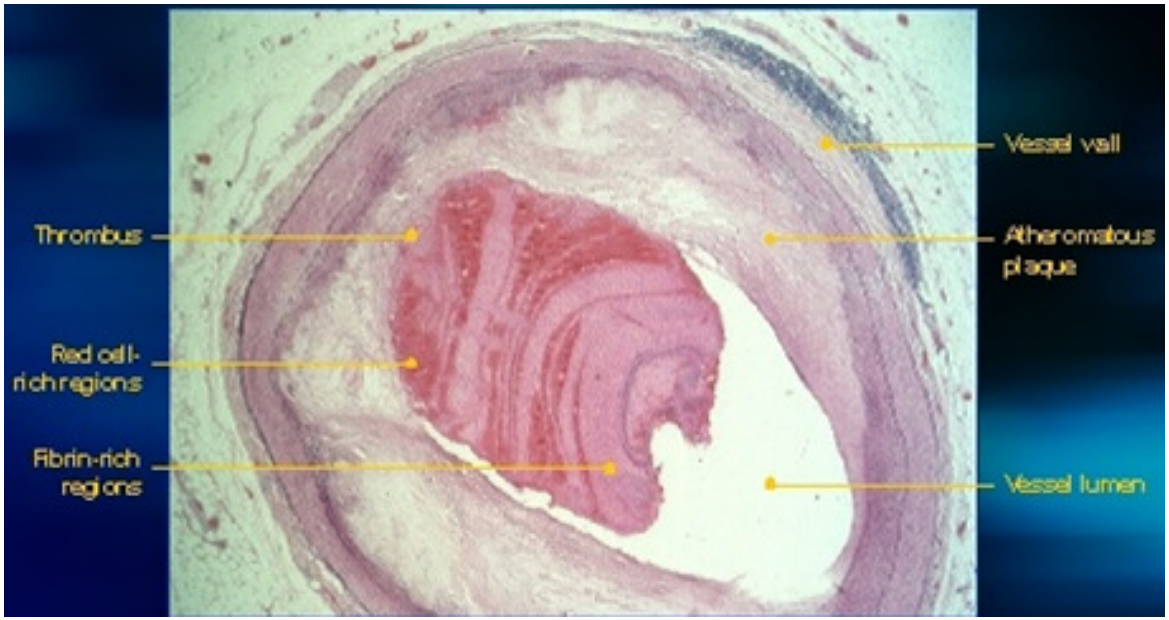
Hôpitaux Universitaires de Genève

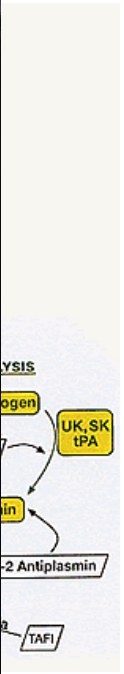
UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Old drugs and new antithrombotic strategies to manage acute coronary syndromes



Jean-Luc Reny
Division of General Internal medicine

Platelet and coagulation targets …



Varga-Szabo D, Pleines I, Nieswandt B. Cell adhesion mechanisms in platelets. Arterioscler Thromb Vasc Biol 2008;28:403-12. enzymeresearch.co.uk

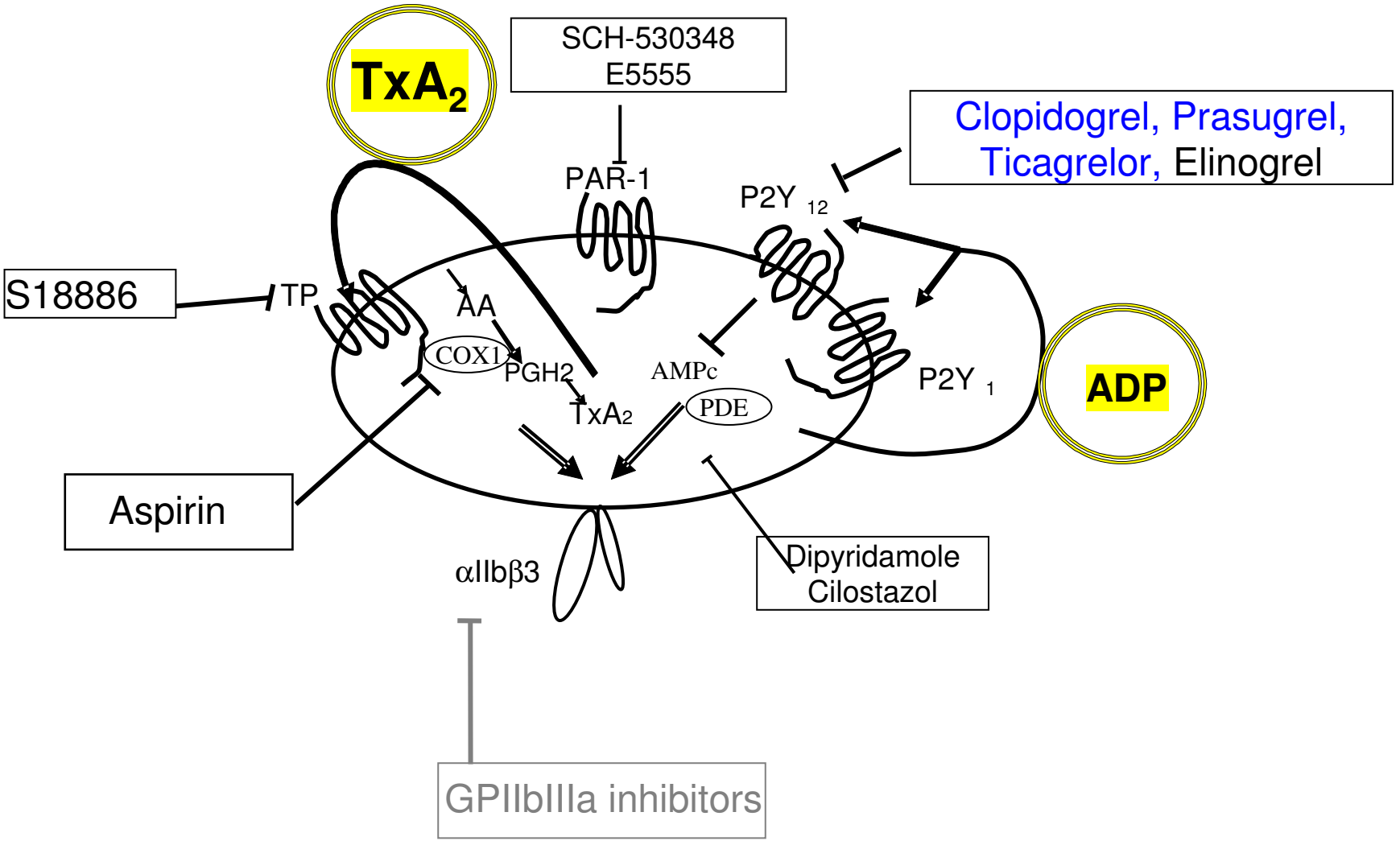
1. « Old » antiplatelet agents: *efficacy and variability*
2. New antiplatets agents: *efficacy and risk*
3. Anticoagulants: *ESC 2010*

Acute coronary syndrome …

- A symptom or group of symptoms compatible with acute myocardial ischaemia
- The term 'acute coronary syndrome' covers a spectrum of acute cardiac conditions from unstable angina to varying degrees of evolving myocardial infarction (MI)

From RF Storey, Sheffield, UK

Platelet targets …



Aspirin …

Lancet. 1979 Dec 22-29;2(8156-8157):1313-5.

Aspirin and secondary mortality after myocardial infarction.

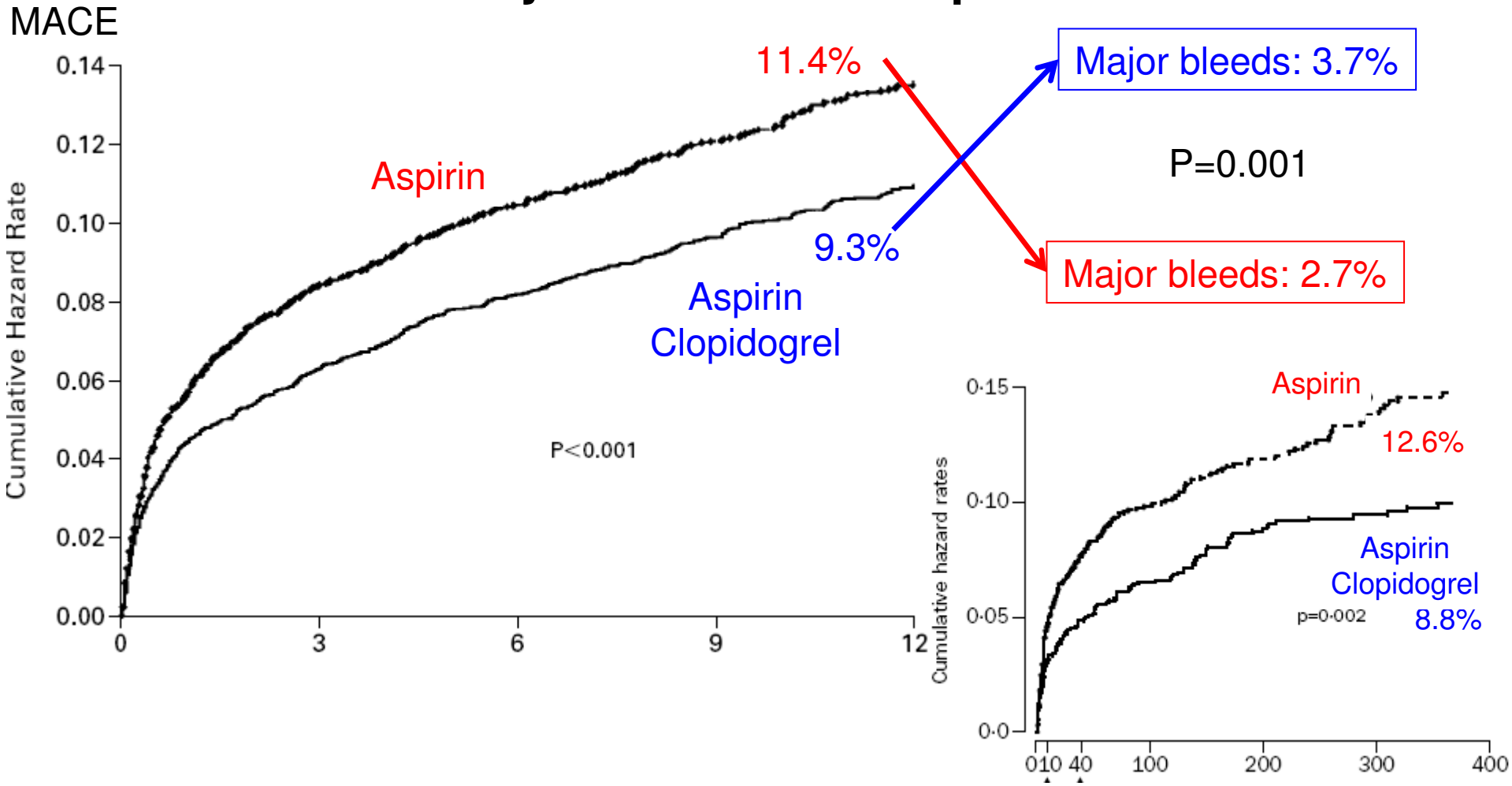
Elwood PC, Sweetnam PM.

