ANTIAGREGANTS

IN ACUTE CORONARY SYNDROME

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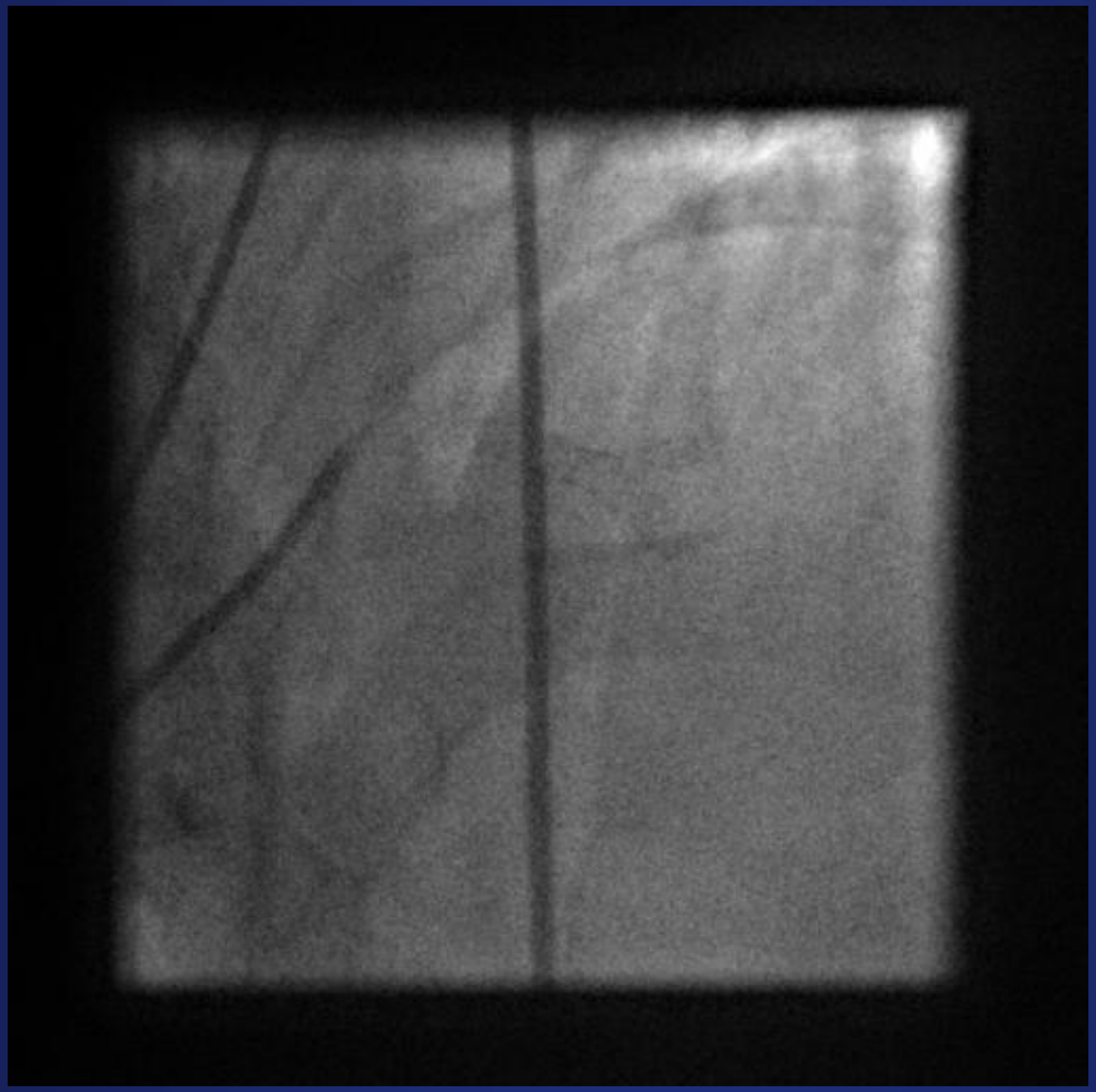
Dual Antiplatelet Therapy

- ASA + Clopidogrel
- I Class of evidence in treatment of ACS
- Beneficial, effective and useful in acute and long term treatment of ACS
- Current standard in patients after stent implantation

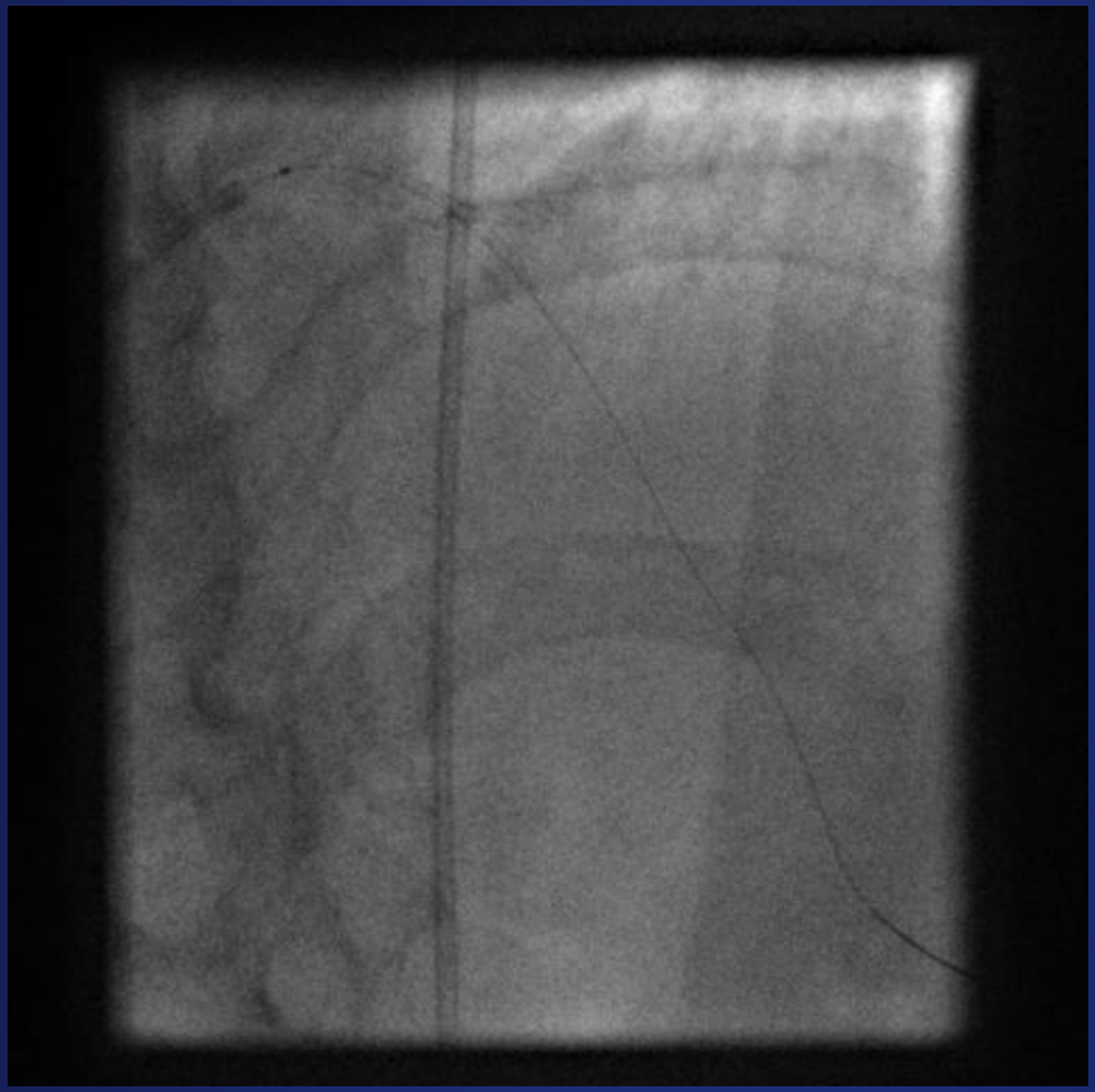
Possible problems:

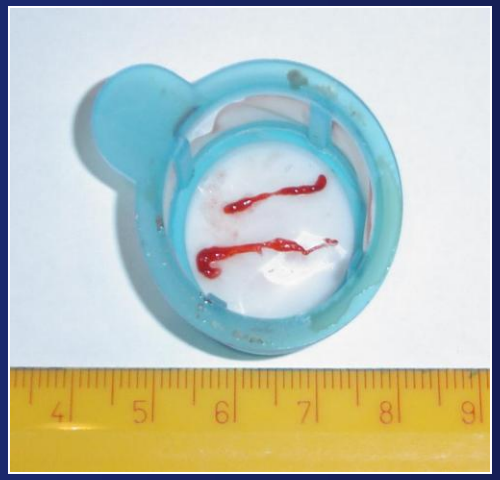
- Increased risk of bleeding
- Risk of stent thrombosis and MI in poor responders

