Thrombus versus Bleeding…

The Art of Balance

Kyung Woo Park, MD, PhD

Seoul National University Hospital, Seoul, Korea

Today's KEY Message

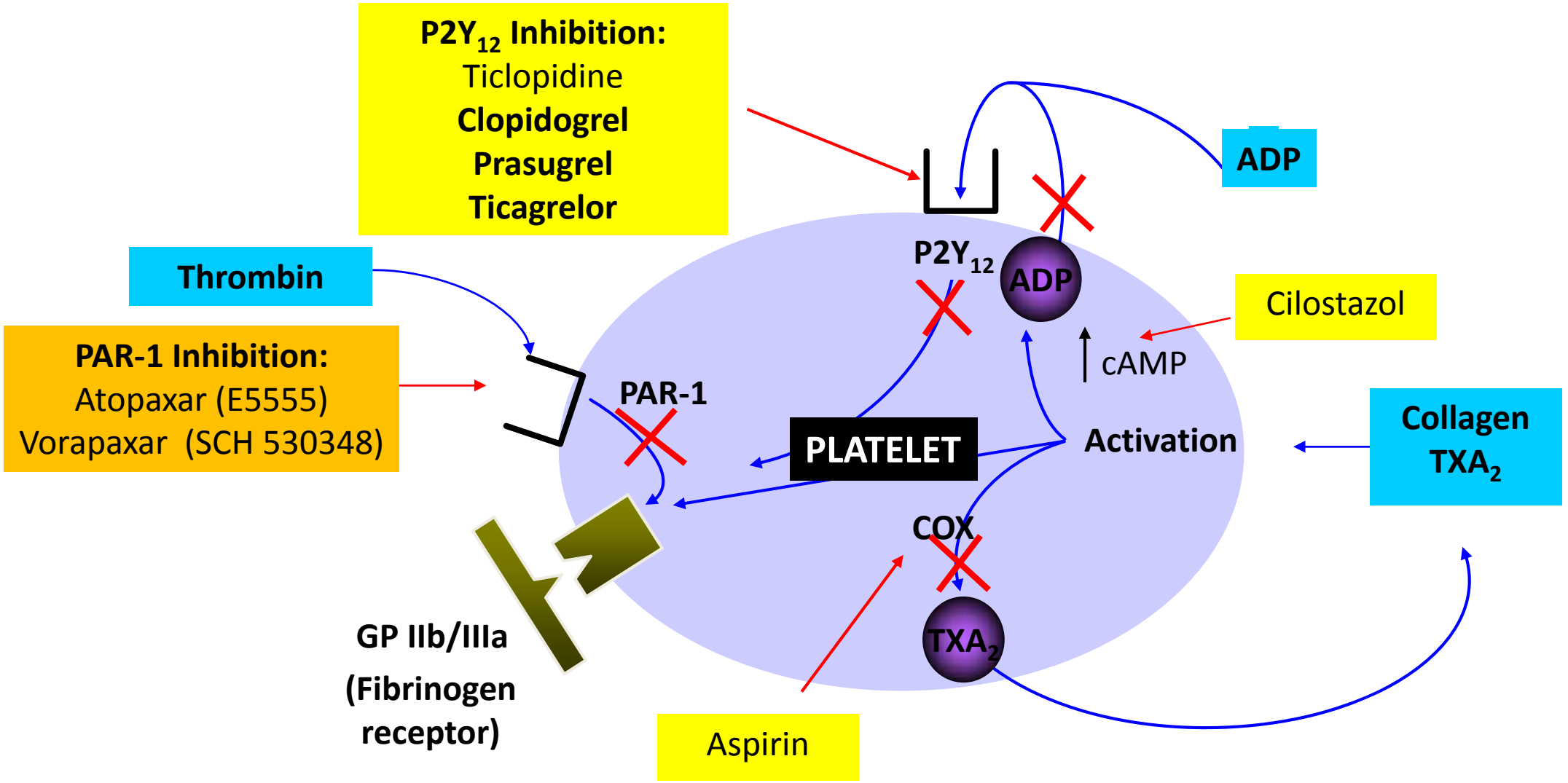
Let's not be penny wise and pound foolish

中庸 (중용)

過猶不及 (과유불급)

小貪大失 (소탐대실)

Oral Anti-Platelet Agents

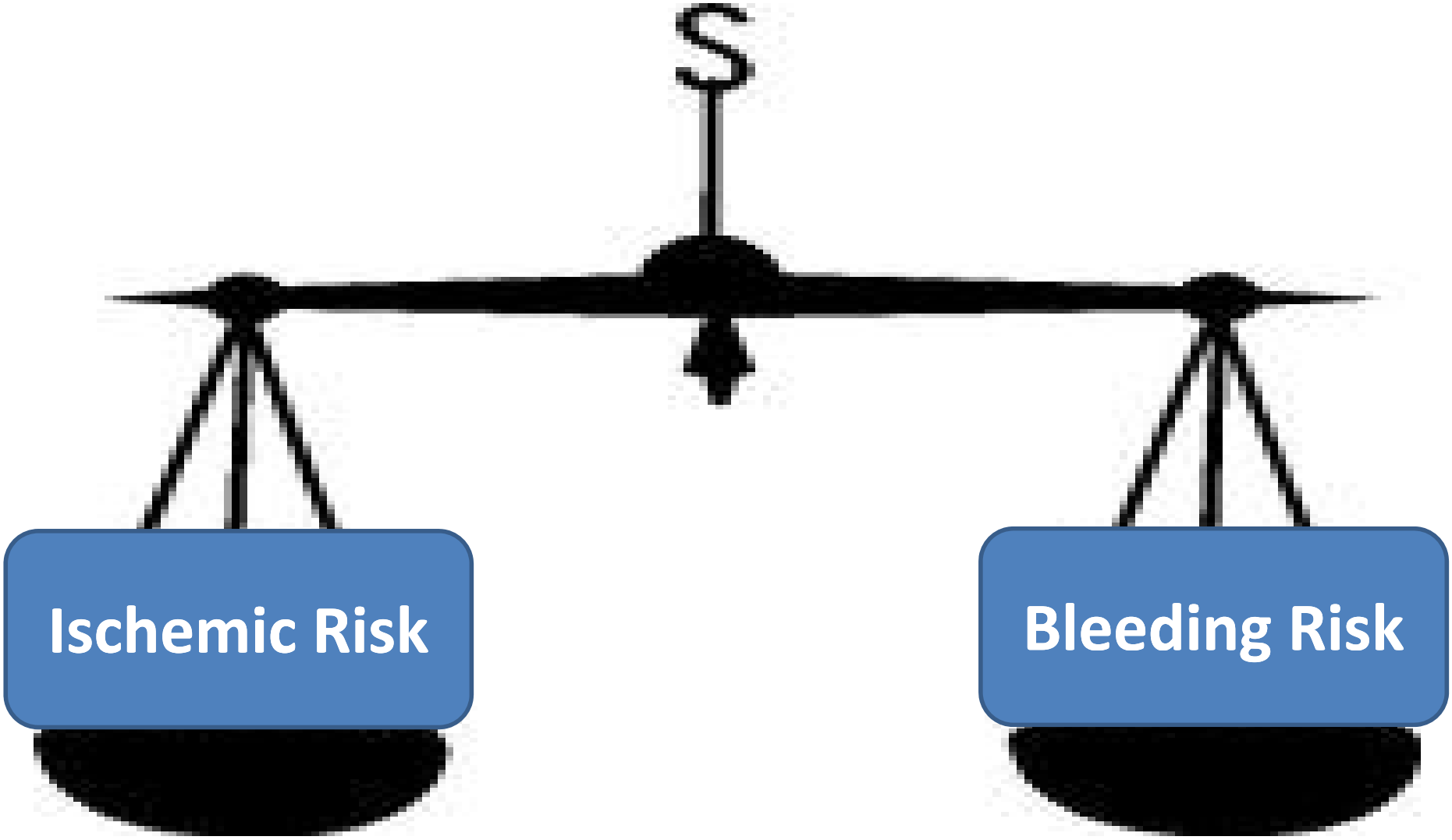



Plavix
75 mg film-coated tablet Clopidogrel
28 film-coated tablets


Effient
(prasugrel) tablets
10 mg


BRILIQUE
90 mg
ticagrelor/tikagrelori

Balance is the KEY



What are the pitfalls of clopidogrel?

1. Variability Issue

a. susceptibility to genetic variation, variation in OPR

b. possible drug interactions (Cytochrome enzymes): PPIs, lipophilic statins, CCBs etc

2. Moderate Efficacy at Best (Compared with newer agents)

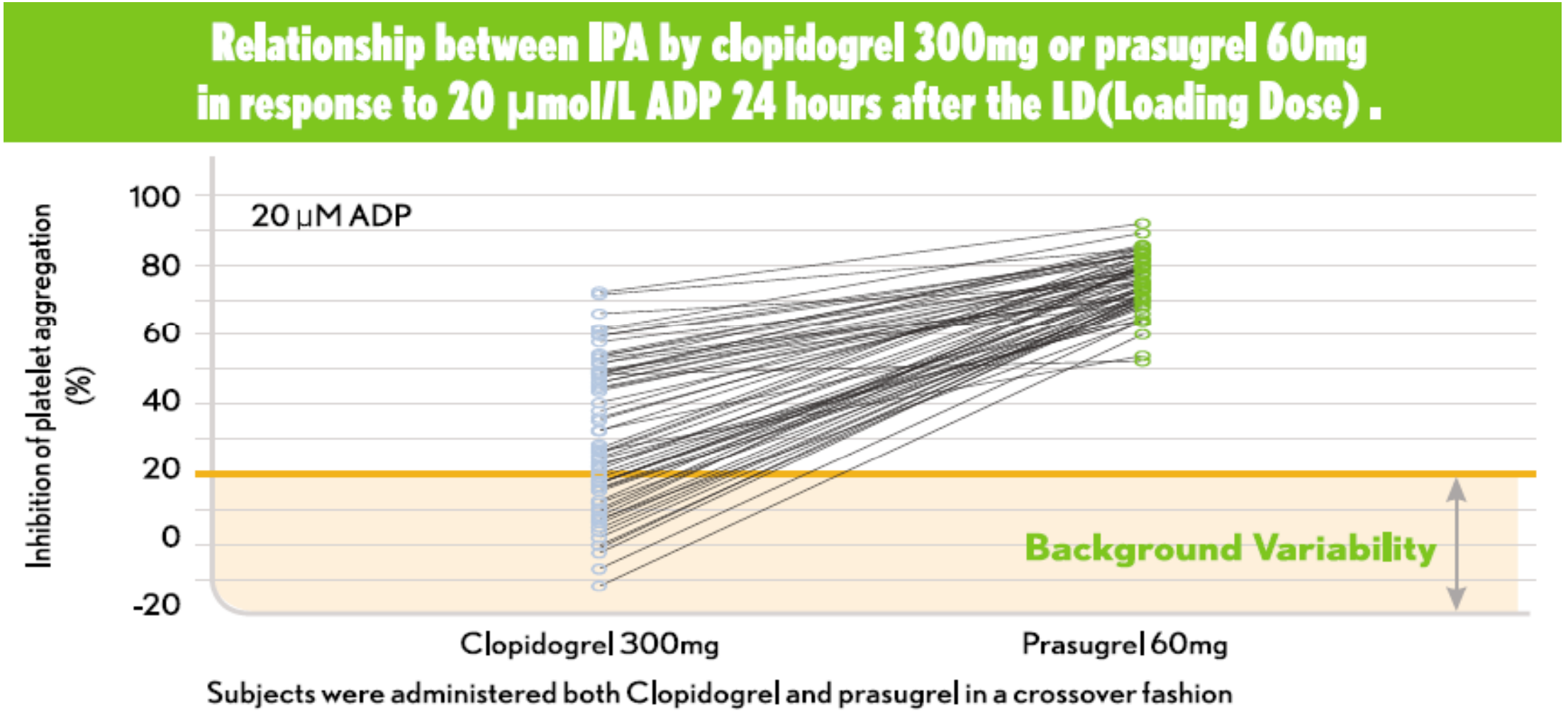
→ In certain situations, it cannot overcome the burden of thombosis

3. Slow onset of Action (To achieve full action)

→ Need agent with faster onset

Q1: Have the newer agents overcome these pitfalls?

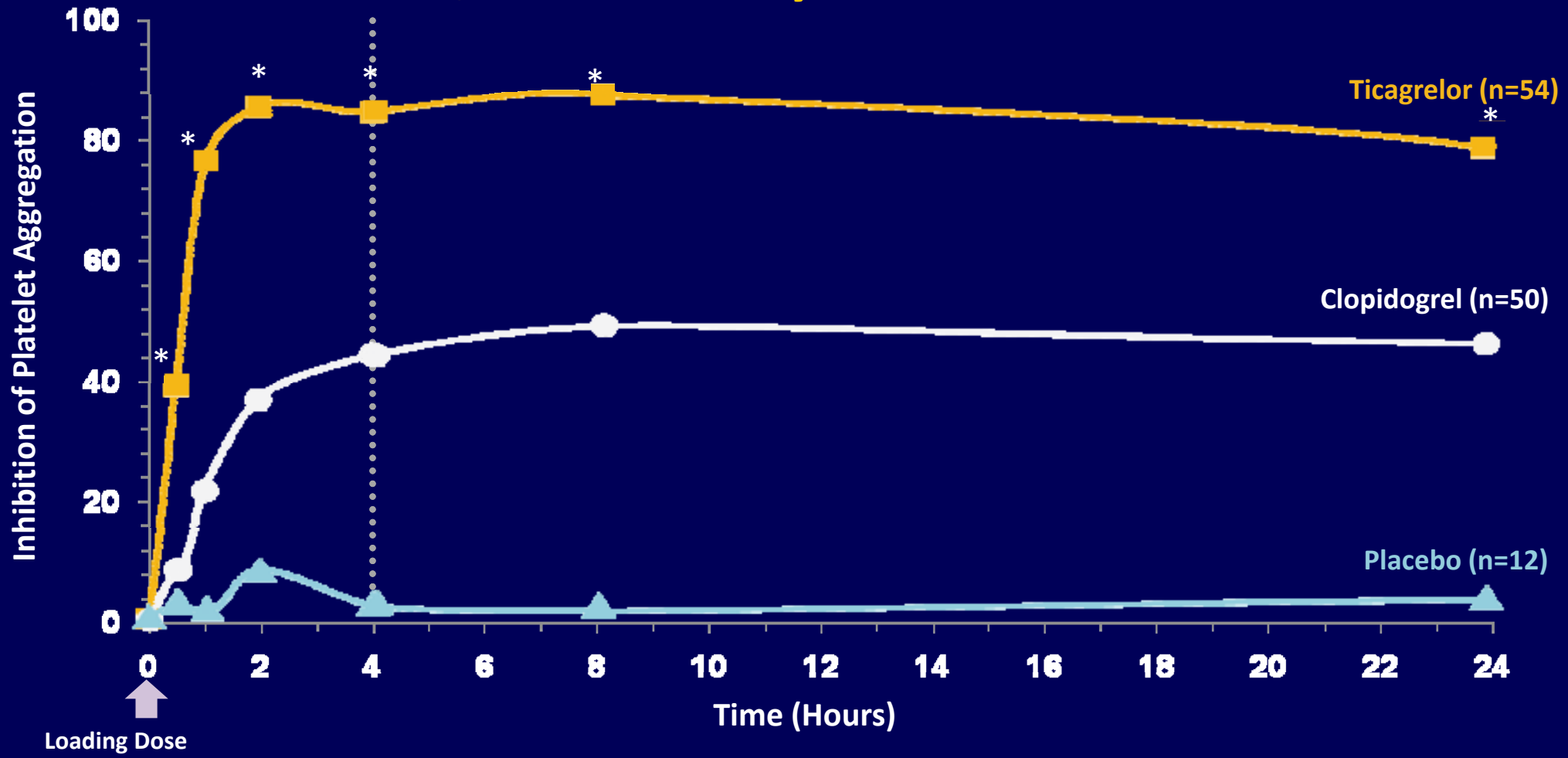
Less Variable Platelet inhibition



Data from. Brandt JT. Et al. Am Heart J. 2007;153:66e9-66e16

Faster Onset

From the ONSET/OFFSET study



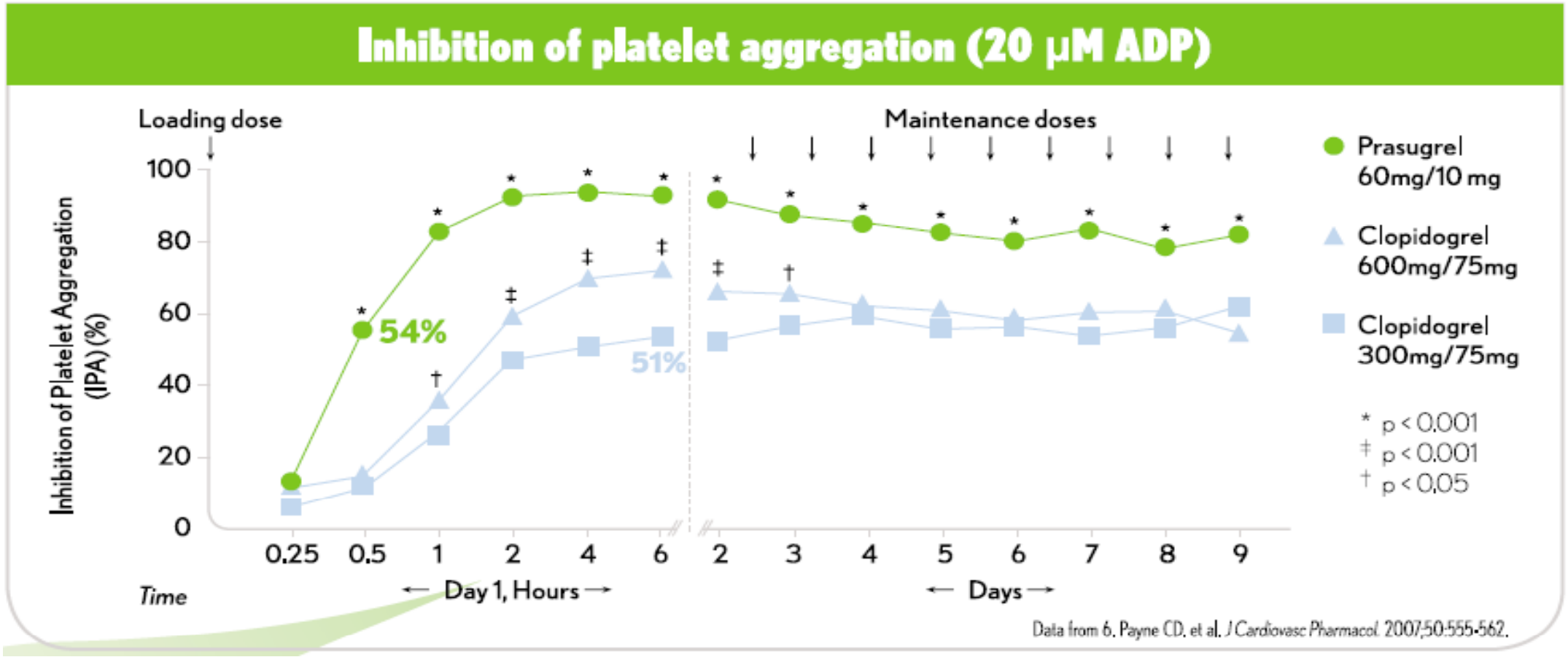
Ticagrelor 180-mg loading dose in Stable CAD patients
Clopidogrel 600-mg loading dose in Stable CAD patients

******P*<0.0001 ticagrelor vs clopidogrel**

CAUTION: ONSET OF ACTION: Pharmacodynamic data were obtained in patients with stable CAD, not from the PLATO pivotal trial, which studied patients with ACS. Data on IPA cannot be directly correlated with clinical outcomes. These data cannot be used to extend promotion into stable CAD patients. Additionally, careful consideration should be given to ensure physical separation of these data from clinical and safety results.

