

TAILORED CLOPIDOGREL LOADING DOSE ACCORDING TO PLATELET REACTIVITY MONITORING DECREASE EARLY STENT THROMBOSIS

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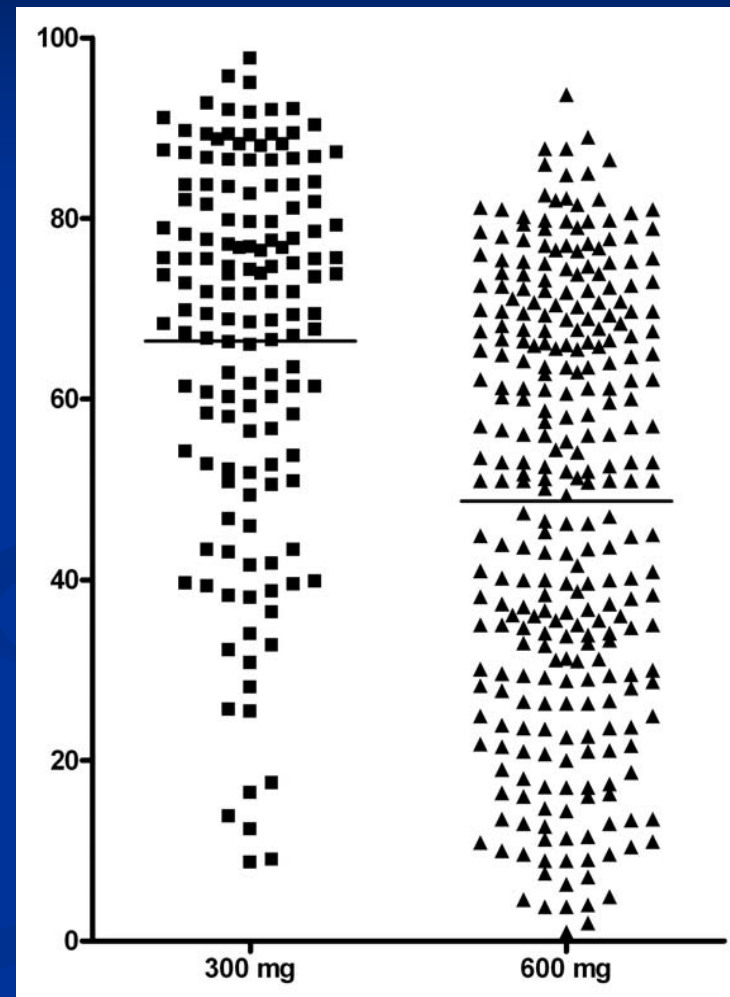


CONFLICT OF INTEREST

- None for any of the author

INTRODUCTION

- Large inter-individual variability in response to clopidogrel in CAD patients
- Variability is related to various factors from genetic to clinic
- Response to clopidogrel is unpredictable



Link between low-response and thrombotic events

Endpoint	Author	Platelet assay	n
Stent thrombosis	Barragan	VASP index	36
	Gurbel	VASP index, ADP aggregometry	120
	Buonamici	ADP- aggregometry	804
	Blindt	VASP index, ADP aggregometry	99
Ischemic events			
CV death, MI, unstable angina, stroke	Gurbel	ADP aggregometry	192
Death, MI, stent thrombosis, stroke, ischemia	Bliden	ADP aggregometry	100
CV death, acute or subacute ST, ACS, ischemic stroke	Cuisset	ADP aggregometry, VASP index	195
Death, MI, TLR	Trenk	ADP aggregometry	802
CV death, MI, urgent TVR	Bonello	VASP index	144
CV death, acute and subacute stent thrombosis, MI	Price	VerifyNow P2Y12	380

