

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

Tailoring Treatment to Risk in Antiplatelet Therapy

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Disclosures

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- **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

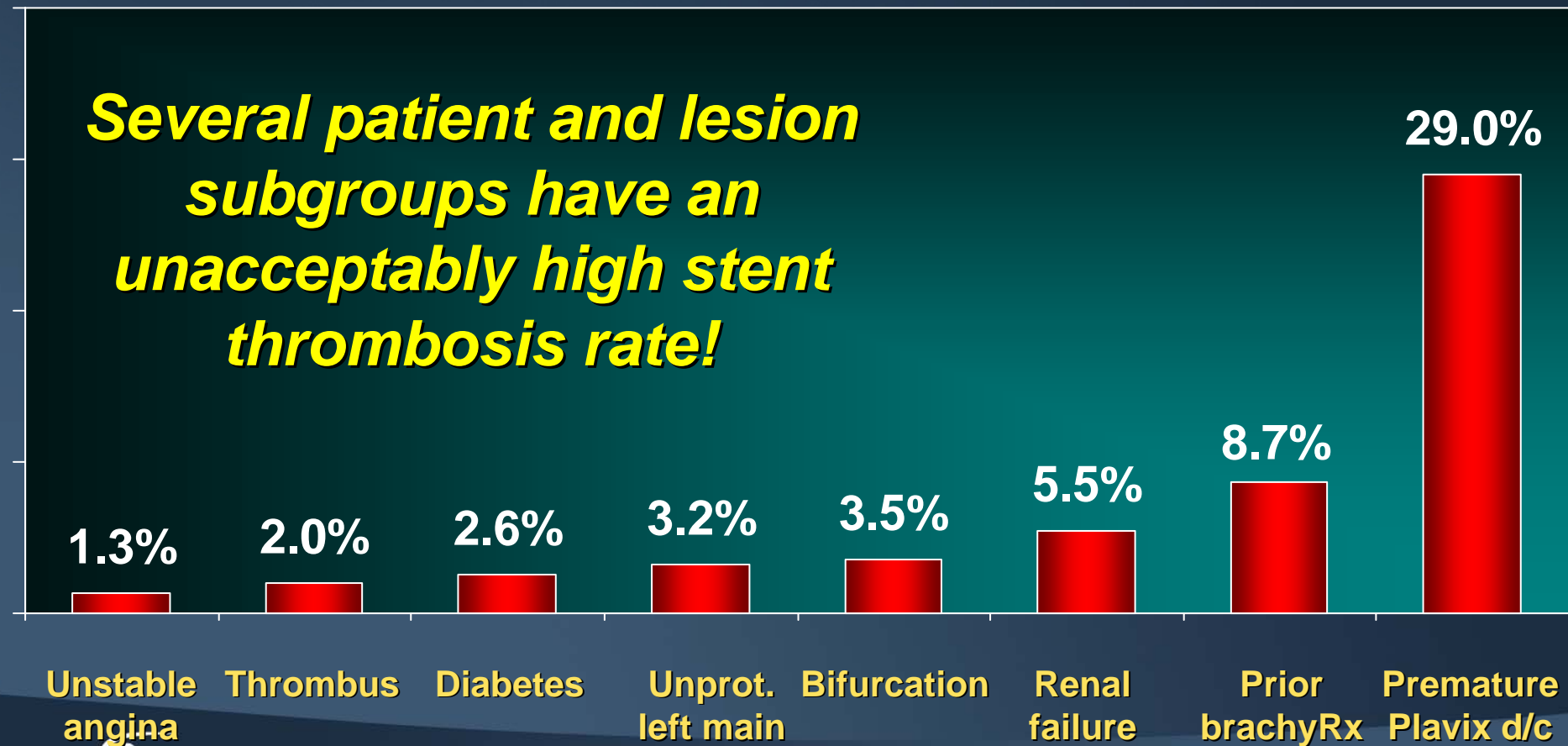


Milan/Siegburg Experience

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

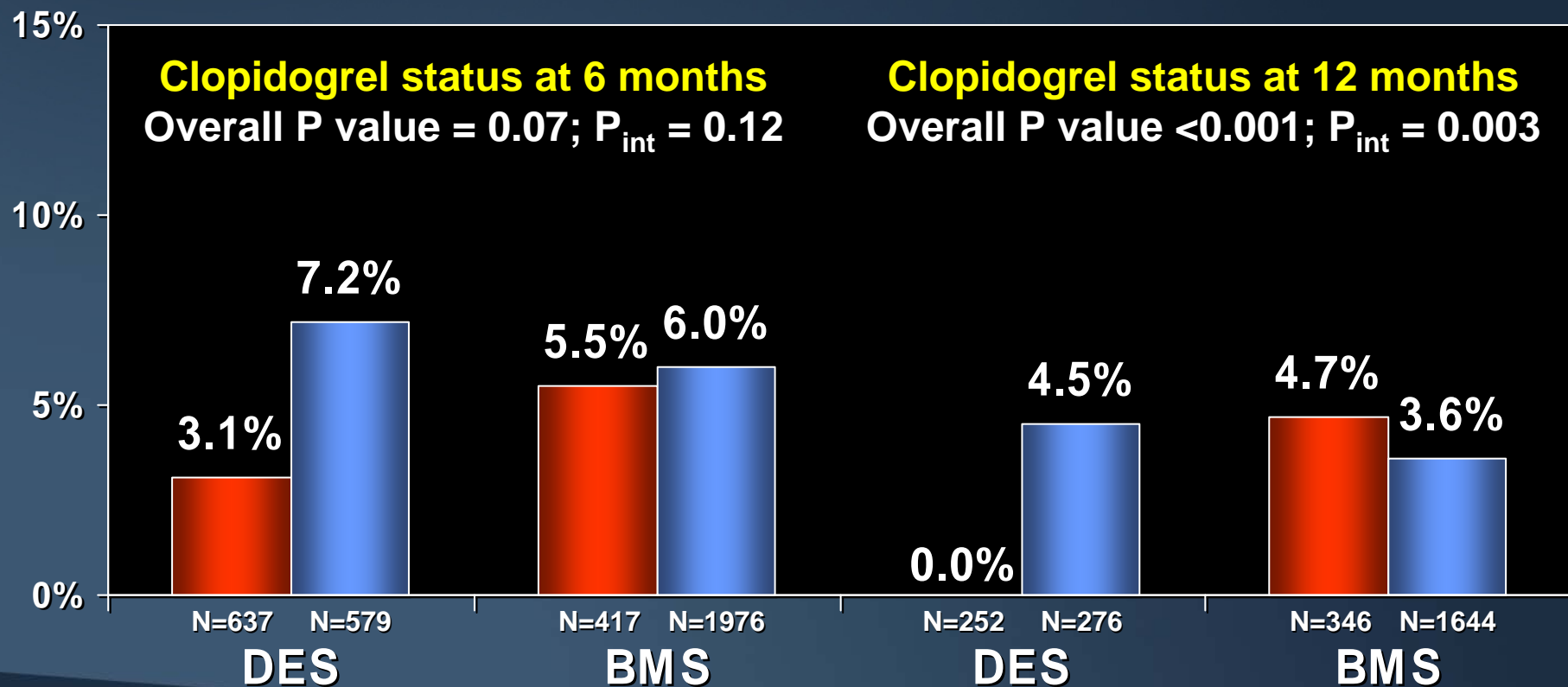
Several patient and lesion subgroups have an unacceptably high stent thrombosis rate!