Adapted from Gurbel PA, et al. *Circulation.* 2009;120:2577–2585.

Prasugrel



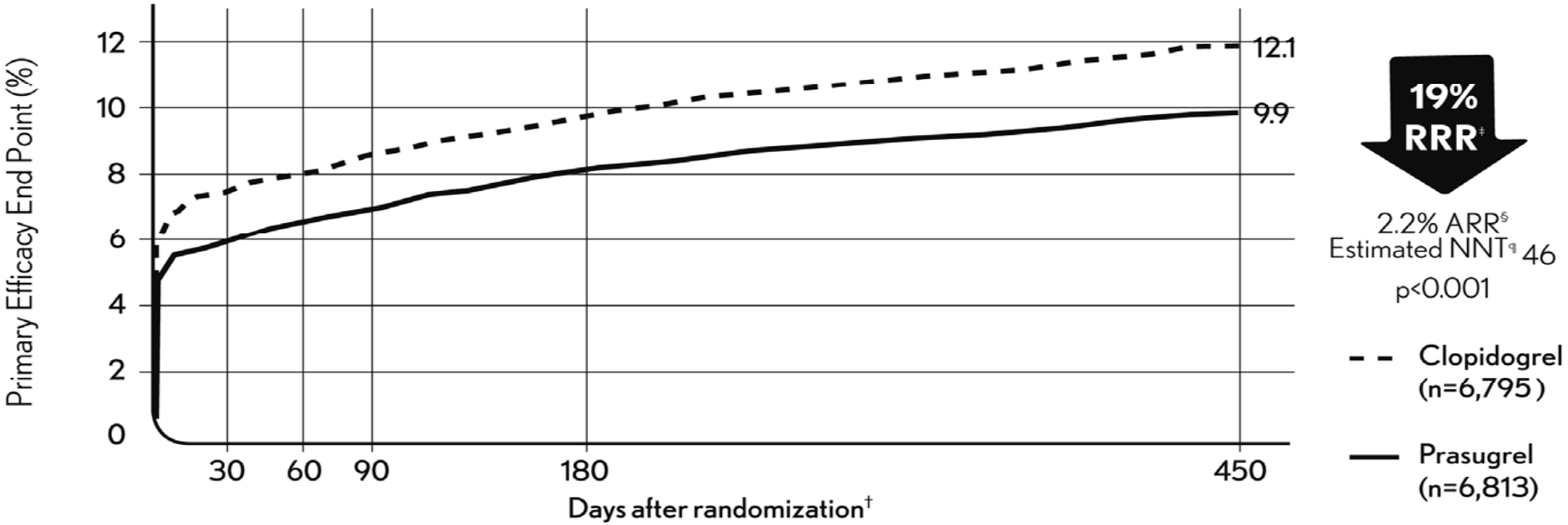
The KFDA approved dose of clopidogrel is 300mg loading dose followed by 75mg once daily maintenance dose in combination with ASA 75 - 325mg daily.

Data from. Pyane CD at al. J Cardiovasc Pharmacol 2007;50:555-562

Q2: Do more potent antiplt agents reduce ischemic events in the heart?

Prasugrel: From TRITON TIMI-38

- Prasugrel demonstrated a significant 19% relative risk reduction in the primary endpoint of cardiovascular death, nonfatal MI or nonfatal stroke compared to clopidogrel in ACS-PCI patients.[7]
- Prasugrel improves cardiovascular outcomes versus clopidogrel in ACS-PCI patients.[7]



† No.at Risk

Days after randomization	0	30	90	180	270	360	450
Clopidogrel	6795	6169	6036	5835	5043	4369	3017
Prasugrel	6813	6305	6177	5951	5119	4445	3085

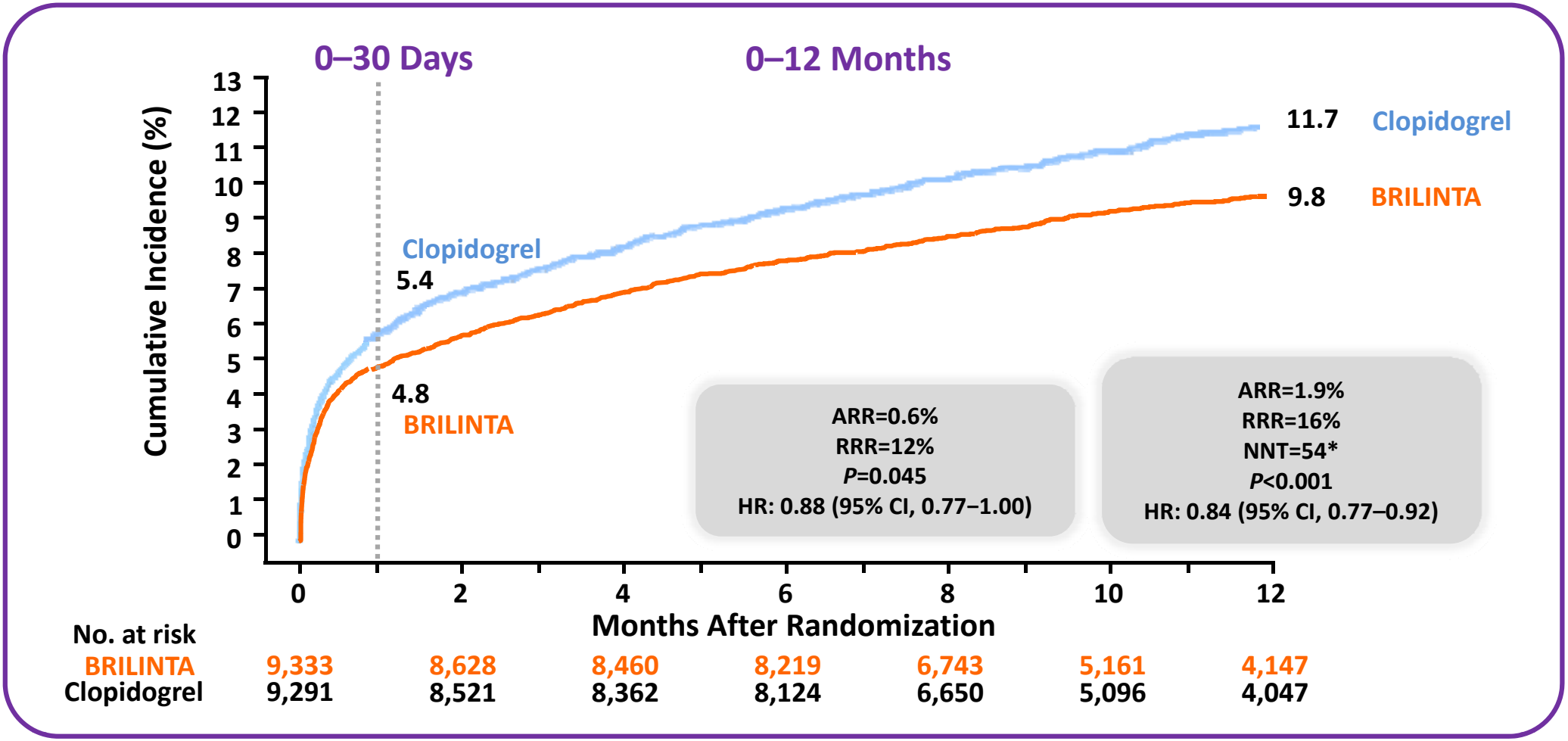
‡RRR: Relative Risk Reduction
§APR: Absolute Risk Reduction
¶NNT: number needed to treat

* Composite primary endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke.

Data from Ref 7. Wiviott SD et al. *N Engl J Med* 2007;357:2001-15.

Prasugrel: From PLATO

Primary Endpoint (Composite of CV Death, MI, or Stroke)



Both groups included aspirin.
*NNT at one year.

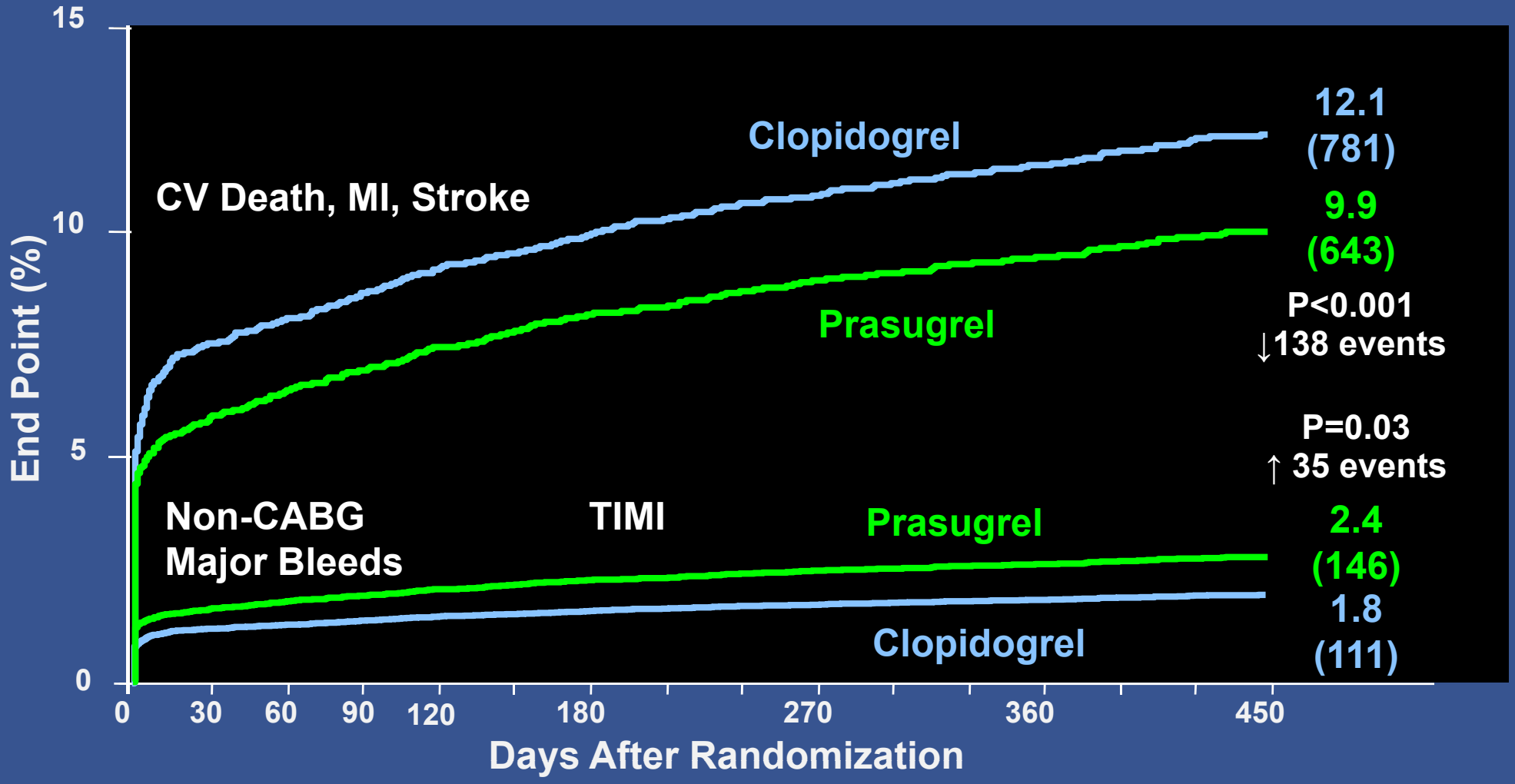
Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

Q3: OK! Great. Is there a price to pay for the improved effect on ischemia?

YES! there is a price to pay

→A Bleeding Tax!!

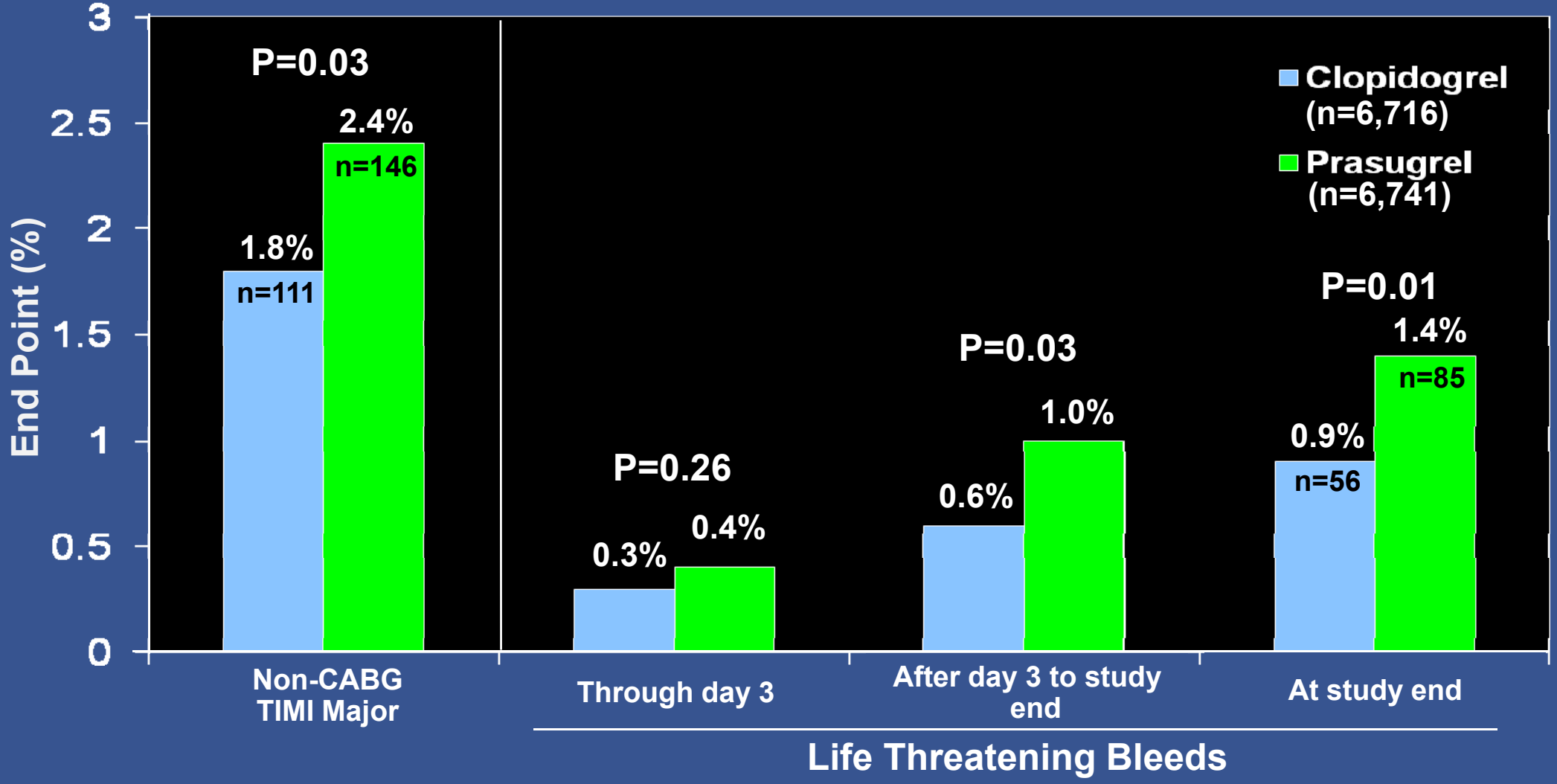
TRITON-TIMI 38: Rates of Key Study End Points (All ACS)



