

Adjusted Clopidogrel Loading Doses According to VASP Phosphorylation Index Decrease Rate of Major Adverse Cardiovascular Events in Patients With Clopidogrel low response: A Multicentre Randomized Prospective Study.

L Bonello, L Camoin-Jau, S Arques, C Boyer, D Panagides, O Wittenberg, MC Siméoni, P Barragan, F Dignat-George, F Paganelli.

Service de cardiologie, Hôpital universitaire nord, Marseille; FRANCE

Laboratoire d'hématologie, INSERM UMRS 608, Hôpital conception; Marseille; FRANCE

Service de cardiologie, Hôpital d'aubagne, Aubagne; FRANCE

Service de cardiologie, Clinique clairval, Marseille; FRANCE

Service de cardiologie, Clinique Bouchard, Marseille; FRANCE

Service de cardiologie, Hôpital privé beaugard, Marseille; FRANCE

Laboratoire de statistique, Faculté de la timone, Marseille; FRANCE

Service de cardiologie, Polyclinique les Fleurs, Ollioules, FRANCE



**Assistance Publique
Hôpitaux de Marseille**





CONFLICT OF INTEREST

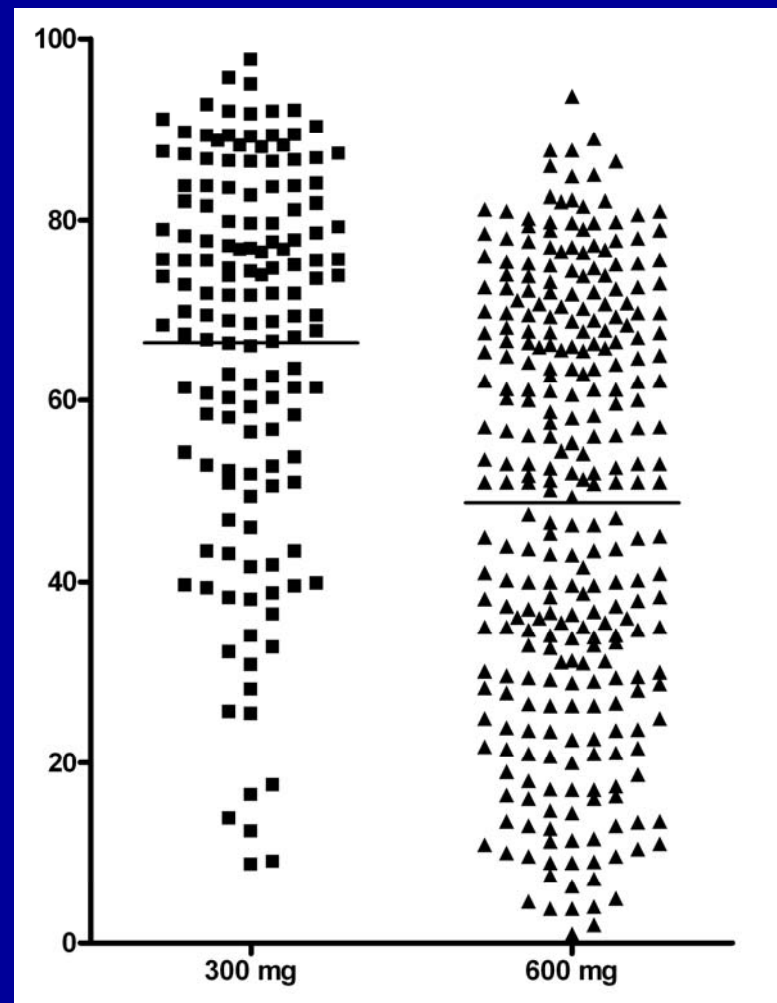
- **None for any author.**
- **This study was supported by a grant from the federation française de cardiologie, Paris, France.**



BACKGROUND

Large inter-individual variability in response to clopidogrel has been observed when a 300 mg loading dose (LD) is used.

A 600 mg LD decrease the mean platelet reactivity (PR) but does not overcome the large inter-individual variability observed.





