Interventional Pharmacology:
Now And The Future

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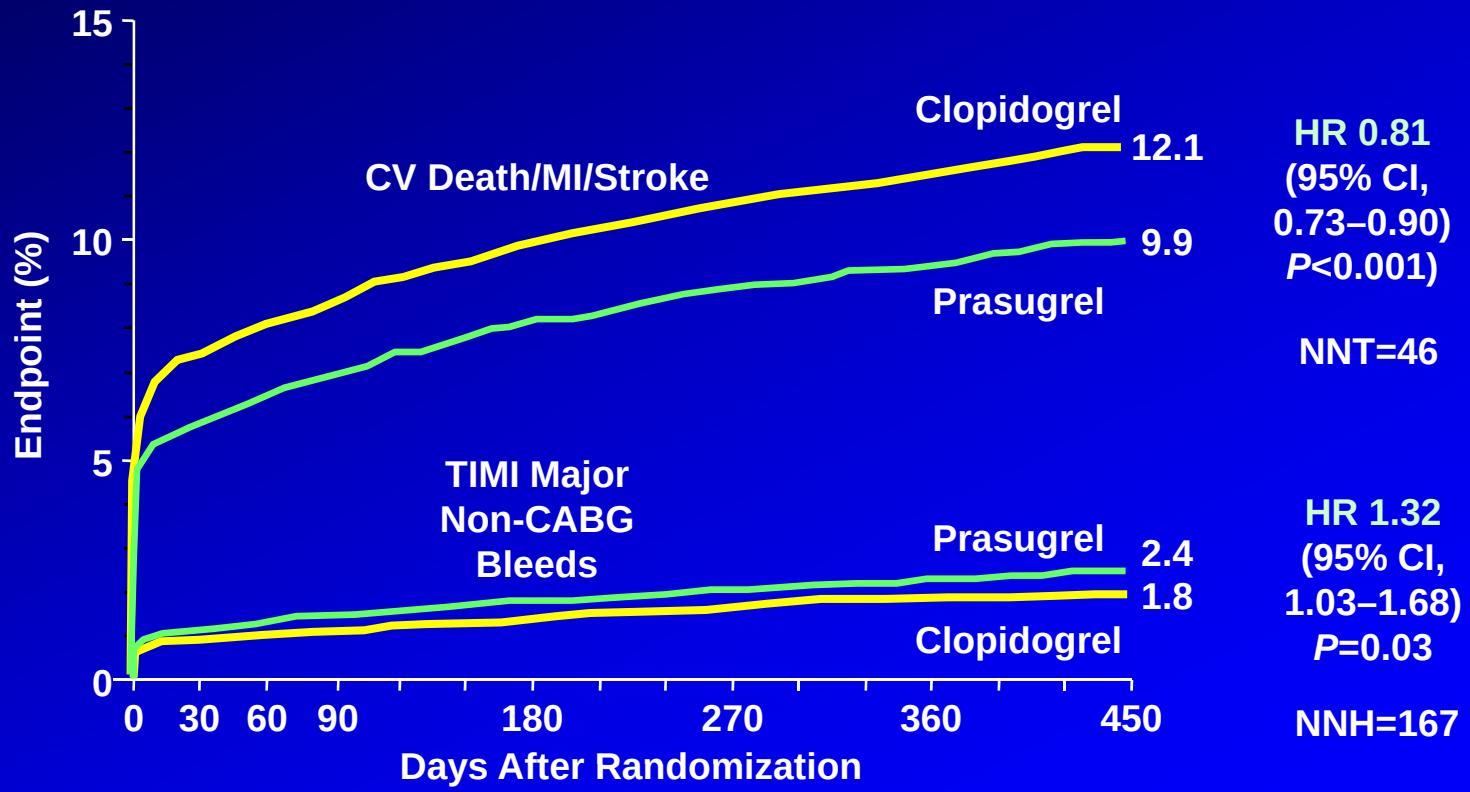
Currently Available Oral Antiplatelet Agents

DRUG	DRUG CLASS	CLINICAL CHARACTERISTICS
Aspirin	COX-1 inhibitor	PO, Irreversible binding
Ticlopidine	$P2Y_{12}$ (ADP) receptor antagonist	PO, Irreversible binding
Clopidogrel	$P2Y_{12}$ (ADP) receptor antagonist	PO, Irreversible binding
Prasugrel	$P2Y_{12}$ (ADP) receptor antagonist	PO, Irreversible binding
Cilostazol	PDE inhibitor; Increase cAMP	PO, Reversible inhibition

COX = cyclooxygenase; ADP = adenosine diphosphate; PDE = phosphodiesterase

Current State Of $P2Y_{12}$ Inhibition: Can We Do Better?

TRITON-TIMI 38: Prasugrel *vs* Clopidogrel in ACS Treated With PCI



Wiviott SD et al. *N Engl J Med*. 2007;357(20):2001-2015.

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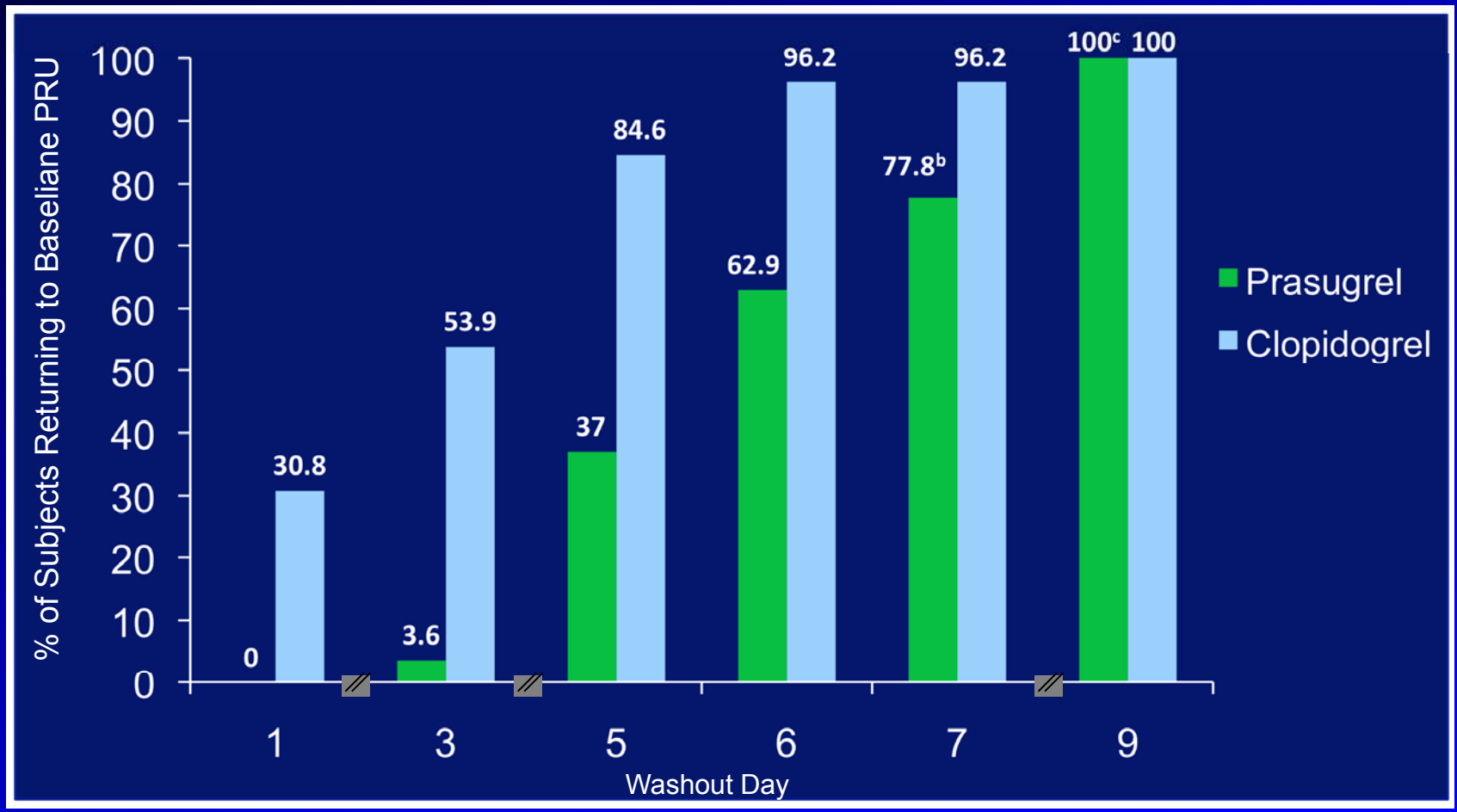
The RECOVERY Trial: Duration Needed To Return To Baseline Function With The Thienopyridines



[a]Return to baseline is defined as the return to within 60 $P2Y_{12}$ reaction units (PRUs) of baseline PRU value determined prior to thienopyridine therapy

