What is the Optimal Antiplatelet Therapy in High Risk Patients After DES?

Tailoring Treatment to Risk in Antiplatelet Therapy

Alexandra Lansky MD

Columbia University Medical Center
Cardiovascular Research Foundation

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Disclosures

- Research support from The Medicines Company
- Speaker's Bureau of Eli Lilly Company/ Daiichi Sankyo

What are the Risks in DES Pts? Predictors of DES Thrombosis

Moreno, JACC 45:954, 2005
N=5030 (10 RCT)

- Number of stents/patient
- Total stent length

Kuchulakanti, Circulation 113:1108, 2006

- Discontinuation of clopidogrel
- Renal failure
- Bifurcation lesions
- In-stent restenosis

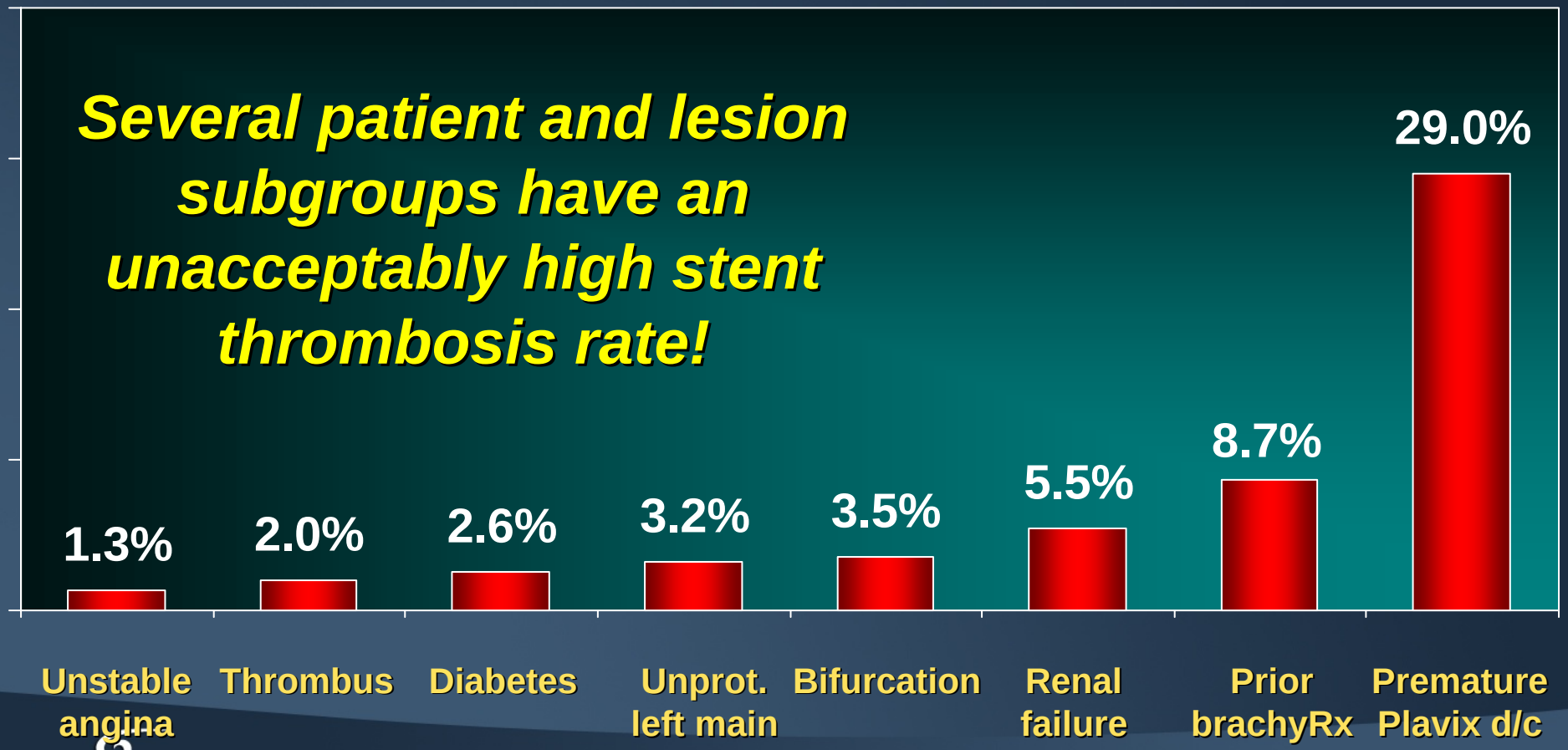
Iakovou and Colombo, JAMA 293:2126, 2005
N=2229 (3 Centers)

- Premature antiplatelet rx d/c
- Renal failure
- Bifurcation lesion
- Diabetes
- ↓ LVEF

Milan/Siegburg Experience

Stent thrombosis after DES (SES or PES) occurred in 29/2229 pts (1.3%) at 9.3±5.6 mos

Iakovou et al. JAMA 2005;293:2126-2130

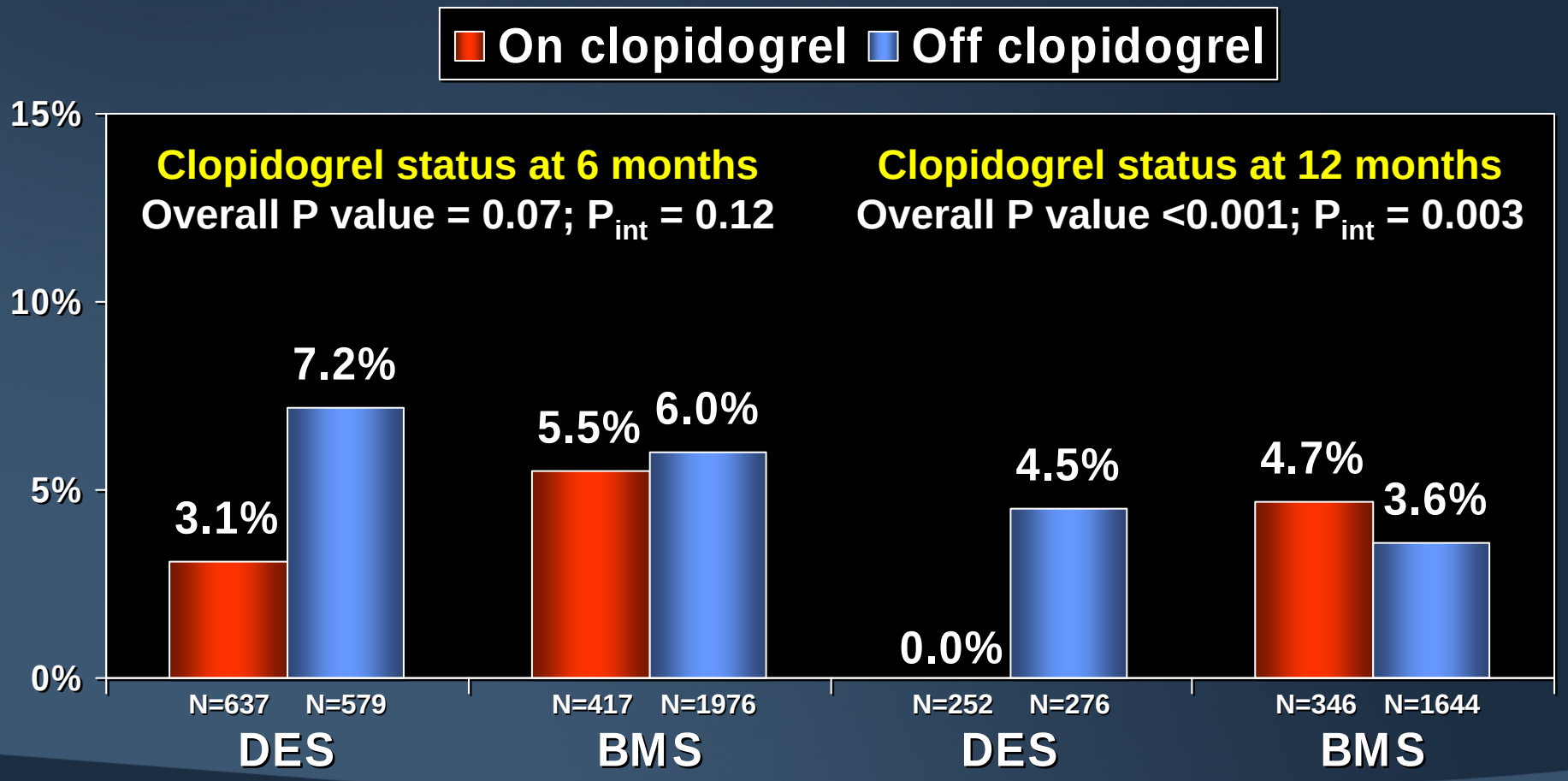


CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Duke Database Death/MI Analysis