Stent thrombosis of LAD bifurcation

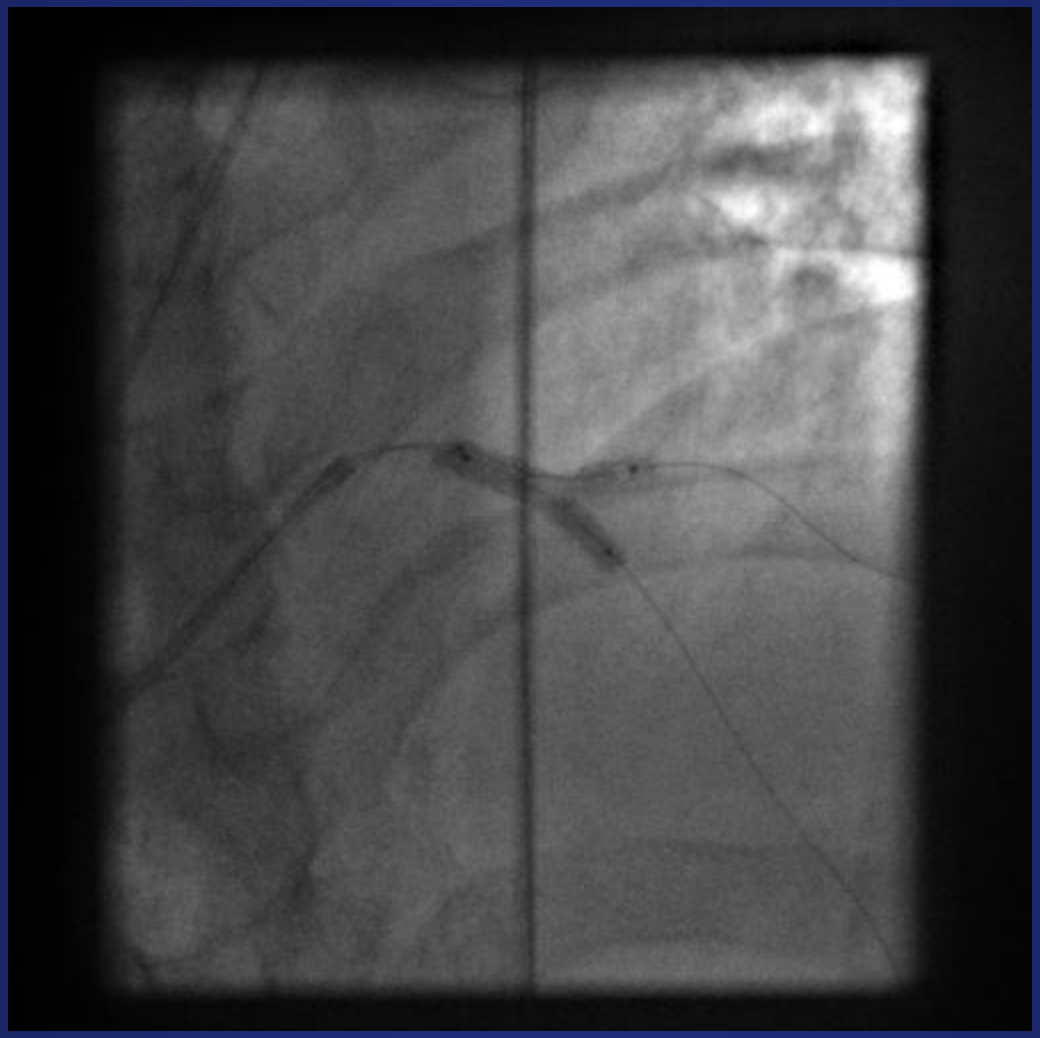


Thrombosuction

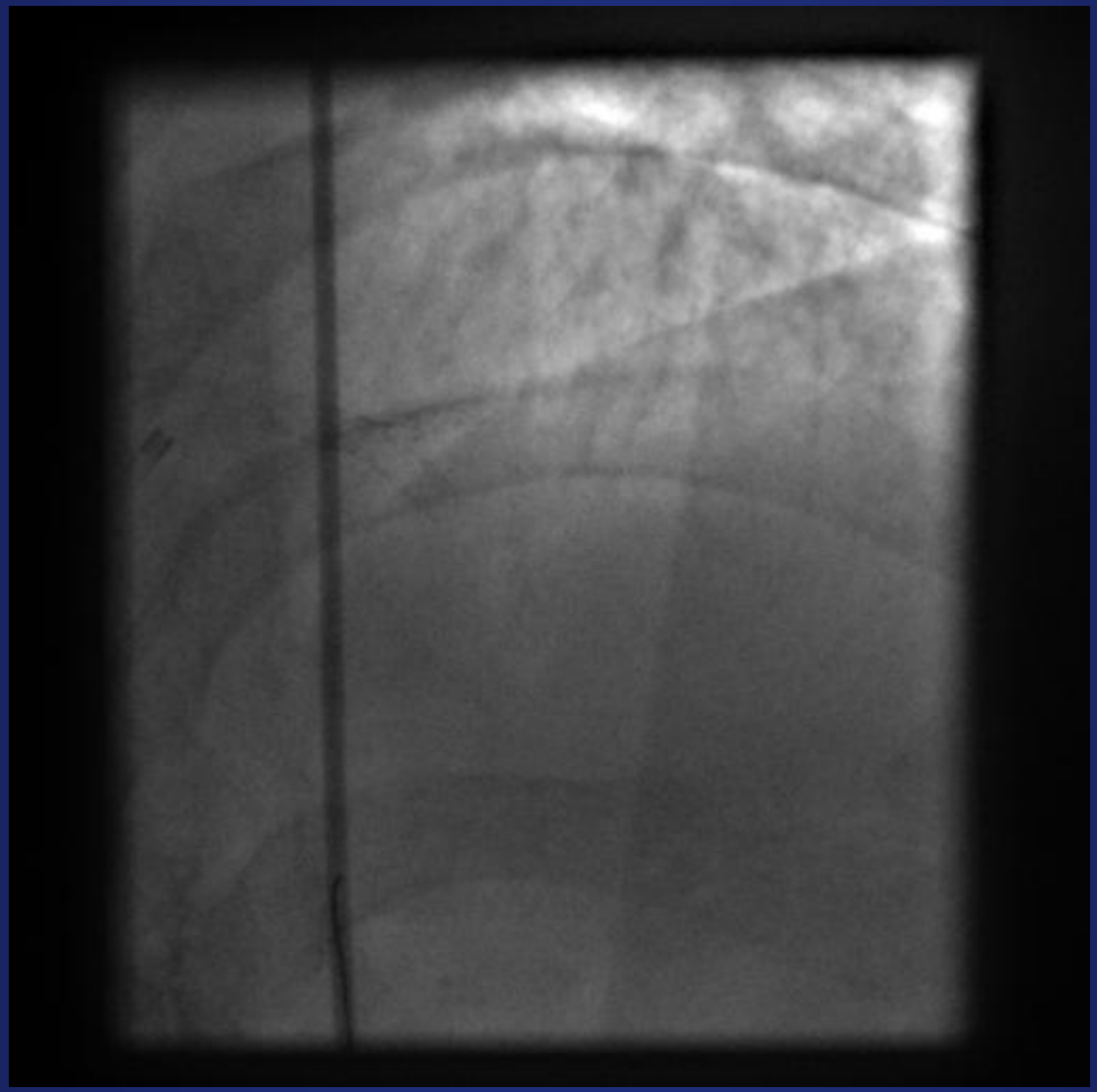




Kissing balloon dilatation

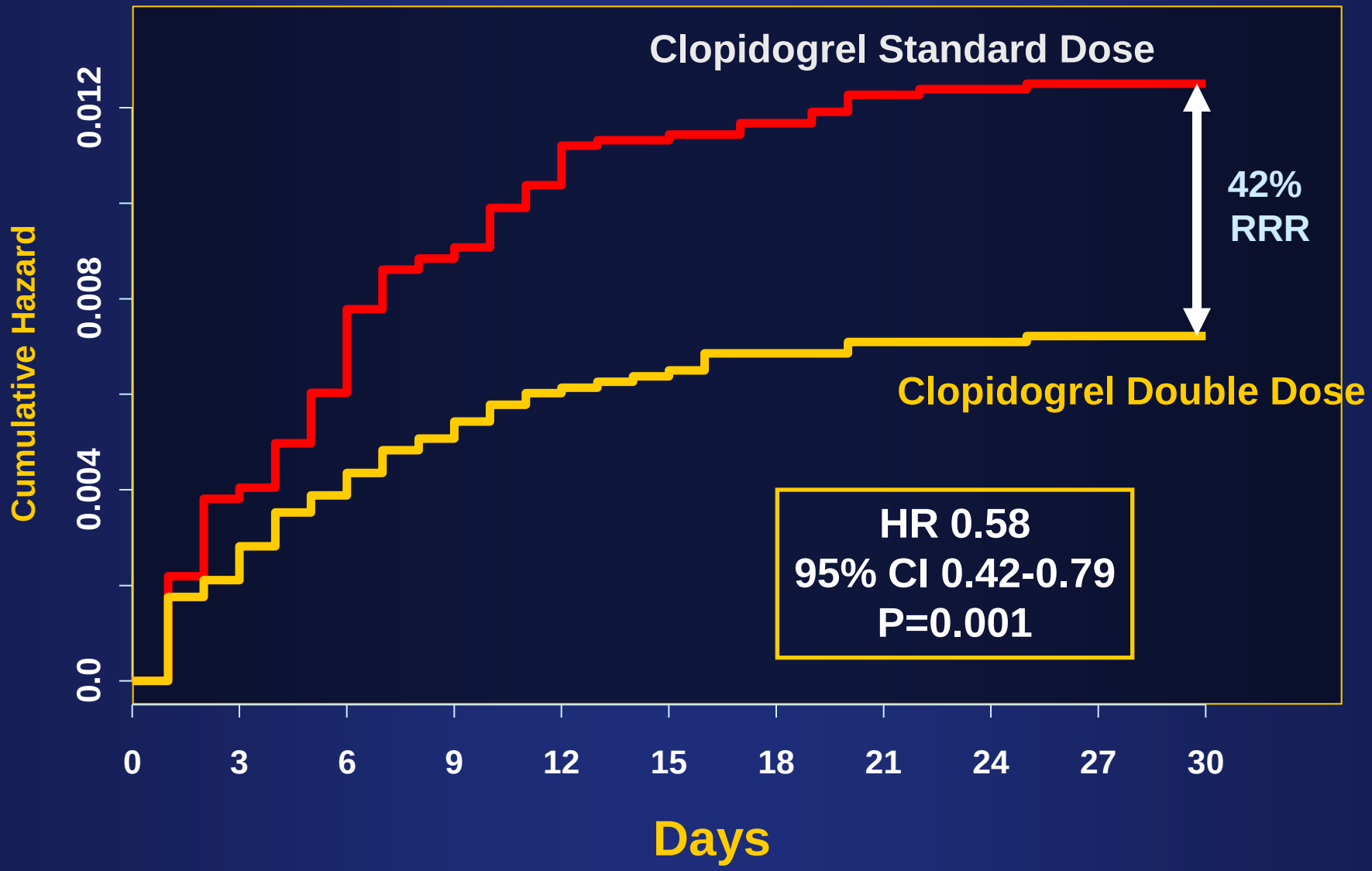


Final Result

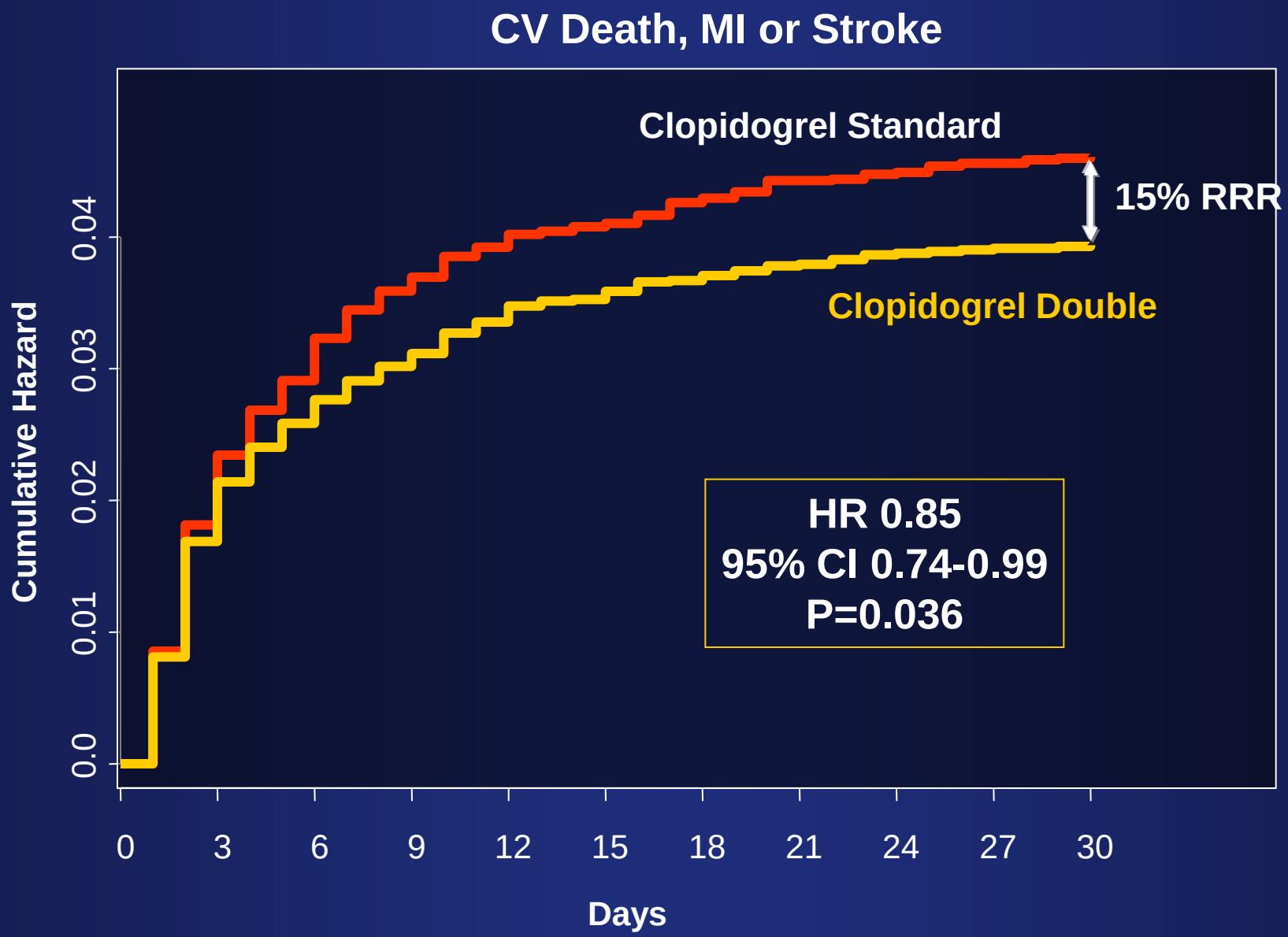


CURRENT

Clopidogrel: Double (600mg and 150mg/d 1wk) vs Standard Dose (300mg) Definite Stent Thrombosis



Clopidogrel: Double vs Standard Dose
Primary Outcome: PCI Patients



Clopidogrel Double vs Standard Dose Bleeding PCI Population

	Clopidogrel				
	Standard N= 8684	Double N=8548	Hazard Ratio	95% CI	P
TIMI Major[1]	0.5	0.5	1.06	0.70-1.61	0.79
CURRENT Major[2]	1.1	1.6	1.44	1.11-1.86	0.006
CURRENT Severe[3]	0.8	1.1	1.39	1.02-1.90	0.034
Fatal	0.15	0.07	0.47	0.18-1.23	0.125
ICH	0.035	0.046	1.35	0.30-6.04	0.69
RBC transfusion ≥ 2U	0.91	1.35	1.49	1.11-1.98	0.007
CABG-related Major	0.1	0.1	1.69	0.61-4.7	0.31

[1]ICH, Hb drop ≥ 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal
[2]Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units
[3]Fatal or ↓Hb ≥ 5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of ≥ 4 units

CURRENT

Conclusions

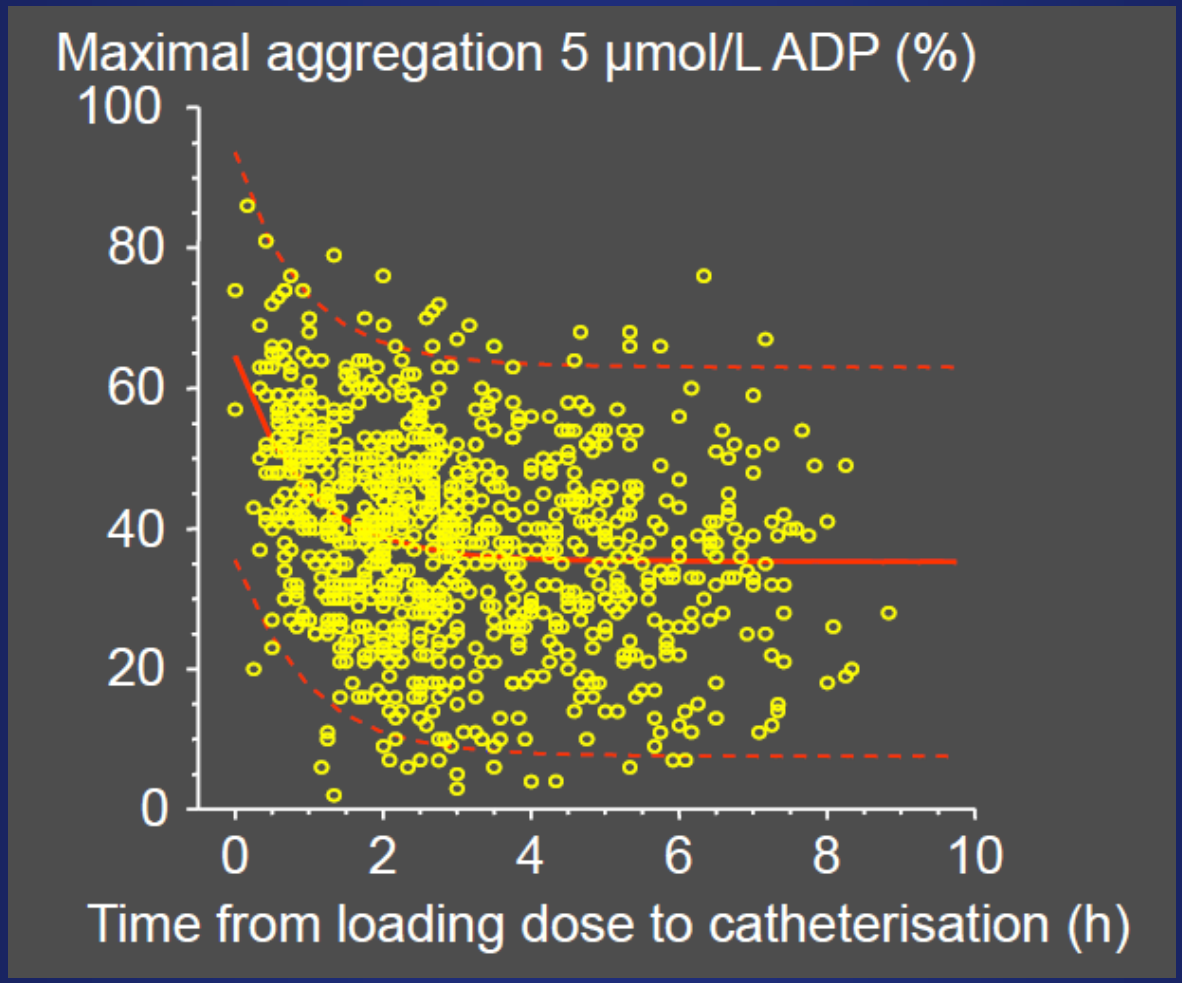
1. Double-dose clopidogrel significantly reduced stent thrombosis and major CV events (CV death, MI or stroke) in PCI.

