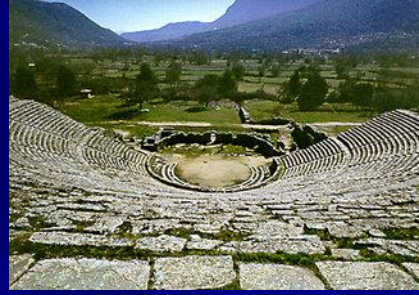
UNIVERSITY OF IOANNINA

ATHEROTHROMBOSIS

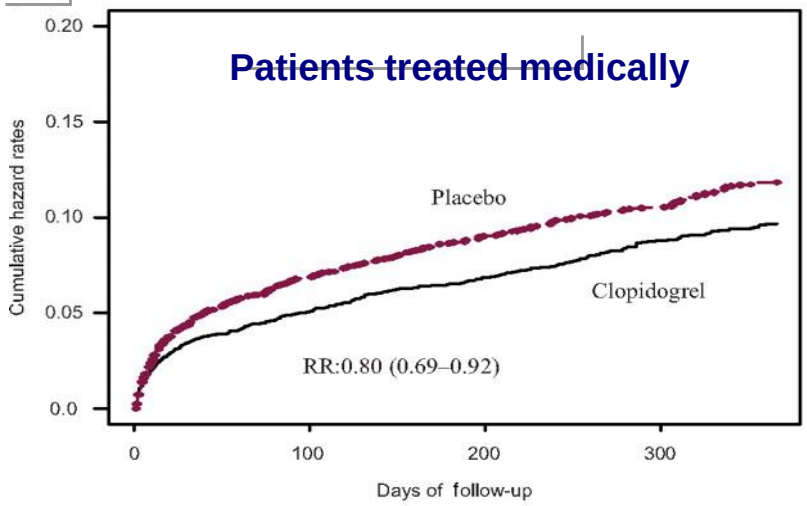
RESEARCH CENTER

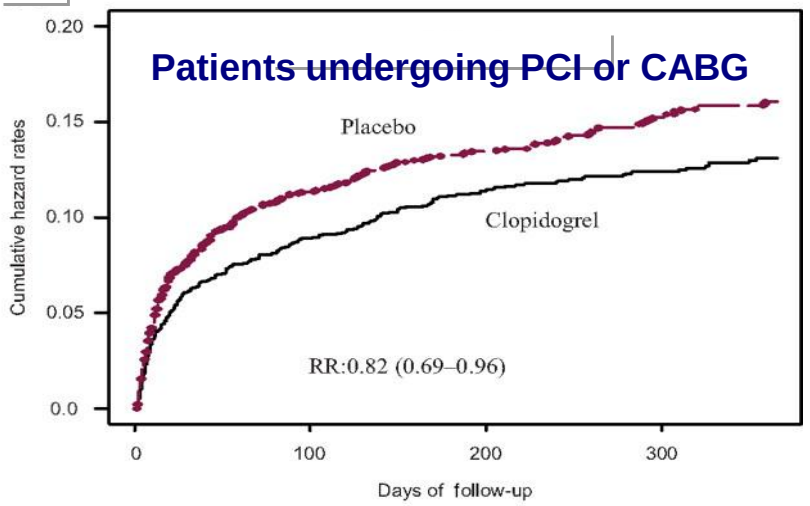


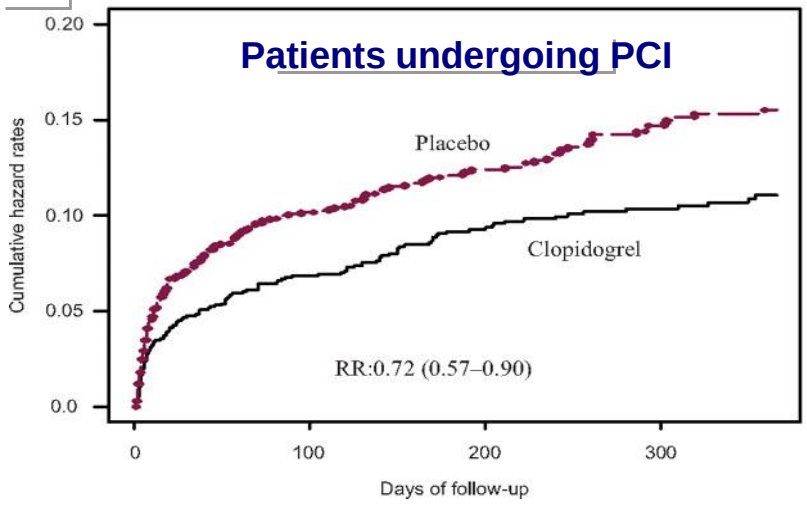
Recent advances in antiplatelet therapy. Is still the need of platelet functional assessment or genotyping?

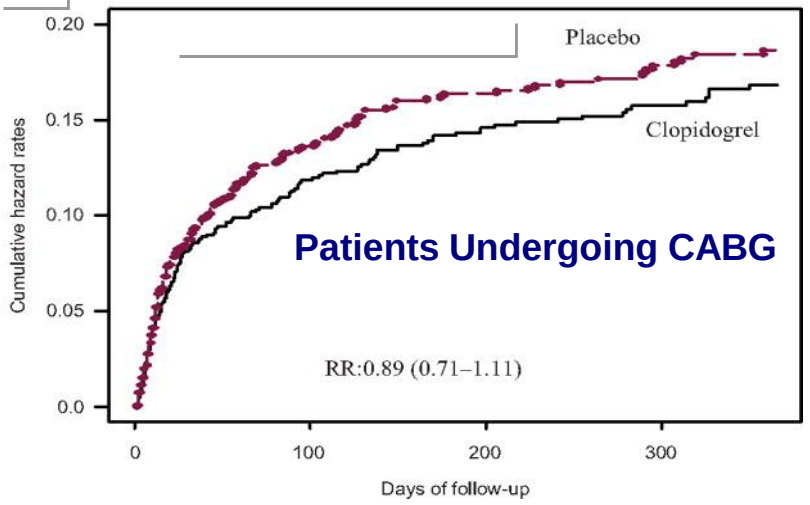
Alexandros D. Tselepis, MD, PhD
Professor of Biochemistry – Clinical Chemistry

Benefit of Clopidogrel + Aspirin vs aspirin in reducing CV death, MI, or Stroke in the CURE trial





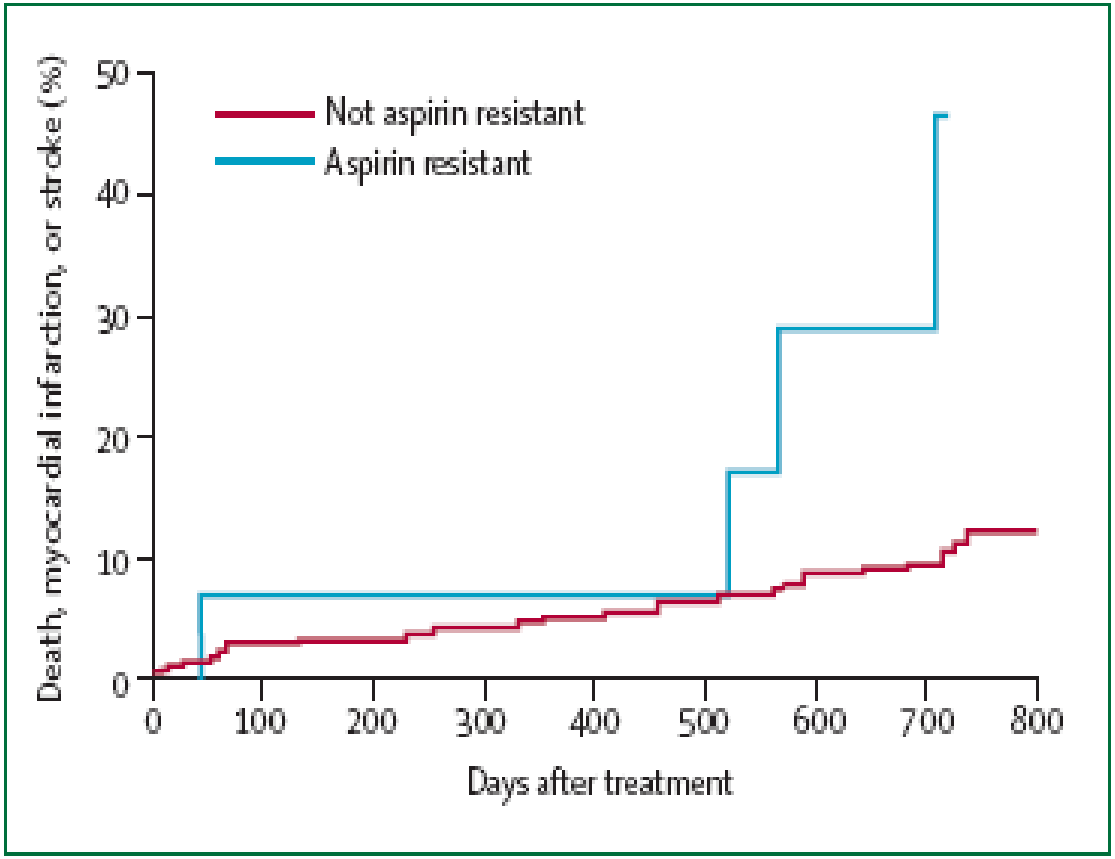




Mehta S R Eur Heart J Suppl 2006;8:G25-G30

Aspirin Resistance

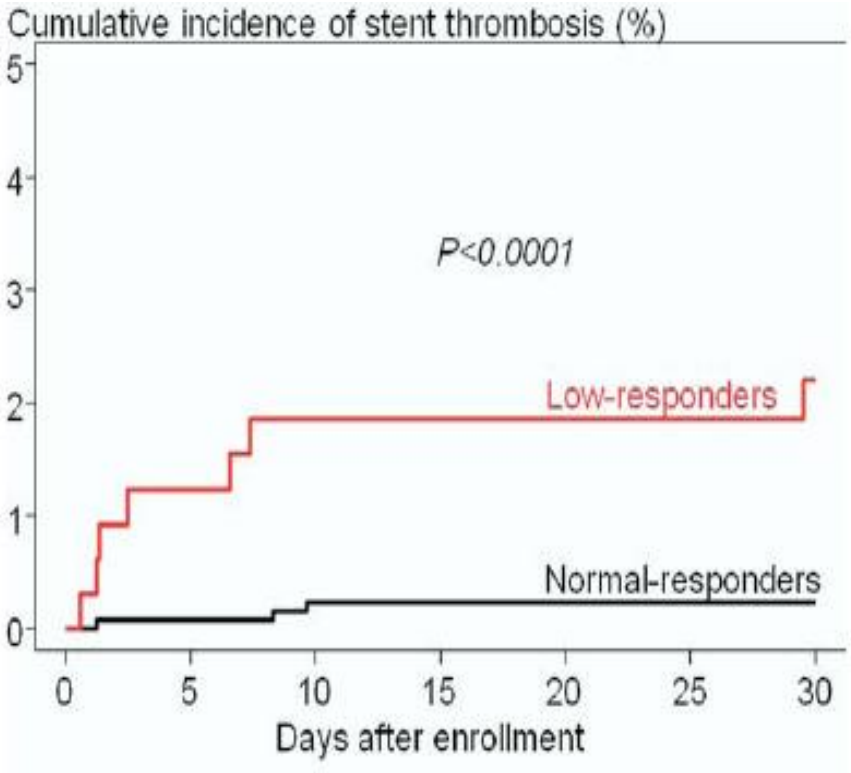
Association between reduced inhibition of agonist induced platelet aggregation and incidence of death, MI, or stroke

