ALPIC2012

Advanced Learning on Platelets & Thrombosis International Course

Bleeding in congenital and drug-induced defects of the platelet $P2Y_{12}$ receptors

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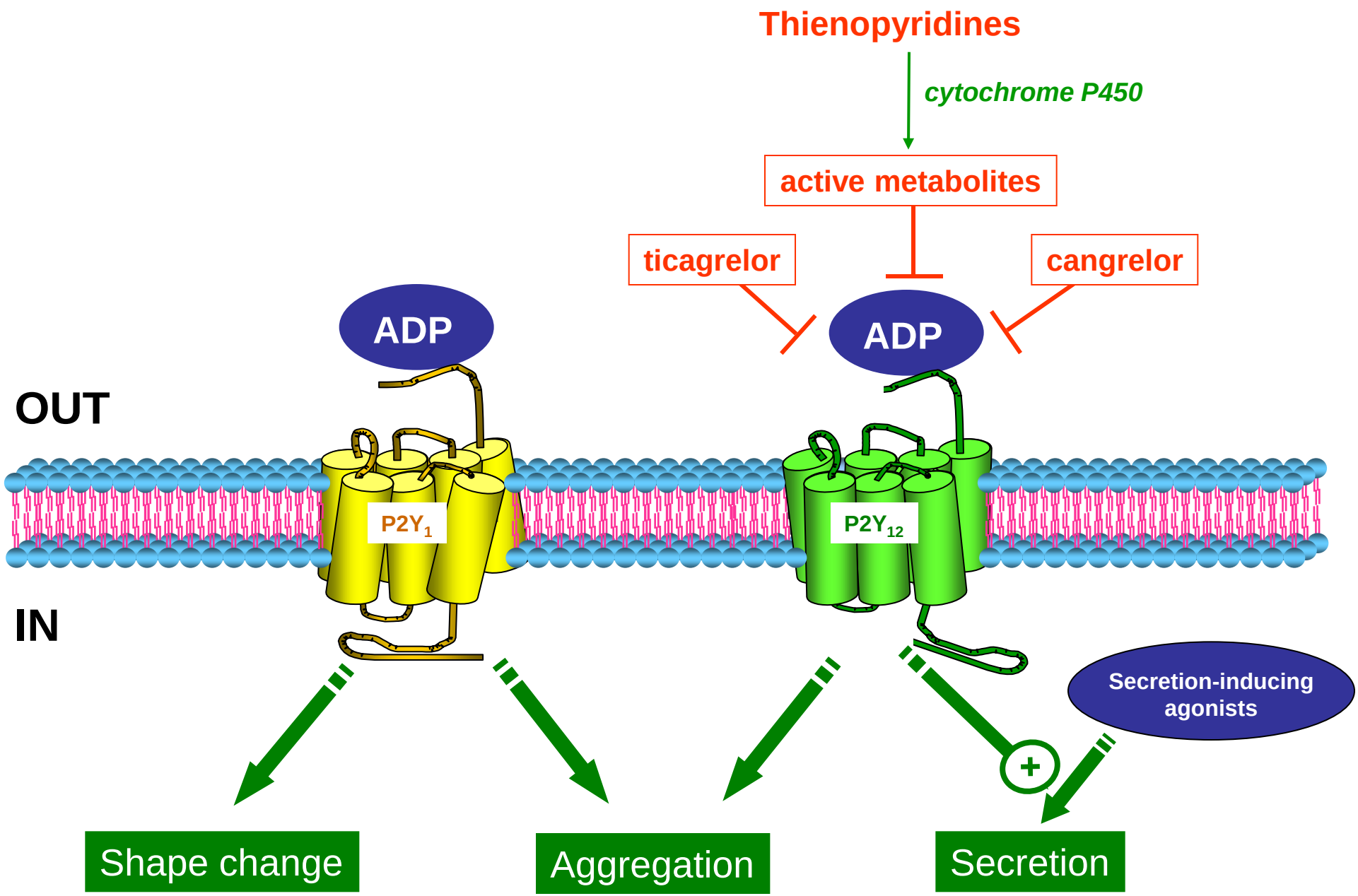
Thienopyridines
cytochrome P450
active metabolites
ticagrelor
cangrelor
ADP
ADP
OUT
IN
P2Y1
P2Y12
Secretion-inducing agonists
+
Shape change
Aggregation
Secretion

$P2Y_{12}$ KO mice

Roles of $P2Y_1$ and $P2Y_{12}$ receptors for ADP in hemostasis

	$P2Y_1$ inhibition (or $P2Y_1$ KO)	$P2Y_{12}$ inhibition (or $P2Y_{12}$ KO)
Platelet aggregation (Borns' aggregometer)		
Shear-induced platelet aggregation		
Platelet thrombus formation on collagen under flow conditions		
Bleeding time (KO-mice)	=/↑	↑↑

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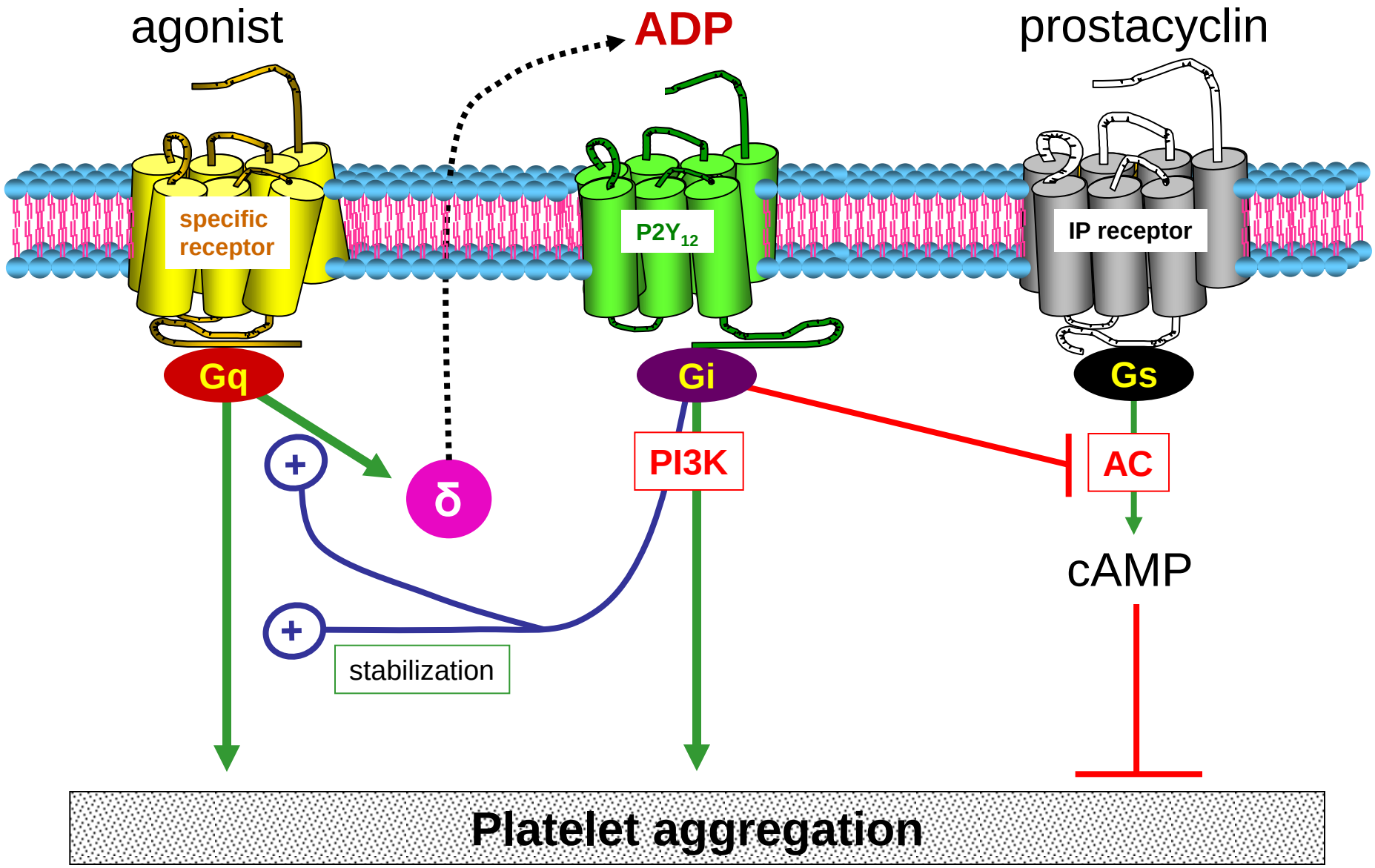
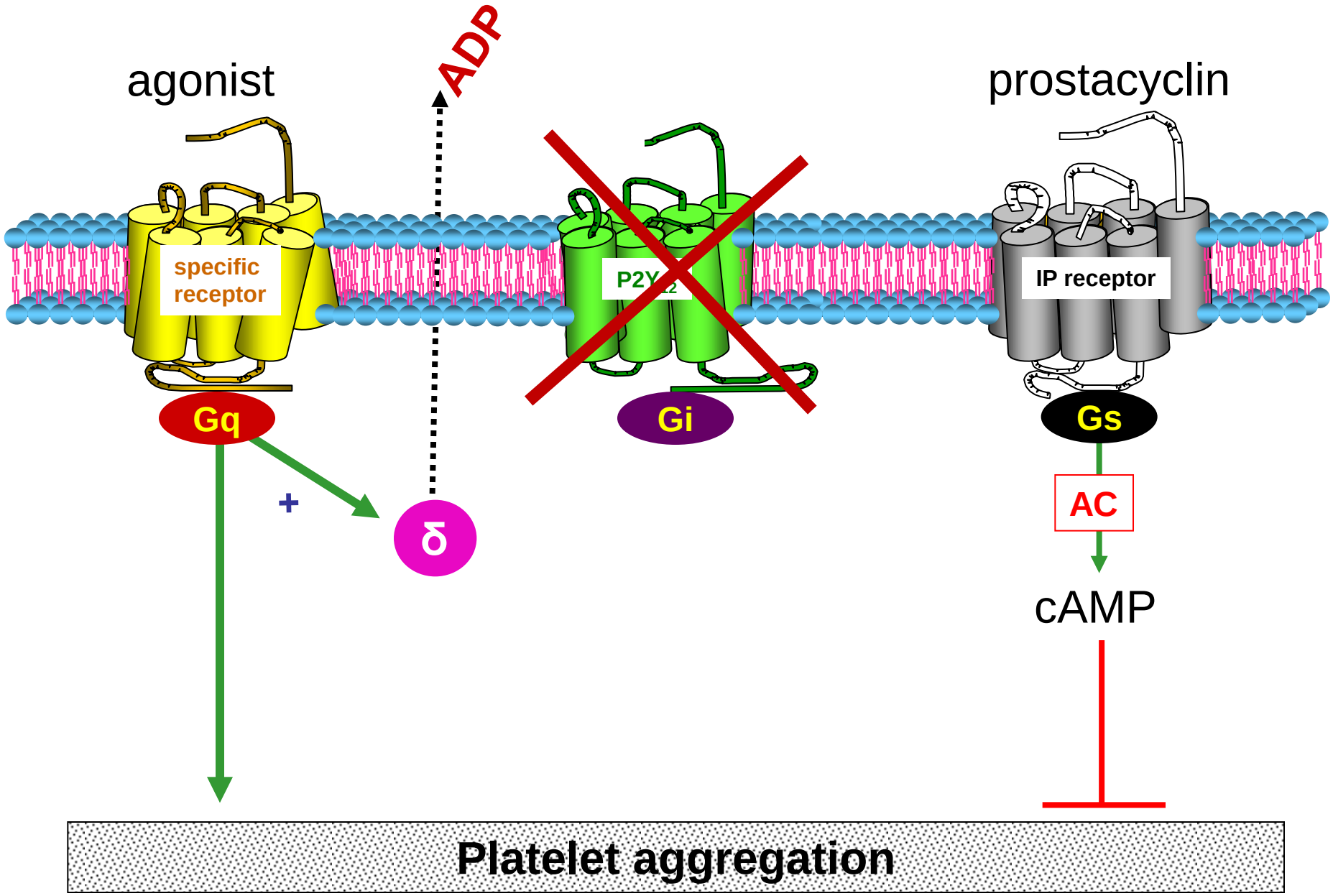
Platelet aggregation (Borns' aggregometer)	↓↓	↓↓
Shear-induced platelet aggregation	↓↓	↓↓
Platelet thrombus formation on collagen under flow conditions	↓↓	↓↓
Bleeding time (KO-mice)	=/↑	↑↑


agonist
ADP
prostacyclin
specific receptor
P2Y12
IP receptor
Gq
Gi
Gs
PI3K
AC
cAMP
stabilization
Platelet aggregation


agonist
ADP
prostacyclin
specific receptor
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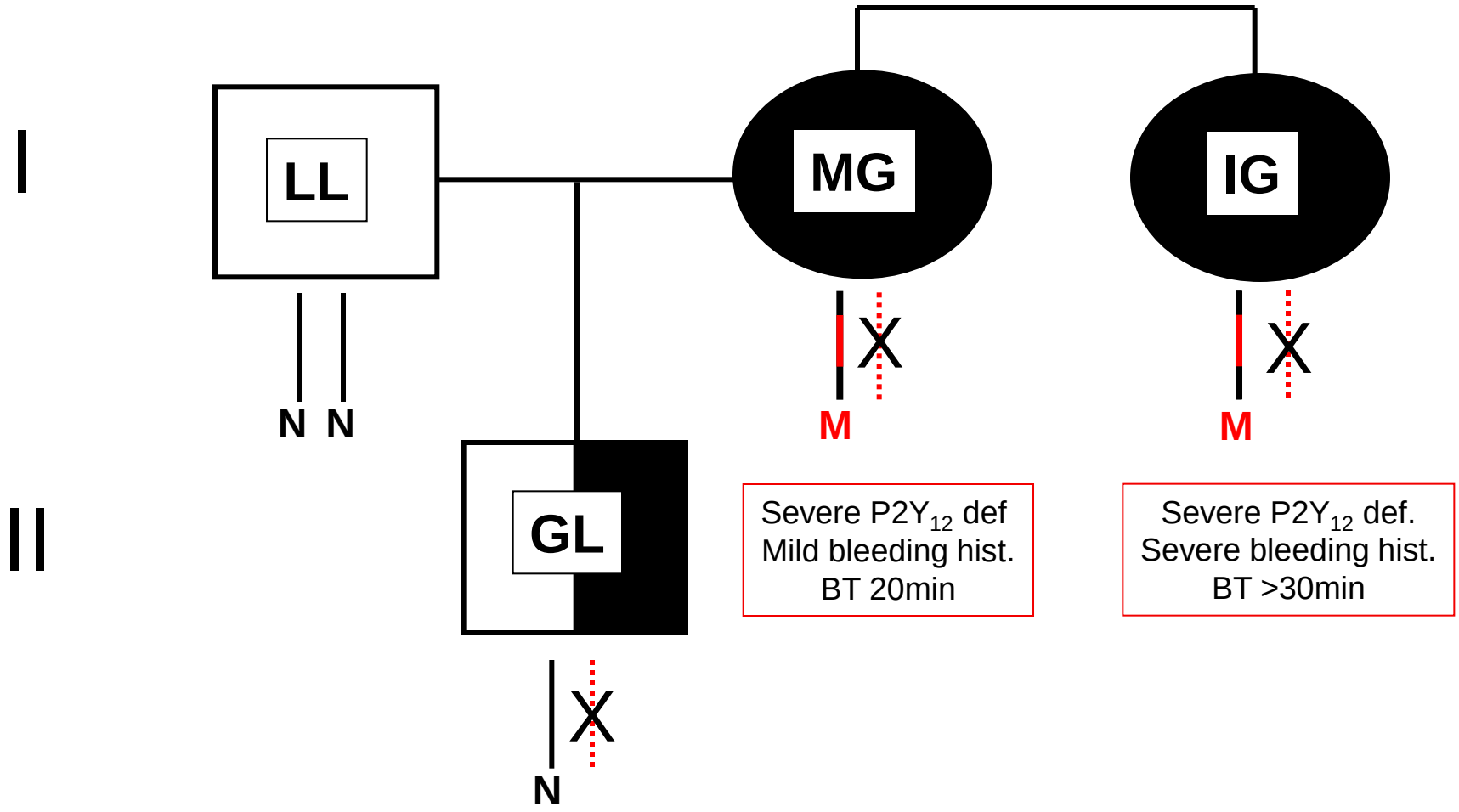
Gq
Gi
Gs
+
α
AC
cAMP
Platelet aggregation

