Dual Antiplatelet Therapy in ACS / PCI

Current Recommendations and Corresponding Data

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Demand

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Rheumatism

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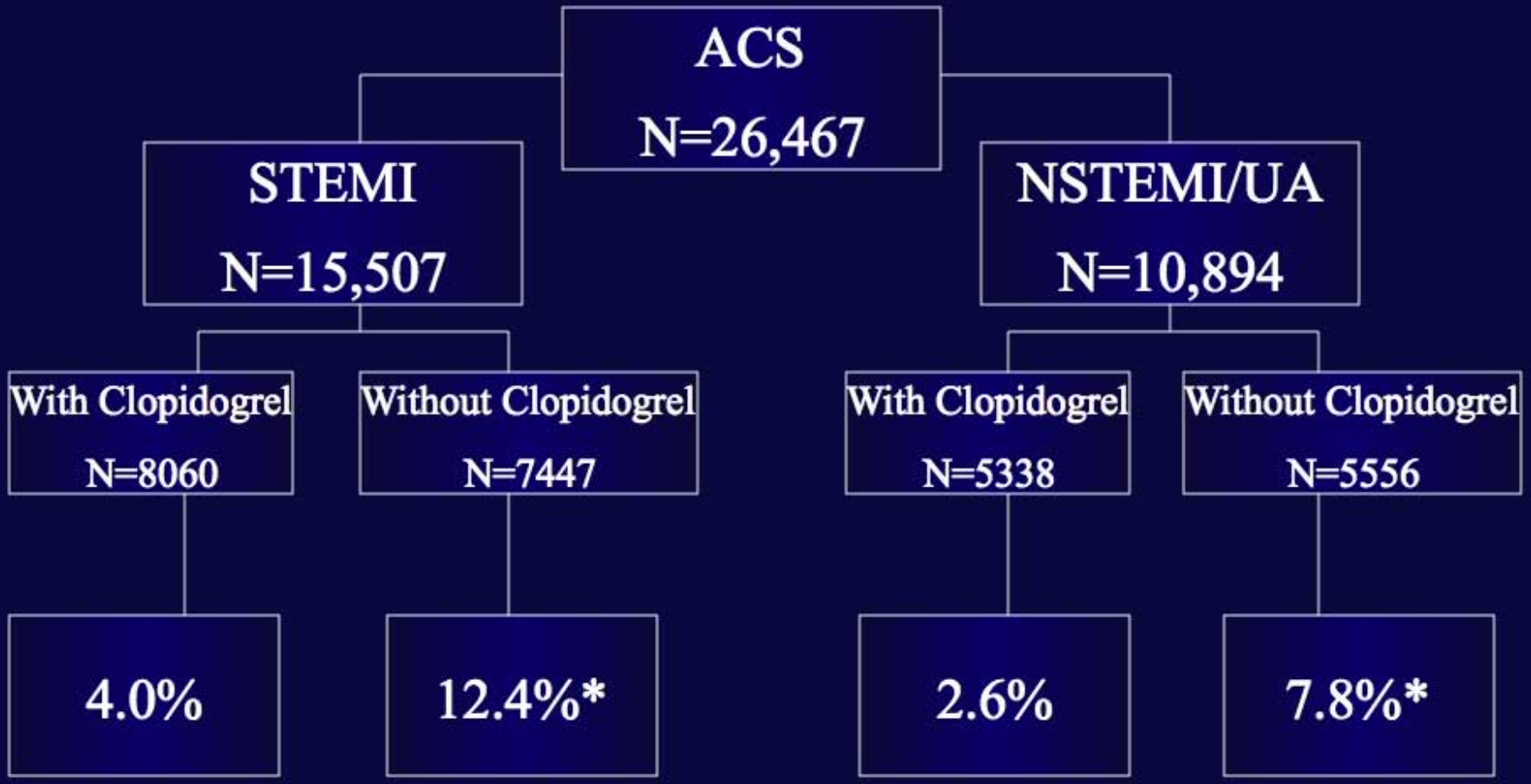
AMIS :Impact of Clopidogrel on in-hospital Mortality

