Upcoming Evidence and Practice of Optimal Antiplatelet Therapy in DES Era?

Polymorphism in Metabolism of Clopidogrel and Its Clinical Implications and Management

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Disclosures

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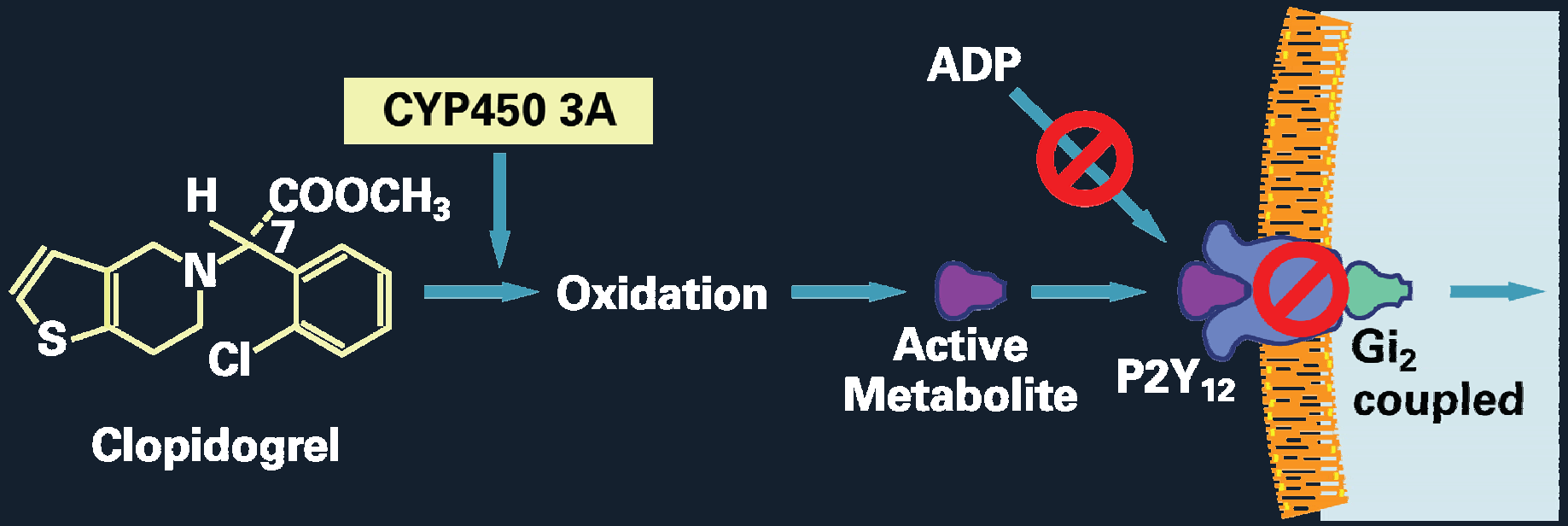
- Speaker's Bureau of Eli Lilly Company/ Daiichi Sankyo

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

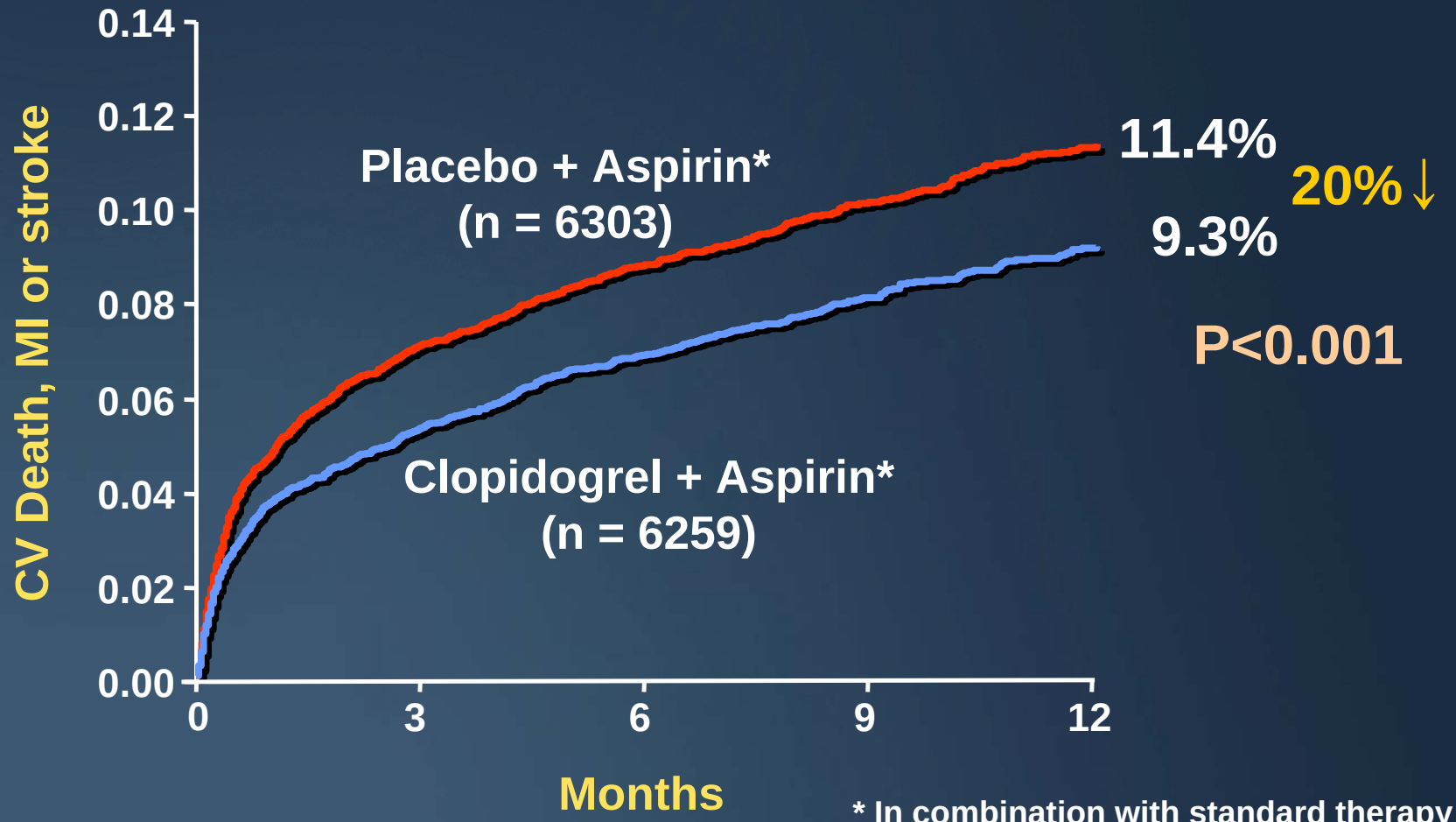


Clopidogrel is a prodrug, 85% hydrolysed to inactive metabolite
Variable intestinal absorption and hepatic P450 activity