Congenital $P2Y_{12}$ deficiency

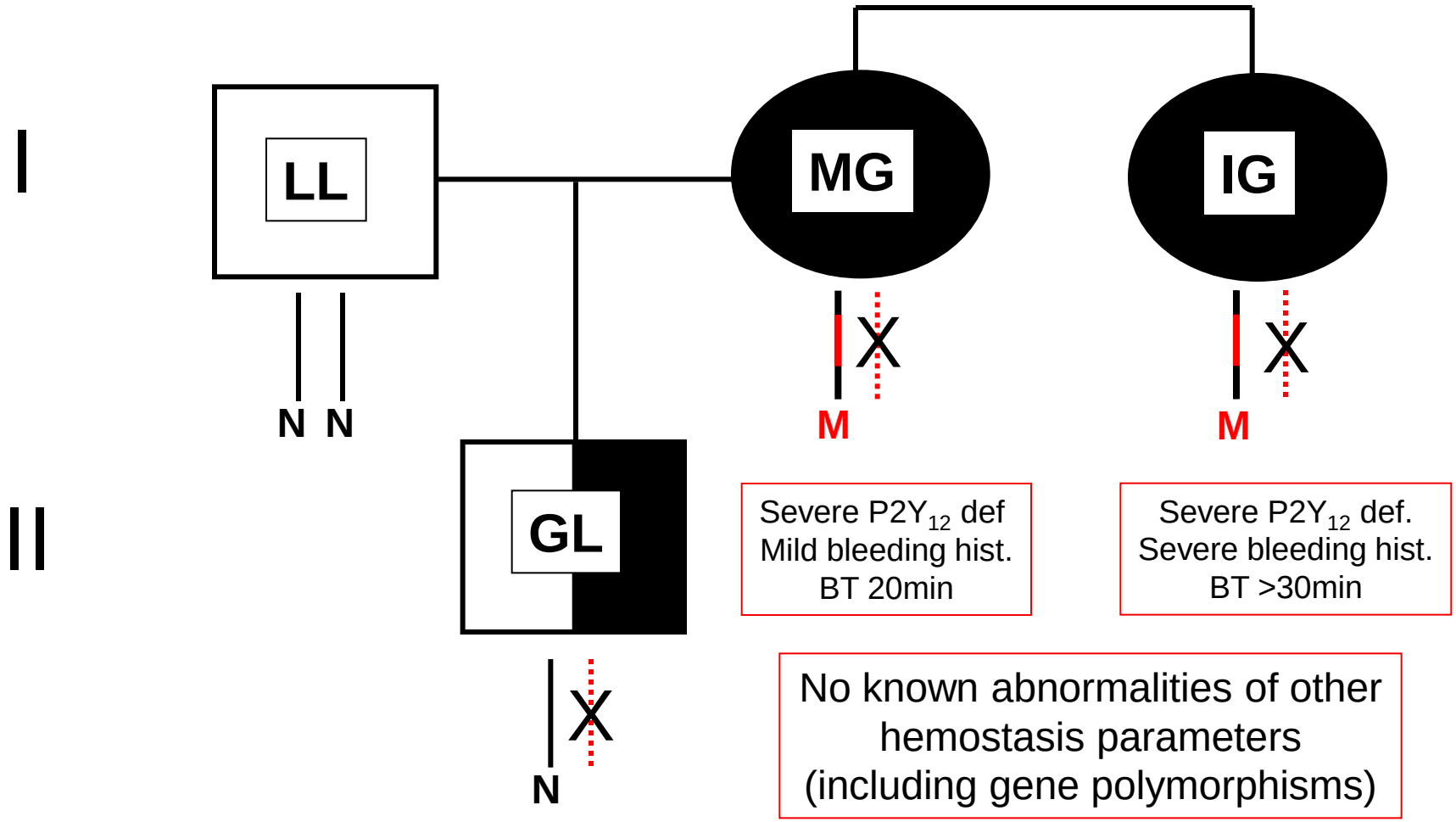
Bleeding Times and Bleeding Scores in 4 patients with inherited, severe $P2Y_{12}$ deficiency

Patient	Bleeding time (min)	Bleeding score*
V.R.	15-20	8
M.G.	>30	13
I.G.	15	7
T.S.	-	16
Normal values	<8	<3

*Bleeding score: Tosetto et al, JTH 2005



Cattaneo M et al, ATVB 2000
Fontana G et al, Haematologica 2009



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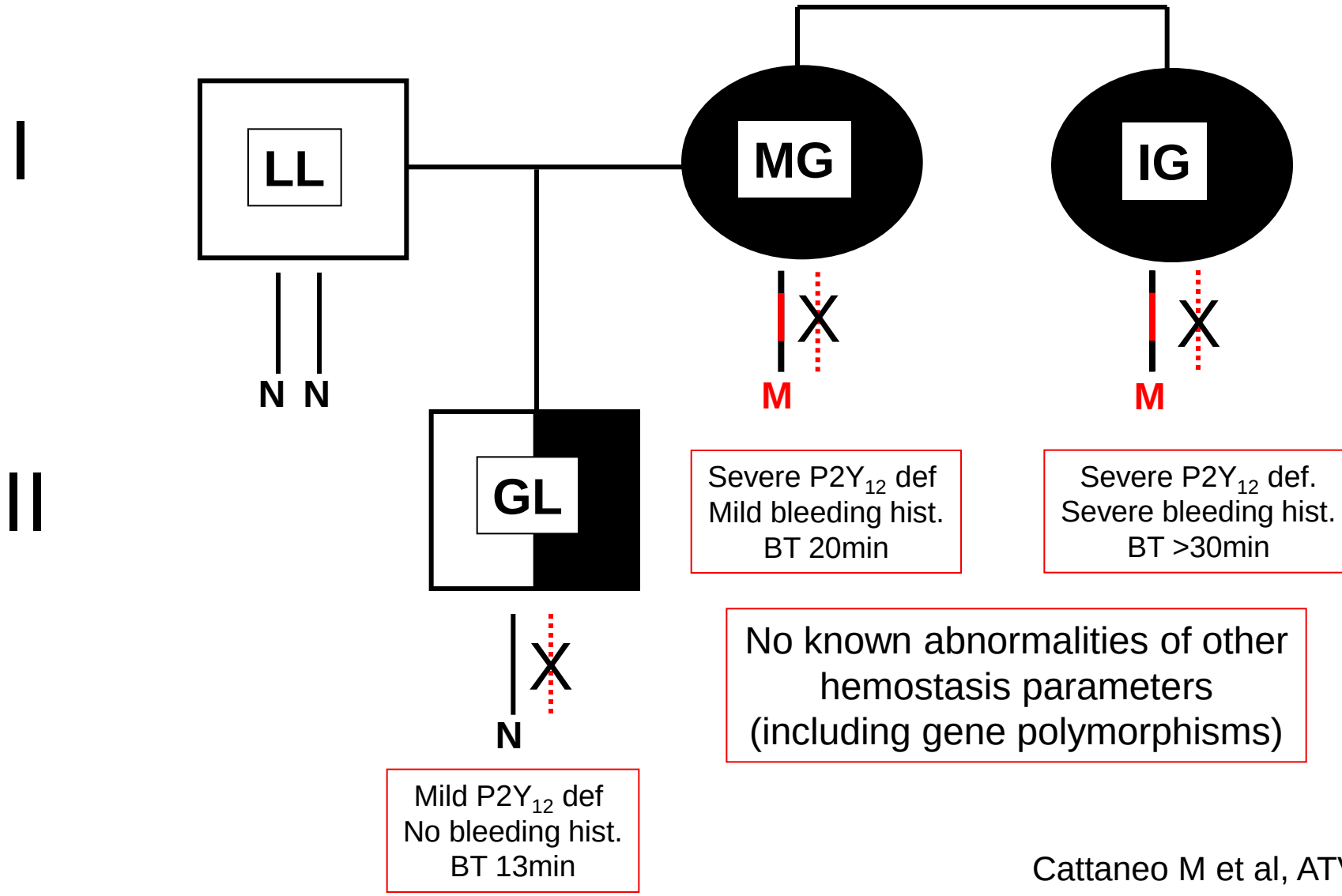


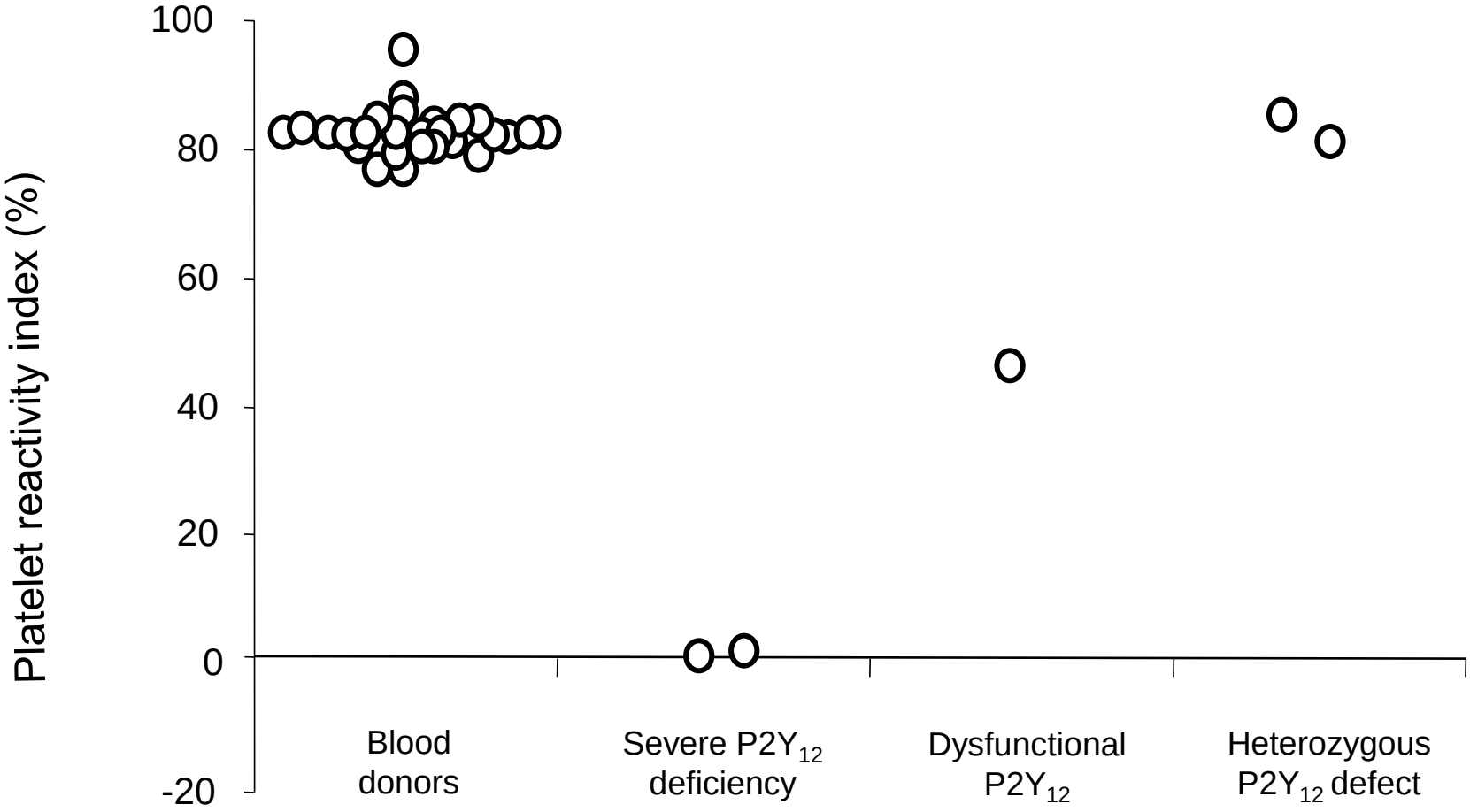
Cattaneo M et al, ATVB 2000
Fontana G et al, Haematologica 2009

Bleeding Times and Bleeding Scores in 1 patient with inherited, $P2Y_{12}$ dysfunction

Patient	Bleeding time (min)	Bleeding score*
A.C	19-20	10

*Bleeding score: Tosetto et al, JTH 2005

VASP phosphorylation assay in patients with congenital P2Y12 defect



Zighetti et al, JTH 2010

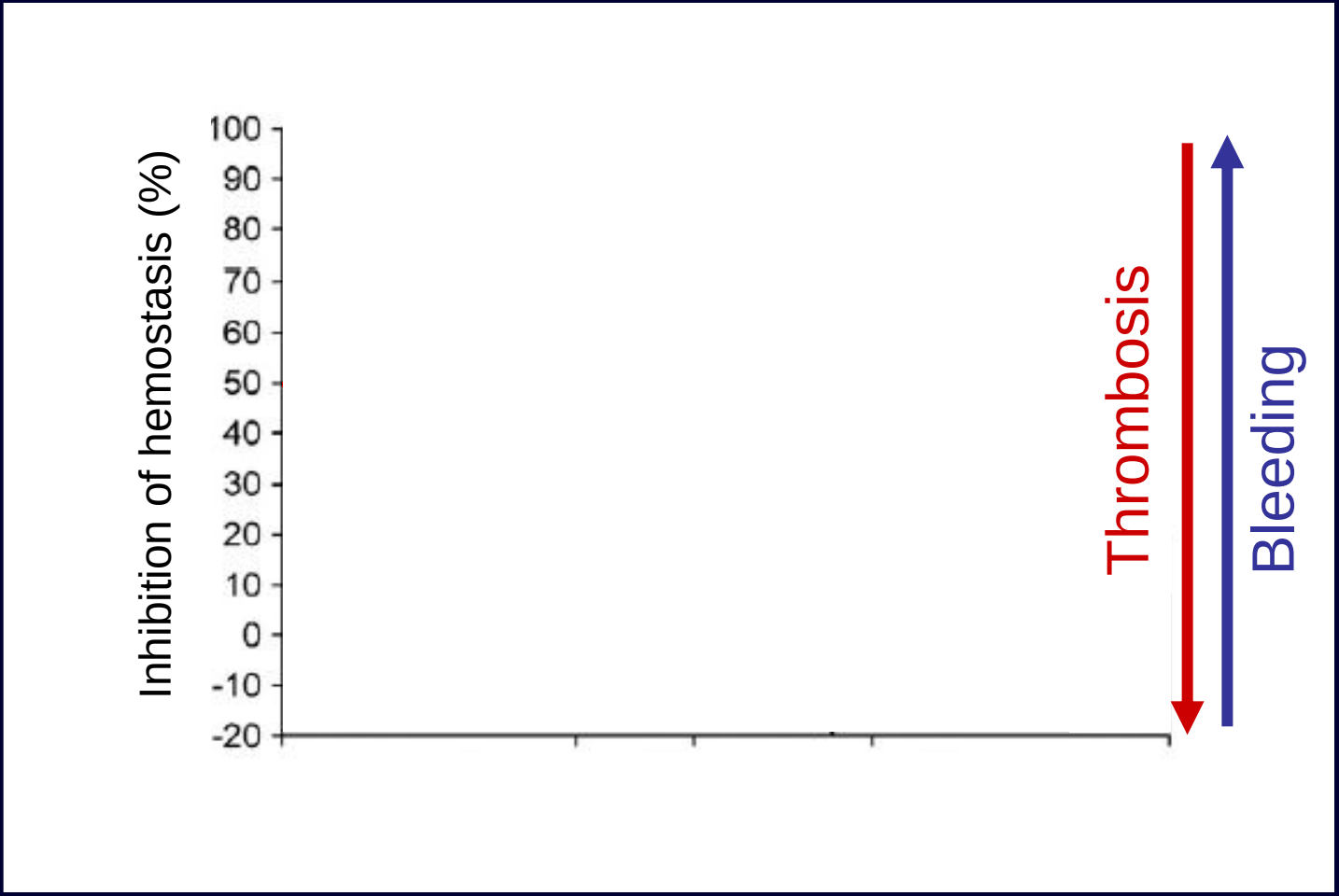
Pharmacological inhibition of $P2Y_{12}$