Threshold of PR to prevent thrombotic events

Author	Test	End-point	n	Follow-up	Cut-off
Barragan	<u>VASP index</u>	ST	46	1 month	50%
Bonello	<u>VASP index</u>	MACE	144	6 months	50%
Frere	<u>VASP index</u>	MACE+ stroke	195	1 months	53%
	LTA 10 μ mol ADP				70%
Blindt	<u>VASP index</u>	ST	99	6 months	48%
Price	VerifyNow P2Y ₁₂	CVD + ST	380	6 months	235 U
Gurbel	LTA 5 μ mol ADP	CVE	297	24 months	46%
	LTA 20 μ mol ADP				59%

AIM

- Does a strategy of platelet monitoring to tailor clopidogrel loading dose translates into a reduction in the rate of stent thrombosis in patients with clopidogrel low-response?

DESIGN

Non-emergent PCI : ACS and Stable angina (n= 1122)

Loading dose (LD) -ASA 250mg
-Clopidogrel 600mg ↓ VASP ≥ 50%

Randomization
(n=429)

CONTROL (n =215)

VASP-guided LD (n =214)

Maintenance dose -ASA 160 mg
-Clopidogrel 75 mg

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

1° endpoint: Definite stent thrombosis (ARC definition)

2° endpoints: MACE including CV death, MI and U-TVR

TIMI major and minor bleeding at 30 days

Baseline characteristics

n , (%)	Control (n = 214)	VASP-guided (n = 215)	p
Sex, male	168 (78.5)	177 (82)	0.4
Age, yrs*	66.8 ± 11	66.1 ± 11.3	0.8
BMI, kg/m ² *	28 ± 5.1	27.9 ± 4.7	0.8
Previous MI	56 (26)	65 (30)	0.4
Present smoking	115 (53.7)	123 (57)	0.9
Dyslipidemia	126 (58.9)	129 (60)	0.8
Diabetes	84 (39)	71 (33)	0.5
Hypertension	132 (61.7)	132 (61.4)	0.2
ACS	112 (52.3)	109 (50.7)	1
n of treated vessels*	1.5 ± 0.6	1.6 ± 0.7	0.2
n of stents	1.8 ± 1	1.9 ± 1.1	0.1
n of DES	0.9 ± 1.1	0.7 ± 1	0.9
GP IIb/IIIa inhibitors	51 (23.8)	51 (23.7)	0.1

