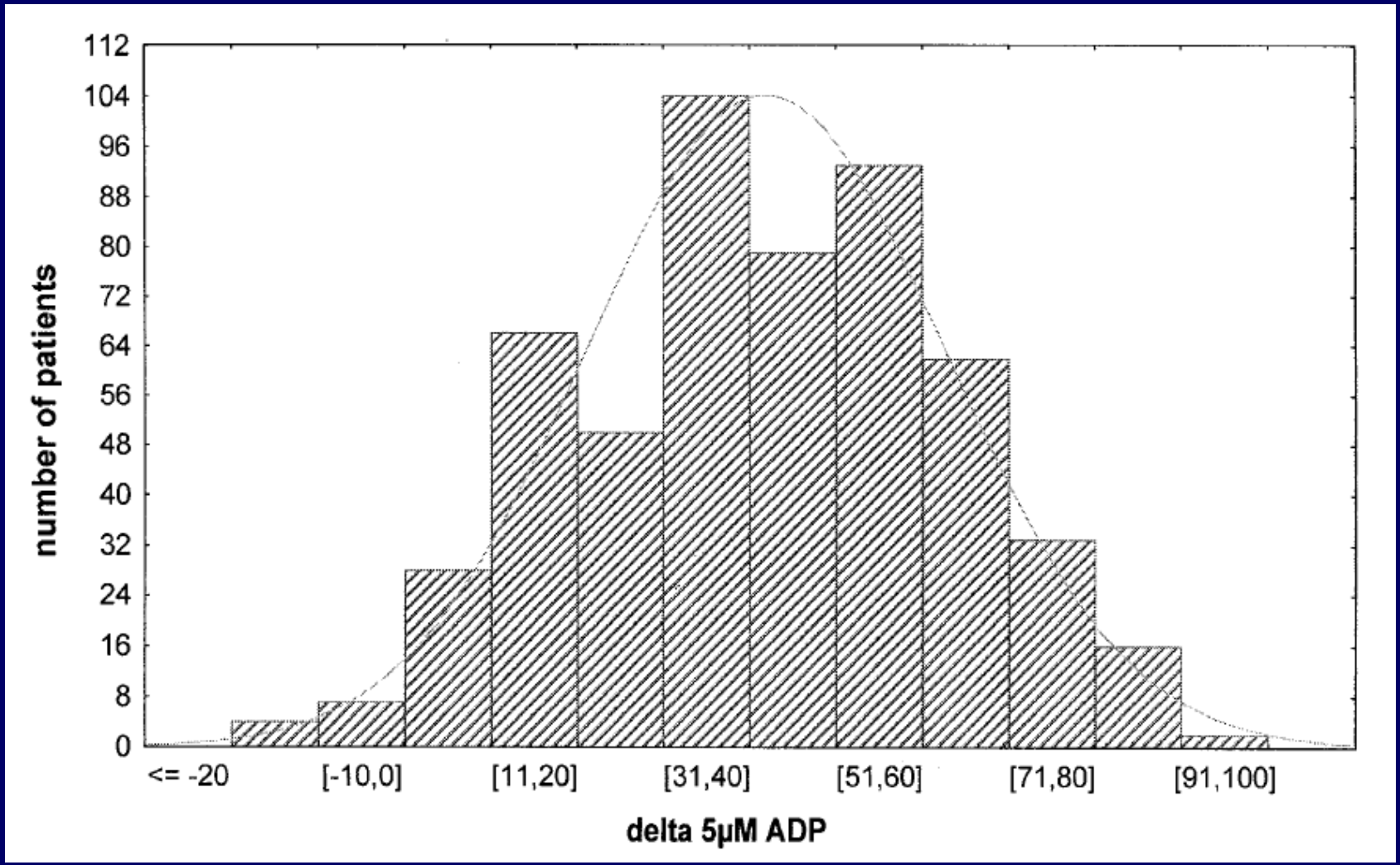
ISAR-CHOICE 2

Randomized Trial of 75 mg vs 150 mg of Daily Clopidogrel in Patients Undergoing PCI

Adnan Kastrati

Deutsches Herzzentrum,
Munich, GERMANY

Variability in Platelet Response to Clopidogrel



Serebruany et al, JACC 2005

Variability Sources

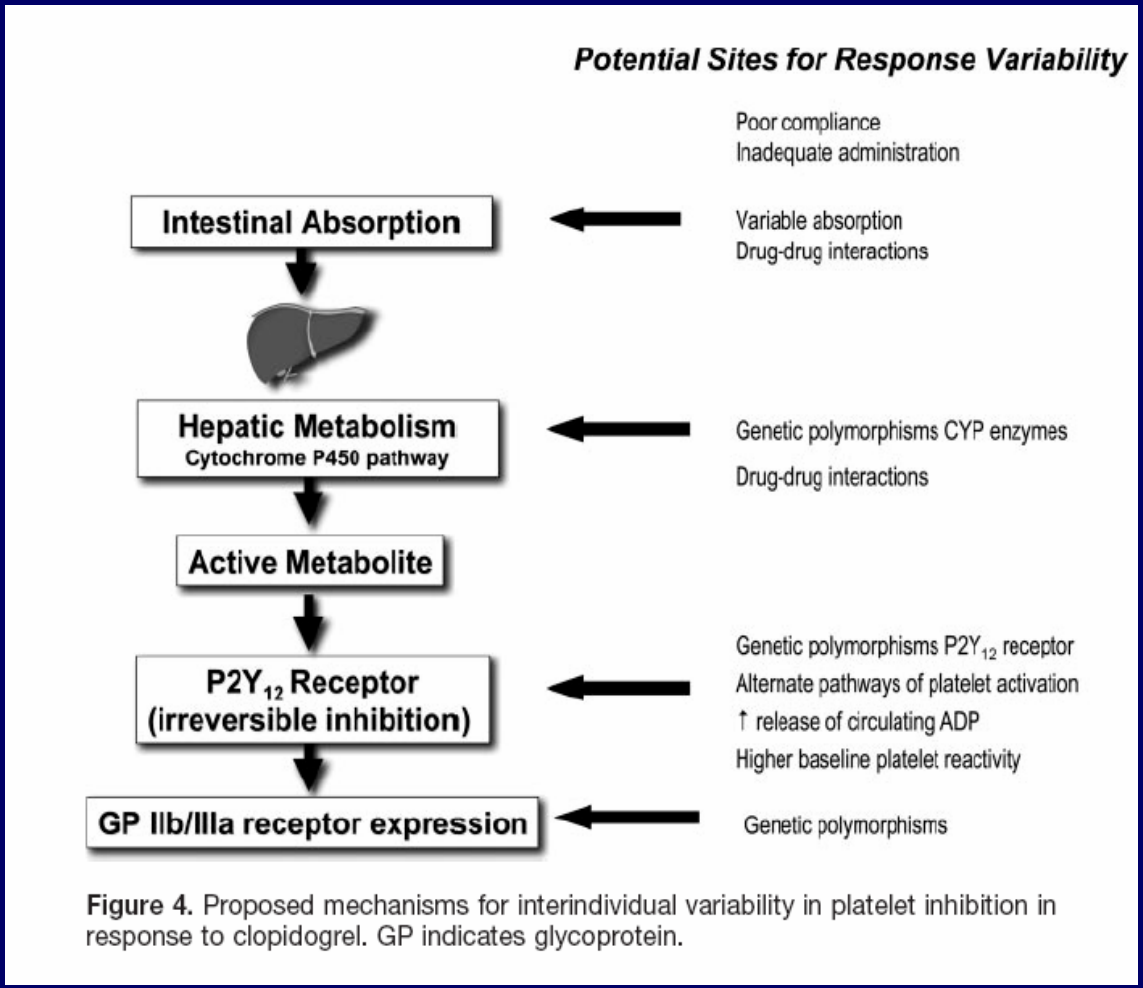


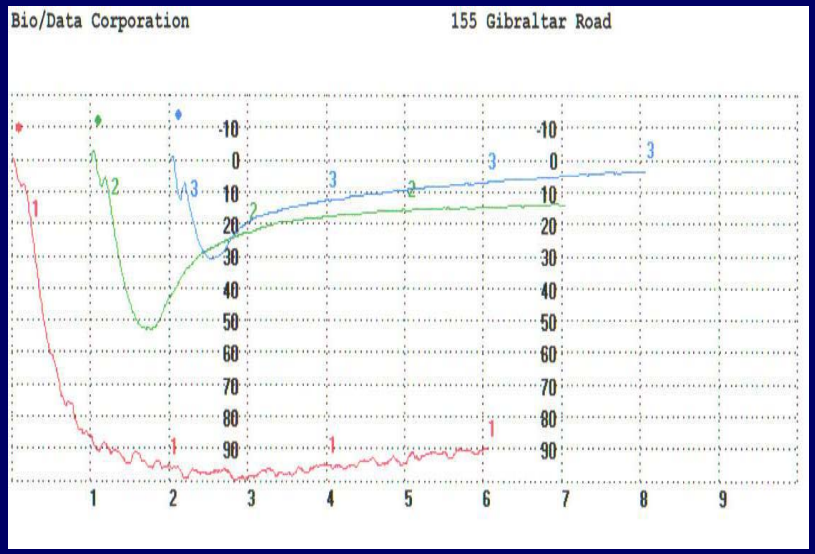
Figure 4. Proposed mechanisms for interindividual variability in platelet inhibition in response to clopidogrel. GP indicates glycoprotein.

O'Donoghue & Wiviott, Circ 2006

How can we measure platelet response to clopidogrel in clinical practice?