Characteristics of the ideal antithrombotic agent

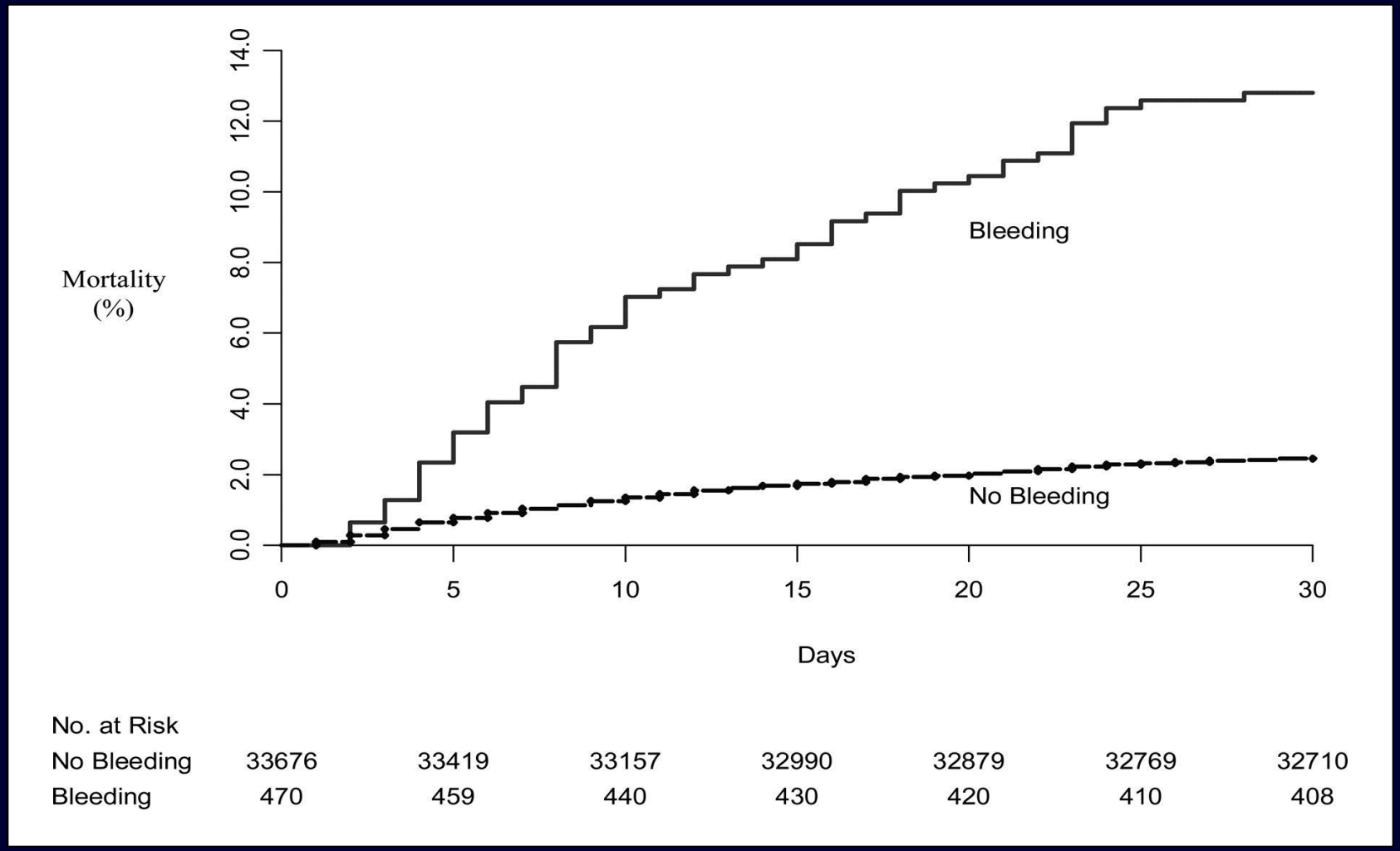
- Potent antithrombotic effect
- Low risk of bleeding complications
- Predictable pharmakodynamic profile, making monitoring unnecessary
- Rapid onset
- Rapid offset*
- Availability of an antidote
- No interaction with food or adjunctive medicines commonly used
- Low cost

** For safety reasons, a drug with rapid offset is generally preferable to a drug with long-lasting effects, although the use of the latter might minimize the negative effects of poor compliance.*

Reletionship between drug-induced inhibition of hemostasis and the risk of thrombosis or bleeding



Kaplan-Meier estimates of mortality during the first 30 days among patients who developed and those who did not develop **major bleeding**



No. at Risk							
No Bleeding	33676	33419	33157	32990	32879	32769	32710
Bleeding	470	459	440	430	420	410	408

Eikelboom, J. W. et al. Circulation 2006;114:774-782

Prognostic Modeling of Individual Patient Risk and Mortality Impact of Ischemic and Hemorrhagic Complications

Assessment From the Acute Catheterization and Urgent Intervention Triage Strategy Trial

Stuart J. Pocock, PhD; Roxana Mehran, MD; Tim C. Clayton, MSc; Eugenia Nikolsky, MD, PhD; Helen Parise, ScD; Martin Fahy, MSc; Alexandra J. Lansky, MD; Michel E. Bertrand, MD; A. Michael Lincoff, MD; Jeffrey W. Moses, MD; E. Magnus Ohman, MD; Harvey D. White, MD, DSc; Gregg W. Stone, MD

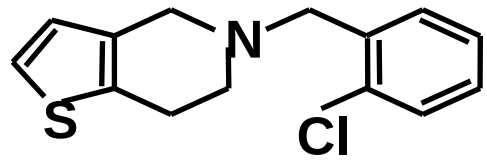
In contrast to the increased risk from non-CABG major bleeding, CABG-related major bleeding was not an independent predictor of subsequent death within 1 year (HR, 1.01; 95% confidence interval, 0.70 to 1.46; $P=0.96$).

Pocock, S. J. et al (ACUITY trial). Circulation 2010;121:43-51

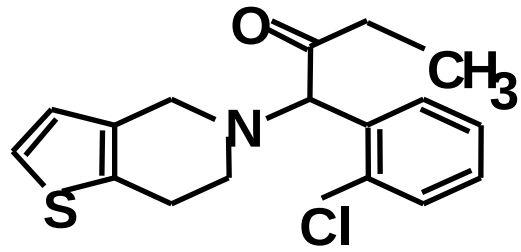
- Non CABG-related bleeding
- CABG-related bleeding

- Non CABG-related bleeding
- CABG-related bleeding

THIENOPYRIDINES

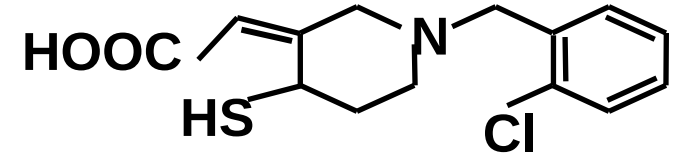


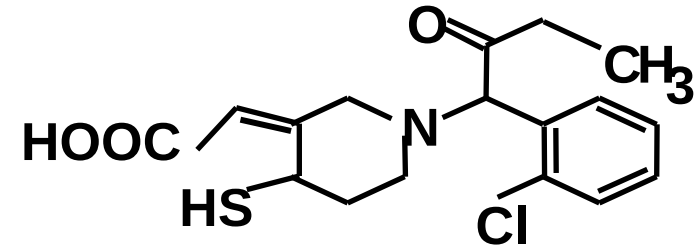
Ticlopidine

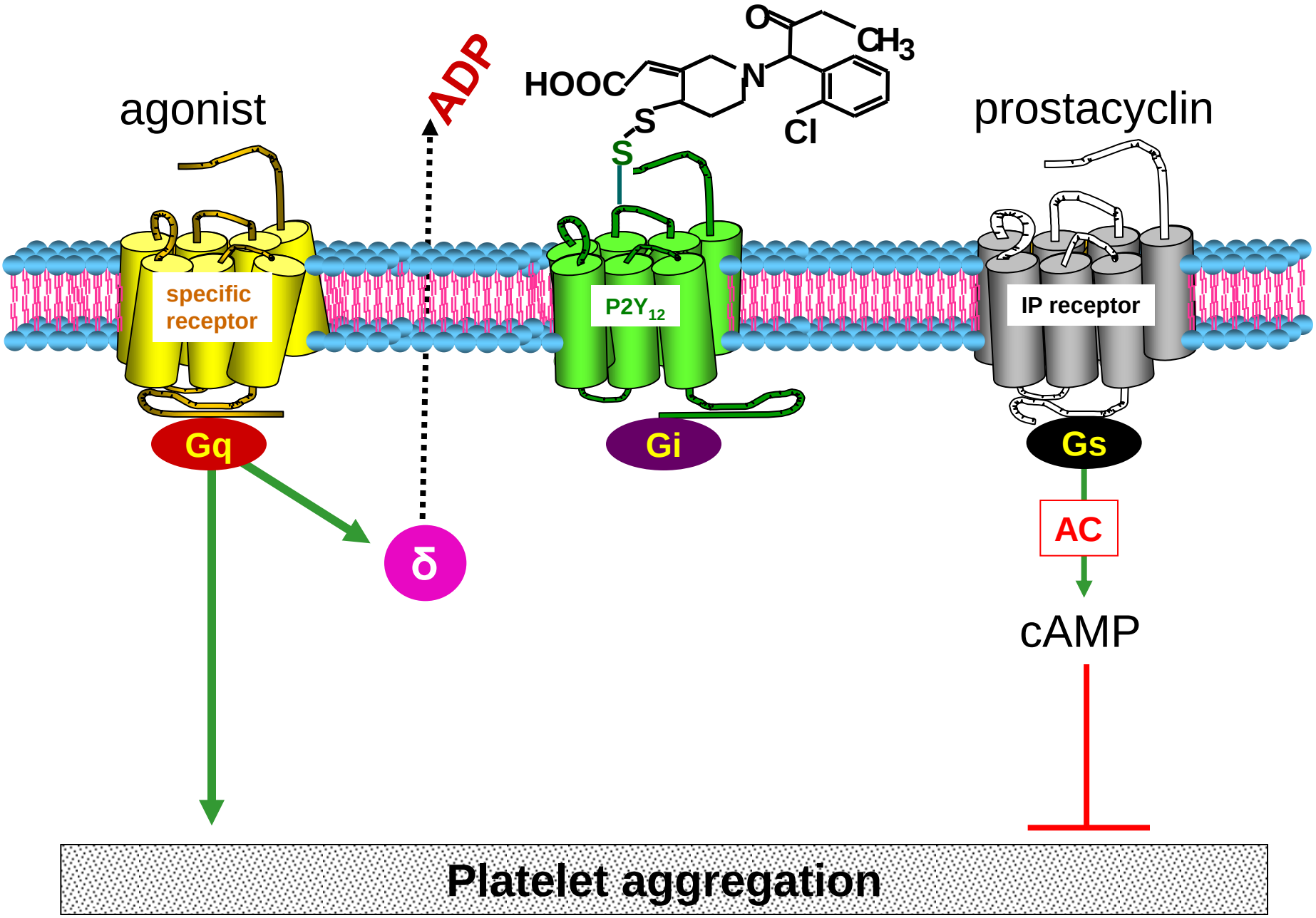


Clopidogrel

ACTIVE METABOLITES






agonist
ADP
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Platelet aggregation

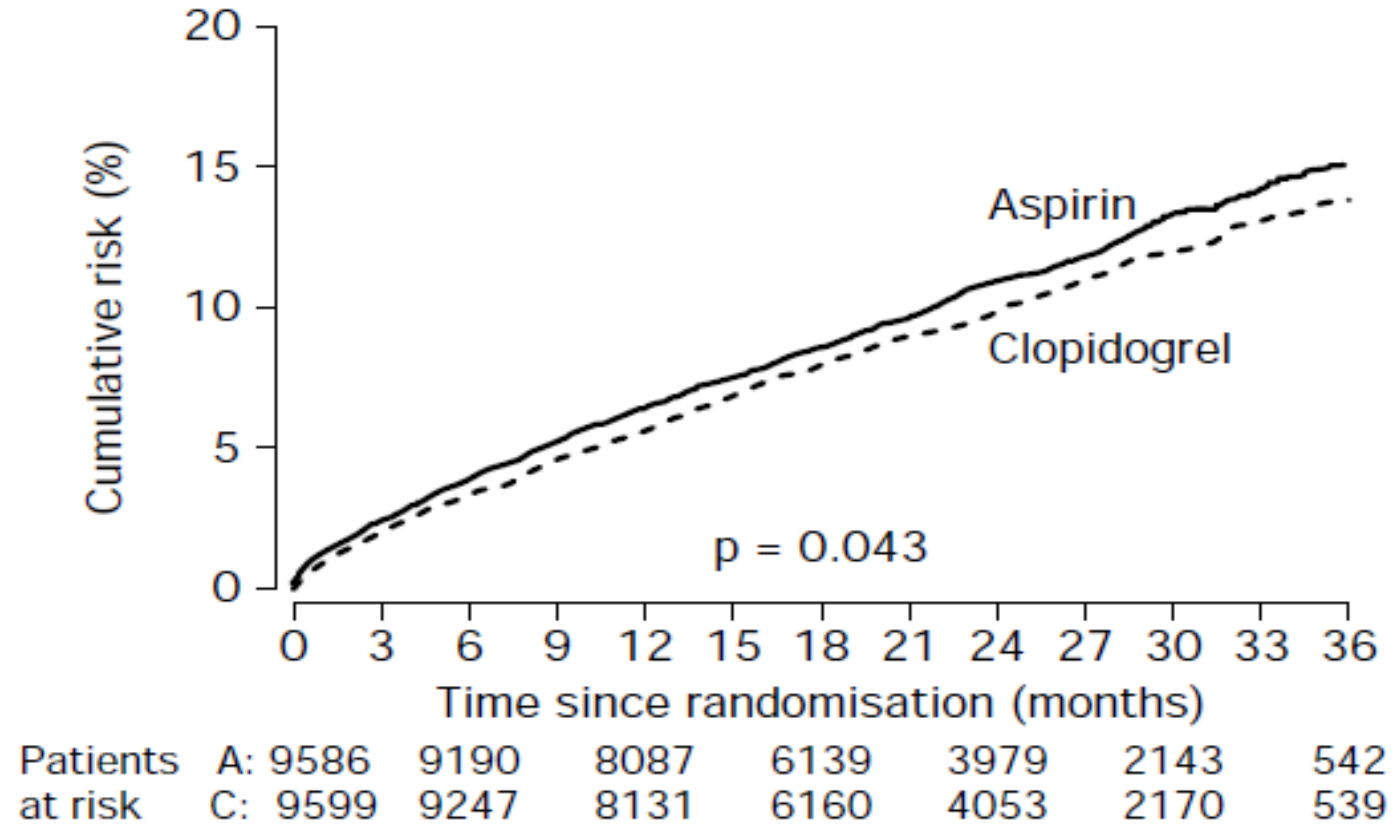

Figure 3: **Cumulative risk of Ischaemic stroke, myocardial infarction, or vascular death**
A=aspirin; C=clopidogrel.

CAPRIE Steering Committee, Lancet 1996

Incidences of adverse clinical events in the two study arms (CAPRIE Study)

Adverse experience	Patients ever reporting		Severe		Study drug permanently discontinued	
	Clopidogrel	Aspirin	Clopidogrel	Aspirin	Clopidogrel	Aspirin
Rash	578 (6·02%)	442 (4·61%)*	25 (0·26%)	10 (0·10%)*	86 (0·90%)	39 (0·41)*
Diarrhoea	428 (4·46%)	322 (3·36%)*	22 (0·23%)	11 (0·11%)	40 (0·42%)	26 (0·27%)
Indigestion/nausea/vomiting	1441 (15·01%)	1686 (17·59%)*	93 (0·97%)	118 (1·23%)	182 (1·90%)	231 (2·41%)*
Any bleeding disorder	890 (9·27%)	890 (9·28%)	132 (1·38%)	149 (1·55%)	115 (1·20%)	131 (1·37%)
Intracranial haemorrhage	34 (0·35%)	47 (0·49%)	30 (0·31%)	41 (0·43%)	20 (0·21%)	32 (0·33%)
Gastrointestinal haemorrhage	191 (1·99%)	255 (2·66%)*	47 (0·49%)	68 (0·71%)*	50 (0·52%)	89 (0·93%)*
Abnormal liver function	285 (2·97%)	302 (3·15%)*	11 (0·11%)	9 (0·09%)	22 (0·23%)	28 (0·29%)

*Statistically significant, $p<0.05$.

