



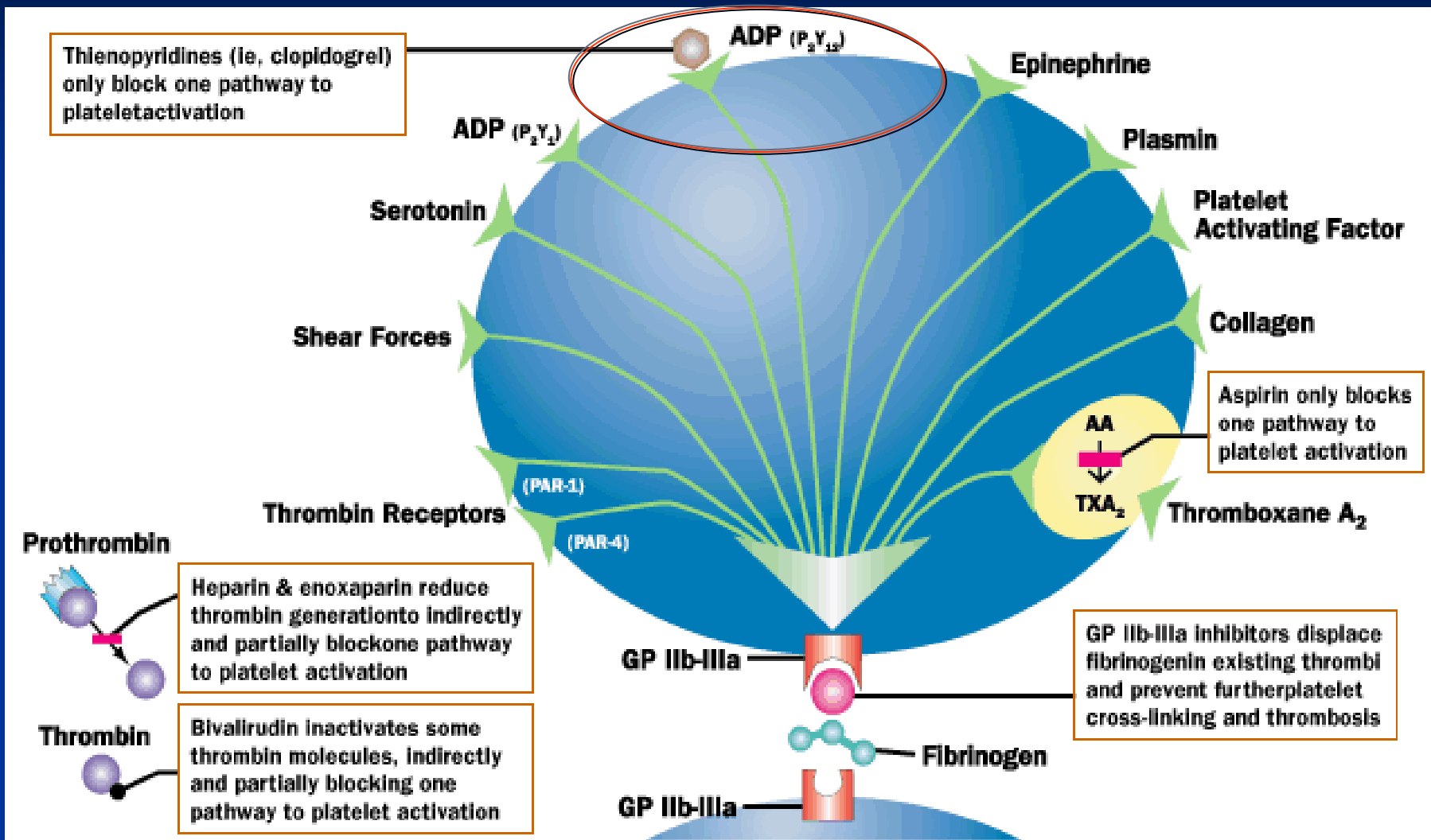
מרכז רפואי רבין
Rabin Medical Center



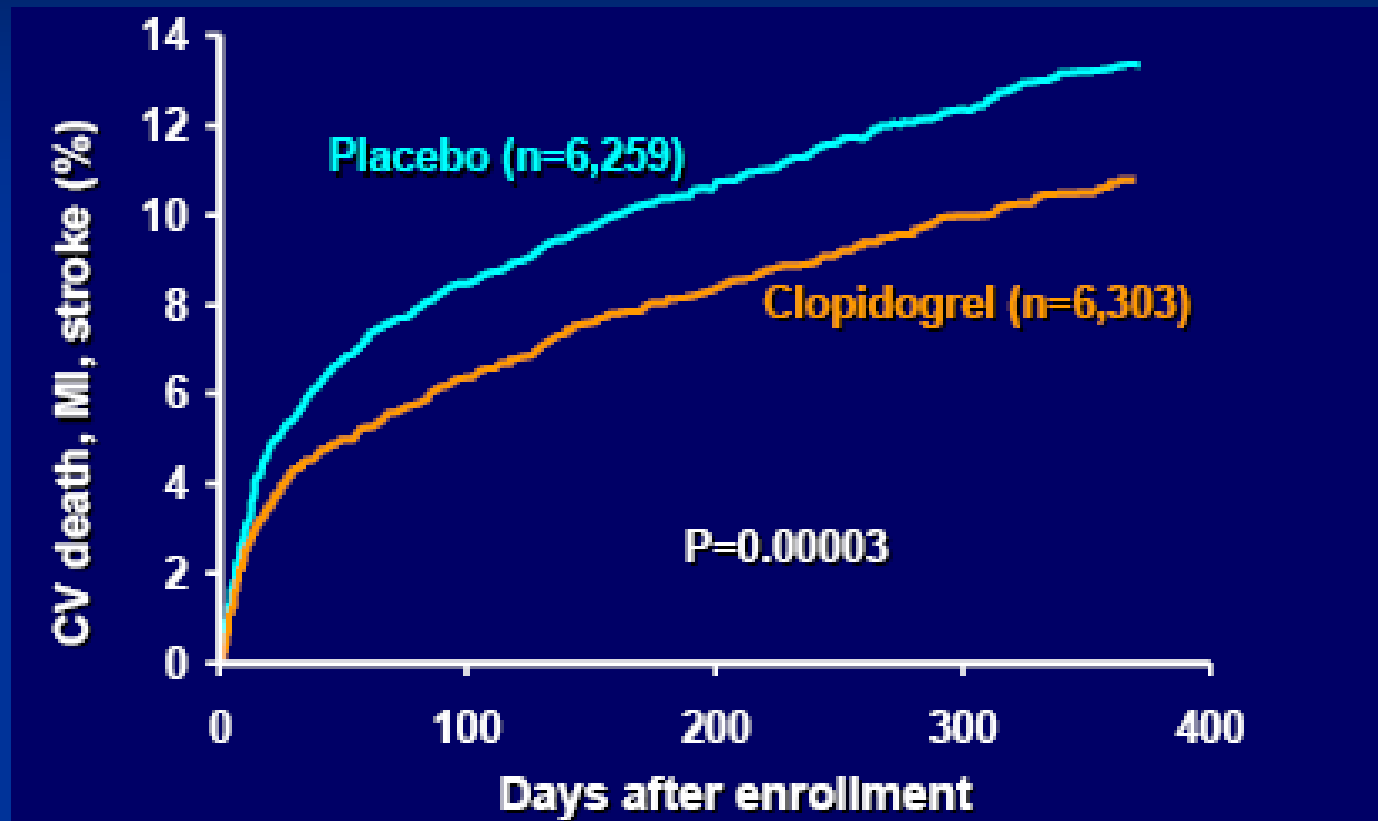
תרופות מעכבות טסיות חדשות

ד"ר אלי לב
מנהל שרות הצנתורים
בי"ח השרון
מרכז רפואי רבין

1. Why should clopidogrel be replaced ?
2. Prasugrel
3. Ticagrelor
4. Conclusions



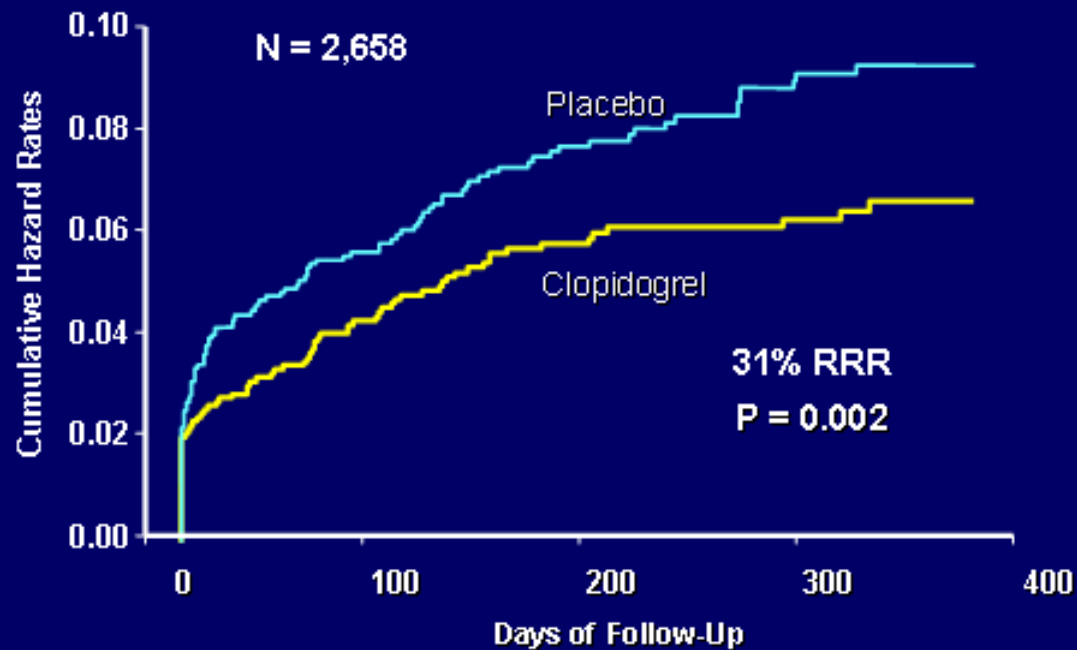
CURE TRIAL – ACS pts



20 % reduction in primary endpoint (N Engl J Med. 2001;345:494-502)

