

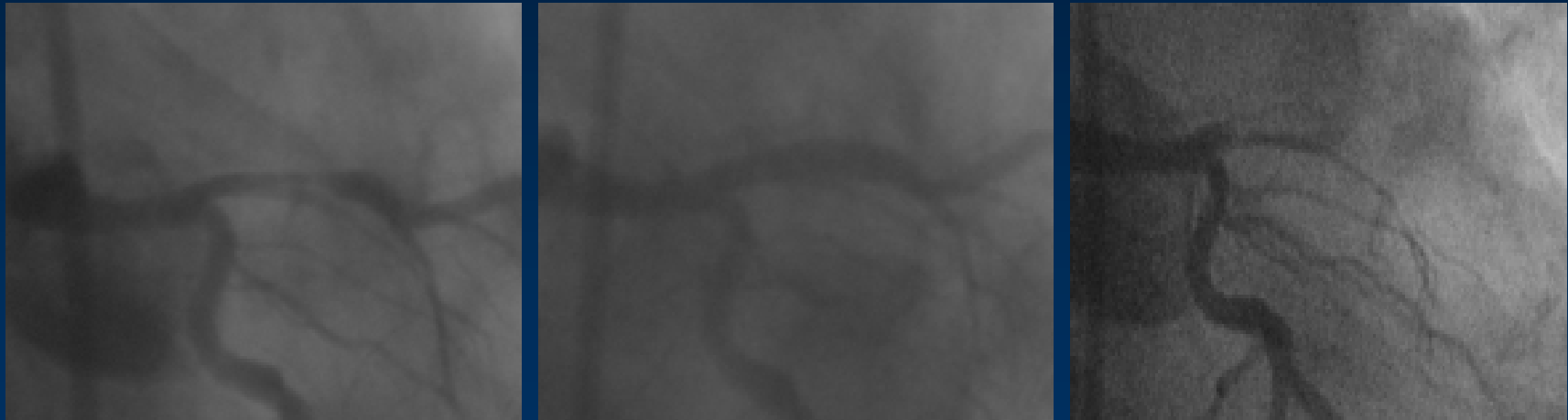
Aspirin & clopidogrel resistance

Cardiovascular Center, SNUH
Hyo-Soo Kim & Jung-Won Seo

서울대학교병원 심혈관센터
김효수, 서정원

- Case (M/51) : SNUH

- D-1 : Clopidogrel loading
- D0 : P-LAD stenting successfully & Aspirin+Clopidogrel maintenance
- D3 : Chest pain & ST-elevation → Subacute stent thrombosis