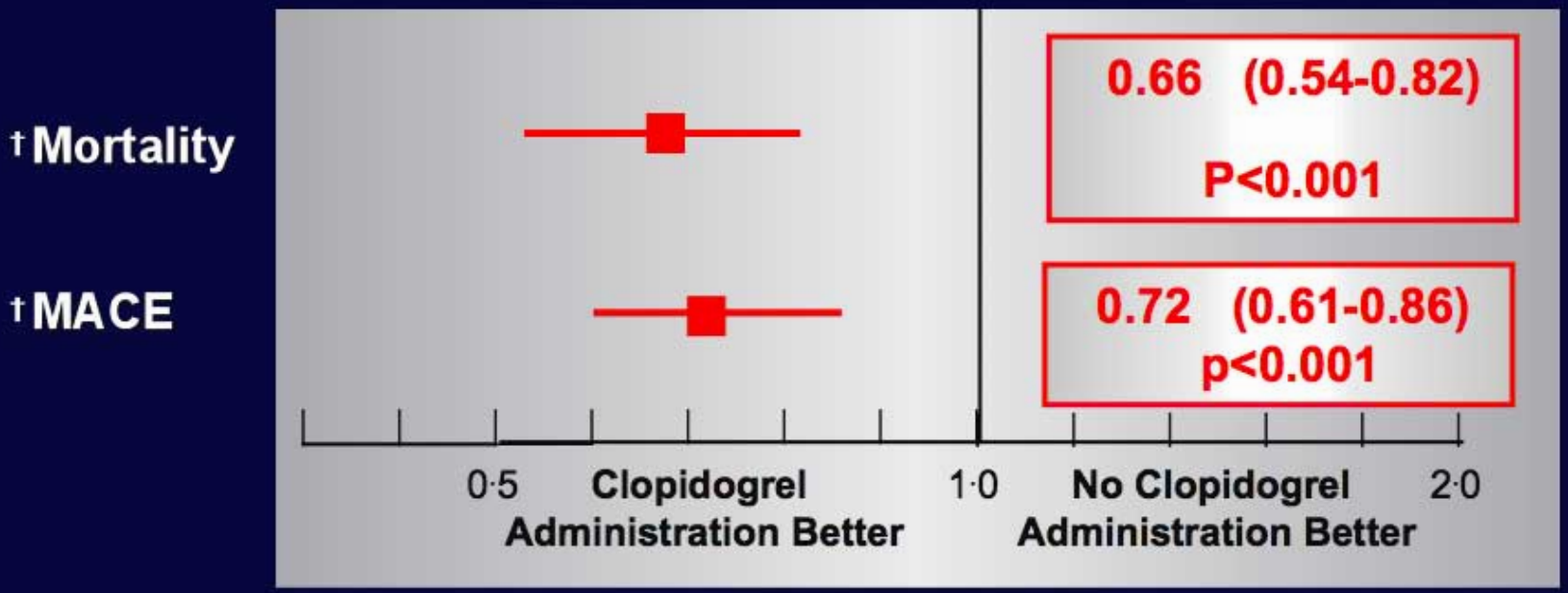


*p<0.001

*p<0.001

Mortality and MACE (death, reinfarction and stroke) Benefit of Clopidogrel Rx

A Acute
M Myocardial
I Infarction in
S Switzerland

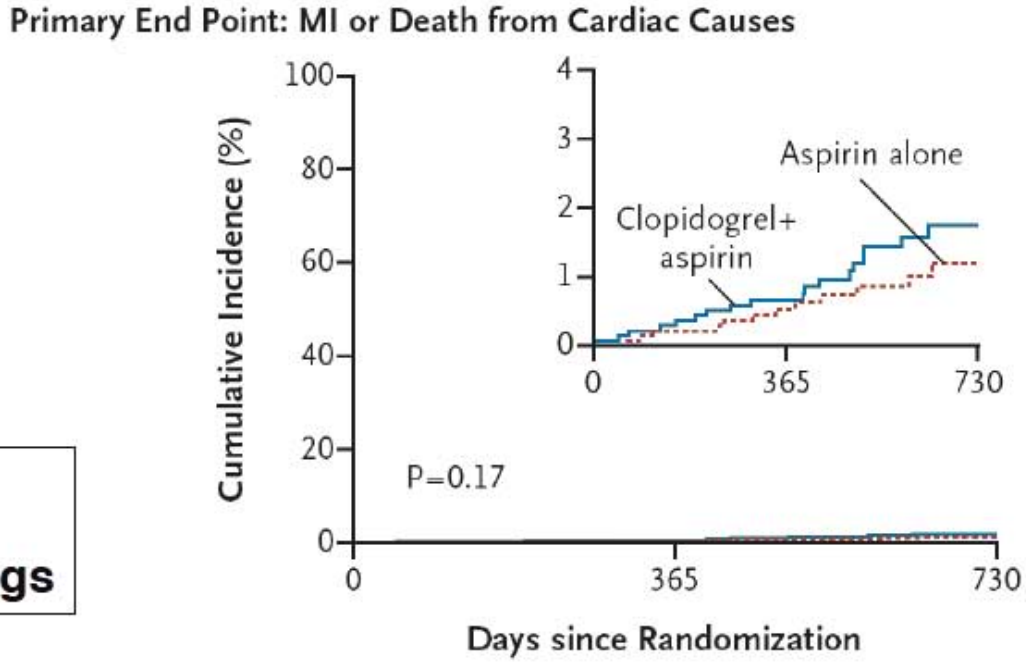


†Adjusted imbalances for all variables by multivariate analysis

Randomized Study: DES LATE

2701 pts / DES / FU 2 years

12 months vs > 12 months DAT



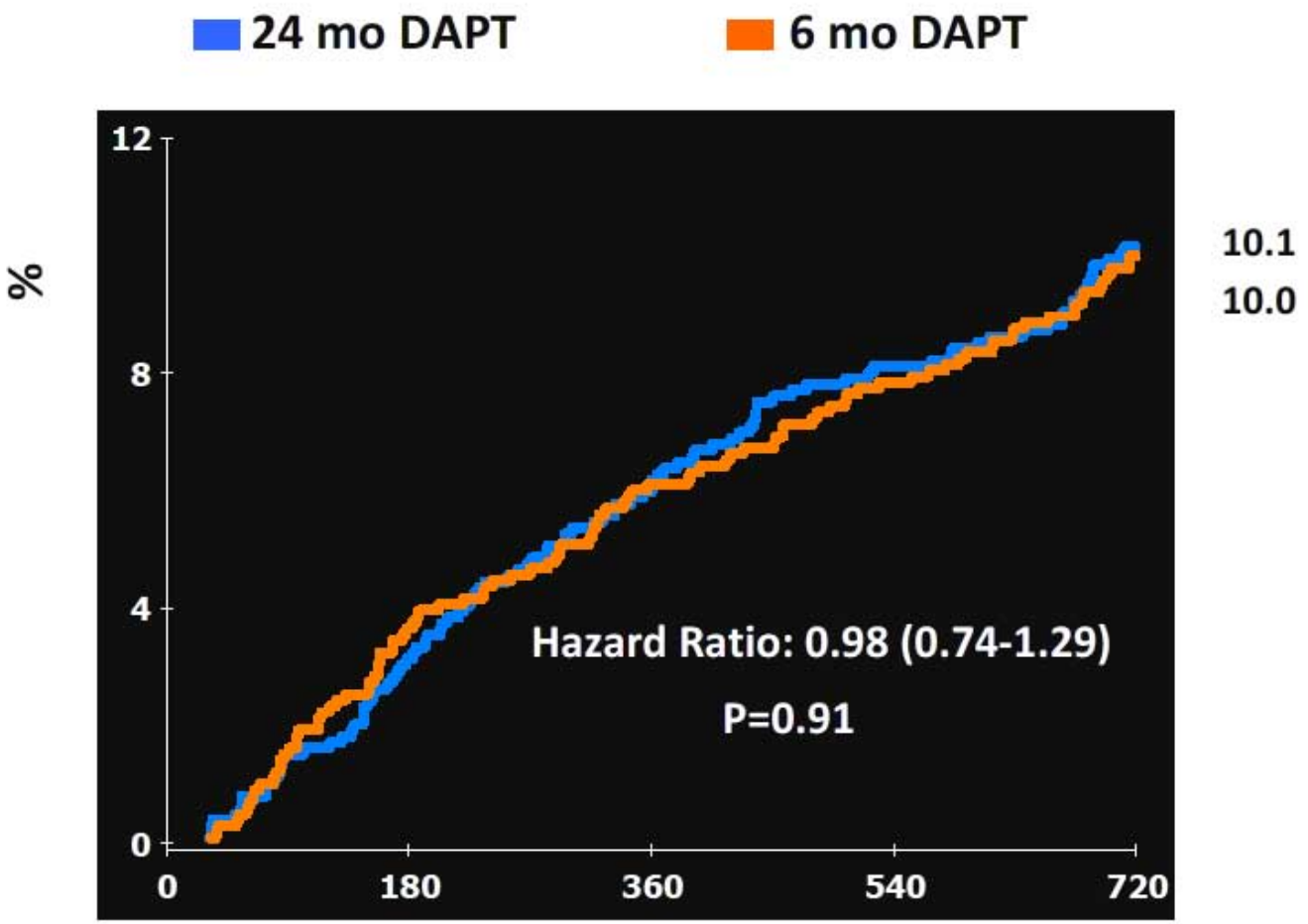
No benefit of long term DAT

No difference in TIMI Major bleedings

Park et al. NEJM 2010

PRODIGY Study

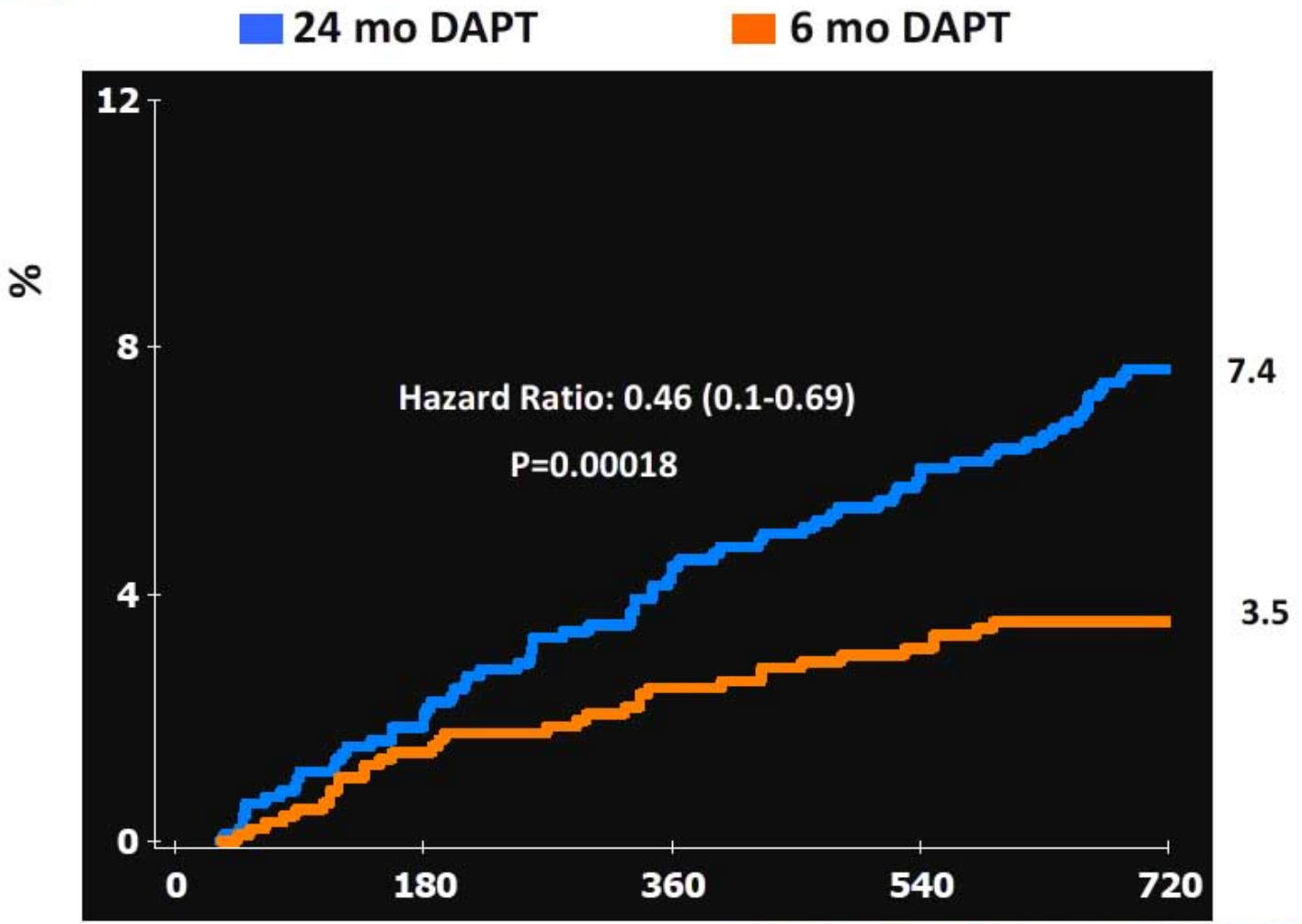
Overall Death, MI or CVA



Valgimigli et al, Circulation 2012

PRODIGY Study

Type II, III or V BARC bleeding