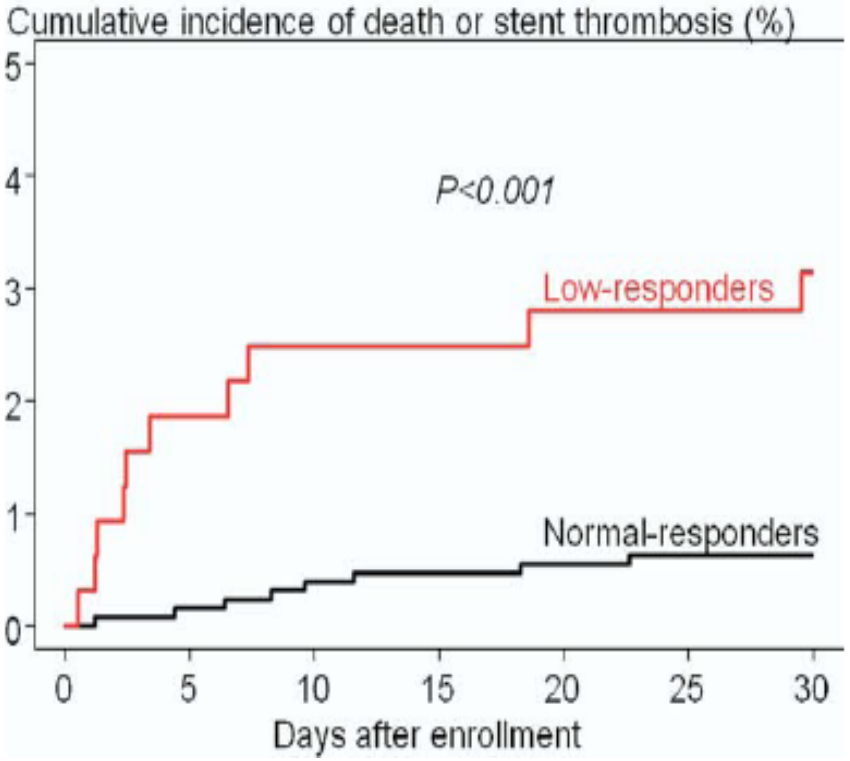


Hankey GJ, et al. Lancet 2006; 367: 606–17

Clopidogrel Resistance

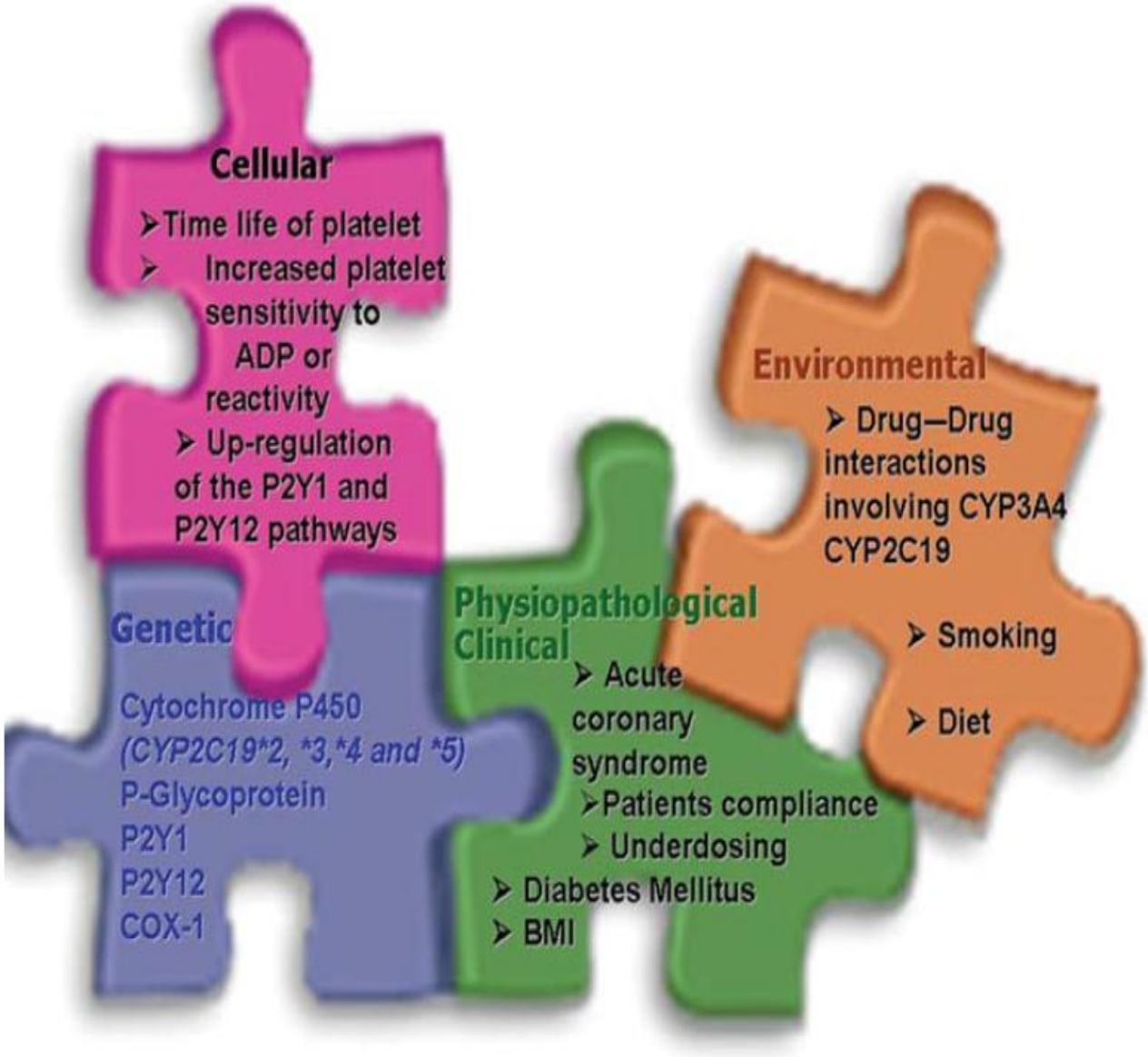
Kaplan-Meier analysis for the cumulative incidence of stent Thrombosis and for the composite of death or stent thrombosis





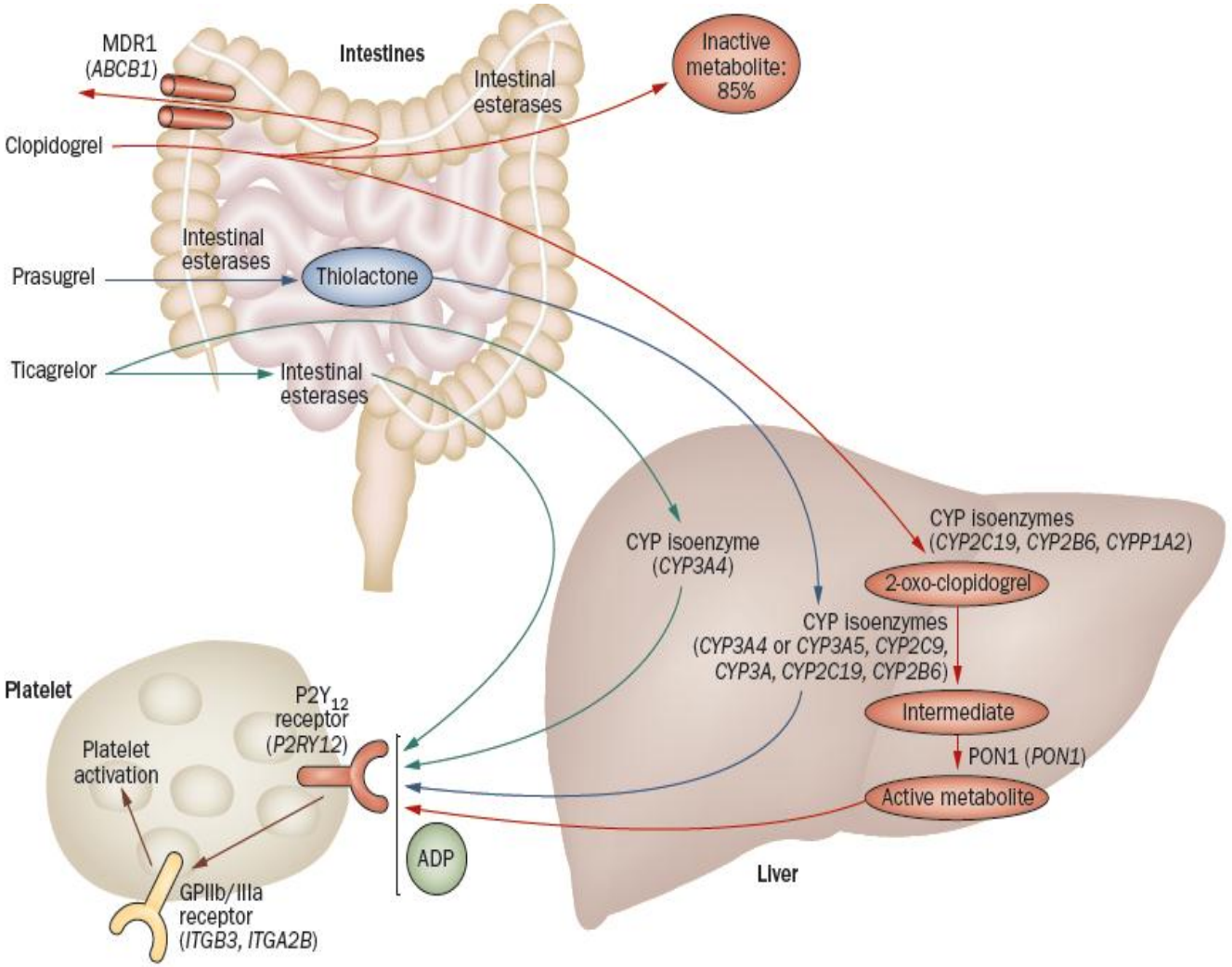
Sibbing D, et al. J Am Coll Cardiol 2009;53:849–56

Factors influencing the variability of antiplatelet drug response



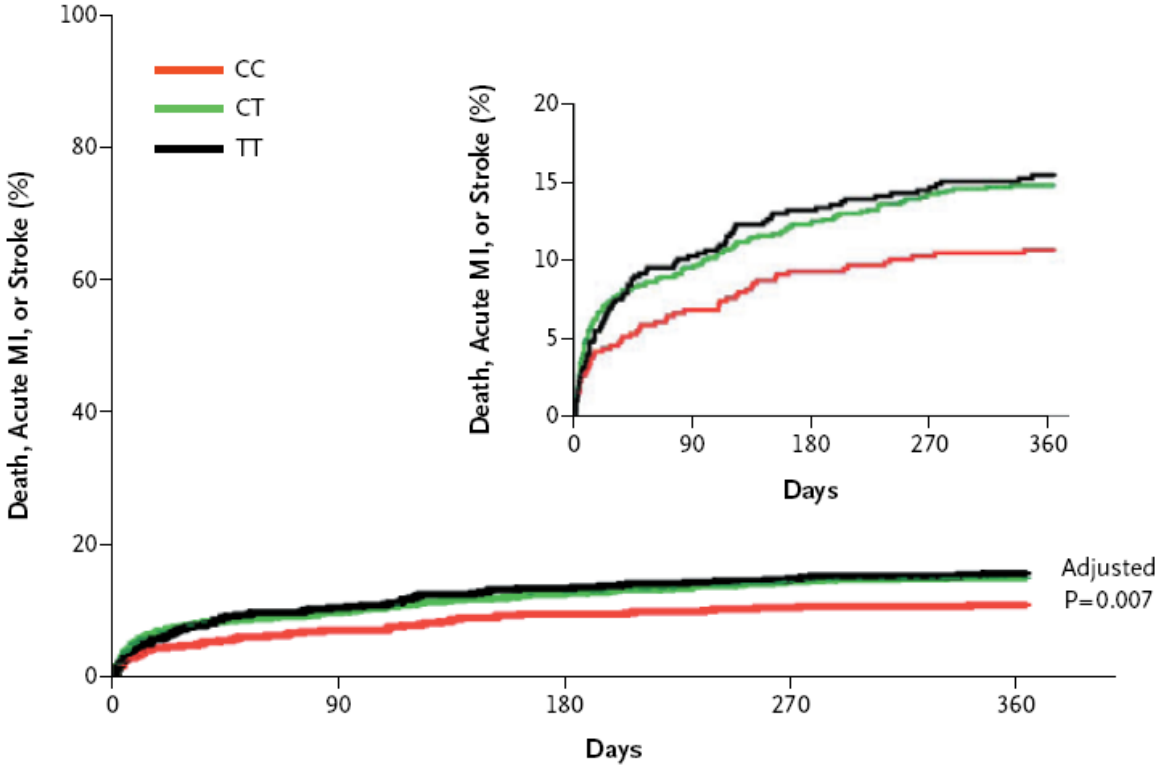
Verstuyft C, et al. Eur Heart J (2009) 30, 1943–1963

Variability in response to thienopyridine platelet inhibition



Ahmad T, et al. Nat. Rev. Cardiol. 8, 560–571 (2011)

Estimated Rates of Death from Any Cause, Nonfatal Myocardial Infarction, or Stroke, according to the type of *ABCB1 C3435T* alleles present



No. at Risk					
CC	564	527	514	509	507
CT	1050	953	925	907	902
TT	574	517	501	493	489

Simon T, et al. N Engl J Med 2009;360:363-75

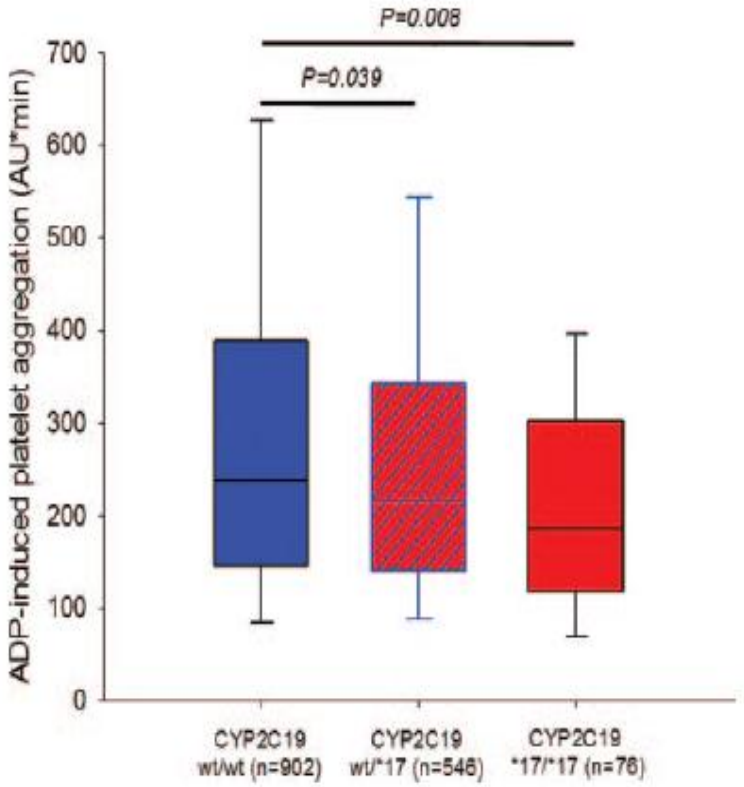
Patient classification by *CYP2C19* genotype

Metabolizer type	Genetic variant
Ultra	*17/*17, *1/*17
Extensive	*1/*1
Intermediate	*1/*2, *1/*3
Poor	*2/*2, *2/*3, *3/*3
Unknown	*2/*17, *3/*17

