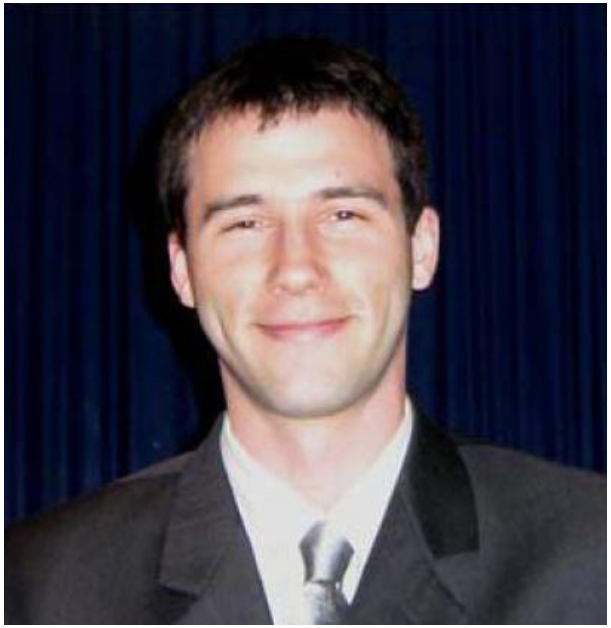
High on-treatment platelet reactivity to thienopyridines .
Is it clinically important in ACS/PCI?



- Thank you Dr laurent BONELLO

High on-treatment platelet reactivity to thienopyridines .
Is it clinically important in ACS/PCI?

Pr PAGANELLI Franck

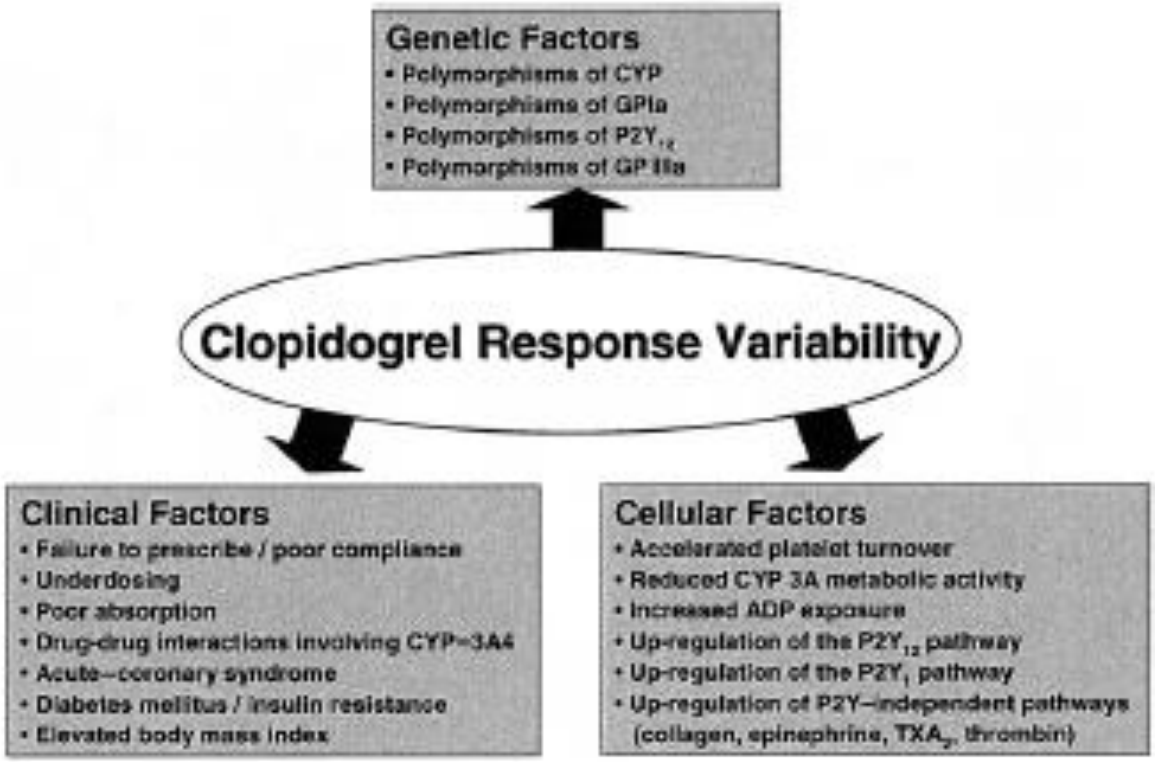
Département de cardiologie

Hôpital nord Marseille

FRANCE

What is HTPR?

Large interindividual variability in clopidogrel responsiveness



Responsiveness is unpredictable

« The optimal definition of resistance or non-responsiveness to any platelet agent should be the failure of the antiplatelet agent to inhibit the target and its action »

Platelet function monitoring in patient with coronary artery disease.
Gurbel PA JACC 2007:50;1822-34

There is a strong link between PR and recurrent thrombotic events: threshold

Author	n	End point	Follow-up	Platelet assay	Cut-off value
Barragan et al.	46	ST	1 month	VASP index	*50 %*
Bonello et al.	144	MACE	6 months	VASP index	*50 %*
Frere et al.	195	MACE + stroke	1 month	VASP index	*53 %*
Blindt et al.	99	ST	6 months	VASP index	*48 %*
Price et al.	380	CV death + MI	6 months	VerifyNow P2Y12	*235 PRU*
Marcussi et al.	683	CV death + MI	12 months	VerifyNow P2Y12	*240 PRU*
Gurbel et al.	297	CVE	24 months	LTA 5µmol ADP	*46 %*

For example

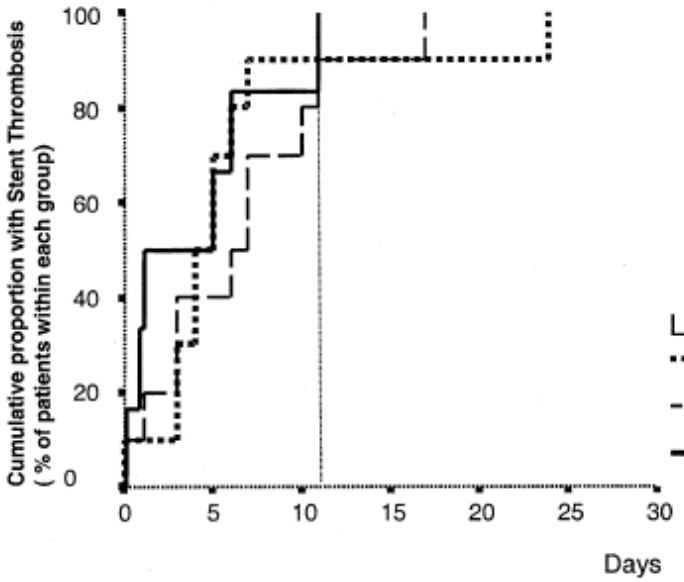
Threshold of VASP index is ≥ 50 %with a high NPV for MACE

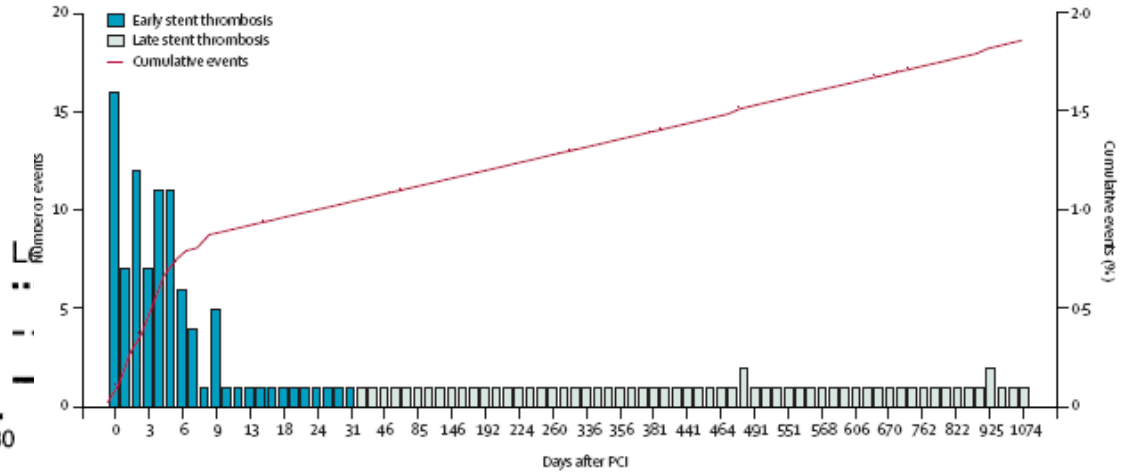
= Definition of High on treatment platelet reactivity (HTPR)

Why is it clinically important ?