Light Transmission Aggregometry

Platelet Aggregation Profiler® PAP 8
(Bio/Data Corporation, USA)

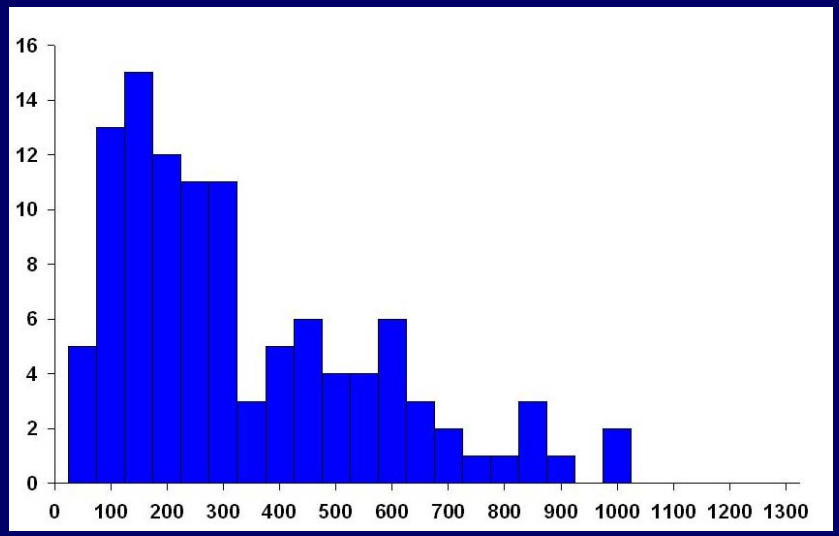


Standard method, but complex, time-consuming and impractical for routine use

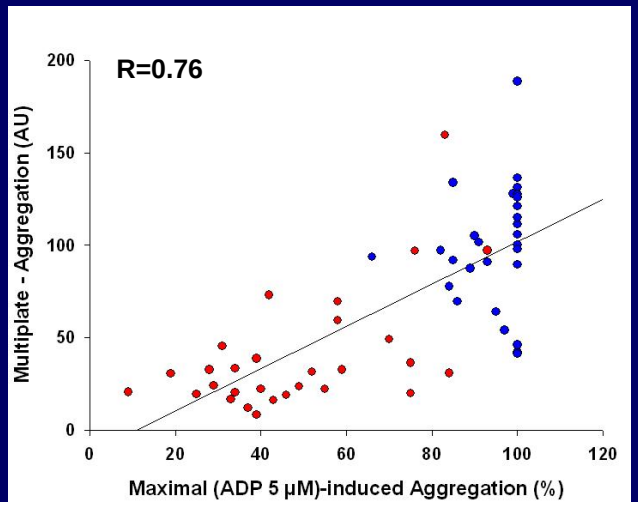
Whole-Blood Aggregometry

Multiple Platelet Function Analyzer®
(Dynabyte GmbH)

No. of pts

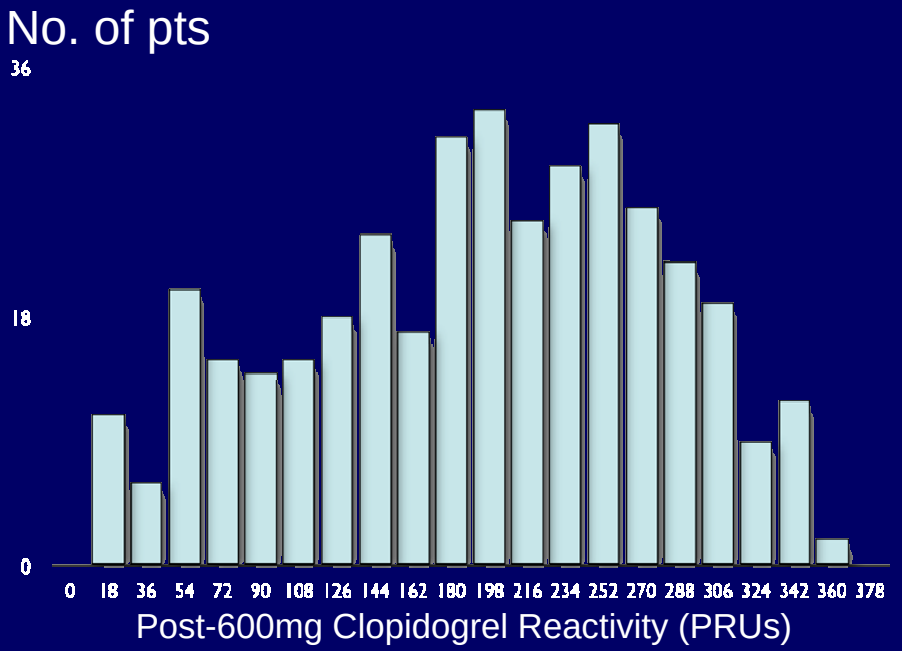


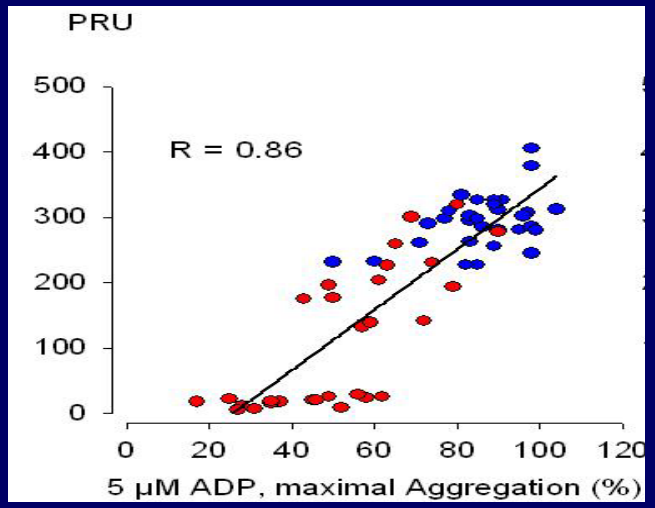
Post-600mg Clopidogrel ADP test (AUC)



Point of Care Assay

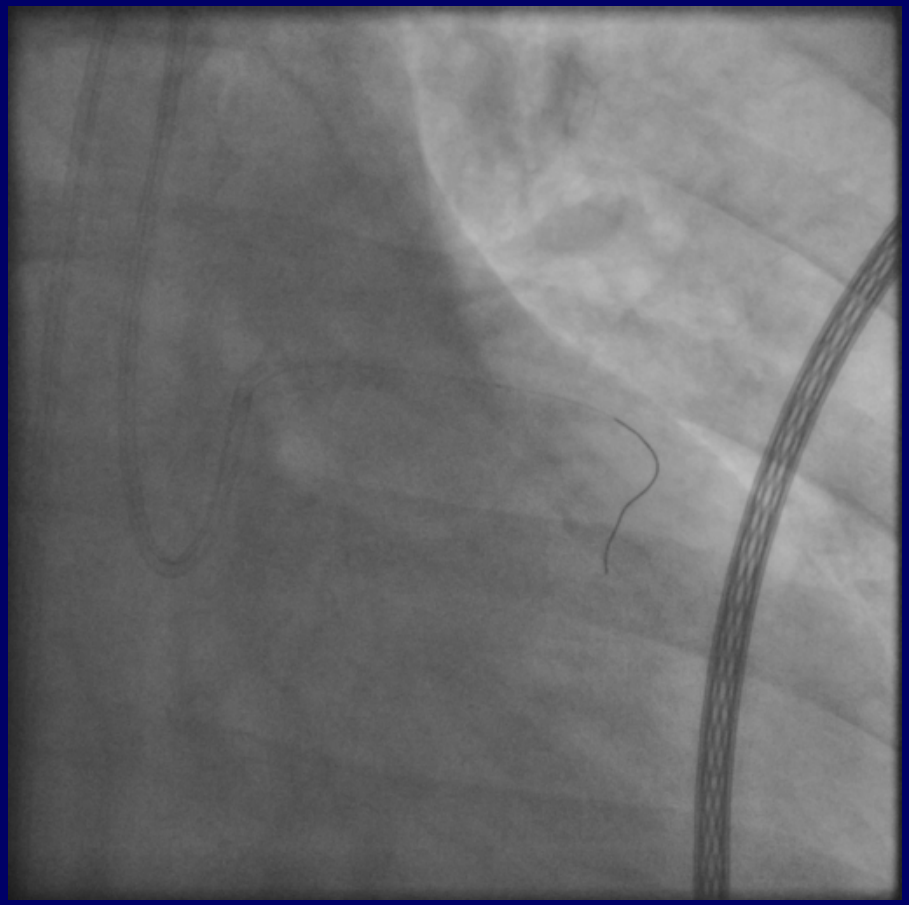
VerifyNow® P2Y12 Assay
(Accumetrics, USA)