Duke Database Death/MI Analysis

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

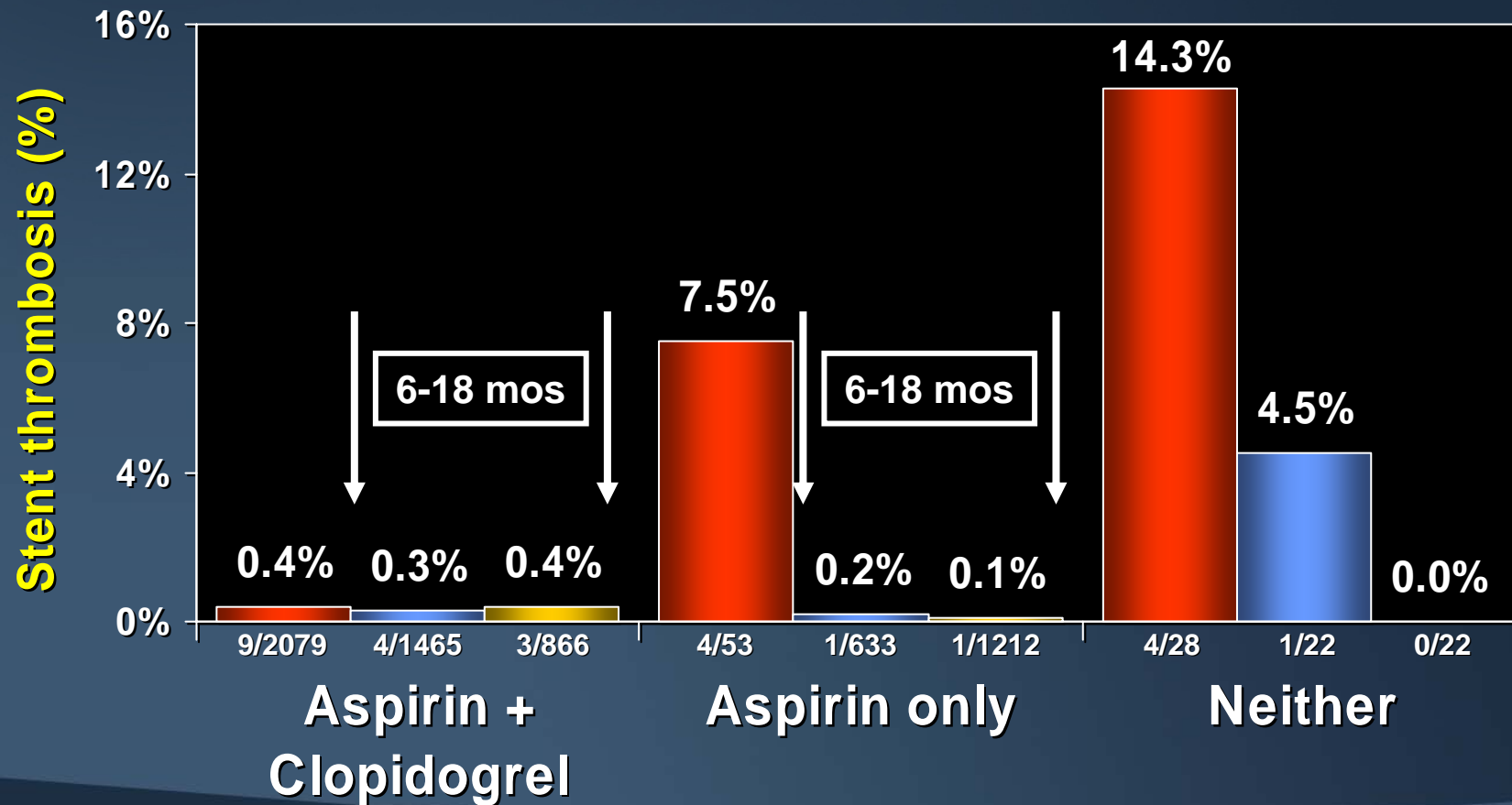
■ On clopidogrel ■ Off clopidogrel



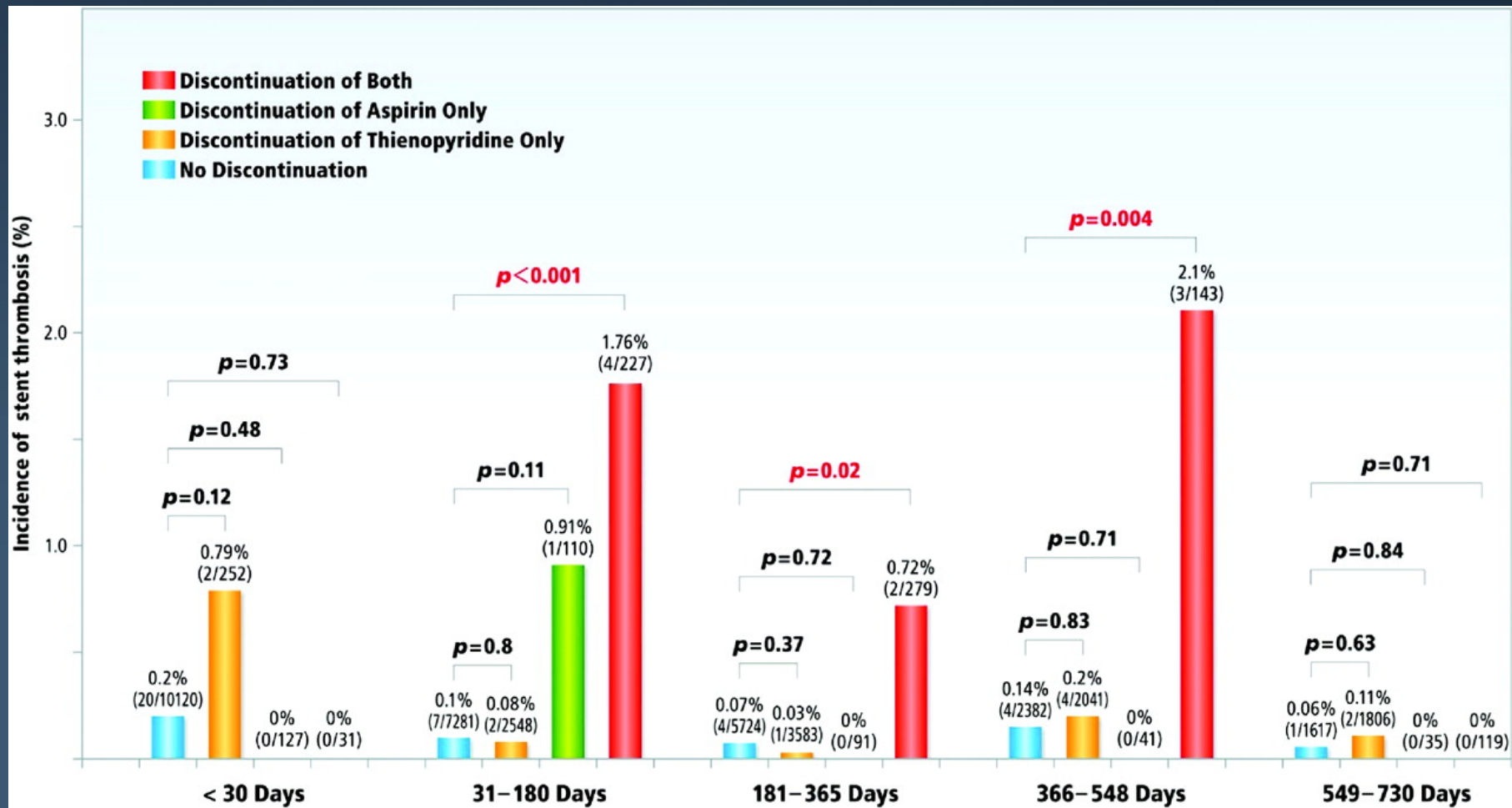
Milan Stent Thrombosis Experience

2,160 consecutive pts with DES implanted

■ 0-6 months
 ■ 6-12 months
 ■ 12-18 months

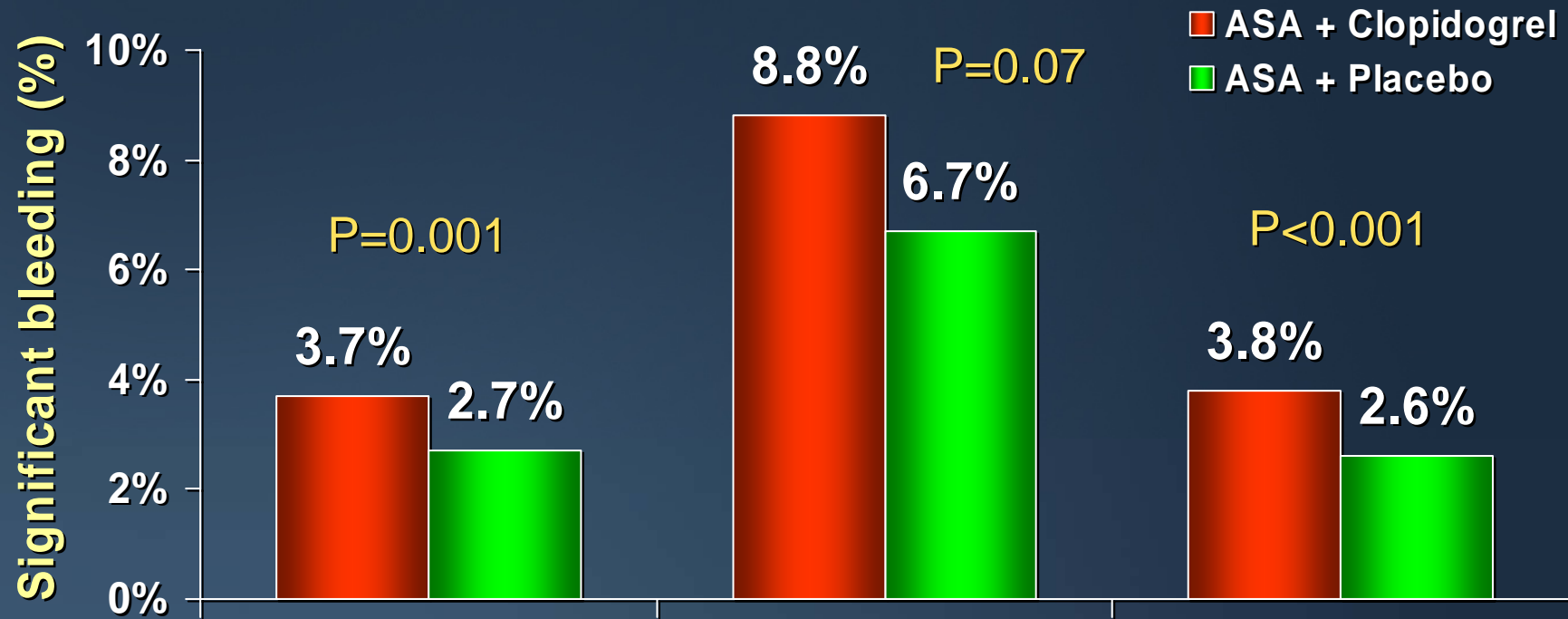


Relationship between thienopyridine and/or aspirin discontinuation and Stent Thrombosis by time interval after stent implantation



Bleeding with Long-Term Clopidogrel

3 Placebo Controlled Trials



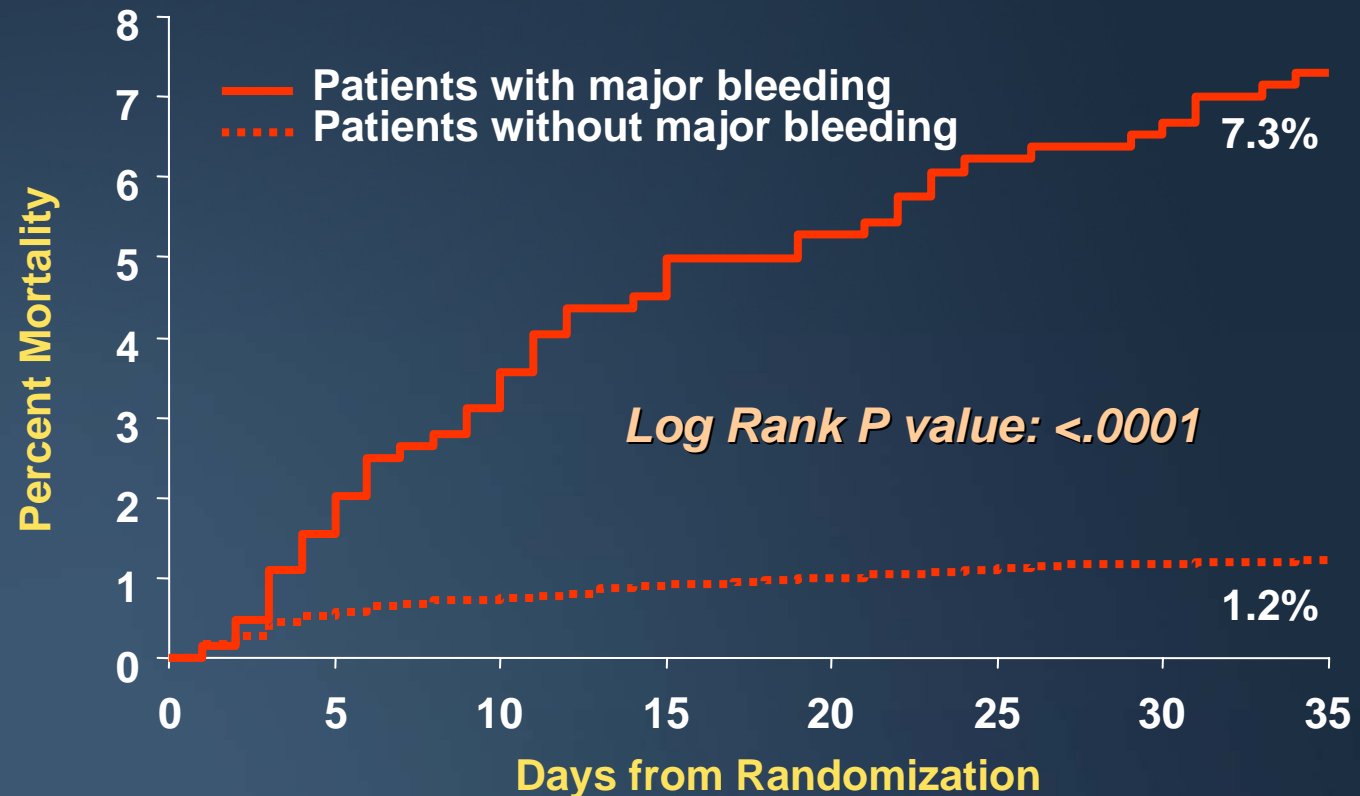
CURE
N=12,563
1 year FU
CURE major bleed
NEJM 2001;345:494-502

