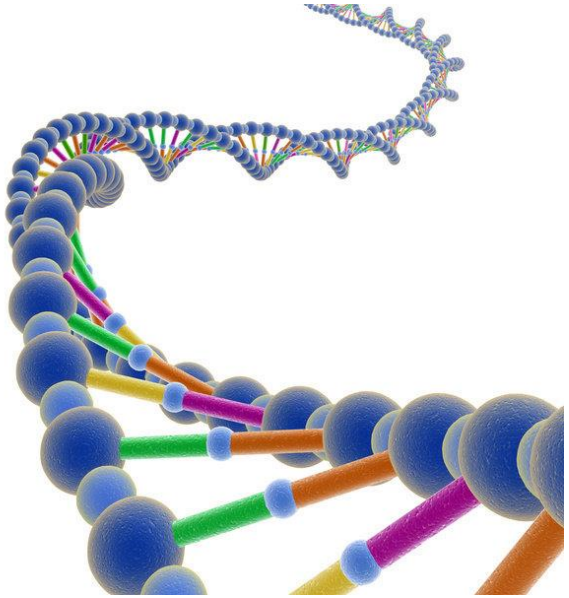
Do We Need Genotyping for Antiplatelet Therapy? : Pros



분당서울대학교병원 순환기내과 서정원

Division of Cardiology, Department of Internal Medicine,
Seoul National University Bundang Hospital

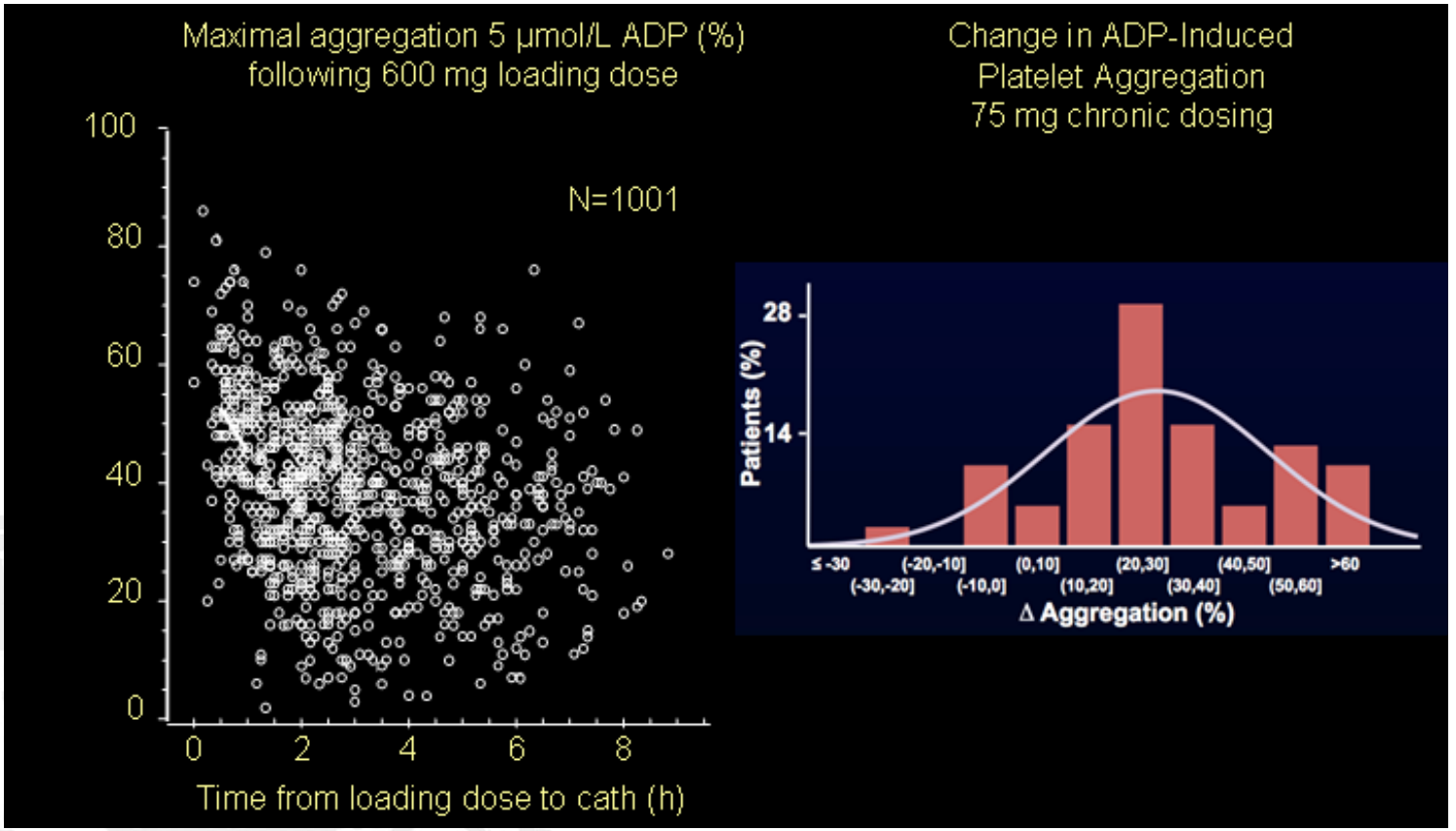
분당서울대학교병원
SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

Contents

- Introduction
- Hyporesponsiveness to clopidogrel
- CYP2C19 genotype
  - Association with responsiveness to clopidogrel
  - Association with clinical outcomes in patients with CHD
- Tailored selection of antiplatelet agents
- Conclusion

The Myth of Procrustes' Bed

Platelet Reactivity Varies Widely Among Patients on Clopidogrel

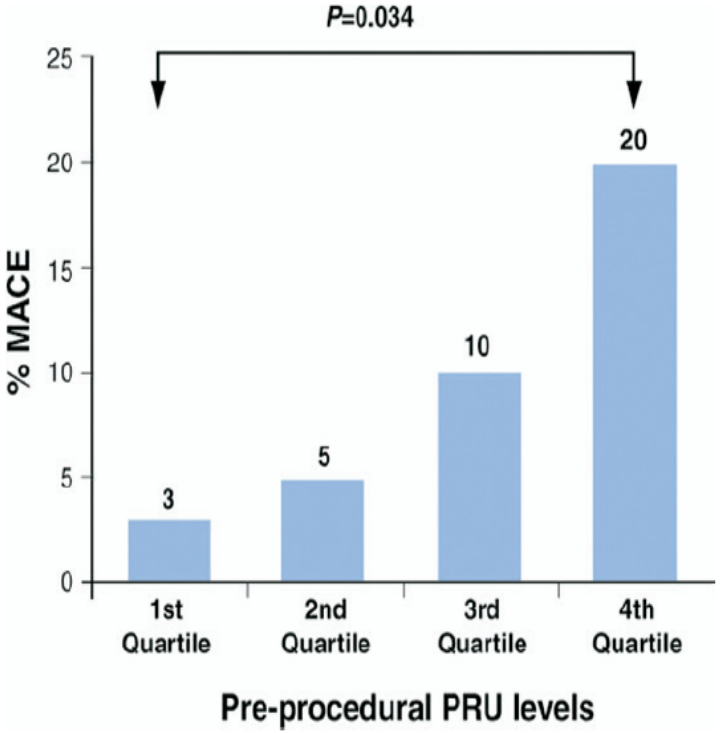


Hochholzer et al. *Circulation* 2005

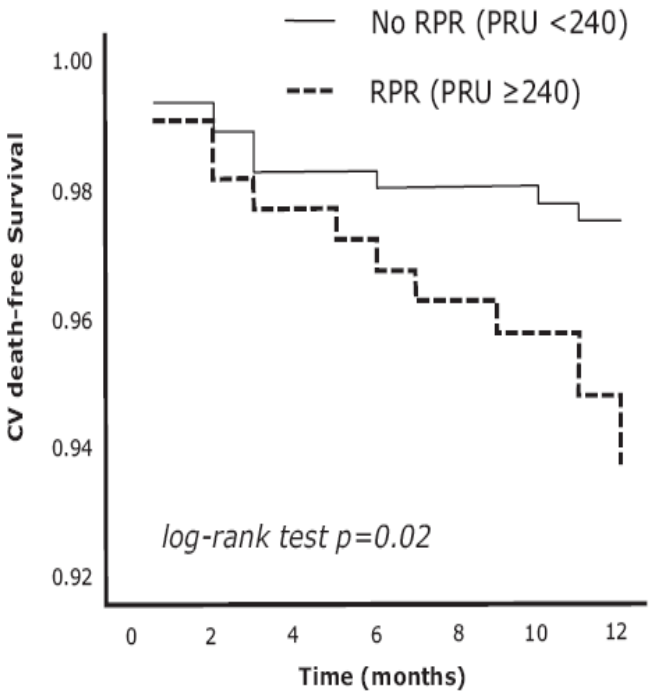
Gurbel P et al, *Circulation* 2003

High On (Post)-treament Platelet Teactivity (HOPR or HPPR)

Clinical Implication of HOPR in Caucasian Population



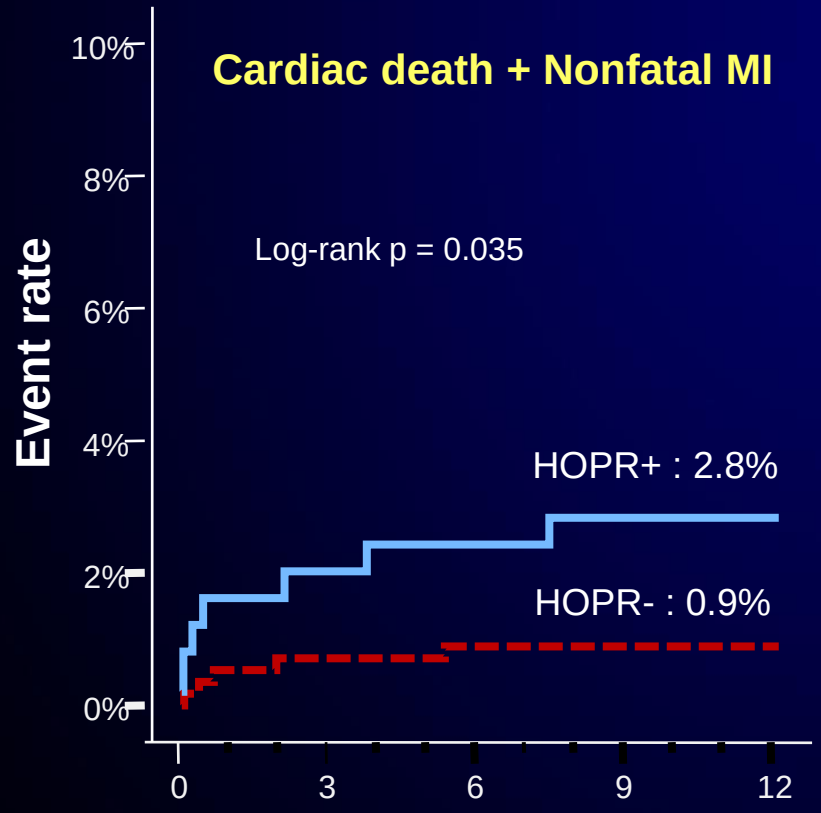
ARMYDA-PRO (JACC, 2008)