Case illustrations

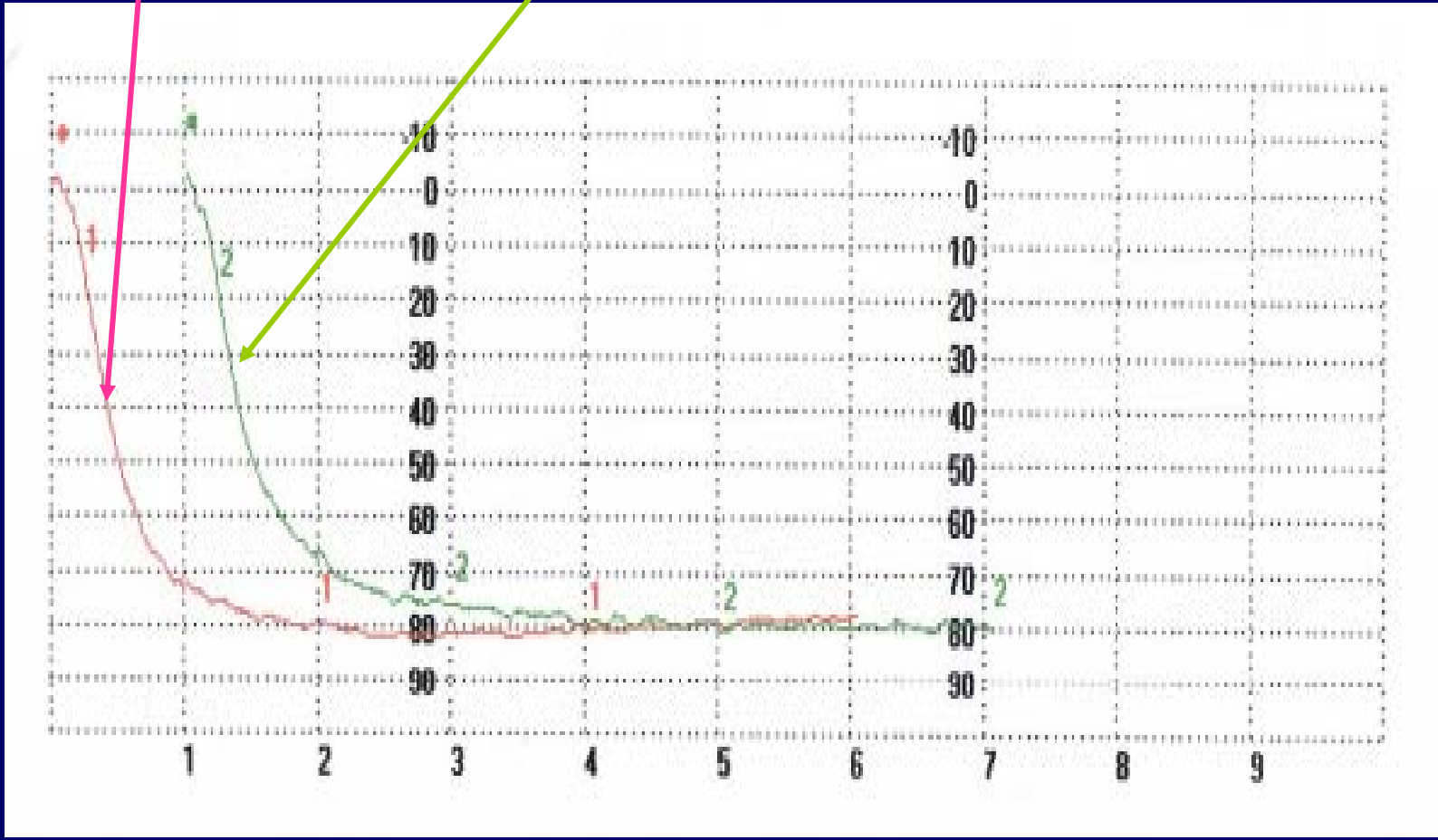
Patient with Stent Thrombosis 72h After Procedure