To avoid stent thrombosis

Stent thrombosis : an early event





Stent thrombosis remains in the vast majority of cases an early (<30 days) event.

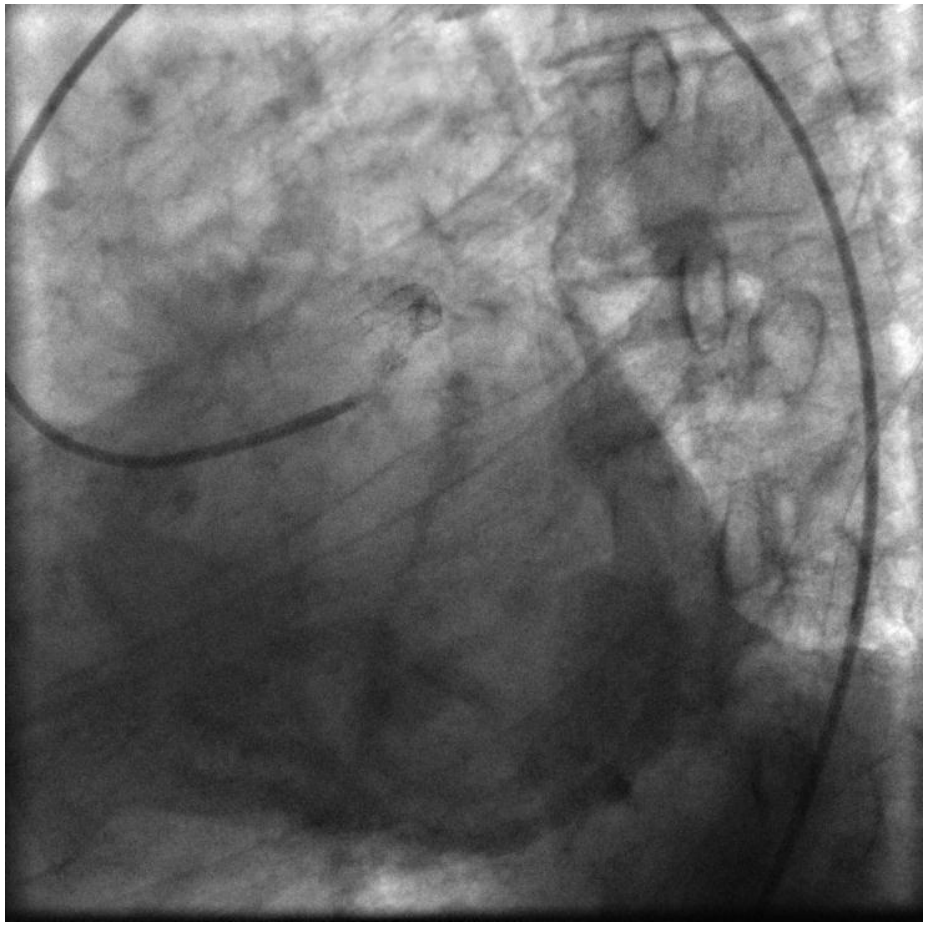
Ong a. et al JACC 2005

Wiviott SD et al. Lancet 2008

STENT thrombosis is

rare =1à 3%

expensive 50% mortality



If we decrease HTPR,

we decrease stent thrombosis

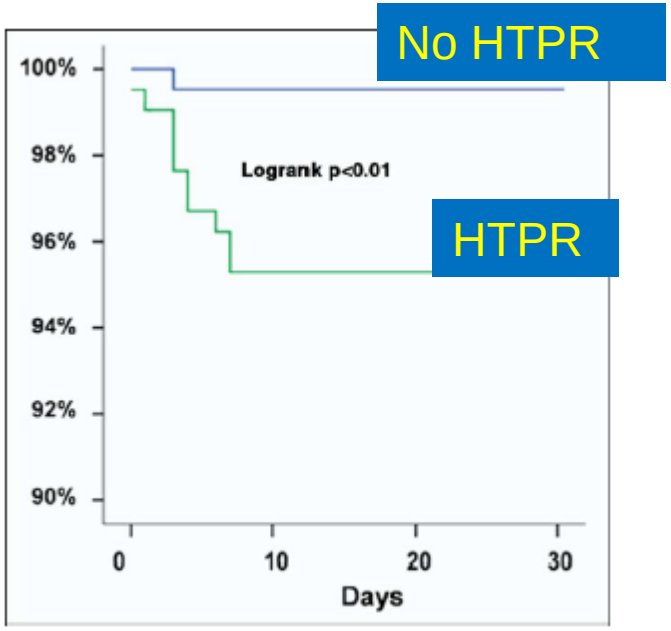


Figure 3. Kaplan-Meier curve of freedom of definite stent thrombosis survival according to groups.

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]

How to detect HTPR?