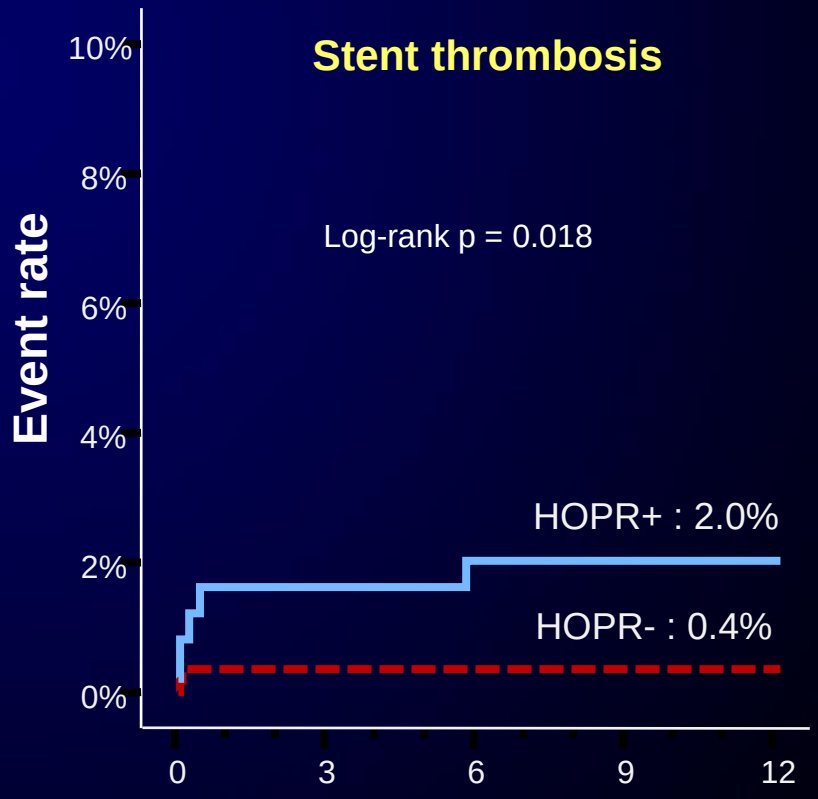
Marcucci, et al. Circulation, 2009

Clinical Implication of HOPR in Korean population

CROSS-VERIFY Registry



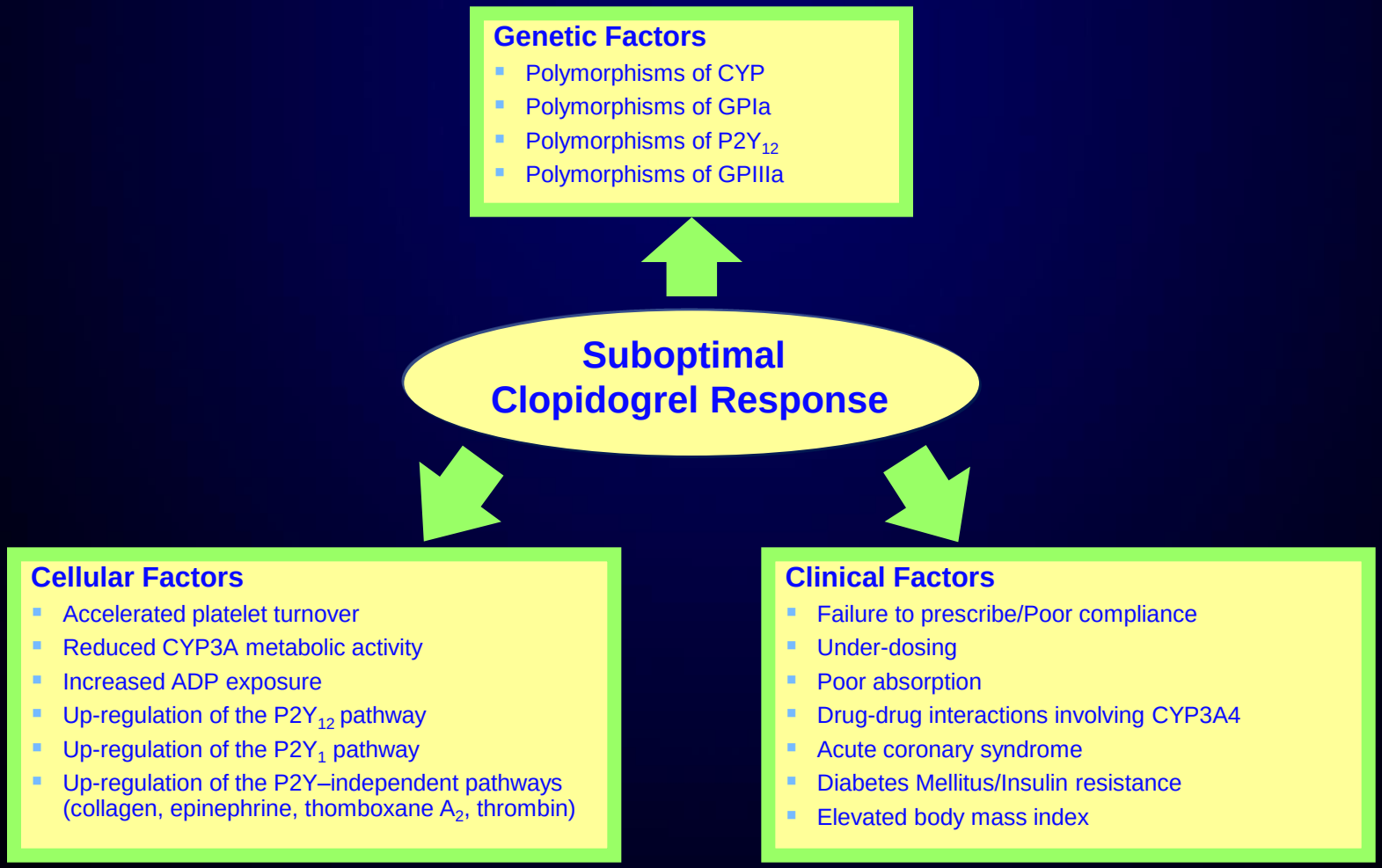
Patients at risks	Months after index procedure				
HOPR +	247	243	241	241	239
HOPR -	562	557	554	552	551



Patients at risks	Months after index procedure				
HOPR+	247	243	242	242	240
HOPR-	562	558	554	552	551

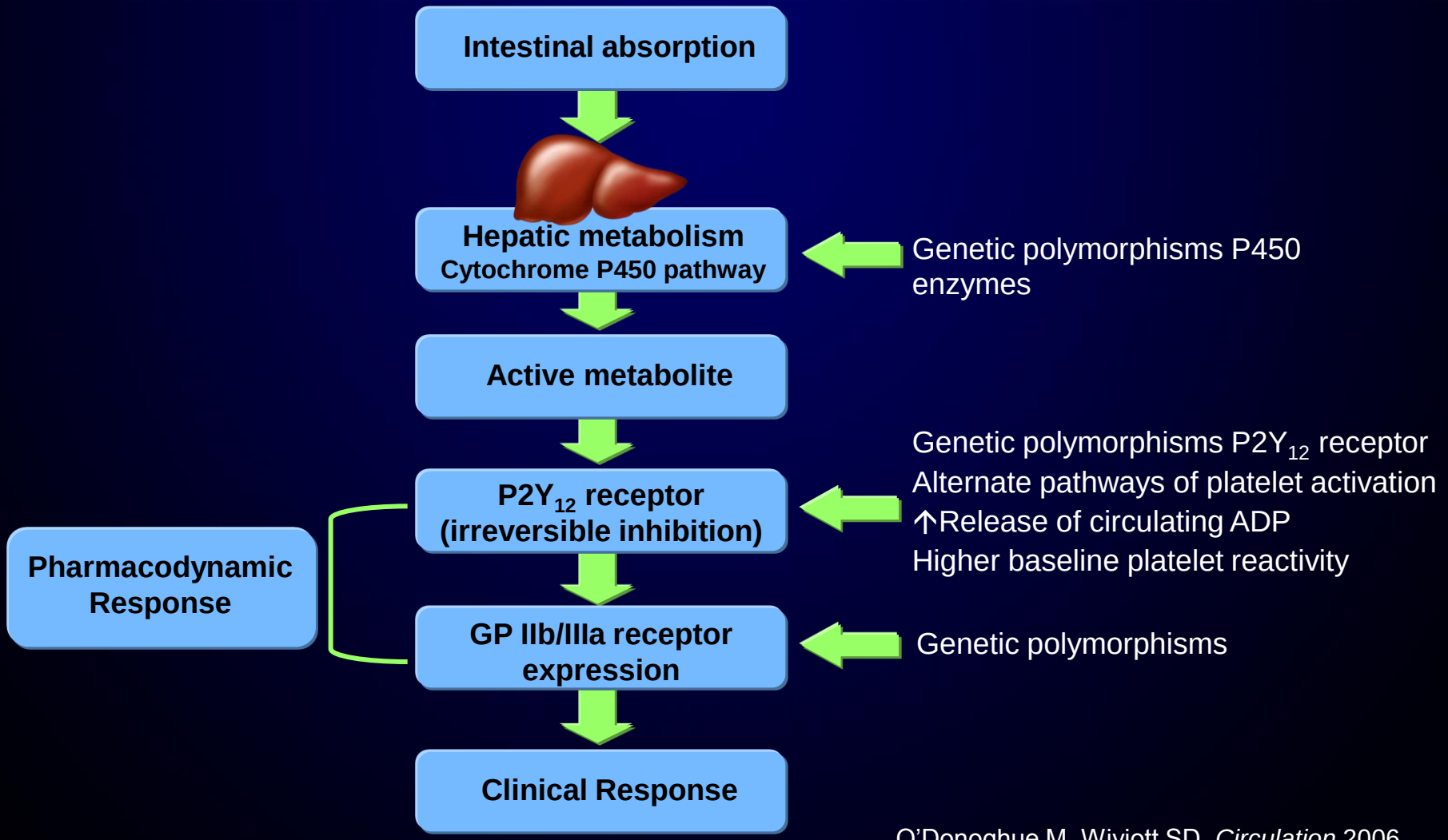
Park KW, Jeon KH, et al. Am J Cardiol. 2011

Mechanisms of Inter-individual Variability in Clopidogrel Responsiveness



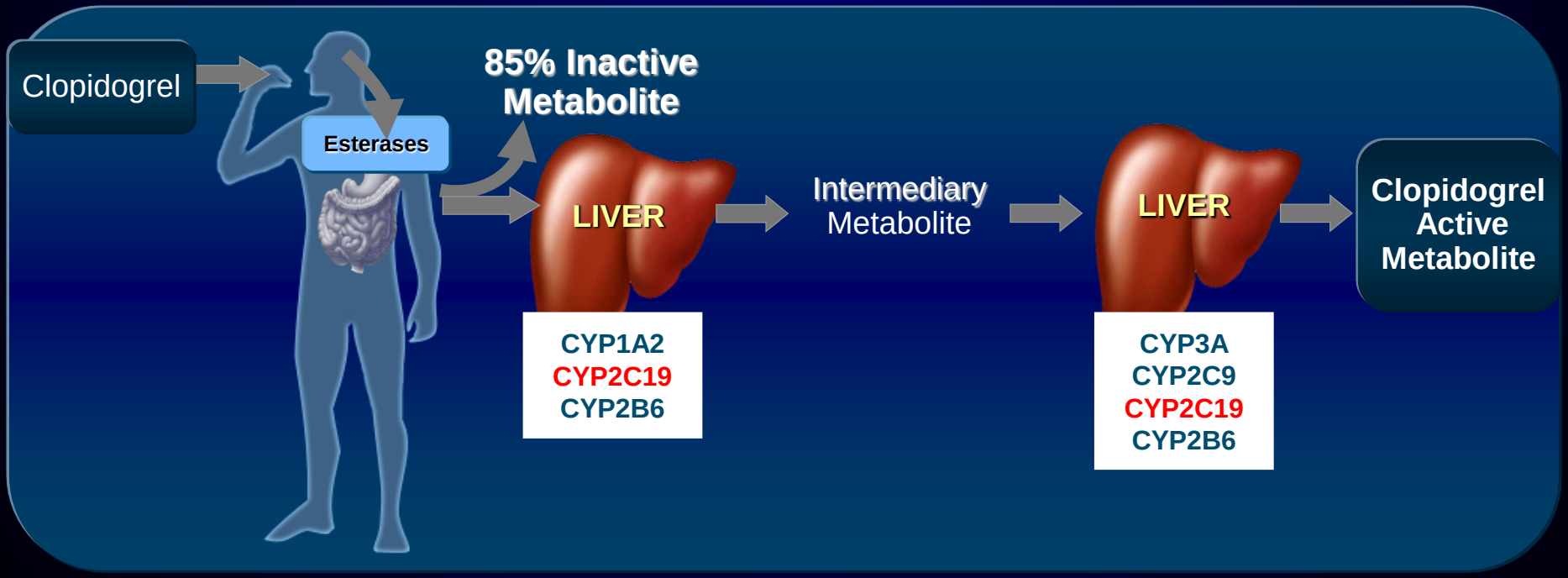
Angiolillio DJ et al. *J Am Coll Cardiol*. 2007;49:1505–16