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

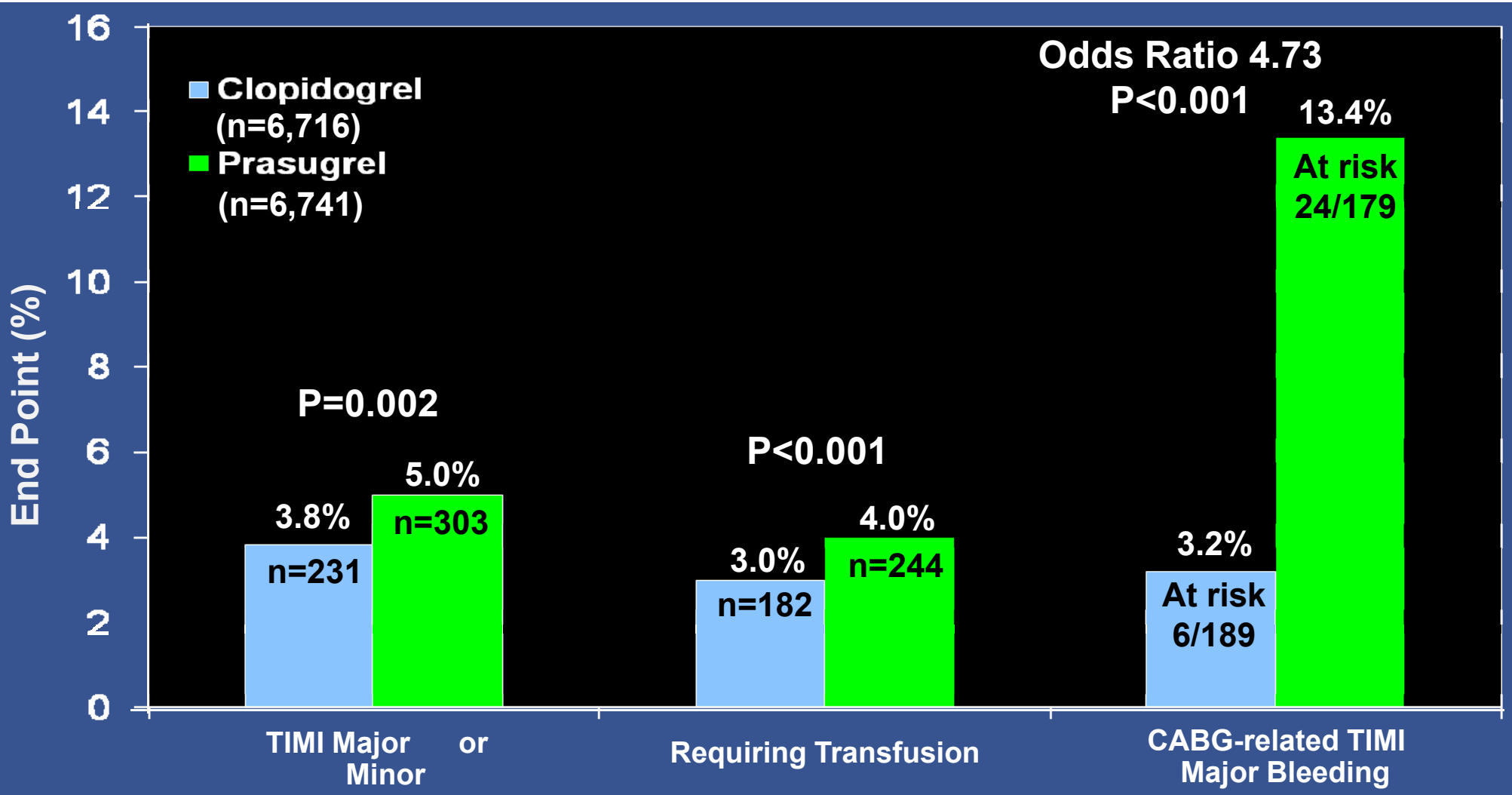
TRITON-TIMI 38: Non-CABG TIMI Major Bleeds at 15 Months (All ACS)



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

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

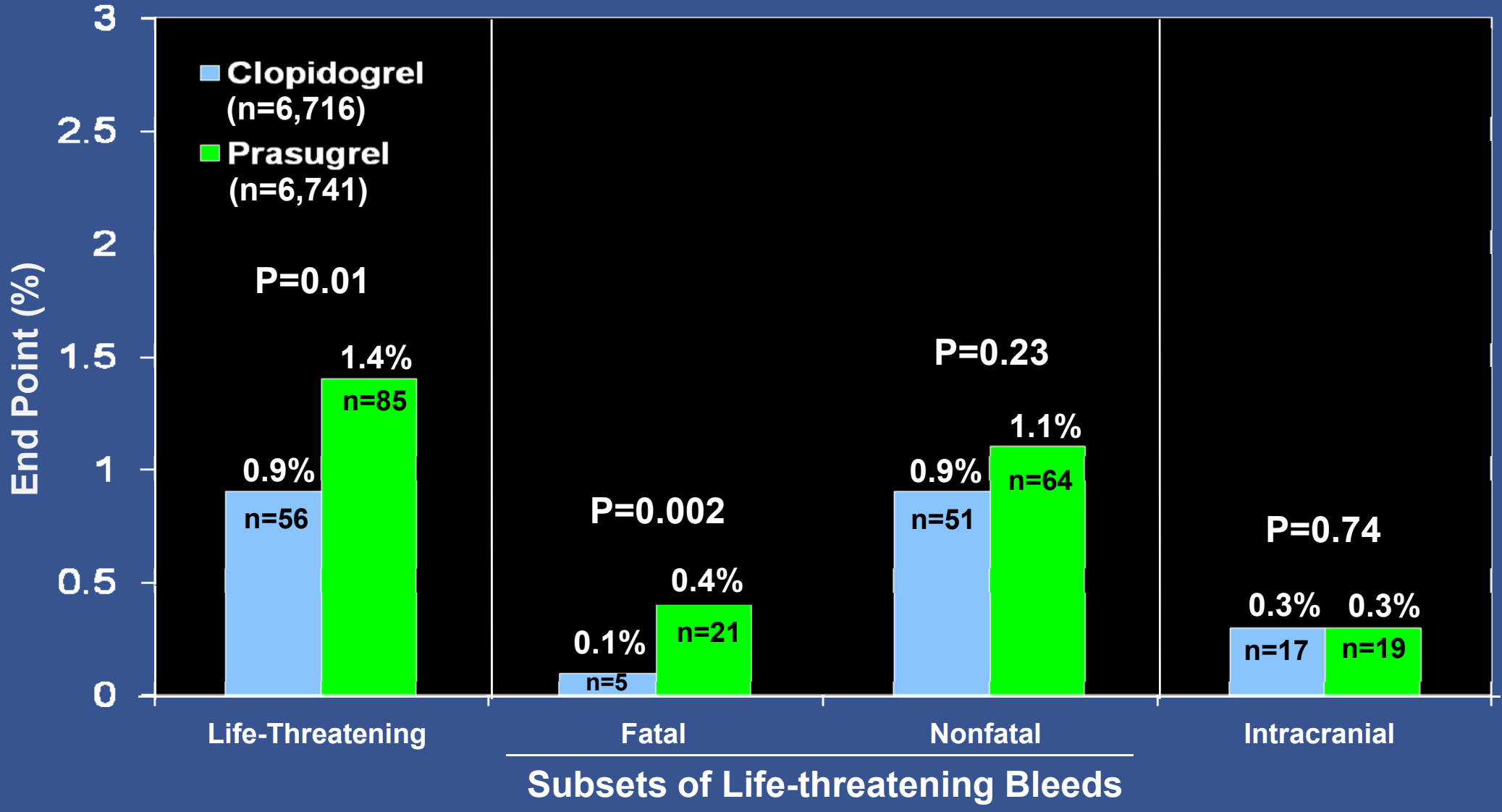
TRITON-TIMI 38: Other TIMI Bleeds at 15 Months (All ACS)



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

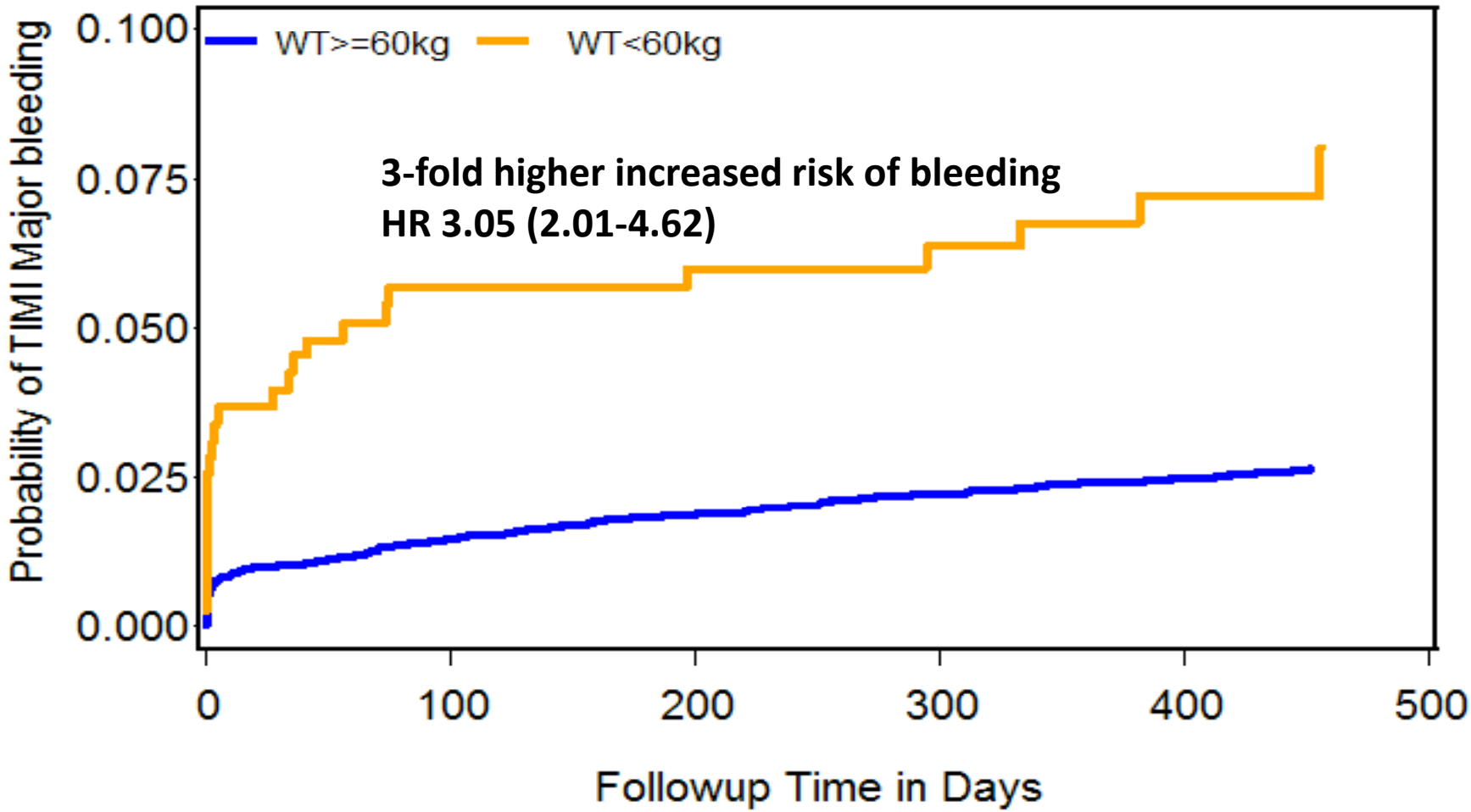
TRITON-TIMI 38: Life Threatening Bleeds at 15 Months (All ACS)



ACS=Acute Coronary Syndrome; HR=Hazard Ratio

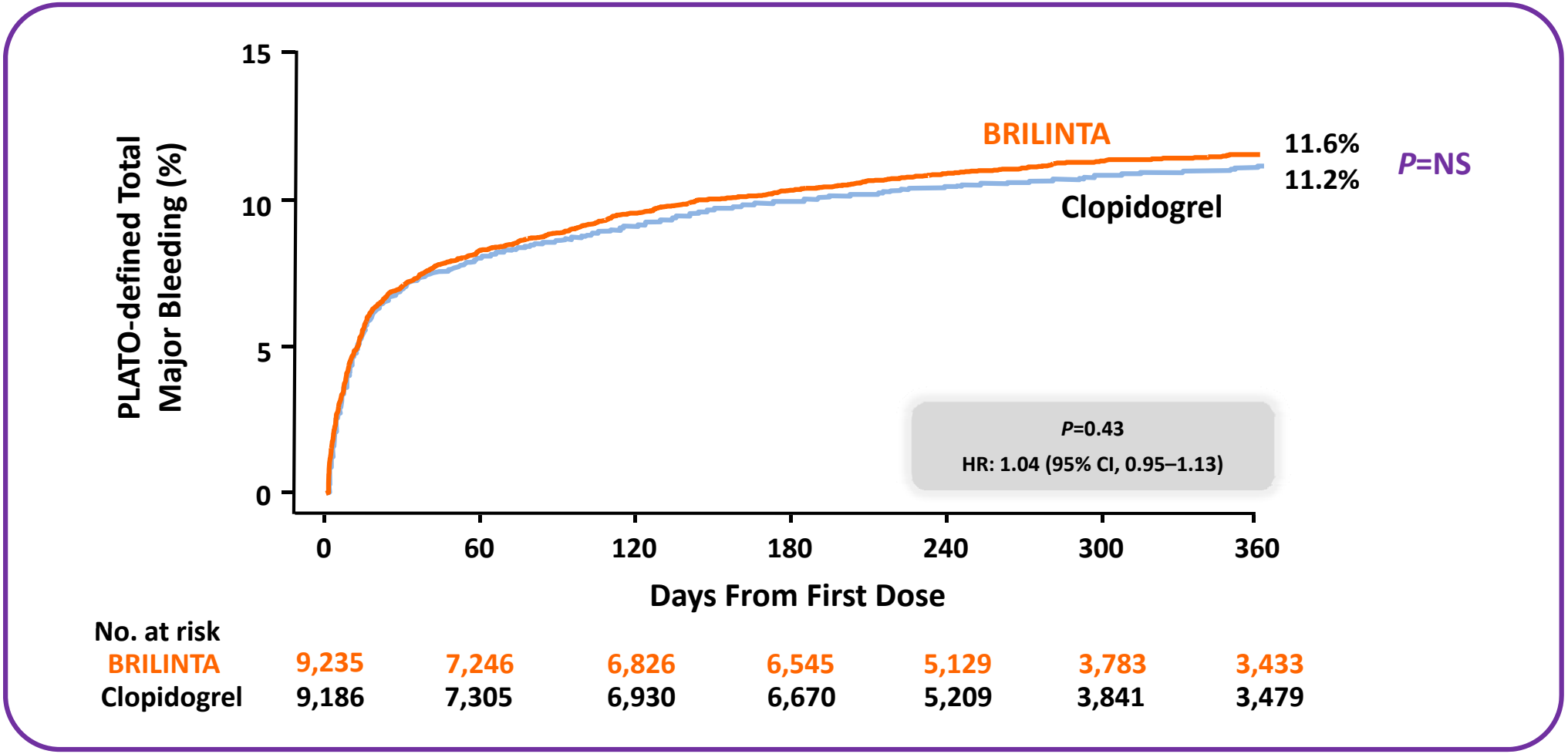
Wiviott SD et al. *New Engl J Med* 2007;357:2001-2015

TRITON-TIMI 38: Impact of Low Bwt.



FDA Advisory Committee Docket. Available at http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4412b1-01-FDA.pdf.

