

9th Angioplasty Summit 2004, Seoul, Korea, April 2004.

Clopidogrel in Cardiovascular Disease

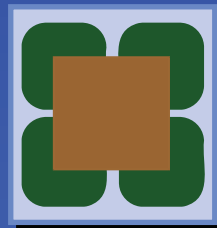
A. Michael Lincoff, M.D.

Associate Professor of Medicine

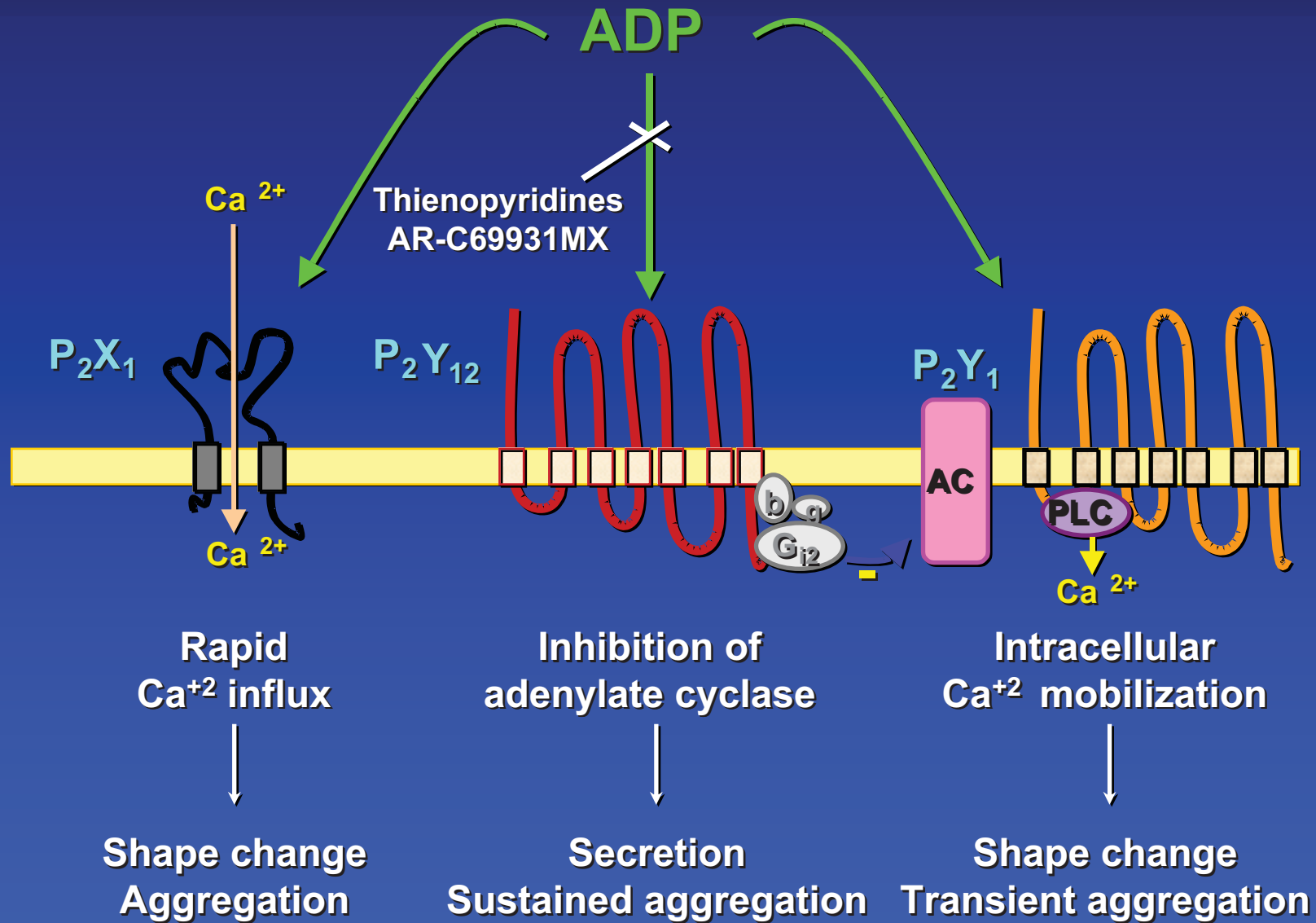
Department of Cardiovascular Medicine

THE CLEVELAND CLINIC FOUNDATION

Cleveland, Ohio



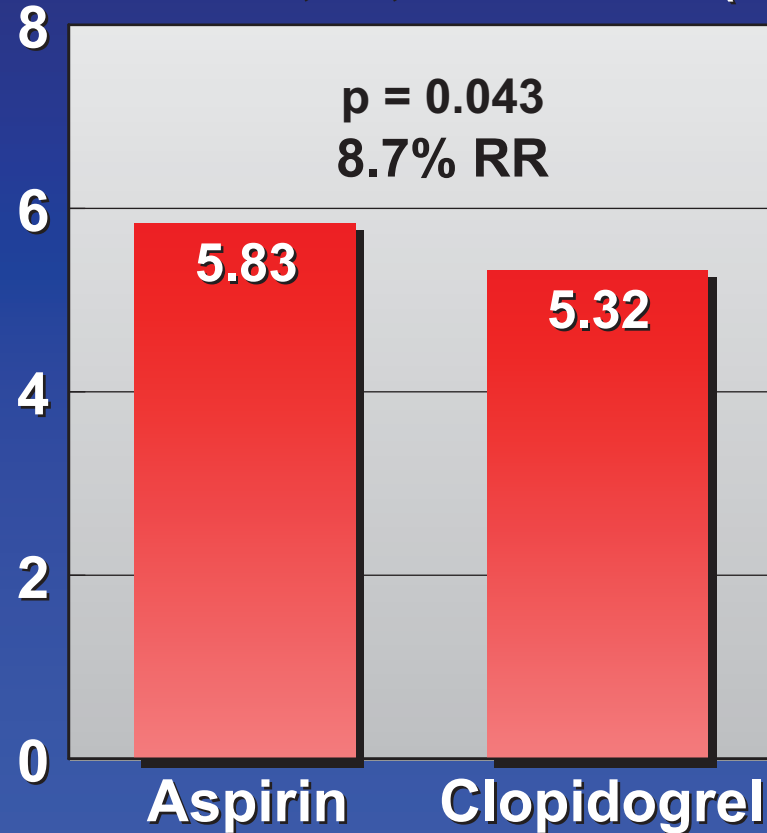
Platelet ADP Receptors



CAPRIE

Clopidogrel vs Aspirin - Randomized Trial

Isch Stroke, MI, Vasc Death (%)



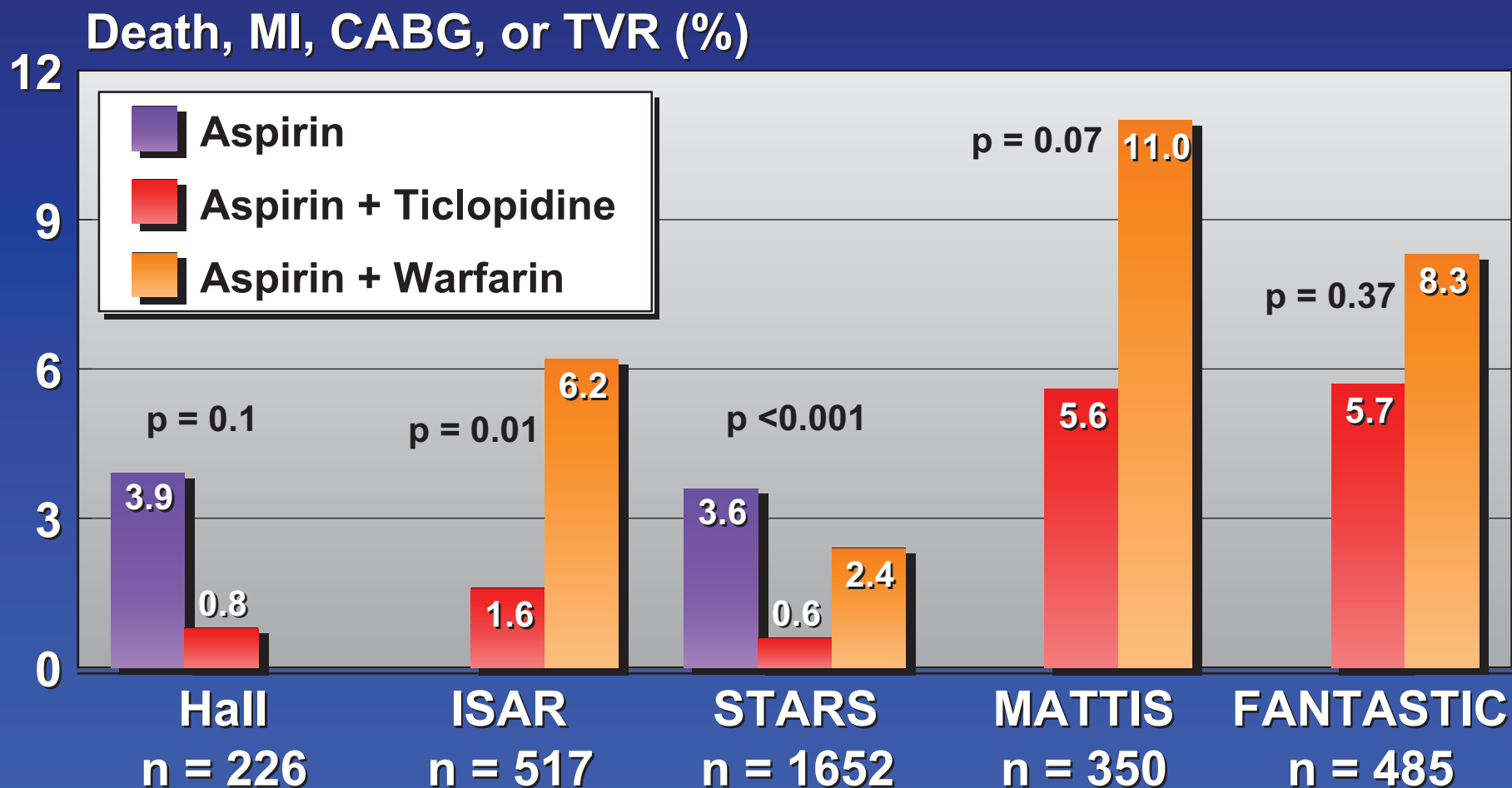
- Randomized, double-blind trial
- Clopidogrel 75 mg qd vs Aspirin 325 mg qd
- 19,185 patients, followed for 1 to 3 yrs (mean 1.91 yrs)
- Entry with MI, stroke, or PVD

CAPRIE Steering Committee. Lancet 1996;348:1329.