CREDO
N=2,116
1 year FU
TIMI major bleed
JAMA 2002;288:2411-20

CHARISMA
N=15,603
2.5 year FU
GUSTO major
+ moderate bleed
NEJM 2006;354:1706-17

Implications of Major Bleeding: ACUITY: 30-day Mortality

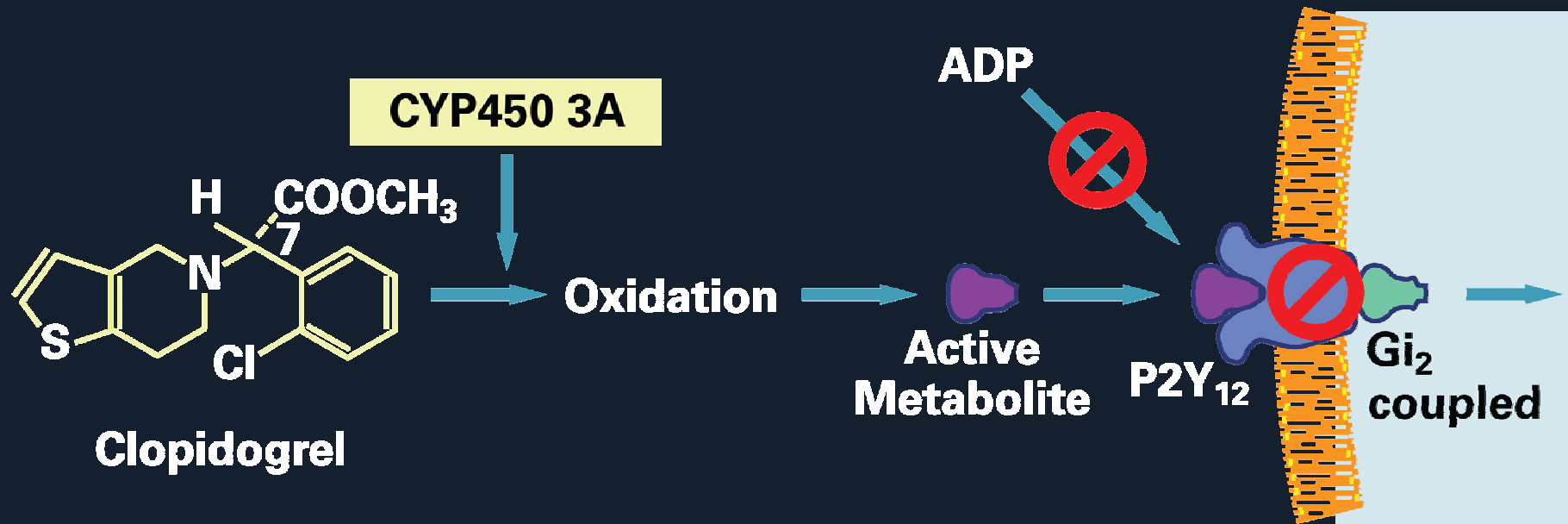
- 30-day mortality by patients with or without major bleeding



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

The Target for Clopidogrel is the Platelet P2Y₁₂ Receptor

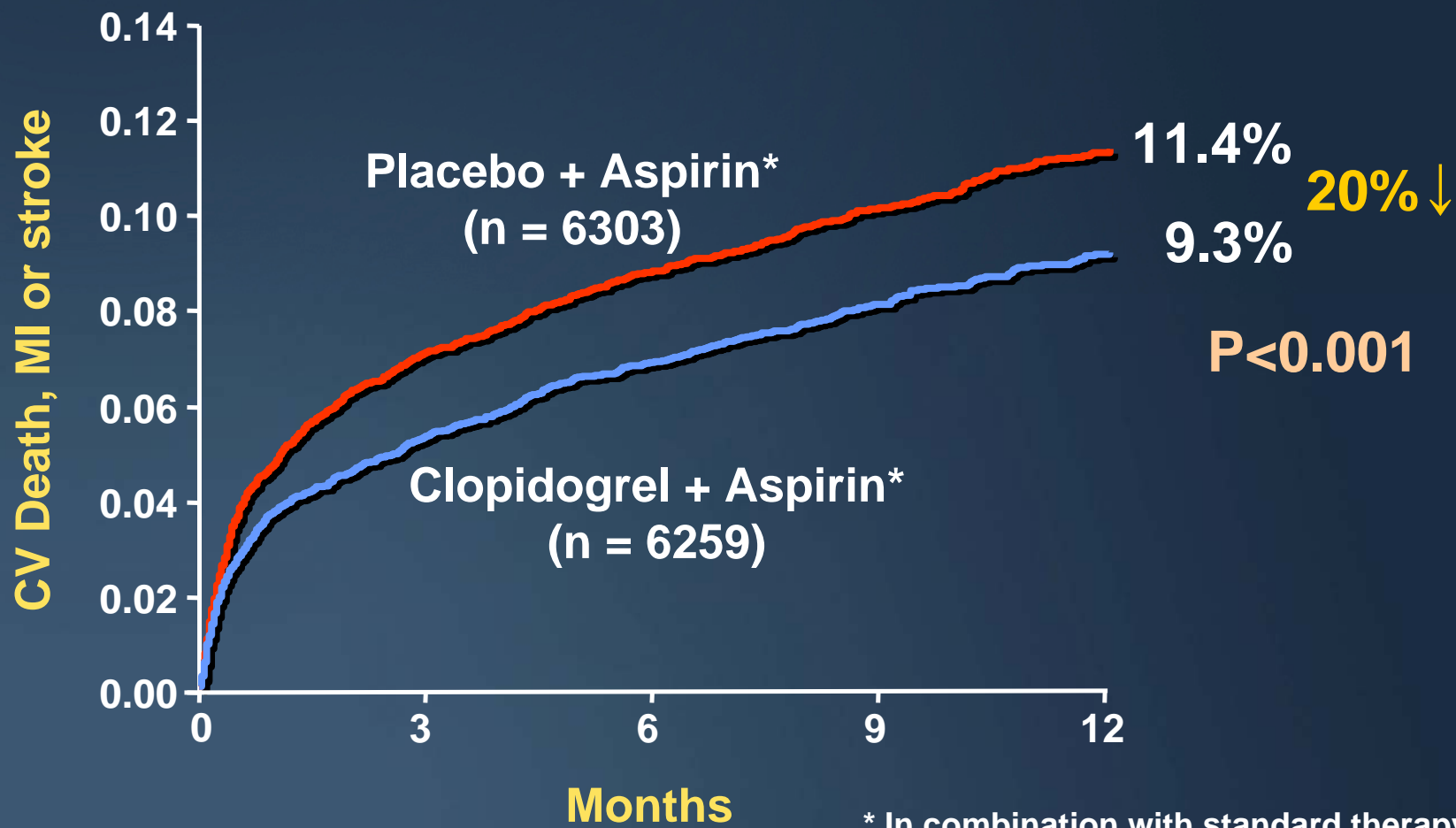


Clopidogrel is a prodrug, 85% hydrolysed to inactive metabolite
Variable intestinal absorption and hepatic P450 activity