Abstract

A randomised controlled double-blind trial of aspirin in the prevention of death was conducted in 1682 patients (including 248 women) who had had a confirmed myocardial infarct (MI). 25% of the patients were admitted to the trial within 3 days of the infarction and 50% within 7 days. Aspirin, 300 mg three times daily, was given for 1 yr. Total mortality was 12.3% in patients given aspirin and 14.8% in those given placebo, a reduction by aspirin of 17%, which was not statistically significant at p less than 0.05. The reduction in specific ischaemic-heart-disease (IHD) mortality was 22% and in total mortality plus IHD morbidity (readmission to hospital for MI in survivors) was 28%.

Dual aspirin-clopidogrel treatment …

CURE study : 12562 NSTEMI patients



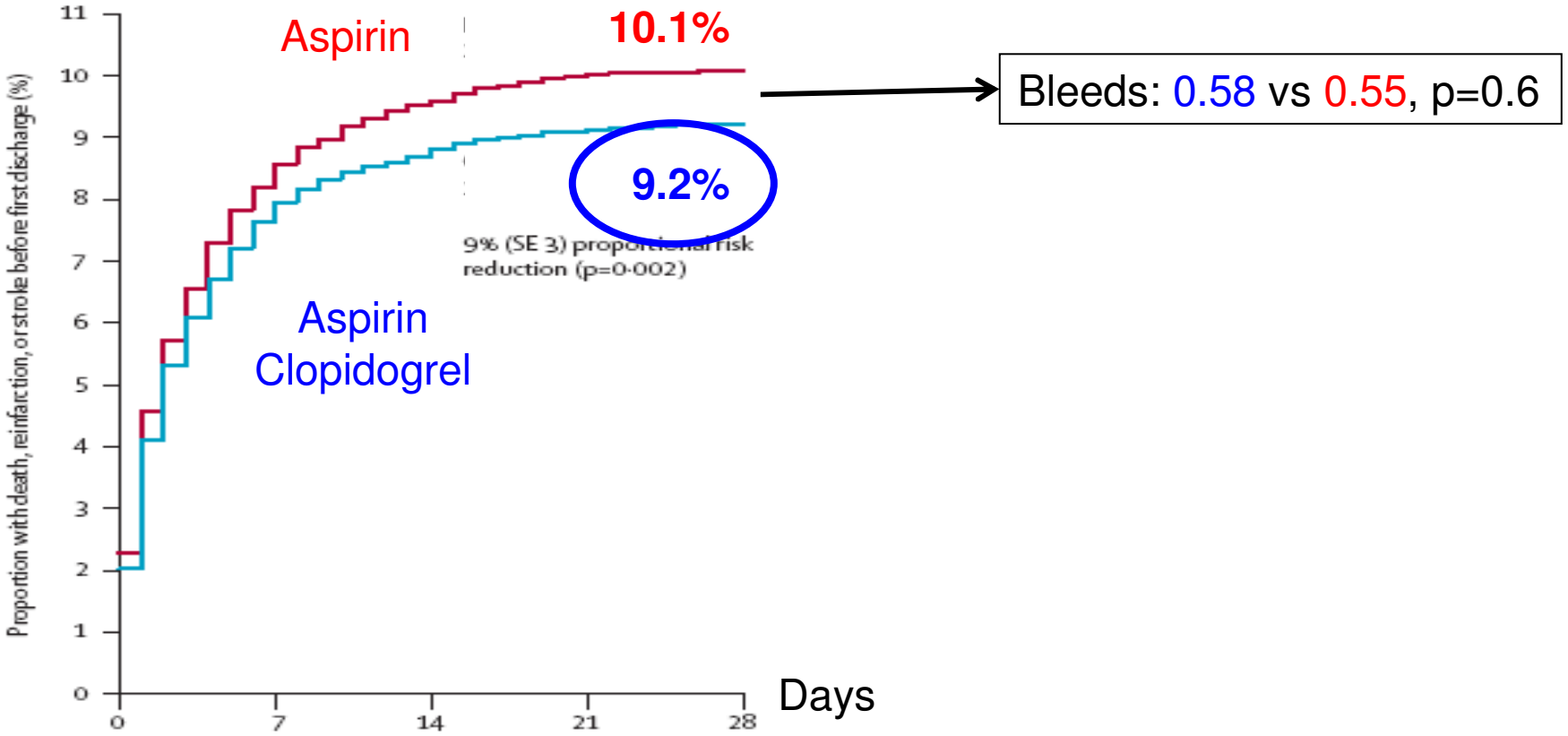
Yusuf S et al *N Engl J Med. 2001; 345: 494-502.*
Mehta SR et al. Lancet. 2001; 358: 527-33.

PCI-CURE.
Bleeds 2.7 vs 2.5%

Dual aspirin-clopidogrel treatment …

COMMIT Study: 45852 STEMI patients

In-hospital MACE

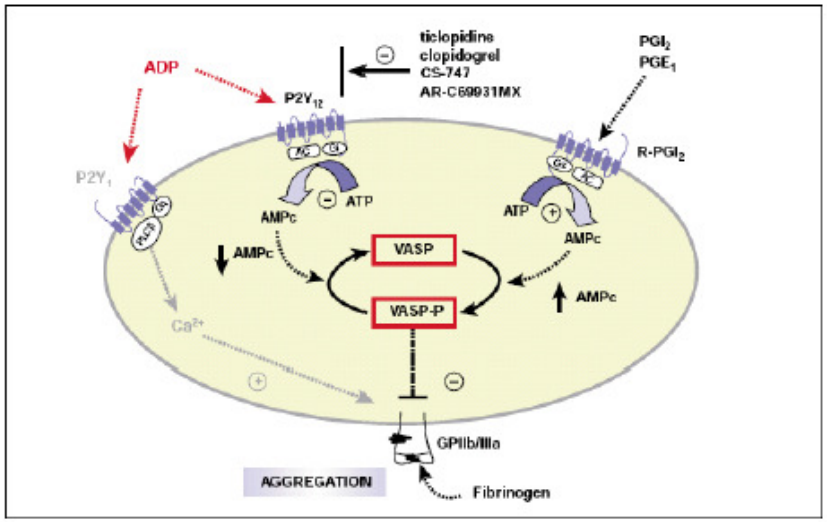


Bleeds: 0.58 vs 0.55, p=0.6

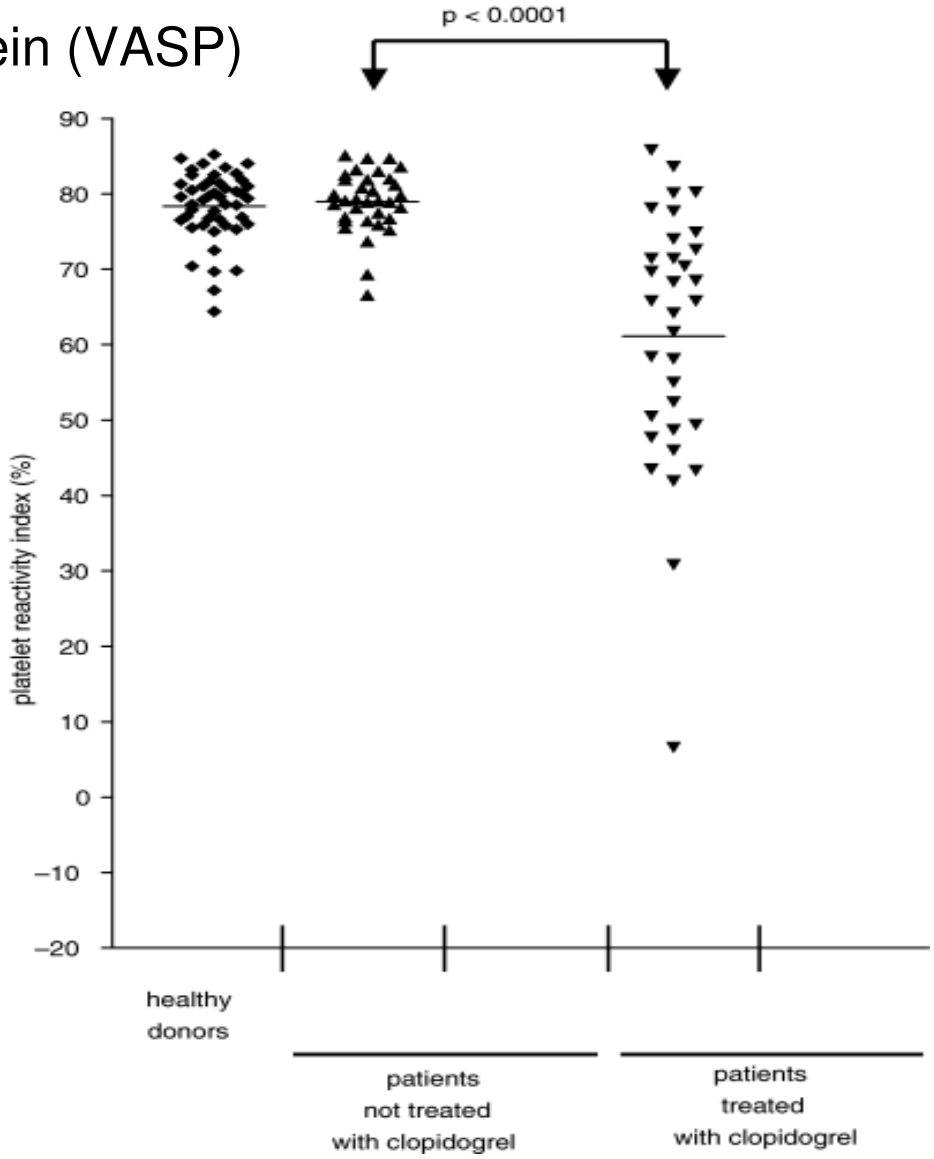
Chen ZM et al. *Lancet. 2005; 366: 1607-21.*

How do platelets respond to clopidogrel ?

