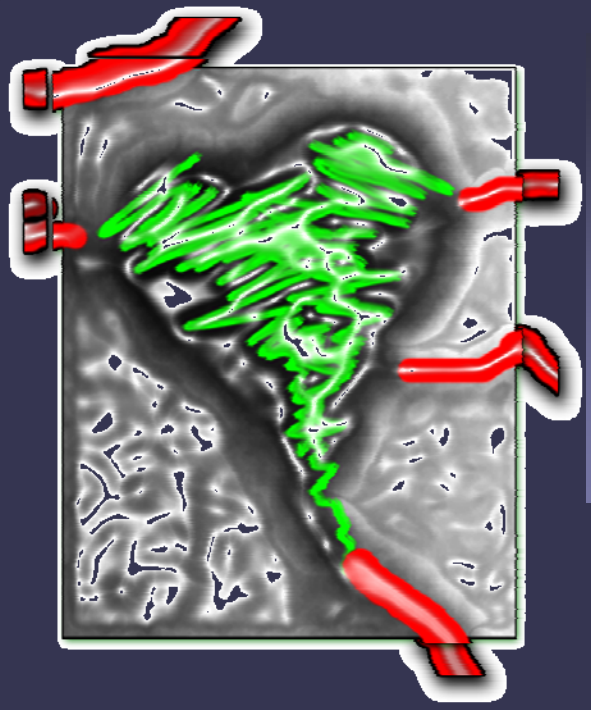
5TH JMC - Joint Meeting with Mayo Clinic



Antiaggregation therapy when it is not effective

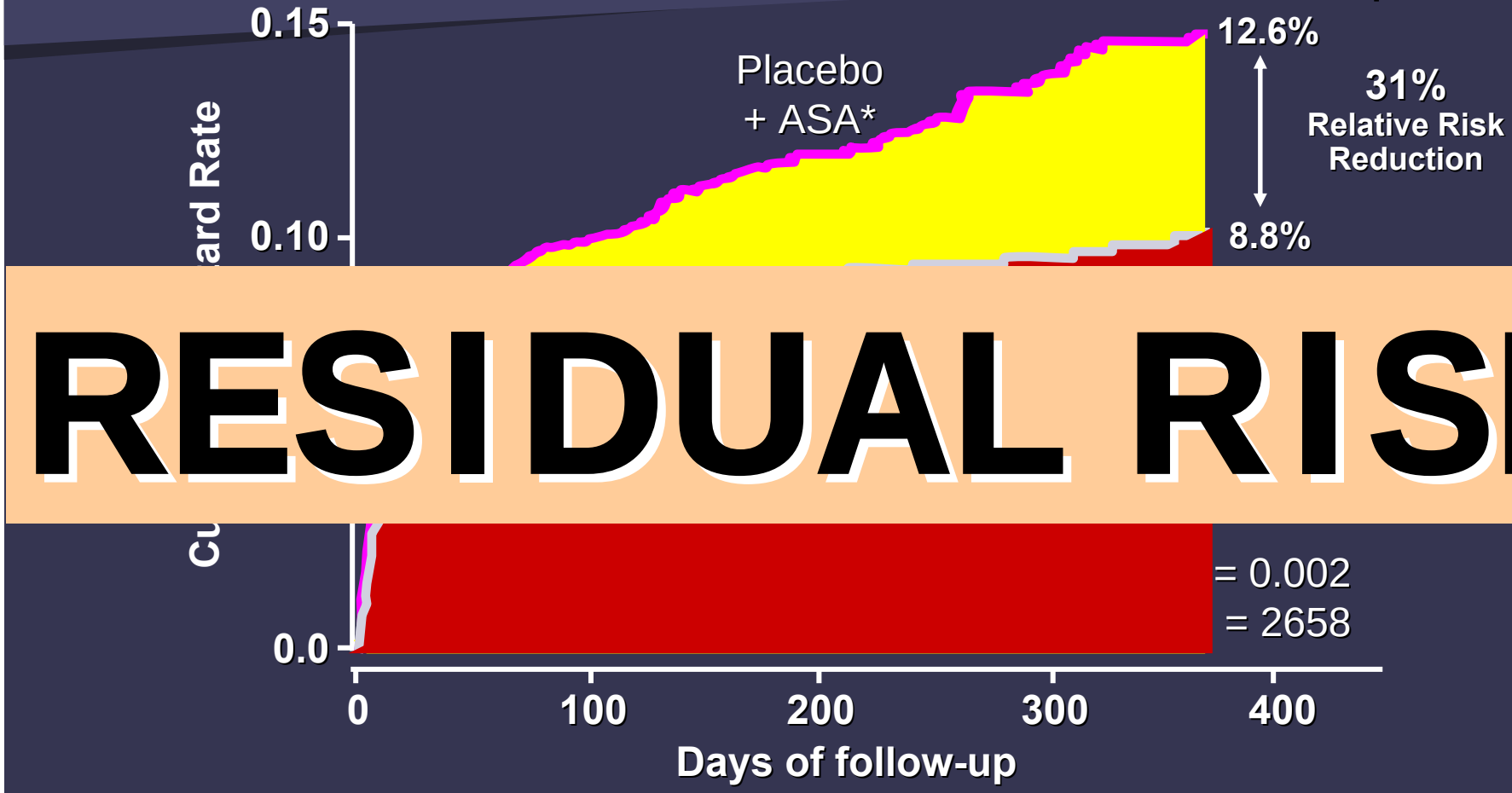
M. Valgimigli, MD, PhD
University of Ferrara
ITALY

Torino 16 Ottobre 2009

PCI-CURE

Early Clopidogrel in PCI Patients

Composite of MI or cardiovascular death from randomization to end of follow-up



RESIDUAL RISK

* In addition to other standard therapies.

Mehta et al for the CURE Investigators. *Lancet.* 2001;358:527

Equations in CV medicine

Residual Risk

≠

Tested Tx is not effective

Equations in CV medicine

Part of Residual Risk

=

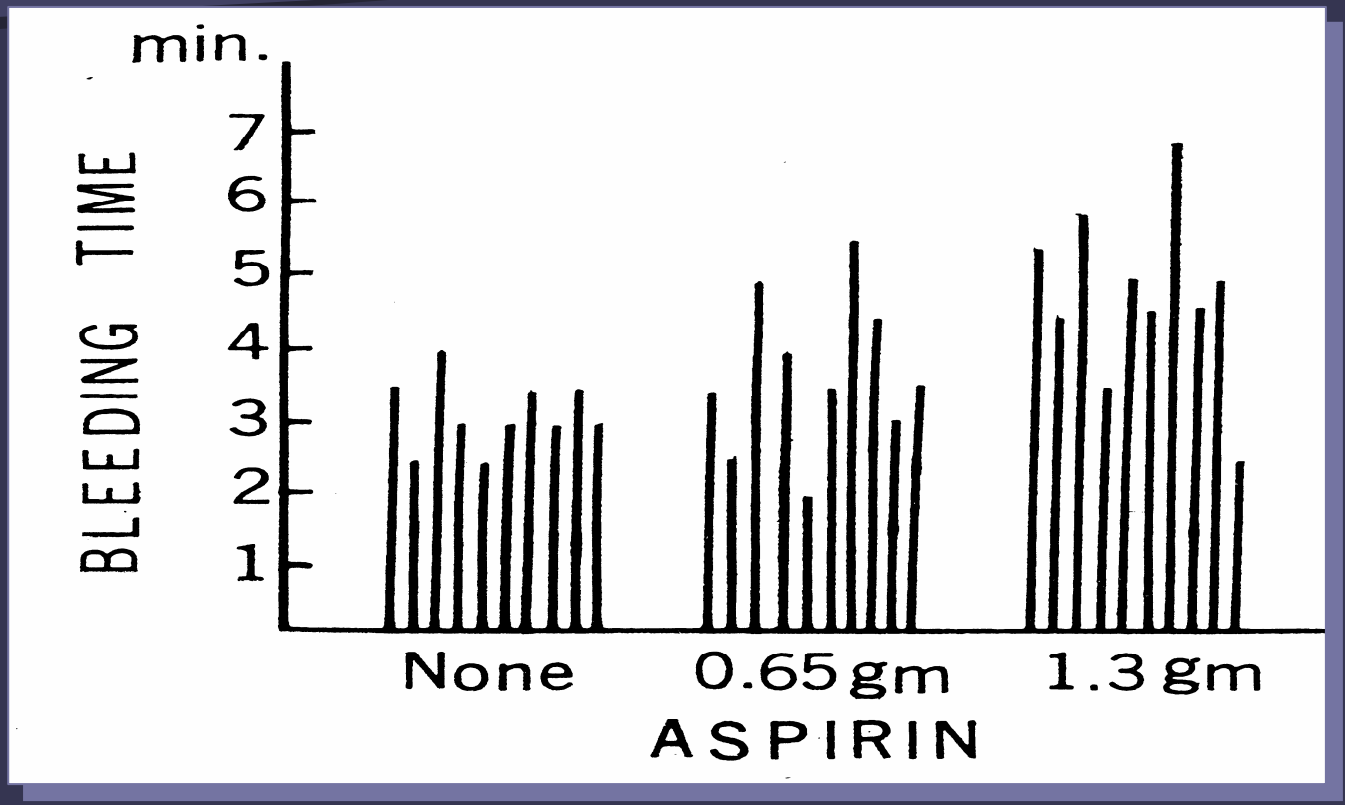
↓efficacy in modulating target receptor(s)