Table 9: **Adverse experiences (number and percentage of patients)**

Follow-up: 1-3 years

CAPRIE Steering Committee, Lancet 1996

Clopidogrel in combination with aspirin

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Antithrombotic Therapy

The Relative Efficacy and Safety of Clopidogrel in Women and Men

A Sex-Specific Collaborative Meta-Analysis

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New York, New York; Boston, Massachusetts; Oxford, England; Beijing, China; Hamilton, Ontario, Canada; La Jolla, California; and Danville, Pennsylvania

Table 1 Design of Trials Included in the Meta-Analysis

Trial, Year	n	Patient Population	Female Sex (%)	Clopidogrel Dosage	Clopidogrel Duration	Follow-Up
CURE, 2001	12,562	Patients who presented with acute coronary syndromes without ST-segment elevation	38.5	300-mg loading dose followed by 75 mg/day	3 to 12 months (mean duration of treatment 9 months)	1 yr
CREDO, 2003	2,116	Patients referred for a planned PCI or coronary angiogram	28.6	300-mg loading dose followed by 75 mg once daily*	12 months	1 yr
CLARITY–TIMI 28, 2005	3,491	Patients who presented within 12 h after the onset of an ST-segment elevation MI	19.7	300-mg loading dose followed by 75 mg once daily	Up to and including the day of coronary angiography†	30 days
COMMIT, 2005	45,852	Patients who presented within 24 h of suspected acute MI	27.8	75 mg daily	Hospital discharge or 28 days (median of ~2 weeks)	Hospital discharge or 28 days (median of ~2 weeks)
CHARISMA, 2006	15,603	Patients with clinically evident cardiovascular disease or multiple risk factors	29.8	75 mg daily	Median of 28 months, maximum of 35 months	Median of 28 months, maximum of 35 months

*Both groups received 75 mg/day of clopidogrel through day 28. †For patients who did not undergo angiography, study drug was to be administered up to and including day 8 or hospital discharge, whichever came first.

CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CLARITY–TIMI 28 = Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction 28; COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction Trial; CREDO = Clopidogrel for the Reduction of Events During Observation; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Berger et al, JACC 2009

Bleeding in patients on DAPT (clopidogrel+ASA) vs ASA alone

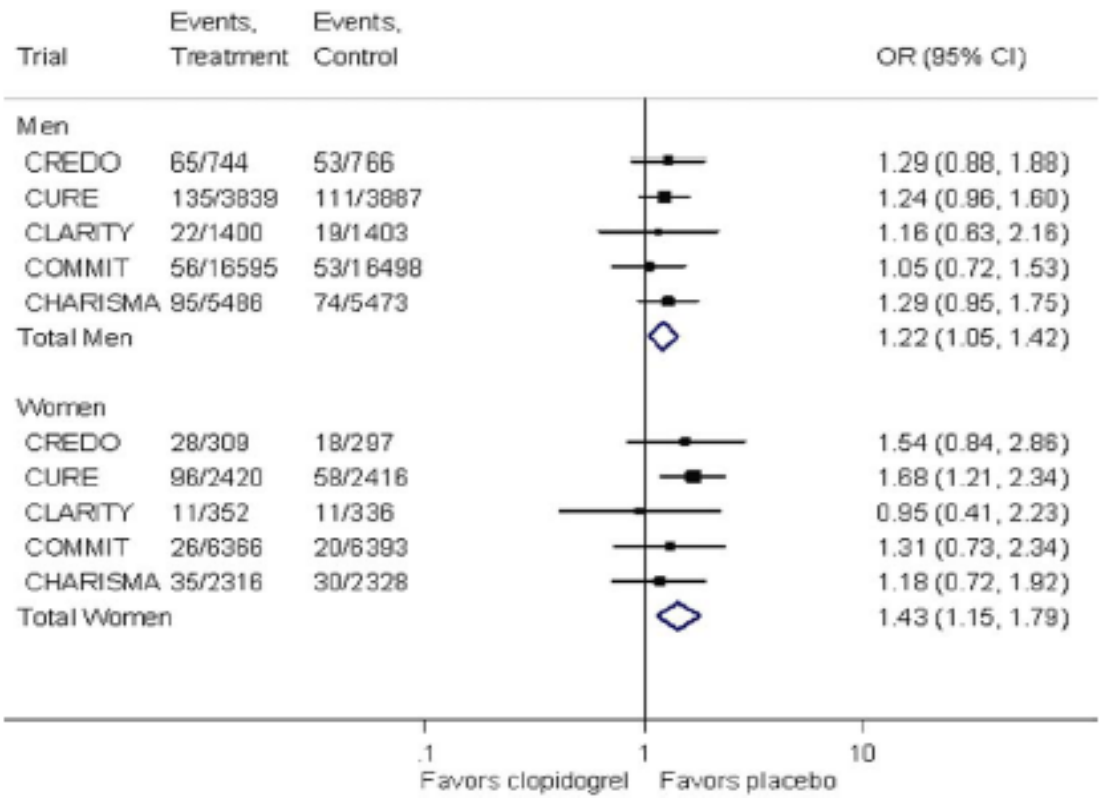


Figure 6 **Effect of Clopidogrel Treatment on the Effect of Major Bleeding**

Pooled ORs are from a random-effects model. Sizes of data markers are proportional to the amount of data contributed by each trial. Abbreviations as in Figure 2.

Berger et al, JACC 2009

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

ABSTRACT

BACKGROUND

Vitamin K antagonists reduce the risk of stroke in patients with atrial fibrillation but are considered unsuitable in many patients, who usually receive aspirin instead. We investigated the hypothesis that the addition of clopidogrel to aspirin would reduce the risk of vascular events in patients with atrial fibrillation.

METHODS

A total of 7554 patients with atrial fibrillation who had an increased risk of stroke and for whom vitamin K–antagonist therapy was unsuitable were randomly assigned to receive clopidogrel (75 mg) or placebo, once daily, in addition to aspirin. The primary outcome was the composite of stroke, myocardial infarction, non–central nervous system systemic embolism, or death from vascular causes.

N Engl J Med 2009;360:2066-78

Relative Risks of Hemorrhage, According to Treatment Group

Table 3. Relative Risks of Hemorrhage, According to Treatment Group.

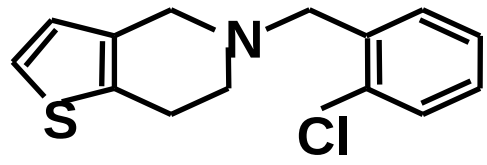
Bleeding	Clopidogrel plus Aspirin		Aspirin		Relative Risk (95% CI)	P Value
	no. of events	%/yr	*no. of events*	%/yr		
Major bleeding	251	2.0	162	1.3	1.57 (1.29–1.92)	<0.001
Severe	190	1.5	122	1.0	1.57 (1.25–1.98)	<0.001
Fatal	42	0.3	27	0.2	1.56 (0.96–2.53)	0.07
Minor bleeding	408	3.5	175	1.4	2.42 (2.03–2.89)	<0.001
Any bleeding	1014	9.7	651	5.7	1.68 (1.52–1.85)	<0.001
Site of major bleeding*						
Gastrointestinal	132	1.1	68	0.5	1.96 (1.46–2.63)	<0.001
Gastrointestinal, with transfusion	117	0.9	61	0.5	1.93 (1.42–2.63)	<0.001
Intracranial	54	0.4	29	0.2	1.87 (1.19–2.94)	0.006
Extracranial	200	1.6	134	1.1	1.51 (1.21–1.88)	<0.001

* Four patients had both intracranial and extracranial bleeding.

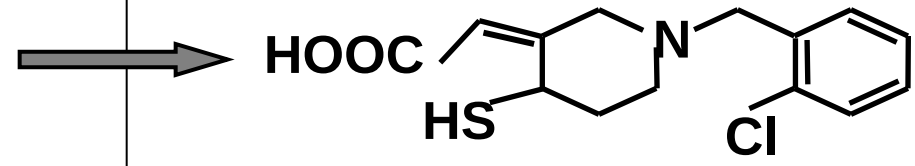
The ACTIVE Investigators. N Engl J Med 2009

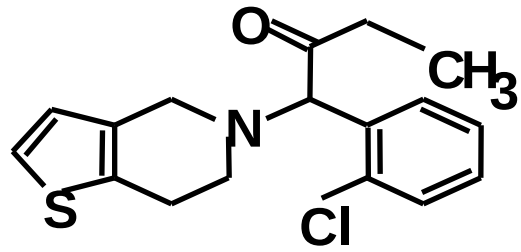
THIENOPYRIDINES

ACTIVE METABOLITES

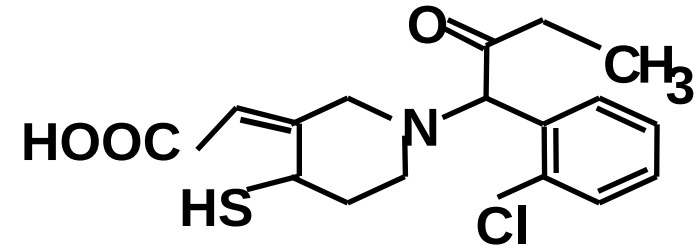


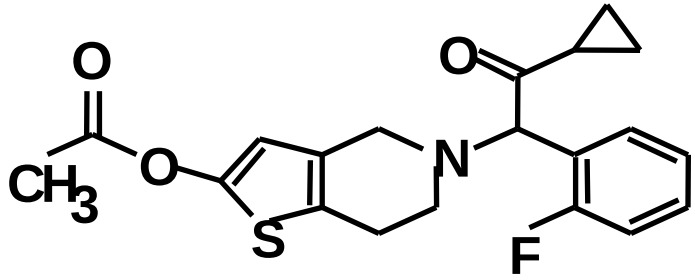
Ticlopidine



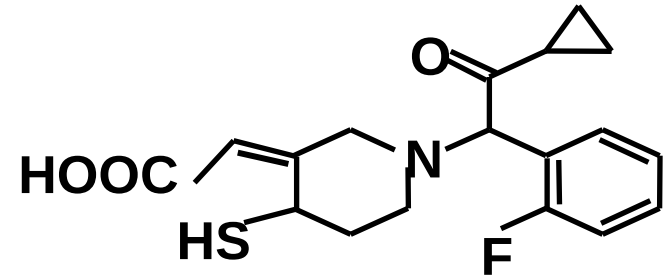


Clopidogrel

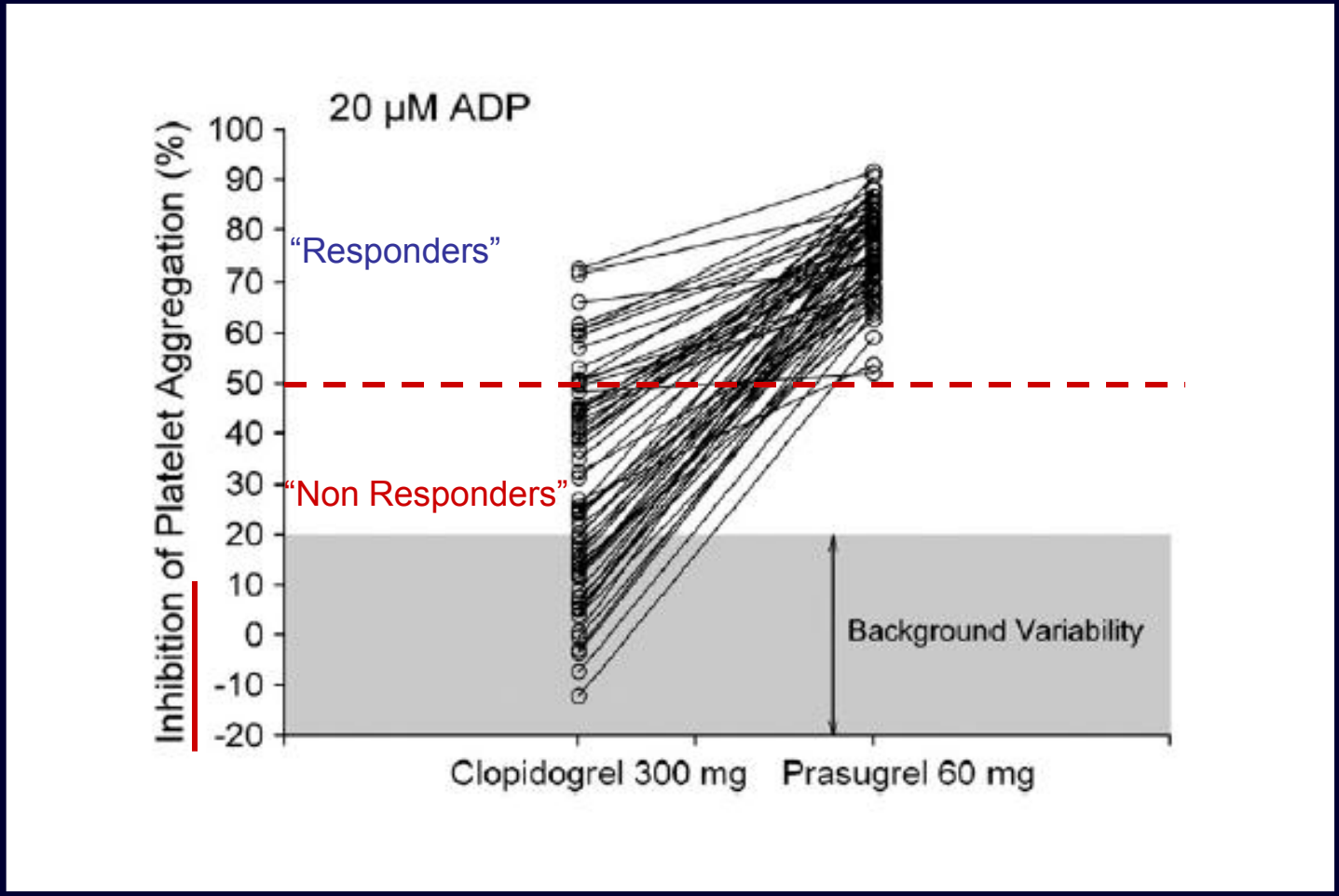




Prasugrel

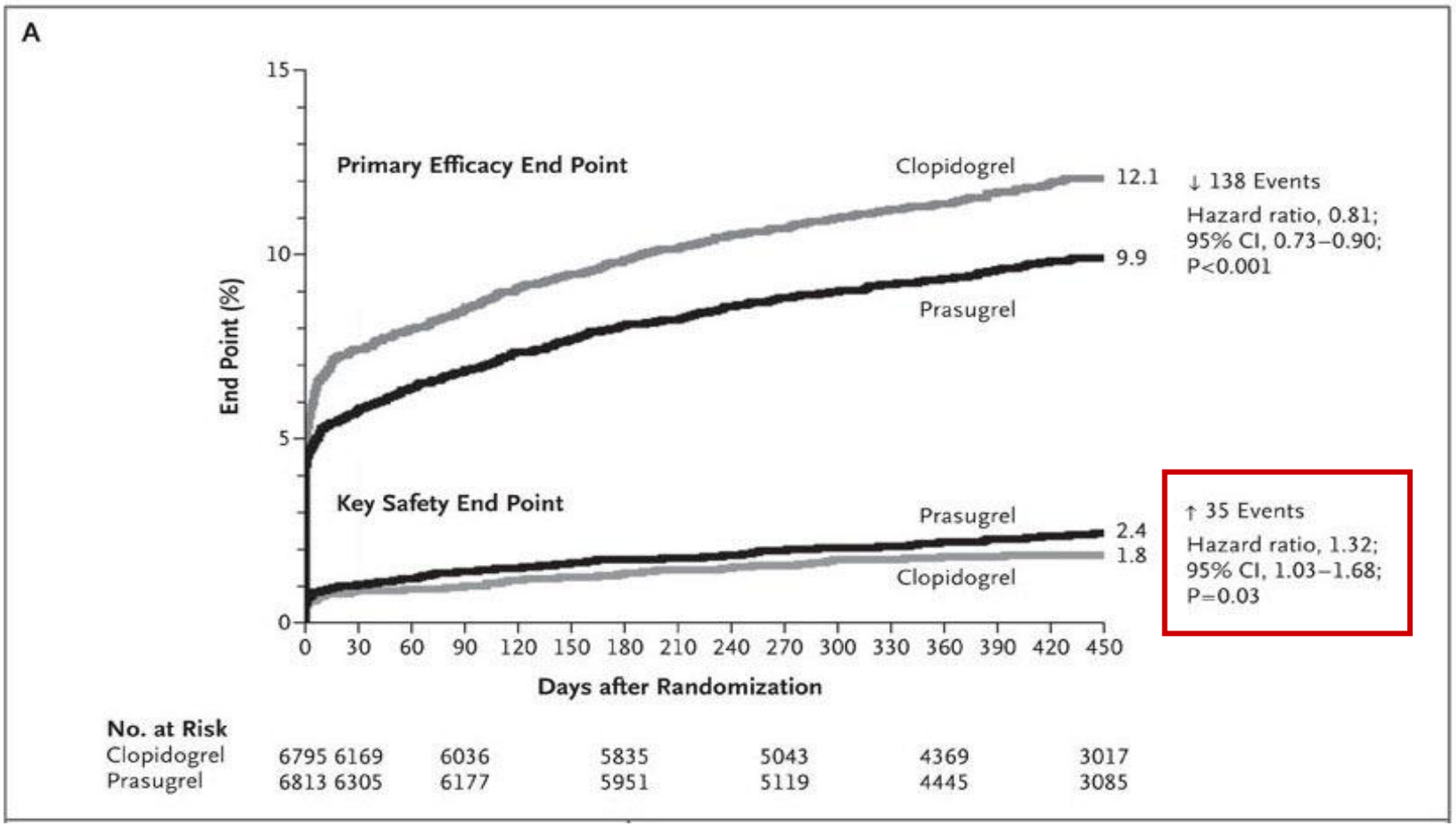


Reletionship between IPA by Clopidogrel 300 mg or Prasugrel 60 mg in response to 20 µM ADP 24 h after the loading dose