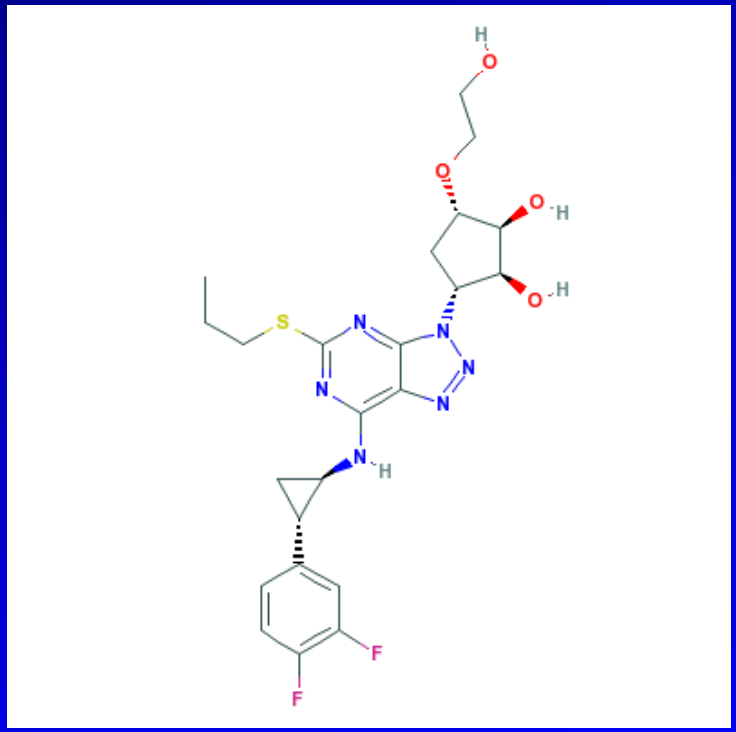
[b]The day on which the proportion of subjects returning to baseline PRU in the prasugrel group is closest to that attained by the clopidogrel group on Washout Period Day 5

[c]The day on which the proportion of subjects returning to baseline PRU in the prasugrel group is closest to that attained by the clopidogrel group on Washout Period Day 7

Price MJ, Angiolillo DJ et al, ACC/i2 2011

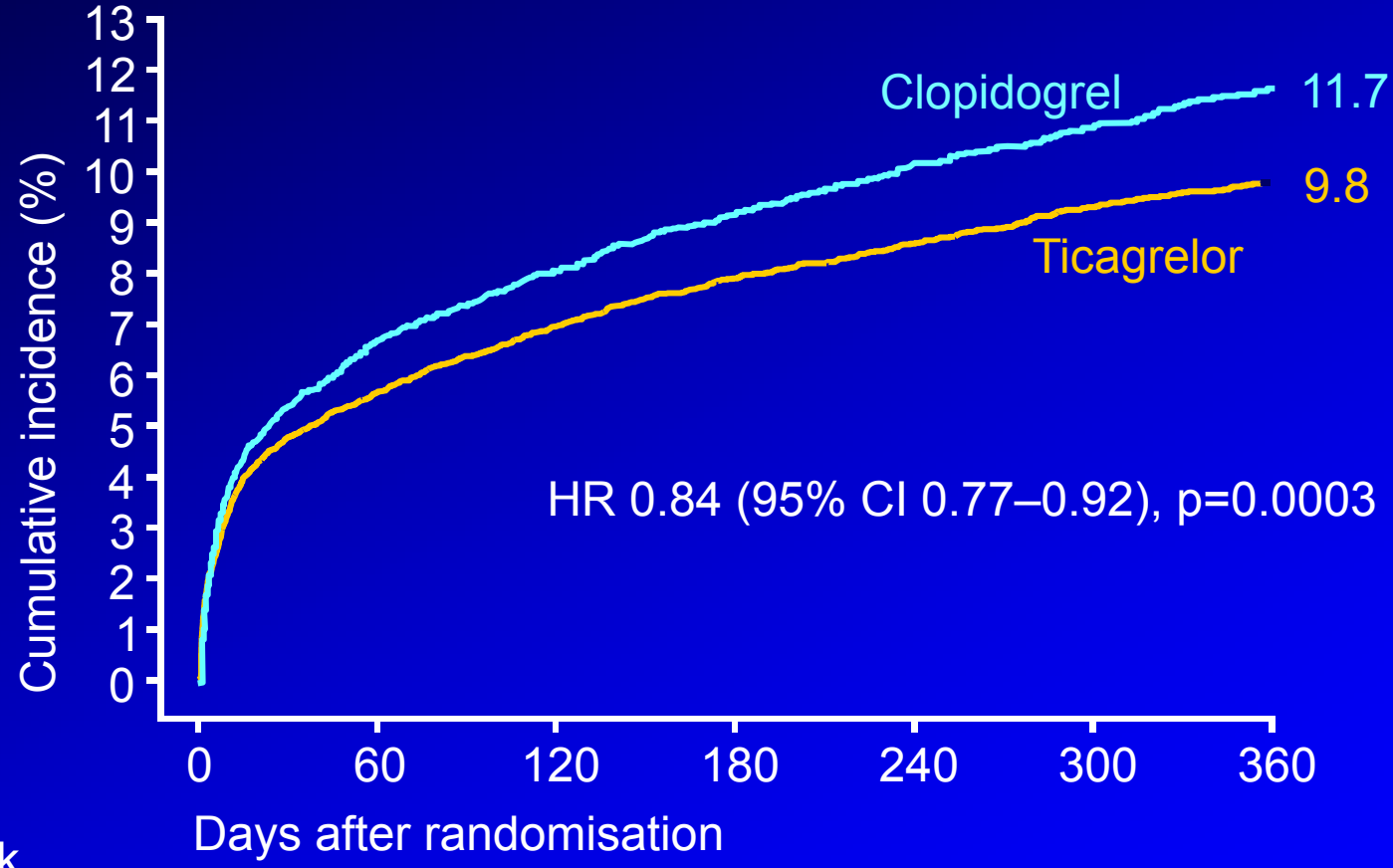
Ticagrelor: Pharmacology

- Class: *Cyclopentyl-triazolo-pyrimidine (CPTP)*
- Mechanism: Direct inhibition of the P2Y12 receptor (no metabolic activation required).
- Onset of action: Rapid, max reached at < 2 hrs
- Administration: Oral
- Plasma $t_{½}$ ≈10-12 hours (bid drug)
- "Off-target" effects: Blocks adenosine reuptake by RBC's



O'Donoghue M, Wiviott SD. Circulation. 2006;114:e600-e606;
Angiolillo DJ et al. Am J Cardiov Drugs. 2007; Teng, Eur J Clin Pharmacol 2010;66:487-496

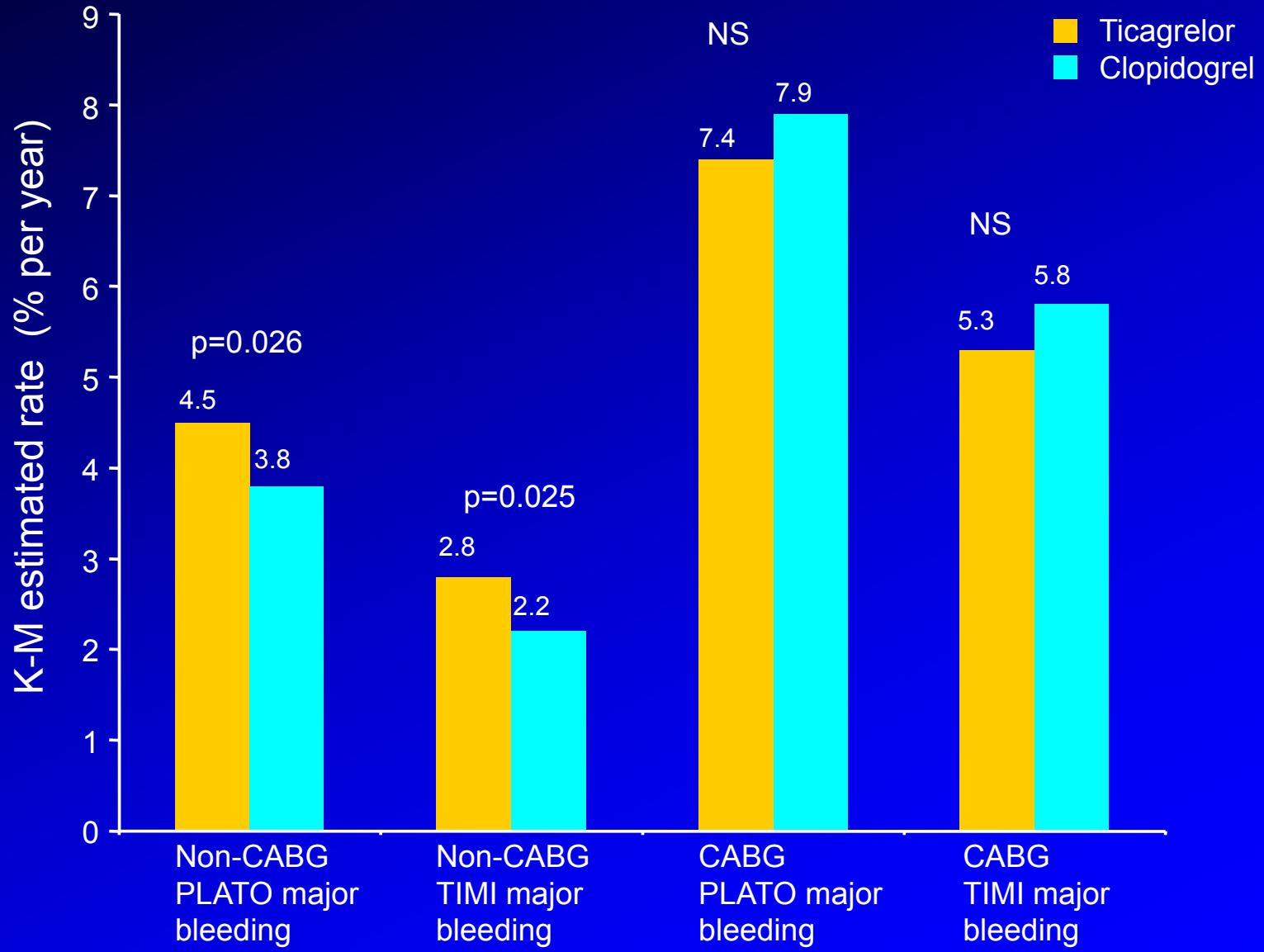
PLATO: Time to first primary efficacy event (CV death, MI or stroke) – Ticagrelor *vs* Clopidogrel