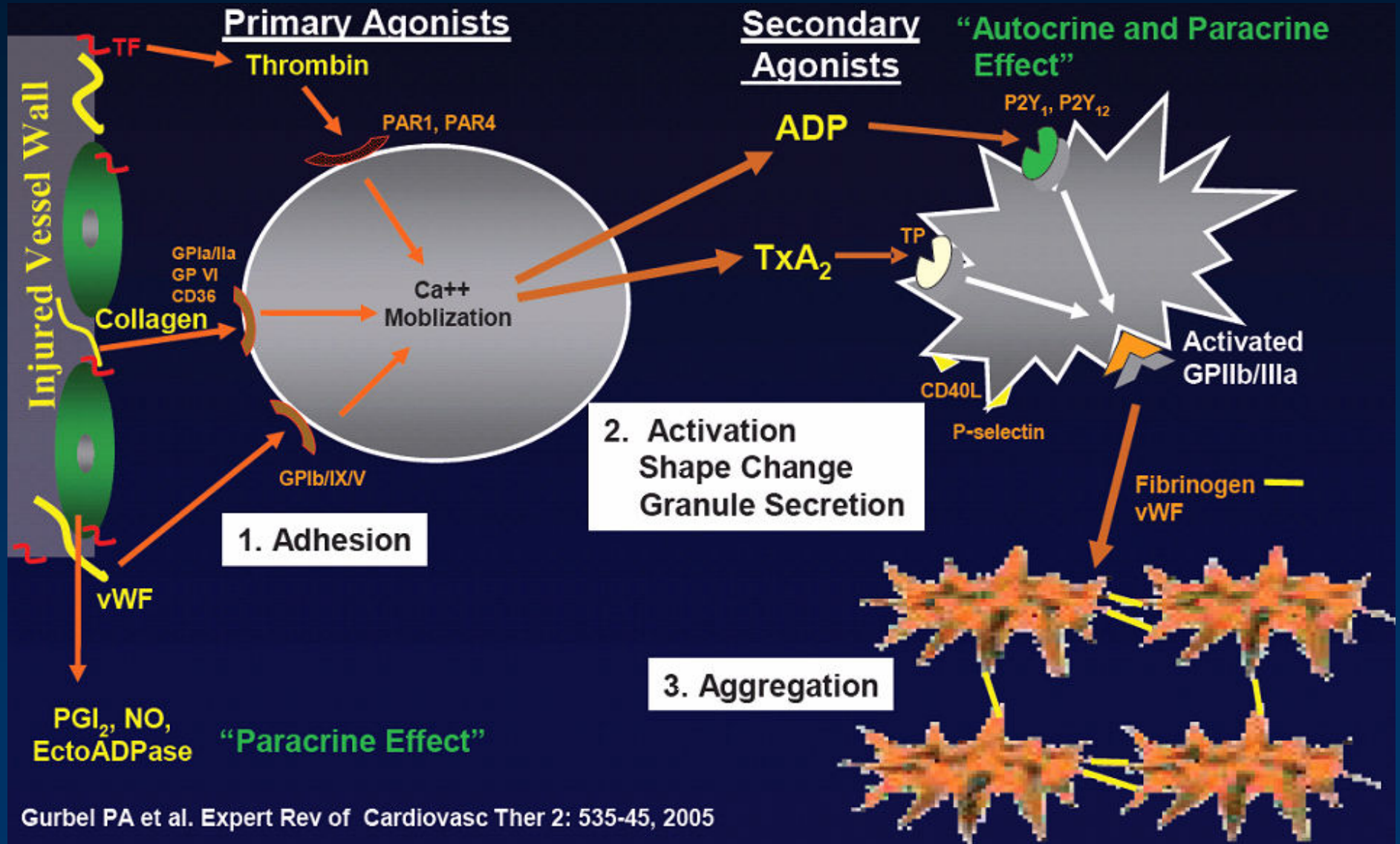


Resistance to Antiplatelet Agents?

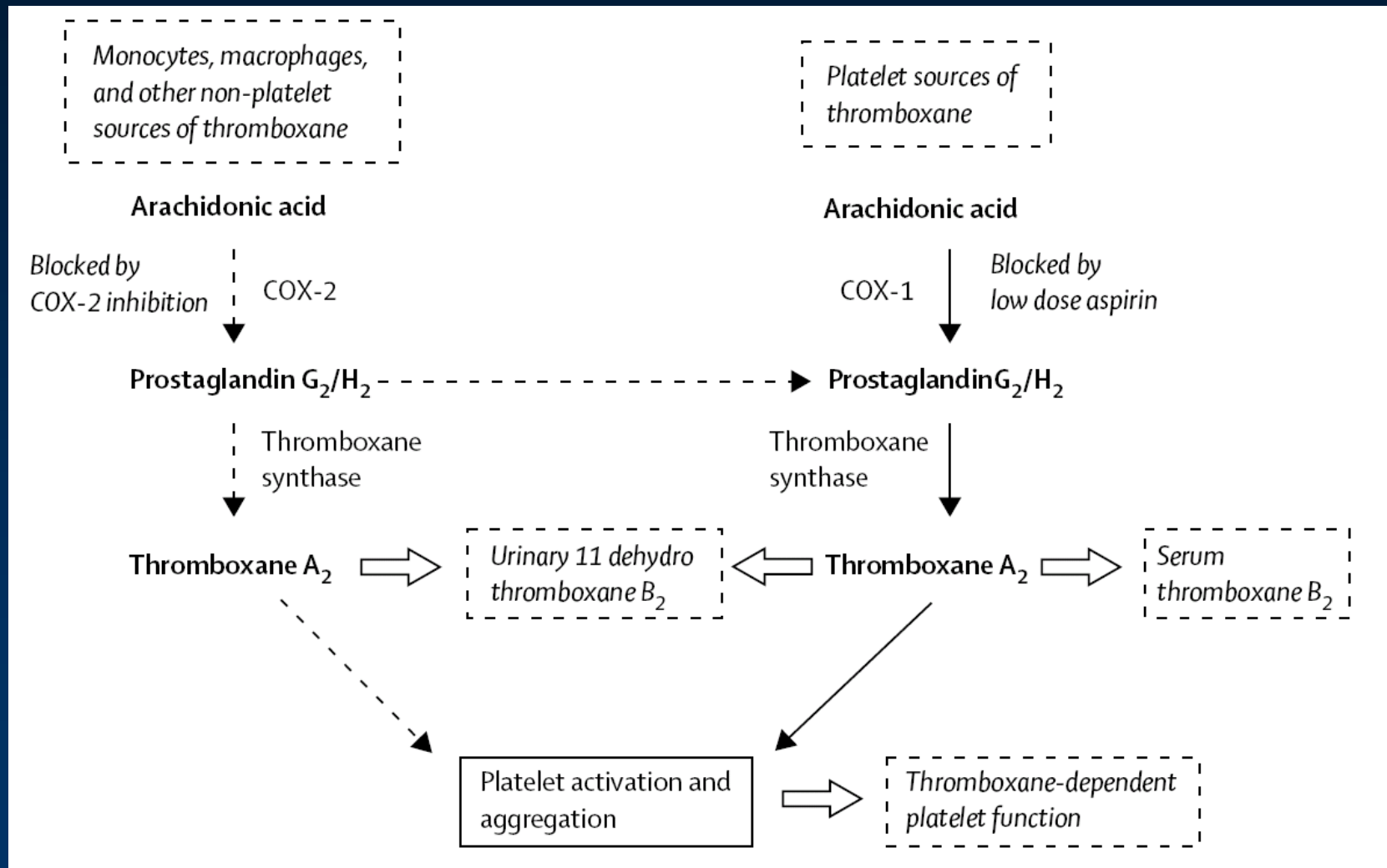
Platelet Adhesion, Activation & Aggregation