PCI-CURE TRIAL – ACS pts

PCI-CURE Overall Results

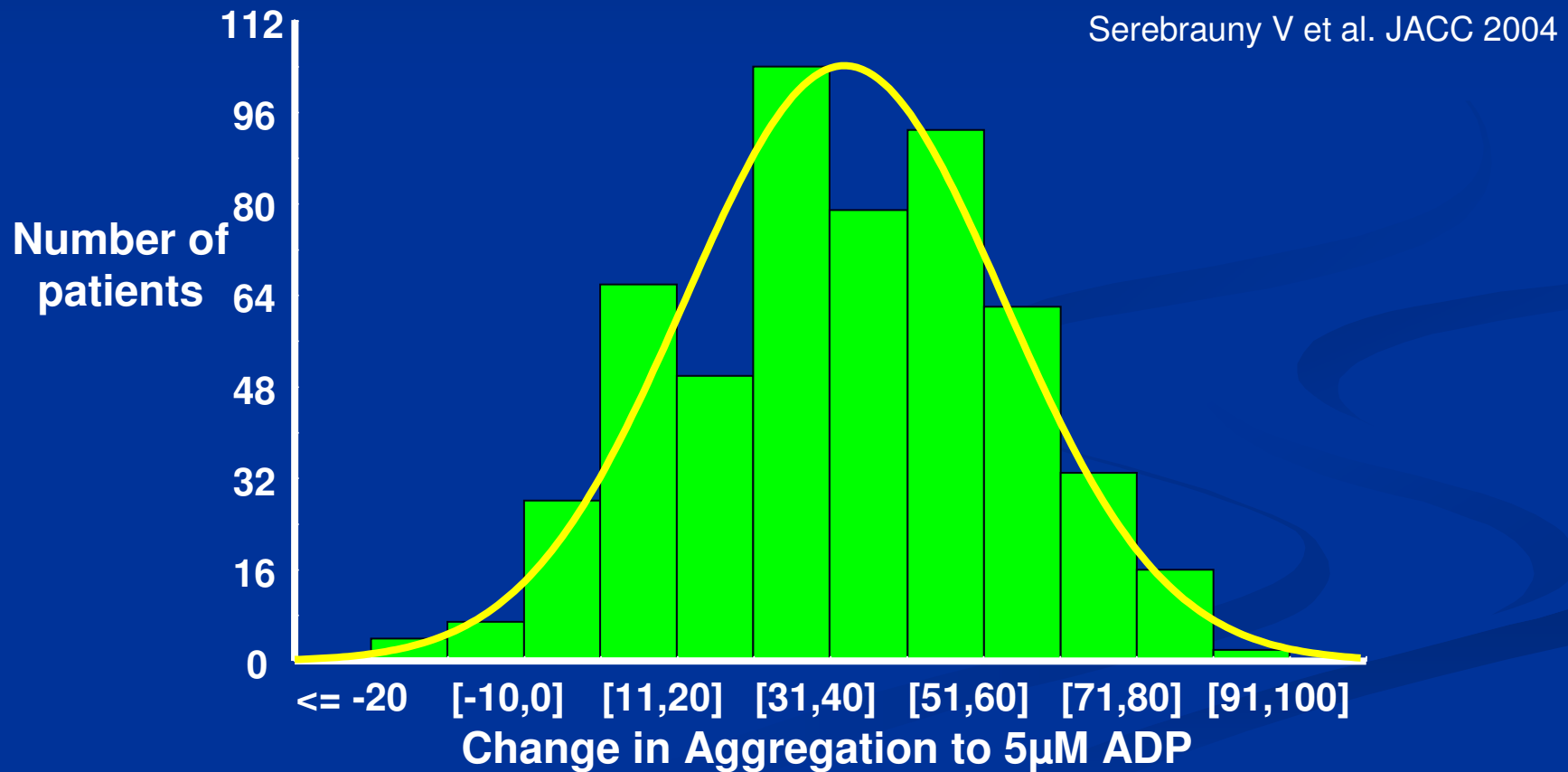


The CURE Investigators. *Lancet* August 2001

UK

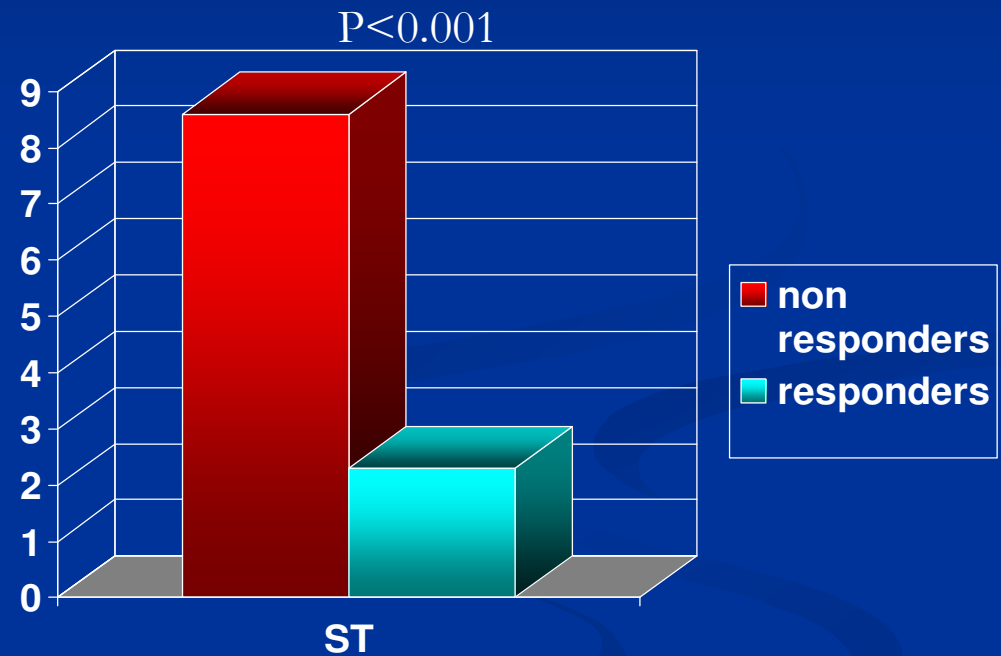
Pretreatment with clopidogrel vs. no pretreatment
Reduction in CV death, MI or urgent TVR
CURE Investigators, Lancet 2001 358: 527-33

Distribution of Response to Clopidogrel (544 patients, platelet aggregation)



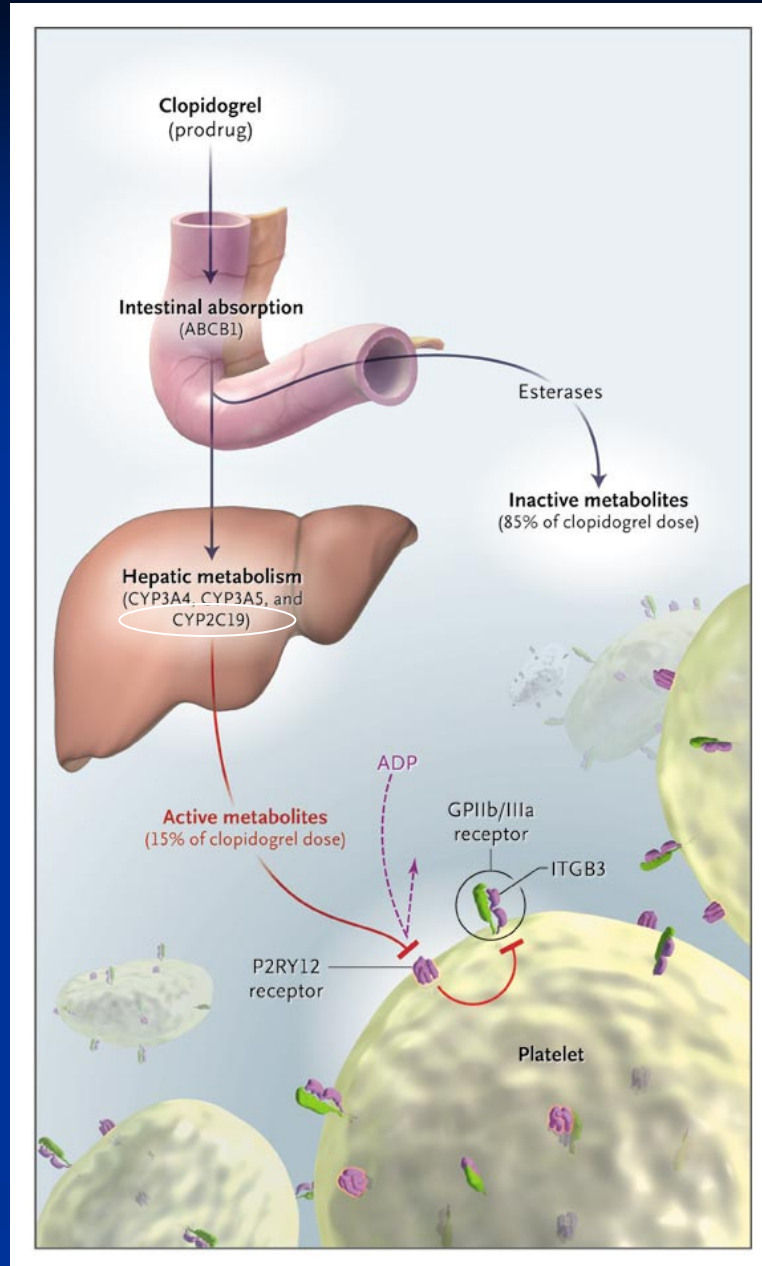
Impact of Clopidogrel Response on Stent Thrombosis

- 804 pts who had successful PCI with DES implantation
- Loaded with 600 mg clopidogrel, platelet reactivity to ADP assessed 12-18 hrs after loading
- 105 pts (13%) not responsive to clopidogrel
- **ST incidence: 8.6% vs. 2.3% (non responders vs responders)**



Buonamici et al , JACC 2007

Clopidogrel metabolism



Efficacy of clopidogrel is hampered by:

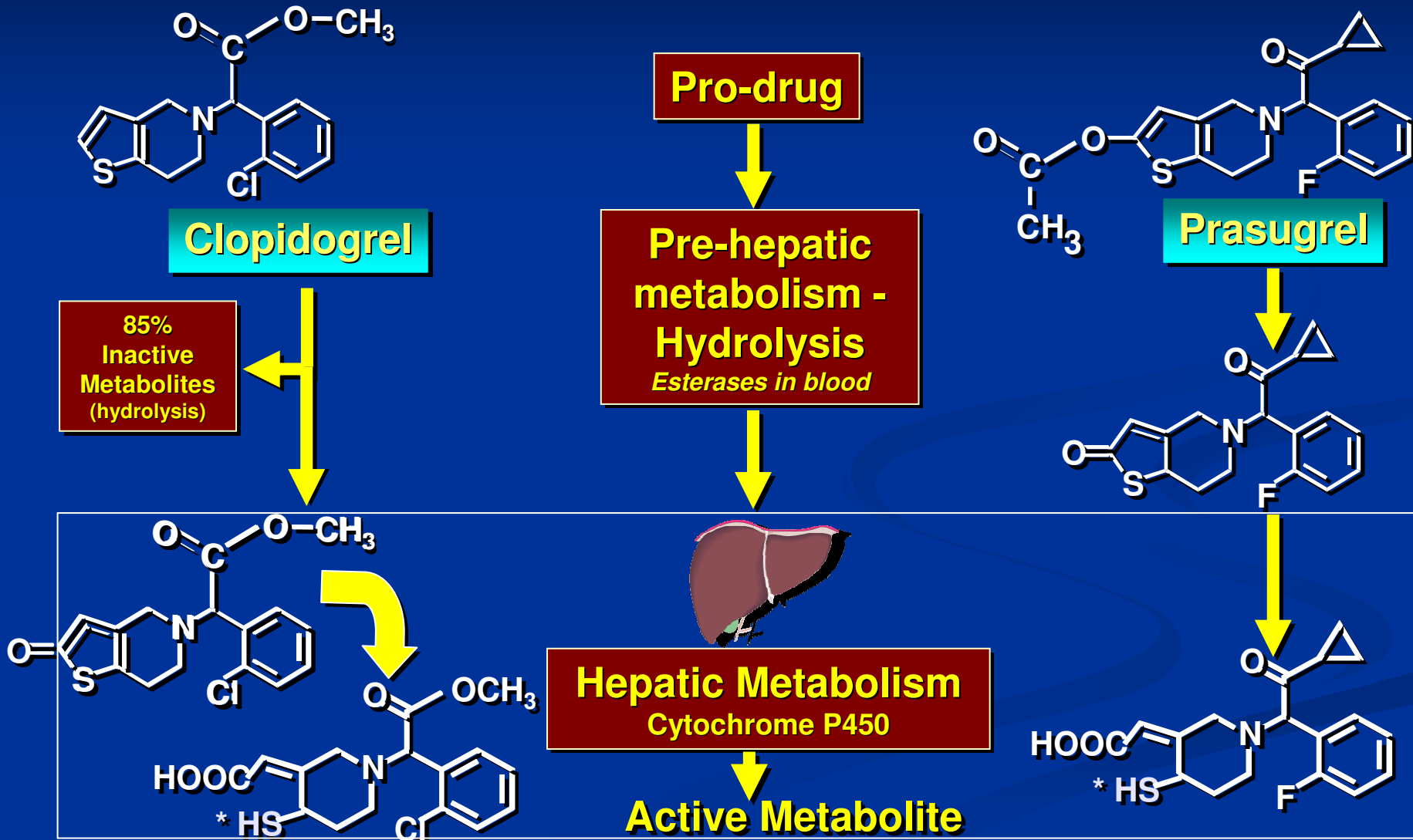
- Wide variability in response (variable platelet inhibition)
- Risk of stent thrombosis and MI in poor responders
- Slow and variable transformation to the active metabolite → interaction with other drugs –PPIs, genetic polymorphisms (about 25-30% carriers)
- Slow onset of action, long withdrawal - Platelet inhibition effect of 600 mg bolus after ~2-4 hrs, of 300 mg bolus after ~4-6 hrs

PRASUGREL (Effient)

- Thienopyridine (3rd generation) – P2Y₁₂ receptor inhibitor
- Prodrug (similar to clopidogrel and ticlopidine) – requires metabolism to form active metabolite
- Pharmacodynamic advantages:
 - Increased IPA
 - Rapid onset of IPA activity (0.5-1 hour after 60 mg loading)
 - More consistent IPA response (less inter-patient variability)
 - Drug response not affected by CYP2C19 polymorphisms (Mega et al, Circulation 2009) nor by ABCB1 polymorphisms (Mega et al, Lancet 2010)

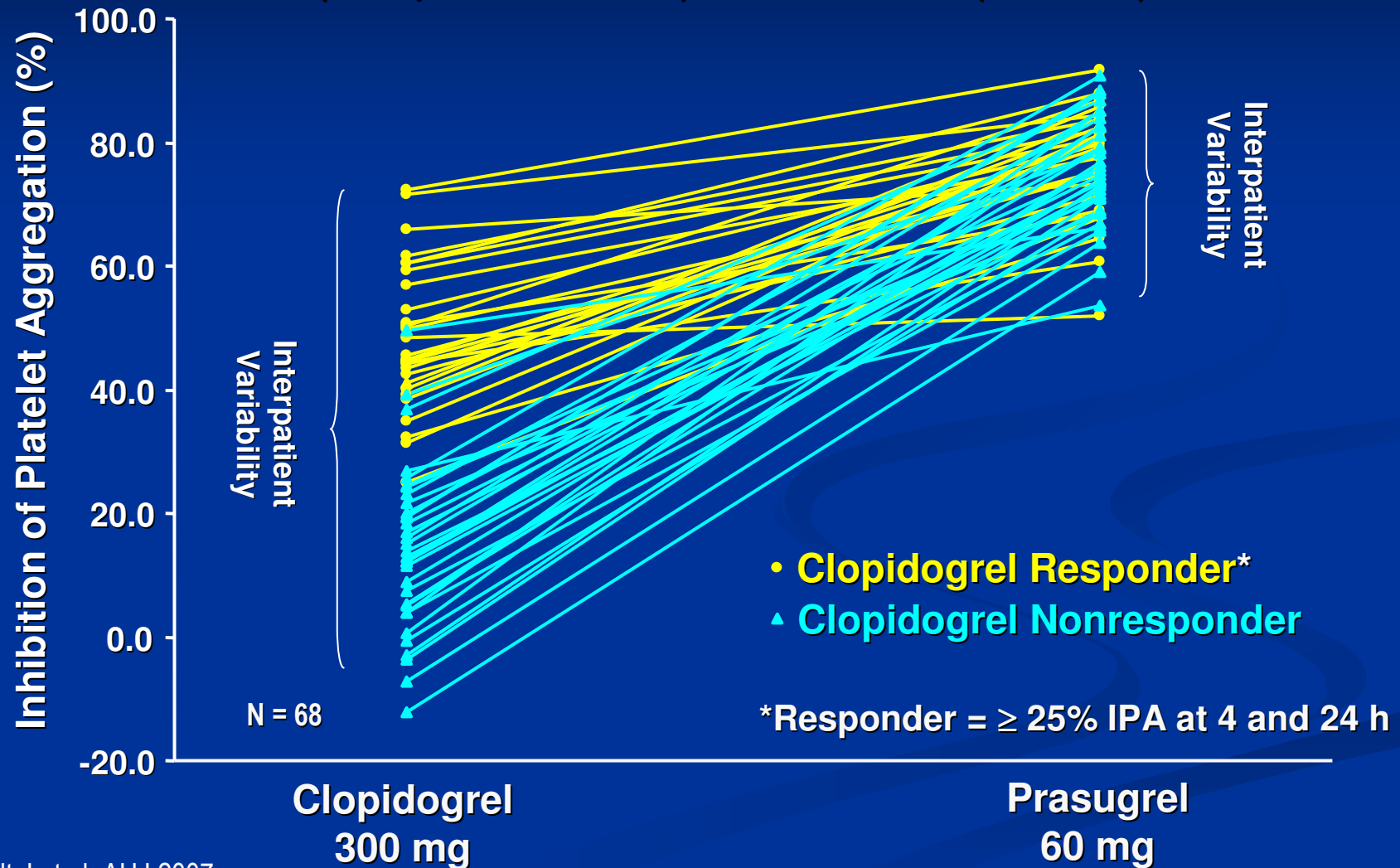
Prasugrel: Active Metabolite Formation Faster Onset of IPA