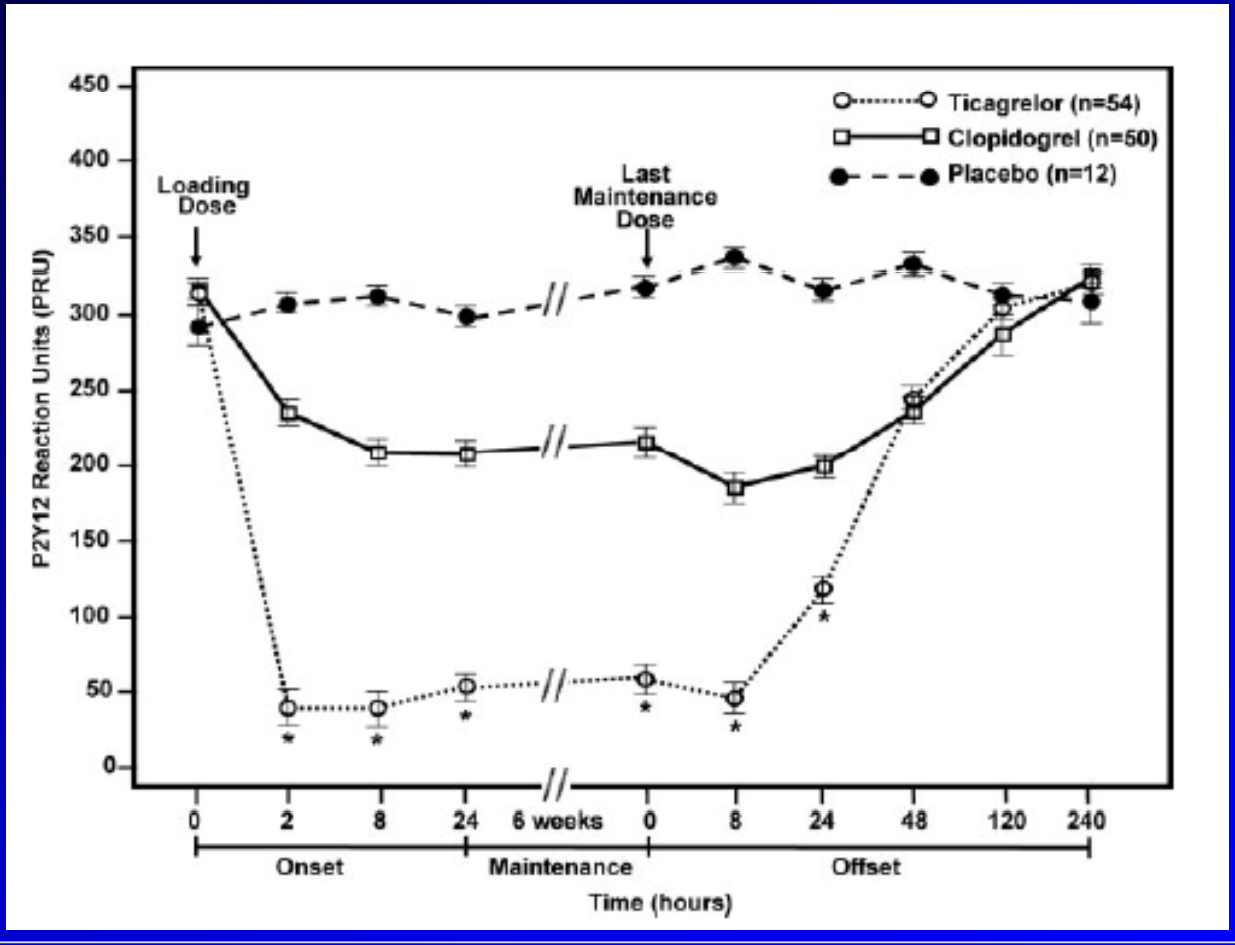
No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

Wallentin L et al, N Engl J Med. 2009;361(11):1045-1057

PLATO: Non-CABG and CABG-related major bleeding



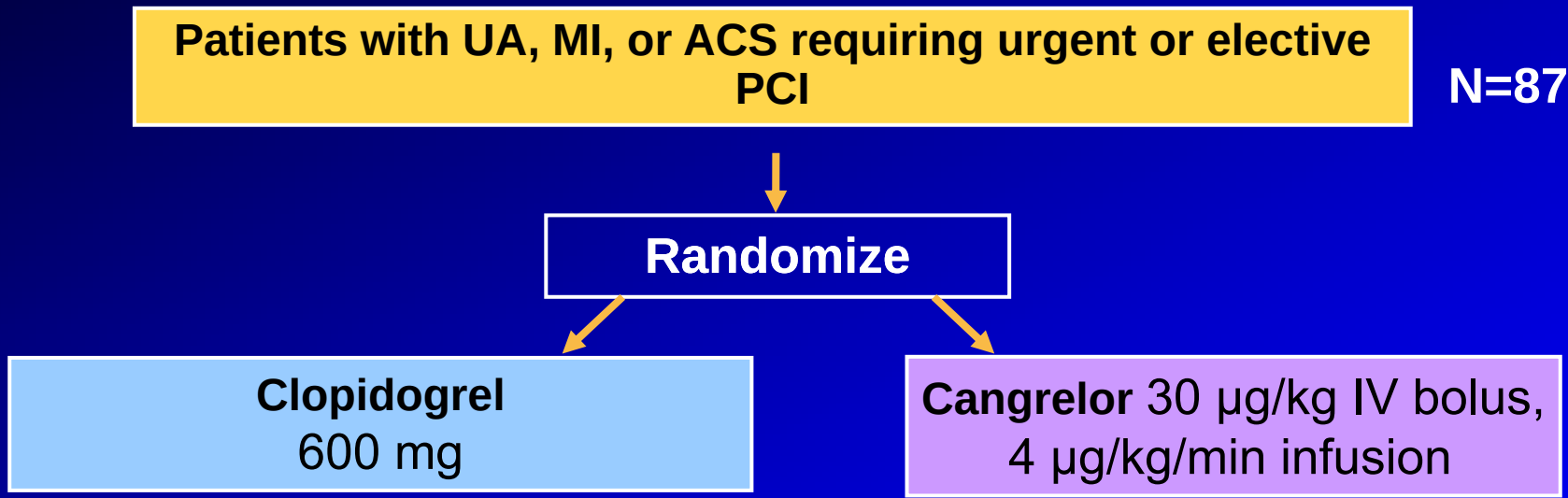
ONSET/OFFSET: Duration Until Complete Recovery After Ticagrelor MD Is Similar To Clopidogrel MD



"ticagrelor should be discontinued 7 days prior to surgery if a patient is to undergo elective surgery and antiplatelet effect is not desired" – EMEA for ticagrelor

Gurbel P et al, Circulation 2009

CHAMPION-PCI: Cangrelor versus Standard Tx to Achieve Optimal Management of Platelet Inhibition



Primary Objective: Superiority of cangrelor versus clopidogrel for PCI

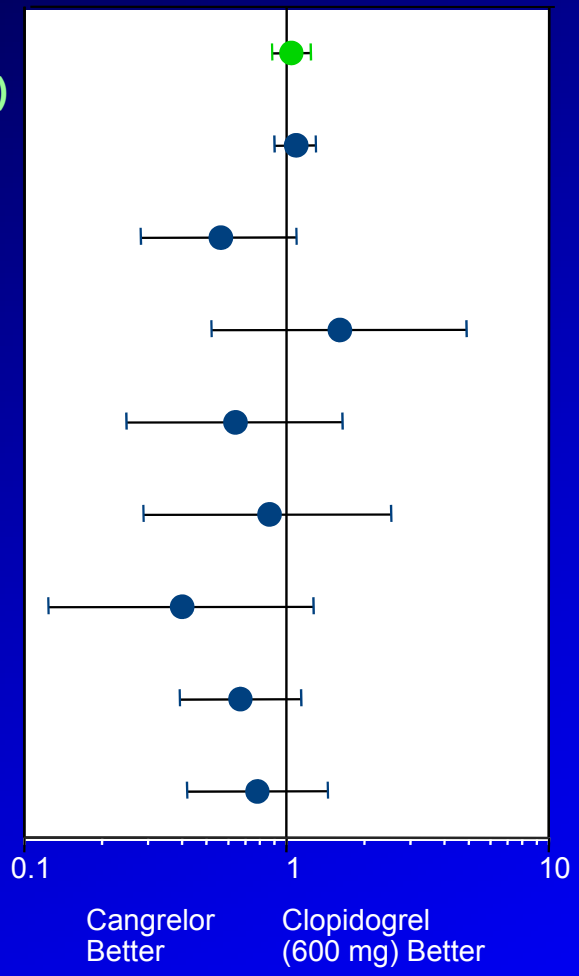
1º end point: all-cause mortality, MI, or IDR at 48 hours
2º end points: all-cause mortality and MI at 48 hours

IDR, ischemia-driven revascularization.