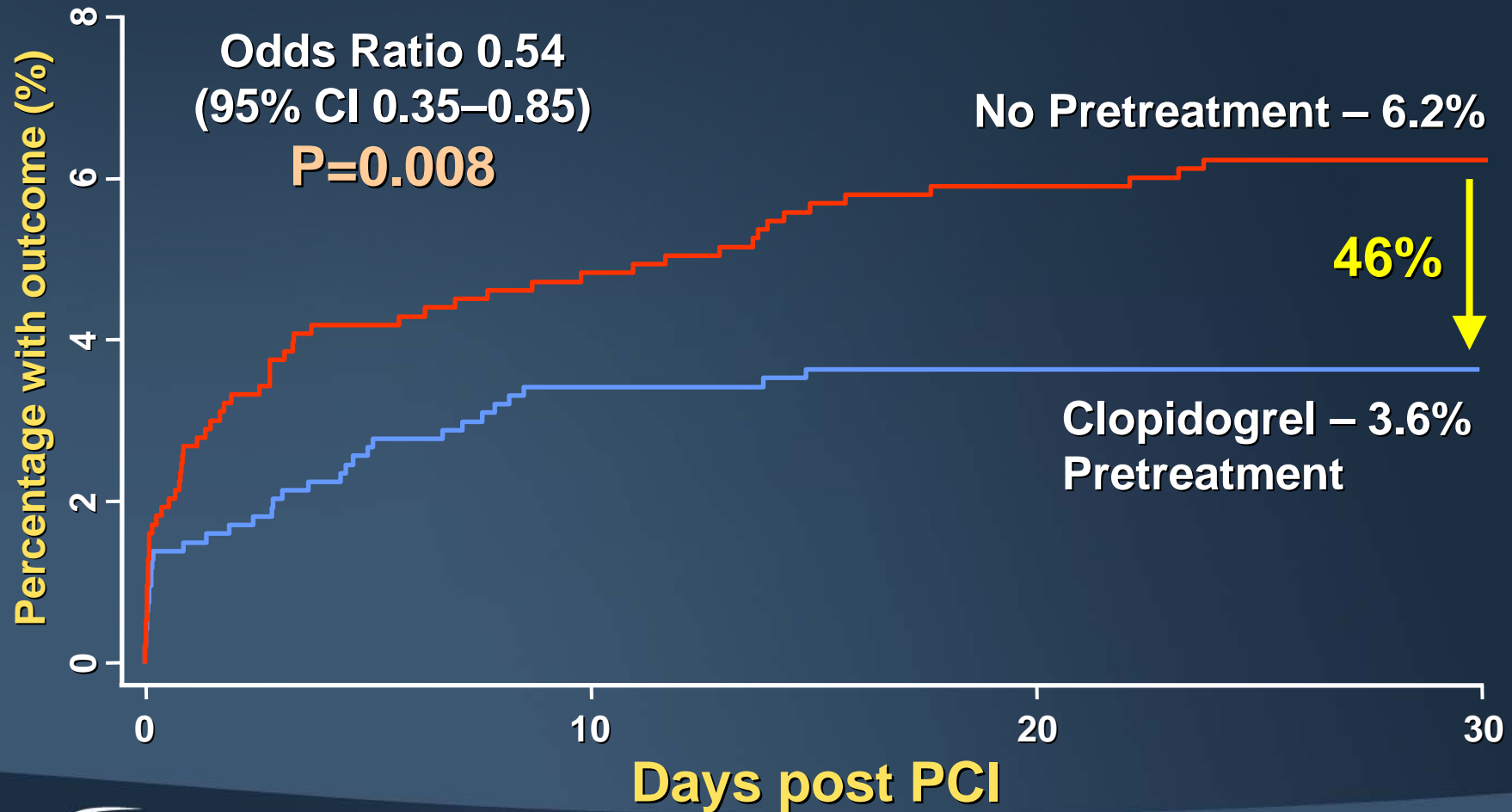
CURE

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



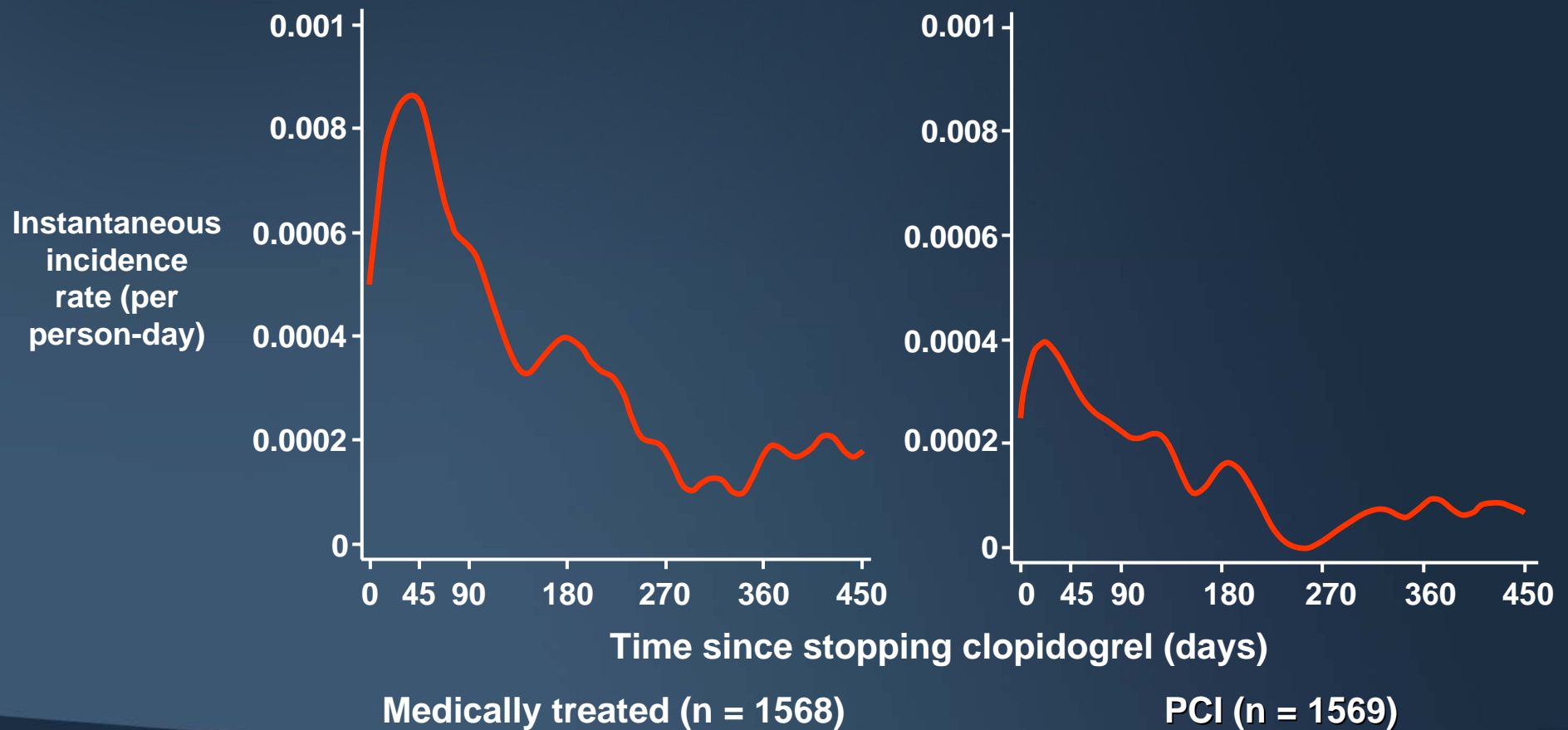
1863 of 3491 pts treated with fibrinolytic and aspirin, randomized to clopidogrel 300/75mg vs. placebo and followed for 30 days

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



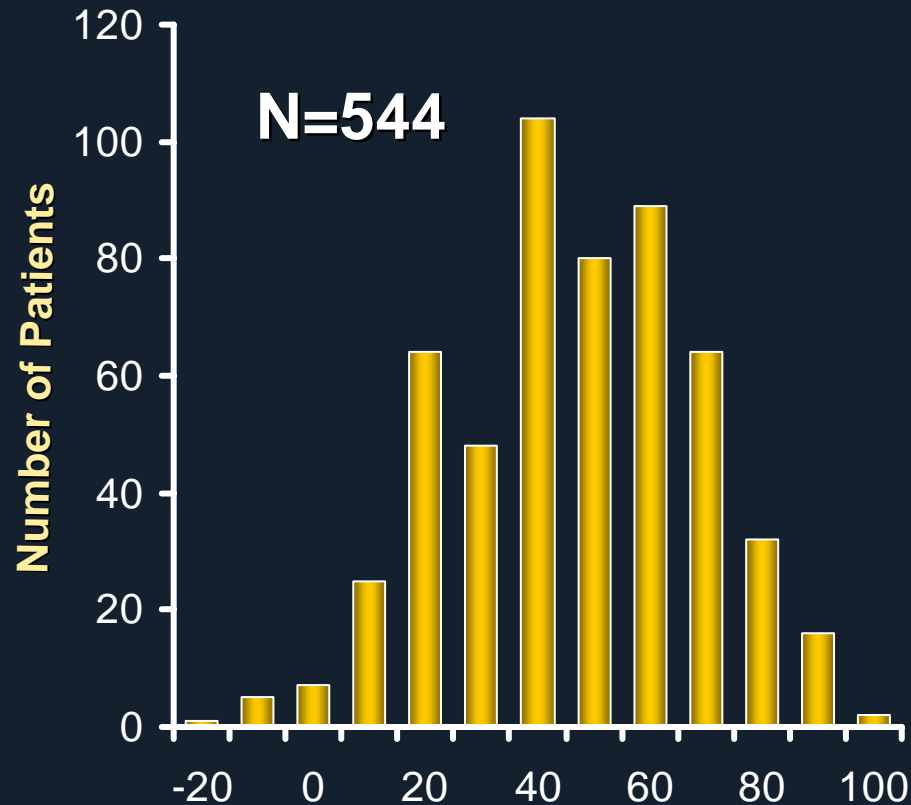
Hazard of death or MI after clopidogrel discontinuation post-ACS

N = 3137 US Veterans Administration patients

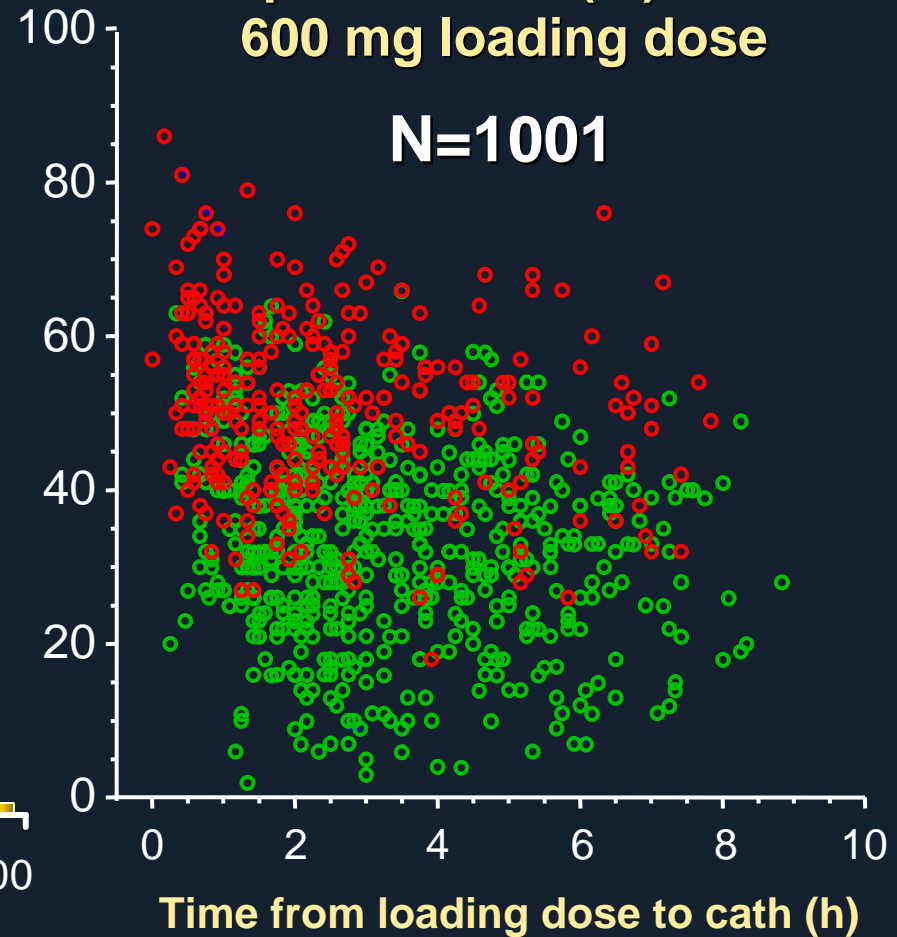


Variability in Clopidogrel Response

Change in 5 $\mu\text{mol/L}$ ADP-induced platelet aggregation with 75 mg chronic dosing



Maximal aggregation to 5 $\mu\text{mol/L}$ ADP (%) after 600 mg loading dose



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

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 P2Y₁₂ receptor inhibitors)



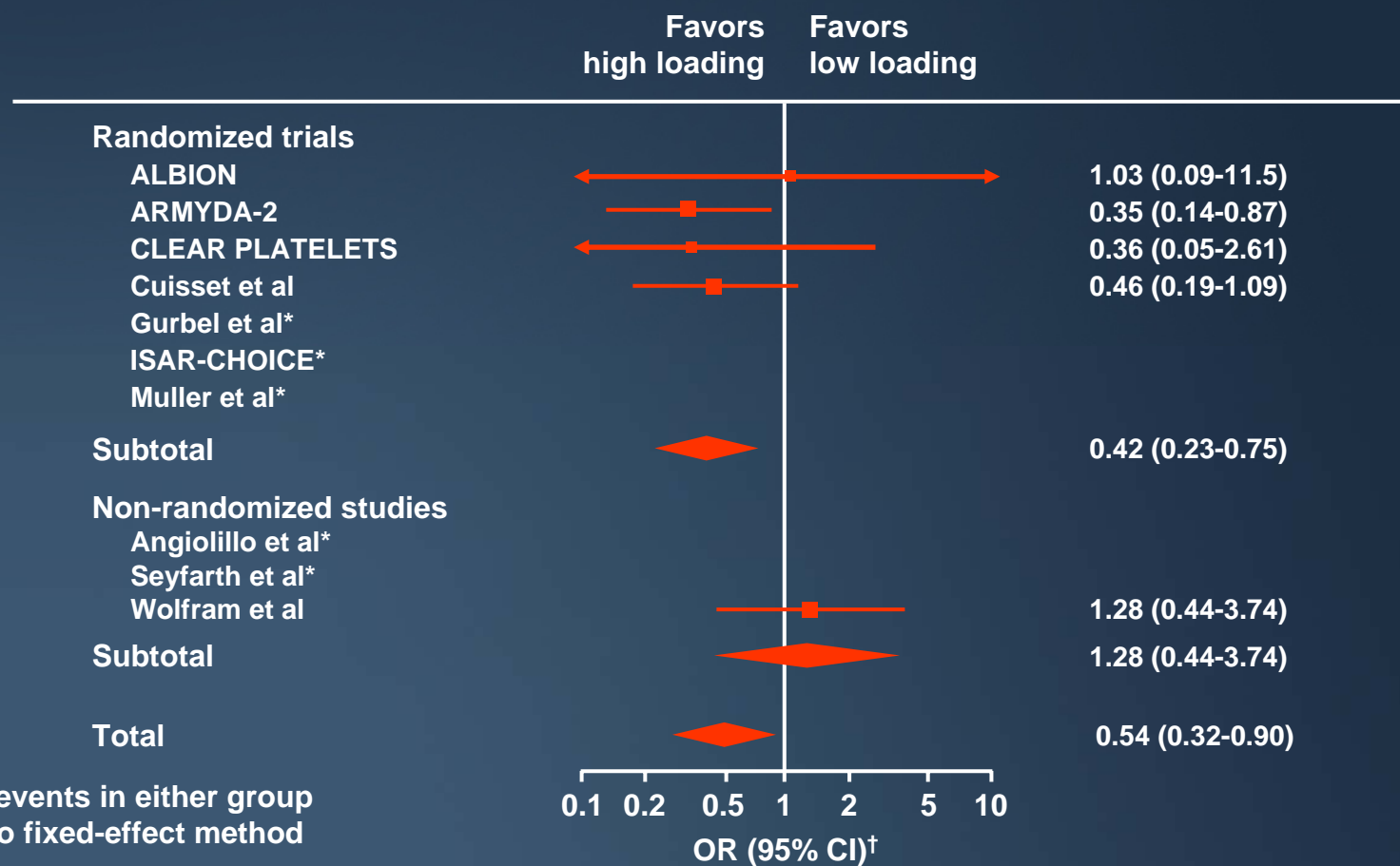
Clopidogrel 600 mg: Inhibition of platelet function at various time points