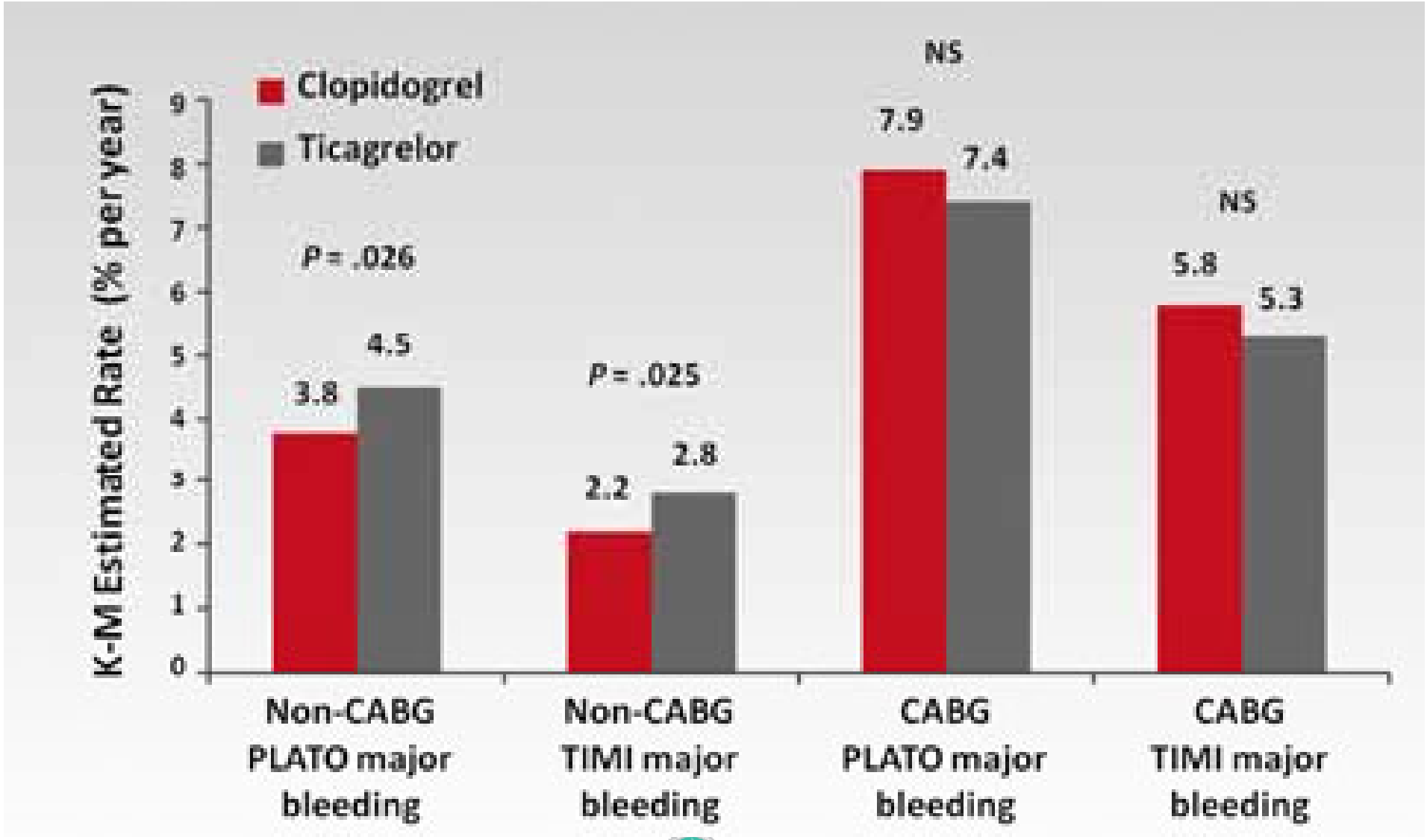
PLATO: Safety Primary Endpoint



Both groups included aspirin.

PLATO :Major Bleeding

Non-CABG and CABG Related



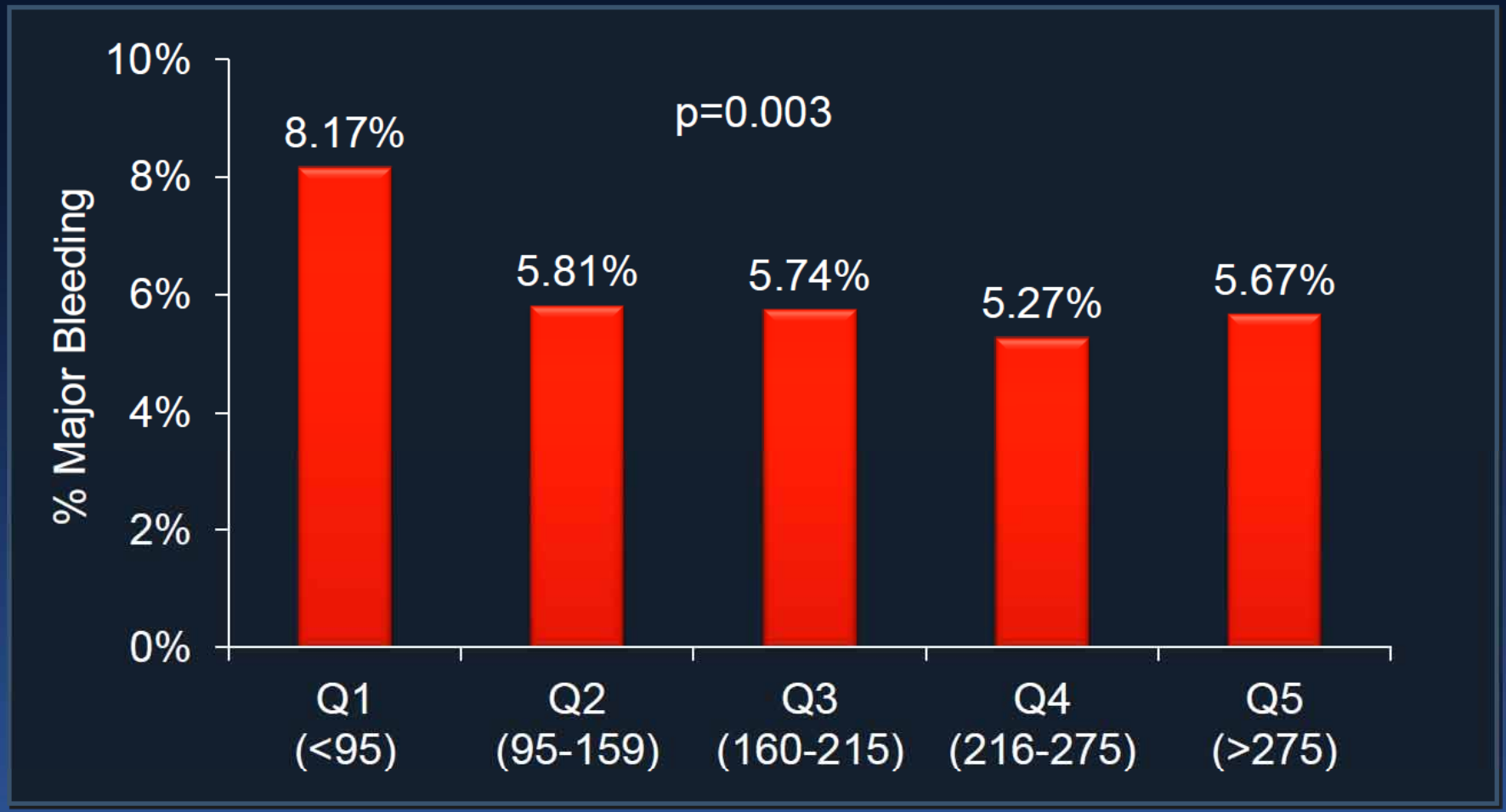
You can't avoid bleeding

→ *If you want stronger inhibition of platelets*

(Universal Finding Including Clopidogrel)

ADAPT DES at 1 Year: Major Bleeding by PRU Quintiles

8,449 PCI pts with VerifyNow PRU after clopidogrel loading



Let's not forget the fragile brain

→ *The brain is more susceptible to bleeding*

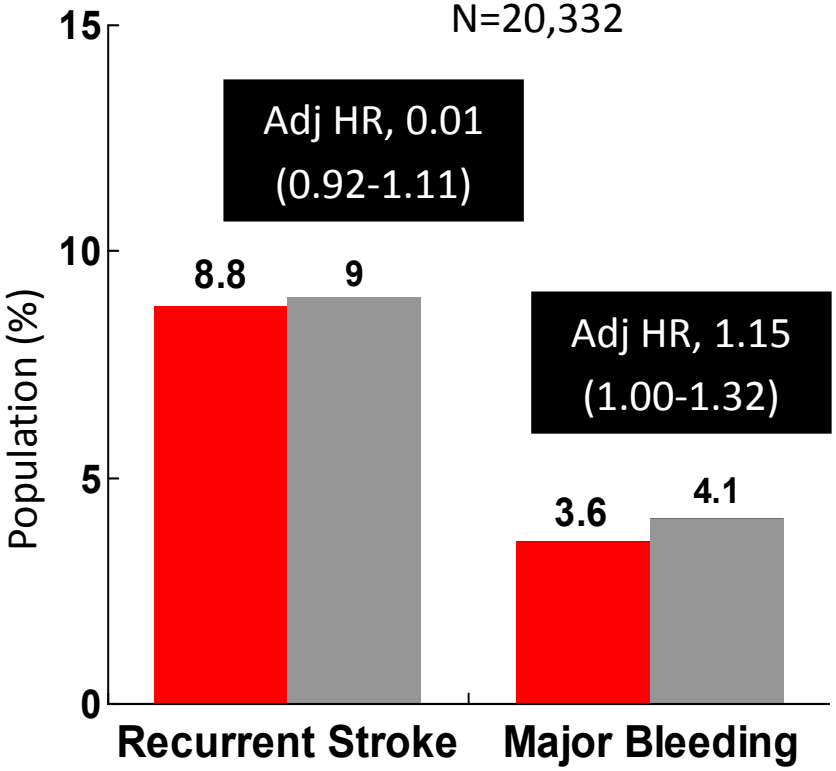
No Ischemic Benefits and Higher Bleeding

With Greater Antiplatelet Therapy in Prior Stroke

Recent isch stroke

PROFESS

N=20,332



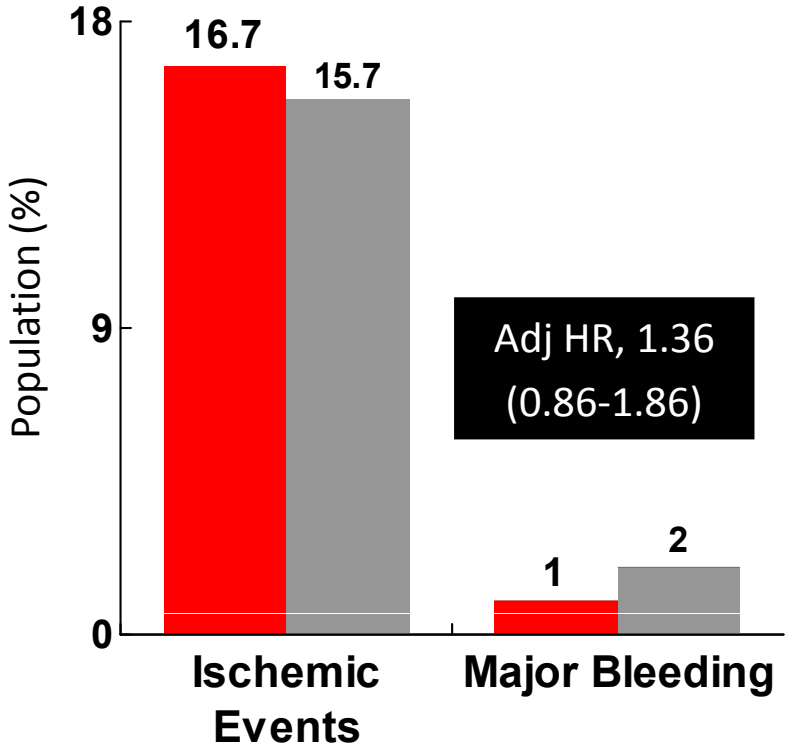
Clopidogrel 75 mg daily

Aspirin (25 mg) + Dipyridamole 200 mg twice daily

Recent isch stroke or TIA

MATCH

N=7599

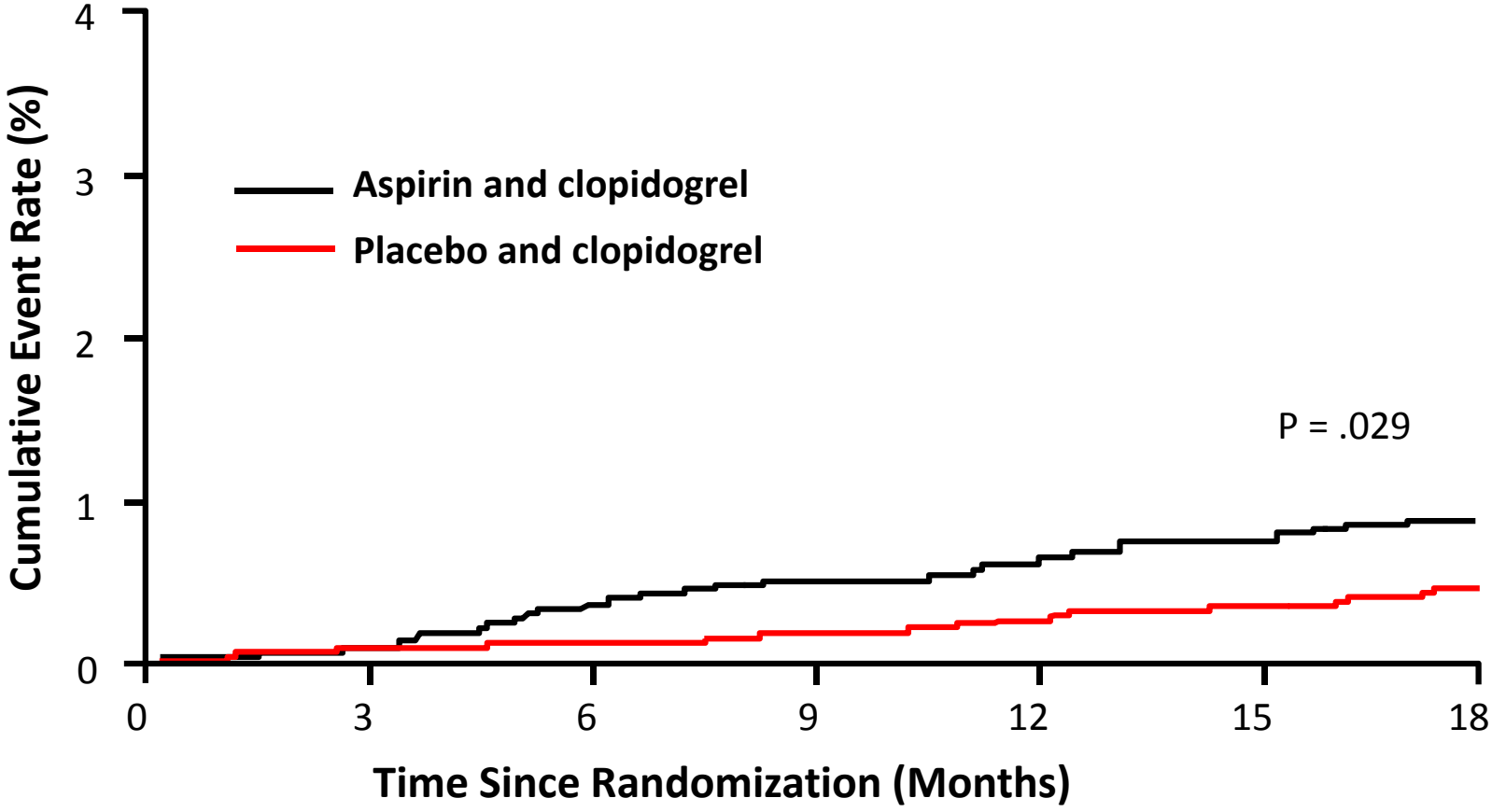


Clopidogrel 75 mg + placebo

Clopidogrel 75 mg + Aspirin 75 mg daily

NEJM2008;359:1238 Lancet2004;364:331

MATCH: Intracranial Hemorrhage



Patients at Risk	3 months	6 months	9 months	12 months	15 months	18 months
Aspirin and clopidogrel	3724	3691	3601	3552	3508	2756
Placebo and clopidogrel	3781	3576	3638	3582	3544	2823

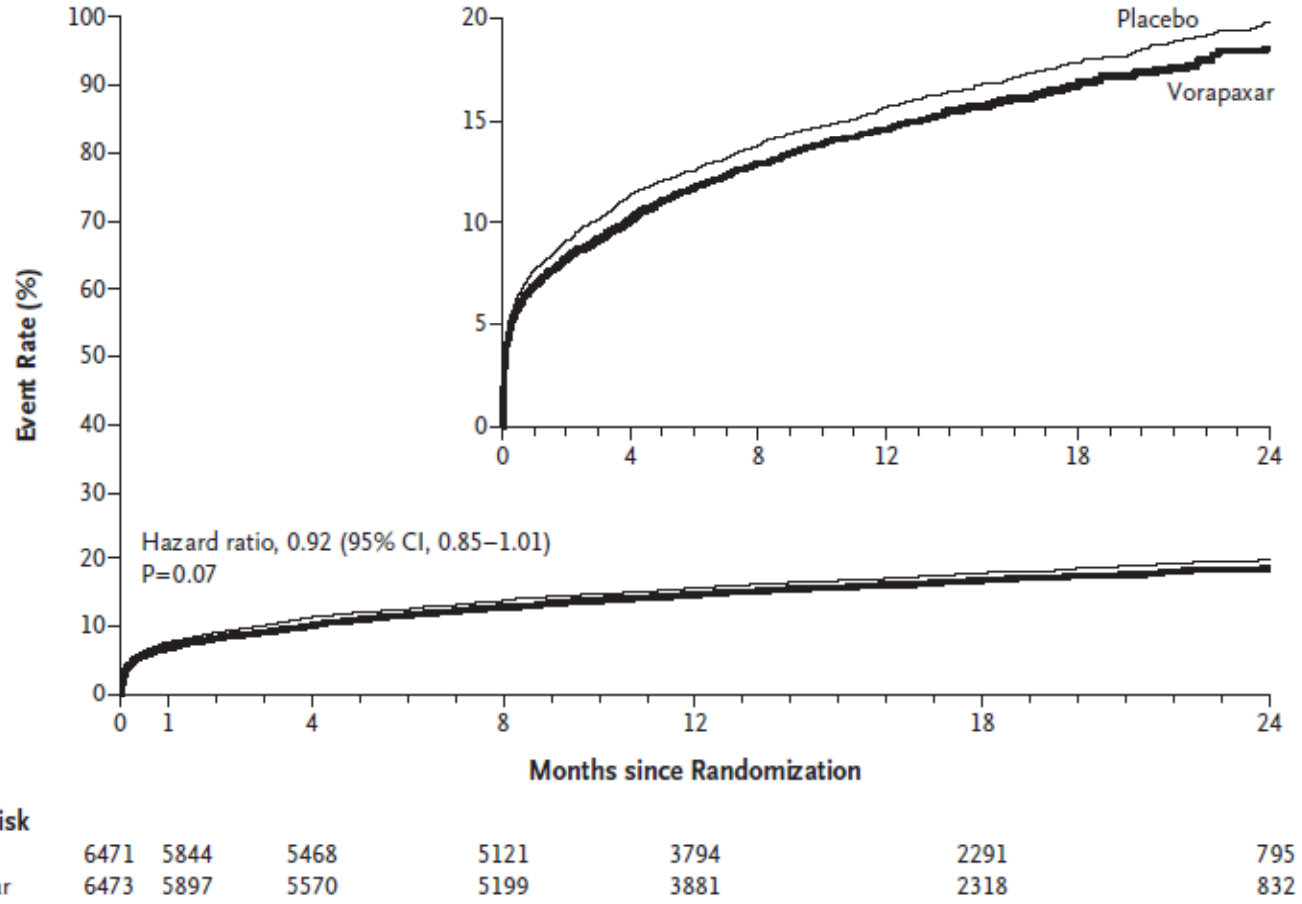
Intracranial Bleeding

- ✓ **Patient history of stroke or TIA**
- ✓ **TRITON-TIMI 38: incidence of stroke in patients with a history of prior TIA or stroke greater with prasugrel + ASA (6.5% total: 4.2% thrombotic, 2.3% ICH) vs clopidogrel + ASA (1.2% total, all thrombotic)**
- ✓ **PLATO: Fatal ICH higher in ticagrelor vs clopidogrel (0.1 vs 0.01; *P*=.02)**