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



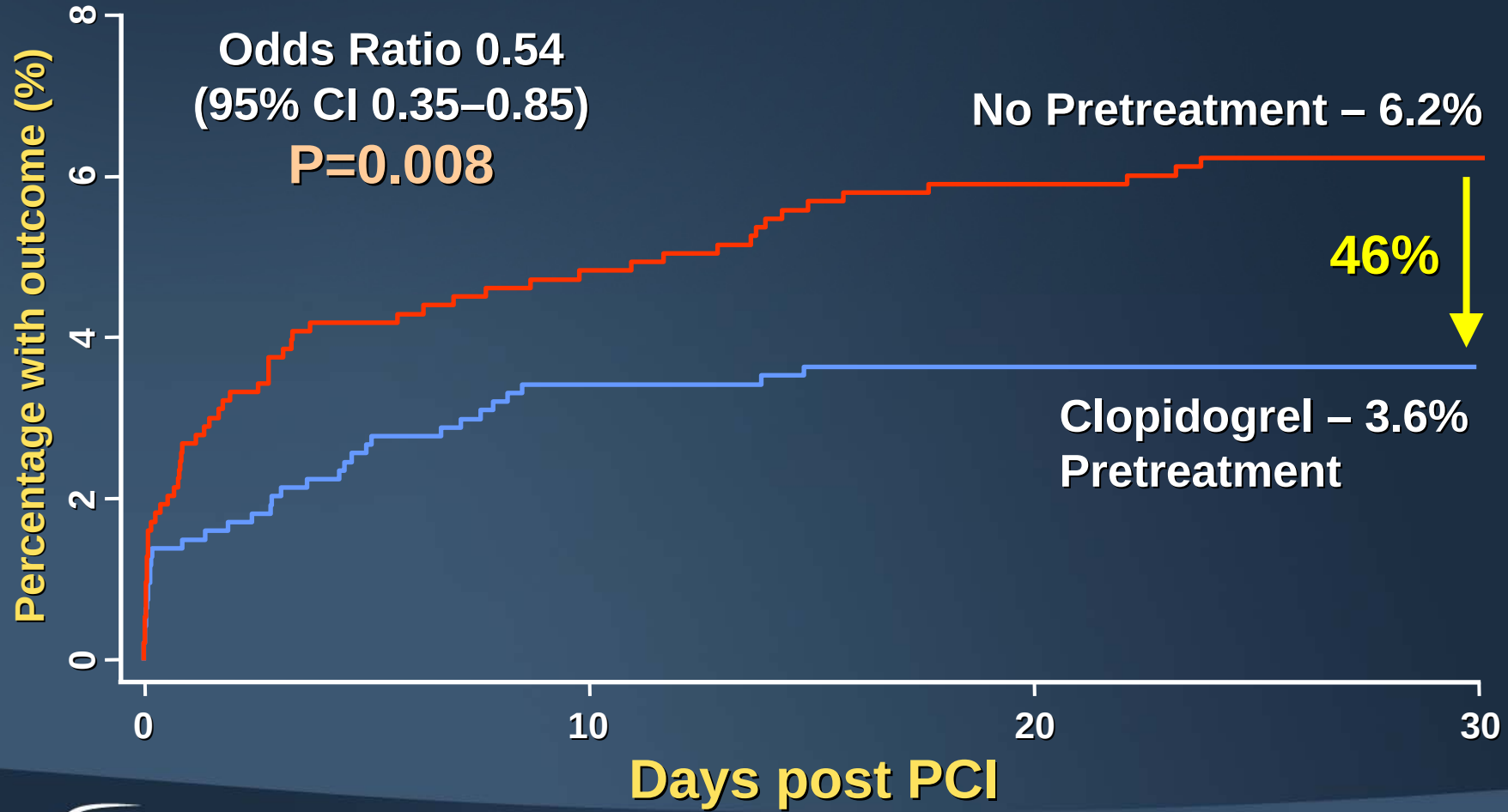
* In combination with standard therapy

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



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

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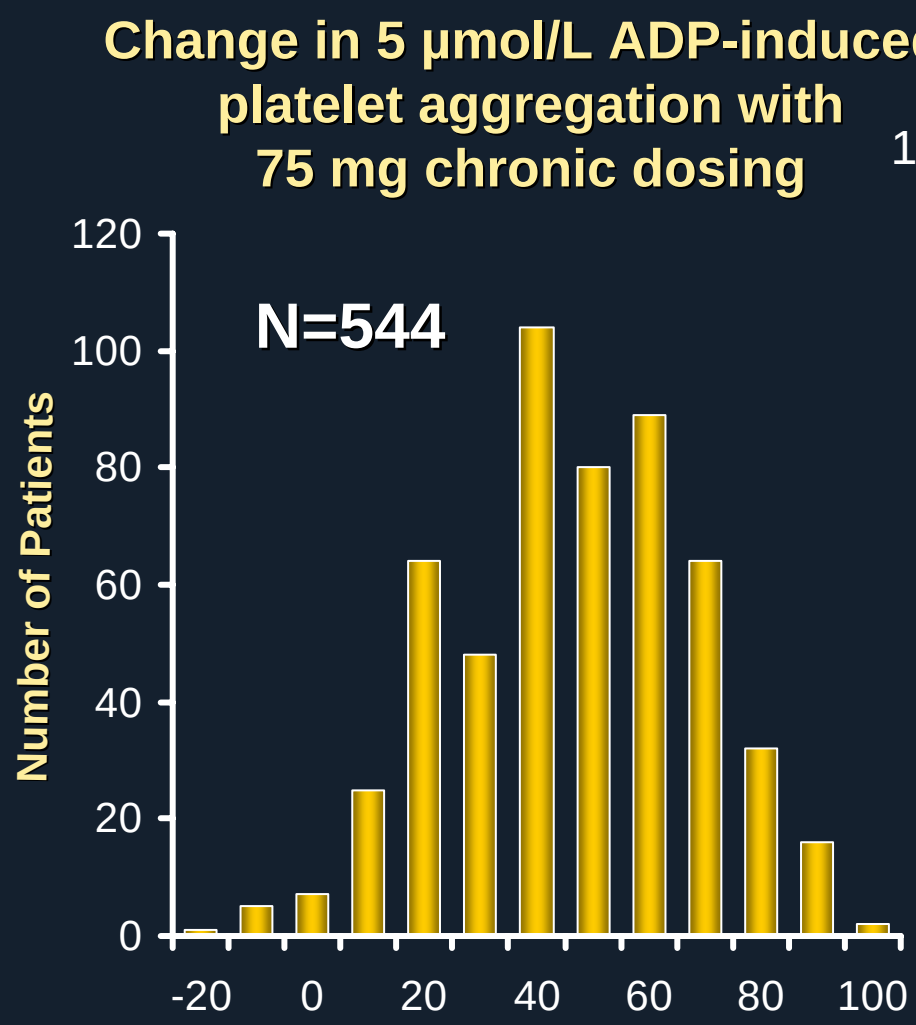
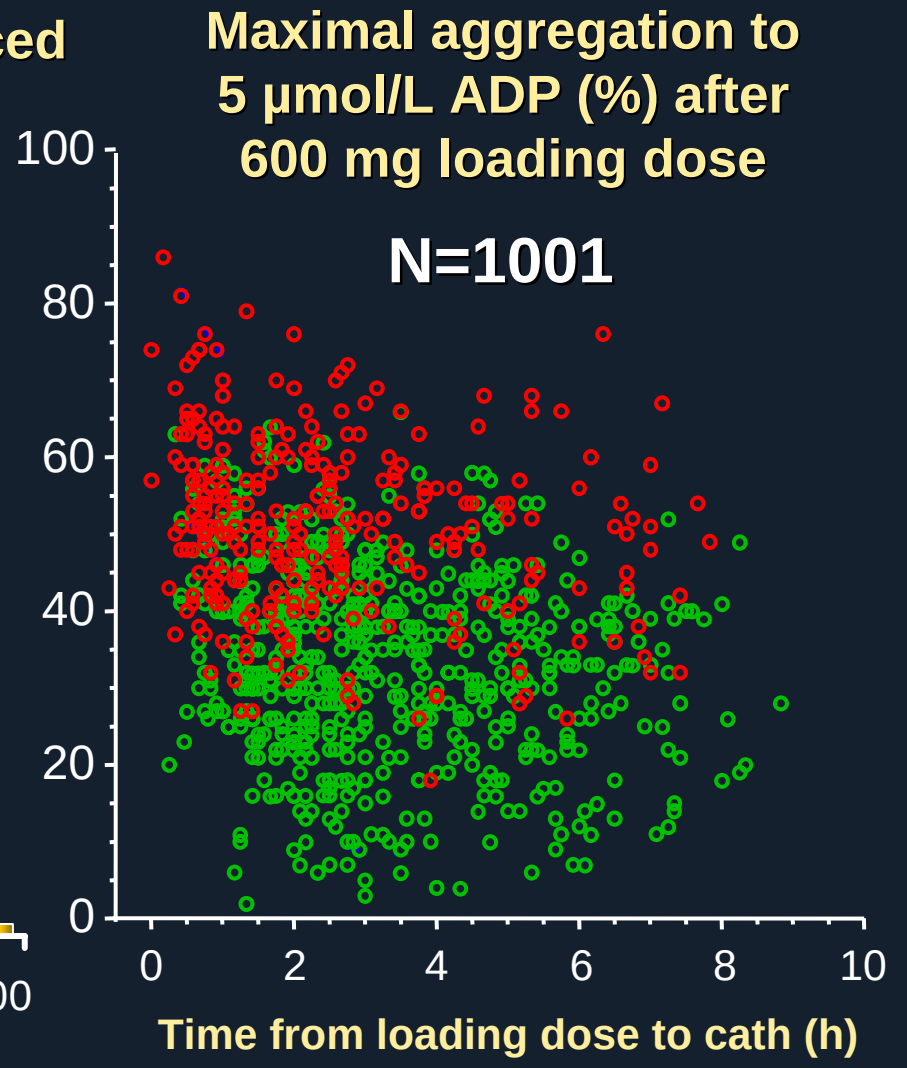
Variability in Clopidogrel Response





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