RESISTENCE TO THE TREATMENT

Issue no.1

Variability in Response

Inter-Individual Variability in Response to Aspirin

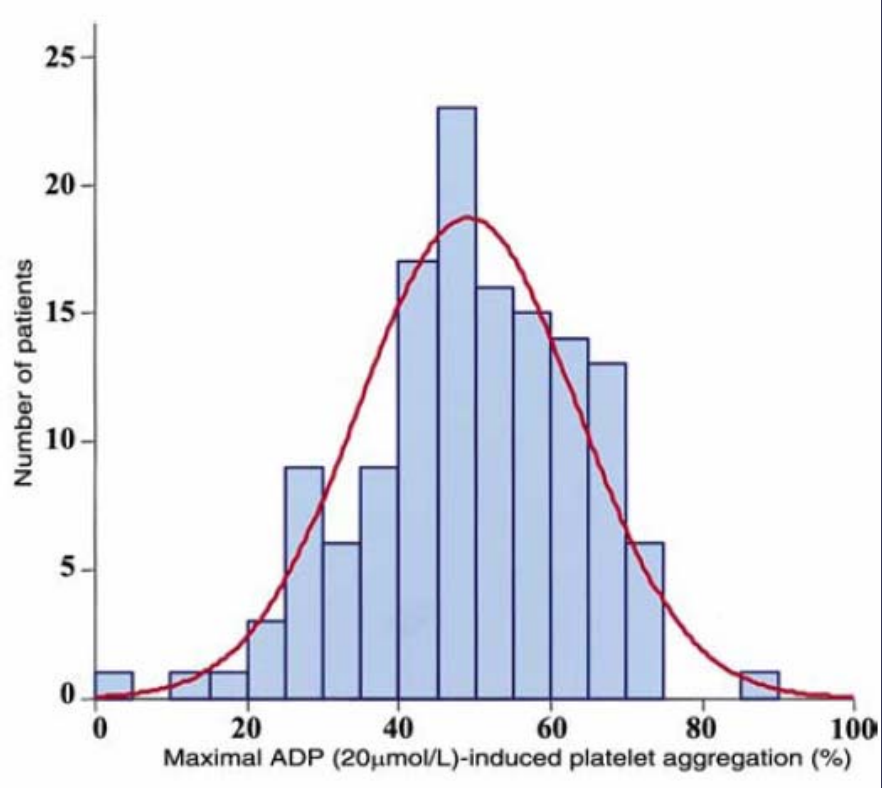


N=10

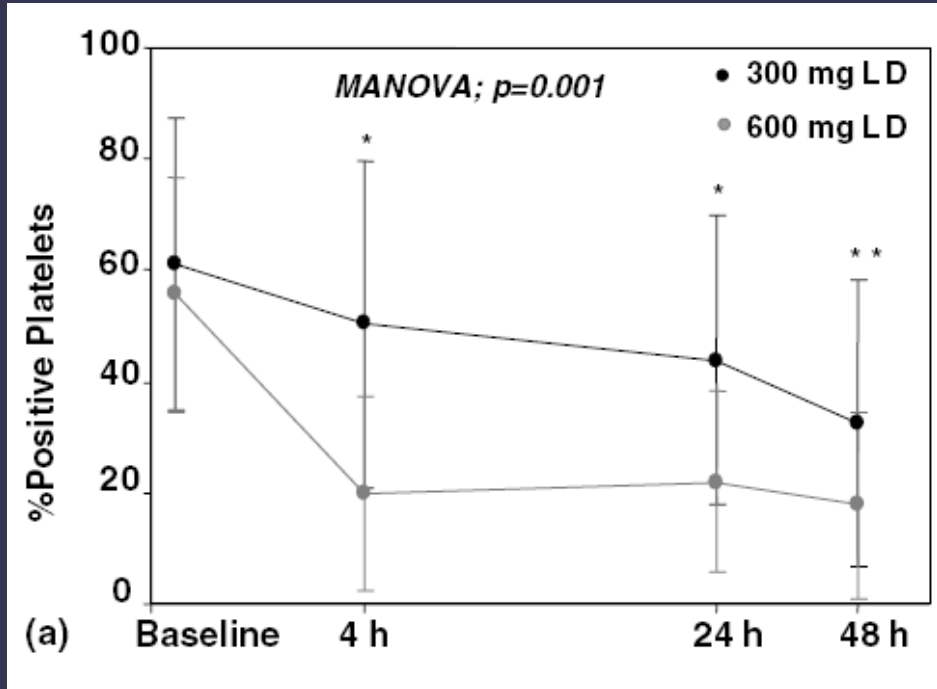
Quick AJ.
American Journal of Medical Science
Sept 1966:265-9

Inter-Individual Variability in Response to Clopidogrel

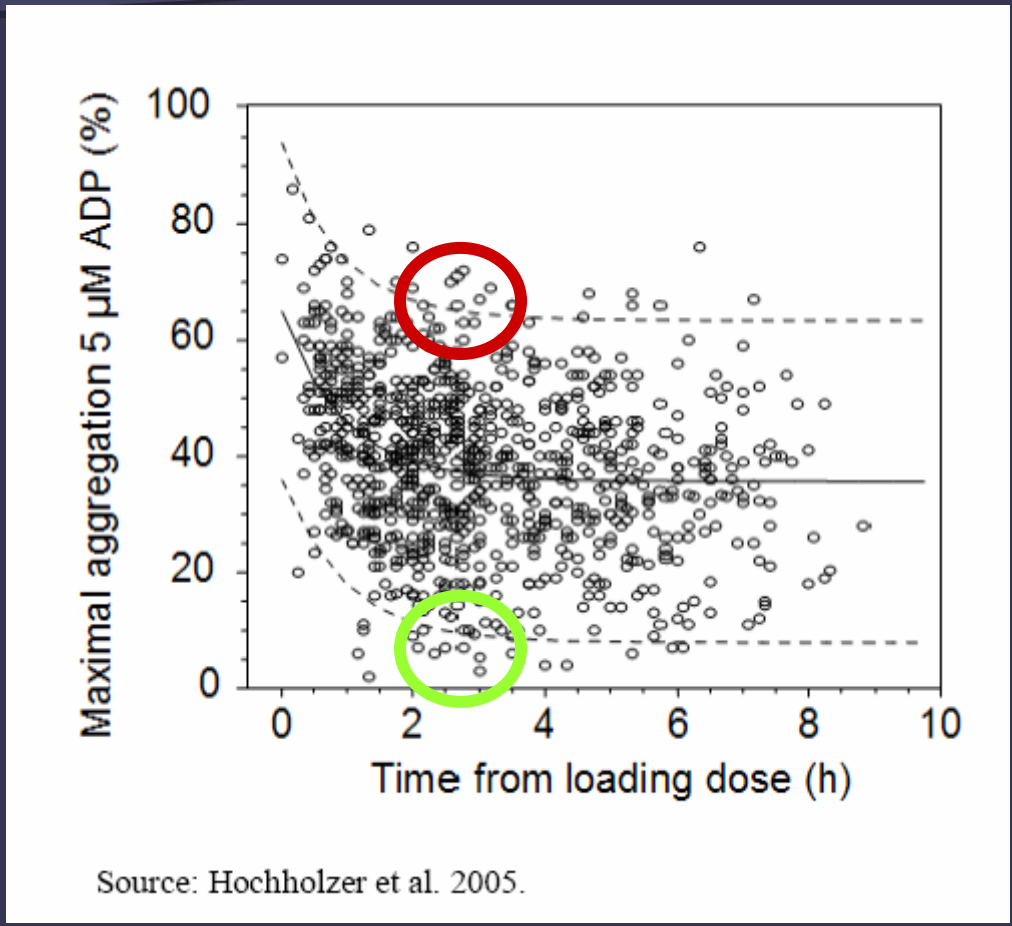
Clopidogrel steady-state di clopidogrel 75 mg



300 or 600 mg loading dose



“600 mg clopidogrel LD..wait 2 hours and you will be fine…”



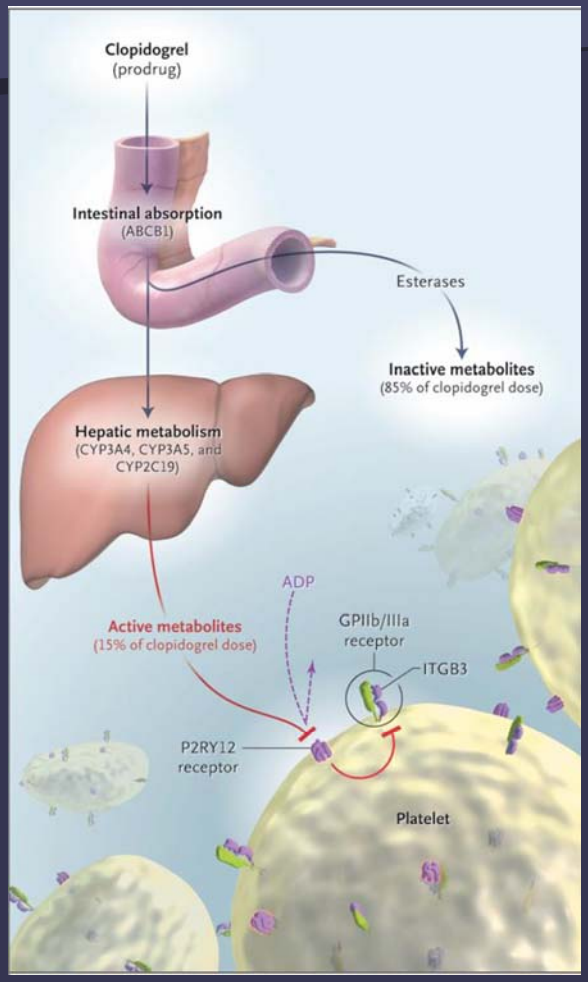
Source: Hochholzer et al. 2005.

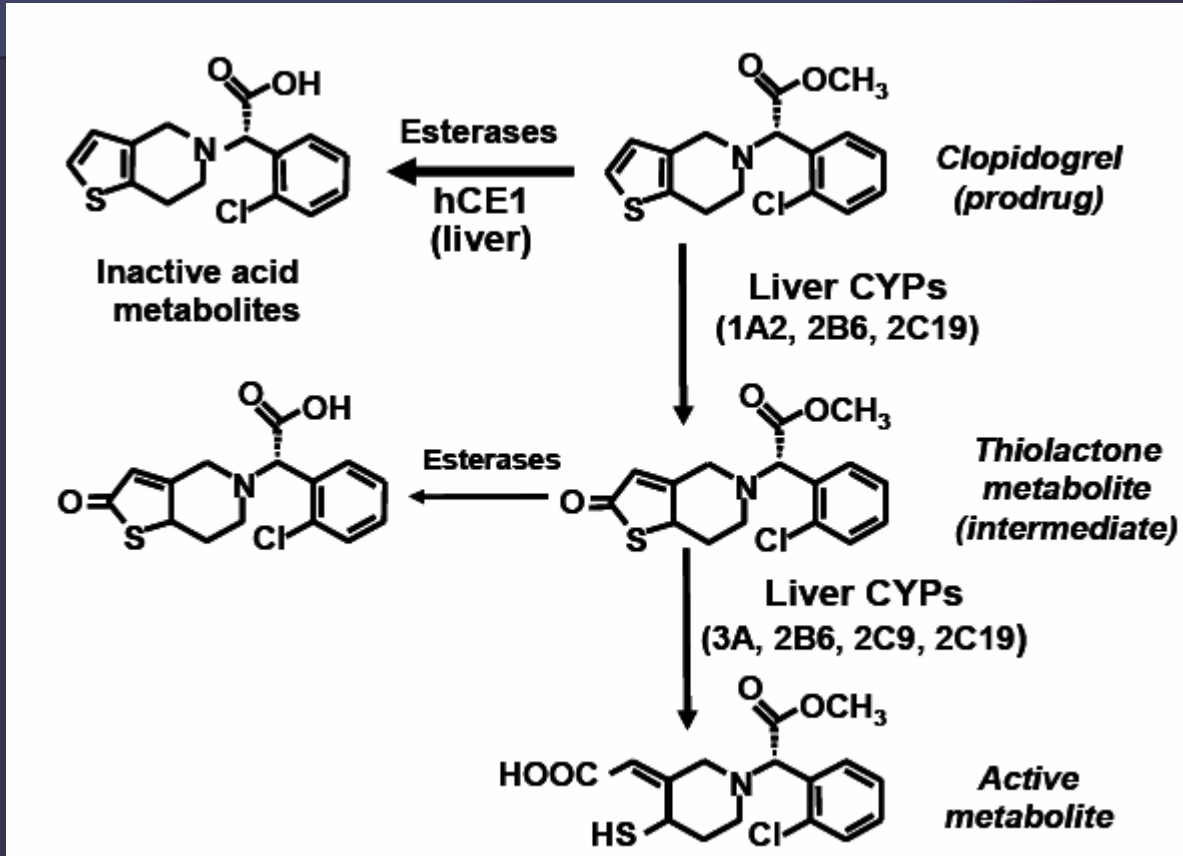
Putative mechanisms for such variability

Clopidogrel

Variable bioavailability of Clopidogrel's active metabolite to reach the target (P2Y12 ADP receptor)

Clopidogrel: a prodrug





Source: Kurihara et al. 2005; Tang et al. 2006.