TRACER

ORIGINAL ARTICLE

Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes



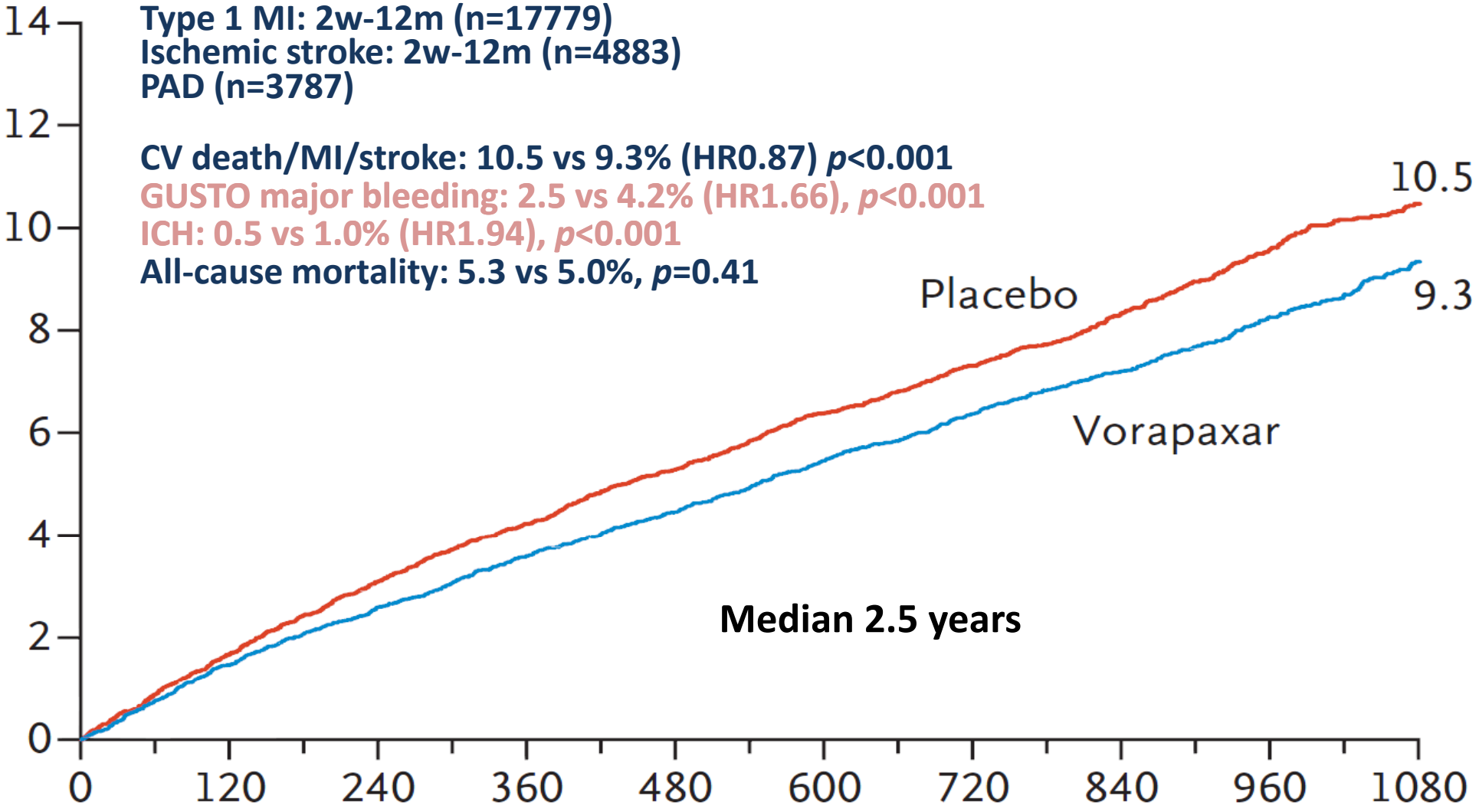
No. at Risk							
Placebo	6471	5844	5468	5121	3794	2291	795
Vorapaxar	6473	5897	5570	5199	3881	2318	832

- Bleeding (p<0.001): GUSTO severe (HR1.66), TIMI major(HR1.53), ICH (HR3.39)
- Total death: HR1.05 (P=0.52)
- In pts with ACS, the addition of vorapaxar to standard therapy did not significantly reduce the primary endpoint but significantly increased the risk of major bleeding.

TRA2°P

Type 1 MI: 2w-12m (n=17779)
Ischemic stroke: 2w-12m (n=4883)
PAD (n=3787)

CV death/MI/stroke: 10.5 vs 9.3% (HR0.87) *p*<0.001
GUSTO major bleeding: 2.5 vs 4.2% (HR1.66), *p*<0.001
ICH: 0.5 vs 1.0% (HR1.94), *p*<0.001
All-cause mortality: 5.3 vs 5.0%, *p*=0.41

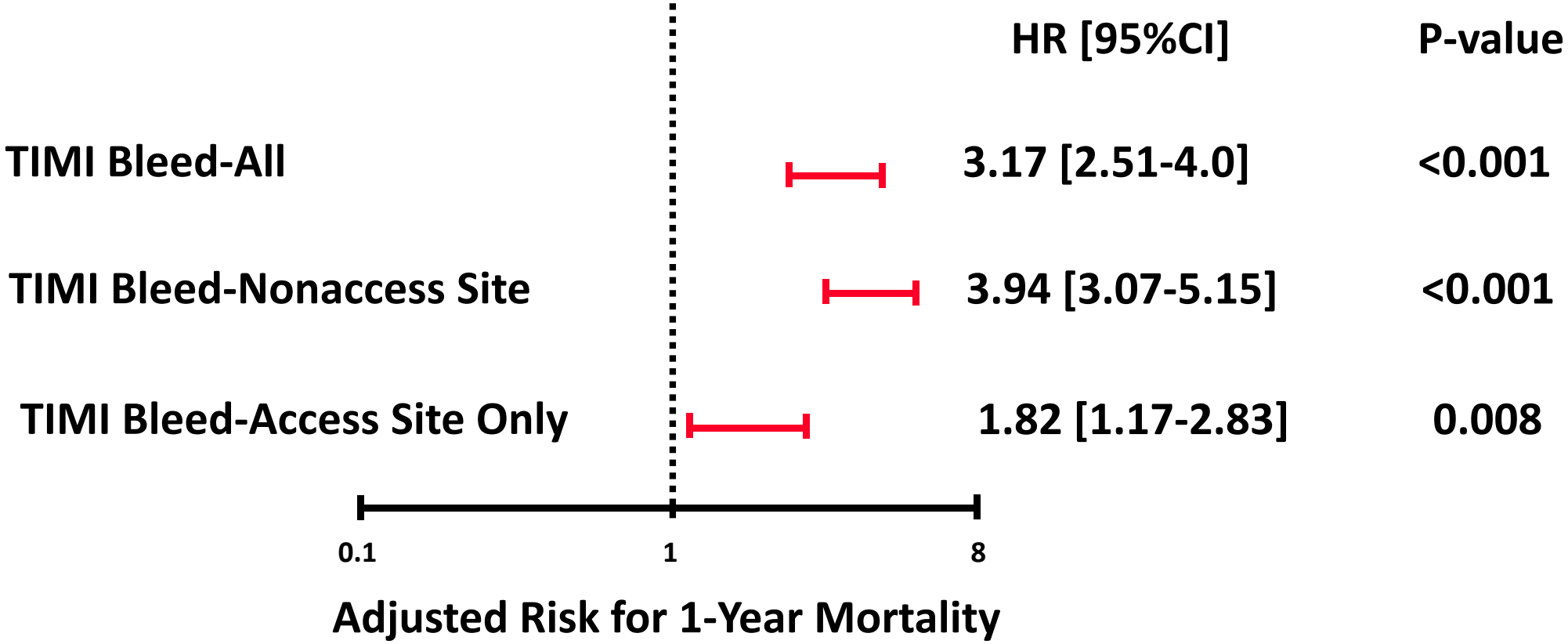


Bleeding is bad (prognosis wise)

“More Bleeding = More Death”

Impact of Bleeding on Mortality after PCI

17,393 patients from REPLACE-2, ACUITY and Horizons



Q4: So where do we compromise?

Lets look for….

1. **Situations with the highest risk of ischemia**

2. **Situations with the highest risk of bleeding**

Lets look for….

1. **Situations with the highest risk of ischemia**

2. **Situations with the highest risk of bleeding**

Korea ST Registry

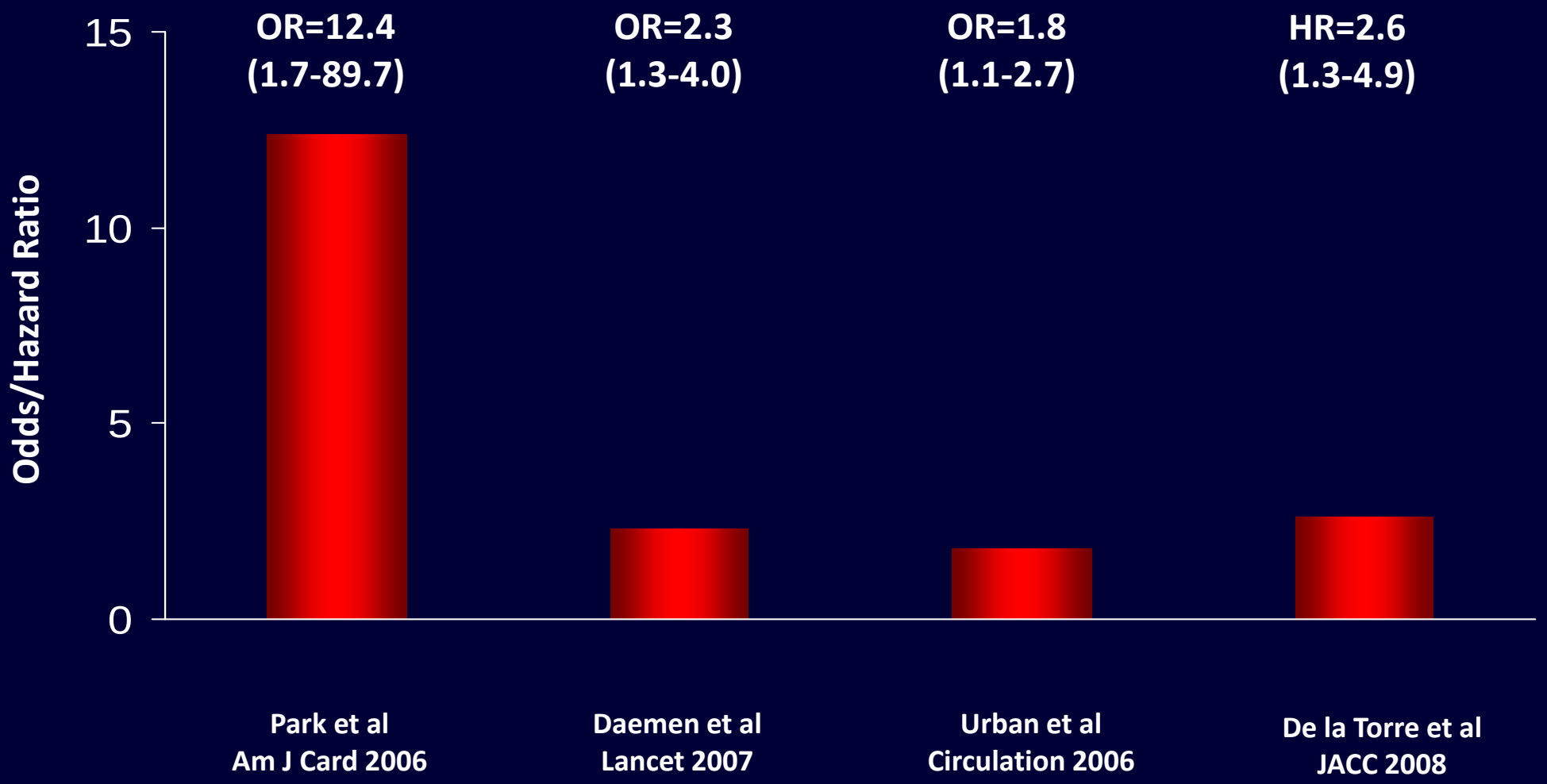
Independent Predictors of ST

	Hazard ratio (95% confidence interval)	p value
Both early and delayed ST		
AMI	3.91(2.66-5.74)	<0.001
Low EF	3.51(2.01-6.13)	<0.001
Stent diameter (per 1mm decrease)	2.71(1.45-5.05)	0.002
DES ISR	4.75(2.32-9.75)	<0.001
Only Early ST		
Bifurcation stenting	2.39 (1.27-4.52)	0.007
Only Delayed ST (Late + VL)		
Younger Age (per decade decrease)	1.8 (1.5-2.1)	<0.001
Hypertension / Anti-HT Med	0.50 (0.27-0.92)	0.025
Diabetes	0.46 (0.22-0.96)	0.038
Renal insufficiency	2.16(1.05-6.31)	0.031
LAD PCI	2.47(1.36-4.51)	0.003

Park KW, Kim HS et al. Circulation J 2011

Seoul National University Hospital, Korea

ACS as Predictor of Stent Thrombosis

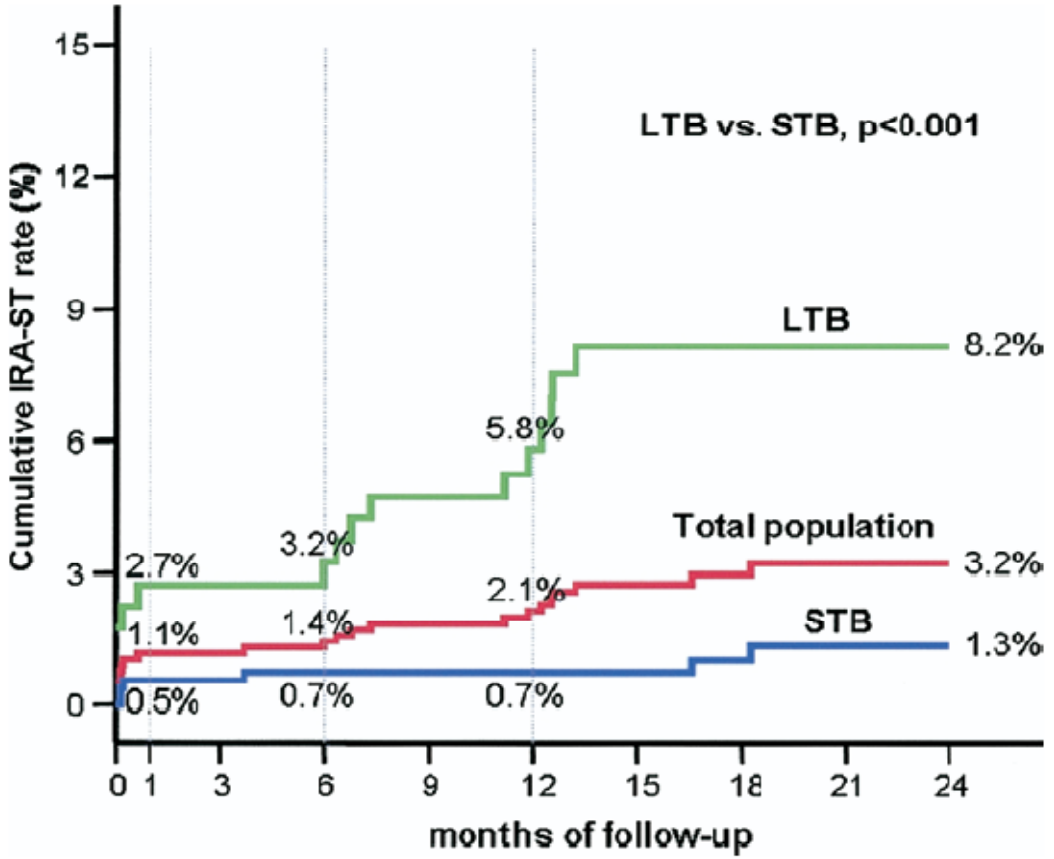


Impact of Thrombus Burden on Risk of Stent Thrombosis With DES in Patients With STEMI