Harrington RA, et al. *N Engl J Med.* 2009;361(24):2318-2329.

CHAMPION PCI: Efficacy End Points at 48 Hr

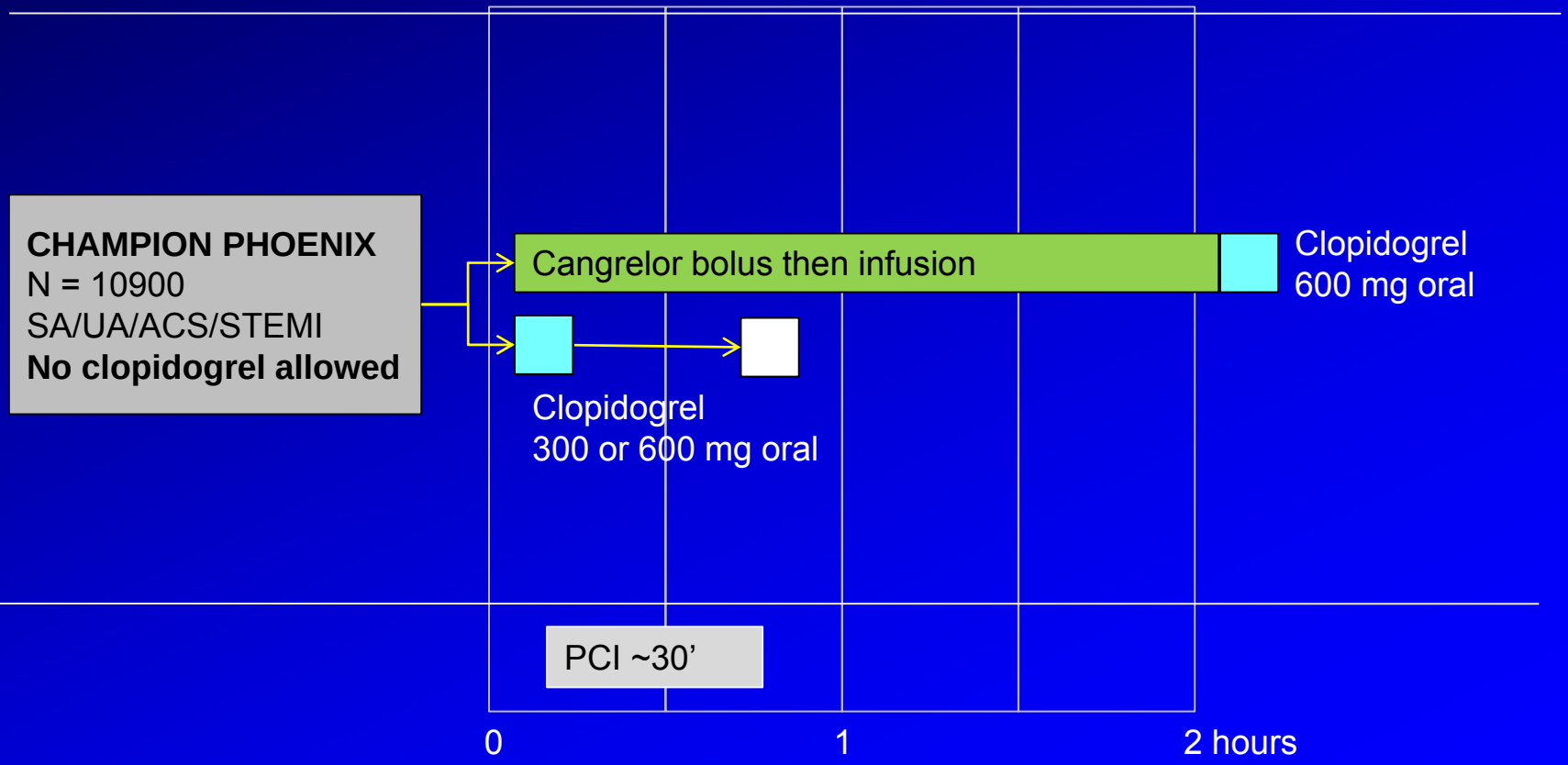
Efficacy mITT	Cangrelor (n=3897)	Clopidogrel (n=3871)	OR (95% CI)	*P* Value
Death/MI/IDR (primary end point)	**7.5%**	**7.1%**	**1.05 (0.88–.24)**	**.59**
MI	7.1%	6.6%	1.09 (0.91–1.29)	.36
IDR	0.3%	0.6%	0.56 (0.28–1.11)	.10
All-cause mortality	0.2%	0.1%	1.59 (0.52–4.87)	.42
Stent thrombosis	0.2%	0.3%	0.63 (0.25–1.63)	.34
Stroke	0.2%	0.2%	0.85 (0.29–2.54)	.77
Q-wave MI	0.1%	0.3%	0.40 (0.12–1.27)	.12
Death/Q-wave MI/ IDR	0.6%	0.9%	0.67 (0.39–1.14)	.14
Death/Q-wave MI/ Stent thrombosis	0.5%	0.6%	0.78 (0.42–1.44)	.42



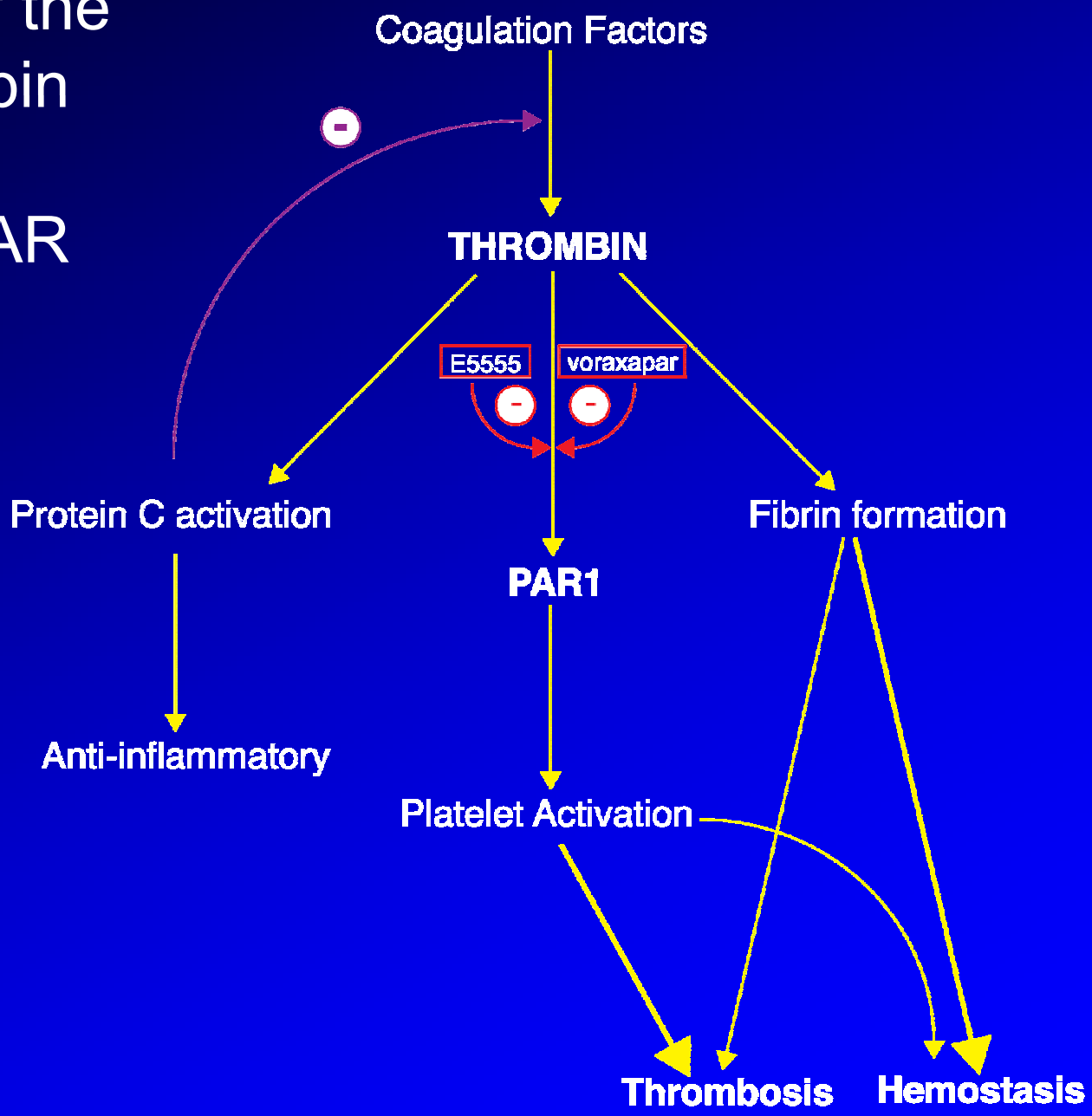
Harrington RA, et al. *N Engl J Med.* 2009;361(24):2318-2329.