Role of TXA2 & ADP

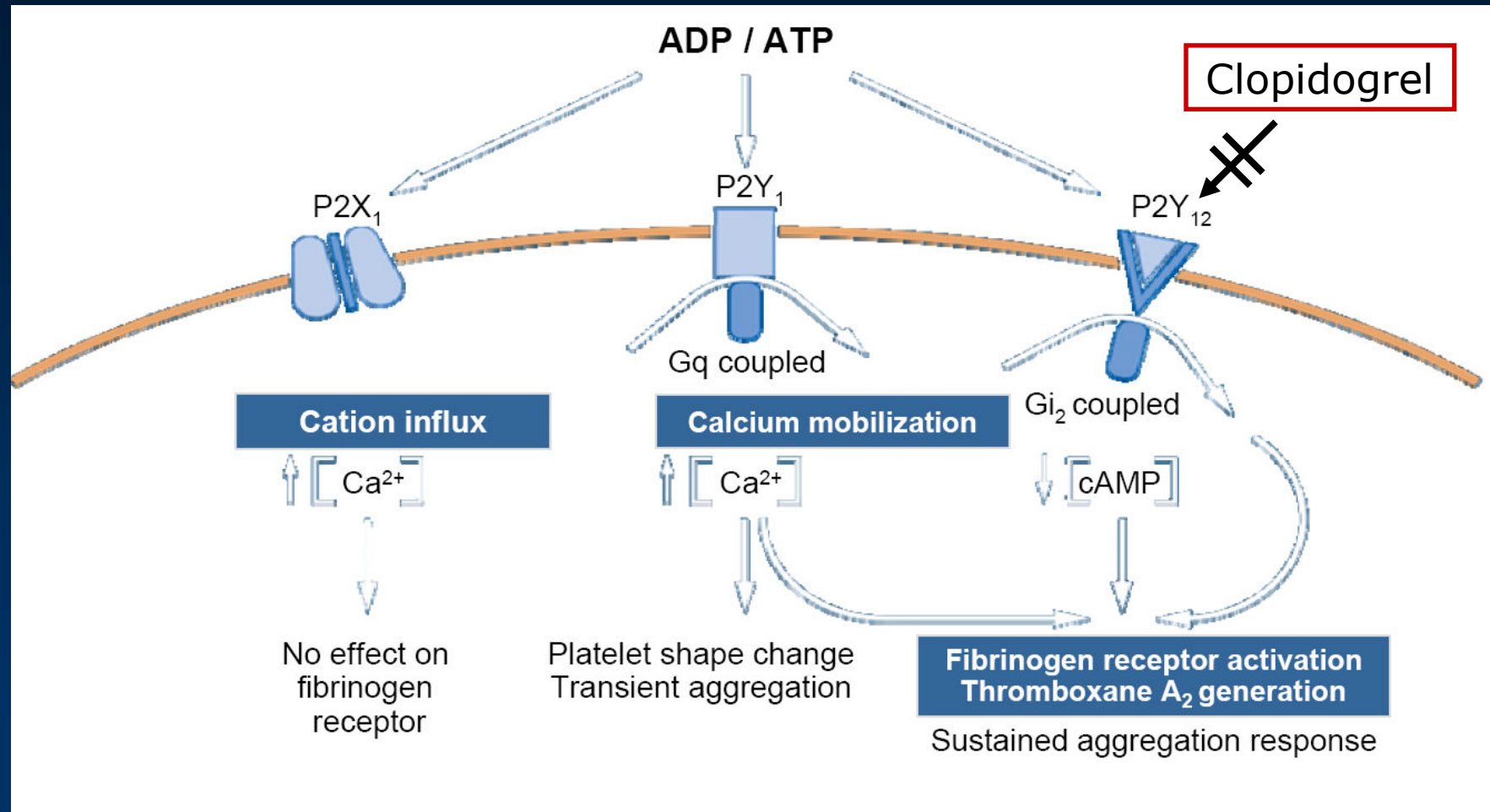
Platelet Adhesion, Activation and Aggregation



Thromboxane A₂



ADP



The role of Aspirin & Clopidogrel

Aspirin in 1° & 2° Prevention of CV disease

Table 1. Features of the 5 Randomized Trials of Aspirin in the Primary Prevention of Cardiovascular Disease

Features	Physicians' Health Study (1988)	British Doctors' Trial (1988)	Thrombosis Prevention Trial (1998)	Hypertension Optimal Treatment Study (1998)	Primary Prevention Project (2001)
Subjects randomized, No.	22 071	5139	5085	18 790	4495
Follow-up, y	5 (mean)	6 (mean)	≥5	4 (mean)	3.6 (mean)
Patient population	Apparently healthy male physicians	Apparently healthy male physicians	Men at high risk for cardiovascular disease	Men and women with hypertension and diastolic blood pressure from 100 to 115 mm Hg	Men and women with ≥1 major cardiovascular risk factor
Age range, y	40-84	50-78	45-69	50-80	50-80+
Female sex, %	0	0	0	47	57.7
Aspirin dosage	325 mg every other day	500 mg/d	75 mg/d (controlled release)	75 mg/d	100 mg/d