By several tests

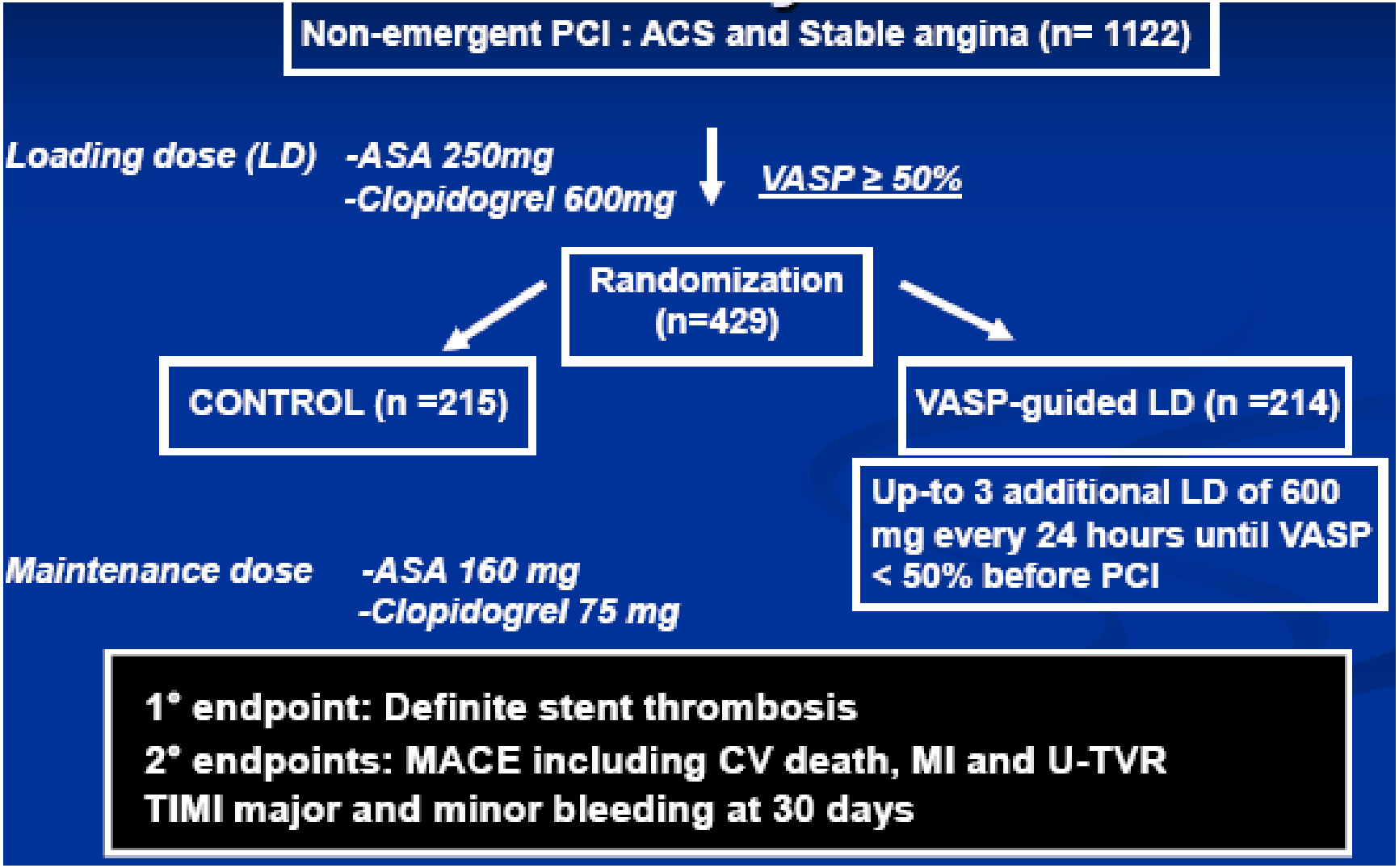
Test	Measure	Advantages	Disadvantages
Light transmission aggregometry (LTA)	Platelet aggregation	Historical gold standard	Time consuming High sample volume
Verify now	Platelet aggregation	Simple to use Point of care Low sample volume	Limited haematocrit and platelet count range
Platelet works	Platelet aggregation	Minimal sample preparation Whole blood assay	Limited studies
Platelet surface P-selectin, platelet surface-activated GP IIb/IIIa, leukocyteplatelet aggregates	Activation dependent changes in platelet surface	Low sample volume Whole blood assays	Requires flow cytometer and experienced technician
Thromboelastography platelet mapping system	Platelet contribution to clot strength	Whole blood assay	Limited studies
Impact cone and platelet analyser	Shear-induced platelet adhesion	Simple to use not widely Rapid result available Point of care Low sample volume No sample preparation Whole blood assay	Not widely available
VASP (vasodilatorstimulated phosphoprotein)	P2Y12 signalling dependent	Low sample volume Whole blood assay Blood samples can be mailed at room temperature to a core laboratory Specificity for P2Y12	Requires flow cytometer and experienced technician

Can we modulate HTPR?

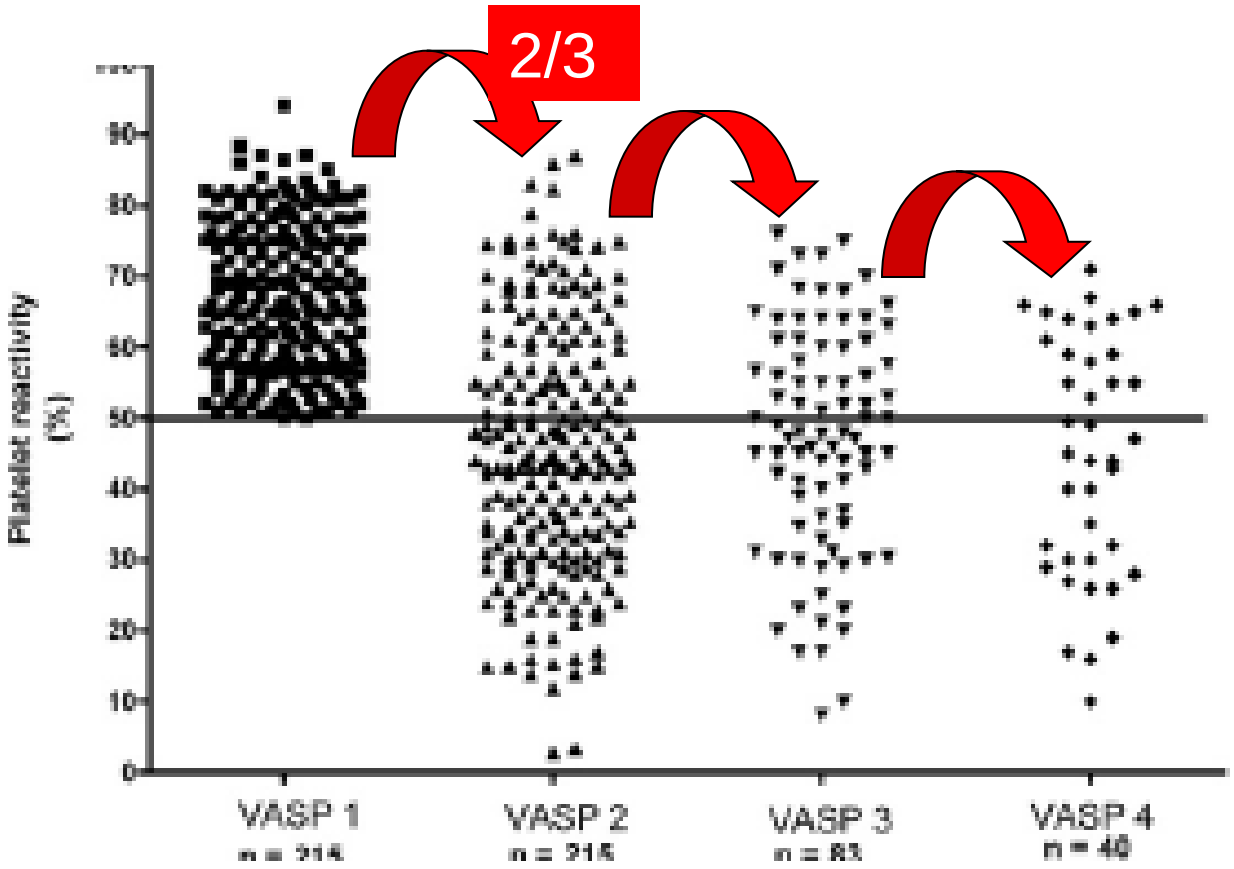
Yes we can …


We Can Do It!
POST FEB. 15 TO FEB. 28
WAR PRODUCTION CO-ORDINATING COMMITTEE

VASP study: multicenter prospective randomized study

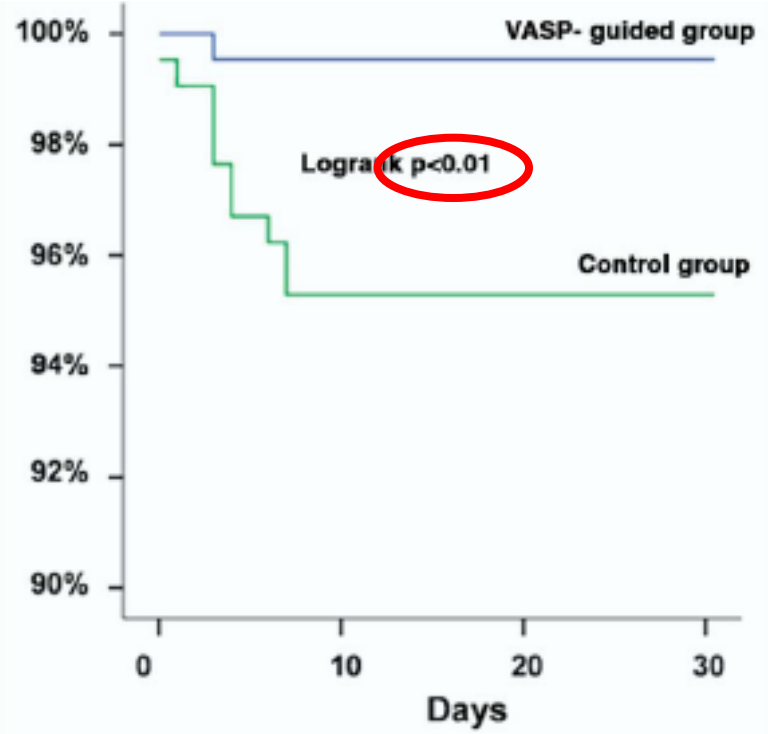


Biological results



Platelet reactivity monitoring enable to the reach therapeutic window in almost all patients