Adjusted death/MI rates at 24 months in patients without events at 6 months



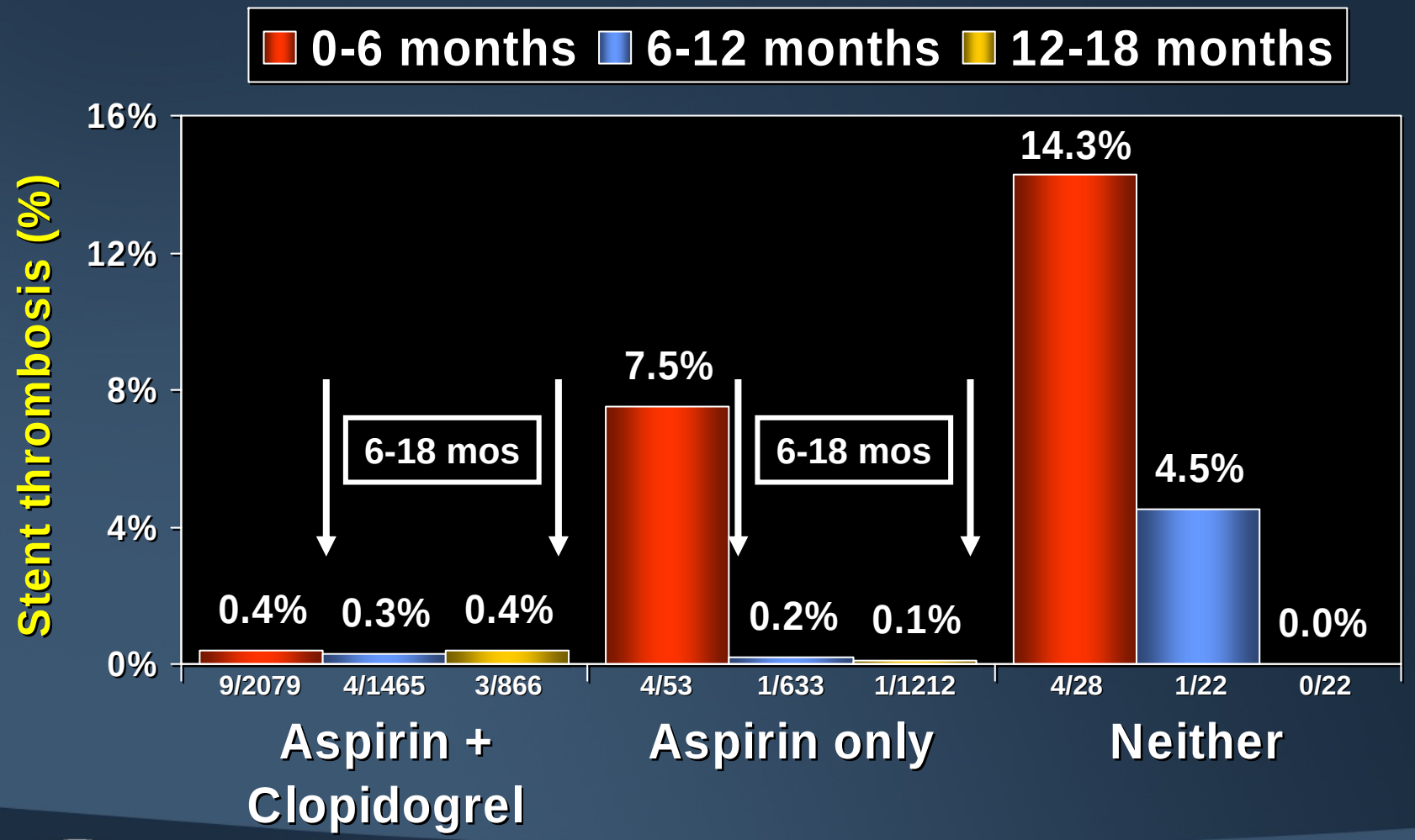
CARDIOVASCULAR RESEARCH FOUNDATION

Eisenstein EL et al. JAMA 2007;297

COLUMBIA UNIVERSITY MEDICAL CENTER

Milan Stent Thrombosis Experience

2,160 consecutive pts with DES implanted

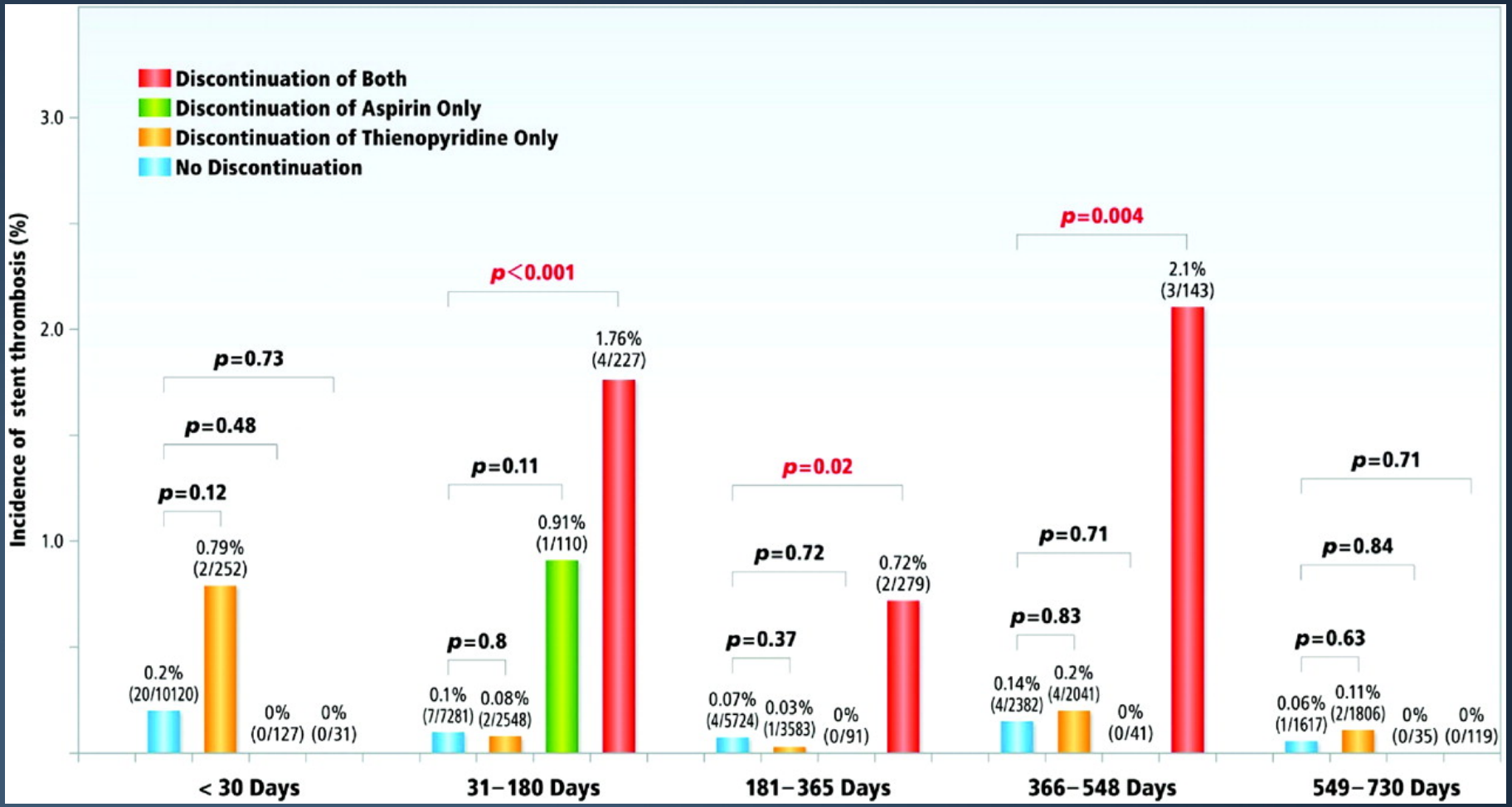


CARDIOVASCULAR RESEARCH FOUNDATION

Colombo A, TCT 2006

COLUMBIA UNIVERSITY MEDICAL CENTER

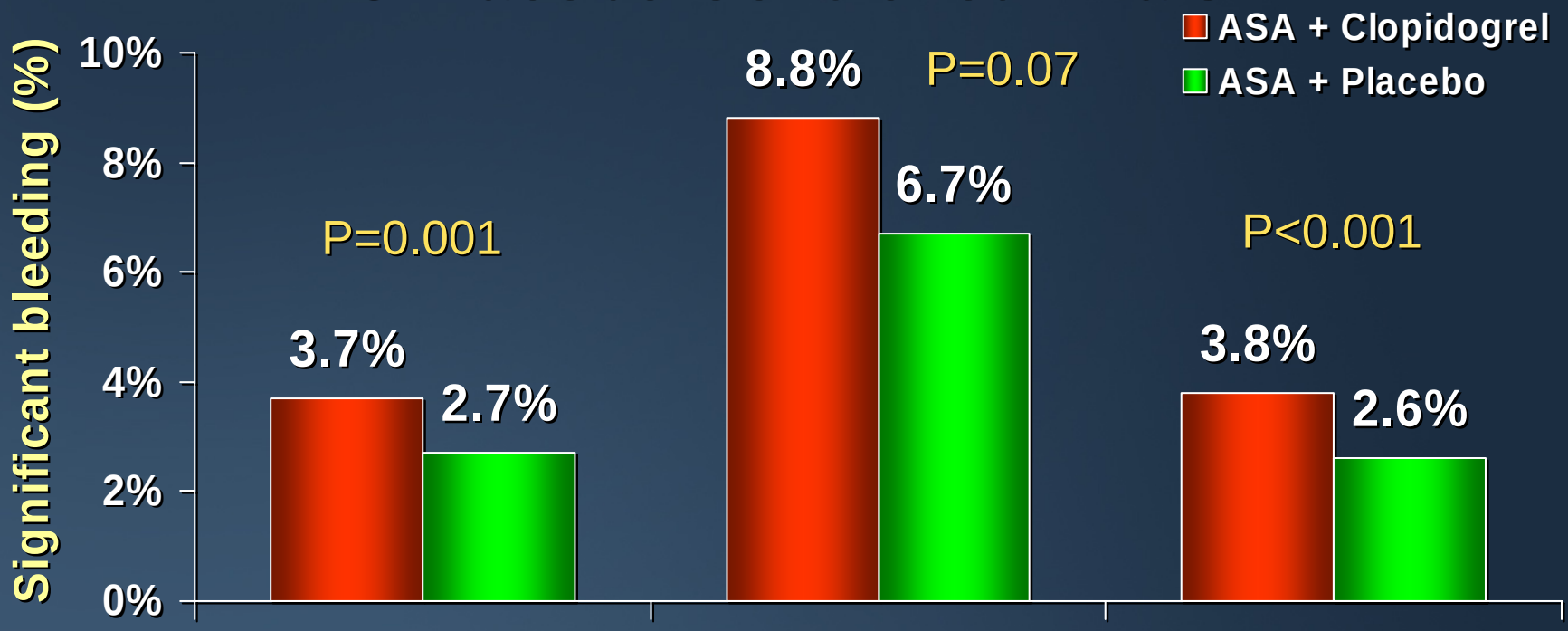
Relationship between thienopyridine and/or aspirin discontinuation and Stent Thrombosis by time interval after stent implantation



Kimura, T. et al. Circulation 2009;119:987-995

Bleeding with Long-Term Clopidogrel

3 Placebo Controlled Trials



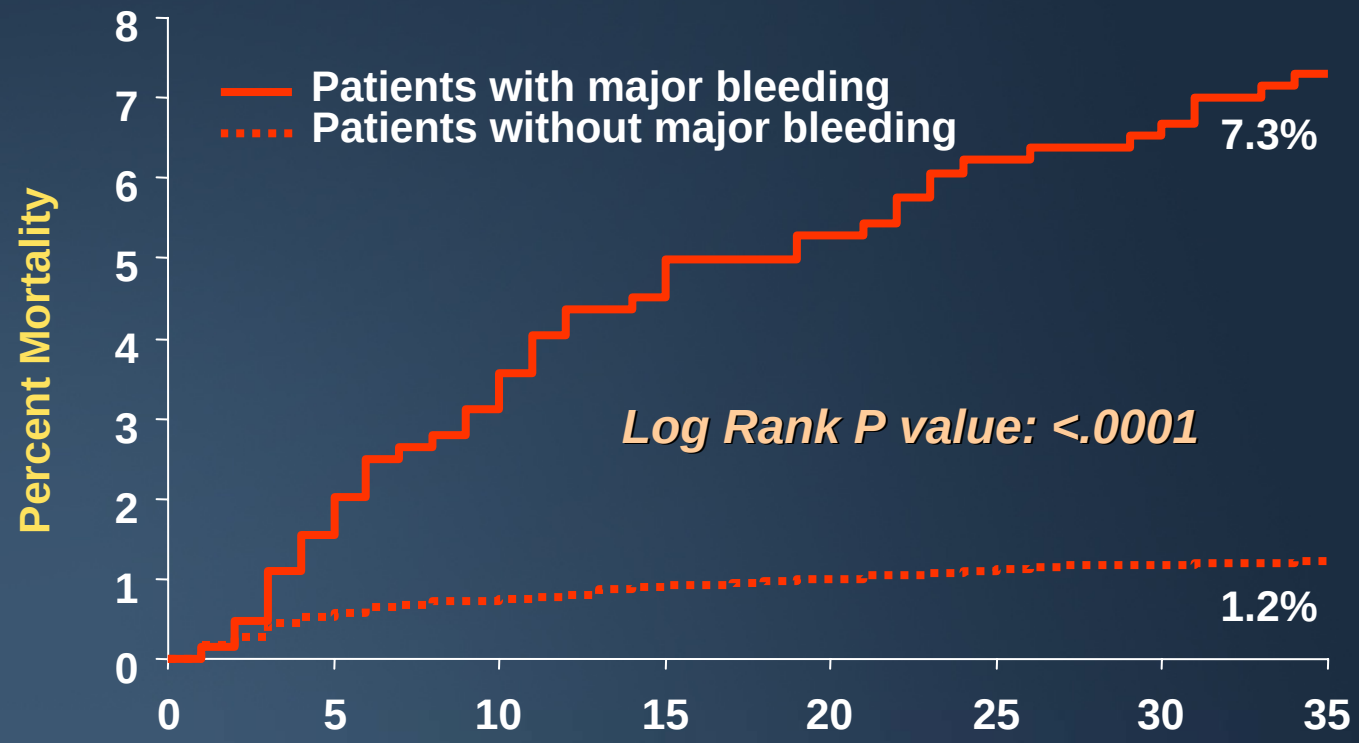
CURE	CREDO	CHARISMA
N=12,563	N=2,116	N=15,603
1 year FU	1 year FU	2.5 year FU
CURE major bleed	TIMI major bleed	GUSTO major + moderate bleed
NEJM 2001;345;494-502	JAMA 2002;288:2411-20	NEJM 2006;354:1706-17

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Implications of Major Bleeding: ACUITY: 30-day Mortality

- 30-day mortality by patients with or without major bleeding

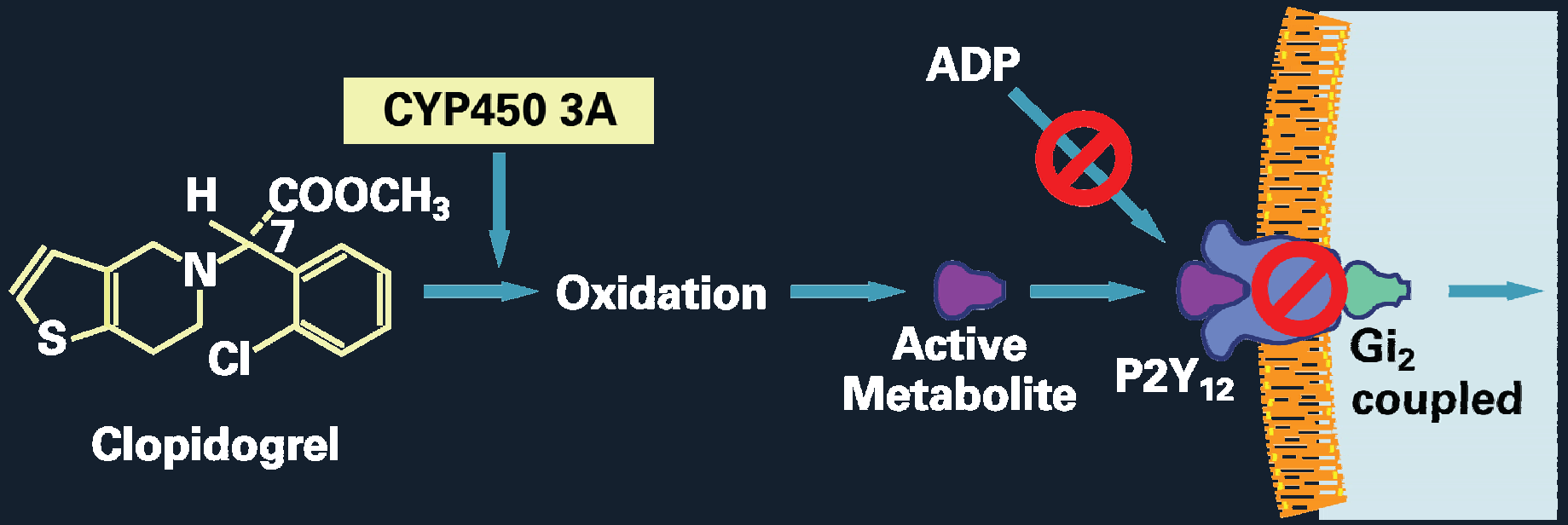


Patients at Risk

Patients with major bleeding:	644	633	623	614	609	602	599	589
Patients without major bleeding:	13169	13009	12975	12951	12933	12911	12864	12761