Sianos G et al. *J Am Coll Cardiol* 2007;50:573-83

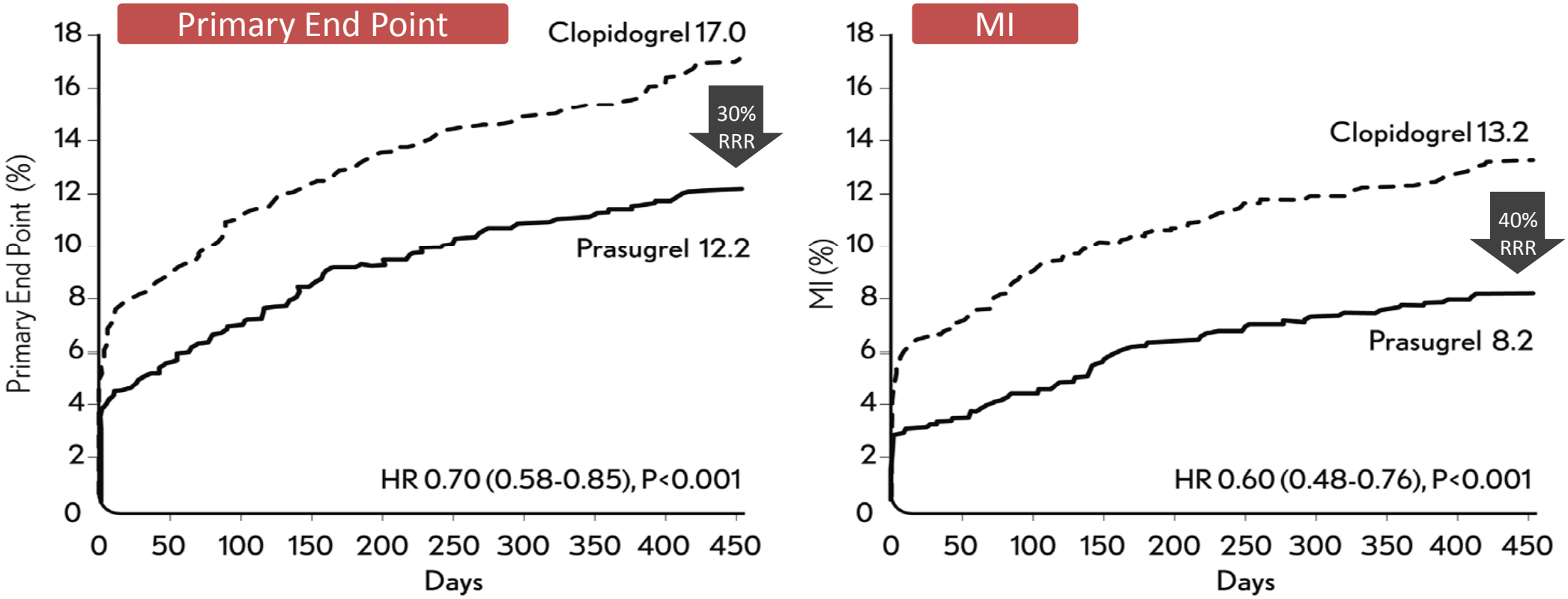
Independent Predictors of ST

Variable	*Hazard Ratio*	*95% CI*
Age	0.6	0.4-0.8
Index ST	6.2	2.1-18.9
Bifurcation	4.1	1.6-10.0
Thrombectomy	0.1	0.01-0.8
Large thrombus	8.7	3.4-22.5



Diabetes

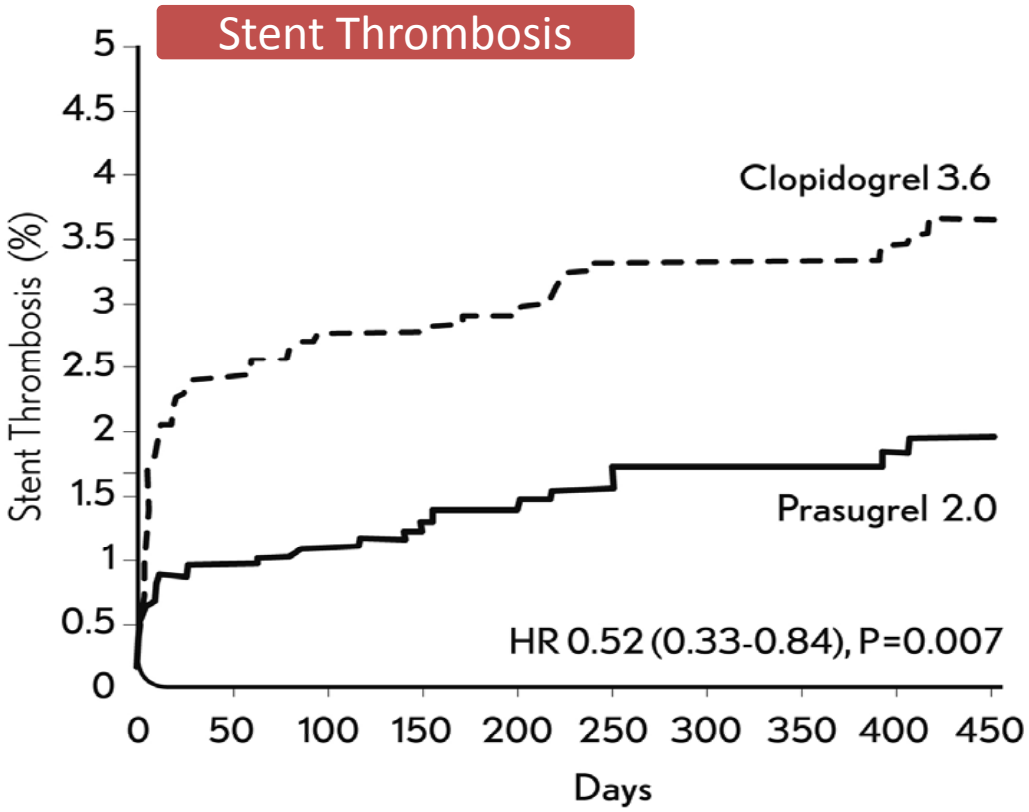
- 30% relative risk reduction of primary efficacy endpoints (CV death, non-fatal MI or stroke) in diabetic patient group vs. 19% relative risk reduction in whole population compared with clopidogrel
- 40% relative risk reduction of myocardial infarction in diabetic patient group vs. 24% relative risk reduction in whole population compared with clopidogrel

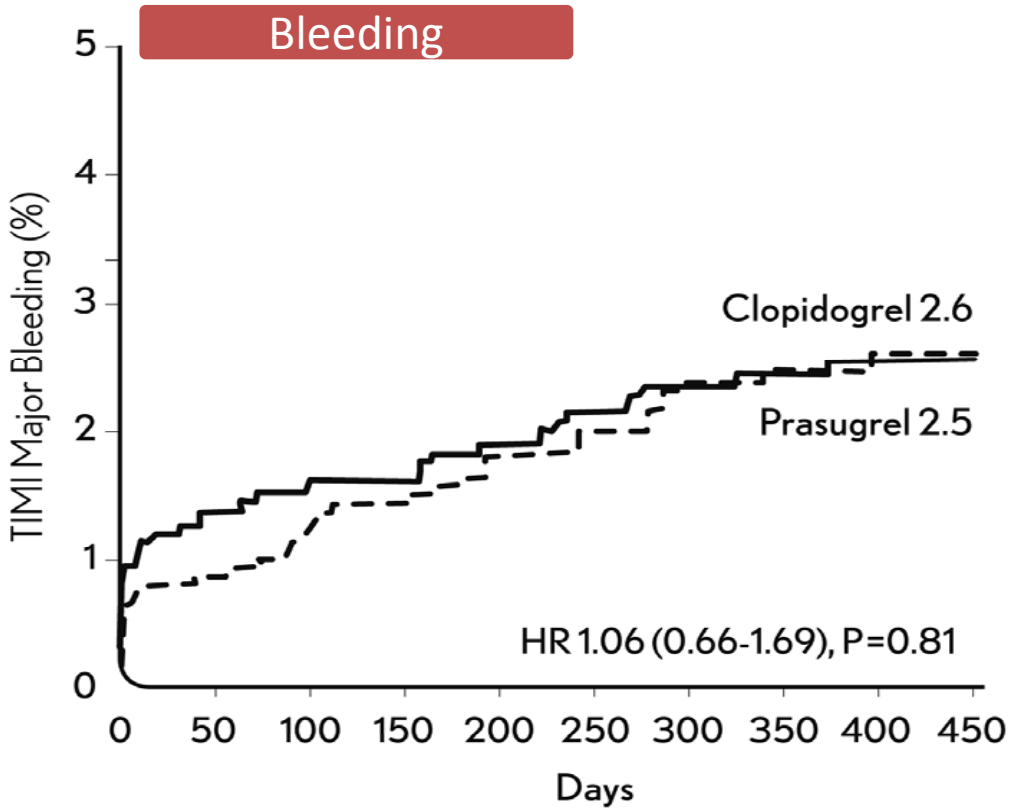


Data from Wiviott SD et al. *Circulation*. 2008;118(16):1626-1636

Diabetes

- 48% relative risk reduction of stent thrombosis diabetic patient group vs. 52% relative risk reduction in whole population compared with clopidogrel
- No increase of major bleeding in diabetic population, leading to a greater net clinical benefit of prasugrel in diabetic patients

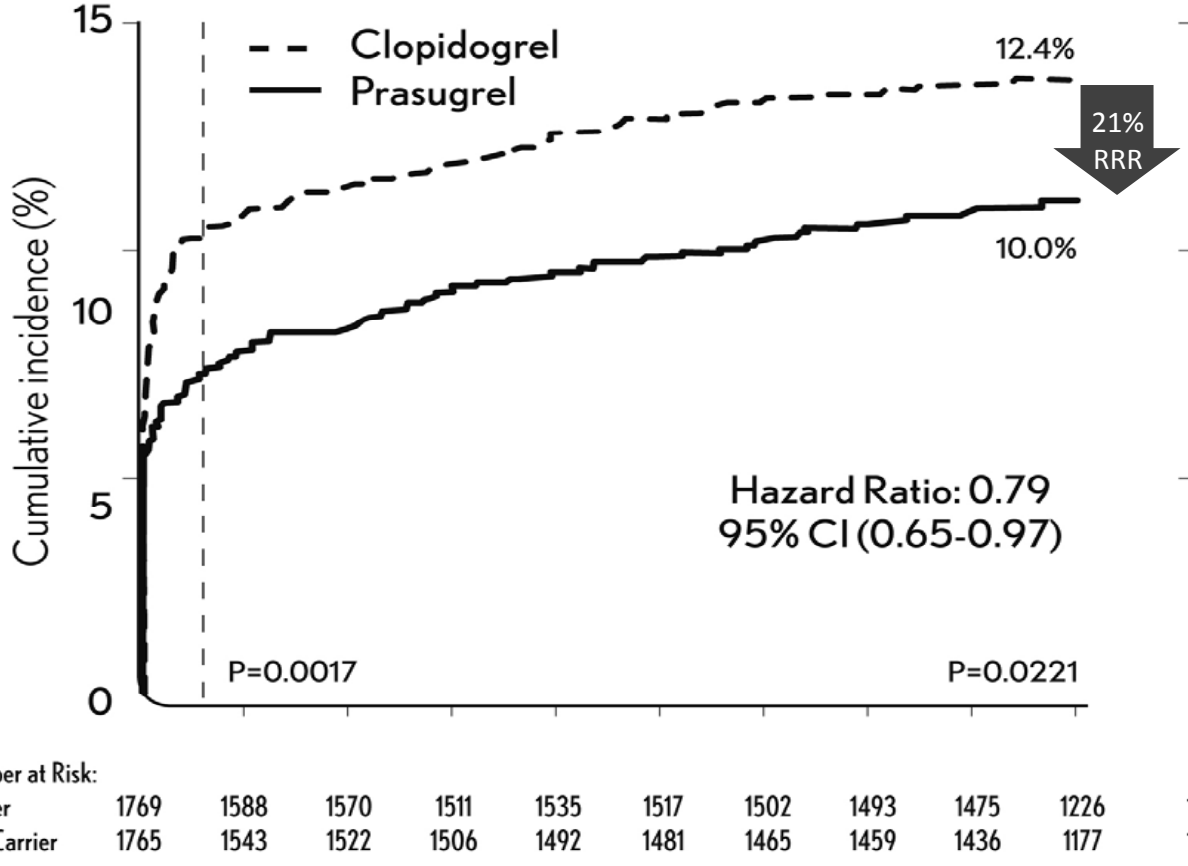




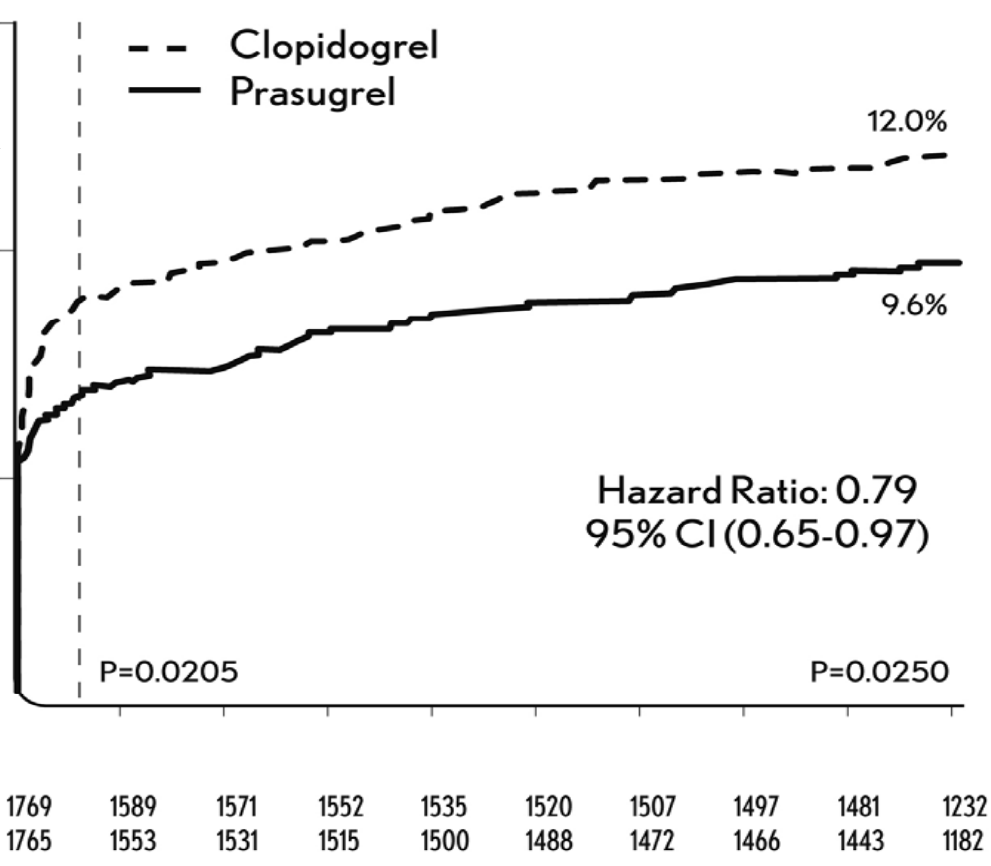
Data from SD Wiviott et al. *Circulation*. 2008;118(16):1626-1636

STEMI

Primary study endpoint (CV death, non-fatal MI or stroke)



Key secondary endpoint (CV death, non-fatal MI, or uTVR)



Number at Risk:

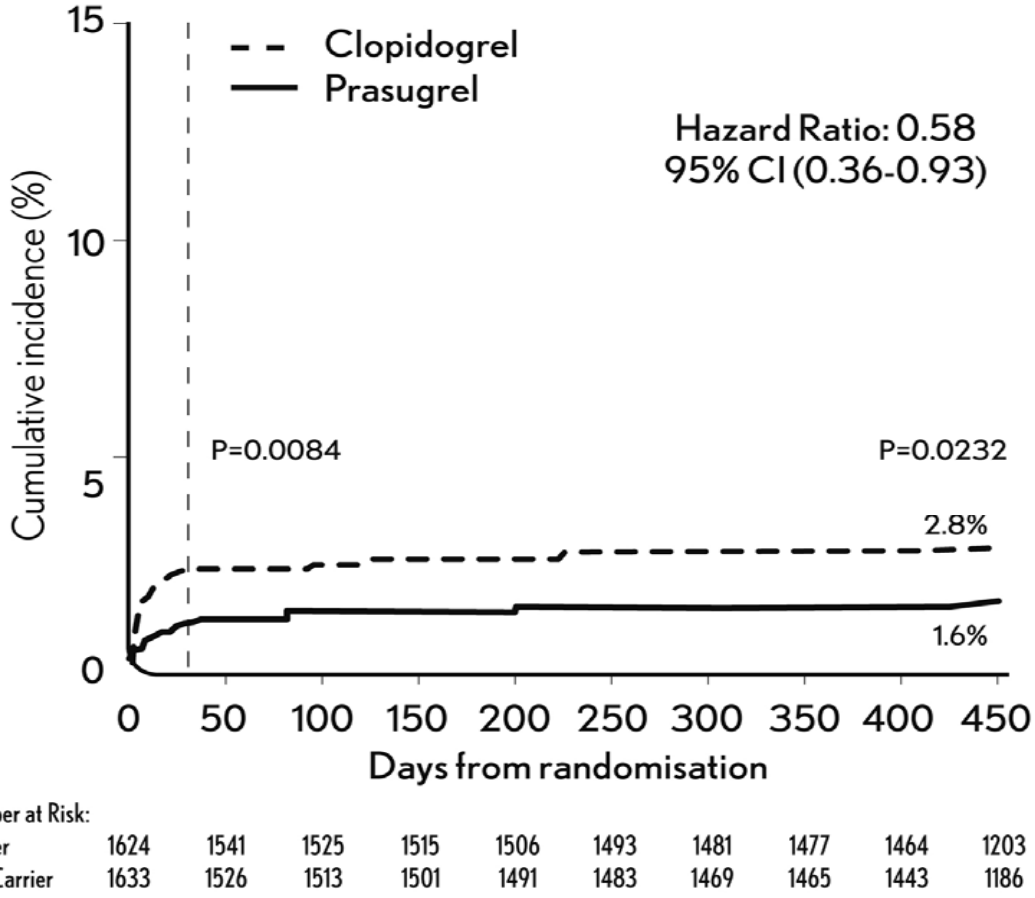
Carrier	1769	1588	1570	1511	1535	1517	1502	1493	1475	1226
Non-Carrier	1765	1543	1522	1506	1492	1481	1465	1459	1436	1177