PR monitoring decreased the rate of thrombotic recurrences without increasing bleedings



End Point	Control Group (n = 214)	VASP-Guided Group (n = 215)	p Value
Major bleeding	2 (0.9%)	2 (0.9%)	1
Minor bleeding	4 (1.9%)	6 (2.8%)	0.8
All	6 (2.8%)	8 (3.7%)	0.8

JACC. 2008. Am J Card. 2009

So must detect HTPR to select patients on high risk stent thrombosis

So we must detect HTPR for adjusting loading dose regarding the test results (monitoring)

Take home message

- HTPR is clinically important to detect patients with high risk of stent thrombosis

- HTPR is clinically important to perform monitoring platelet inhibition

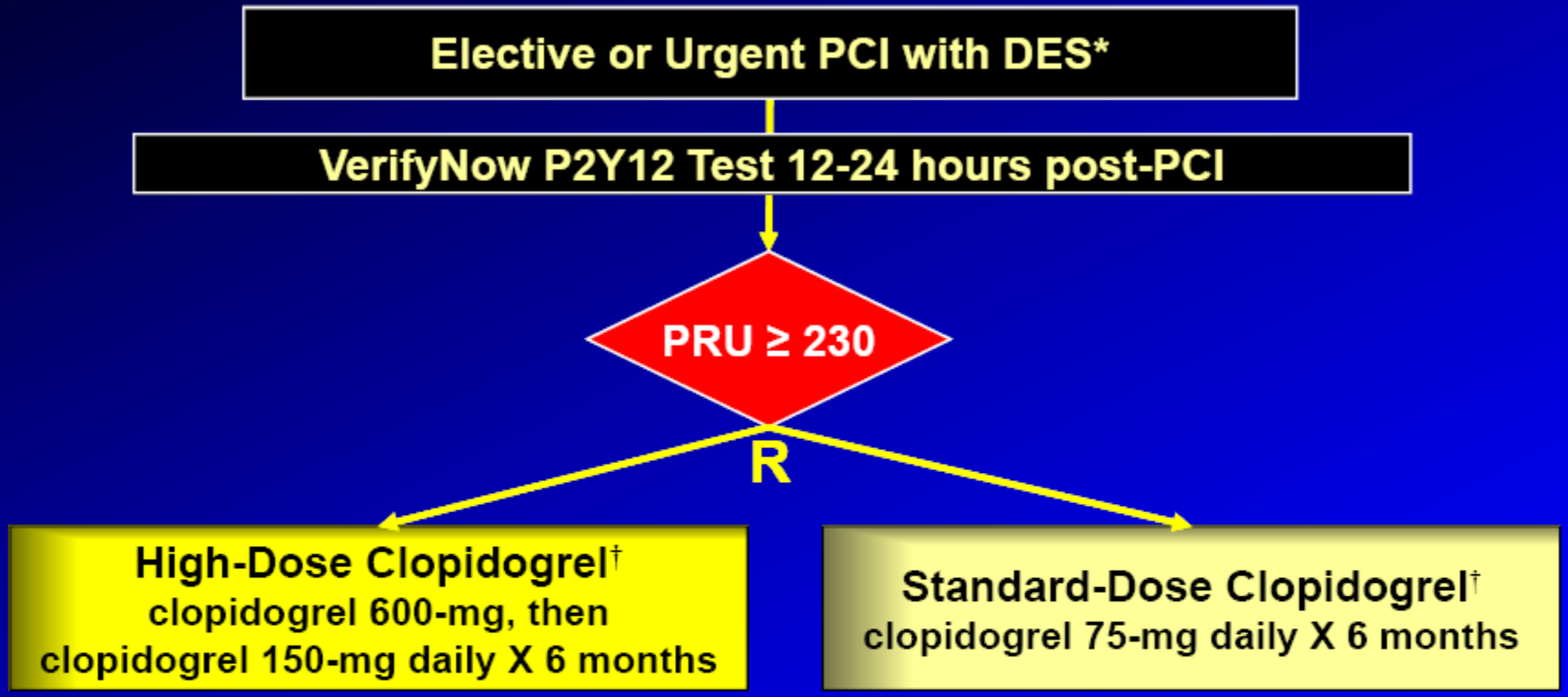
Thank you for your attention

Question 1

- Mr PAGANELLI
- In the GRAVITAS, we detect HTPR but there is no significant difference in MACE

- HTPR doesn’t work ?

GRAVITAS Study Design



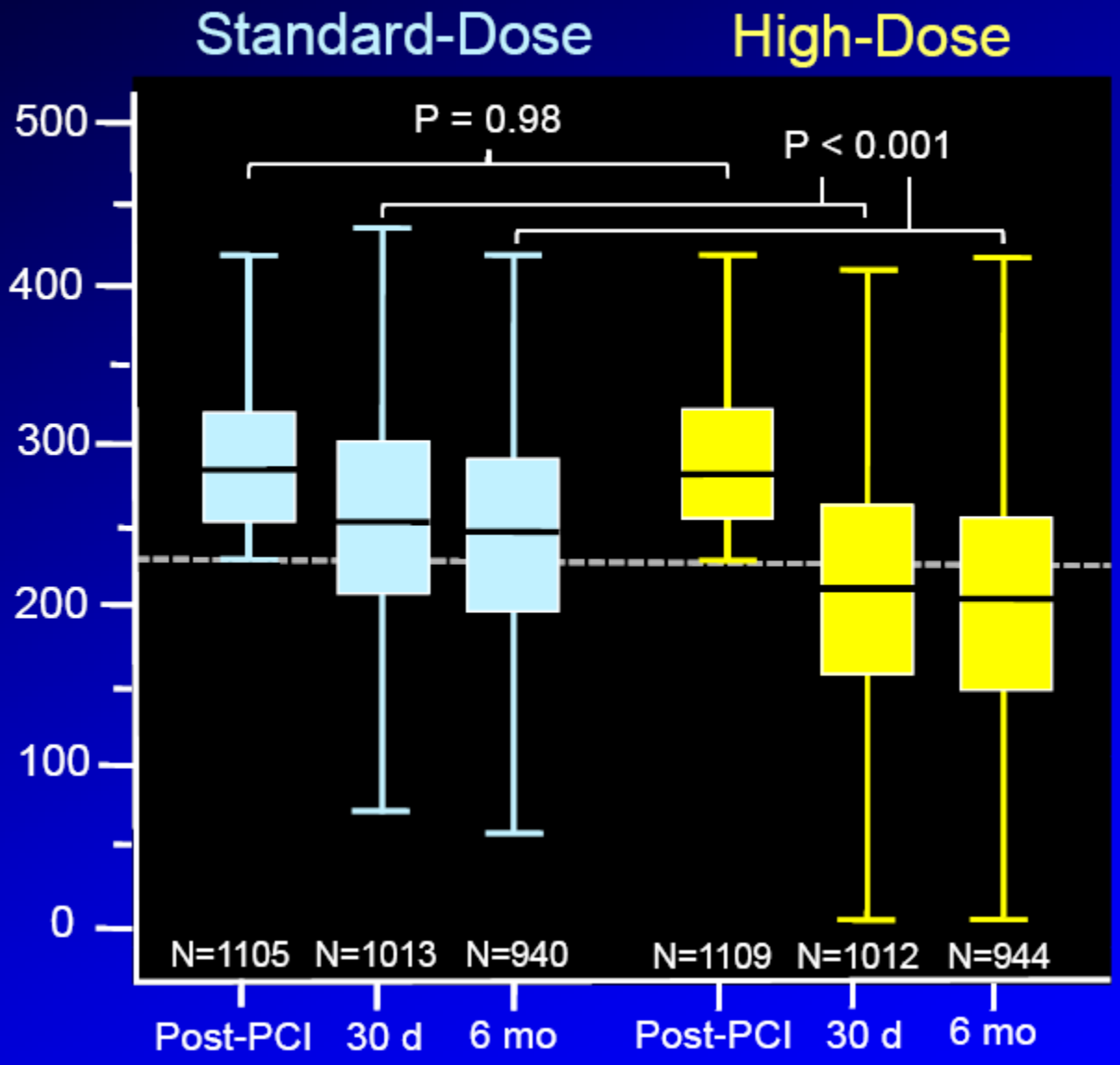
Primary Efficacy Endpoint: CV Death, Non-Fatal MI, Stent Thrombosis at 6 mo
Key Safety Endpoint: GUSTO Moderate or Severe Bleeding at 6 mo
Pharmacodynamics: Repeat VerifyNow P2Y12 at 1 and 6 months