Manoukian et al, *JACC* 2007;49

The Target for Clopidogrel is the Platelet $P2Y_{12}$ Receptor

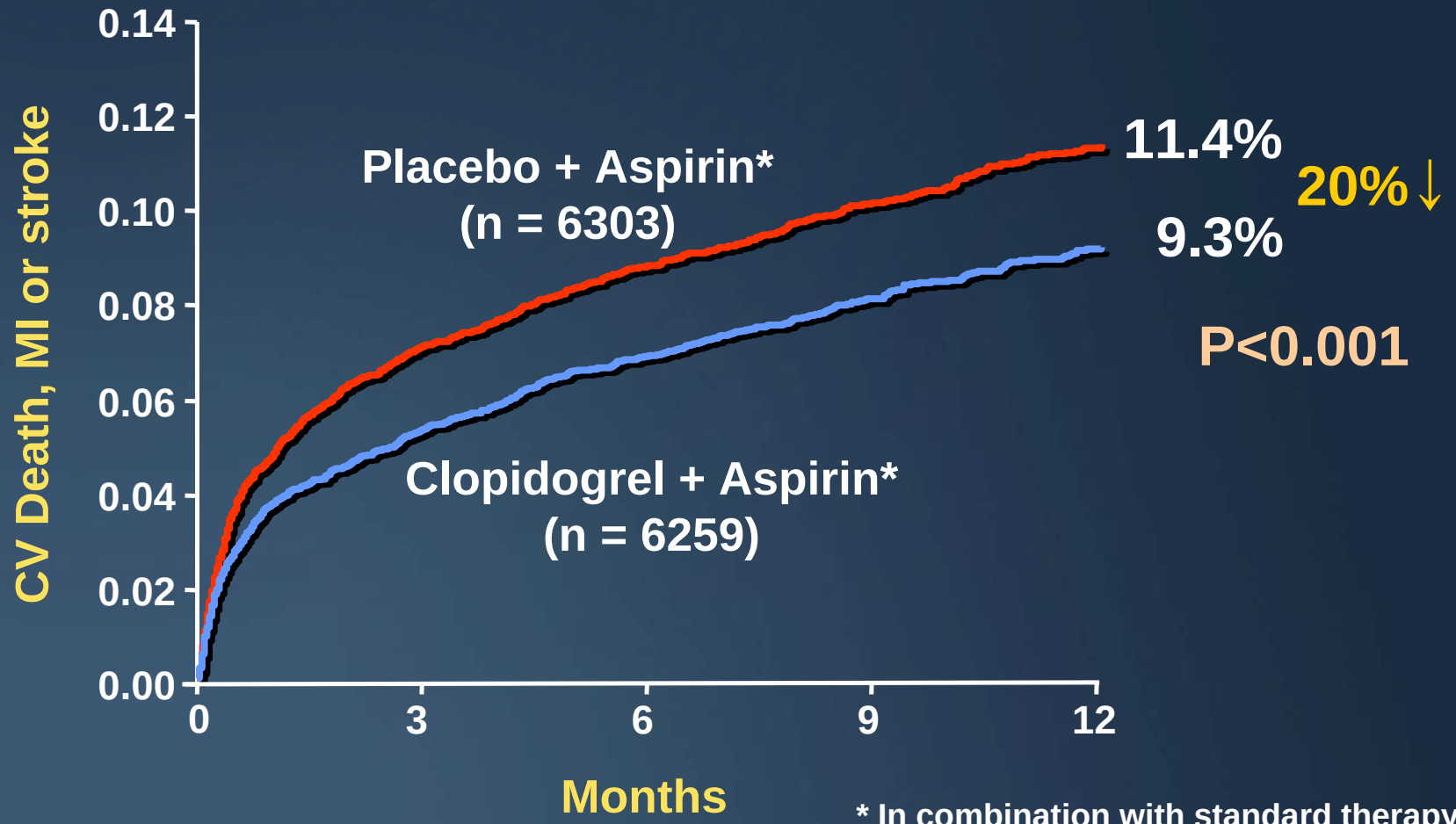


Clopidogrel is a prodrug, 85% hydrolysed to inactive metabolite
Variable intestinal absorption and hepatic P450 activity

CURE

12,562 pts with ACS were treated with aspirin and randomized to clopidogrel vs. placebo and followed for up to 12 months

Primary endpoint = CV Death, MI, or Stroke



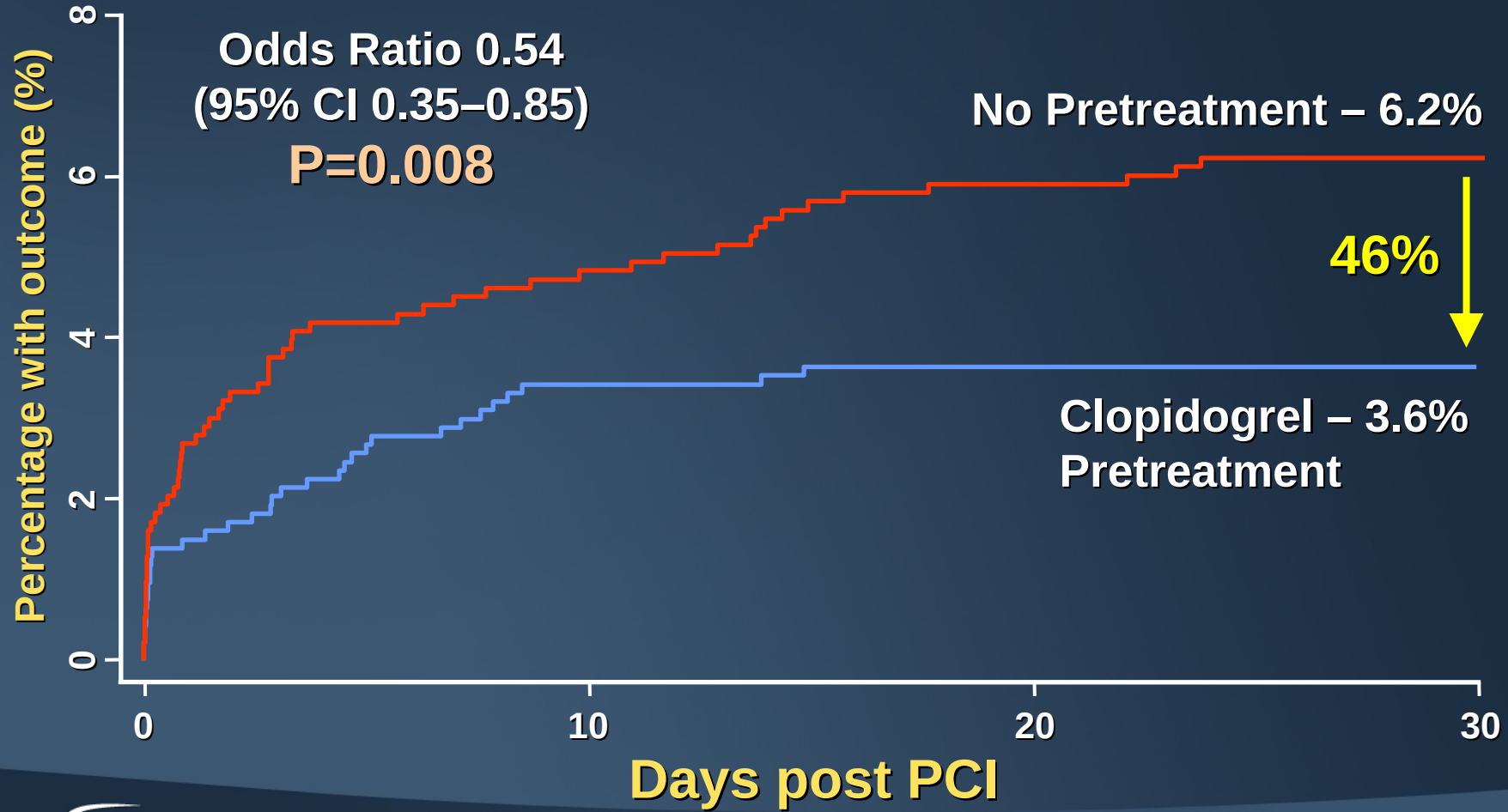
* In combination with standard therapy

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

PCI – CLARITY TIMI 28

1863 of 3491 pts treated with fibrinolytic and aspirin, randomized to clopidogrel 300/75mg vs. placebo and followed for 30 days