VAsodilator-Stimulated Phosphoprotein (VASP)



Platelet reactivity index
(PRI, %)



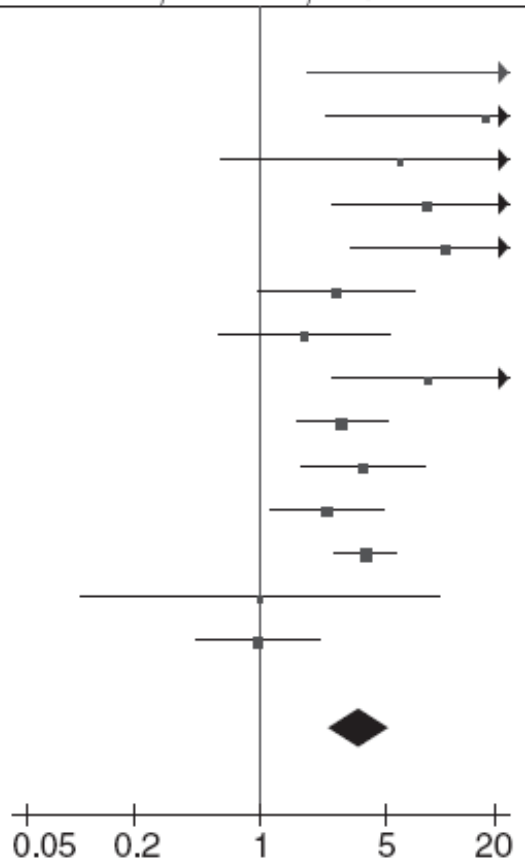
Aleil B et al. *J Thromb Haemost* 2005

Clopidogrel biological response and events …

Study or Subgroup	Non-responders Events	Total	Responders Events	Total	Weight	Risk ratio IV, Random, 95% CI	Year
Gurbel 2003	0	29	0	63		Not estimatable	2003
Muller 2003	2	12	0*	93	1.5%	36.15 (1.84–36.15)	2003
Matetzky 2004	6	15	1	45	3.0%	18.00 [2.35, 137.71]	2004
Mobley 2004	2	11	1	33	2.4%	6.00 [0.60, 59.93]	2004
Campo 2006	7	14	3	51	6.3%	8.50 [2.52, 28.69]	2006
Cuisset 2006	9	23	3	83	6.3%	10.83 [3.19, 36.75]	2006
Hochholzer 2006	7	199	8	603	7.9%	2.65 [0.97, 7.22]	2006
Schwonberg 2007	4	14	6	37	7.1%	1.76 [0.58, 5.32]	2007
Frere 2007	11	54	3	127	6.2%	8.62 [2.50, 29.69]	2007
Angiolillo 2007	17	45	17	128	12.2%	2.84 [1.59, 5.08]	2007
Buonamici 2007	9	105	16	699	9.9%	3.74 [1.70, 8.25]	2007
Geisler 2008	15	312	13	638	10.5%	2.36 [1.14, 4.90]	2008
Gurbel 2008	54	101	27	196	14.3%	3.88 [2.62, 5.76]	2008
Liu 2008	1	13	2	26	2.4%	1.00 [0.10, 10.04]	2008
Yong 2009	7	49	21	142	9.9%	0.97 [0.44, 2.13]	2009
Total (95% CI)		996		2964	100.0%	3.53 [2.39, 5.20]	
Total events	151		121				

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 27.20$, d.f. = 13 ($P = 0.01$); $I^2 = 52\%$

Test for overall effect: $Z = 6.36$ ($P < 0.00001$)



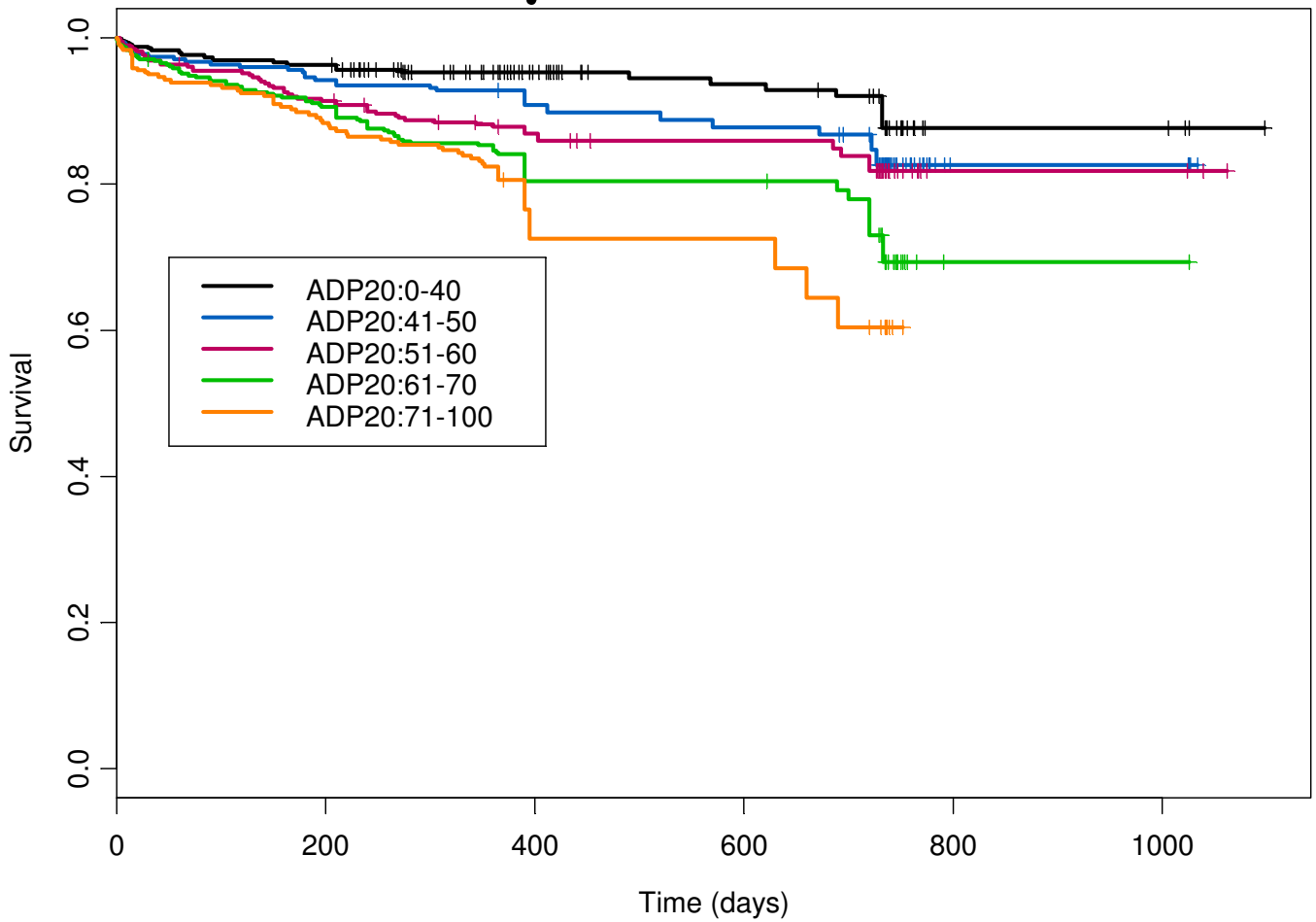
Residual platelet Hyperreactivity (clo) : RR = 3.5 [2.4-5.2]

One test (ADP Agg), heterogeneity … related to IIbIIIa inhibitors?

Combescure C et al. J Thromb Haemost. 2010; 8: 923-33.

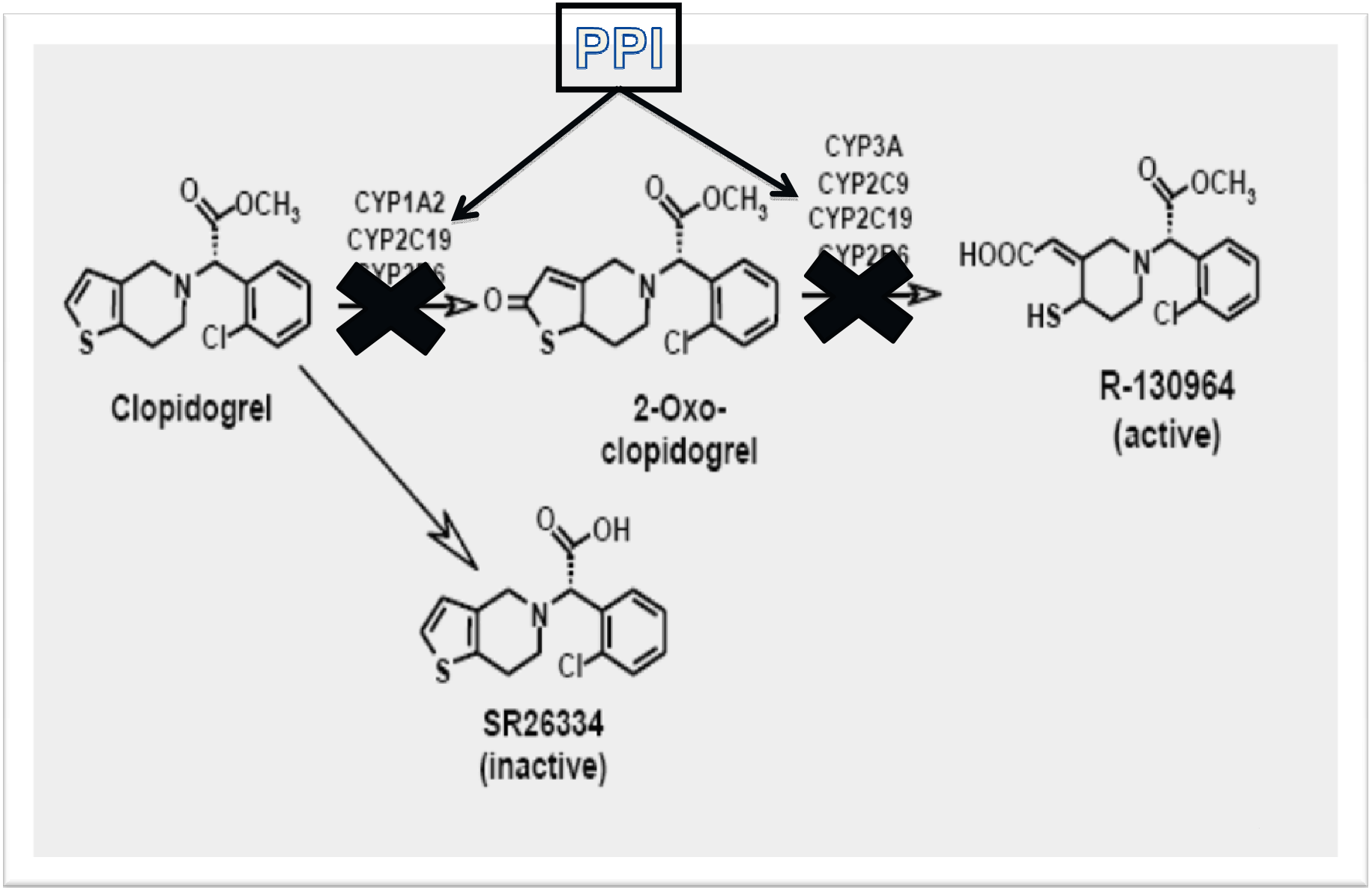
Clopidogrel response variability: short term or long term effect ?…