2. In patients not undergoing PCI, double dose clopidogrel was not significantly different from standard dose (70% had no significant CAD or stopped study drug early for CABG).

3. There was a modest excess in CURRENT-defined major bleeds but no difference in TIMI major bleeds, ICH, fatal bleeds or CABG-related bleeds.

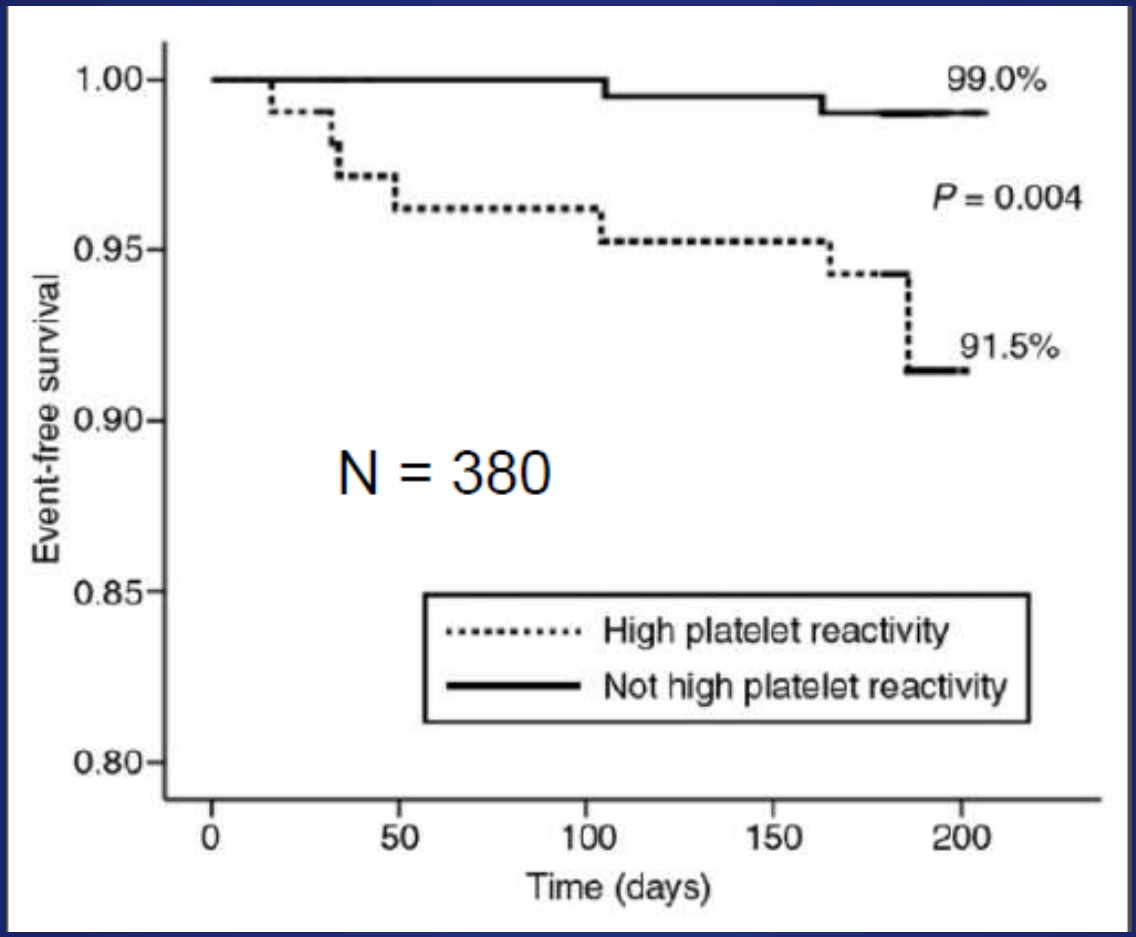
4. No significant difference in efficacy or bleeding between ASA 300-325 mg and ASA 75-100 mg

Platelet Aggregation after Clopidogrel Loading



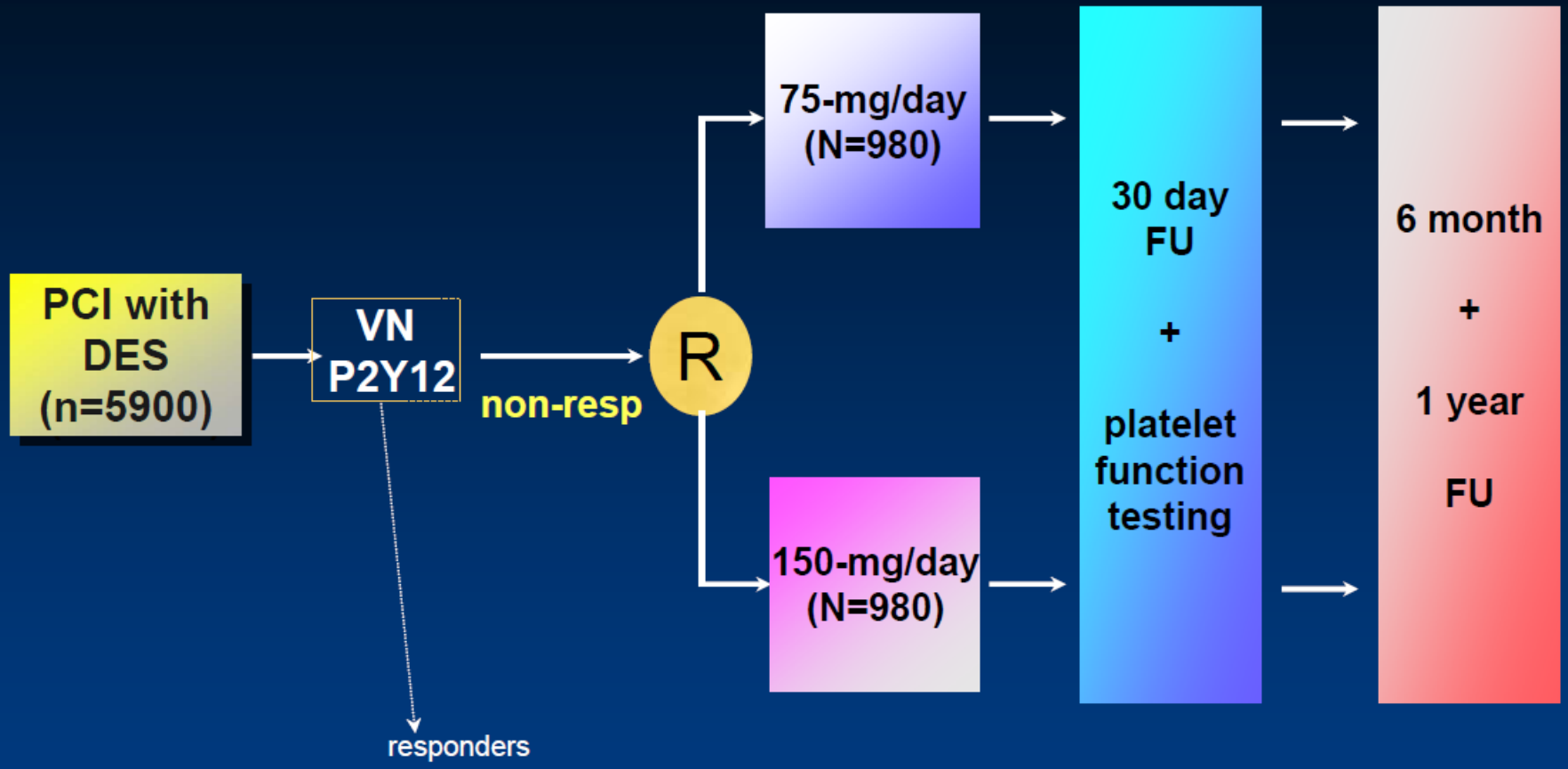
Hochholzer W et al, Circulation 2005

Survival free of cardiovascular death, infarction and stent thrombosis depending on platelet reactivity



Price MJ et al. Eur heart J 2008

GRAVITAS: Gauging Responsiveness With A VerifyNow assay- Impact On Thrombosis And Safety

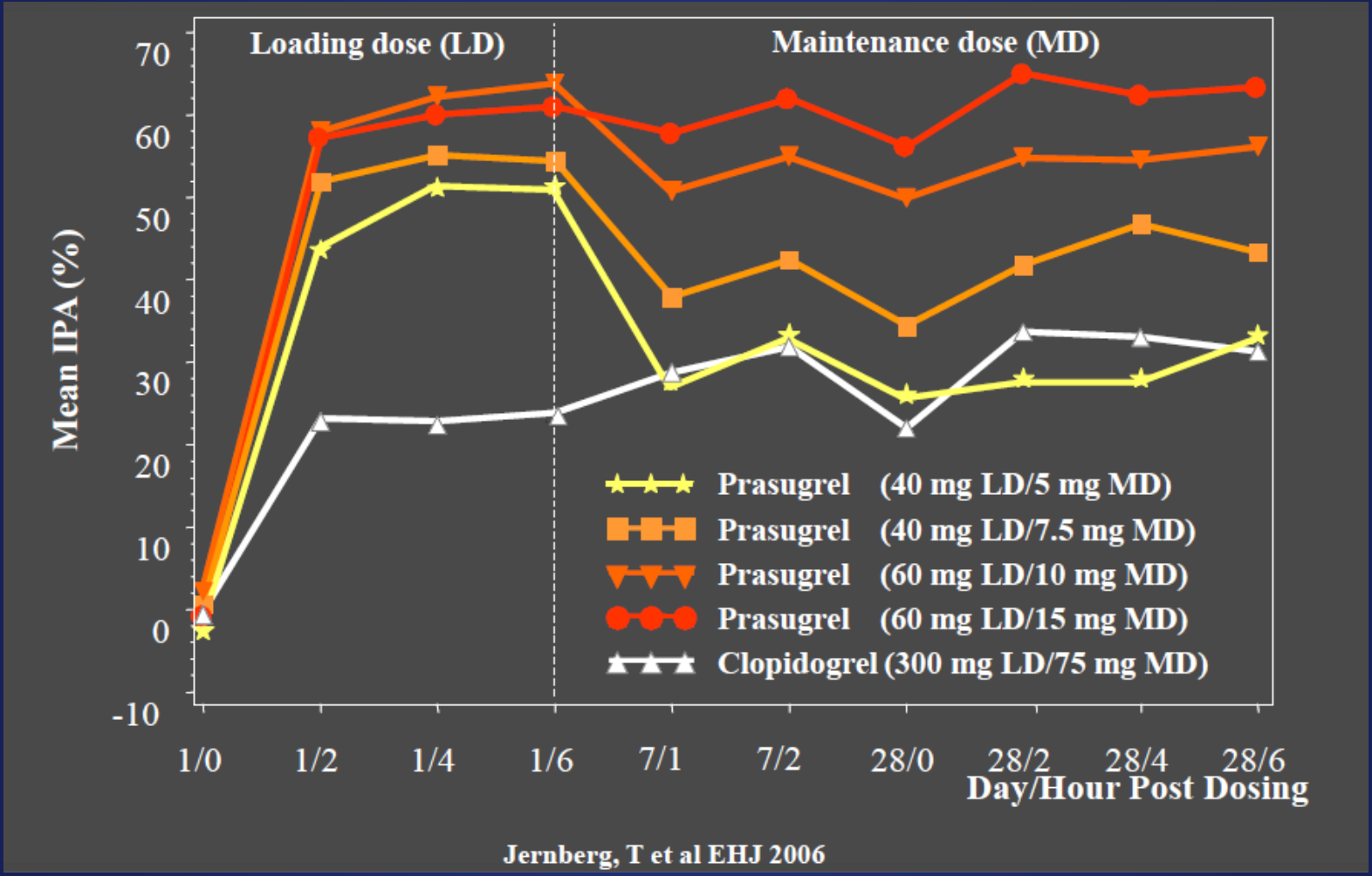


Primary Clinical Endpoint: 6-month cardiac death, non-fatal MI, stent thrombosis
Secondary Endpoint: 30-day &1 year cardiac death, non-fatal MI, stent thrombosis
Primary Physiologic Endpoint: Change in PRU at 30 days

PI: Matthew J. Price, MD

Coordinating Site: Scripps Clinic

Inhibition of Platelet Aggregation



Jernberg, T et al EHJ 2006

TRITON TIMI-38
STENT ANALYSIS

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA ↓ **N= 13,608**

Double-blind

CLOPIDOGREL	**PRASUGREL**
300 mg LD/ 75 mg MD	**60 mg LD/ 10 mg MD**

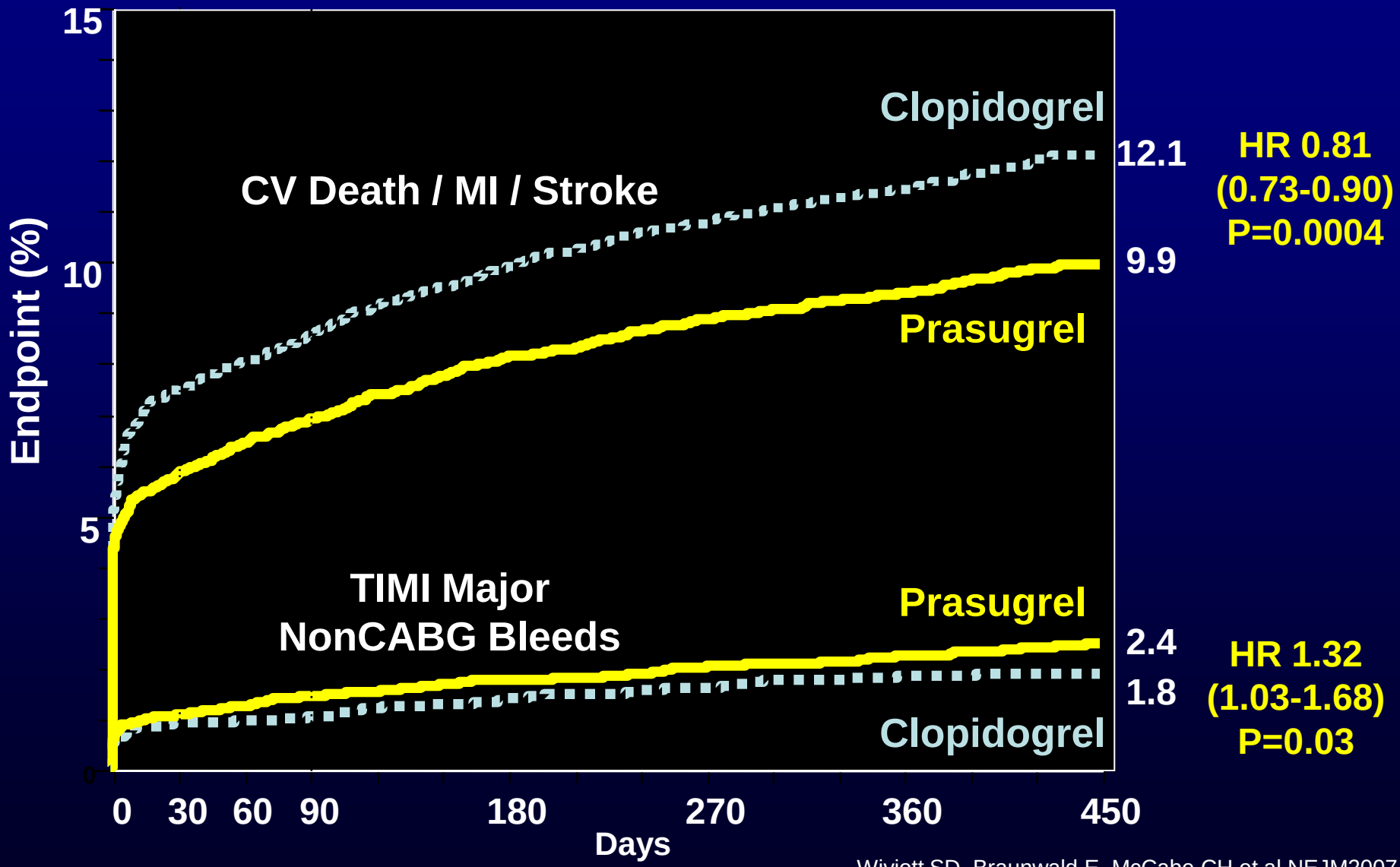
Duration of therapy: 6-15 months

1º endpoint:	**CV death, MI, Stroke**
2º endpoint:	**Stent Thrombosis**
Safety endpoints:	**TIMI major bleeds, Life-threatening bleeds**