Brandt et al, Am Heart J 2007

Cumulative Kaplan-Meier Estimates of the Rates of Key Study End Points during the Follow-up Period, in TRITON-TIMI 38

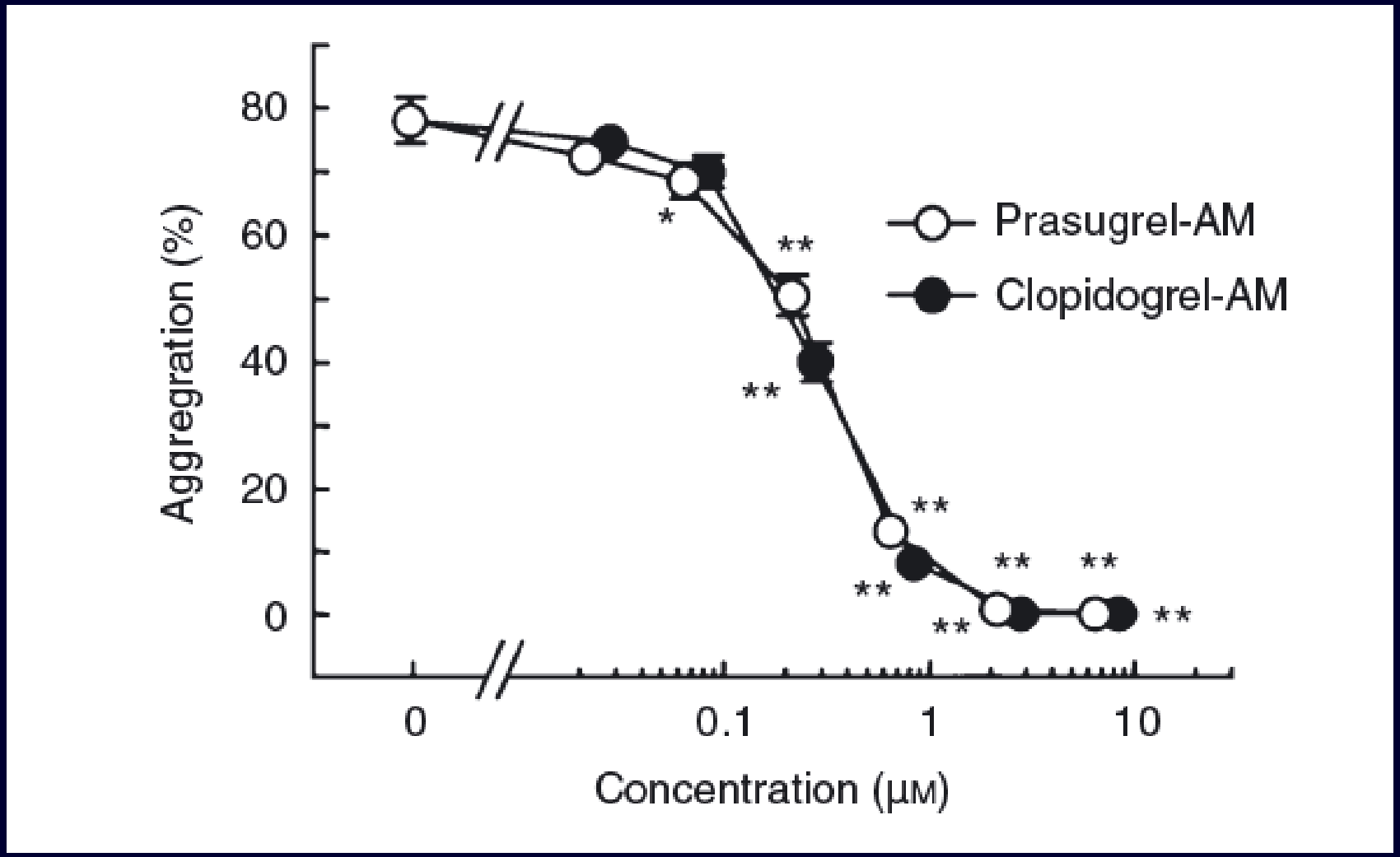


Wiviott S et al. N Engl J Med 2007

The current view

- Prasugrel is **more potent** than Clopidogrel
- Prasugrel is probably **too potent** because its use is associated with higher incidence of major bleedings, compared to Clopidogrel
- Therefore, caution should be taken in using Prasugrel, especially in patients at risk of bleeding (e.g., patients with previous cerebrovascular accidents), who should be treated with Clopidogrel

Effects of Prasugrel and Clopidogrel active metabolites (AM) on human platelet aggregation induced by ADP (10 μM)



Sugidachi et al, JTH 2007

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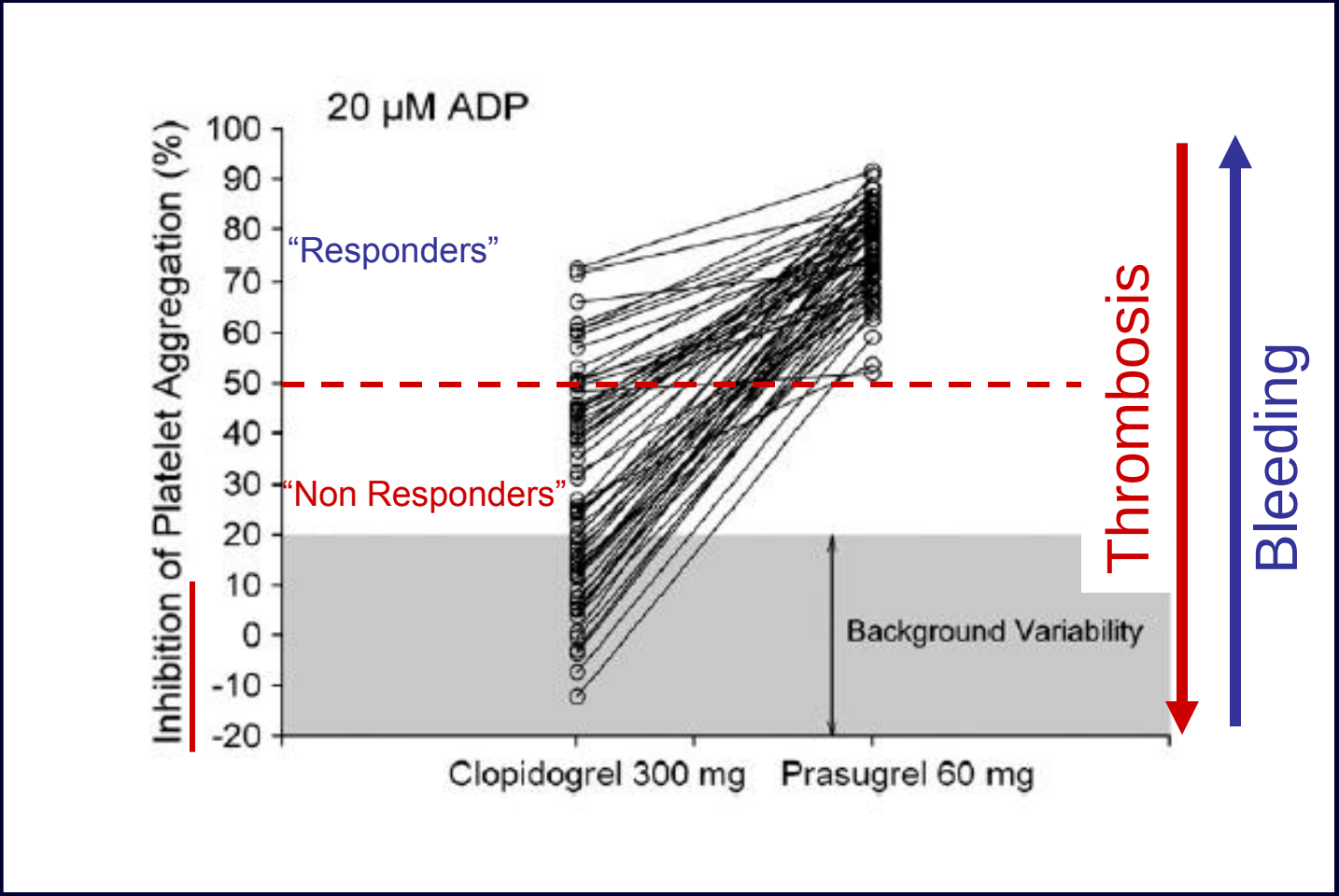

Brandt et al, Am Heart J 2007

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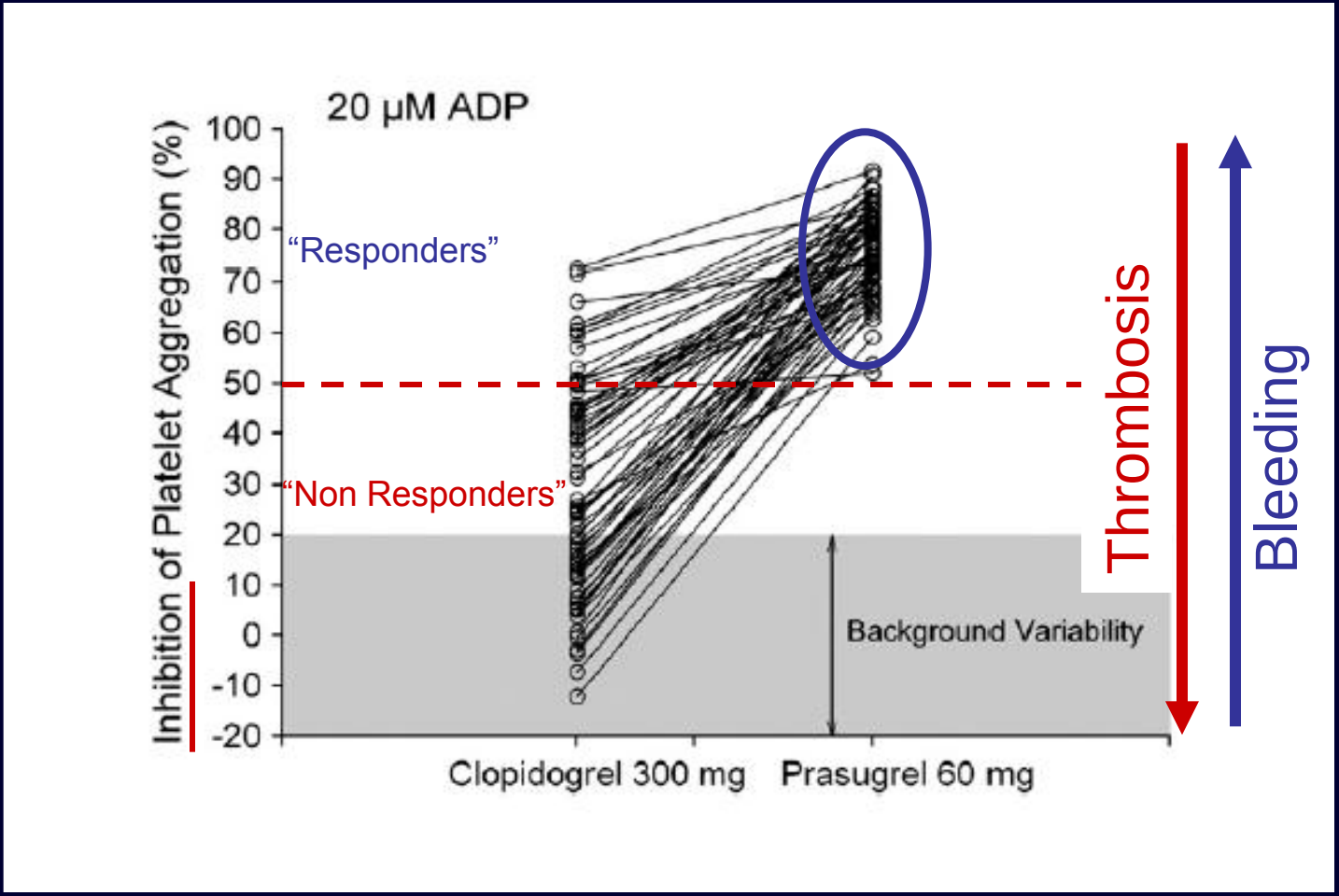

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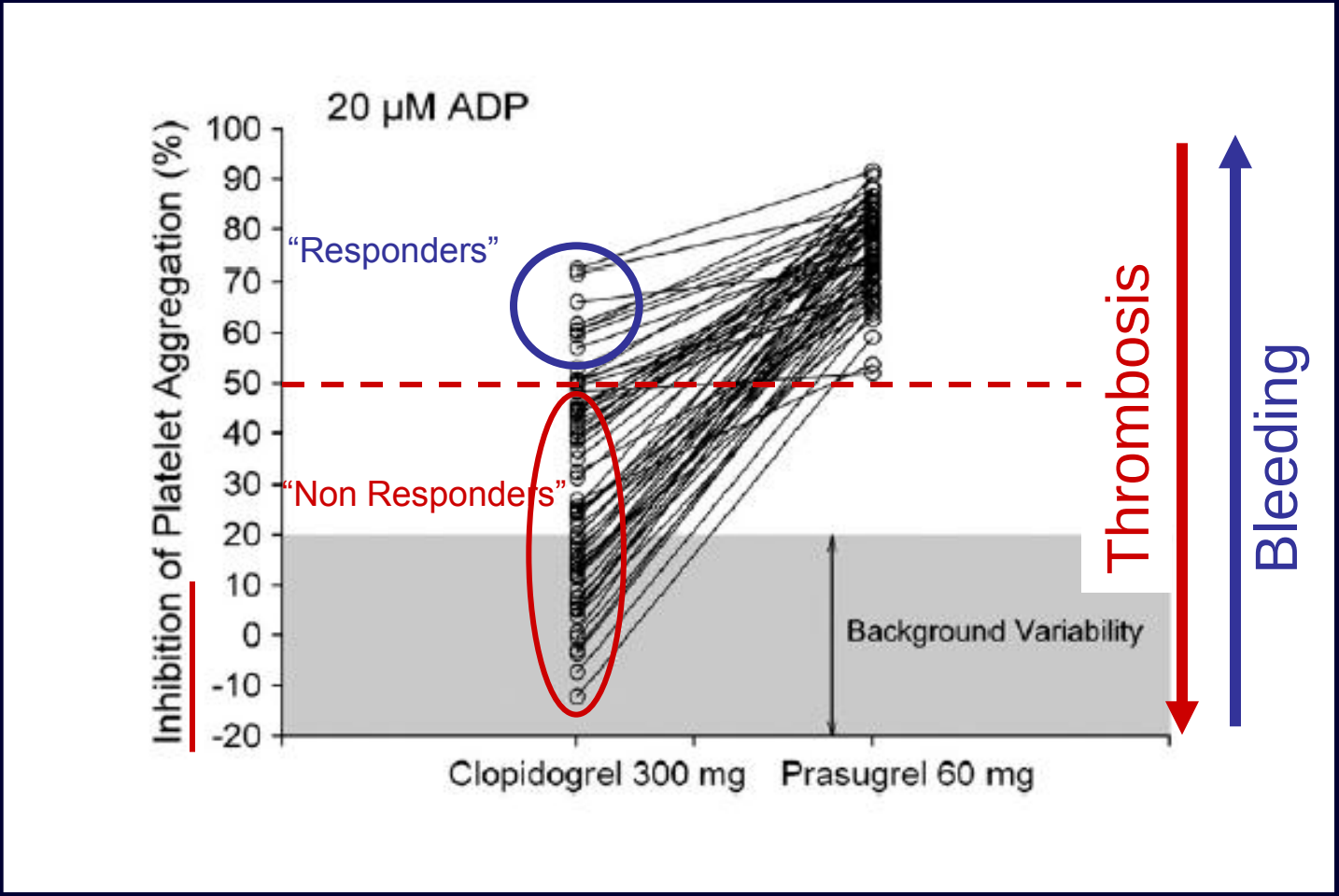
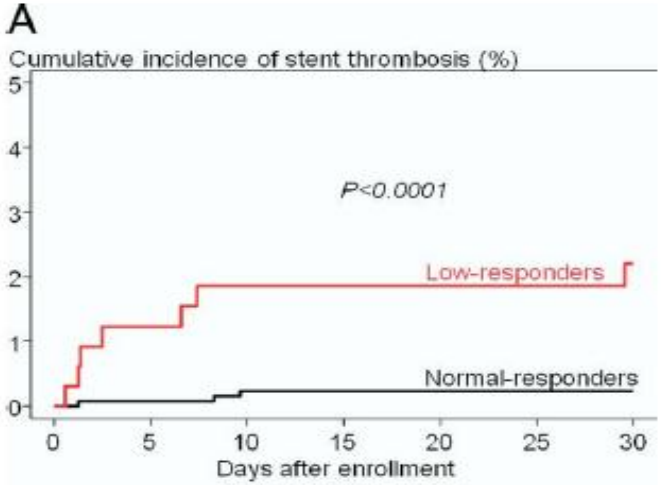