Clopidogrel Metabolism Pathway



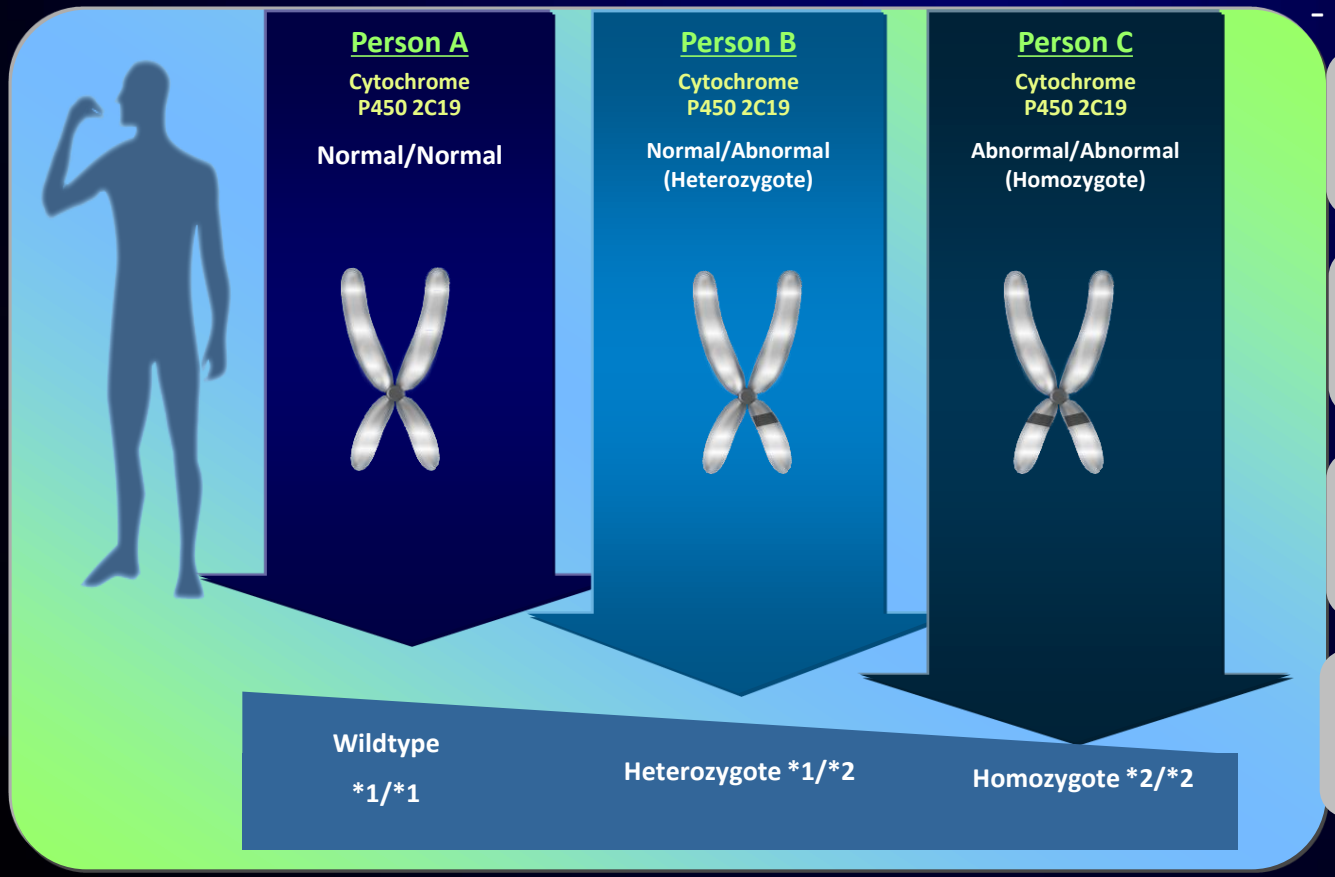
O'Donoghue M, Wiviott SD. *Circulation* 2006

Role of Cytochrome P450 system in the metabolism of clopidogrel



Cytochrome P450 2C19 Polymorphisms & Antiplatelet Effects

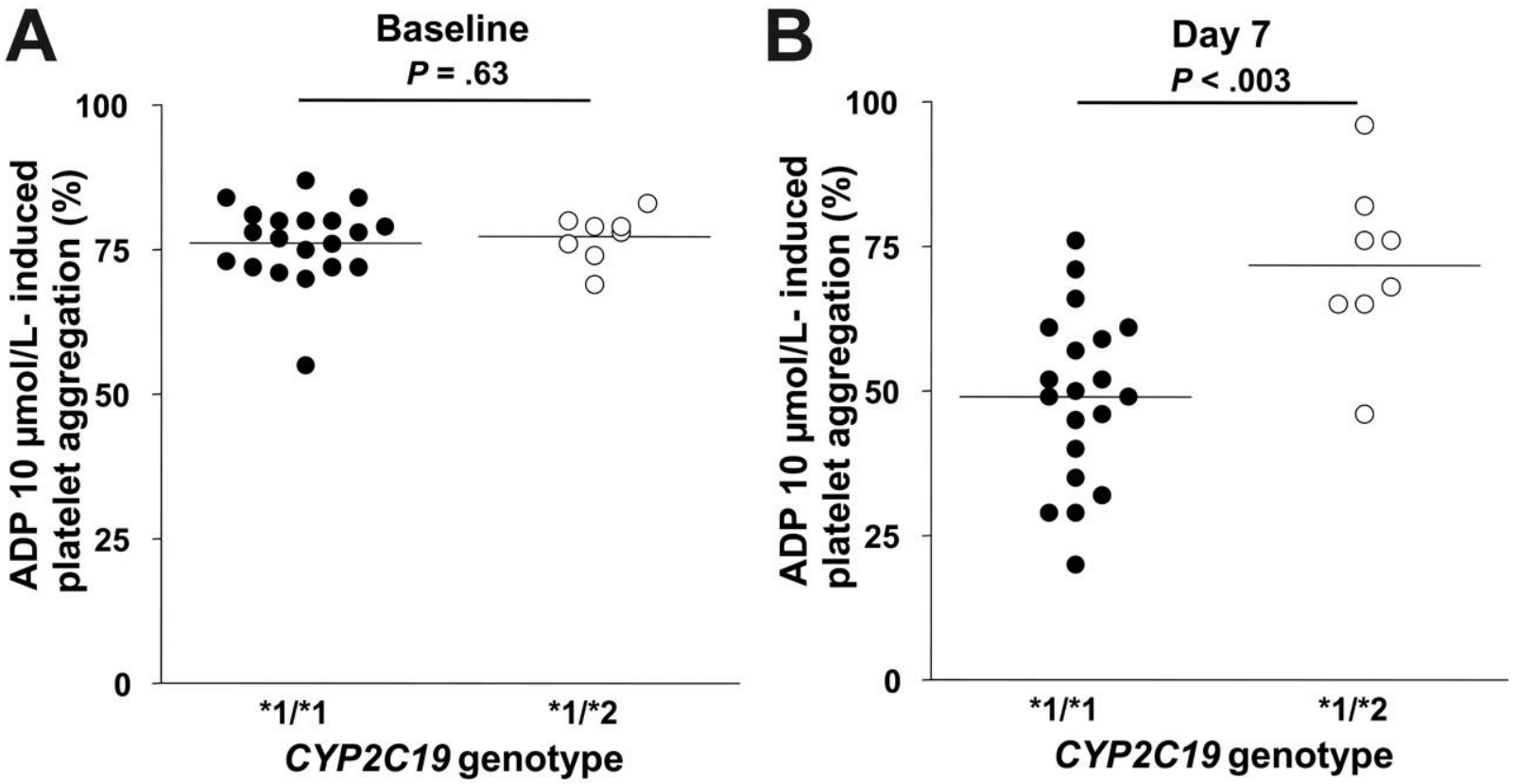
- Wild type (*1)
- Loss-of-function (*2, *3)
- Gain-of-function (*17)



Extensive metabolism	CYP2C19*1/*1
Intermediate metabolism	CYP2C19*1/*2 or *1/*3
Poor metabolism	CYP2C19*2/*2, *2/*3 or 3/*3 Also *4,*5
Ultrarapid	CYP2C19*17/*17,

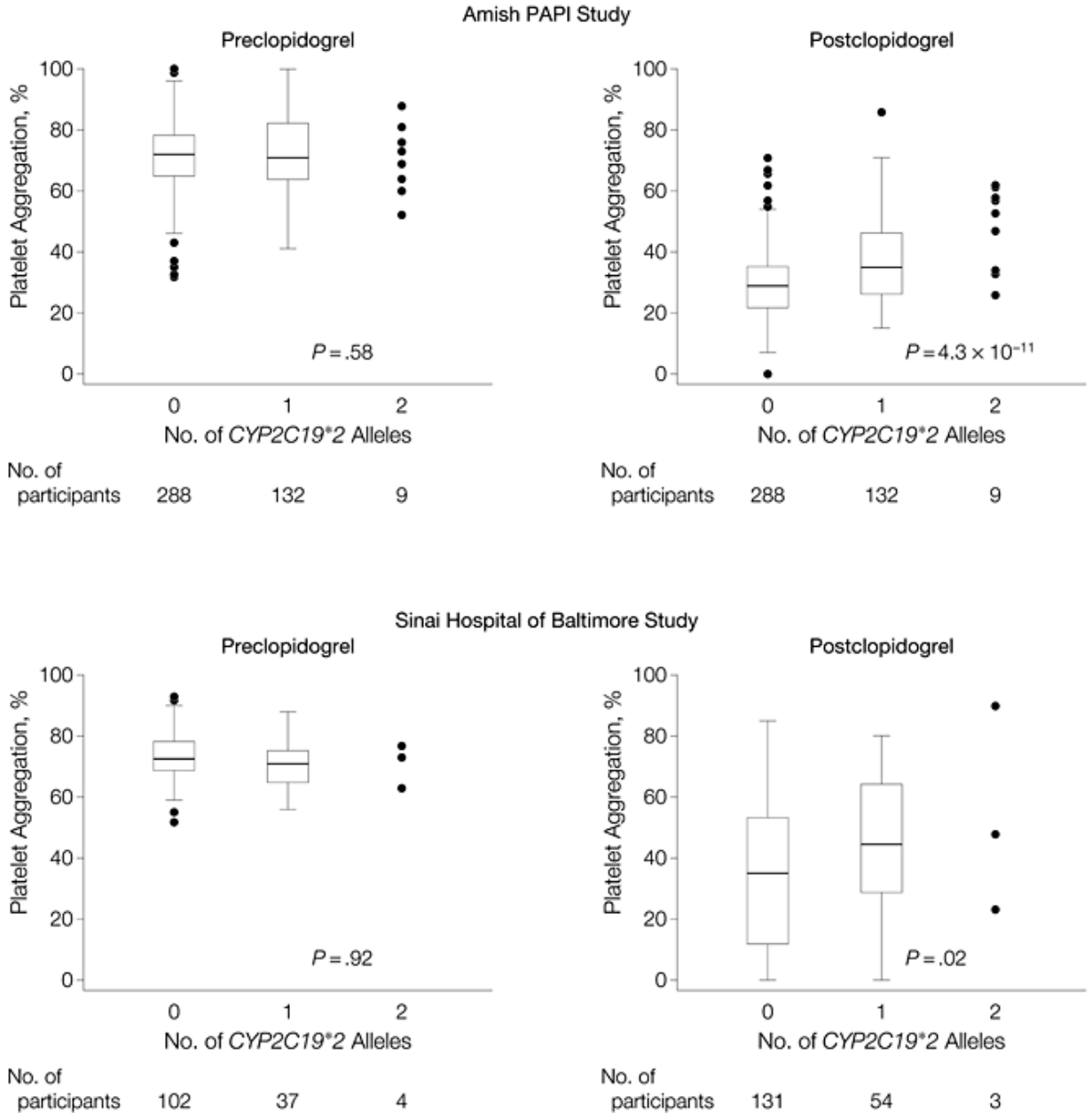
Kim KA, Park PW, Hong SJ, Park J-Y. *Clin Pharmacol Ther.* 2008;84:236–42

CYP2C19 LOF Polymorphism & Response to Clopidogrel



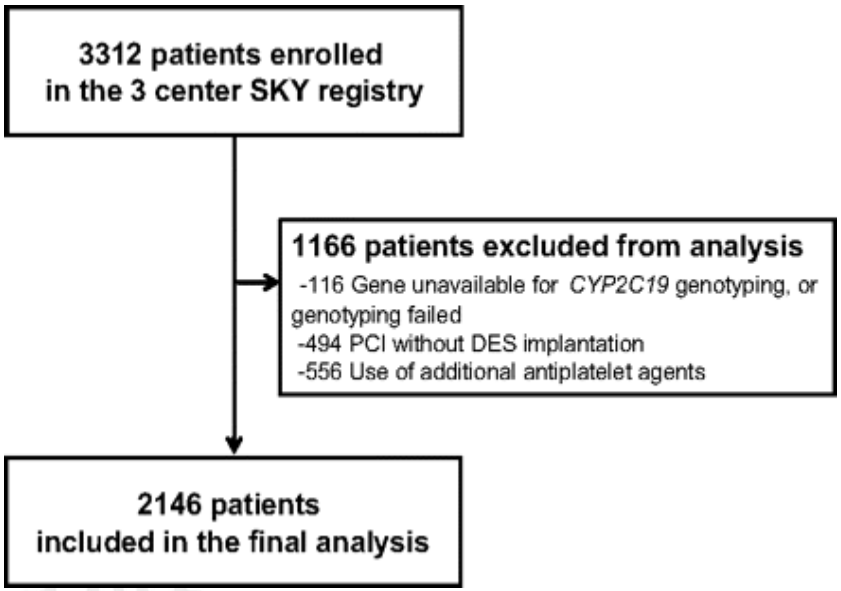
Hulot JS, et al. *Blood* 2006;108:2244-7

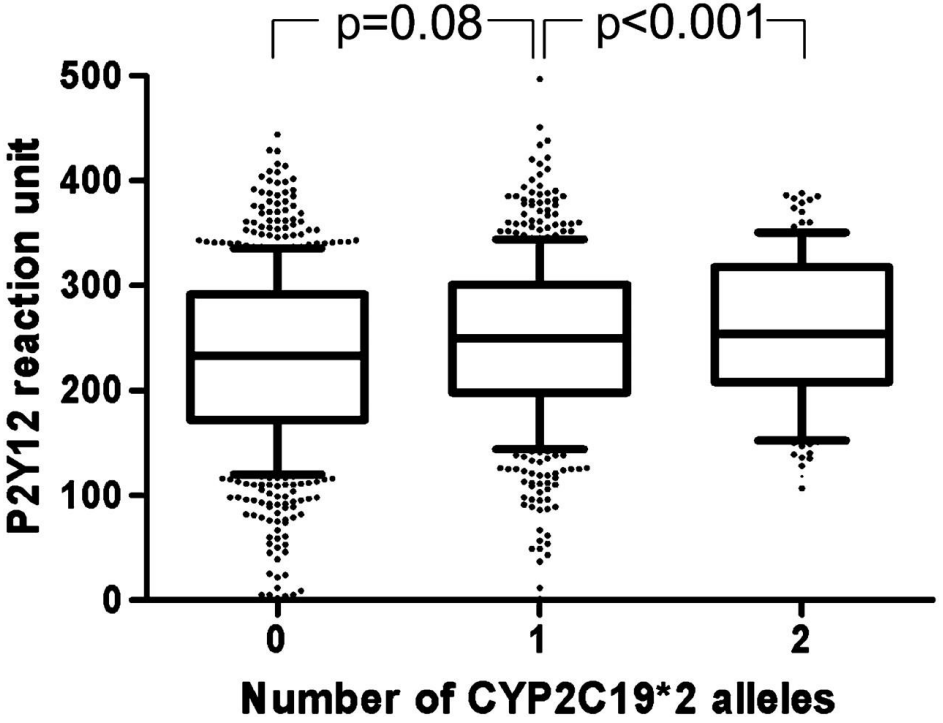
CYP2C19 LOF Polymorphism & Response to Clopidogrel



Shuldiner AR, et al. JAMA 2009;302:849-57

Korean Data : SKY registry





Oh IY, et al. Heart 2012;98:139-144

CYP2C19 polymorphism is associated with low responsiveness to clopidogrel, How about clinical outcomes?