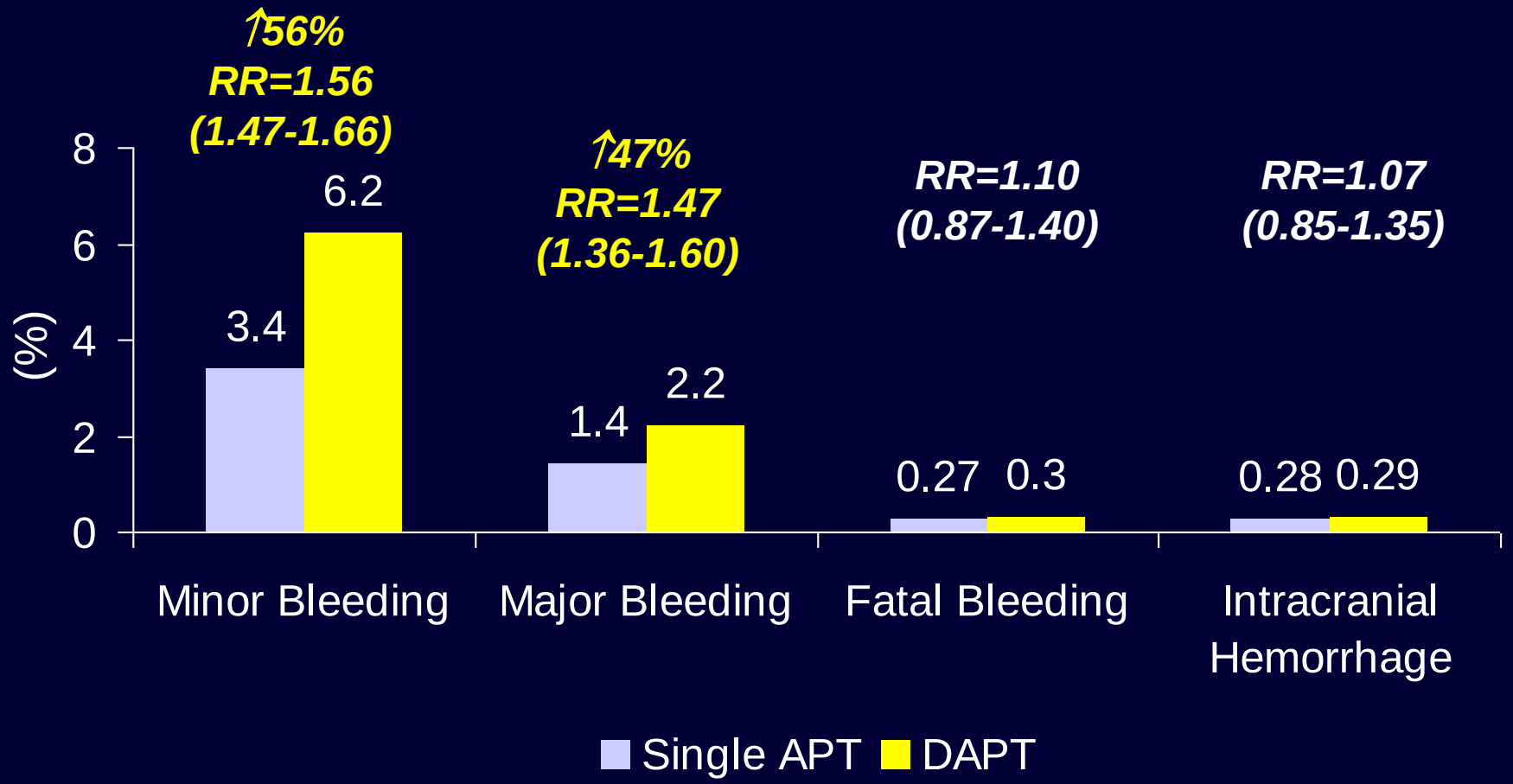


Valgimigli et al, Circulation 2012

Risk of Bleeding With DAPT

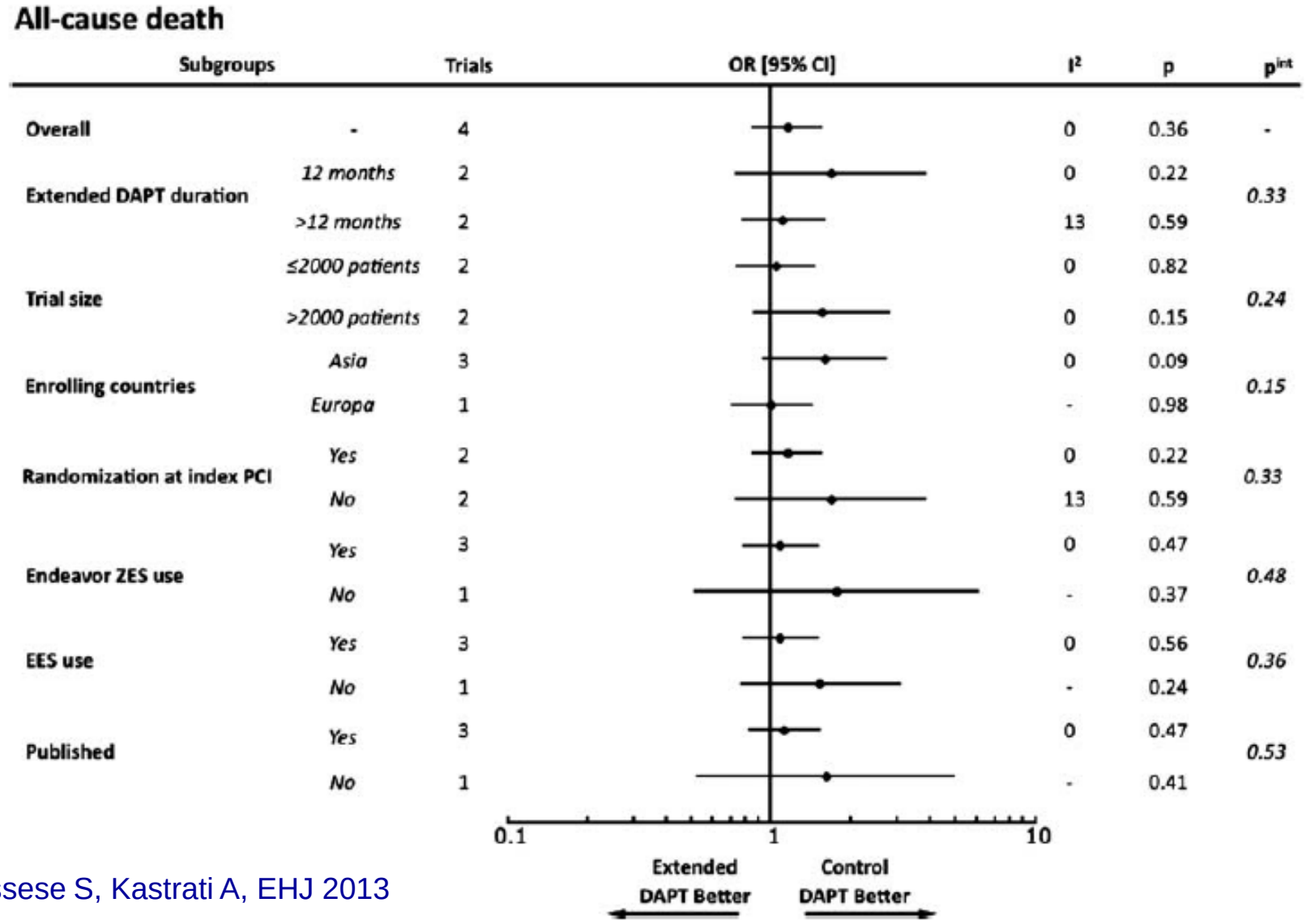
Serebruany VL et al. *Fund & Clin Pharmacology* 2008;22:315-21

18 RCTs With 129,314 Patients Comparing Single versus Dual Antiplatelet Therapy



Extended dual antiplatelet therapy after PCI with DES

a meta-analysis of randomized trials



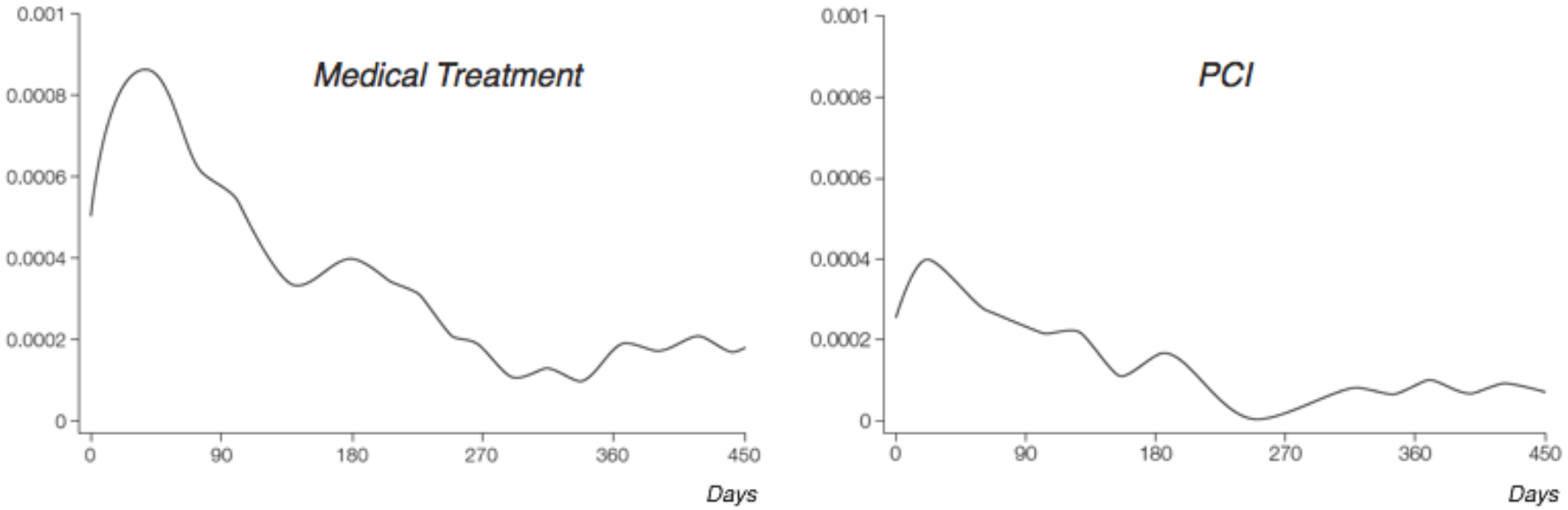
Cassese S, Kastrati A, EHJ 2013

Clopidogrel Cessation

Death or MI

VA pts with ACS	**3137**
• Medical therapy	1568
• PCI	1569

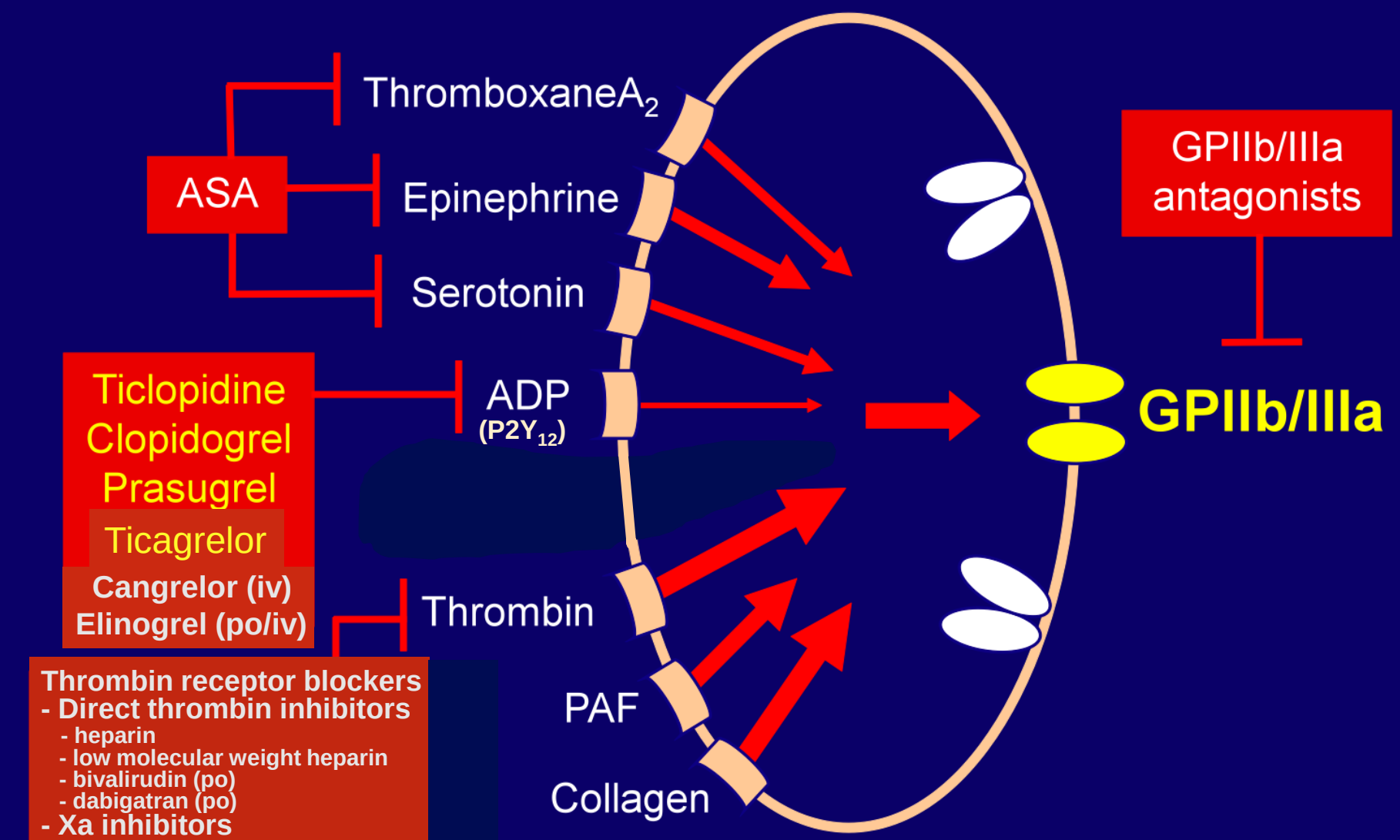
Incidence per Day and Patient After Stop of Clopidogrel



