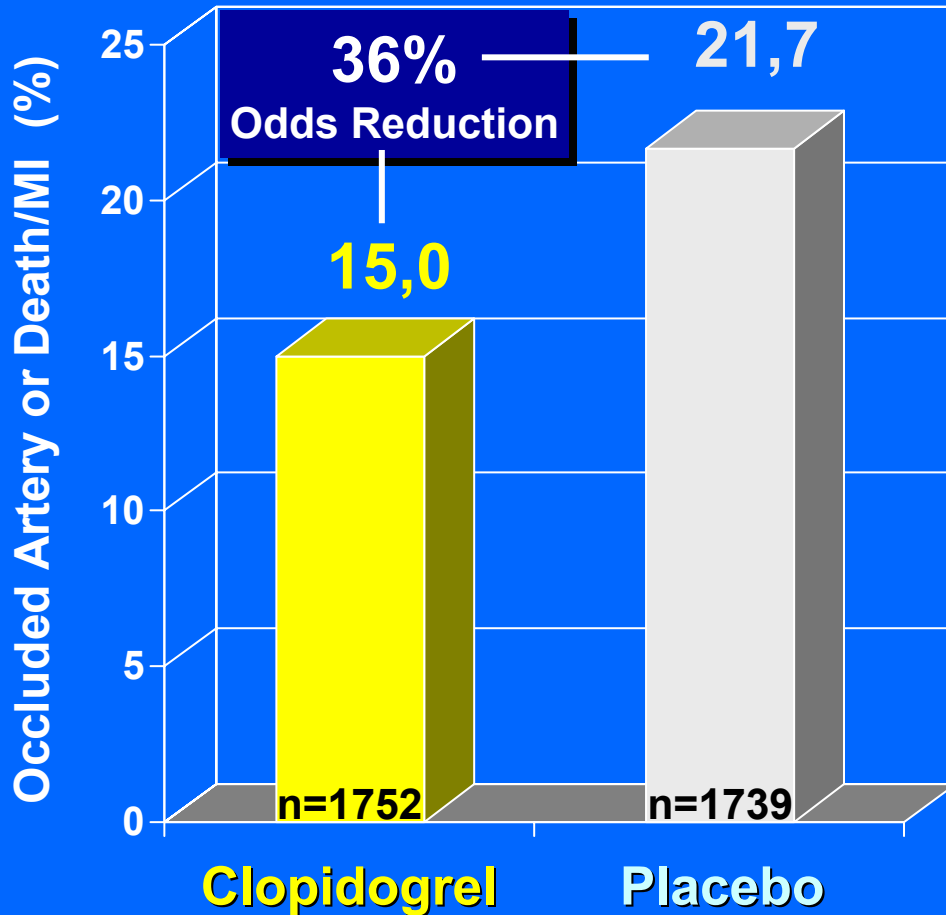
[†]All patients received ASA 75–162 mg/day plus other standard care

Interventions

Parameter	Clopidogrel	Placebo
Sx onset to fibrinolytic	2.7 hrs	2.6 hrs
Fibrinolytic to study drug	10 mins	10 mins
Median # doses of study med	4	4
Angiography	93.9%	94.2%
Study drug to angiography	3.5 days	3.5 days
Coronary revascularization	62.8%	62.4%
PCI	57.2%	56.6%
CABG	5.9%	6.0%

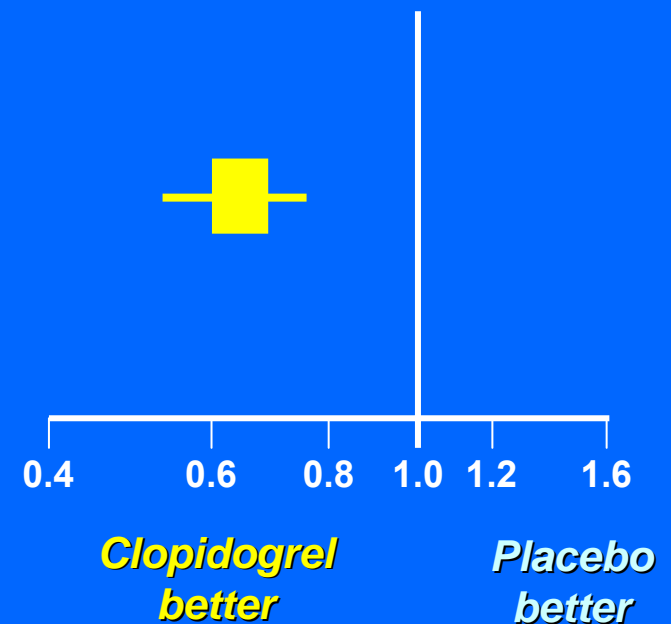
Primary Endpoint:

Occluded Artery (or D/MI thru Angio/HD)



Odds Ratio 0.64
(95% CI 0.53-0.76)