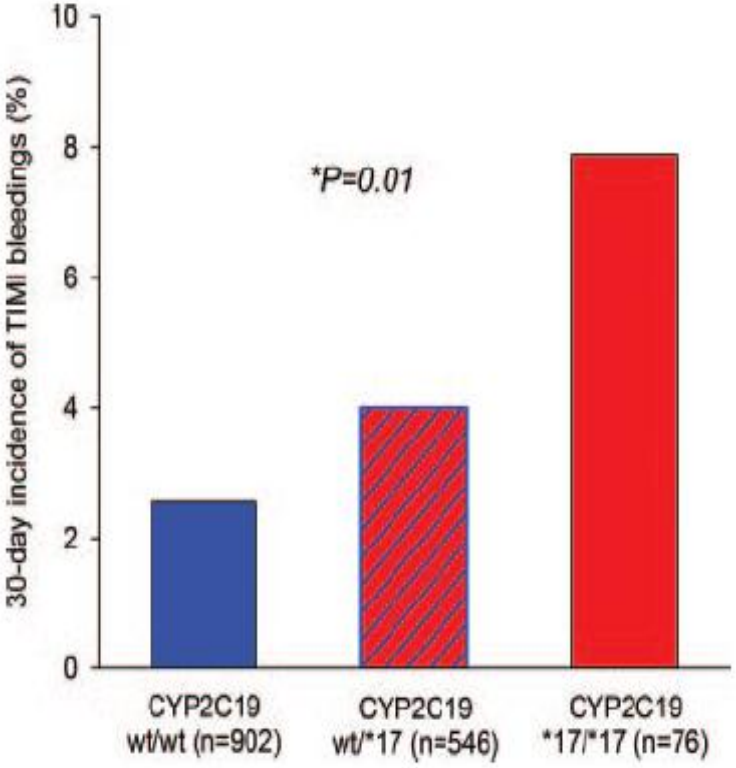
Ahmad T, et al. Nat. Rev. Cardiol. 8, 560–571 (2011)

*CYP2C19*17* genotypes

Platelet aggregation

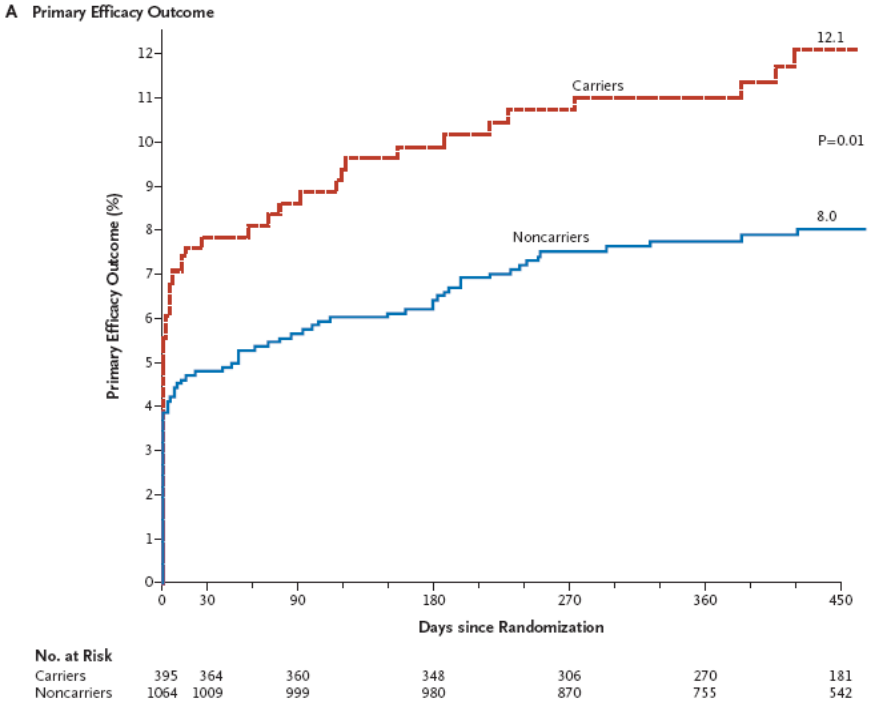


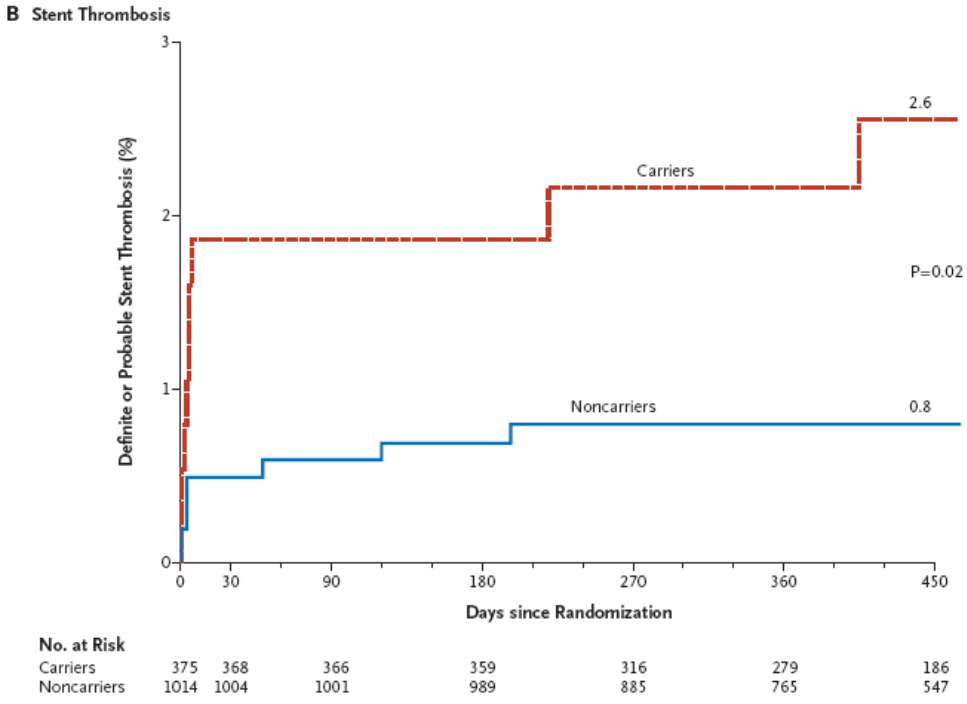
Incidence of TIMI bleedings



Sibbing D, et al. Circulation. 2010;121:512-518

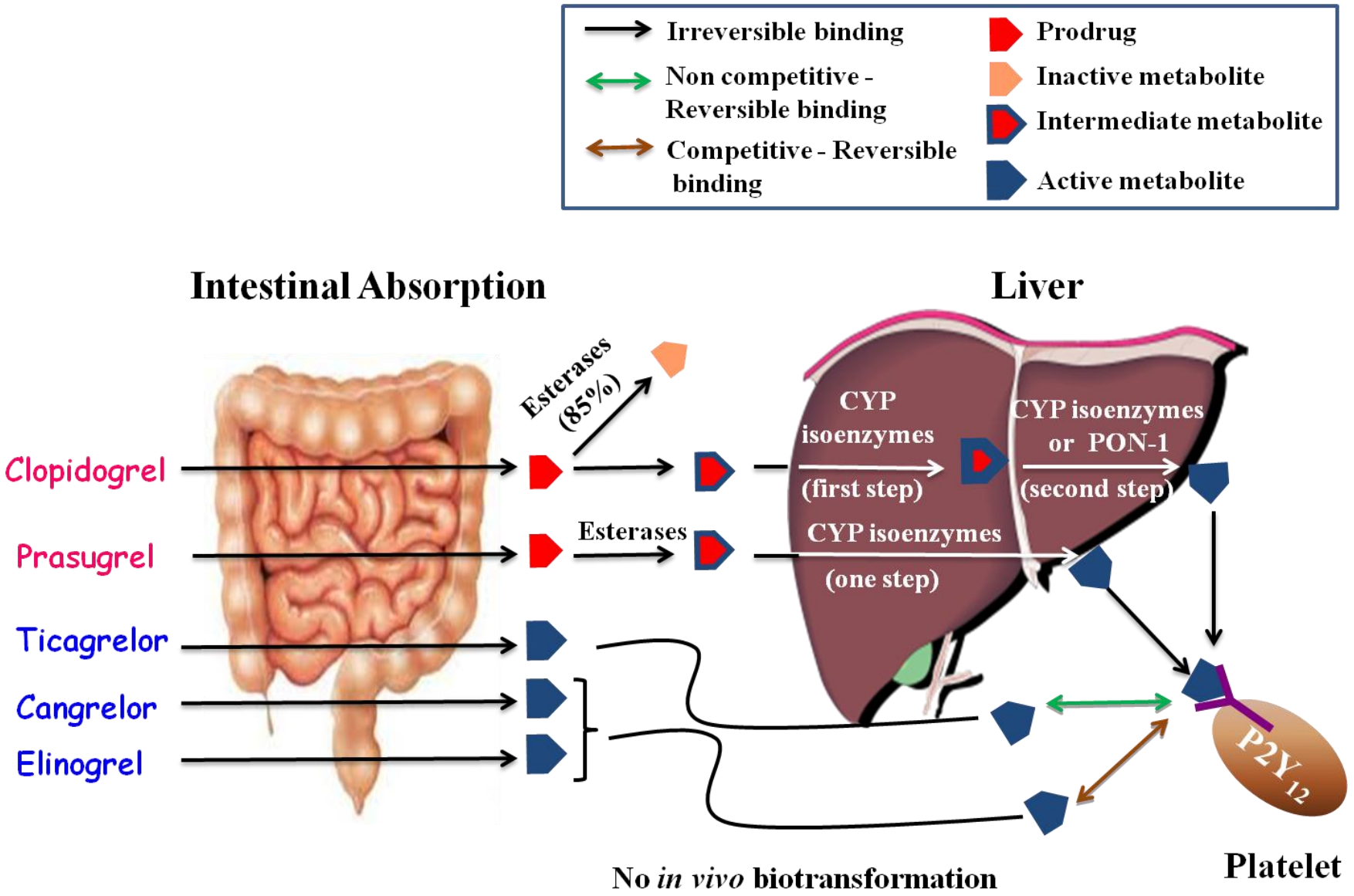
Association between the *CYP2C19*2* Reduced-Function Allele and the Primary Efficacy Outcome or Stent Thrombosis in Subjects Receiving Clopidogrel





Mega JL, et al. N Engl J Med 2009;360:354-62

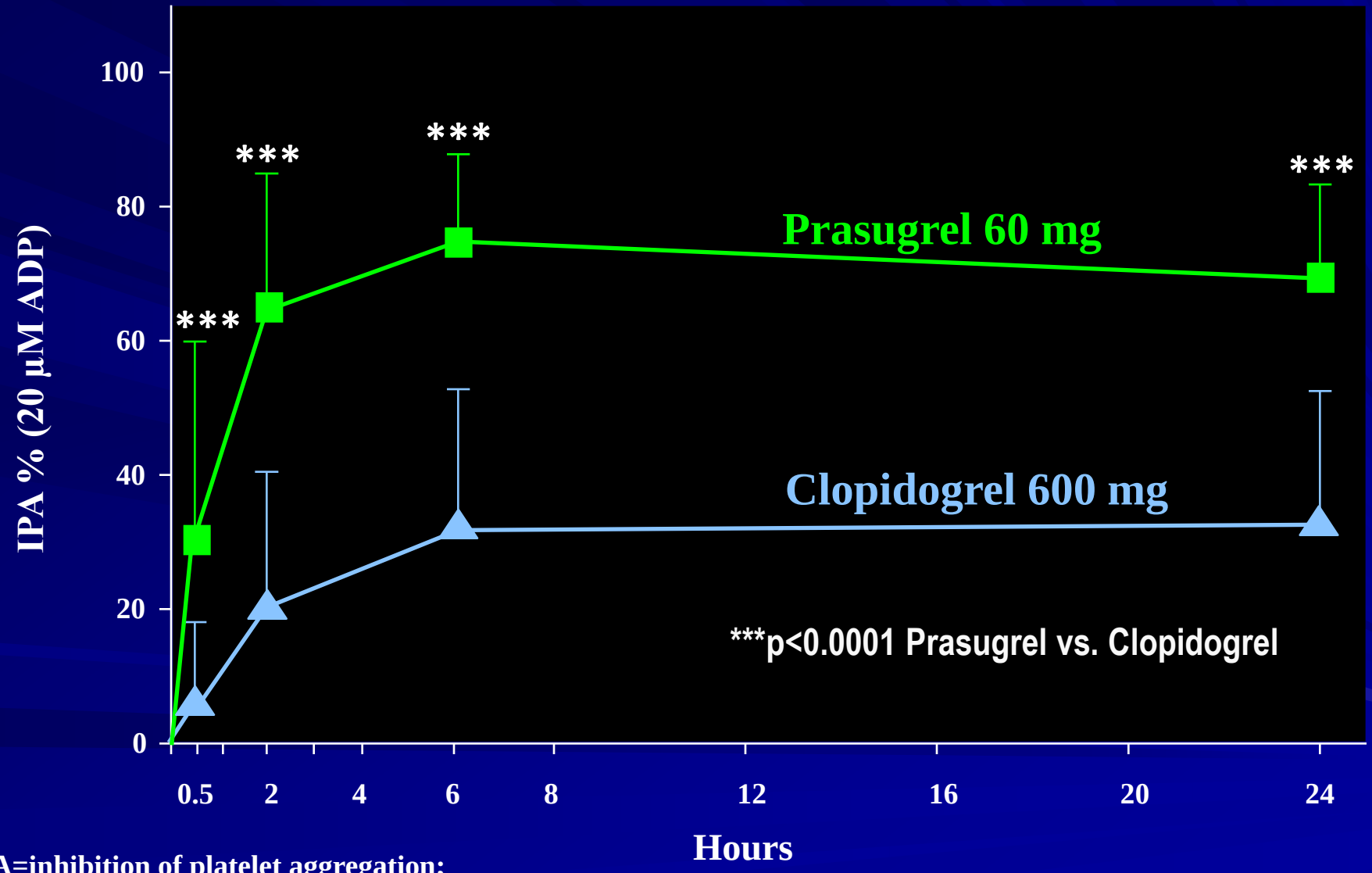
$P2Y_{12}$ antagonists



Kalantzi KI, et al. Exp Rev Clin Pharm. 2012, Accepted

Prasugrel

Inhibition of Platelet Aggregation After Loading Dose in Patients With Elective PCI