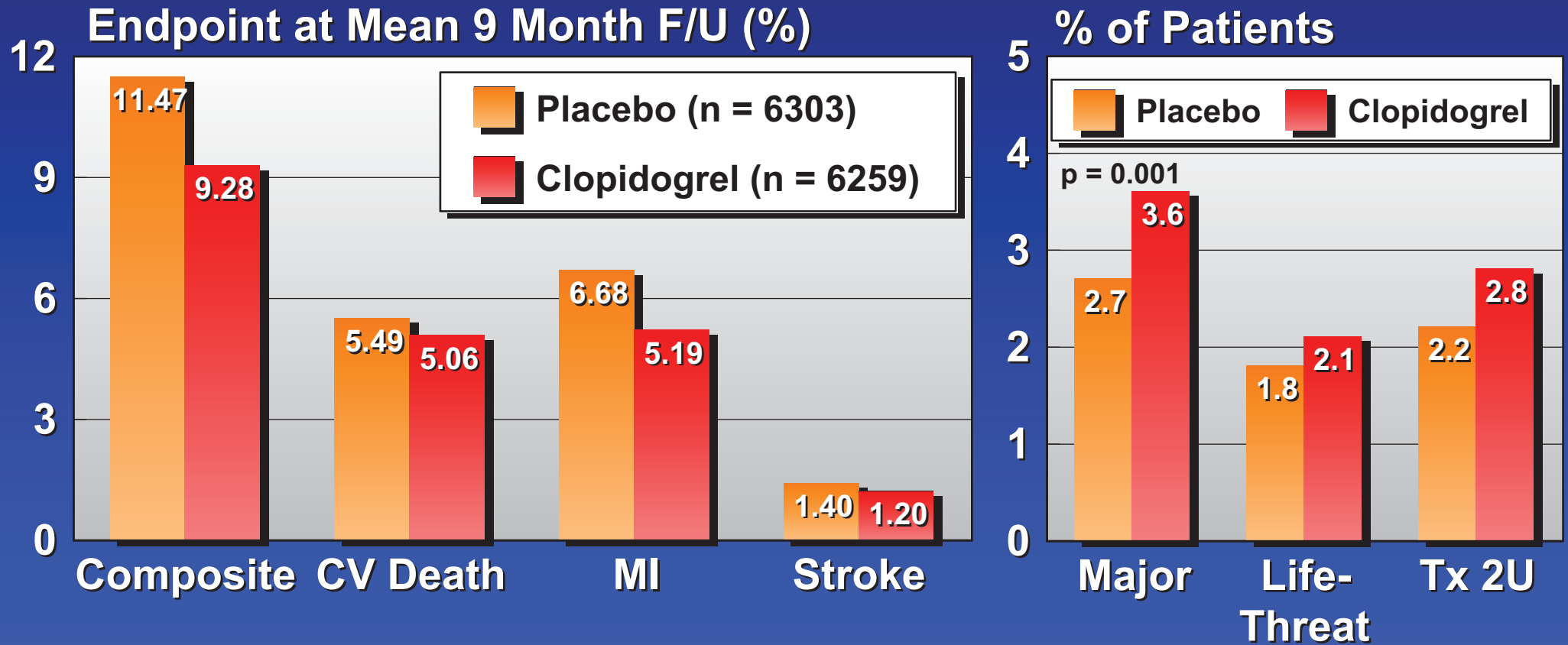
Ticlopidine in Stenting

Randomized Trials



CURE Trial

Clopidogrel in Non-ST Elevation ACS



CURE Investigators. NEJM 2001;345:494.

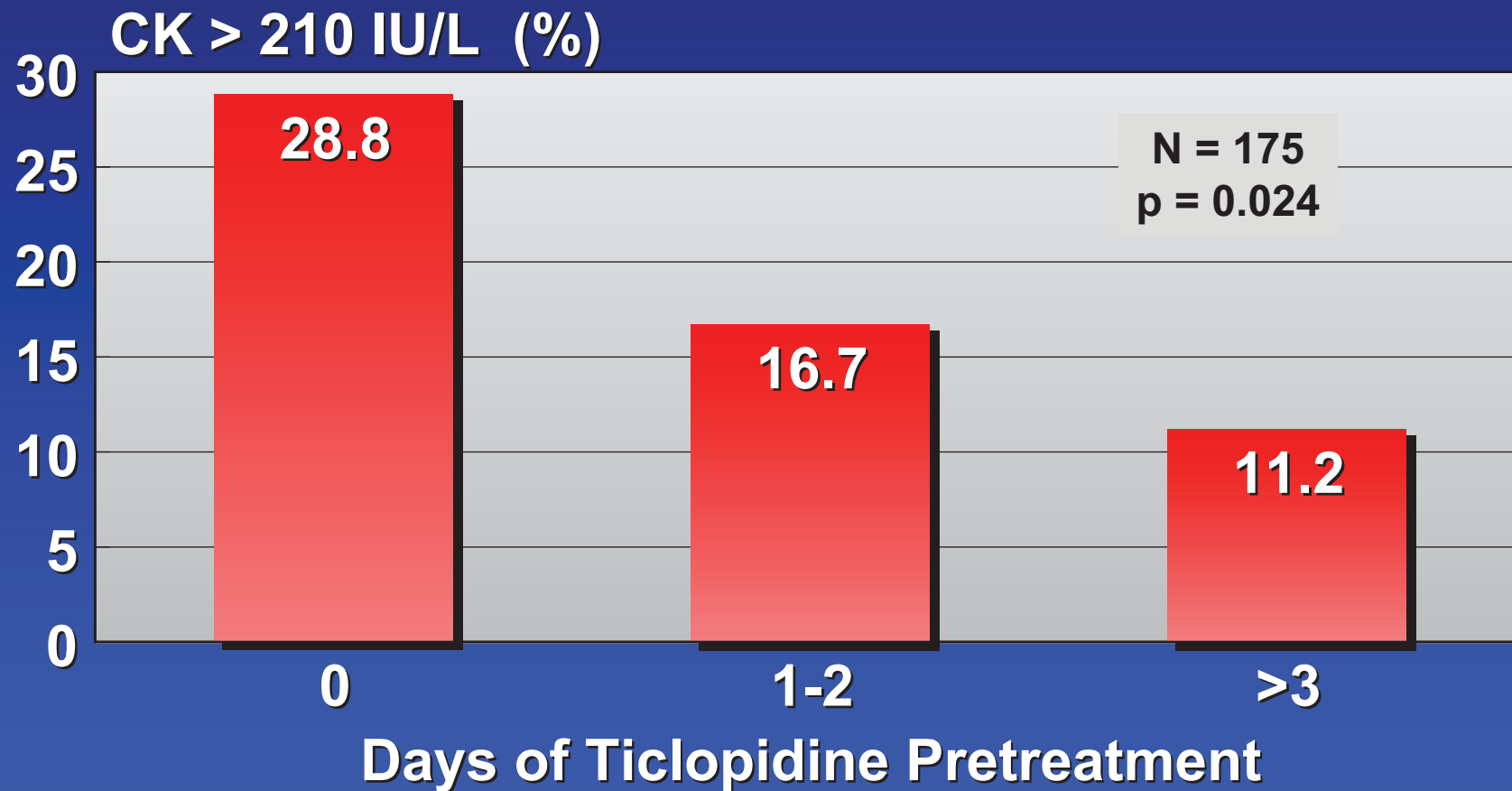


Clopidogrel in CAD

- ◇ **When should it be started**
- ◇ **What else is needed**
- ◇ **When should it be stopped**
- ◇ **The future**

Ticlopidine and Stenting

Pretreatment - Cleveland Clinic Experience

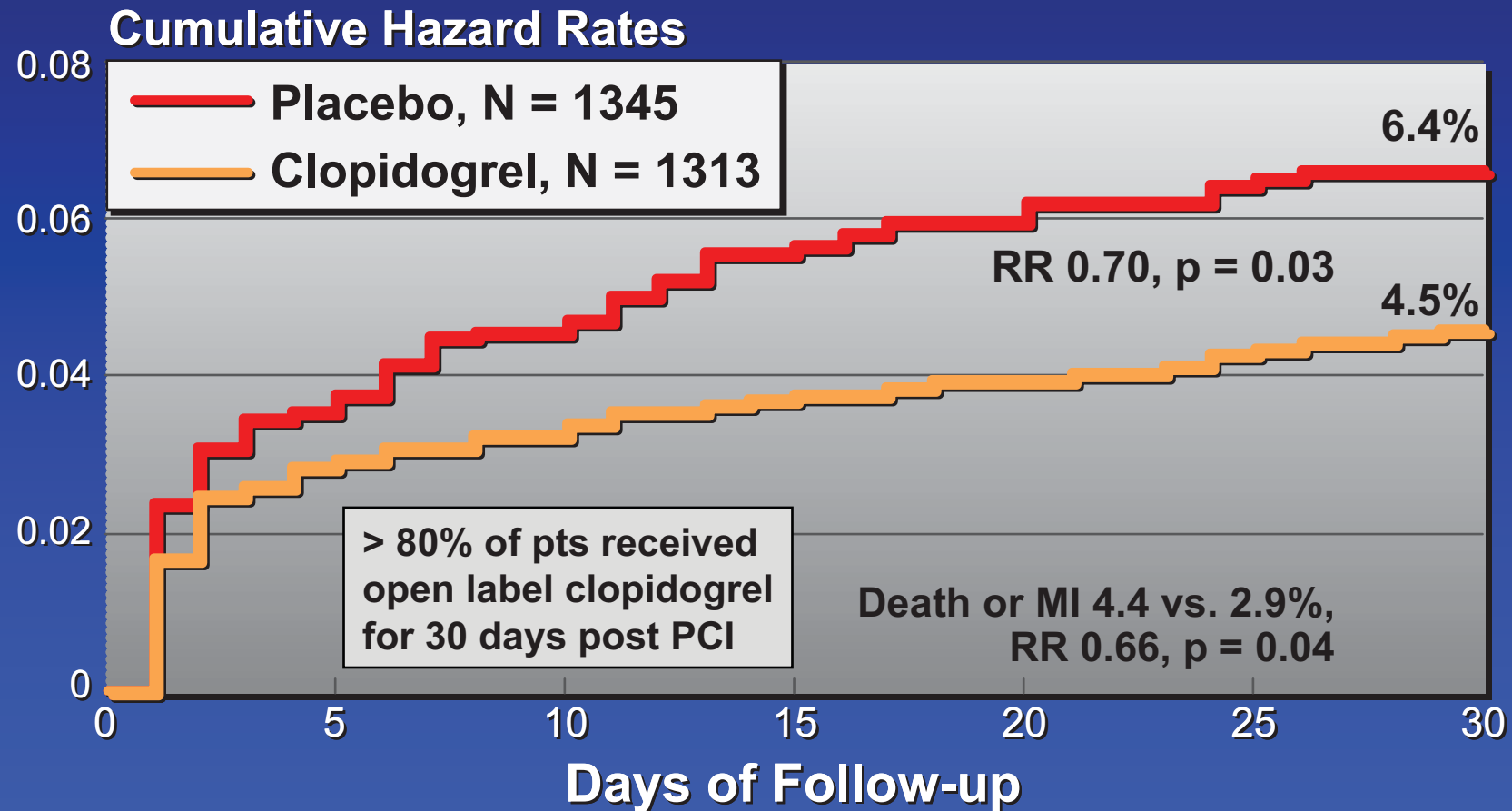


Steinhubl et al. JACC 1998;32:1366.