Reduced-Function *CYP2C19* Genotype and Risk of Adverse Clinical Outcomes Among Patients Treated With Clopidogrel Predominantly for PCI

A Meta-analysis

Figure 1. Study Selection Flow Diagram

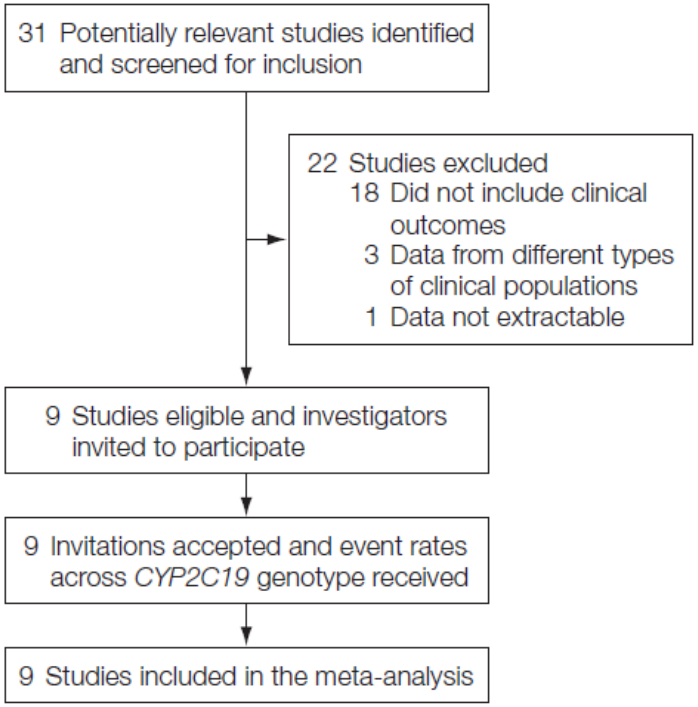


Table 2. Pooled Baseline Characteristics by *CYP2C19* Genotype Status[a]

	No. of Participants (%)[b]			
		Reduced-Function *CYP2C19* Alleles		
Characteristics	Overall (n = 9685)	None (n = 6923)	1 (n = 2544)	2 (n = 218)
Age, weighted mean, y	64.2	64.1	64.6	63.7
Male sex	7204 (74.4)	5180 (74.8)	1852 (72.8)	172 (78.9)
Diabetes	2724 (28.1)	1926 (27.8)	739 (29.0)	58 (27.1)
Current smoker	2524 (26.1)	1821 (26.3)	648 (25.5)	55 (25.2)
ACS at presentation	5278 (54.5)	3820 (55.2)	1339 (52.6)	119 (54.6)
PCI at presentation	8847 (91.3)	6336 (91.5)	2316 (91.0)	195 (89.4)
White race[c]	4781 (95.8)	3399 (95.9)	1277 (95.7)	105 (92.9)

Abbreviations: ACS, acute coronary syndrome; FAST-MI, French Registry of Acute ST-Segment Elevation and Non-ST-Elevation Myocardial Infarction; ISAR, Intracoronary Stenting and Antithrombotic Regimen; PCI, percutaneous coronary intervention.

[a] There were no significant differences for the categorical variables across *CYP2C19* genotype.

[b] Data are presented as No. of participants (%) unless otherwise indicated.

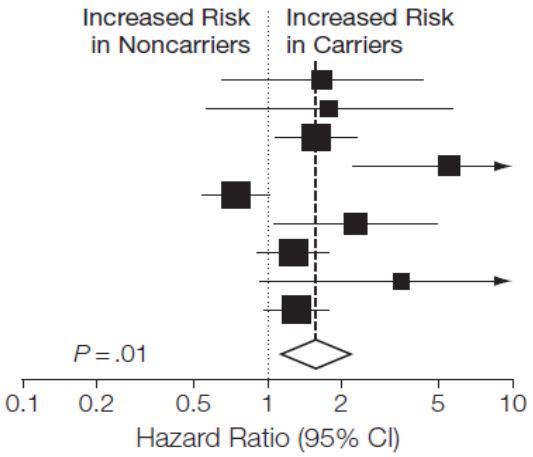
[c] Data on race (self-reported) were not captured uniformly in ISAR and FAST-MI (see footnotes c and d in Table 1). White race denominators for overall, none, 1, and 2 reduced-function *CYP2C19* alleles are 4992, 3545, 1334, and 113, respectively.

JAMA. 2010;304(16):1821-1830

Cardiovascular death, MI, or ischemic stroke by CYP2C19 genotype

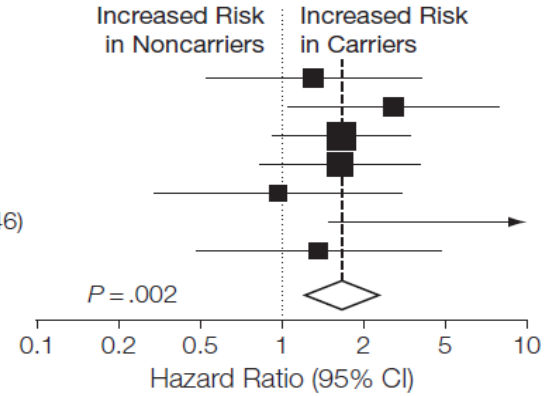
B Carriers of 1 *CYP2C19* Reduced-Function Alleles vs Noncarriers

	CYP2C19 Reduced-Function Alleles, No. of Events/ No. of Individuals at Risk		Hazard Ratio (95% CI)
	1	None	
CLARITY-TIMI 28	8/73	10/150	1.64 (0.65-4.17)
EXCELSIOR	5/226	7/554	1.75 (0.56-5.53)
TRITON-TIMI 38	42/357	83/1064	1.55 (1.07-2.25)
AFIJI	13/64	11/186	5.42 (2.23-13.18)
FAST-MI	53/577	193/1573	0.73 (0.54-0.99)
RECLOSE	13/221	14/525	2.25 (1.06-4.78)
ISAR	52/633	119/1805	1.25 (0.90-1.73)
CLEAR-PLATELETS	5/63	4/160	3.45 (0.93-12.89)
Intermountain	65/330	141/906	1.29 (0.96-1.73)
Overall	**256/2544**	**582/6923**	**1.55 (1.11-2.17)**



C Carriers of 2 *CYP2C19* Reduced-Function Alleles vs Noncarriers

	CYP2C19 Reduced-Function Alleles, No. of Events/ No. of Individuals at Risk		Hazard Ratio (95% CI)
	2	None	
TRITON-TIMI 38	4/38	83/1064	1.35 (0.49-3.69)
AFIJI	2/9	11/186	2.85 (1.07-7.59)
FAST-MI	10/58	193/1573	1.75 (0.92-3.32)
RECLOSE	2/26	14/525	1.73 (0.83-3.62)
ISAR	3/47	119/1805	0.96 (0.30-3.04)
CLEAR-PLATELETS	1/5	4/160	14.27 (1.57-129.46)
Intermountain	3/14	141/906	1.41 (0.45-4.41)
Overall	**25/197**	**565/6219**	**1.76 (1.24-2.50)**

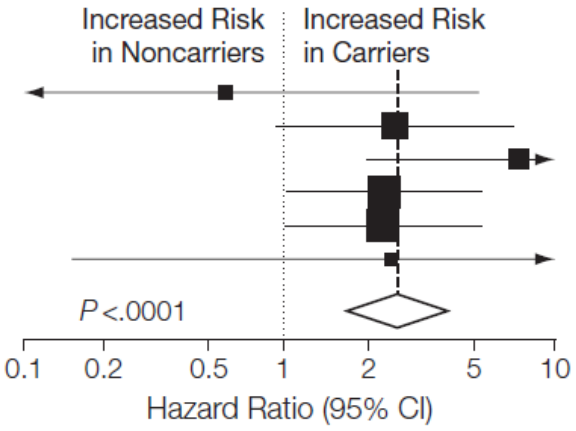


JAMA. 2010;304(16):1821-1830

Stent thrombosis by CYP2C19 genotype

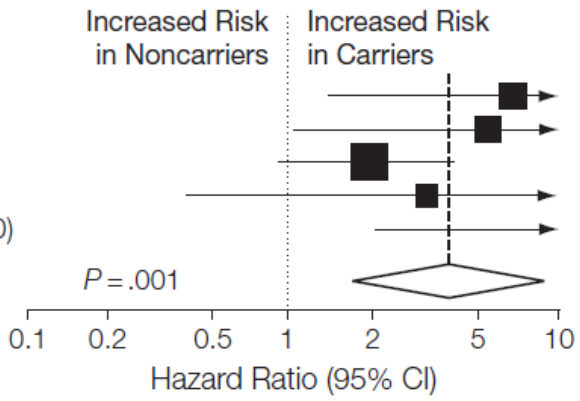
B Carriers of 1 *CYP2C19* Reduced-Function Alleles vs Noncarriers

	CYP2C19 Reduced-Function Alleles, No. of Events/ No. of Individuals at Risk		Hazard Ratio (95% CI)
	1	None	
EXCELSIOR	1/226	4/554	0.61 (0.07-5.44)
TRITON-TIMI 38	7/339	8/1014	2.65 (0.96-7.30)
AFIJI	7/53	4/162	7.75 (2.10-28.60)
RECLOSE	11/221	11/525	2.41 (1.05-5.55)
ISAR	10/633	12/1805	2.39 (1.03-5.54)
CLEAR-PLATELETS	1/63	1/160	2.57 (0.16-40.99)
Overall	**37/1535**	**40/4220**	**2.67 (1.69-4.22)**



C Carriers of 2 *CYP2C19* Reduced-Function Alleles vs Noncarriers

	CYP2C19 Reduced-Function Alleles, No. of Events/ No. of Individuals at Risk		Hazard Ratio (95% CI)
	2	None	
TRITON-TIMI 38	2/36	8/1014	6.79 (1.42-32.53)
AFIJI	1/8	4/162	5.46 (1.05-28.38)
RECLOSE	2/26	11/525	1.95 (0.92-4.13)
ISAR	1/47	12/1805	3.21 (0.42-24.60)
CLEAR-PLATELETS	1/5	1/160	34.41 (2.15-551.50)
Overall	**7/122**	**36/3666**	**3.97 (1.75-9.02)**

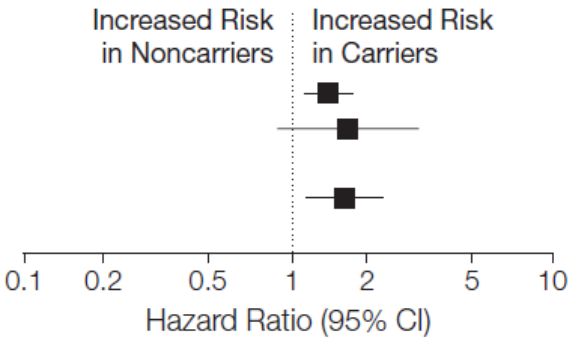


JAMA. 2010;304(16):1821-1830

Timing of Events for CV Death, MI, or Ischemic Stroke and Stent Thrombosis

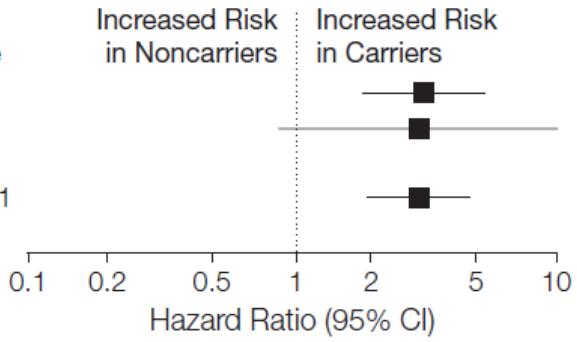
Cardiovascular Death, Myocardial Infarction, or Stroke