30 day Endpoint: CV Death, MI, or Stroke post PCI



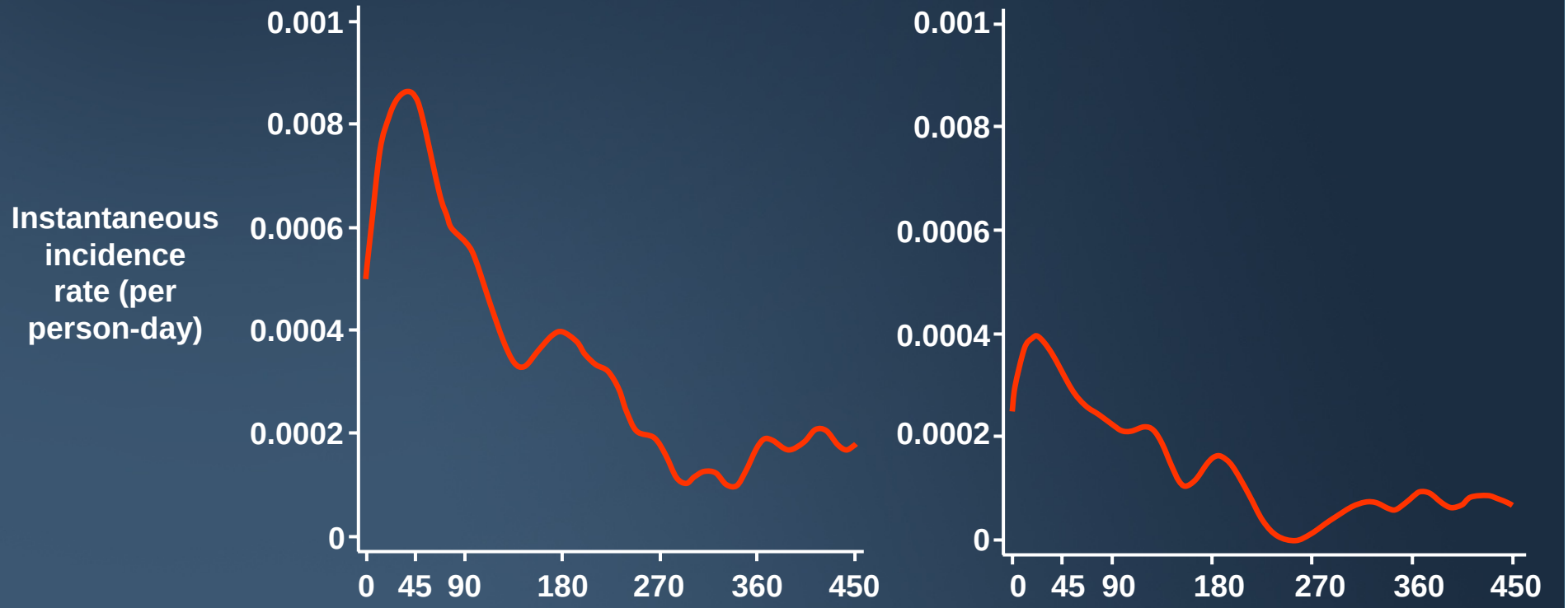
CARDIOVASCULAR RESEARCH FOUNDATION

Sabatine MS et al. JAMA. 2005;294:1224-1232

COLUMBIA UNIVERSITY MEDICAL CENTER

Hazard of death or MI after clopidogrel discontinuation post-ACS

N = 3137 US Veterans Administration patients

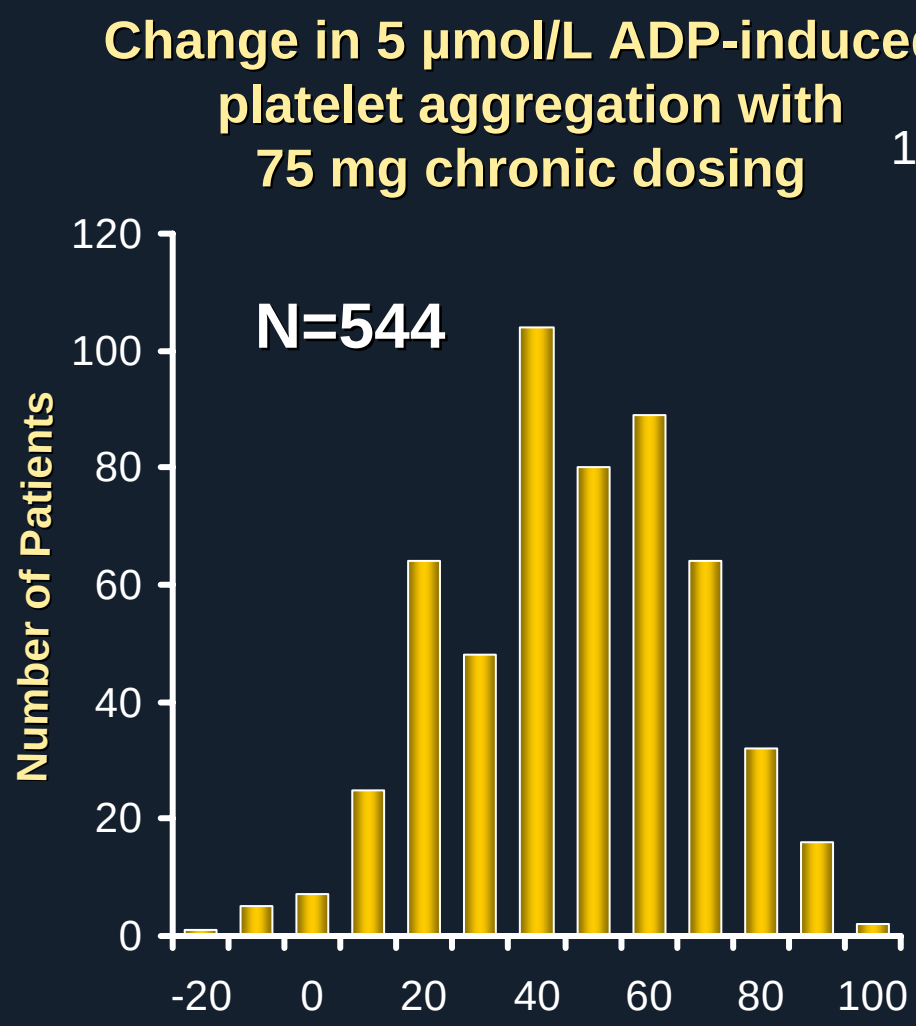


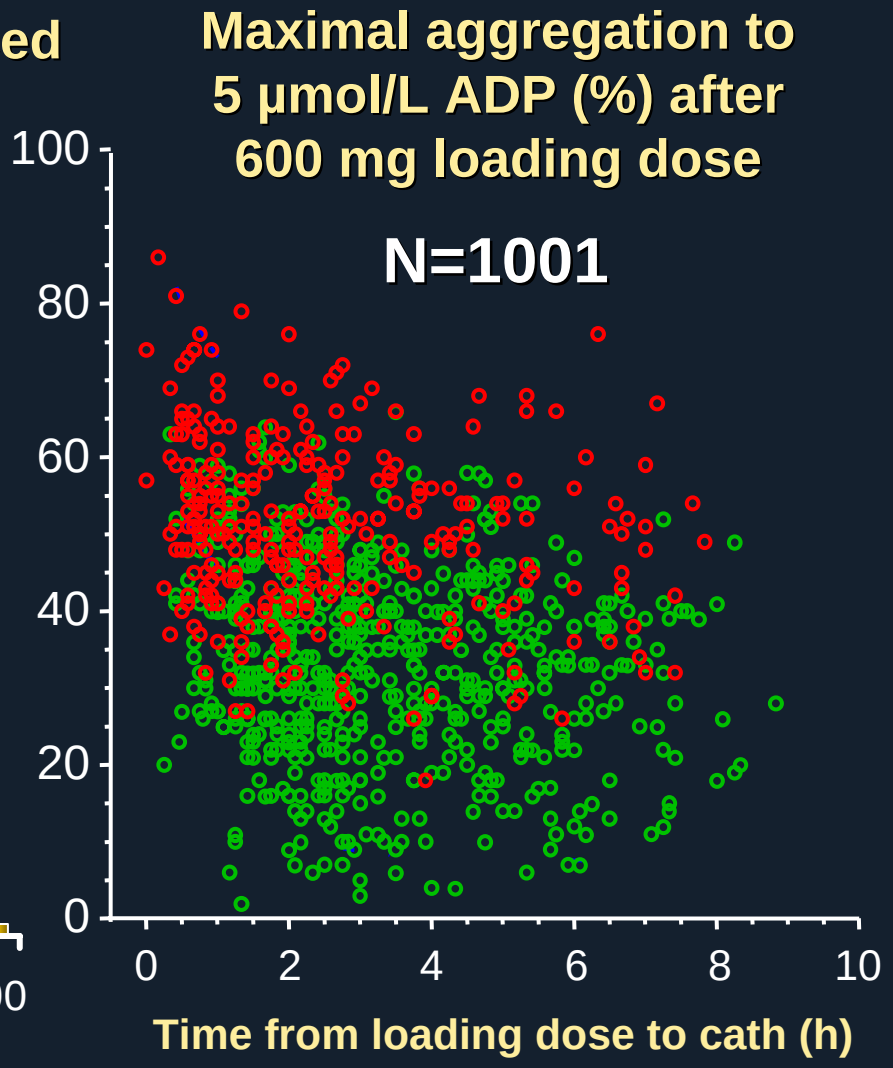
Ho PM et al. *JAMA*. 2008;299:532-9.

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Variability in Clopidogrel Response





CARDIOVASCULAR RESEARCH FOUNDATION

Serebruany V et al. JACC 2005;45:246-51

Hochholzer W et al. Circ 20051;11:2560-4

COLUMBIA UNIVERSITY MEDICAL CENTER

Mechanisms of Clopidogrel Response Variability

	Functional Parameter
Platelet Function	Accelerated platelet turn over
	Increased sensitivity to ADP and collagen
Bioavailability	Non compliance
	Poor absorption
	Drug-drug interaction (Statins, ompeprazole)
	Under dosing
Genetic Polymorphism	Cytochrome P450 (CYP2C19)
	$P2Y_{12}$
	$P2Y_1$
Other Factors	Diabetes
	Hypercholesterolemia, smoking, BMI

Clopidogrel Non-responsiveness Implications on Stent Thrombosis

	N	Functional Parameter	Clinical Relevance
Mueller et al. Thromb Haemost 2003	105	↓ inhibition of platelet aggregation	Stent thrombosis
Barragan et al. CCI 2003	36	↑ $P2Y_{12}$ reactivity ratio (VASP-levels)	Stent thrombosis
Gurbel et al. JACC 2005	120	↑ $P2Y_{12}$ reactivity ratio; ↑ platelet aggregation; ↑ stimulated GPIIb/IIIa expression	Stent thrombosis
Ajzenberg et al. JACC 2005	49	↑ shear-induced platelet aggregation	Stent thrombosis
Buonamici et al JACC 2007	804	↑ platelet aggregation	Stent thrombosis

CARDIOVASCULAR RESEARCH FOUNDATION

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

COLUMBIA UNIVERSITY MEDICAL CENTER

Overcoming Suboptimal Antiplatelet Drug Response

- ✓ **Modifying dosage of currently approved drugs**

  (e.g. higher dose)

- ✓ **Adding other agents with antiplatelet properties**

  (e.g. cilostazol)

- ✓ **Using new drugs**

  (e.g. novel $P2Y_{12}$ receptor inhibitors)

Clopidogrel 600 mg: Inhibition of platelet function at various time points

	Time (hours)				
Assay	**<1 (n = 98)**	**1 to <2 (n = 185)**	**2 to <4 (n = 341)**	**4 to <6 (n = 173)**	**≥6 (n = 204)**
5 μmol/L ADP					
% aggregation	51	41	37*	36*	35*
% inhibition	5	25	32*	35*	37*
20 μmol/L ADP					
% aggregation	67	58	52*	50*	50*
% inhibition	8	20	30*	32*	32*
P-selectin, % inhibition	26	56	62*	66*	65*
Activated GP IIb/IIIa, % inhibition	2	20	28*	33*	31*

*P = NS: 2 to <4 vs 4 to <6 vs ≥6 hours by 1-way ANOVA

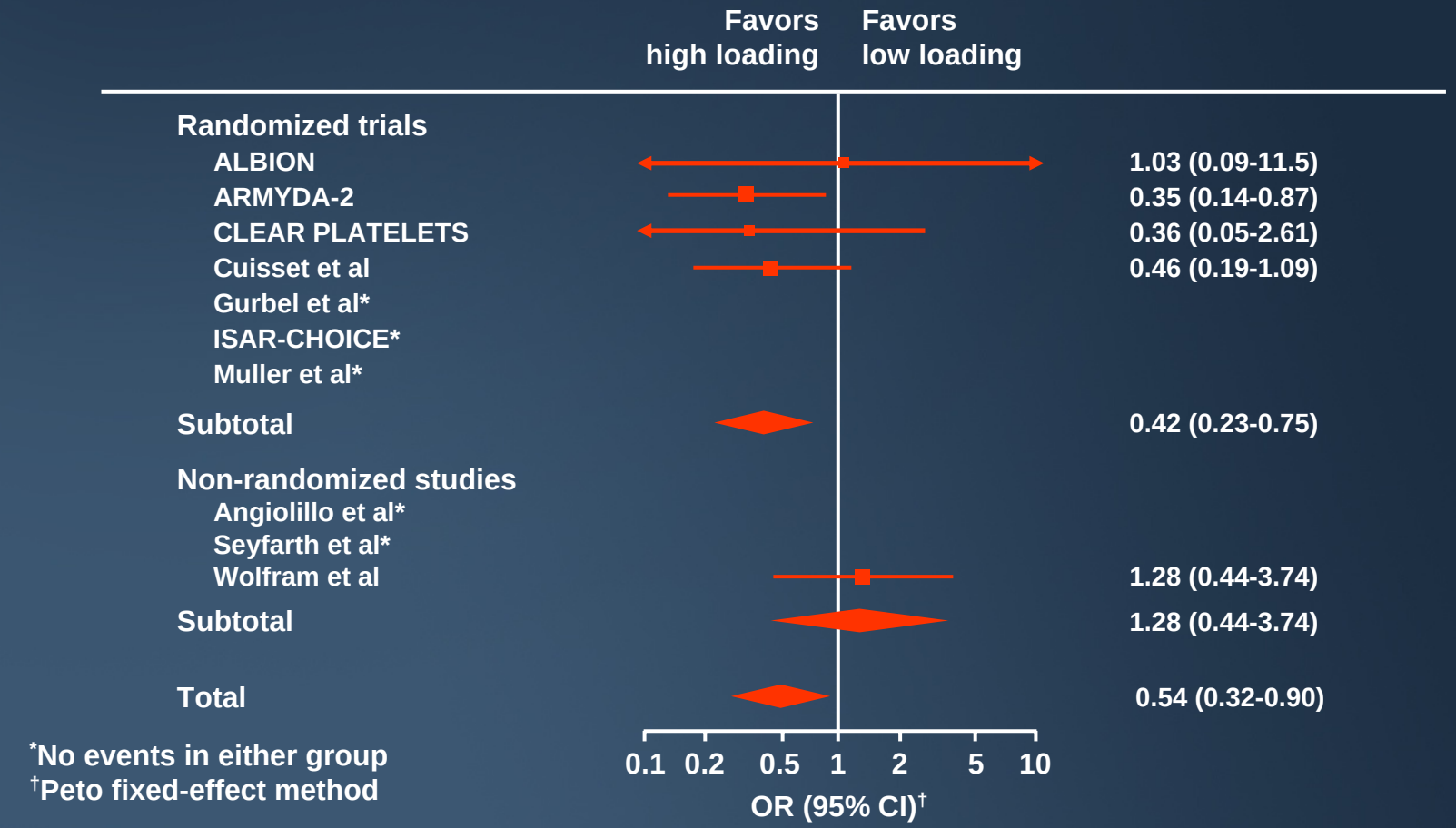
CARDIOVASCULAR RESEARCH FOUNDATION

Hochholzer W et al. *Circulation*. 2005;111:2560-4.

COLUMBIA UNIVERSITY MEDICAL CENTER

Clopidogrel 600 mg vs 300 mg loading dose

Meta-analysis; N = 1567; Primary endpoint: Cardiac death or MI at 1 month



*No events in either group
†Peto fixed-effect method

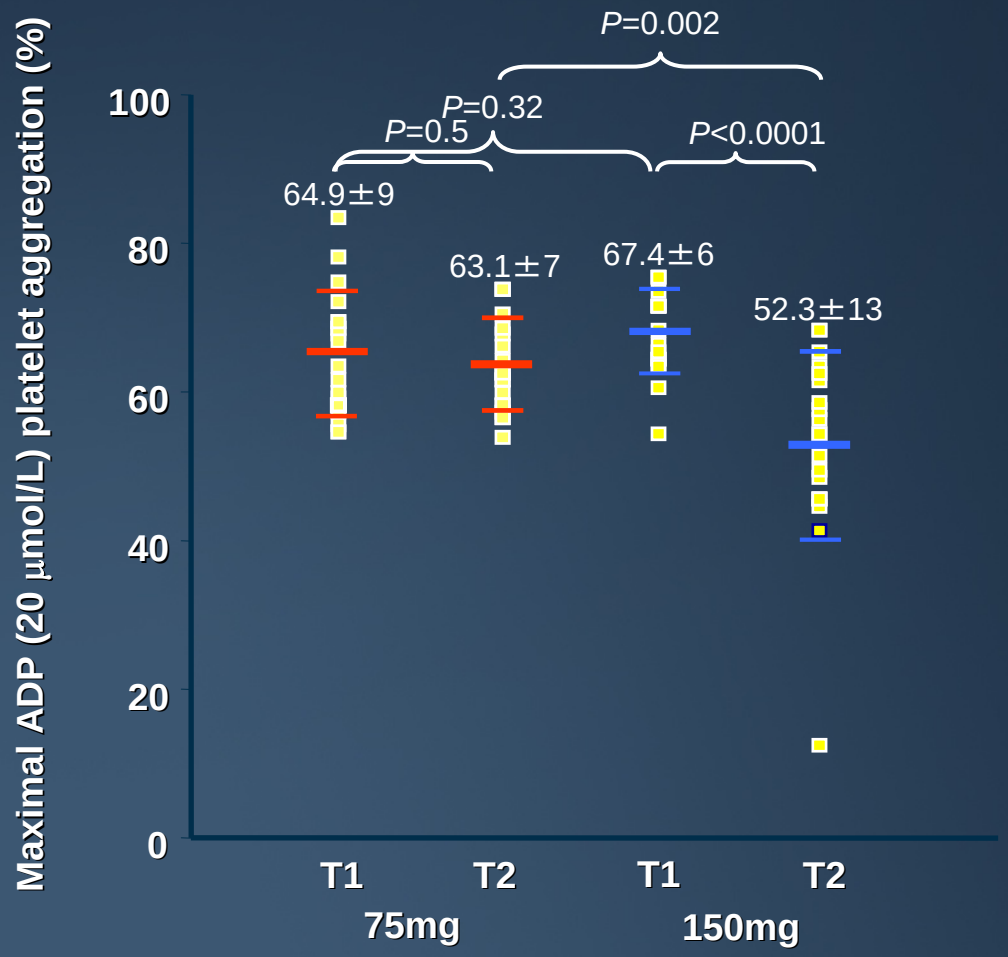
Lotrionte M et al. *Am J Cardiol*. 2007;100:1199-206.