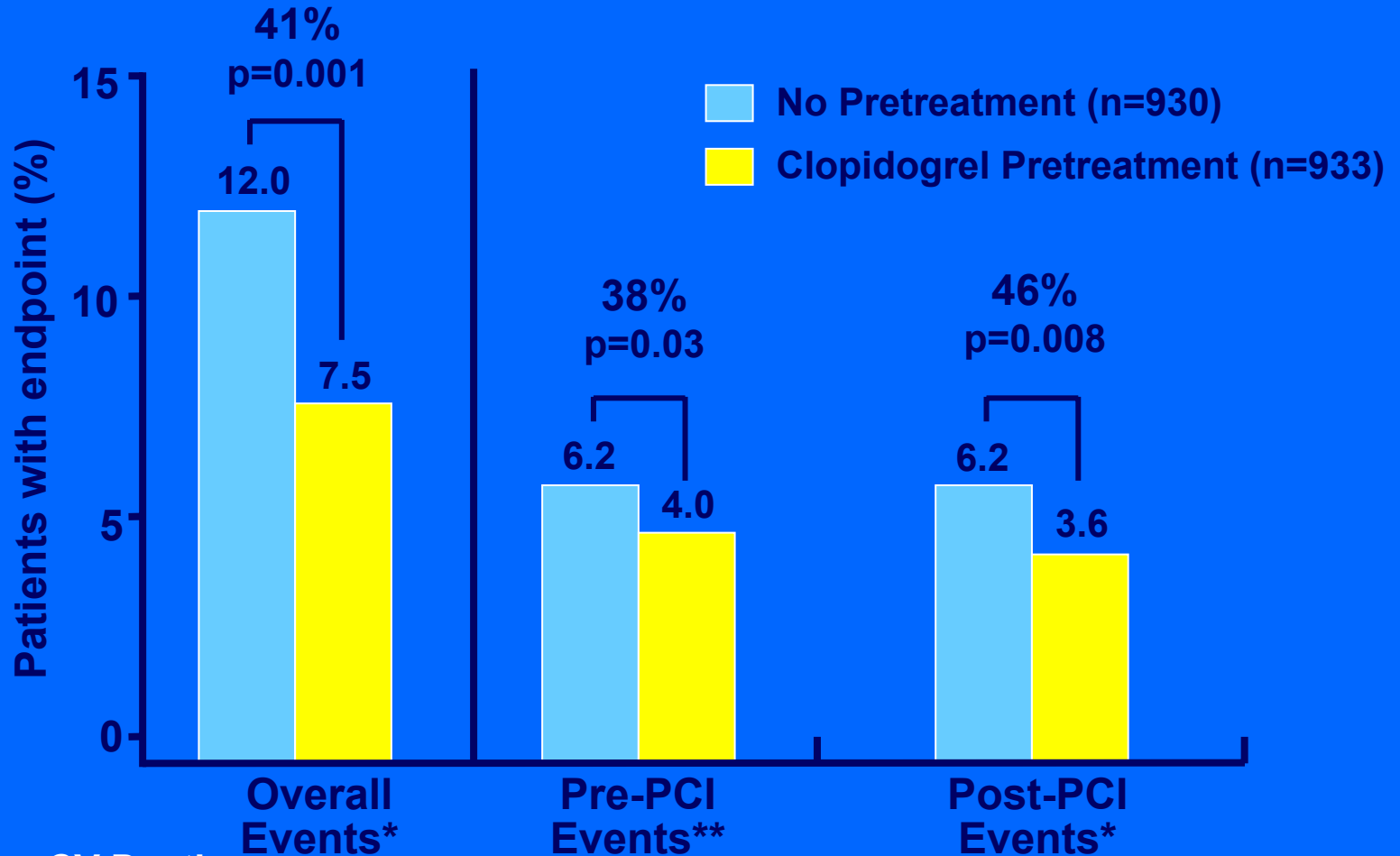
$P=0.00000036$



PCI-CLARITY: Purpose

To test the hypothesis that in patients undergoing PCI after initial pharmacologic therapy for STEMI, clopidogrel pretreatment hours to days before PCI is superior to clopidogrel pretreatment initiated at the time of PCI in preventing major cardiovascular events

PCI-CLARITY: Overall Results

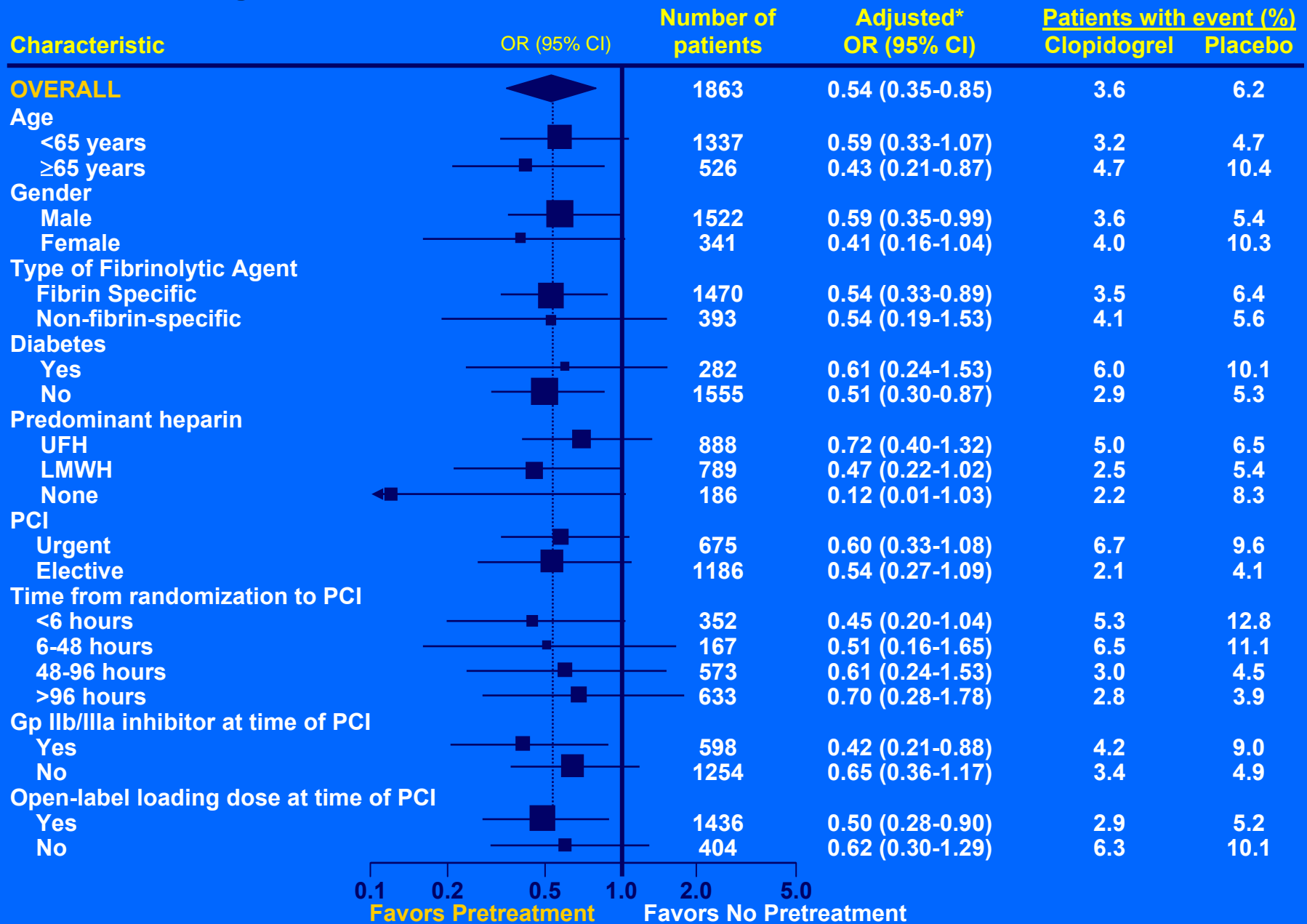


*MI, Stroke, or CV Death

**MI or Stroke

Overall events includes events from randomization through 30 days. Percent reduction based on odds ratio for event rates. Odds ratios adjusted for propensity score for likelihood of PCI, type of lytic, initial type of heparin, and infarct location.