Putative mechanisms for such variability

Aspirin

Incompletely understood !!

Variability in response to ASA

- ASA, even low doses, inhibits arachidonic acid–induced aggregation and thromboxane B2 production by 99%
- Inhibition of urinary thromboxane excretion and platelet activation in pathways indirectly related to cyclooxygenase-1 is less pronounced and more variable (inhibition of 0% to 100%).
- Measured covariates may contribute modestly to variability in ASA response phenotypes.
- Dose issue for regimen lower than 160 mg reported some studies, i.e. diabetic patients.
- Phenotypes indirectly related to cyclooxygenase-1 were strongly heritable across races

Putative mechanisms for such variability

Aspirin

COX-1 effect on PLTs

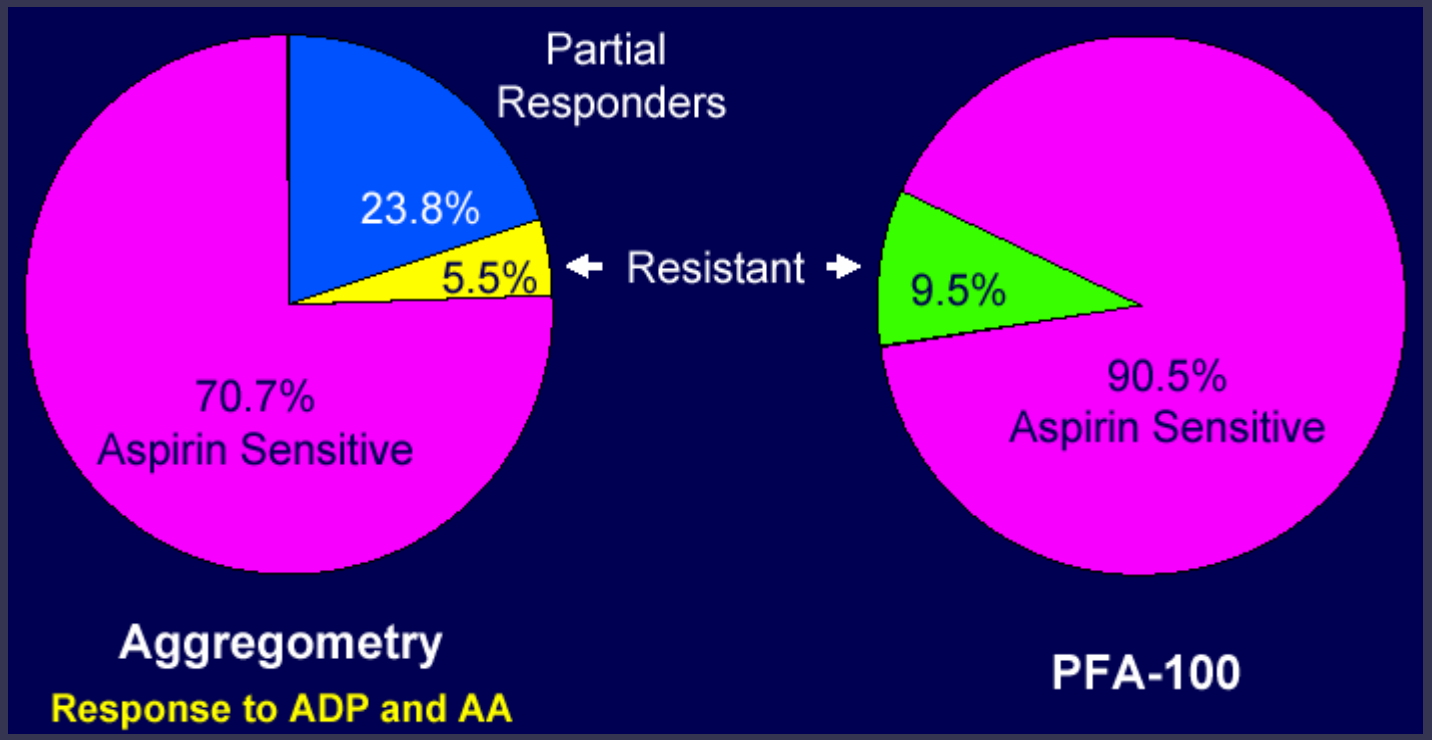
No-little variability

Non-COX-1 effect on PLTs

great variability
Possible dose-related

Prevalence of ASA Resistance

325 patients with stable CVD taking ASA 325 mg >7days



ASA-R: mean aggregation ≥70% with μM 10 ADP & ≥20% with 0.5 mg/ml AA

Gum PA et al. *Am J Cardiol* 2001;88:230-235

Aspirin History

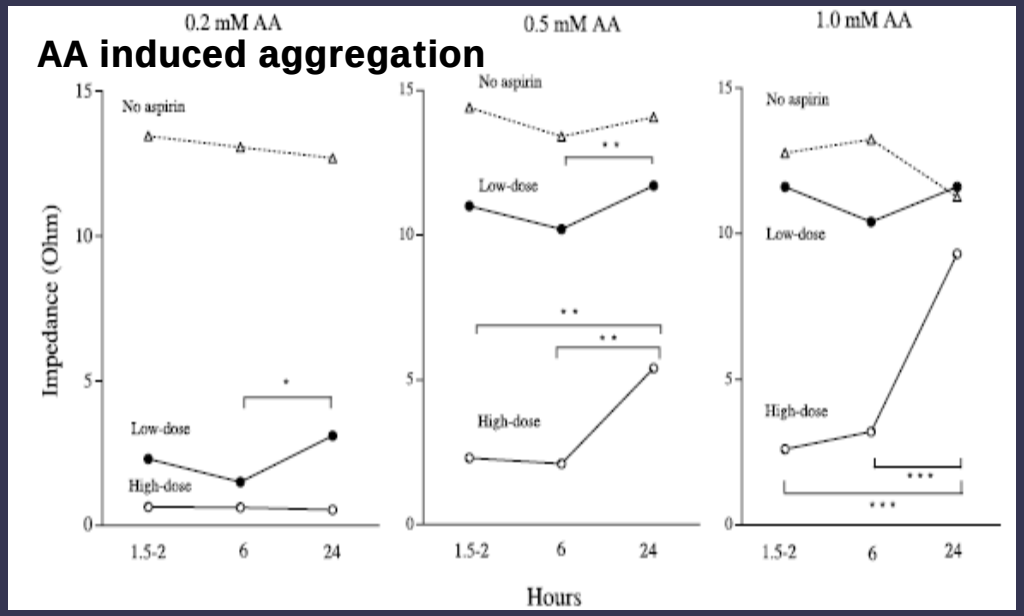
Due to problems with the original Aspirin powder being counterfeited, it became the first pharmaceutical agent ever sold in pill form in early 1900's.

First pill in USA was 5 grains (~325 mg).

Aspirin....100 years after

Emerging concept

Once daily administration may not cover 24 hour PLT inhibition



Thromb Haemost. 2006 ;5(4):652-8.

Rapid turnover of circulating platelets may be responsible

ASA Dose Comparison Primary Outcome and Bleeding

	ASA 75-100 mg	ASA 300-325 mg	HR	95% CI	P
CV Death/MI/Stroke					
PCI (2N=17,232)	4.2	4.1	0.98	0.84-1.13	0.76
No PCI (2N=7855)	4.7	4.4	0.92	0.75-1.14	0.44
Overall (2N=25,087)	4.4	4.2	0.96	0.85-1.08	0.47
Stent Thrombosis	2.1	1.9	0.91	0.73-1.12	0.37
TIMI Major Bleed	1.03	0.97	0.94	0.73-1.21	0.71
CURRENT Major Bleed	2.3	2.3	0.99	0.84-1.17	0.90
CURRENT Severe Bleed	1.7	1.7	1.00	0.83-1.21	1.00

No other significant differences between ASA dose groups

GI Bleeds: 30 (0.24%) v 47 (0.38%), P=0.051

CURRENT Clopidogrel Dose Comparison

2 Significant Interactions:

1. PCI v No PCI (P=0.016)

2. ASA dose (P=0.043)

ASA Resistance: Long-term Clinical Studies

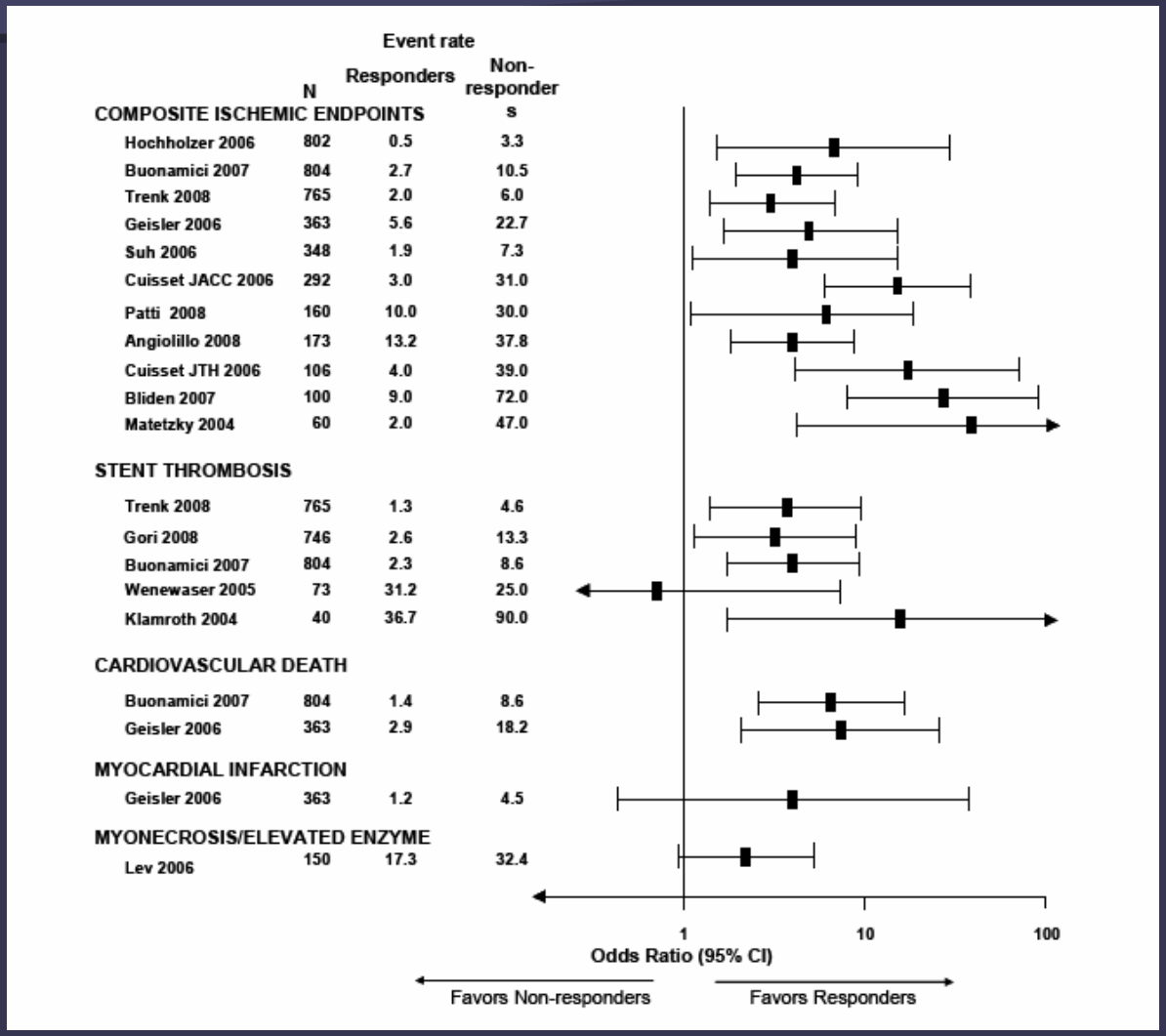
Pts	ASA dose	Test	F/U	End-point	Results
Stroke[1] (n=180)	1500 mg	Plt Reactivity	24 m	Stroke/MI/ Vascular death	10-fold lower risk in ASA responders
PVD[2] (n=100)	100 mg	Whole blood aggregometry	18 m	Arterial Occlusion	87% higher risk in ASA-R
CVD/CVA[3] (n=53) TIA	100 mg	PFA-100	>60 m	Recurrent CVA/ TIA	Recurrent CVA 34% ASA-R vs. 0% no recurrent events
Subgroup HOPE[4] (n=967)	75-325 mg	Urinary 11-dehydro TX B2	5 yrs	MI/Stroke/ CVDeath	1.8 times higher risk in upper vs. lower quartile
CVD[5] (n=326)	325 mg	Optical platelet aggregation	679±185 days	Death/MI/CVA	24% ASA-R vs. 10% ASA-S [HR 3.12 (95% CI 1.1-8.9, p=0.03)