Carrier	1769	1589	1571	1552	1535	1520	1507	1497	1481	1232
Non-Carrier	1765	1553	1531	1515	1500	1488	1472	1466	1443	1182

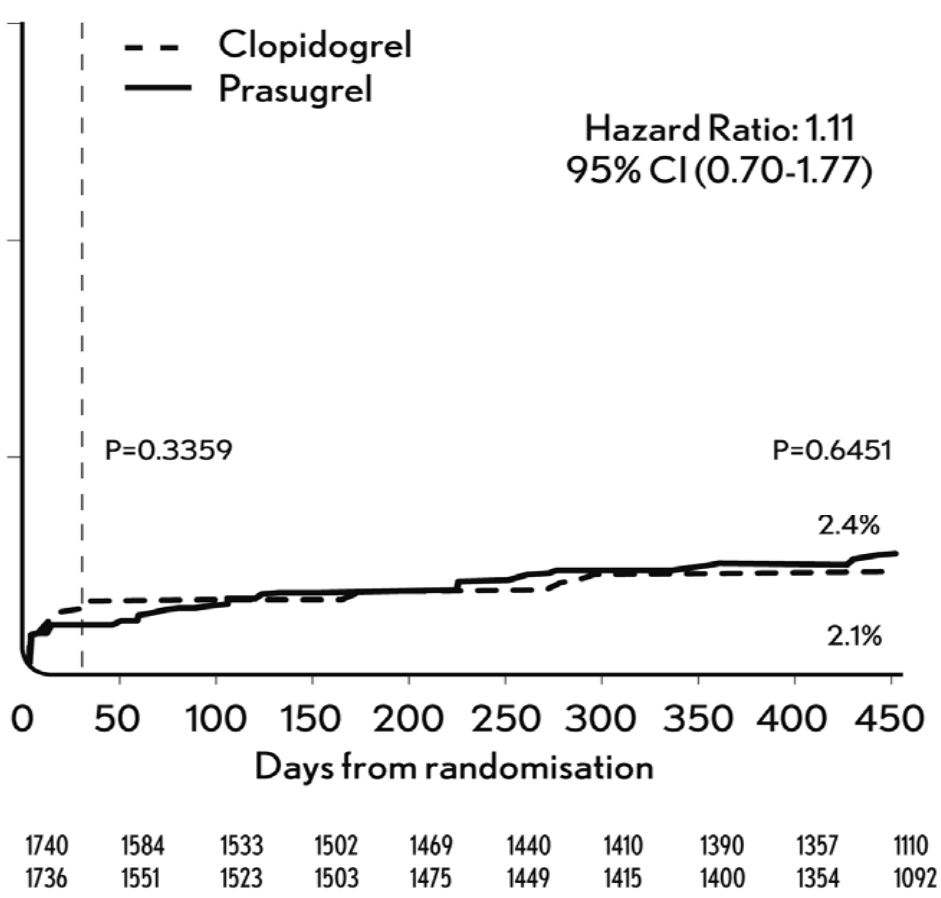
Data from Montalescot G et al. *Lancet* 2009;373(9665):723-731

STEMI

Stent thrombosis



Non-CABG related TIMI major bleeding



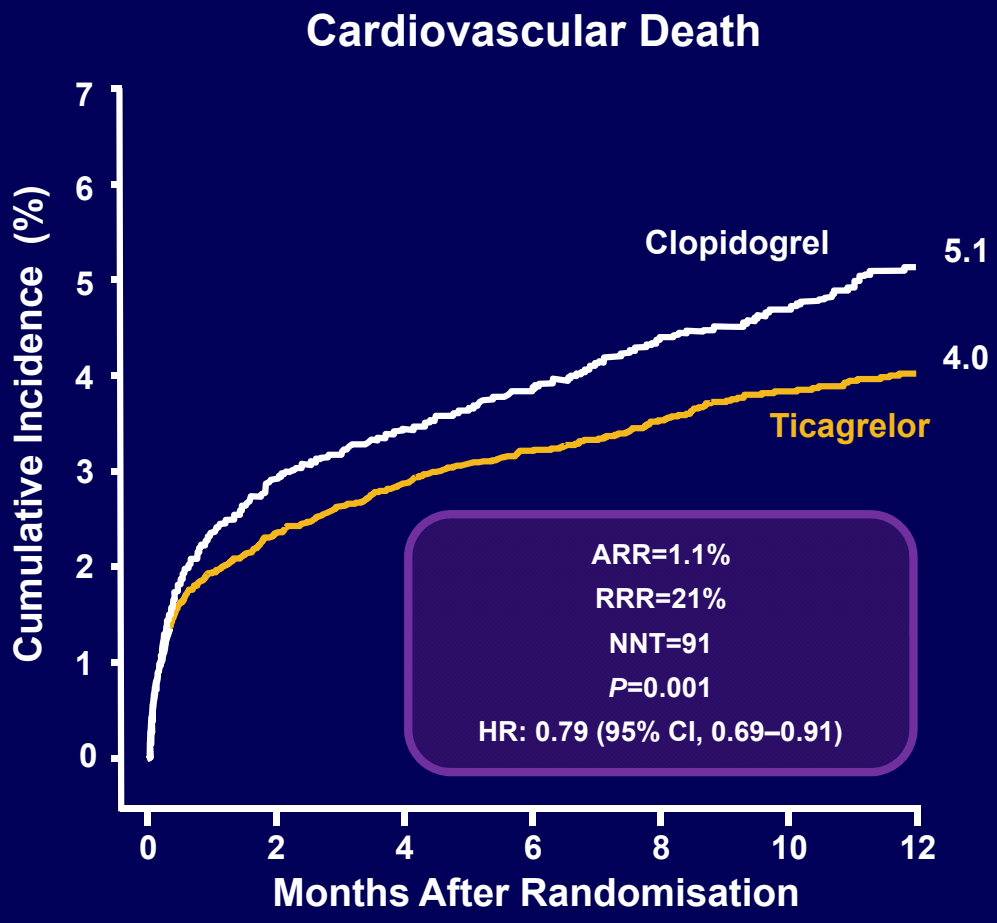
Number at Risk:

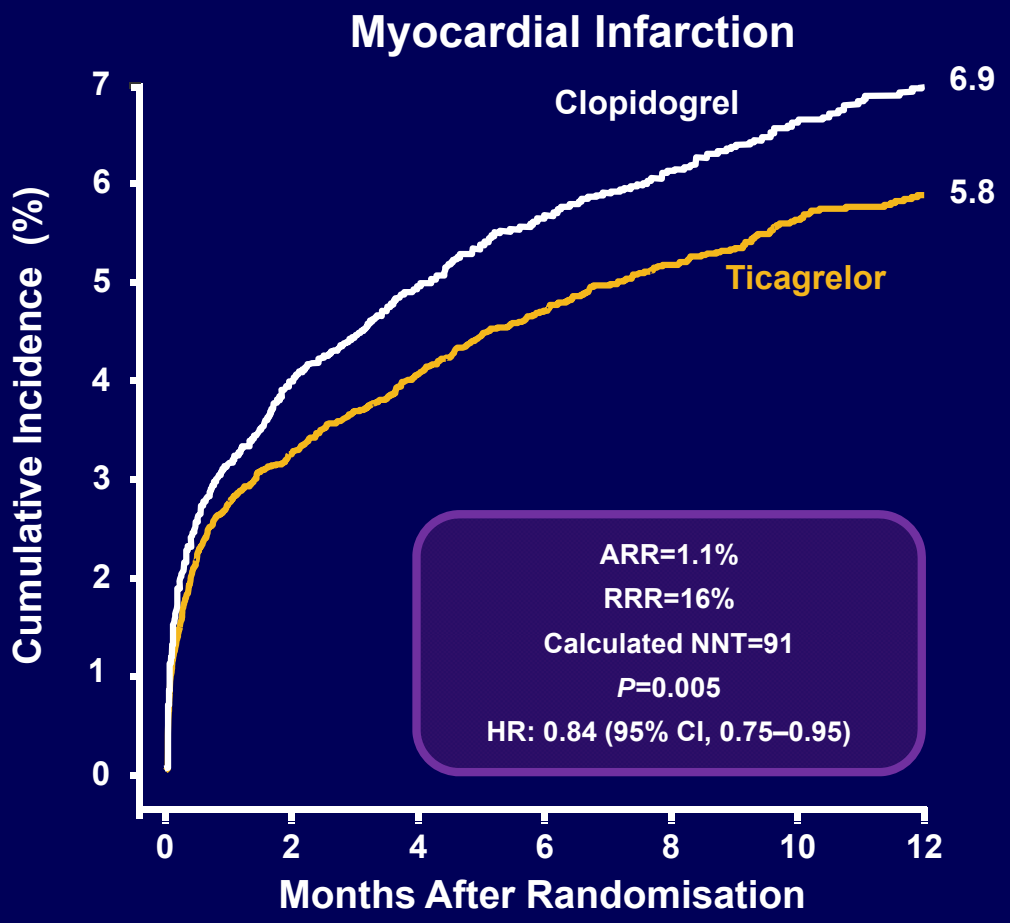
Carrier	1624	1541	1525	1515	1506	1493	1481	1477	1464	1203
Non-Carrier	1633	1526	1513	1501	1491	1483	1469	1465	1443	1186

Carrier	1740	1584	1533	1502	1469	1440	1410	1390	1357	1110
Non-Carrier	1736	1551	1523	1503	1475	1449	1415	1400	1354	1092

Data from Montalescot G et al. *Lancet* 2009;373(9665):723-731

PLATO: Secondary Efficacy Endpoints





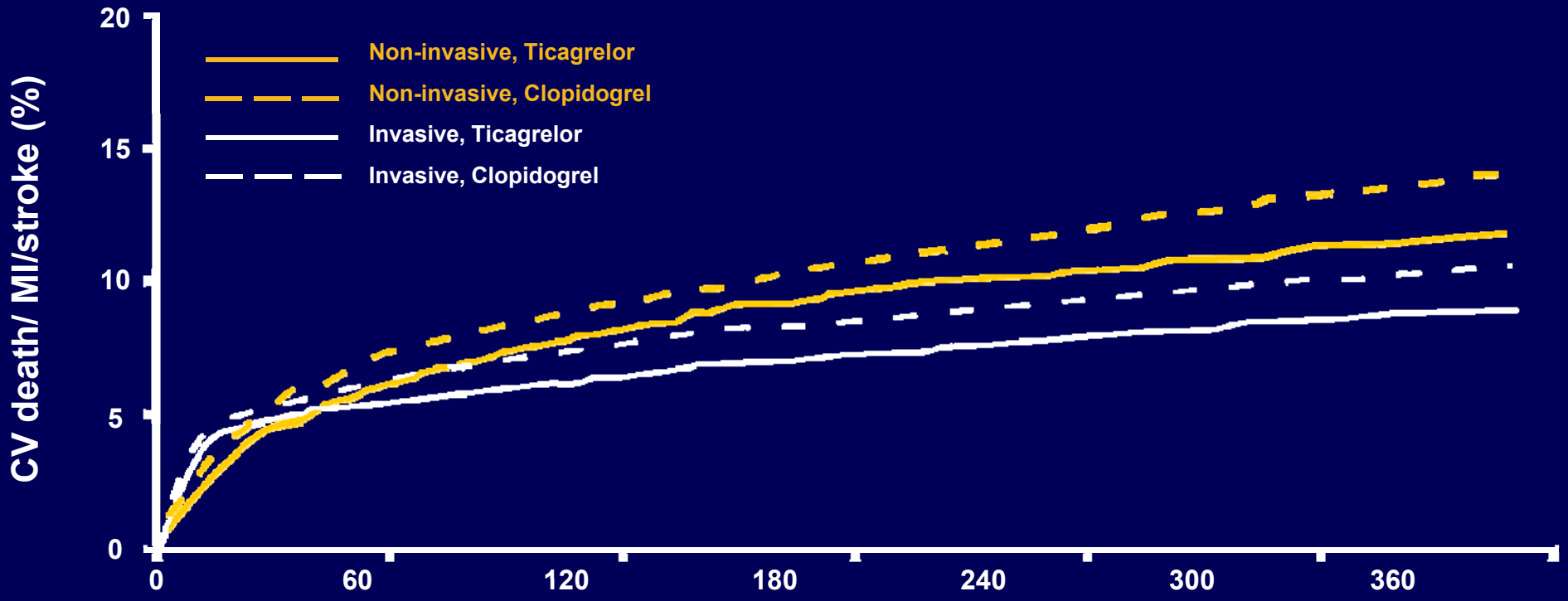
Rate of stroke for Ticagrelor was not different from clopidogrel (1.3% vs 1.1%), *P*=0.225.

Both groups included aspirin.

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.
Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057. Supplement.
BRILIINTA: Summary of Product Characteristics, 2010.

PLATO Non-invasive: Results

Time to first primary efficacy event (composite of CV death, MI or stroke)



Number at risk							
Invasive							
Ticagrelor	6,732	6,134	5,972	4,889	3,735	3,735	3,048
Clopidogrel	6,676	6,034	5,881	4,815	3,680	3,680	2,965
Non-invasive							
Ticagrelor	2,601	2,326	2,247	1,854	1,426	1,426	1,099
Clopidogrel	2,615	2,328	2,243	1,835	1,416	1,416	1,109

James SK, et al. *BMJ.* 2011 Jun 17;342:d3527

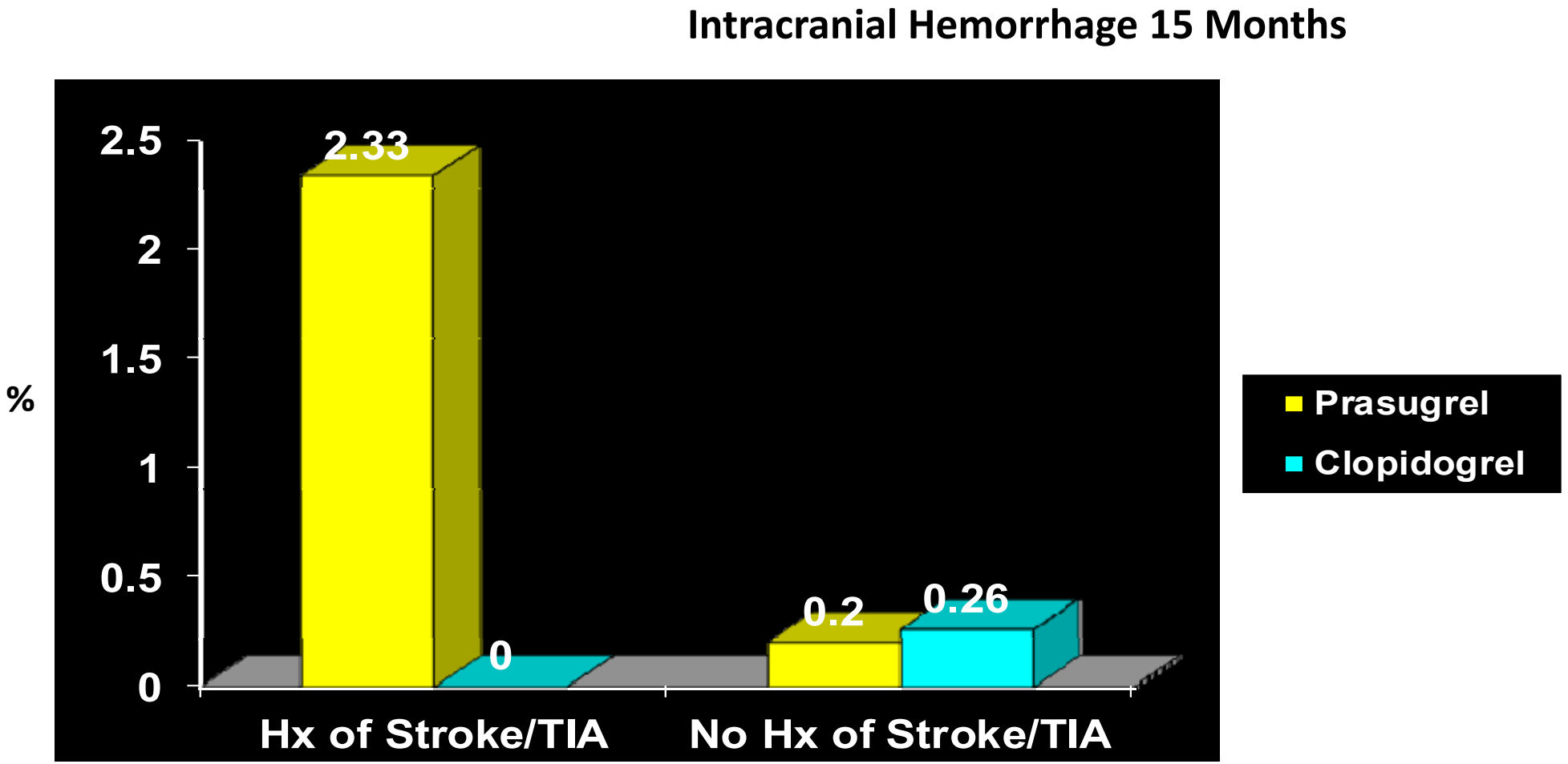
Lets look for….