Brandt et al, Am Heart J 2007



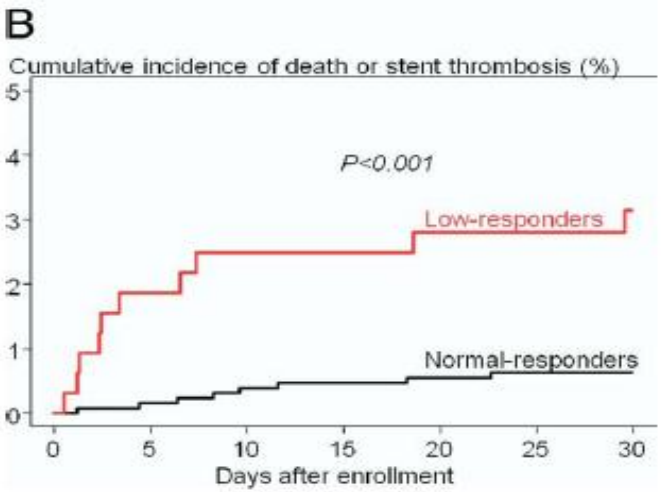


Figure 1 **Kaplan-Meier Analysis**

Kaplan-Meier analysis for the cumulative incidence of stent thrombosis **(A)** and for the composite of death or stent thrombosis **(B)**.

Sibbing et al, JACC 2009

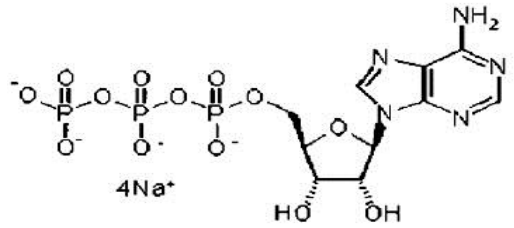
Incidence of non-CABG-related TIMI major + TIMI minor bleeding events in studies comparing prasugrel treated patients with clopidogrel treated patients, or good responders with low responders to clopidogrel.

Group 1	Group 2	Total n.of patients	Non-CABG-related TIMI major + TIMI minor bleeding events (% increase in group 1 *vs* group 2)	p
Prasugrel	Clopidogrel	13,467	32%	.002
clopidogrel Responders	clopidogrel low responders	1,608	42%	.25

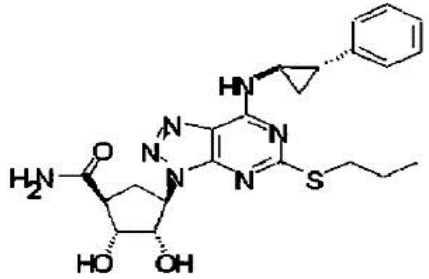
Conclusion

- It is not true that Prasugrel is “more potent” than Clopidogrel: the real difference is that, in contrast with Clopidogrel, Prasugrel effectively inhibits $P2Y_{12}$-dependent platelet function in the VAST MAJORITY OF TREATED PATIENTS
- Therefore, the higher efficacy and lower safety of Prasugrel compared to Clopidogrel are simply explained by the fact that Prasugrel protects from MACE and exposes to the risk of bleeding MORE PATIENTS than Clopidogrel

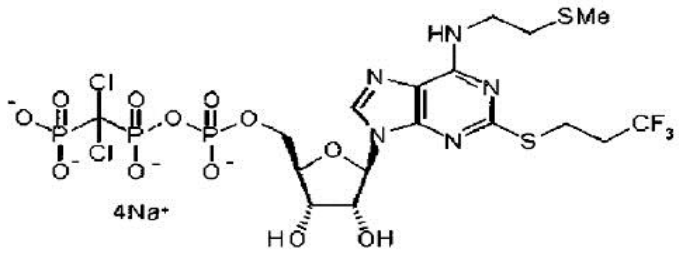
Short-acting, direct $P2Y_{12}$ antagonists



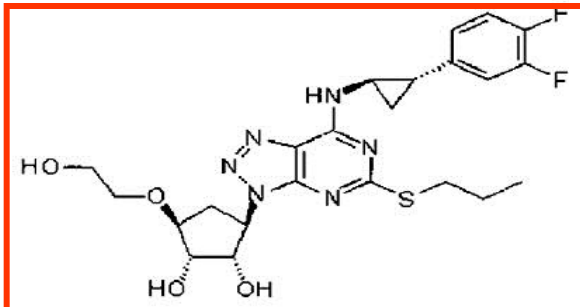
ATP



AR-C109318XX

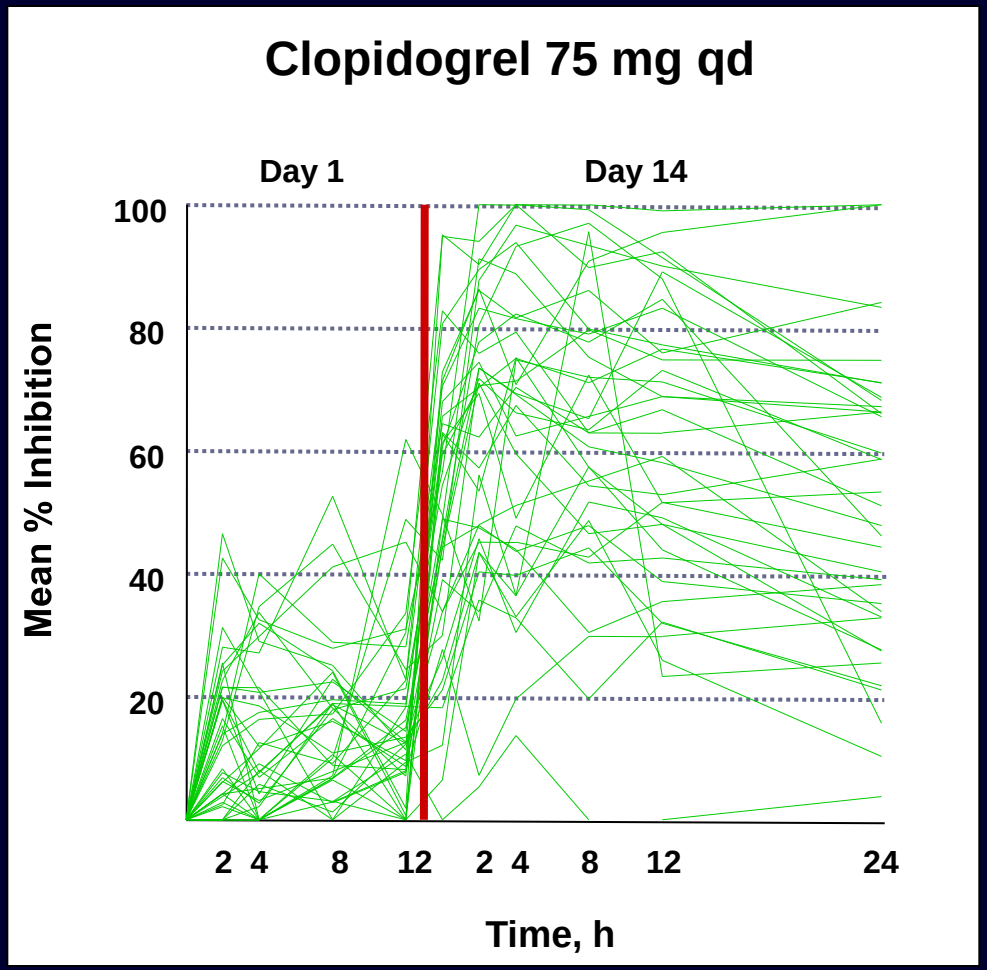


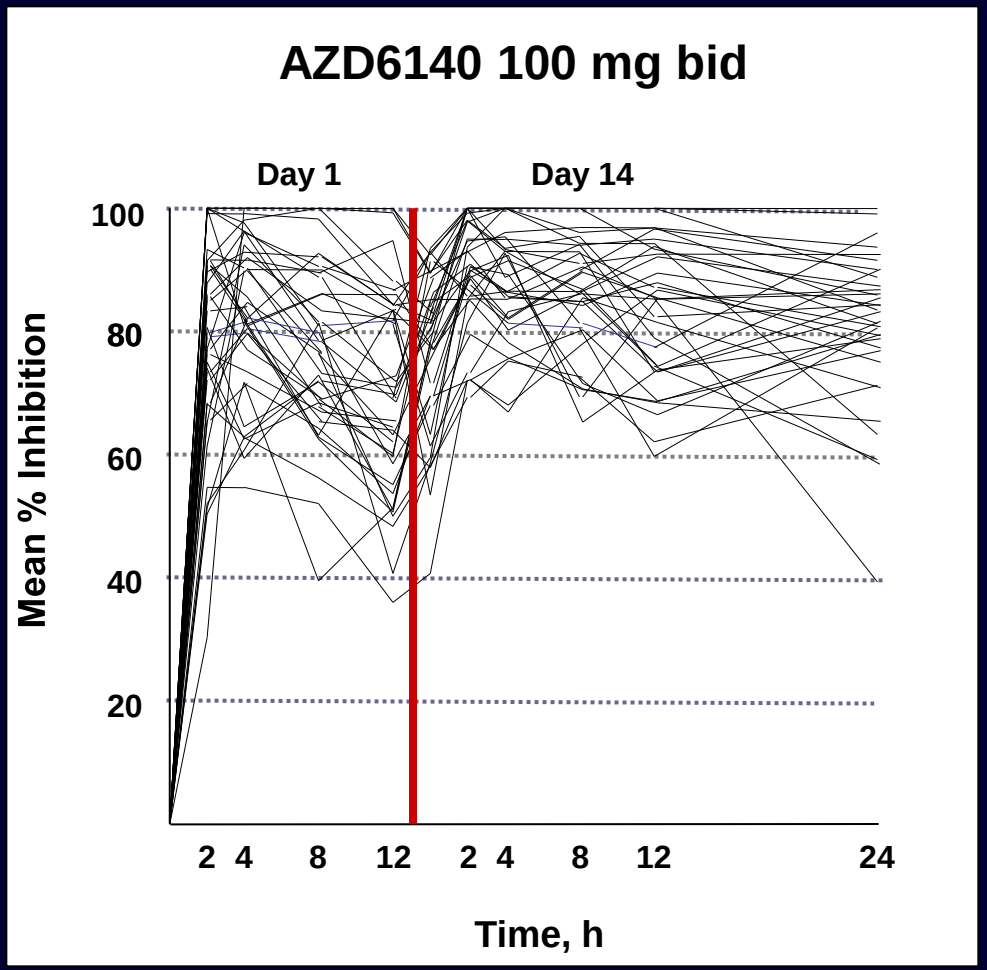
AR-C69931MX
(Cangrelor)



AZD6140
(Ticagrelor)

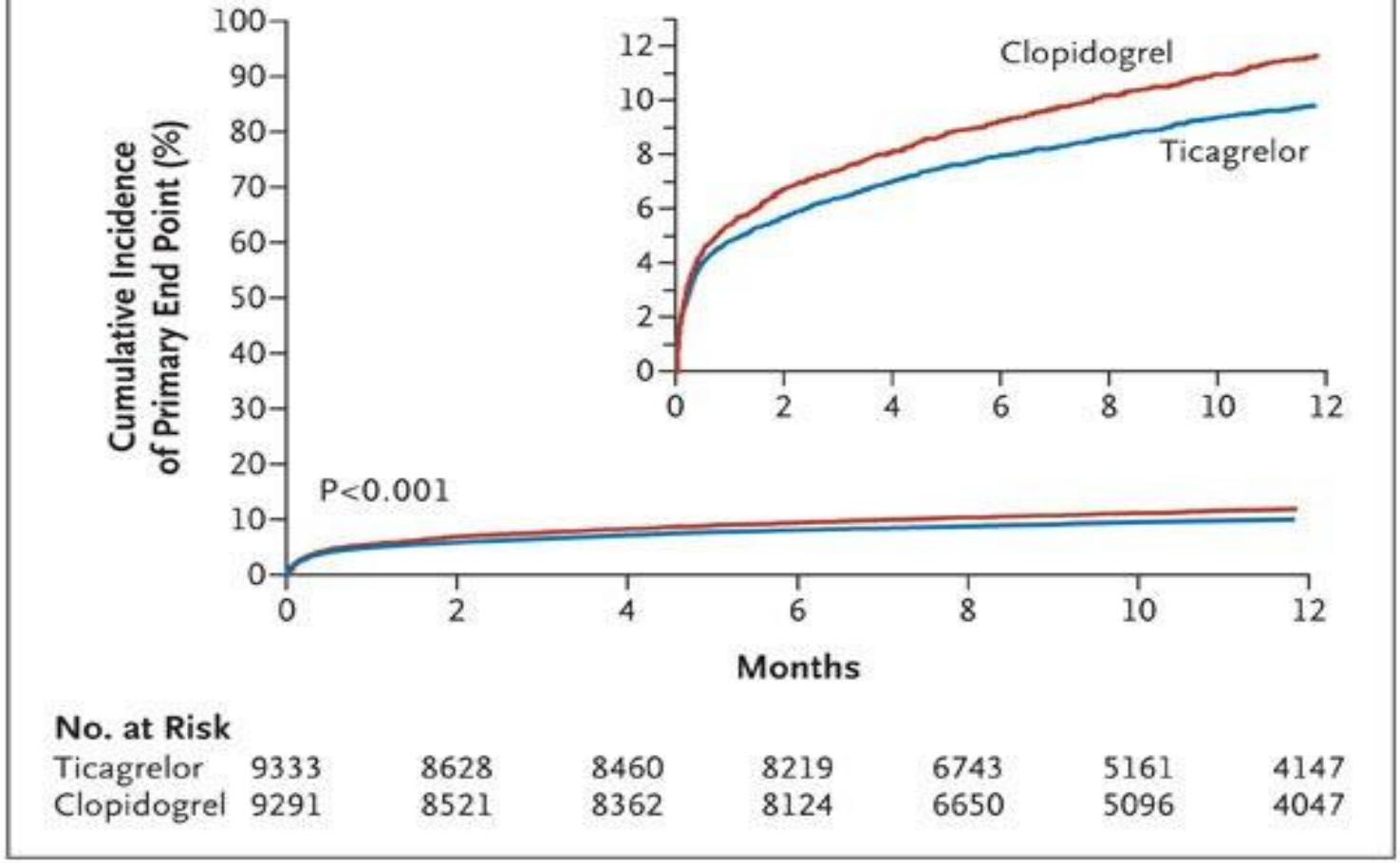
DISPERSE Study: Faster and More Consistent IPA With AZD6140 Than With Clopidogrel (Final Extent)





Husted S. Presented at ESC 2005.