1. Grotemeyer KH, et al. *Thromb Res* 1993; 71:397-403
2. Mueller MR, et al. Thromb Haemost 1997; 78:1003-1007
3. Grundmann K, et al. *J Neurol* 2003; 250: 63-66
4. Eikelboom JW, et al. *Circulation* 2002; 105:1650-1655
5. Gum PA, et al. *J Am Coll Cardiol* 2003; 41:961-965

Clopidogrel poor responsiveness and outcomes

Study	Instrument	Reagent	Setting	N	Clinical endpoint	Cut-off	Low-response rate	Hazard ratio
Hochholzer (JACC 2006)	LTA (PAP4)	5 µM ADP	Elective PCI	802	MACE (death, MI, target lesion revascularisation)	aggregation > median	50%	6.7
Geisler (EHJ 2006)	LTA (Chronolog)	20 µM ADP	PCI	379	MACE (death, MI, stroke)	aggregation > 70%	5.80%	4.9
Buonamici (JACC 2007)	LTA (APACT 4)	10 µM ADP	DES implantation	804	definite/probable stent thrombosis	aggregation > 70%	13%	3.1
Marcucci (Circulation 2009)	VerifyNow	P2Y12 assay	PCI/ACS	683	CV death / nonfatal MI	>240 PRU (ROC analysis)	32%	2.55/3.36
Price (EHJ 2008)	VerifyNow	P2Y12 assay	DES implantation	380	stent thrombosis (definite, probable, possible), CV death, nonfatal MI	> 235 PRU (ROC analysis)	32%	ND
Patti (JACC 2008)	VerifyNow	P2Y12 assay	PCI	160	MACE (death, MI, target lesion revascularisation)	PRU in upper quartile	25%	6.1
Bonello (JTH 2007)	VASP	P2Y12 assay	PCI	144	MACE (death, stroke, revascularization)	PRI >50%	80%	ND
Sibbing (JACC 2009)	Multiplate	6.4 µM ADP	DES	1608	Stentthrombosis (definite)	Upper quintile (416 AU*min)	20%	10.95

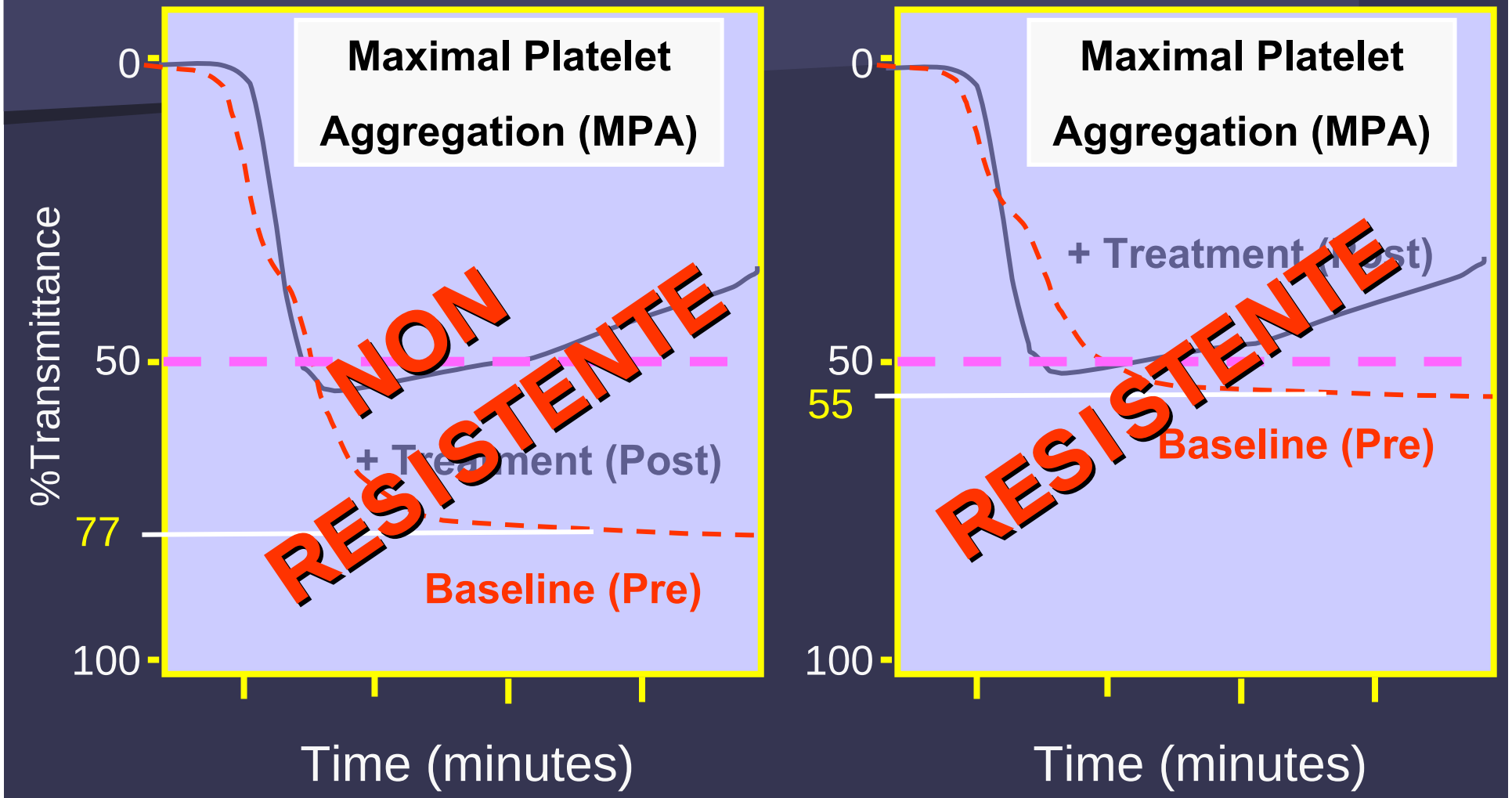
Clopidogrel poor response: Consistent results across studies



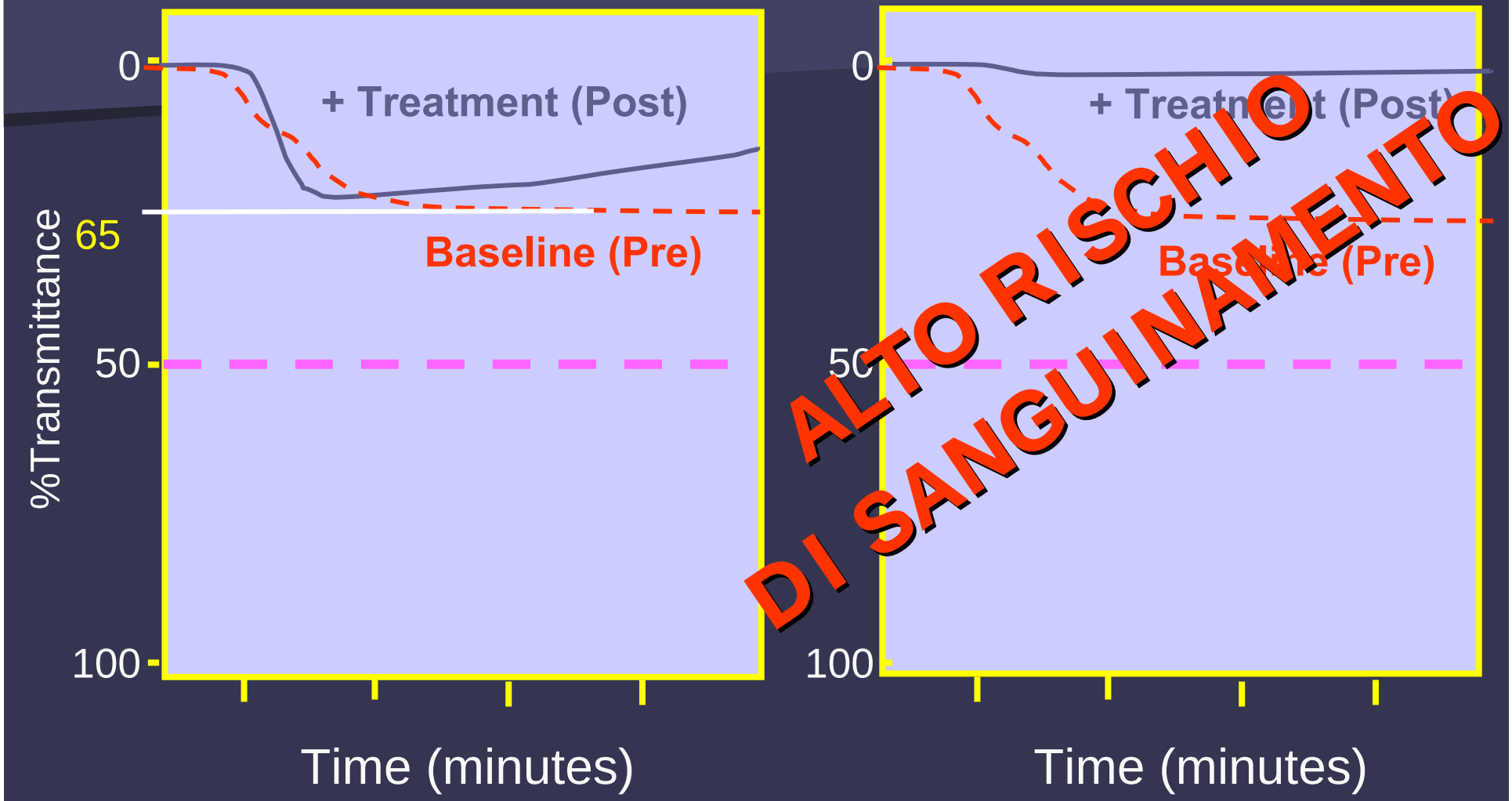
Resistance to a drug

- Not always drug's fault !!
- Not necessarily associated to worse outcomes !!