Arch Int Med 2003;163:2006-10

Table 2. Randomized Placebo-Controlled Trials of Low-Dose Aspirin Therapy (≤325 mg/d) in Secondary Prevention of Myocardial Infarction and Stroke*

Source	Aspirin Dosage, mg/d	No. of Subjects	Mean Age, y	Male, %
Elwood et al, ⁹ 1974	300/0	615/624	55.2/54.8	100/100
Lewis, ¹⁴ 1985	324/0	625/641	56.1/56.2	100/100
The RISC Group, ¹¹ 1990	75/0	189/199	58.5/58.0	100/100
Zaijia et al, ¹³ 1991	50/0	216/211	58.9/60.1	81/65
The SALT Collaborative Group, ¹² 1991	75/0	676/684	67.1/66.8	65.4/66.2
Farrell et al, ¹⁰ 1991	300/0	806/814	60.0/59.5	75/71
Overall total	...	6300	59.5†	83.8†

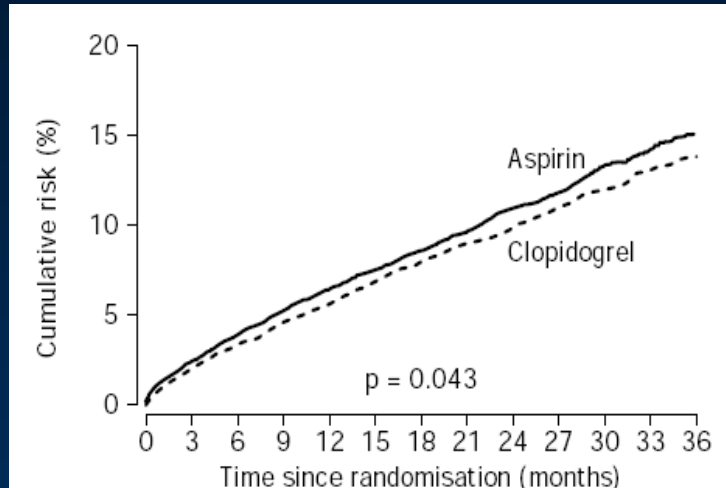
*Data are for aspirin/control groups.
†Weighted mean.

심근 경색의 10년 내 발생 위험도가 10% 를 넘는 건강한 군에서 아스피린의 장기 요법의 득이 실보다 큰 것으로 나타났다.