Results of LT Aggregometry 20h After 600 mg of Clopidogrel

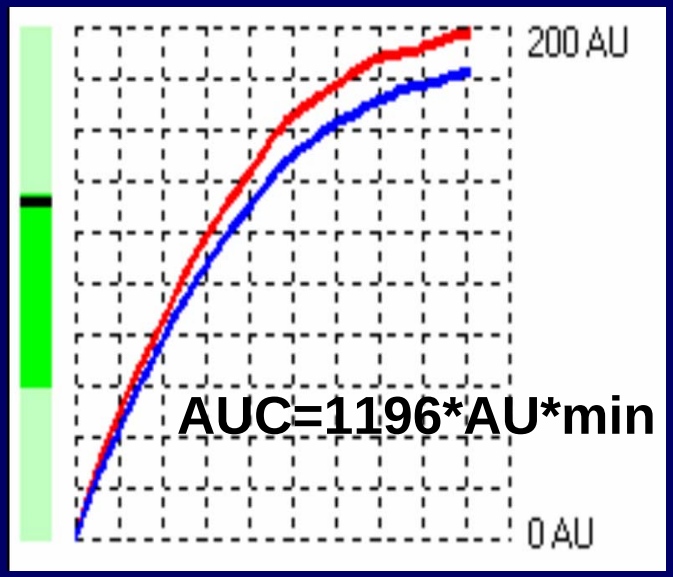
ADP 5μM

ADP 20μM

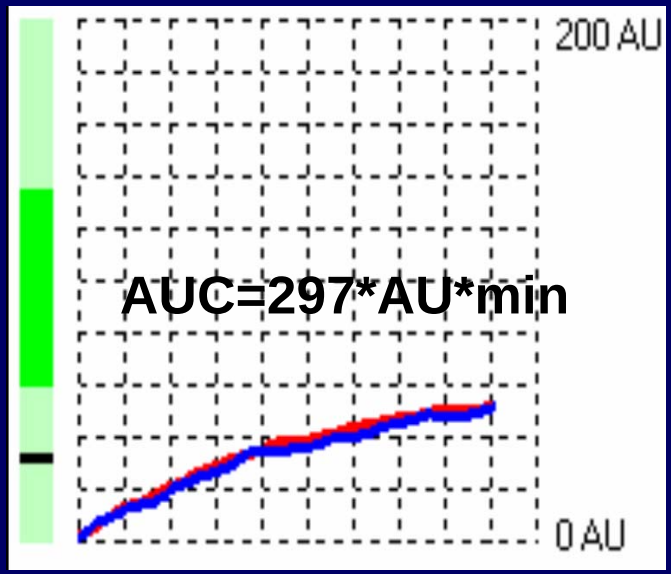


Results of Whole Blood Aggregometry 20h After 600 mg of Clopidogrel

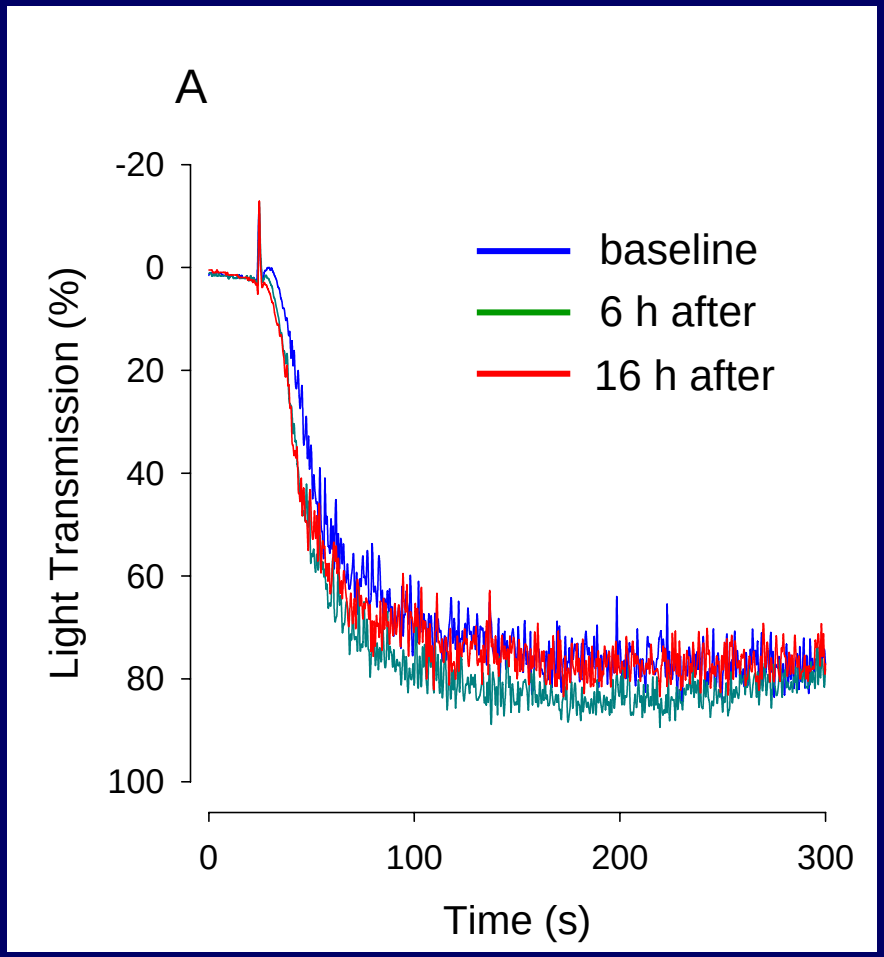
ST patient

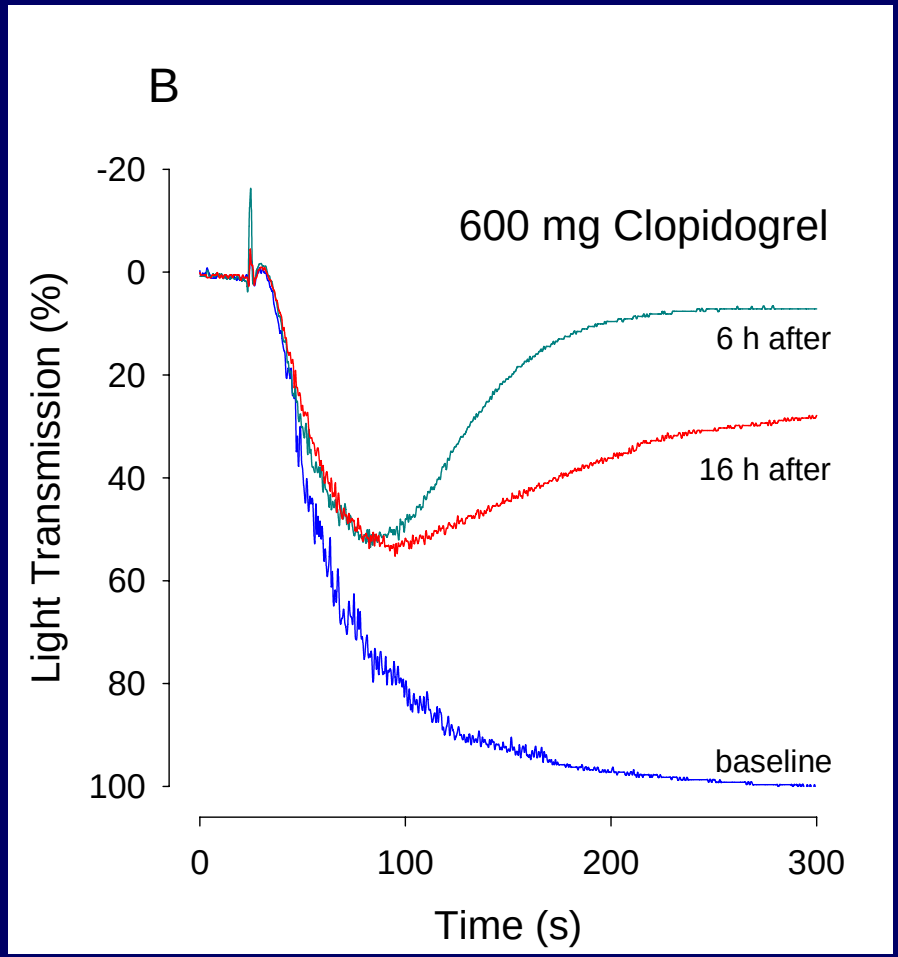


Control



A Patient with Stent Thrombosis and Clopidogrel Resistance



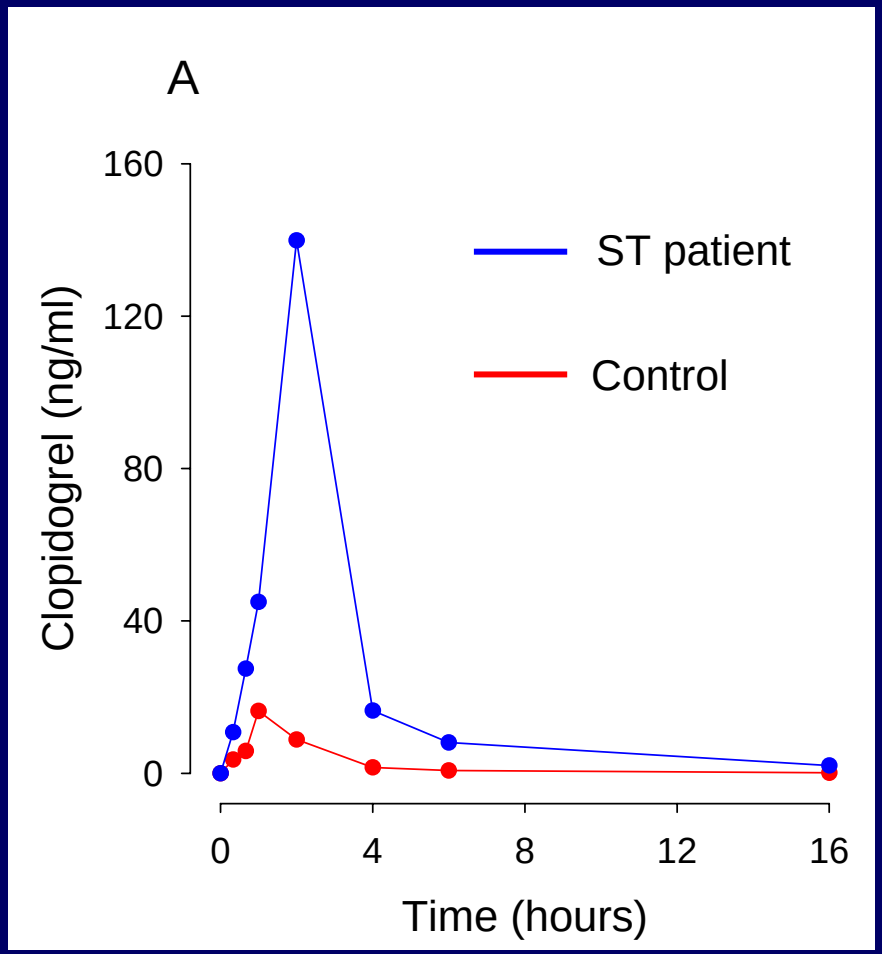


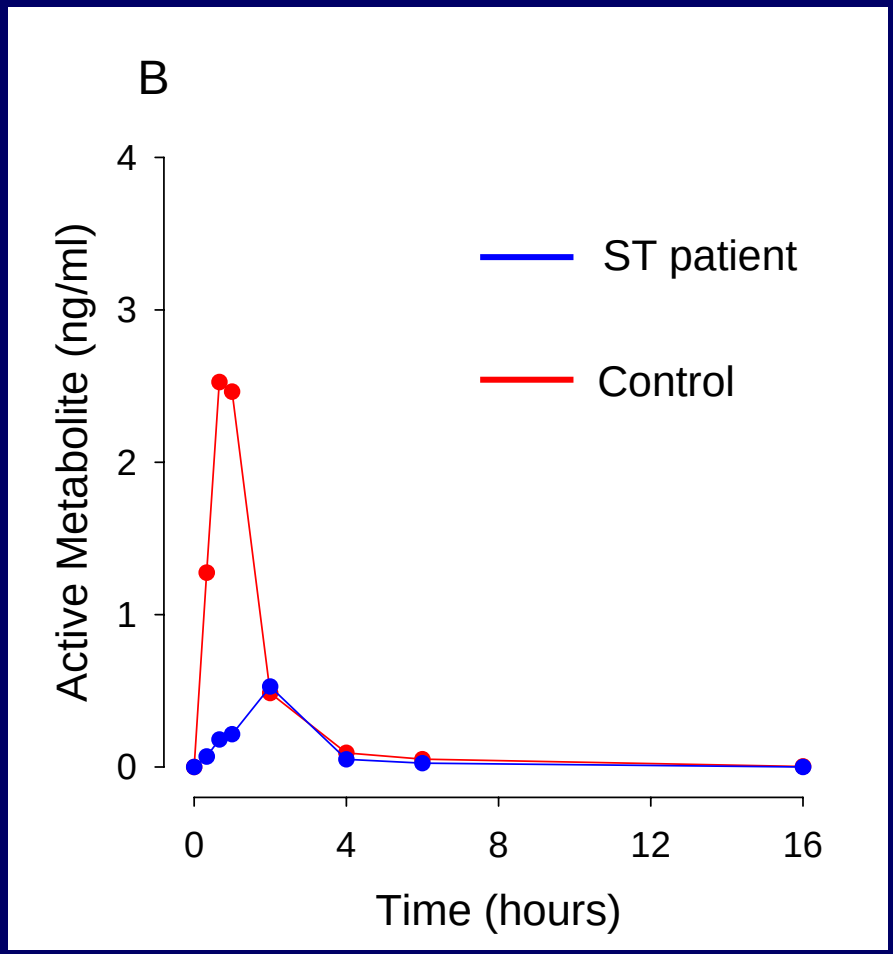
Stent Thrombosis Patient

Control Individual

Beckerath et al, Thromb Haemost 2005