PHOENIX – Trial schematic

- Randomized, double blind, double dummy, superiority
- Cangrelor (bolus +infusion for 2 hr) compared to usual care clopidogrel
- Primary efficacy endpoint : Death/MI/IDR/ST at 48hr

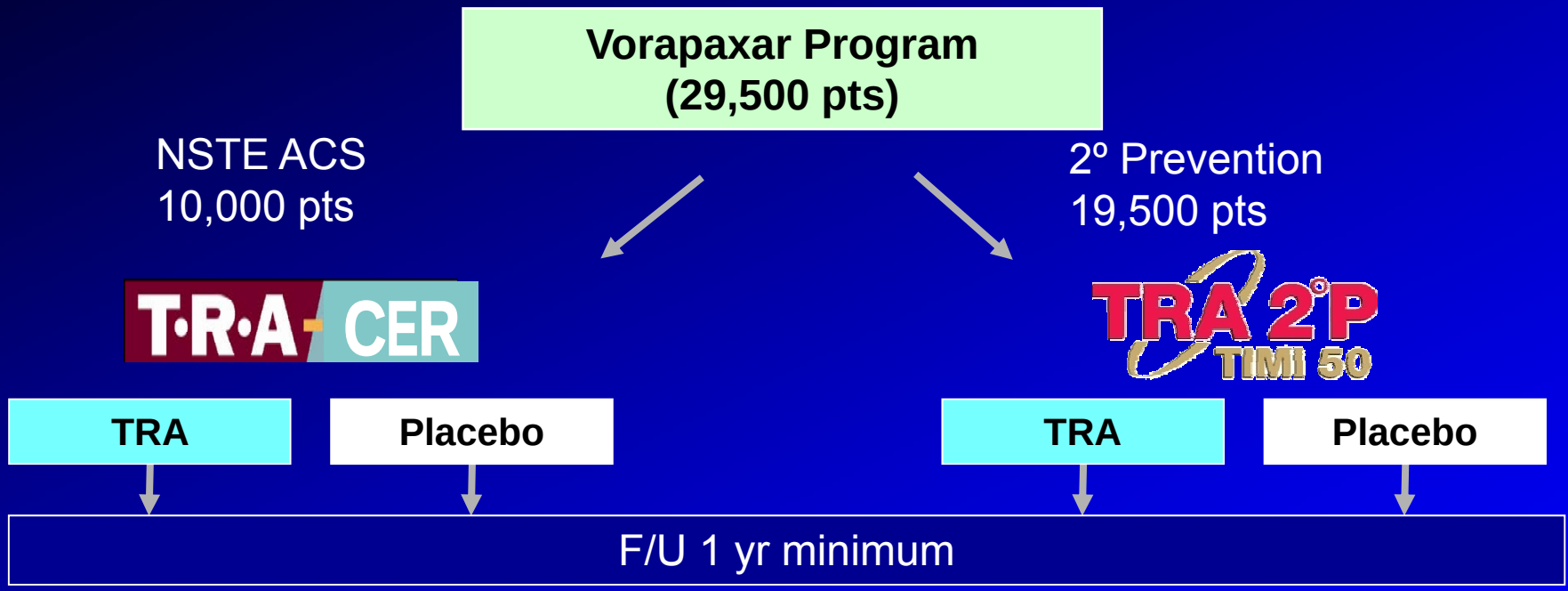


The Promise of the Platelet Thrombin Receptor Antagonists (PAR inhibitors)



From Price and Angiolillo, Topol's Interventional Cardiology, 7th Edition

Vorapaxar: Thrombin Receptor Antagonism



Primary Endpoint: CV death, MI, stroke, urgent revascularization and recurrent ischemia w/ rehospitalization

ClinicalTrials.gov
Identifier: NCT00527943.

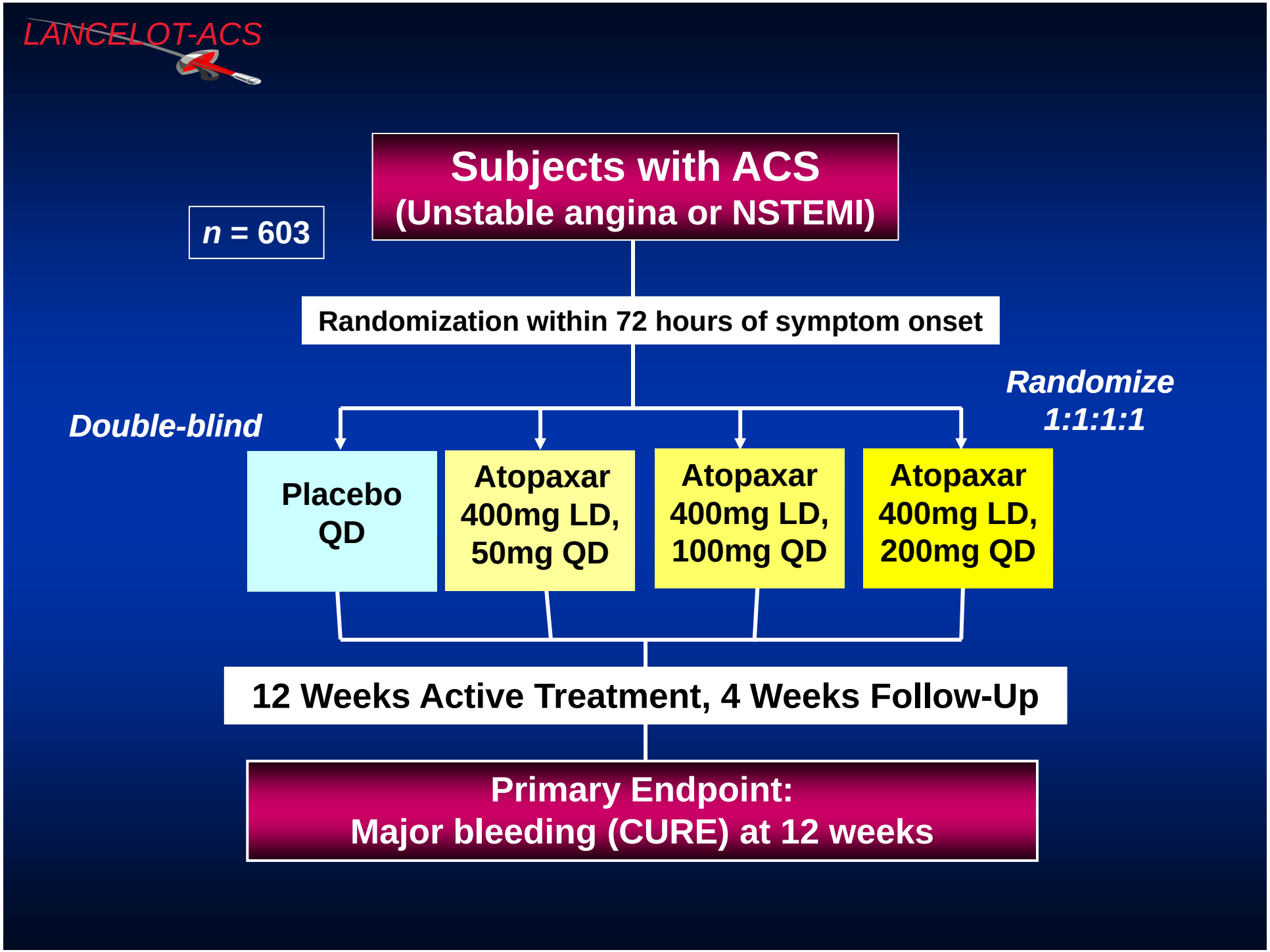
Primary Endpoint: CV death, MI, stroke, and urgent revascularization

ClinicalTrials.gov
Identifier: NCT00526474.

Vorapaxar…Not So Much?