CLOVIS meta-analysis on 3538 individual pts data



Reny JL, Fontana P, Fabbro-Peray P, Laporte S, van Werkum JW, Ten Berg JM, Geisler T, Gawaz M, Gurbel PA, Cuisset T, Alessi MC, Yong G, Angiolillo DJ, Campo G1, Combescure C , Unpublished

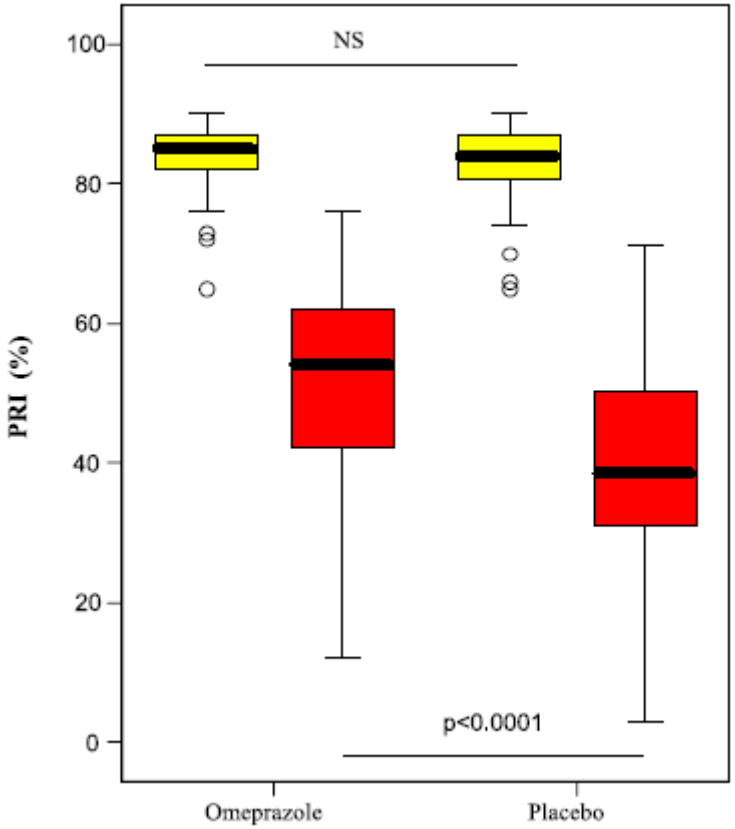
Clopidogrel and drug interaction …



From RL Talbert, Austin, USA

Clopidogrel and Omeprazole …

OCLA randomised controlled trial



conflicting data on clinical relevance but …

FDA, EMEA, MHRA-UK warnings on PPI use in clopidogrel treated patients

Gilard M et al. J Am Coll Cardiol. 2008; 51: 256-60.

Response to clopidogrel and ischemic events: CYP 2C19 genotype … or platelet phenotype

CYP 2C19 Loss of function	Sibbing D Eur H J 2009	Mega JL NEJM 2009	Simon T NEJM 2009	Collet JP Lancet 2009
N	2485	1459	2208	259
Se	30%	36%	26%	58%
Sp	73%	74%	71%	75%

VASP P2Y12 PRI	Blindt R TH 2007	Frere C JTH 2007	Bonello L JTH 2007
N	99	195	144
PRI cut-off	48%	53%	50%
Se	80%	92%	100%
Sp	73%	49%	25%

CYP2C19 and clopidogrel efficacy ?

- related to the biological response
- relation to clinical clinical efficacy ….

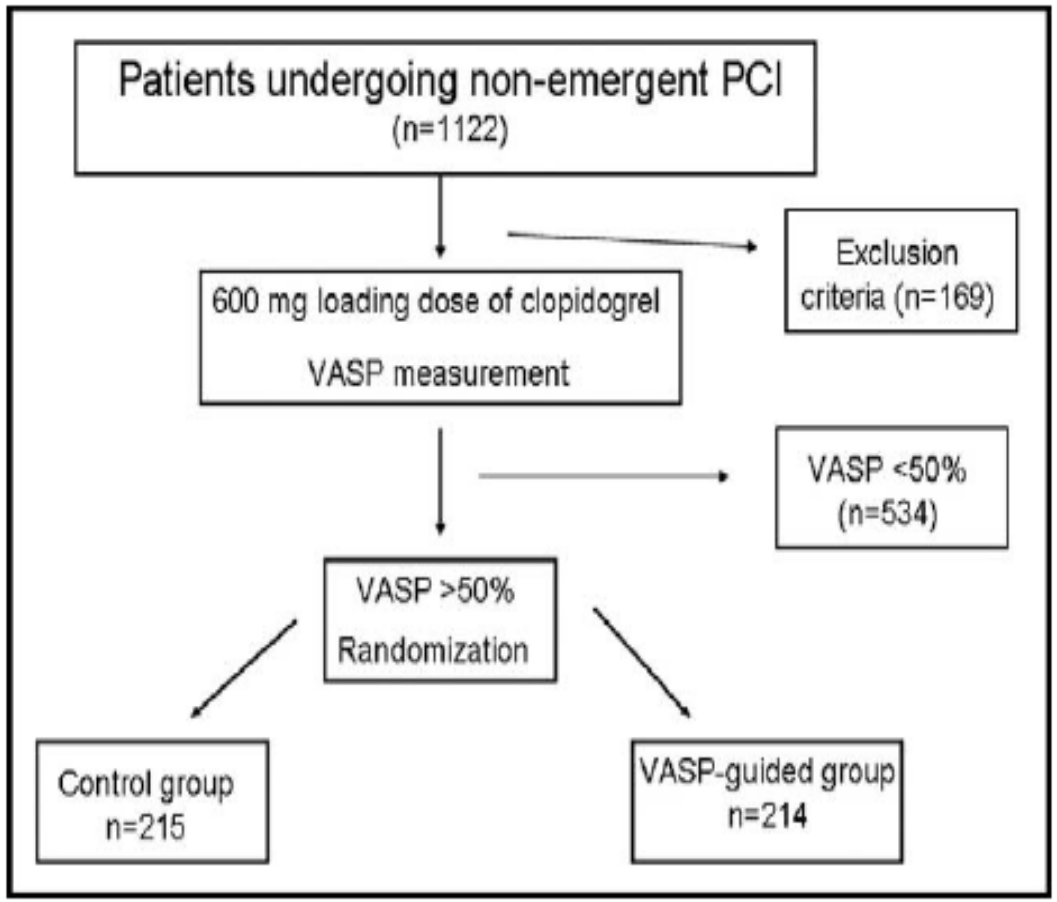
29 Aug 2010 ESC Stockholm

CURE ACTIVE: Efficacy and Safety of Clopidogrel compared with Placebo according to CYP2C19 Genotype in over 6000 patients with Non-ST-elevation Acute Coronary Syndromes (CURE trial) and atrial fibrillation (ACTIVE trial)

Guillaume Pare, Shamir R. Mehta, Salim Yusuf, Sonia S. Anand, Stuart J. Connolly, Jack Hirsh, Katy Simonsen, Deepak L. Bhatt, Keith A.A. Fox, John W. Eikelboom

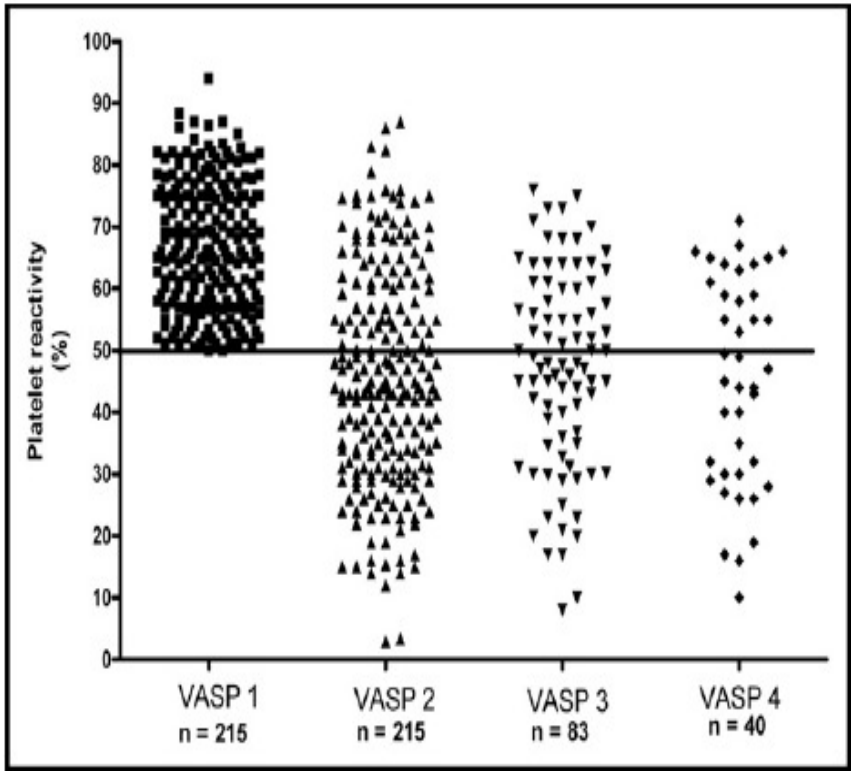
"The primary finding was that there was no relationship between allele status and placebo event rates, and for the most part, no relationship to treatment effect**.** **Clopidogrel was effective in preventing ischemic events and caused more bleeding than placebo, regardless of allele status in CURE**."

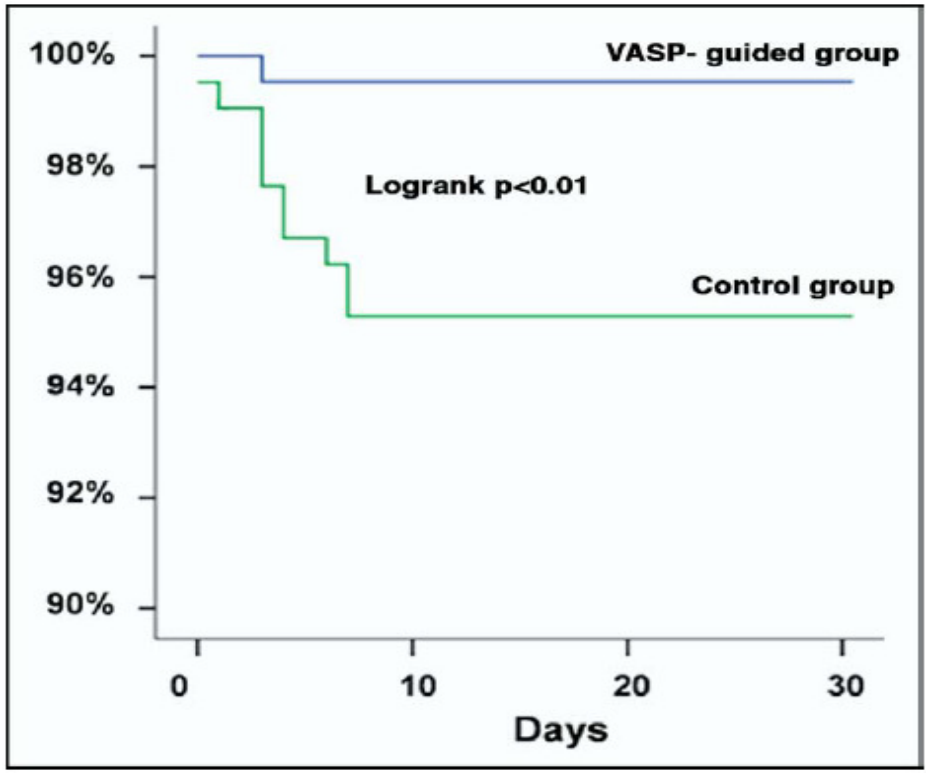
Residual platelet hyperreactivity… A tailored clopidogrel dosing



Bonello L et al. Am J Cardiol. 2009; 103: 5-10.