	CYP2C19 Reduced-Function Alleles, No. of Events/ No. of Individuals at Risk		Hazard Ratio (95% CI)	Overall *P* Value
	1 or 2	None		
0 to 30 Days	183/2762	348/6923	1.36 (1.11-1.65)	.003
31 Days to end of follow-up	113/1712	246/4316	1.61 (0.88-2.94)	.123
0 Days to end of follow-up	281/2762	582/6923	1.57 (1.13-2.16)	.006



Stent Thrombosis

	CYP2C19 Reduced-Function Alleles, No. of Events/ No. of Individuals at Risk		Hazard Ratio (95% CI)	Overall *P* Value
	1 or 2	None		
0 to 30 Days	32/1674	28/4220	2.94 (1.75-4.94)	<.0001
31 Days to end of follow-up	12/820	13/2023	2.80 (0.83-9.39)	.096
0 Days to end of follow-up	44/1674	40/4220	2.81 (1.81-4.37)	<.00001



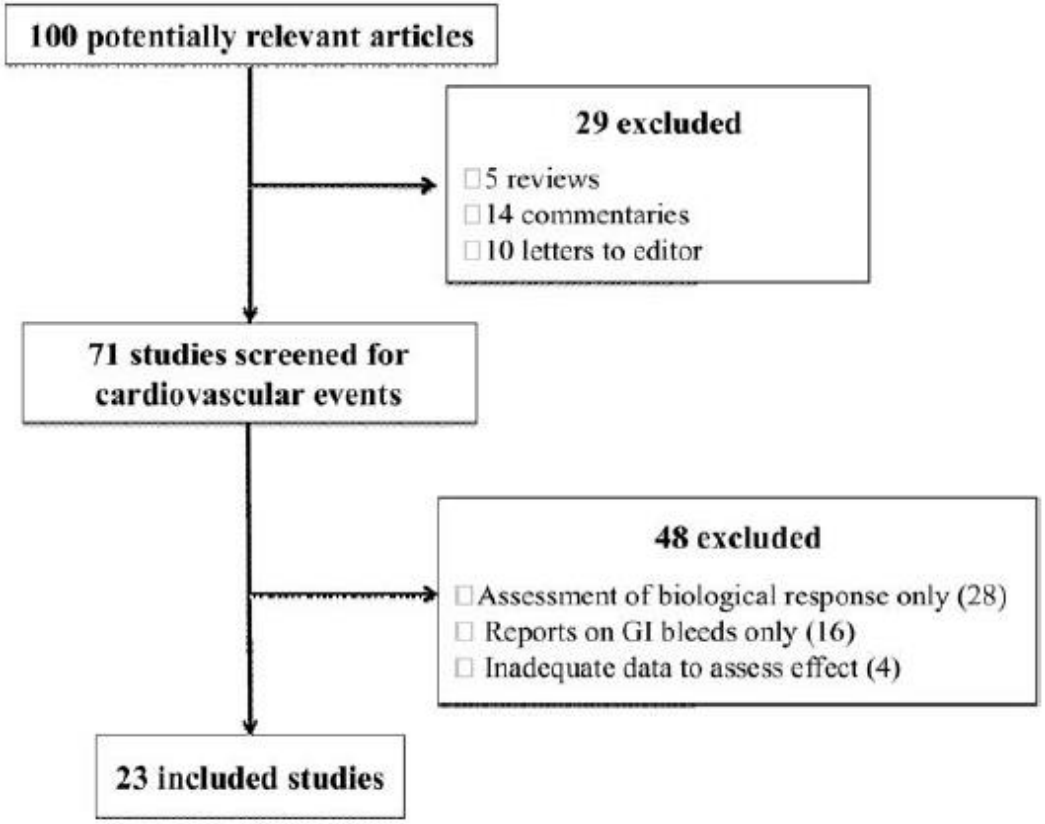
JAMA. 2010;304(16):1821-1830

Cardiovascular Risk in Clopidogrel-Treated Patients According to Cytochrome P450 2C19*2 Loss-of-Function Allele or Proton Pump Inhibitor Coadministration

A Systematic Meta-Analysis

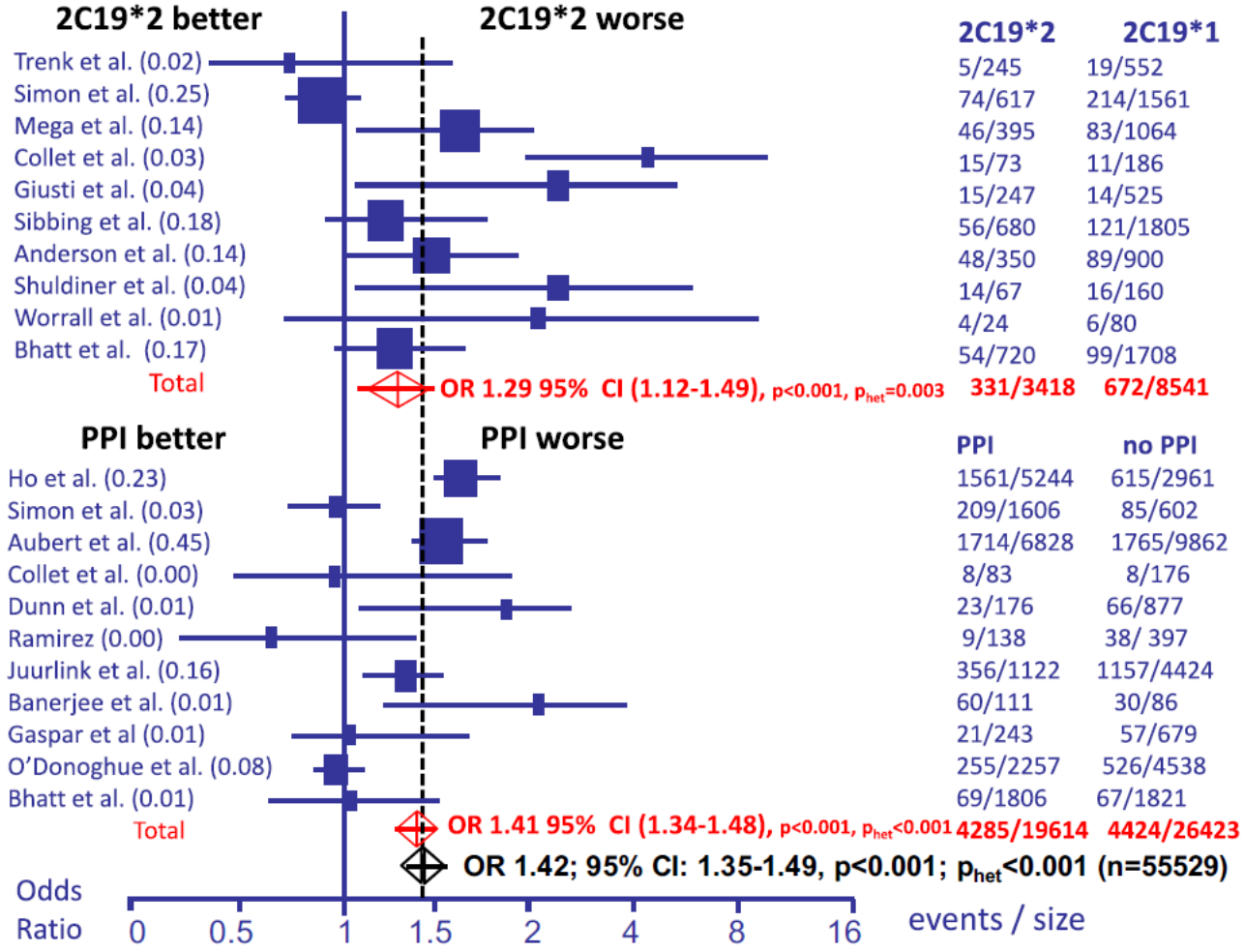
Jean-Sébastien Hulot, MD, PHD,* Jean-Philippe Collet, MD, PHD,† Johanne Silvain, MD,† Ana Pena, PHD,† Anne Bellemain-Appaix, MD,† Olivier Barthélémy, MD,† Guillaume Cayla, MD,† Farzin Beygui, MD, PHD,† Gilles Montalescot, MD, PHD†

Paris, France



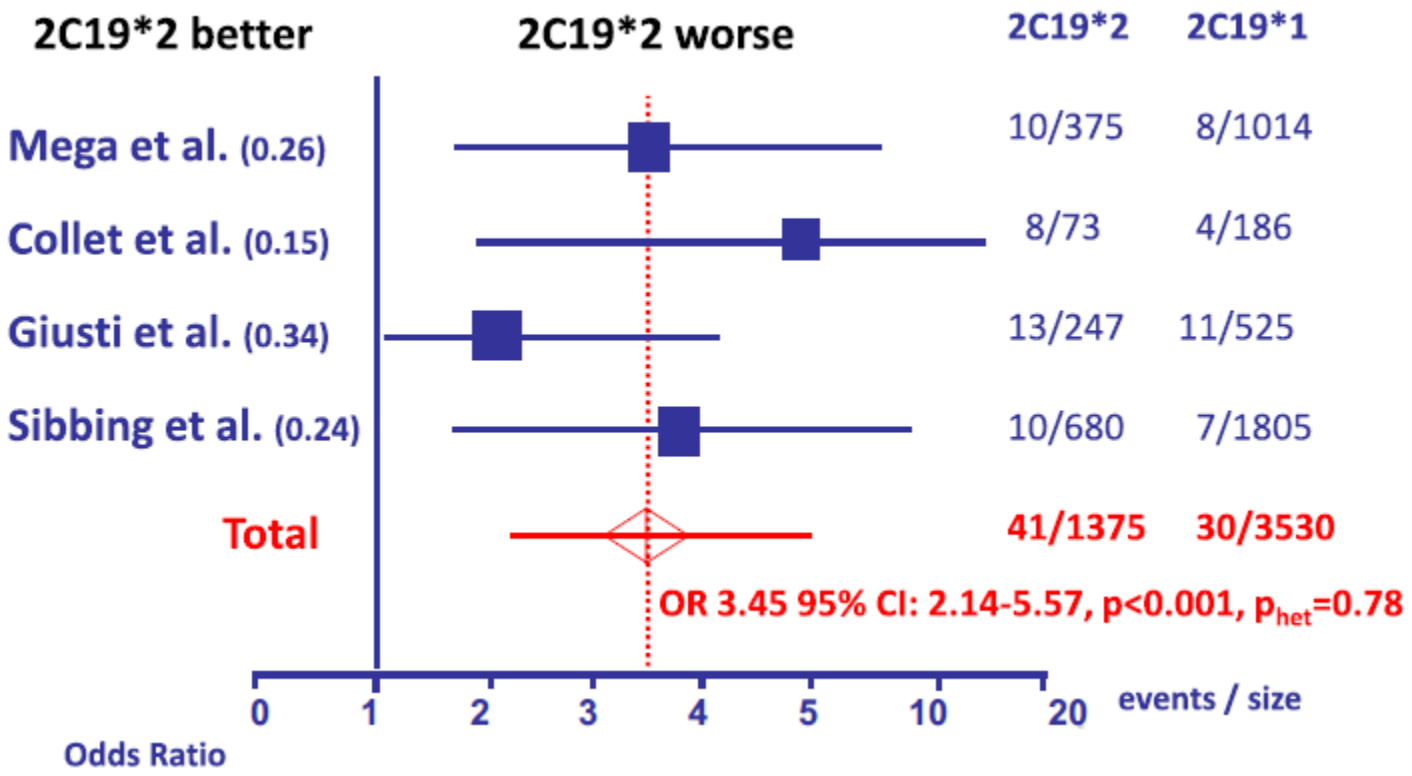
JACC Vol. 56, No. 2, 2010
July 6, 2010:134–43

ORs for MACE According to CYP2C19*2 Allele (n=11,959) and PPI use (n=46,037)