PCI CURE

Clopidogrel in Non-ST Elevation ACS Death, MI, Urgent Revascularization



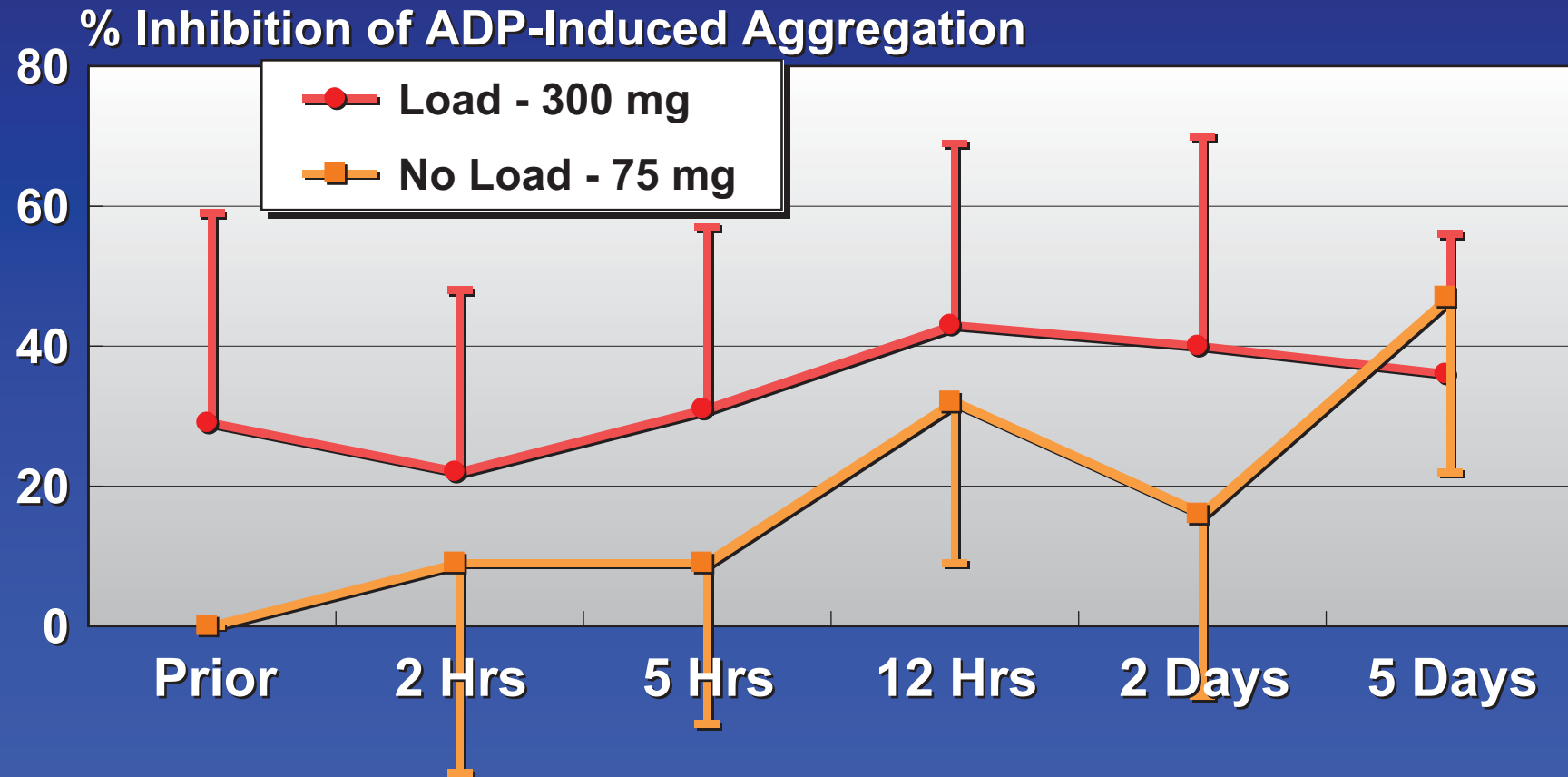
Mehta et al, Lancet 358:527–33, 2001



Platelet Inhibition - Pre-PCI Clopidogrel

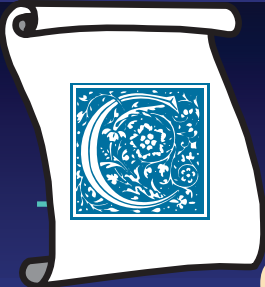
PRONTO Trial

100 pts randomized: clopidogrel load (3-24 hrs prior) or no load



Gurbel et al. Am Heart J 2003;145:239.



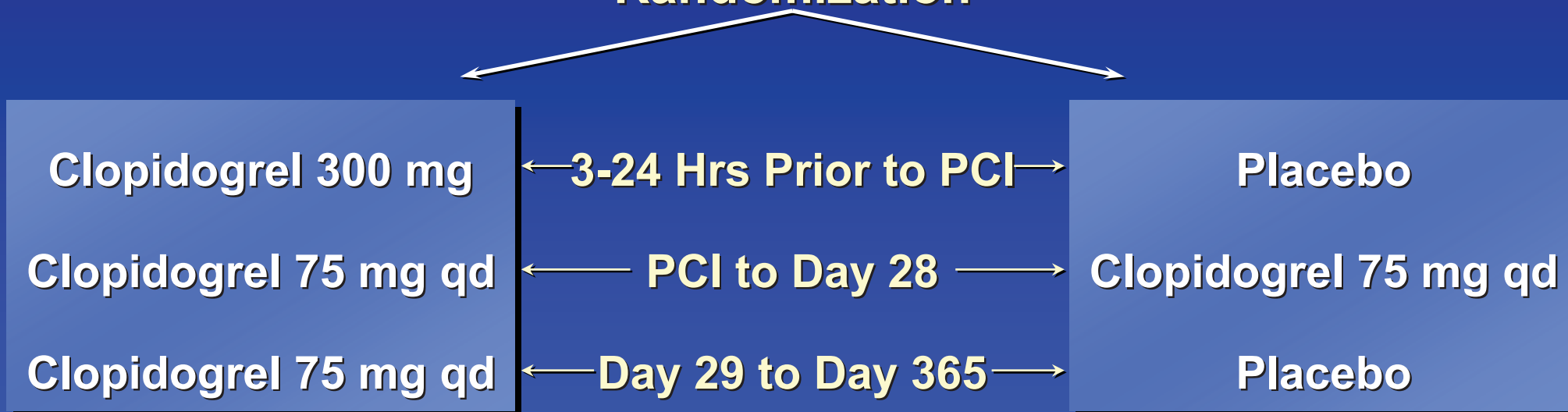


CREDO Trial

Clopidogrel PreRx and Prolonged Rx in PCI

N = 2116 Patients (6/99 - 4/01): Planned PCI
All patients received aspirin

Randomization

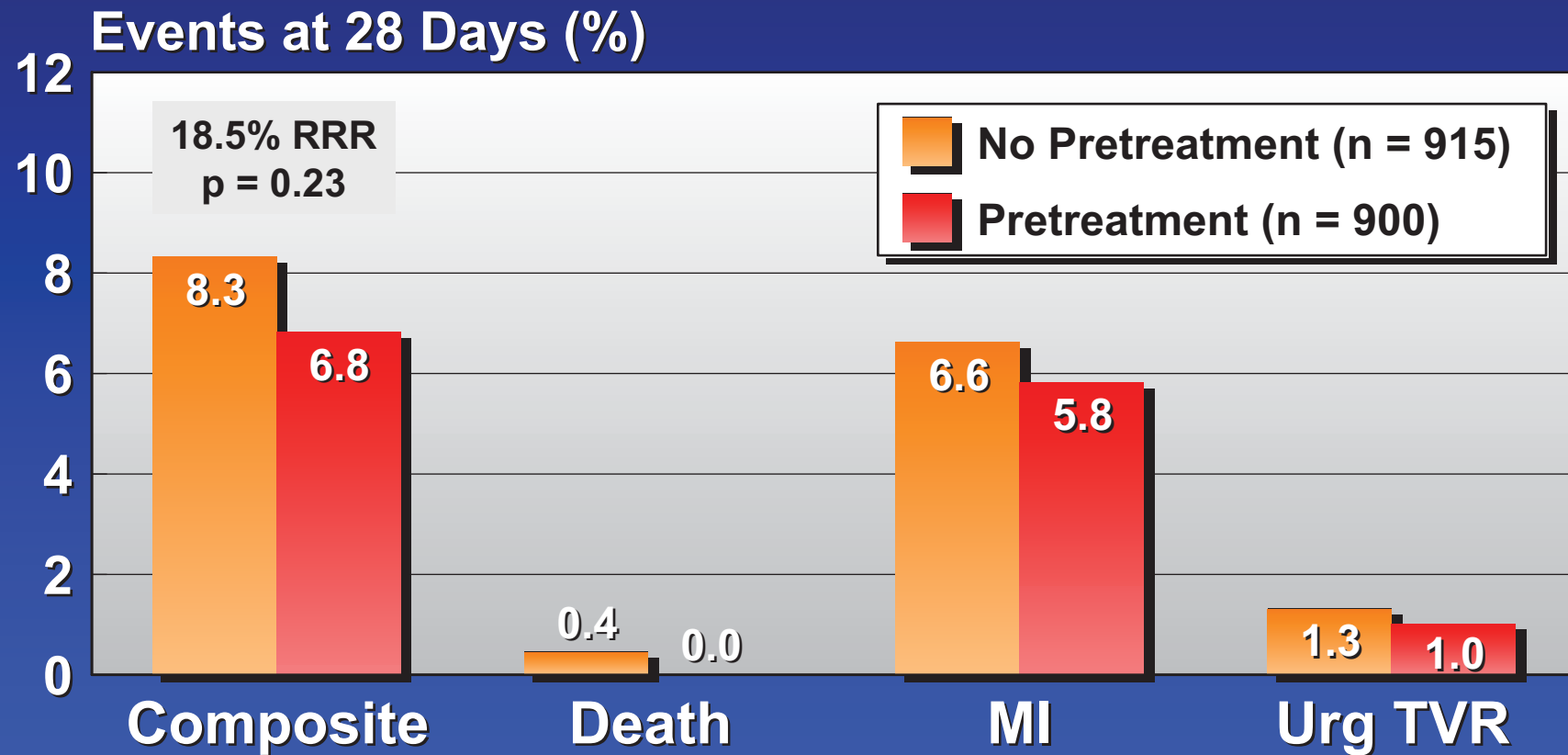


- 28 Day Endpoint: Death, MI, Urgent TVR •
- 1 Year Endpoint: Death, MI, Stroke •



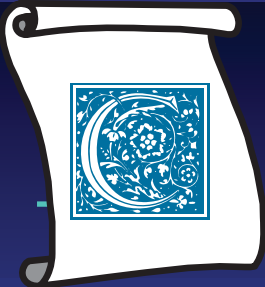
CREDO Trial

28-Day Endpoint



Steinhubl et al. JAMA 2002;288:2411.