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

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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

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

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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

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

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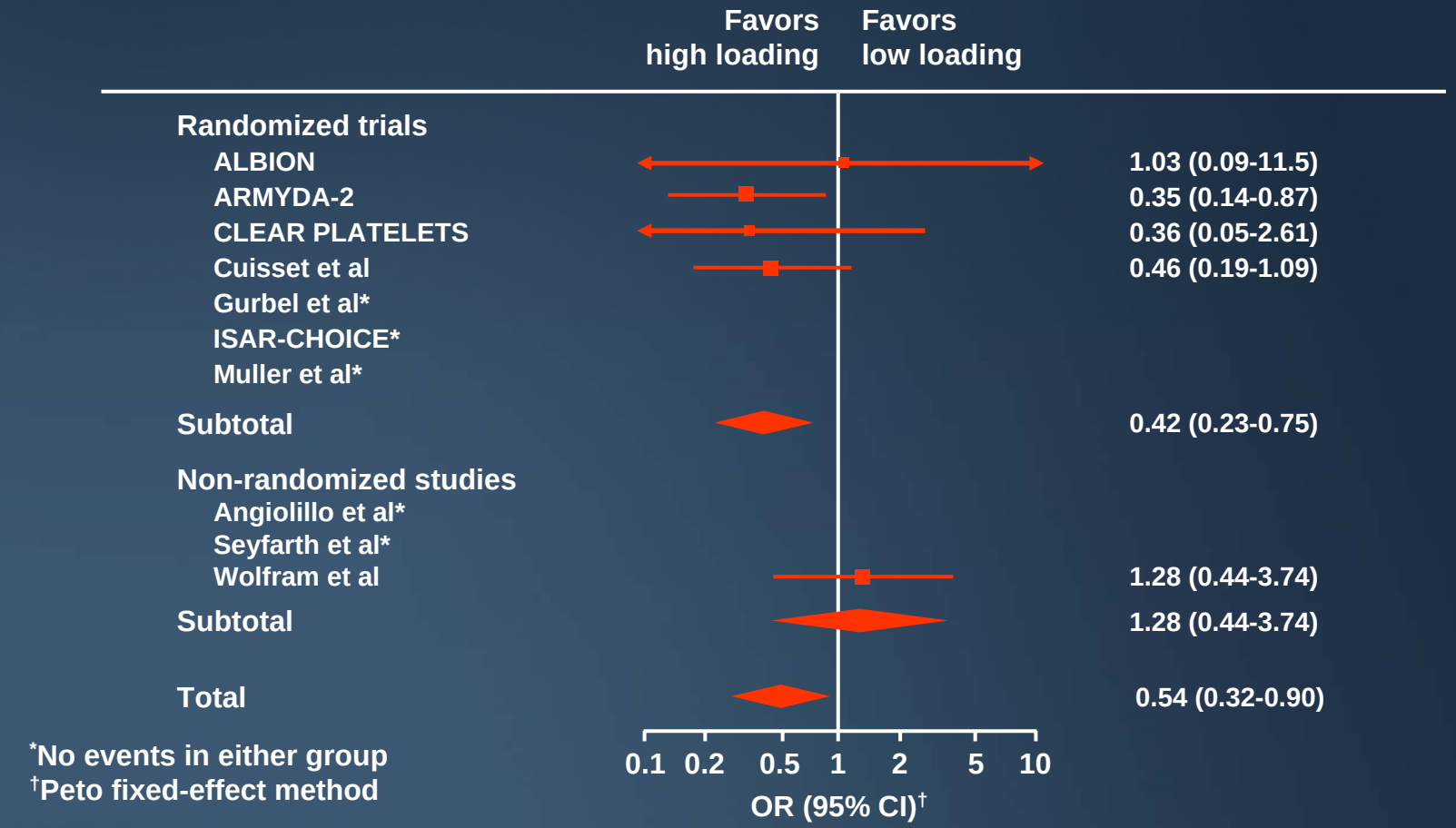
Clopidogrel 600 mg vs 300 mg loading dose