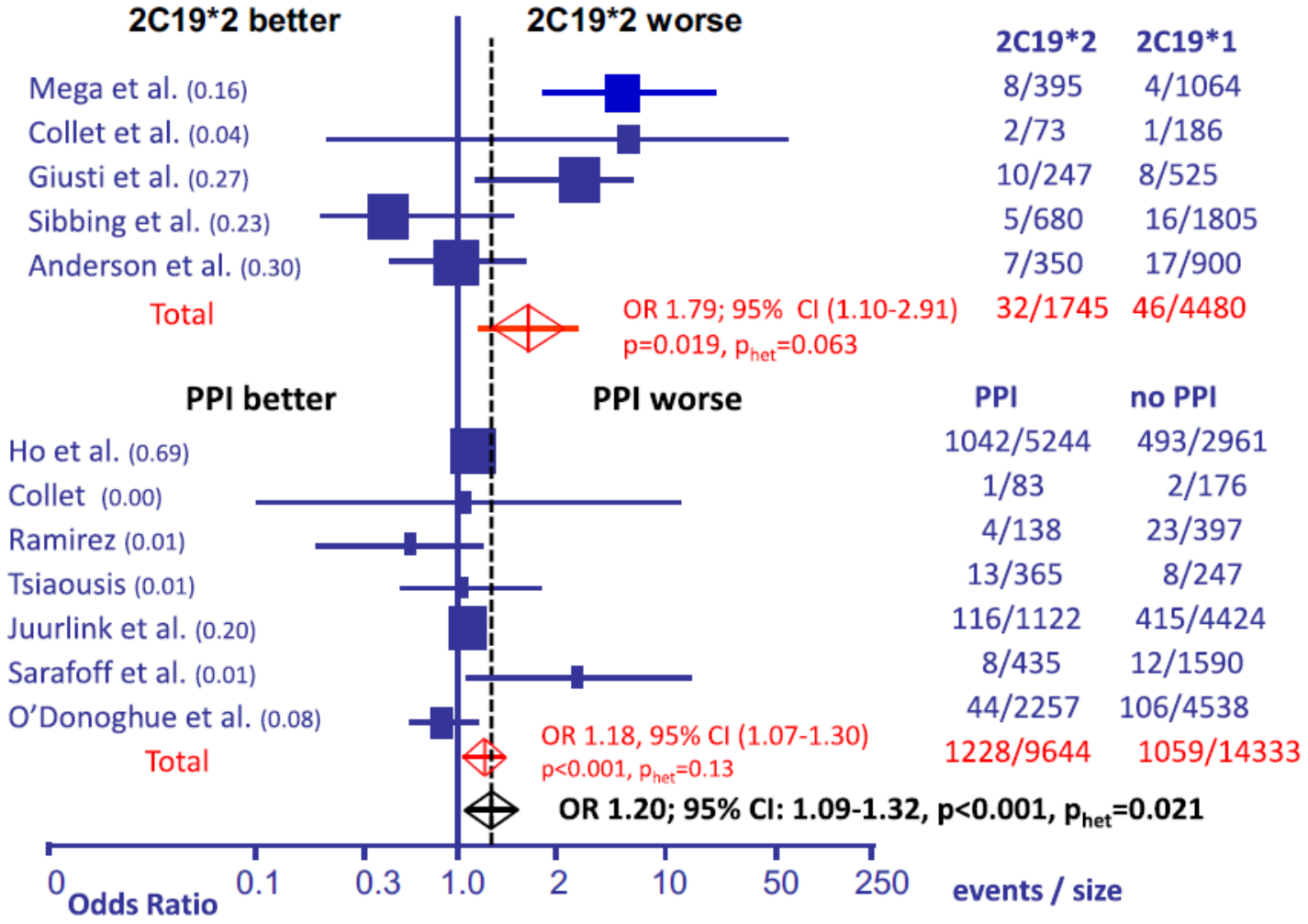
JACC Vol. 56, No. 2, 2010
July 6, 2010:134–43

ORs for Stent Thrombosis (n=4,905) According to CYP2C19*2 Allele



JACC Vol. 56, No. 2, 2010
July 6, 2010:134–43

ORs for Death According to CYP2C19*2 Allele (n=6,225) and PPI Use (n=23,997)



JACC Vol. 56, No. 2, 2010
July 6, 2010:134–43

CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events

A Systematic Review and Meta-analysis

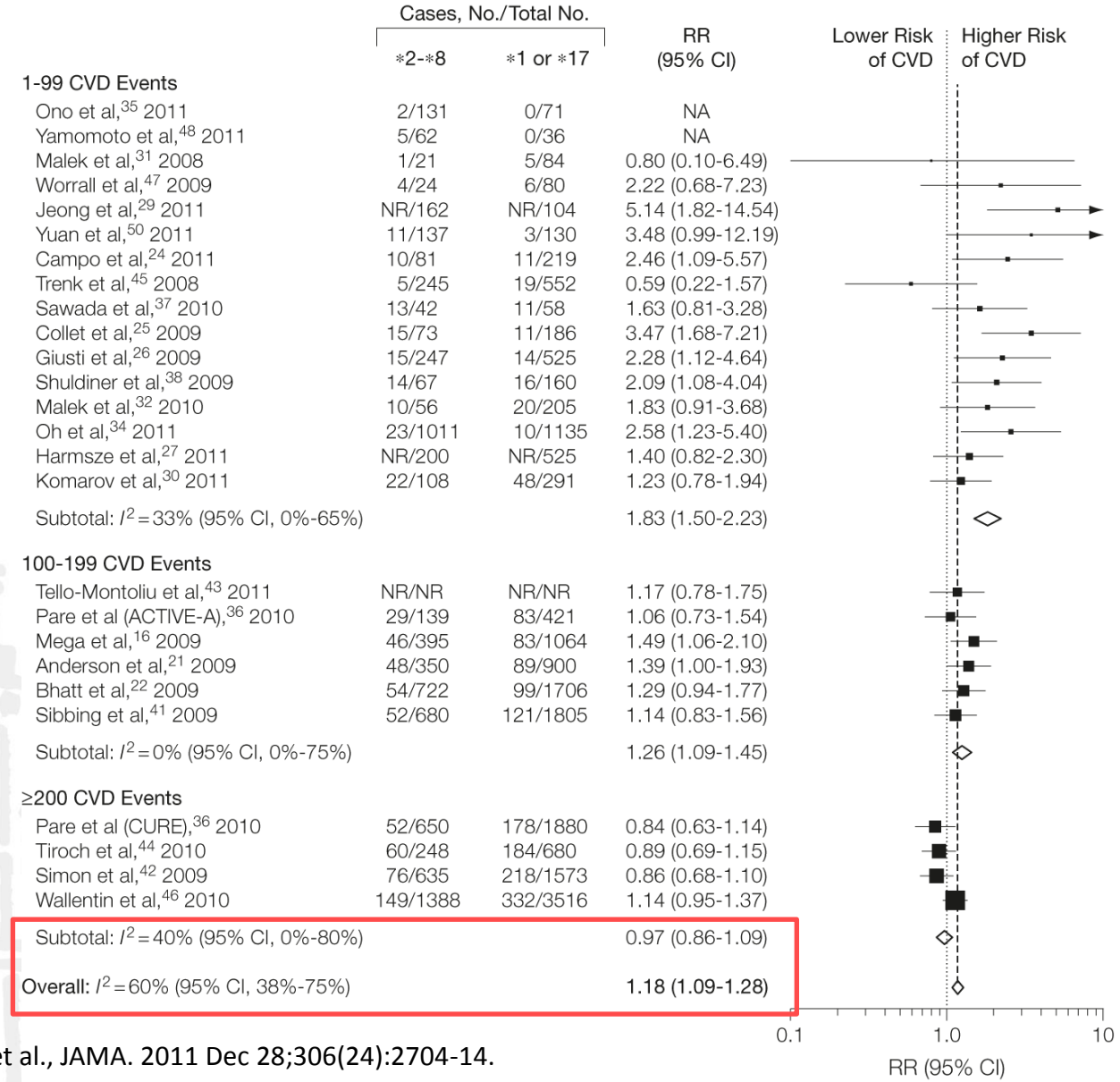
- 32 studies of 42,016 patients
  - 3545 CVD events
  - 579 STs
  - 1413 bleeding events

✓ 6 studies were randomized trials (“effect modification” design)

✓ 26 reported individuals exposed to clopidogrel ("treatment-only" design).

JAMA. 2011;306(24):2704-2714

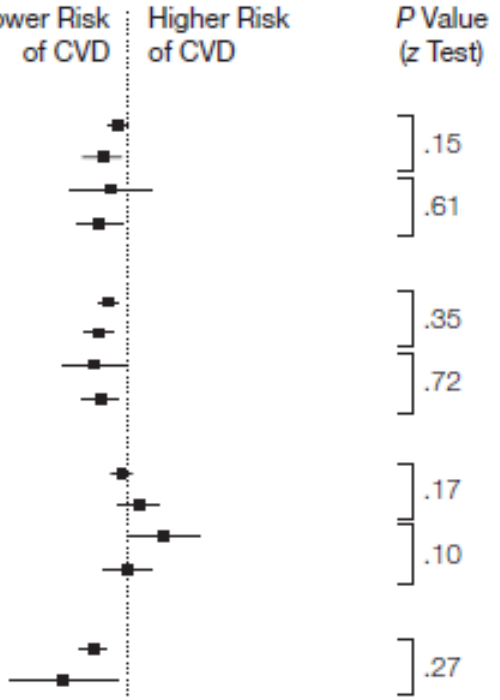
CYP2C19 Genotype and Clinical Outcomes: Treatment-Only Analysis



Holmes MV et al., JAMA. 2011 Dec 28;306(24):2704-14.

CYP2C19 Genotype and Clinical Outcomes: Effect-Modification Analysis

Trial	Cases, No./Total No. Clopidogrel	Cases, No./Total No. Placebo	RR (95% CI)	*P* Value (*z* Test)
ACTIVE-A[36, 54]				
Original RCT	832/3772	924/3782	0.89 (0.81-0.98)	.15
Genetic substudy	112/560	153/574	0.75 (0.61-0.93)	
*2 or *3	29/139	35/139	0.83 (0.54-1.28)	.61
*1 or *17	83/421	118/435	0.73 (0.57-0.93)	
CURE[19, 36]				
Original RCT	582/6259	719/6303	0.80 (0.72-0.90)	.35
Genetic substudy	230/2530	311/2486	0.73 (0.62-0.85)	
*2 or *3	52/650	78/673	0.69 (0.49-0.96)	.72
*1 or *17	178/1880	233/1813	0.74 (0.61-0.89)	
CHARISMA[20, 22]				
Original RCT	534/7802	573/7801	0.93 (0.83-1.05)	.17
Genetic substudy	153/2428	138/2434	1.11 (0.89-1.39)	
*2 or *3	54/722	36/708	1.47 (0.98-2.21)	.10
*1 or *17	99/1706	102/1726	0.98 (0.75-1.28)	
CLARITY-TIMI 28[33, 53]				
Original RCT	262/1752	377/1739	0.69 (0.60-0.80)	.27
Genetic substudy	NR/NR	NR/NR	0.49 (0.28-0.88)	



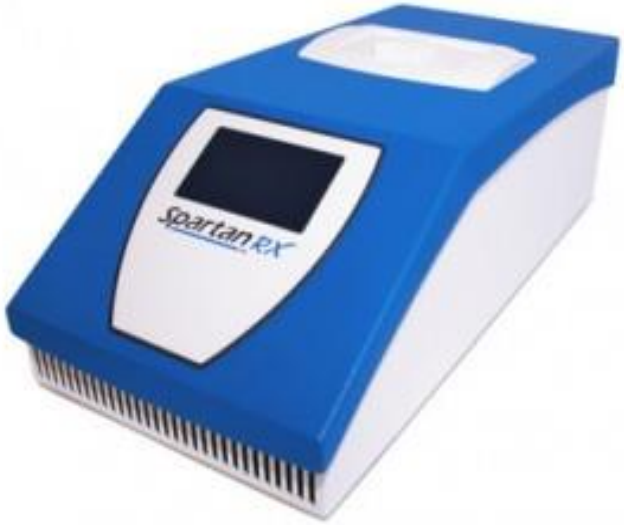
Overall, there was no significant association of CYP2C19 genotype with cardiovascular events.

Holmes MV et al., JAMA. 2011 Dec 28;306(24):2704-14.

Limitation

- The analysis included patients in whom there is relatively little to no benefit of clopidogrel.
- The current meta-analysis included outcomes that occurred in patients who were no longer taking clopidogrel.
- It included outcomes such as elective TLR and non-CV death, in which clopidogrel has no clear effect.
- Conversely, the authors excluded studies that focused solely on ST, even though this outcome is clinically important.