1. Situations with the highest risk of ischemia

2. **Situations with the highest risk of bleeding**

TRITON-TIMI 38

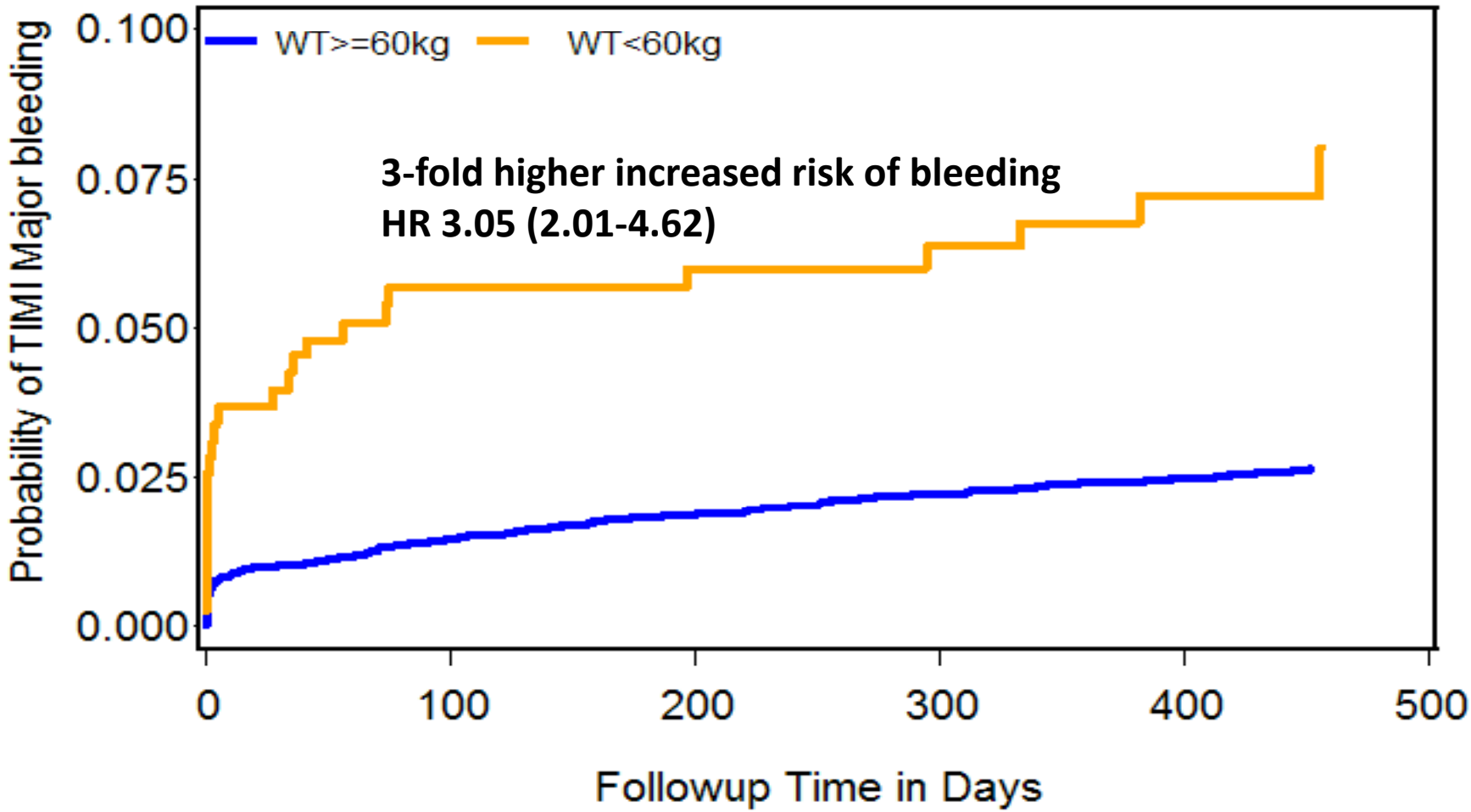
Impact of History of Stroke or TIA



FDA Advisory Committee Docket. Available at http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4412b1-01-FDA.pdf.

TRITON-TIMI 38

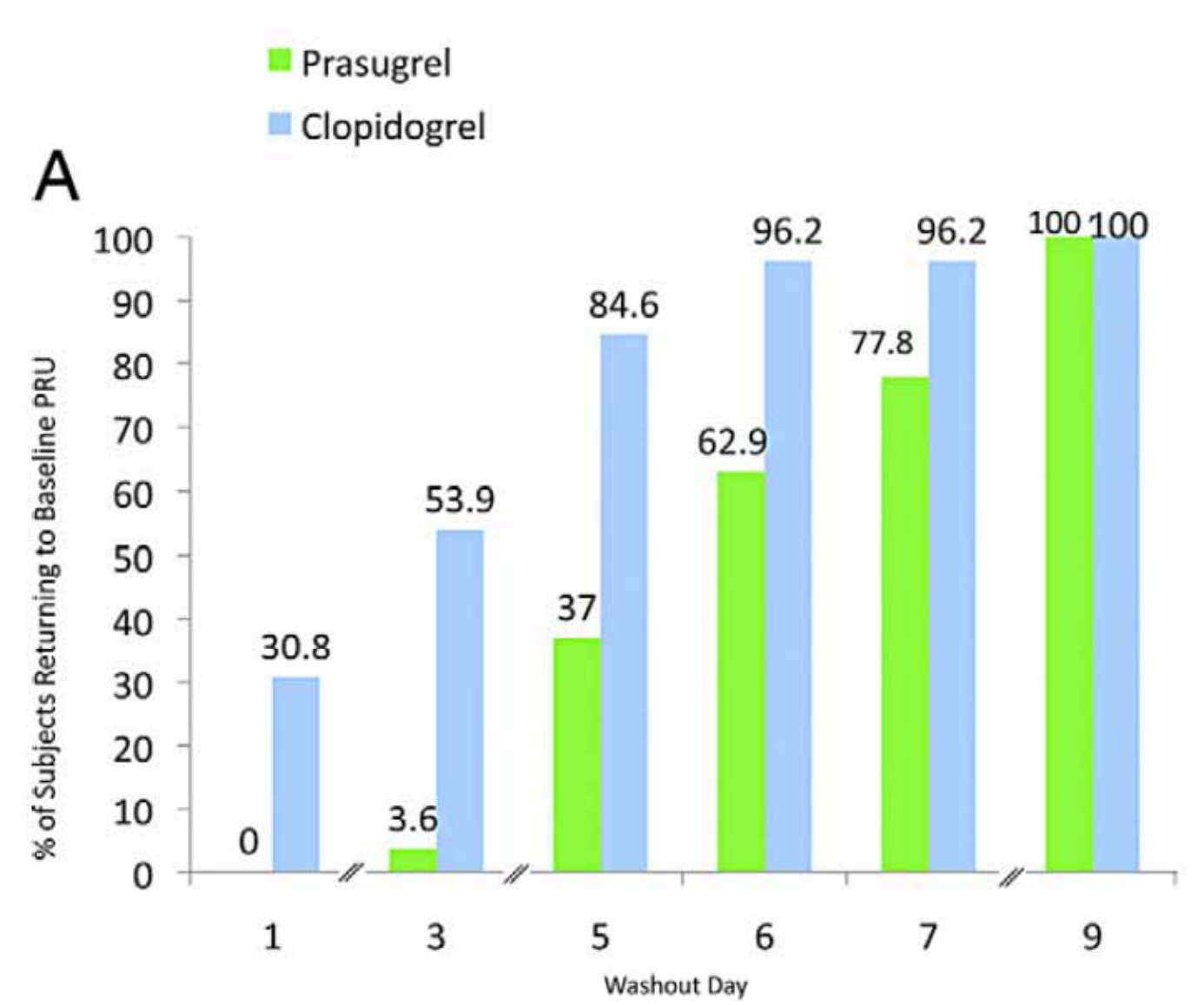
Impact of Low Bwt.



FDA Advisory Committee Docket. Available at http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4412b1-01-FDA.pdf.

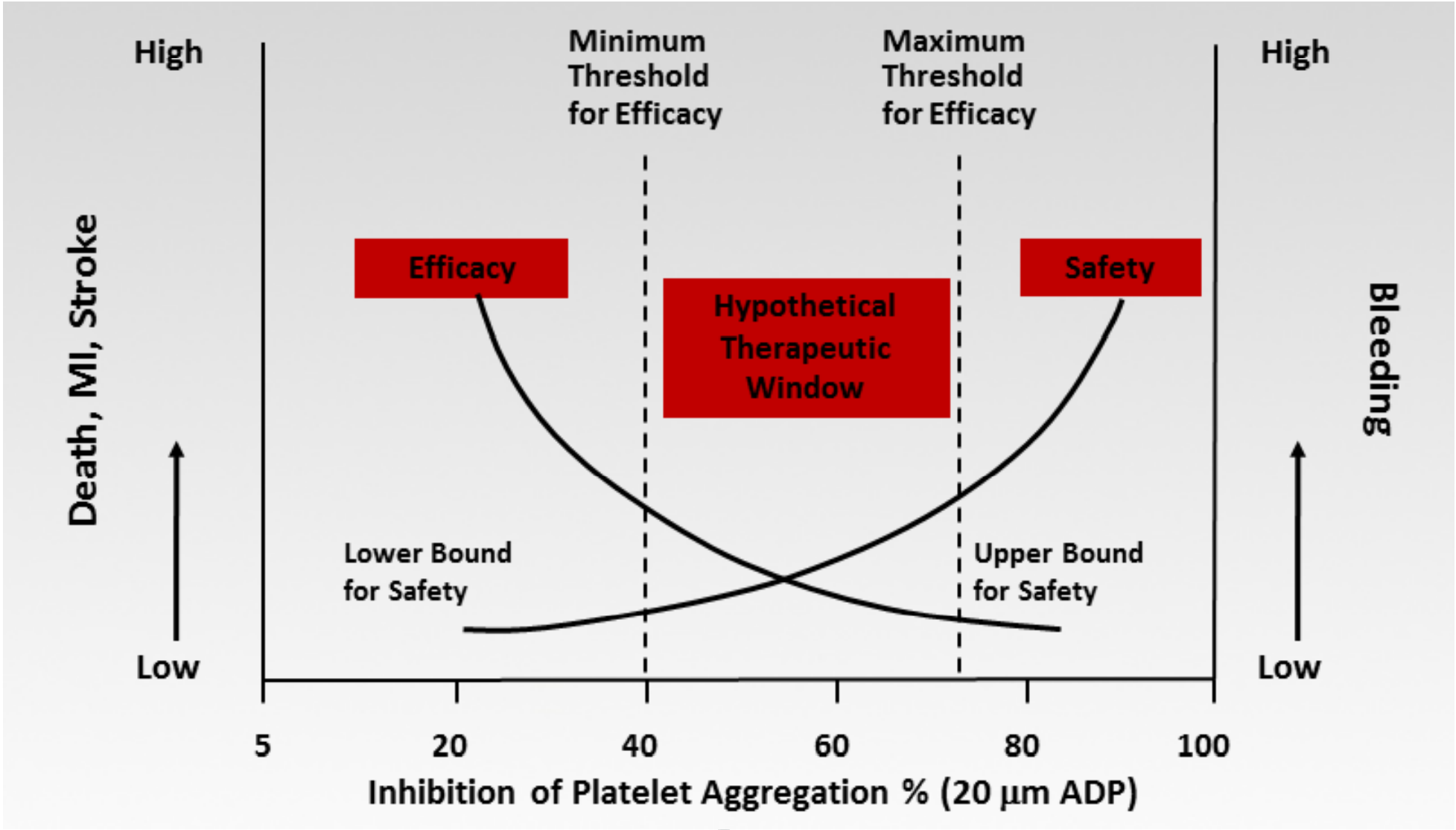
RECOVER study

Recovery of platelet fxn after drug discontinuation



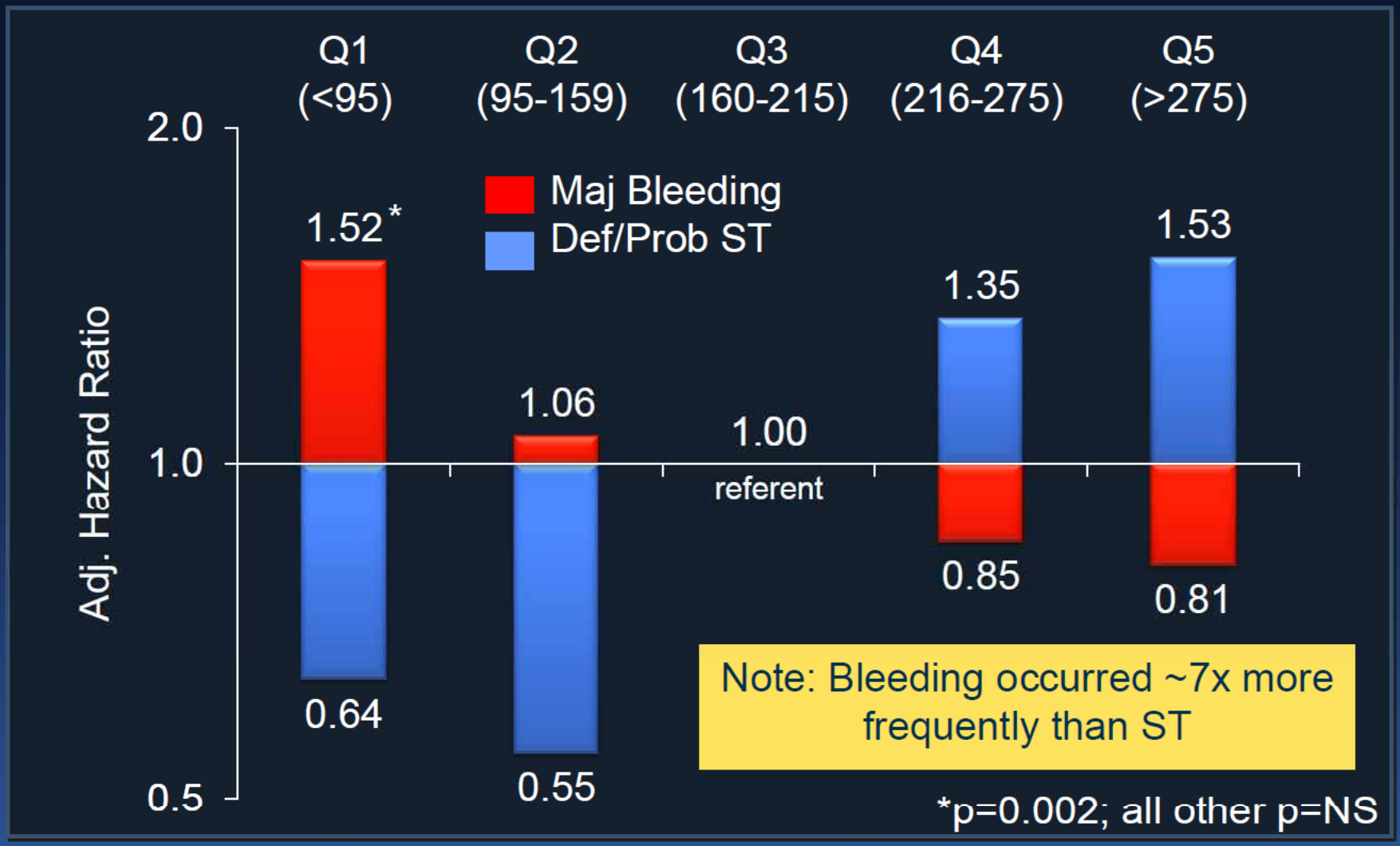
Price M et al. JACC 2012

Balance between ischemia and bleeding



Becker RC. et al. *J Thromb Thrombolysis* 2009;28:513-514

ADAPT DES at 1 Year:
MV Analysis of ST and Maj Bleeding by PRU



Summary

1. More potent antiplatelet agents reduces ischemic outcomes in the heart!
2. However, there is a bleeding tax.
3. Let's also not forget the fragile brain
4. Therefore, stronger is not always better → need balance
5. Always consider both the risk of ischemia and the risk of bleeding

Summary

ACS

↓

Default antiplt:
newer agent

↓

If high risk of bleeding or S/E to newer agent
→ Clopidogrel

Stable Angina

↓

Default antiplt:
Clopidogrel

↓

If high risk of thrombosis or prior ST
→ + Cilo or
Could consider new agent

It’s all about BALANCE!

Let’s not be penny wise and pound foolish