Sem Vasc Med 3:113, 2003

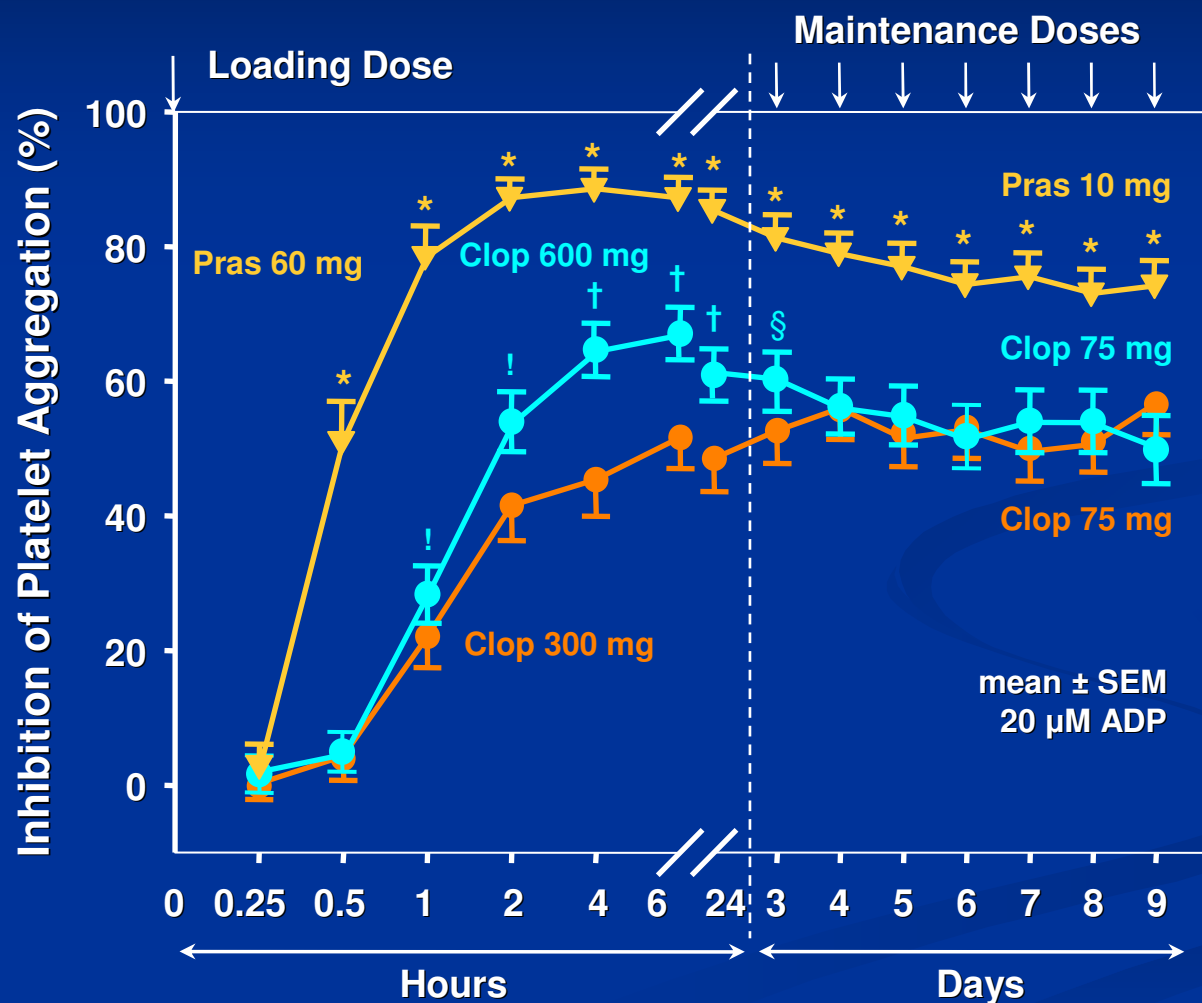


Healthy Volunteer Crossover Study

IPA (20 μ M ADP) at 24 H (n=68)



Prasugrel 10 mg MD vs. Clopidogrel 75 mg MD: Higher IPA During Maintenance Dosing



* $P < 0.001$ vs. Clop 300 mg or 600 mg LD
 † $P < 0.001$ vs. Clop 300
 ‡ $P < 0.05$ vs. Clop 300
 § $P < 0.05$ vs. Clop 300/75

TRITON TIMI-38 Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA ↓ n=13,500

Double-blind

CLOPIDOGREL
300 mg LD / 75 mg MD

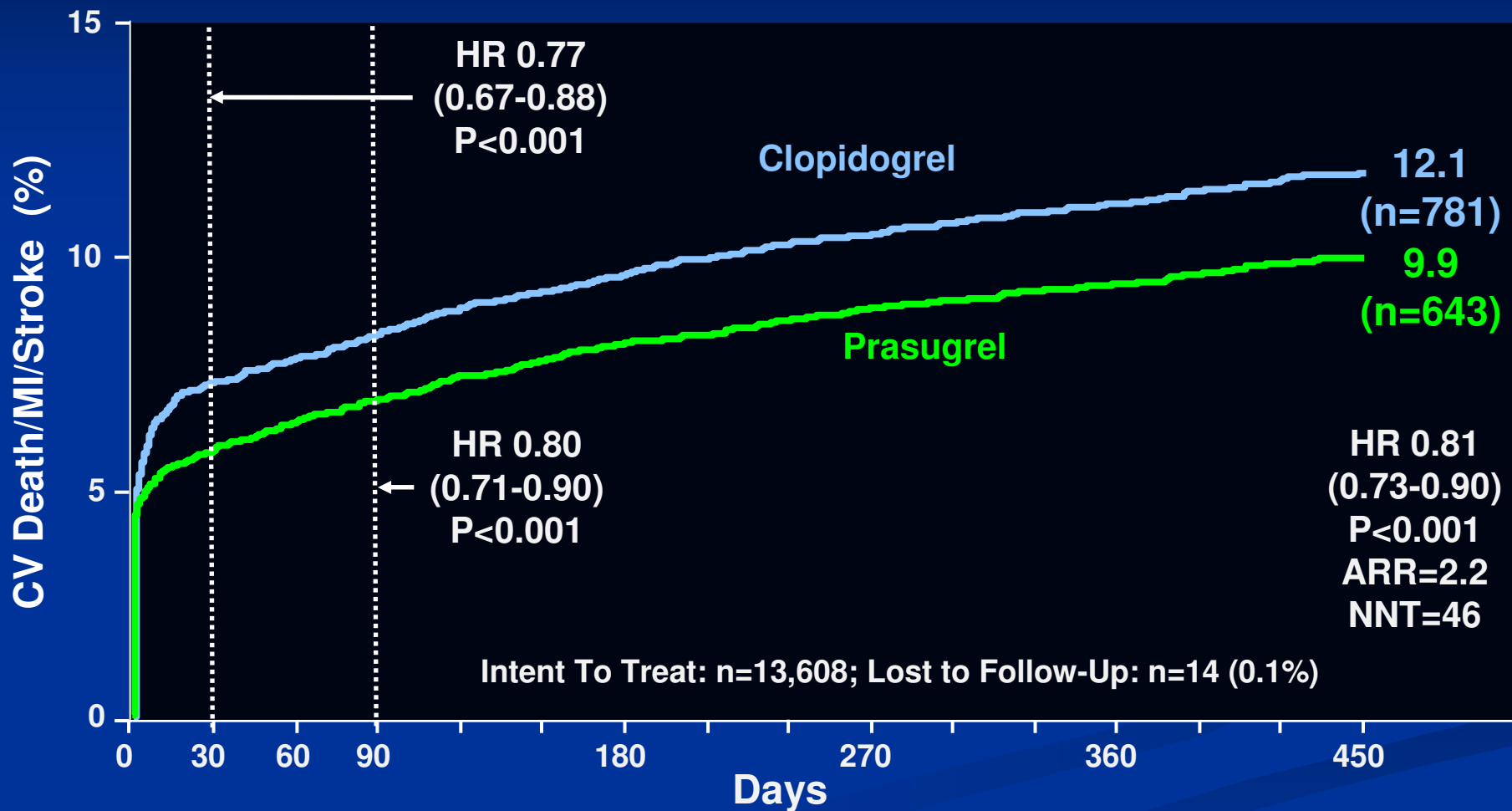
PRASUGREL
60 mg LD / 10 mg MD

Median duration of therapy: 12 months

1° endpoint: CV death, MI, Stroke

2° endpoints: CV death, MI, Stroke, Rehosp-Recurrent Ischemia
CV death, MI, UTVR

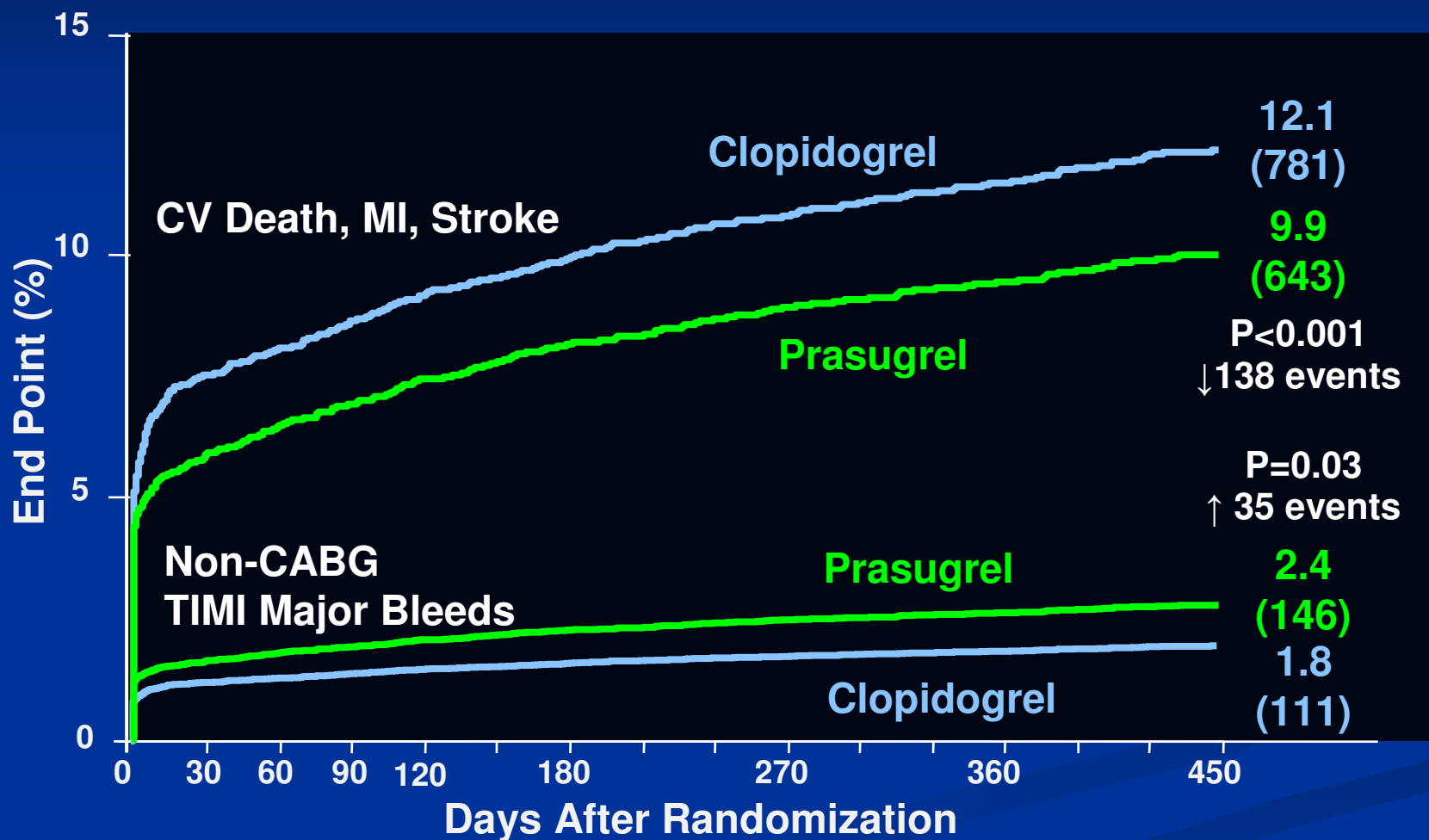
TRITON-TIMI 38: Primary End Point All ACS Population



ACS=Acute Coronary Syndrome; ARR=Absolute Risk Reduction; CV=Cardiovascular; HR=Hazard Ratio; MI=Myocardial Infarction; NNT=Number Needed to Treat

Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

TRITON-TIMI 38: Rates of Key Study End Points (All ACS)