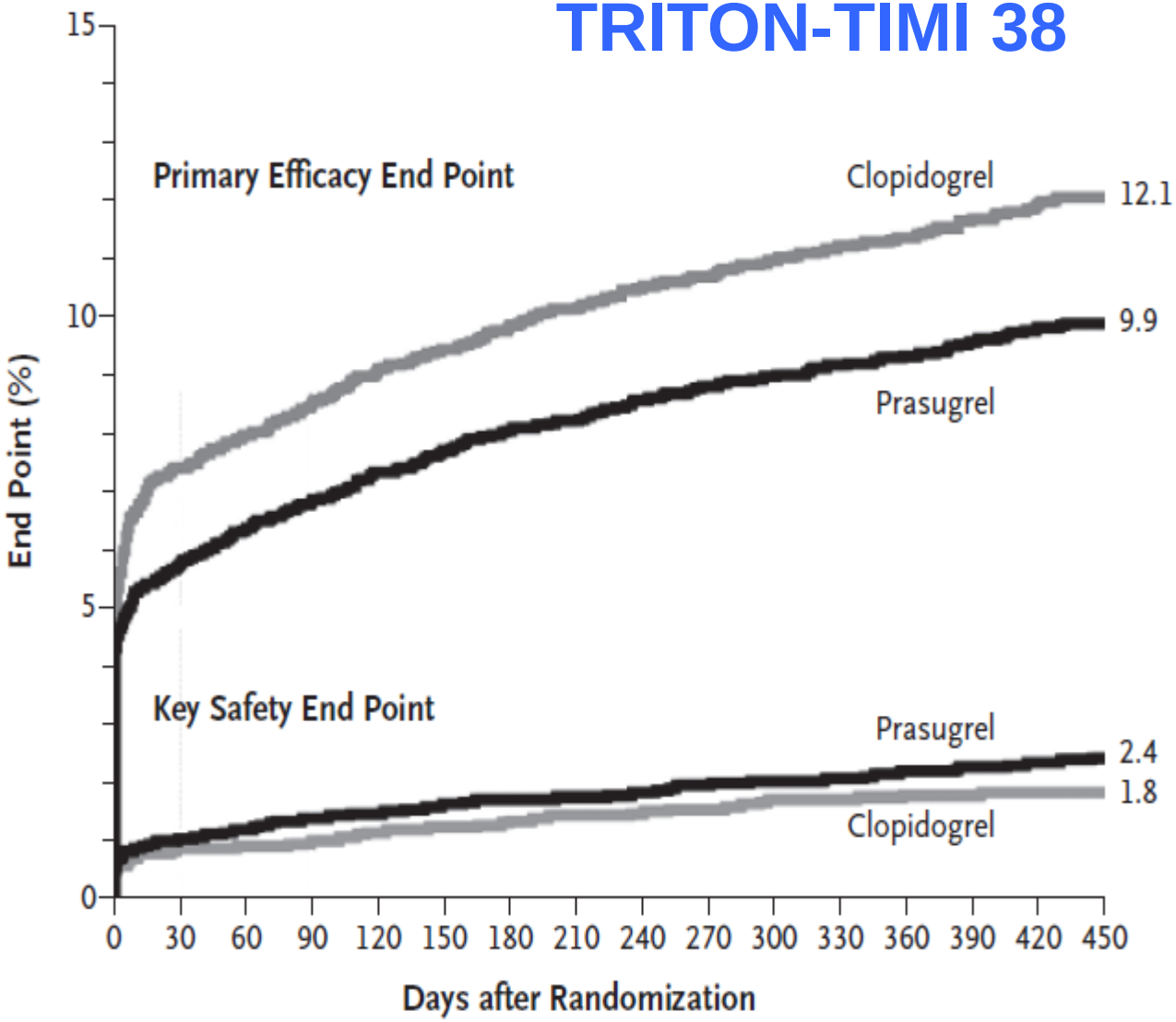
IPA=inhibition of platelet aggregation;
PCI=Percutaneous coronary intervention

Wiviott SD et al. *Circulation* 2007;116(25):2923-2932

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 15, 2007 VOL. 357 NO. 20

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

TRITON-TIMI 38



↓ 138 Events

Hazard ratio, 0.81;
95% CI, 0.73–0.90;
P<0.001

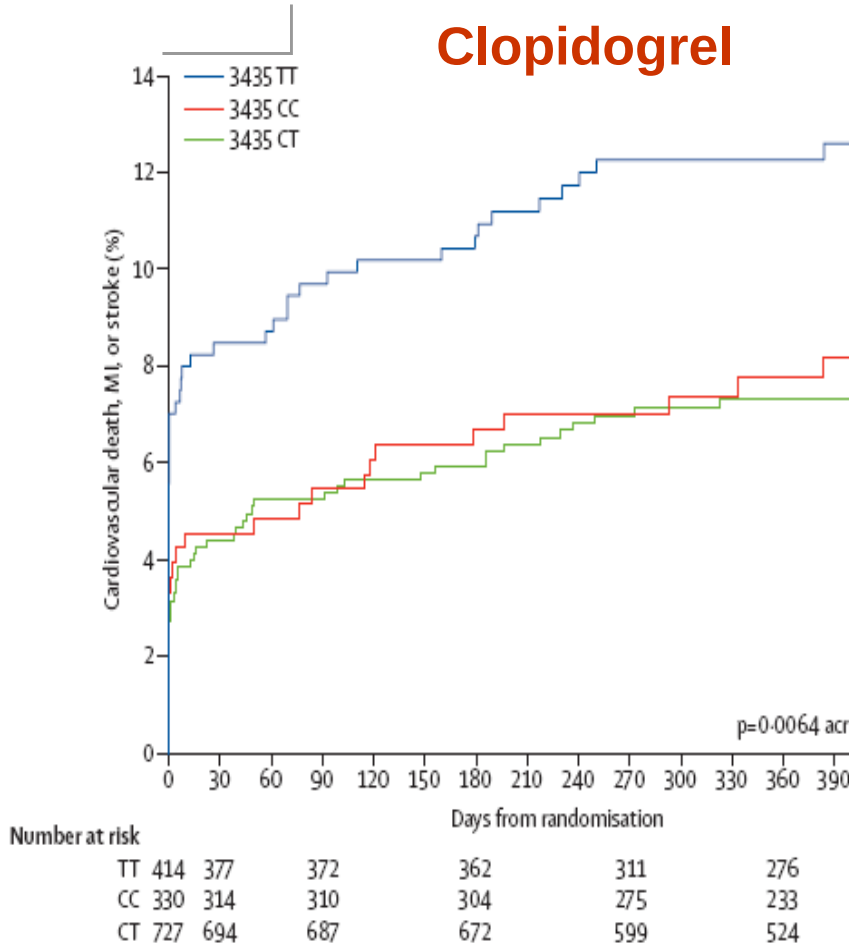
↑ 35 Events

Hazard ratio, 1.32;
95% CI, 1.03–1.68;
P=0.03

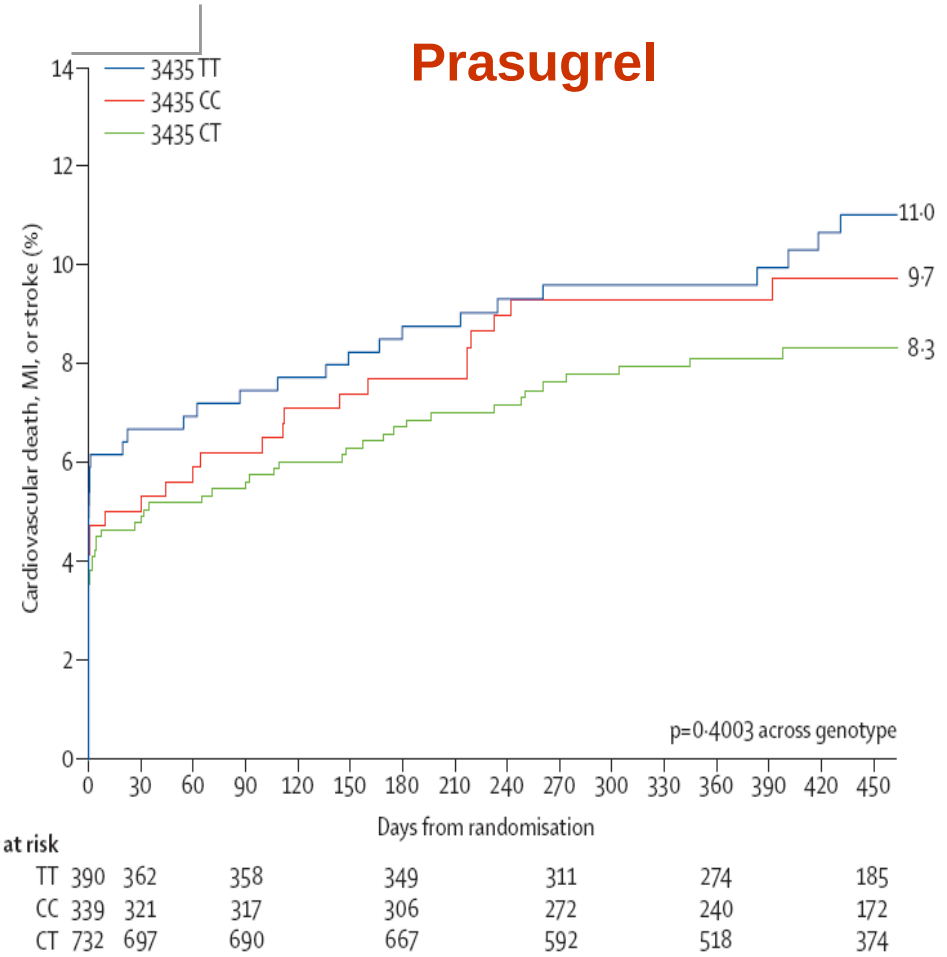
TRITON–TIMI 38 trial: A pharmacogenetic analysis

ABCB1 3435C→T and CV outcomes in patients treated with clopidogrel or prasugrel

Clopidogrel

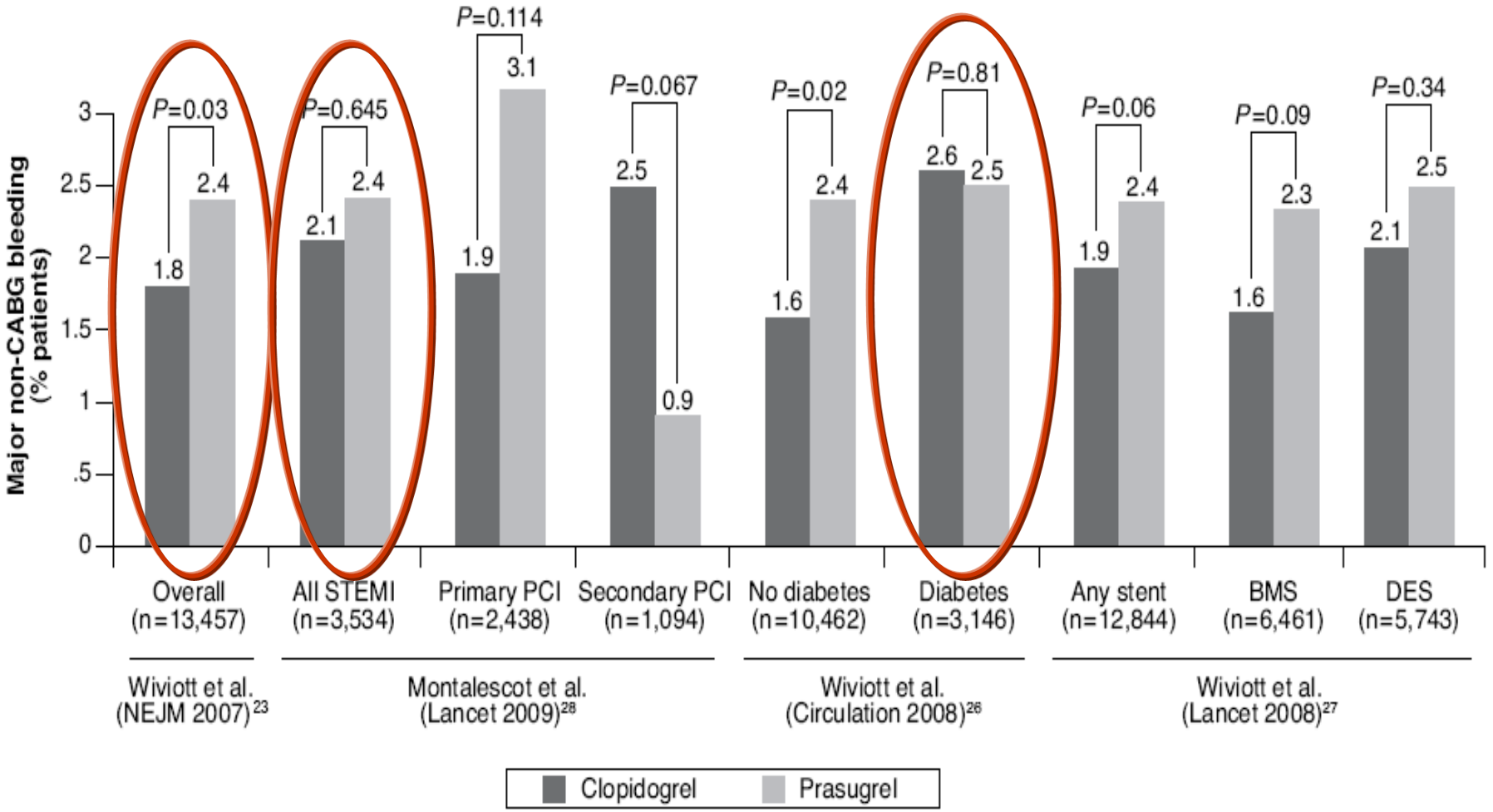


Prasugrel



Mega JL, et al. Lancet 2010

The Incidence of the Primary Safety End Point of Non-CABG-Related Major TIMI Bleeding in the TRITON-TIMI 38 Study



Spinler SA, et al. J Manag Care Pharm. 2009;15(5):383-95.