Discontinuation of long term clopidogrel therapy induces platelet rebound hyperaggregability between 2 and 6 weeks post cessation.
(Diehl P, Clinical Research in Cardiology, April 2011)

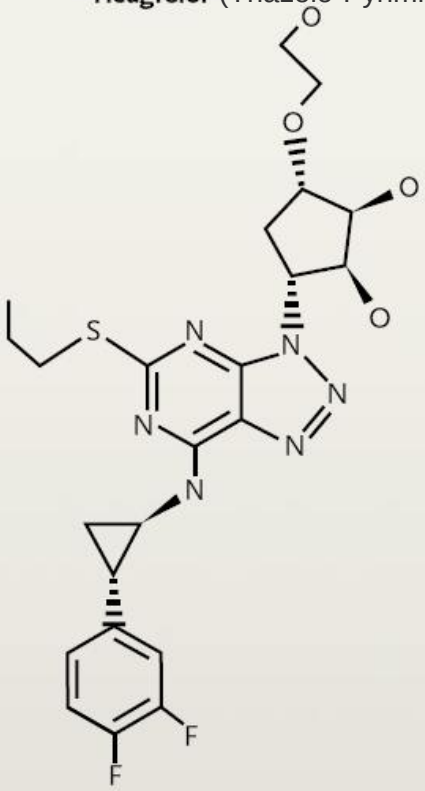
Ho PM, JAMA. 2008;299:532-539

Platelet activating substances and targets for inhibition

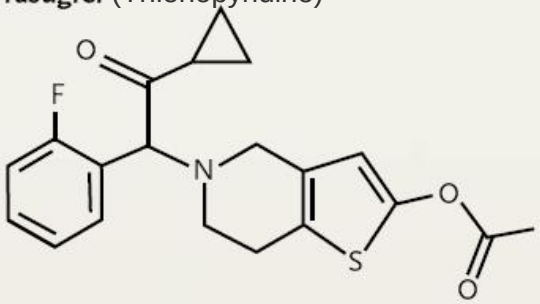


Adapted from Gawaz M, Blood Platelets. 1° Ed. New York:Thieme; 2001

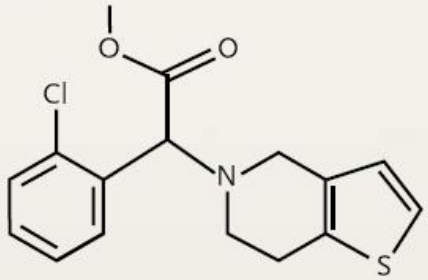
Ticagrelor (Triazolo-Pyrimidine)



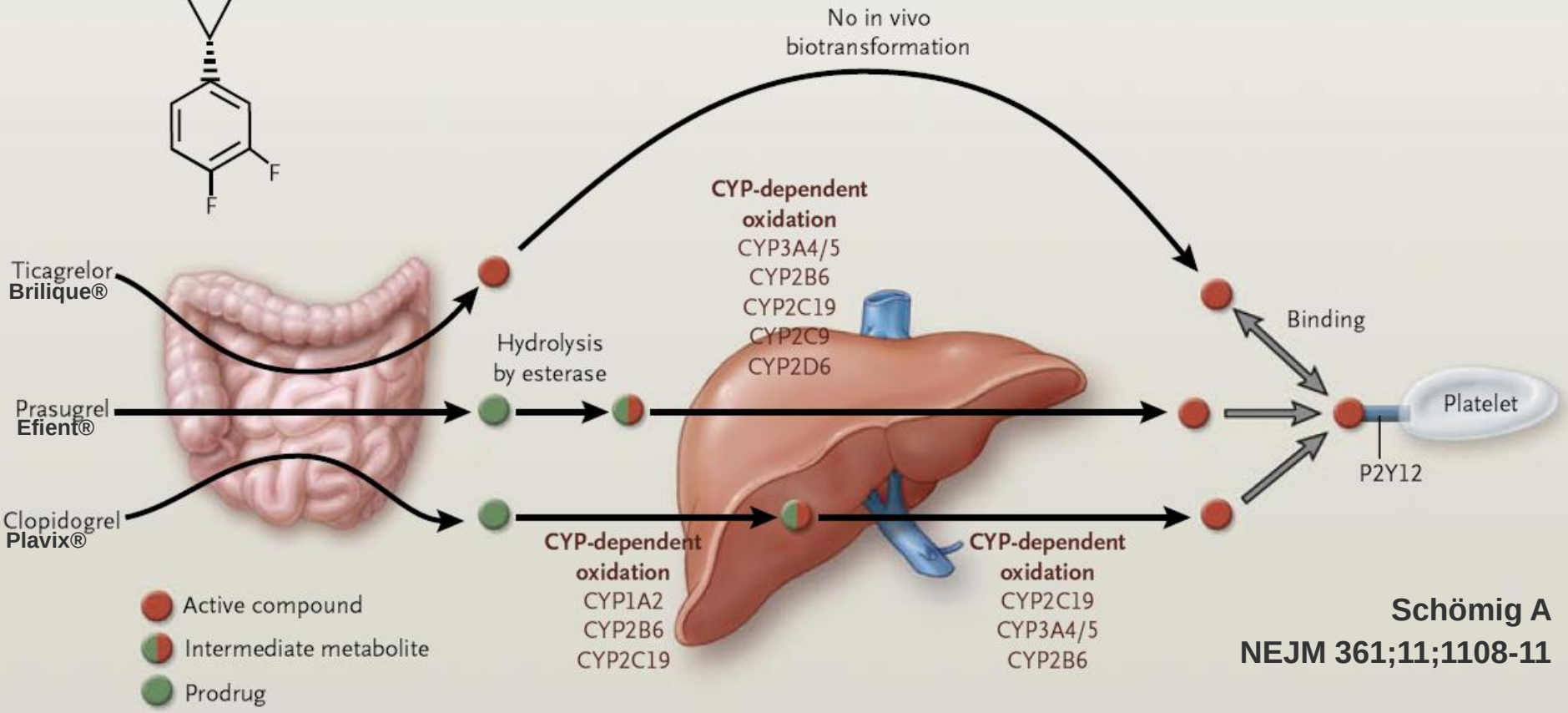
Prasugrel (Thienopyridine)



Clopidogrel (Thienopyridine)



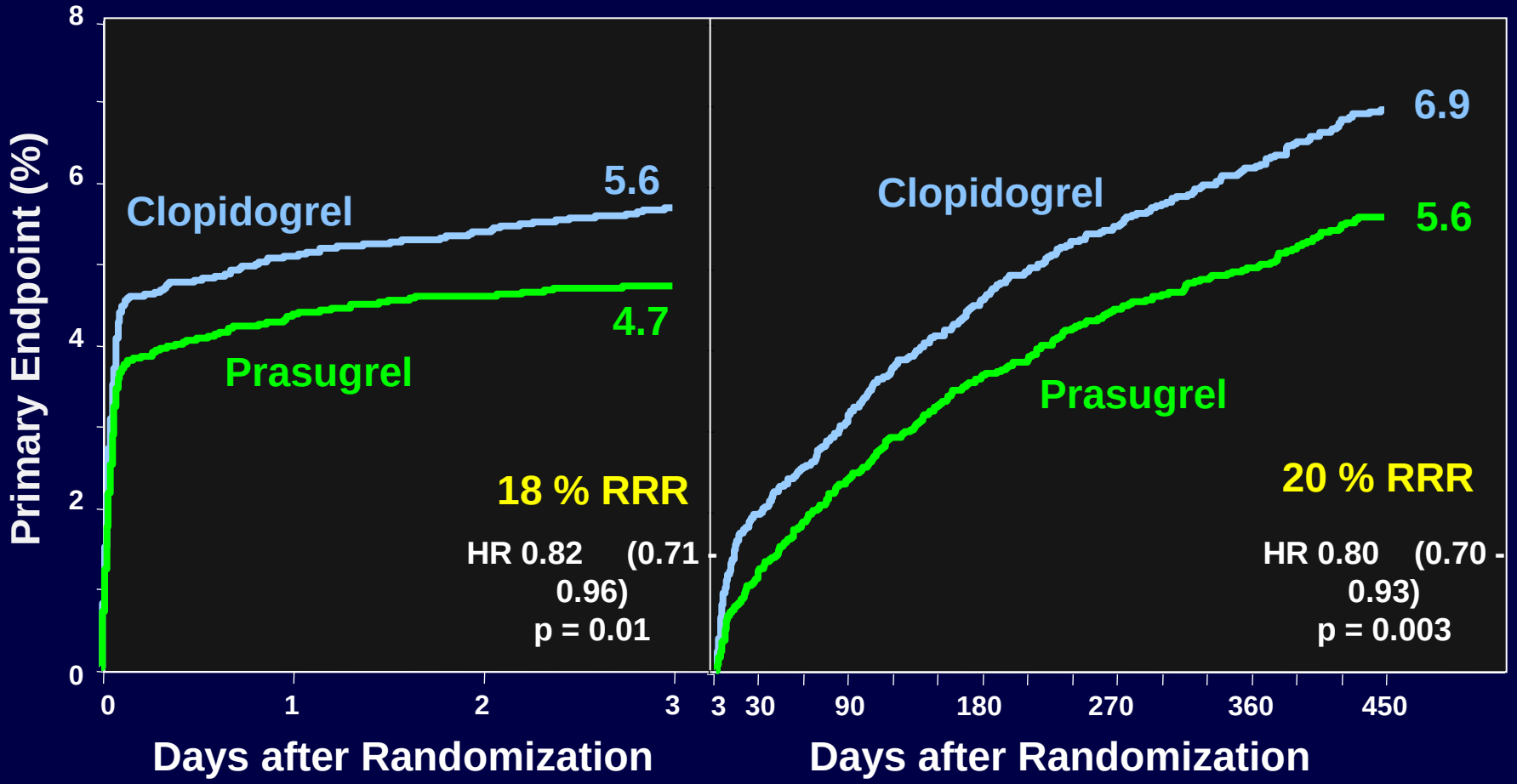
Oral Antiplatelet Agents
(via receptor $P2Y_{12}$)