CREDO Trial

28-Day Endpoint by Pretreatment Duration

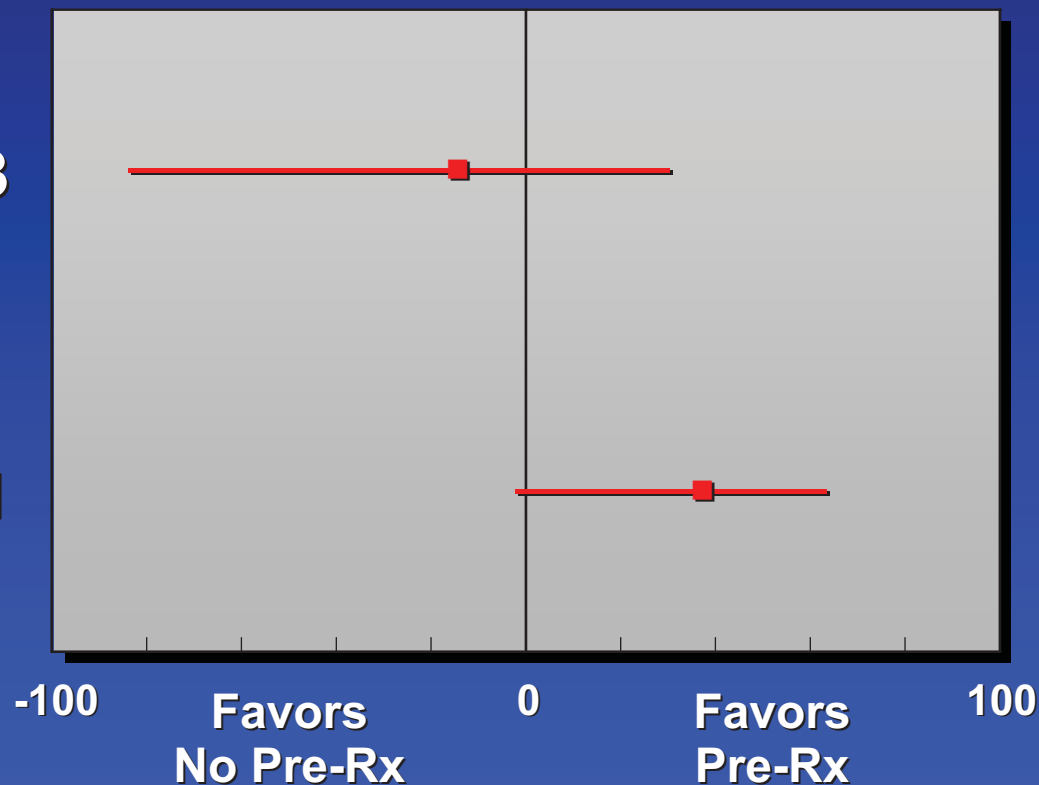
3 - <6 Hrs
Prior to PCI

893

6 - 24 Hrs
Prior to PCI

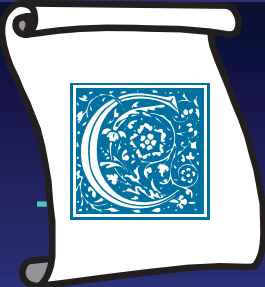
851

RRR & 95% CI



Steinhubl et al. JAMA 2002;288:2411.