TRITON TIMI-38

Prasugrel should not be administered in:

- ✓ **Patients with previous stroke**
- ✓ **>75 years old**
- ✓ **Weighing <60 kg**

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ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.04.017

High On-Treatment Platelet Reactivity After Prasugrel Loading Dose and Cardiovascular Events After Percutaneous Coronary Intervention in Acute Coronary Syndromes

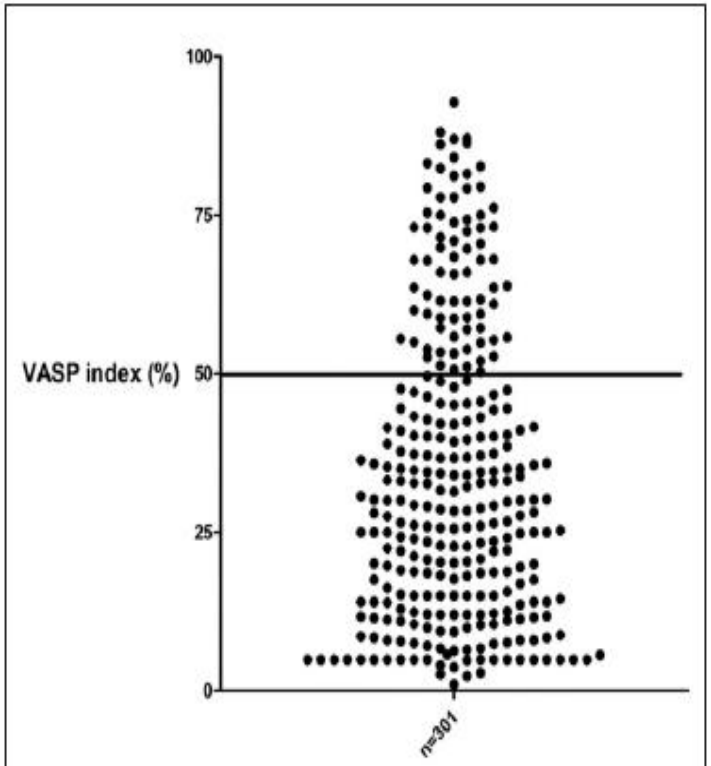


Figure 1 VASP Index After Prasugrel LD

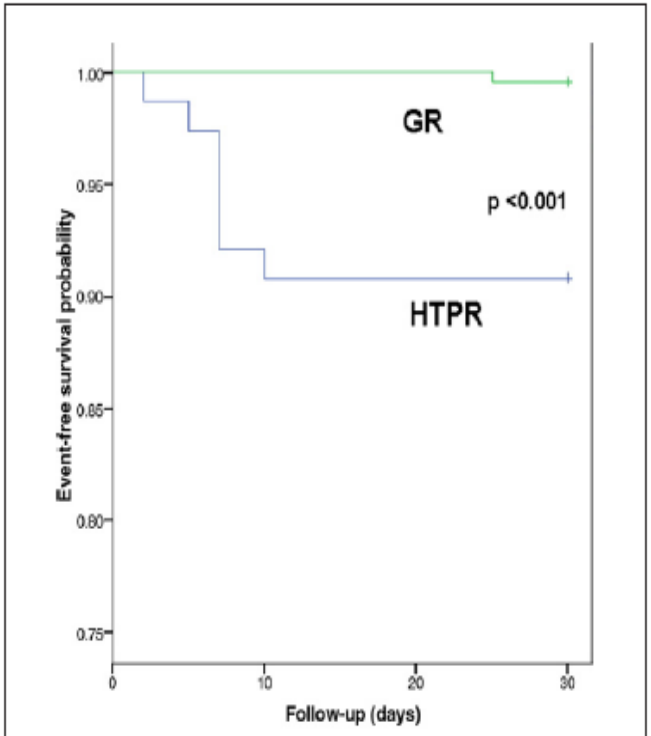
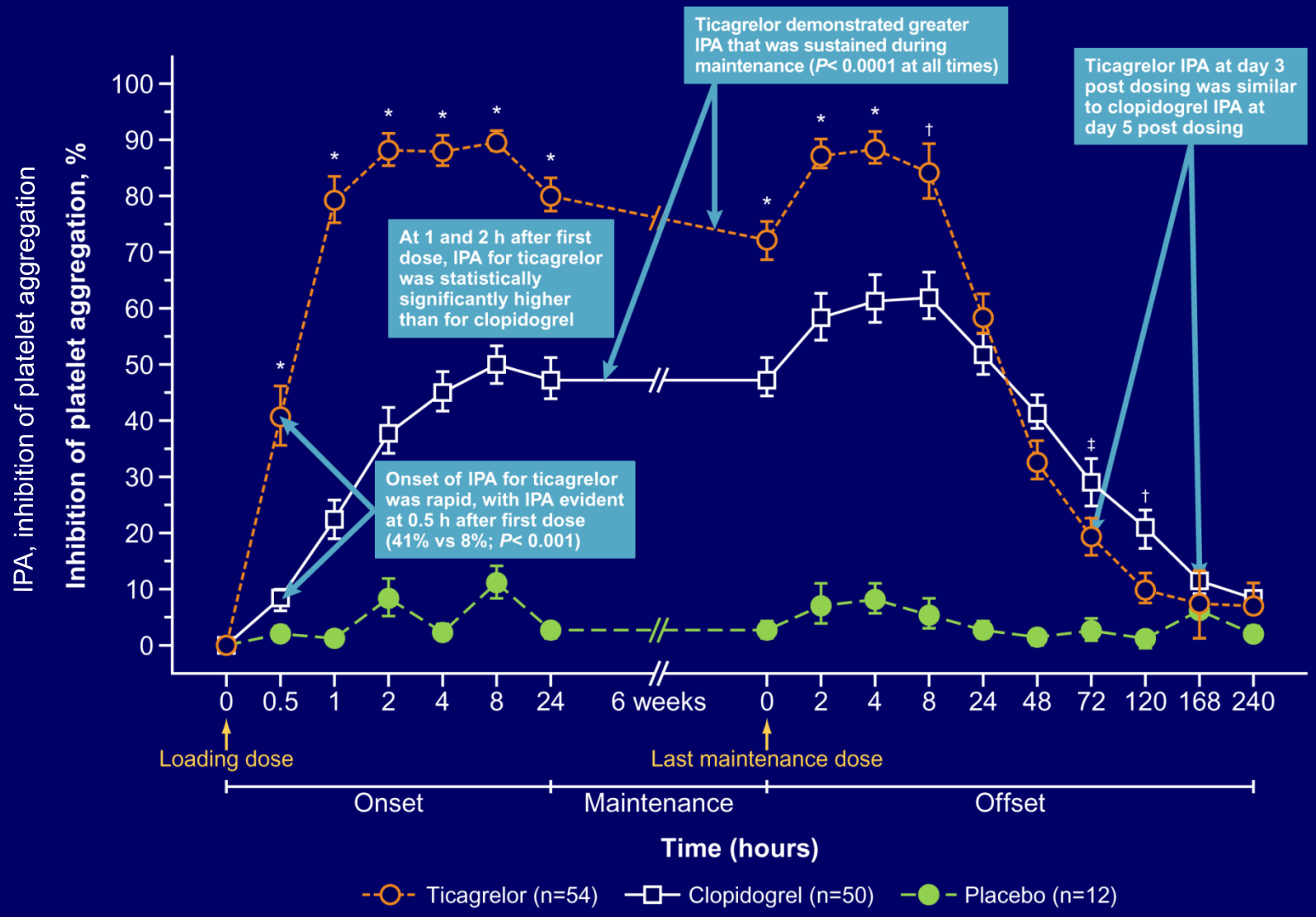


Figure 3 Kaplan-Meier Analysis of Survival Free From Thrombotic Events Comparing GR and Patients With HTPR

Ticagrelor

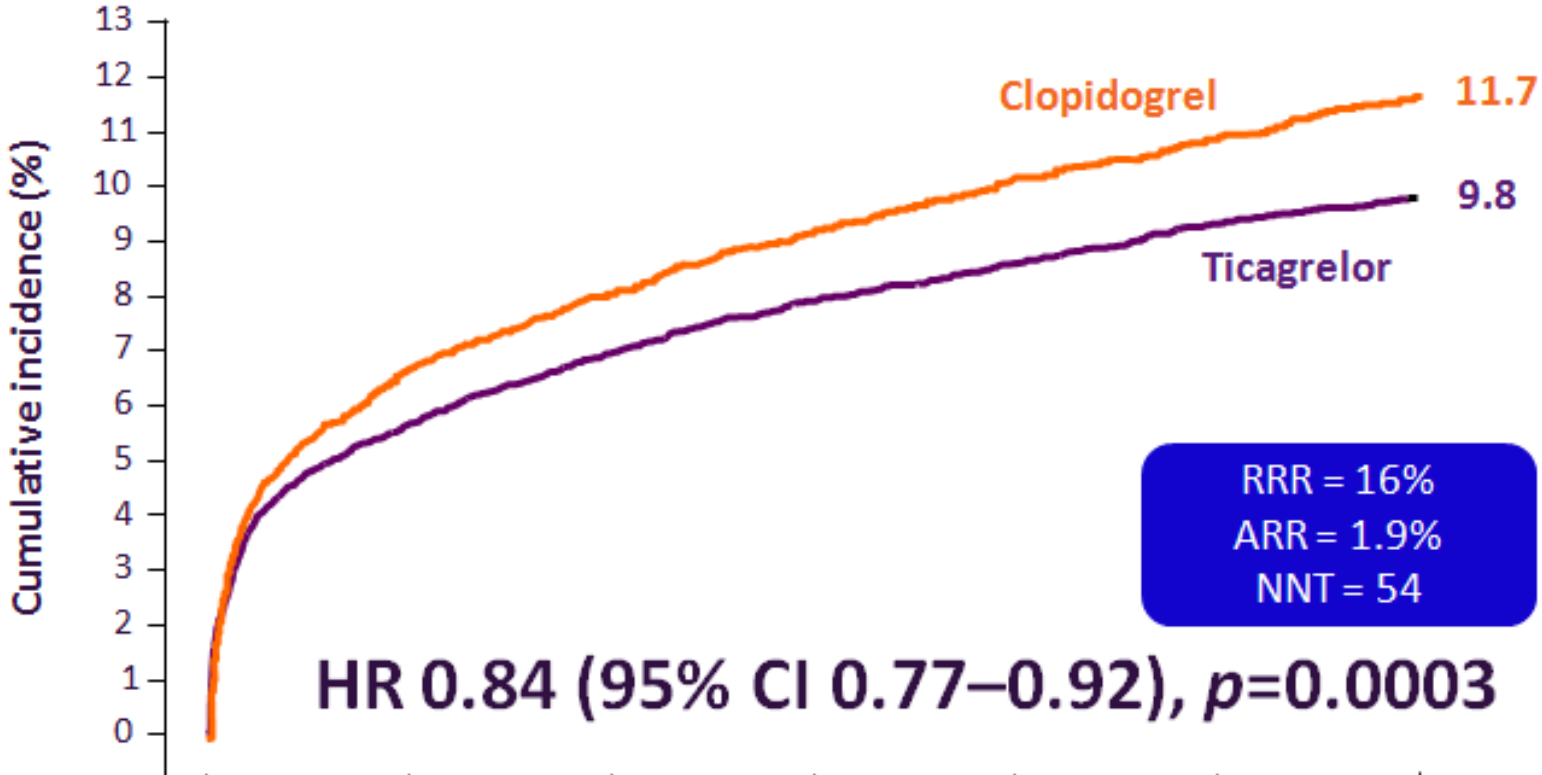
Inhibition of platelet reactivity



Gurbel PA, et al. Circulation 2010;121;1188-1199

PLATO

Kaplan-Meier estimate of time to first primary efficacy endpoint (composite of CV death, MI or stroke)