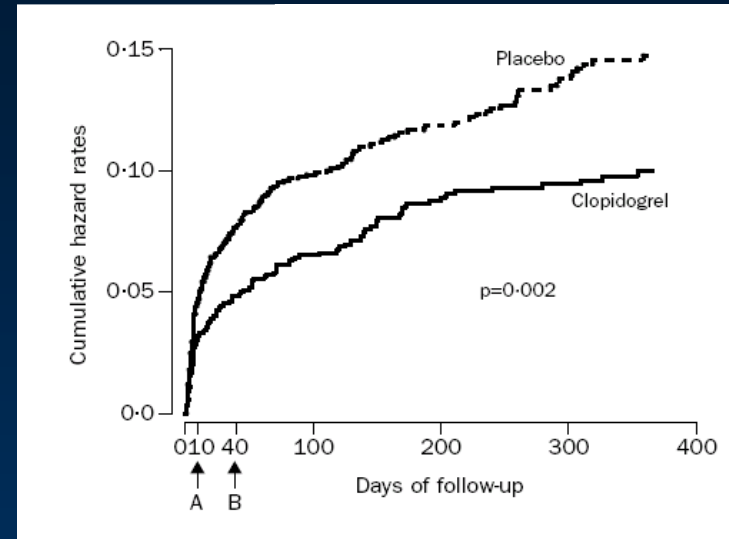
Arch Int Med 2002;162:2197-2002

Clopidogrel in UA, high risk pts

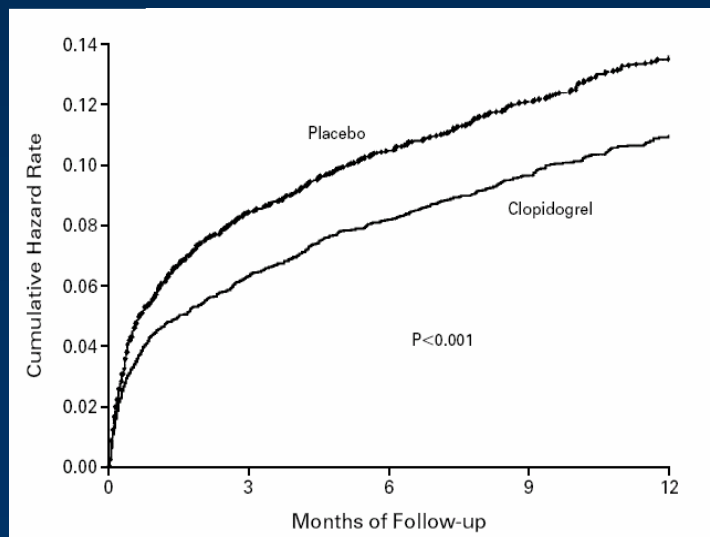
CAPRIE



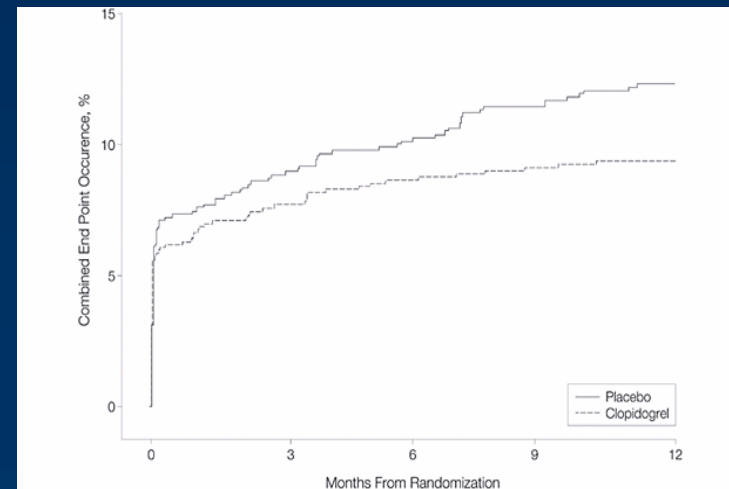
PCI-CURE



CURE



CREDO



Dual antiplatelet agents after stenting

Randomized Multicenter Comparison of Conventional Anticoagulation Versus Antiplatelet Therapy in Unplanned and Elective Coronary Stenting

The Full Anticoagulation Versus Aspirin and Ticlopidine (FANTASTIC) Study

A RANDOMIZED COMPARISON OF ANTIPLATELET AND ANTICOAGULANT THERAPY AFTER THE PLACEMENT OF CORONARY-ARTERY STENTS

ALBERT SCHÖMIG, M.D., FRANZ-JOSEF NEUMANN, M.D., ADNAN KASTRATI, M.D., HELMUT SCHÜHLEN, M.D.,
RUDOLF BLASINI, M.D., MARTIN HADAMITZKY, M.D., HANNA WALTER, M.D.,
EVA-MARIA ZITZMANN-ROTH, M.D., GERT RICHARDT, M.D., ECKHARD ALT, M.D.,
CLAUS SCHMITT, M.D., AND KURT ULM, PH.D.