Schömig A
NEJM 361;11;1108-11

TRITON-TIMI 38: Landmark Analysis for Primary Efficacy Endpoint

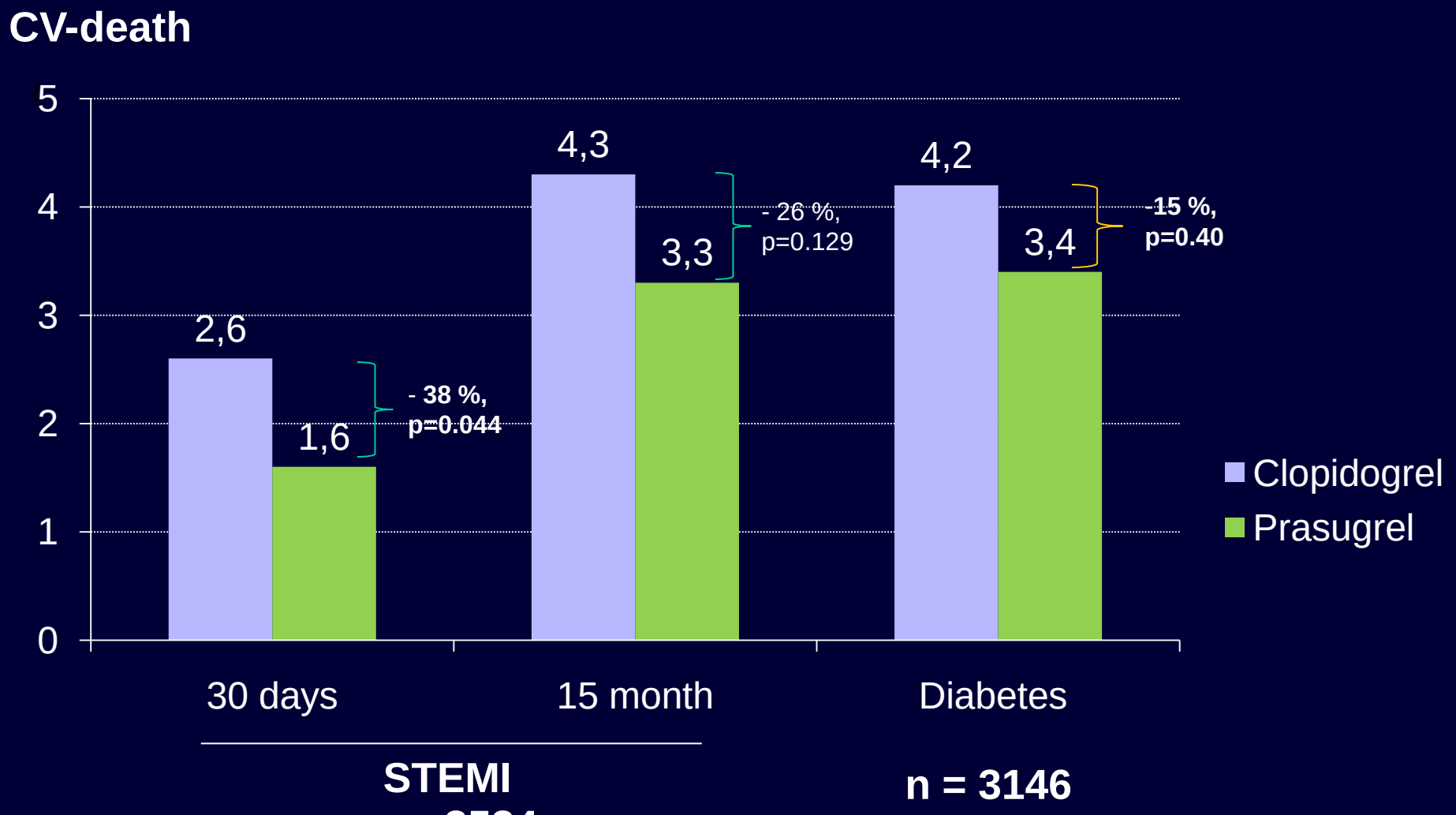
Cardiovascular Death, Nonfatal Myocardial Infarction, Nonfatal Stroke



- Hazard ratios based on Kaplan-Meier estimates; HR = Hazard ratio

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

Mortality benefit in TRITON

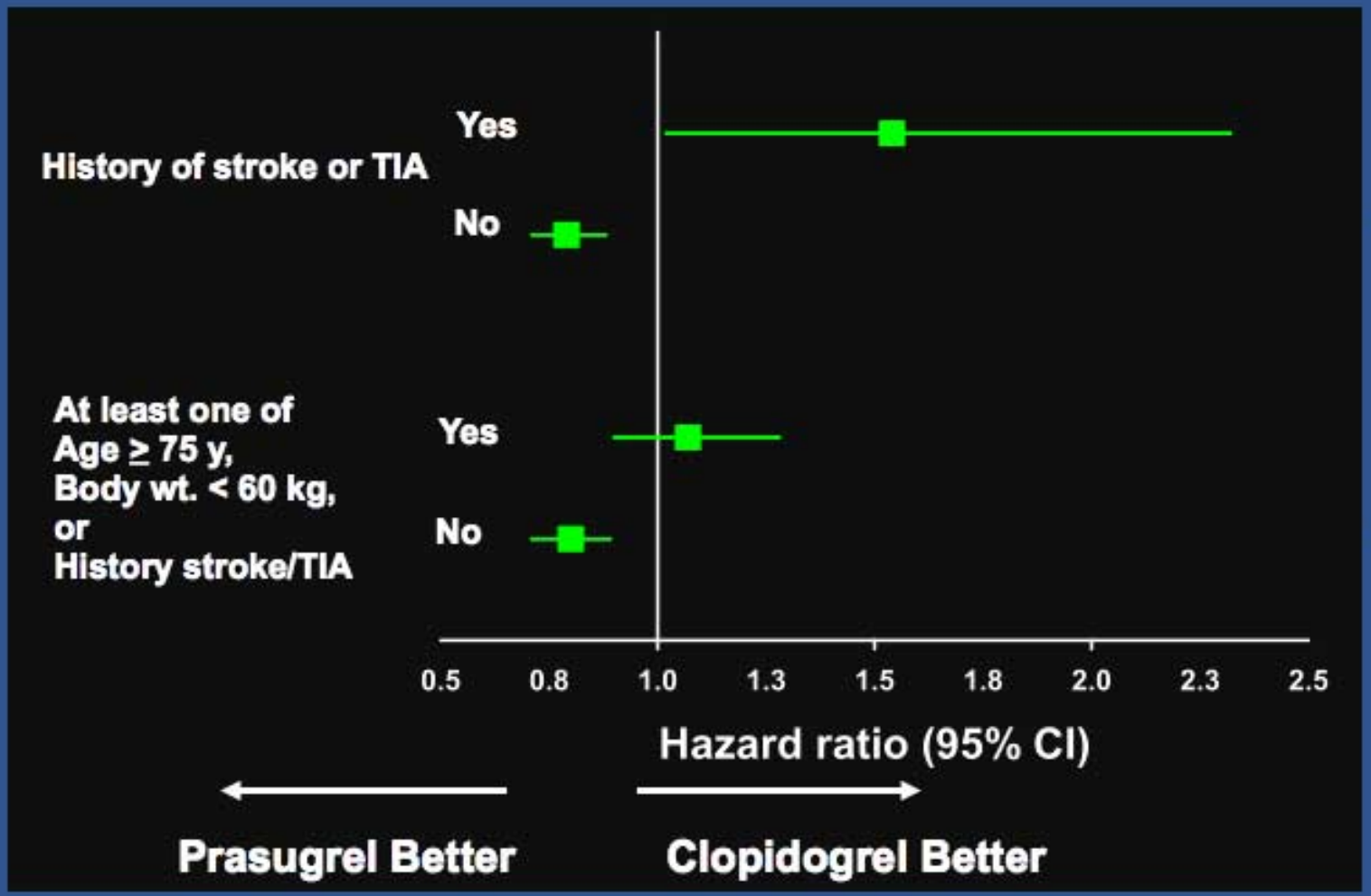


STEMI
n = 3534

n = 3146

Montalescot et al, 2009 Lancet 373
Wiviott et al. 2008 Circulation 118

Any cause death, Nonfatal MI, Nonfatal Stroke, Non-CABG TIMI Major Bleed: Post-hoc Analysis Selected Subgroups*



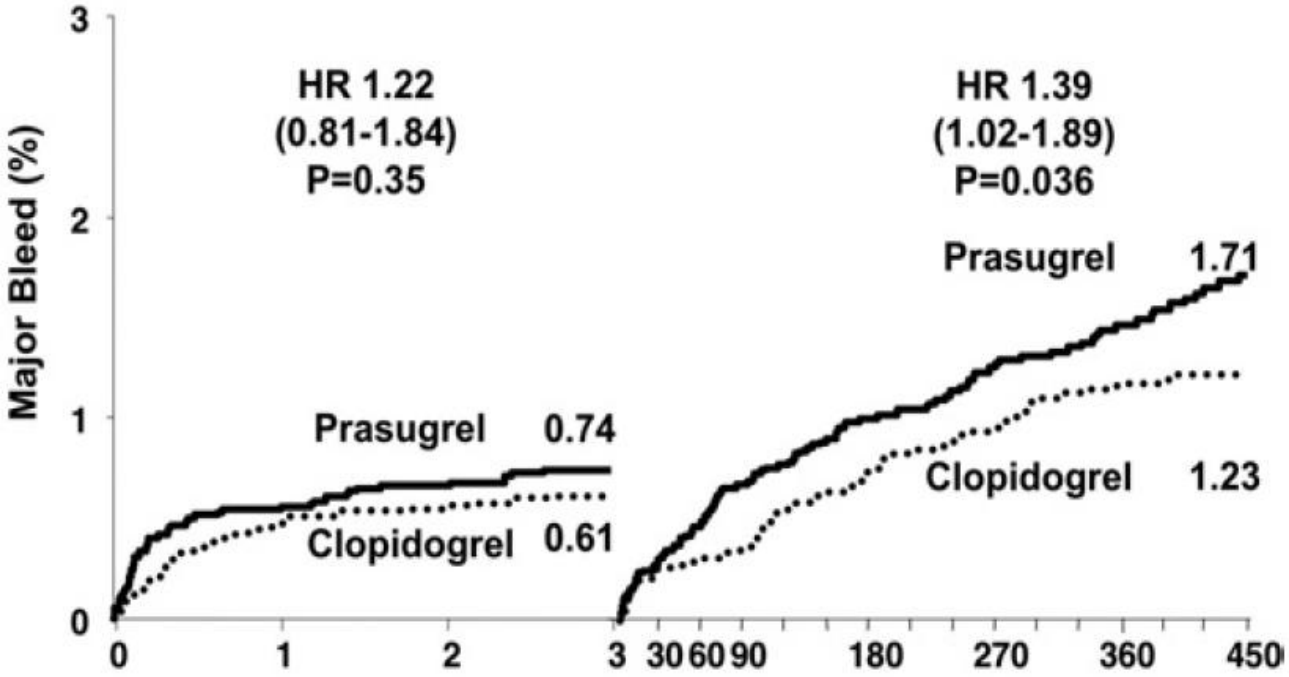
	P** value	P*** interaction
History of stroke or TIA: Yes	0.04	-
History of stroke or TIA: No	<0.001	0.006
At least one of Age ≥ 75 y, Body wt. < 60 kg, or History stroke/TIA: Yes	0.43	-
At least one of Age ≥ 75 y, Body wt. < 60 kg, or History stroke/TIA: No	<0.001	0.006