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



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

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

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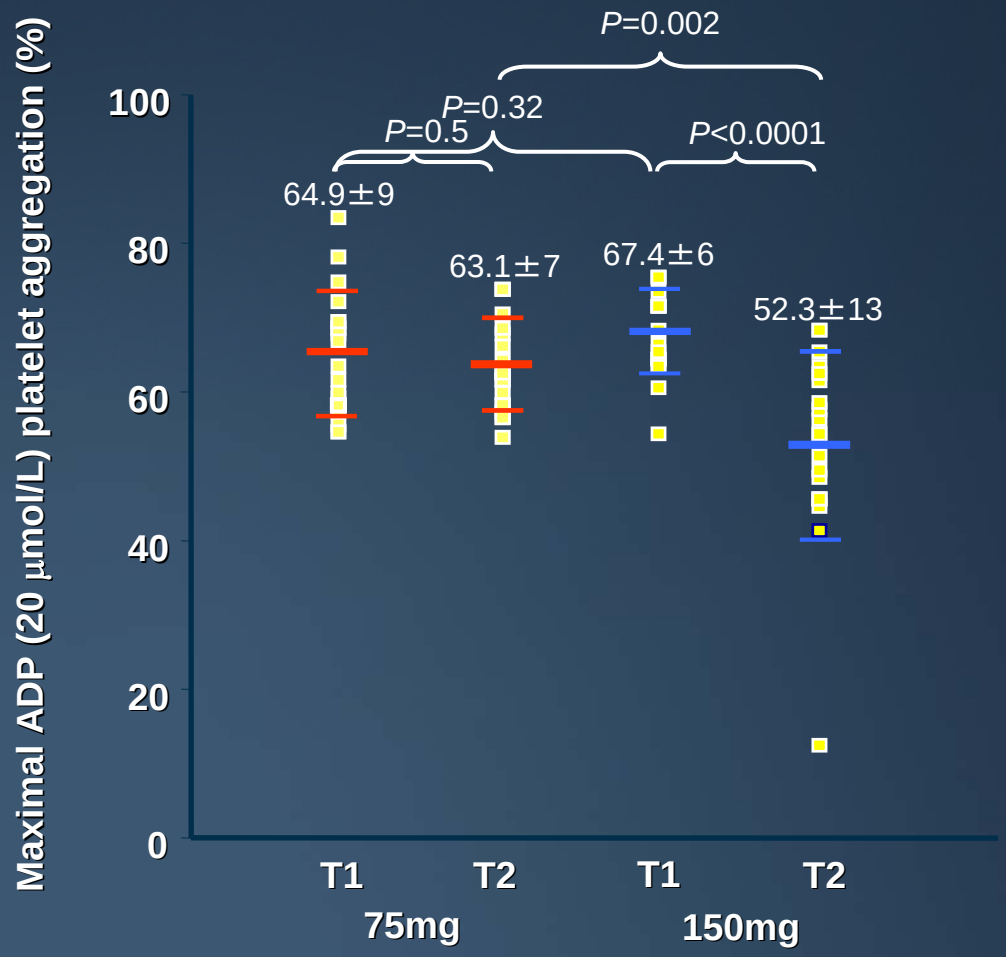
OPTIMUS Study:
(Optimizing anti-Platelet Therapy In diabetes MellitUS)

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



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

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Overcoming Suboptimal Antiplatelet Drug Response

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  (e.g. higher dose)

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  (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

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

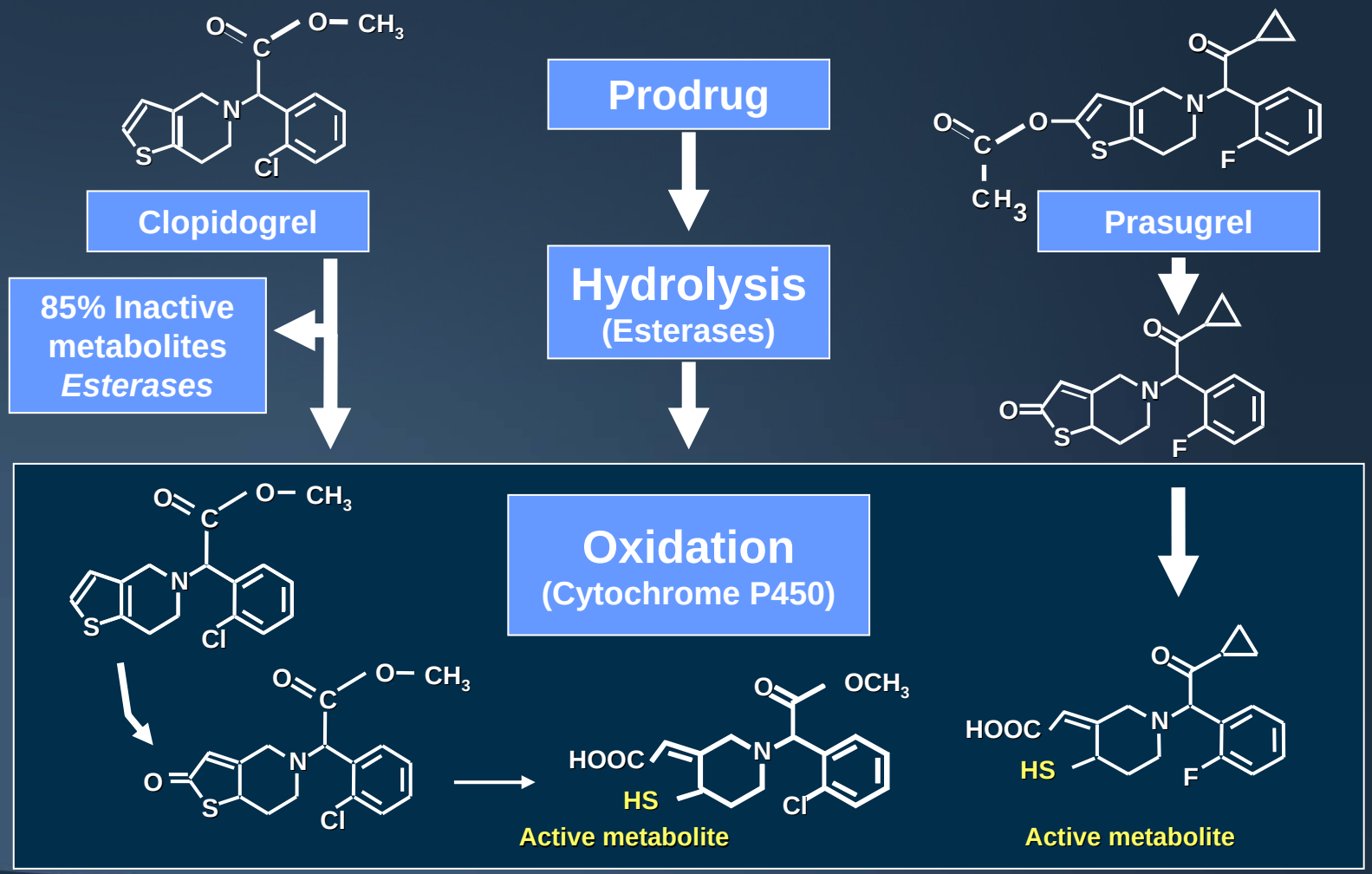
Novel $P2Y_{12}$ ADP receptor antagonist

More potent and less variability!!