Link between low response and stent thrombosis / ischemic events

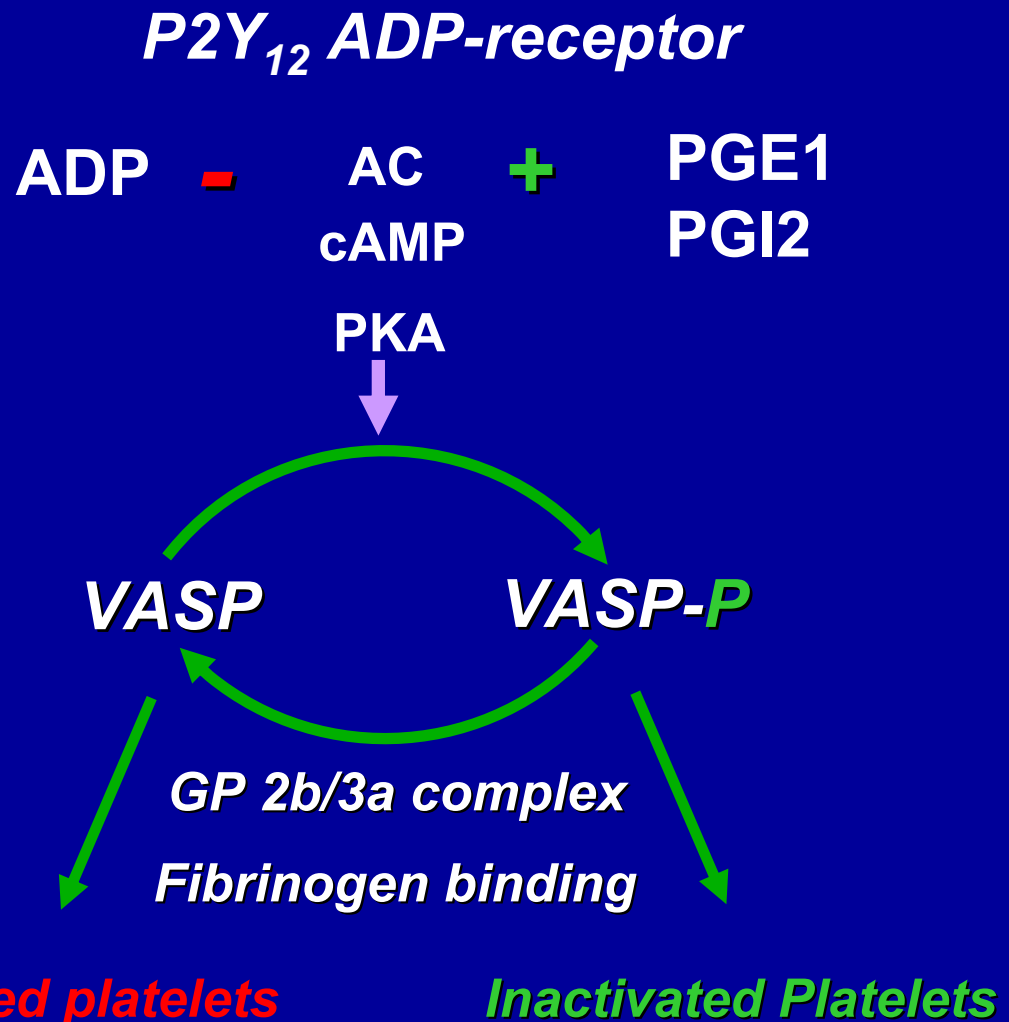
End-point	Author	Journal / year	n
Stent thrombosis	Barragan et al.	CCI 2003	36
	Gurbel et al.	JACC 2005	120
	Ajenberg et al.	JACC 2005	49
	Buonamici et al.	JACC 2007	804
	Blindt et al.	TH 2007	99
Ischemic events	Matetzky et al.	Circ 2004	60
	Geiser et al.	EHJ 2006	379
	Gurbel et al.	JACC 2005	192
	Bliden et al.	JACC 2007	100
	Cuisset et al.	JTH 2006	106
	Hochholzer et al.	JACC 2006	802
	Bonello et al.	JTH 2007	144



VASP index

VASP index : standardized and reproducible.

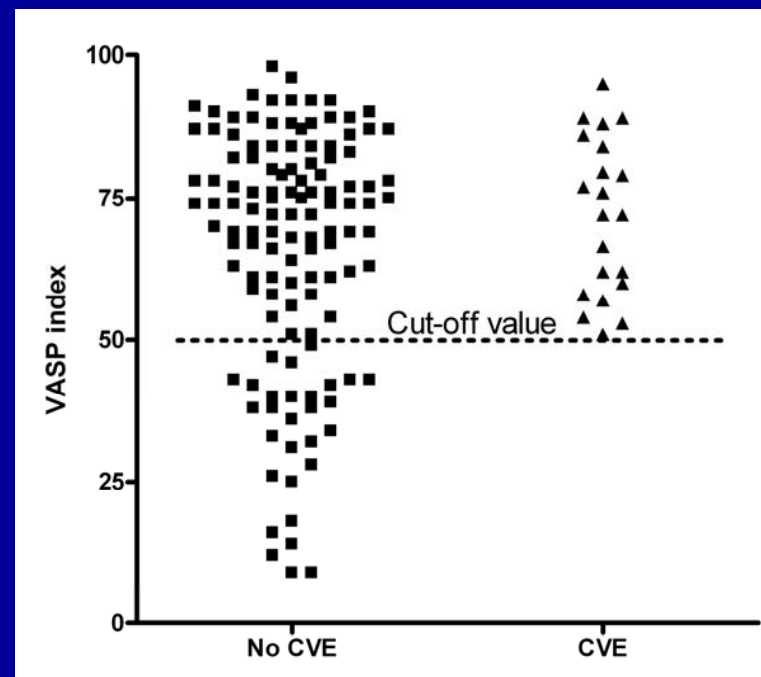
Highly specific of the response to clopidogrel.