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

OPTIMUS Study:
(Optimizing anti-Platelet Therapy In diabetes MellitUS)

Primary Endpoint: Maximal ADP (20 μmol/L) Platelet Aggregation



Angiolillo DJ et al. *Circulation.* 2007;115:708-16.

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Overcoming Suboptimal Antiplatelet Drug Response

- ✓ **Modifying dosage of currently approved drugs**

  (e.g. higher dose)

- ✓ **Adding other agents with antiplatelet properties: triple therapy**

  (e.g. cilostazol)

- ✓ **Using new drugs**

  (e.g. novel $P2Y_{12}$ receptor inhibitors)

Clinical Evidence for Triple Therapy: Cilostazol

	N	Study and Population	Result Summary
OPTIMUS II *Angiolillo DJ et al. Eur Heart Journal 2008; 29:2202-11*		**Cilostazol vs Placebo on background of ASA and Clopidogrel in DM pts**	**Reduction in $P2Y_{12}$ reactivity Index (PRI) (p<0.001)**
ACCEL RESISTANCE *Jeong, Y.-H. et al. J Am Coll Cardiol 2009;53:1101-1109*	**60**	**Cilostazol (100mgx2) vs High Maintenance Dose Clopidogrel (150mg) in AMI pts With Clopidogrel Resistance**	**Reduction in ADP platelet aggregation with Cilostazol (p<0.001, 20 μmol/L; p=0.012, 5 μmol/L)**
KAMIR trial *Kang-Yin Chen TCT 2008*	**4910**	**Adjusted clinical outcomes at 8 months for Triple vs Dual antiplatelet therapy in AMI**	**Reduced MACE** **OR 0.79[0.63-0.98]**
DECREASE SJ Park TCT 2008	**965**	**Twelve-month propensity matched risk of events after DES of Triple versus Dual antiplatelet therapy**	**Reduced Stent thrombosis HR 0.124 [0.016-0.996]**
Yalin Han Am Heart J 2009	**1212**	**Prospective randomized study of Cilostazol vs placebo on background of ASA and Clopidogrel after PCI. Endpoint 1 yr MACCE**	**Reduction in 1yr MACCE 10.3% vs 15.1%;p=0.01)**
DECLARE DM Seung-Whan Lee	**400**	**Randomized study of triple vs dual antiplatelet Rx in PCI DM pts. 9 month events. Primary endpoint: TLR**	**Reduced TLR (p=0.034); MACE (p=0.066); cilostazol predicts lower TLR, RS, MACE**

Overcoming Suboptimal Antiplatelet Drug Response

- ✓ **Modifying dosage of currently approved drugs**

  (e.g. higher dose)

- ✓ **Adding other agents with antiplatelet properties: triple therapy**

  (e.g. cilostazol)

- ✓ **Using new drugs**

  (e.g. novel $P2Y_{12}$ receptor inhibitors)

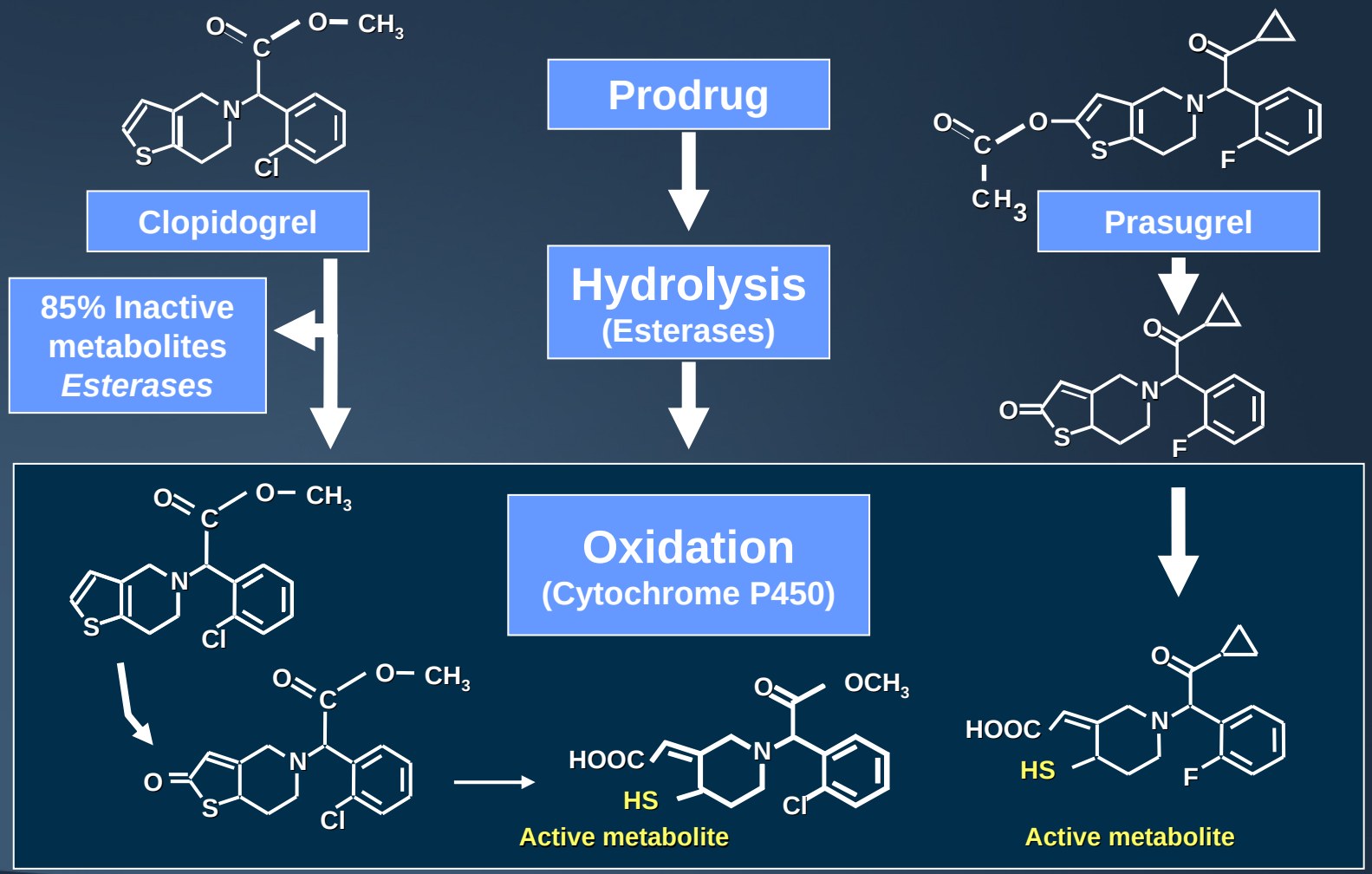
Novel $P2Y_{12}$ ADP receptor antagonist

More potent and less variability!!

Drug	Type	Route	Action	Dose	Mean platelet inhibition (time required)	Trials (phase III)
Prasugrel (CS-747)	Thienopyridine (3^{rd} generation) - requires hepatic conversion to active metabolite	Oral	Irreversible binding	60 mg loading dose, 10 mg maintenance dose	≈ 70% (< 1 hour)	TRITON
Cangrelor (ARC-669931MX)	ATP analogue- Direct inhibition	Parenteral	Competitive binding	4 µg/kg/min	≈ 95% (few minutes)	CHAMPION
Ticagrelor (AZD-6140)	Cyclopetyl-triazolopy-rimidine- Direct inhibition	Oral	Competitive binding	90 mg/twice daily	≈ 95% (2-4 hours)	PLATO

Elinogrel (PRT060128): reversible; IV & oral; effects within seconds; Phase II (INNOVATE-PCI)

Prasugrel: Thienopyridine, orally administered as prodrug (more efficiently metabolized vs clopidogrel), irreversible inhibition of P2Y12 receptor, >70% platelet inhibition in<1hour

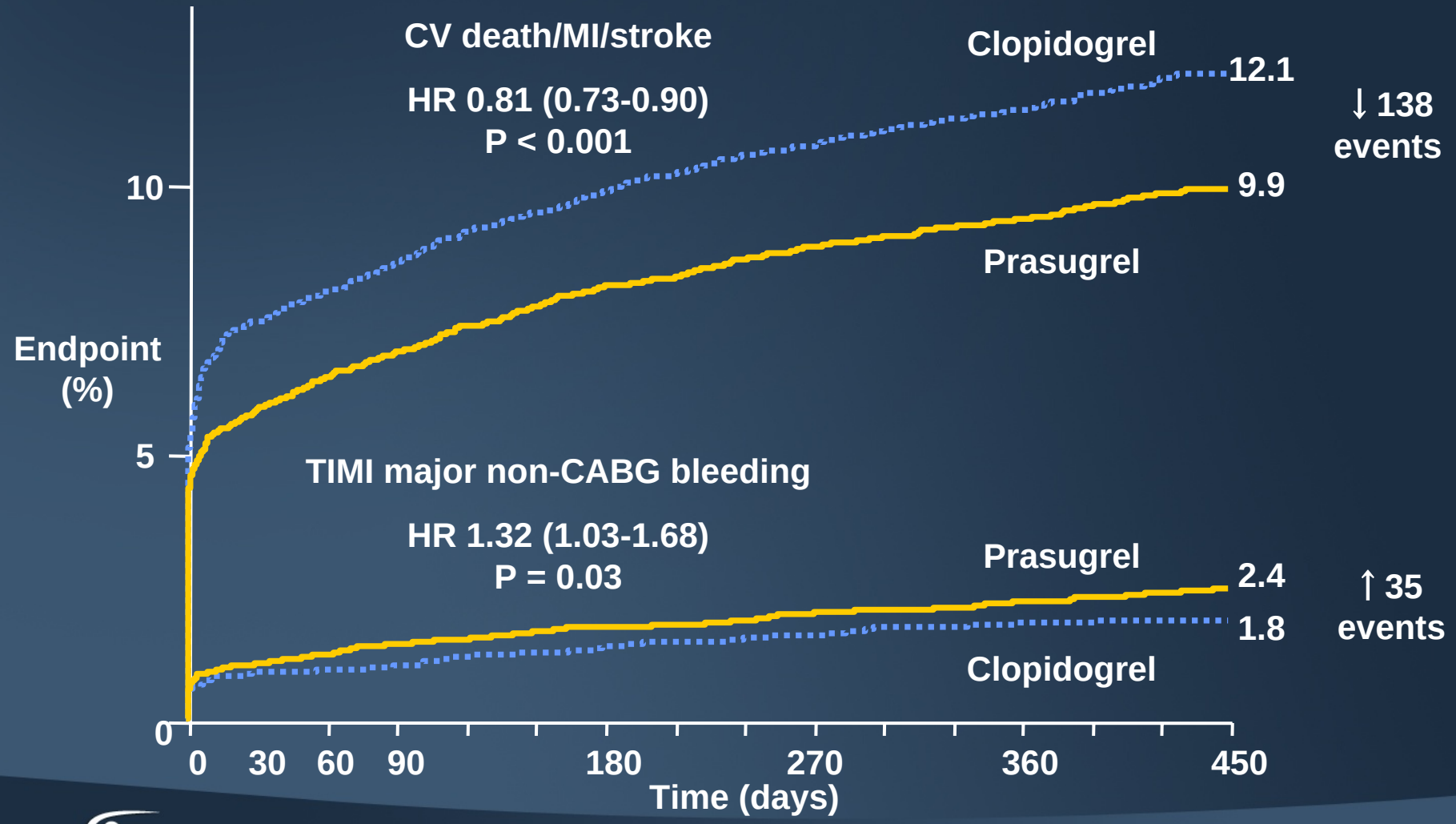


Angiolillo DJ, Capranzano P. *Am Heart J*. 2008;156:S10-S15;
Herbert JM, Savi P. *Sem Vasc Med.* 2003;3:113-22.