Light Transmittance Aggregometry



Light Transmittance Aggregometry

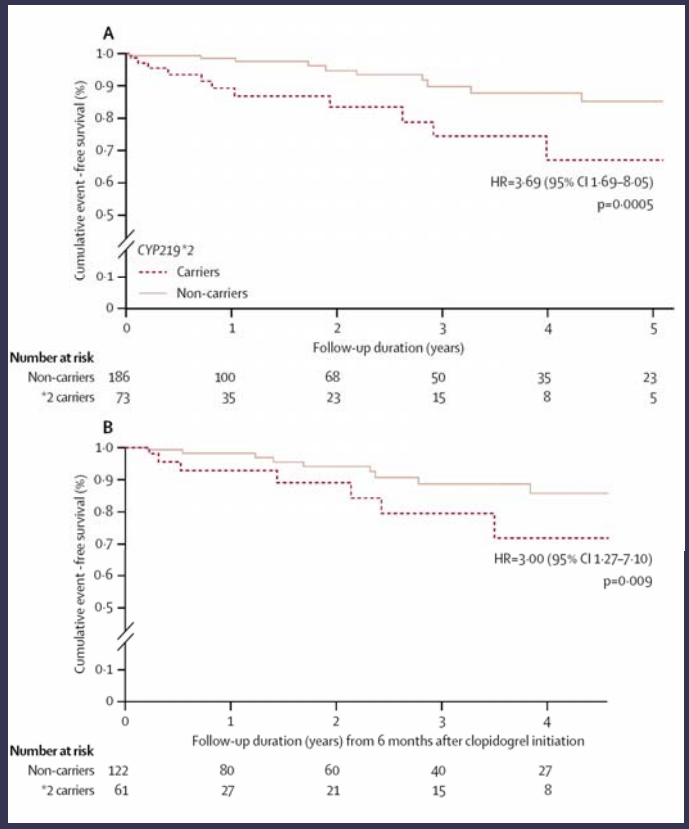


Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study

Jean-Philippe Collet, Jean-Sébastien Hulot, Anna Pena, Eric Villard, Jean-Baptiste Esteve, Johanne Silvain, Laurent Payot, Delphine Brugier, Guillaume Cayla, Farzin Beygui, Gilbert Bensimon, Christian Funck-Brentano, Gilles Montalescot

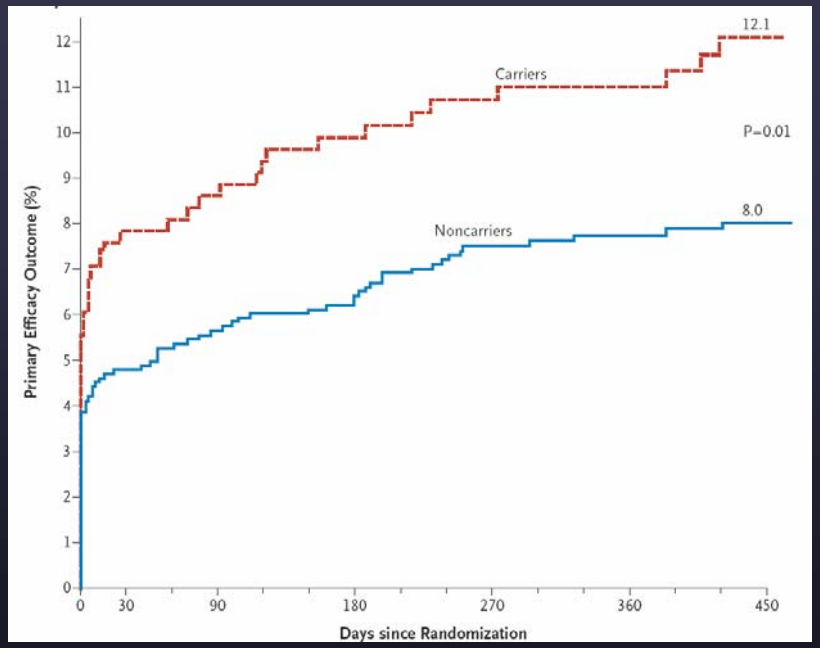
Of the 259 patients, 186 (72%) were wild-type homozygotes (*1/*1), 64 (25%) were heterozygotes (*1/*2), and nine (3%) were homozygous (*2/*2) with respect to the *2 allelic variant.

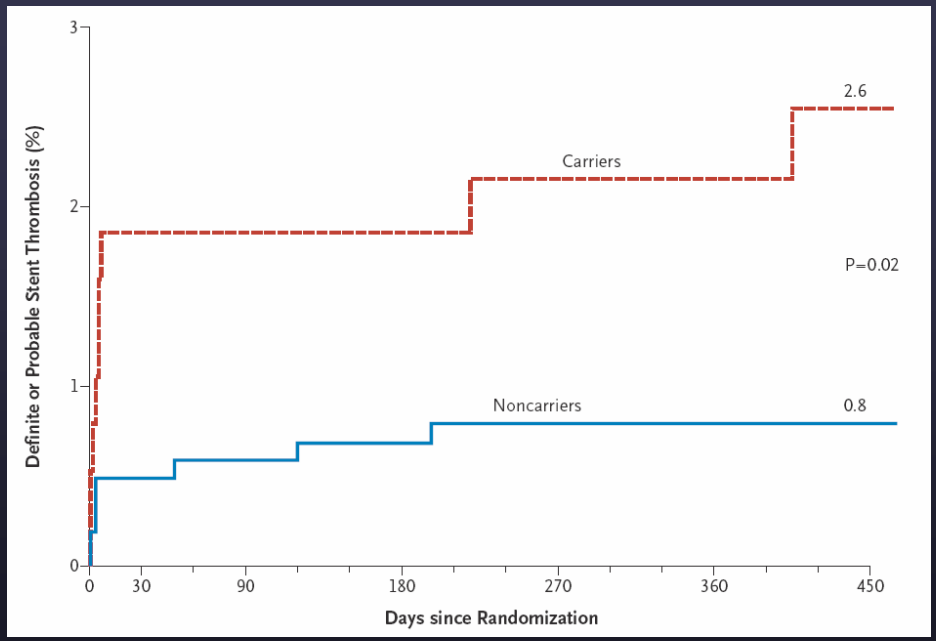
	*CYP2C19**2 allele*		p value
	Non-carriers (N=186)	Carriers (N=73)	
Primary endpoint (death, non-fatal myocardial infarction, urgent revascularisation)			
Absolute number of events (n)	11	15	
Event rate per 100 patient-years	2·89	10·90	
Unadjusted HR (95% CI)	1·0	3·69 (1·69–8·05)	0·0005
Adjusted HR (95% CI)*	1·0	5·38 (2·32–12·47)	<0·0001
Cardiovascular death			
Absolute number of events (n)	1	2	
Event rate per 100 person-years	0·26	1·45	
Unadjusted HR (95% CI)	1·0	5·74 (0·52–63·48)	0·10
Adjusted HR (95% CI)*	†	†	
Myocardial infarction			
Absolute number of events (n)	6	10	
Event rate per 100 patient-years	1·58	7·27	
Unadjusted HR (95% CI)	1·0	4·54 (1·64–12·53)	0·001
Adjusted HR (95% CI)*	1·0	5·57 (1·94–16·01)	0·001
Urgent revascularisation			
Absolute number of events (n)	4	3	
Event rate per 100 patient-years	1·05	2·18	
Unadjusted HR (95% CI)	1·0	1·94 (0·43–8·73)	0·38
Adjusted HR (95% CI)*	1·0	3·24 (0·69–15·09)	0·13
Definite stent thrombosis‡			
Absolute number of events (n)	4	8	
Event rate per 1000 person-years	1·14	6·79	
Unadjusted HR (95% CI)	1·0	6·02 (1·81–20·04)	0·0009
Adjusted HR (95% CI)*	1·0	6·04 (1·75–20·80)	0·004
Ischaemic endpoint not related to stent thrombosis‡§			
Absolute number of events (n)	7	6	
Event rate per 100 patient-years	1·99	5·09	
Unadjusted HR (95% CI)	1·0	2·38 (0·79–7·13)	0·11
Adjusted HR (95% CI)*	1·0	3·31 (1·05–10·47)	0·04



Cytochrome P-450 Polymorphisms and Response to Clopidogrel

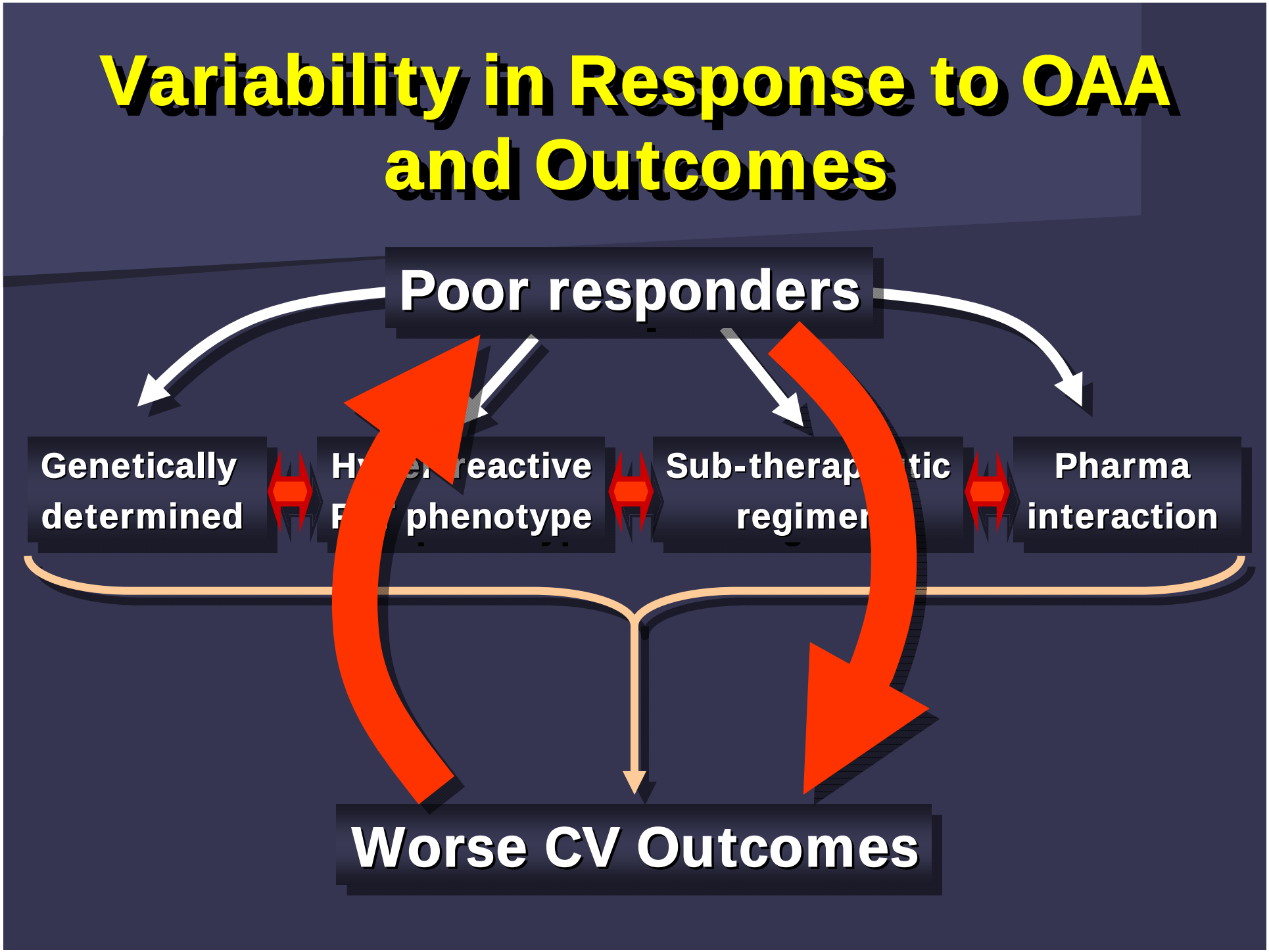
95% of poor response due to a single SNP *2