Platelet reactivity monitoring

VASP after first LD

66 ± 11

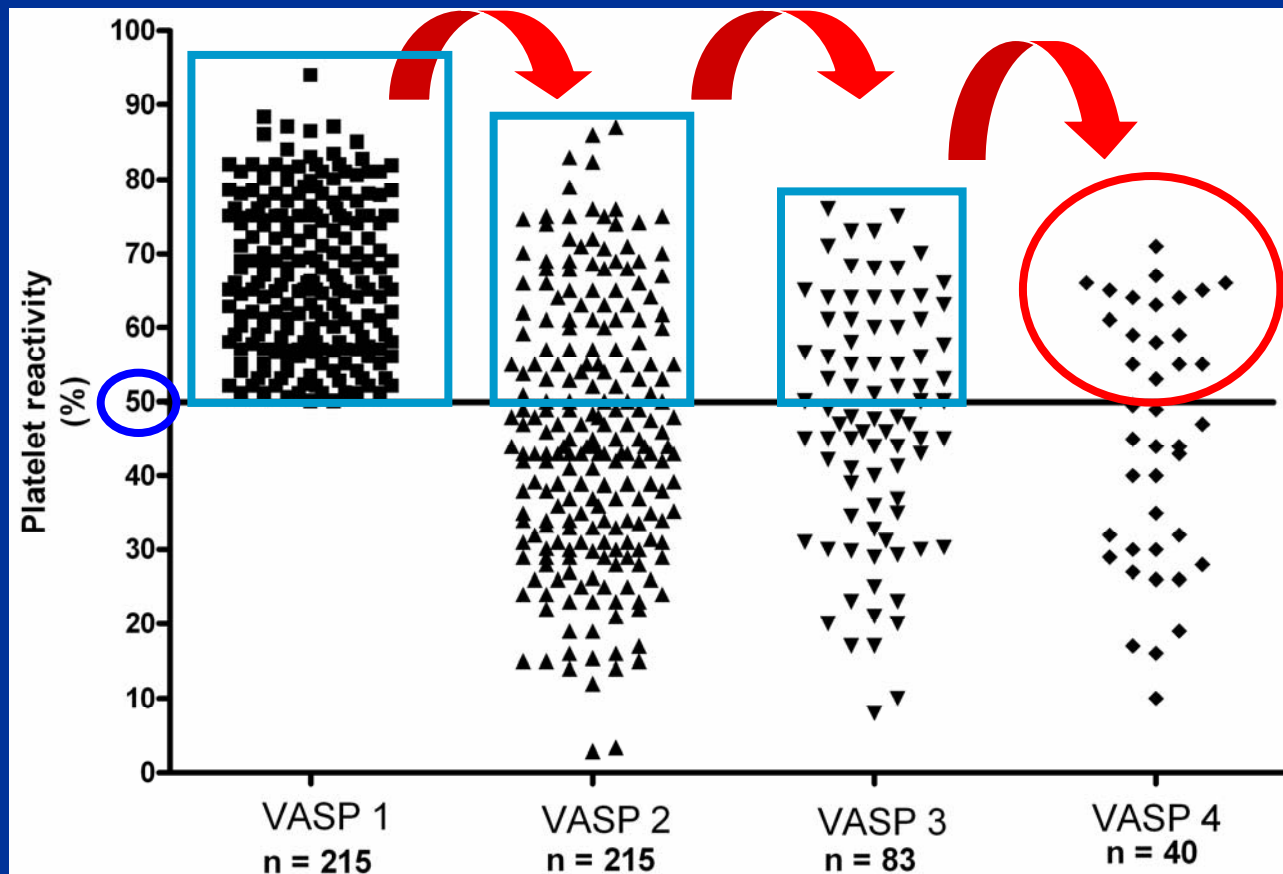
67 ± 10

VASP after sensitization

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$37 \pm 12^\dagger$

$\dagger p < 0.01$



Early definite stent thrombosis during one month follow-up.