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

TRITON-TIMI 38: Treatment effects on primary efficacy and key safety endpoints N=13,608

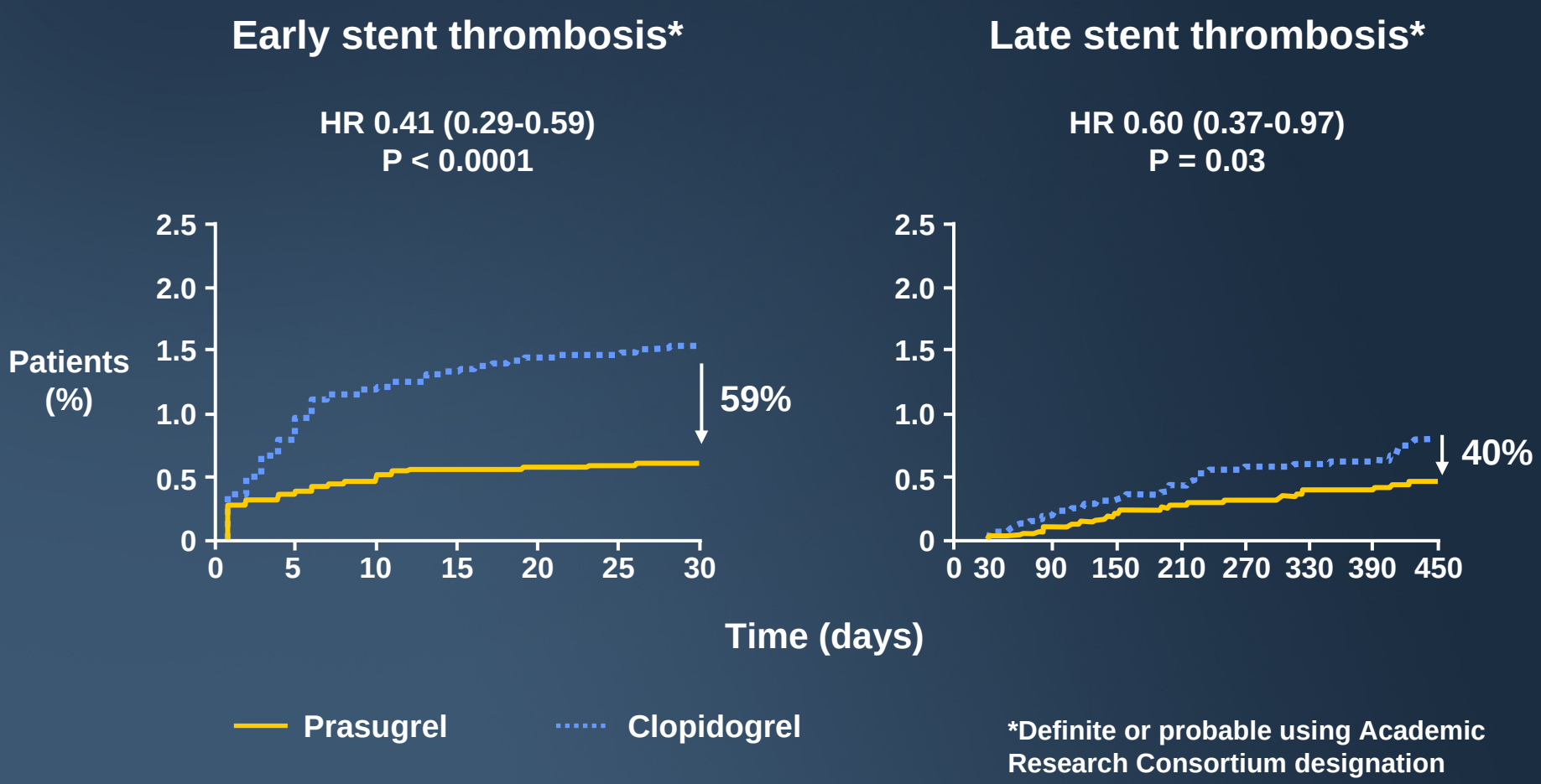


CARDIOVASCULAR RESEARCH FOUNDATION

Wiviott SD et al. *N Engl J Med.* 2007;357:2001-15.

COLUMBIA UNIVERSITY MEDICAL CENTER

TRITON-TIMI 38: Stent thrombosis for all patients receiving at least one intracoronary stent



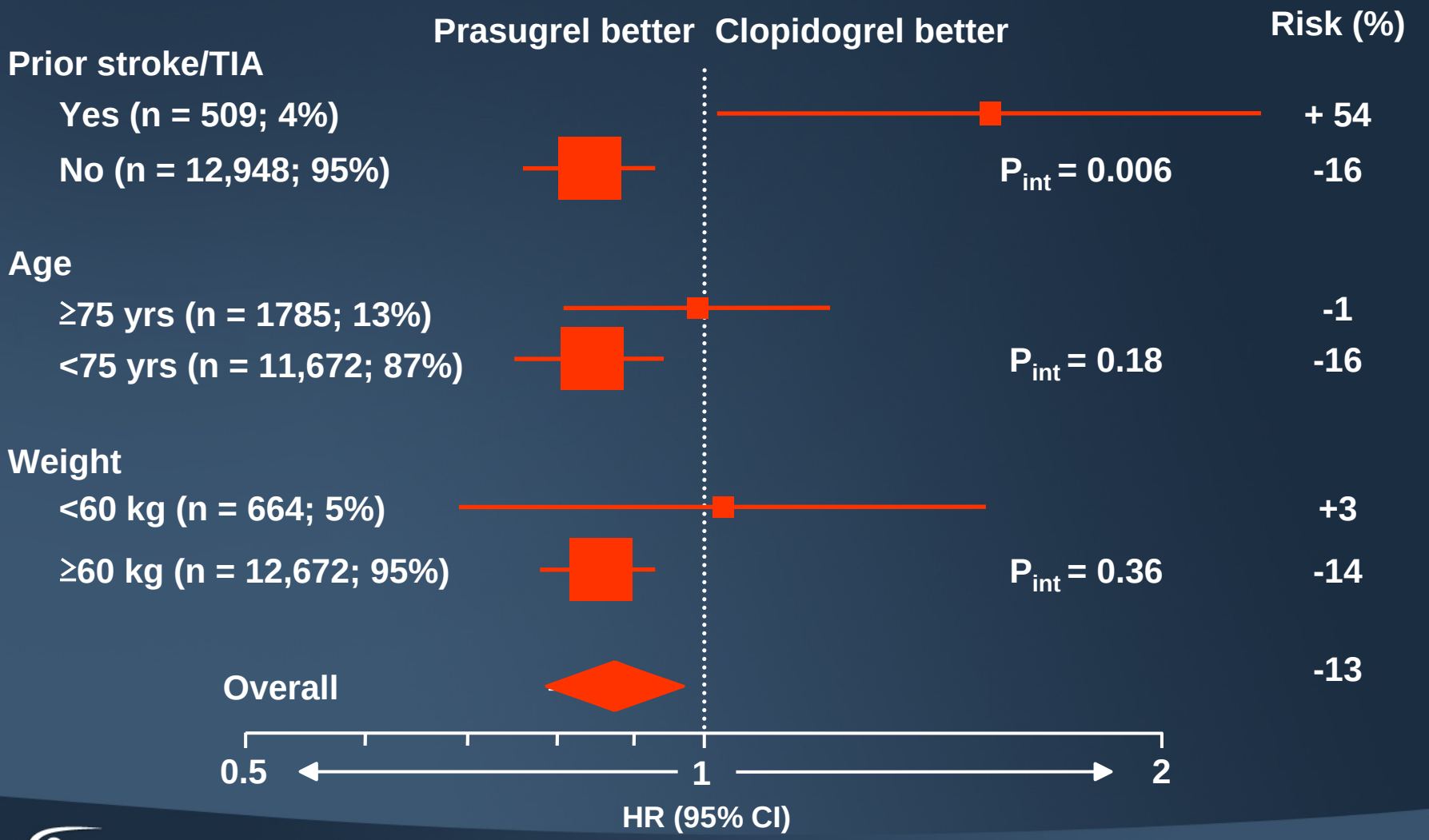
*Definite or probable using Academic Research Consortium designation

CARDIOVASCULAR RESEARCH FOUNDATION

Wiviott SD et al. *Lancet*. 2008;371:1353-63.

COLUMBIA UNIVERSITY MEDICAL CENTER

TRITON-TIMI 38 post hoc analysis: Net clinical benefit in subgroups at increased bleeding risk



CARDIOVASCULAR RESEARCH FOUNDATION

Courtesy of SD Wiviott, MD; Wiviott SD et al. *N Engl J Med*. 2007;357:2001-15.

COLUMBIA UNIVERSITY MEDICAL CENTER

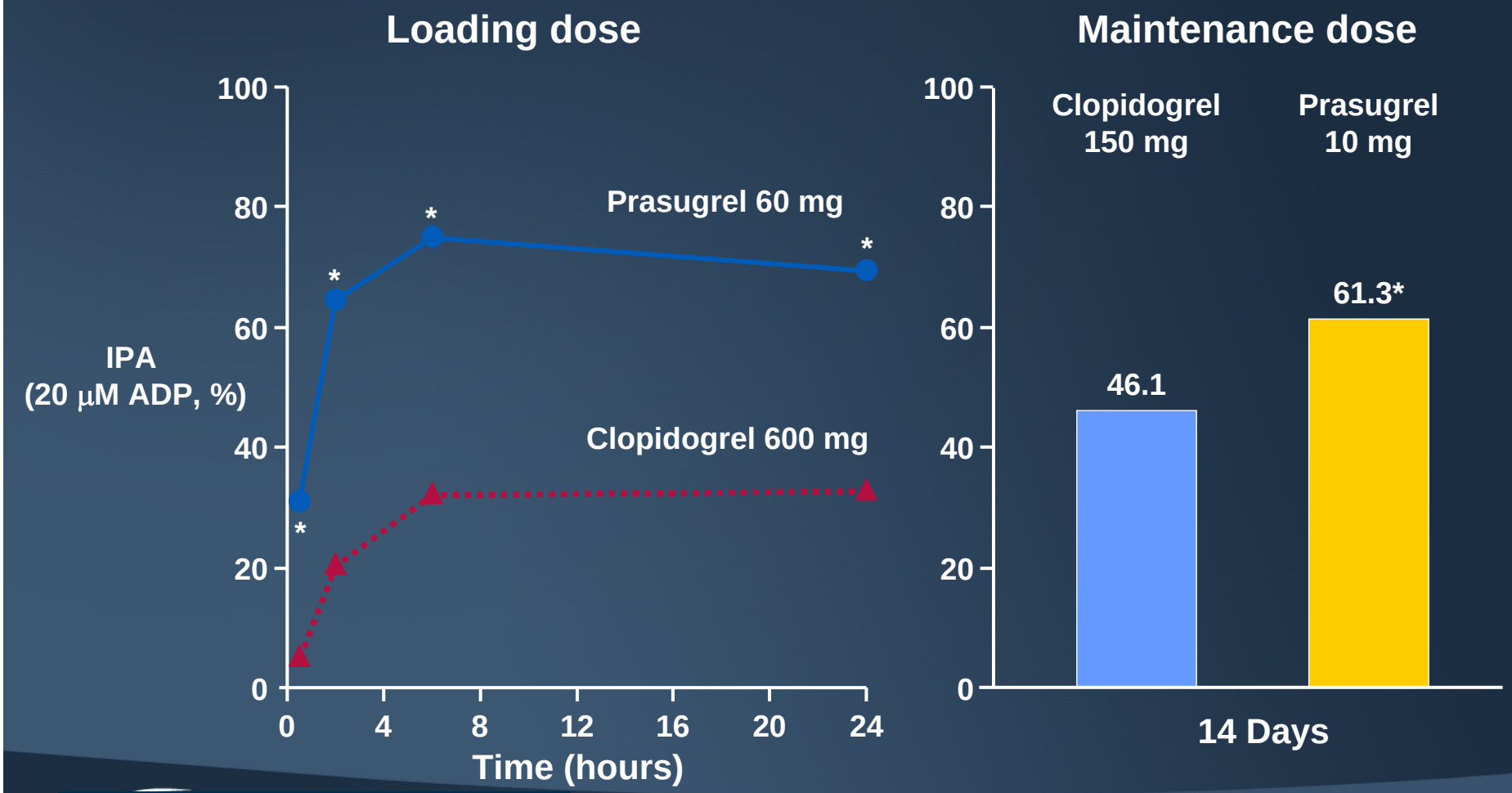
TRITON-TIMI-38

	Prasugrel (n=6813)	Clopidogrel (n=6795)	HR [95%CI]	P
CV death, MI, stroke	9.9%	12.1%	0.81 [0.73, 0.90]	<0.001
- CV death	2.1%	2.4%	0.89 [0.70, 1.12]	0.31
- Nonfatal MI	7.3%	9.5%	0.76 [0.67, 0.85]	<0.001
- Non fatal stroke	1.0%	1.0%	1.02 [0.71, 1.45]	0.93
Urgent TVR	2.5%	3.7%	0.66 [0.54, 0.81]	<0.001
Death, all-cause	3.0%	3.2%	0.95 [0.78, 1.16]	0.64
TIMI bleed, major or minor	5.0%	3.8%	1.31 [1.11, 1.56]	0.002
- Major, non CABG related	2.4%	1.8%	1.32 [1.03, 1.68]	0.03
- Life-threatening	1.4%	0.9%	1.52 [1.08, 2.13]	0.01
- Fatal	0.4%	0.1%	4.19 [1.58, 11.11]	0.002
- Major, CABG related	13.4%	3.2%	4.73 [1.90, 11.82]	<0.001
- Requiring transfusion	4.0%	3.0%	1.34 [1.11, 1.63]	<0.001