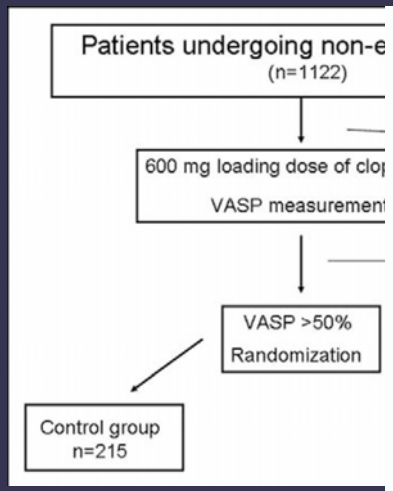
Mega, New Eng J Med 2009

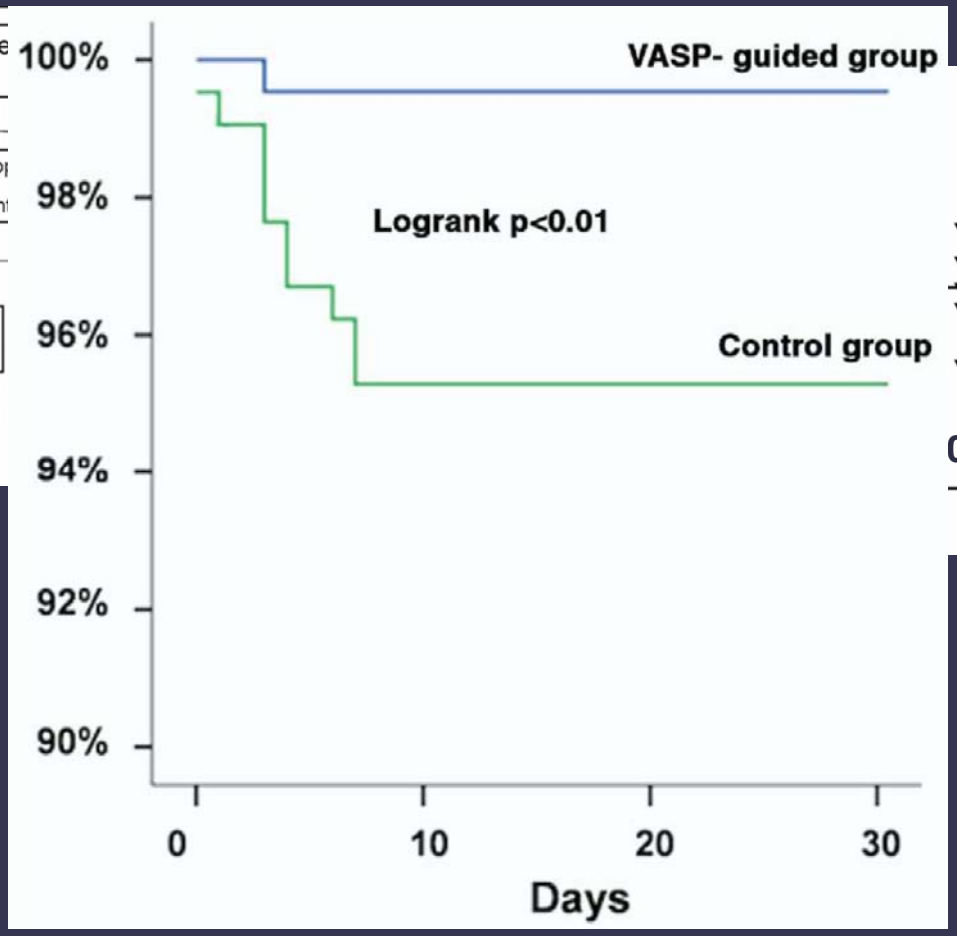
Variability in Response to OAA and Outcomes

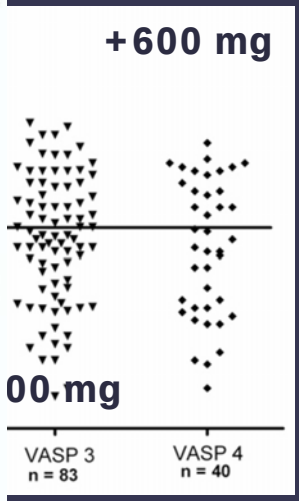


Tailored *Clopidogrel* Loading Dose According to Platelet Reactivity Monitoring to Prevent Acute and Subacute Stent Thrombosis

Laurent Bonello, MD[a,e,*], Laurence Camoin-Jau, PhD[d,e], Sébastien Armero, MD[a], Olivier Com, MD[a], Stéphane Arques, MD[f], Caroline Burignat-Bonello, MD[b], Marie-Paule Giacomoni, MD[c], Roland Bonello, MD[c], Frédéric Collet, MD[c], Philippe Rossi, MD[c], Paul Barragan, MD[g], Françoise Dignat-George, PhD[d,e], and Franck Paganelli, MD[a]







Am J Cardiol 2009;103:5–10

Patients selection

Screening

- **Patients scheduled to undergo elective CAG/PCI for silent ischemia, stable angina or low risk NSTEACS**

Eligibility

-Undergoing PCI
-CK, CK-MB and Tp I/T persistently –ve
-No controindications to Gp IIb/IIIa blockers
-Aspirin and/or Clopidogrel poor response as assessed by VerifyNow™ Aspirin and P2Y12 assays (Accumetrics, USA)

Valgimigli et al, Circulation 2009

Response evaluation

Aspirin Poor Response

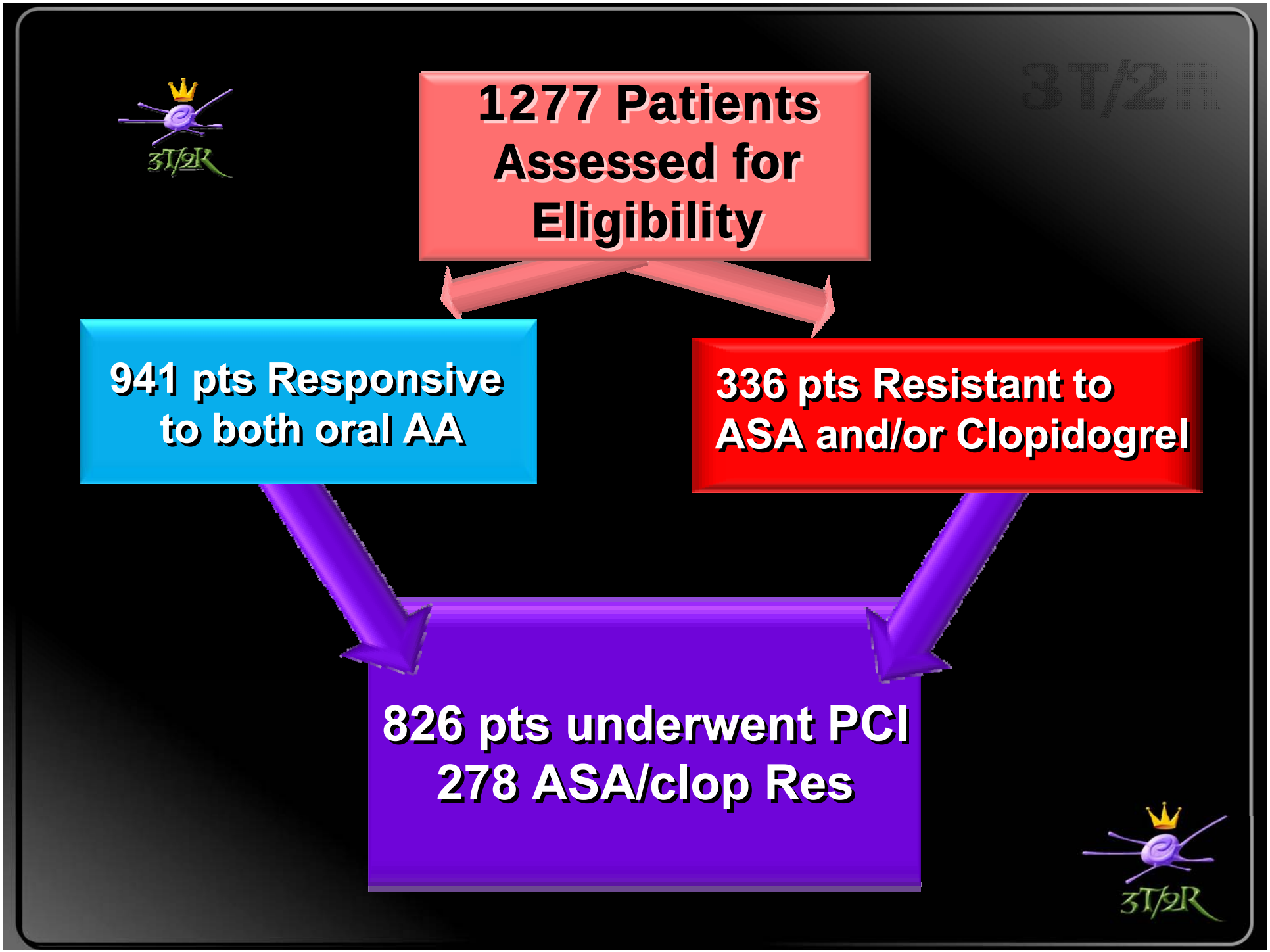
- Aspirin reaction units (ARU) >550
  - ASA orally 80 mg for at least 5 days *And/Or*
  - i.v. 500 mg ASA 15 mins or more before

Clopidogrel Poor Response

- < 40% platelet inhibition
  - 600 mg clopidogrel LD at least 2 hours before *Or*
  - 300 mg clopidgrel LD at least 6 hours before *Or*
  - 75 mg clopidogrel MD for at least 7 days