A Patient with Stent Thrombosis and Failed Clopidogrel Metabolism





Clopidogrel

Active Metabolite

Beckerath et al, Thromb Haemost 2005

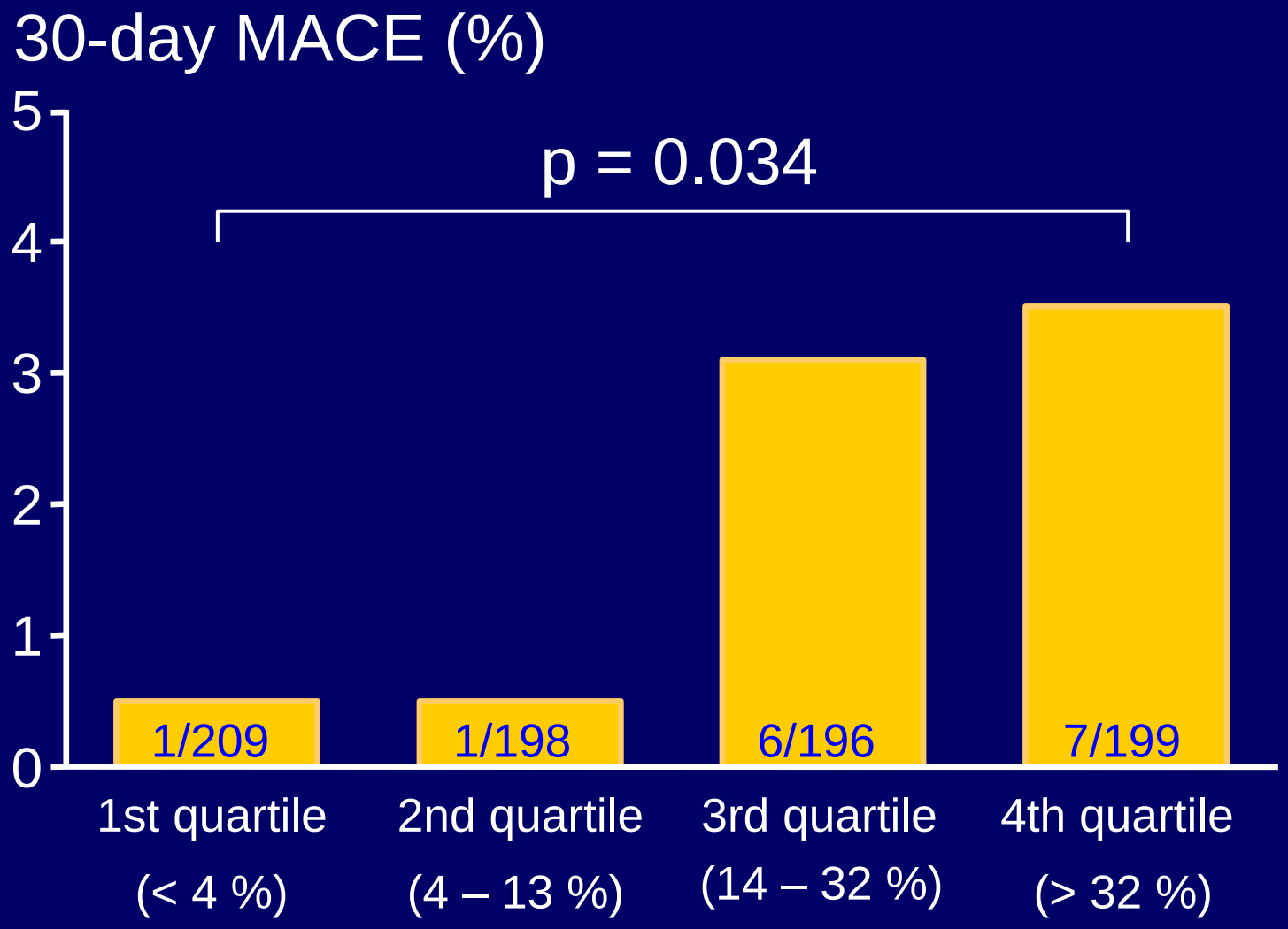
Study Evidence

Clinical Relevance of Nonresponse to Clopidogrel

EXCELSIOR Sudy
802 pts

600mg of clopidogrel
Light transmission aggregometry (5µM ADP)
prior to PCI

Platelet Aggregation During PCI and Outcome



EXCELSIOR, JACC 2006

Clinical Relevance of Nonresponse to Clopidogrel

RECLOSE Trial
804 DES pts

600mg of clopidogrel
Light transmission aggregometry
(ADP 10µmol)
Non-respondent pts – upper 10% of aggregation