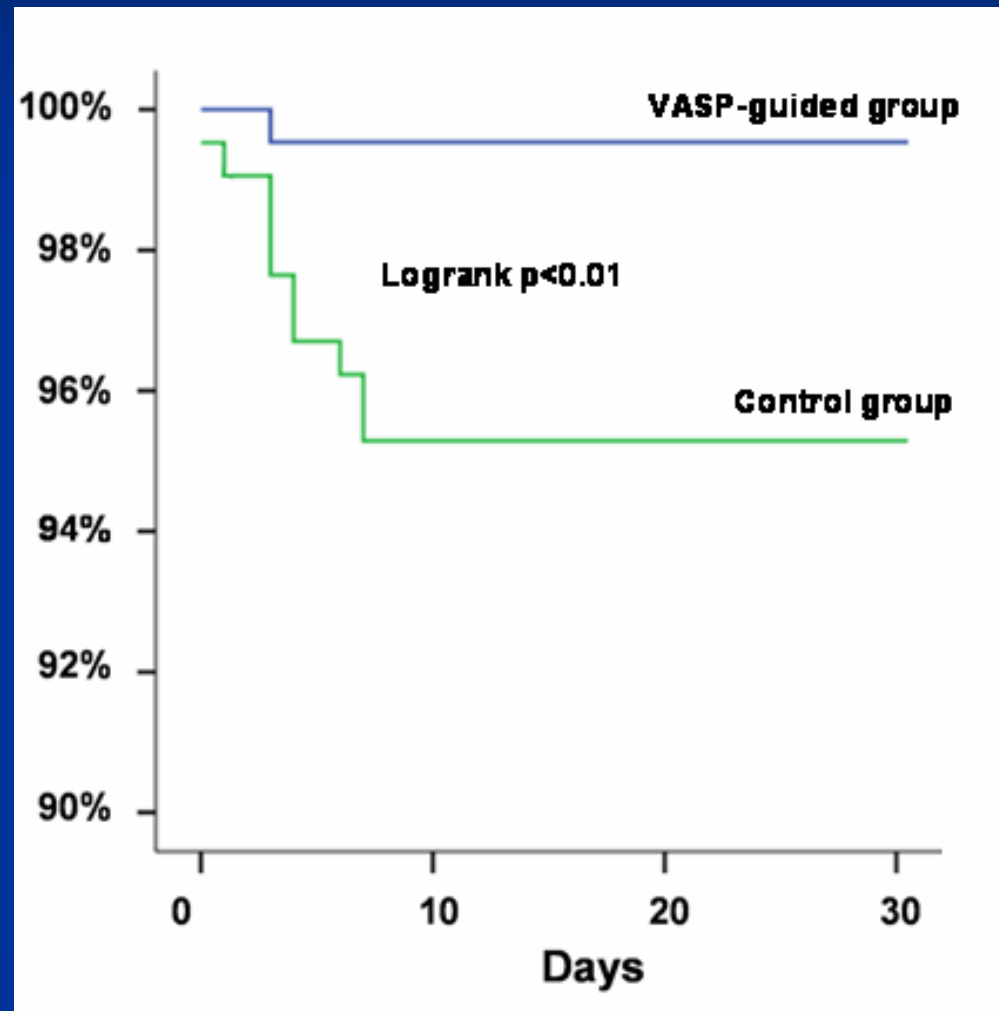
	Control group	VASP-guided group	
Endpoint n, (%)	(n= 214)	(n= 215)	p
Acute stent thrombosis	2 (0.9)	0	0.25
Sub-acute stent thrombosis	8 (3.7)	1 (0.5)	0.02
Early DST	10 (4.7)	1 (0.5)	0.01

-2 patients presented recurrent sub acute stent thrombosis (2 recurrences for each, 1 in the control group and 1 in the VASP guided group.

-GP IIb/IIIa inhibitor were used in half of patients presenting with early stent thrombosis.

Timing of early stent thrombosis

All early stent thrombosis occurred during the first 7 days



Secondary end-point: MACE

Endpoint n, (%)	Control (n= 214)	VASP-guided (n= 215)	p
Cardiovascular death	4 (1.8)	0	0.06
Myocardial infarction	10 (4.8)	1 (0.5)	0.01
Urgent revascularization	5 (2.3)	0	0.06
All MACE	19 (8.9)	1 (0.5)	< 0.001

Secondary end-point: TIMI bleeding

	Control (n= 214)	VASP-guided (n= 215)	p
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

No difference in bleeding complication between the 2 groups

No intra-cerebral bleeding, no fatal bleeding

Majority of patients had PCI through the radial access (55.6%)

CONCLUSION 1

- Adjusted LD of clopidogrel according to PR monitoring decrease the rate of stent thrombosis at 30 days in patients with clopidogrel low-response without increasing bleedings.

CONCLUSION 2

- Patients could be divided in 3 groups according to VASP index:
 - Good-responders: $VASP < 50$ % after a first bolus of 600 mg of clopidogrel (55%)
 - Low-responders: $VASP > 50$ % after the first bolus but could be sensitized with up-to three additional LD (37%)
 - Resistant: $VASP > 50$ % despite up-to 2400 mg of clopidogrel (8%)

CONCLUSION 3

- Paradigm shift ?
 - Therapeutic window for anti platelet therapy in patients undergoing PCI to prevent ischemic events without increasing bleedings is emerging and support the need for platelet reactivity monitoring.

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