Point-of-care genetic testing



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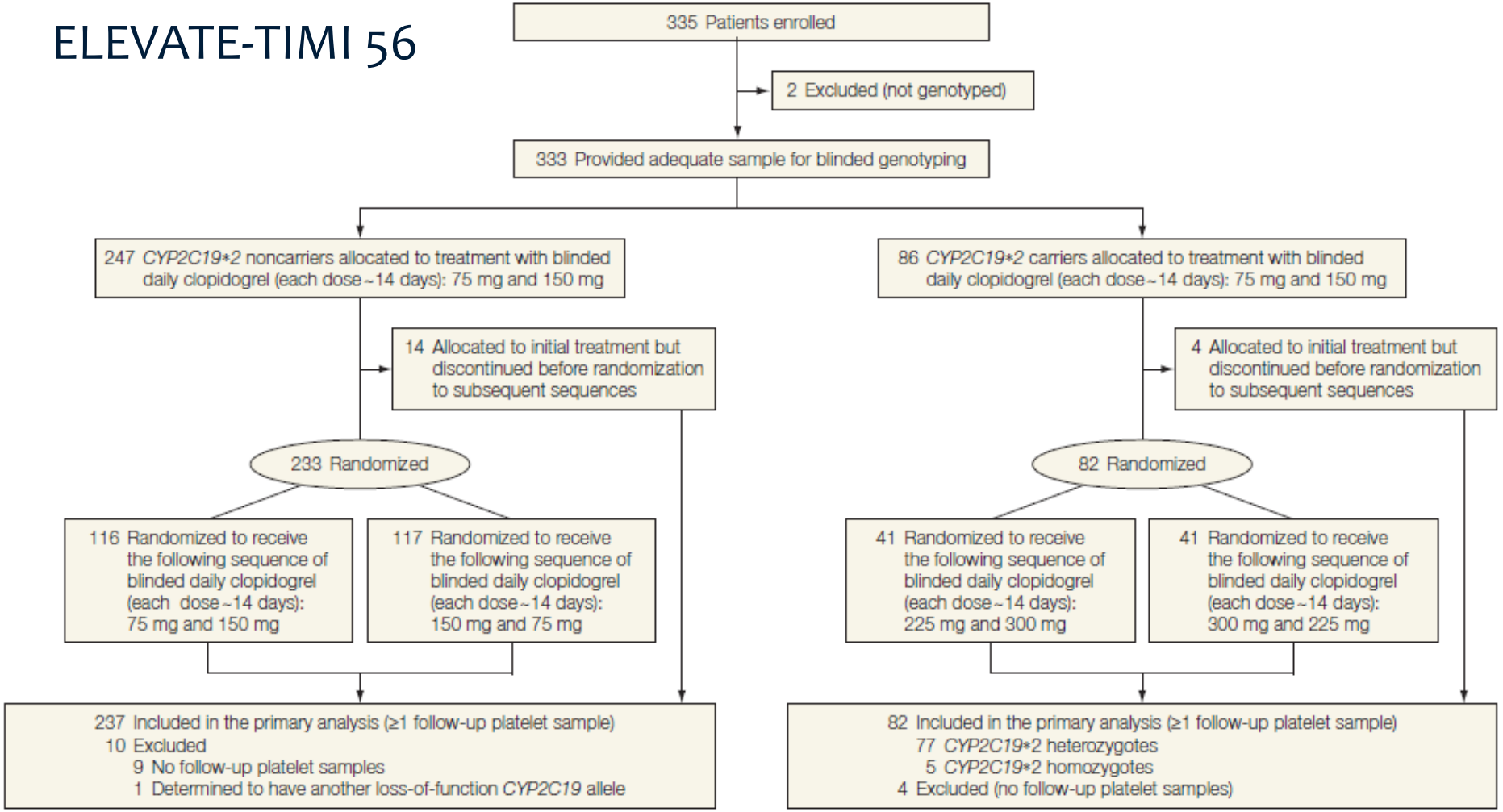
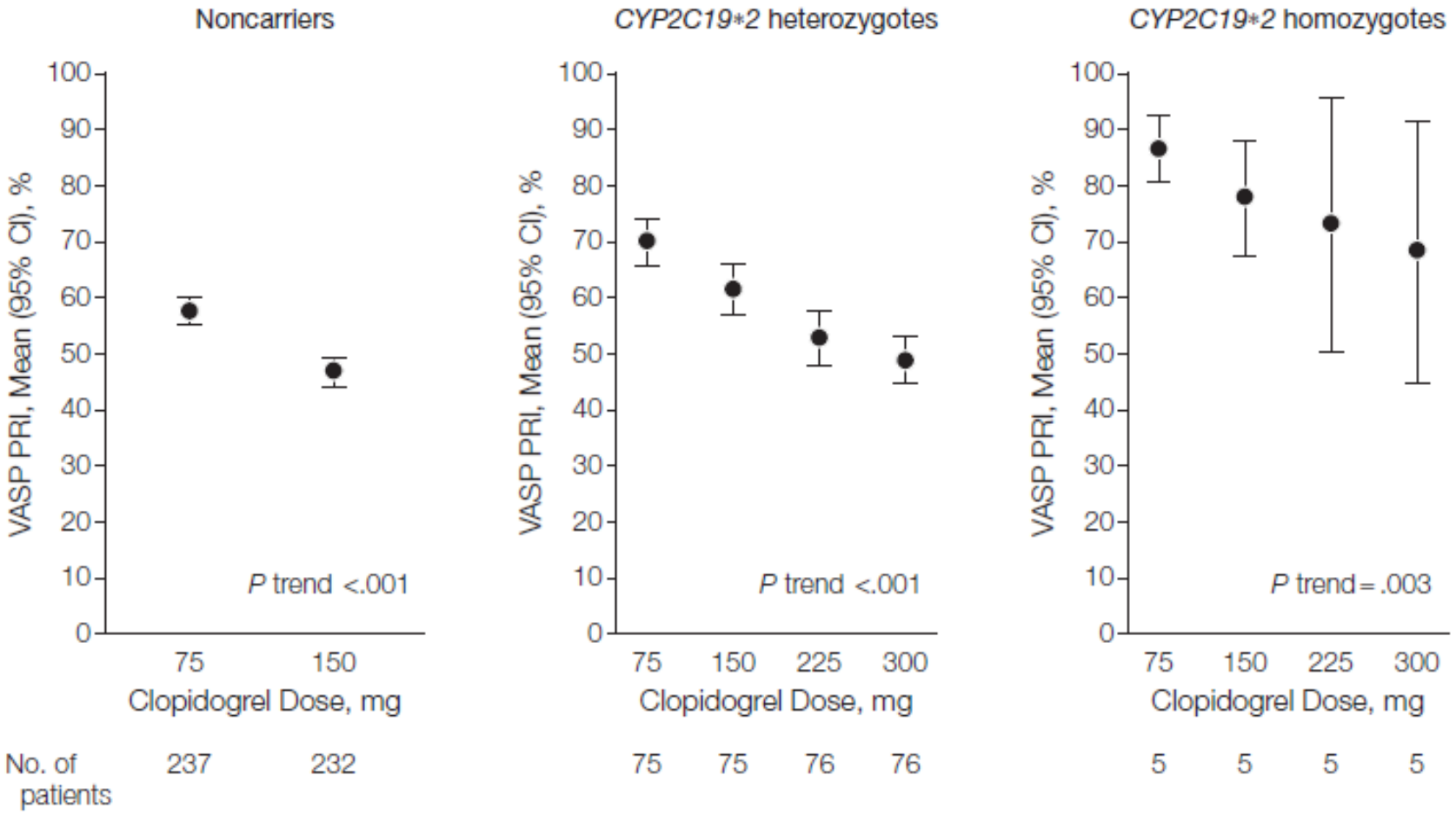
Dosing Clopidogrel Based on *CYP2C19* Genotype and the Effect on Platelet Reactivity in Patients With Stable Cardiovascular Disease

ELEVATE-TIMI 56



JAMA. 2011;306(20):2221-2228
Published online November 16, 2011. doi:10.1001/jama.2011.1703

On-treatment platelet reactivity across genotype and clopidogrel daily dose



VASP PRI indicates vasodilator-stimulated phosphoprotein phosphorylation assay platelet reactivity index.

JAMA. 2011;306(20):2221-2228
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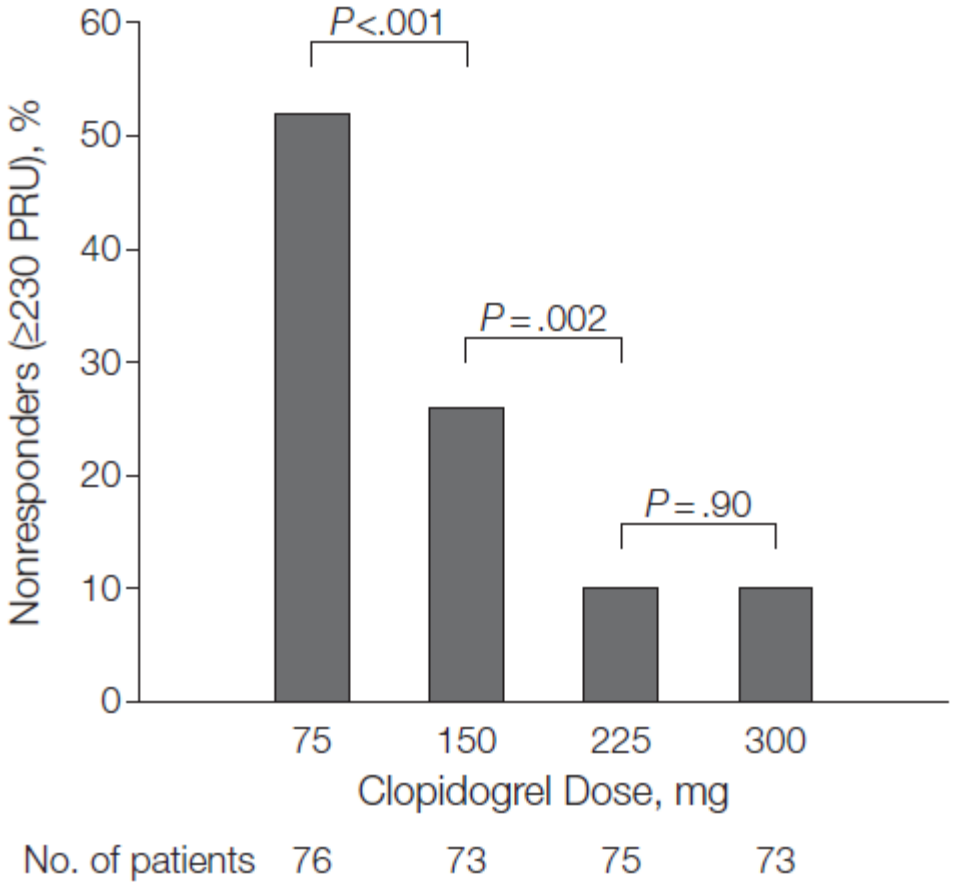
Figure 3. Clopidogrel Nonresponders Among *CYP2C19**2* Heterozygotes Across Daily Doses of Clopidogrel



Nonresponders were defined using the VerifyNow $P2Y_{12}$ assay with a prespecified cut point of ≥230 $P2Y_{12}$ reaction units (PRU).

JAMA. 2011;306(20):2221-2228
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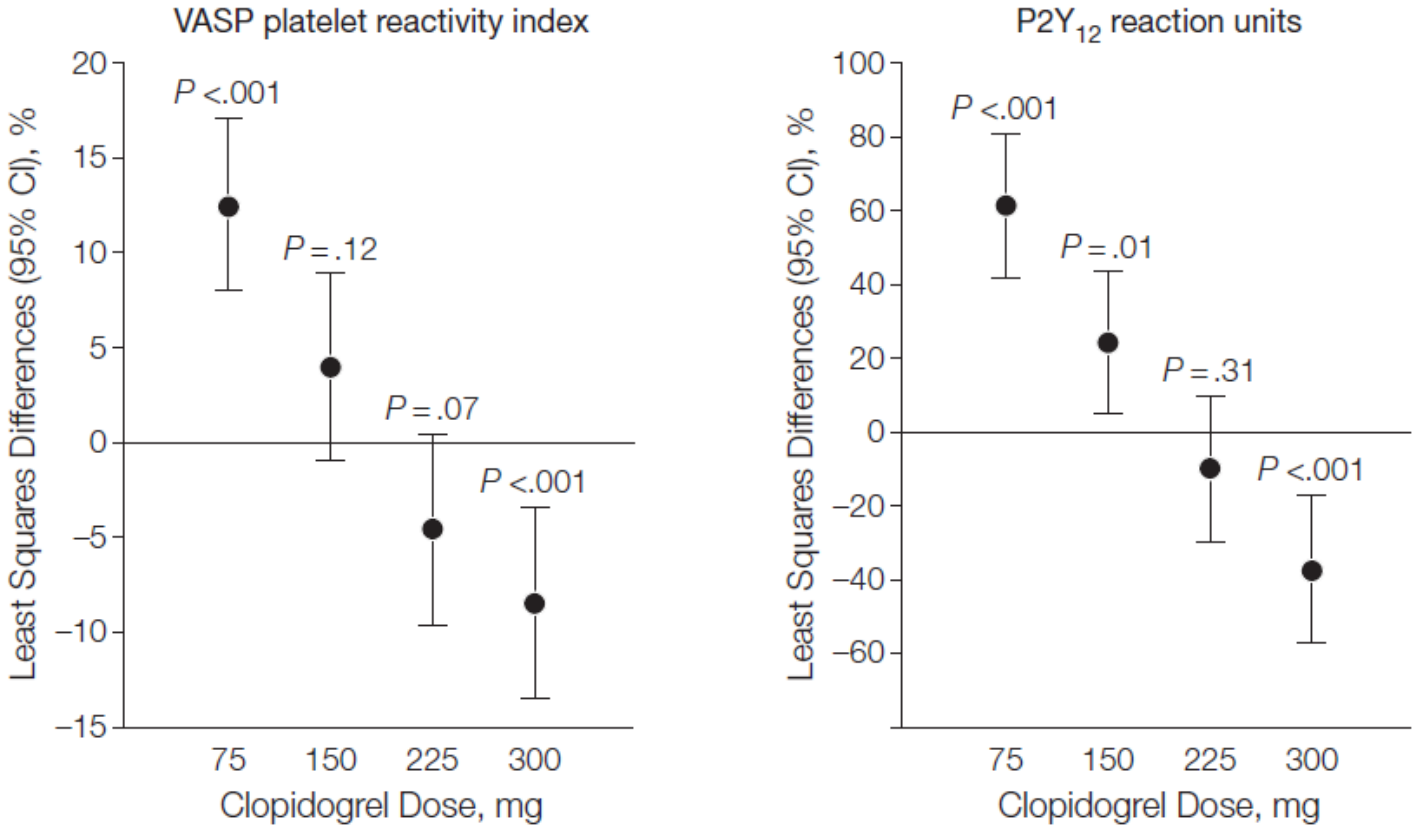
Figure 4. Difference in Platelet Reactivity Between *CYP2C19*2* Heterozygotes Treated With Increasing Doses of Clopidogrel vs Noncarriers Treated With 75 mg of Clopidogrel Daily



Data are reported as least squares differences and 95% confidence intervals for platelet reactivity between *CYP2C19*2* heterozygotes at clopidogrel doses of 75 mg (n=76), 150 mg (n=73), 225 mg (n=75), and 300 mg (n=73) and noncarriers at 75 mg of clopidogrel (n=237). Differences in least squares means were tested using asymptotic methods (normal z test). VASP indicates vasodilator-stimulated phosphoprotein phosphorylation assay.