DEFINITION OF LOW-RESPONSE using VASP index

The negative predictive value of the VASP index to predict MACE after PCI was 100% using the cut-off value of 50% of PR.



Therefore we defined low response as a post-treatment platelet reactivity $\geq 50\%$ using the VASP index in the present study.



AIM

- ***Clinical impact of loading dose adjustment according to platelet monitoring in patients with low-response to clopidogrel.***



STUDY DESIGN

Non-emergent PCI : ACS and Stable angina (n=406)

Loading dose (LD) ASA 250mg
Clopidogrel 600mg

VASP \geq 50%

Randomization
(n=162)

CONTROL (n=84)

VASP-guided LD (n=78)

Up-to 3 additional LD of 600 mg every 24 hours until VASP < 50% before PCI

Maintenance dose ASA 160 mg
Clopidogrel 75 mg

1° endpoint: MACE (CV death, MI, revascularization) at 30 days

2° endpoints: TIMI major and minor bleeding at 30 days



BASELINE CHARACTERISTICS

Baseline characteristics <i>n, (%)</i>	Control (n=84)	VASP-guided (n=78)	p
Sex, female/male	17/67	19/59	0.5
Age, yrs (mean \pm SD)	66.6 \pm 11.1	66.3 \pm 10.1	0.9
BMI, kg/m ² (mean \pm SD)	27.2 \pm 5.1	27.6 \pm 5.1	0.6
Previous myocardial infarction	20 (24)	22 (28)	0.5
Cardiovascular risk factors			
Current smoker	35 (42)	27 (35)	0.4
Dyslipidemia	45 (54)	41 (53)	0.9
Diabetes mellitus	36 (43)	31 (40)	0.7
Hypertension	51 (61)	47 (60)	1
PCI indication			
Silent ischemia	18 (21)	14 (18)	0.6
Stable angina	27 (32)	27 (35)	0.7
ACS	40 (48)	35 (45)	0.7



PROCEDURAL CHARACTERISTICS

Procedural data (mean +/-SD)	Control	VASP-guided	p
LVEF, %	59.4 ± 12.1	58.7 ± 13.2	0.7
Number of diseased vessels	2.1 ± 1.1	2.4 ± 1.3	0.1
Number of treated vessels	1.4 ± 0.6	1.5 ± 0.7	0.4
Number of stents per patient	2 ± 1	2.2 ± 1.2	0.3
Number of DES per patient	0.96 ± 1.1	0.97 ± 1.1	0.9
Stent length per patient, mm	29 ± 15	33 ± 18	0.1
GP IIb/IIIa inhibitors, n (%)	17 (20)	13 (17)	0.6