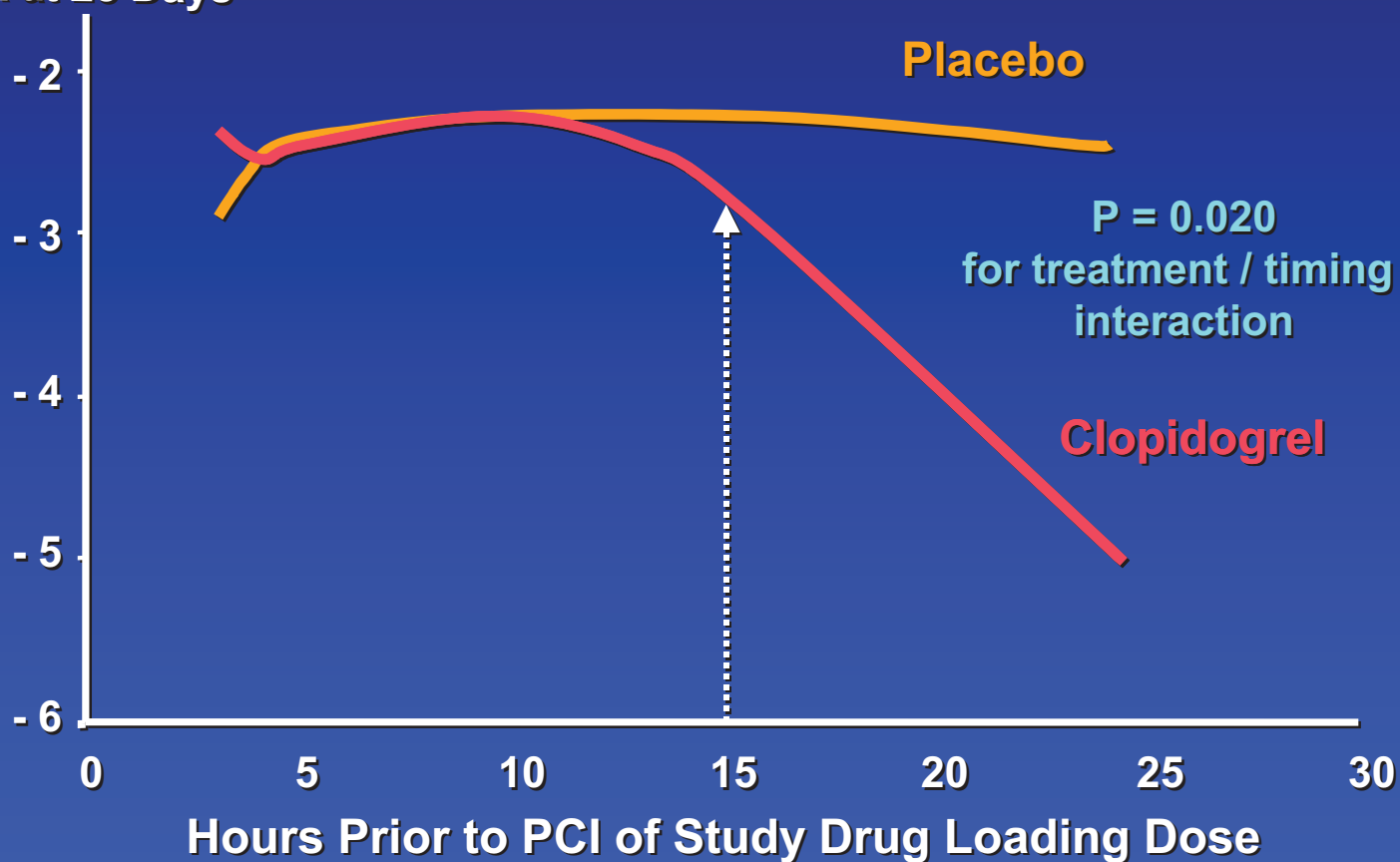




CREDO Trial

Loading Dose Timing and Risk of MACE

Log Odds of Death, MI
or UTVR at 28 Days



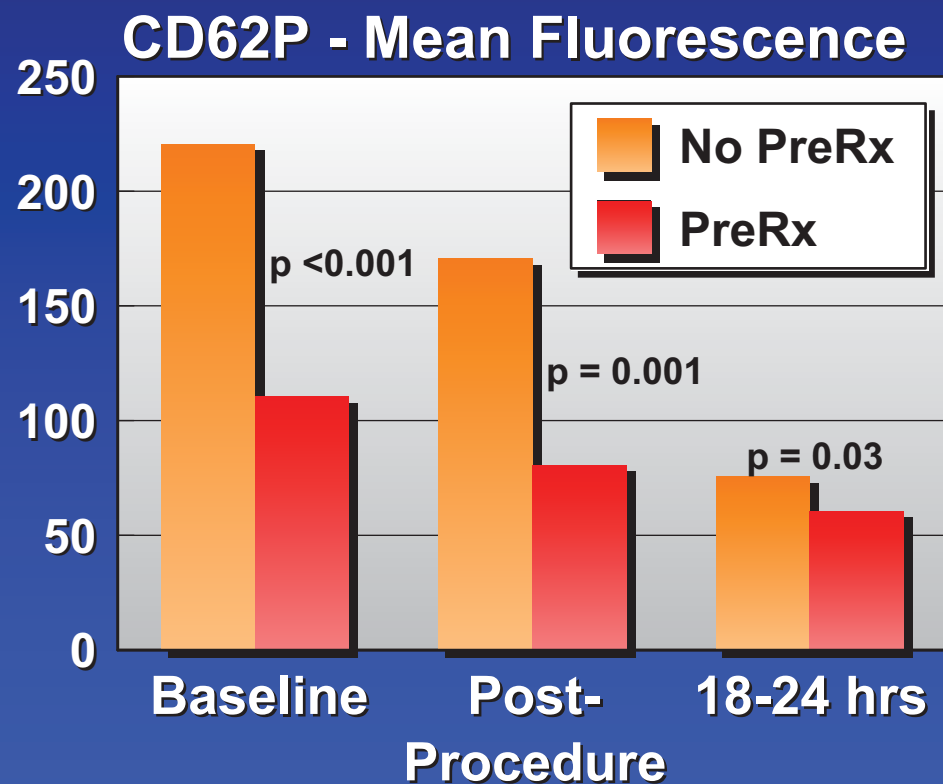
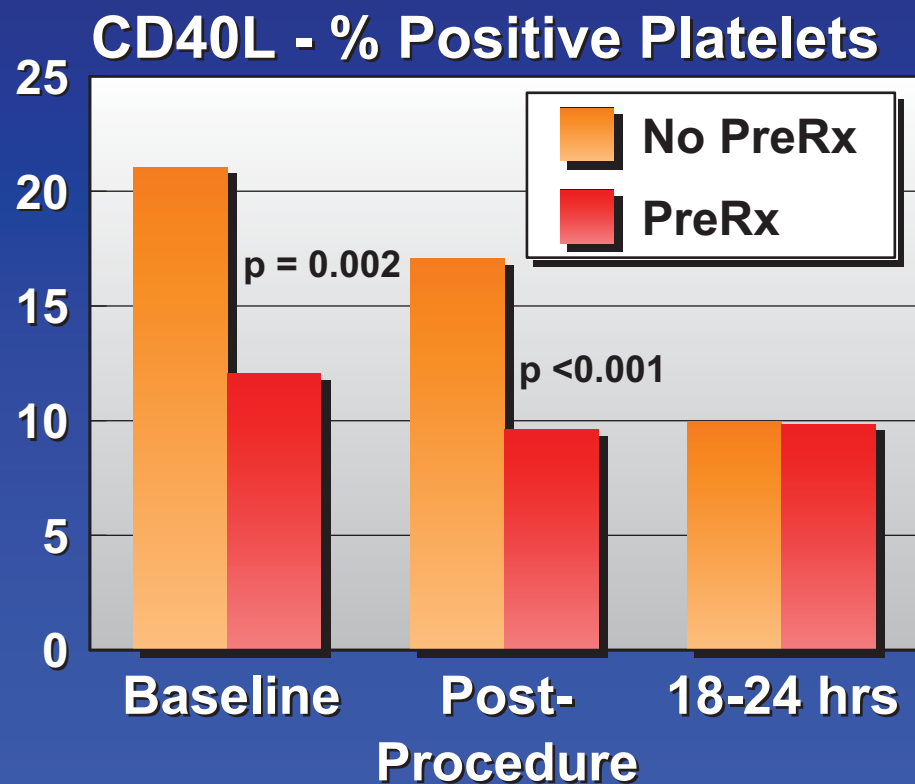
Courtesy of S. Steinhubl, MD



Clopidogrel Pretreatment and Inflammation

Activated CD40L and CD62P Expression during PCI

79 pts in prospective non-randomized study of pretreatment (dose >24 hrs pre-PCI) vs no pretreatment

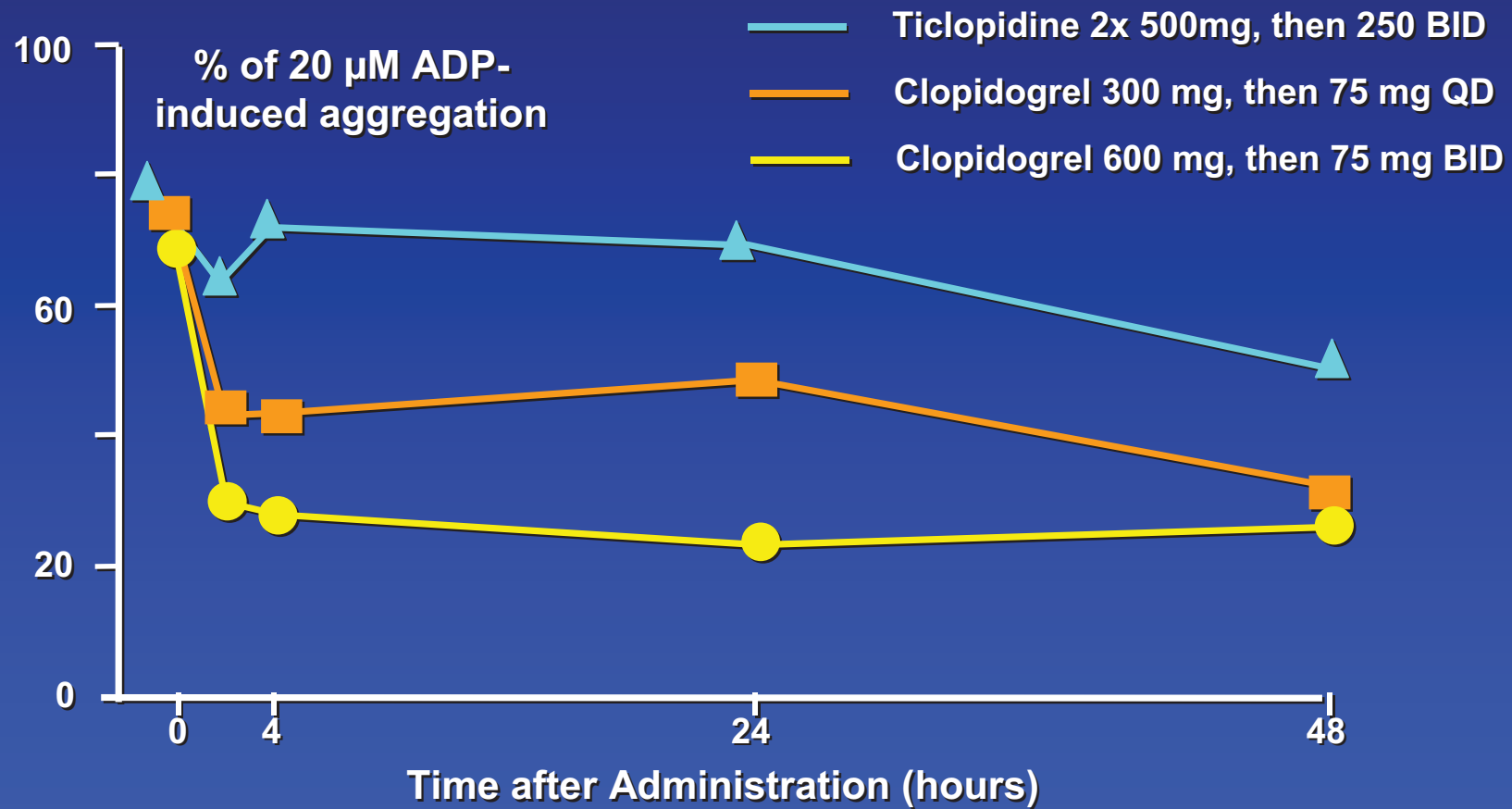


Quinn et al. A J Cardiol 2004;93:679.



Clopidogrel Loading

Clopidogrel Loading Dose



Muller I. Heart 2001;85:92-3.



CURE - CABG and Bleeding

Major Bleeding within 7 Days after CABG

Last Study Rx Dose Before CABG	Clopidogrel + ASA	Placebo + ASA
> 5 days (n = 910)	4.4%	5.3%
≤ 5 days (n = 912)	9.6%*	6.3%

*P = 0.06

Clopidogrel in CAD

- ◇ **When should it be started**
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Clopidogrel Pretreatment

Benefit Independent of GP IIb/IIIa Inhibition

GPIIb/IIIa Inhibitor

Yes



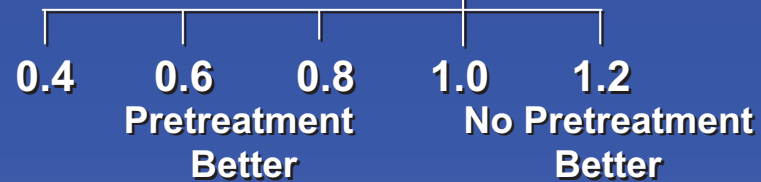
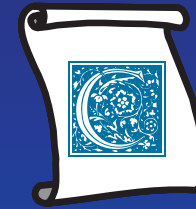
No



Yes



No



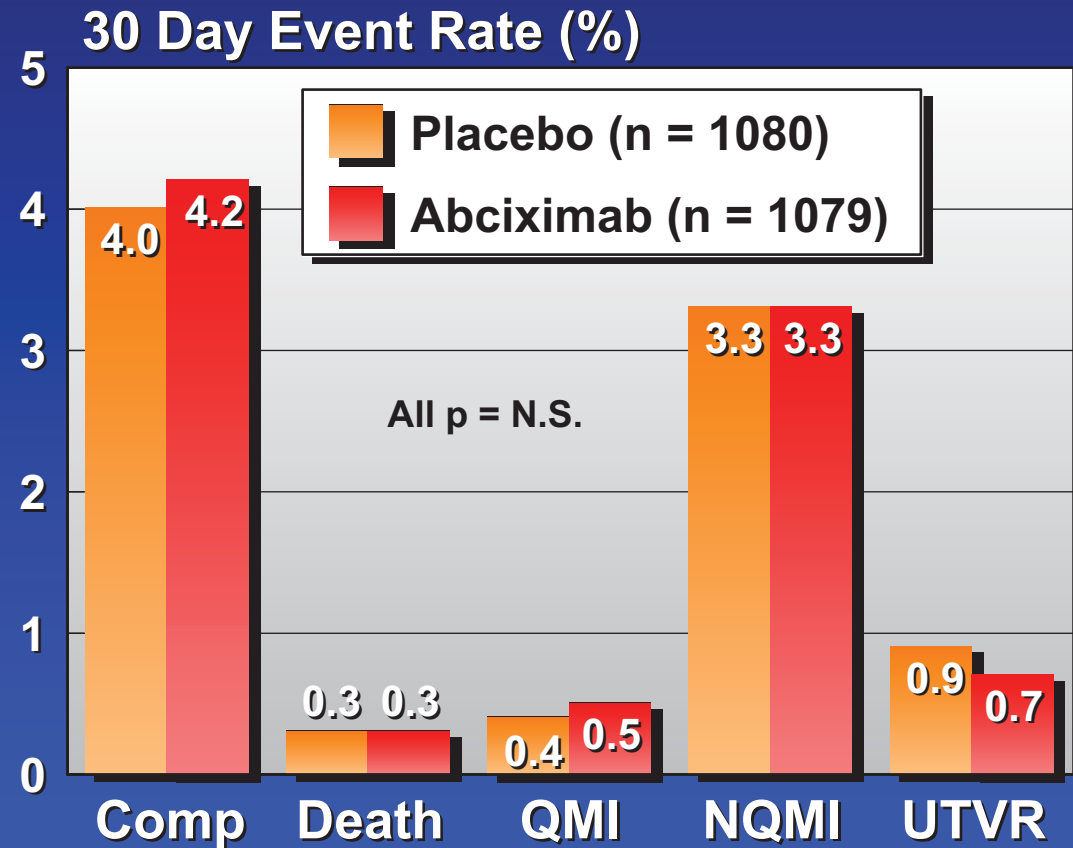
Courtesy of Steve Steinhubl, M.D.