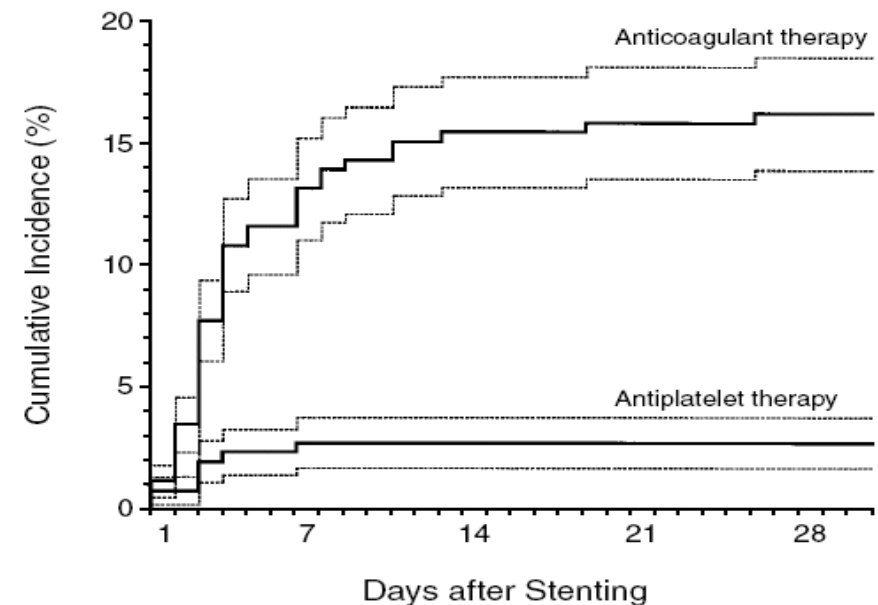
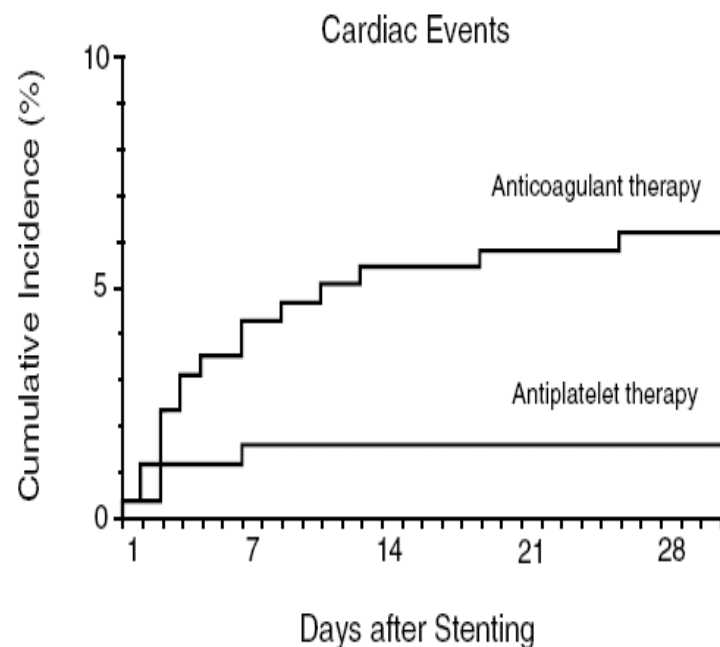
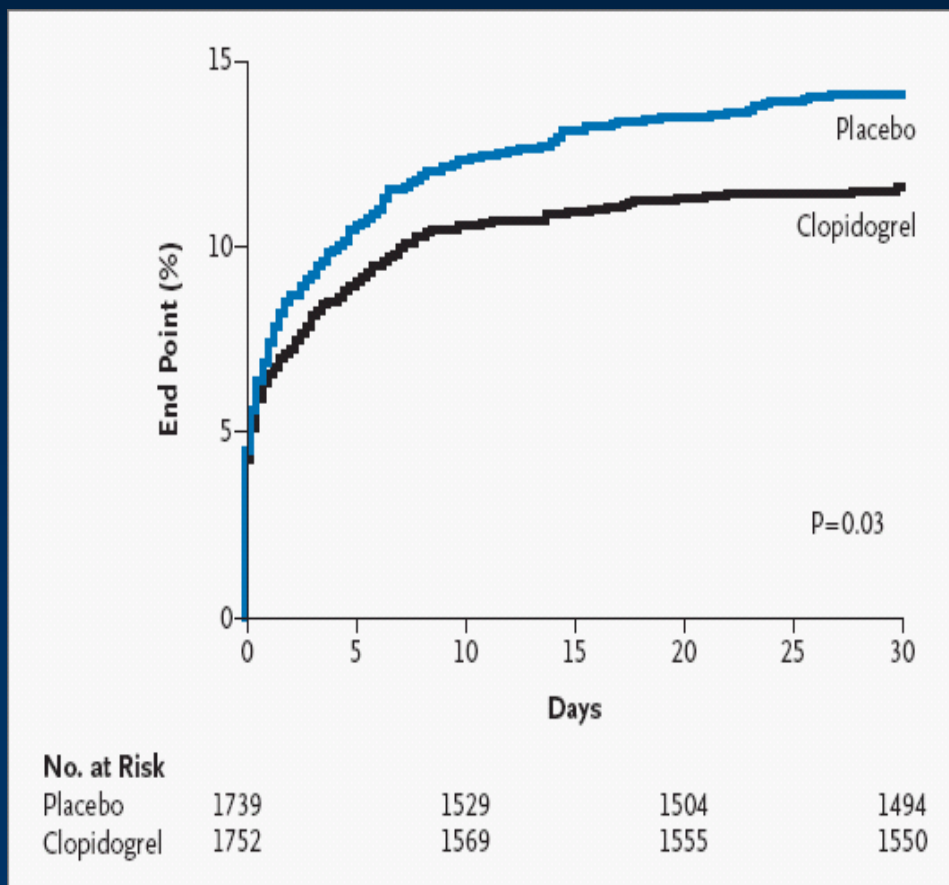


Figure 2. Cumulative Incidence of Any Cardiac or Noncardiac Event, Whichever Occurred First.

Clopidogrel in AMI regardless of stenting

CLARITY-TIMI28 (NEJM 2005)

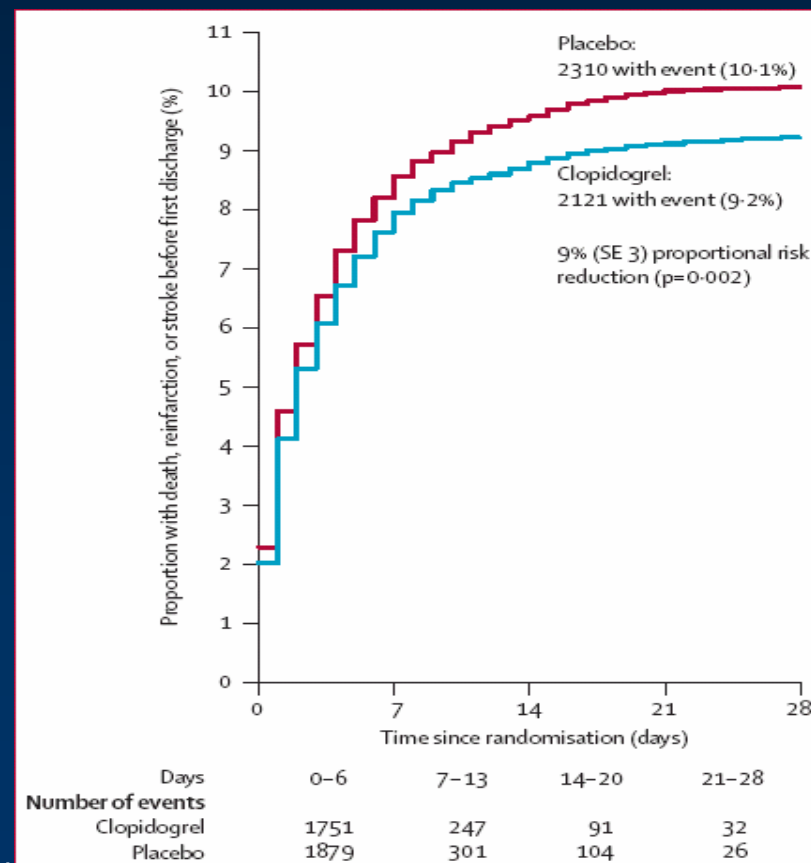
- CLARITY-TIMI-28 (The Clopidogrel as Adjunctive Reperfusion Therapy)