Wiviott SD et al. NEJM 2007;357:2001-15

PRINCIPLE-TIMI 44: Inhibition of platelet aggregation with loading and maintenance doses

201 pts undergoing elective PCI randomized to a loading dose of 600 mg clopidogrel vs. 60 mg prasugrel



*P < 0.0001 vs clopidogrel
IPA = inhibition of platelet aggregation

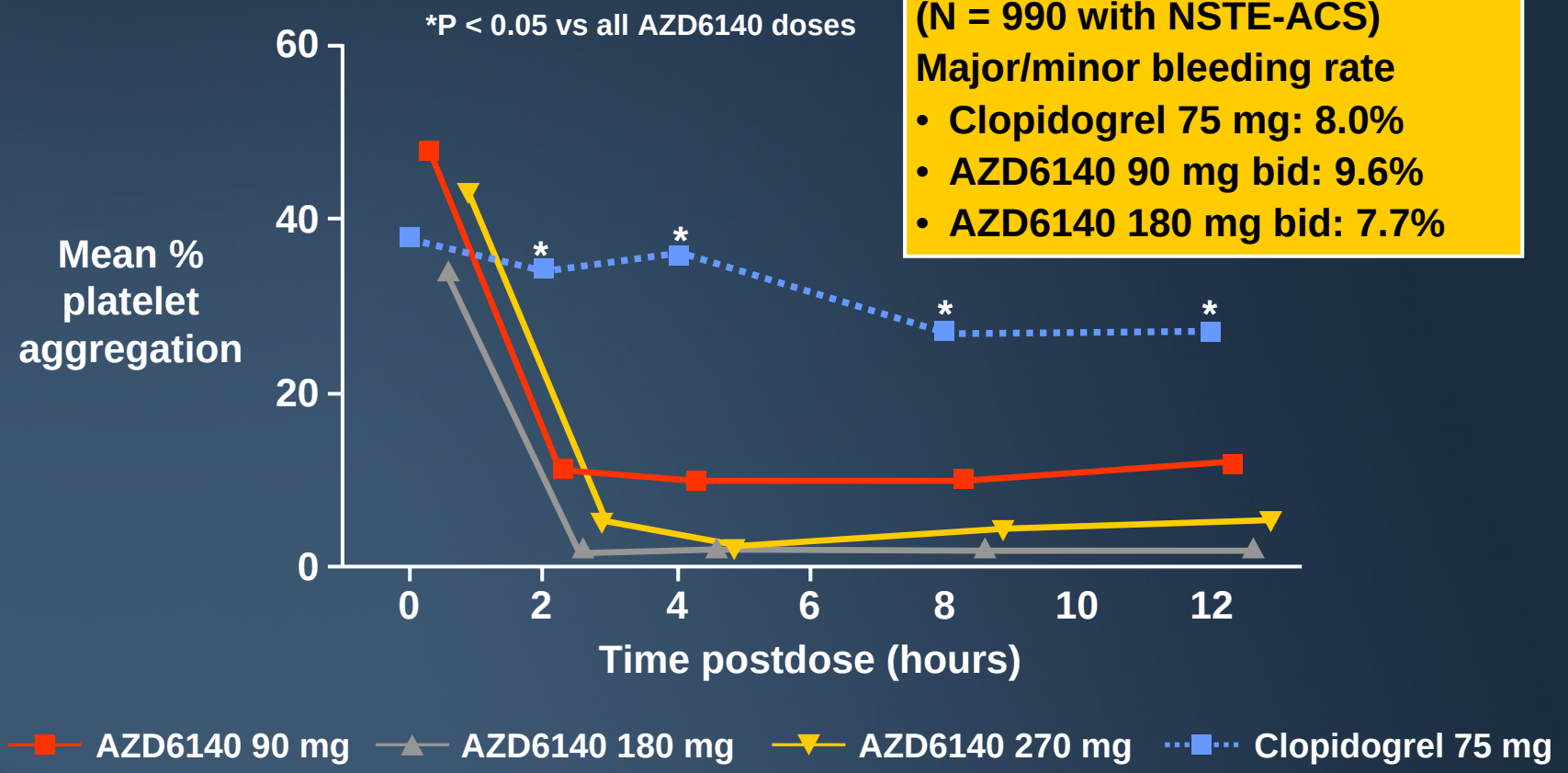
Wiviott SD et al. *Circulation.* 2007;116:2923-32.

Columbia University Medical Center

Ticagrelor/AZD6140
DISPERSE-2: Dose Optimization Study

Oral, direct-acting cyclopentyltriazolopyrimidine
reversible inhibition of P2Y12 receptor

Clopidogrel-pretreated cohort (n = 44)



All patients
(N = 990 with NSTE-ACS)
Major/minor bleeding rate

- **Clopidogrel 75 mg: 8.0%**
- **AZD6140 90 mg bid: 9.6%**
- **AZD6140 180 mg bid: 7.7%**

CARDIOVASCULAR RESEARCH FOUNDATION

Cannon CP et al. *J Am Coll Cardiol*. 2007;50:1844-51.
Storey RF et al. *J Am Coll Cardiol.* 2007;50:1852-6.

COLUMBIA UNIVERSITY MEDICAL CENTER

PLATO: Study design

N ~ 18,000 with UA/NSTEMI or STEMI scheduled for primary PCI

AZD6140
180 mg loading dose*
90 mg bid maintenance dose

12 months

Clopidogrel
300 mg loading dose†
75 mg maintenance dose

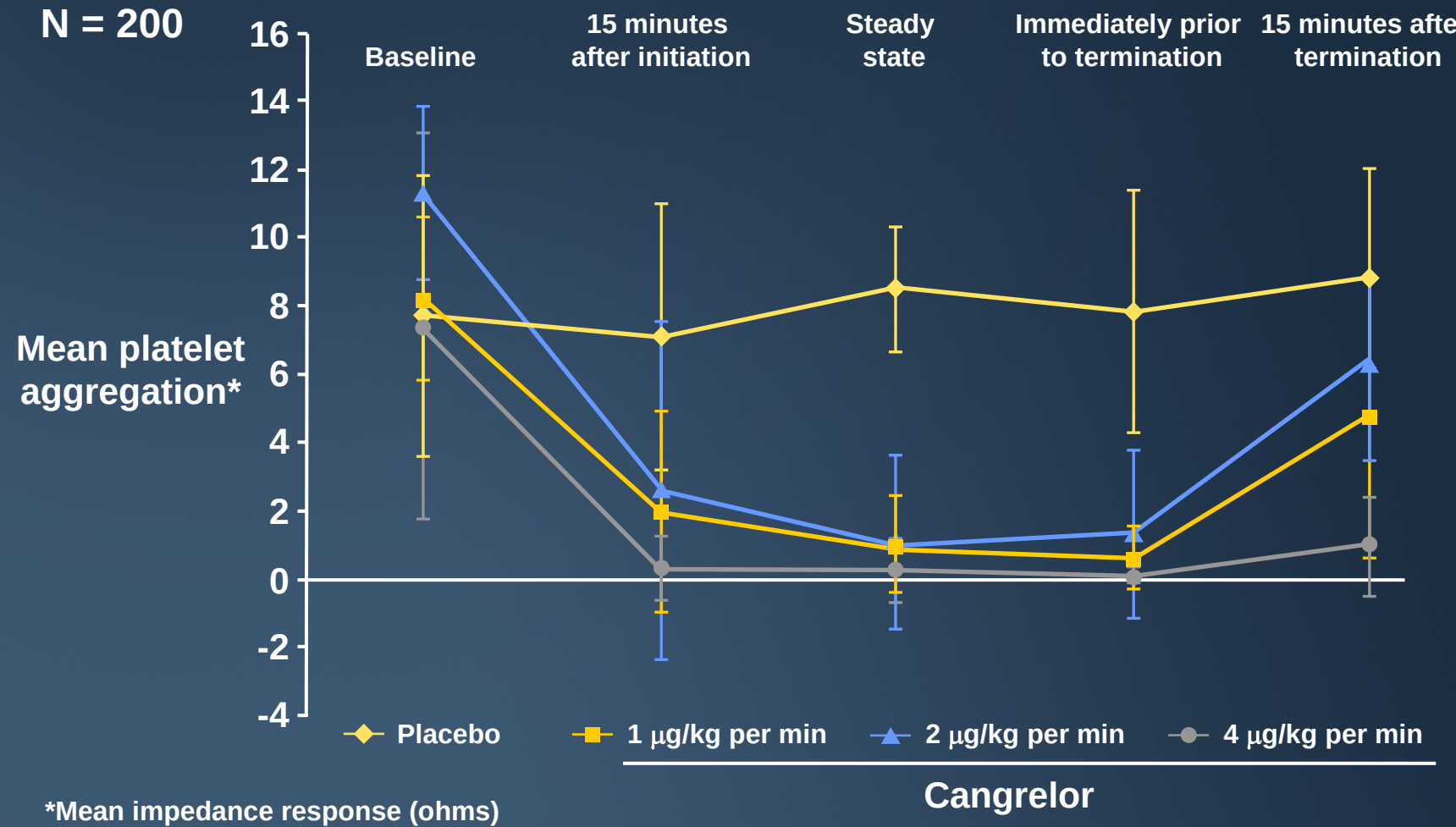
Primary endpoint:
CV death, MI, stroke

***Additional 90 mg allowed pre-PCI**
†In clopidogrel-naïve patients (no loading dose if pretreated); Additional 300 mg allowed in either clopidogrel group pre-PCI

Storey RF. *Eur Heart J Suppl.* 2008;10(suppl D):D30-D37.

Cangrelor: Dose finding study

Intravenous, direct-acting ATP analog, reversible inhibitor of P2Y12 receptor, plasma half-life 2.6-3.3 minutes



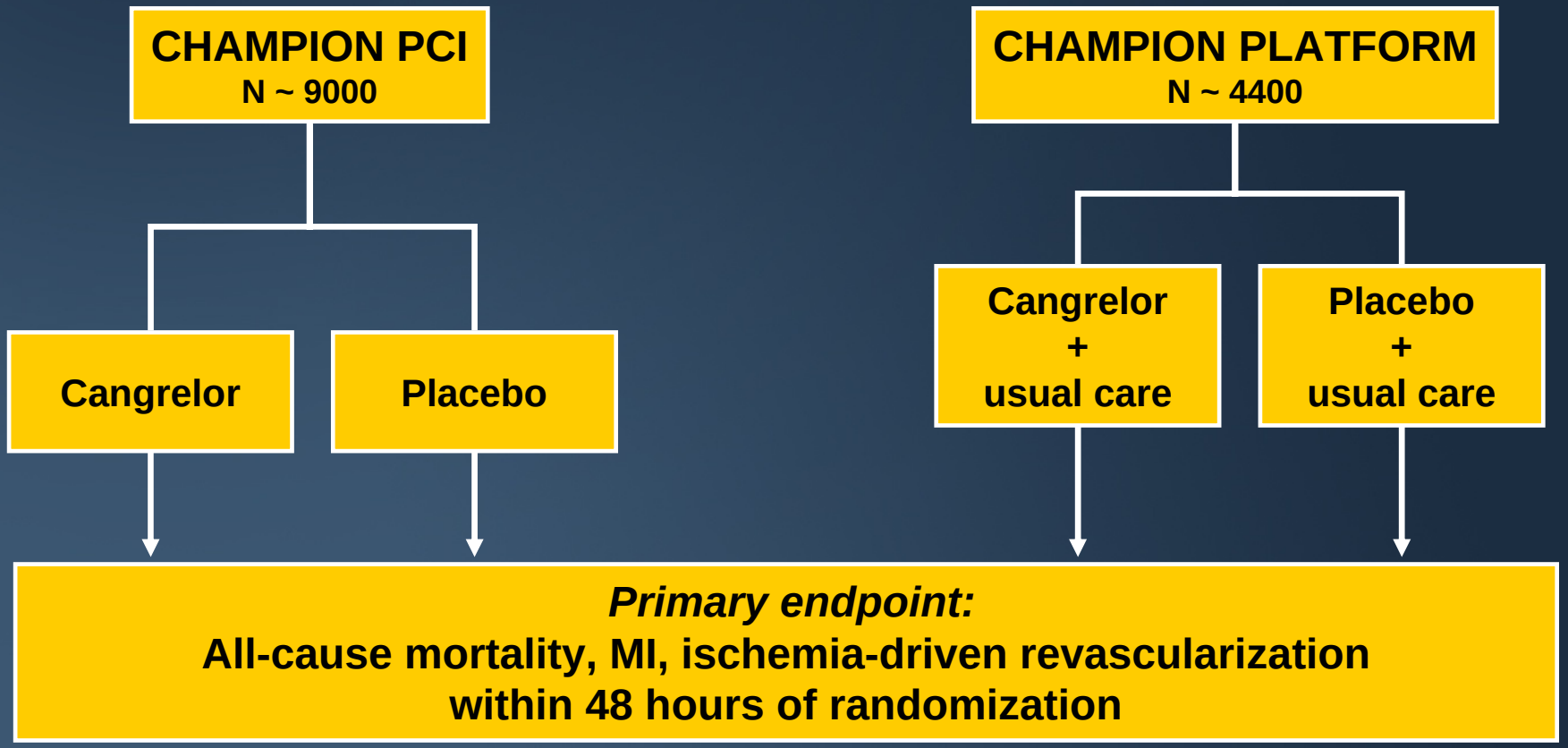
*Mean impedance response (ohms)

Greenbaum AB et al. *Am Heart J.* 2006;151:689.e1-10.