Drug	Type	Route	Action	Dose	Mean platelet inhibition (time required)	Trials (phase III)
Prasugrel (CS-747)	Thienopyridine (3rd 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.

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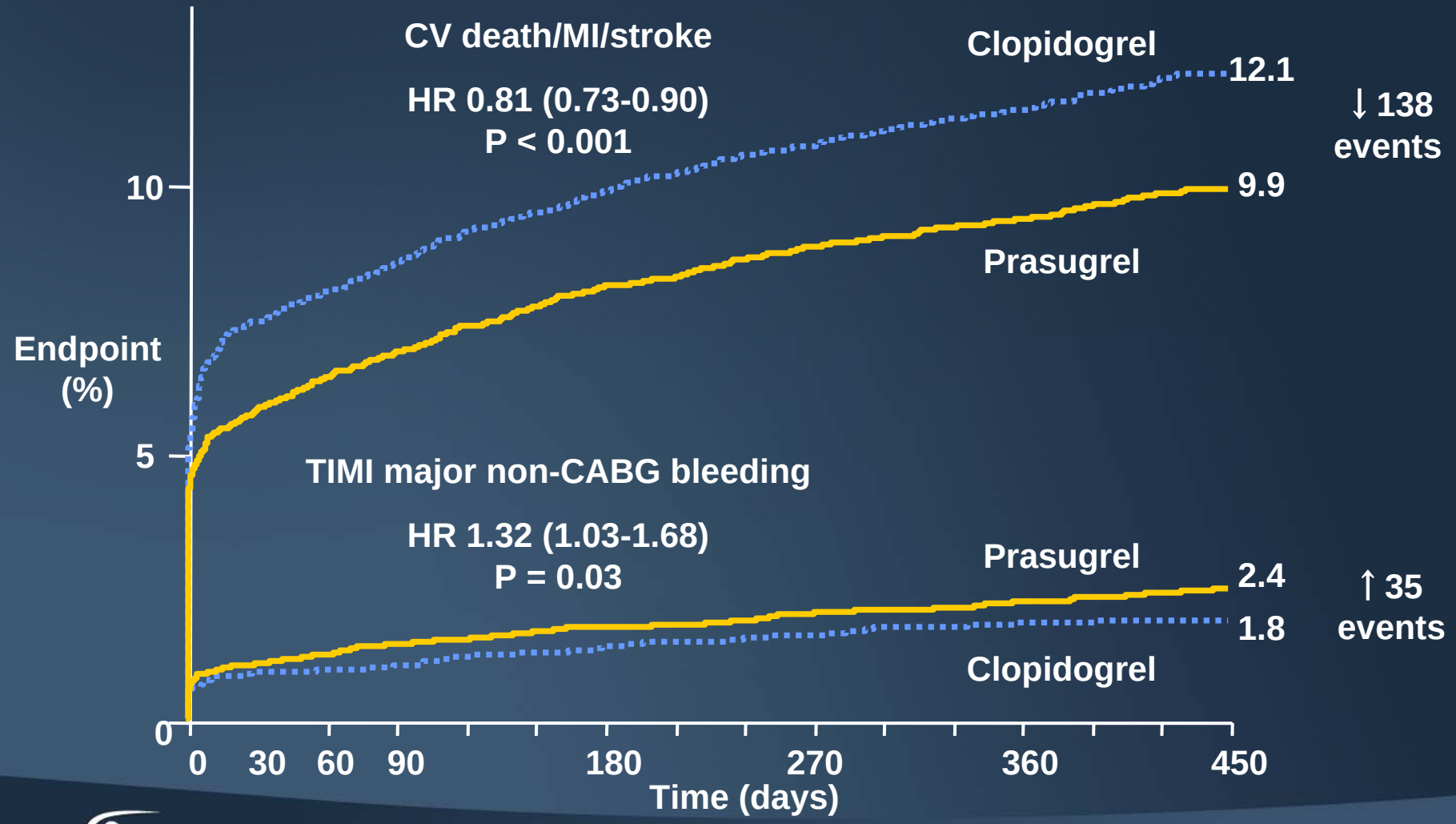
TRITON-TIMI 38: Treatment effects on primary efficacy and key safety endpoints N=13,608



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

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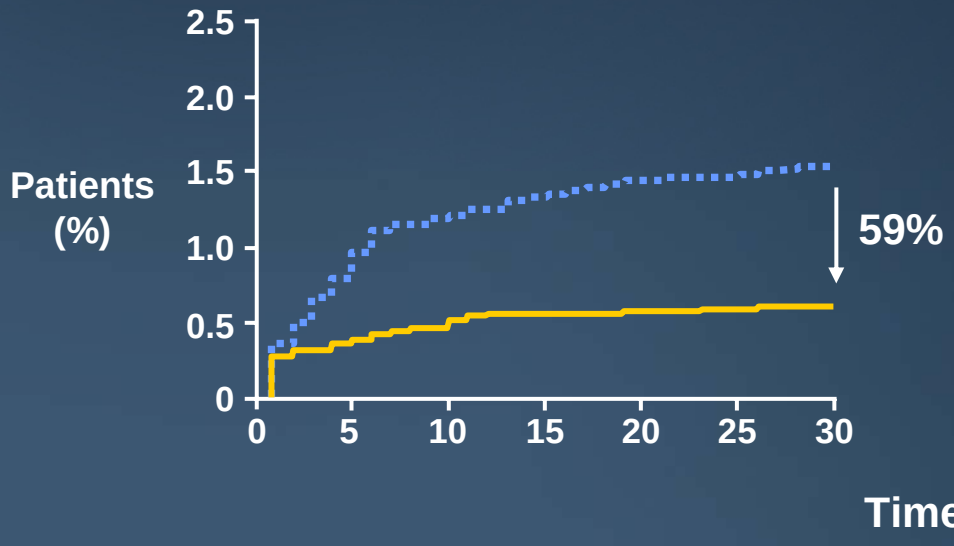
TRITON-TIMI 38: Stent thrombosis for all patients receiving at least one intracoronary stent