LBCT of Dr. Antoniucci at ACC ‘07

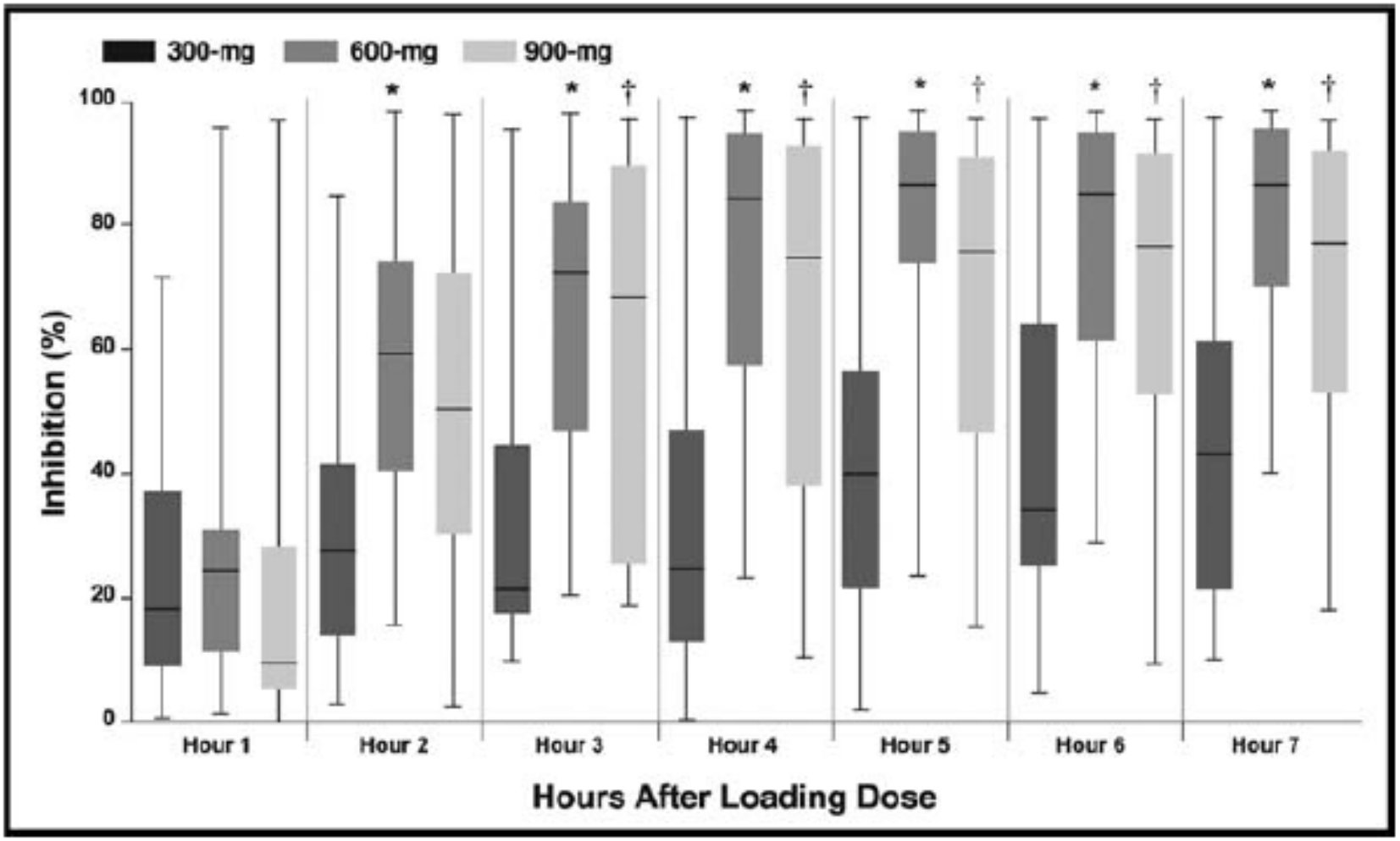
RECLOSE Trial
Primary End Point

Six- month FU	Overall n=804	Resp. n=699	Non- Resp. n=105	p value
❖ Definite/probable stent thrombosis	25 (3.1)	16 (2.3)	9 (8.6)	< 0.001
➢ Definite	11 (1.4)	9 (1.3)	2 (1.9)	0.612
➢ Probable	14 (1.7)	7 (1.0)	7 (6.7)	< 0.001
Time of stent thrombosis				
➢ Early	0	0	0	
➢ Subacute	16 (2.0)	12 (1.7)	4 (3.8)	0.152
➢ Late	9 (1.1)	4 (0.6)	5 (4.8)	< 0.001

Evidence on Increased Loading Dose

Platelet Inhibition After 300, 600 and 900 mg of Clopidogrel

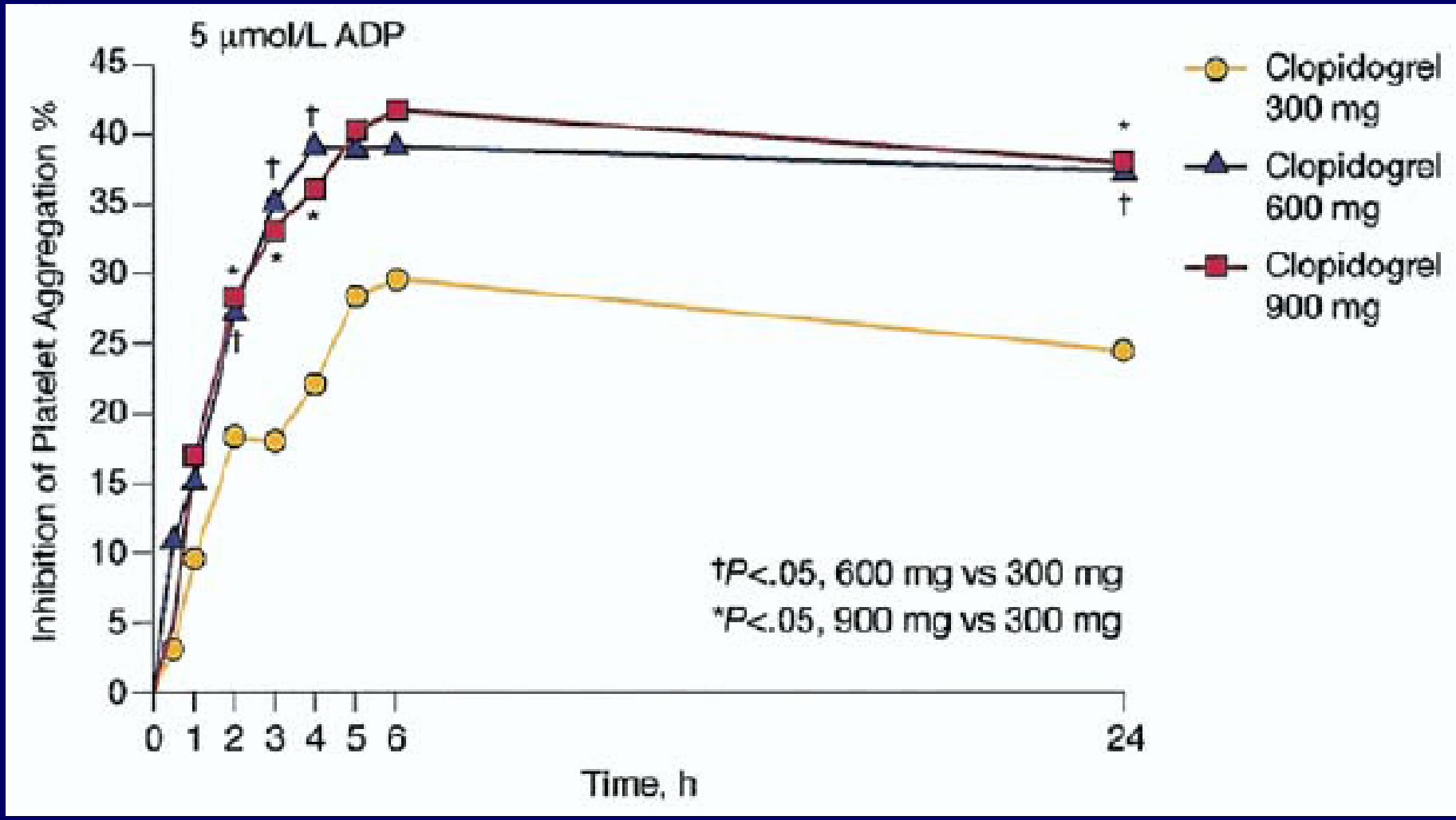
n=45, point of care test (Accumetrics)