Cumulative Kaplan-Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point

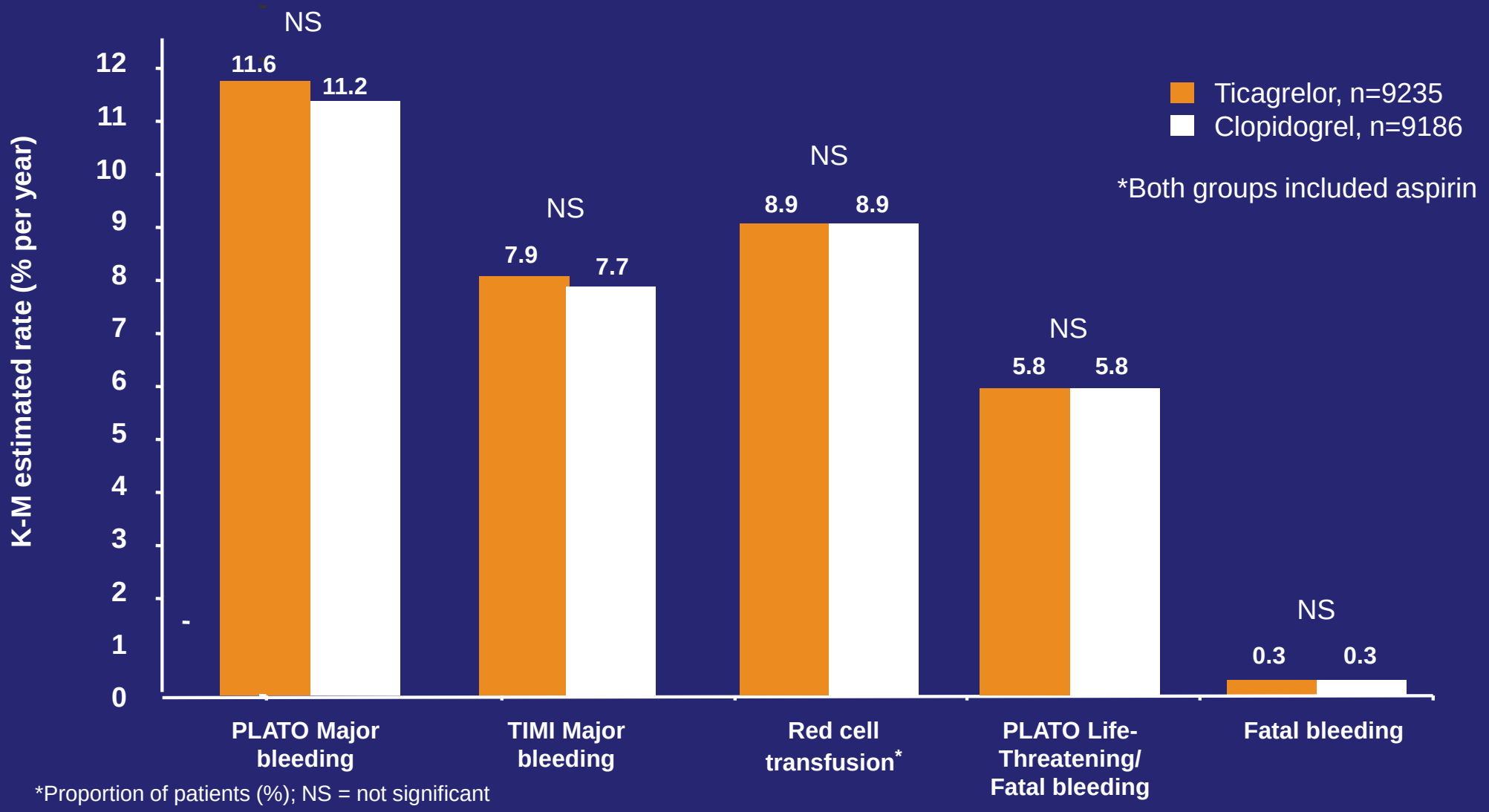


No. at Risk

Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

Wallentin L et al. N Engl J Med 2009;361:1045-1057

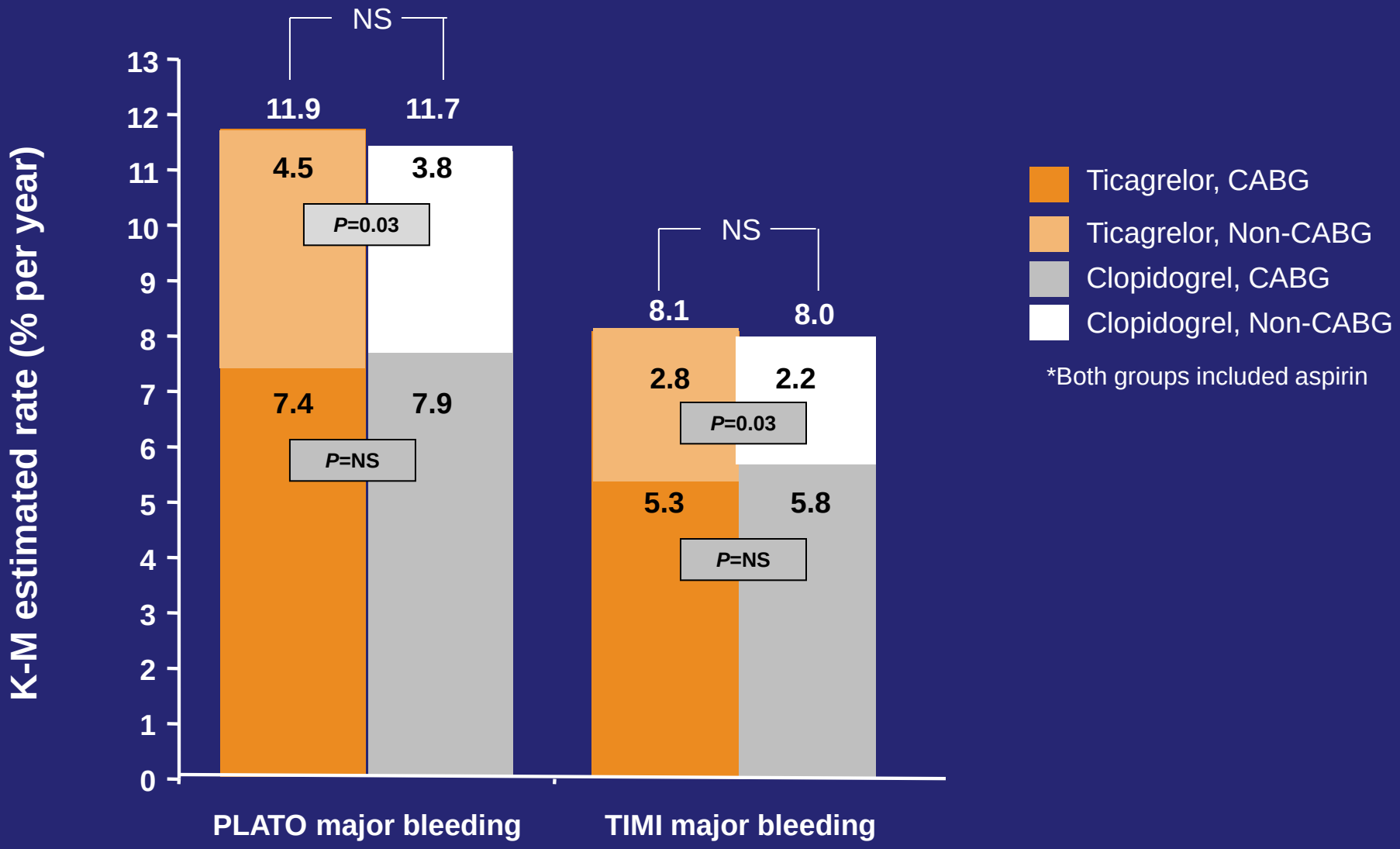
Total Major bleeding in PLATO



*Proportion of patients (%); NS = not significant

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057

Major bleeding: CABG and non-CABG*†



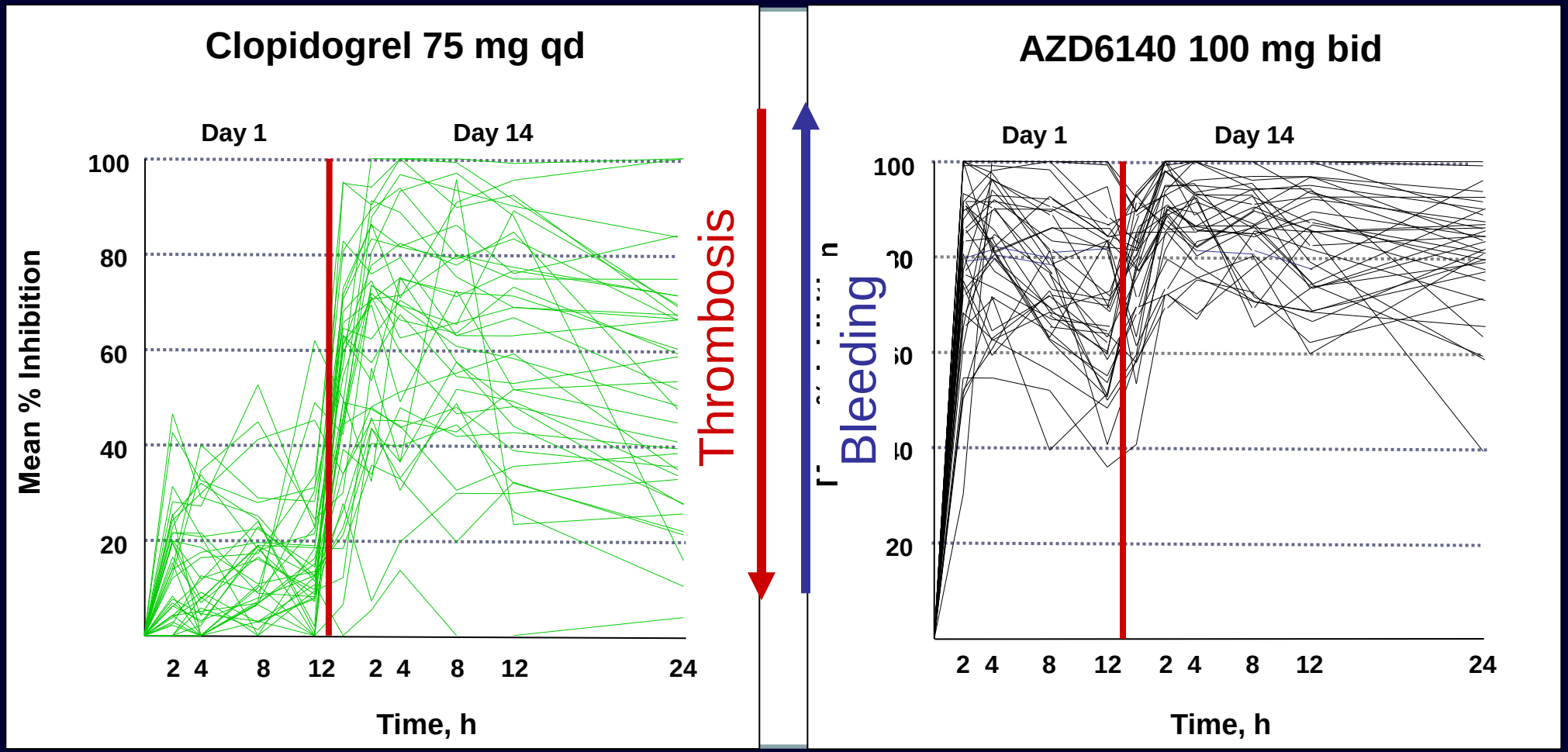
†Study drug was stopped; NS=not significant; CABG=coronary artery bypass graft; K-M=Kaplan Meier;
Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057

Incidence of the primary end-point and non-CABG-related TIMI-major bleeding events in patients who received ticagrelor vs patients who received clopidogrel in the PLATO trial.

Events	Ticagrelor no/total (%)	Clopidogrel no/total (%)	Hazard Ratio (95% C.I.)	p
Primary end point (composite of vascular death, myocardial infarction or stroke)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77-0.92)	<0.001
Non-CABG-related major bleedings, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03-1.53)	0.03

Wallentin and PLATO Investigators, NEJM 2009

DISPERSE Study: Faster and More Consistent IPA With AZD6140 Than With Clopidogrel (Final Extent)



Husted S. Presented at ESC 2005.

- Non CABG-related bleeding
- CABG-related bleeding

Use of clopidogrel and bleeding risk in patients undergoing CABG

Table 1 Results of meta-analysis

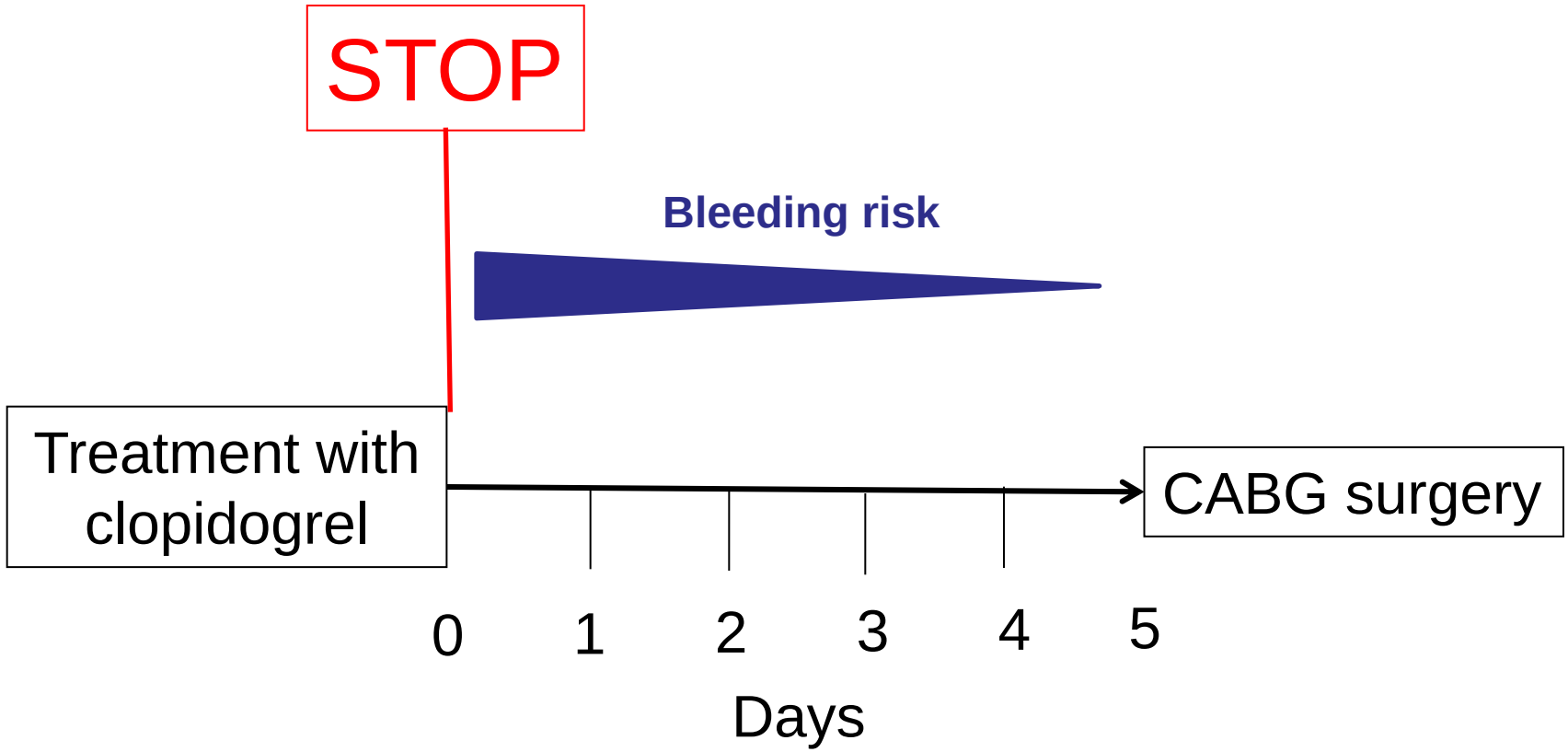
	No in analysis			Heterogeneity values		Overall effect	
Outcome	CL	NCL	WMD/OR (95% CI)	χ^2	χ^2 p value	Z	Z p value
Blood loss	427	2636	323.62 (137.19 to 510.04)	325.94	<0.01	3.40	<0.01
Overall transfusion risk	767	2021	4.90 (2.79 to 8.59)	64.73	<0.01	5.54	<0.01
Overall transfusion requirement	1542	1239	1.36 (0.80 to 1.92)	1208.14	<0.01	4.78	<0.01
Mortality	333	1005	1.01 (0.41 to 2.48)	1.76	0.78	0.02	0.98
Adverse events	296	874	1.53 (1.02 to 2.32)	3.18	0.53	2.04	0.04
Length of stay	229	1994	1.18 (0.24 to 2.12)	31.87	<0.01	2.47	0.01
Re-exploration rate	445	2649	6.76 (3.37 to 13.56)	2.63	0.85	5.38	<0.01
Ventilation requirement	210	597	2.81 (1.63 to 4.86)	3.97	0.14	3.70	<0.01

CI, confidence interval; CL, clopidogrel group; NCL, non-clopidogrel group (control); OR, odds ratio; WMD, weighted mean difference; Z, value for test for overall effect.