Residual platelet hyperreactivity…
A tailored clopidogrel dosing





no difference in the rate of major bleeding (0.9% vs 0.9%, p = 1).

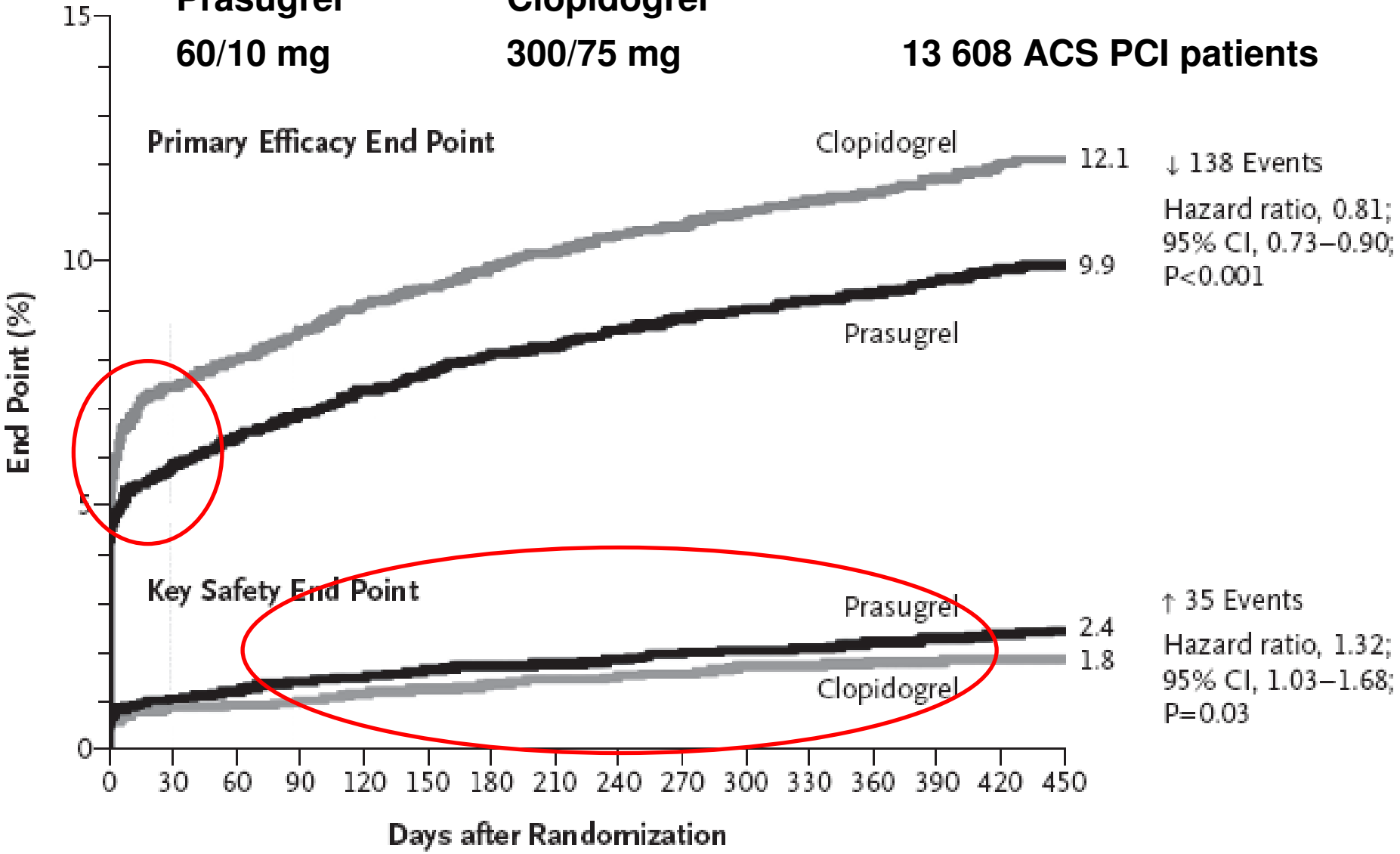
Bonello L et al. Am J Cardiol. 2009; 103: 5-10.

1. « Old » antiplatelet agents: *efficacy and variability*
2. New antiplatets agents: *efficacy and risk*
3. Anticoagulants: *ESC 2010*

Prasugrel in Triton-TIMI 38 …

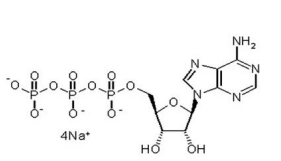
Prasugrel **Clopidogrel**

60/10 mg **300/75 mg** **13 608 ACS PCI patients**

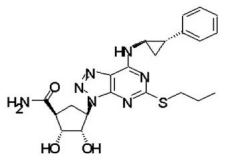


Wiviott SD, et al, *N Engl J Med* 2007;357:2001

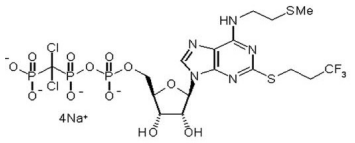
Ticagrelor …



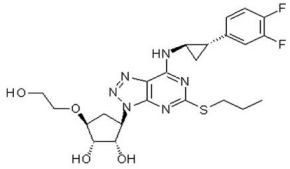
ATP



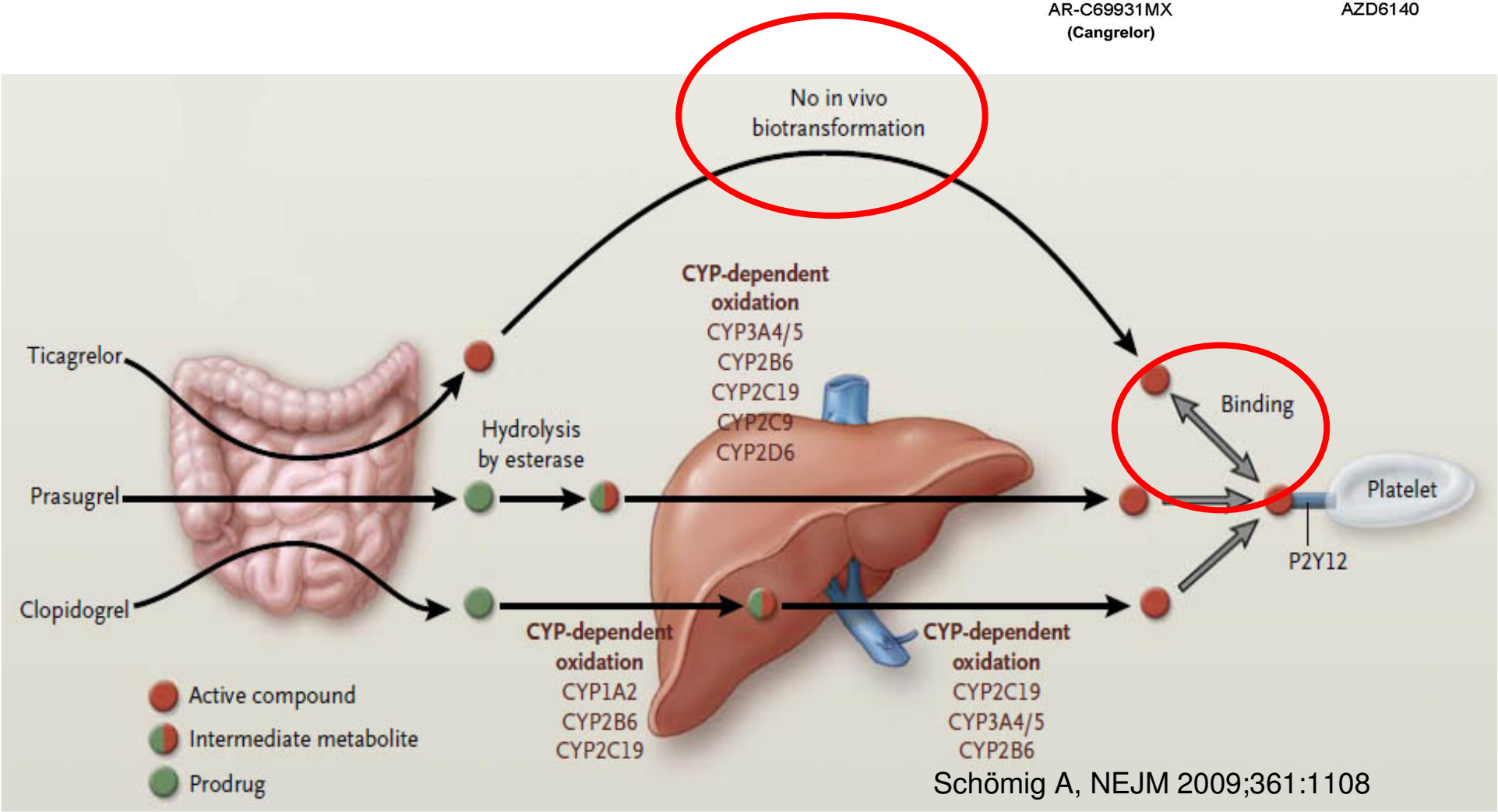
AR-C109318XX



AR-C69931MX
(Cangrelor)