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Cangrelor: Ongoing clinical trials



Storey RF. *Eur Heart J Suppl.* 2008;10(suppl D):D30-D37.
NIH. www.clinicaltrials.gov.

Antiplatelet Therapy in ACS/STEMI/PCI

- Patients should be adequately pre-loaded with clopidogrel prior to angiography and PCI
  - 600 mg given ≥2-6 hours pre cath (or in ER ASAP for STEMI)
- Continue clopidogrel 75 mg per day
  - 1 year (minimum) in pts with ACS/STEMI
  - Higher dose considered in high risk patients
- Triple Therapy
  - High risk patients including restenosis risk
- Prasugrel is more potent and rapid acting than clopidogrel and has greater anti-ischemic efficacy but more bleeding
  - Should be the preferred agent in pts at low risk for bleeding

Tailored antiplatelet therapy to Patient risk

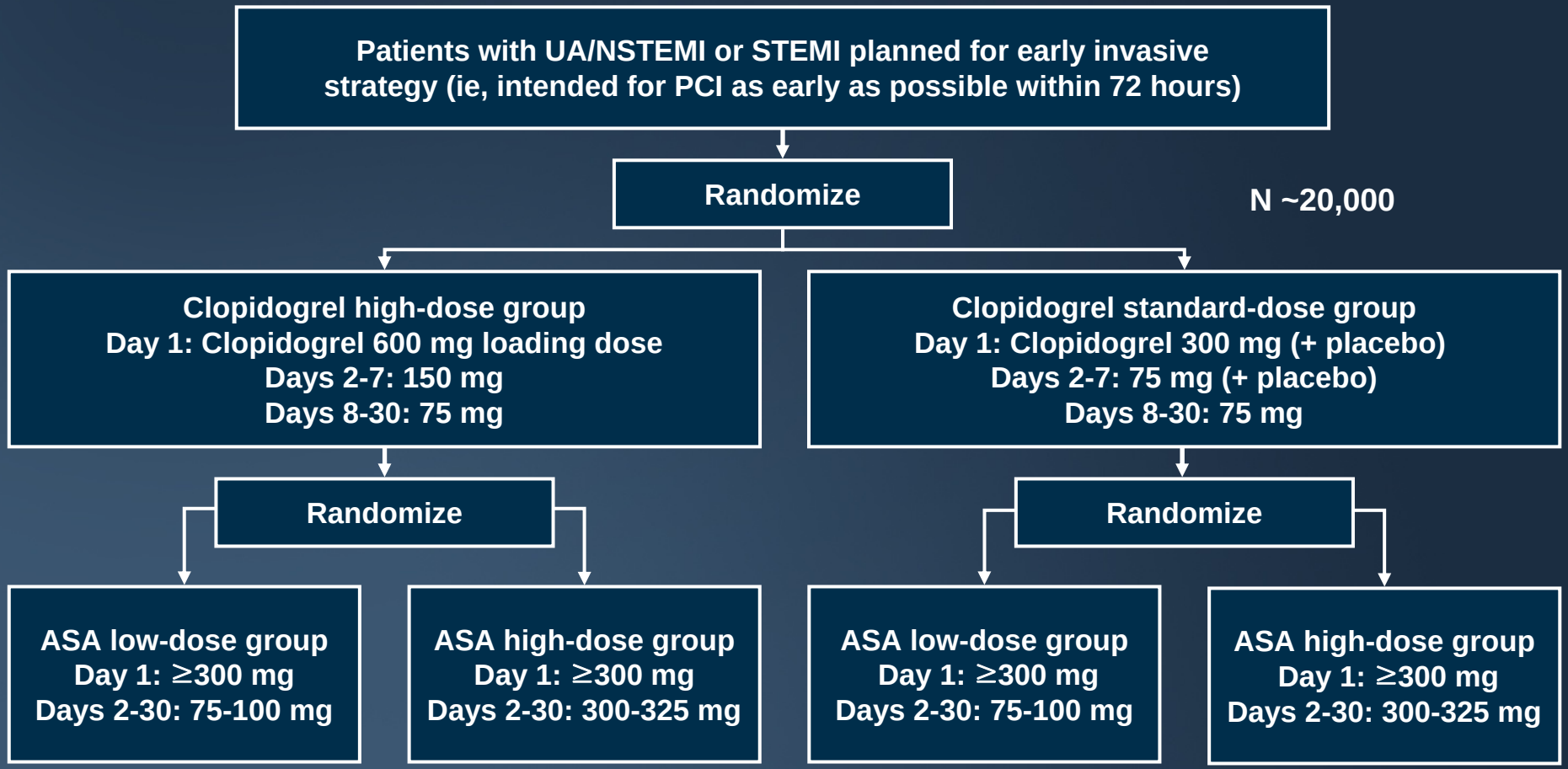
Prolonged DAPT > 1 year:

1) Multiple hospitalizations for ACS?
2) Broad atherosclerotic burden, including PAD?
3) Prior MI?
4) VBT, complex lesion, multiple stents

DAPT for no more than 1 year :

1) Prior bleeding?
2) Prior stroke?
3) Economic restraints?

CURRENT-OASIS 7: Study design



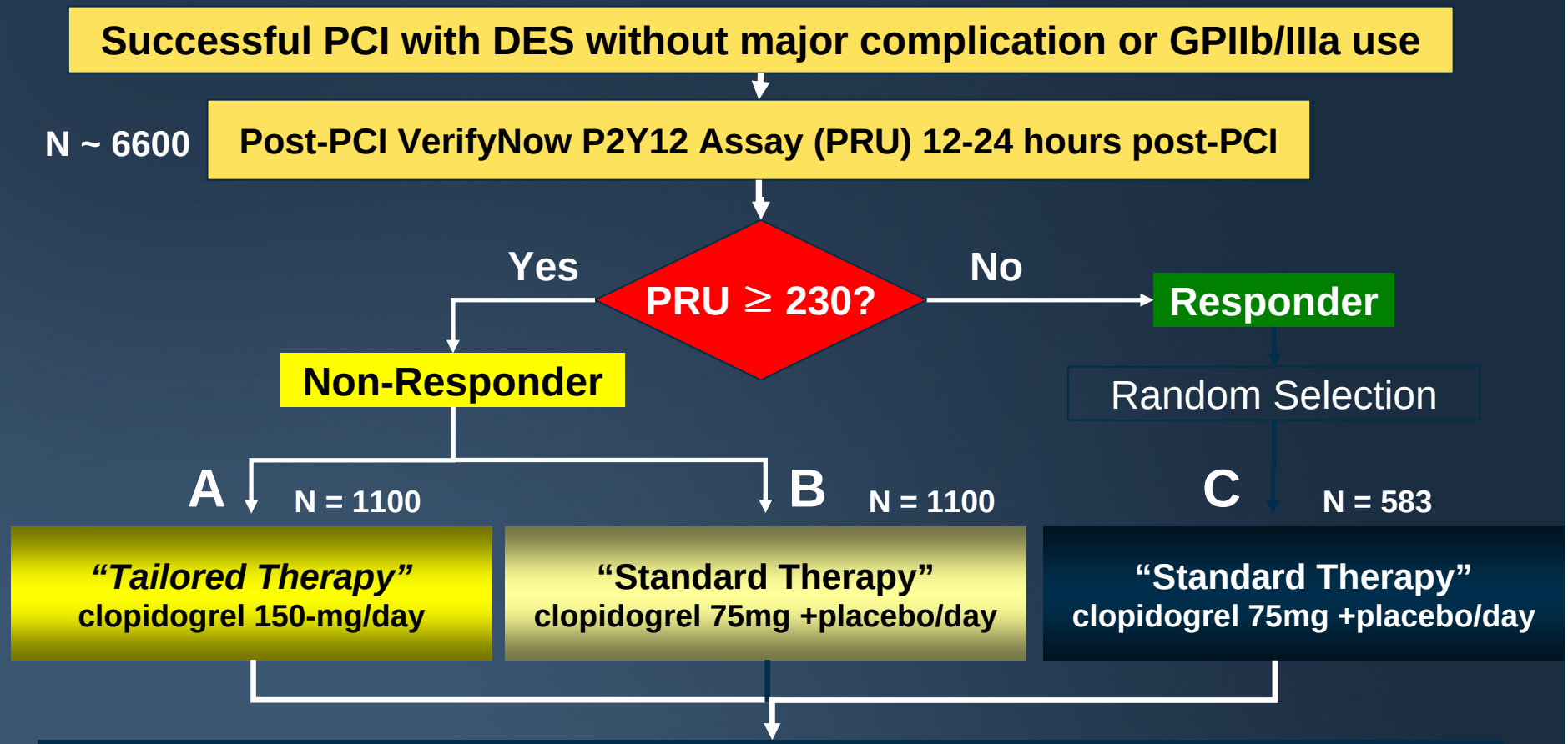
Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events-Organization to Assess Strategies in Ischemic Syndromes
Primary outcome: CV death, MI, stroke at 30 days

CARDIOVASCULAR RESEARCH FOUNDATION

Mehta SR et al. *Am Heart* ,2008;156:1080-1088.e1.

COLUMBIA UNIVERSITY MEDICAL CENTER

GRAVITAS



Primary Endpt: 6 month CV Death, Non-Fatal MI, ARC Def/Prob Stent Thrombosis

CARDIOVASCULAR RESEARCH FOUNDATION

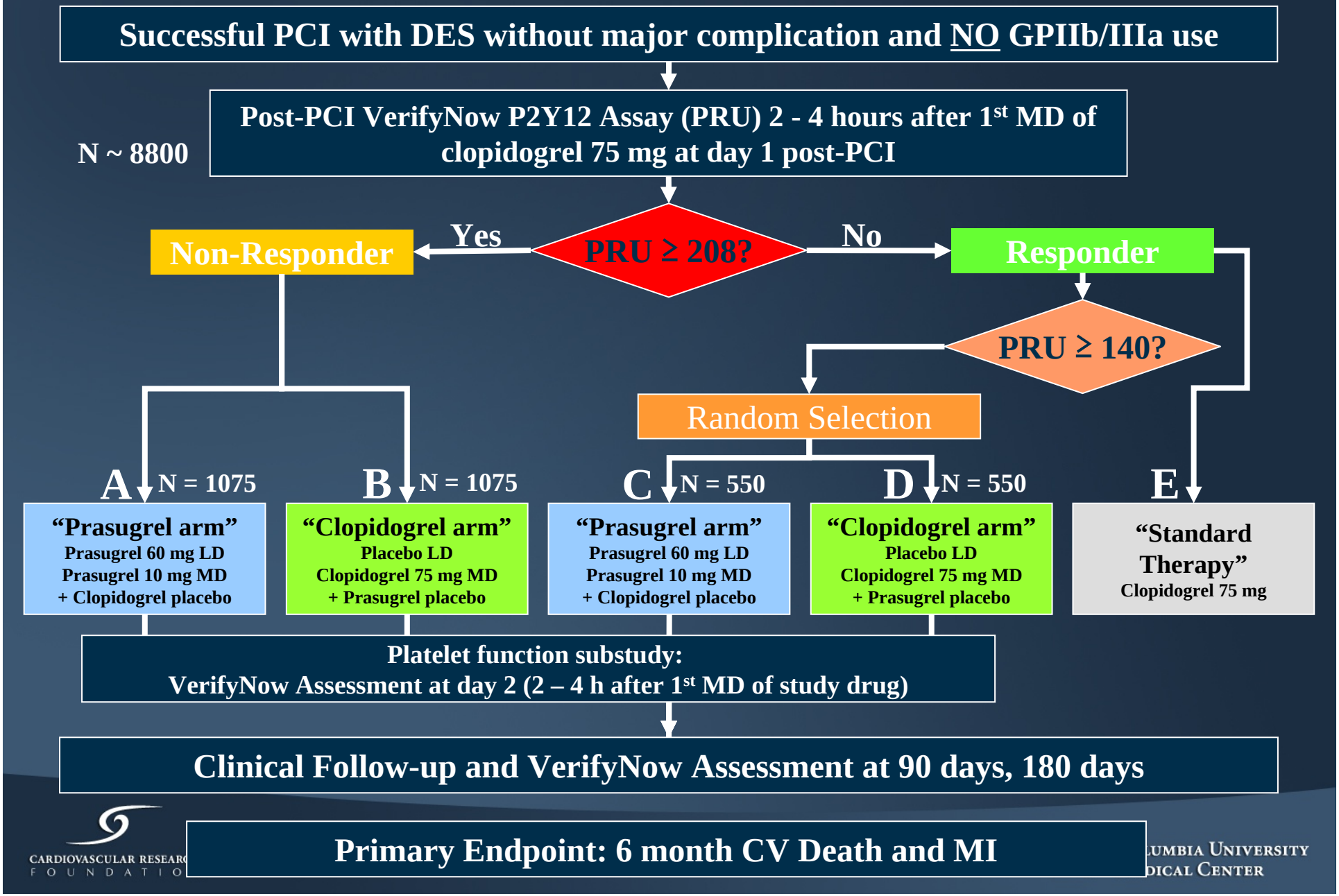
Study PI: Matthew J. Price, MD

Coordinating Center: Scripps Advanced Clinical Trials

COLUMBIA UNIVERSITY MEDICAL CENTER

TRIGGER-PCI

Courtesy of F.J. Neumann



CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER