Why all patients are not equal for antiplatelet therapy ?

P. COMMEAU, MD , PhD
OLLIOULES

Disclosure

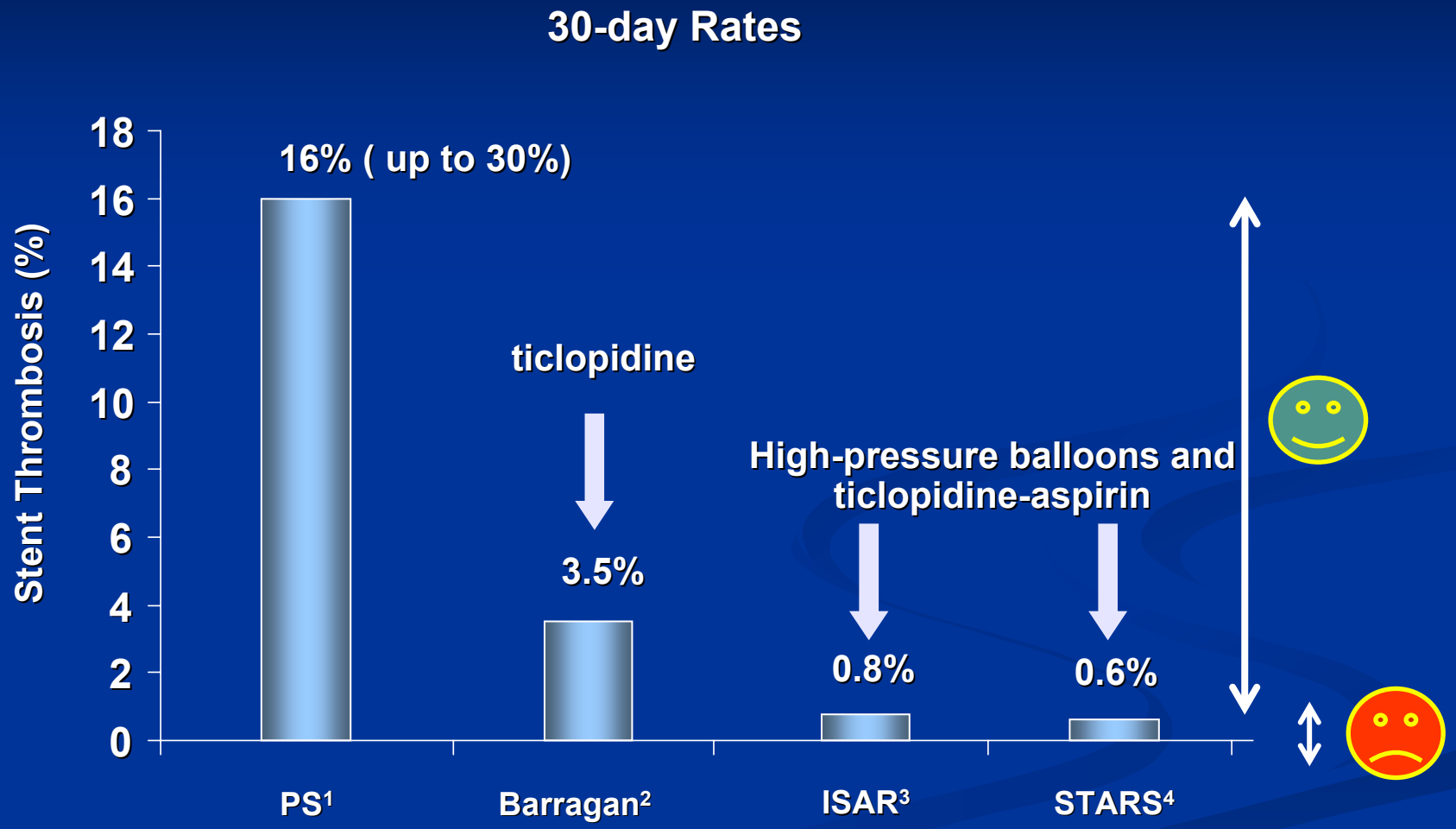
- Consultant and trainor for :
  - MEDTRONIC
  - CORDIS
  - EV3
  - ABBOTT
  - BIOTRONIK
  - BOSTON

In principle, we are equal !

- Recommendations from Societies , Group of experts , administration office and health department are:
  - Clopidogrel 75 mg whichever CV pathology (stenting, ACS, peripheral disease…) we have to treat and no matter the patient to treat (age, sex, weight, diabetes…)
  - Loading dose of Clopidogrel : 300 or 600 or 900mg ?
  - Aspirin : from 75 mg in Europe to 325 mg in USA ?
- My question is :

  do you prescribe the same dose of coumadin for each of your patients with mitral mechanical

Bare-Metal Stent Thrombosis

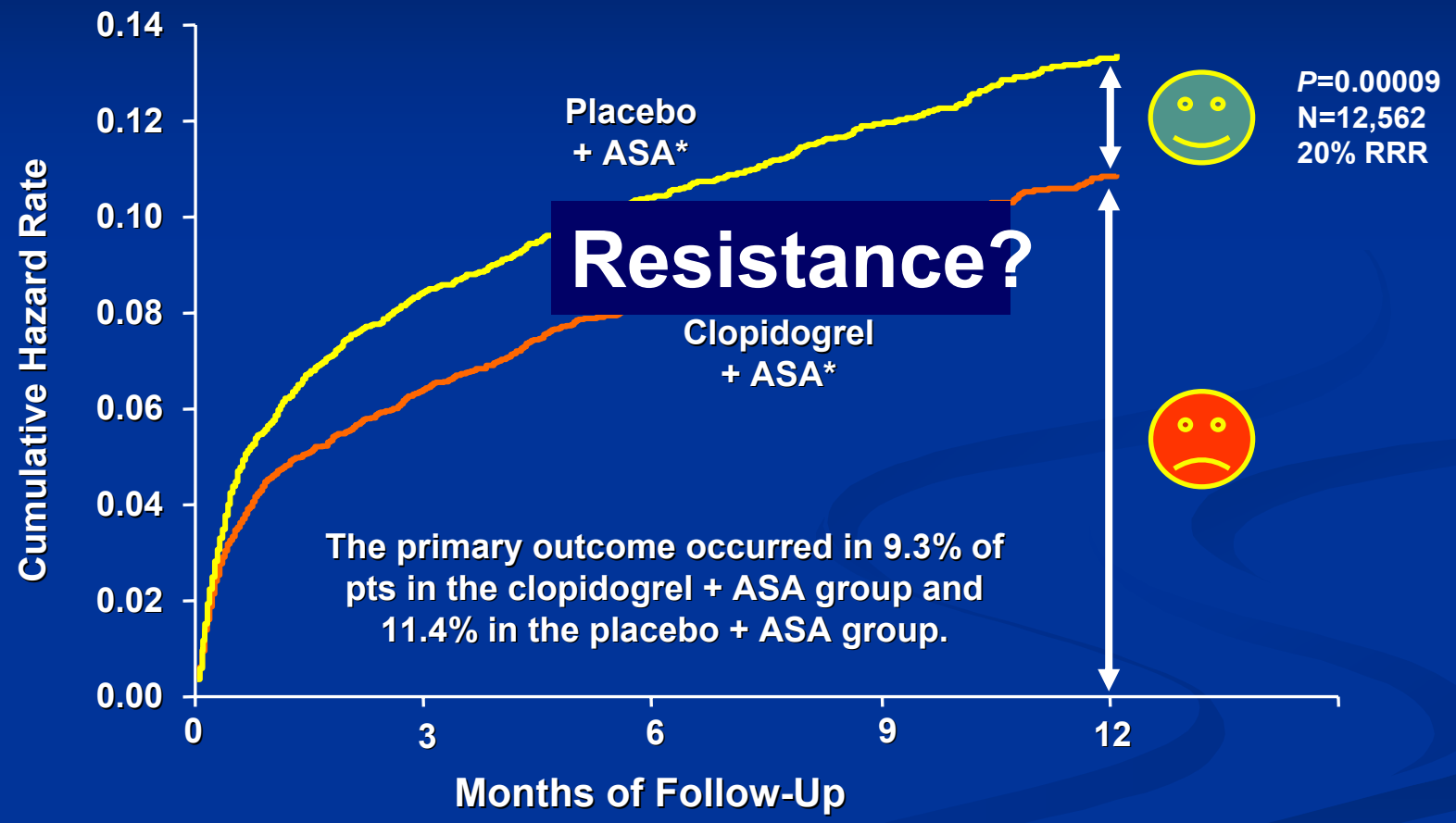


1. Schatz RA et al. *Circulation*. 1991;83:148-61. 2. Barragan et al. *Cathet Cardiovasc Diagn.* 1994;32:133–138. 3. Schömig A et al. *New Engl J Med.* 1996;334:1084-9. 4. Leon MB et al. *N Engl J Med*. 1998;339:1665-71.

MEET 2008

CURE

Primary Endpoint—MI/Stroke/CV Death

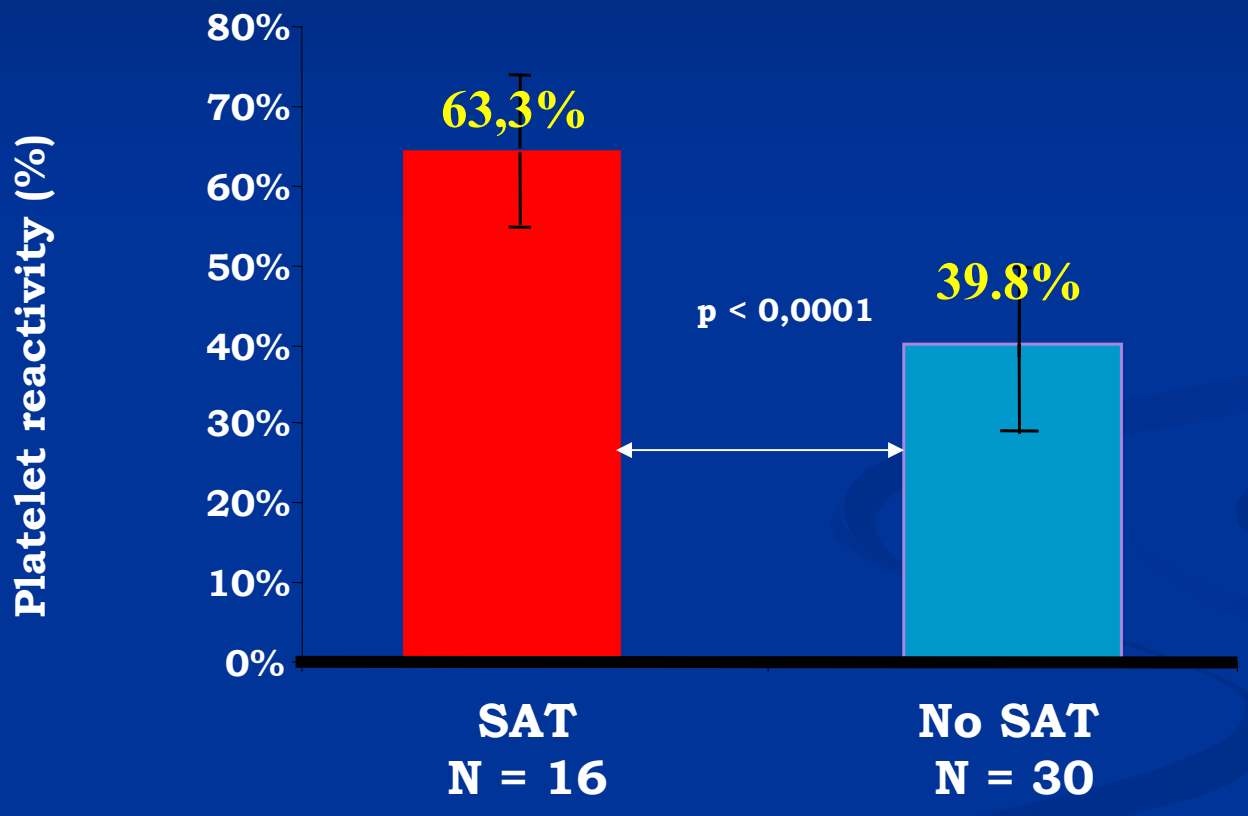


*Other standard therapies were used as appropriate.

Yusuf S et al. *N Engl J Med.* 2001;345:494-502.

CLOPIDOGREL « RESISTANCE »

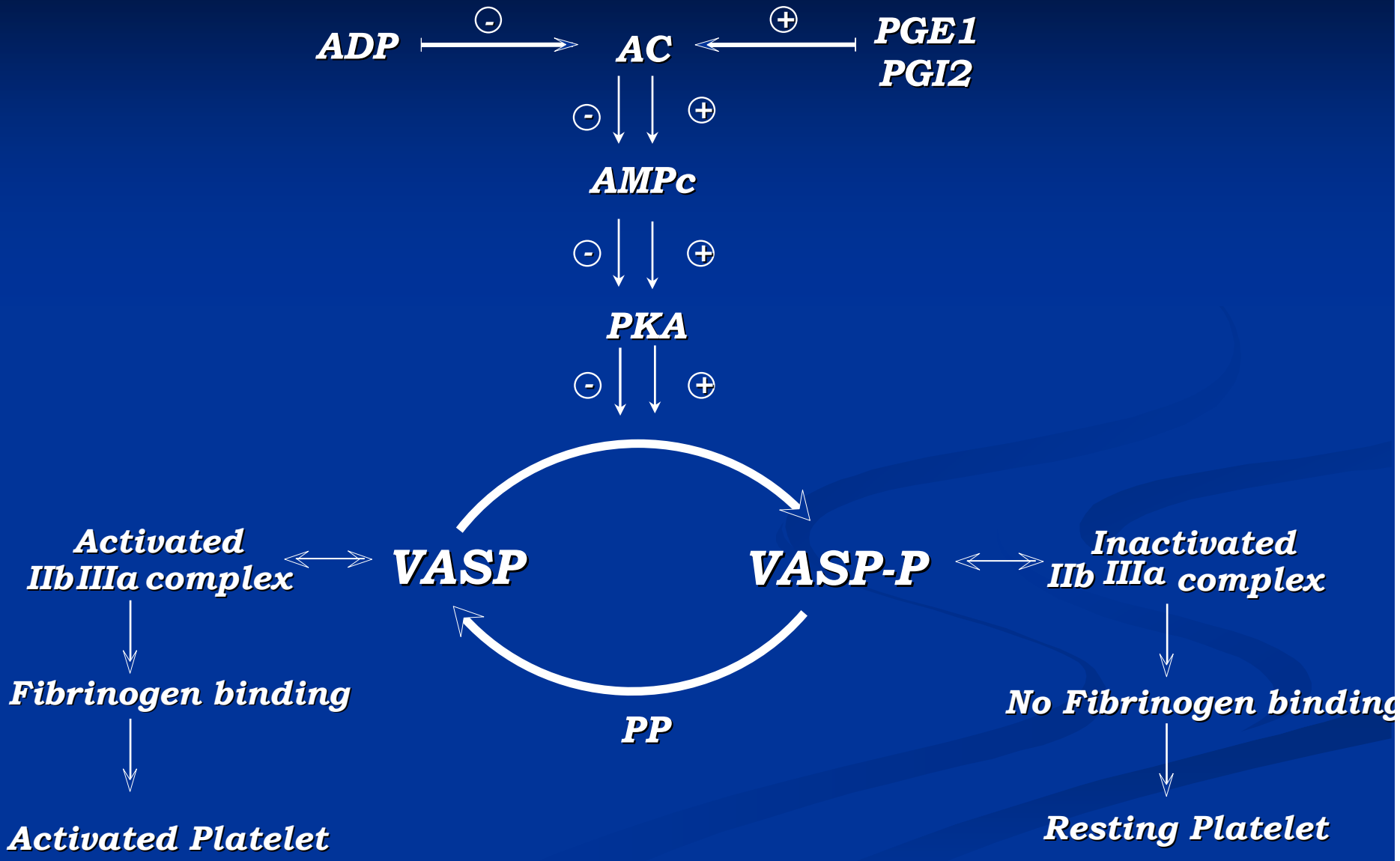
Sub-Acute Thrombosis is associated with high platelet reactivity



Cut-off : 50 % of PRI

Barragan P. et al, Catheter Cardiovasc Interv 2003; 59 : 295-302

Regulation Cascade of VASP Phosphorylation



Horstrup et al. Eur J Biochem 1994, 225 : 21-7

The Flow Cytometric Measurement of VASP Phosphorylation

① Is capable of detecting a significant decrease of platelet reactivity in patients treated with ticlopidin or clopidogrel regimen.

② Revealed an important inter-individual variability of response and a progressive platelet inhibition as a function of time.

③ Allows us to find a strong correlation between a thienopyridine resistance and coronary SAT.