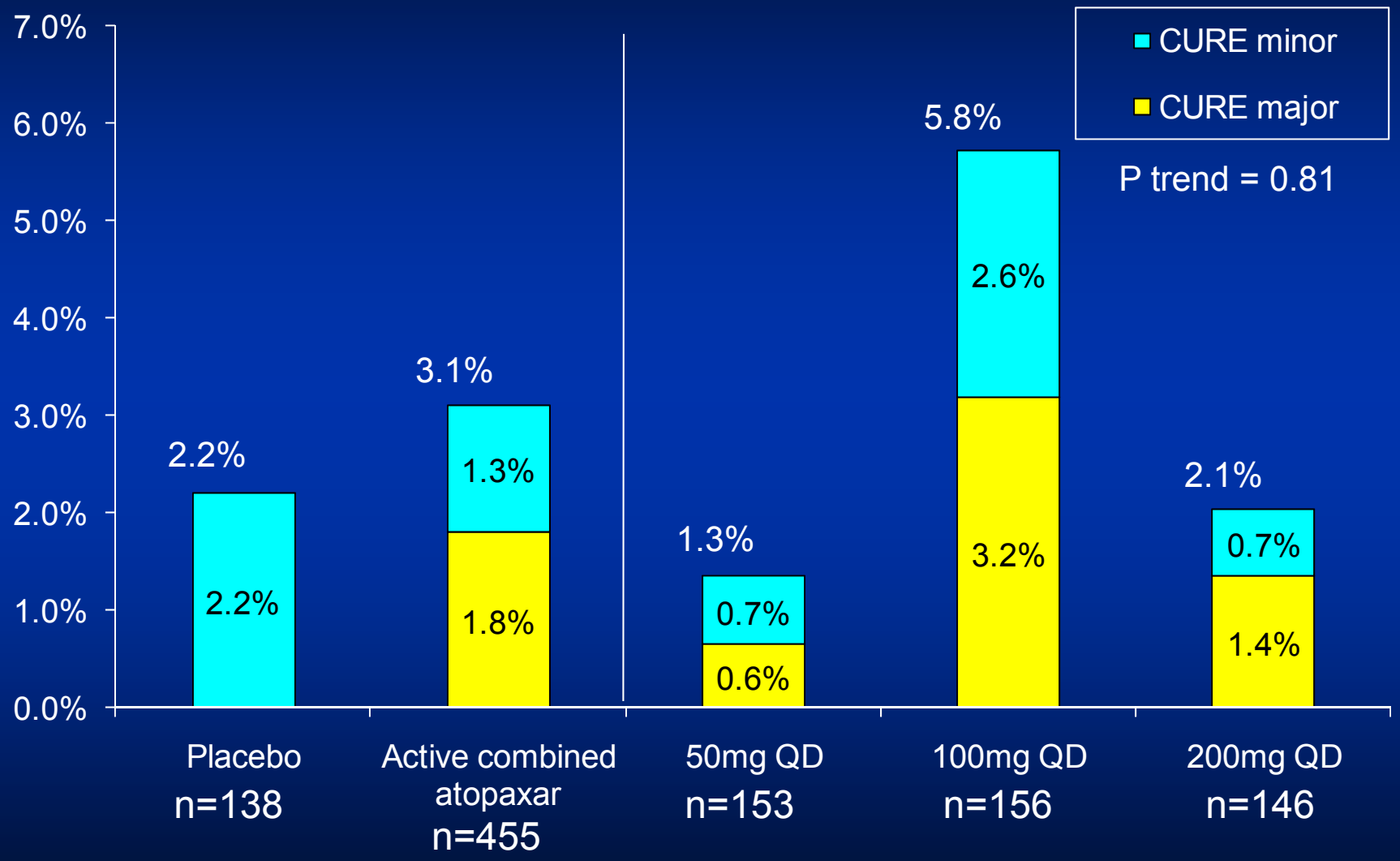
In the TRACER study, patients will discontinue study drug and investigators are to begin now to close out the study in a timely and orderly fashion.

In the TRA-2P study, study drug…will be immediately discontinued in patients who experienced a stroke prior to entry into the study or during the course of the study.


LANCELOT-ACS
Subjects with ACS
(Unstable angina or NSTEMI)
n = 603
Randomization within 72 hours of symptom onset
Double-blind
Randomize
1:1:1:1
Placebo
QD
Atopaxar
400mg LD,
50mg QD
Atopaxar
400mg LD,
100mg QD
Atopaxar
400mg LD,
200mg QD
12 Weeks Active Treatment, 4 Weeks Follow-Up
Primary Endpoint:
Major bleeding (CURE) at 12 weeks

LANCELOT-ACS

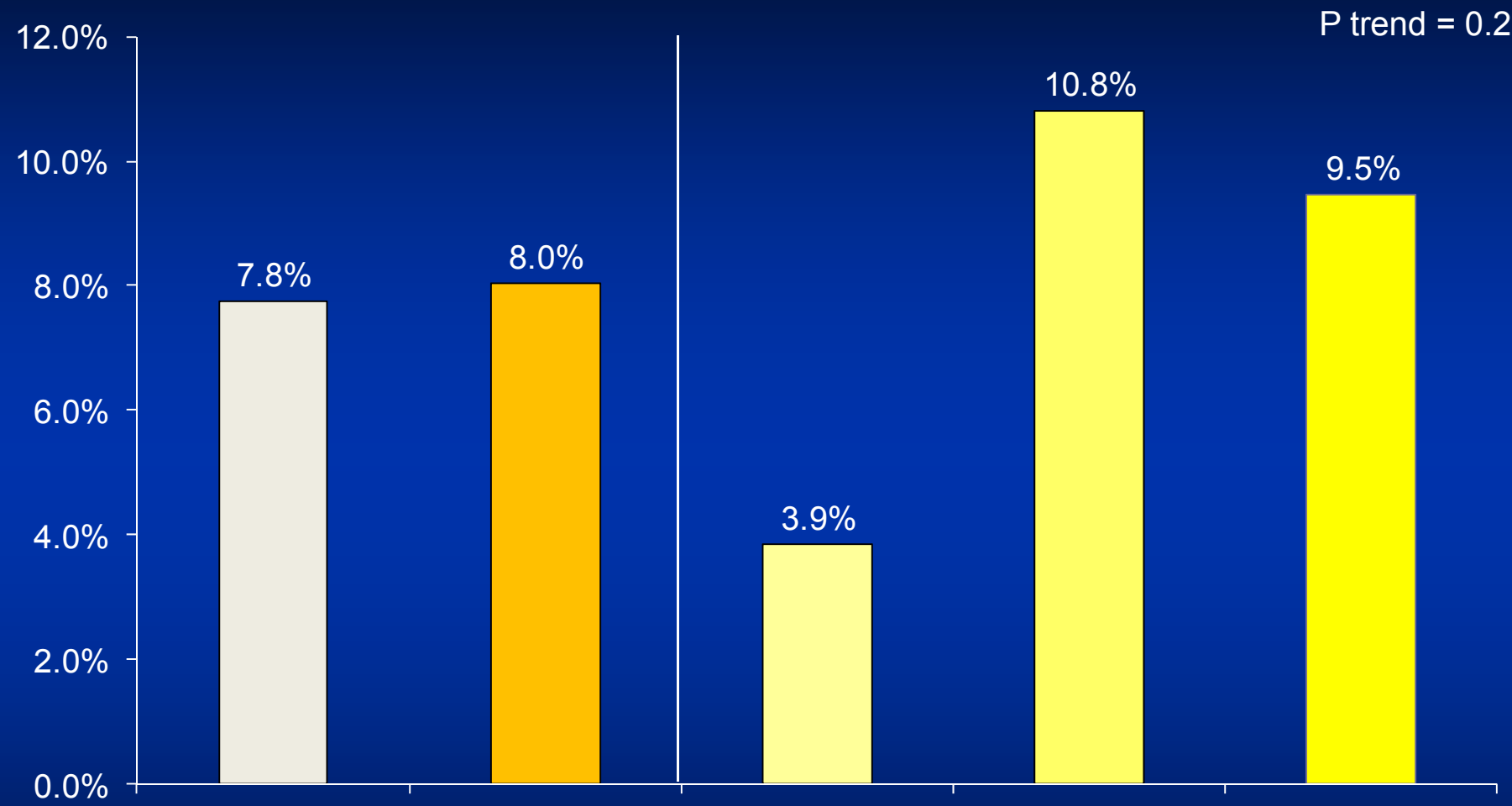
Incidence of any CURE Bleeding



Relative Risk (95% CI) vs. placebo	Active combined atopaxar	50mg QD	100mg QD	200mg QD
	RR 1.42 (0.44-4.8) P = 0.63	RR 0.60 (0.11-3.00) P = 0.62	RR 2.65 (0.78-10.3) P = 0.13	RR 0.95 (0.18-5.04) P = 0.99