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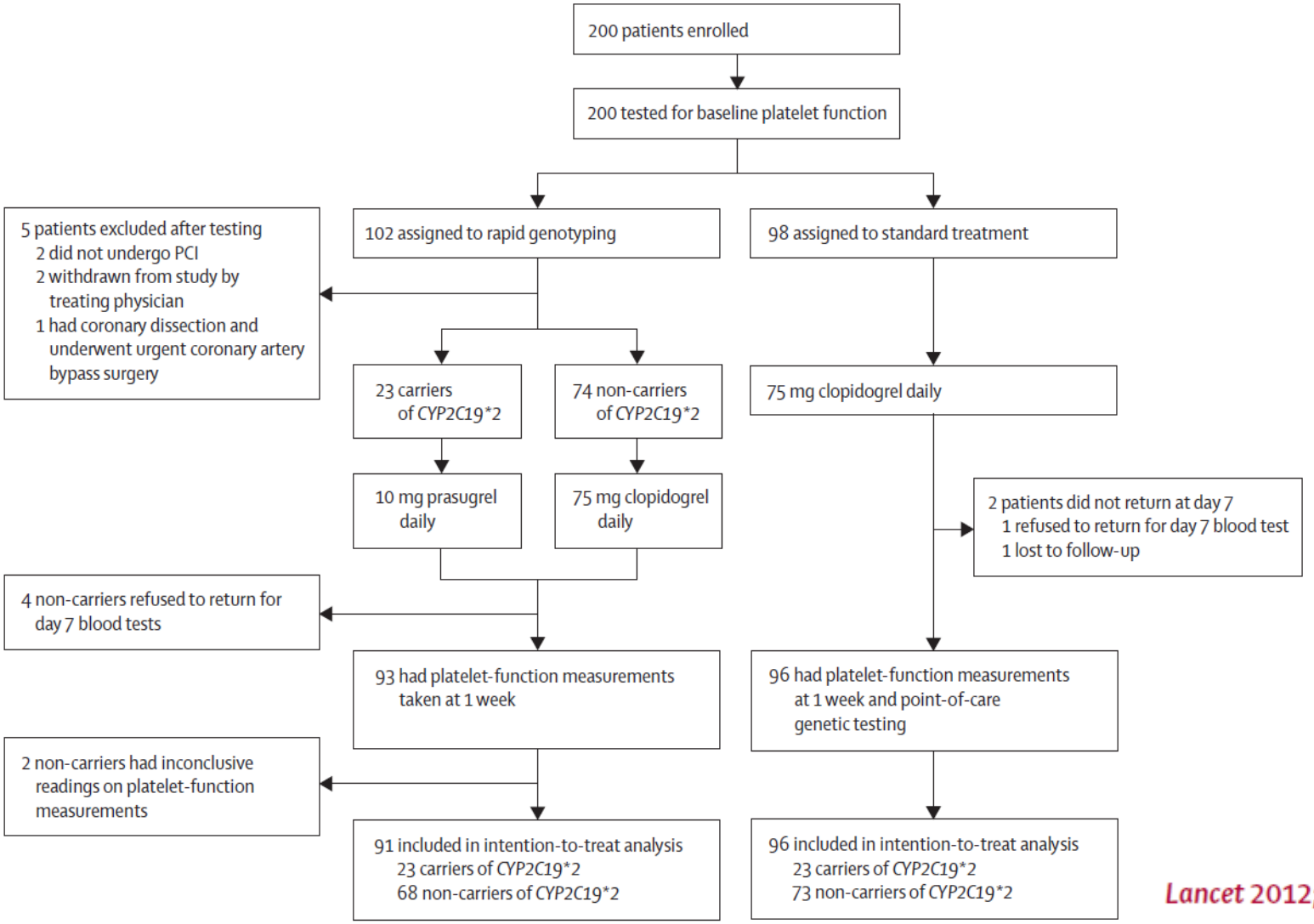
Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial

Jason D Roberts, George A Wells, Michel R Le May, Marino Labinaz, Chris Glover, Michael Froeschl, Alexander Dick, Jean-Francois Marquis, Edward O'Brien, Sandro Goncalves, Irena Druce, Alexandre Stewart, Michael H Gollob, Derek Y F So



Lancet 2012; 379: 1705–11

Primary and secondary outcomes in CYP2C19*2 carriers

	Rapid genotyping (n=23)	Standard treatment (n=23)	p value
Primary outcome			
Patients with PRU values >234 at day 7	0	7 (30%)	0·0092
Secondary outcomes			
Patients with PRU values >208 at day 7	1 (4%)	11 (48%)	0·0017
Baseline PRU	198·7 (80·7)	198·7 (91·9)	0·9986
PRU at day 7	75·6 (57·3)	207·3 (55·8)	<0·0001
Platelet inhibition at day 7	73·3% (20·3)	27·0% (13·4)	<0·0001
Change in PRU from baseline to day 7	123·09 (77·2)	−8·48 (74·0)	<0·0001

Data are n (%) or mean (SD). PRU=P2Y12 reactivity unit.

Table 2: Primary and secondary outcomes in *CYP2C19*2* carriers

Lancet 2012; 379: 1705–11

Platelet function outcomes in all patients

	Rapid genotyping (n=91)	Standard treatment (n=96)	p value*	p value†
Baseline PRU	154·7 (98·0)	160·2 (101·7)	0·7098	0·2646
PRU at day 7	125·3 (74·8)	163·9 (78·4)	0·0007	<0·0001
Patients with PRU values >234 at day 7	9 (10%)	16 (17%)	0·1735	0·0672
Patients with PRU values >208 at day 7	14 (15%)	30 (31%)	0·0106	0·0008
Platelet inhibition at day 7	56·5% (24·5)	43·9% (22·9)	0·0003	<0·0001

Data are mean (SD) or n (%). PRU=P2Y12 reactivity unit. *Unadjusted p value. †p value based on imputation analysis for missing data and adjusted for acute coronary syndrome, diabetes, smoking status, bodyweight, and use of proton-pump inhibitor.

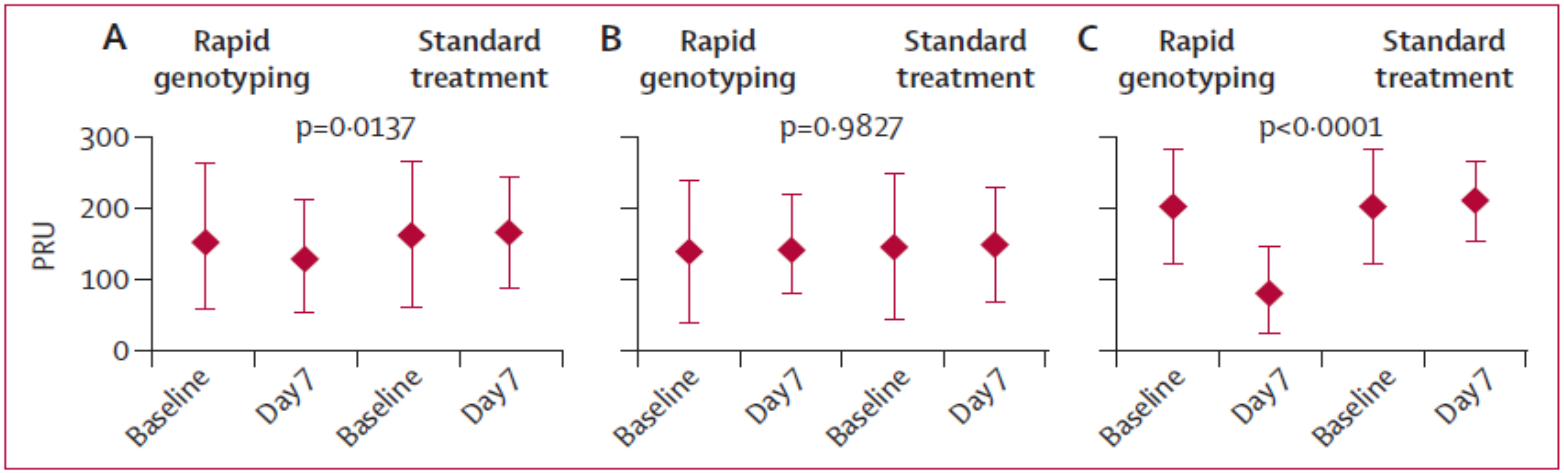
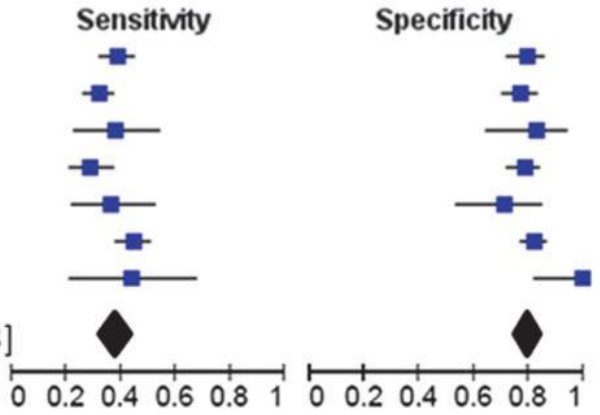


Figure 2: **PRU values at baseline and at day 7**
Values given for the whole cohort (A), non-carriers of *CYP2C19*2* (B), and carriers of *CYP2C19*2* (C). p values correspond to analyses for comparison of change in platelet reactivity from baseline to day 7 between rapid genotyping and standard treatment groups. PRU=P2Y12 reactivity units.

Sensitivity and specificity of the 2C19*2 polymorphisms for detecting HOPR, as based on VASP assay performed in clopidogrel-treated patients

Study	*2C HTPR + TP	*2C HTPR - FP	*2NC HTPR + FN	*2NC HTPR - TN	Sensitivity	Specificity
BONELLO 2010	103	31	154	123	0.40 [0.34, 0.46]	0.80 [0.73, 0.86]
BONELLO 2012	102	42	205	149	0.33 [0.28, 0.39]	0.78 [0.71, 0.84]
BONELLO-PALOT 2009	17	5	26	25	0.40 [0.25, 0.56]	0.83 [0.65, 0.94]
CUISSET 2011	46	40	105	155	0.30 [0.23, 0.38]	0.79 [0.73, 0.85]
FONTANA 2008	17	10	28	26	0.38 [0.24, 0.53]	0.72 [0.55, 0.86]
FONTANA 2011	122	46	143	225	0.46 [0.40, 0.52]	0.83 [0.78, 0.87]
TELLO-MONTOLIU 2012	9	0	11	20	0.45 [0.23, 0.68]	1.00 [0.83, 1.00]
Summarized results					0.38[0.32,0.43]	0.80[0.77,0.83]



Fontana P, et al. JAHA 2013;2:e000131

CYP2C19 genotype should be regarded as one of risk factors.

"Personalized" antiplatelet therapy based on CYP2C19 genotyping needs more clinical evidence.

Summary

- CYP2C19 polymorphism is associated with poor responsiveness to clopidogrel & cardiovascular outcomes after PCI.
- Point-of-care genetic assay may be useful in identifying patients with increased thrombotic risk.
- We need more data for “Tailored antiplatelet strategy by genotype”

"Here's my sequence..."

Journey Toward Personalized Patient Care

Best clinical practice might be selecting a best clinical trial for the patient, during our journey toward a genuine tailored therapy