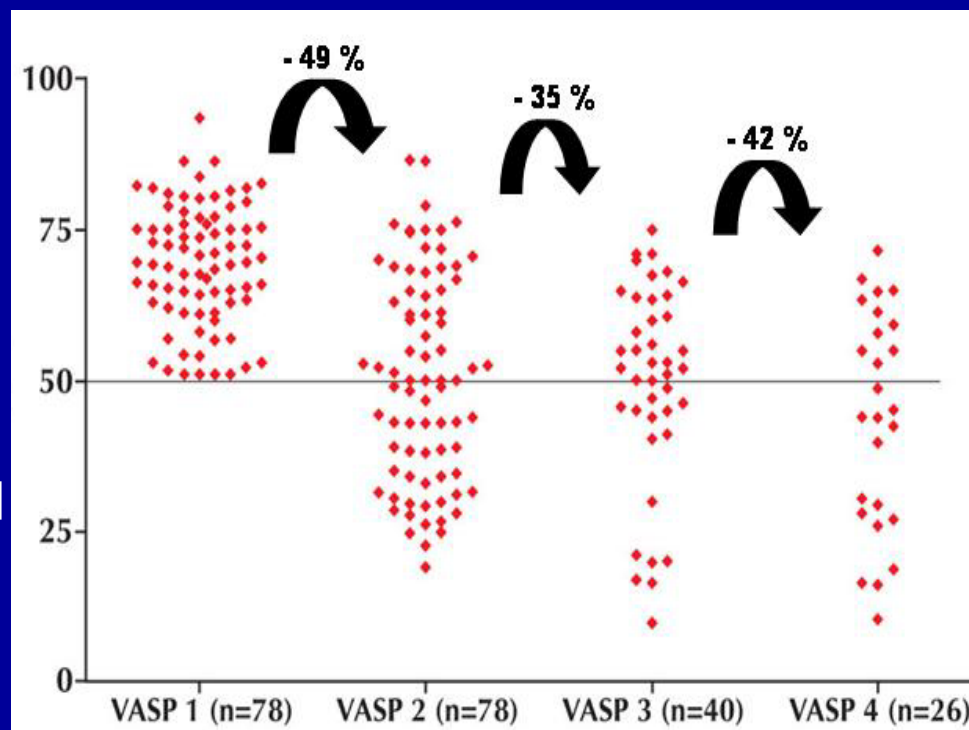


PLATELET MONITORING

<i>Mean ±SD</i>	Control	VASP-guided	p
VASP after first LD, %	68 ±11	69 ±10	0.4
VASP after adjustment, %	—	38 ±14*	*<0.001

-Each additional bolus of 600 mg of clopidogrel decreased the number of patients with low response from 35 to 49%.

-Despite 2400 mg of clopidogrel 11 (14%) patients remained low-responders.



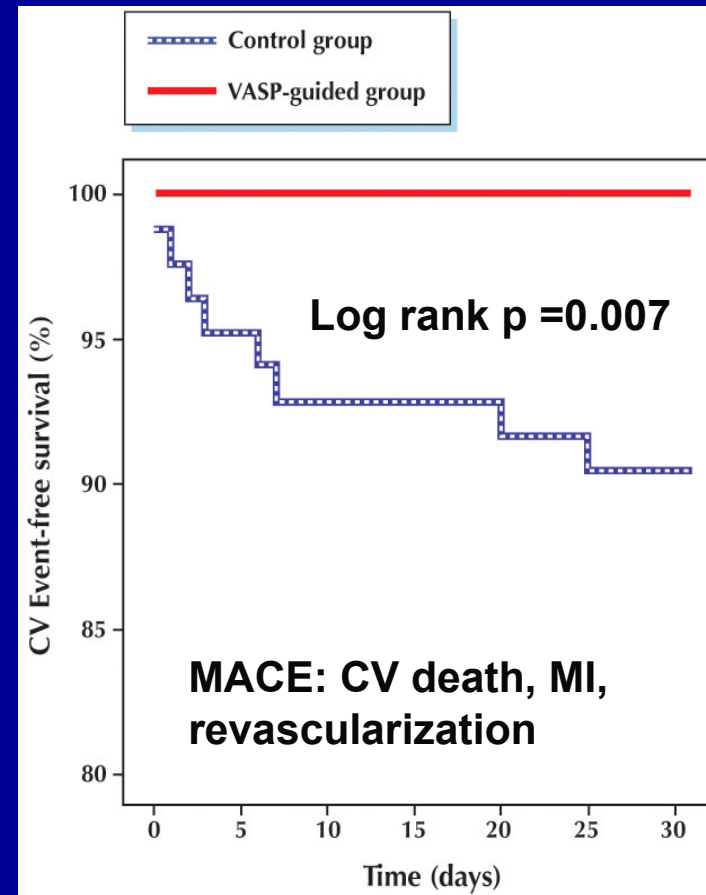


PRIMARY-END POINT : EFFICACY

MACE; n (%)	Control (n=84)	VASP-guided (n=78)
Cardiovascular death	2 (2)	0
Acute and Sub-acute stent thrombosis	4 (5)†	0
Revascularization	2 (2)	0
Overall MACE	8 (10)*	0

† p =0.059

* p =0.007





BLEEDING

Bleeding, n (%)	Control (n=84)	VASP-guided (n=78)
TIMI Major	1	1
TIMI Minor	3 (4)	2 (3)
All, n (%)	4 (5)	3 (4)

Using additional clopidogrel LD in patients with low-response and according to platelet monitoring was safe.



CONCLUSION

- **Adjusted loading dose of clopidogrel according to platelet monitoring using VASP assay is:**
 - **Feasible, safe**
 - **Efficacious in reducing post-PCI MACE.**
- **Reaching a post-treatment platelet reactivity <50% using the VASP index seems optimal to prevent MACE in patients.**