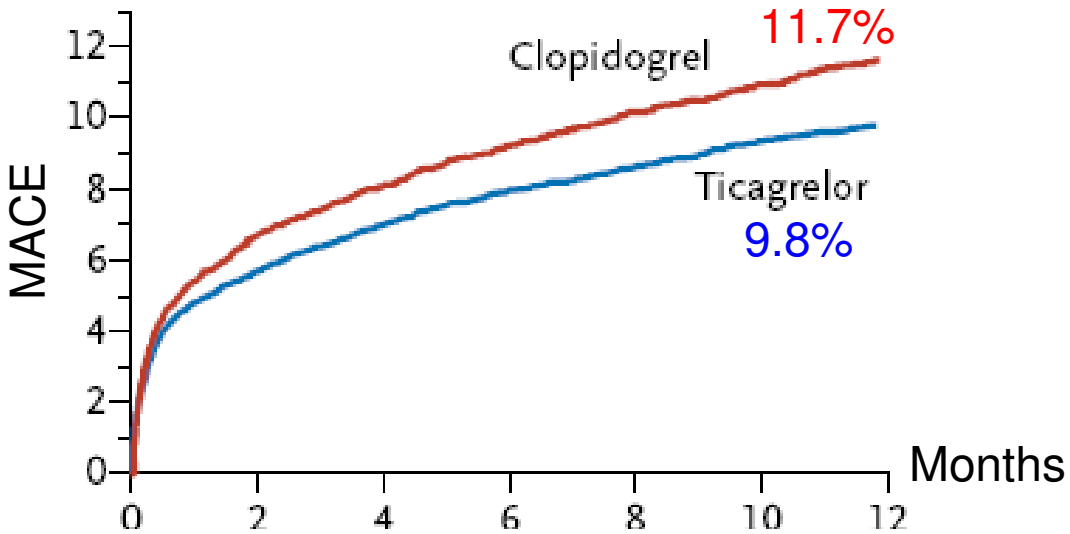
AZD6140



Schömig A, NEJM 2009;361:1108

Ticagrelor vs Clopidogrel …

PLATO: 18,624 NSTEMI-STEMI

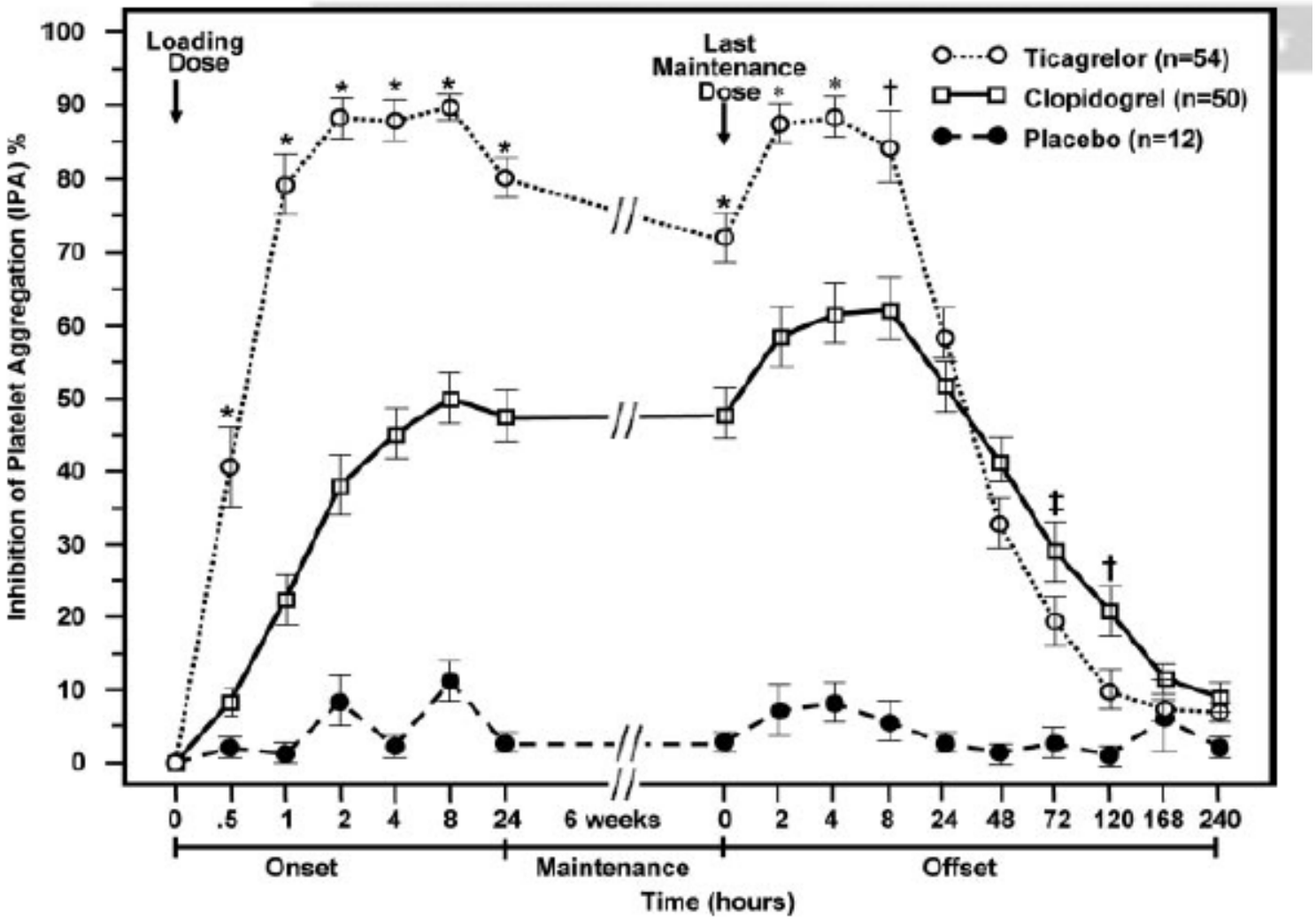


Secondary safety end points — no./total no. (%)				
Non–CABG-related major bleeding, study criteria	362/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
Non–CABG-related major bleeding, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03, 1.53)	0.03
CABG-related major bleeding, study criteria	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32
CABG-related major bleeding, TIMI criteria	446/9235 (5.3)	476/9186 (5.8)	0.94 (0.82–1.07)	0.32
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)	1.11 (1.03–1.20)	0.008
Major or minor bleeding, TIMI criteria‡	946/9235 (11.4)	906/9186 (10.9)	1.05 (0.96–1.15)	0.33
Dyspnea — no./total no. (%)				
Any	1270/9235 (13.8)	721/9186 (7.8)	1.84 (1.68–2.02)	<0.001
Requiring discontinuation of study treatment	79/9235 (0.9)	13/9186 (0.1)	6.12 (3.41–11.01)	<0.001