*Kaplan-Meier estimates intention-to-treat cohort
**Tests hazard ratio =1.0 within subgroups
***Tests equality hazard ratio between subgroups

Early and Late Risks of Prasugrel Over Clopidogrel in ACS Patients Undergoing PCI

Antman E et al. *J Am Coll Cardiol* 2008;51:2028-33

Major Bleeding

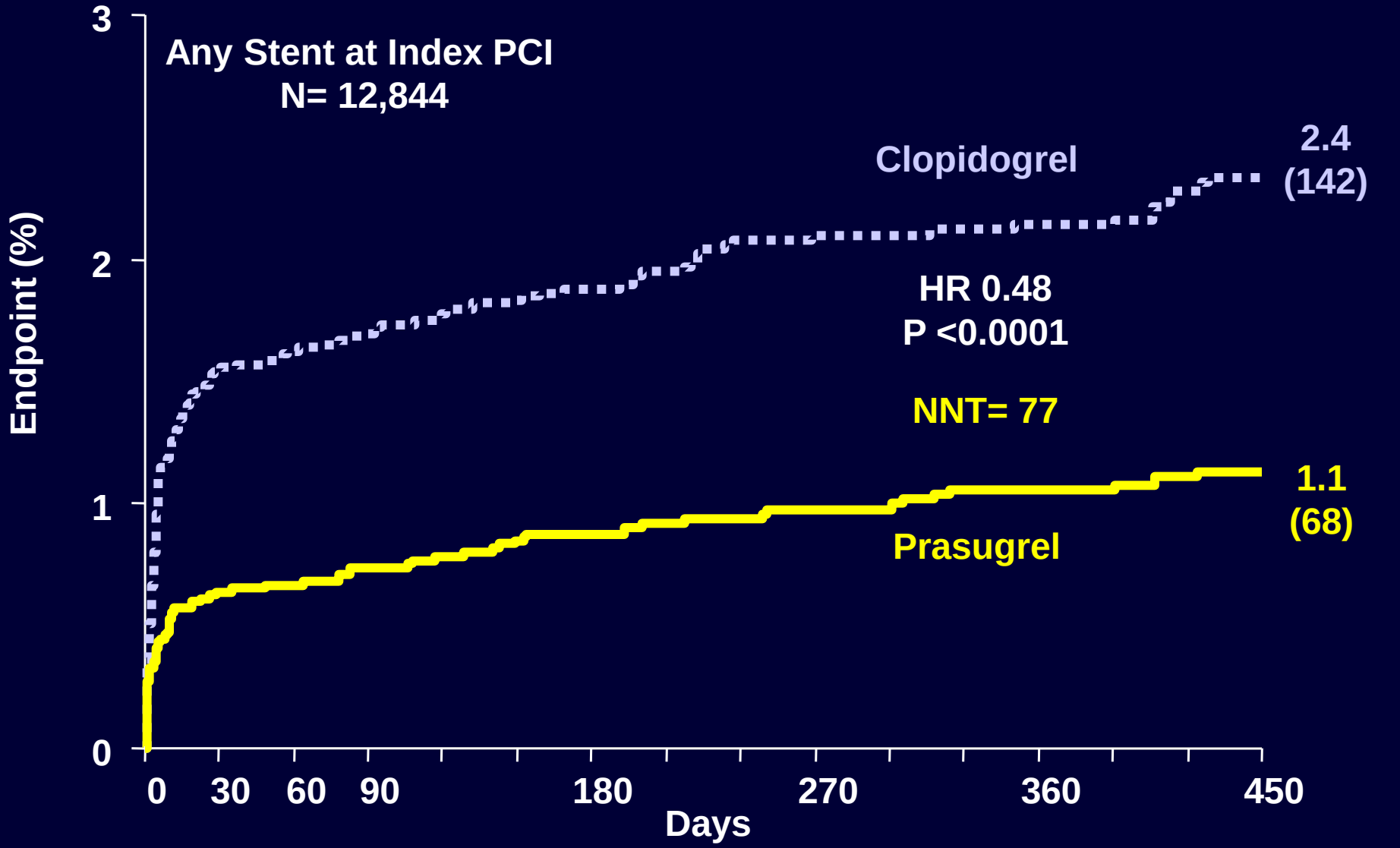


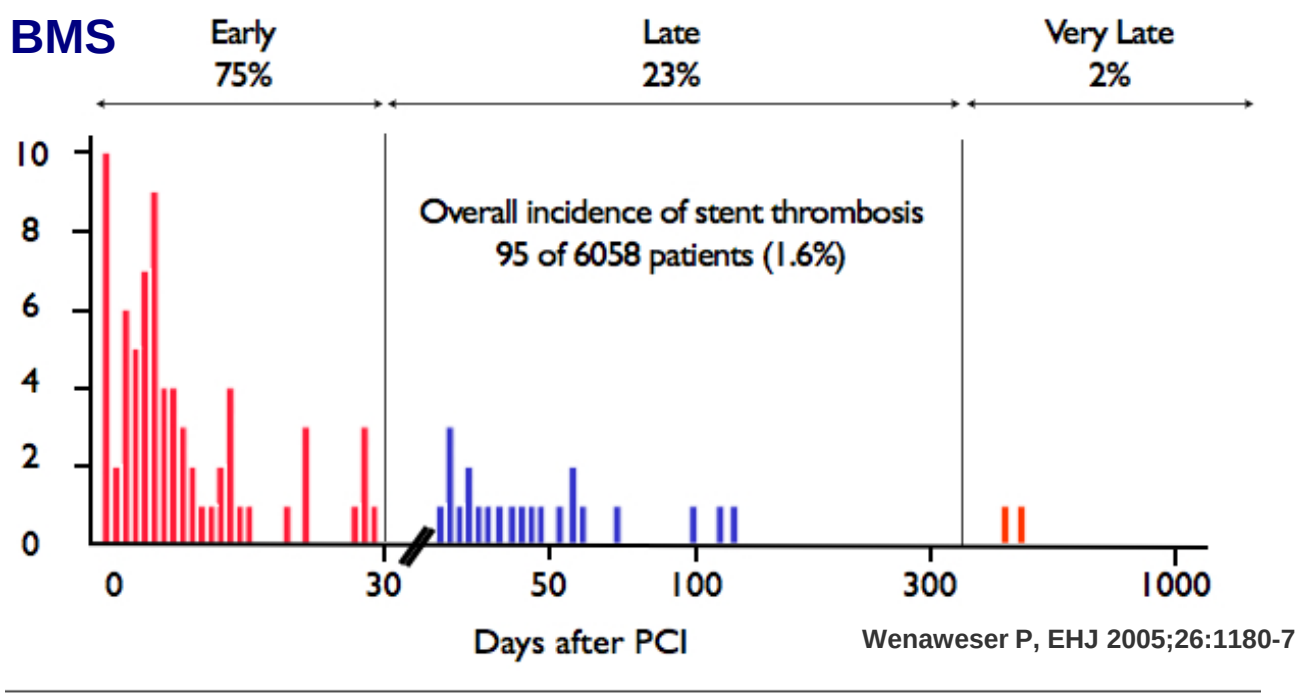
0-3 Days **3-450 Days**

Triton-TIMI 38 – Prasugrel vs. Clopidogrel

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

Stent Thrombosis (ARC Definite + Probable)