PCI-CLARITY: Consistent Results for Primary Endpoint Across Subgroups

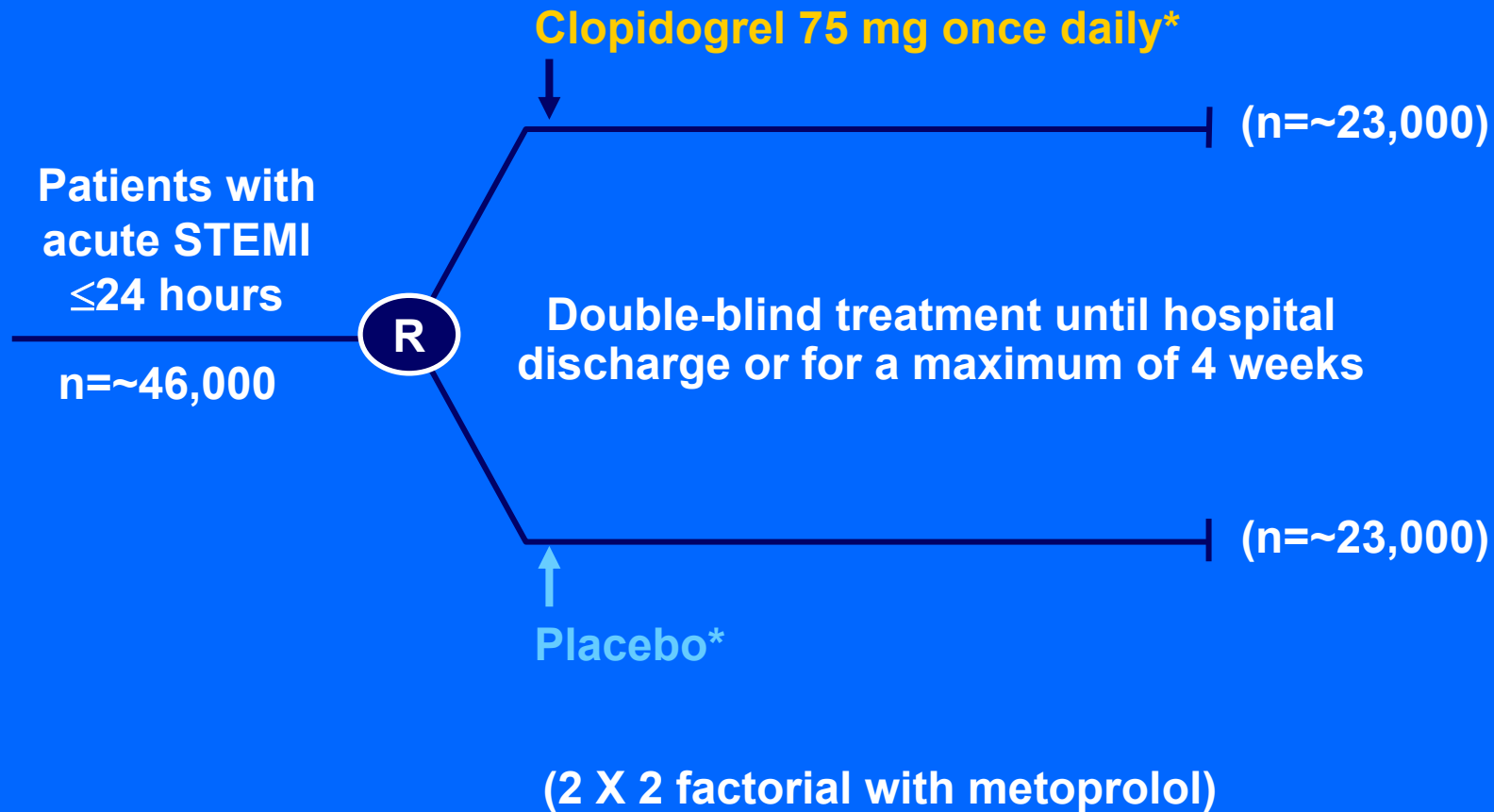


COMMIT/CCS-2: Clopidogrel and Metoprolol in Myocardial Infarction Trial

Purpose:

To determine whether adding clopidogrel can produce a further reduction in mortality and the risk of vascular events in hospitalized patients admitted with acute STEMI¹