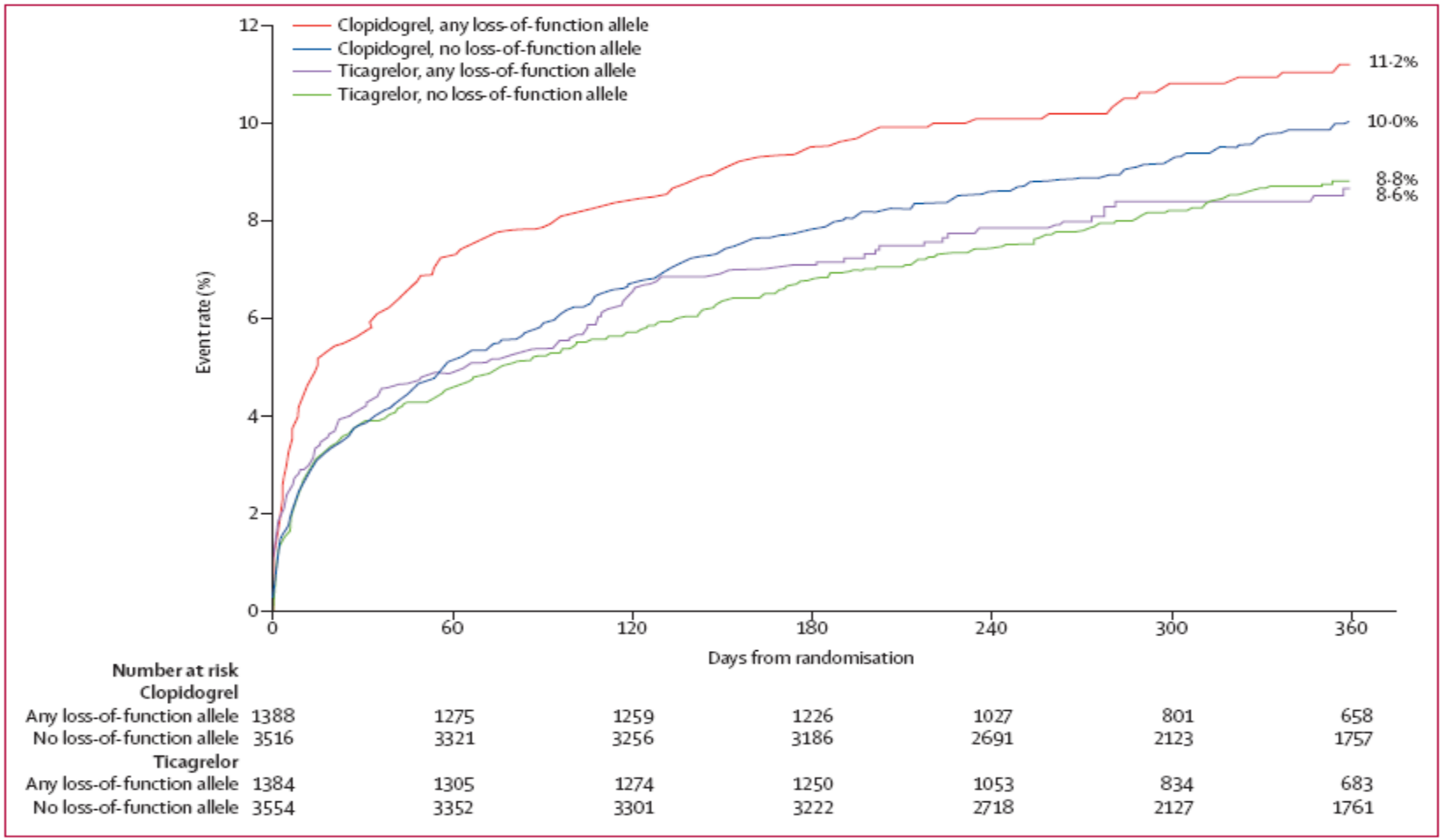


No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

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

The PLATO trial: A genetic substudy

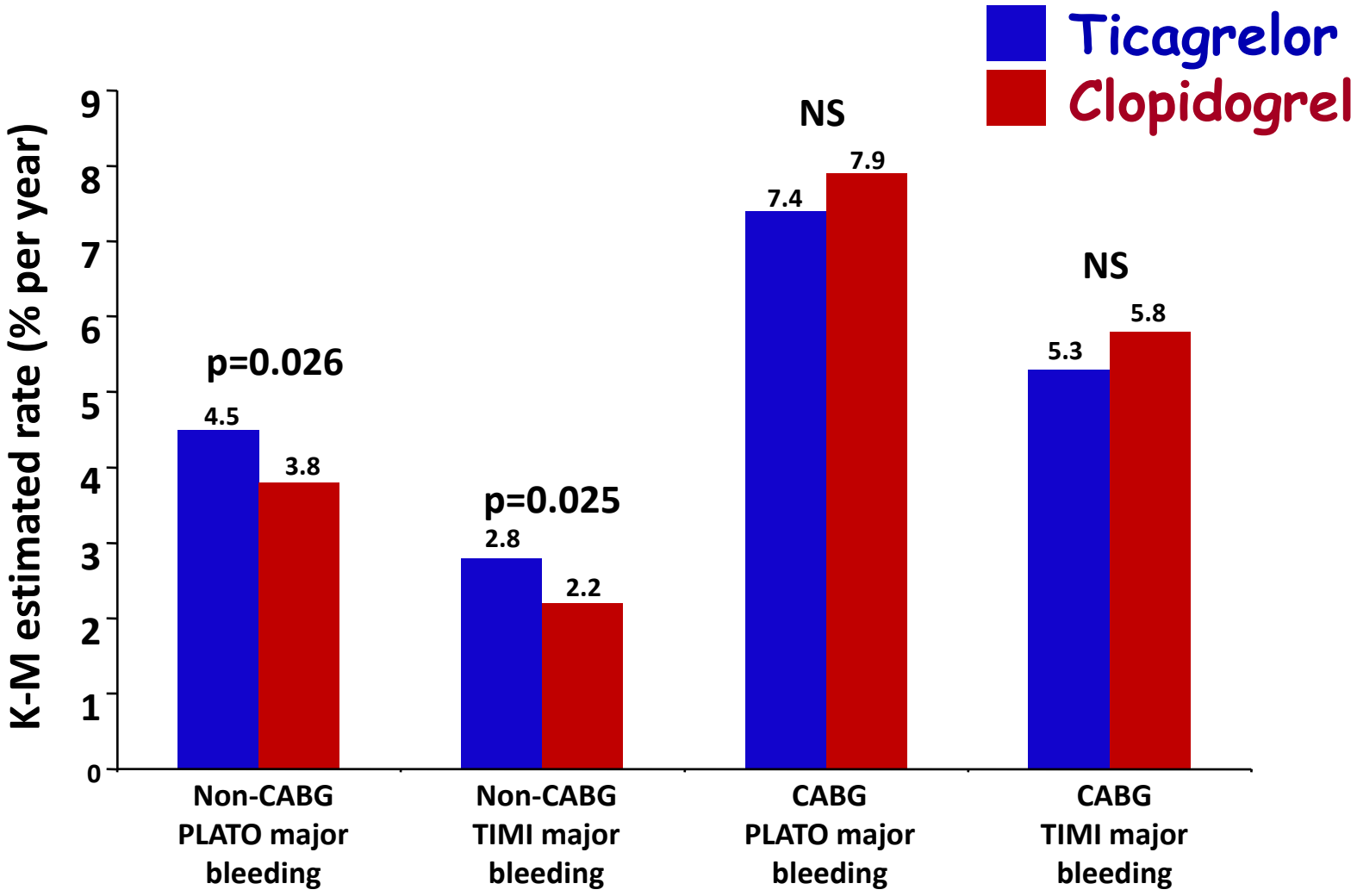
Kaplan-Meier estimates of events of the primary efficacy outcome in relation to the *CYP2C19* genotype



Number at risk							
Clopidogrel							
Any loss-of-function allele	1388	1275	1259	1226	1027	801	658
No loss-of-function allele	3516	3321	3256	3186	2691	2123	1757
Ticagrelor							
Any loss-of-function allele	1384	1305	1274	1250	1053	834	683
No loss-of-function allele	3554	3352	3301	3222	2718	2127	1761

Wallentin L, et al. Lancet 2010; 376: 1320–28

Non-CABG & CABG related bleeding



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

Dyspnea in PLATO trial

All patients	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value*
Dyspnea, %			
Any	13.8	7.8	<0.001
With discontinuation of study treatment	0.9	0.1	<0.001

Is Tailored Treatment a Solution to Overcome Clopidogrel Resistance?

Consensus and Future Directions on the Definition of High On-Treatment Platelet Reactivity to ADP

- **The absolute level of platelet reactivity during treatment (on-treatment platelet reactivity) is proposed to be a better measure of thrombotic risk than responsiveness to clopidogrel**

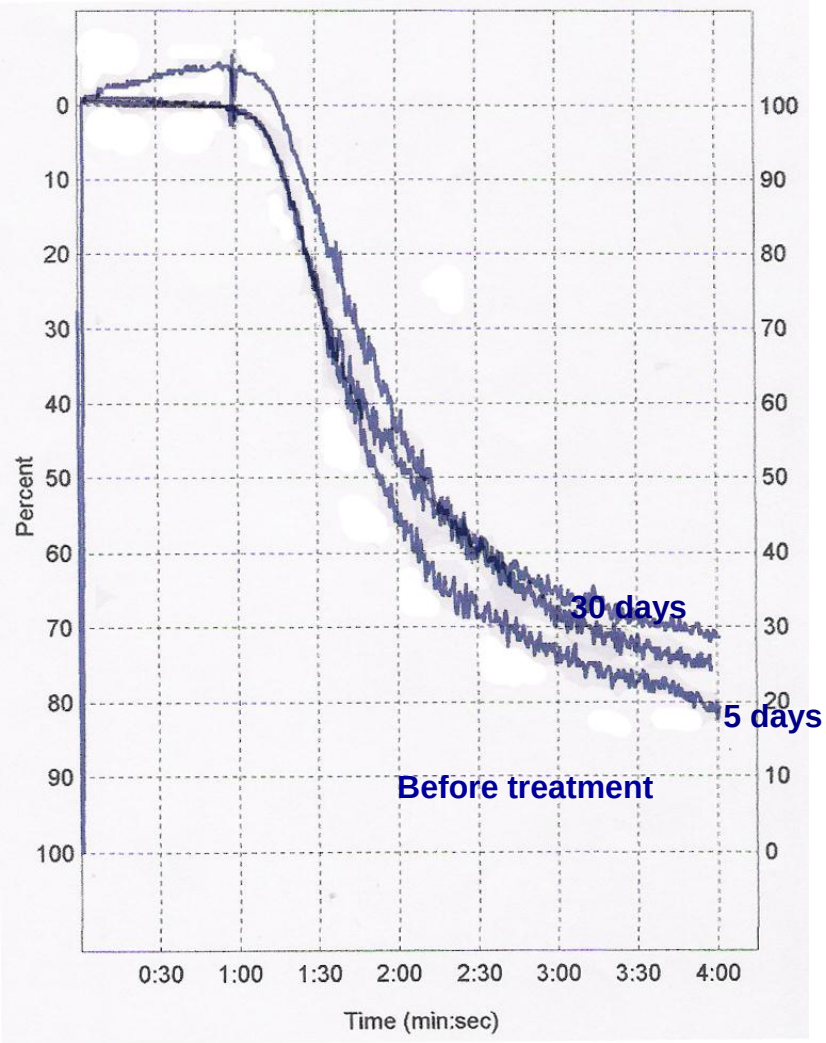
- **At the present time, high on-treatment platelet reactivity in the setting of PCI has been defined by ROC analyses using the following criteria:**
  - **PRI > 50% by VASP-P analysis**
  - **> 235 to 240 P2Y12 reaction units by VerifyNow P2Y12 assay**
  - **> 46% maximal 5-µM ADP-induced aggregation**
  - **> 468 arbitrary aggregation units/min in response to ADP by Multiplate analyzer**

Bonello L, et al. JACC. 2010;56:919–33

Residual Platelet Reactivity

High Residual Platelet Reactivity

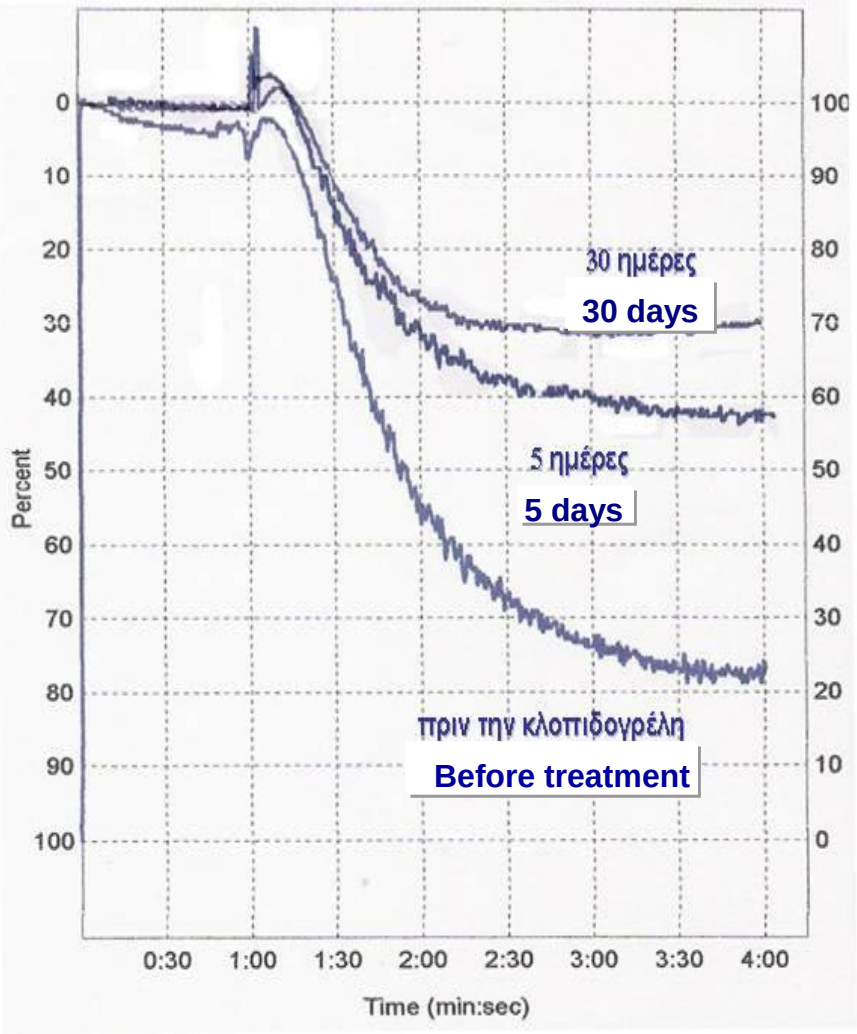
HRPR



Kalantzi KI, et al. J Thromb Haemost. 2011;9:875-878

Low Residual Platelet Reactivity

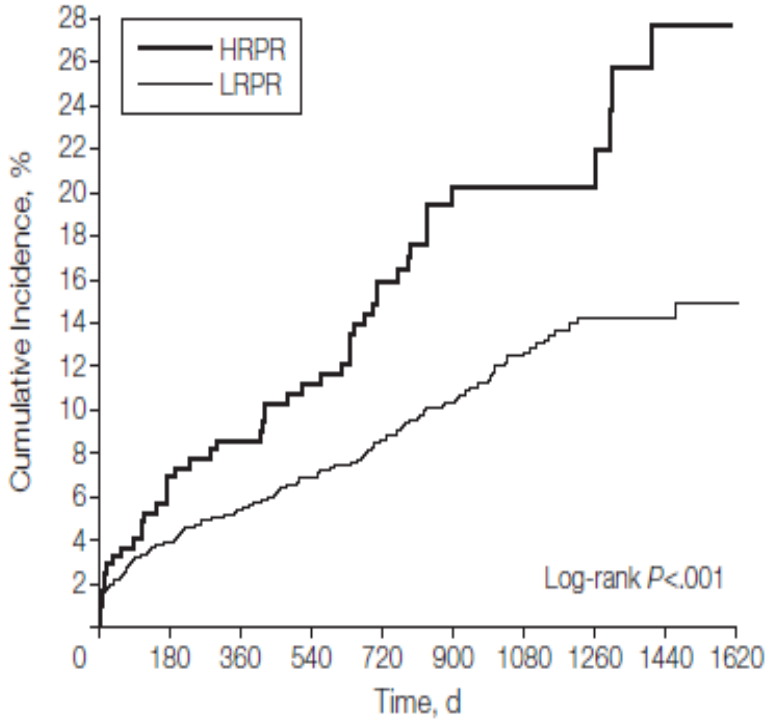
LRPR



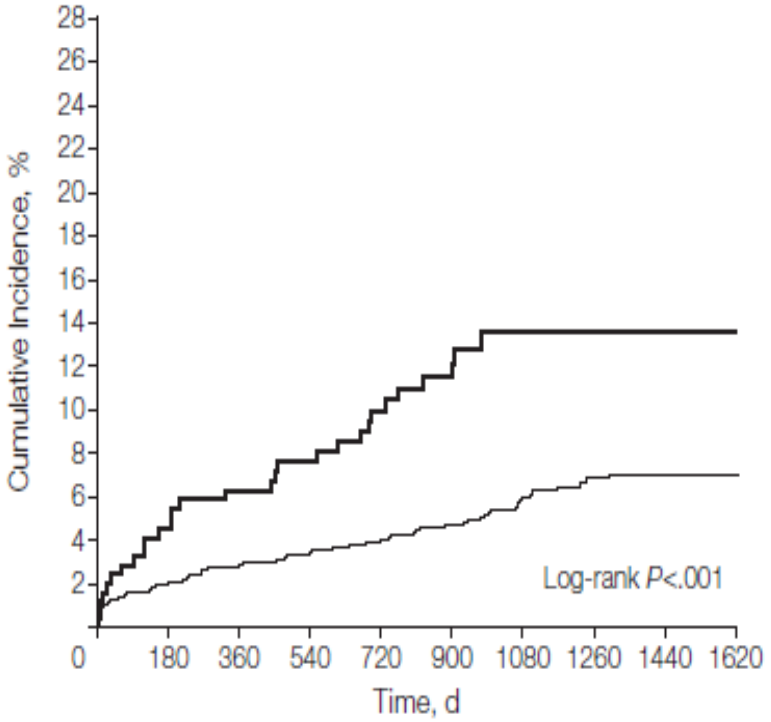
Kalantzi KI, et al. *Platelets*. 2012; In Press