Wiviott SD, Antman EM et al AHJ 2006

TRITON TIMI-38

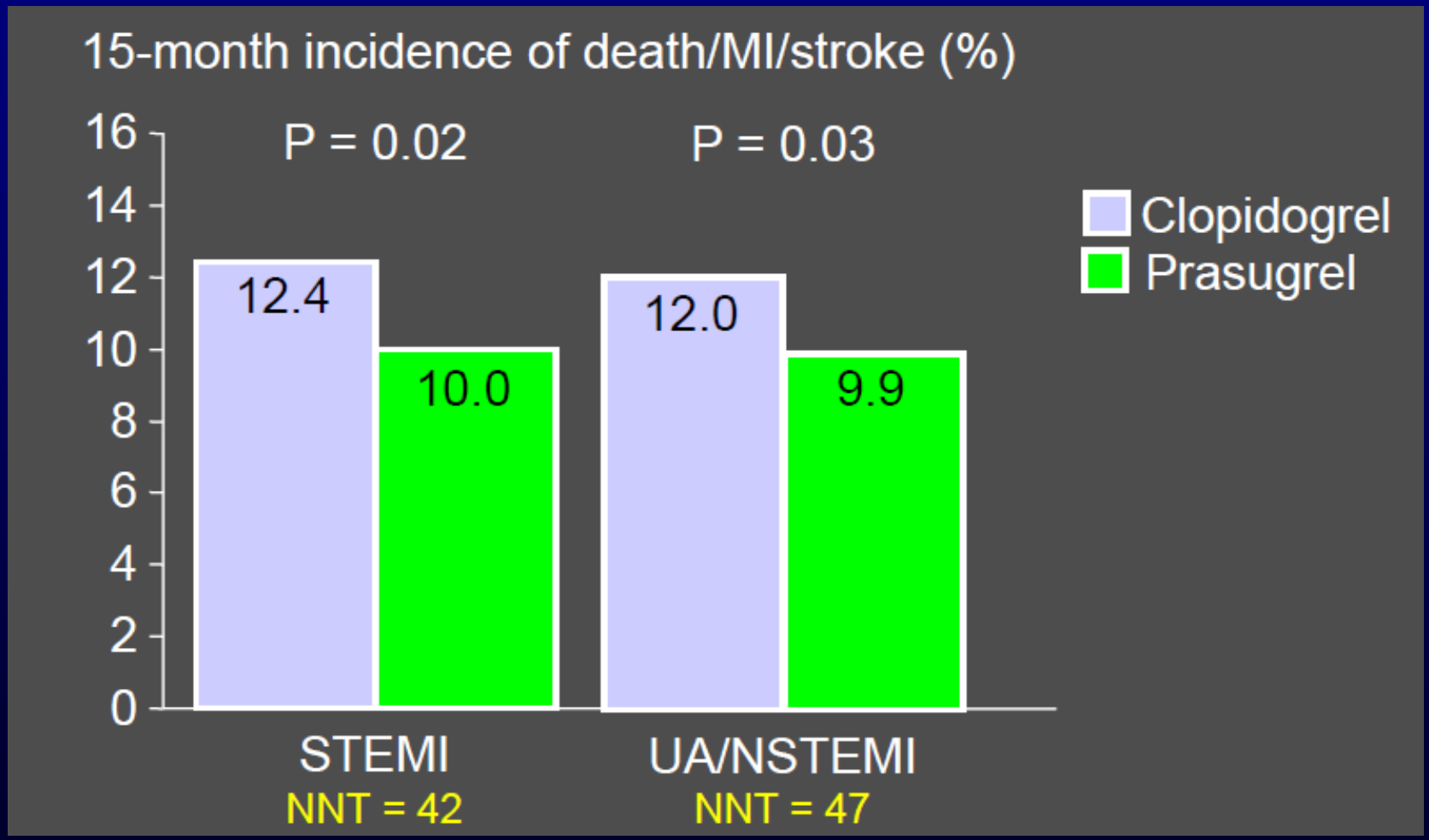
Main Trial: Primary Results



Wiviott SD, Braunwald E, McCabe CH et al NEJM2007

TRITON TIMI-38

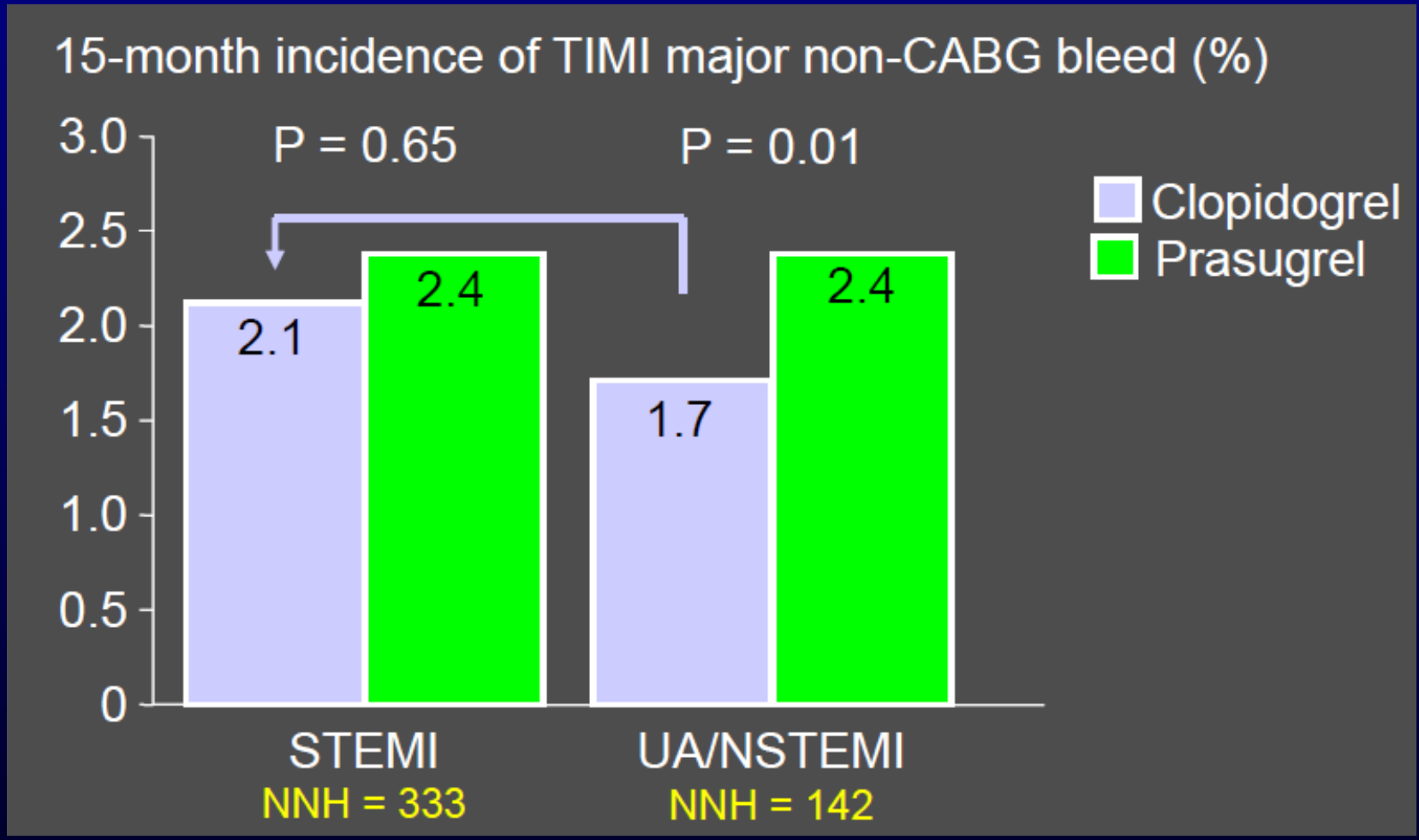
Prasugrel in STEMI and UA/NSTEMI



Wiviott SD, Braunwald E, McCabe CH et al NEJM2007

TRITON TIMI-38

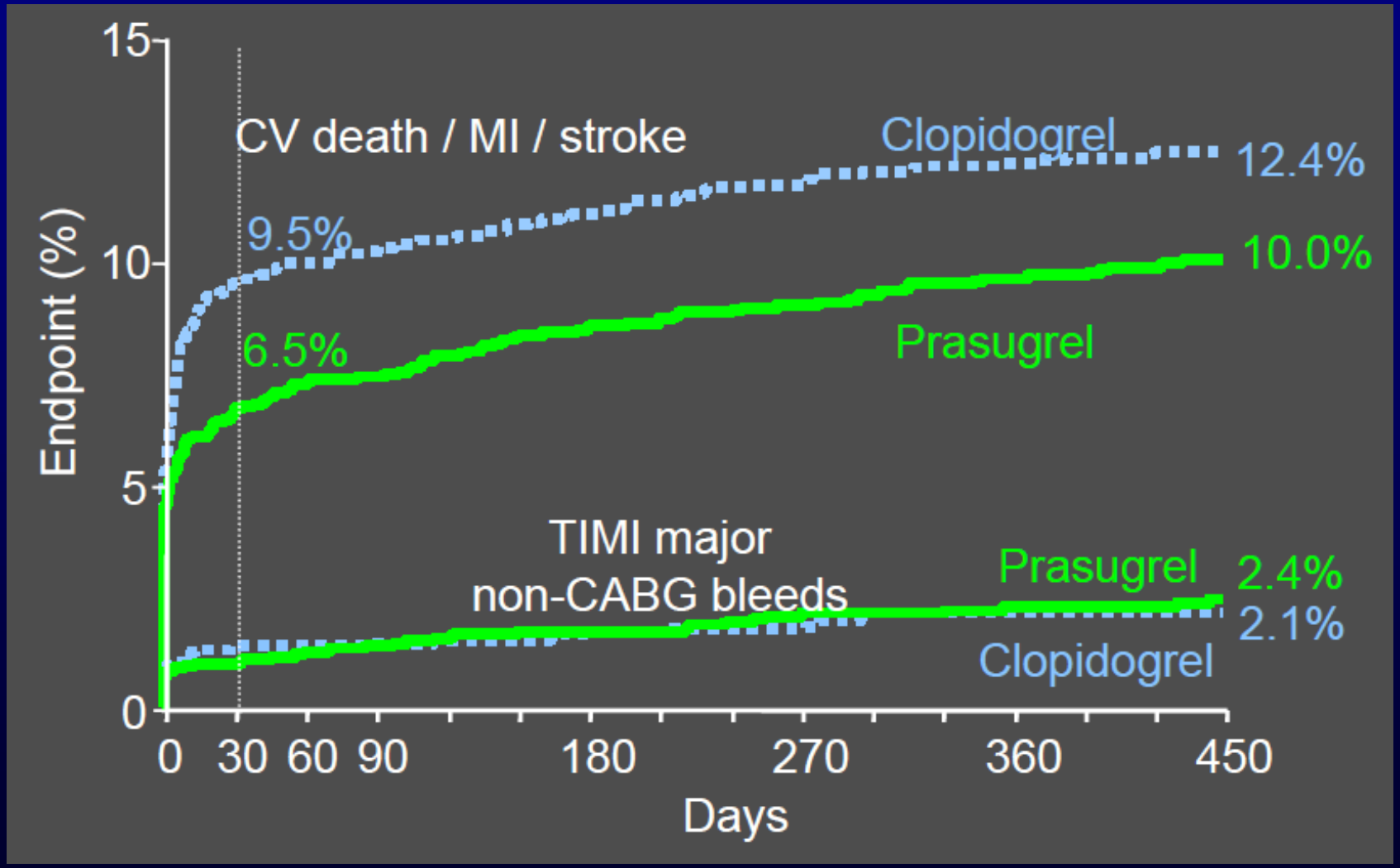
Safety Profile of Prasugrel in STEMI vs UN/NSTEMI