Assay	Time (hours)				
	<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

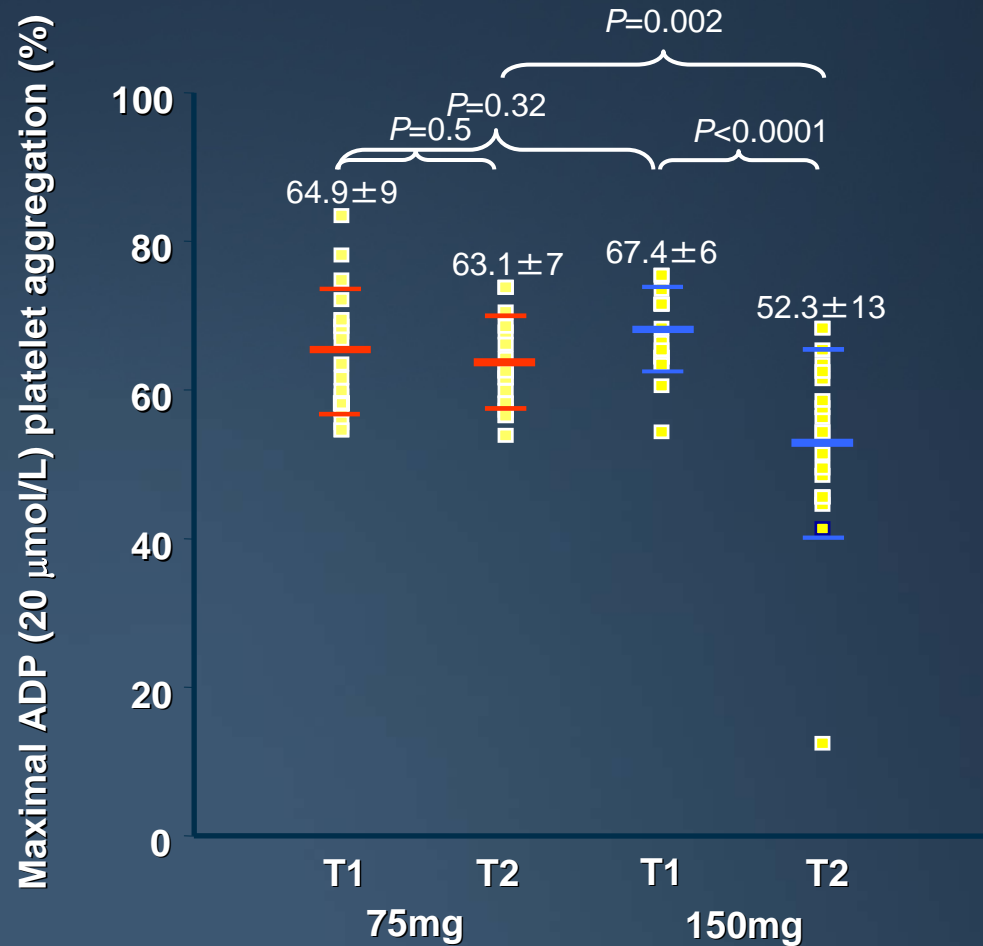
Clopidogrel 600 mg vs 300 mg loading dose

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



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

Primary Endpoint: Maximal ADP (20 $\mu\text{mol/L}$) Platelet Aggregation



Overcoming Suboptimal Antiplatelet Drug Response

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(e.g. cilostazol)
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Clinical Evidence for Triple Therapy: Cilostazol

	N	Study and Population	Result Summary
OPTIMUS II Angiolillo DJ et al. <i>Eur Heart Journal</i> 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. <i>J Am Coll Cardiol</i> 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 <i>Am Heart J</i> 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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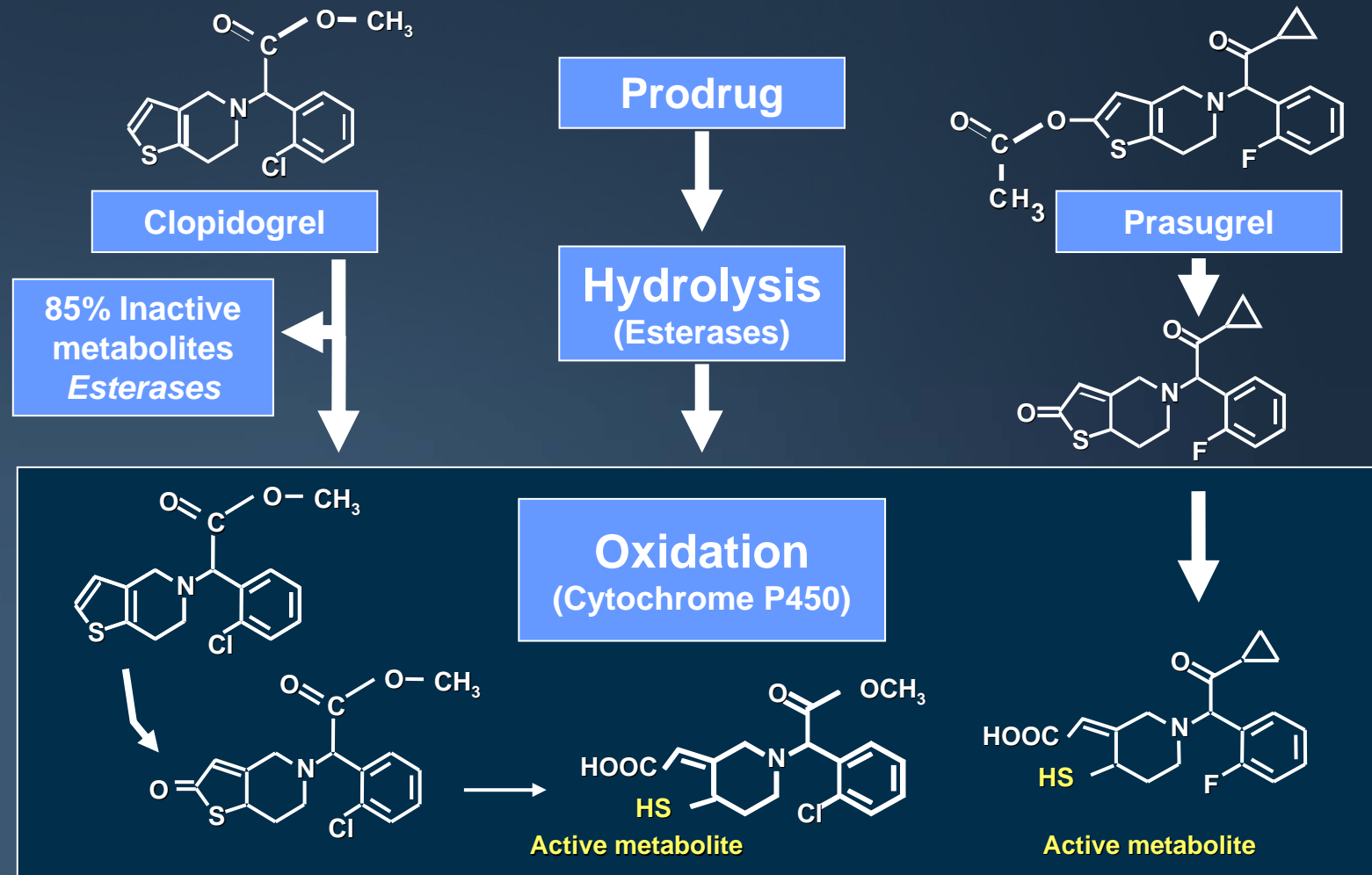
Novel P2Y₁₂ ADP receptor antagonist

More potent and less variability!!

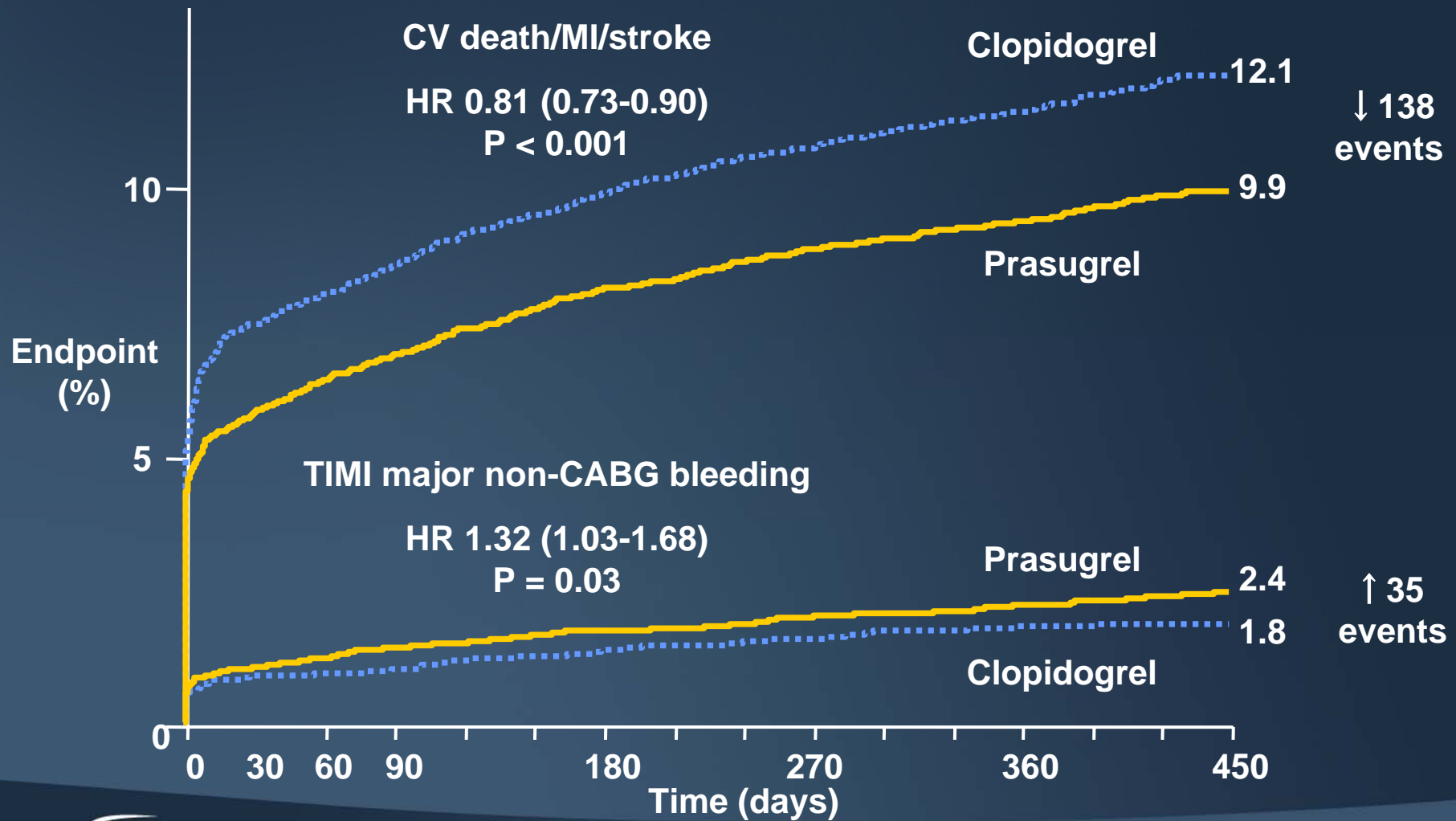
Drug	Type	Route	Action	Dose	Mean platelet inhibition (time required)	Trials (phase III)
Prasugrel (CS-747)	Thienopyridine (3 rd generation) - requires hepatic conversion to active metabolite	Oral	Irreversible binding	60 mg loading dose, 10 mg maintenance dose	≈ 70% (< 1 hour)	TRITON
Cangrelor (ARC-669931MX)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