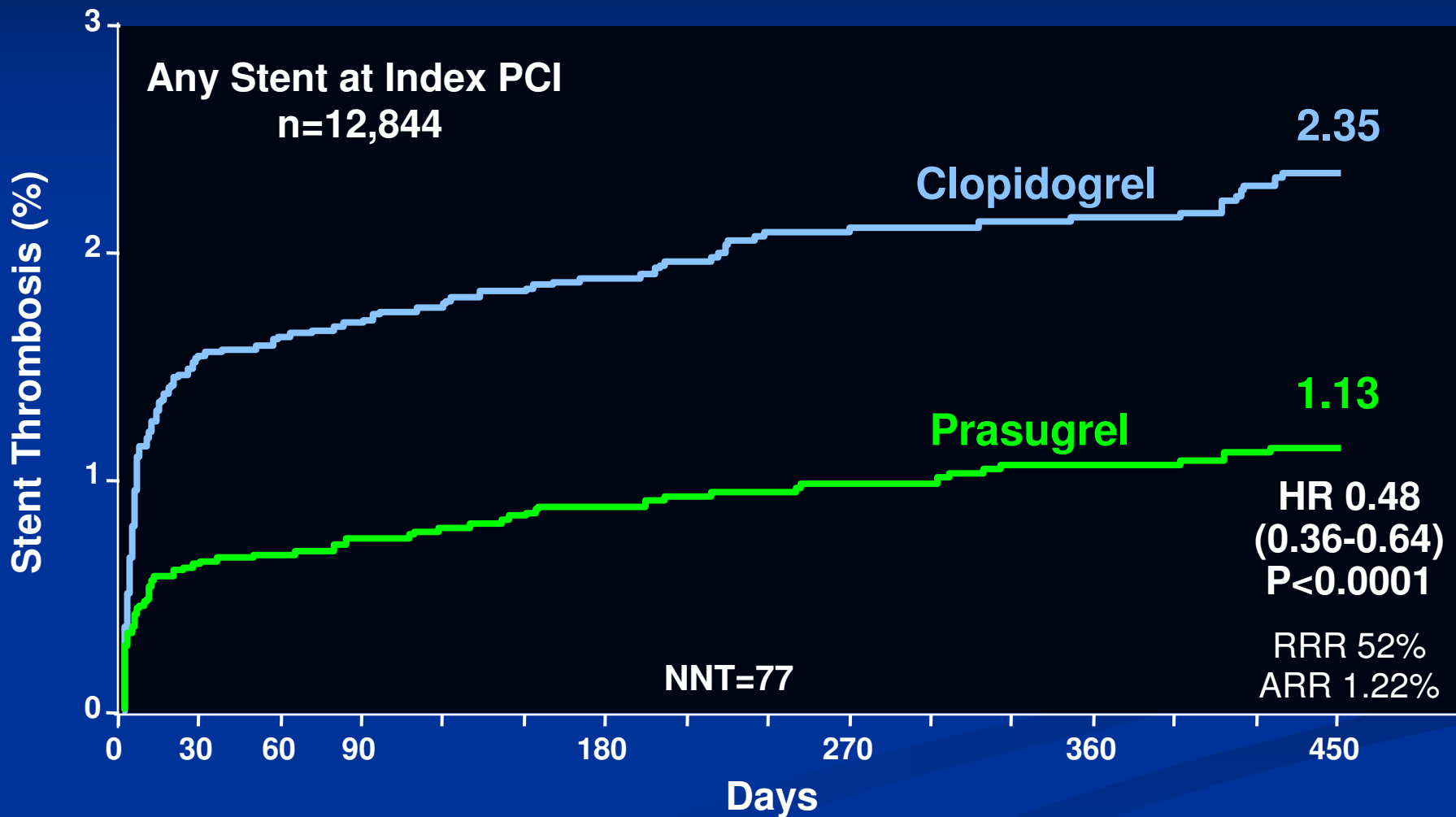


CABG=Coronary Artery Bypass Graft surgery; CV=Cardiovascular; MI=Myocardial Infarction;
TIMI=Thrombolysis In Myocardial Infarction

Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

TRITON-TIMI 38: ARC

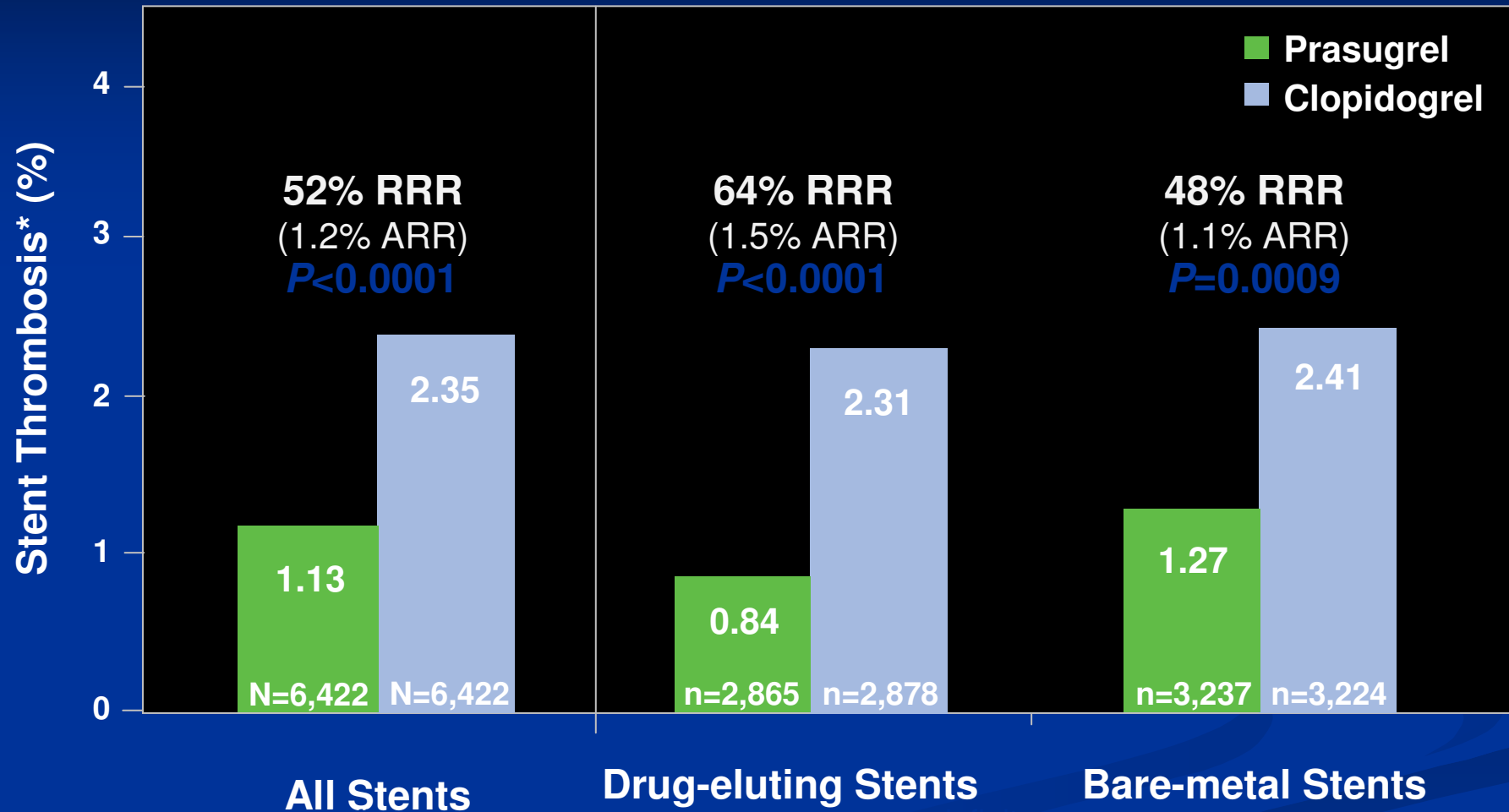
Definite/Probable Stent Thrombosis:



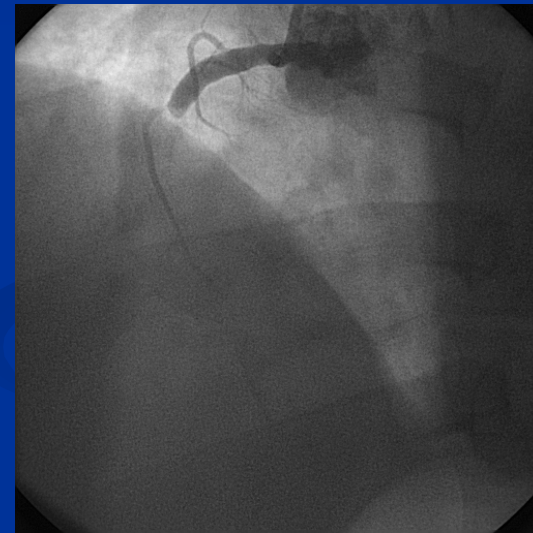
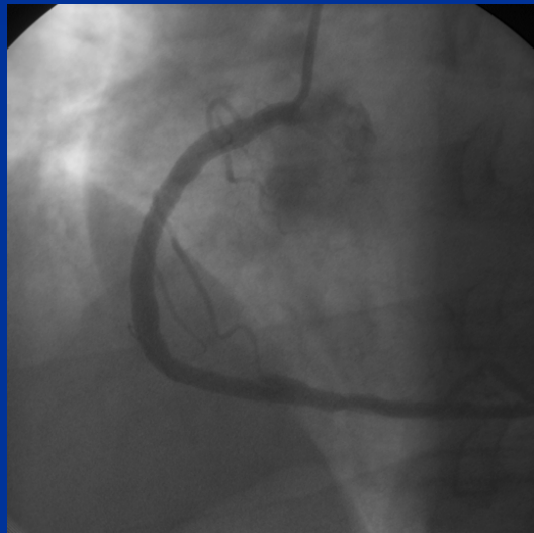
ARC=Academic Research Consortium; ARR=Absolute Risk Reduction; HR=Hazard Ratio;
NNT=Number Needed to Treat; PCI=Percutaneous Coronary Intervention;
RRR=Relative Risk Reduction