Wiviott SD, Braunwald E, McCabe CH et al NEJM2007

TRITON TIMI-38

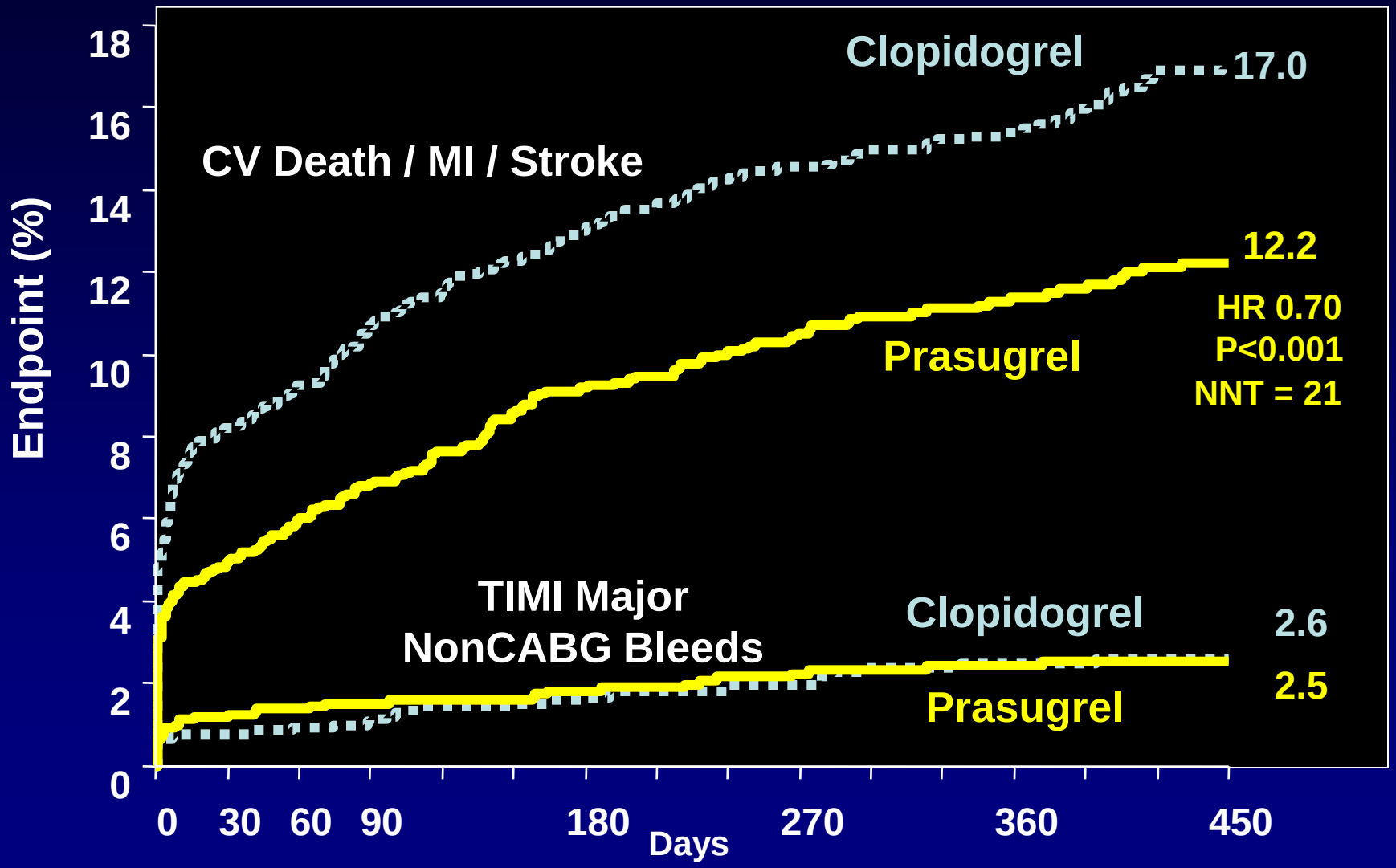
Net Clinical Benefit in STEMI



Montalescot G et al. Lancet 2009

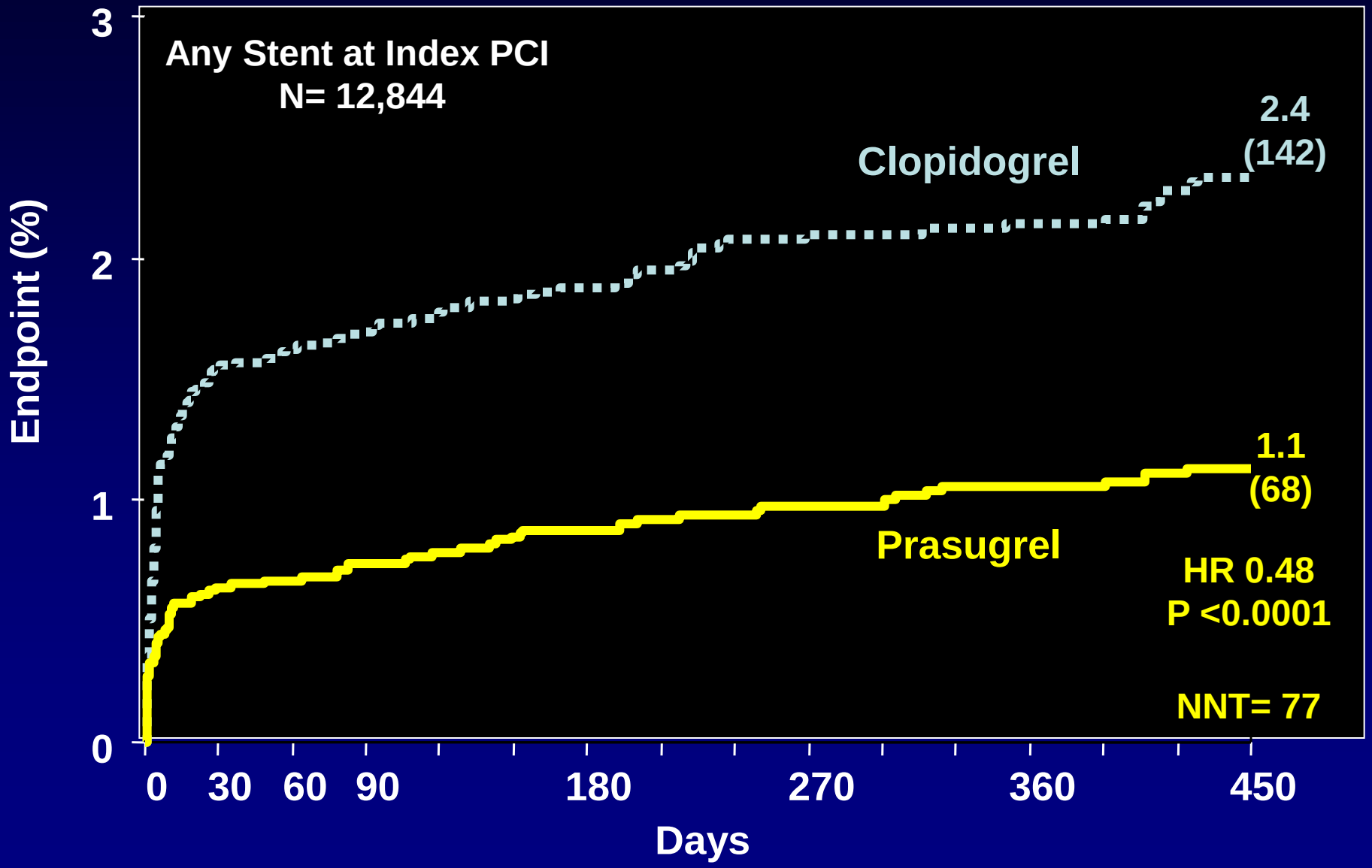
Diabetic Subgroup

N=3146



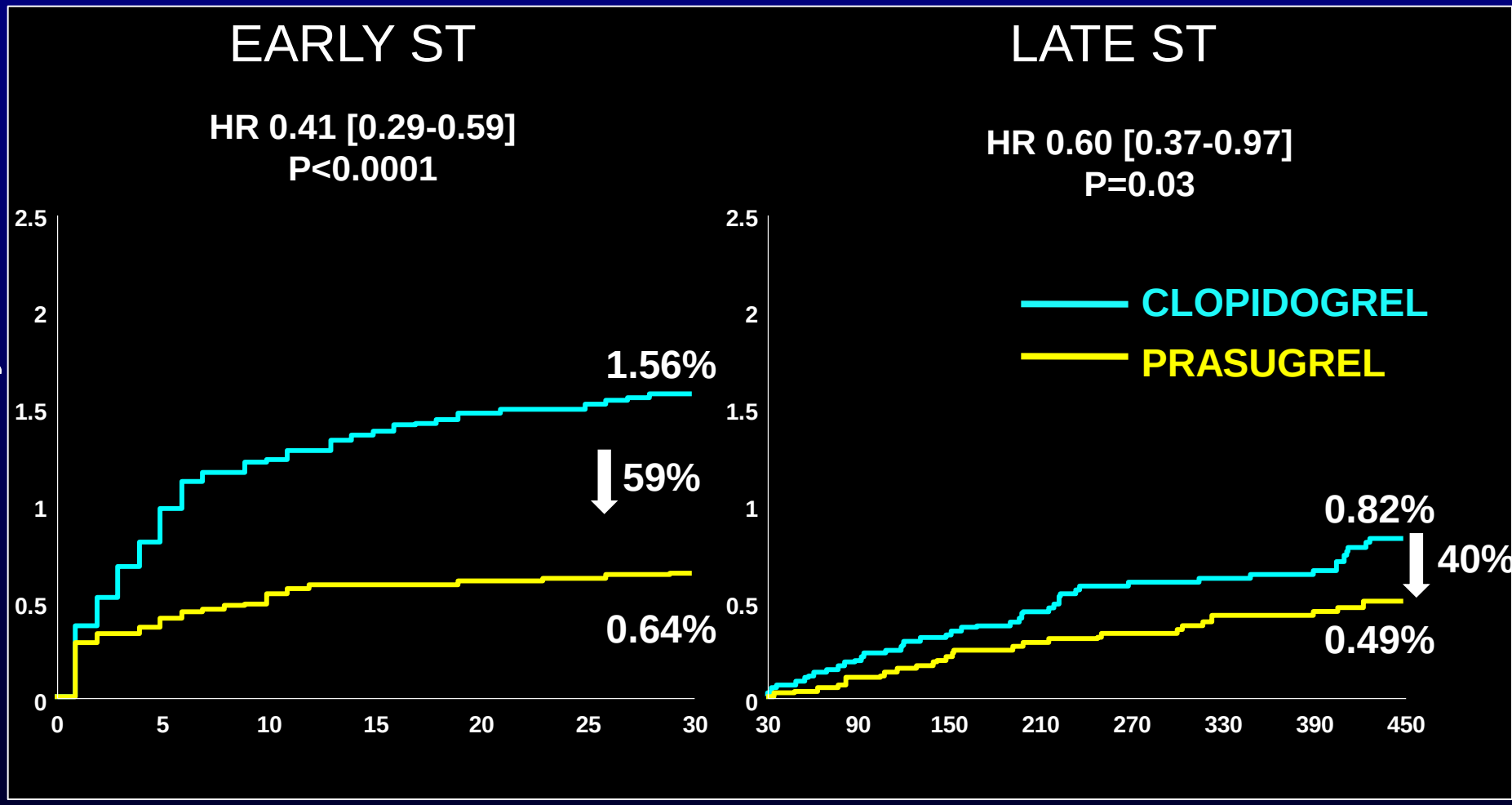
Wiviott et al NEJM 2007

Stent Thrombosis
(Definite + Probable)



TRITON TIMI·38
STENT ANALYSIS

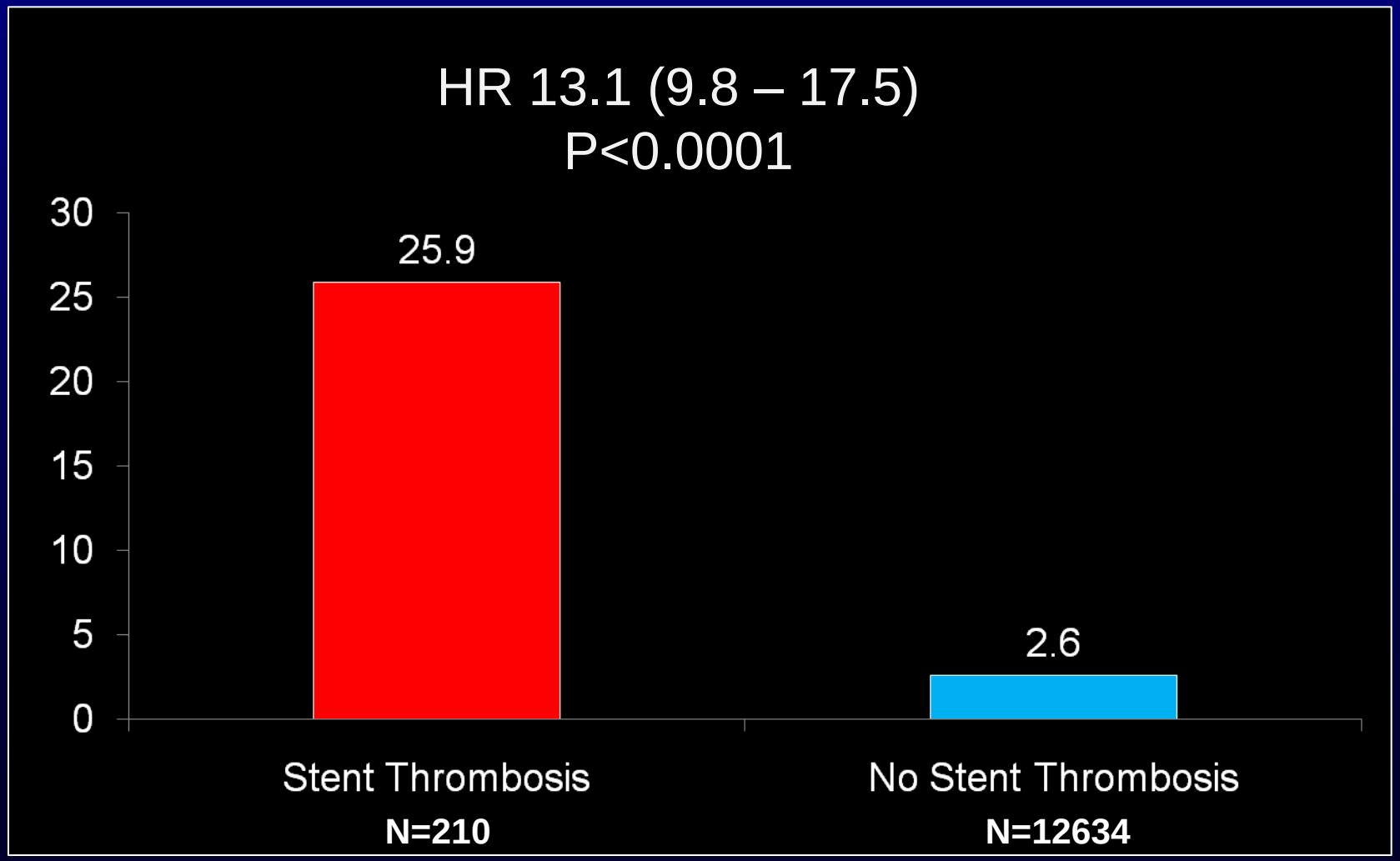
Definite/Probable ST: Any Stent (N=12844)