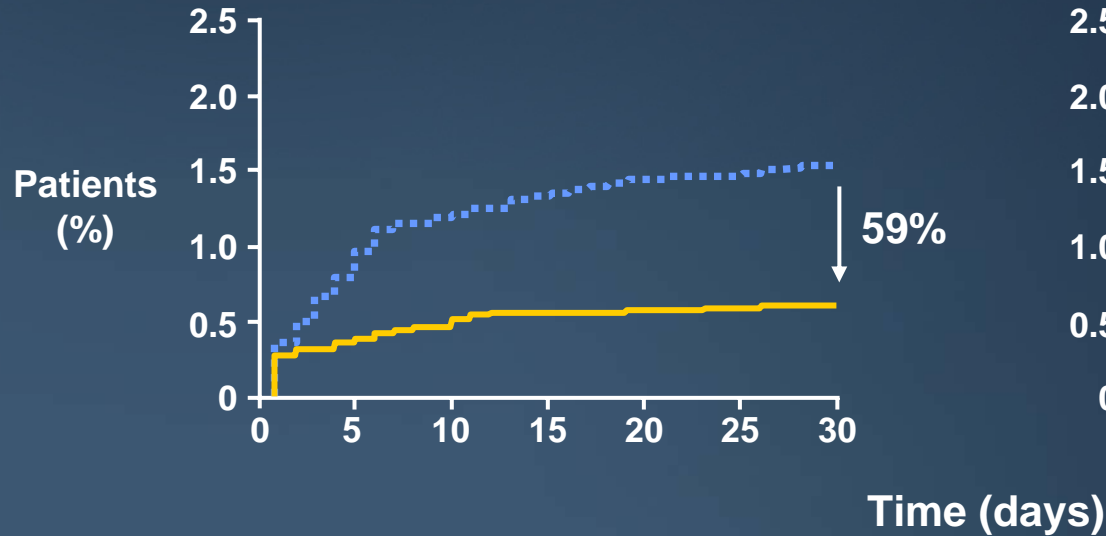
TRITON-TIMI 38: Treatment effects on primary efficacy and key safety endpoints N=13,608



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

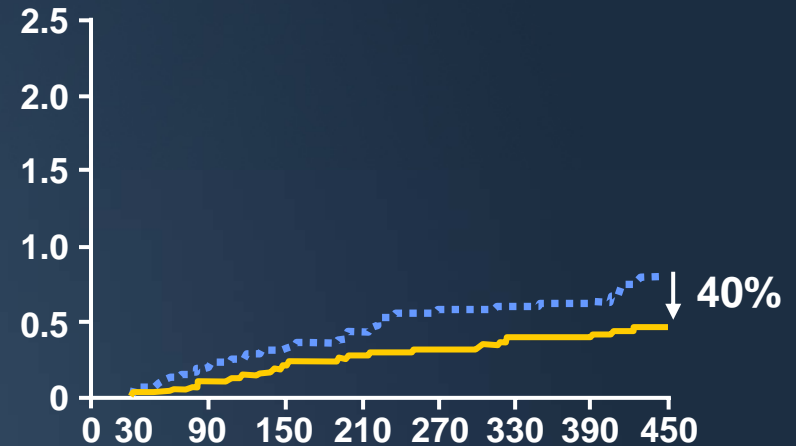


— Prasugrel

..... Clopidogrel

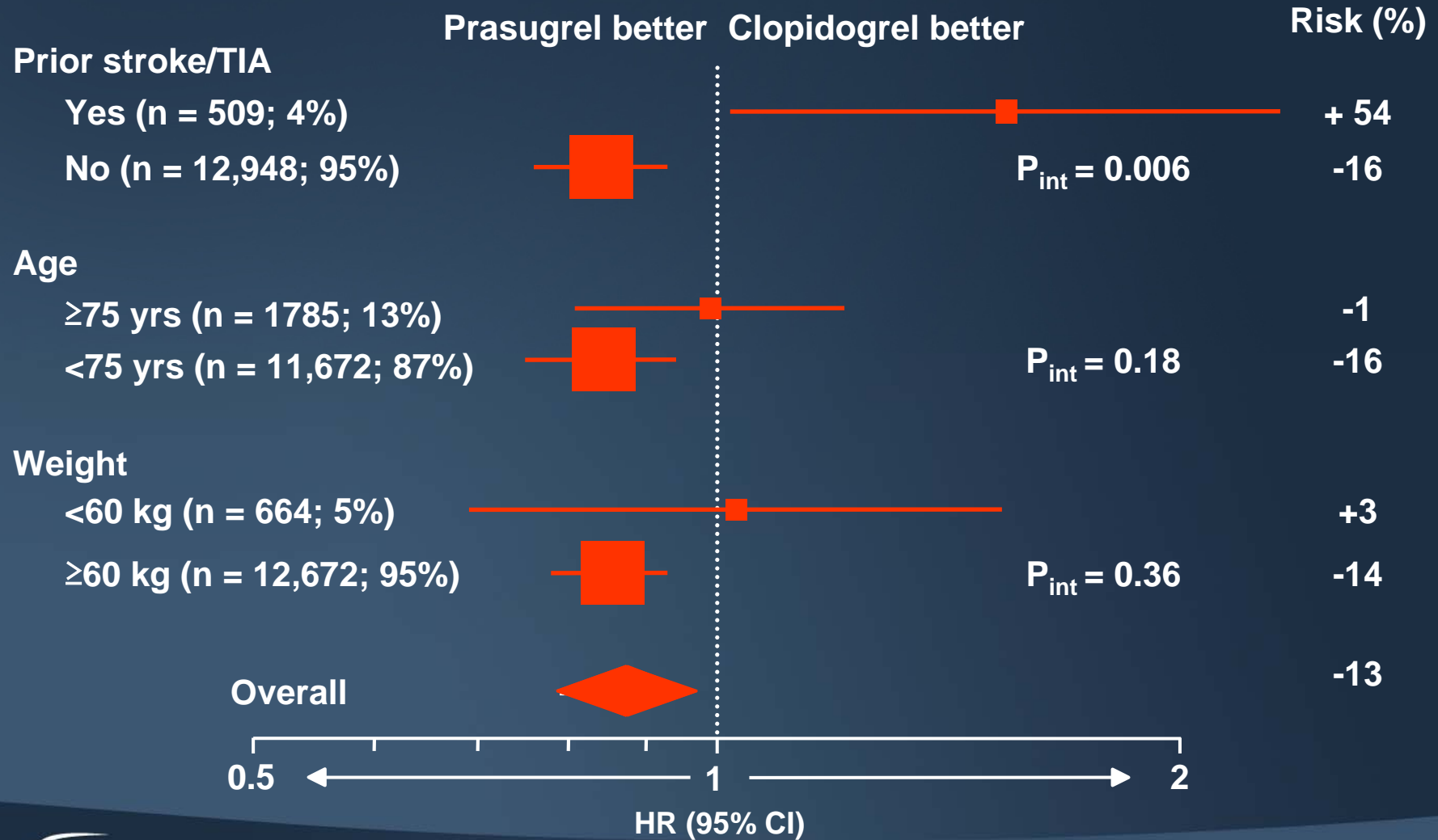
Late stent thrombosis*

HR 0.60 (0.37-0.97)
P = 0.03



*Definite or probable using Academic Research Consortium designation

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

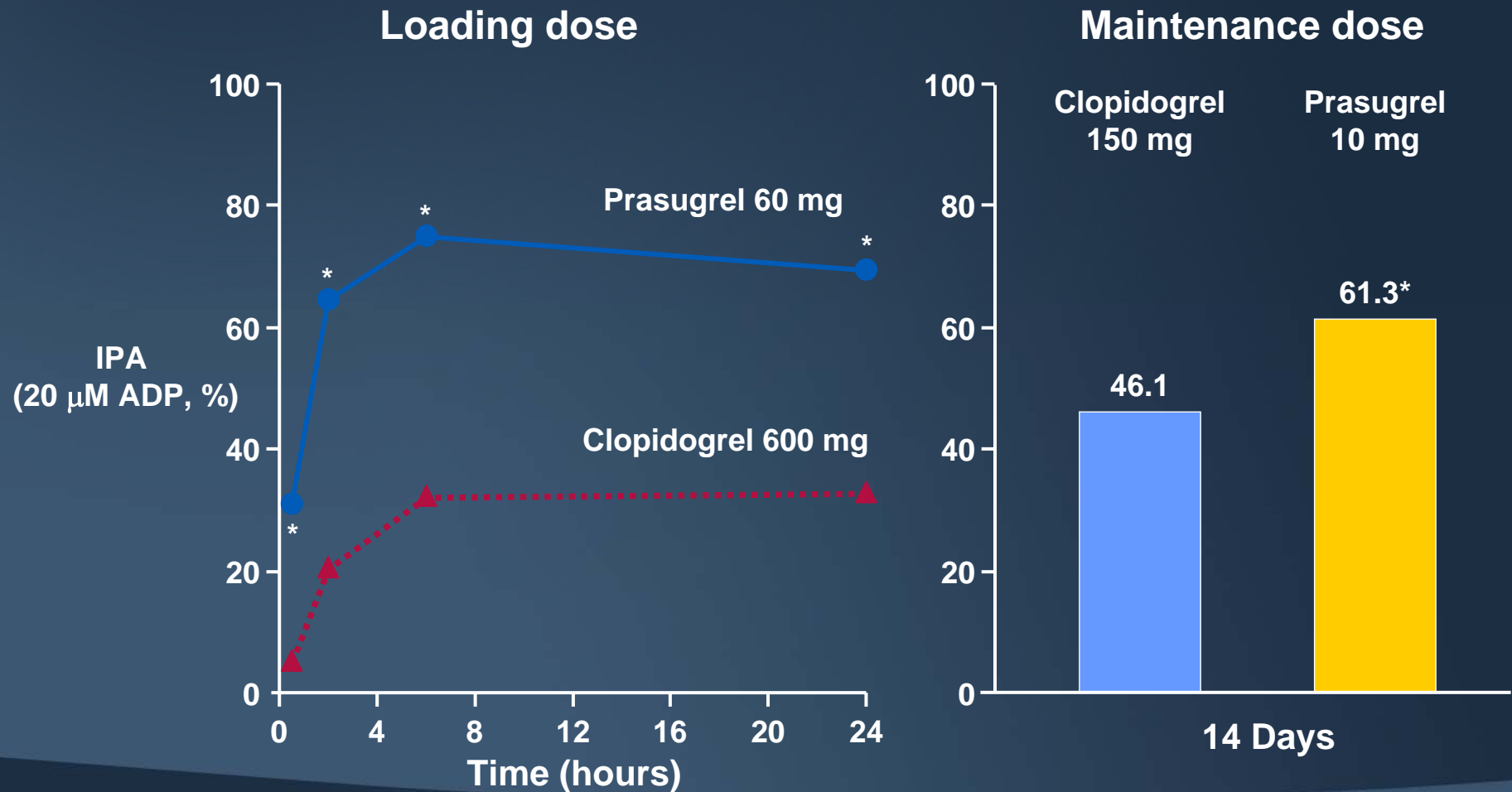


TRITON-TIMI-38

	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

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.