The Responsiveness to Clopidogrel and Stent Thrombosis 2–ACS (RECLOSE 2–ACS) study

Primary End Point events

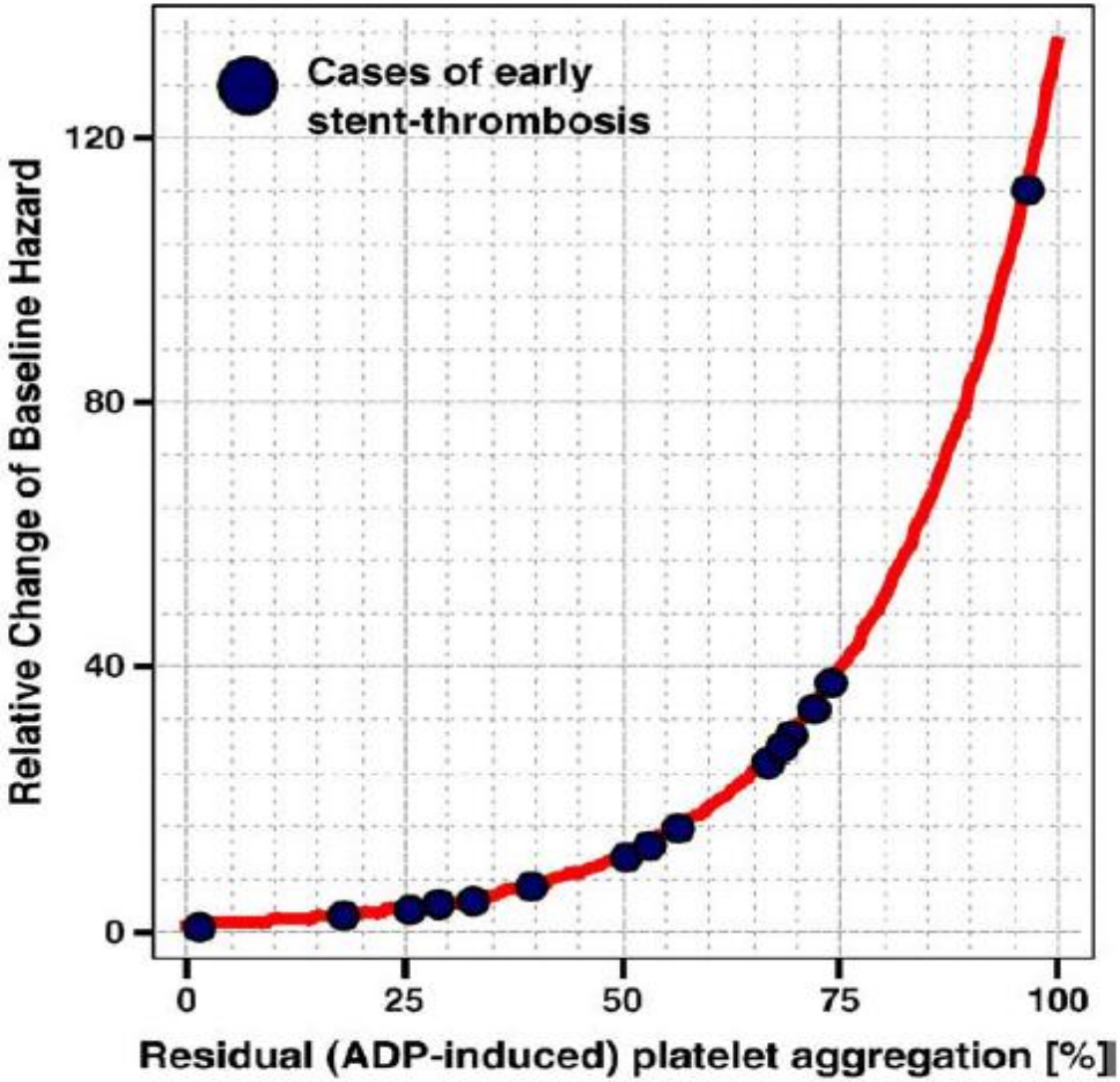


Cardiac mortality



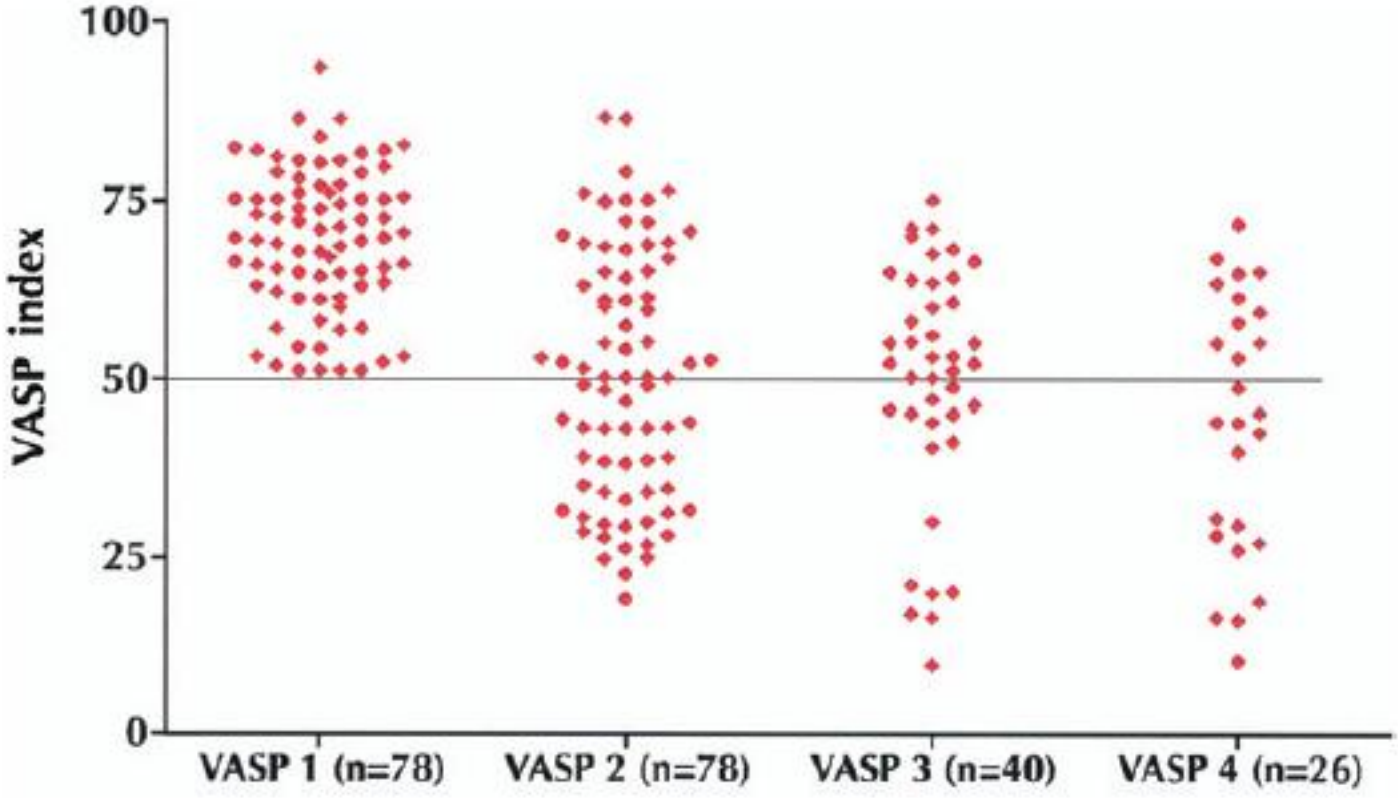
Parodi G, et al. JAMA. 2011;306(11):1215-1223

Hazard for early stent thrombosis increases with higher post-treatment platelet aggregation



Geisler T, et al. Eur Heart J. 2010

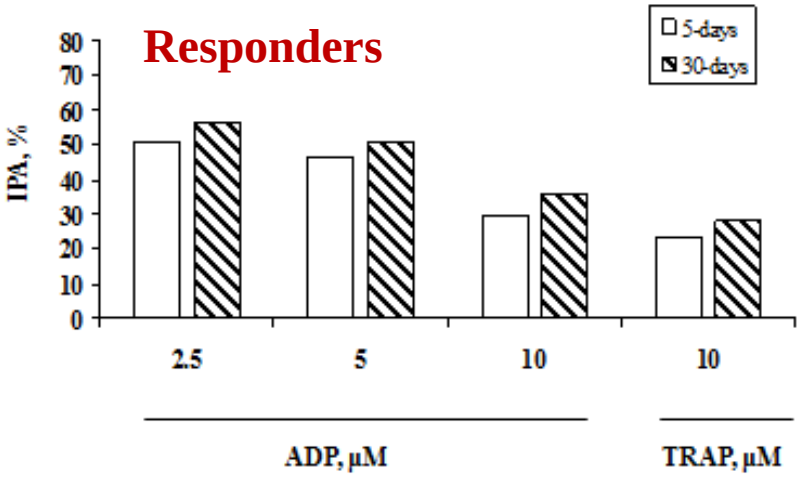
Effects of Each Additional Bolus of Clopidogrel on the VASP Index in the VASP-Guided Group

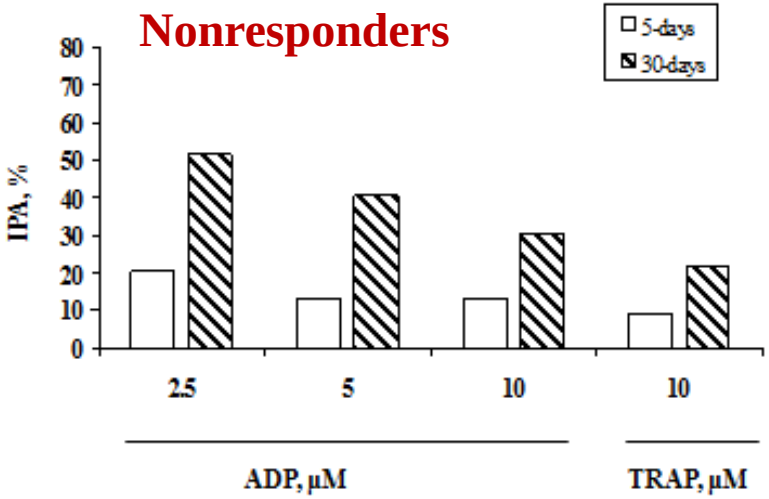


After the initial dose up to 3 additional boluses of 600 mg may be given in 24 h increments
The VASP index was assessed after 12 h until a VASP index below 50% was obtained

Bonello et al. J Am Coll Cardiol 2008;51:1404–11

The clopidogrel-induced platelet inhibition are improved in clopidogrel non-responders at 30 days of therapy with 75 mg/day





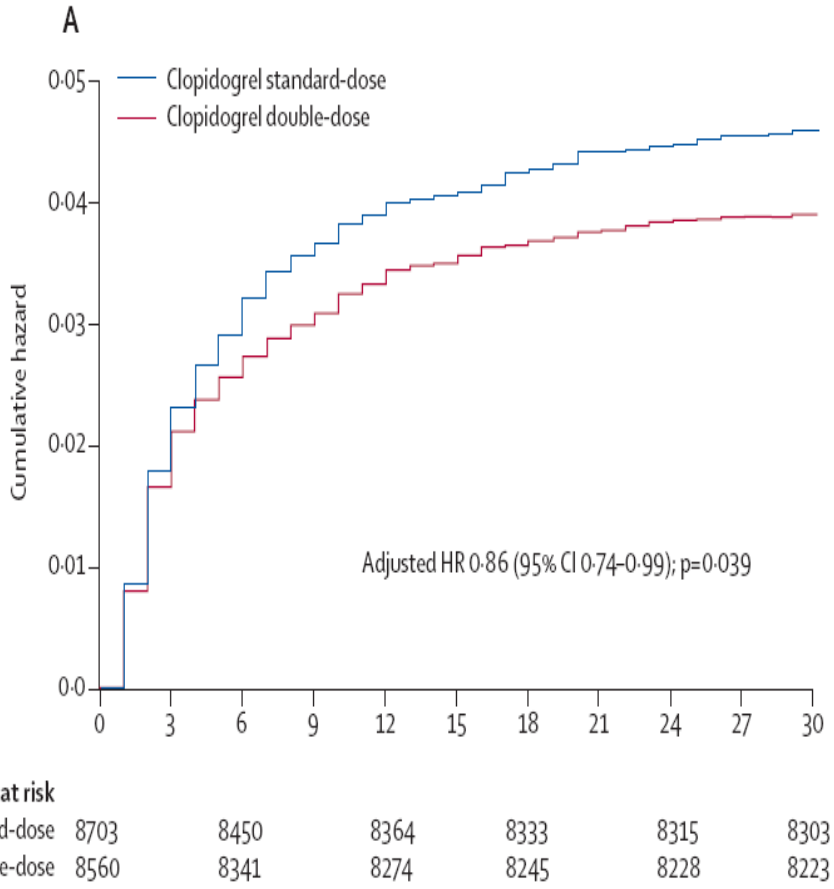
Kalantzi KI, et al. J Thromb Haemost. 2011;9:875-878

Kalantzi KI, et al. *Platelets*. 2012; In Press

CURRENT–OASIS 7

In patients undergoing PCI for ACS, a 7-day double-dose clopidogrel regimen was associated with a reduction in CV events and stent thrombosis compared with the standard dose.