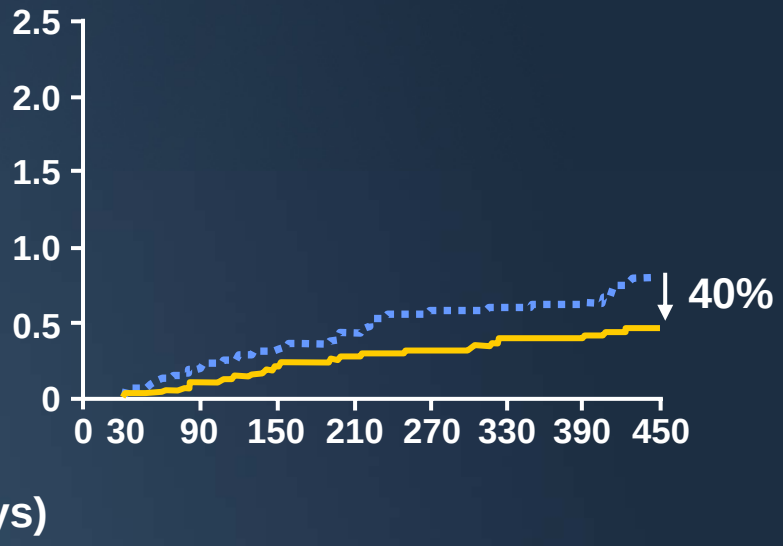
Early stent thrombosis*

HR 0.41 (0.29-0.59)
P < 0.0001



Late stent thrombosis*

HR 0.60 (0.37-0.97)
P = 0.03



Time (days)

Prasugrel

Clopidogrel

*Definite or probable using Academic Research Consortium designation

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

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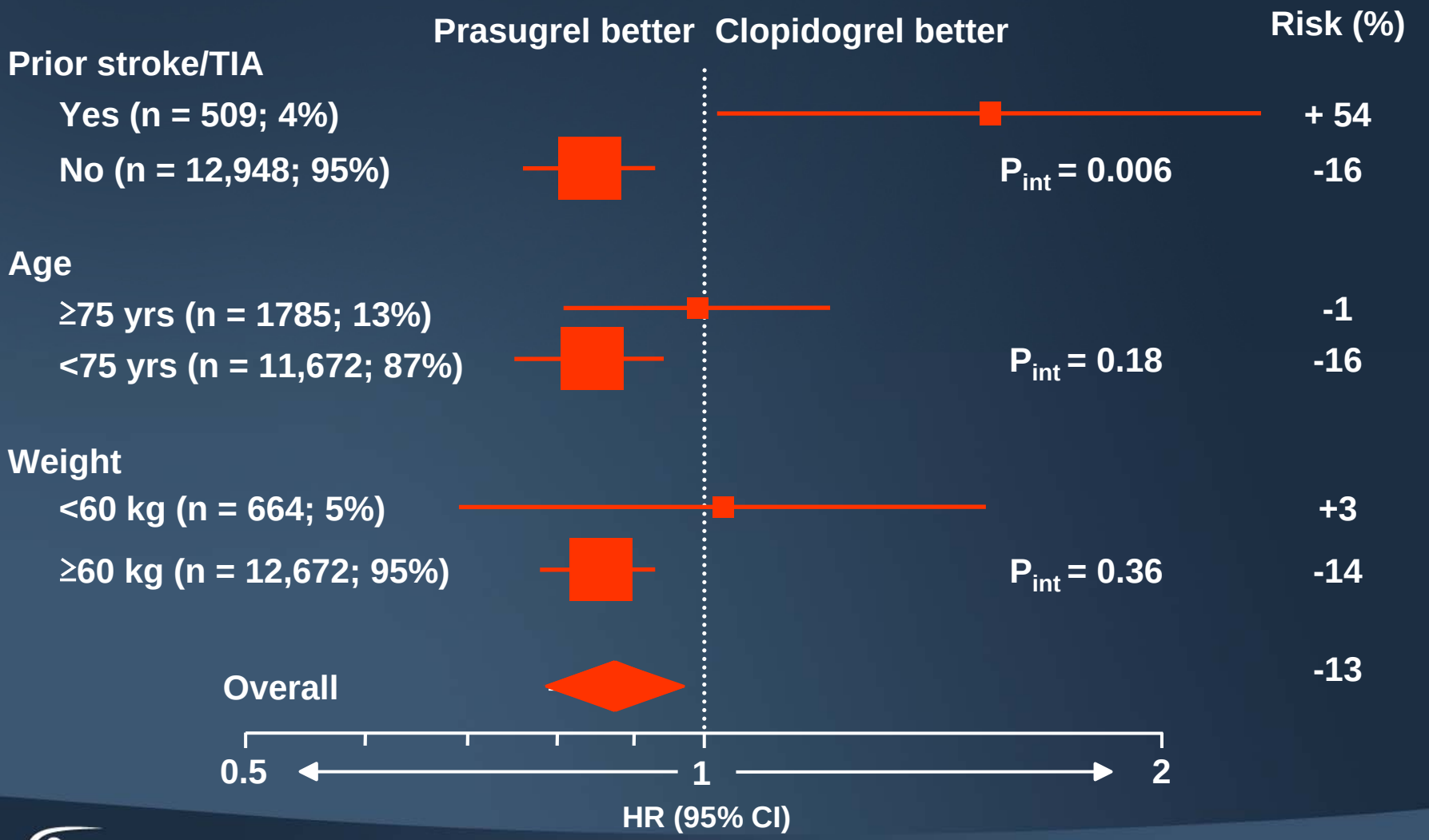
TRITON-TIMI 38 post hoc analysis: Net clinical benefit in subgroups at increased bleeding risk