COMMIT/CCS-2

(Lancet 2005, n=45,852)

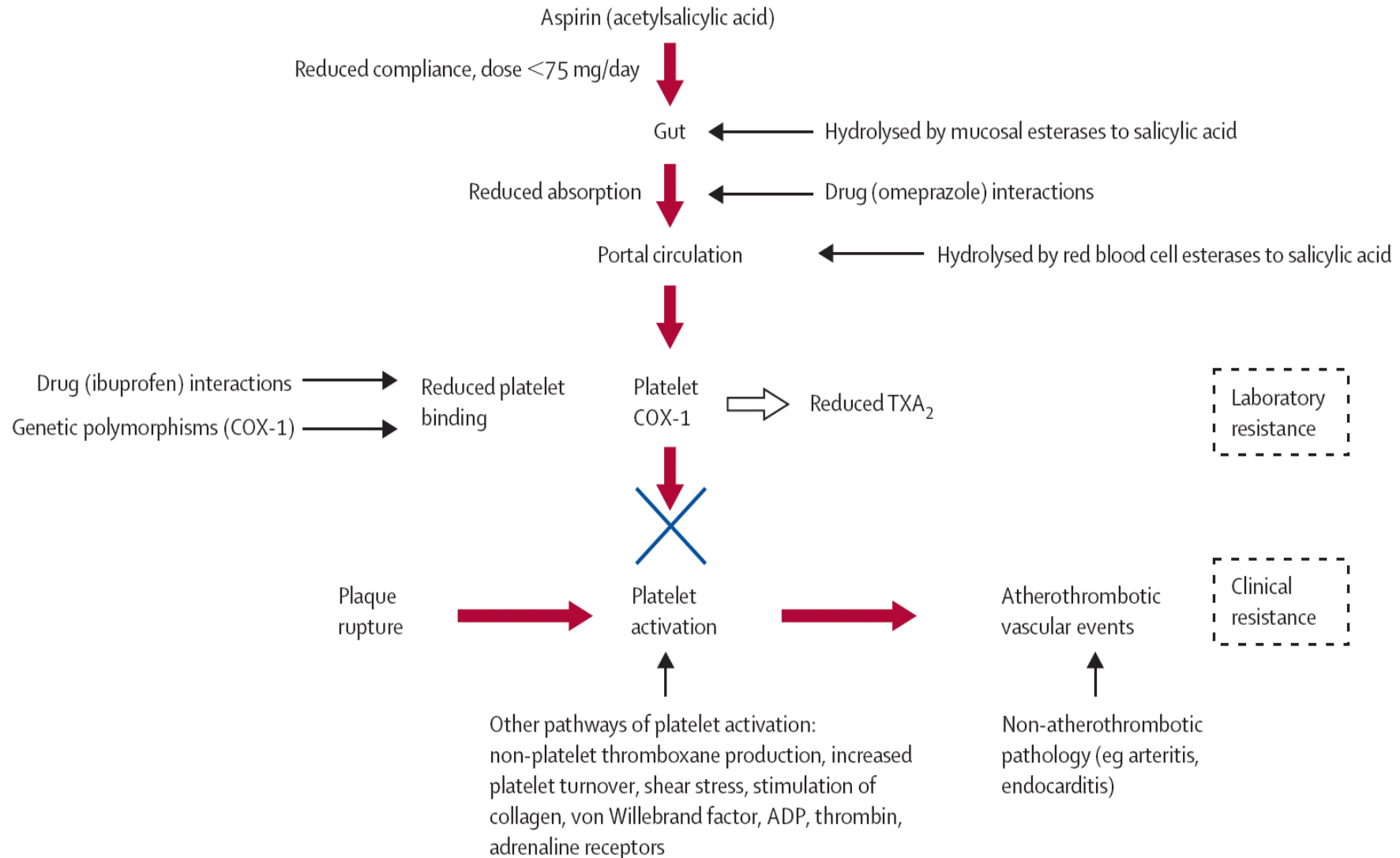
- COMMIT/CCS-2 (The Clopidogrel and Metoprolol in Myocardial infarction Trial/Second Chinese Cardiac Study)