ISAR - REACT

Abciximab vs Placebo with Clopidogrel Pre-Rx

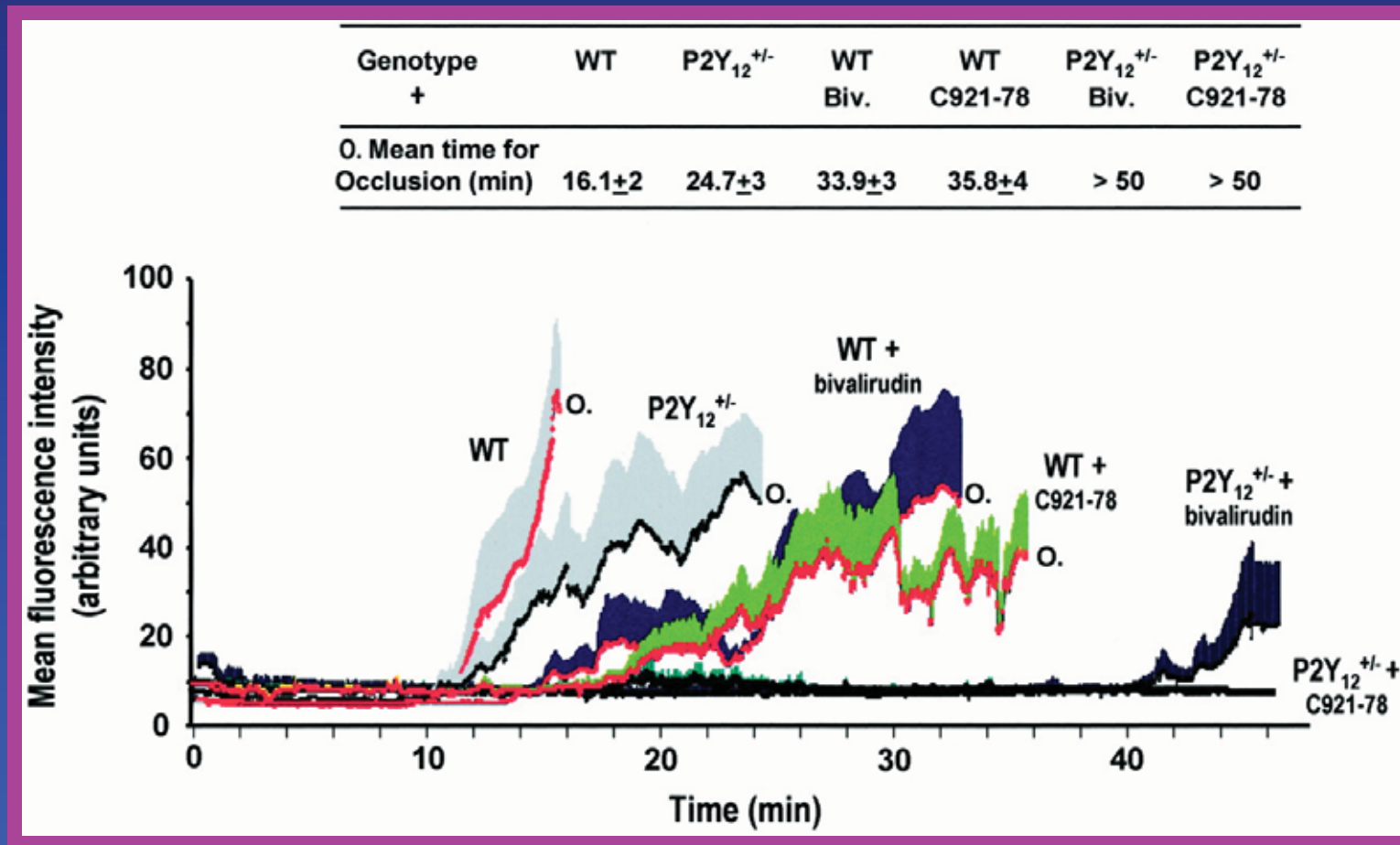
Exclusions:

- ◇ ACS with ST Δ 's or \uparrow Tn
- ◇ DM with insulin Rx
- ◇ SVG PCI
- ◇ occlusion, thrombus
- ◇ EF < 30%
- ◇ hemodynamic instability



ADP P2Y₁₂ Receptor Inhibition

Synergy with Thrombin or Factor Xa Inhibition Arterial Thrombosis in the FeCl₃-injury model

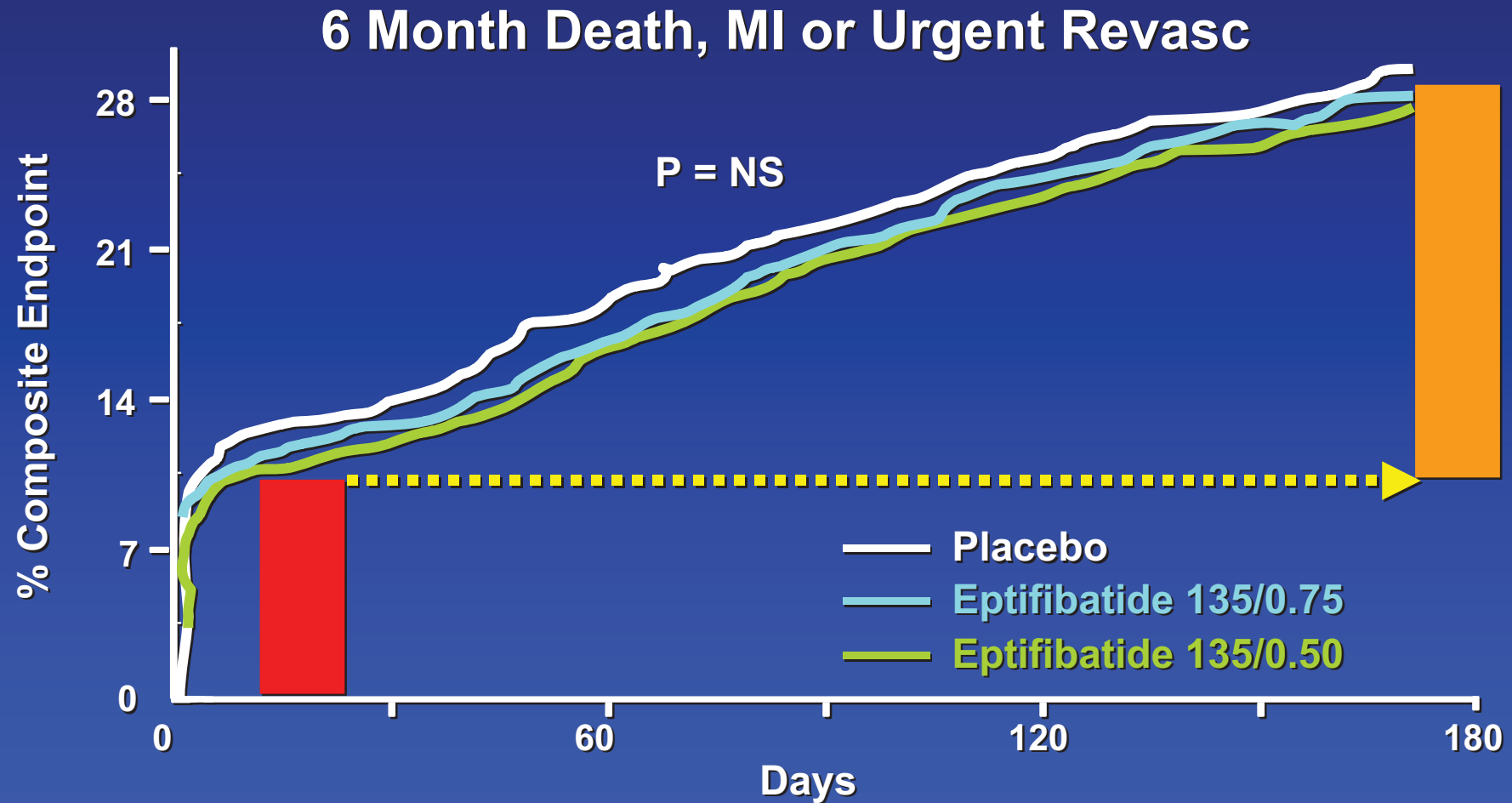


Andre et al. *Circulation* 2003;108:2697.

Clopidogrel in CAD

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IMPACT II: Long-Term Ischemic Events