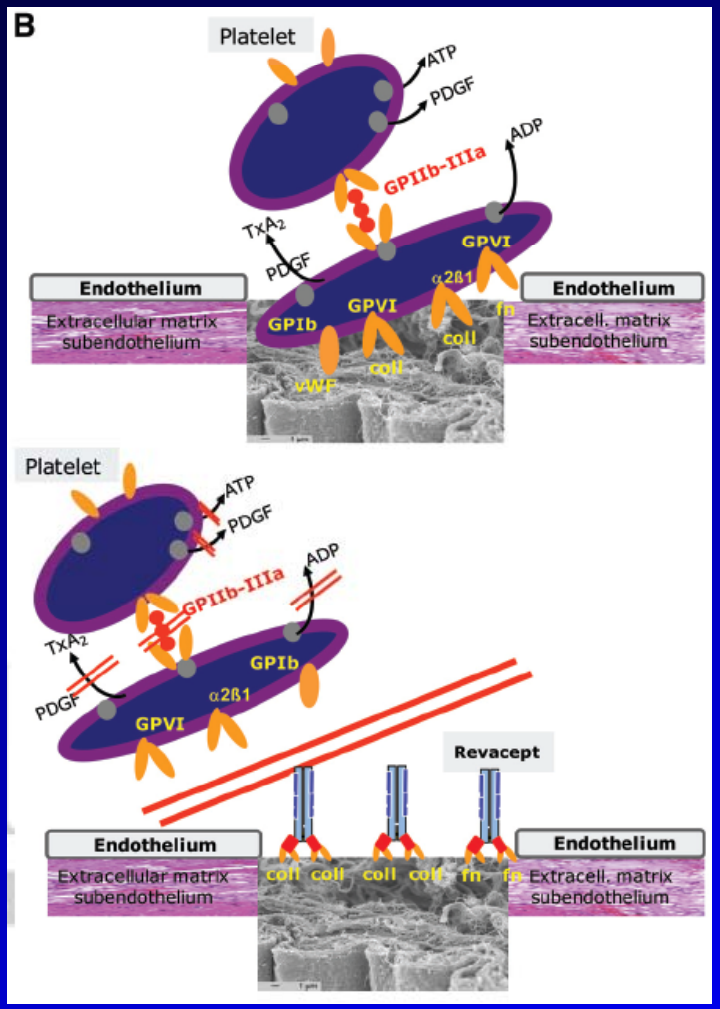
LANCELOT-ACS

Incidence of CV death, MI, Stroke, or Recurrent ischemia



RR (95% CI) vs. placebo				
	RR 1.04 (0.55-1.97) P = 0.93	RR 0.50 (0.16-1.27) P = 0.18	RR 1.40 (0.68-2.86) P = 0.37	RR 1.22 (0.58-2.57 P = 0.63

The Pipeline: New Targets For Platelet Adhesion and Activation



Revacept:

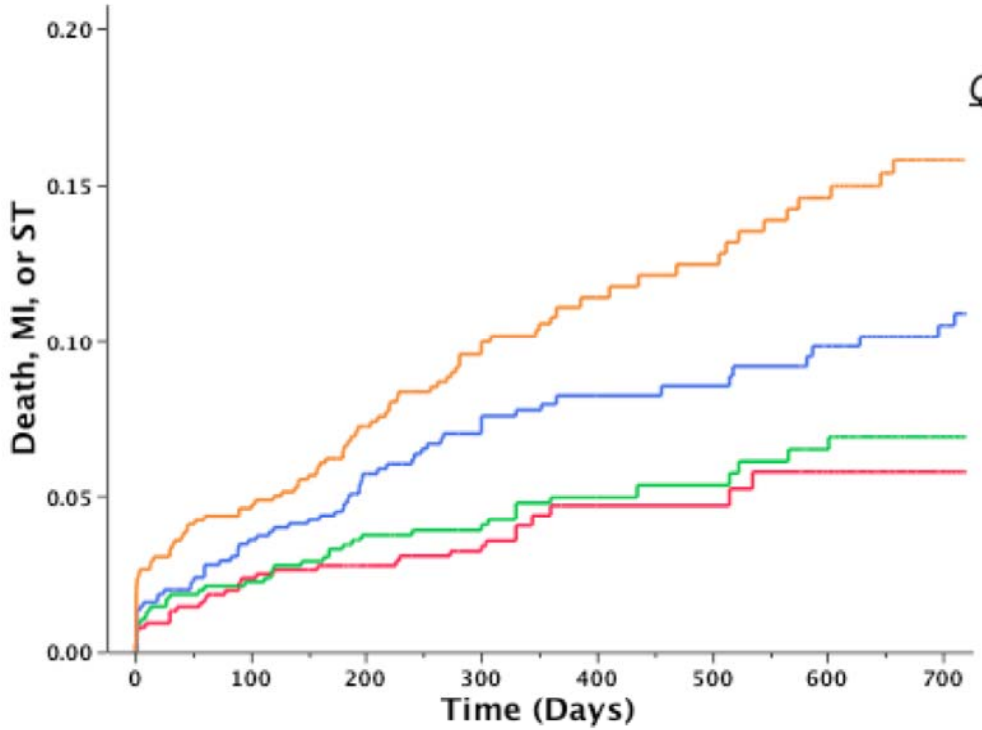
- a dimeric GPVI/Fc fusion protein and the extracellular domain of the human GPVI platelet receptor.
- binds to collagen and fibronectin in atherosclerotic stable or ruptured plaques

Ungerer M et al, Circulation 2011

Can We Do Better With our CURRENT Agents?

Meta-Analysis of OTR and Ischemic Events Post-PCI: Increasing Risk With Greater Residual Reactivity

N=3,041



Quartile	Event Rate	P-value*
Q4	15.8%	<0.001
Q3	10.9%	0.02
Q2	6.9%	0.97
Q1	5.8%	–

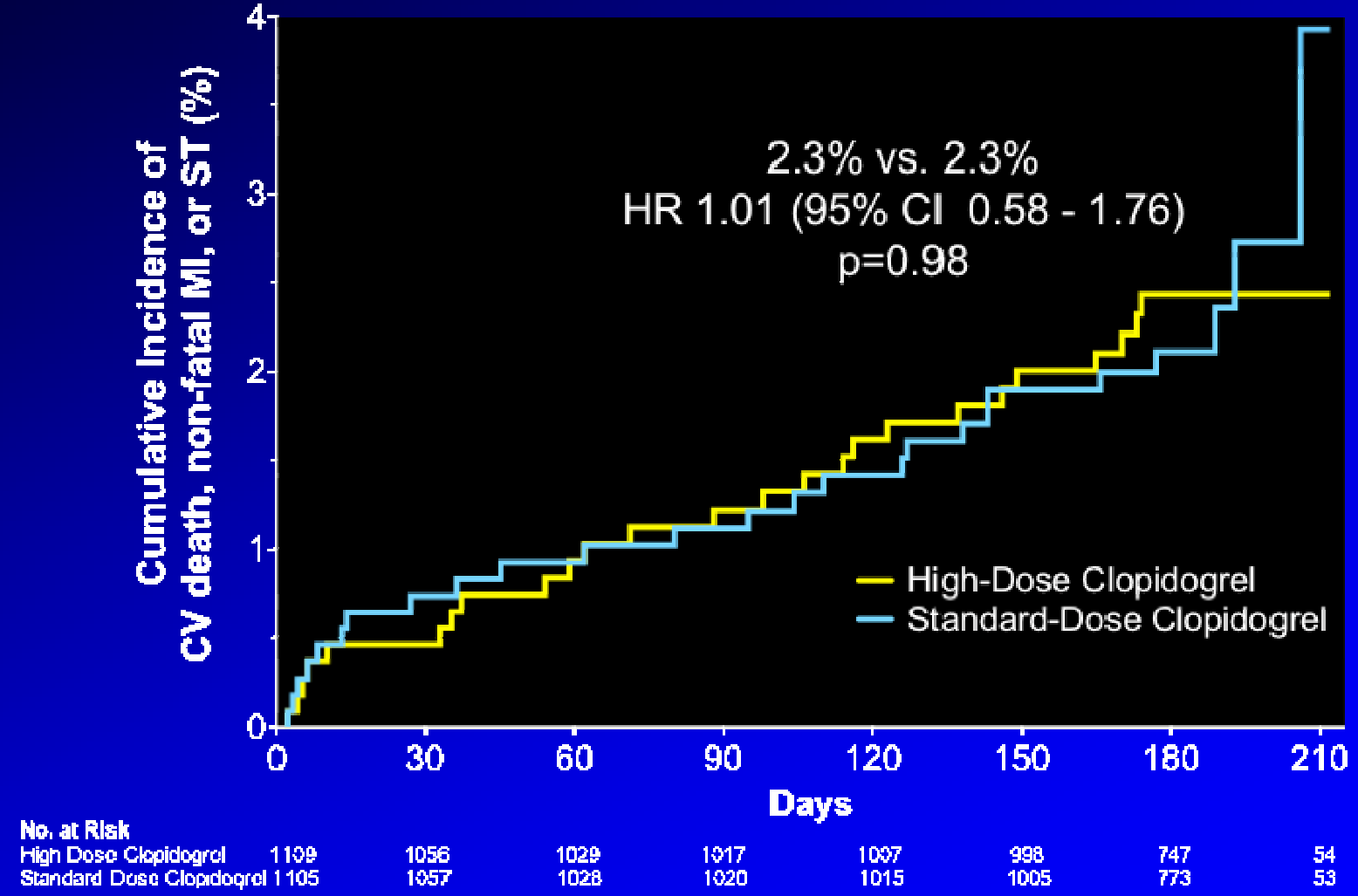
No. at risk

Q1	765	639	179	169
Q2	761	611	249	237
Q3	757	595	294	271
Q4	758	588	252	224

P-values adjusted for multiple comparisons

Brar S, ACC 2011 (in press)

GRAVITAS: Standard- *vs* High-Dose Clopidogrel in Patients with High Reactivity after PCI (≥ 230 PRU)



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

Price MJ et al, JAMA 2011;305(11):1097-1105.