Barragan et al. , CCI 2003

Detection of clopidogrel « resistance »
Platelet assays

- P2Y12 Signaling-Dependent
  - VASP phosphorylation analysis
- ADP as stimulus
  - Standart aggregometry
  - VerifyNow P2Y12 test
  - Cytometry: receptors GPIIb-IIIa, P-Selectin, leucocytes-Pq aggregates
  - TEG

Michelson Eur Heart J 2006; 8G3

Bibliography VASP/P2Y12

Updated 2008

2008

Bonello et al — JACC, 2008; 51: 1404-1411
Morel et al — Thromb Haemost 99:448-451
Gilard et al — JACC 51: 256-60
Sbrana et al — Cytometry 74:30-39
Wallentin et al — Eur Heart J 29:21-30

2007

Wiviott et al — Circulation 116:2923-32
Good et al — Heart 93, 5-105
Angiolillo et al — TCT2007
Lev et al — Am Heart J 154:694.e1-694.e7
Blindt et al — Thromb Haemost 98:1329-1334
Lortie et al — **SFAR 2007**
Jakubowski et al — **Eli Lilly - CRT 2007**
Cattaneo — J Thromb Haemost 5:879-881
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Fontana et al. — Thromb Haemost [Epub ahead of print]
Dropinski et al. — Thromb Haemost 98:201-209
Paniccia et al — J Thromb Haemost 5:1839-1847
Bonello et al — J Thromb Haemost 5:1630-1636
Mueller et al — Thromb Res [Epub ahead of print]
Schumacher et al — JPET 322:369-377
Cuisset et al — Thromb Res [Epub ahead of print]
Morel et al — Ann Cardiol Ang 56:21-29
Cattaneo — Expert Rev Cardiol Ther 5:45-55
Gurbel — Thromb Res [Epub ahead of print]
van Werkum et al — J Thromb Haemost 5:881-883
Angiolillo et al — Circulation 115:708-716
Aleil et al — J Thromb Haemost 5:879-881
Cuisset et al — Thromb Haemost 97:212-217

2006

von Beckerath et al — JTH 95:910-911
Gaussem — Thérapie 61:1-5
Pampuch et al — Thromb Haemost, 96:767-773
Gurbel & Tantry — Nat Clin Pract Cardiovasc Med 3:387-395
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Gilard et al — J Thromb Haemost 4:2508-2509
Cauwenberghs et al — Transfusion 46:1018-1028
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Montalescot et al — JACC 48:931-938

2005

Aleil et al — J Thromb Haemost 3:85-92
Aleil et al — Thromb & Haemost 94:886-887
Gurbel et al — J Am Coll Cardiol 46:1827-1832

2003

Barragan et al. — Cathet Cardiovasc Intervent 59:295-302

STUDY DESIGN

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

Loading dose (LD) *ASA 250mg*
Clopidogrel 600mg

VASP ≥ 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

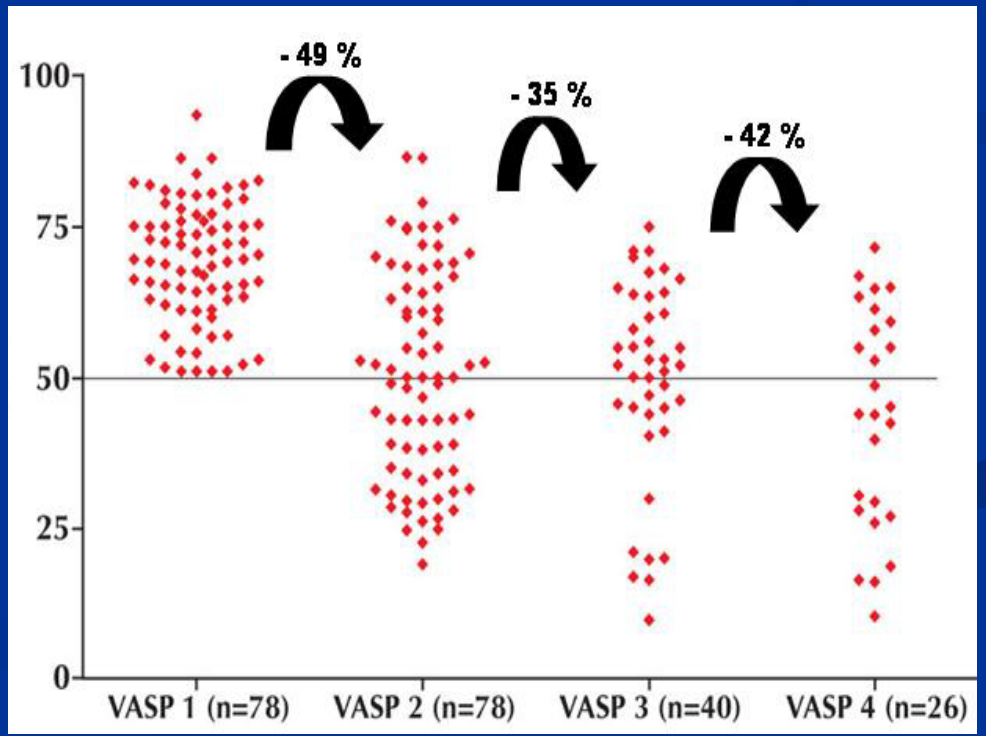
Bonello et al. JACC. 2008; 51: 1404-1411

PLATELET MONITORING

Mean ±SD	Control	VASP-guided	p
Time between first LD and VASP measurement, hrs	25 ±13	24 ±13	0.7
VASP after first LD, %	68 ±11	69 ±10	0.4
VASP after adjustment, %	–	38 ±14*	*<0.001

-Each additionnal 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.

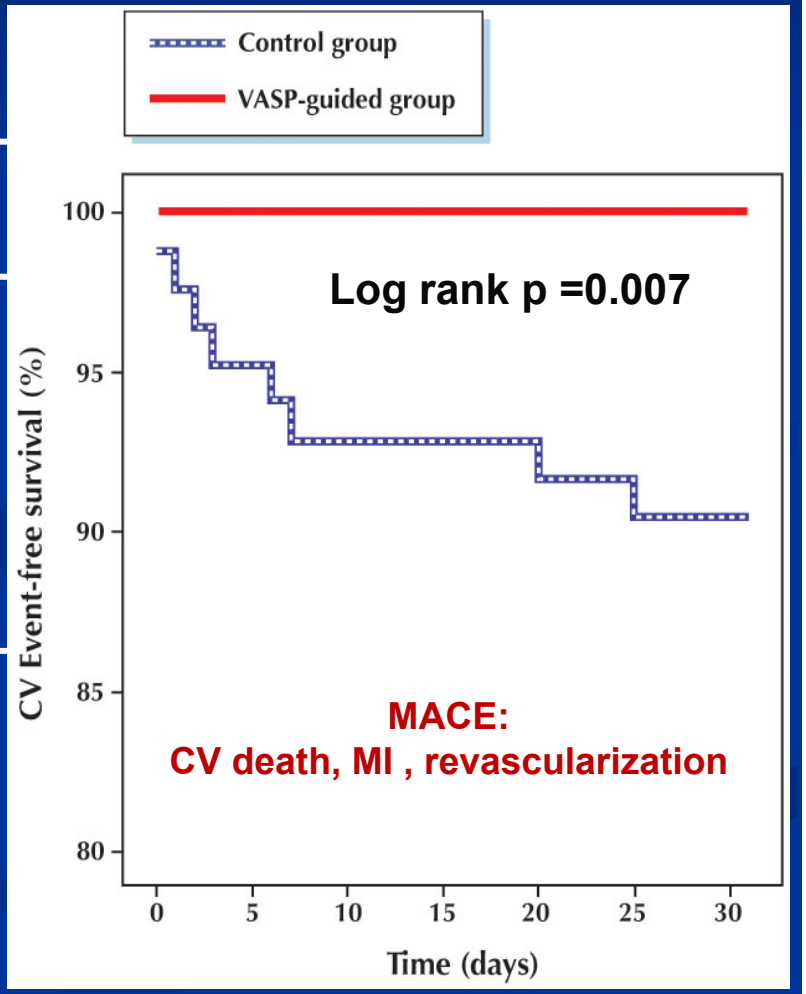


Bonello et al. JACC. 2008; 51: 1404-1411

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

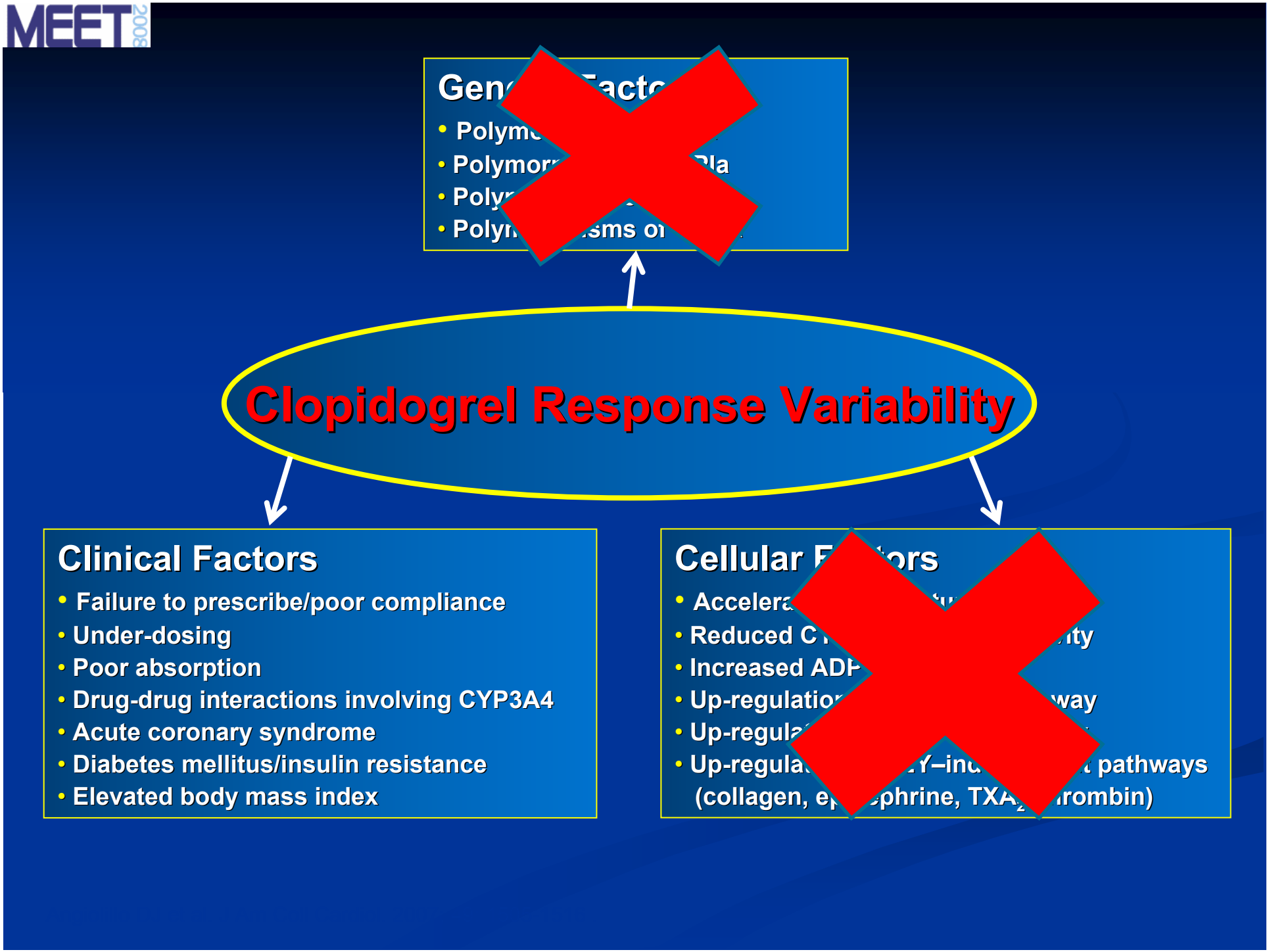


Bonello et al. JACC. 2008; 51: 1404-1411

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)

Bonello et al. JACC. 2008; 51: 1404-1411


Gen Facto
• Polym
• Polymor Pla
• Poly
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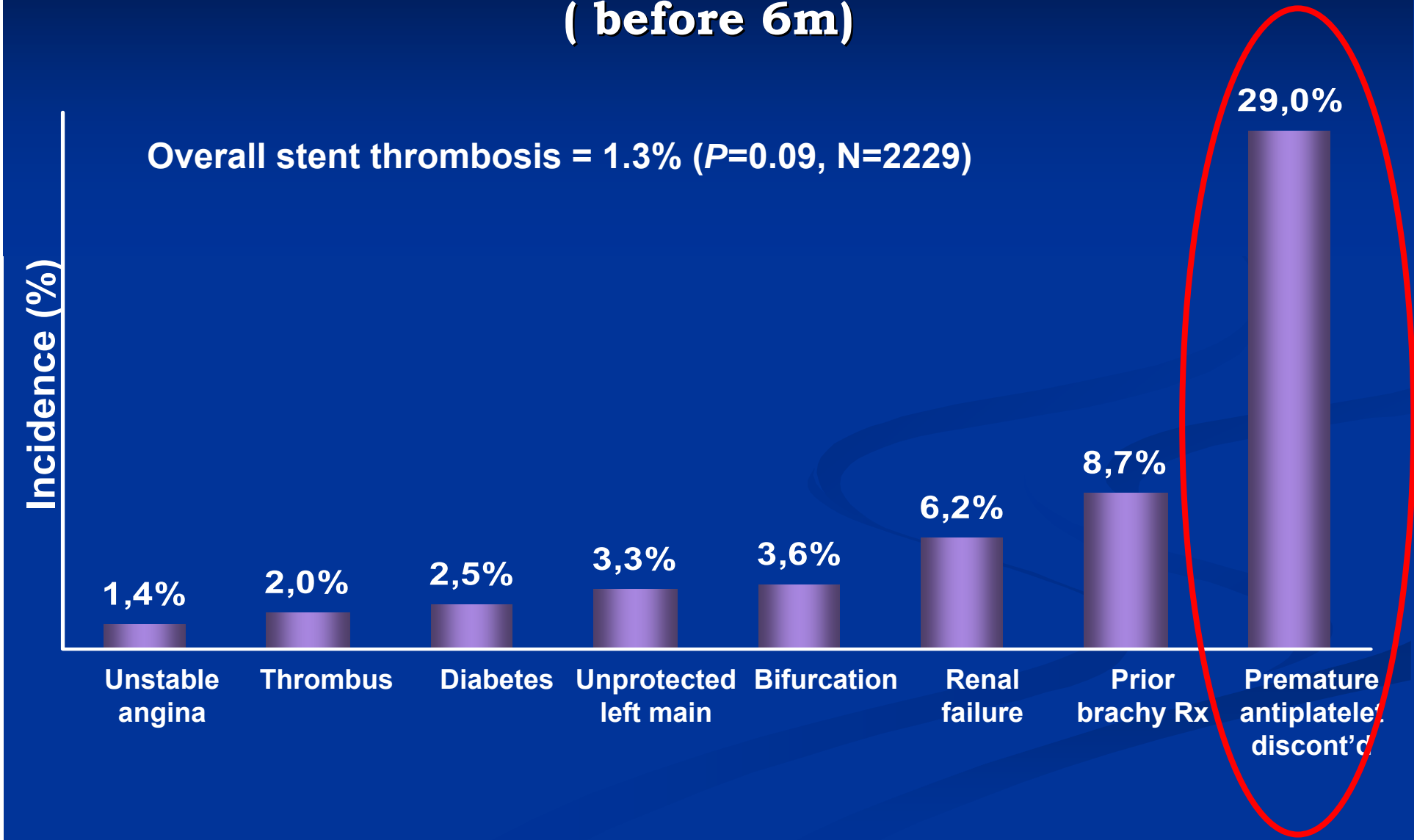
Clopidogrel Response Variability
Clinical Factors
• Failure to prescribe/poor compliance
• Under-dosing
• Poor absorption
• Drug-drug interactions involving CYP3A4
• Acute coronary syndrome
• Diabetes mellitus/insulin resistance
• Elevated body mass index
Cellular F ors
• Accelera
• Reduced C ity
• Increased ADP
• Up-regulatio way
• Up-regula
• Up-regula Y–ind t pathways
(collagen, e ephrine, TXA2 hrombin)

Stent Thrombosis
Early Discontinuation of Anti-platelet Therapy (before 6m)



Iakovou et al. *JAMA*. 2005;293:2126.

Premature Cessation of Thienopyridine Therapy (<30d)

- PREMIER registry: MI and DES, 19 centers, 500 subjects
- Early discontinuation associated with mortality (7.5% vs 0.7%, p<0.0001)

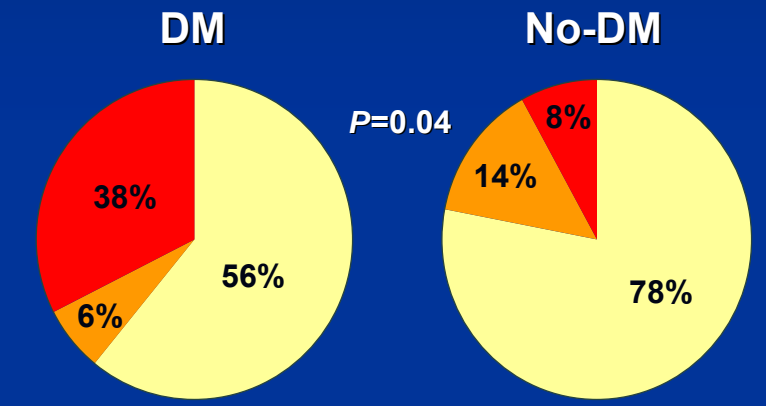
Factors related to premature cessation:

- Older age
- Not having completed high school
- Not being married
- Not receiving discharge instructions for medication use
- Not being referred for cardiac rehabilitation
- Greater likelihood of having preexistent cardiovascular disease or anemia
- Not seeking health care because of cost

Spertus JA. Circulation 2006;48:2584-91.

Influence of Diabetes Mellitus on Clopidogrel-induced Antiplatelet Effects

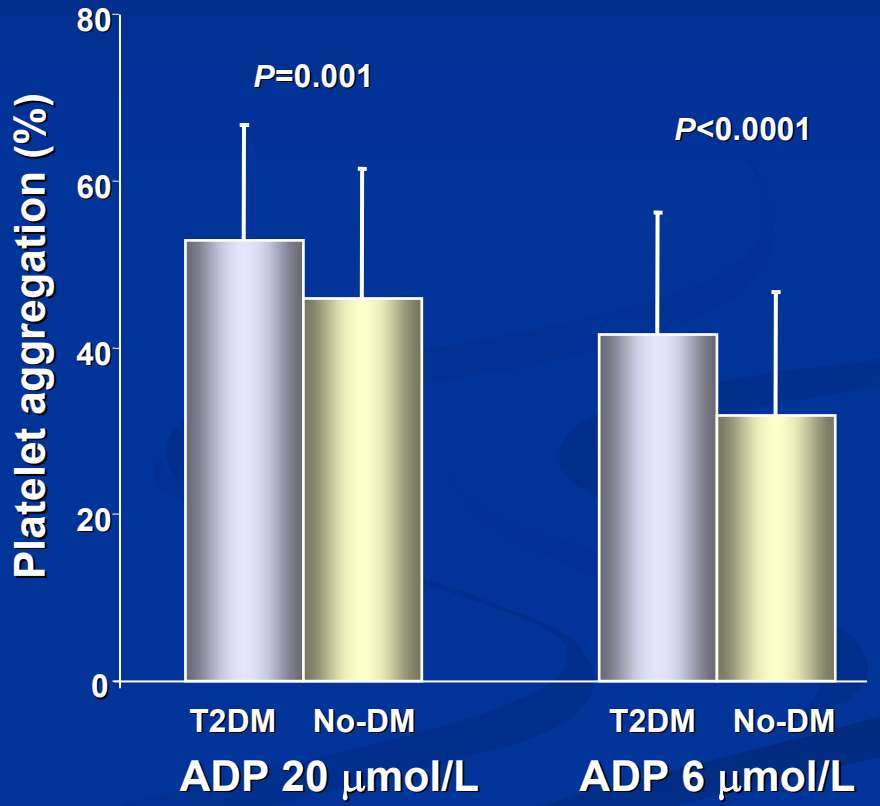
Acute phase of treatment



24 hrs post 300 mg LD

- Non-responders (Platelet inhibition <10%)
- Low responders (Platelet inhibition 10-29%)
- Responders (Platelet inhibition >30%)

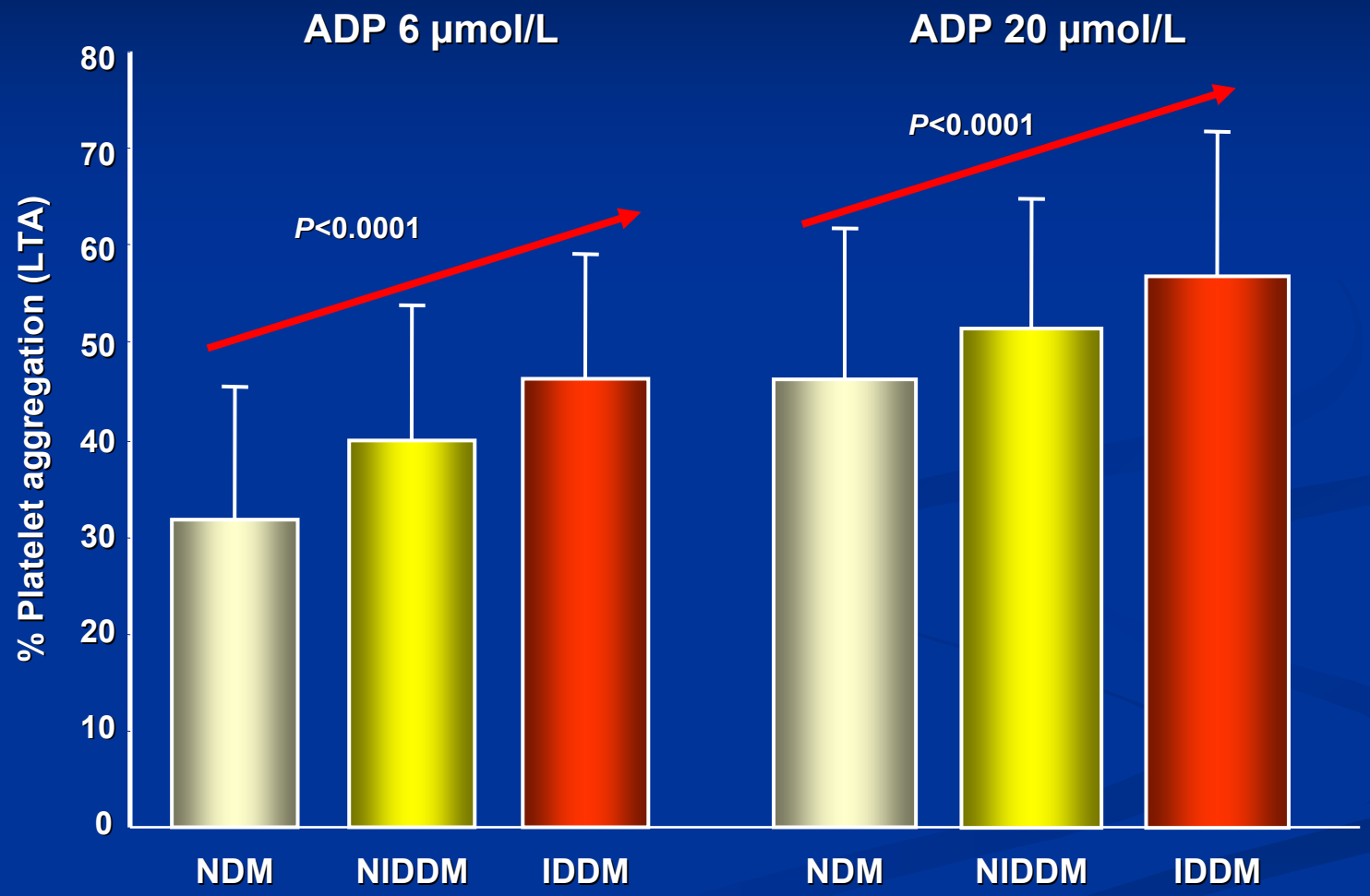
Long-term phase of treatment



Angiolillo DJ et al. *Diabetes.* 2005;54:2430-5.

Angiolillo DJ et al. *J Am Coll Cardiol* 2006;48 298-304.

Platelet Function According to Hypoglycemic Treatment

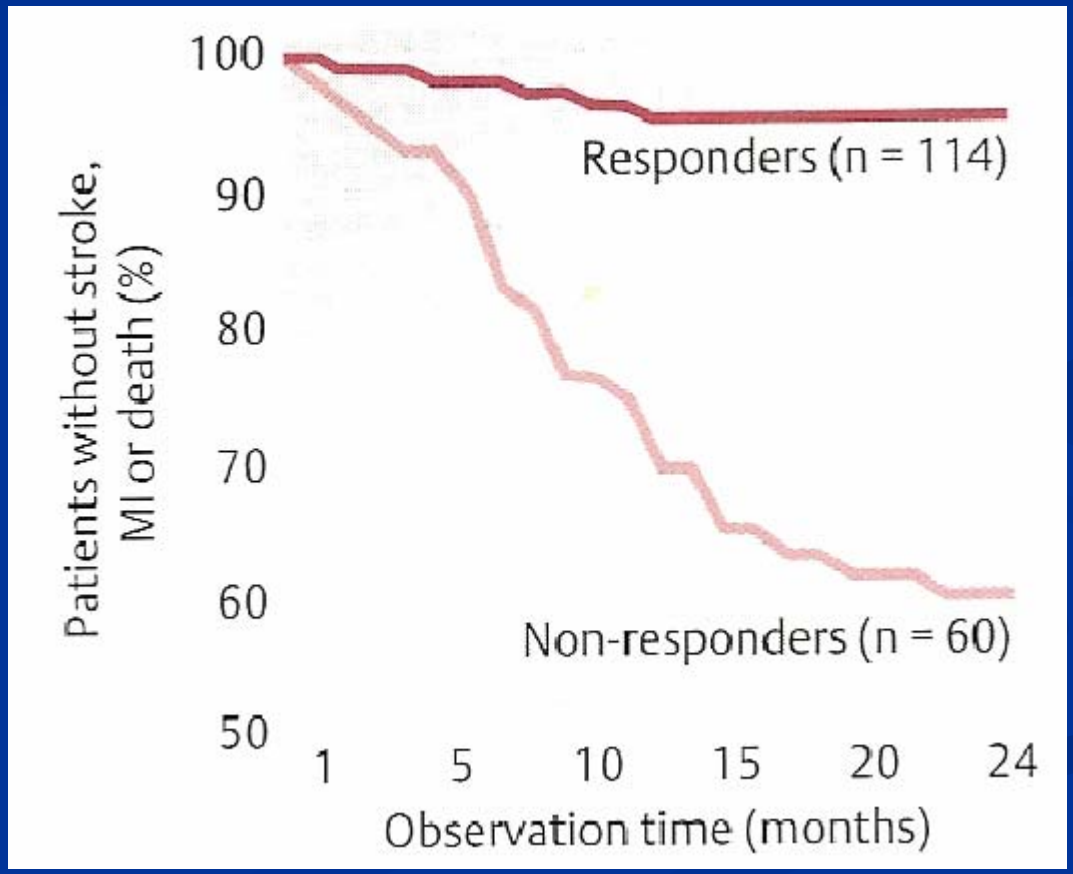


Angiolillo DJ et al. *J Am Coll Cardiol.* 2006;48:298-304.

ASPIRIN "RESISTANCE"

ASPIRINE :

Pilote Study including 180 post-stroke patients



Grotemeyer. Thromb Res 1993;71:397-403

A prospective , blinded determination of the Natural History of Aspirine Resistance among Stable Patients with Cardiovascular Disease

326 pts with 325 mg ASA alone Optical aggr.
ADP + AA(1.6mmole/l)

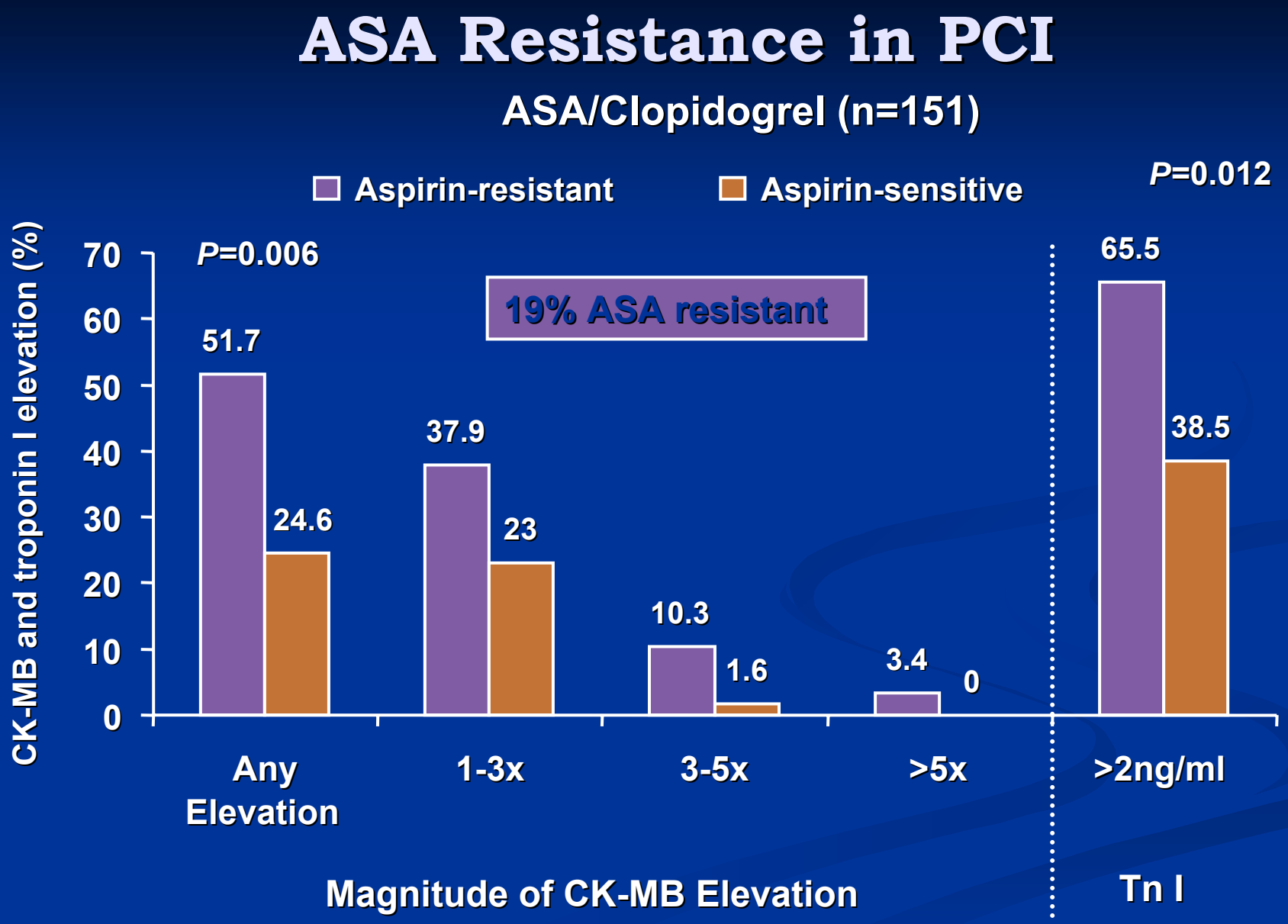
N=17
(5 %)

P< 0.009

N=309

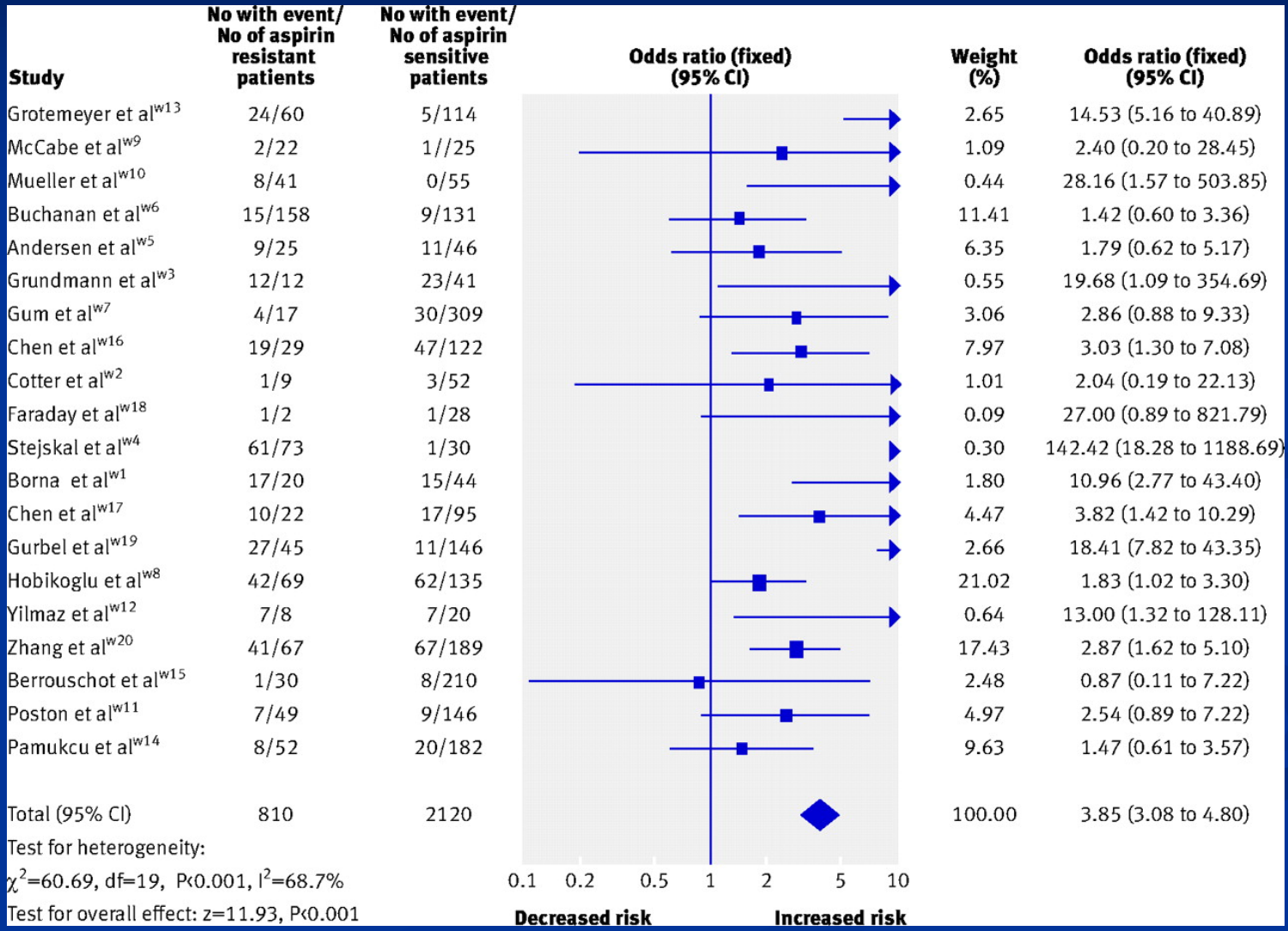
P.Gum et al. JACC 2003, 41:961-5

ASA Resistance in PCI



Chen W-H. *J Am Coll Cardiol.* 2004;43:1122-6.

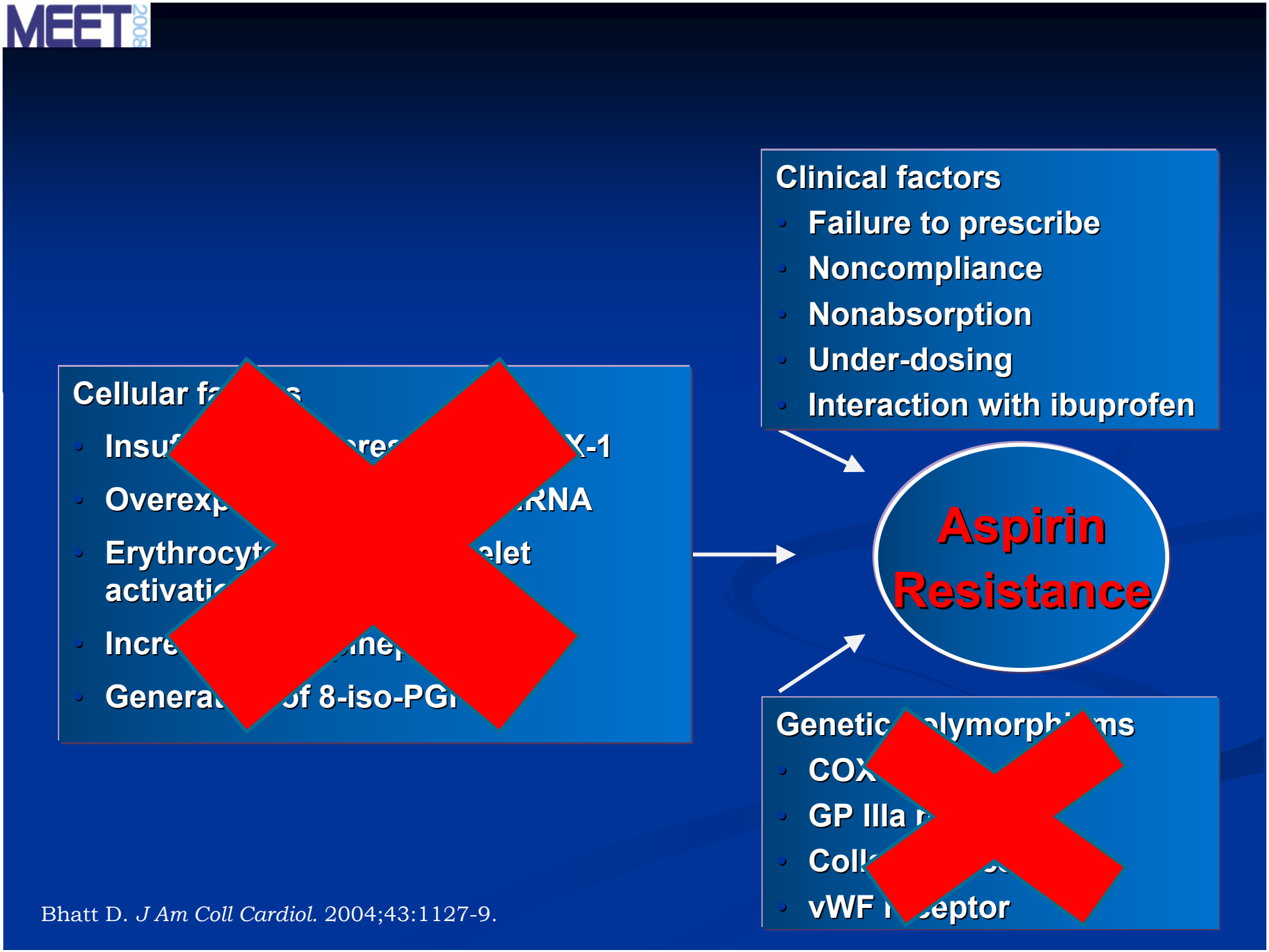
Risk of any cardiovascular event in aspirin resistant patients



Study	No with event/ No of aspirin resistant patients	No with event/ No of aspirin sensitive patients	Weight (%)	Odds ratio (fixed) (95% CI)
Grotemeyer et al[w13]	24/60	5/114	2.65	14.53 (5.16 to 40.89)
McCabe et al[w9]	2/22	1//25	1.09	2.40 (0.20 to 28.45)
Mueller et al[w10]	8/41	0/55	0.44	28.16 (1.57 to 503.85)
Buchanan et al[w6]	15/158	9/131	11.41	1.42 (0.60 to 3.36)
Andersen et al[w5]	9/25	11/46	6.35	1.79 (0.62 to 5.17)
Grundmann et al[w3]	12/12	23/41	0.55	19.68 (1.09 to 354.69)
Gum et al[w7]	4/17	30/309	3.06	2.86 (0.88 to 9.33)
Chen et al[w16]	19/29	47/122	7.97	3.03 (1.30 to 7.08)
Cotter et al[w2]	1/9	3/52	1.01	2.04 (0.19 to 22.13)
Faraday et al[w18]	1/2	1/28	0.09	27.00 (0.89 to 821.79)
Stejskal et al[w4]	61/73	1/30	0.30	142.42 (18.28 to 1188.69)
Borna et al[w1]	17/20	15/44	1.80	10.96 (2.77 to 43.40)
Chen et al[w17]	10/22	17/95	4.47	3.82 (1.42 to 10.29)
Gurbel et al[w19]	27/45	11/146	2.66	18.41 (7.82 to 43.35)
Hobikoglu et al[w8]	42/69	62/135	21.02	1.83 (1.02 to 3.30)
Yilmaz et al[w12]	7/8	7/20	0.64	13.00 (1.32 to 128.11)
Zhang et al[w20]	41/67	67/189	17.43	2.87 (1.62 to 5.10)
Berrouschot et al[w15]	1/30	8/210	2.48	0.87 (0.11 to 7.22)
Poston et al[w11]	7/49	9/146	4.97	2.54 (0.89 to 7.22)
Pamukcu et al[w14]	8/52	20/182	9.63	1.47 (0.61 to 3.57)
Total (95% CI)	810	2120	100.00	3.85 (3.08 to 4.80)

Test for heterogeneity:
χ^2=60.69, df=19, P<0.001, I^2=68.7%
Test for overall effect: z=11.93, P<0.001

Krasopoulos G. et al. BMJ 2008



Bhatt D. *J Am Coll Cardiol.* 2004;43:1127-9.