*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs

†placebo-controlled All patients received aspirin (81-162mg daily)

GRAVITAS

Pharmacodynamics: Effect of SD vs HD Clopidogrel

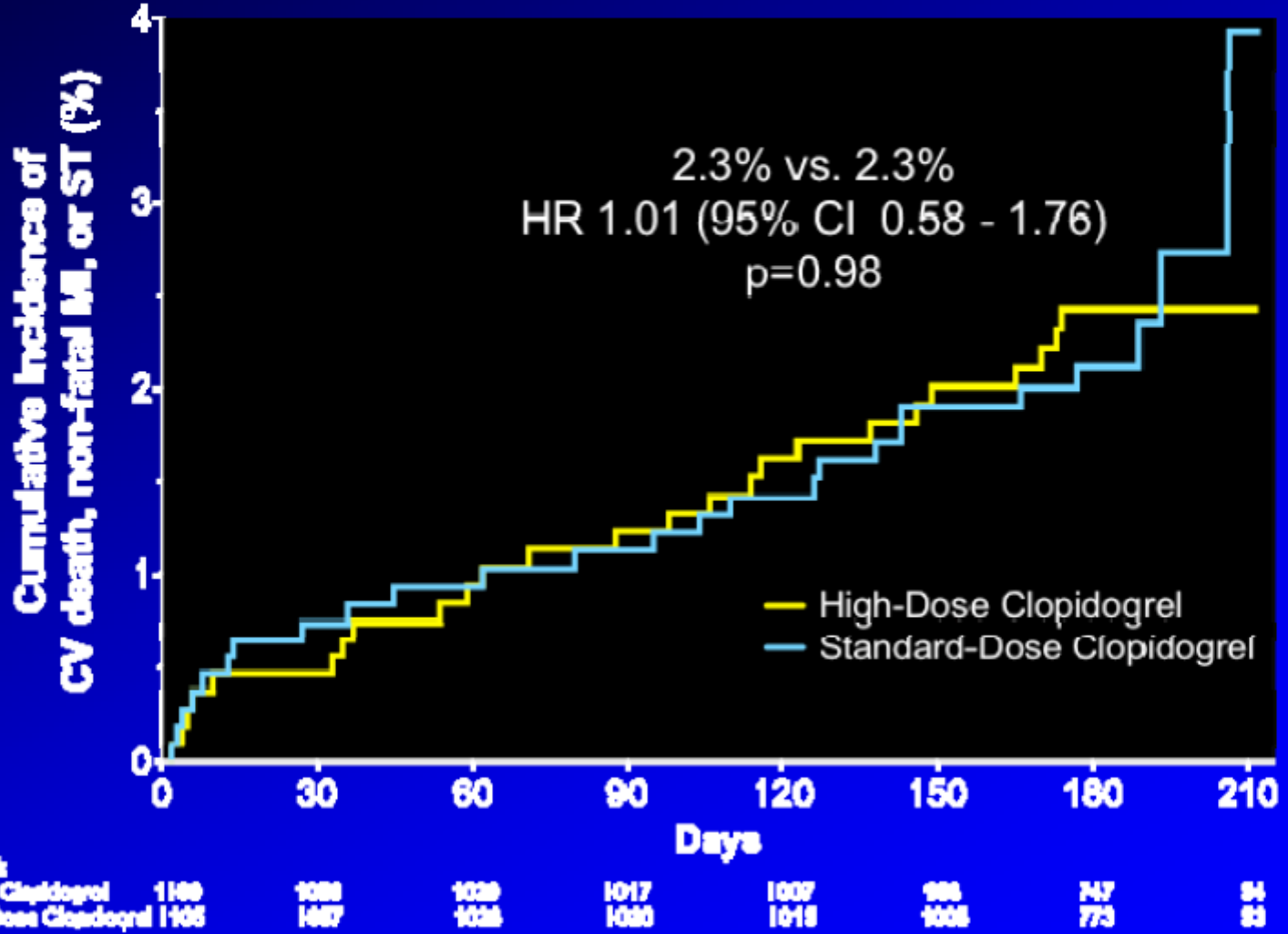


Persistently high reactivity @ 30 days: 62% vs 40%, p<0.001

ITT population

GRAVITAS

Primary Endpoint: CV Death, MI, Stent Thrombosis



No. at Risk								
High Dose Clopidogrel	1149	1088	1029	1017	1007	986	747	94
Standard Dose Clopidogrel	1105	1057	1026	1000	1018	1006	773	93