Wiviott SD et al. *Lancet* 2008;371:1353-1363

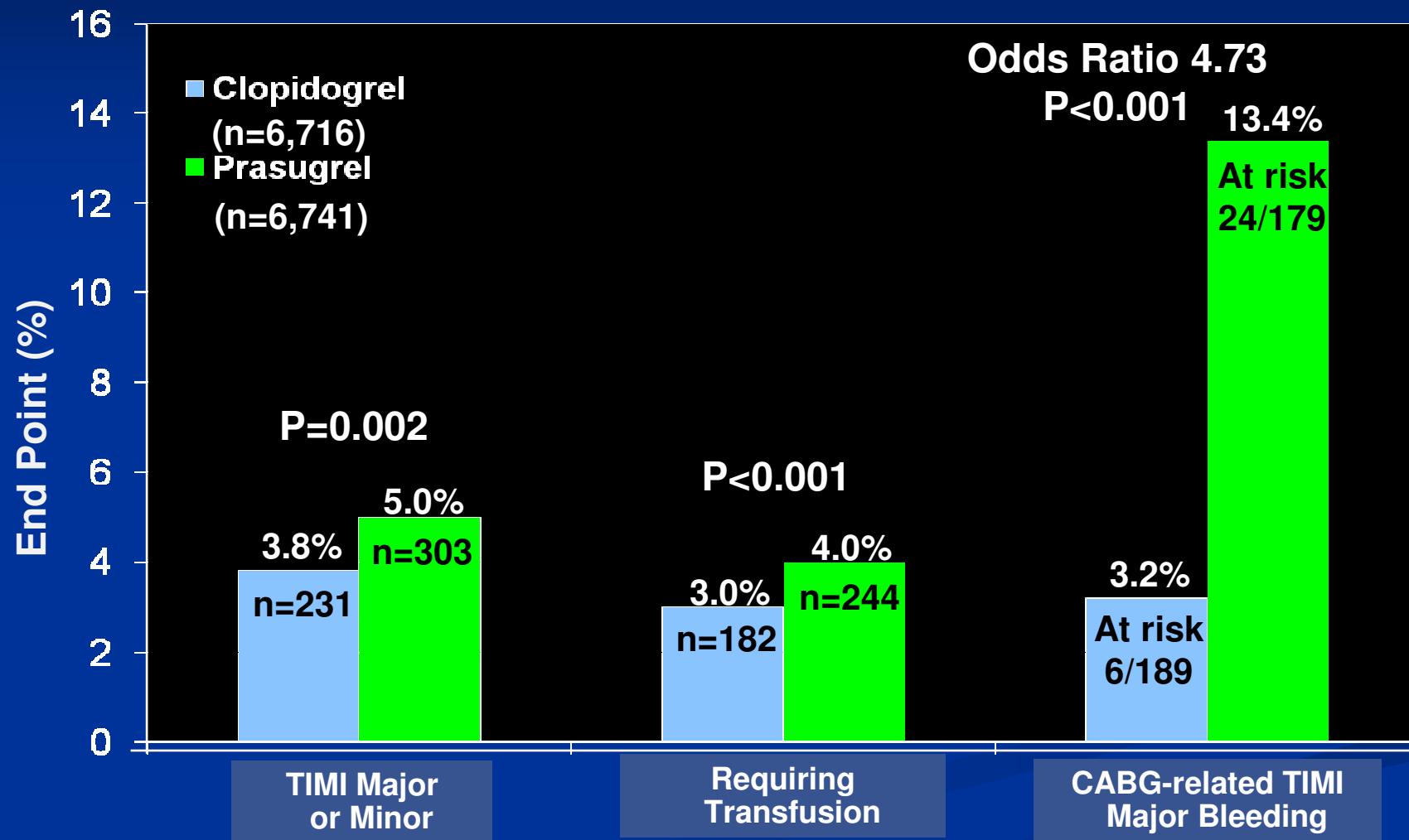
Stent Thrombosis Rates at End of Study



Stent Thrombosis



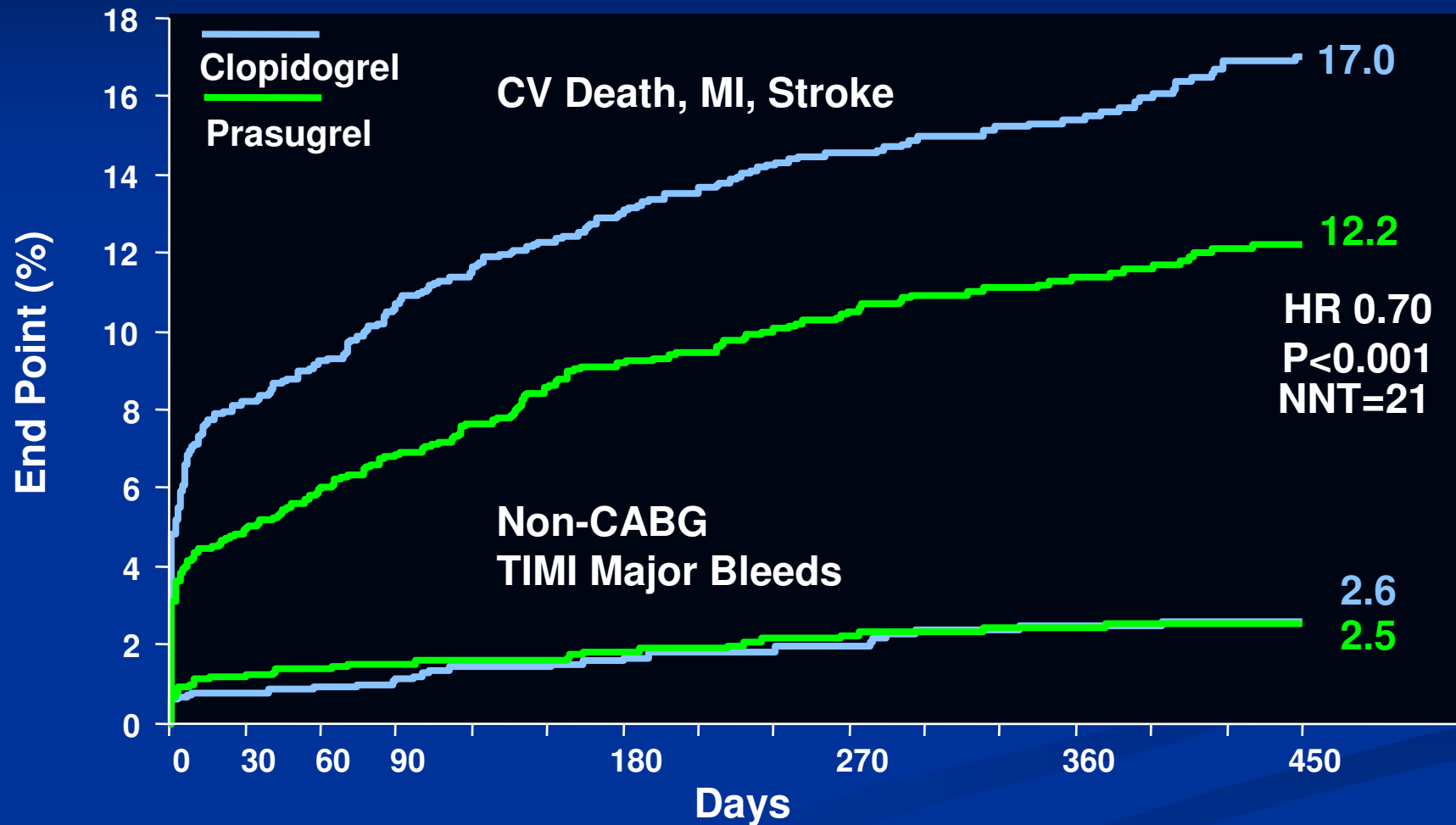
TRITON-TIMI 38: Other TIMI Bleeds at 15 Months (All ACS)



ACS=Acute Coronary Syndrome; CABG=Coronary Artery Bypass Graft surgery; HR=Hazard Ratio; TIMI=Thrombolysis In Myocardial Infarction

Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

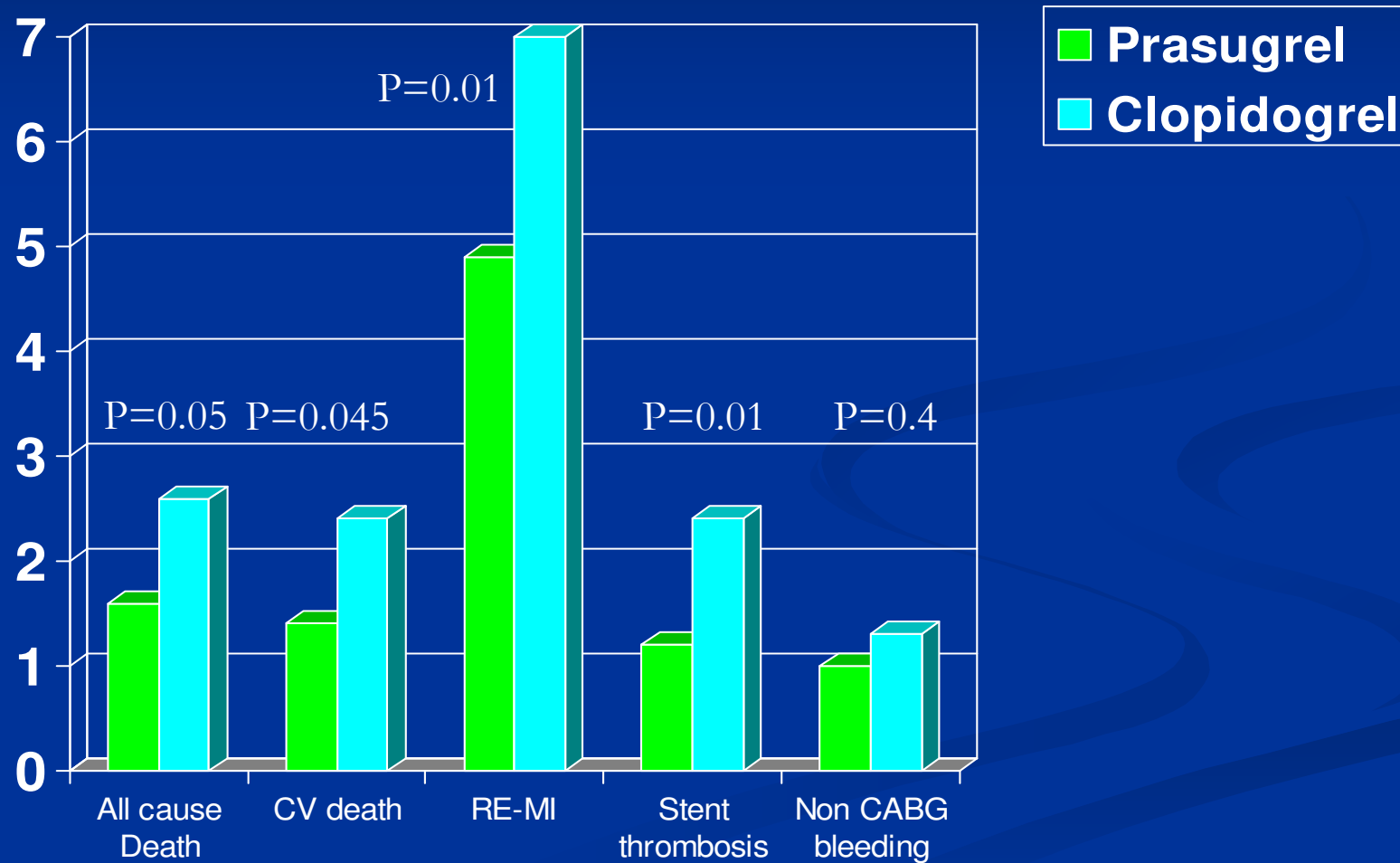
TRITON-TIMI 38: Diabetic Subgroup Analysis (n=3,146)



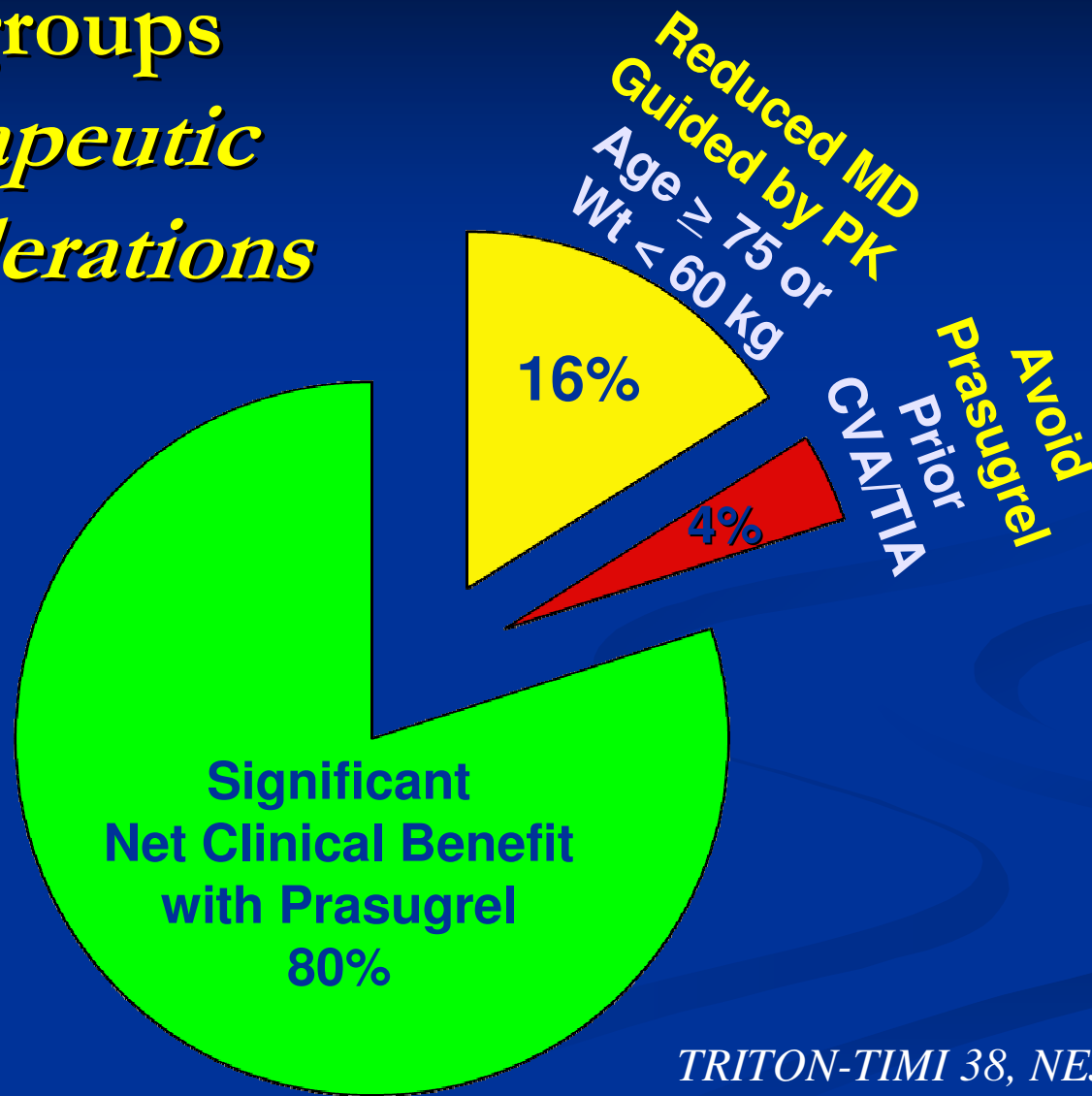
CABG=Coronary Artery Bypass Graft surgery; CV=Cardiovascular; HR=Hazard Ratio; MI=Myocardial Infarction; NNT=Number Needed to Treat; TIMI=Thrombolysis In Myocardial Infarction

Adapted from Antman EM et al. American Heart Association Scientific Sessions; 2007, Nov 4-7; Orlando, FL

TRITON-TIMI 38: STEMI Subgroup Analysis (n=3,534)



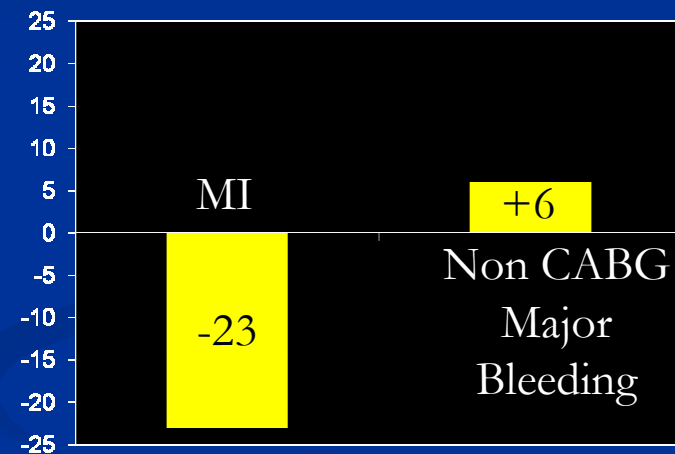
Bleeding Risk Subgroups *Therapeutic Considerations*



TRITON-TIMI 38, NEJM 2007

TRITON-TIMI 38: Clinical Implications

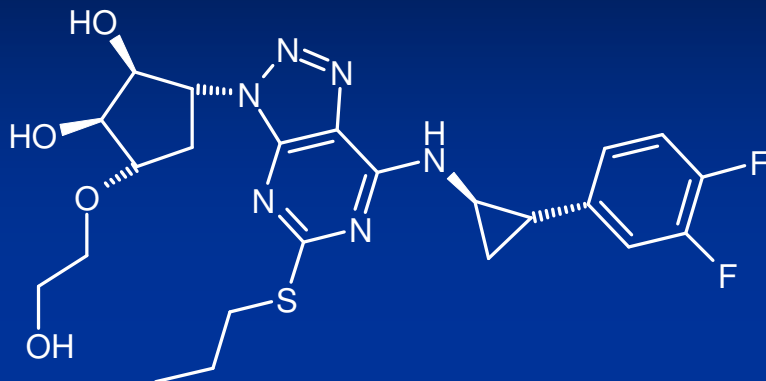
- For every 1,000 patients treated with prasugrel compared with clopidogrel
 - 23 MI's are prevented
 - 6 more non-CABG TIMI major bleeds are experienced
- Over 15 months
 - Number needed to treat is 46 to prevent one CV death, nonfatal MI or nonfatal stroke
 - Number needed to harm is 167 to cause one non-CABG TIMI major bleed