Purkayasta et al, Heart 2006

New $P2Y_{12}$ inhibitors *vs* clopidogrel in CABG surgery - 1

- When the clinical conditions of the patients allow it, clopidogrel is usually withheld for 5 days before CABG, in order to restore the hemostatic competency of the patient.


STOP
Bleeding risk
Treatment with clopidogrel
CABG surgery
0
1
2
3
4
5
Days

New $P2Y_{12}$ inhibitors *vs* clopidogrel in CABG surgery - 1

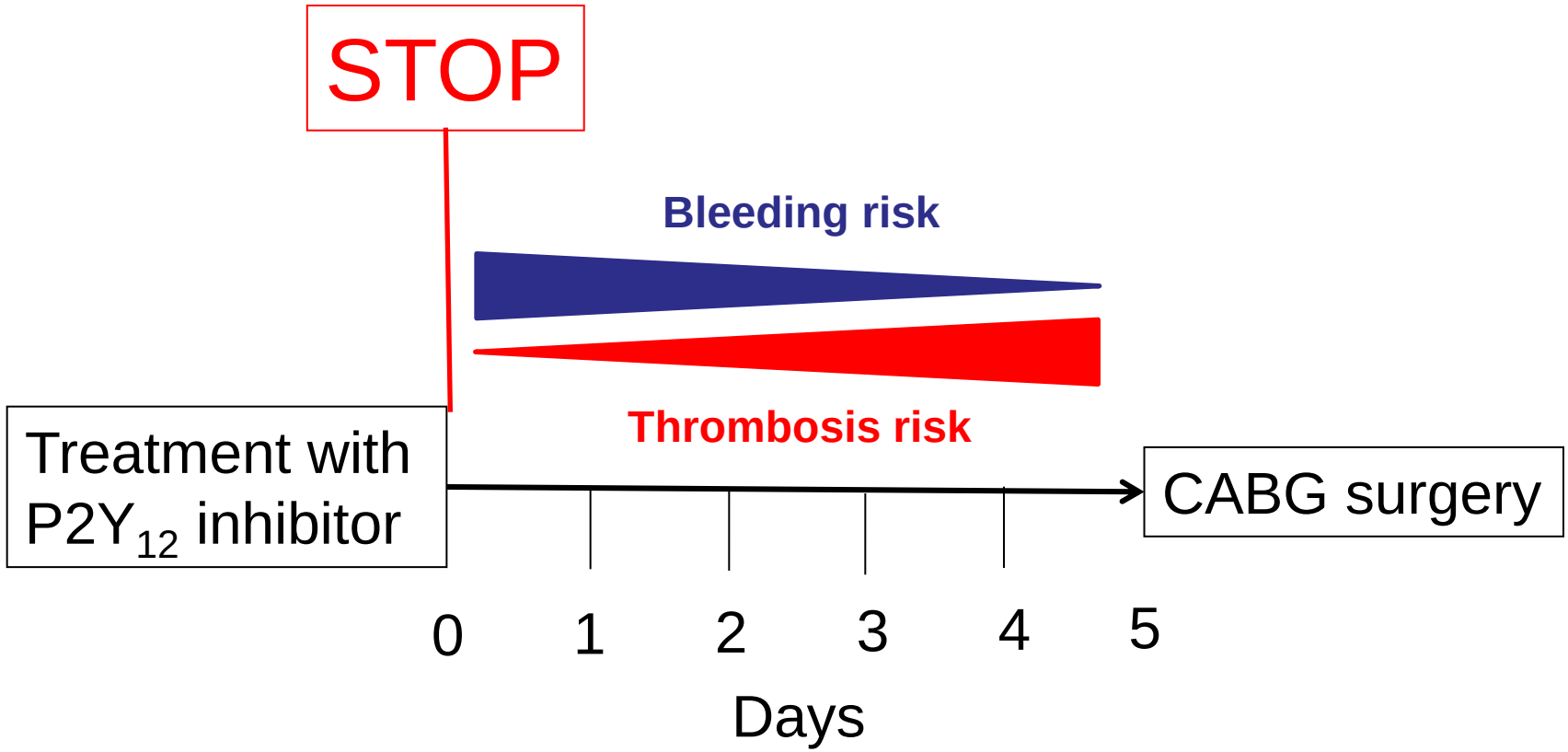
- When the clinical conditions of the patients allow it, clopidgrel is usually withheld for 5 days before CABG, in order to restore the hemostatic competency of the patient.
- This procedure was followed for patients undergoing CABG in both arms of RCTs that compared the new $P2Y_{12}$ antagonists to clopidogrel.

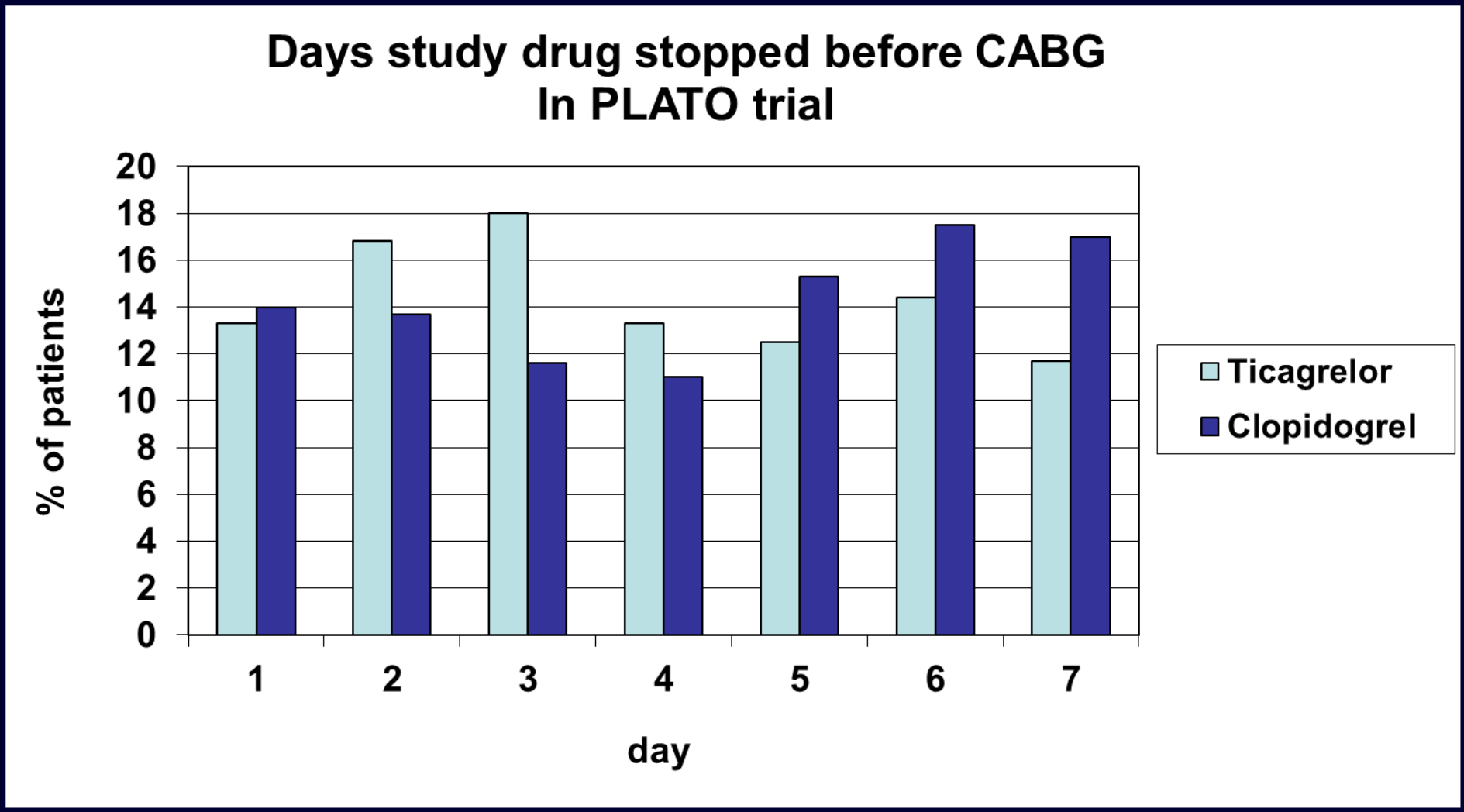
New $P2Y_{12}$ inhibitors *vs* clopidogrel in CABG surgery - 2

- Therefore, the incidence of CABG-related bleeding is not the relevant end-point to be considered when comparing new anti-$P2Y_{12}$ drugs to clopidogrel in CABG surgery, for the simple reason that patients were off-treatment when they undewent CABG.

New $P2Y_{12}$ inhibitors *vs* clopidogrel in CABG surgery - 2

- Therefore, the incidence of CABG-related bleeding is not the relevant end-point to be considered when comparing new anti-$P2Y_{12}$ drugs to clopidogrel in CABG surgery, for the simple reason that patients were off-treatment when they undewent CABG.
- Differences among $P2Y_{12}$ antagonists in this setting should be evaluated on the basis of the time needed to withhold treatment before surgery to restore adequate hemostatic competency.


STOP
Bleeding risk
Thrombosis risk
Treatment with
P2Y12 inhibitor
CABG surgery
0
1
2
3
4
5
Days


Days study drug stopped before CABG
In PLATO trial
% of patients
20
18
16
14
12
10
8
6
4
2
0
1
2
3
4
5
6
7
day
Ticagrelor
Clopidogrel

Incidence of TIMI-major CABG-related bleeding events in patients who received prasugrel vs patients who received clopidogrel in the TRITON TIMI-38 trial.

Events	Prasugrel no/total (%)	Clopidogrel no/total (%)	OR (95% C.I.)	p
CABG-related major bleedings, TIMI criteria	24/179 (13.4)	6/189 (3.2)	4.73 (1.90-11.82)	<0.001

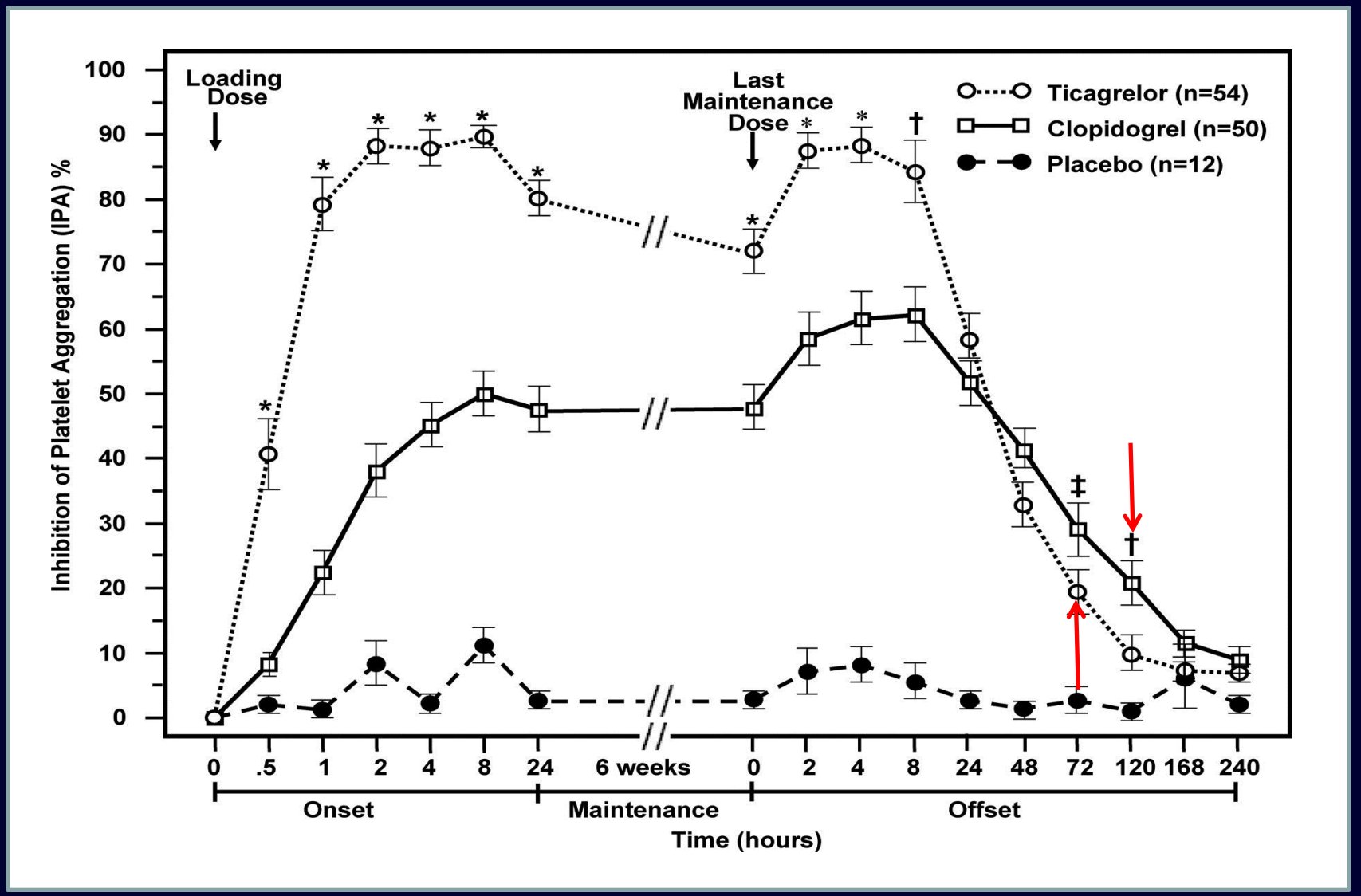
Prasugrel witheld for a median of ?? days before surgery
Clopidogrel: witheld for a median of ?? days before surgery

Incidence of TIMI-major CABG-related bleeding events in patients who received ticagrelor vs patients who received clopidogrel in the PLATO trial.

Events	Ticagrelor no/total (%)	Clopidogrel no/total (%)
CABG-related major bleedings, TIMI criteria	446/931 (47.9)	476/968 (49.2)

Ticagrelor: witheld for a median of ?? days before surgery
Clopidogrel: witheld for a median of ?? days before surgery

IPA (%; 20 {micro}mol/L ADP, final extent) by protocol time and treatment



Gurbel, P. A. et al. Circulation 2009;120:2577-2585

Conclusion

- Patients with congenital, severe $P2Y_{12}$ defects have a moderate (severe in some cases) bleeding diathesis
- The incidence of bleeding in clopidogrel-treated patients is similar to that of aspirin-treated patients
- DAPT (clopidogrel+aspirin) is associated with increased bleeding, compared to aspirin alone
- DAPT with prasugrel or ticagrelor instead of clopidogrel is associated with increased bleeding (likely due to good inhibition of platelet function in the vast majority of treated patients)