Platelet function analyzer (PFA)-100®

One

Pipette 800 µL blood

Two

Insert cassette

Three

Start the test

VerifyNow

VerifyNow predicts clinical outcomes

- Aspirin assay: Chen *JACC* 2004;43:1122–6
- P2Y12 assay: Price *ACC* 2007
- GPIIb-IIIa assay: Steinhubl *Circ* 2001;103:2572–8

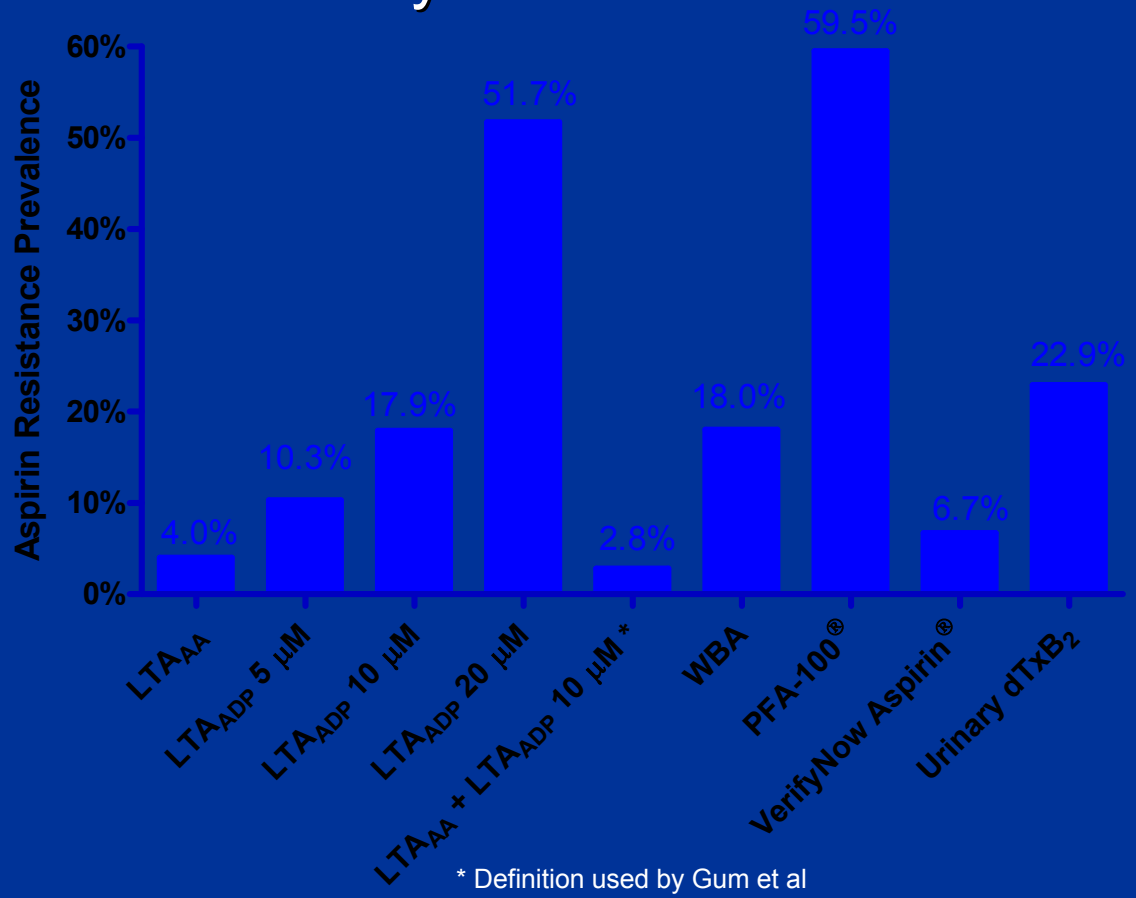
The assessment of ASA resistance is highly assay-dependant

N=125 stable patients

Gurbel et al. Circulation 2007.115: 3156-3164.

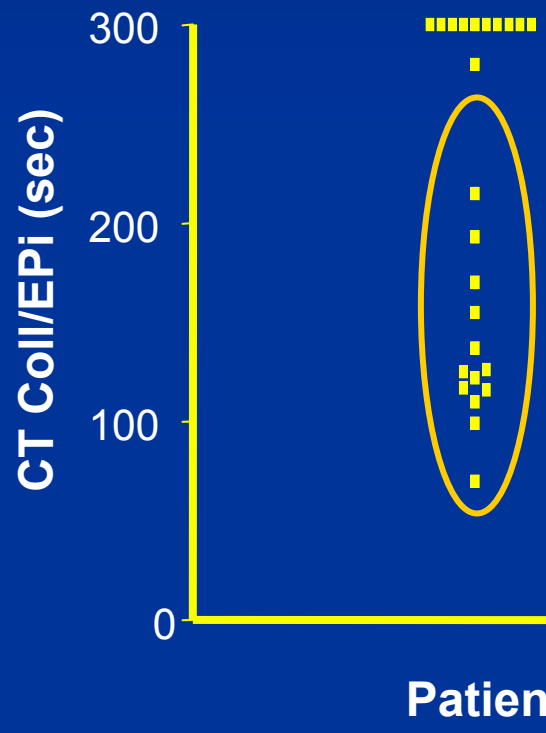
Results

- Prevalence of resistance varied according to the platelet function assay used



* Definition used by Gum et al

PFA-100 and ASA resistance



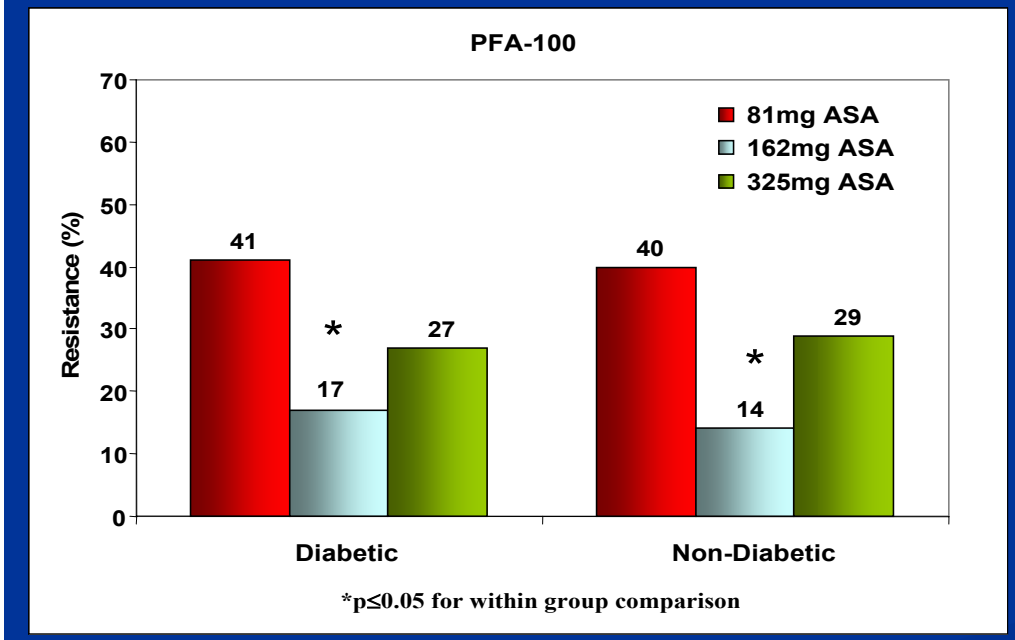
- Patients (n =100)
- Mean ASA duration > 3 months
- ASA 160 mg/day

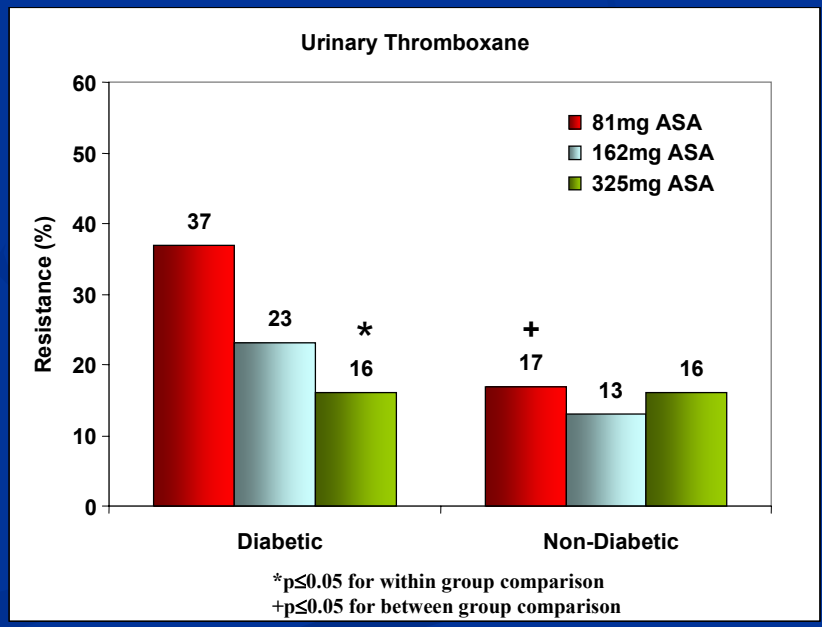
30 % of patients had a normal Closure time= Resistance ASA

Personal data

ASA resistance AND diabetes

- Low dose aspirin may not provide adequate platelet inhibition in diabetic patients.
- But, there are limited data quantifying the prevalence of platelet aspirin resistance in diabetic patients.





Watala C. Blood platelet reactivity and its pharmacological modulation in people with diabetes mellitus. *Current Pharmaceutical Design.* 2005;11:2331-2365

Thrombosis Research (2005) 116, 465–470

ELSEVIER

THROMBOSIS RESEARCH

intl.elsevierhealth.com/journals/thre

Regular Article

Effect of increasing doses of aspirin on platelet function as measured by PFA-100 in patients with diabetes

Adnan Abaci[a,*], Yucel Yilmaz[b], Mustafa Caliskan[b], Fahri Bayram[c], Mustafa Cetin[d], Ali Unal[d], Servet Cetin[b]

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[b]Department of Cardiology, Erciyes University School of Medicine, Kayseri, Turkey
[c]Department of Endocrinology, Erciyes University School of Medicine, Kayseri, Turkey
[d]Department of Hematology, Erciyes University School of Medicine, Kayseri, Turkey

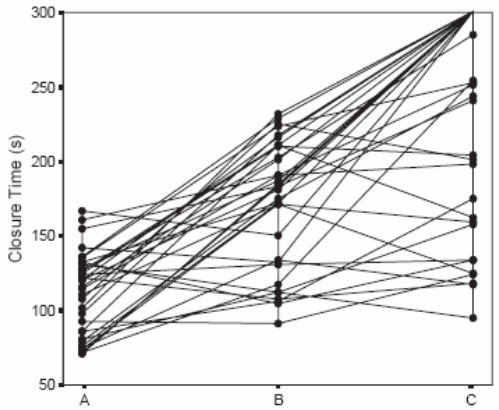


Figure 1 Closure times before (A), after 100 mg (B) and 300 mg (C) doses of aspirin in 34 patients in which the closure times did not exceeded the upper limit of 300 s. *$p<0.05$ (100 mg vs. before treatment and 300 mg vs. 100 mg).

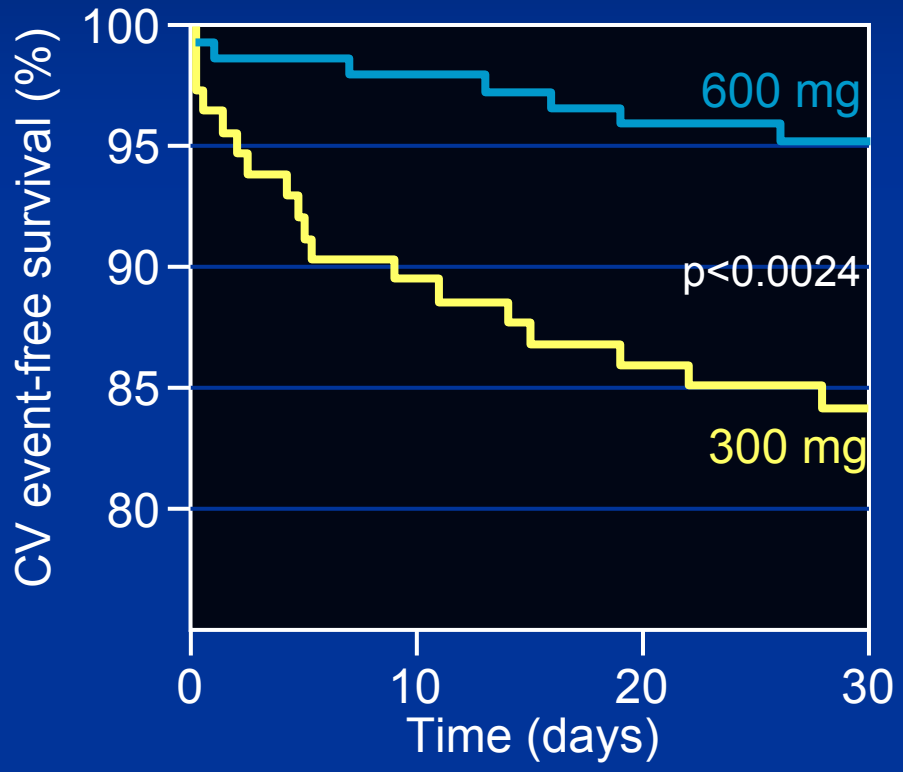
Prevalence of aspirin resistance may be related to aspirin dose and aspirin resistance can be overcome in some patients by increasing the aspirin dose

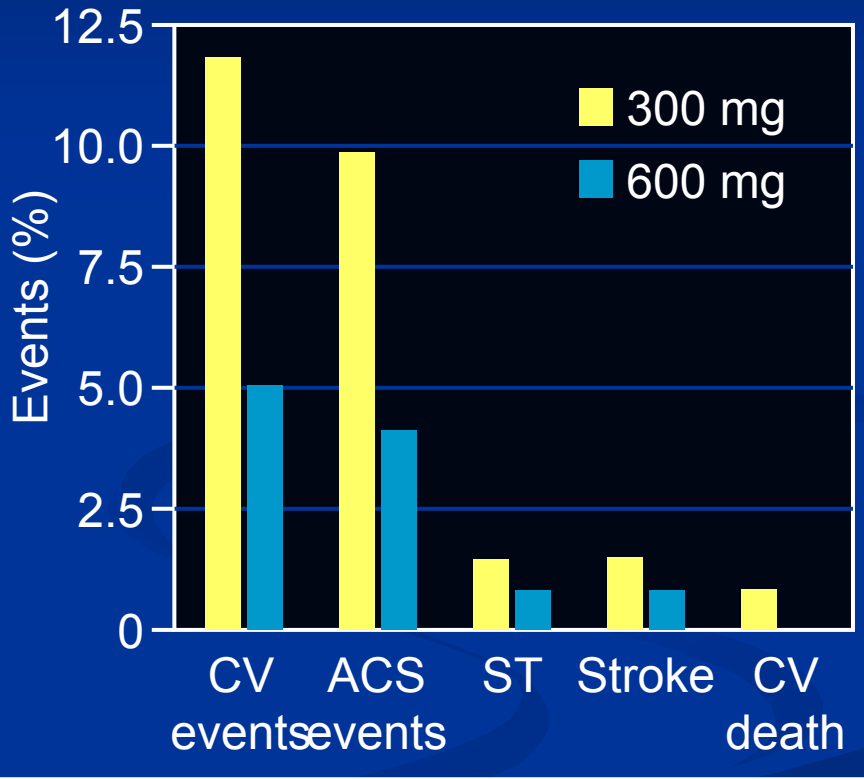
MEET 2008

Are an higher dose or a new (more effective) drug able to eradicate drug resistance?