Wallentin et al. N Engl J Med. 2009; 361: 1045-57

Ticagrelor vs Clopidogrel …

ONSET-OFFSET study

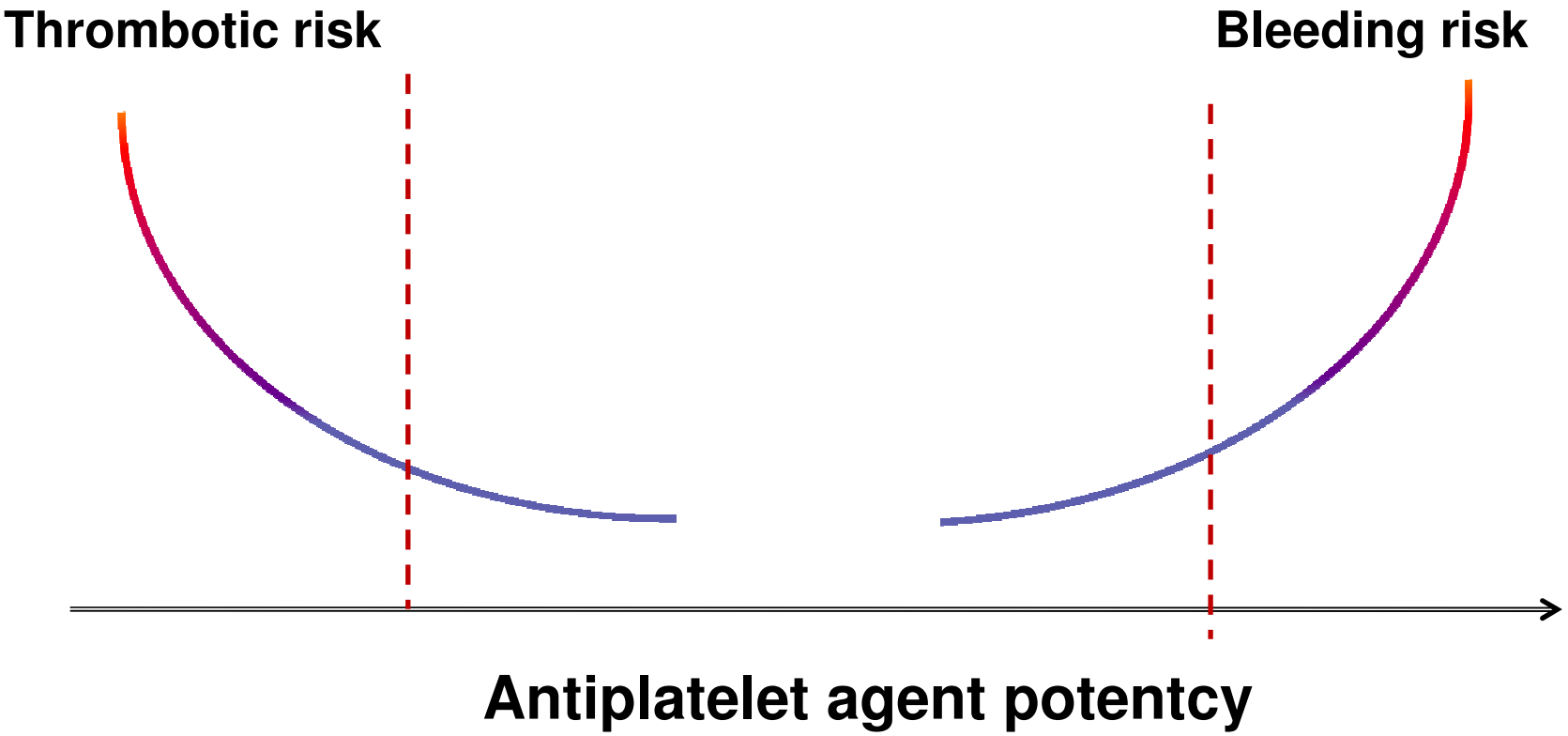


Gurbel PA et al, *Circulation* 2009;120:2577

Others …

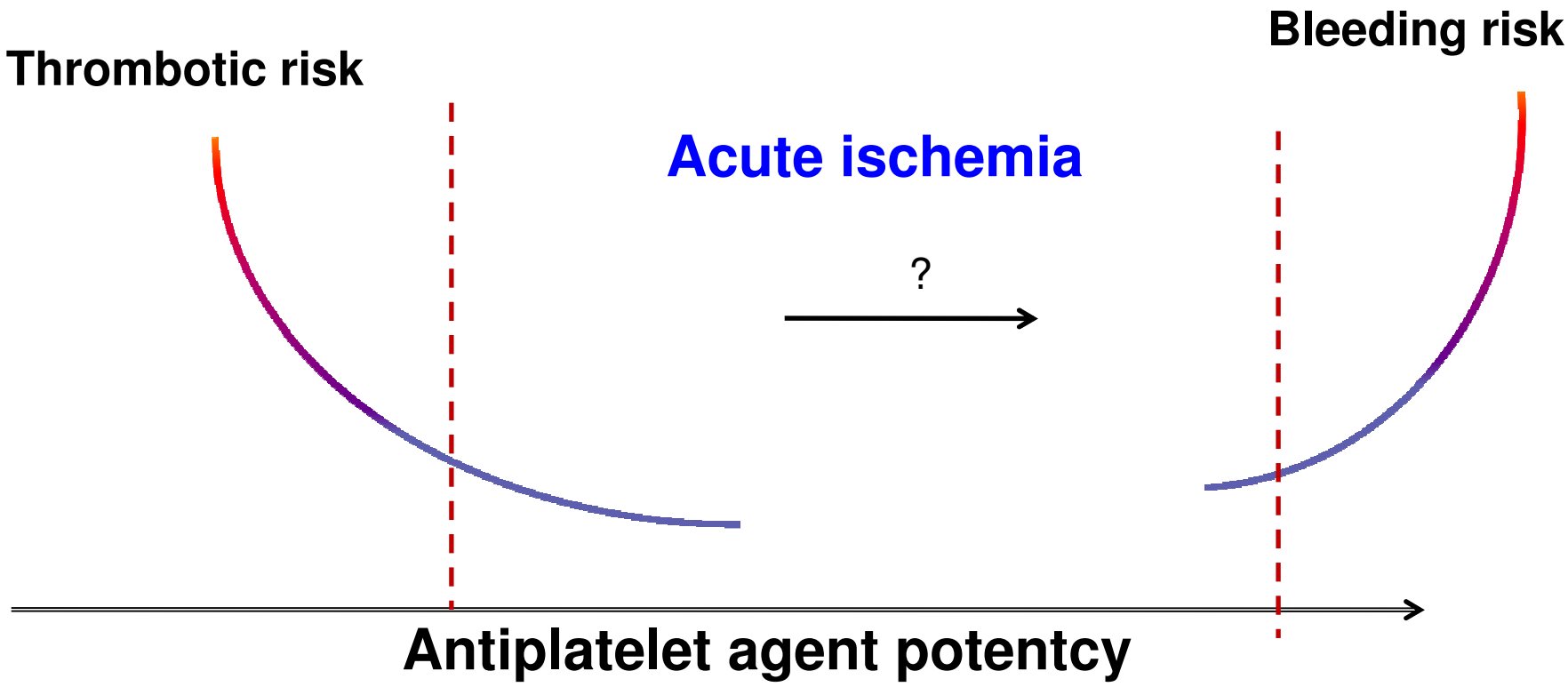
- Elinogrel: large Phase II completed
- Cangrelor:
  - IV, fast onset, fast offset
  - not better than clopidogrel for PCI patients
  - Bridging therapy ?
- S18886: phase III in stroke stopped early
- SCH-530348
  - Phase II prometteuse mais manque de puissance
  - TRA.CER : 10 000 patients SCA => 2011
  - TRA 2°P - TIMI 50 : 19 500 patients
    CI,AIC,AOMI stables => 2010

How much platelet inhibition ?...



Adapted from P Fontana, Geneva

How much platelet inhibition ?...



Antiplatelet agents : summary

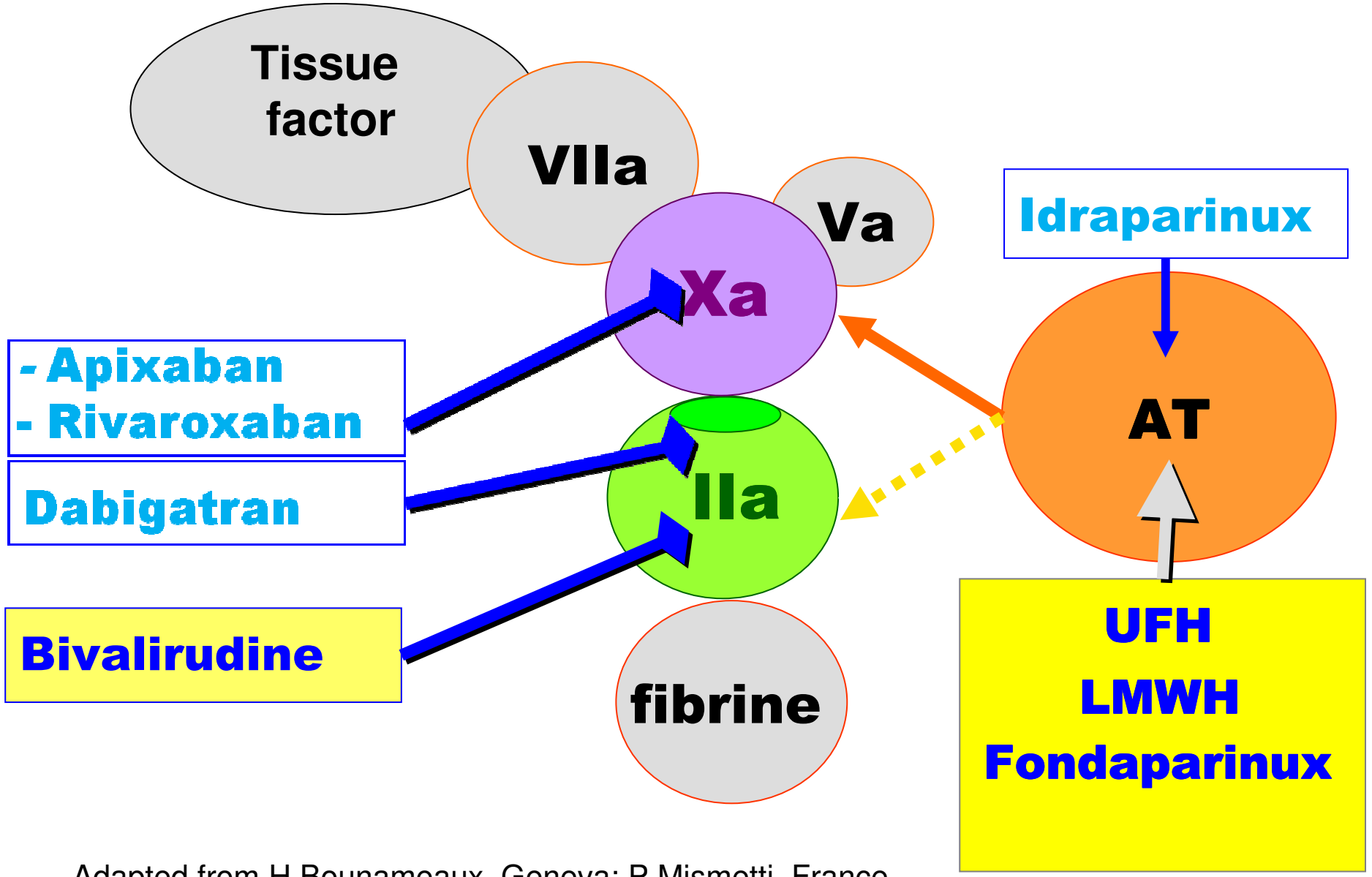
NSTE-ACS			
Antiplatelet therapy			
	ASA	I	C
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Clopidogrel (for 9–12 months after PCI)	I	B
	Prasugrel[d]	IIa	B
	Ticagrelor[d]	I	B
STEMI			
Antiplatelet therapy			
	ASA	I	B
	Clopidogrel[f] (with 600 mg loading dose as soon as possible)	I	C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

- short term objective : decrease thrombosis
- long term objective : balance thrombosis/bleeds

Wijns W et al. Guidelines on myocardial revascularization. Eur Heart J. 2010.

1. « Old » antiplatelet agents: *efficacy and variability*
2. New antiplatets agents: *efficacy and risk*
3. Anticoagulants

Anticoagulants …



Adapted from H Bounameaux, Geneva; P Mismetti, France

Vitamin K antagonists

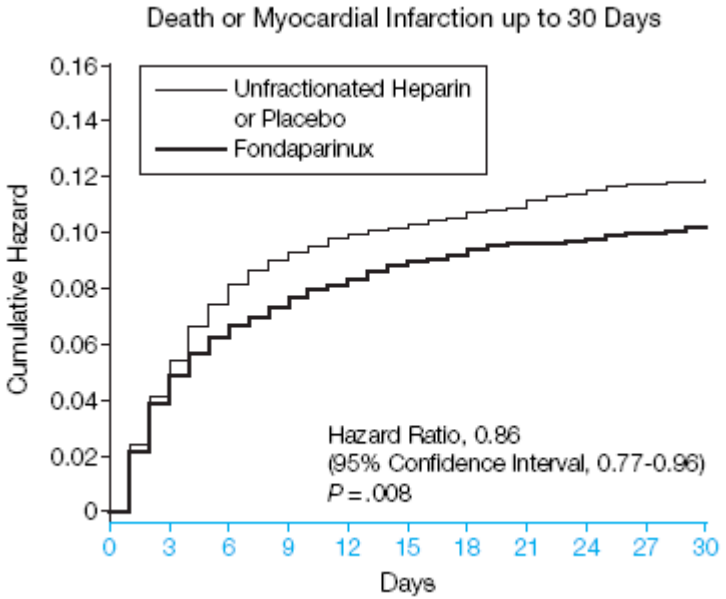
Karl Link

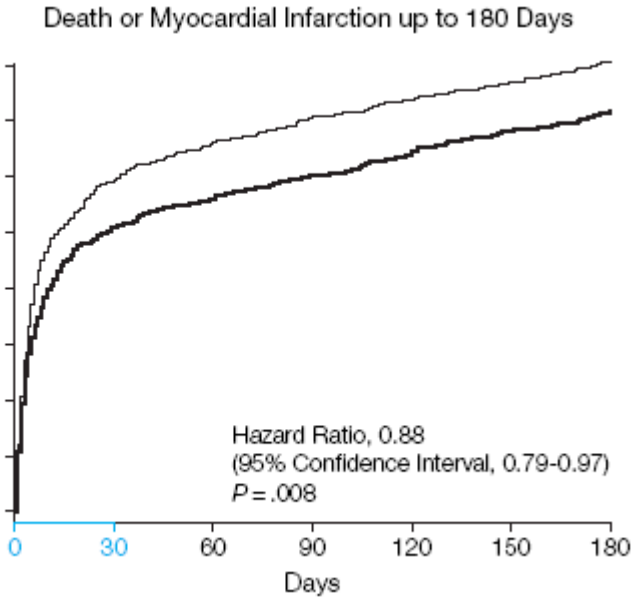
- 1920s cattle bleeding
- 1934-40 3,3'-methylene-bis[4-hyfroxycoumarin => dicoumarol
- 1948 warfarin as rodent killer
- 1955 warfarin for… Eisenhower MI
- 1960 clinical trials…

Wardrop D, Keeling D. The story of the discovery of heparin and warfarin. Br J Haematol 2008; 141: 757-63.