Price et al, AJC 2006

Platelet Inhibition After 300, 600 and 900 mg of Clopidogrel

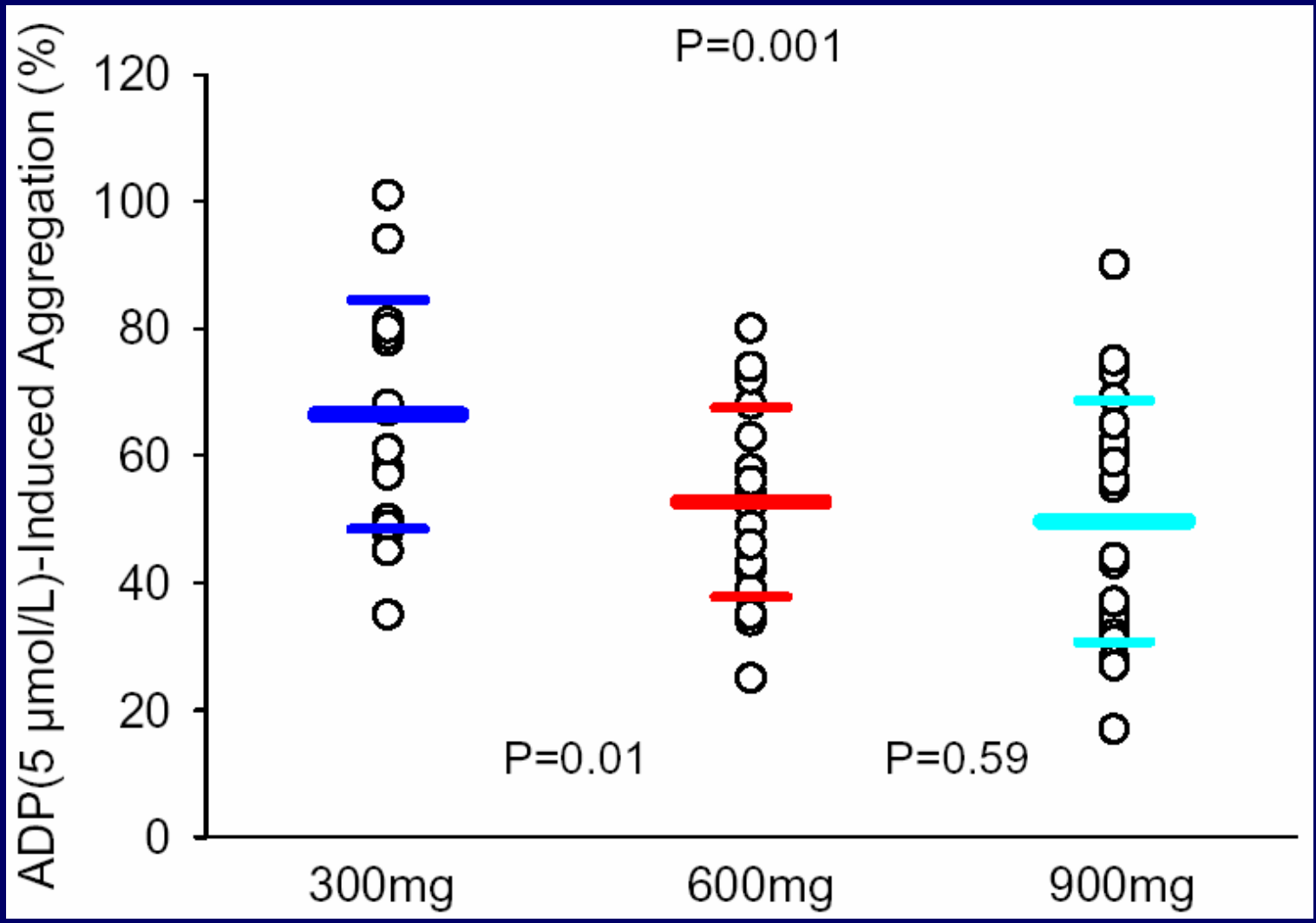
n=103, optical aggregometry



ALBION trial, JACC 2006

Platelet Inhibition After 300, 600 and 900 mg of Clopidogrel

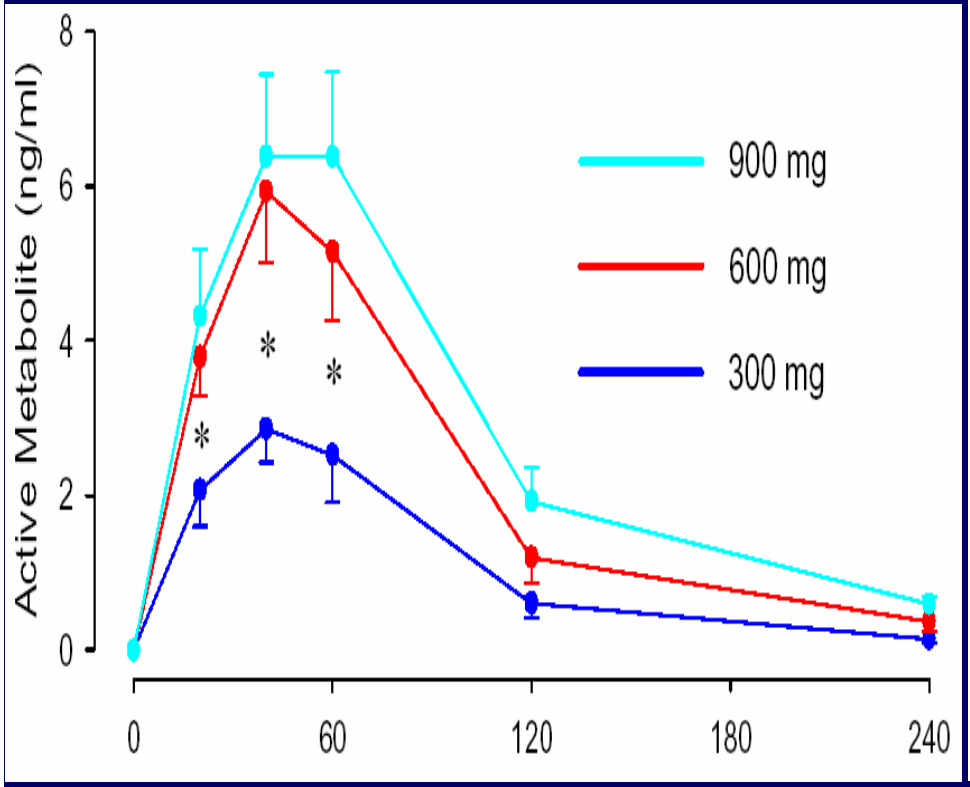
n=60, optical aggregometry



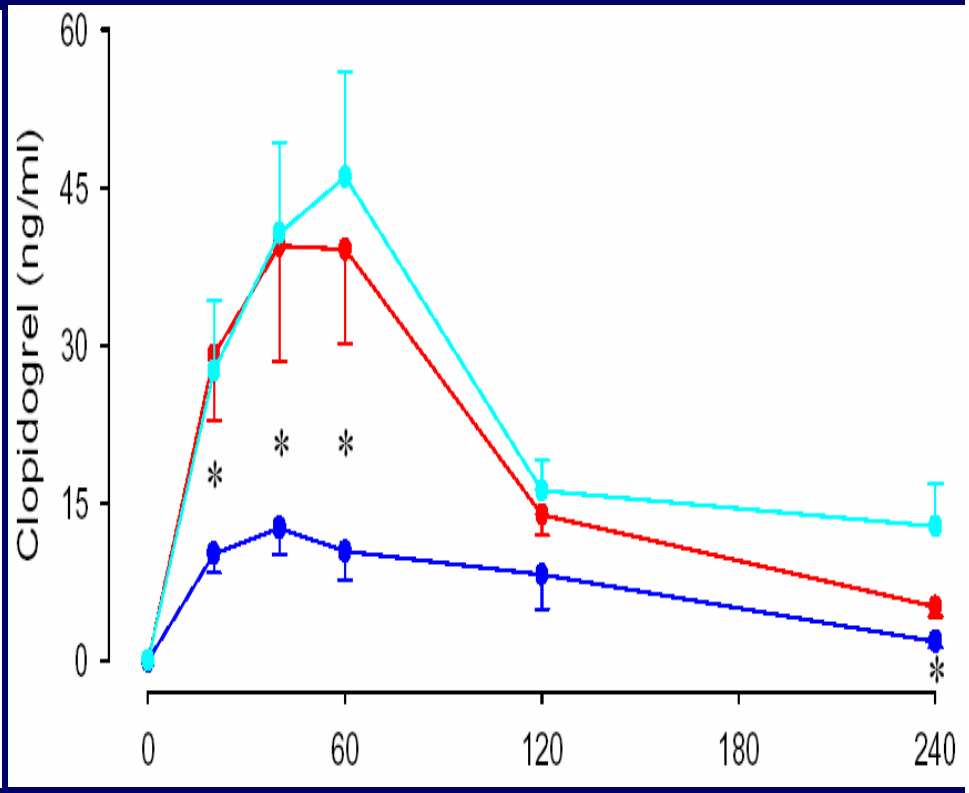
ISAR-CHOICE, Circulation 2005

Plasma Concentrations

Active metabolite



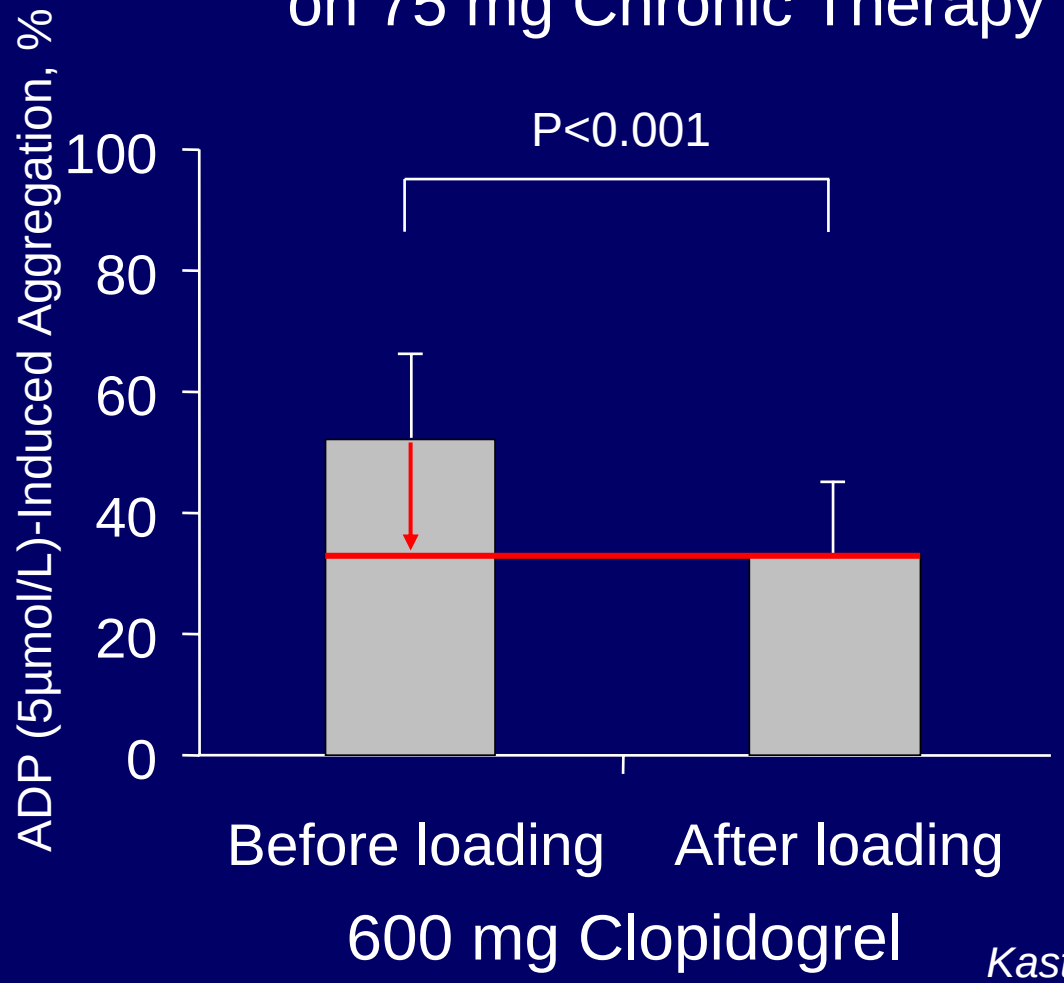
Clopidogrel



ISAR-CHOICE, Circulation 2005

Evidence on Increased Maintenance Dose

Are Clopidogrel Maintenance Doses >75 mg More Effective?



Kastrati et al, Circulation 2004

ISAR-CHOICE 2
- A Double Blind Study-

60 Patients

	150 mg	75 mg
No. of patients	31	29

Study Protocol

Daily 150 or 75 mg clopidogrel

0

30 days

600 mg clopidogrel

assessment of platelet function

(optical aggregometry, 5 & 20 µmol/L ADP

Point of care test: Verify Now)

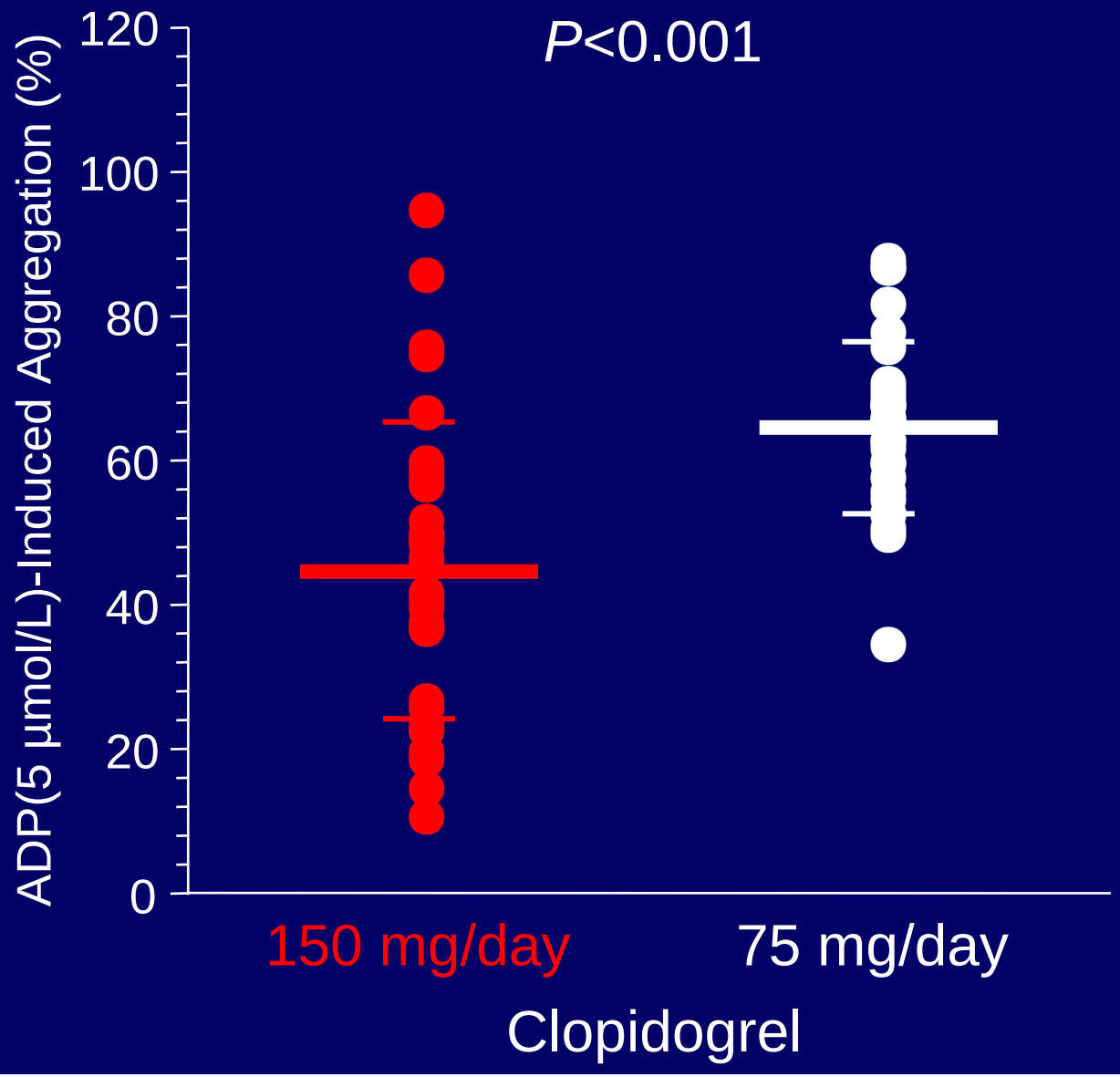
Baseline Characteristics

	150 mg n=31	75 mg n=29	P
Age, y	63.0±7.5	65.4±6.9	0.20
Women	3 (9.7)	2 (6.9)	0.70
Weight, kg	89.2±17.4	82.8±9.8	0.09
Height, cm	176.2±6.8	174.8±6.5	0.41
Platelet count, 10^9/L	217±65	223±44	0.70
Arterial hypertension	14 (45.2)	15 (51.7)	0.61
Hypercholesterolemia	16 (51.6)	142 (48.3)	0.80
Active smoker	3 (9.7)	2 (6.9)	0.70
Diabetes	7 (22.6)	10 (34.5)	0.31