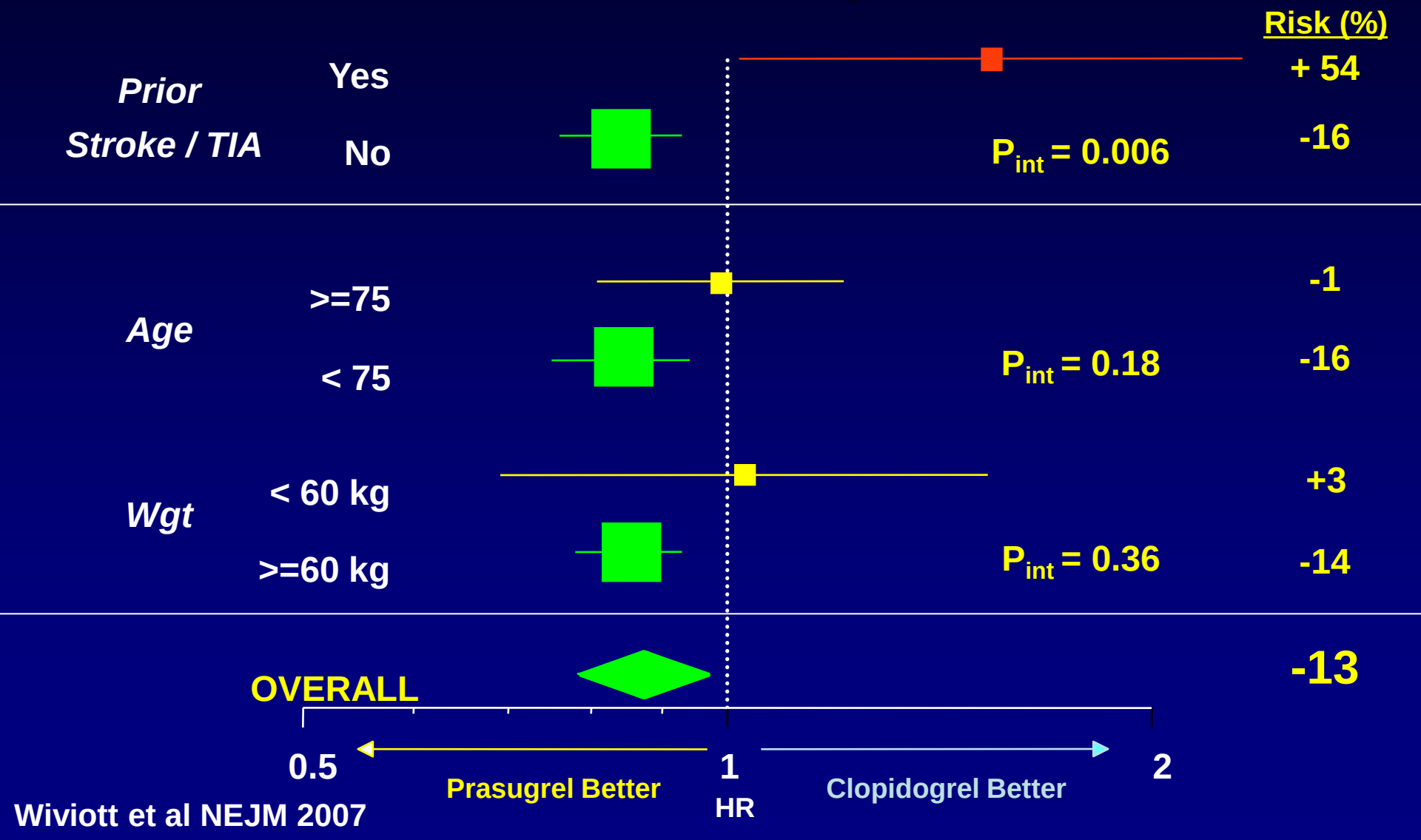
TRÎTON TIMI·38
STENT ANALYSIS

Death Following ST

Mortality During Follow up (%) Post-Stent Thrombosis

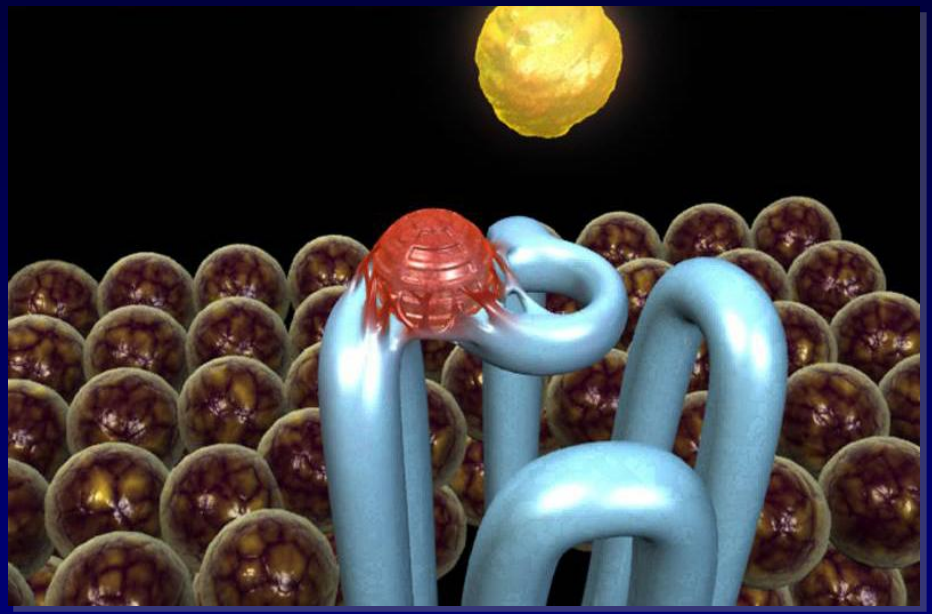


Net Clinical Benefit
Bleeding Risk Subgroups
Post-hoc analysis

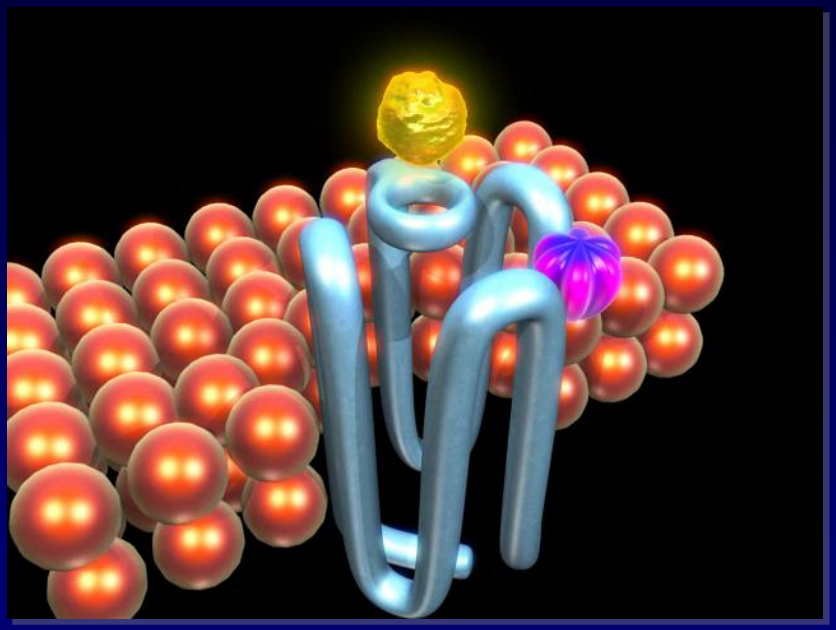


Wiviott et al NEJM 2007

Irreversible inhibition - Thienopyridines



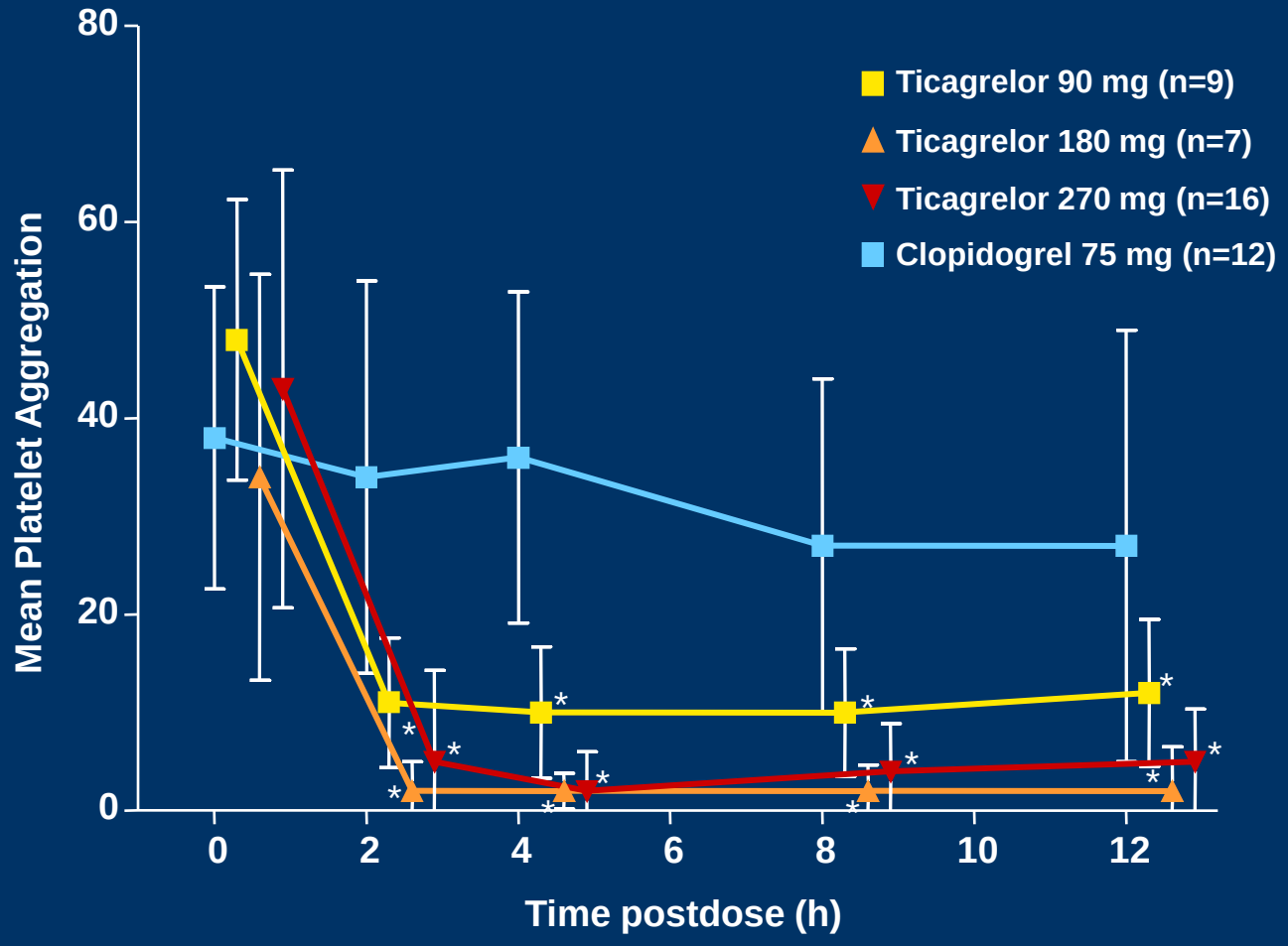
Reversible inhibition – Ticagrelor



- **Thienopyridines act by binding covalently to the P2Y12 receptor, causing a structural change, and rendering the receptors permanently inactivated**

P Savi, et al. Proc Natl Acad Sci USA 2006; 103:11069-11074.

DISPERSE-2 PK/PD Substudy:
Suppression of Platelet Aggregation in Clopidogrel-Pretreated Patients (N=44)



*P<0.05 for AZD6140 vs clopidogrel.

Storey RF et al. *J Am Coll Cardiol*. 2007;50:1852-1856.

PLATO study design

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

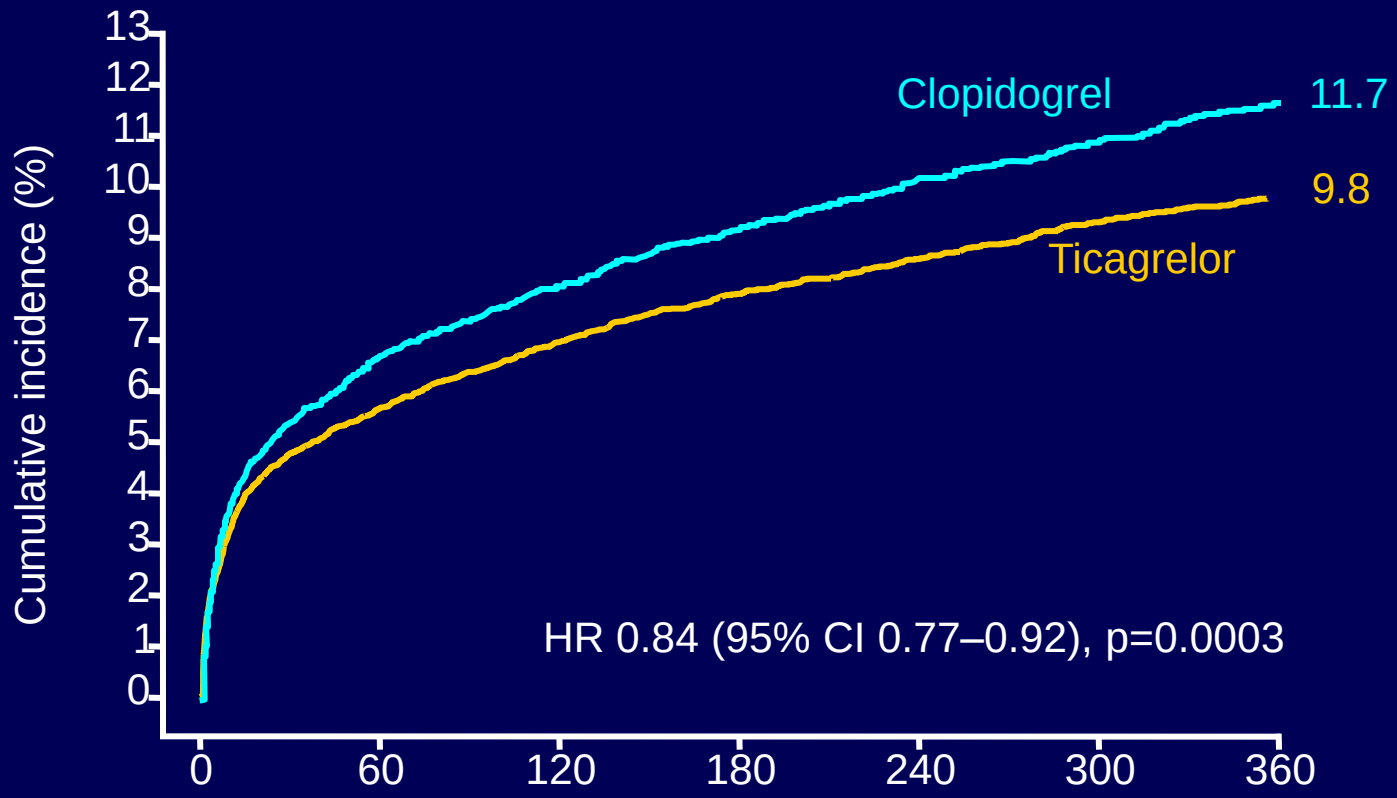
6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack

K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

PLATO



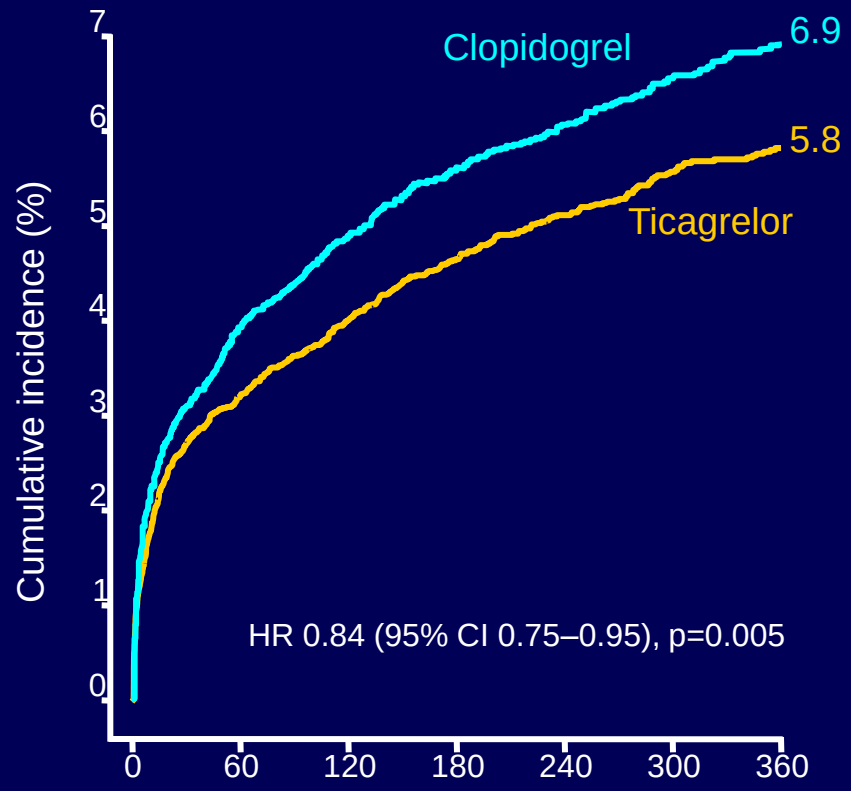
No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Secondary efficacy endpoints over time

PLATO

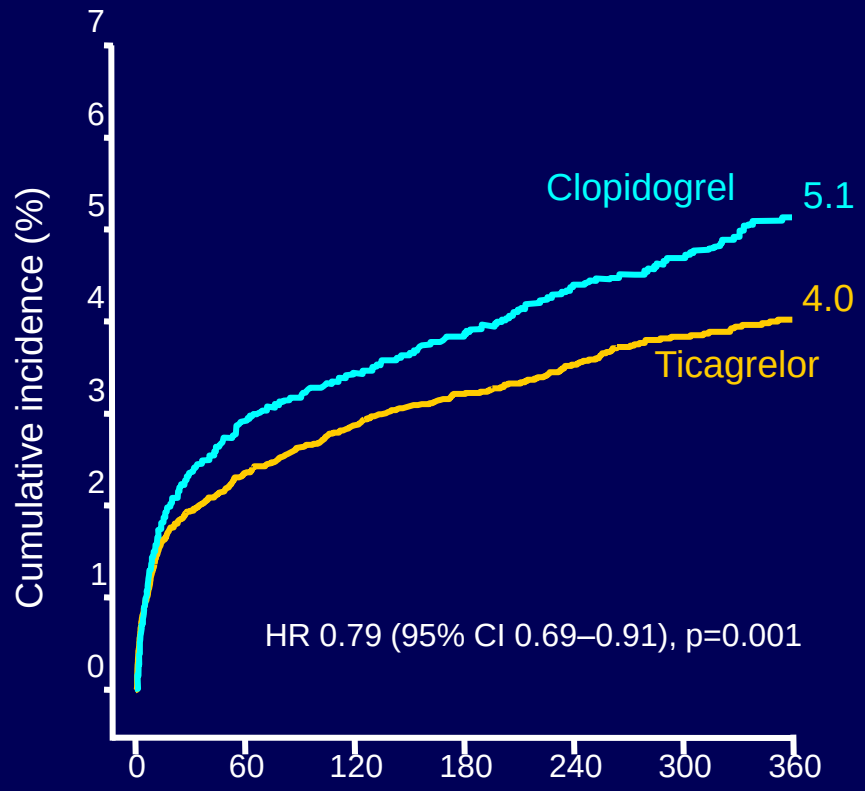
Myocardial infarction



No. at risk

Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

Cardiovascular death



	9,333	8,294	8,822	8,626	7119	5,482	4,419
	9,291	8,865	8,780	8,589	7079	5,441	4,364

Stent thrombosis

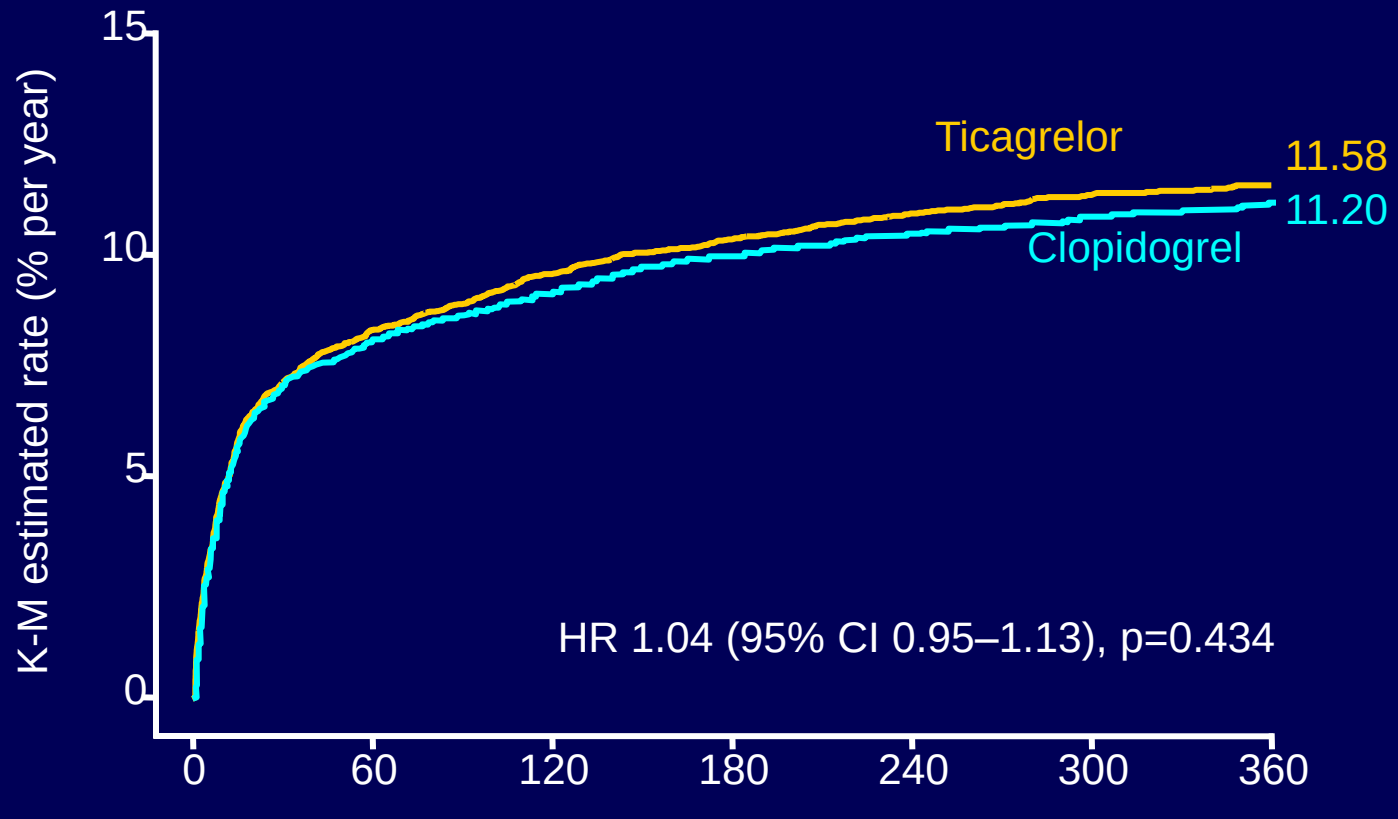
(evaluated in patients with any stent during the study)

	Ticagrelor (n=5,640)	Clopidogrel (n=5,649)	HR (95% CI)	p value
Stent thrombosis, n (%)				
Definite	71 (1.3)	106 (1.9)	0.67 (0.50–0.91)	0.009
Probable or definite	118 (2.1)	158 (2.8)	0.75 (0.59–0.95)	0.02
Possible, probable, definite	155 (2.8)	202 (3.6)	0.77 (0.62–0.95)	0.01

*Time-at-risk is calculated from first stent insertion in the study or date of randomisation

Time to major bleeding – primary safety event

PLATO



No. at risk							
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

Holter monitoring & Bradycardia related events

PLATO

Holter monitoring at first week	Ticagrelor (n=1,451)	Clopidogrel (n=1,415)	p value
Ventricular pauses ≥3 seconds, %	5.8	3.6	0.01
Ventricular pauses ≥5 seconds, %	2.0	1.2	0.10

Holter monitoring at 30 days	Ticagrelor (n= 985)	Clopidogrel (n=1,006)	p value
Ventricular pauses ≥3 seconds, %	2.1	1.7	0.52
Ventricular pauses ≥5 seconds, %	0.8	0.6	0.60

Bradycardia-related event, %	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value
Pacemaker Insertion	0.9	0.9	0.87
Syncope	1.1	0.8	0.08
Bradycardia	4.4	4.0	0.21
Heart block	0.7	0.7	1.00

Other findings

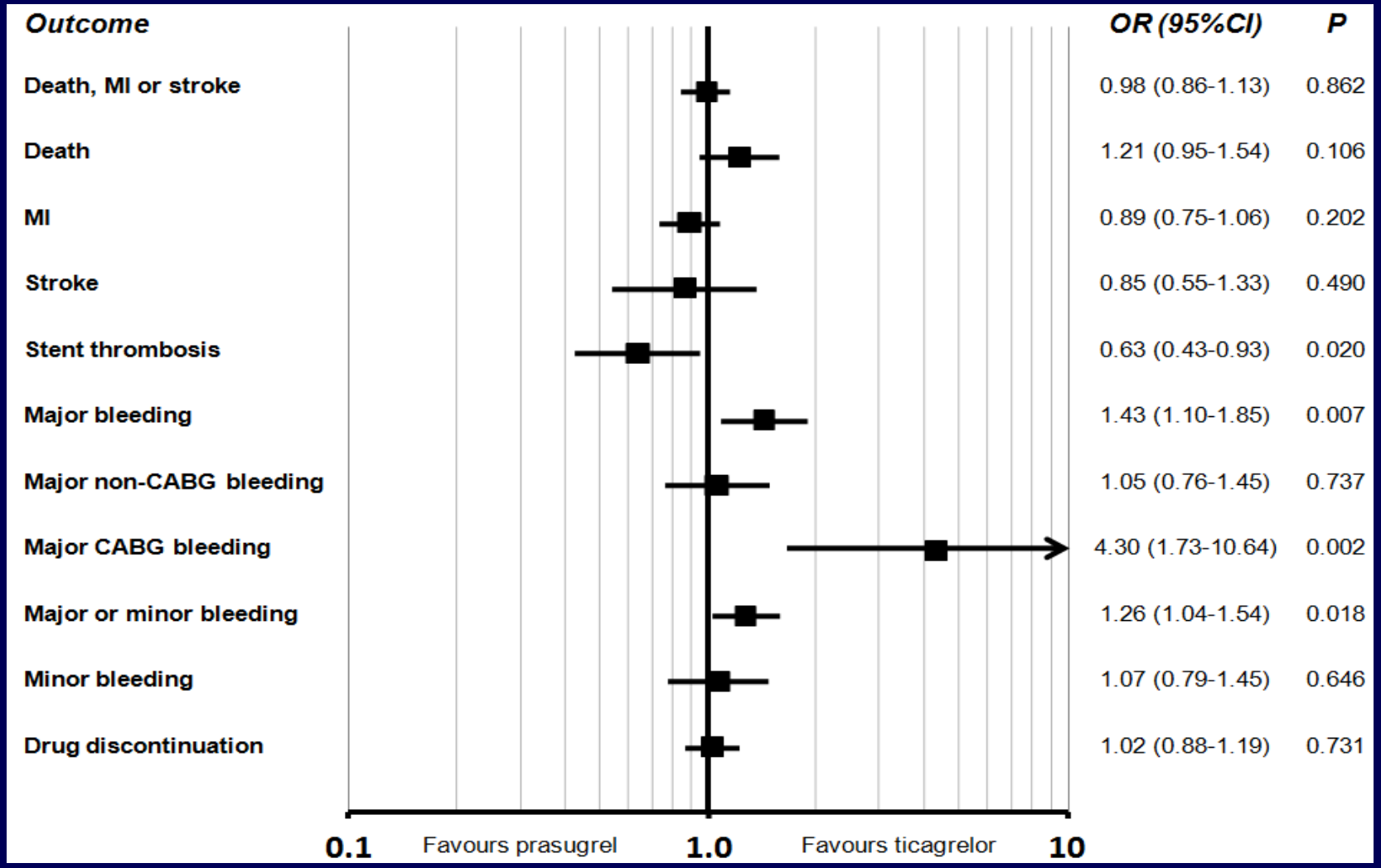
All patients	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value*
Dyspnoea, %			
Any	13.8	7.8	<0.001
With discontinuation of study treatment	0.9	0.1	<0.001
Neoplasms arising during treatment, %			
Any	1.4	1.7	0.17
Malignant	1.2	1.3	0.69
Benign	0.2	0.4	0.02

*p values were calculated using Fischer's exact test

Conclusions

- Reversible, more intense $P2Y_{12}$ receptor inhibition for one year with ticagrelor in comparison with clopidogrel in a broad population with ST- and non-ST-elevation ACS provides
  - Reduction in myocardial infarction and stent thrombosis
  - Reduction in cardiovascular and total mortality
  - No change in the overall risk of major bleeding

Indirect comparison Prasugrel vs. Ticagrelor



Funnel plots comparing prasugrel vs. ticagrelor for the risk of key clinical events. Odds ratios (OR) <1.0 favor prasugrel, whereas odds ratios>1.0 favor ticagrelor.