Valgimigli et al, Circulation 2009

3T/2R


1277 Patients Assessed for Eligibility
941 pts Responsive to both oral AA
336 pts Resistant to ASA and/or Clopidogrel
826 pts underwent PCI
278 ASA/clop Res

Trial Design

Aspirin + Clopidogrel

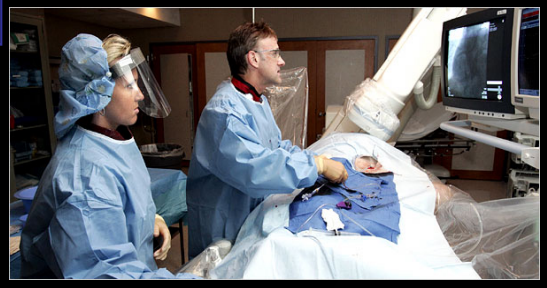
UFH or Bivalirudin

1:1

Double Blind

Tirofiban*

Bail-out Placebo



Placebo

Bail-out Tirofiban

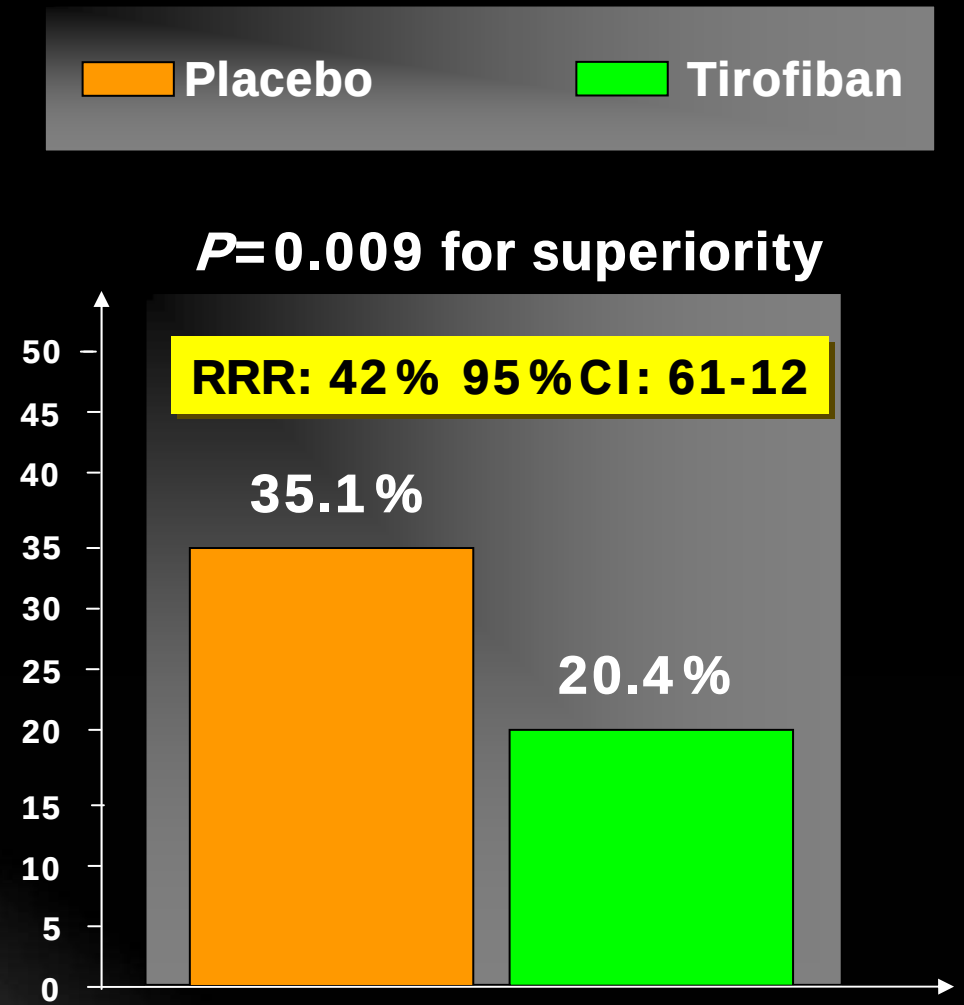
Blood sampling: **Hb, PLT, Tp; CK-MB mass @ 6, 12, 18 or 24 hrs**