Clopidogrel 600 mg vs 300 mg loading dose

292 consecutive NSTE ACS stent patients received
300 or 600 mg loading dose of clopidogrel



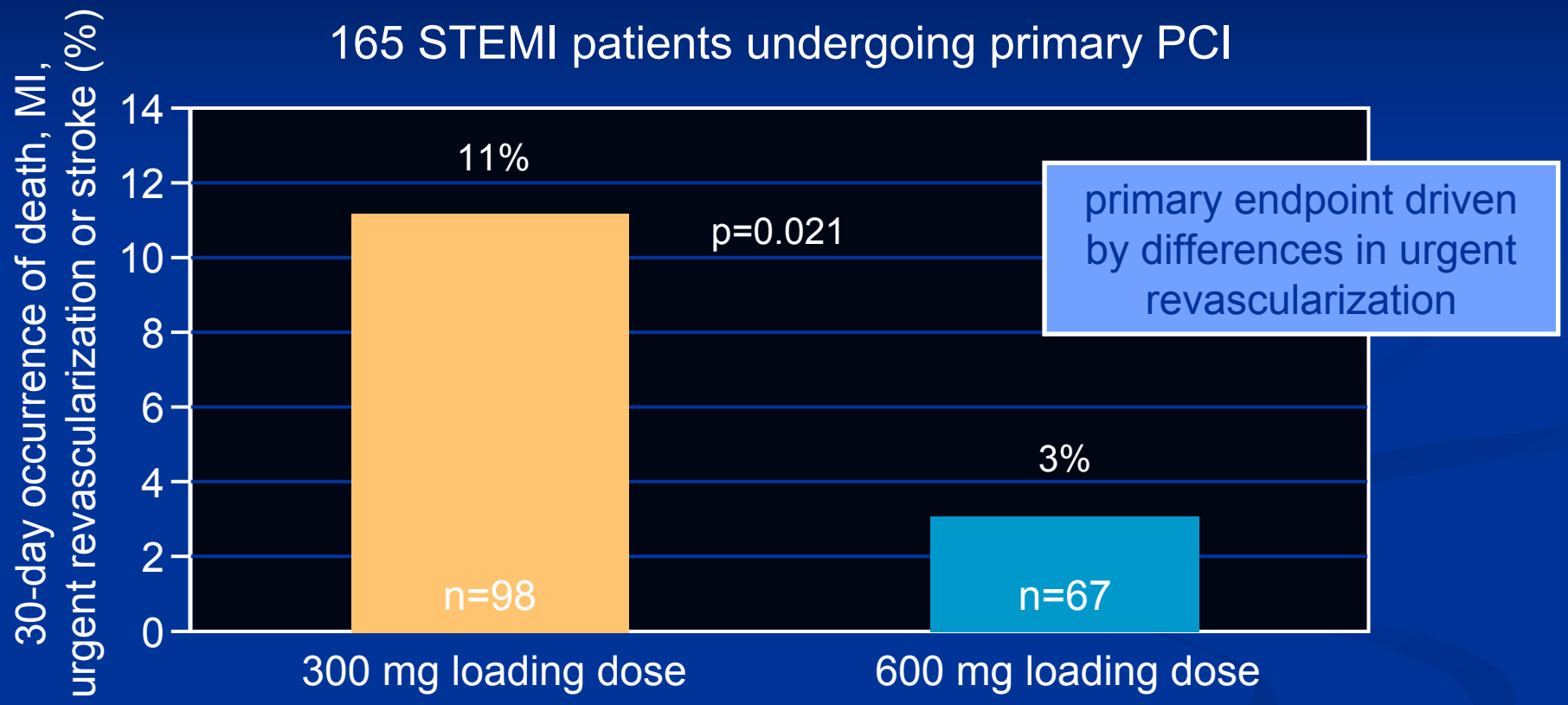


A 600mg loading dose of clopidogrel reduced the occurrence of subsequent events

ST = Stent thrombosis

Cuisset *et al.* J Am Coll Cardiol 2006; 48:1339–45

High loading dose of clopidogrel significantly reduced urgent revasc. after primary PCI

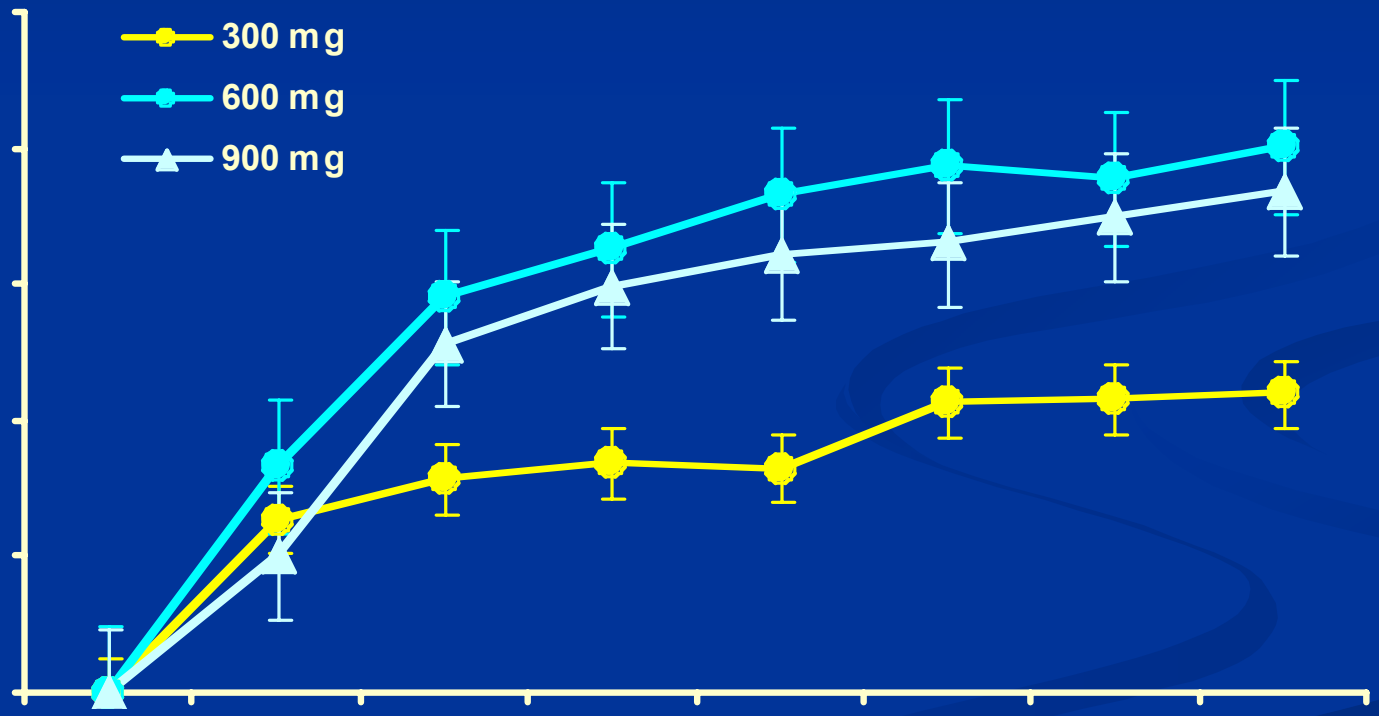


600 mg loading dose may be more effective than a 300 mg loading dose

Jung *et al.* Am J Cardiol 2006; Oct 22-27 (TCT Abstracts)

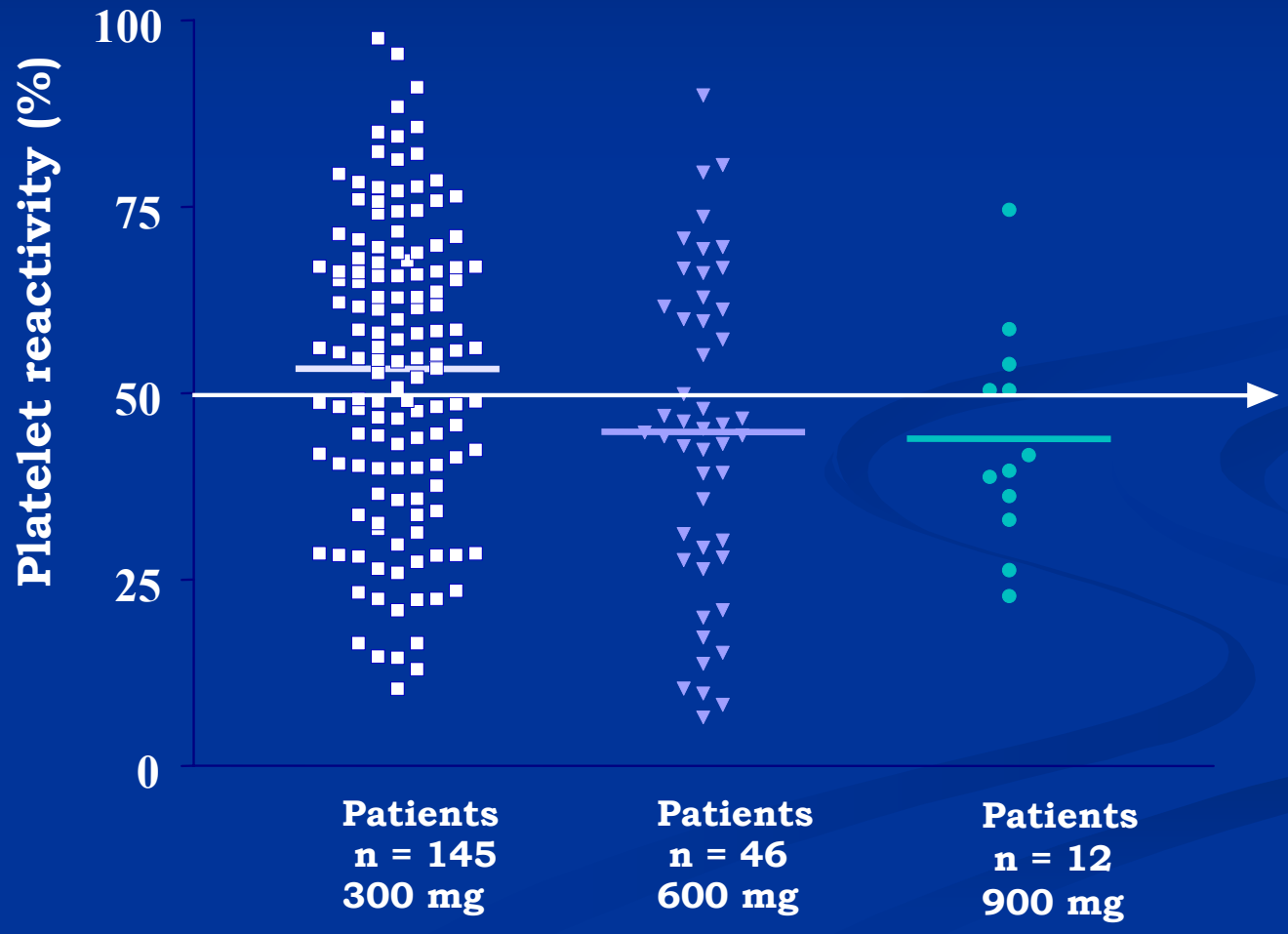
Measured Effect of Different Loading Doses of Clopidogrel (VerifyNow)

* p < 0.01 (600- or 900-mg vs. 300-mg)



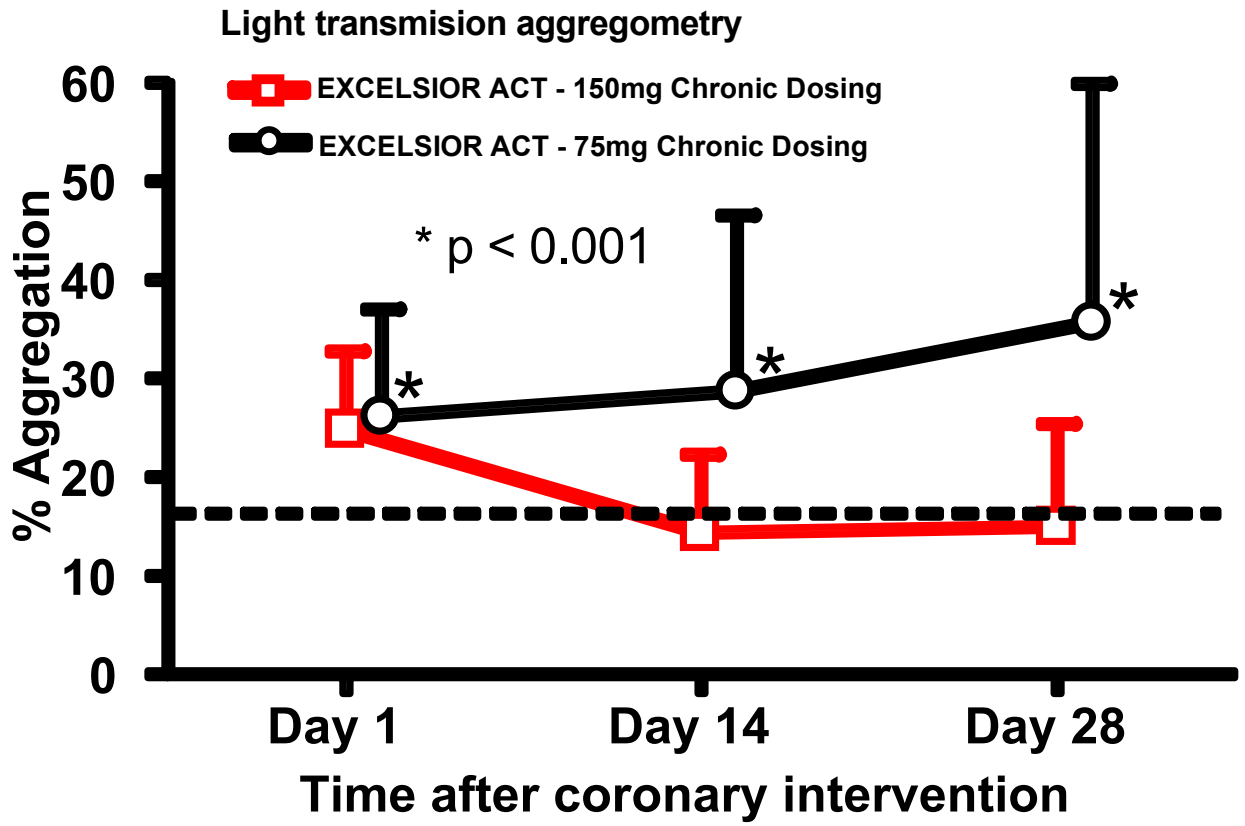
Price, AJC 2006

A standart dose of clopidogrel for every patients ?