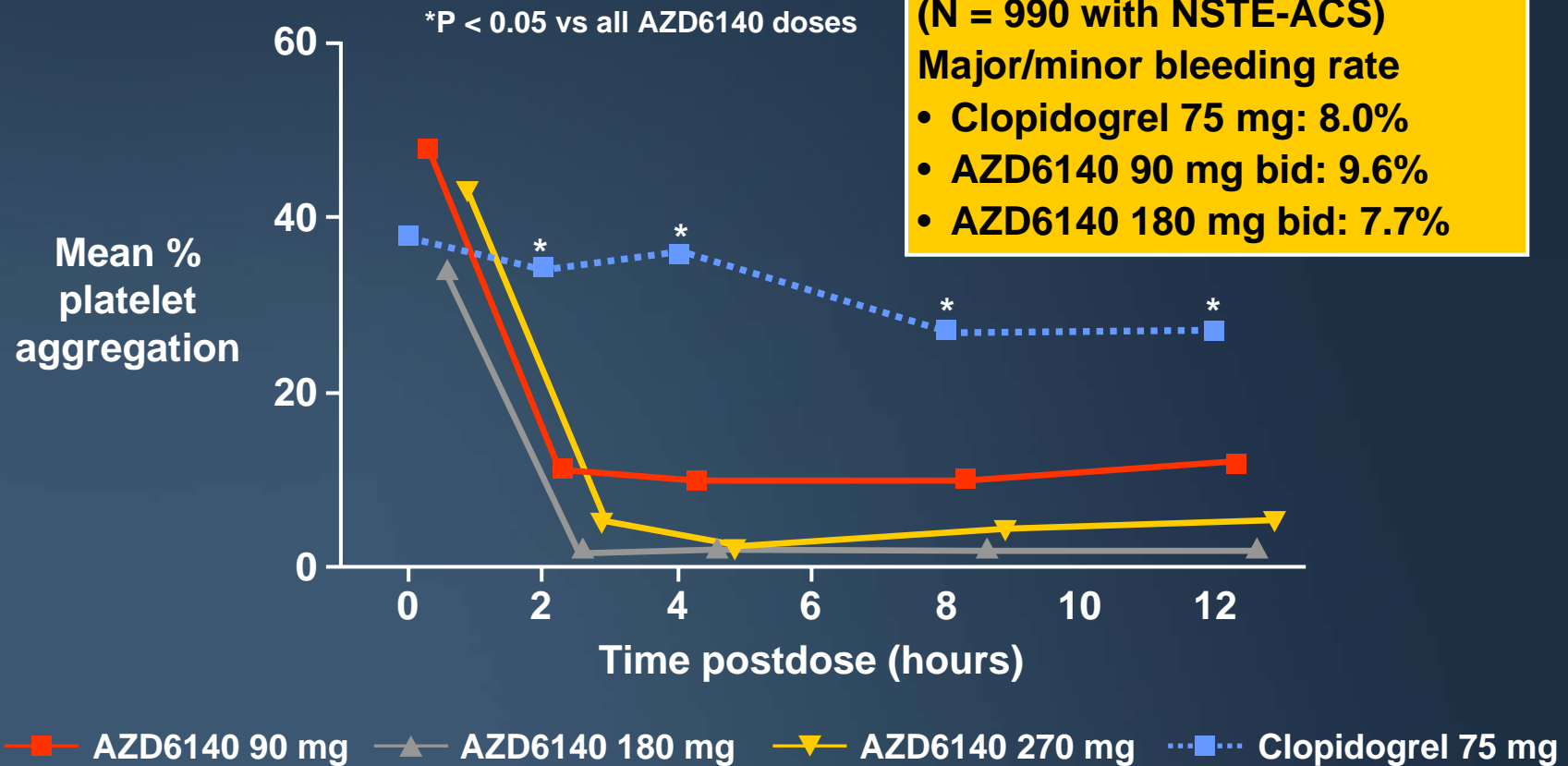
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Ticagrelor/AZD6140

DISPERSE-2: Dose Optimization Study

Oral, direct-acting cyclopentyltriazolopyrimidine
reversible inhibition of P2Y12 receptor

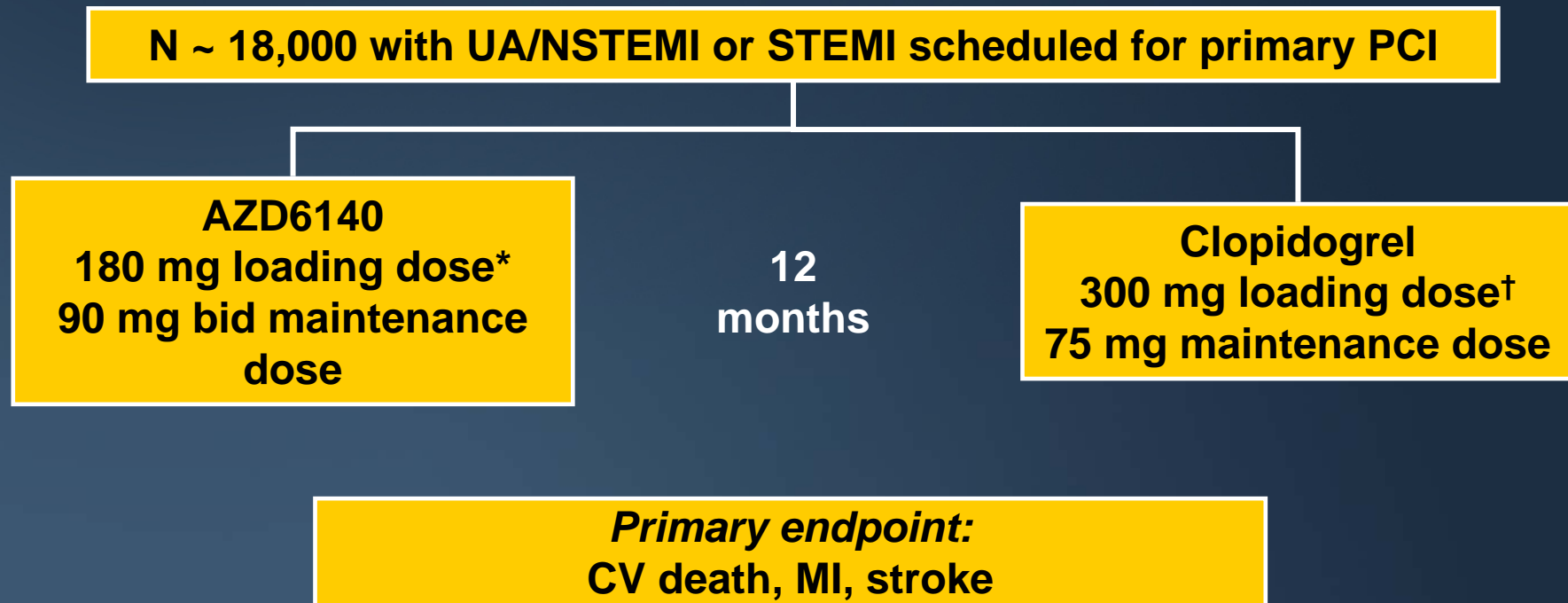
Clopidogrel-pretreated cohort (n = 44)



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

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

PLATO: Study design



*Additional 90 mg allowed pre-PCI

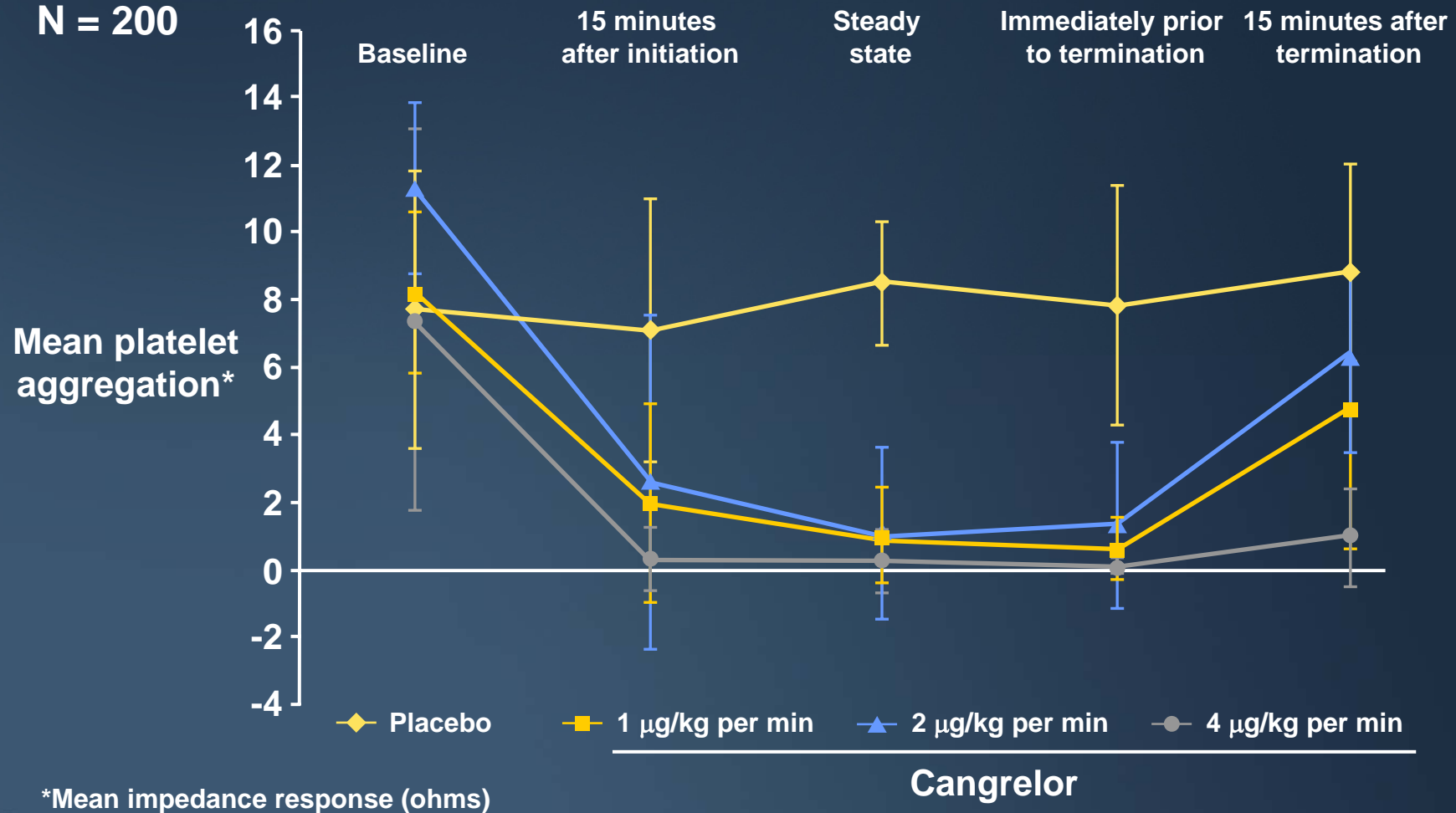
†In clopidogrel-naïve patients (no loading dose if pretreated);