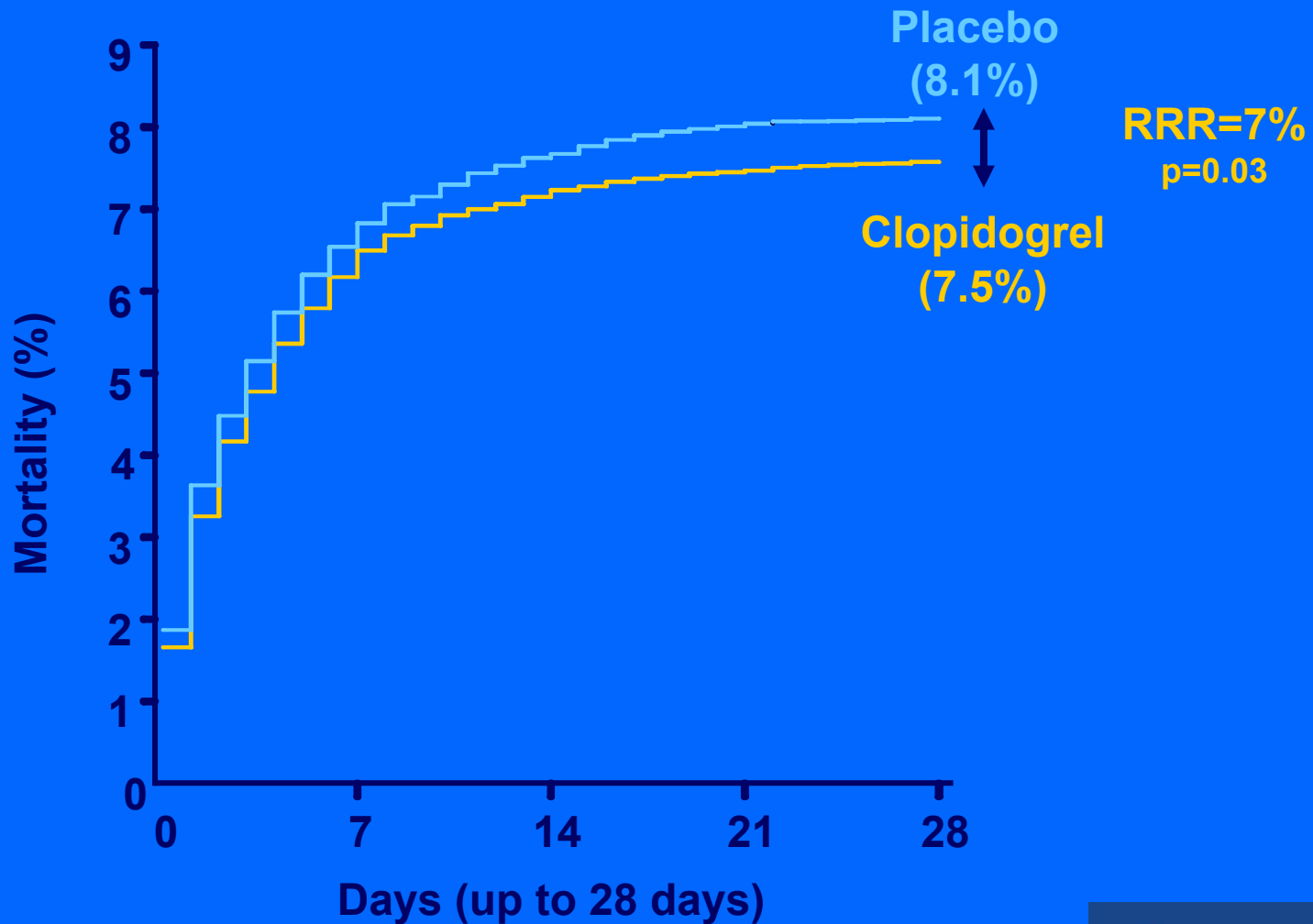
Study Design



*All patients received a background of ASA 162 mg/day during the study



Mortality



Complementary Results of CLARITY, CLARITY-PCI and COMMIT for Patients with STEMI

- Significant improvement in coronary perfusion and clinical outcomes versus standard care (CLARITY, CLARITY-PCI)
- Significant reduction in mortality for patients receiving clopidogrel versus standard care alone (COMMIT)
- No significant increase in major bleeding or ICH (COMMIT and CLARITY)