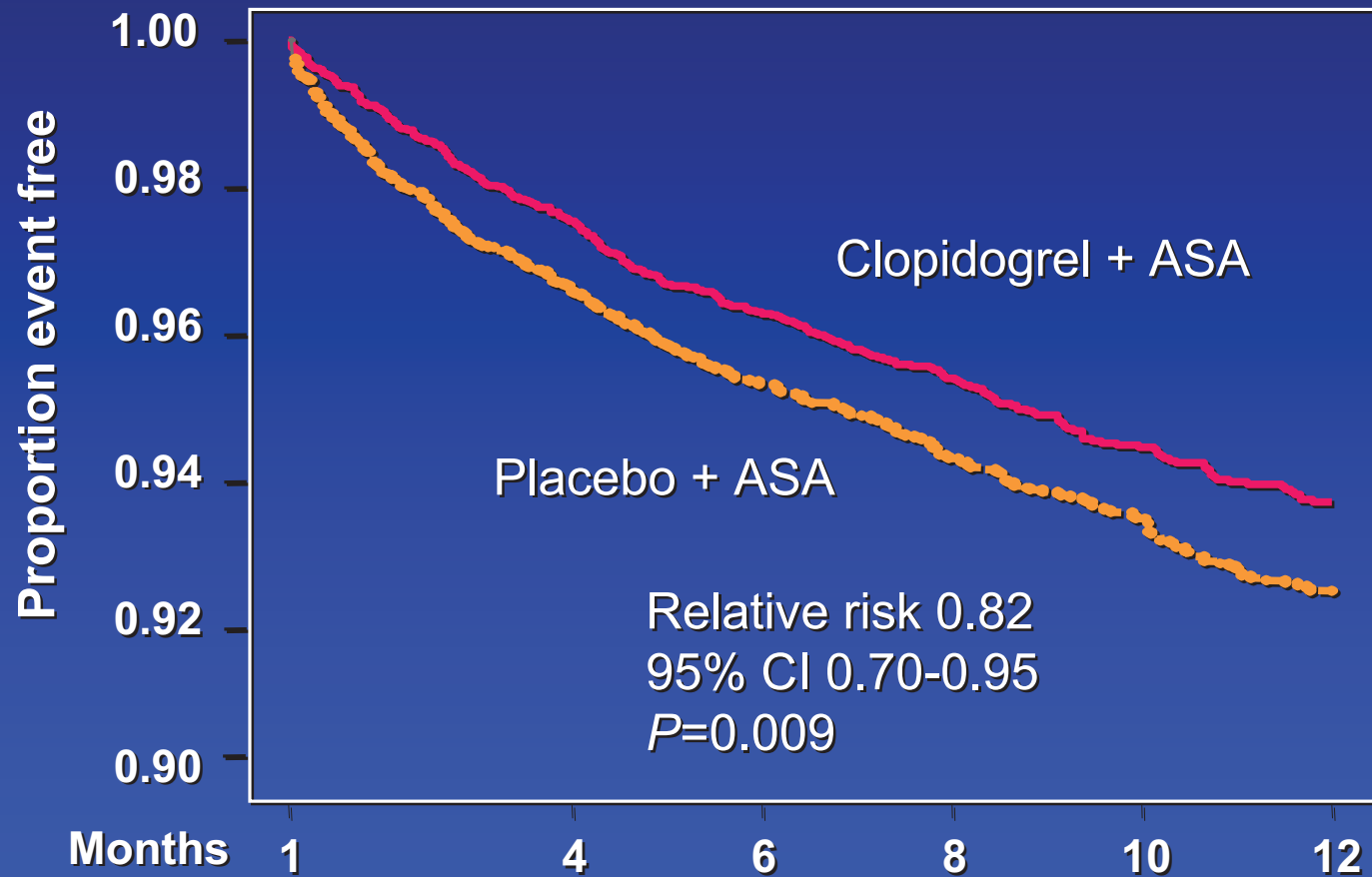


IMPACT II Investigators, Lancet 1997;349:1422.



CURE Trial

MACE (CV Death, MI or Stroke): 31 Days - 1 Year



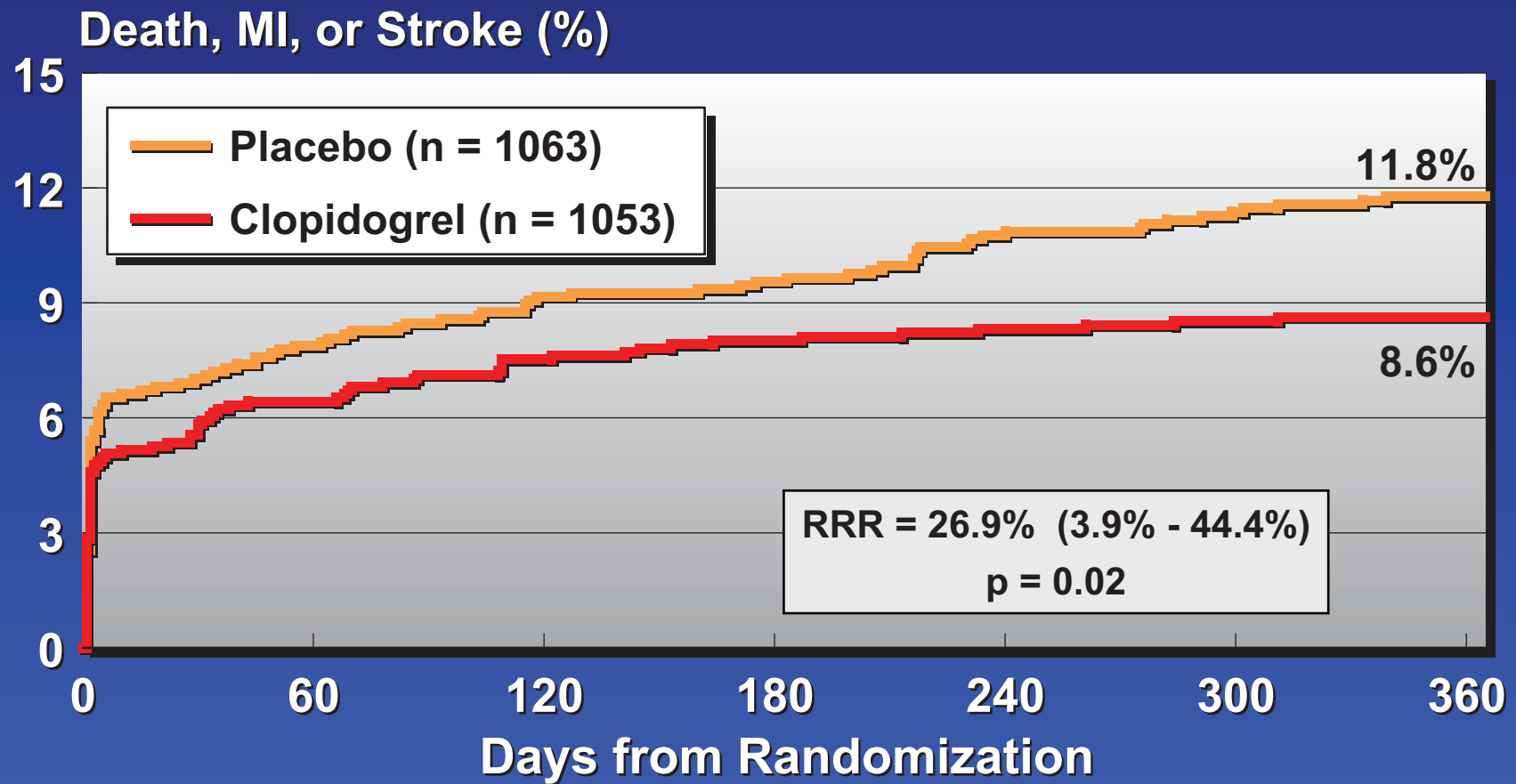
CURE Investigators. NEJM 2001;345:494.





CREDO Trial

1-Year Outcome

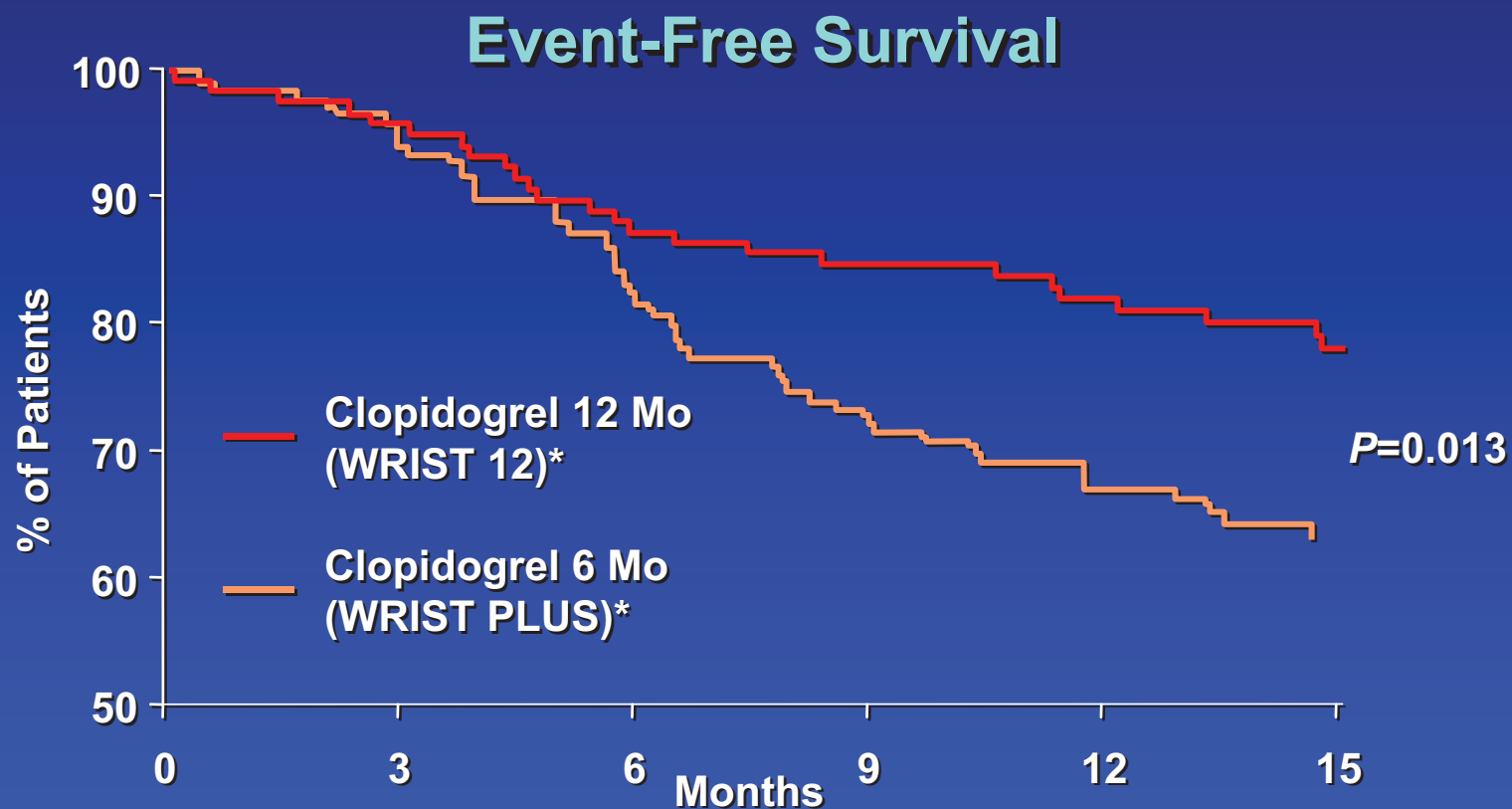


Steinhubl et al. JAMA 2002;288:2411.