Prasugrel – Current Status

- Approved by FDA – 07/2009
- Class I indication for patients with STEMI (as an alternative to clopidogrel) by both AHA/ACC and ESC guidelines.
- Recommended for STEMI and diabetes by UK - NICE

TICAGRELOR (Brilinta): an oral reversible P2Y₁₂ antagonist



Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**

Not a prodrug; does not require metabolic activation

Rapid onset of inhibitory effect on the P2Y₁₂ receptor

Greater and more consistent inhibition of platelet aggregation vs clopidogrel

Not affected by CYP2C19 and ABCB1 polymorphisms (Wallentin et al, Lancet 2010)

- **Reversibly bound**

Degree of inhibition reflects plasma concentration

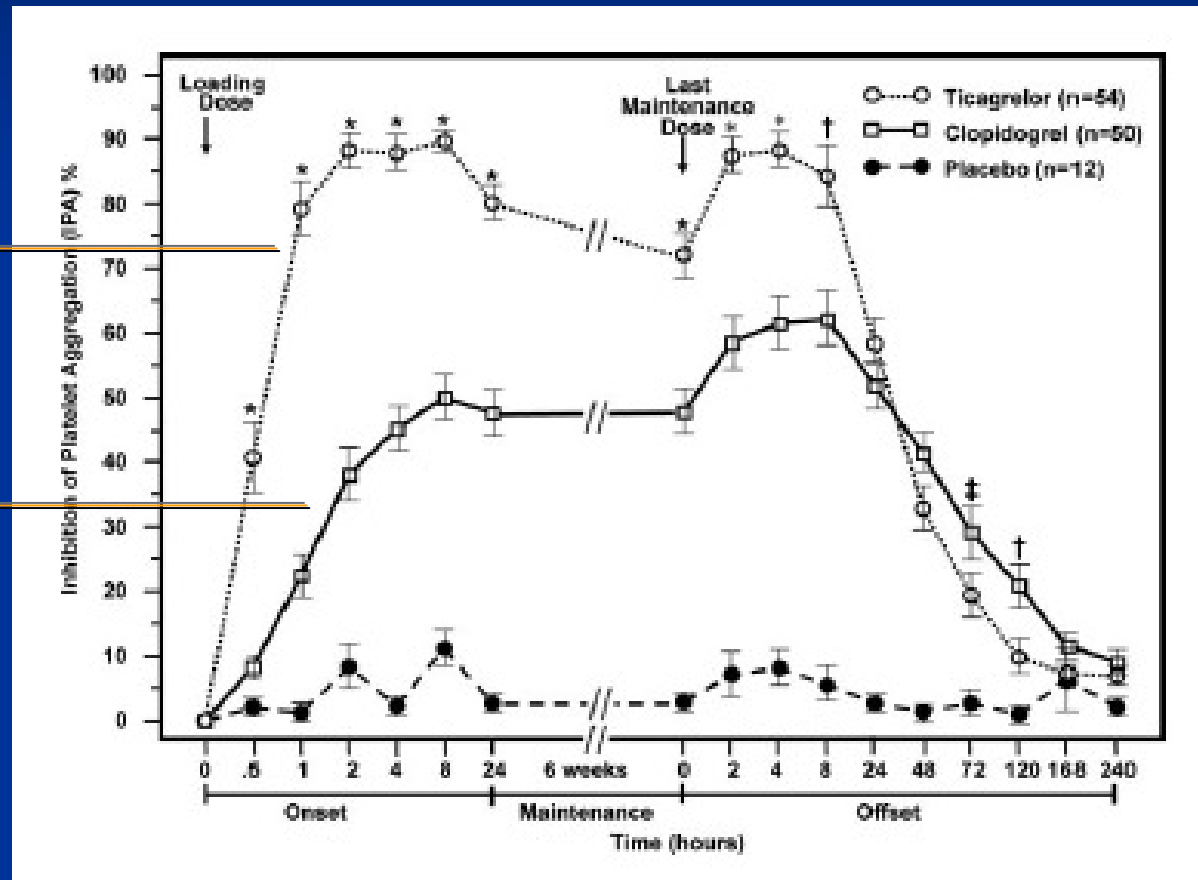
Faster offset of effect than clopidogrel

Functional recovery of all circulating platelets

Pharmacodynamics of ticagrelor – onset offset study

Ticagrelor

Clopidogrel



PLATO study design

UA/NSTEMI (moderate-to-high risk) STEMI (if primary PCI)
All receiving ASA; 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

Key secondary: • CV death + MI + Stroke in patients intended for invasive management

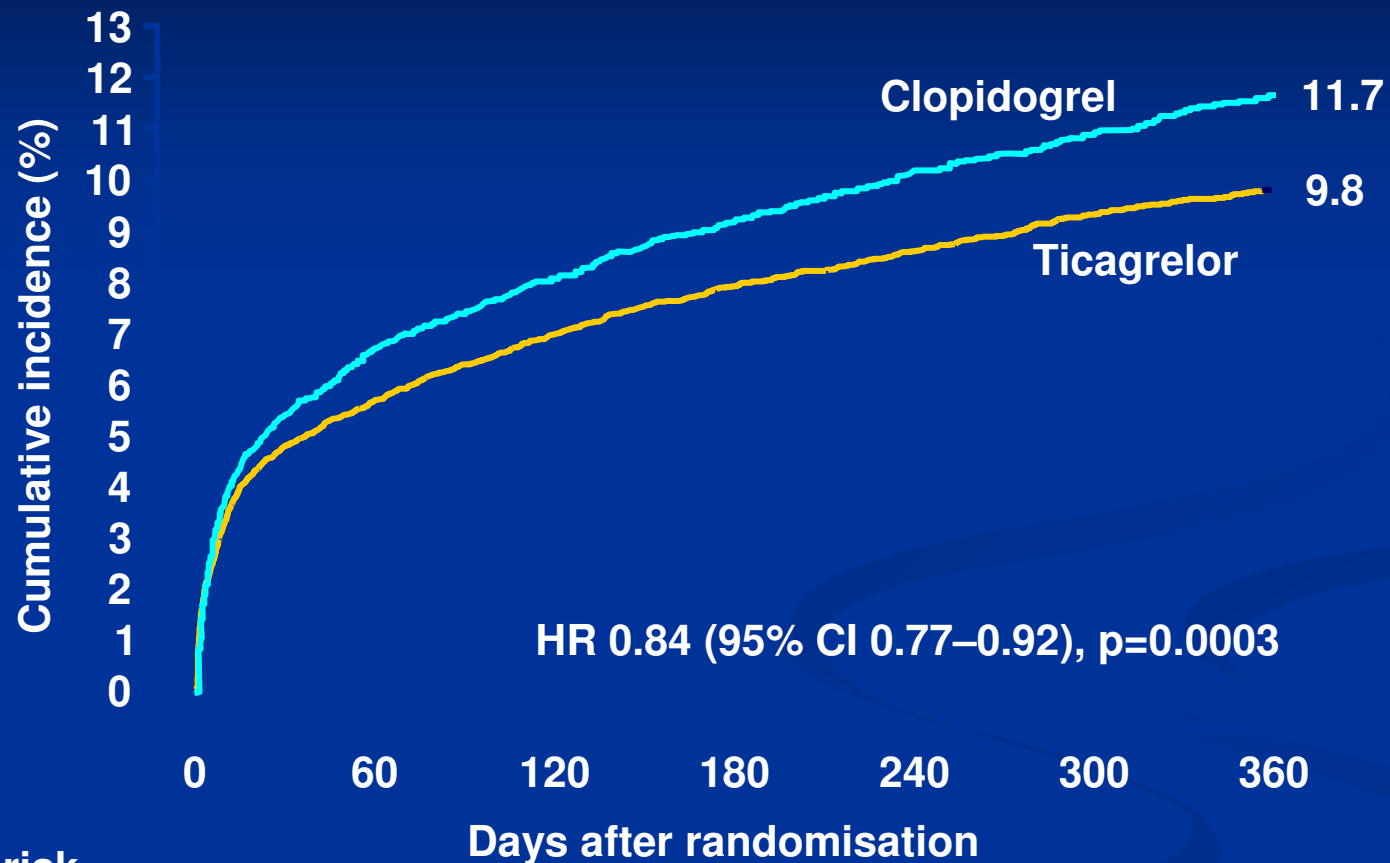
• Total mortality + MI + Stroke

• CV death + MI + Stroke + recurrent ischaemia + TIA + arterial thrombotic events

• MI alone / CV death alone / Stroke alone / Total mortality

Primary safety: • Total major bleeding

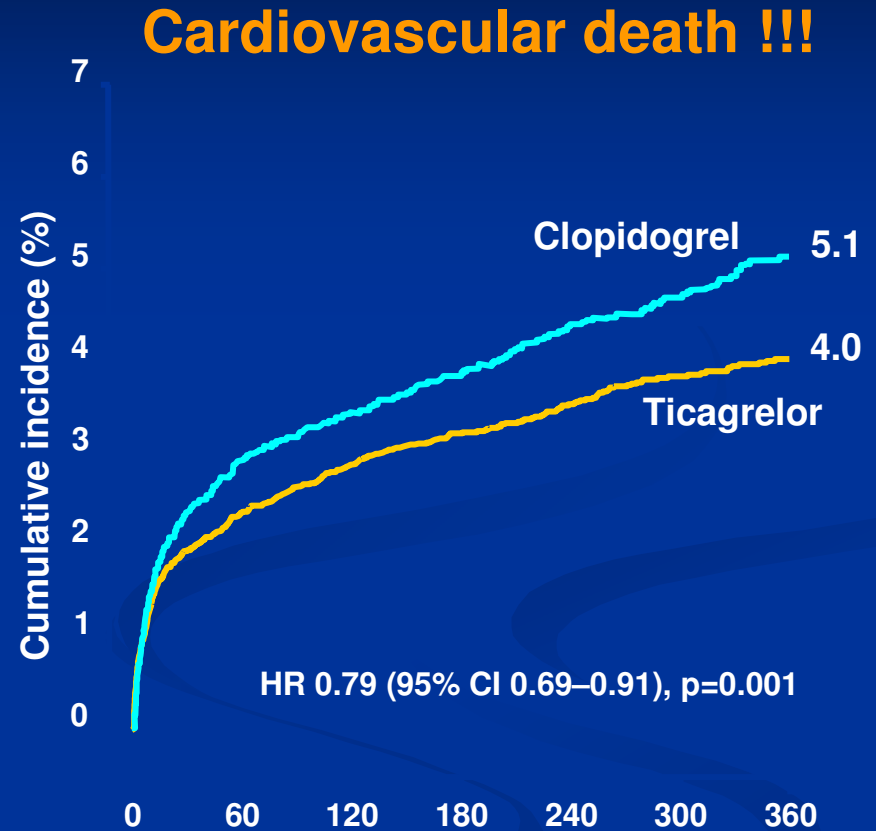
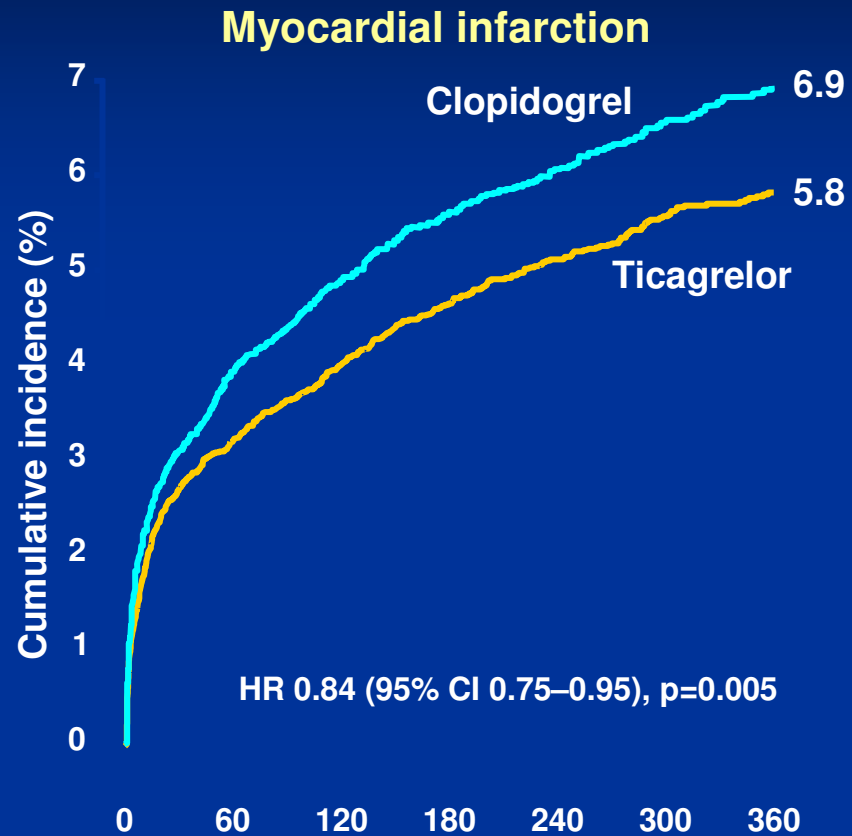
K-M estimate of primary efficacy event (composite of CV death, MI or stroke)



No. at risk	Days after randomisation						
	0	60	120	180	240	300	360
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