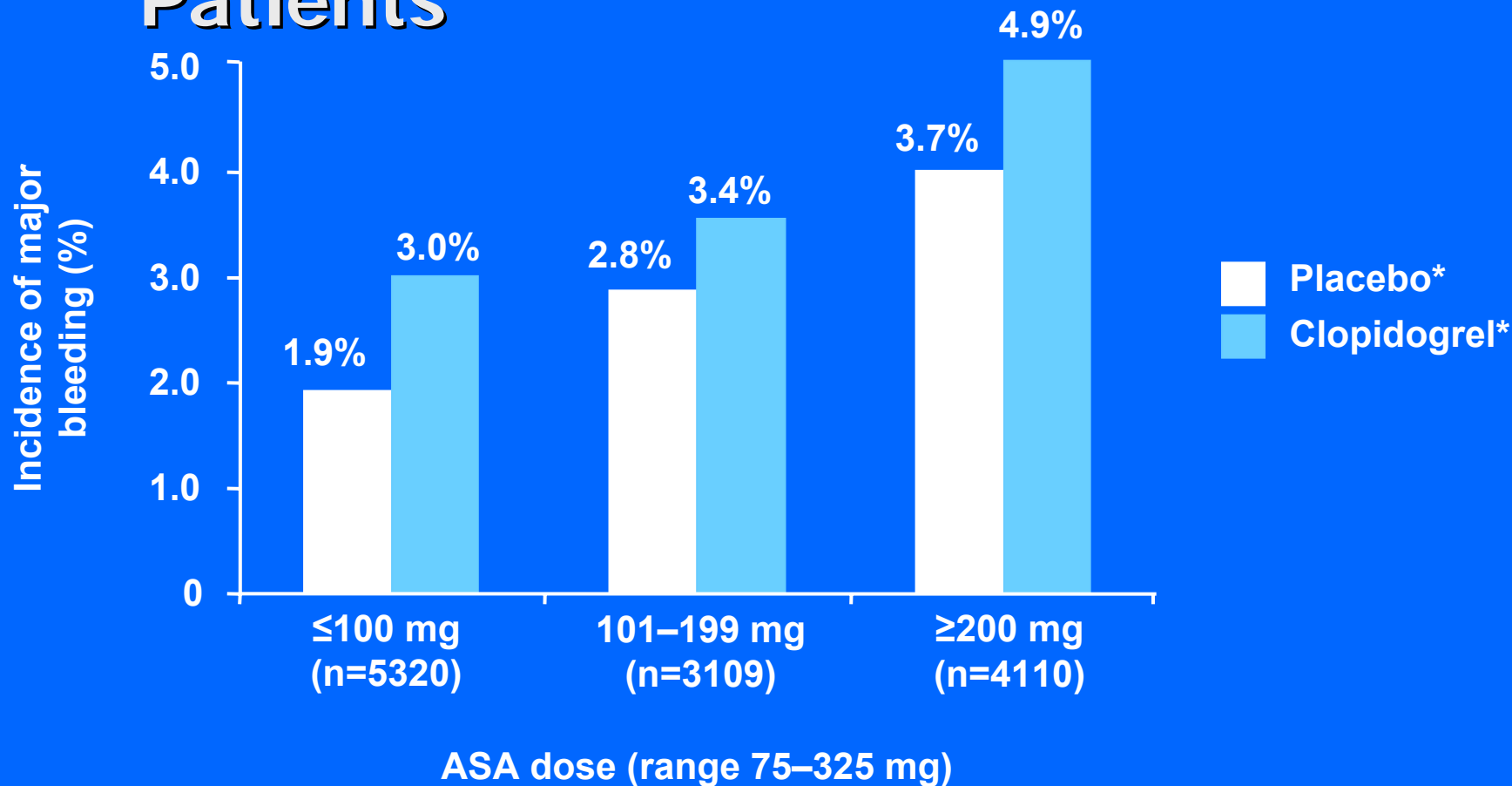
Safety Profile of Clopidogrel

CURE: Safety Profile of Clopidogrel in ACS Patients

Event	Placebo* (n=6303)	Clopidogrel* (n=6259)	p value
Major bleeding	2.7%	3.7%	0.001
Life-threatening bleeding	1.8%	2.2%	0.13
Fatal	0.2%	0.2%	—
Causing a 5 g/dL drop in hemoglobin	0.9%	0.9%	—
Requiring transfusion ≥ 4 units blood	1.0%	1.2%	—
Causing hemorrhagic stroke	0.1%	0.1%	—
Requiring surgery	0.7%	0.7%	—
Hypotension requiring inotropic agents	0.5%	0.5%	—
Non life-threatening bleeding	0.9%	1.5%	0.002

*On a background of standard therapy (including ASA)

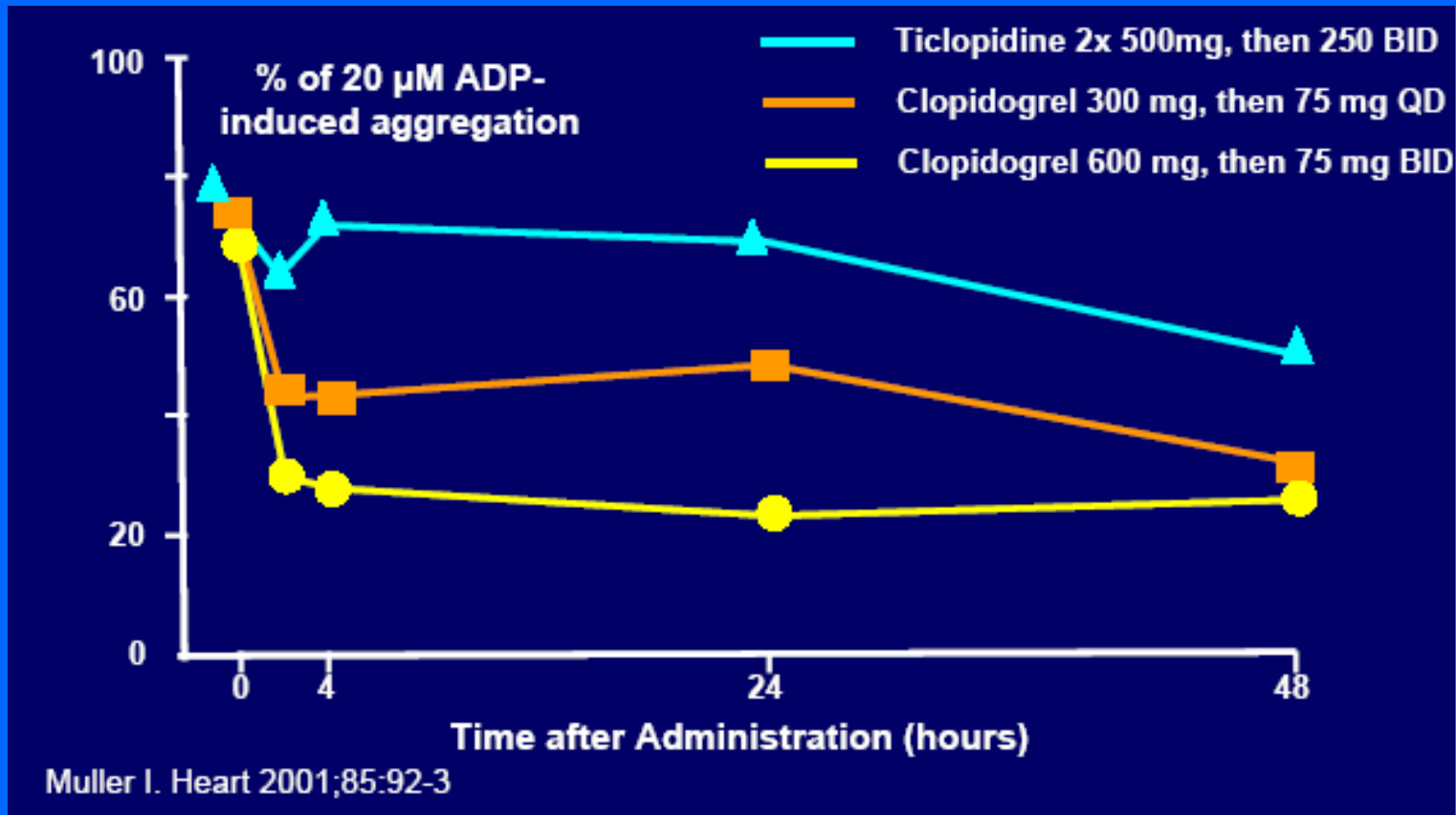
CURE: Relationship Between Major Bleeding and ASA Dose in ACS Patients



*On a background of standard therapy (including ASA)