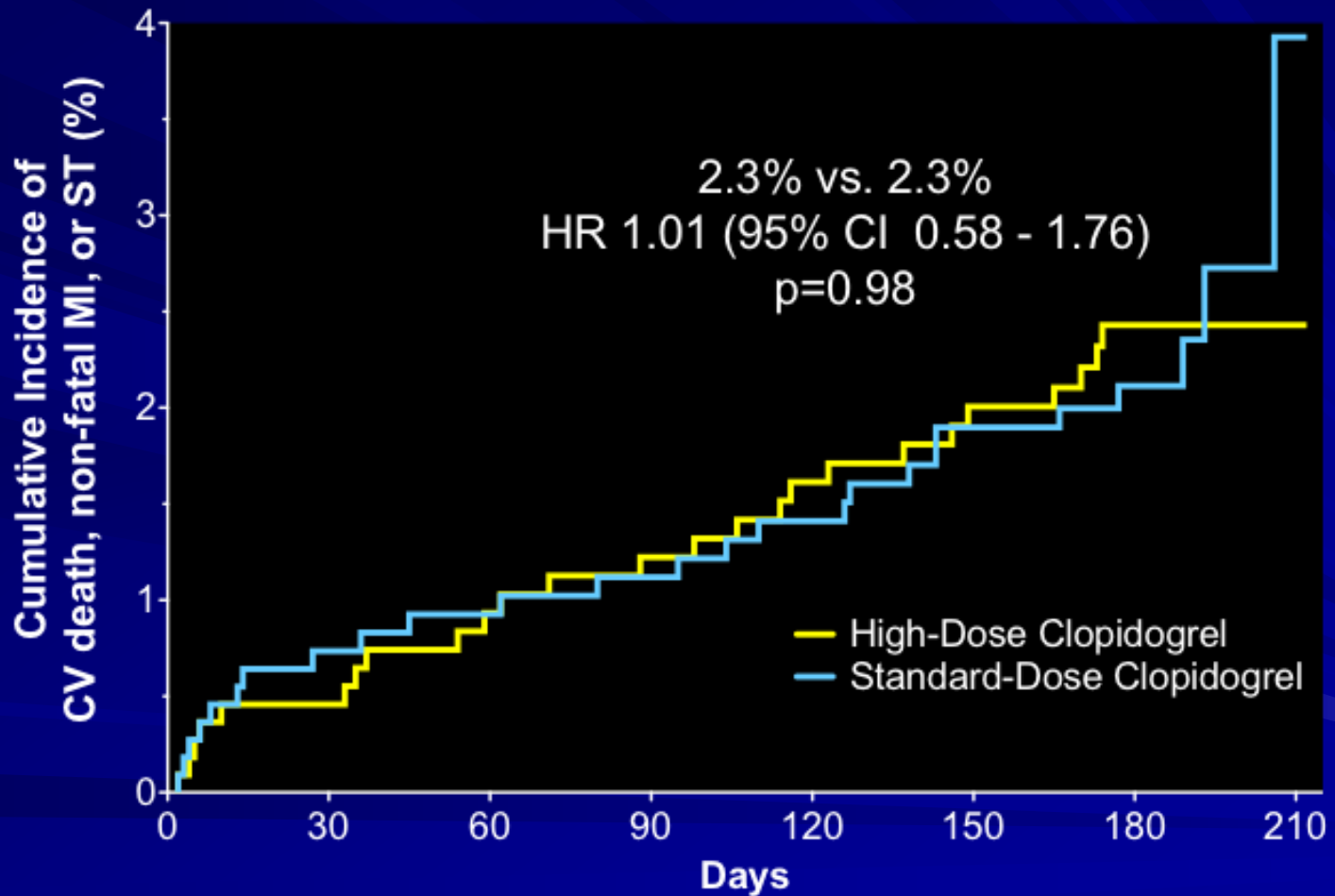
A double-dose clopidogrel regimen can be considered for all patients with ACS treated with an early invasive strategy and intended early PCI



Mehta SR. Lancet. 2010; 376: 1233–43.

GRAVITAS

Primary Endpoint: CV Death, MI, Stent Thrombosis



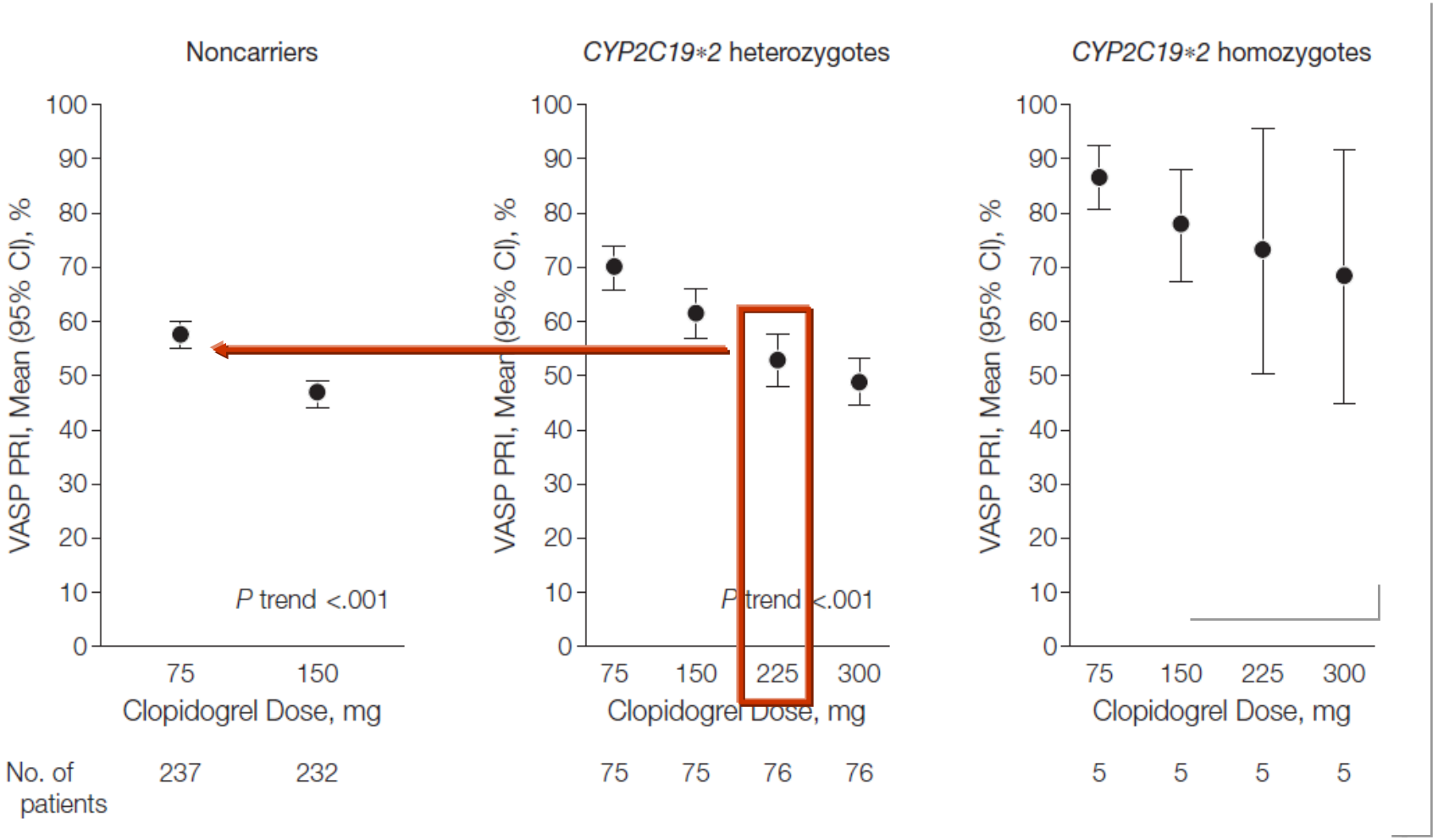
No. at Risk								
High Dose Clopidogrel	1109	1056	1029	1017	1007	998	747	54
Standard Dose Clopidogrel	1105	1057	1028	1020	1015	1005	773	53

Price MJ, et al. JAMA. 2011;305(11):1097-1105

ELEVATE-TIMI 56

333 patients with stable CVD

On-Treatment Platelet Reactivity Across Genotype and Clopidogrel Daily Dose



Mega JL, et al. JAMA 2011;306(20):2221-2228

Ongoing clinical trials on outcomes of genome-guided antiplatelet therapies

Study	Hypothesis	Patients	Duration	End points	Therapies	Effect on clinical practice
GIANT[115]	Modifying therapies according to responder (**1*) vs nonresponder (**2*) *CYP2C19* genotype will affect CV outcomes	Patients with STEMI treated by PCI, genotyped for **1* and **2* Decisions regarding therapies made by physician Estimated enrollment of 1,500 patients	1 year	Primary: death, MI, stent thrombosis Secondary: MACCE	Either continue with clopidogrel or prasugrel, increase dose of clopidogrel, or switch to clopidogrel or prasugrel	Patients with STEMI treated with PCI might benefit from choice of antiplatelet therapies on the basis of *CYP2C19* genotype
GeCCO[116]	Patients who are *CYP2C19* extensive metabolizers have similar benefit from prasugrel and clopidogrel therapies	Patients with a recently verified ACS (with or without PCI) hospitalization using clopidogrel or prasugrel Estimated enrollment of 14,600 patients	6 months	Primary: CVD, MI, CVA Secondary: hospitalizations for other CV events, health-care-resource utilization, cost-effectiveness, hospitalization for bleeding	Patients receiving clopidogrel 75 mg daily who are extensive metabolizers Patients receiving 5–10 mg per day of prasugrel	Patients with ACS who are *CYP2C19* extensive metabolizers might not gain any benefit from use of prasugrel vs clopidogrel
TARGET PCI[117]	Modifying therapies according to *CYP2C19* genotype or platelet-function testing will affect CV outcomes	Patients undergoing nonemergent PCI randomly allocated to standard therapy vs guided therapy Estimated enrollment of 1,500 patients	6 months	Primary: MACE Secondary: Bleeding, platelet-measurement phenotypes	Guided: patients tested with PFT or genotype analysis are switched to prasugrel if *CYP2C19*2* carrier or PRU >230 Standard therapy: 75 mg of clopidogrel	After PCI, patients might benefit from switching of antiplatelet therapies to prasugrel if they have a poor metabolizer genotype or HRPR

Ahmad T, et al. Nat. Rev. Cardiol. 8, 560–571 (2011)

Ongoing clinical trials on outcomes of platelet function-guided antiplatelet therapies

Study		Clinical Trials.gov Identifier	Patients (n)	Outcome	Thienopyridine Therapy	Randomization
GRAVITAS*	Gauging responsiveness With A VerifyNow Assay-Impact on Thrombosis And Safety	NCT00645918	ACS-PCI-DES (2783)	6 month CV death, non-fatal MI or ST	75 mg qd vs 150 mg qd or prasugrel 10 mg	Dose adjustment of clopidogrel among deemed non responders to 75 mg of clopidogrel identified with the VerifyNow® POC
ARCTIC	Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy	NCT00827411	Elective PCI – DES (2500)	12 months Composite end point of death, M, stroke, Urgent revascularization, ST	Therapy based on maintenance test results	Use of the VerifyNow® POC for aspirin& clopidogrel and subsequent dose adjustment in non responders versus standard care
DANTE	Dual Antiplatelet Therapy Tailored on the Extent of Platelet Inhibition	NCT00774475	Unstable or NSTEMI–PCI (442)	6 and 12 months CV death, nonfatal MI, TVR by PCI or CABG	75 mg qd v 150 mg qd	Dose adjustment of clopidogrel among deemed non responders to 75 mg of clopidogrel identified with the VerifyNow® POC
TOPAS -1	Tailoring of Platelet Inhibition to Avoid Stent Thrombosis	NCT00914368	Previous PCI or stenting for CAD (450)	To establish cut off level of platelet inhibition that separates patients with or without previous stent occlusion	600 mg LD 75 mg qd for 6 months	VerifyNow® P2Y12 (PRU)
TRIGGER-PCI	Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel	NCT00910299	Elective PCI 2150	CV death, non fatal MI	Prasugrel 60/10 mg vs Clopidogrel 600 mg/75 mg	Dose adjustment of clopidogrel among deemed non responders to 75 mg identified with the VerifyNow® POC
ASCET	Testing Platelet Reactivity in Patients with stable CHD on Aspirin, whereafter Randomisation to Clopidogrel or Aspirin and repeated Platelet Testing	NCT 00222261	Stable CAD (1001)	24 months Combined Death, AMI, ACS, Stroke	Clopidogrel 75 mg/d	Aspirin or Clopidogrel as monotherapy

CONCLUSION

- The new P2Y12 antagonists, prasugrel and ticagrelor, are characterized by more potent antiplatelet effects and reduce recurrent ischemic event rates compared with clopidogrel among ACS patients
- These antagonists are associated with an increased risk of bleeding, therefore the potential benefits associated in terms of reduction of ischemic events need to be kept in perspective with known bleeding complications
- It is questionable whether individualizing antiplatelet therapy should be based on genetic testing, platelet function testing, or both.
- The results of ongoing large-scale outcome studies, which are evaluating the safety and efficacy of individualizing antiplatelet treatment strategies, are needed before their routine application into clinical practice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