Observed event rates are listed; P value by log rank test

GRAVITAS

GRAVITAS study

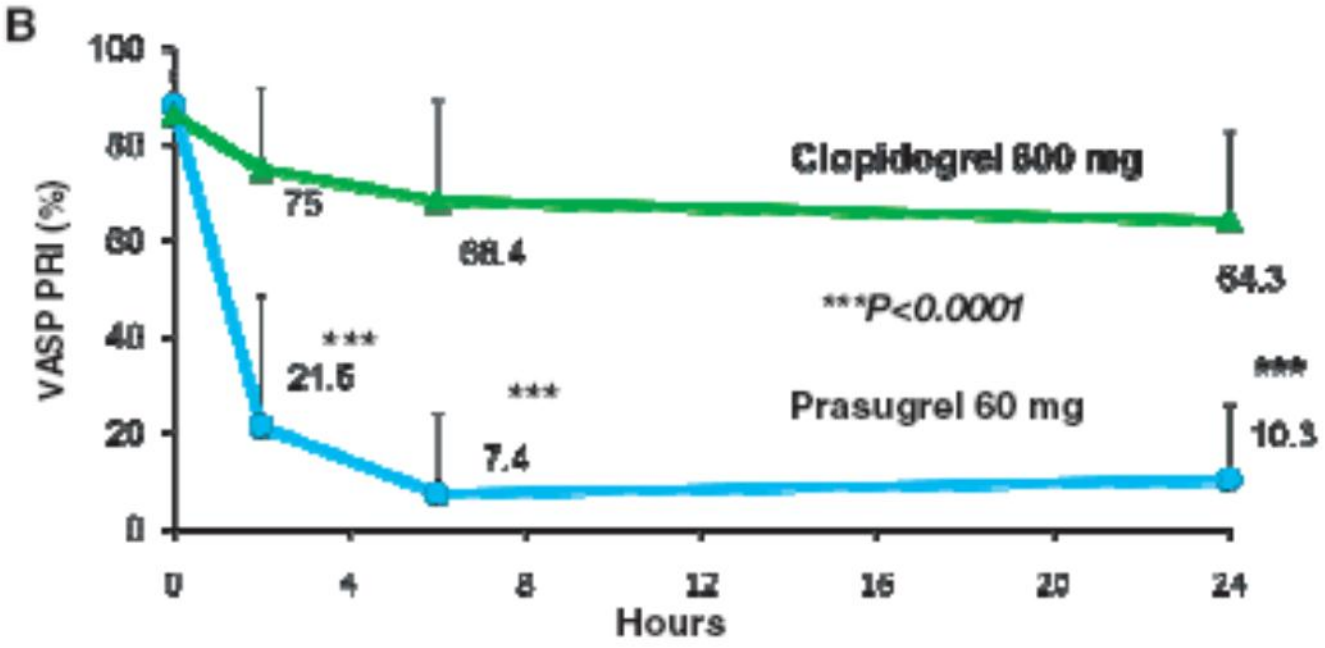
- Detection of HTPR, decrease HTPR

but there is no monitoring …to reach the gold value

- Stable angina unpower study …

Question 2

- Mr PAGANELLI, there is now a new platelet agent « prasugrel » which is superior to clopidogrel so do we need perform HTPR if our patient on prasugrel treatment?



Prasugrel decrease HTPR… more than clopidogrel 75mg more than clopidogrel 150 mg

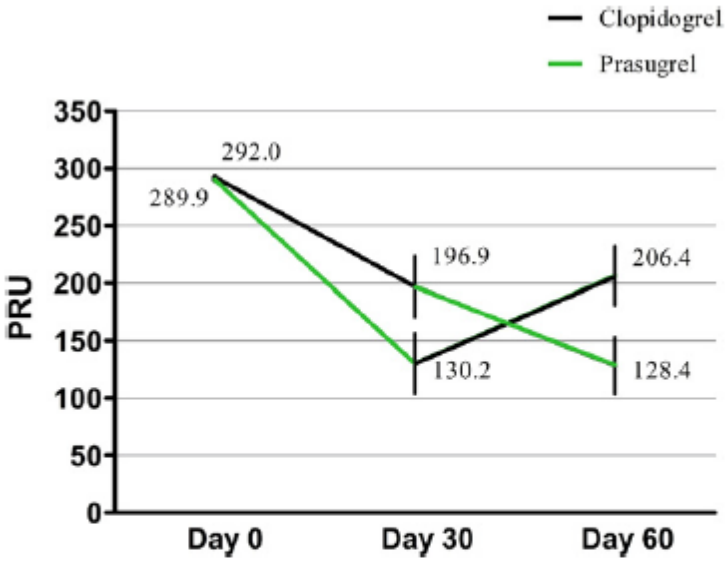
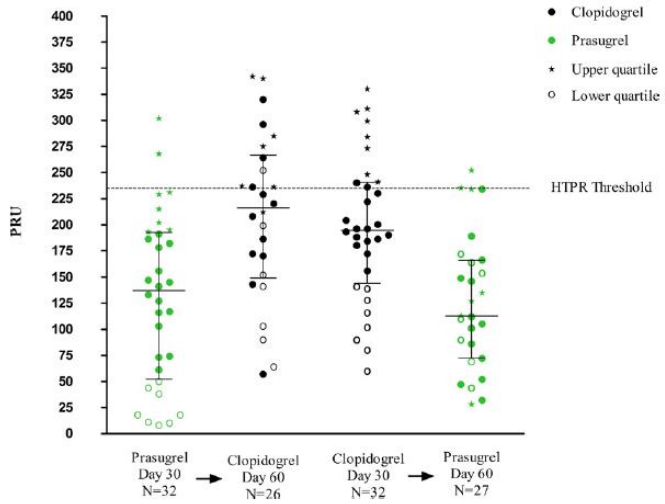


Figure 2. PR by Treatment Sequence

Data for the pre-crossover and post-crossover periods are depicted. Least-squares estimates and 95% confidence intervals are presented. **Black line** indicates clopidogrel; **green line** indicates prasugrel. PR = platelet reactivity; PRU = platelet reactivity unit(s).



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DOI: 10.1016/j.jcin.2010.12.011

Prasugrel Overcomes High On-Clopidogrel Platelet Reactivity Post-Stenting More Effectively Than High-Dose (150-mg) Clopidogrel

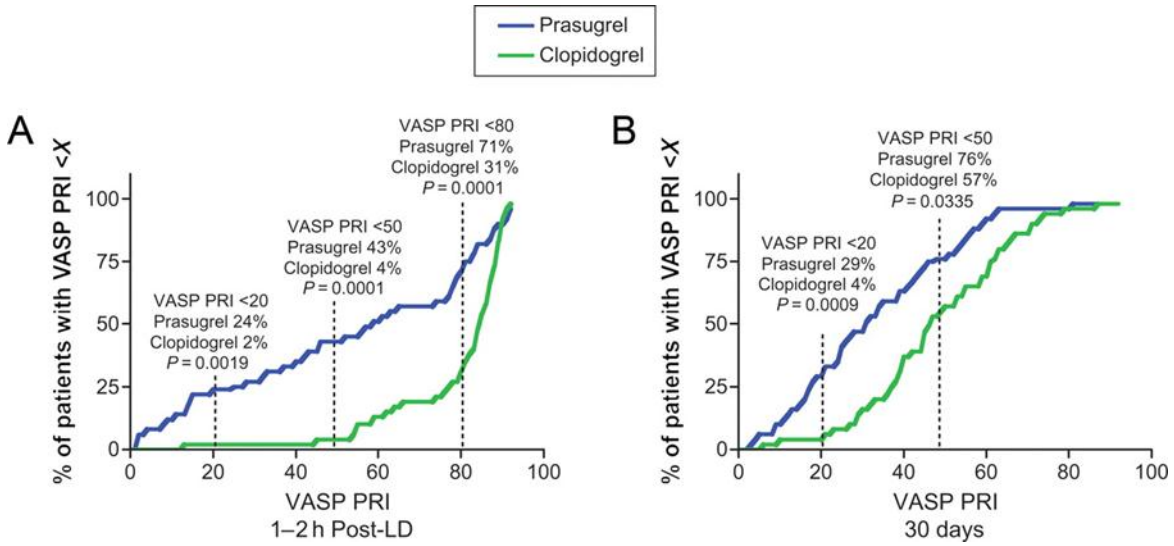
The Importance of *CYP2C19*2* Genotyping

Dimitrios Alexopoulos, MD,* Gerasimos Dimitropoulos, MD,* Periklis Davlouros, MD,* Ioanna Xanthopoulou, MD,* George Kassimis, MD,* Eleana F. Stavrou, PHD,† George Hahalis, MD,* Aglaia Athanassiadou, PHD†

Patras, Greece

- But there is biologic prasugrel resistance
- There is also HTPR with prasugrel

For example in TRITON-TIMI 38



Also in our study

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doi:10.1016/j.jacc.2011.04.017