K-M estimates of time to secondary efficacy endpoints



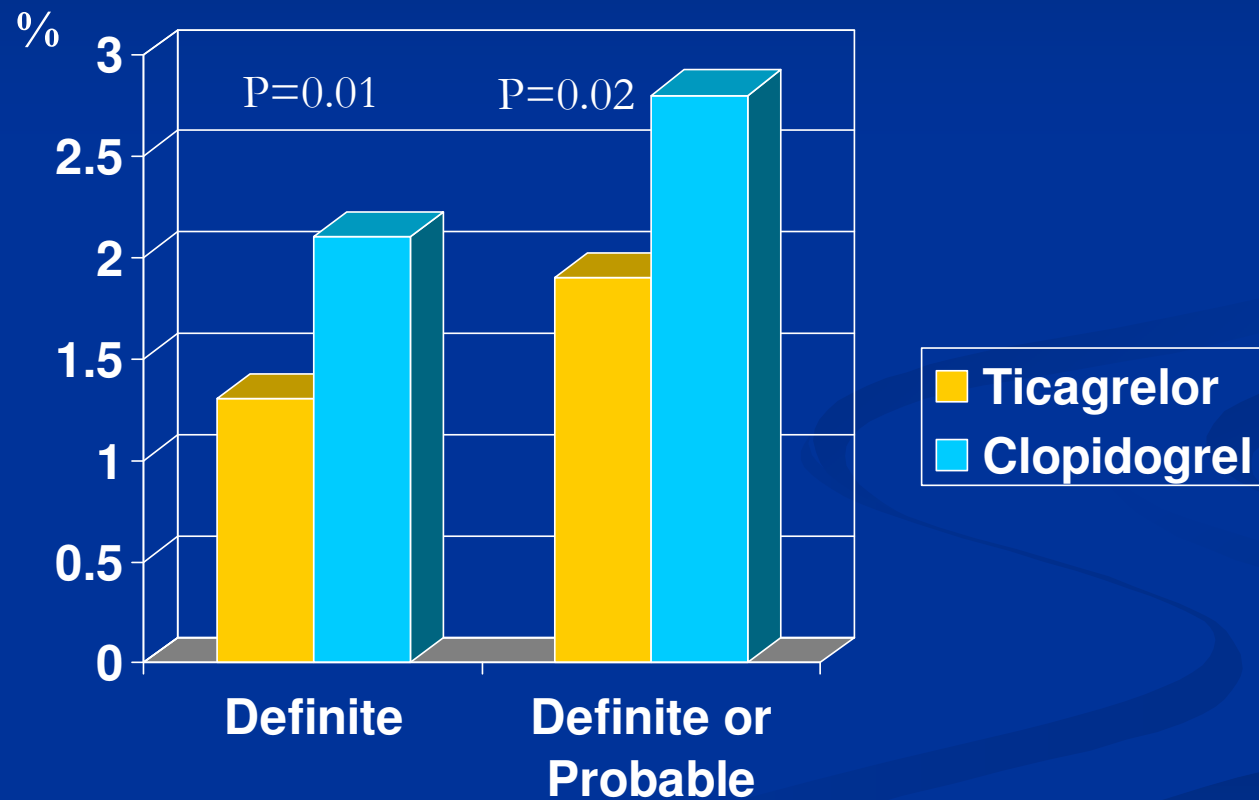
No. at risk

	0	60	120	180	240	300	360
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

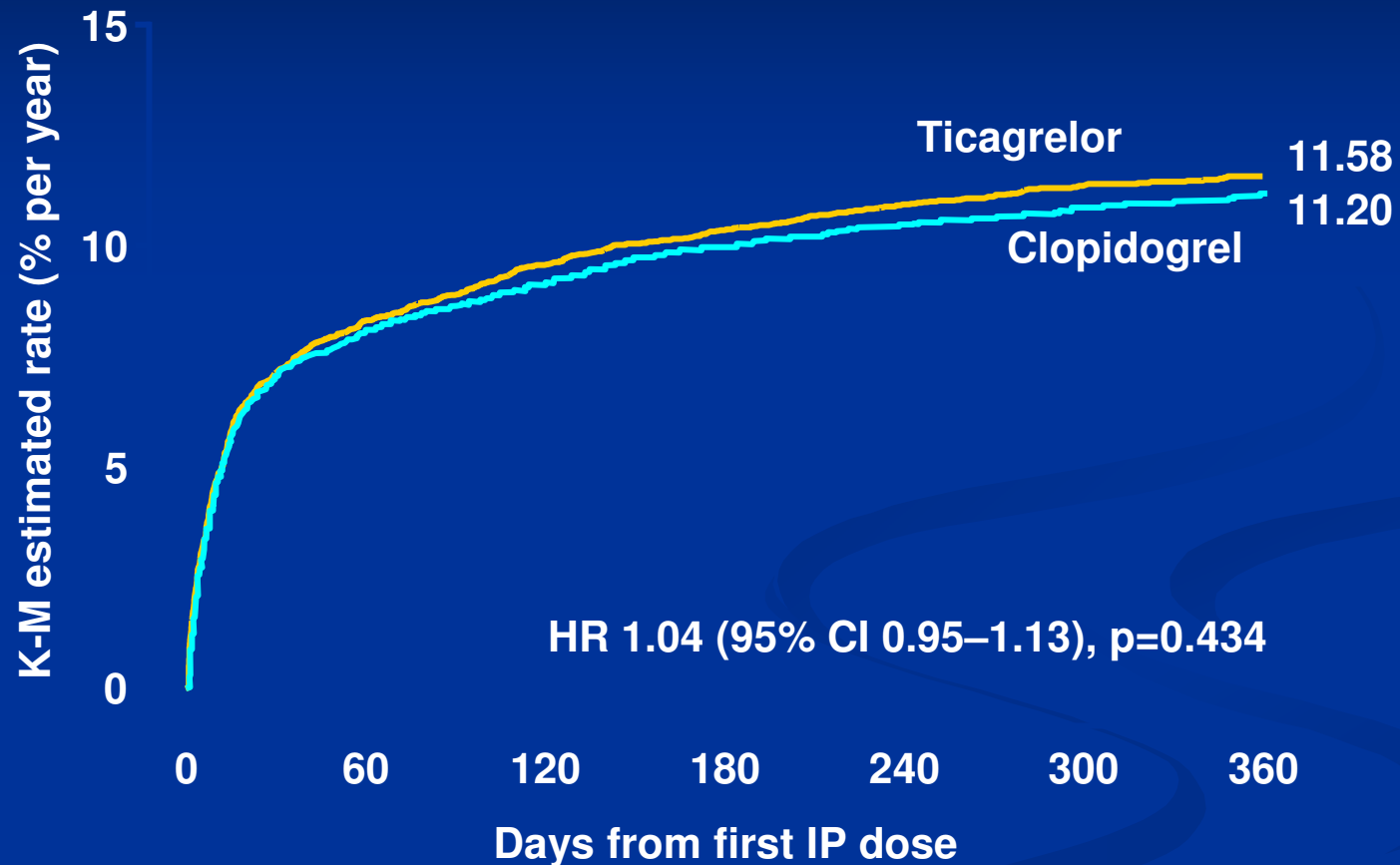
	0	60	120	180	240	300	360
Ticagrelor	9,333	8,294	8,822	8,626	7,119	5,482	4,419
Clopidogrel	9,291	8,865	8,780	8,589	7,079	5,441	4,364

Stent thrombosis

Evaluated in patients with any stent during the study



Major bleeding – primary safety event

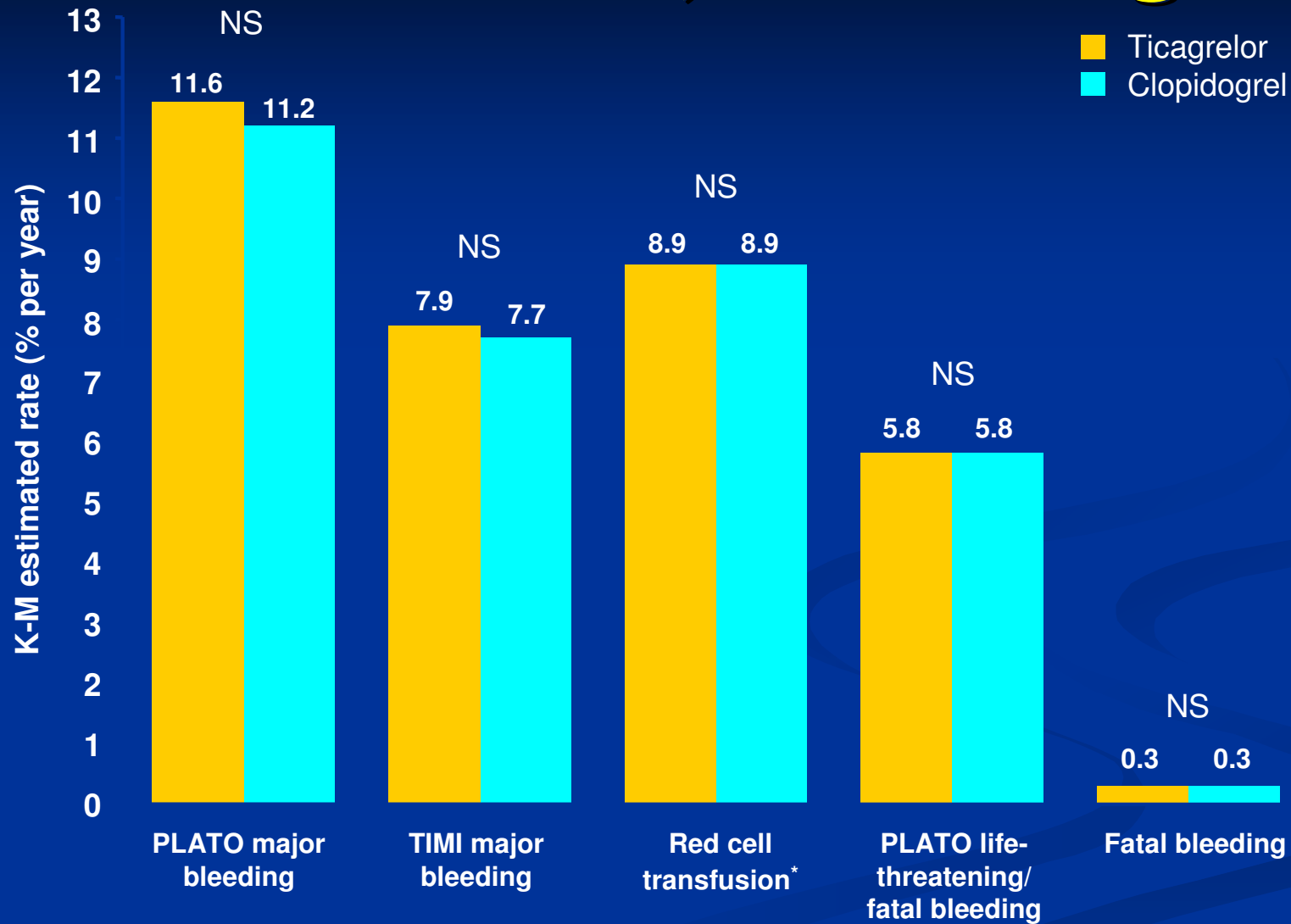


No. at risk

Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
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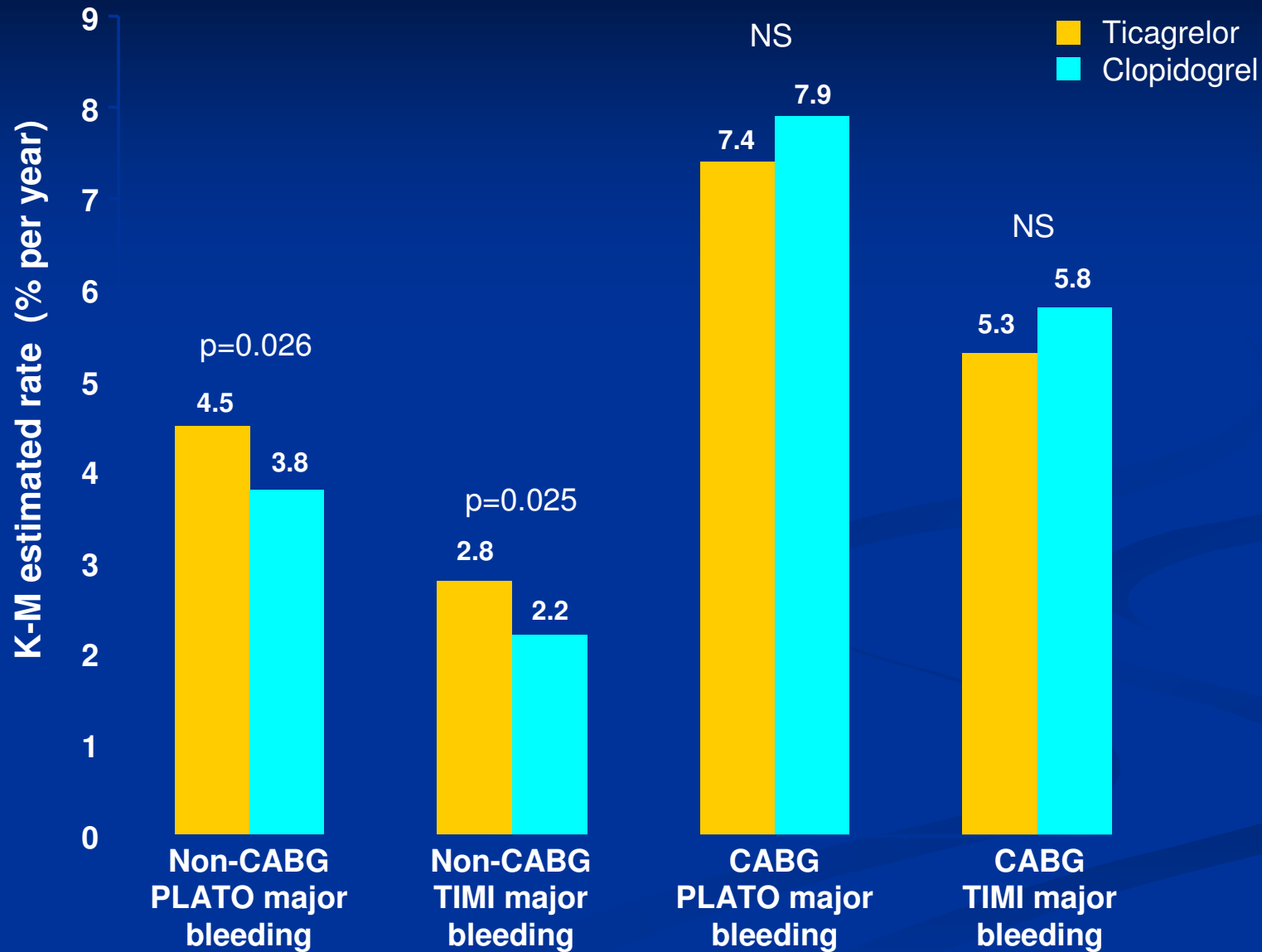
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479
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Total major bleeding



Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. NEJM 2007;357:2001-15; *Proportion of patients (%); NS = not significant

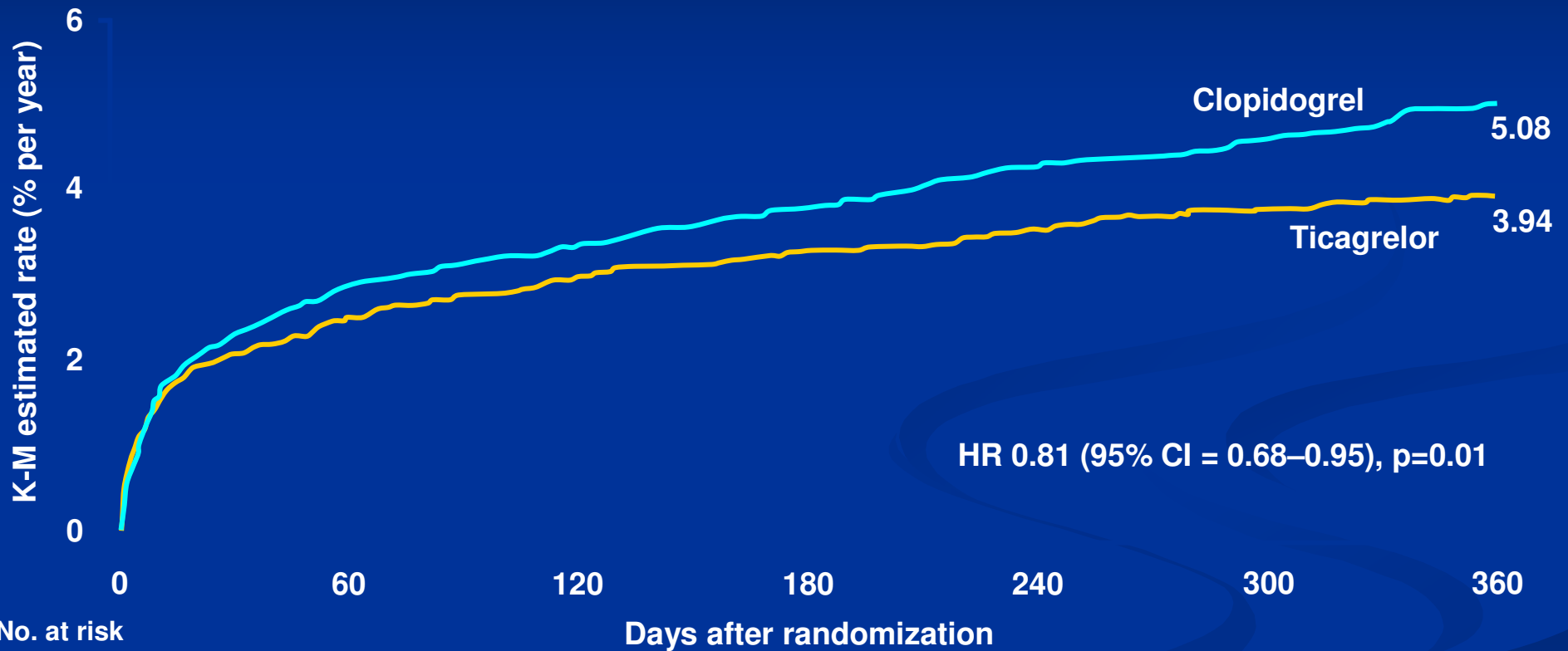
Non-CABG and CABG-related major bleeding



Other findings

All patients	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value*
Dyspnoea, %			
Any	13.8	7.8	<0.001
Requiring discontinuation of study treatment	0.9	0.1	<0.001

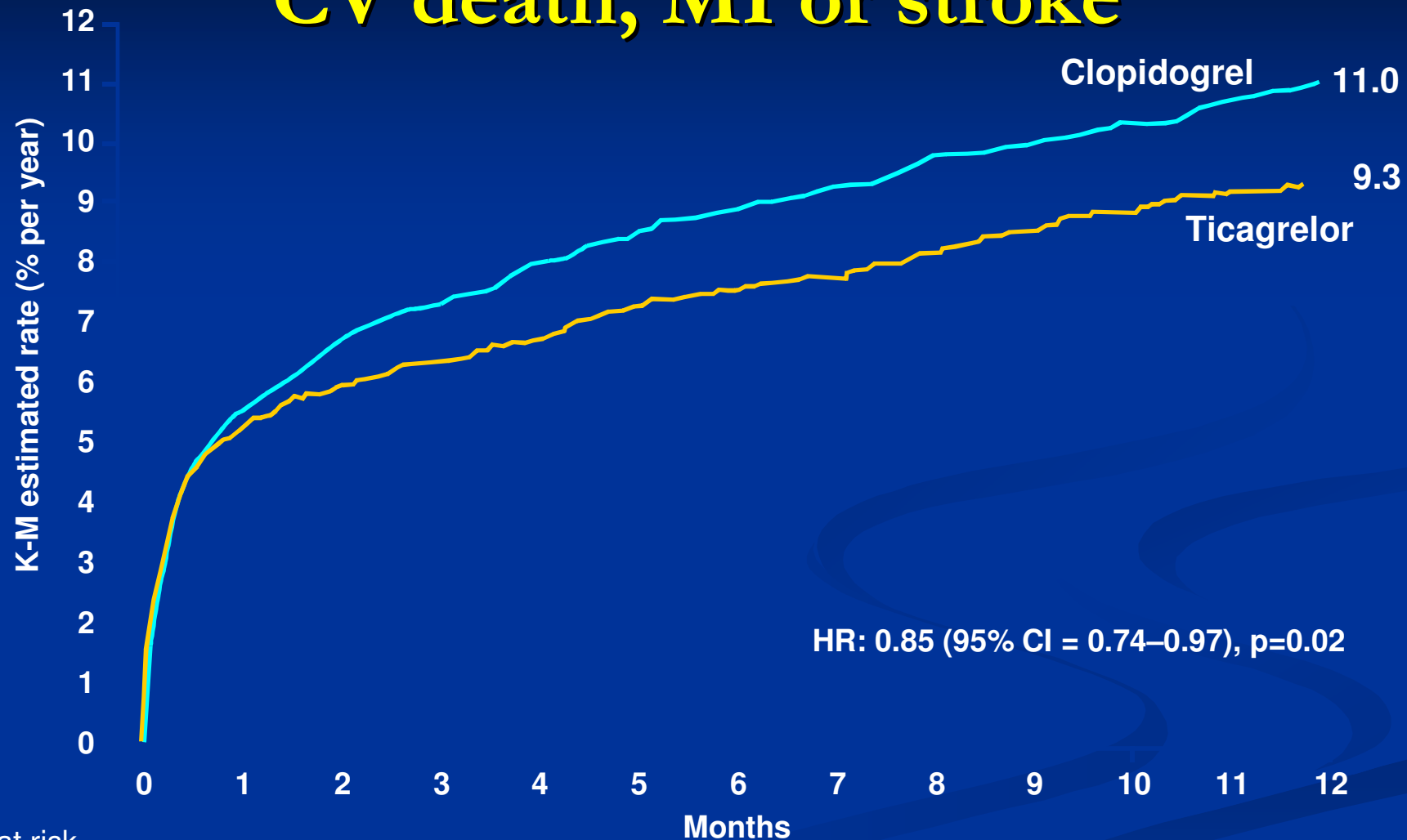
Plato Invasive - All-cause mortality



	0	60	120	180	240	300	360
No. at risk							
Ticagrelor	6,732	6,439	6,375	6,241	5,141	3,951	3,233
Clopidogrel	6,676	6,376	6,331	6,209	5,114	3,917	3,164

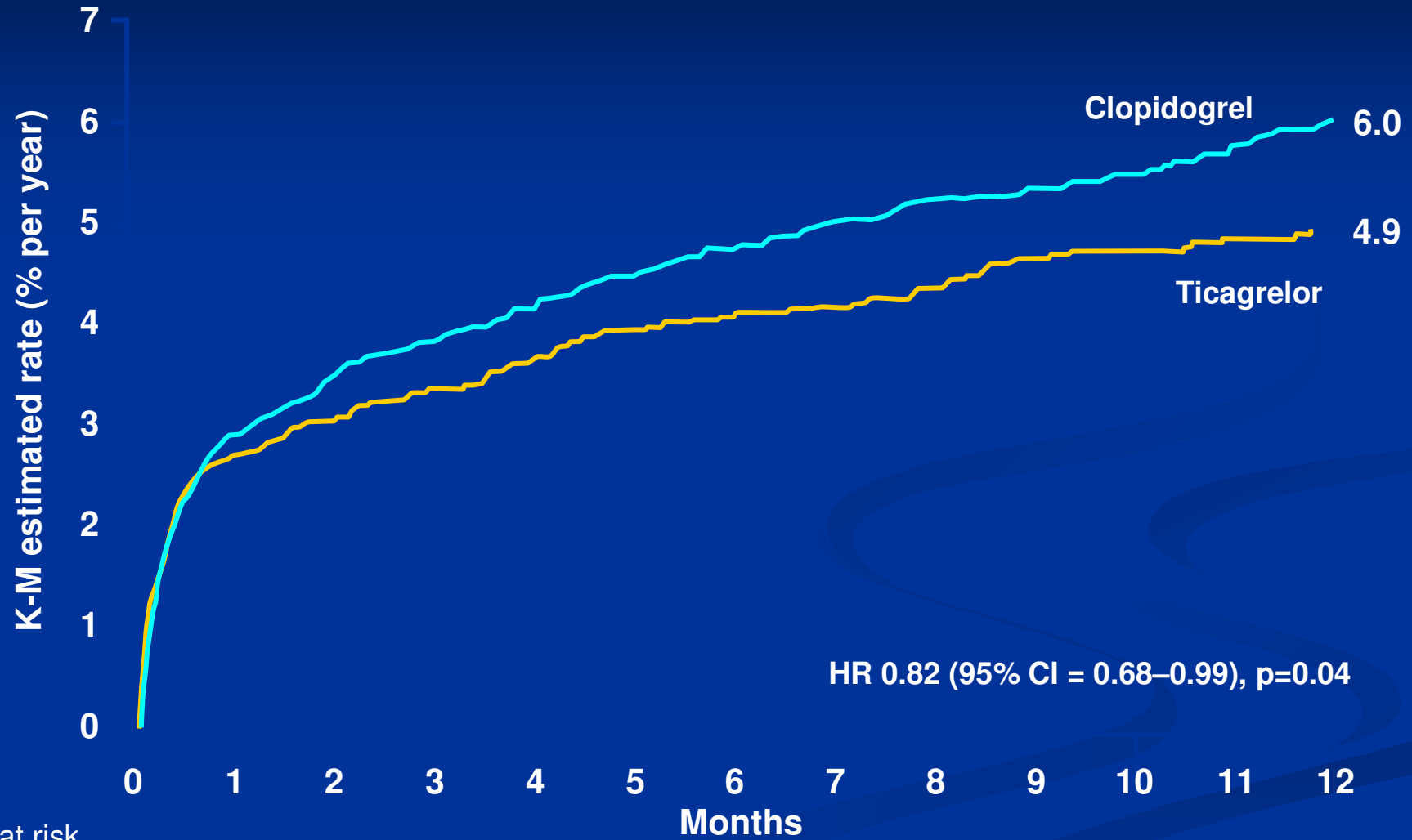
Cannon et al, Lancet 2010

PLATO STEMI - Primary endpoint: CV death, MI or stroke



No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12
Ticagrelor	4,201	3,887	3,834	3,732	3,011	2,297	1,891						
Clopidogrel	4,229	3,892	3,823	3,730	3,022	2,333	1,868						

PLATO STEMI - All cause mortality



HR 0.82 (95% CI = 0.68–0.99), p=0.04

No. at risk

Ticagrelor	4,201	4,005	3,962	3,876	3,150	2,413	1,993
Clopidogrel	4,229	4,029	3,989	3,912	3,195	2,471	1,980

Therapeutic considerations

- Based on 1,000 patients admitted to hospital for ACS, using ticagrelor instead of clopidogrel for 12 months resulted in:
 - 14 fewer deaths
 - 11 fewer myocardial infarctions
 - 6–8 fewer cases with stent thrombosis
 - **No increase in bleedings requiring transfusion**
 - 10 patients may switch to thienopyridine treatment because of reversible symptoms of dyspnoea
- **Treating 54 patients with ticagrelor instead of with clopidogrel for one year will prevent one event of CV death, MI or stroke**

Ticagrelor - Conclusions and Current Status

- Tested in a mod.-high risk ACS, including STEMI
- Reduction in MI and stent thrombosis
- **Reduction in CV and total mortality !!**
- **No change in the overall risk of major bleeding !!**
- FDA Advisory Committee recommended US FDA approval of Ticagrelor (Brilinta) for ACS in 07/2010

Conclusions - general

- New anti-platelet drugs – specifically ADP receptor antagonists - have been proven to be effective in large phase III trials
- More intense, predictable and rapid platelet inhibition translates to reduced ischemic complications (compared with clopidogrel)
- Bleeding price – especially for prasugrel
- Special subgroups benefit the most (e.g. STEMI, diabetes)
- The various alternatives will create an opportunity for “personalized medicine” based on thrombotic / bleeding risk

THANK YOU