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

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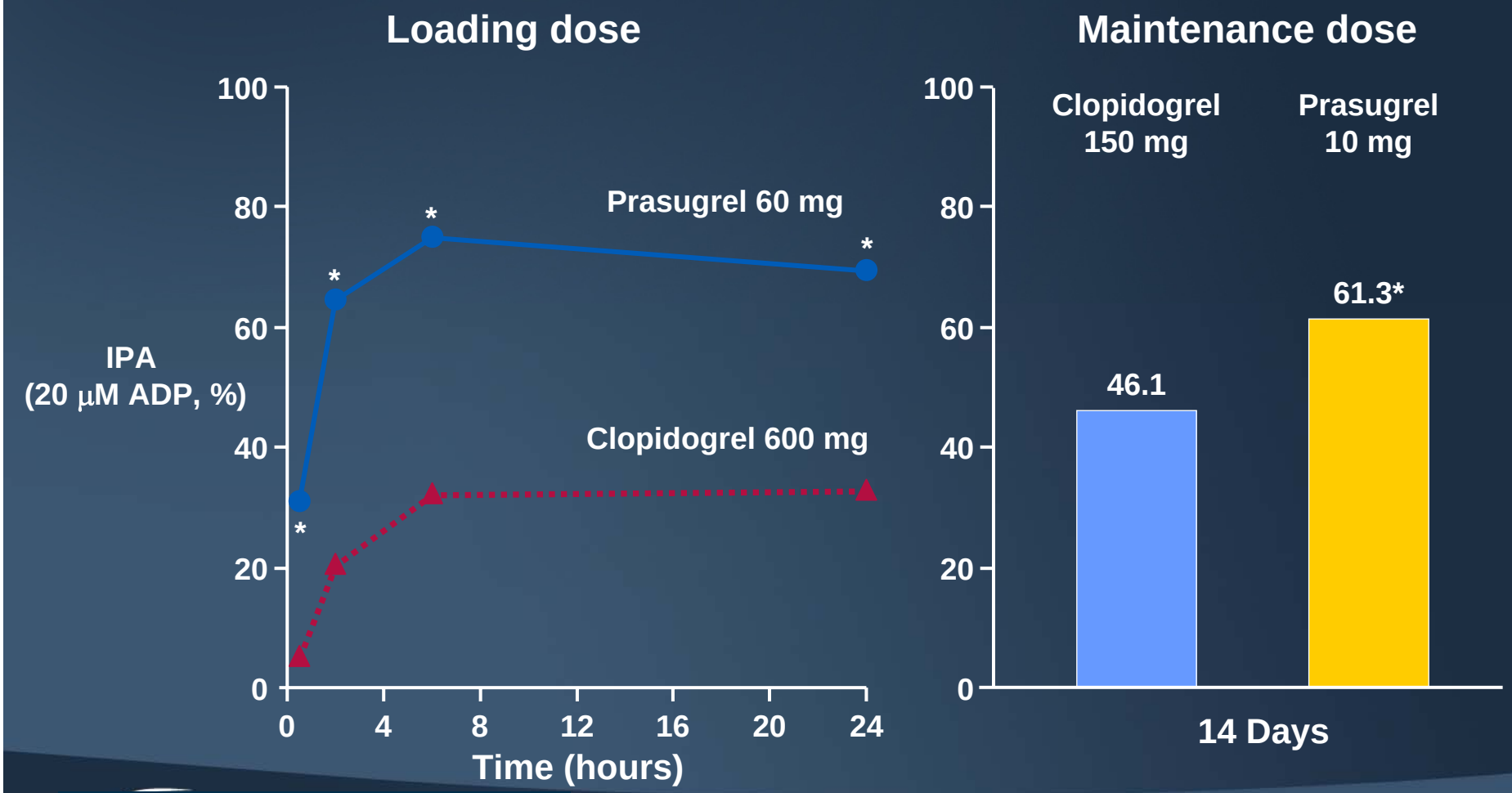
PRINCIPLE-TIMI 44: Inhibition of platelet aggregation with loading and maintenance doses

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.

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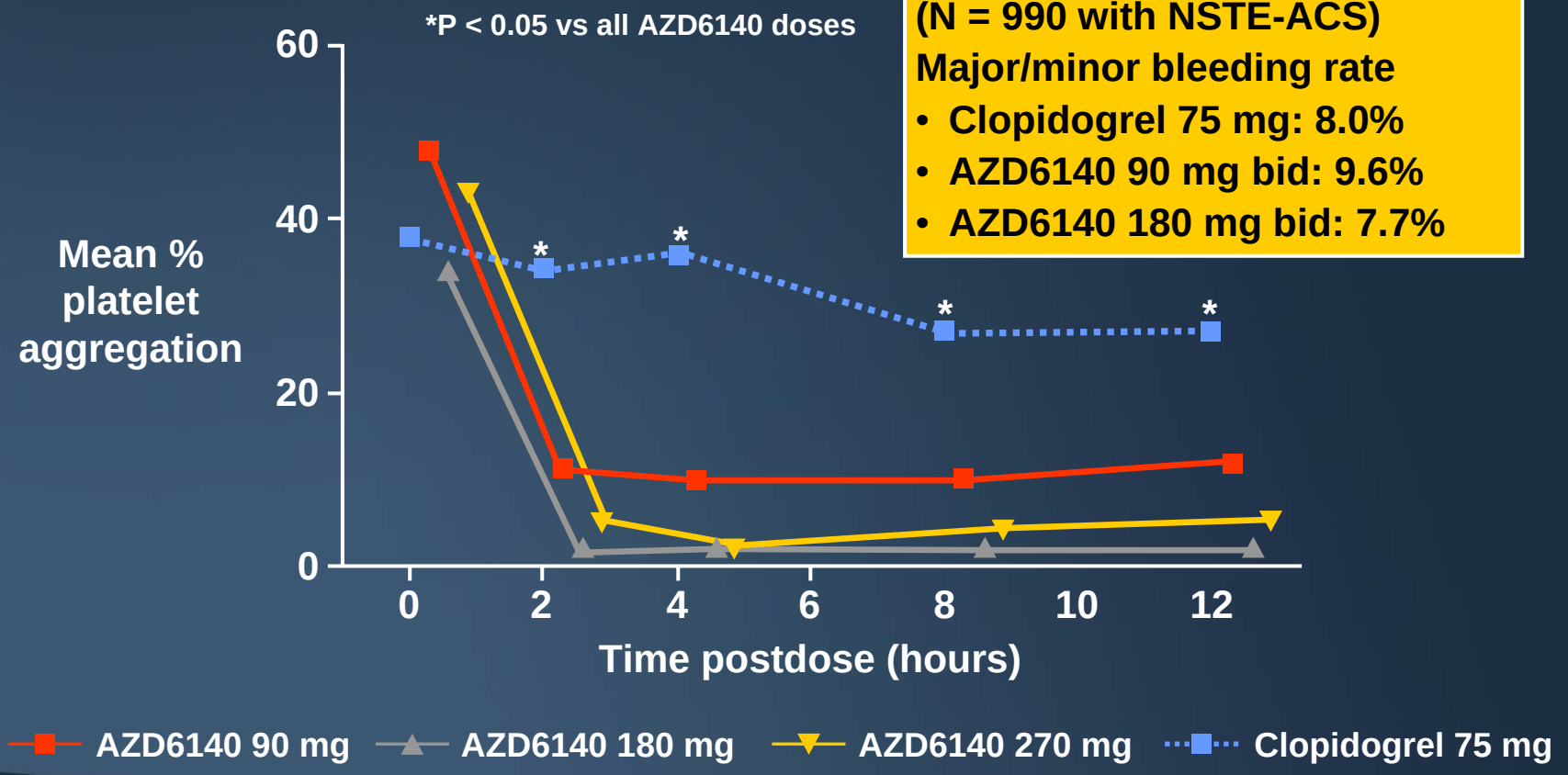
Ticagrelor/AZD6140
DISPERSE-2: Dose Optimization Study

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%**

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

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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