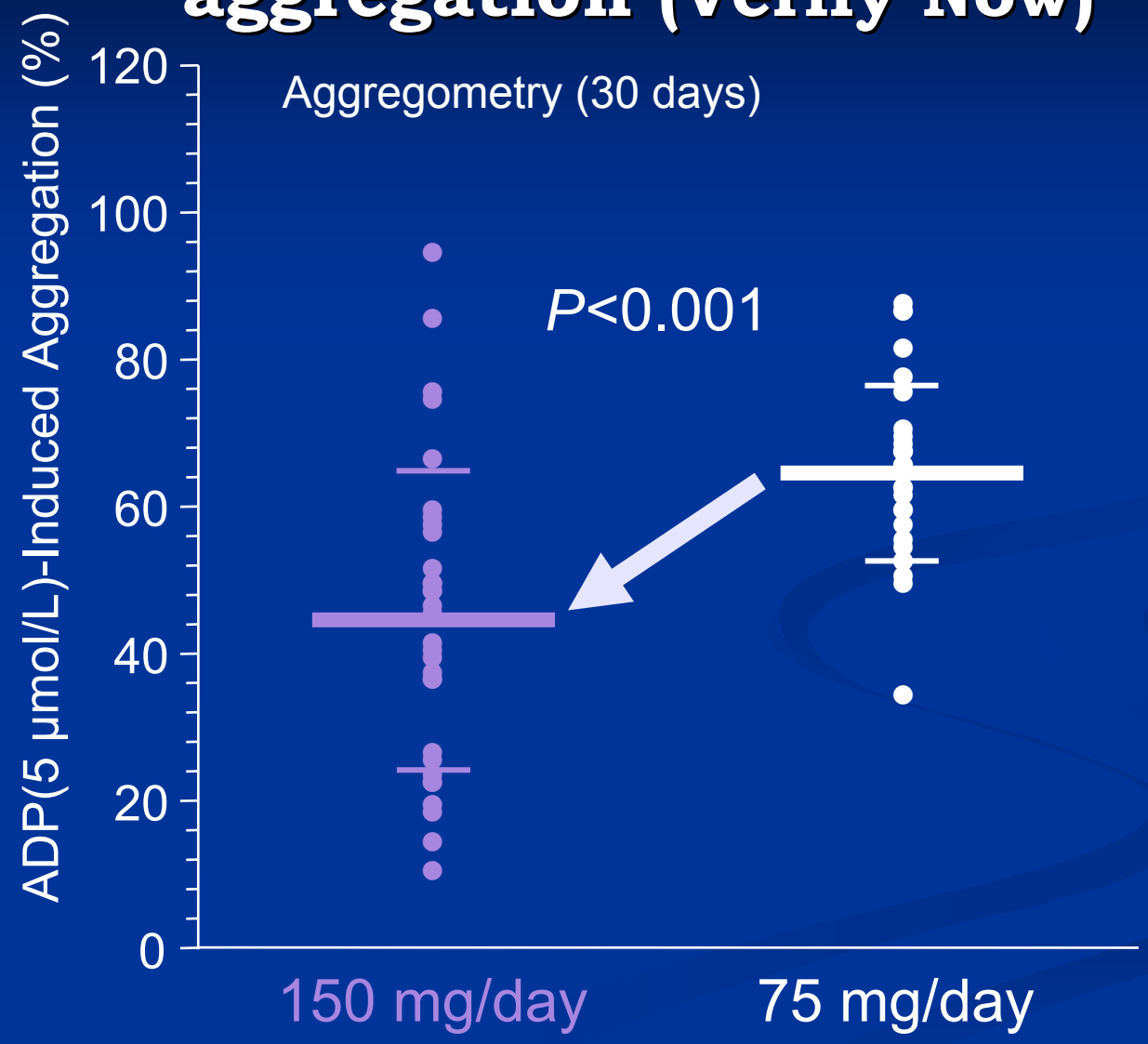
Personal Data

Response to Chronic Dosing with 75 vs 150 mg



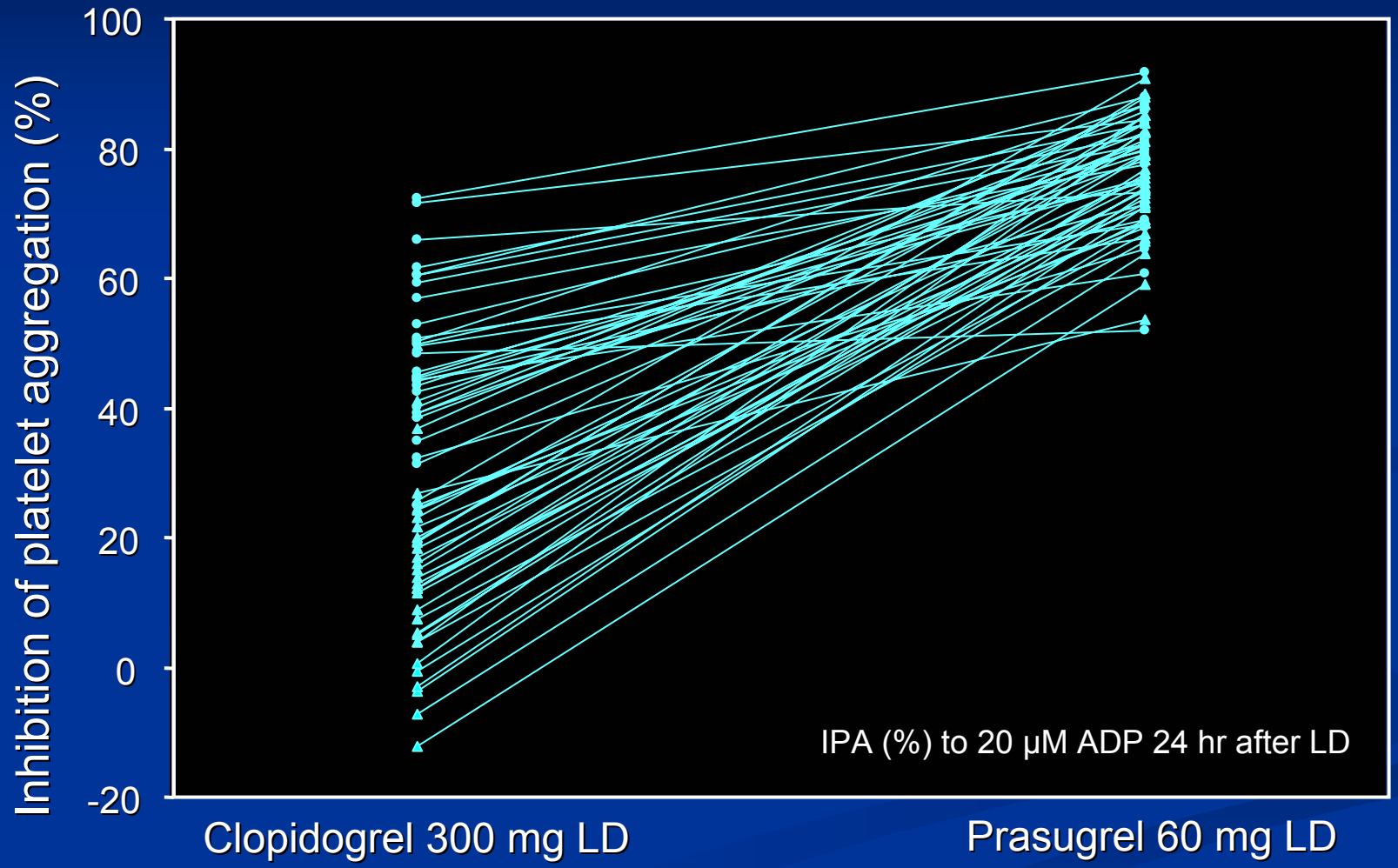
FJ Neumann et al, ACC 2007

Increasing Chronic Dose decreases platelet aggregation (Verify Now)



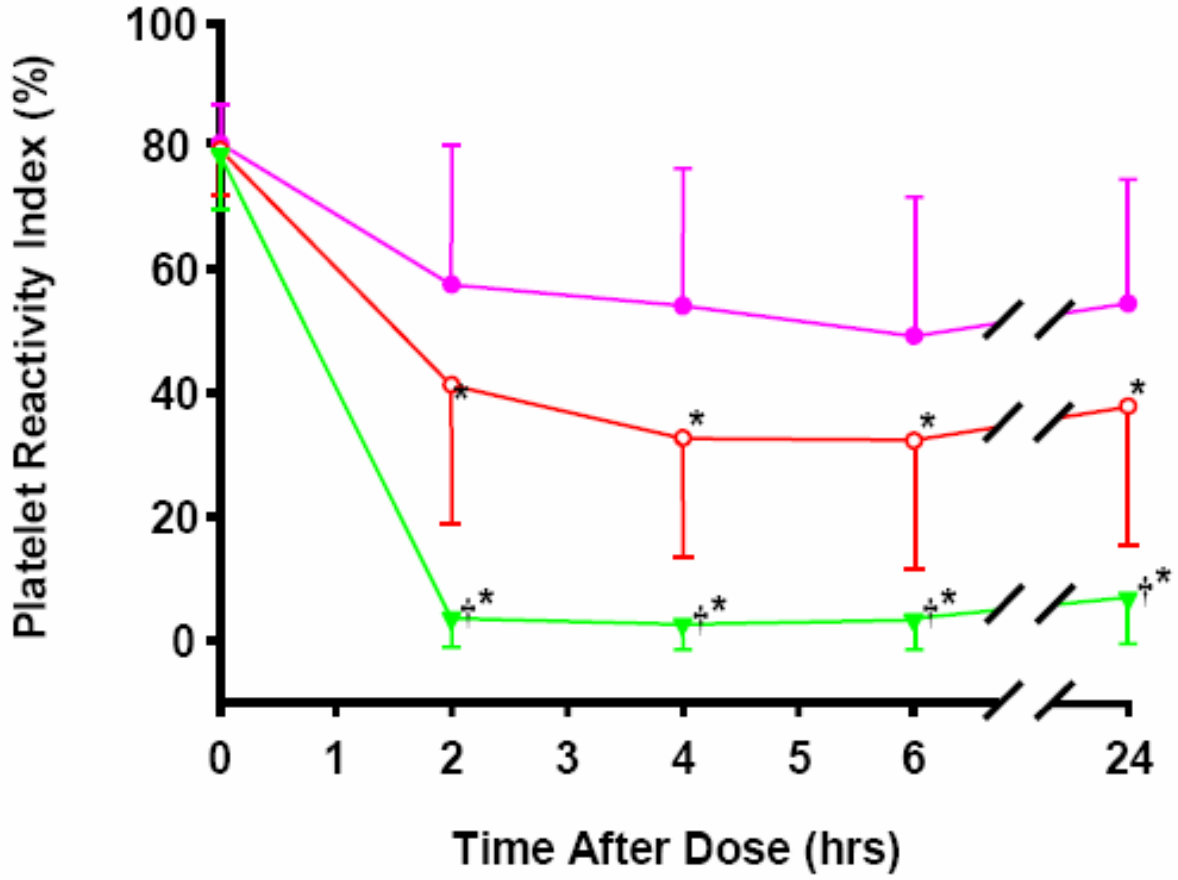
Beckerath N et al., ESC 2006

Clopidogrel/prasugrel crossover study



Brandt JT et al. *Am Heart J* 2007;153:66.e9–e16.

VASP : Clopidogrel vs Prasugrel



* = p<0.001 vs. Clop 300 mg

† = p<0.001 vs. Clop 600 mg

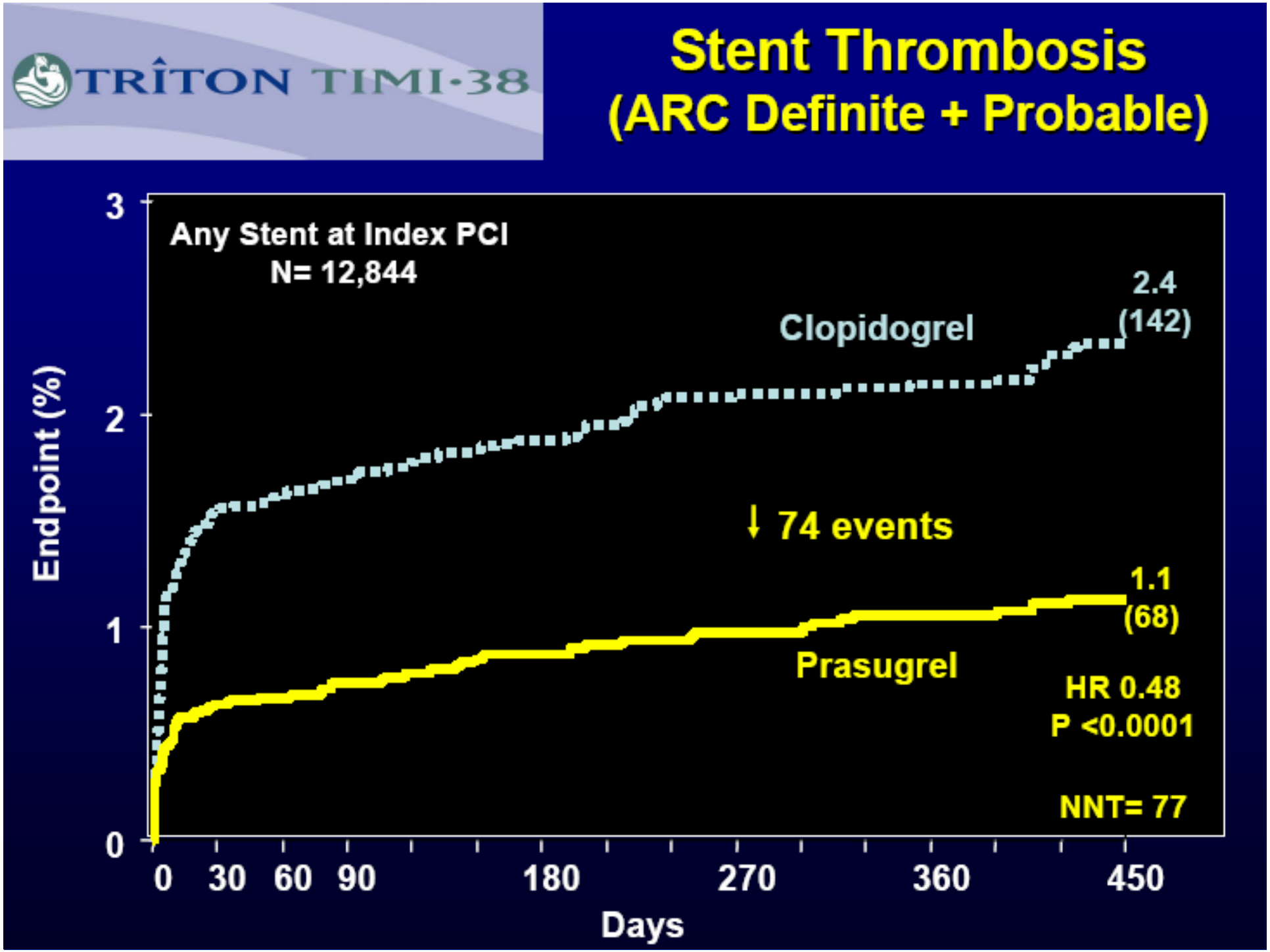
Clop 300 mg (n=36)

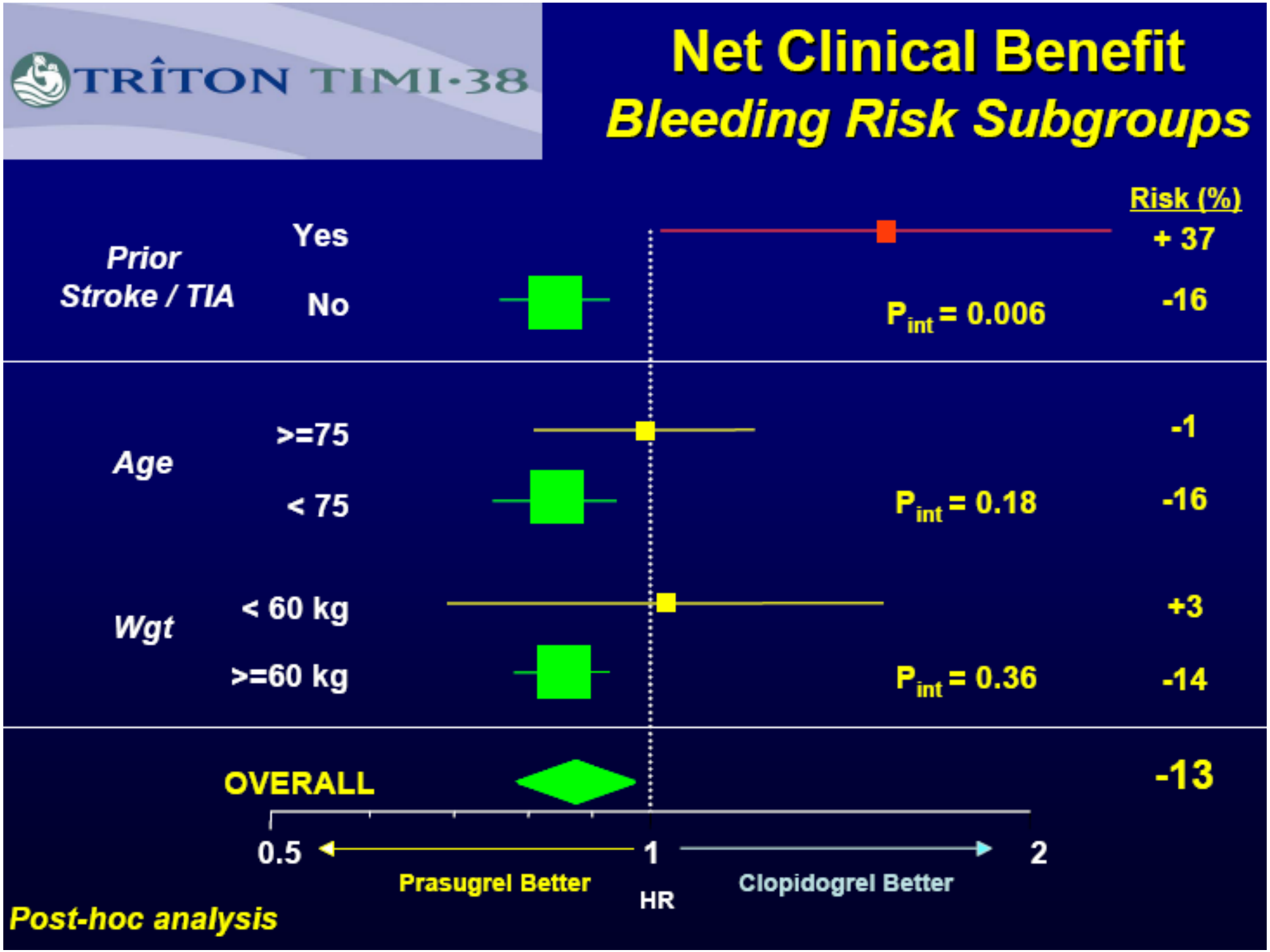
Clop 600 mg (n=35)

Pras 60 mg (n=35)

Mean ± SD

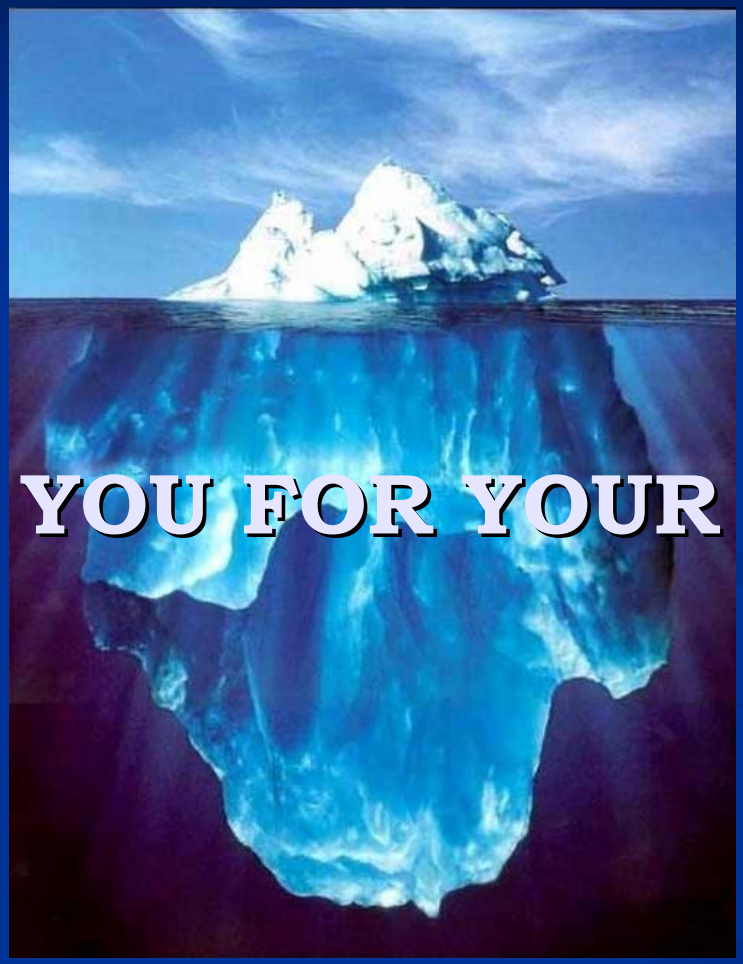
J.Jabukowski CRT 2007


TRÎTON TIMI·38
Stent Thrombosis
(ARC Definite + Probable)
Any Stent at Index PCI
N= 12,844
Clopidogrel
2.4
(142)
74 events
1.1
(68)
Prasugrel
HR 0.48
P <0.0001
NNT= 77
Endpoint (%)
0
1
2
3
0
30
60
90
180
270
360
450
Days


TRÎTON TIMI-38
Net Clinical Benefit
Bleeding Risk Subgroups
Risk (%)
Prior Stroke / TIA
Yes
+ 37
No
-16
P int = 0.006
Age
>=75
-1
< 75
-16
P int = 0.18
Wgt
< 60 kg
+3
>=60 kg
-14
P int = 0.36
OVERALL
-13
0.5
1
2
Prasugrel Better
HR
Clopidogrel Better
Post-hoc analysis