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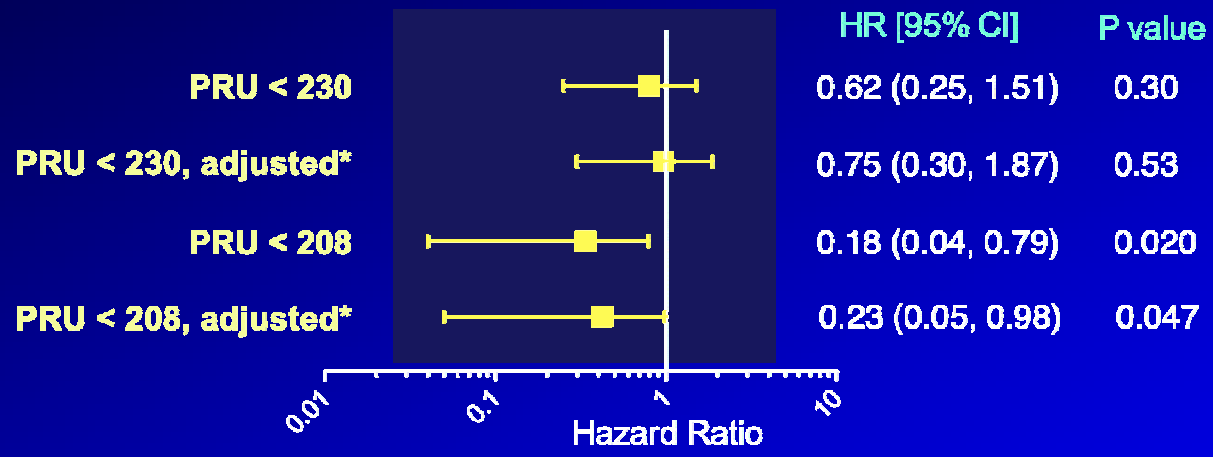
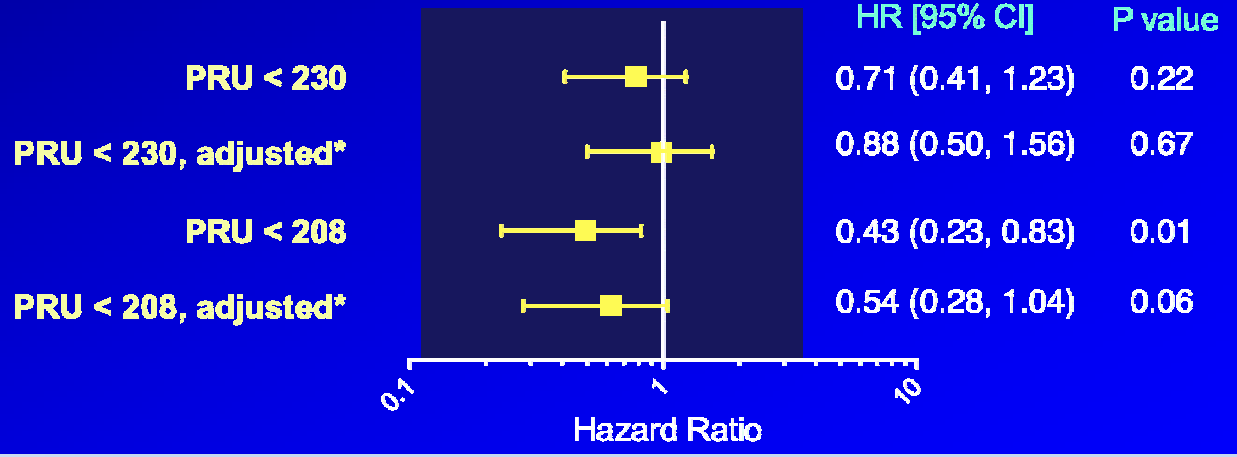
GRAVITAS: Hazard of Primary Endpoint According To *Achieved Reactivity* (Baseline or 30 days)

CV Death, MI or ST at 60 Days

N=2796

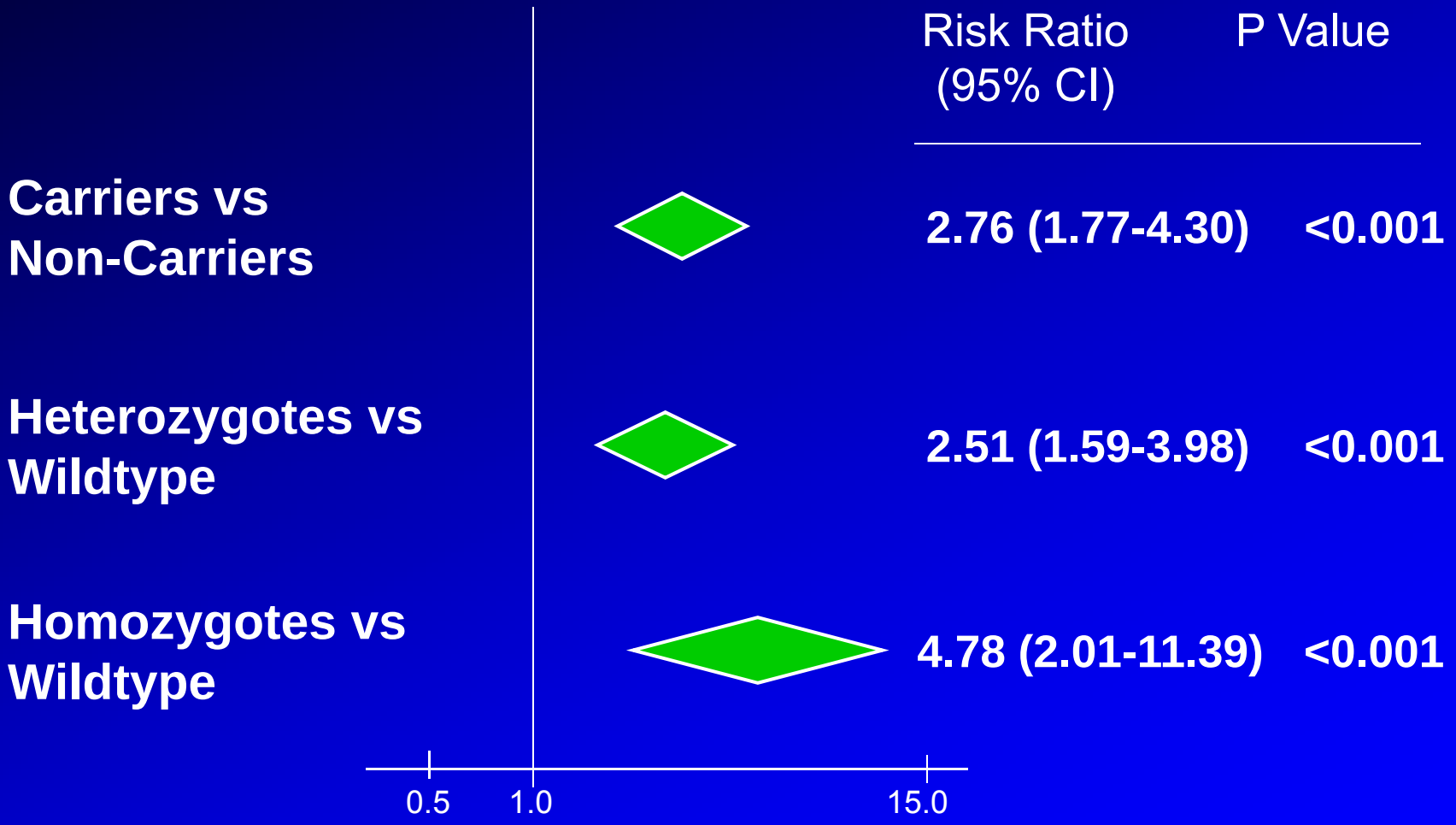


CV Death, MI or ST at 6 Months



Cox regression using OTR as a time-varying covariate
Price MJ et al, *in submission*

CYP2C19 and Stent Thrombosis In Clopidogrel-Treated Patients: A Collaborative Meta-analysis



N=5,772

Mega JL et al. JAMA. Oct 27 2010;304(16):1821-1830

Mega JL et al, AHA 2009

Bedside Genotyping Has (Almost) Arrived!
Sample to result turn-around times < 4 hrs

- Nanosphere (3 - 4 hrs), Spartan (1 hr), Quest (1 hr)
- Whole Blood/Buccal Swab
- Includes nucleic acid purification step
- Can run single samples (no need to batch)
- Minimal pipetting – run in cath lab, holding area, or clinical lab

Now And The Future: The Challenge

- Ischemic events are frequent after PCI for ACS.
- Novel antiplatelet agents in the pipe line do not appear to overcome all the limitations with the current agents.
- Individualized antiplatelet therapy may allow us to use our current drugs more smartly.
  - *Rapid* genotyping platforms will help.
  - Adequately powered RCT's using more potent agents in elective PCI will require very large sample sizes, need special attention to net clinical benefit.
  - The absence of data is not the same as the data of absence!