Additional 300 mg allowed in either clopidogrel group pre-PCI

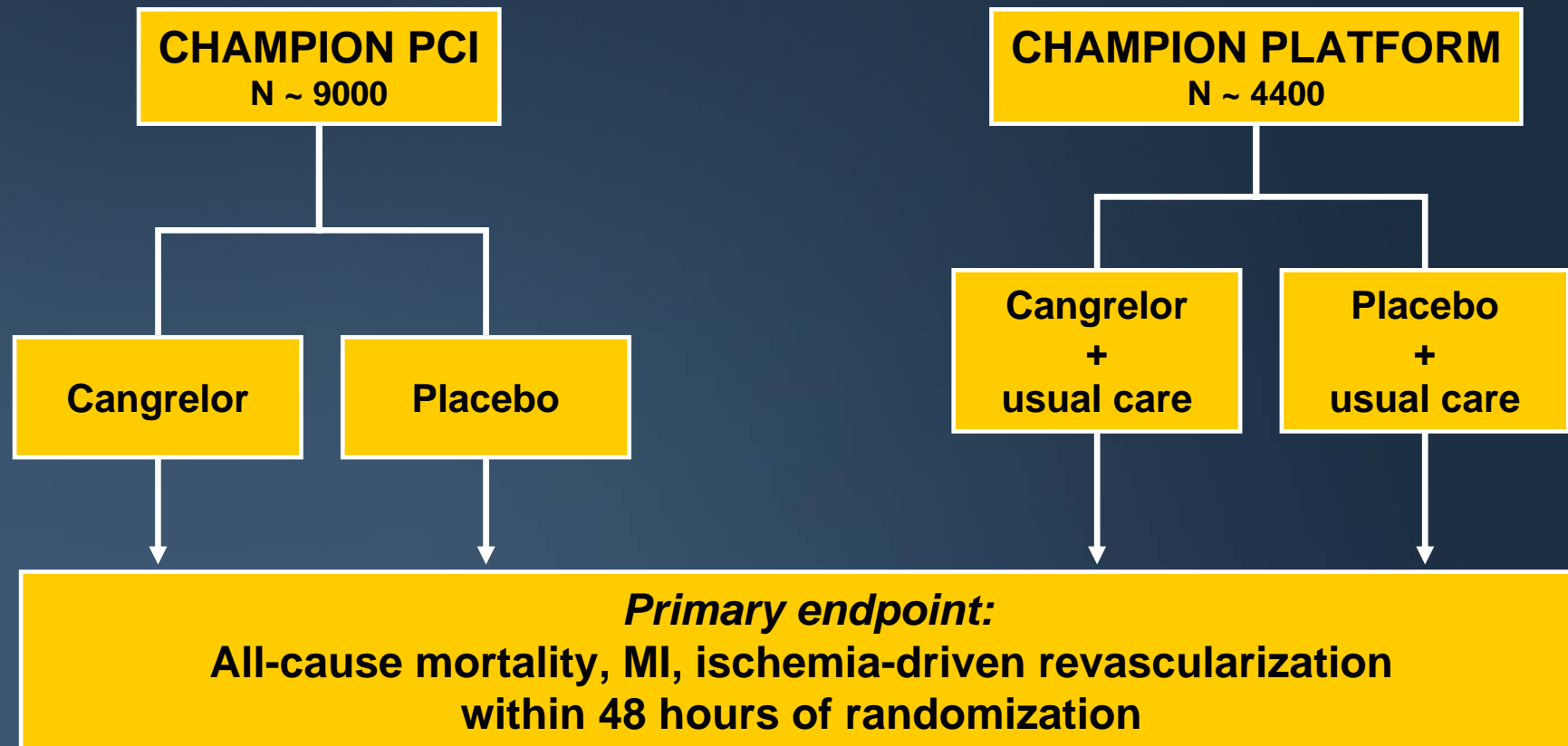
Cangrelor: Dose finding study

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

N = 200



Cangrelor: Ongoing clinical trials



Antiplatelet Therapy in ACS/STEMI/PCI

- Patients should be adequately pre-loaded with clopidogrel prior to angiography and PCI
 - 600 mg given \geq 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

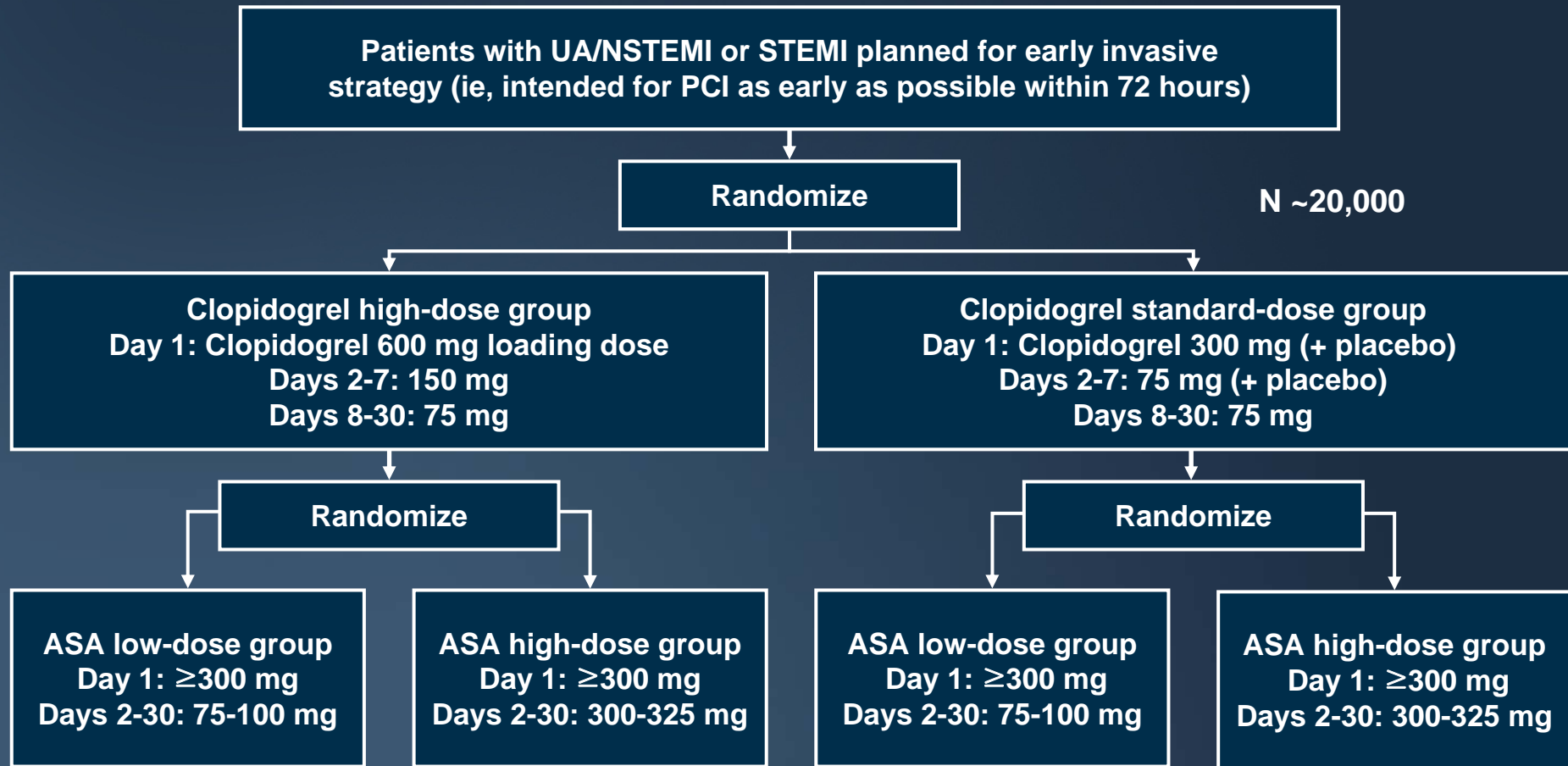
Prolonged DAPT > 1 year:

- 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



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

GRAVITAS

Successful PCI with DES without major complication or GPIIb/IIIa use

N ~ 6600

Post-PCI VerifyNow P2Y12 Assay (PRU) 12-24 hours post-PCI

Yes

PRU \geq 230?

No

Responder

Non-Responder

Random Selection

A

N = 1100

B

N = 1100

C

N = 583

"Tailored Therapy"
clopidogrel 150-mg/day

"Standard Therapy"
clopidogrel 75mg +placebo/day

"Standard Therapy"
clopidogrel 75mg +placebo/day

Clinical Follow-up And VerifyNow Assessment at 30 days, 6 months

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

TRIGGER-PCI

Courtesy of F.J. Neumann

Successful PCI with DES without major complication and NO GPIIb/IIIa use

N ~ 8800

Post-PCI VerifyNow P2Y12 Assay (PRU) 2 - 4 hours after 1st MD of clopidogrel 75 mg at day 1 post-PCI

Non-Responder

Yes

PRU \geq 208?

No

Responder

PRU \geq 140?

Random Selection

A N = 1075

B N = 1075

C N = 550

D N = 550

E

“Prasugrel arm”
Prasugrel 60 mg LD
Prasugrel 10 mg MD
+ Clopidogrel placebo

“Clopidogrel arm”
Placebo LD
Clopidogrel 75 mg MD
+ Prasugrel placebo

“Prasugrel arm”
Prasugrel 60 mg LD
Prasugrel 10 mg MD
+ Clopidogrel placebo

“Clopidogrel arm”
Placebo LD
Clopidogrel 75 mg MD
+ Prasugrel placebo

“Standard Therapy”
Clopidogrel 75 mg

Platelet function substudy:
VerifyNow Assessment at day 2 (2 – 4 h after 1st MD of study drug)

Clinical Follow-up and VerifyNow Assessment at 90 days, 180 days

Primary Endpoint: 6 month CV Death and MI