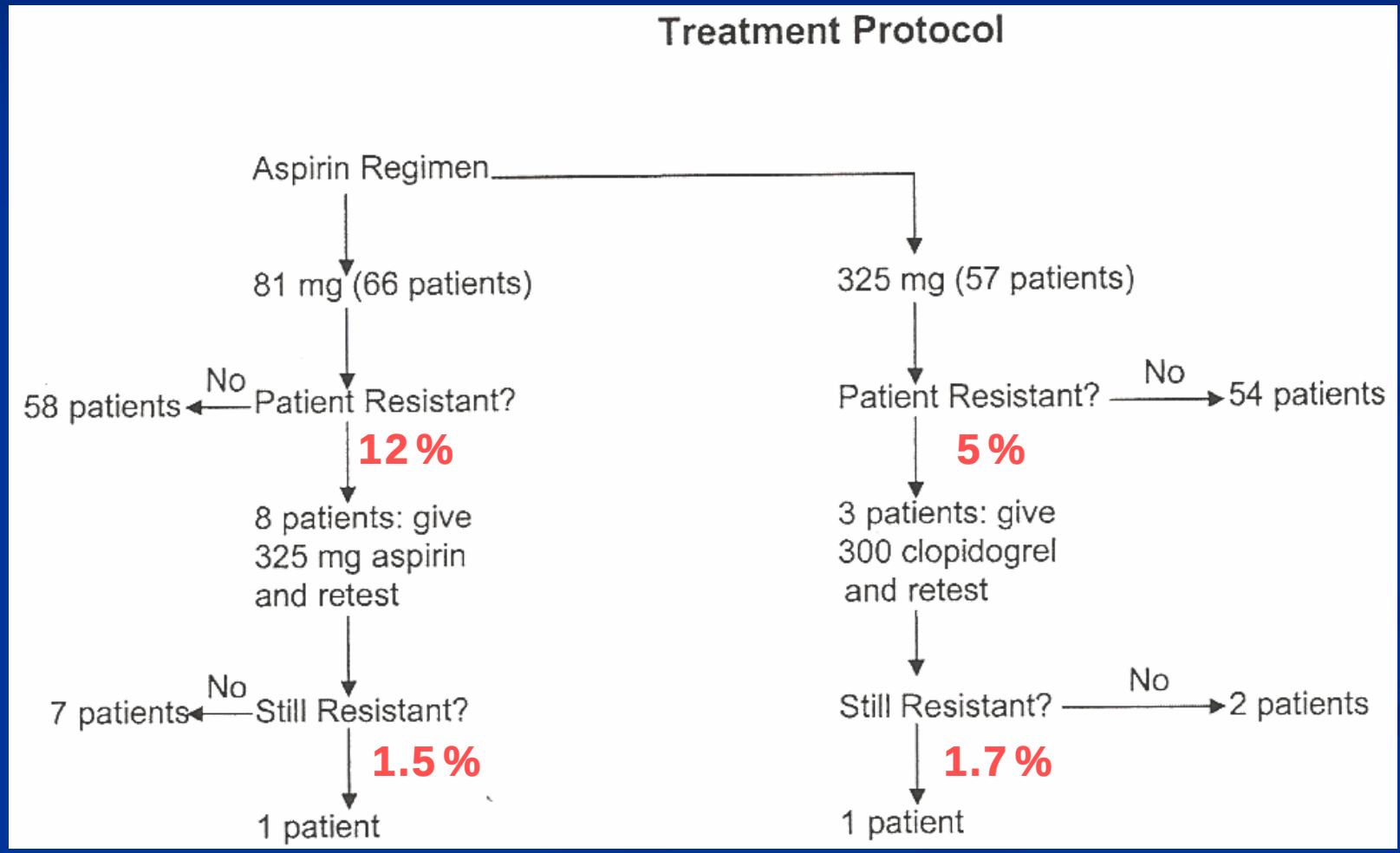
Conclusions

- Platelet function tests have demonstrated interpatient response variability (also referred to as ‘resistance’) to aspirin and clopidogrel
- A number of small but strong clinical studies suggest that a patient’s response variability to aspirin and/or clopidogrel can predict clinical outcome
- Monitoring antiplatelet therapy by point-of-care methods (ie, use at or near the bedside, easy to use without special skills, no sample processing, no pipetting, rapid readout) would be clinically advantageous
- To solve this patient variability , 2 solutions:
  - To adjust the dose by testing the Clopidogrel and Aspirin activity
  - To use Prasugrel except for the patients with history of stroke or TIA



THANK YOU FOR YOUR ATTENTION

Frequency of Aspirin Resistance in a Community Hospital



Mirkhel et al. Am J Cardiol 2006;98:577-579

Platelet function tests for measuring response to aspirin

Thromboxane as the end point

- Serum thromboxane B_2
- Urinary 11-dehydro thromboxane B_2

Arachidonic acid as the stimulus

- Platelet aggregometry (turbidimetric)
- Platelet aggregometry (impedance)
- VerifyNow Aspirin assay
- Plateletworks
- Platelet surface activated GP IIb/IIIa, platelet surface P-selectin, leucocyte–platelet aggregates (flow cytometry)
- TEG PlateletMapping System
- Impact cone and plate(let) analyser
- ThromboVision T-Guide

Other

- PFA-100
- PlaCor PRT

Modified from Michelson. *Eur Heart J* 2006;8:G53.

Platelet function tests for measuring response to clopidogrel

$P2Y_{12}$-specific

- VASP phosphorylation (flow cytometry)

ADP-stimulated

- Platelet aggregometry (turbidimetric)
- Platelet aggregometry (impedance)
- VerifyNow P2Y12 assay
- Plateletworks
- Platelet surface activated GP IIb/IIIa, platelet surface P-selectin, leucocyte-platelet aggregates (flow cytometry)
- TEG PlateletMapping System
- Impact cone and plate(let) analyser
- ThromboVision T-Guide

Other

- ?PFA-100
- ?PlaCor PRT

Modified from Michelson. *Eur Heart J* 2006;8:G53.

SSC/ISTH Working Party on Aspirin Resistance

1. A clinically meaningful definition of aspirin resistance needs to be developed, based on data linking aspirin-dependent laboratory tests to clinical outcomes in patients
2. The correct treatment, if any, of aspirin resistance is unknown, because no published studies address the clinical effectiveness of altering therapy based on a laboratory finding of aspirin resistance
3. Therefore, other than in research trials, it is not currently appropriate to test for aspirin resistance in patients or to change therapy based on such tests

Michelson et al. *J Thromb Haemost* 2005;3:1309–11.

- Same conclusions for clopidogrel
- Similar conclusions reached by ACCP (Patrono C et al. *Chest* 2004;126:234S–264S)
- Similar conclusions reached by ESC (Patrono C et al. *Eur Heart J* 2004;25:166–81)

2006 ACC/AHA PCI guidelines

Class IIb recommendation (based on Level C evidence):

In patients in whom subacute stent thrombosis may be catastrophic or lethal, platelet aggregation studies may be considered and the maintenance dose of clopidogrel increased from 75 mg to 150 mg/day if <50% inhibition of platelet aggregation is demonstrated

Smith SC et al. *Circulation* 2006;113:156–75.

Conclusions II

Although the correct treatment of aspirin or clopidogrel ‘resistance’ is not definitively known (because no published studies address the clinical effectiveness of altering therapy based on a laboratory finding of ‘resistance’), the following are treatment options:

- No change in treatment (to avoid potential bleeding without known additional antithrombotic benefit)
- Consider non-compliance
- Consider interference by other drugs (NSAIDs for aspirin, statins for clopidogrel)
- Increase the doses of aspirin and/or clopidogrel?
- Add a GP IIb/IIIa antagonist?

Conclusions III

- The novel $P2Y_{12}$ antagonists prasugrel, AZD6140 and/or cangrelor may address the problem of platelet response variability or 'resistance' because, compared with clopidogrel, they have:
  - A more rapid onset of action
  - Greater platelet inhibitory effects
  - Less platelet response variability
- Phase III trials of these drugs are currently in progress

Concept of aspirin resistance

- Aspirin may not benefit all patients equally
- No consensual definition of aspirin resistance exists
- It is generally accepted that:

incomplete suppression of platelet aggregation as assessed by platelet function assays constitutes biochemical unresponsiveness of platelets to the inhibitory action of aspirin

Platelet function testing
The Gold Standard

- Many tests are available to assess inhibition of platelet function induced by aspirin

- Light transmission aggregometry (LTA)
  - Current gold standard
  - Evaluates luminosity as aggregation occurs in platelet-rich plasma (PRP) in response to AA
  - Use limited to specialized laboratories because:
    - poorly standardized
    - requires manipulation by a skilled technician

Other platelet function assays available

Laboratory testing

- Whole blood aggregometry (WBA)
  - Preferred agonist: AA
- Serum measurement of TxB_2
- Urinary measurement of $dTxB_2$
- Flow cytometry
- Platelet count drop (PCD)

Point-of-care assays

- PFA-100®
  - Using the COLL-EPI cartridge
- VerifyNow Aspirin®
  - Using AA cartridge
- Thromboelastograph (TEG®)
- Cone and Plate(let) Analyzer
- AspirinWorks®
  - Standardized urinary $dTxB_2$
- PlateletWorks®
  - Standardized PCD

Definitions of aspirin resistance

- AA-induced LTA (LTA_{AA})
  - Platelet aggregation ≥ 20%
- ADP-induced LTA (LTA_{ADP})
  - Platelet aggregation ≥ 70%
- AA-induced WBA
  - Impedance ≥ 3 Ω
- PFA-100®
  - closure time ≤ 193 sec
- VerifyNow Aspirin®
  - Platelet aggregation ≥ 550 Aspirin Response Units
- Urinary levels of $dTxB_2$
  - ≥ 67.9 ng/mmol of creatinine

Aspirin Resistance

Understanding the Problem: Possible Mechanisms

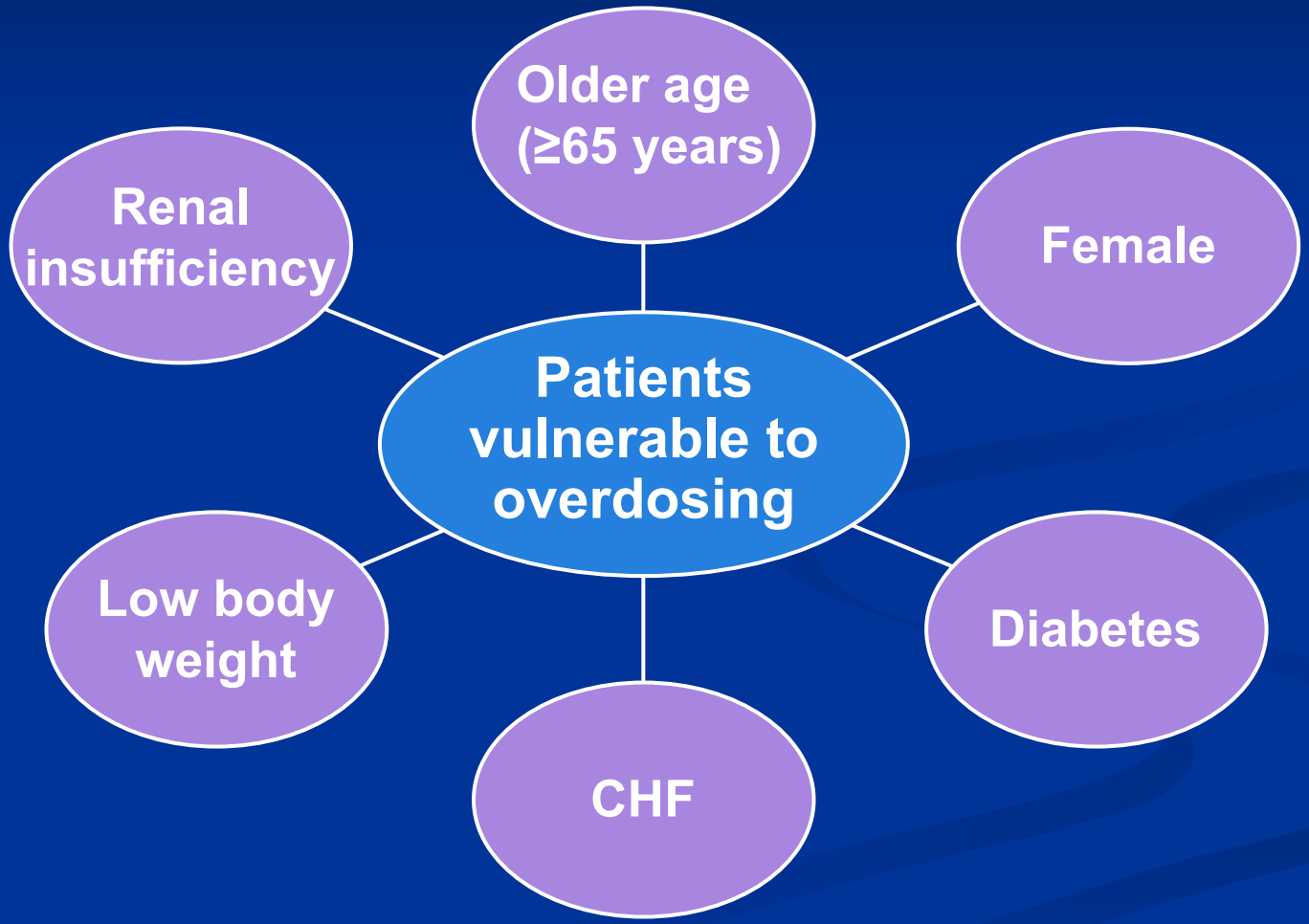
- Extrinsic Mechanisms
  - Accentuation of platelet function by exogenous substances (cigarette smoke)
  - Other drugs blocking aspirin's acetylation of COX-1 (NSAIDs)
  - Increased platelet turnover
  - Inadequate aspirin dosing

Aspirin Resistance

Understanding the Problem: Possible Mechanisms

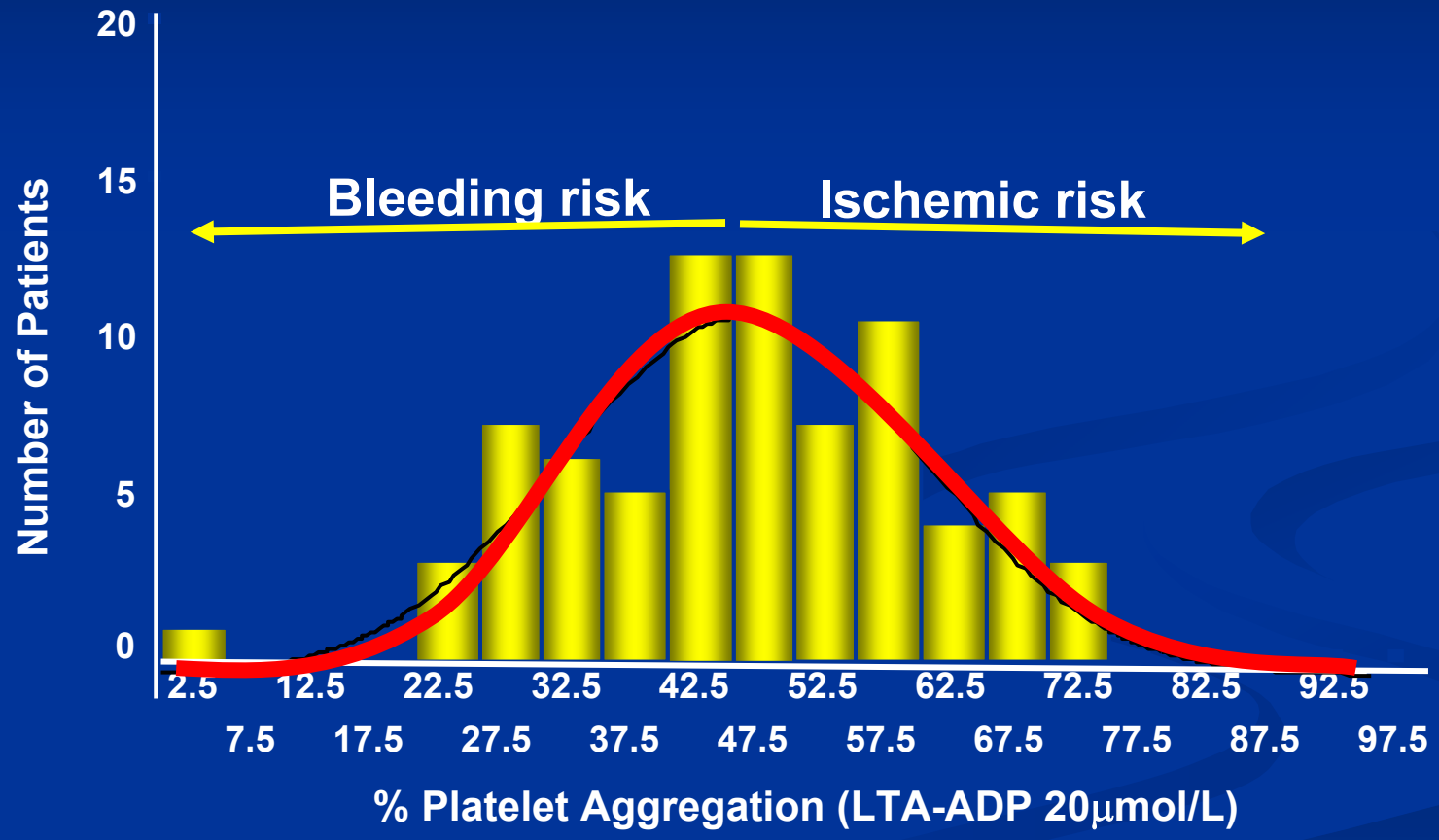
- Intrinsic Mechanisms
  - Inducible COX-2 in platelets that is not inhibited by low-dose aspirin
  - Polymorphisms of COX-1 that alter the structure of the active site and prevent acetylation
  - Production of TXA precursors by other nucleated cells and transfer of these to platelets
  - Polymorphisms of IIb/IIIa receptor that make platelets less dependant on TXA for activation

Major predictors of overdosing



Alexander KP et al. *JAMA*. 2005;294:3108-16.

Individual Response Variability to Dual Antiplatelet Therapy in the Steady State Phase of Treatment



Angiolillo DJ et al. *Am J Cardiol.* 2006;97:38-43.