Clinical F-UP: **30-d, 4, 8 and 12 months**

Valgimigli et al, Circulation 2009

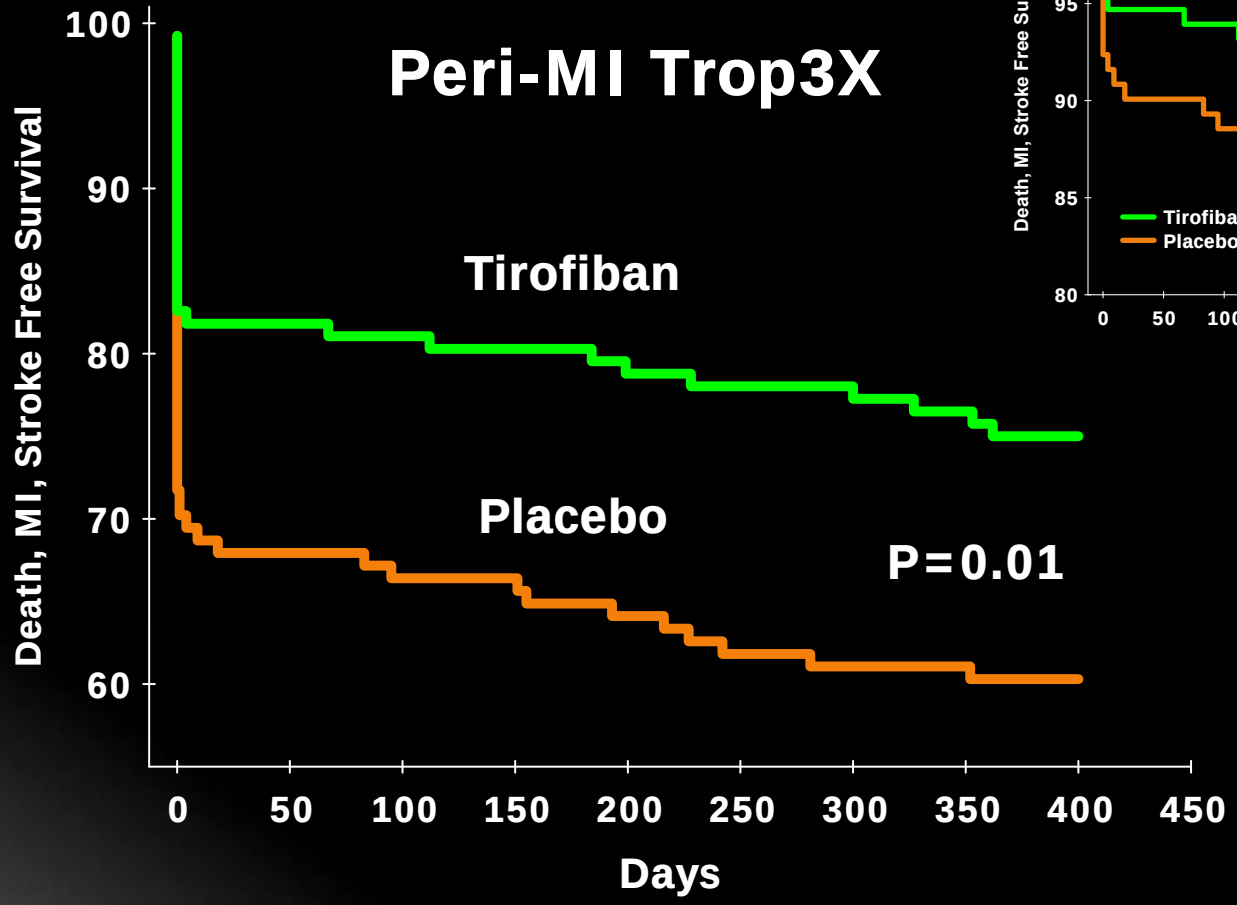
Primary Endpoint

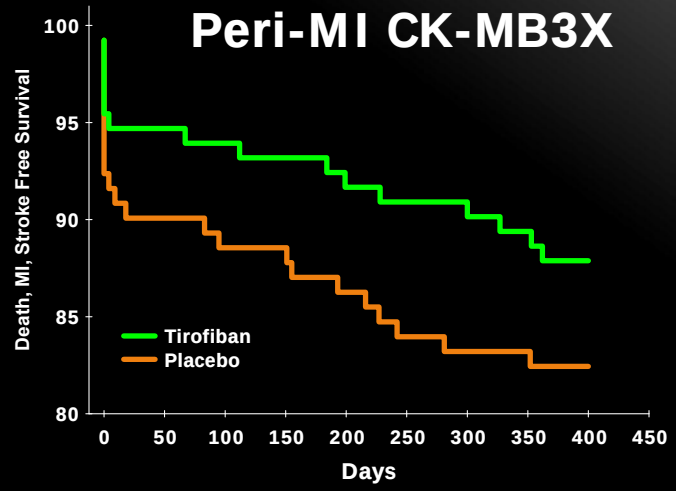
Tp >3×ULN w/in 48 hs



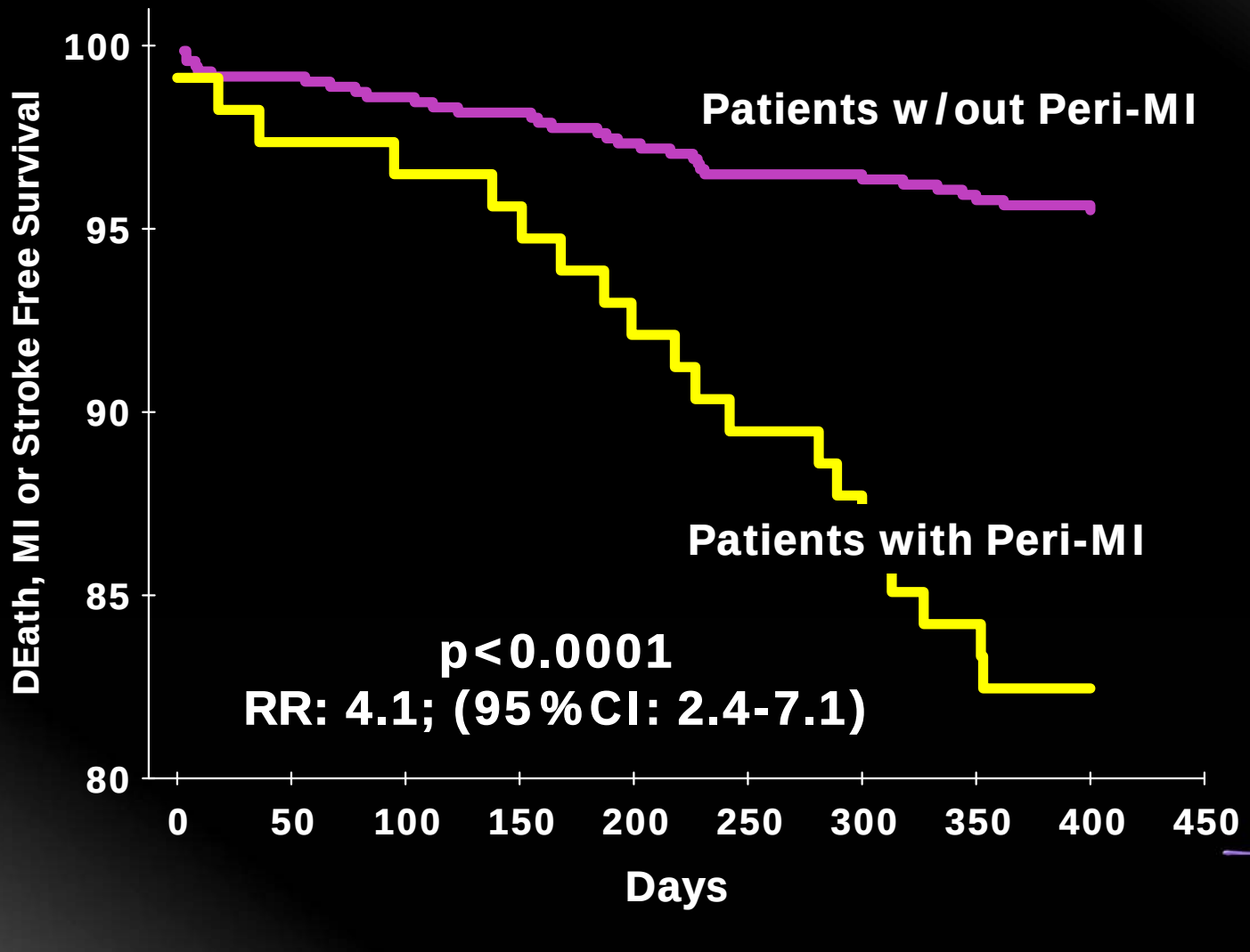
Valgimigli et al, Circulation 2009

1-Year Outcome



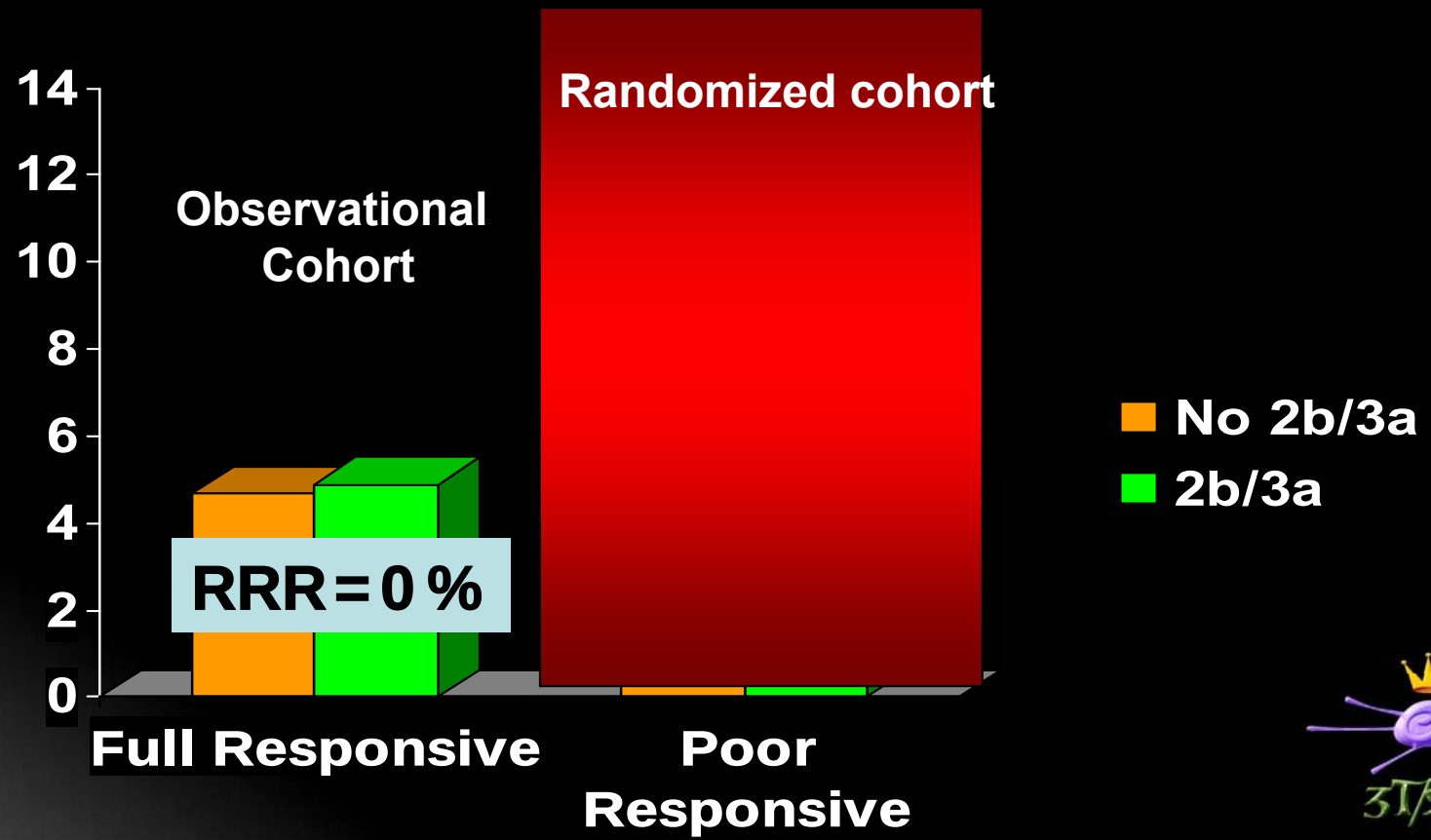


Impact of peri3XTp elevation on outcomes



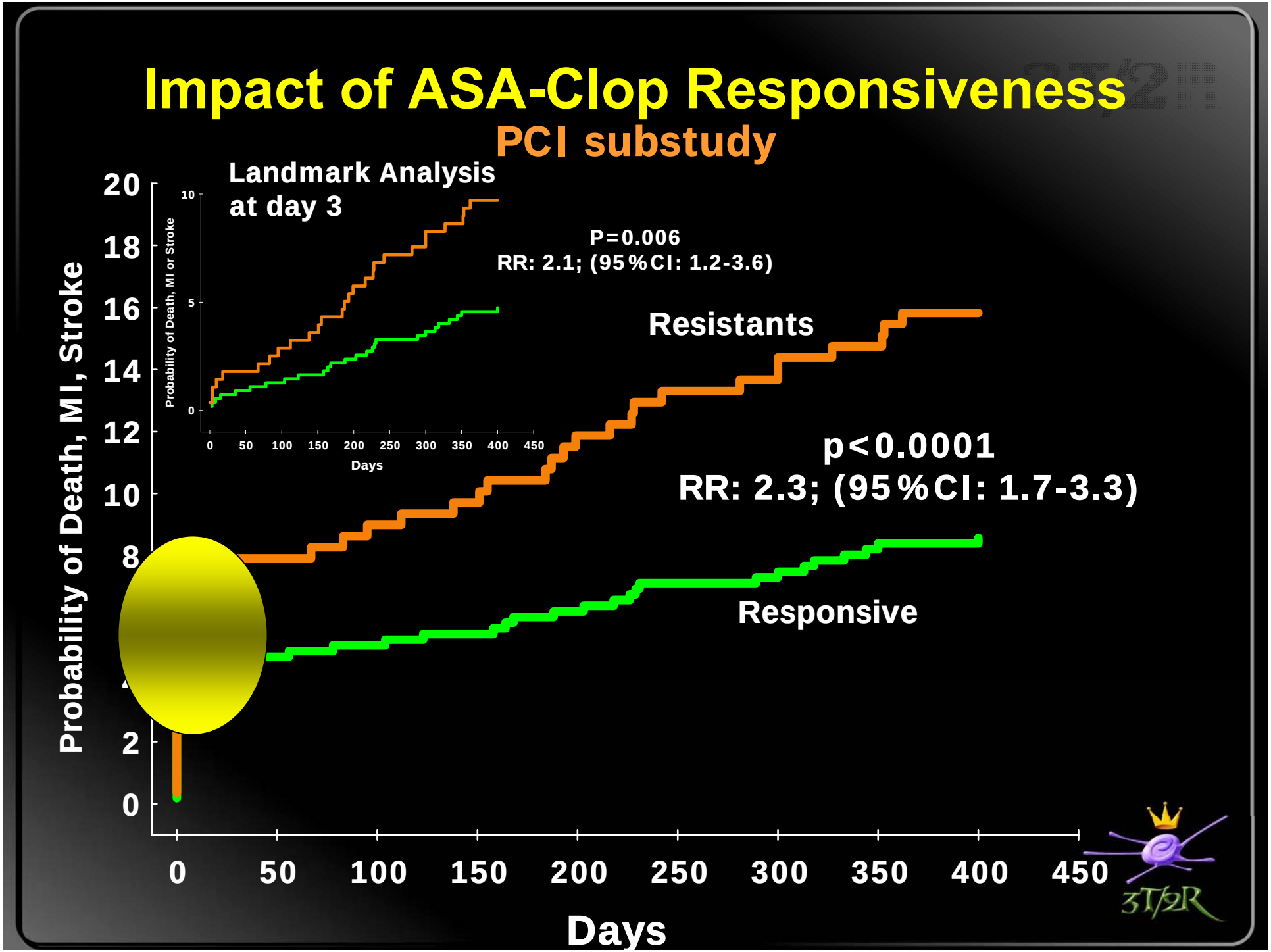
Rate of Peri >CK-MB×3 based on responsiveness status and use of GPI

In the non-randomized cohort GPI was used in 11% of patients



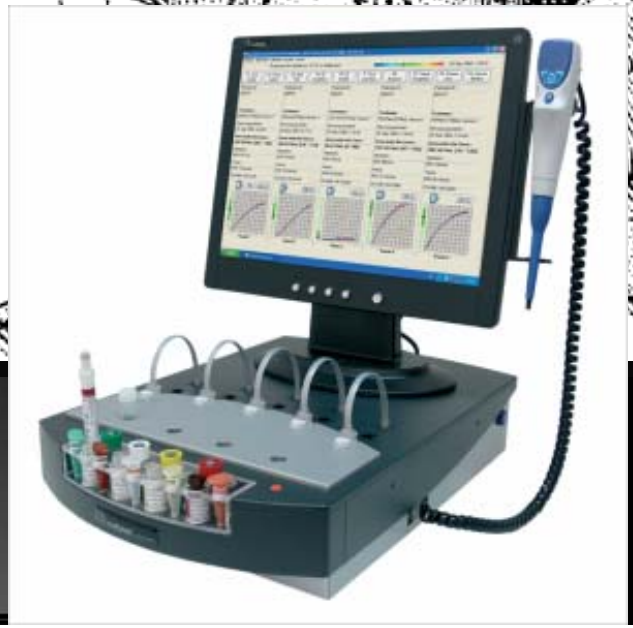
Impact of ASA-Clop Responsiveness

PCI substudy



The knowledge and art of Tailoring

Phenotype



Genotype