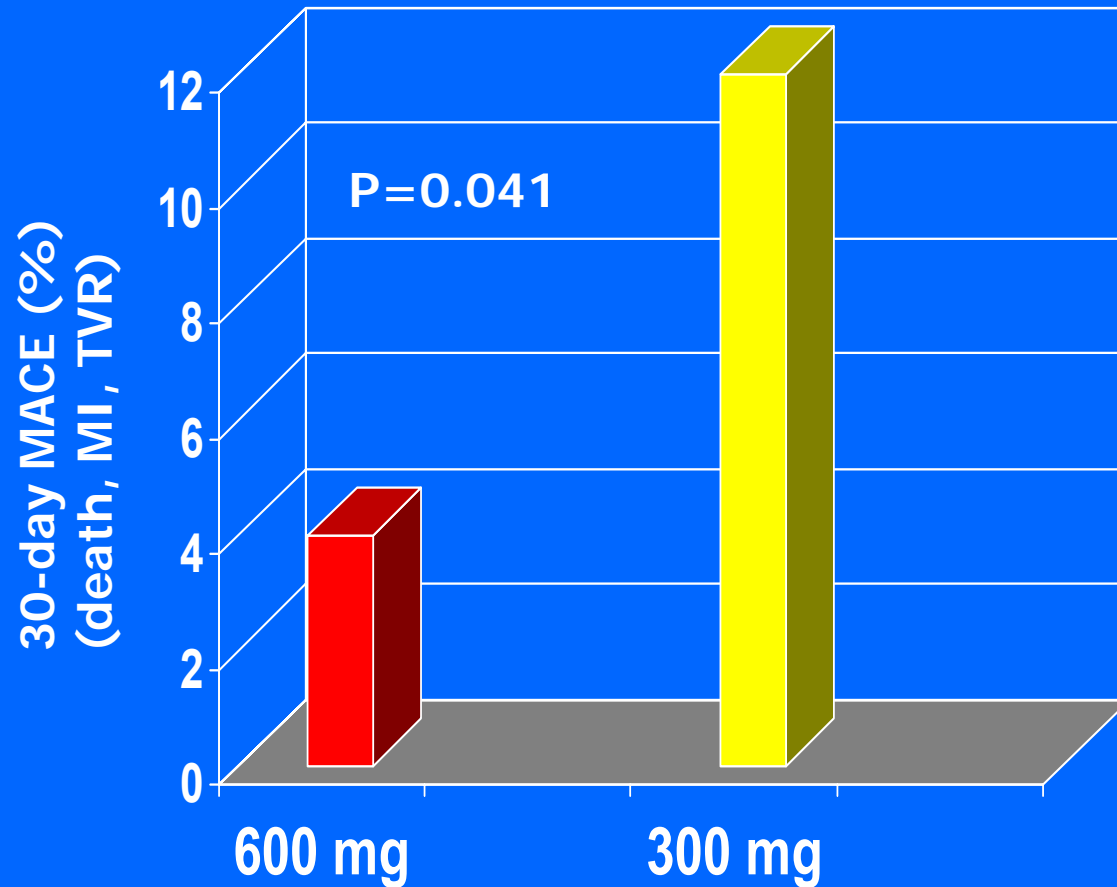
Clopidogrel Loading Dose

Thienopyridines Loading Doses and Platelet Aggregation

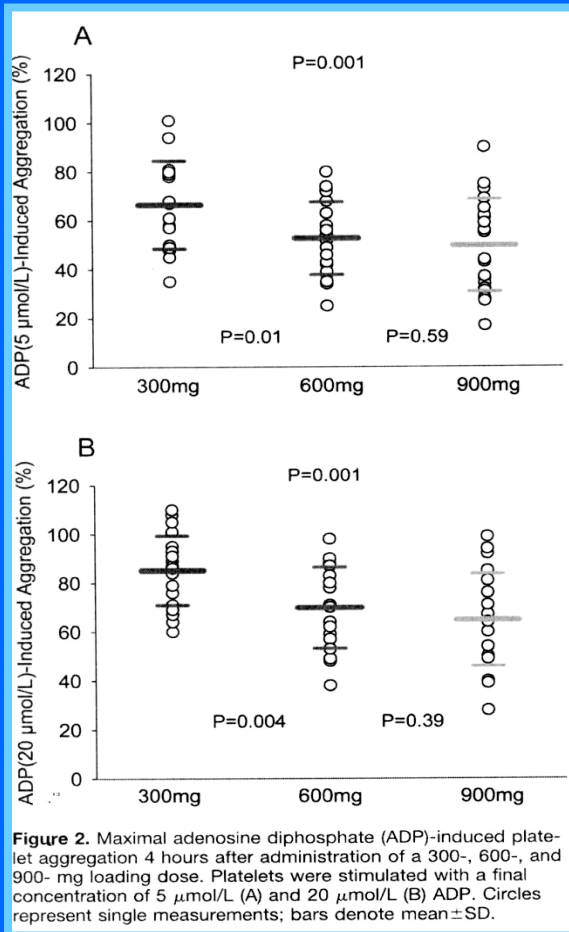


ARMYDA-2: Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty

255 pts with stable CAD or NSTEMI-ACS prior to PCI

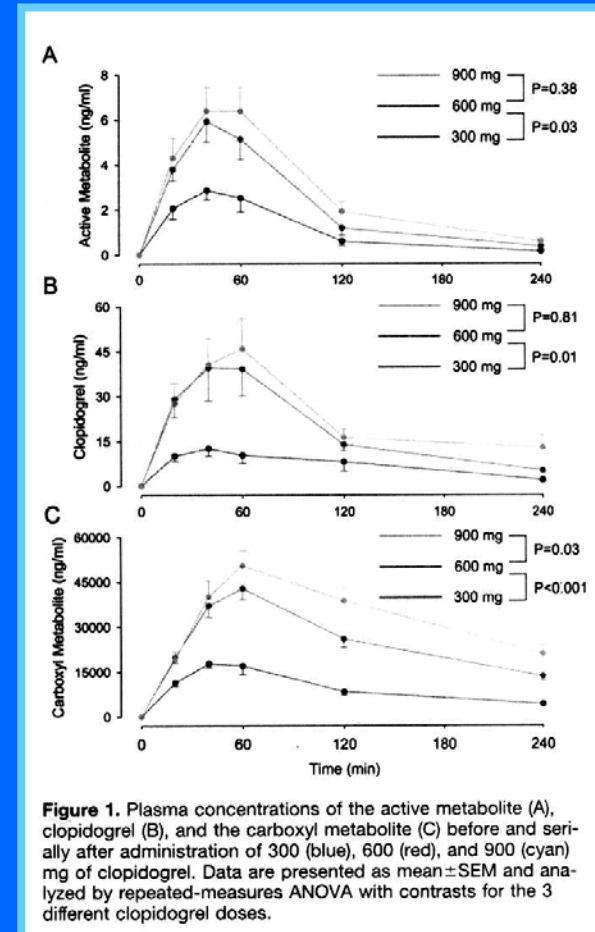


Clopidogrel Loading Before PCI: Do We Use the Right Dose?