Zoccai GB. EuroPCR 2010

European Heart Journal (2010) **31**, 2501–2555
doi:10.1093/eurheartj/ehq277

ESC/EACTS GUIDELINES

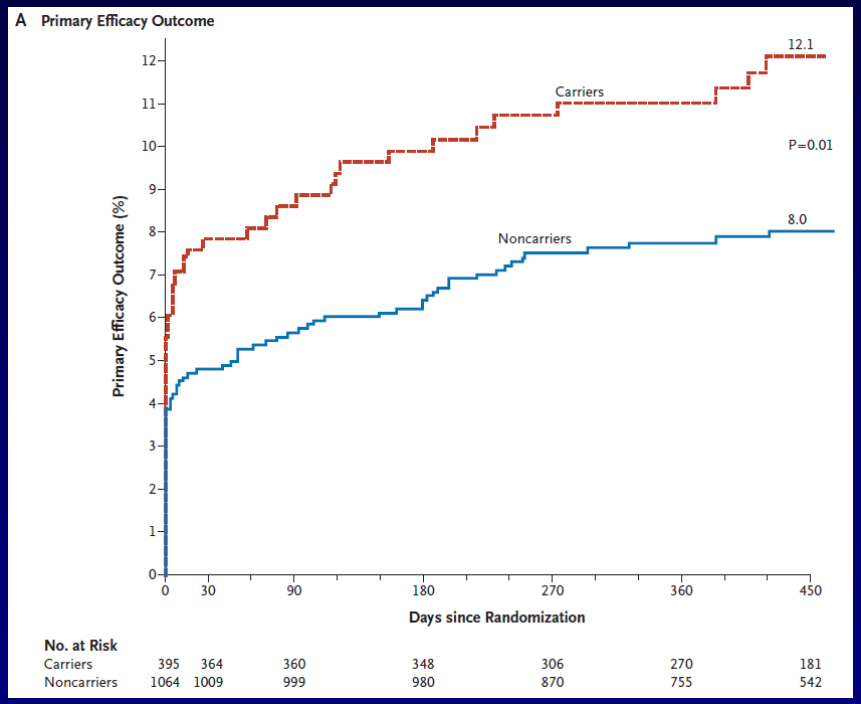
Guidelines on myocardial revascularization

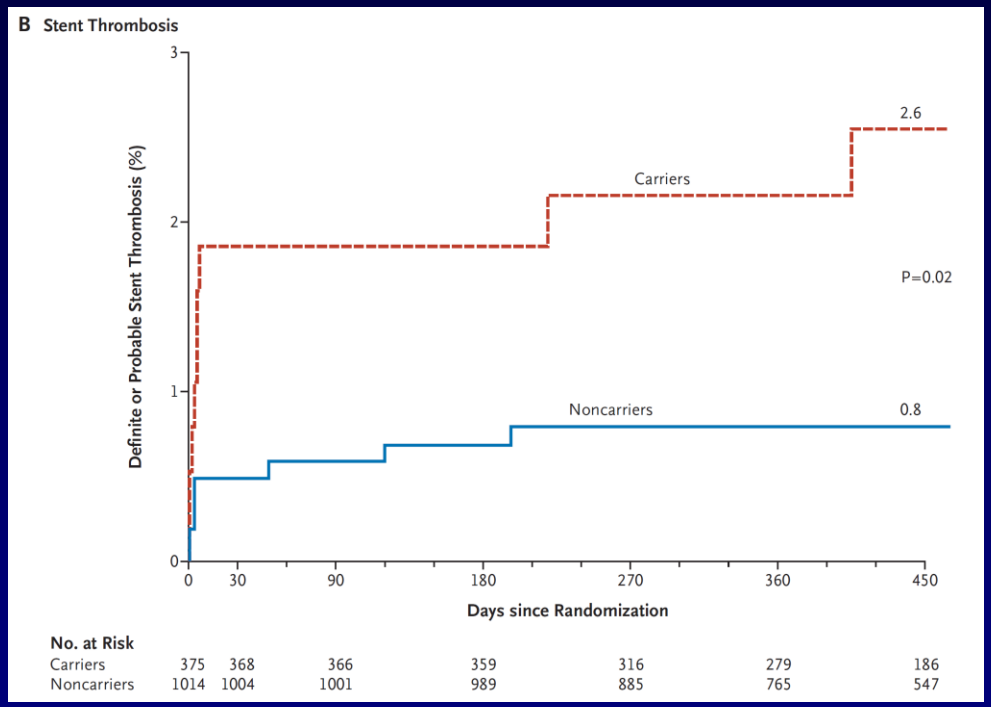
The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

NSTE-ACS			
Antiplatelet therapy			
	ASA	I	C
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Clopidogrel (for 9–12 months after PCI)	I	B
	Prasugrel[d]	IIa	B
	Ticagrelor[d]	I	B

STEMI			
Antiplatelet therapy			
	ASA	I	B
	Clopidogrel[f] (with 600 mg loading dose as soon as possible)	I	C
	Prasugrel[d]	I	B
	Ticagrelor[d]	I	B

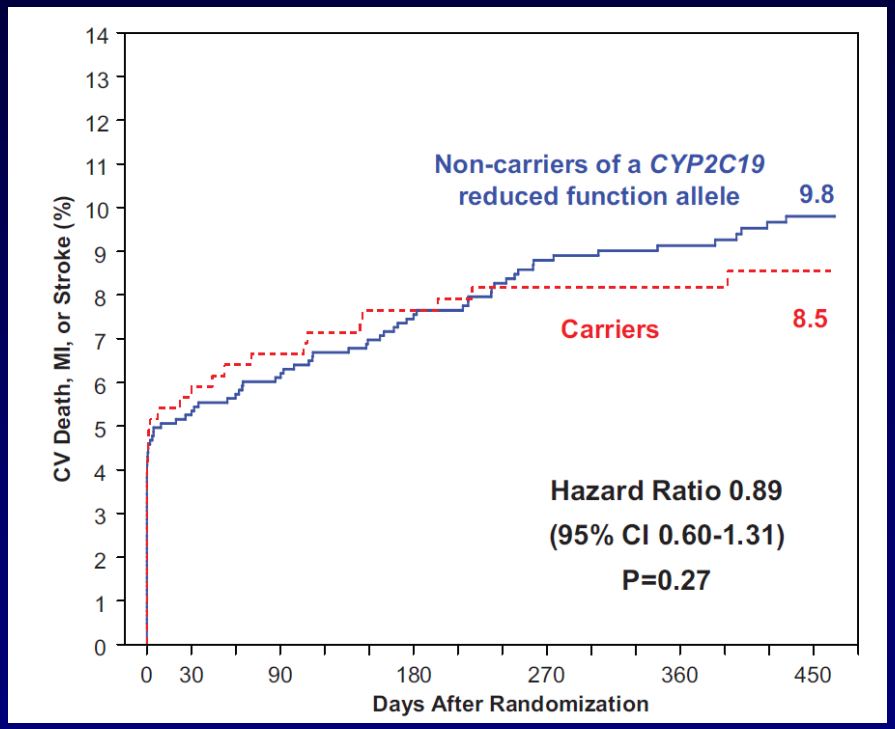
CYP2C19 Polymorphism and Response to Clopidogrel

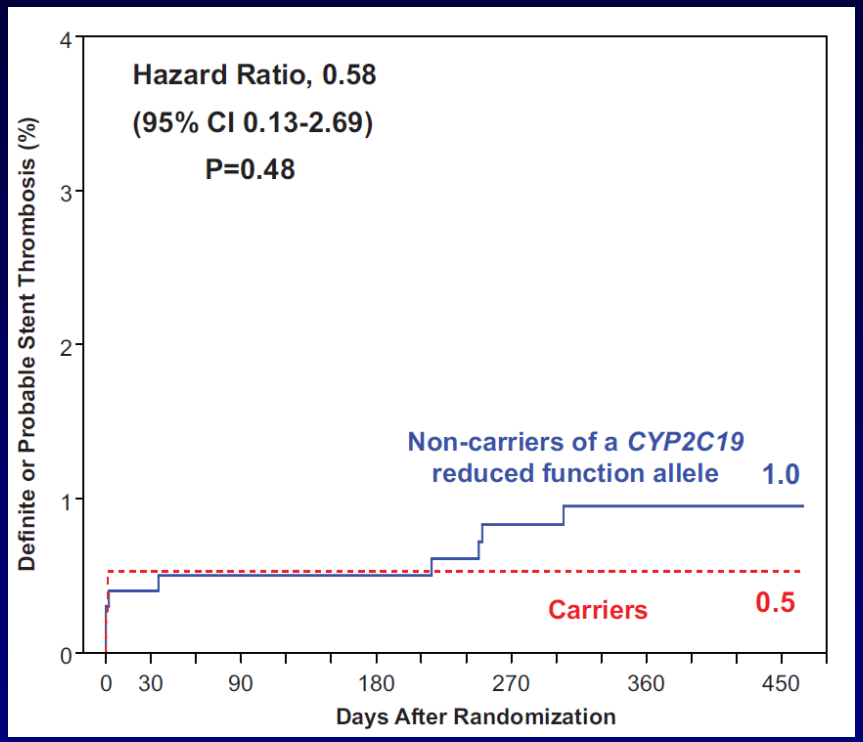




Mega et al. *N Engl J Med* 2009;360:354-62.

CYP2C19 Polymorphism and Response to Prasugrel

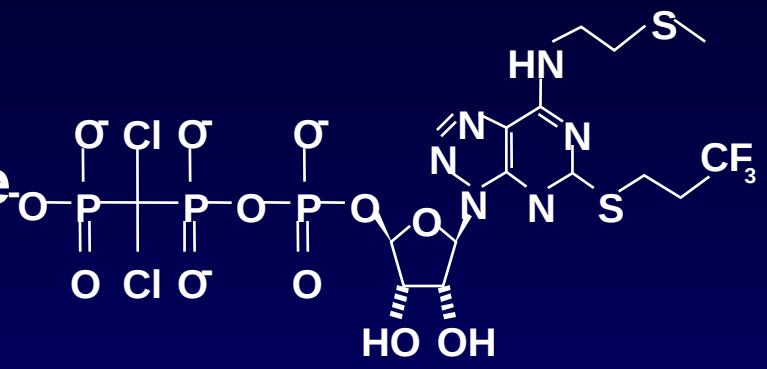




Mega et al. *Circulation*. 2009;119:2553-2560

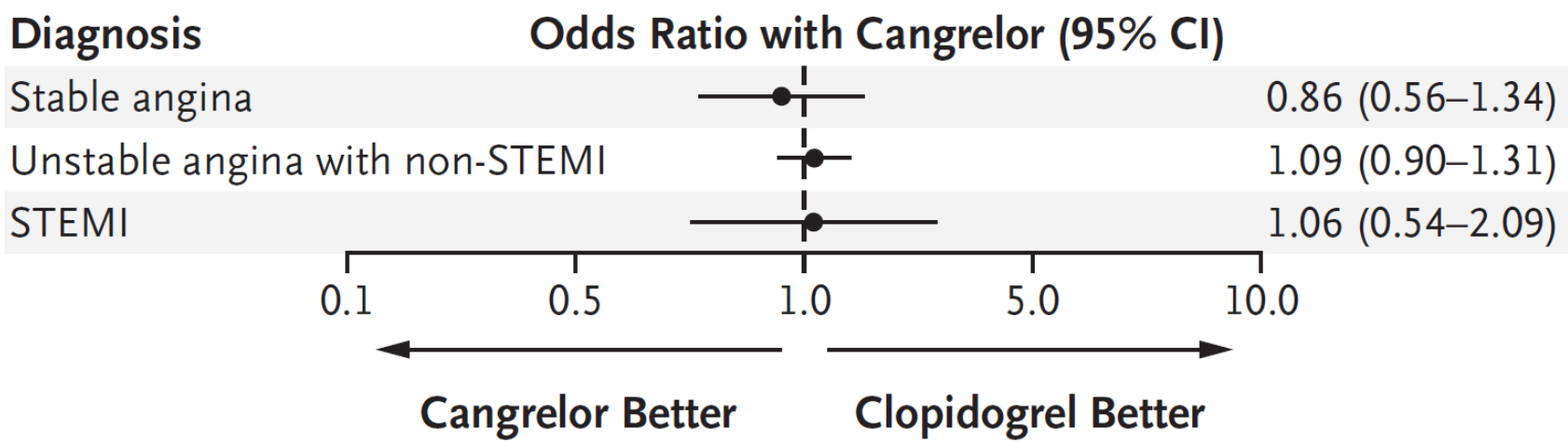
Cangrelor (AR-C69931MX)

- **Parenteral** ADP-$P2Y_{12}$ receptor antagonist
- ATP analogue



- **Direct** and **Reversible** $P2Y_{12}$ inhibitor
- **More potent** than clopidogrel ~90% inhibition of platelet aggregation at 1 - 4 mcg/kg/min iv
- Plasma half-life of 5-9 min.; 20 min. for return to normal platelet function

CHAMPION Trial: Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition PCI



Harrington et al. *N Engl J Med* 2009;361:2318-29.

INNOVATE PCI: treatment with oral and intravenous *Elinogrel* in setting of non-urgent PCI

- Second phase trial
- Evaluation of clinical effectiveness, safety and tolerability

Rao et al. *ESC Congress* 2010

ANTIAGREGANTS

IN ACUTE CORONARY SYNDROME

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