CLINICAL RESEARCH **Interventional Cardiology**

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

Laurent Bonello, MD,*† Michel Pansieri, MD,‡ Julien Mancini, MD,§‖ Roland Bonello, MD,¶ Luc Maillard, MD,# Pierre Barnay, MD,‡ Philippe Rossi, MD,** Omar Ait-Mokhtar, MD,* Bernard Jouve, MD,†† Frederic Collet, MD,¶ Jean Pascal Peyre, MD,‡‡ Olivier Wittenberg, MD,§§ Axel de Labriolle, MD‖‖ Elise Camilleri, MD,¶¶ Edouard Cheneau, MD,## Elma Cabassome, MD,* Françoise Dignat-George, PHD,†*** Laurence Camoin-Jau, PHD,†*** Franck Paganelli, MD*

Marseille, Avignon, Aix-en-Provence, Marignane, Montauban, and Martigues, France

25%....
The same value

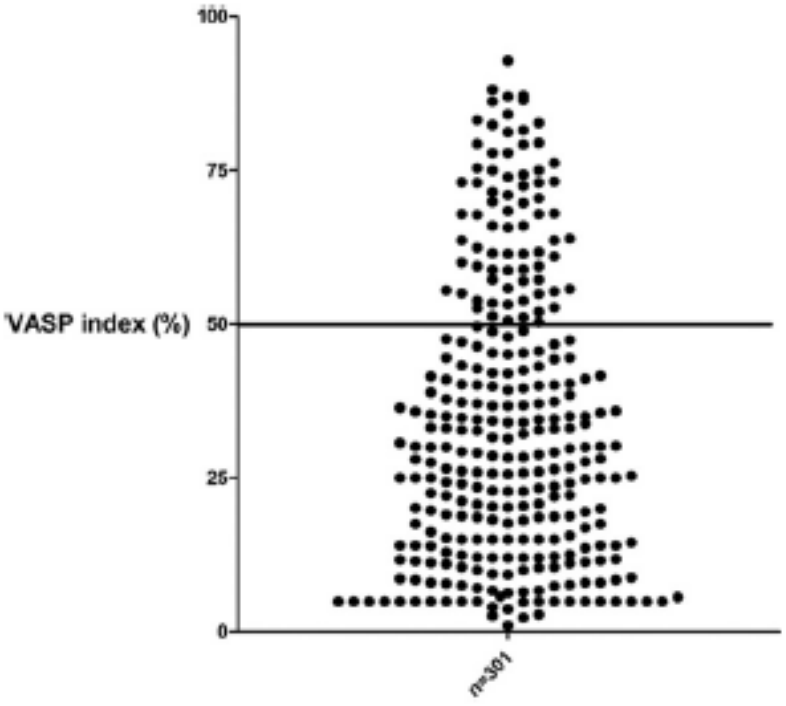


Figure 1 **VASP Index After Prasugrel LD**

Although the vast majority of patients had platelet reactivity (PR) below 50%, 25.2% were considered to have high on-treatment platelet reactivity (HTPR). LD = loading dose; VASP = vasodilator-stimulated phosphoprotein.

HTPR is clinically very important to detect MACE

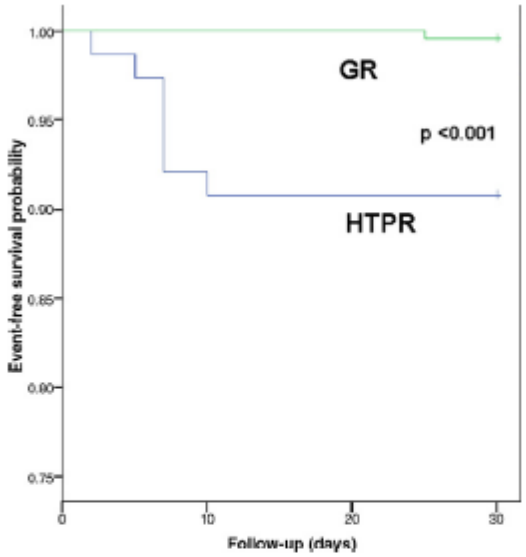


Figure 3 Kaplan-Meier Analysis of Survival Free From Thrombotic Events Comparing GR and Patients With HTPR

Good responders (GR) had significantly higher survival free from major adverse cardiac events than patients with high on-treatment platelet reactivity (HTPR) (log p < 0.001).

Table 2 1-Month Outcomes in GR (VASP Index <50%) and in Patients With HTPR (VASP Index ≥50%)

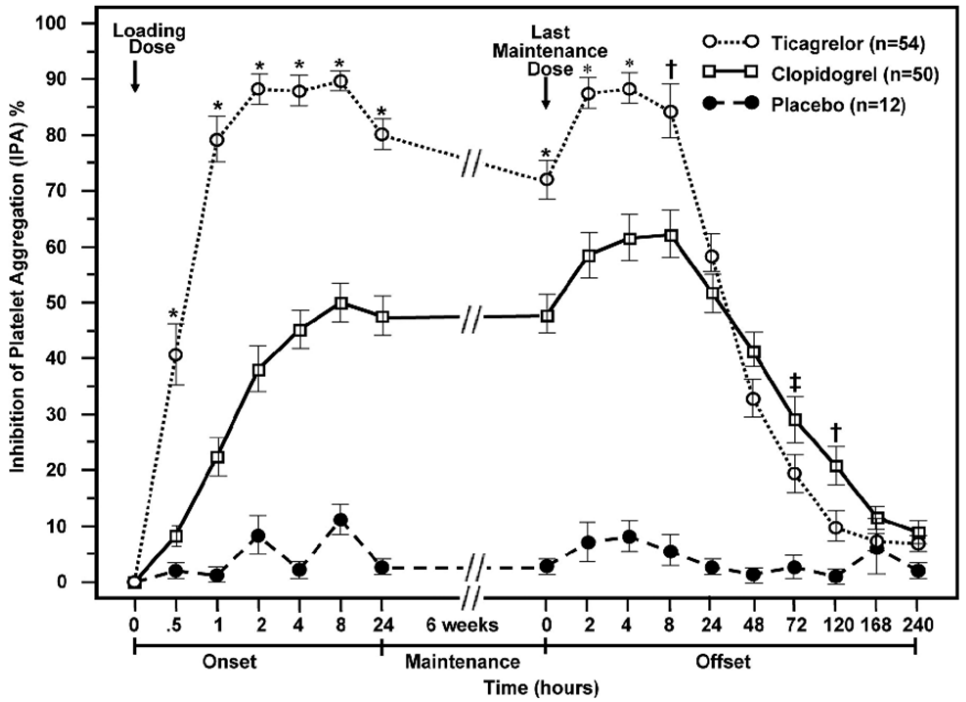
Outcome	GR (n = 225)	HTPR (n = 76)	p Value
CV death	1	0	
Recurrent ACS	0	4	
Stent thrombosis	0	3	
All MACE	1	7	<0.001
Major TIMI bleeds	2	0	
Minor TIMI bleeds	2	1	
All TIMI bleeds	4	1	0.70

ACS = acute coronary syndromes; GR = good responders; HTPR = high on-treatment platelet reactivity; MACE = major adverse cardiac event(s); TIMI = Thrombolysis in Myocardial Infarction; VASP = vasodilator-stimulated phosphoprotein; other abbreviations as in Table 1.

So we must monitoring patients with prasugrel to detect HTPR …

Question 3

- Mr PAGANELLI, there is now a new platelet agent « ticagrelor » which is superior to clopidogrel so do we need HTPR with ticagrelor ?