Novel $P2Y_{12}$ ADP Receptor Antagonist

Drug	Type	Route	Action	Dose	Mean Platelet Inhibition (Time Required)	Trials (Phase III)
Prasugrel (CS-747)	Thienopyridine (3rd gen) – requires hepatic conversion to active metabolite	Oral	Irreversible binding	60 mg loading dose, 10 mg maintenance dose	≈ 70% (<1 hour)	TRITON
AZD6140	Cyclopetyl-triazolopy-rimidine – Direct inhibition	Oral	Competitive binding	90 mg bid	≈ 95% (2-4 hours)	PLATO
Cangrelor (ARC-669931MX)	ATP analogue – Direct inhibition	Parenteral	Competitive binding	4 μg/kg/min	≈ 95% (few minutes)	CHAMPION

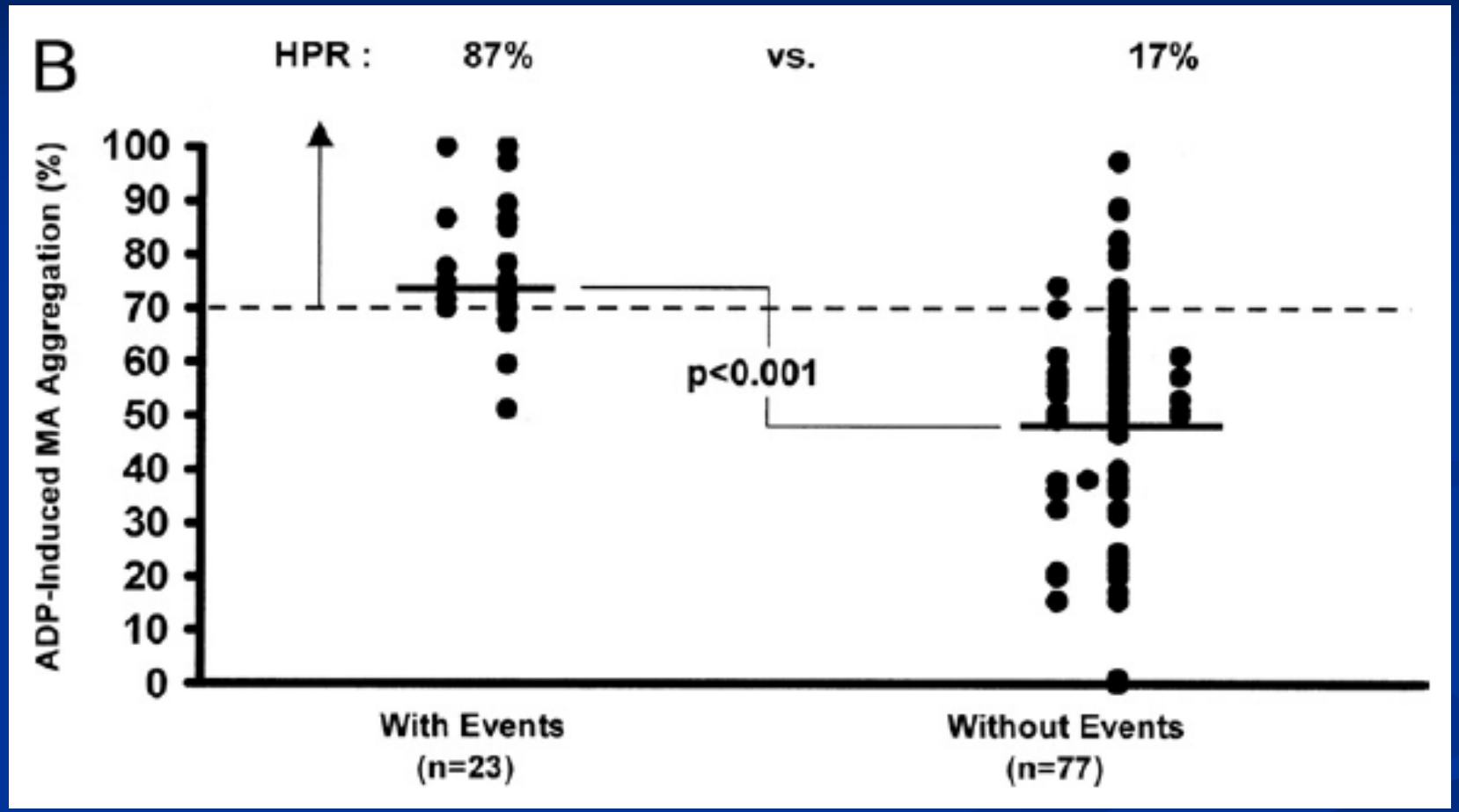
More potent and less variability!!

Angiolillo DJ et al. J Am Coll Cardiol. 2007; 49: 1505-1516 .

MECHANISMS OF CLOPIDOGREL RESISTANCE

- Drug interactions with Cyt P450
- ADP P2Y12 receptor polymorphisms
- $P1^{A2}$ polymorphisms
- Defects in signaling downstream from P2Y12

Clopidogrel 'resistance' by TEG PlateletMapping System vs. clinical outcomes



CAD patients (n = 100) undergoing PCI on chronic ASA 75 mg qd, clopidogrel 75 mg qd.
Events = MACE over 1 year. HPR, high platelet reactivity; MA, clot strength.

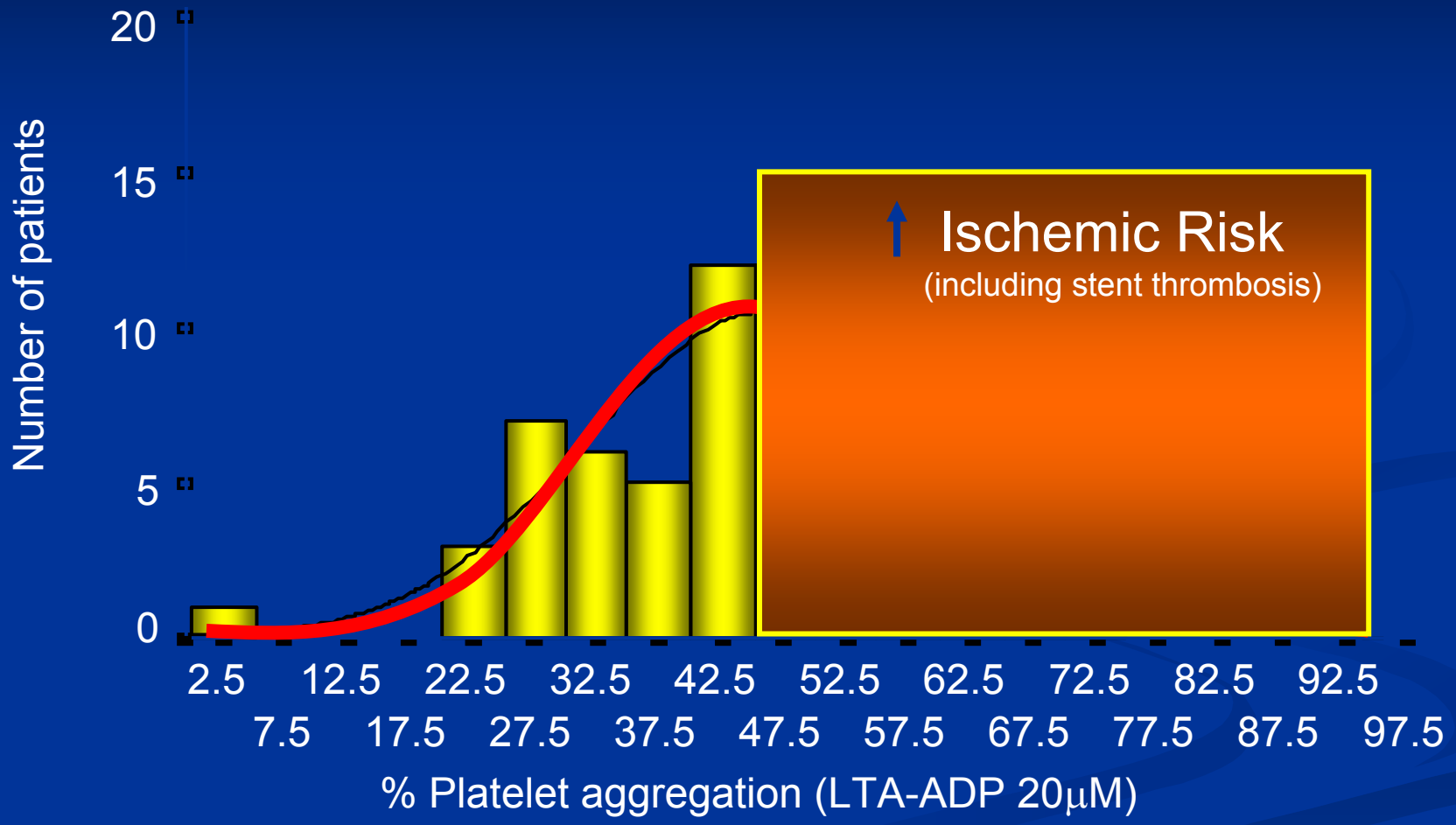
Bliden KP et al. *J Am Coll Cardiol* 2007;49:657–66.

Incidence of death/MI at various time periods after stopping clopidogrel

Patients	Mean duration of clopidogrel treatment (d)	Death/MI after stopping treatment (d)		
		0–90	91–180	181–270
Medically treated (n=1568)	302	163	57	26
PCI treated (n=1569)	278	73	29	8

Ho PM et al. *JAMA* 2008; 299:532-539.

Individual response variability to dual antiplatelet therapy

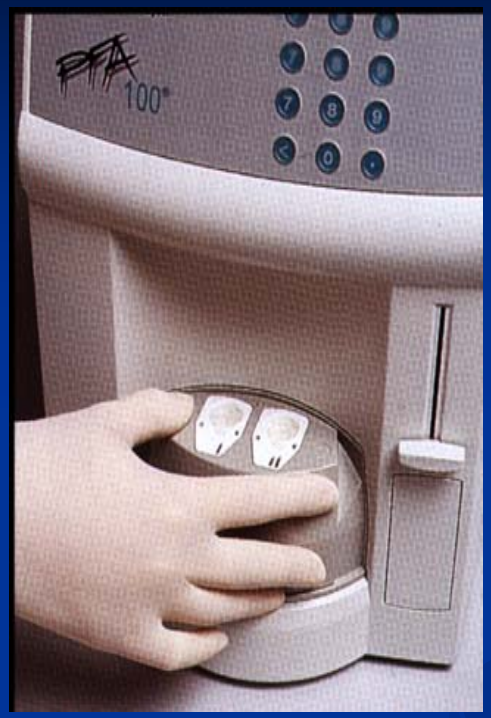


Angiolillo DJ et al. Am J Cardiol 2006; 97: 38-43

Resistant Platelets: What Can Be Done?

- Uniformity of definition
- Improvement of laboratory assays (POC)
- Correlation of laboratory assays with clinical events
- Evaluation of new therapeutic strategies
- In the future…customized patient Rx (pharmacogenomics)

PFA-100



Excellente technique,reproductible, rapide
Excellente corrélation avec l'agrégométrie standart

* **Gum et al . Am J Cardial 2001;88:230-5**
* **Homoncik et al . Thromb Haemost 2000;83:316-21**

Resistance to Thienopyridines: 3 investigational levels

1)The Biochemical Level

2)The Genetic Level

3)The Functional Level (Signal transduction)

Resistance to Thienopyridines: 3 investigational levels

1) The Biochemical Level

- Clopidogrel is a prodrug and must be metabolized by isoensymes of cytochrome P 450 for which there are some functional polymorphisms.
- Some patients might not produce enough active metabolits.

Resistance to Thienopyridines: * 3 investigational levels

2)The Genetic Level

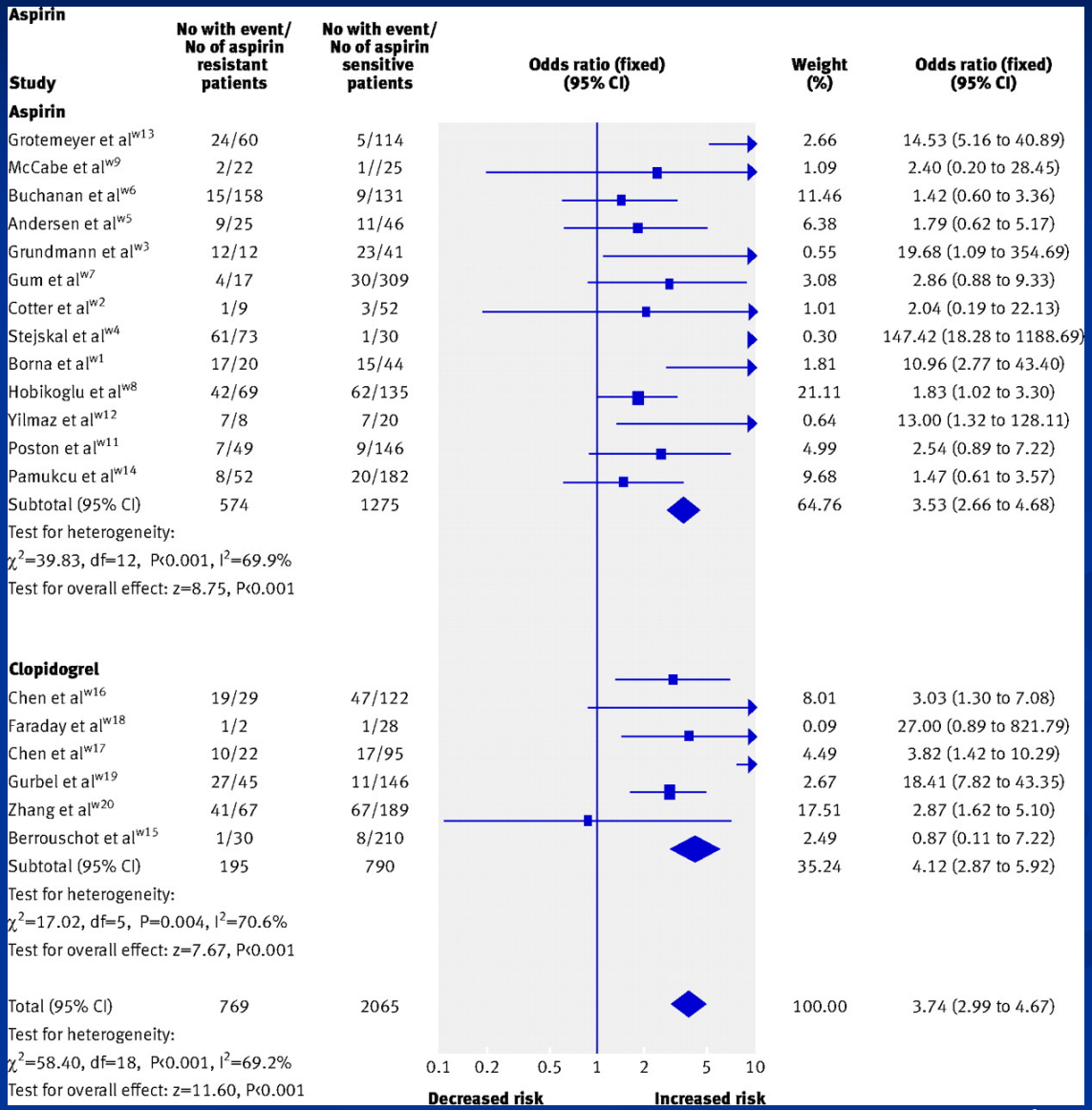
- The Clopidogrel target, the ADP receptor, P2Y12 is also Polymorphic.
- So the platelets might be more or less sensible to ADP, and consequently to its inhibitor (Clopidogrel)

Resistance to Thienopyridines: 3 investigational levels

3)The Functional Level (Signal transduction)

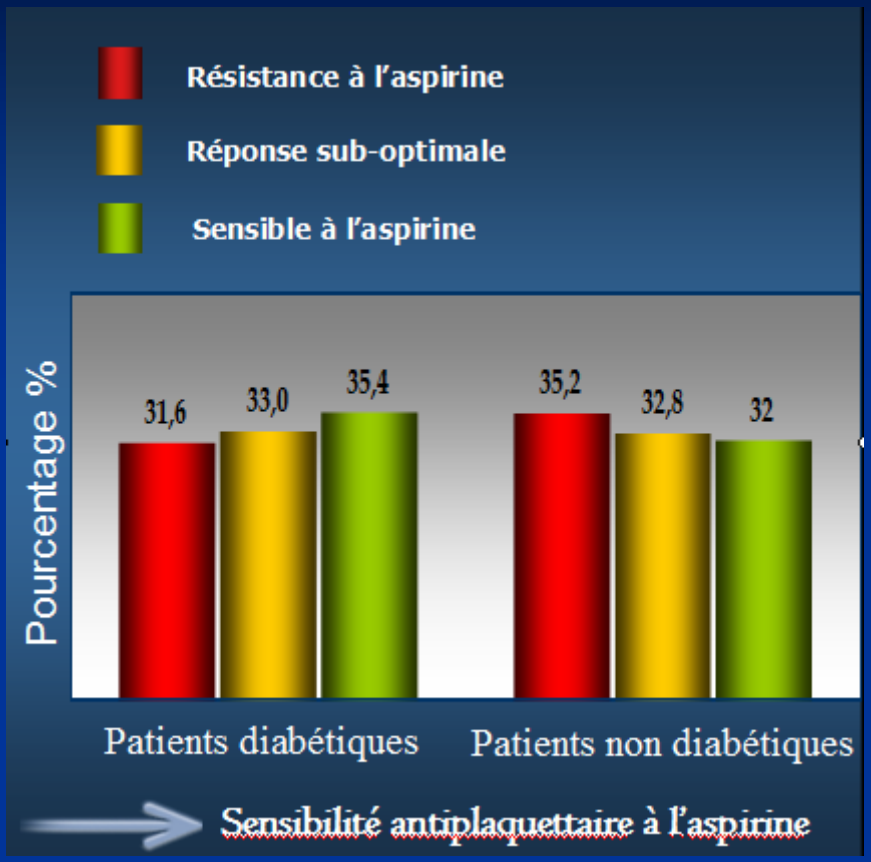
- The signal transduction requires several enzymatic reactions inducing the transconformation of the fibrinogen receptor (GP 2b-3a).
- Among these reactions , the **phosphorylation of VASP** is an interesting factor because at the end of the enzymatic cascade.

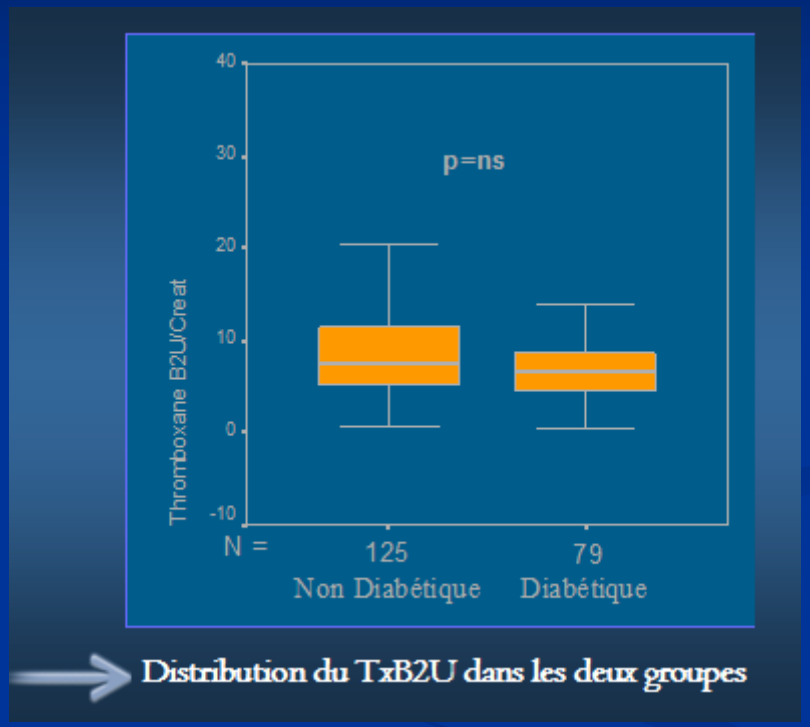
Risks of any cardiovascular event in aspirin resistant and aspirin sensitive patients treated with aspirin alone, and aspirin and clopidogrel (with or without an inhibitor of platelet glycoprotein IIb/IIIa)



Krasopoulos G. et al. BMJ 2008

Variable platelet response to aspirin in coronary artery patients with type 2 diabetes: is it a real problem?





this study did not show a higher proportion of aspirin nonresponsiveness in diabetic patients. This discrepancy with the almost literature was probably explained by the higher dosage of aspirin in our population (250 mg/day).

Addad et al; Arch Cardiovasc Disease Jan 2008