Effects of Fondaparinux on Mortality and Reinfarction in Patients With Acute ST-Segment Elevation Myocardial Infarction

The OASIS-6 Randomized Trial





But…

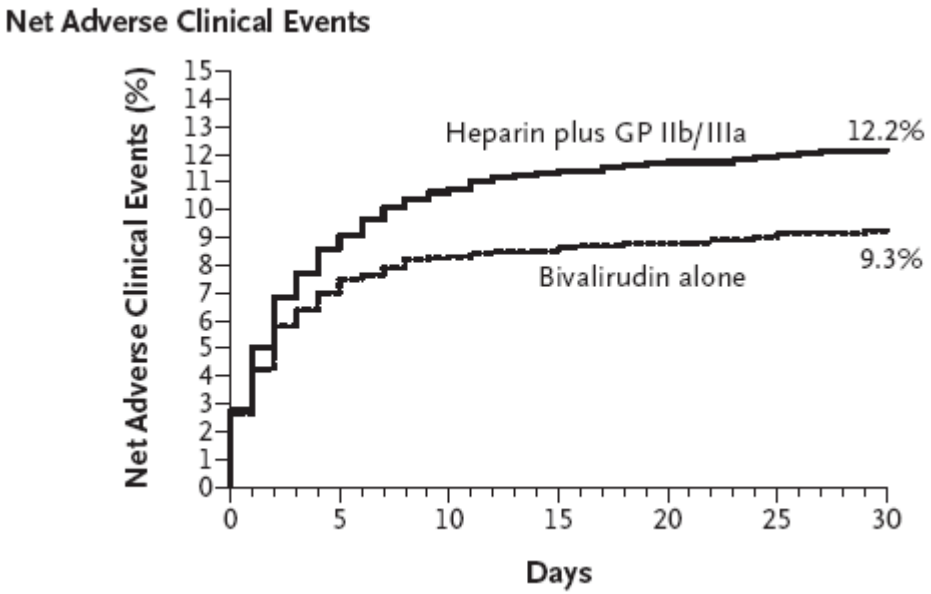
	No. (%) of Patients		Hazard Ratio (95% Confidence Interval)	*P* Value	*P* Value for Interaction
	Unfractionated Heparin	Fondaparinux			
30 Days					
Death or reinfarction					
No primary PCI	184 (13.8)	153 (11.5)	0.82 (0.66-1.02)	.08	.03
Primary PCI	97 (5.1)	115 (6.1)	1.20 (0.91-1.57)	.19	

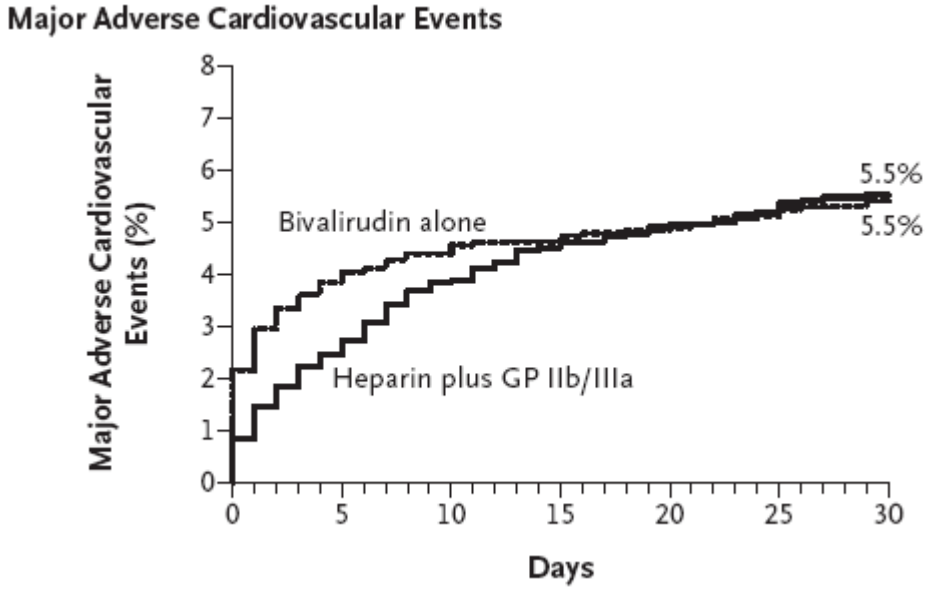
Yusuf S et al. JAMA. 2006; 295: 1519-30.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bivalirudin during Primary PCI in Acute Myocardial Infarction





Stone GW et al. N Engl J Med. 2008; 358: 2218-30

Anticoagulants: summary …

NSTE-ACS			
Anticoagulation			
Very high-risk of ischaemia[e]	UFH (+GPIIb–IIIa antagonists) or	I	C
	Bivalirudin (monotherapy)	I	B
Medium-to-high-risk of ischaemia[e]	UFH	I	C
	Bivalirudin	I	B
	Fondaparinux	I	B
	Enoxaparin	IIa	B
Low-risk of ischaemia[e]	Fondaparinux	I	B
	Enoxaparin	IIa	B
STEMI			
Anticoagulation			
	Bivalirudin (monotherapy)	I	B
	UFH	I	C
	Fondaparinux	III	B

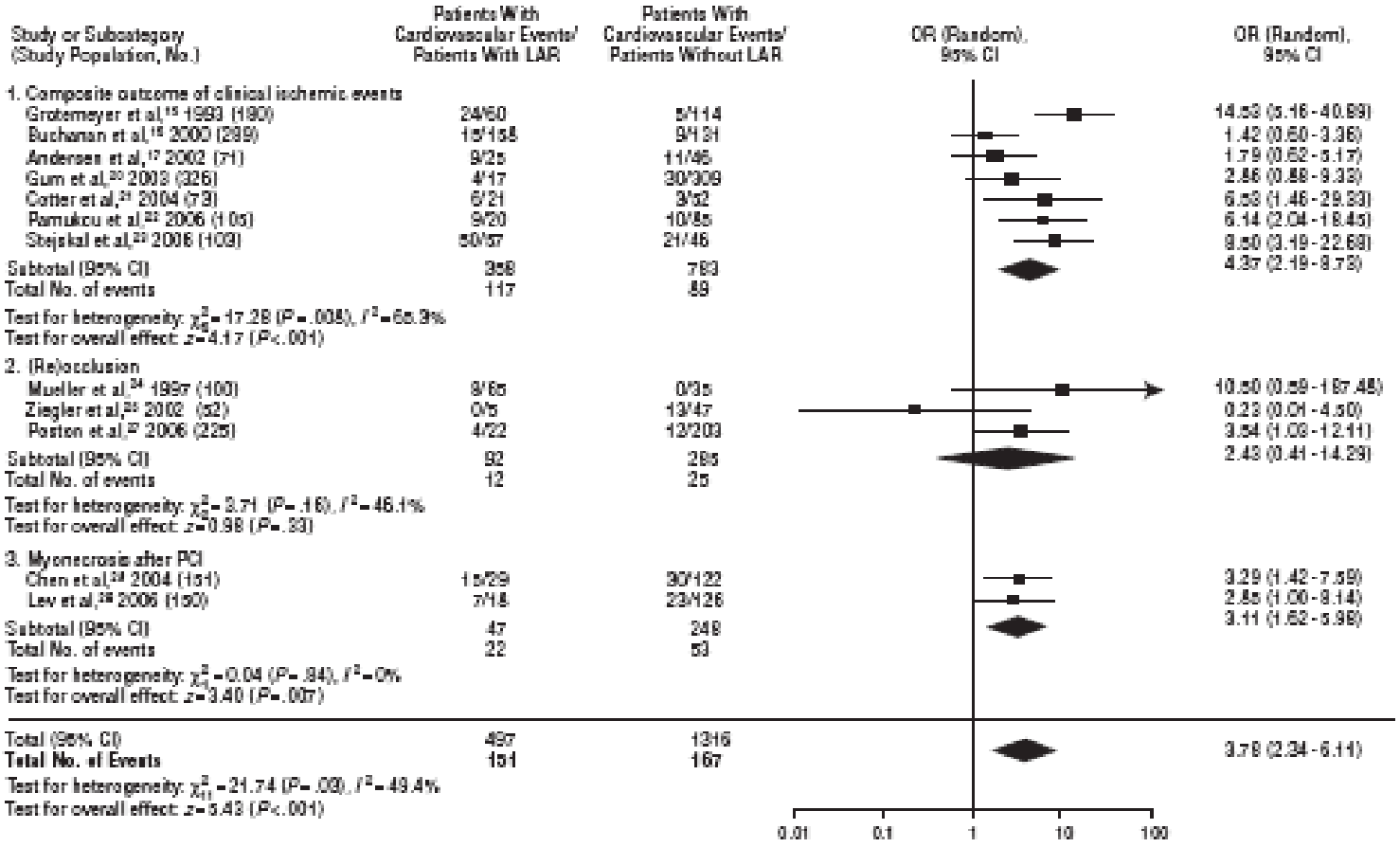
Wijns W et al. Guidelines on myocardial revascularization. Eur Heart J. 2010.

Conclusion …

- Antiplatelet agents
  - The stronger not always the better
  - Individual tailoring ? Acute or stable ?
- Anticoagulants

Thank your for your attention

Aspirin biological response and events …



Residual platelet Hyperreactivity (asa) : OR= 3.8 [2.3-6.1]

Several different tests, heterogeneity

Snoep J et al, Arch Intern Med. 2007; 167:1593

Ki (μM) values of PPIs

Marker Reaction	Omeprazole (Prilosec)	Esomeprazole (Nexium)	Lansoprazole (Prevacid)	Pantoprazole (Protonix)	Rabeprazole (Aciphex)
S-Mephenytoin	6.2	8.6	0.45	69.4	21.3
4-Hydroxylation	2.4	7.9	0.74	15.3	18.8

Higher Ki values indicate lower affinity for 2C19

26% of SPS3 patients take either PPI or H_2 blocker

Li XQ, et al. Drug Metabol Disposit 2004;32:821-7

THEME

"CITATION"

(XXXX)

CYP2C19 and clopidogrel efficacy ?

- related to the biological response
- relation to clinical clinical efficacy ….

29 Aug 2010 ESC Stockholm

CURE ACTIVE: Efficacy and Safety of Clopidogrel compared with Placebo according to CYP2C19 Genotype in over 6000 patients with Non-ST-elevation Acute Coronary Syndromes (CURE trial) and atrial fibrillation (ACTIVE trial)

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"The primary finding was that there was no relationship between allele status and placebo event rates, and for the most part, no relationship to treatment effect**.** **Clopidogrel was effective in preventing ischemic events and caused more bleeding than placebo, regardless of allele status in CURE**."

Table …

xxxxx	xx	xx	xx	xx	xx
Xxx	x	x	x	x	x

xxx

Figure …

xxx