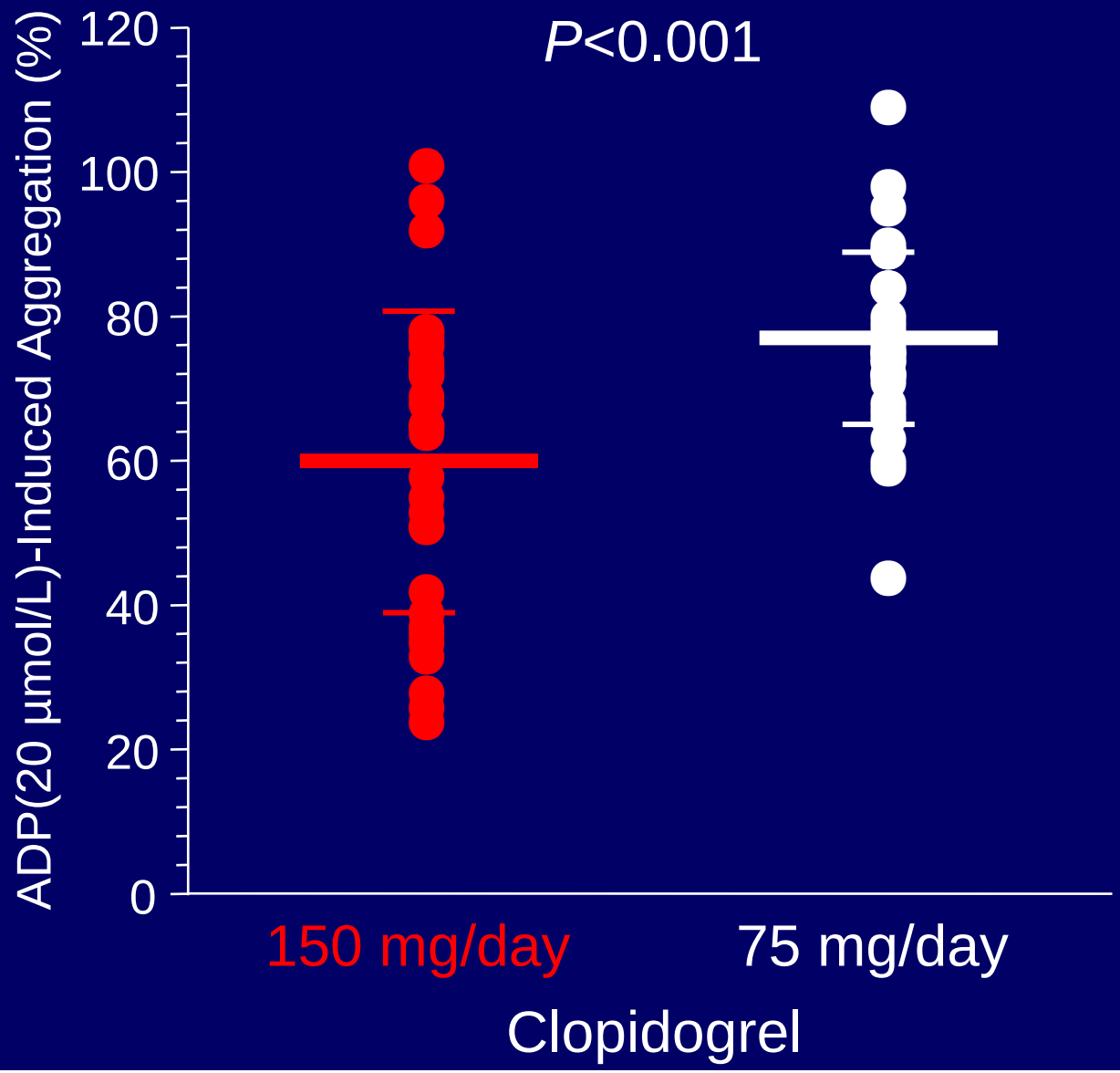
Baseline Medications

	150 mg n=31	75 mg n=29	P
Aspirin	31 (100)	29 (100)	1.00
Beta-blockers	28 (90.3)	28 (96.6)	0.33
ACE-inhibitors	27 (87.1)	26 (89.7)	0.76
Statins	31 (100)	28 (96.6)	0.48

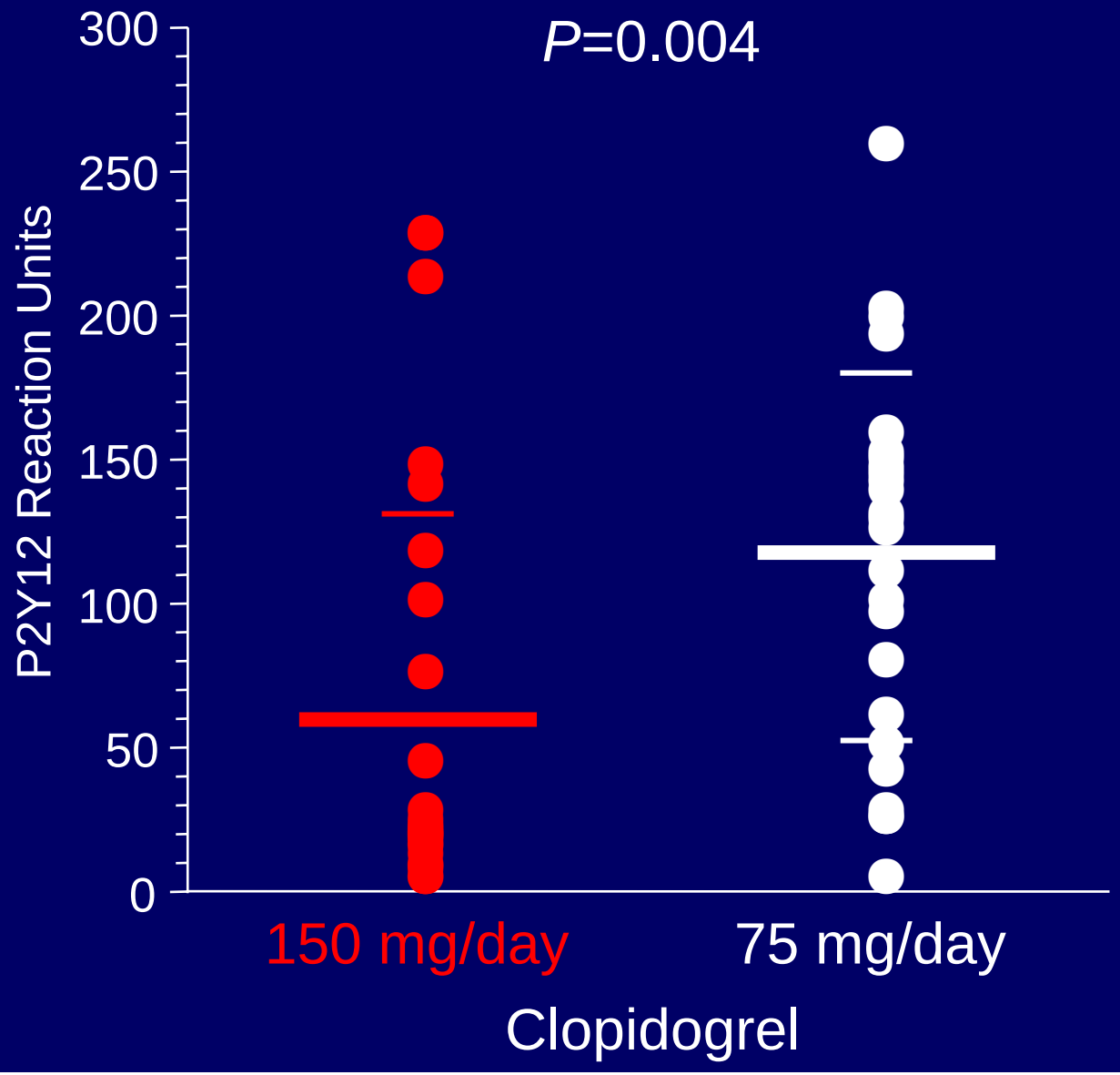
Aggregometry (30 days)



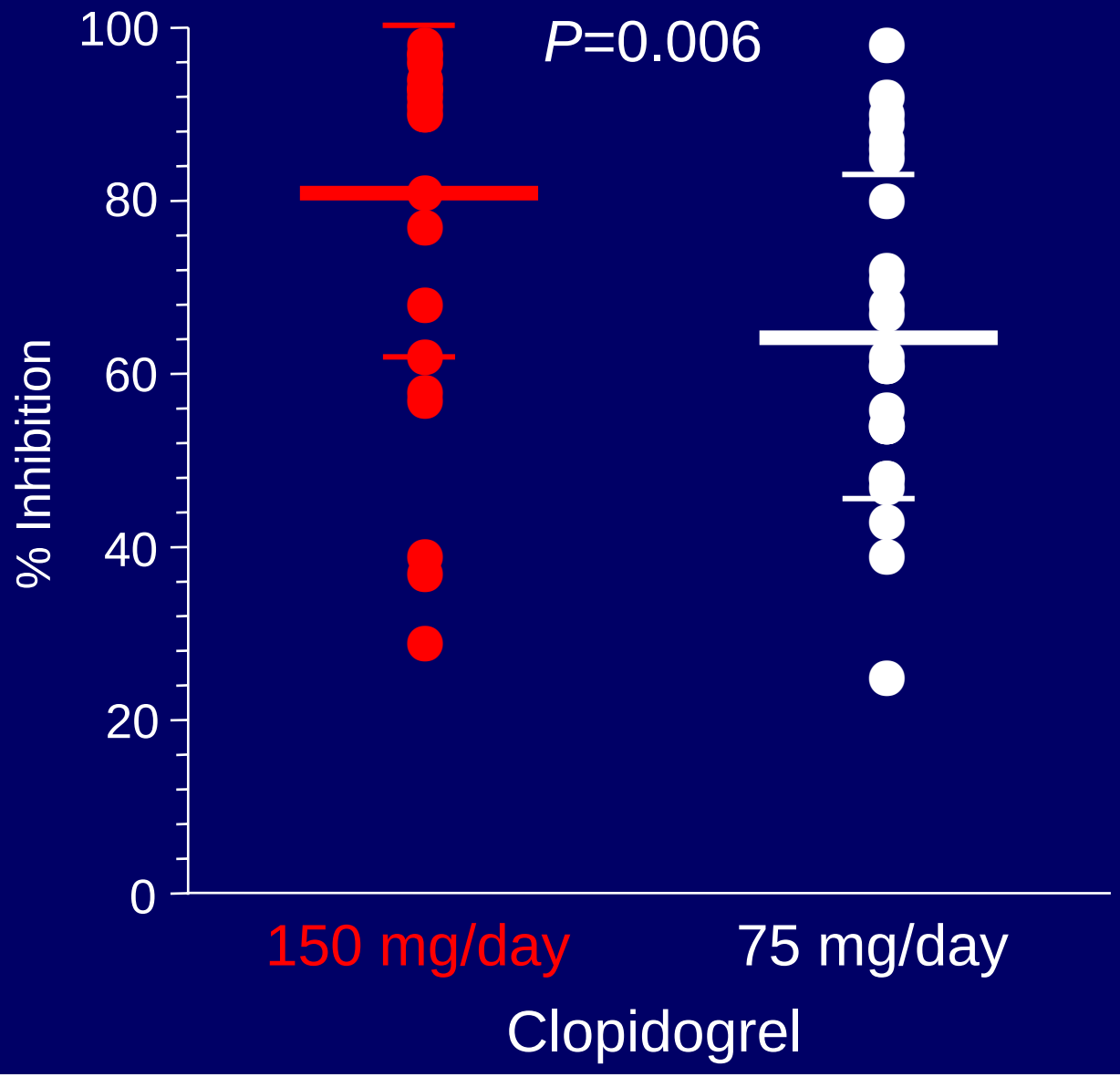
Aggregometry (30 days)



VerifyNow™ P2Y12 Assay (30 days)



VerifyNow™ P2Y12 Assay (30 days)



Conclusions, I

- A low platelet response to clopidogrel is observed in a relevant proportion of patients.
- Increase in the loading dose of clopidogrel up to 600 mg is able to improve significantly platelet response to clopidogrel.

Conclusions, II

- Doubling maintenance dose to 150 mg leads to stronger platelet inhibition.
- This maintenance dose may turn out to be useful in high risk patients or patients with limited response to clopidogrel.
- The clinical efficacy and safety of this increased dose regimen need to be evaluated in specifically designed RCTs.