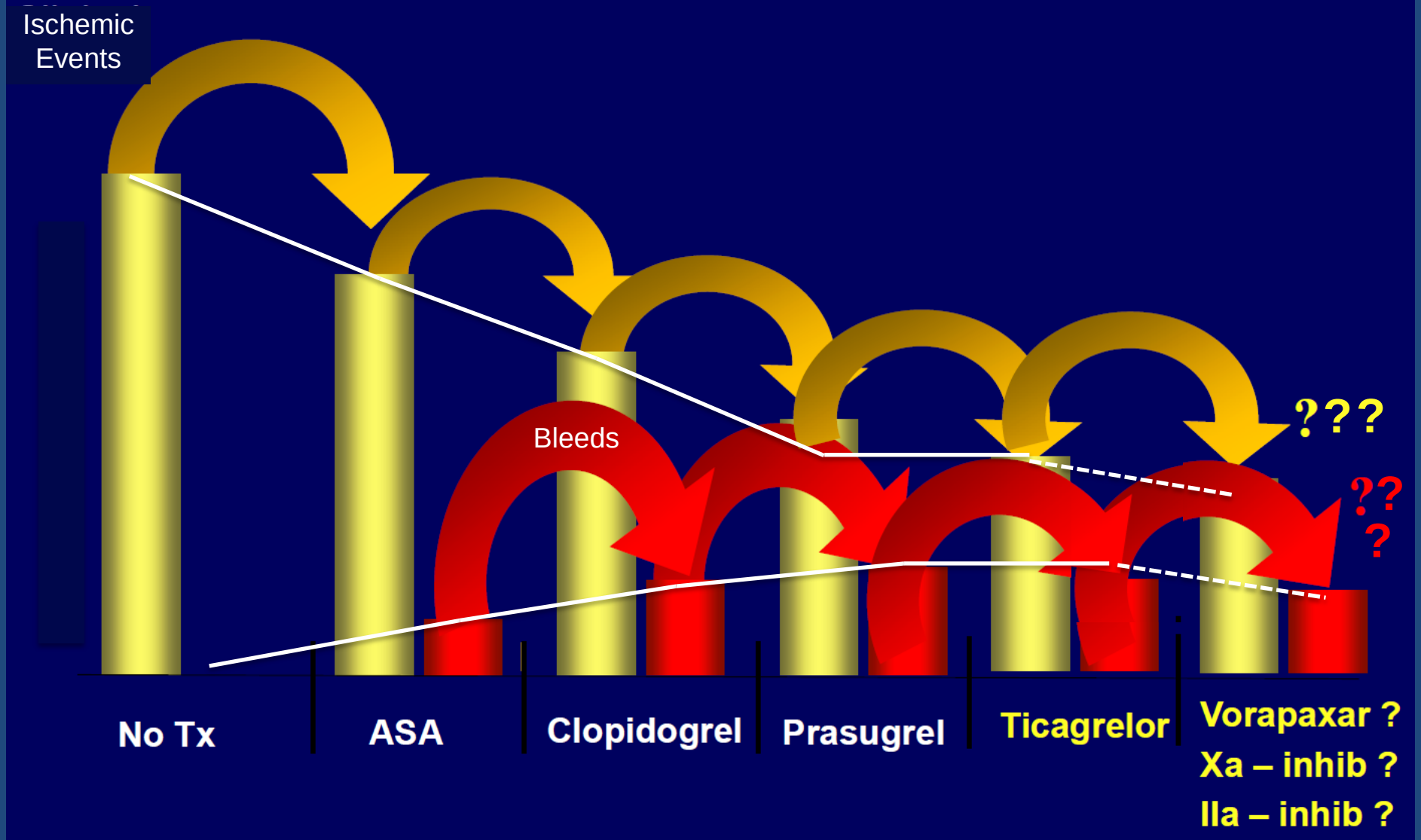
Coronary Stent Thrombosis

Before DES Introduction

Togni M, Windecker S, Meier B
Curr Interv Cardiol Rep 3: 306-310, 2001

..... in particular, the risk of late stent thrombosis driven by inhibitory effects on endothelial regrowth, or late toxic effects on vascular cells, may be encountered with stent-based drug delivery .....

Development of Oral Anti-Platelet Therapy



Vorapaxar (Thrombin-Receptor (PAR-1) Antagonist) in ACS (TRACER)

- **Death (cardiovascular)**
- **MI**
- **Stroke**

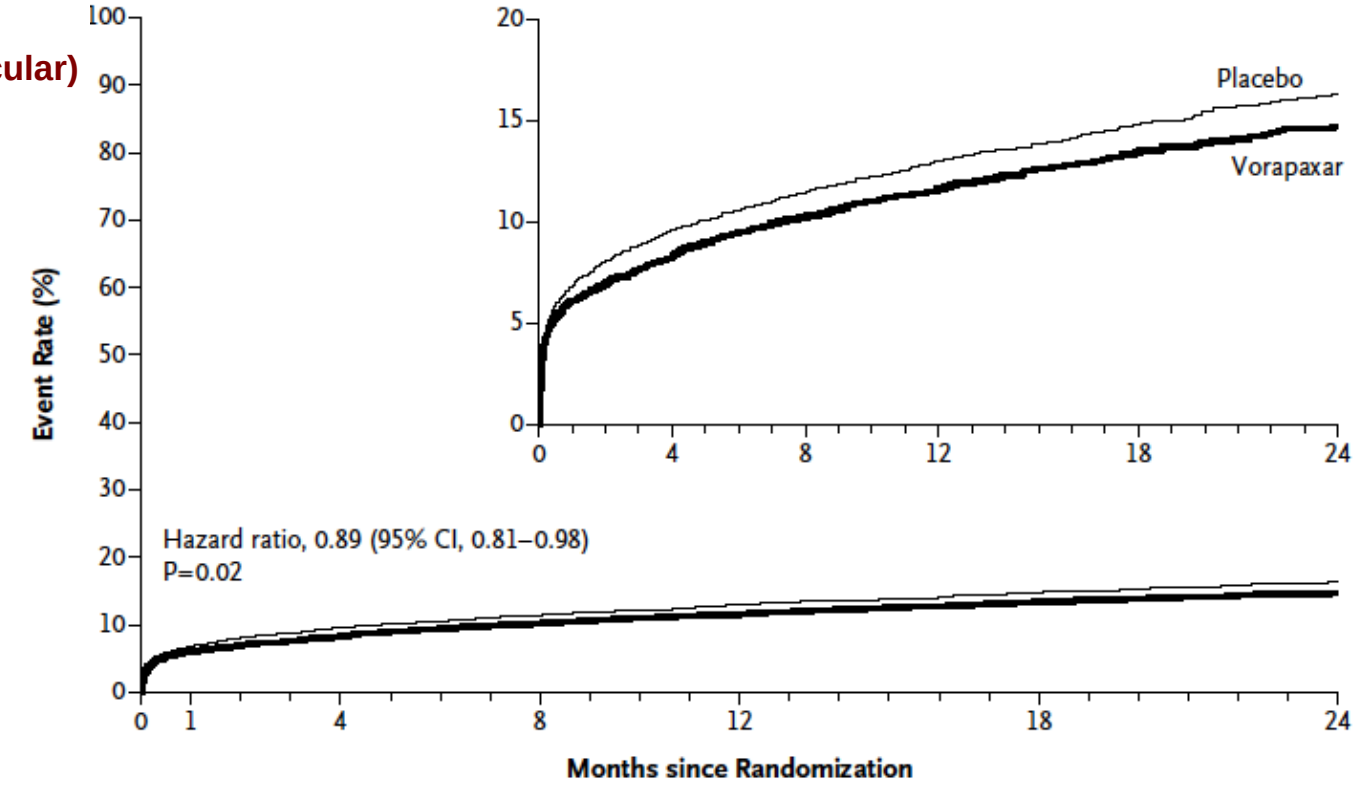


Figure 1. Study End Points.

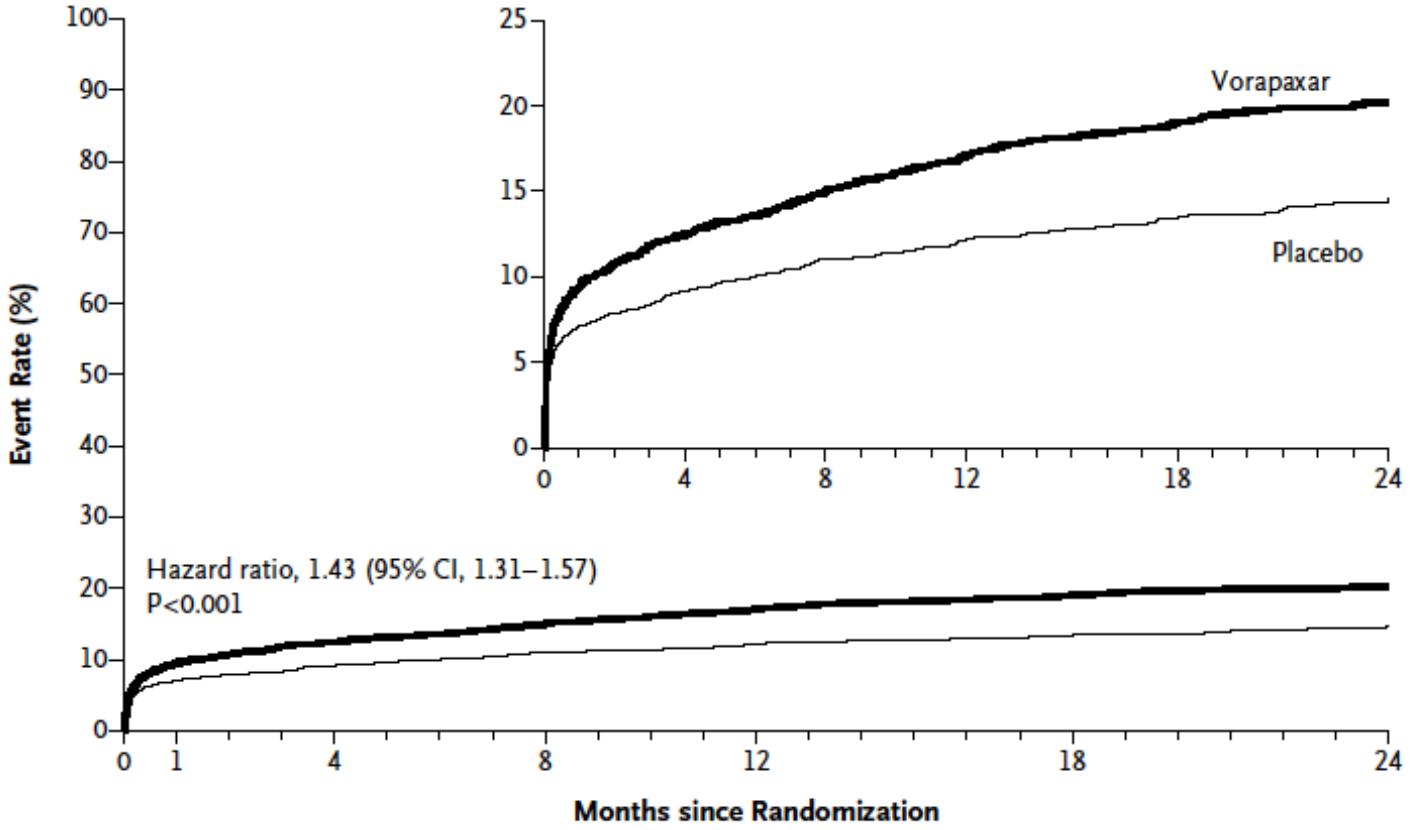
Shown are Kaplan–Meier event rates at 2 years in the two study groups for the primary efficacy end point (a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) (Panel A) and the key secondary efficacy end point (a composite of death from cardiovascular causes, myocardial infarction, or stroke) (Panel B).