Clopidogrel and Brachytherapy

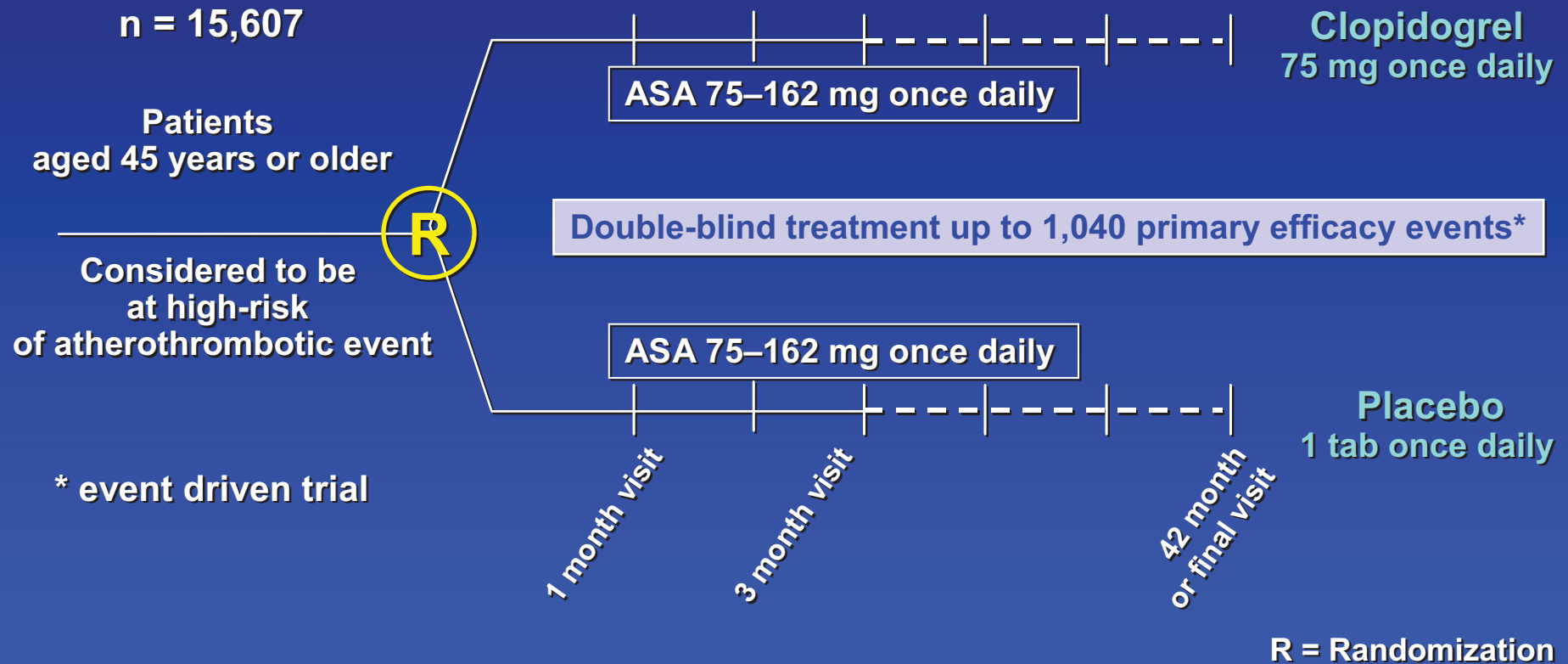
6-Months vs 1-Year of Clopidogrel Therapy



Waksman et al. Circulation 2002;106:776.



Secondary or High-Risk Primary Prevention



Clopidogrel in CAD

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Clopidogrel

Ongoing Trials (> 85,000 Patients)

Trial	# Patients	Population
ACTIVE	14,000	Atrial fibrillation
ARCH	1500	Aortic arch atheroma
CAMPER	2000	Peripheral arterial intervention
CASPAR	1460	Peripheral artery bypass surgery
CHARISMA	15,200	2° and high-risk 1° prevention
CLARITY	2200	Acute STEMI
COMMIT	40,000	Acute STEMI
MATCH	7600	High-risk stroke or TIA
WATCH	1587	Heart failure

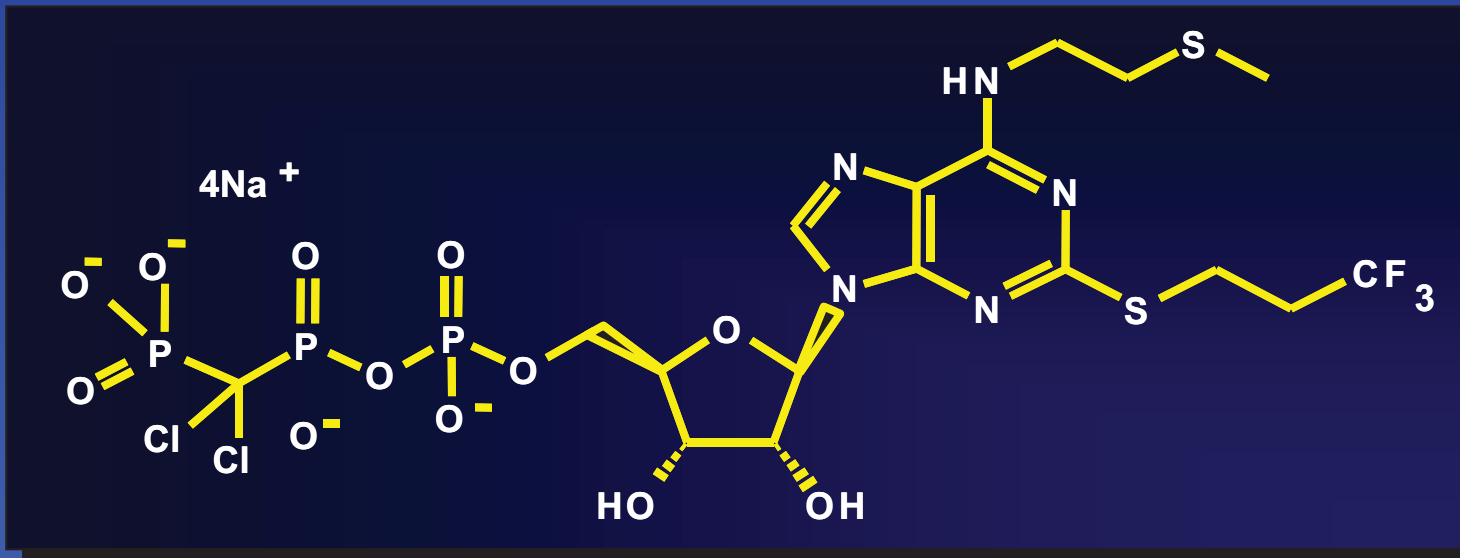
Bhatt and Topol, Nature Reviews Drug Discovery 2003;2:15.



Cangrelor (AR-C69931MX)

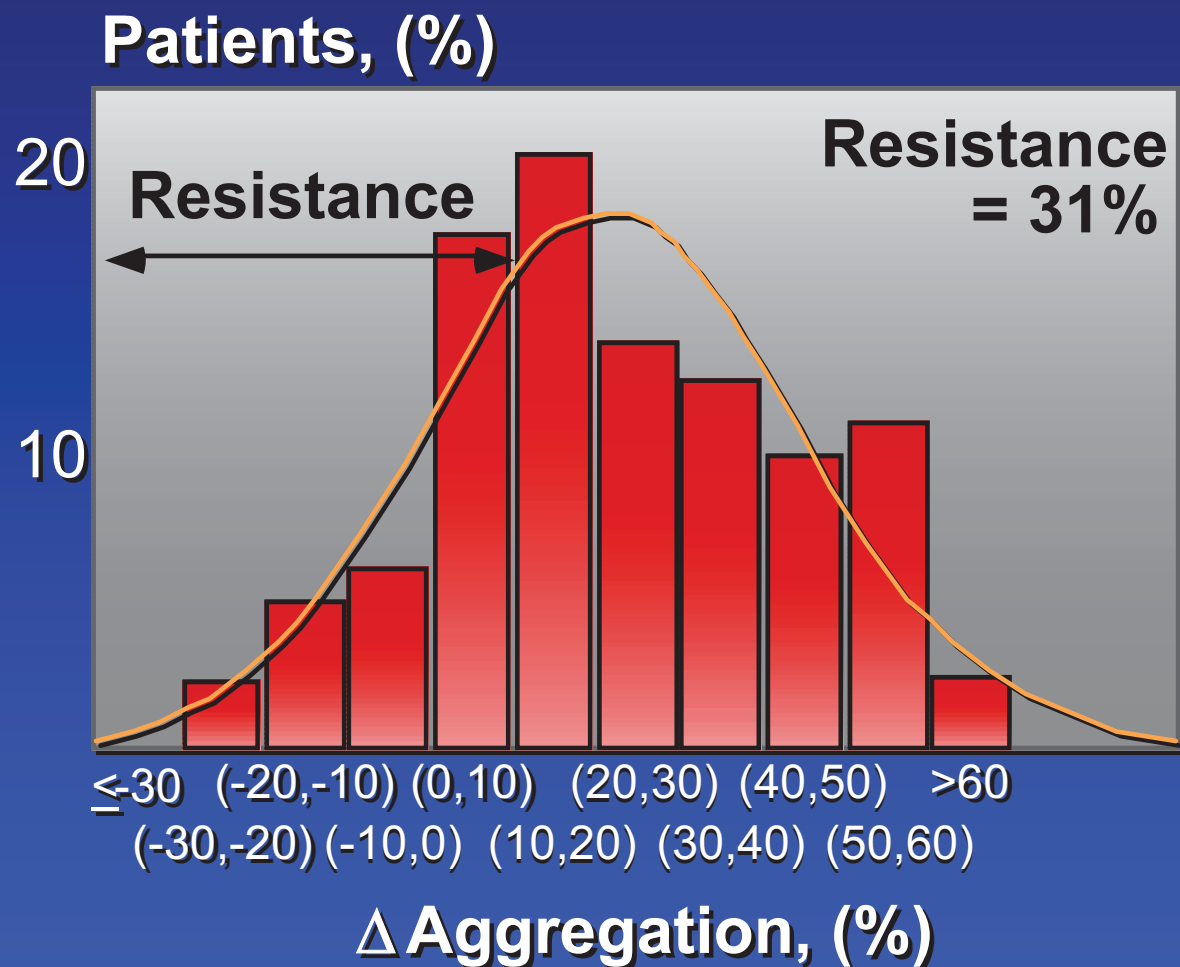
Parenteral ADP-P₂Y₁₂ Inhibitor

- ◇ ATP analog; molecular weight <1000 daltons
- ◇ Plasma half-life 5-9 minutes
- ◇ Return of normal platelet function within 20 minutes



Clopidogrel Response

Inter-Individual Variation



92 patients
undergoing elective
stenting.
Clopidogrel 300 mg
at time of stent, then
75 mg daily.

LTA with 5 μ M ADP
and 20 μ M ADP at
baseline, 2 hrs, 24
hrs, day 5 and 30.
Non-responders
with < 10% change.

Clonidogrel in CAD

Summary

- ◇ Adequate ADP-receptor blockade prior to PCI associated with ↓ MACE, with and without GPIIb/IIIa antagonists.
- ◇ Long-term therapy significantly reduces the risk of atherothrombotic events after PCI.
- ◇ Variability of response may be important factor
- ◇ New parenteral agents may enhance pretreatment and outcomes