Gurbel. CIRC 2010

Sorry

- There is no ticagrelor in France
- So we can’t perform this kind of study …

Take home message (2)

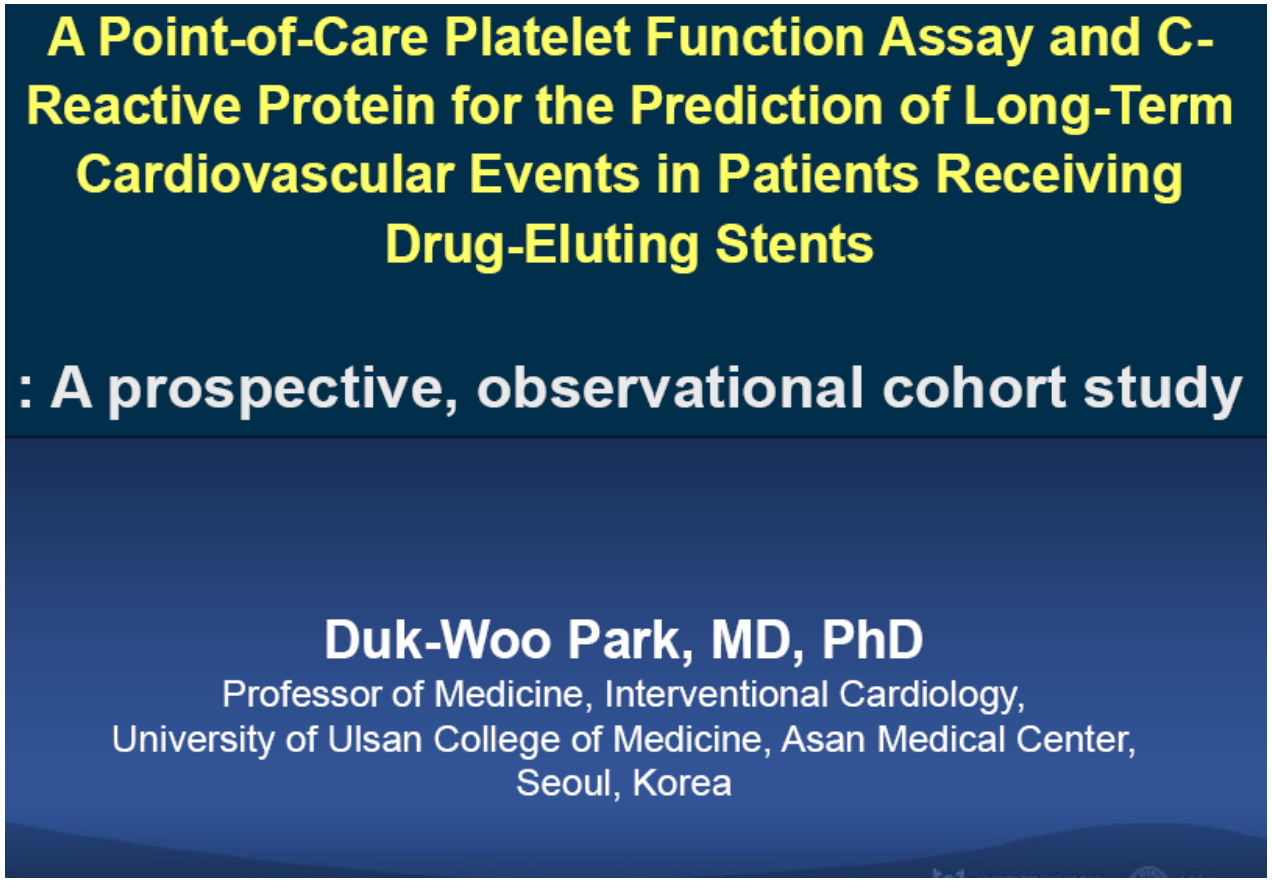
- HTPR is clinically important to detect patients with high risk of stent thrombosis

- HTPR is clinically important to perform monitoring platelet inhibition
- Despite GRAVITAS study
- Even with prasugrel

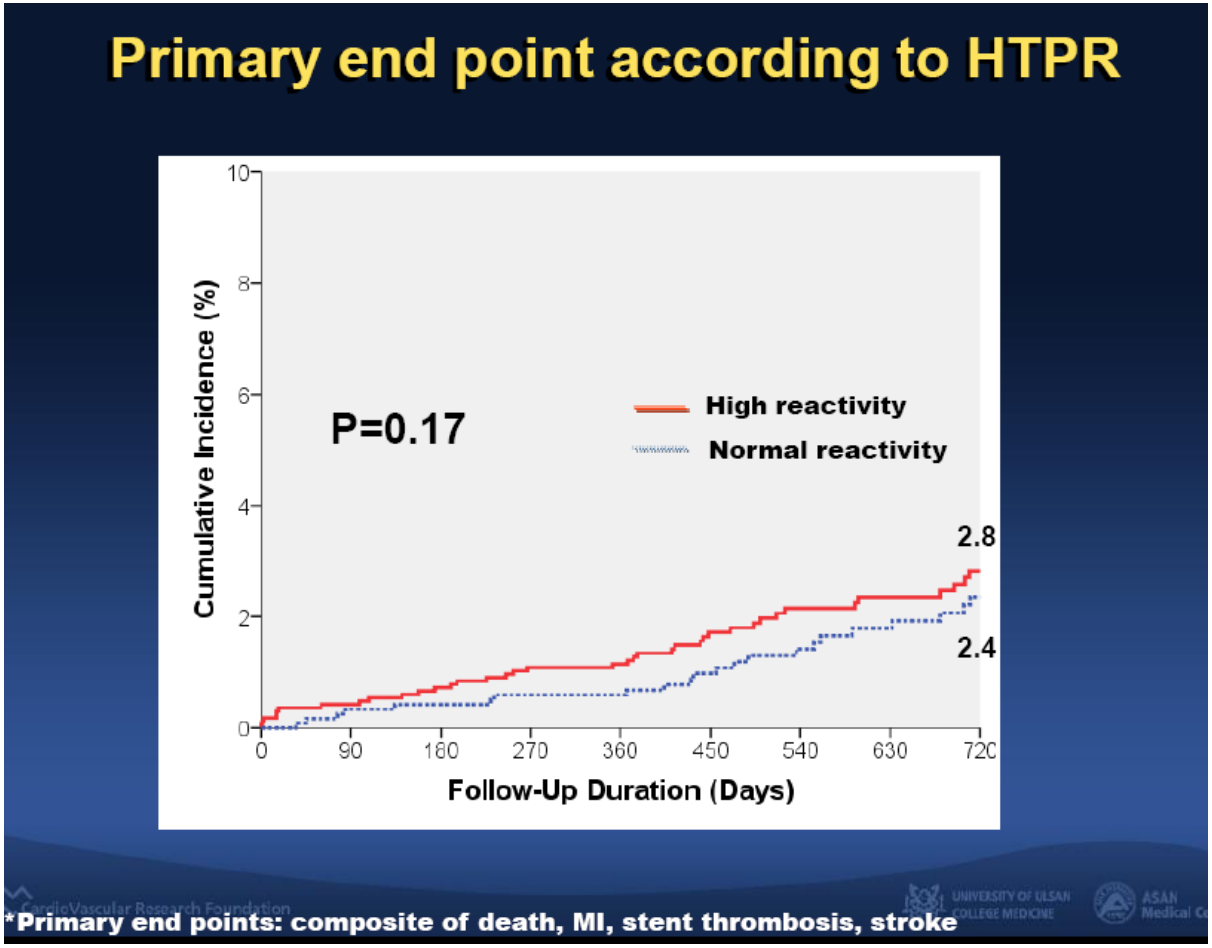
BACK UP

- Thank you Pr Paganelli, but the Asian cohort (Pr PARK) don’t support the predictive value of HTPR (VerifyNow)
- So HTPR is really necessary ?

Thank for your question….



Results no link with outcome



No ACS patients