Merck (MSD)

Tricoci P, N Engl J Med 2012;366:20-33

Vorapaxar (Thrombin-Receptor (PAR-1) Antagonist) in ACS (TRACER)

TIMI Bleeding



No. at Risk

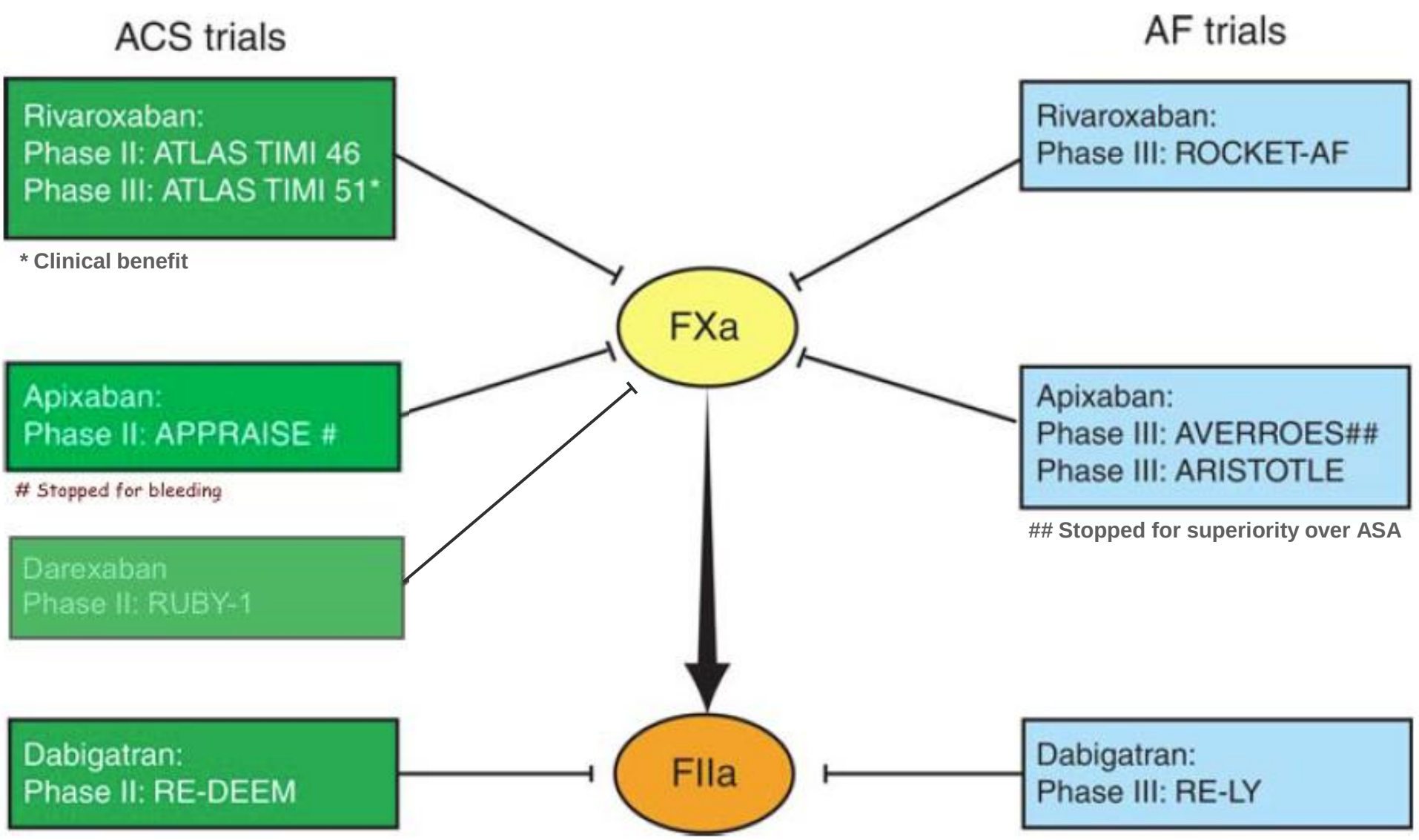
Placebo	6441	5320	4877	4385	3147	1806	573
Vorapaxar	6446	5257	4772	4219	2950	1663	548

Figure 2. Risk of Bleeding.

Shown are Kaplan–Meier event rates at 2 years in the two study groups for Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria for moderate or severe bleeding (Panel A) and for Thrombolysis in Myocardial Infarction (TIMI) criteria for clinically significant bleeding (Panel B).

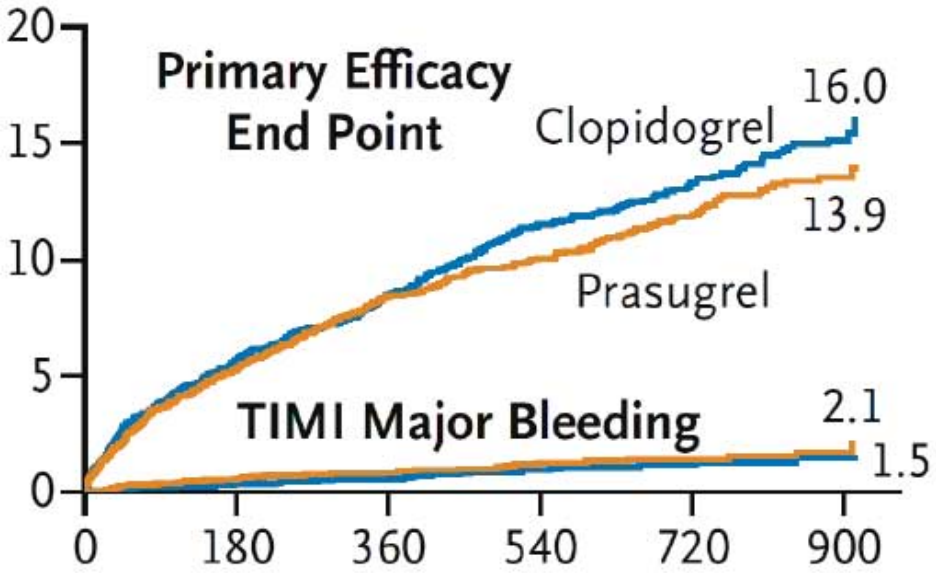
Tricoci P, N Engl J Med 2012;366:20-33

ACS / AF and New Oral Anticoagulants



Moser M, Bode C, European Heart Journal (2011) 32, 2734–2735

TRILOGY study (< 75 y.o, n=7243)
ACS patients medically managed with prasugrel



+ 0.6% absolute
Idem TRITON / PLATO at 1 year

No benefit of Prasugrel in ACS patients medically managed

Roe et al, NEJM 2012

Local Guidelines for Antiplatelet Therapy in ACS patients

ST-elevation MI

Peri-Procedural

ASA 250-500 mg iv
Prasugrel 60 mg loading dose irrespective of preloading with clopidogrel

Post-Procedural

Prasugrel 10 mg* for ≥1 year
ASA indefinitely

Non ST-elevation MI (or severe (un)stable CAD)

Peri-Procedural

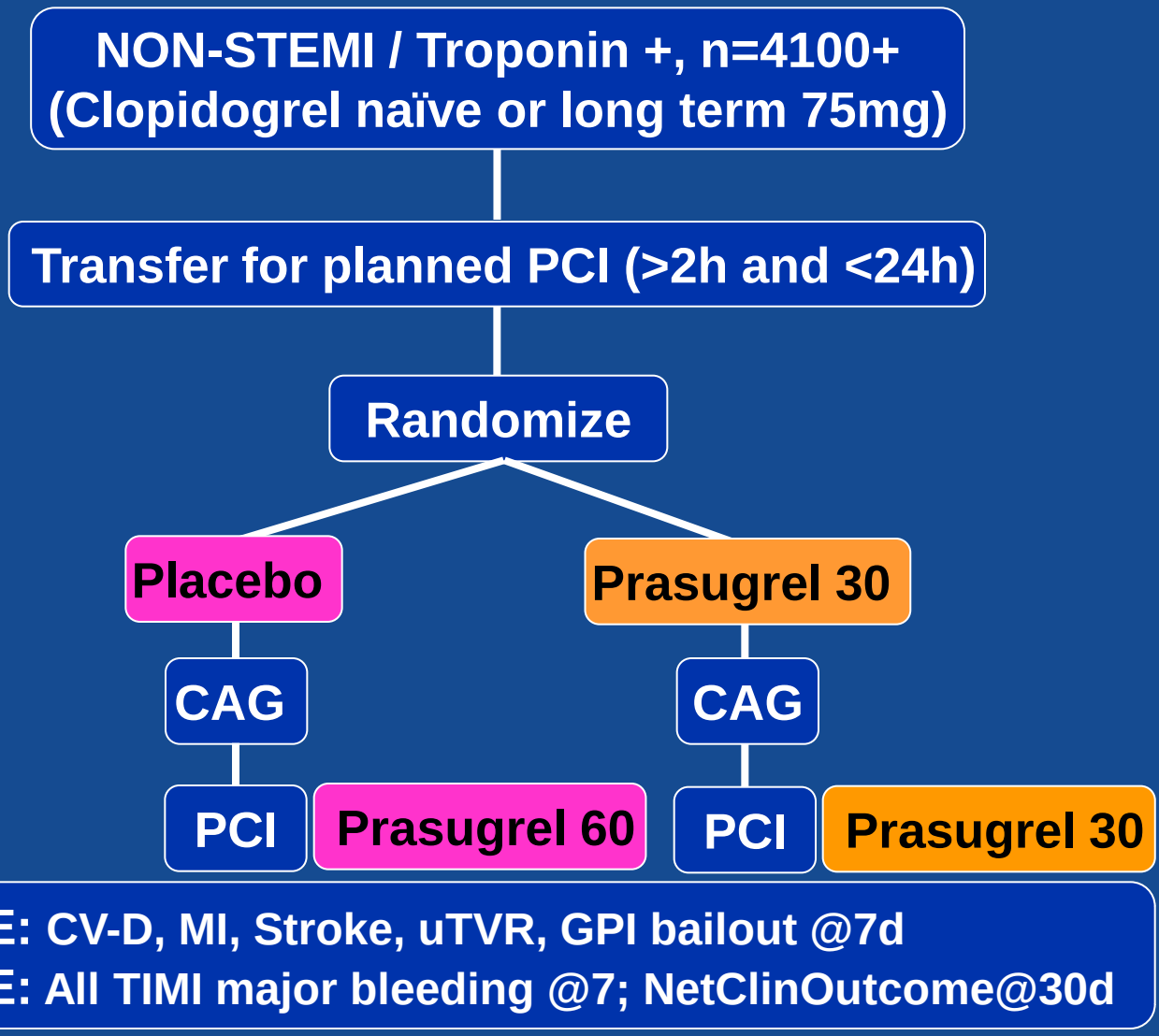
ASA 250-500 mg iv
Clopidogrel 600 mg or prasugrel 60 mg or ticagrelor 180 mg loading dose

Post-Procedural

Clopidogrel 75 mg 2x1 for 1 week
followed by 75 mg for ≥1 year
or
Prasugrel 10 mg* for ≥1 year
or
Ticagrelor 90 mg 2x1 for ≥1 year
ASA indefinitely

**5mg in patients with age >75 years or weight <60kg*
Contraindication: history of stroke (to be rediscussed)

Trial Design



Upstream + Transfer to PCI (>2h to <24h)

Cathlab

30d FU

Stopped prematurely because of pre PCI bleedings