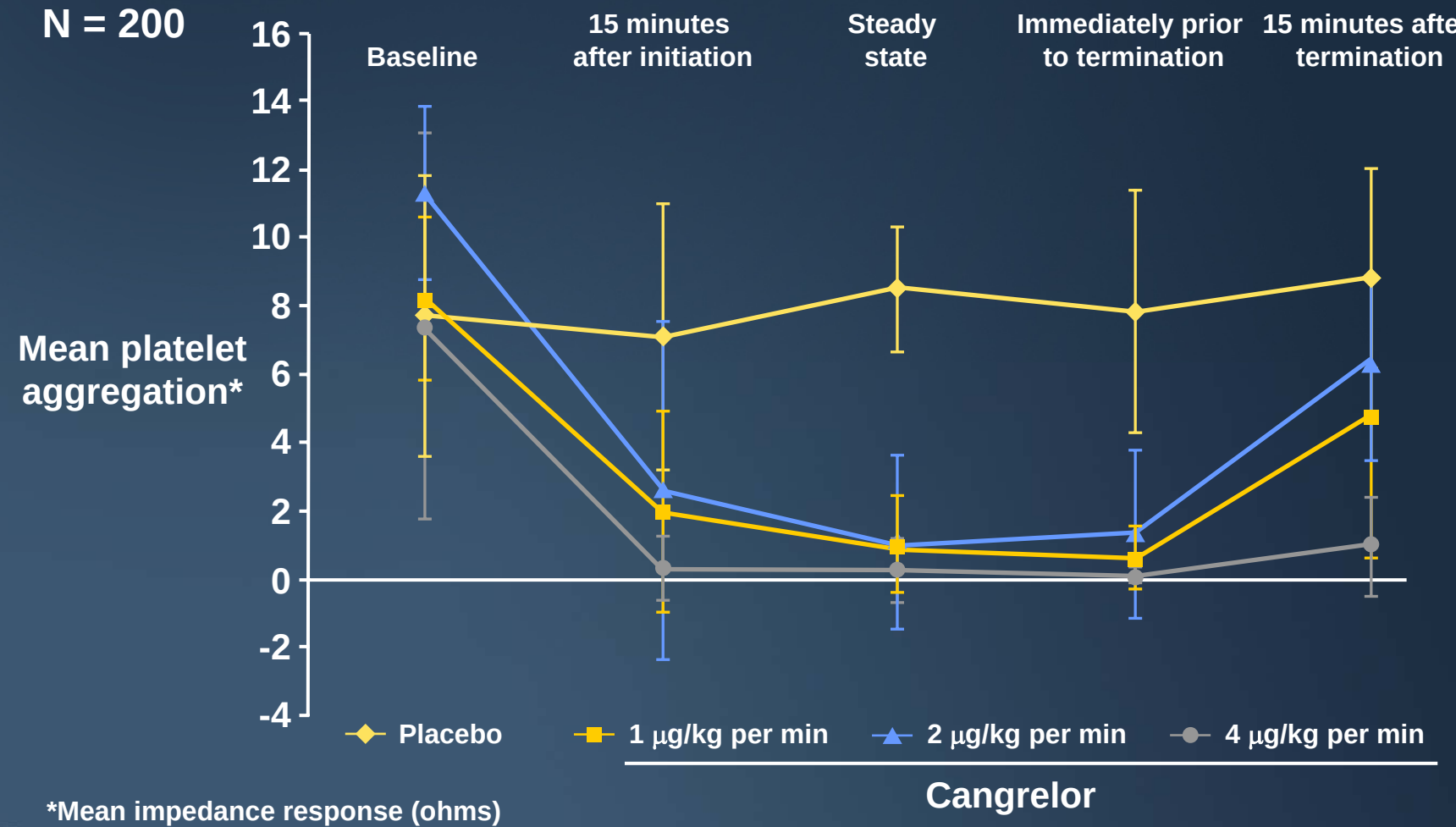
Primary endpoint:
CV death, MI, stroke

***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.

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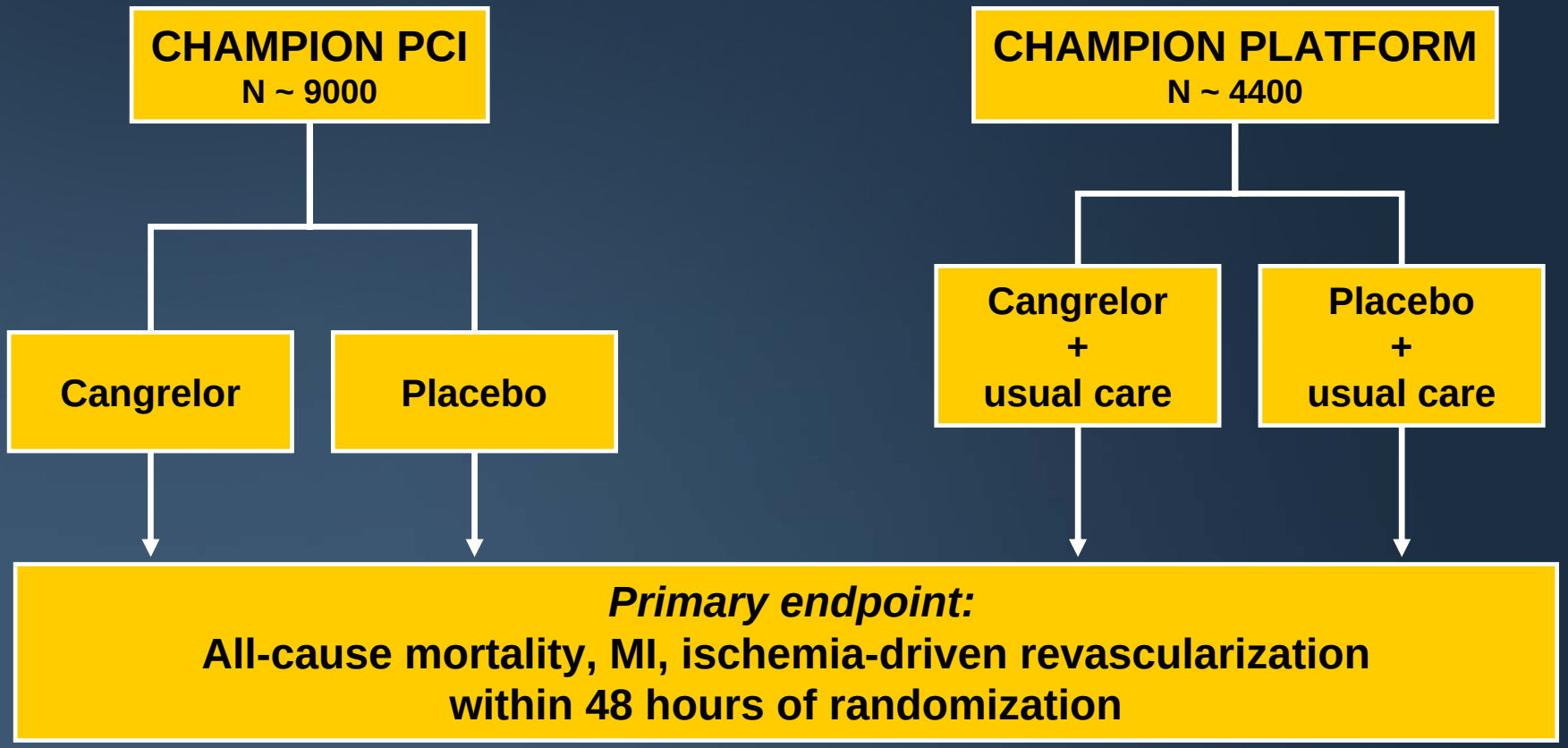
Cangrelor: Ongoing clinical trials



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

Thienopyridines 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