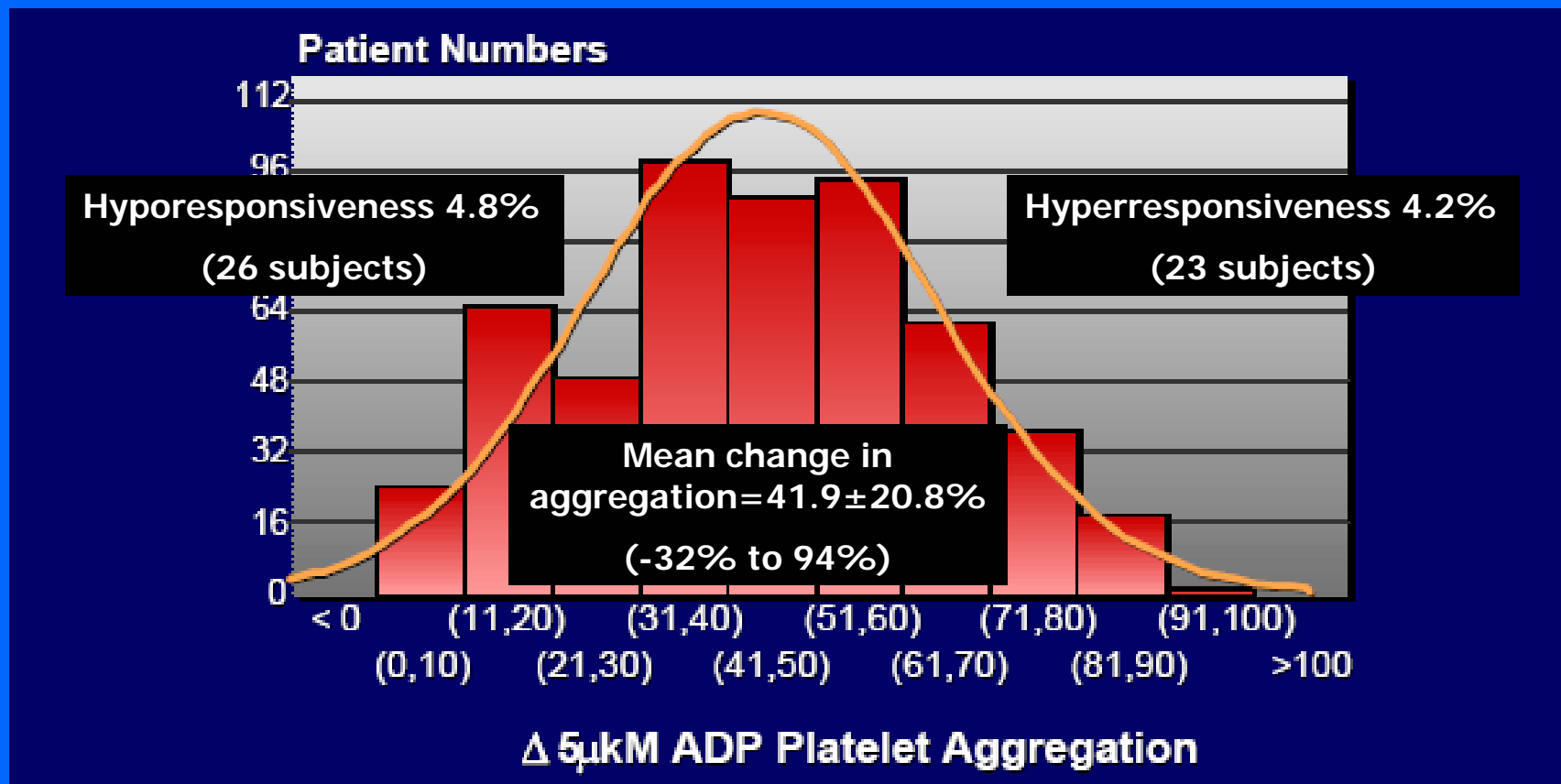
Advantage of 600 mg loading dose over 300 mg. No additional suppression of platelet function after 900 mg loading dose because of limited clopidogrel absorption.

Beckerath N et al., Circulation 2005; 112: 2946-50



Clopidogrel Resistance

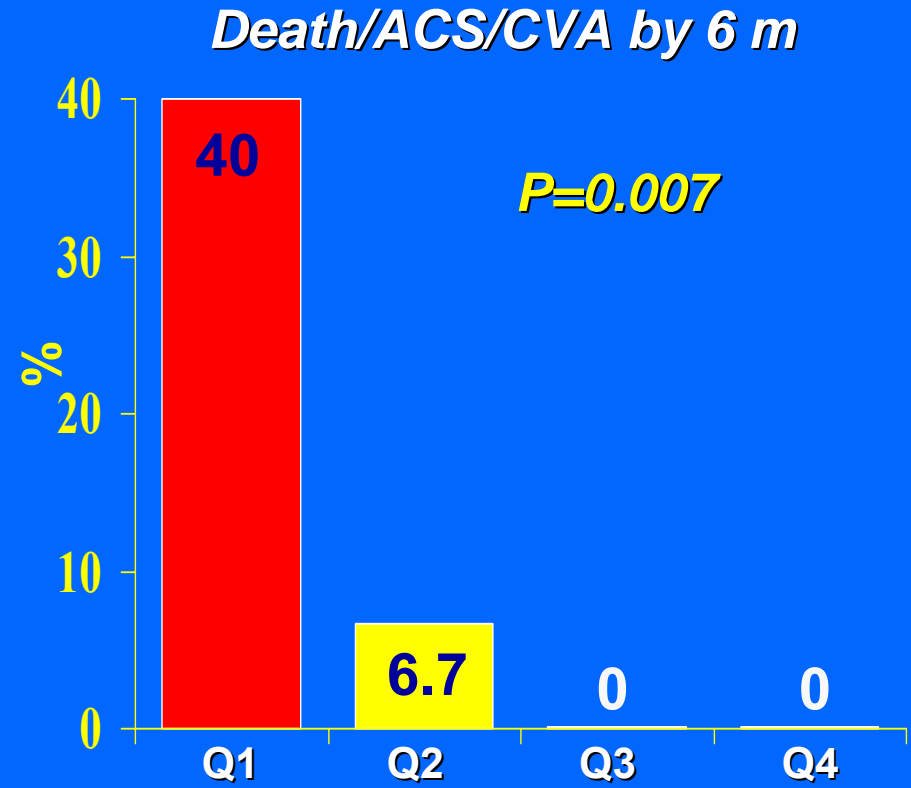
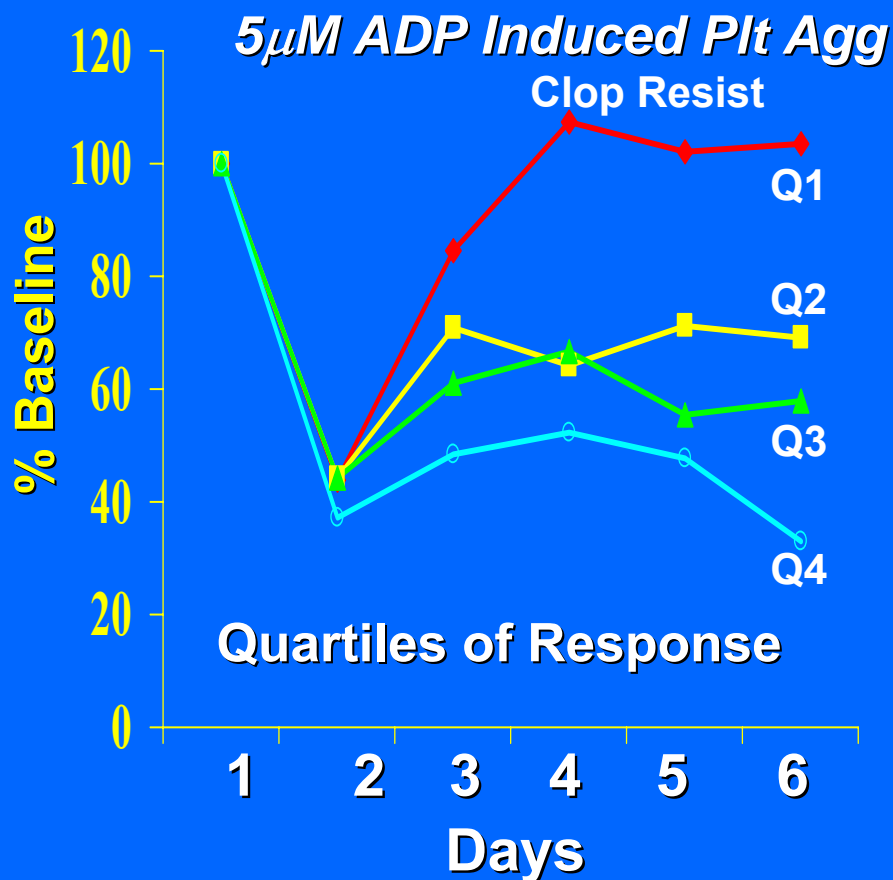
Variability in Platelet Responsiveness to Clopidogrel among 544 Individuals



P=NS for hyper-, hypo- and standard responders to Clopidogrel in regard to demographics, clinical characteristics and medications

Clopidogrel Resistance is Associated with Increased Risk of Ischemic Events

N = 60 Primary PCI for STEMI



Does platelet responsiveness to Clopidogrel has an effect on periprocedural events in PCI patients?

Studies underway:

- CAVIAR Trial
- RESISTOR Trial

Predictors of Stent Thrombosis

Table 3. Independent Predictors of Stent Thrombosis

Variables	Hazard Ratio (95% Confidence Interval)	P Value
Subacute stent thrombosis		
★ Premature antiplatelet therapy discontinuation ★	161.17 (26.03-997.94)	<.001
Renal failure	10.06 (3.13-32.35)	<.001
Bifurcation lesion	5.96 (1.90-18.68)	.002
Diabetes	5.84 (1.74-19.55)	.004
Left ventricular ejection fraction per 10% decrease	1.12 (1.06-1.19)	<.001
Stent length, per 1-mm increase	1.03 (1.00-1.05)	.01
Late stent thrombosis		
★ Premature antiplatelet therapy discontinuation ★	57.13 (14.84-219.96)	<.001
Bifurcation lesion	8.11 (2.50-26.26)	.001
Left ventricular ejection fraction per 10% decrease	1.06 (1.01-1.12)	.03
Cumulative stent thrombosis		
Premature antiplatelet therapy discontinuation	89.78 (29.90-269.60)	<.001
Renal failure	6.49 (2.60-16.15)	<.001
Bifurcation lesion	6.42 (2.93-14.07)	<.001
Diabetes	3.71 (1.74-7.89)	.001
Left ventricular ejection fraction per 10% decrease	1.09 (1.05-1.13)	<.001

Conclusions

Thienopiridines in STEMI after CLARITY-PCI

- Antiplatelet therapy with thienopiridines is primary pharmacologic facilitation in STEMI patients who undergo PCI and/fibrinolysis
- Clopidogrel in combination with aspirin is cornerstone in STEMI reperfusion treatment with reduction of adverse cardiovascular events seen prior and after PCI (CLARITY-PCI)
- There is no increase in major bleeds with clopidogrel in STEMI patients, however the dose of ASA is crucial
- The loading dose of Clopidogrel in STEMI patients treated by means of primary PCI is not well established (ESC – 600 mg, AHA/ACC – 300 mg). Probably higher dose (900 mg) is not clinically beneficial
- Clopidogrel resistance may be an issue, however more clinical data are needed