Causes of Aspirin & Clopidogrel Resistance

Aspirin resistance

Hankey GJ, Einkelboom JW. *Lancet*. 2006



Causes of Aspirin Resistance

- Reduced bioavailability of aspirin
 - Poor compliance
 - Inadequate dose
 - Reduced absorption or increased metabolism

- Altered binding to COX-1
 - Concurrent intake of certain NSAID (ibuprofen, indomethacin)

- Other sources of TX production
 - Not blocked by aspirin (ex. COX-2 in monocytes, macrophages, EC)

- Alternative pathways of PLT activation
 - Not blocked by aspirin (ex. RBC)
 - Increased PLT sensitivity to collagen & ADP

Causes of Aspirin Resistance

- ❑ Increased turnover of PLT
 - By BM in response to stress (ex. CABG)
 - Newly formed PLT unexposed to aspirin during the 24hr dose interval (aspirin half life 20min)

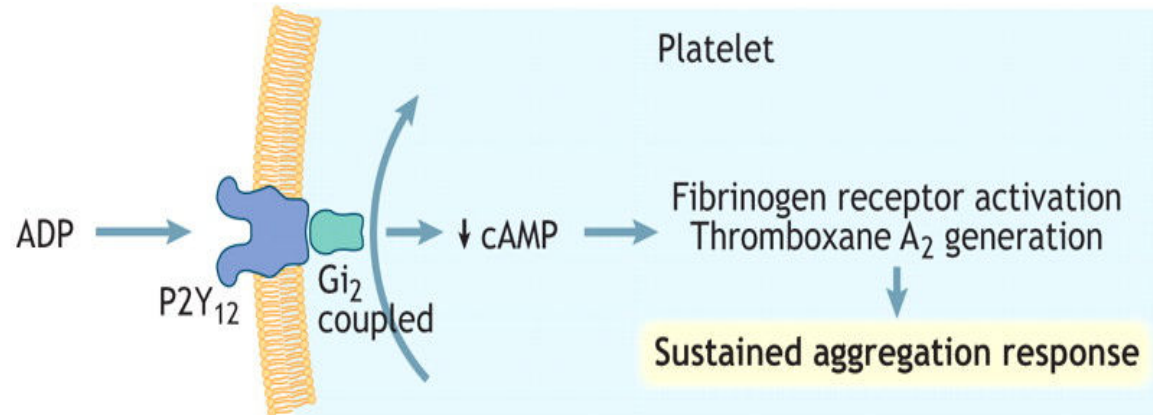
- ❑ Genetic polymorphism
 - COX-1, COX-2, TXA2 synthase etc.
 - PLT Rc (Ia/IIa, Ib/V/IX, IIb/IIIa, collagen,vWF)
 - Factor XIII

- ❑ Loss of the antiplatelet effect of aspirin with prolonged administration (Tachyphylaxis)

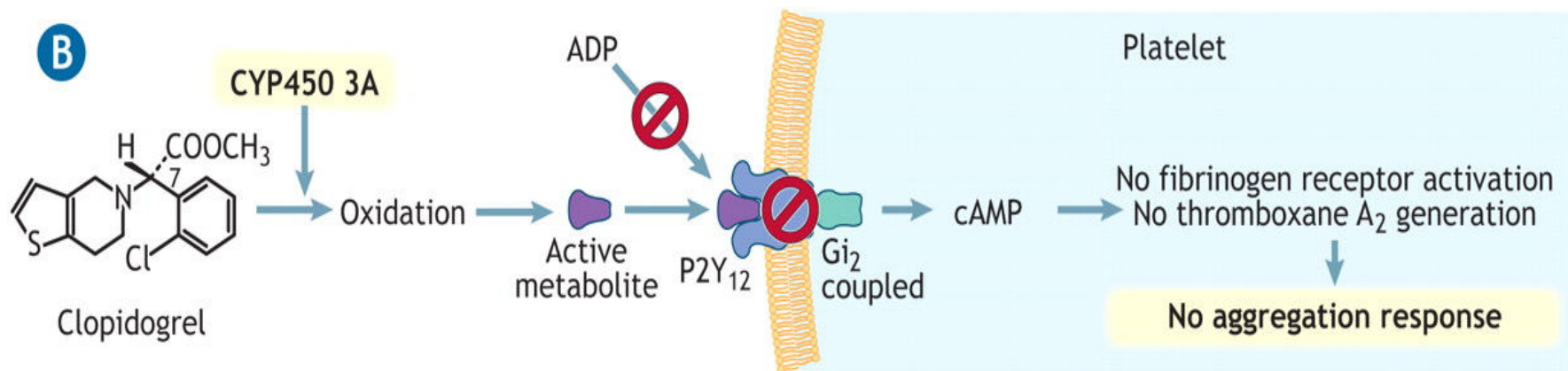
- ❑ Non-atherothrombotic causes of vascular events

Clopidogrel : mechanism

A



B



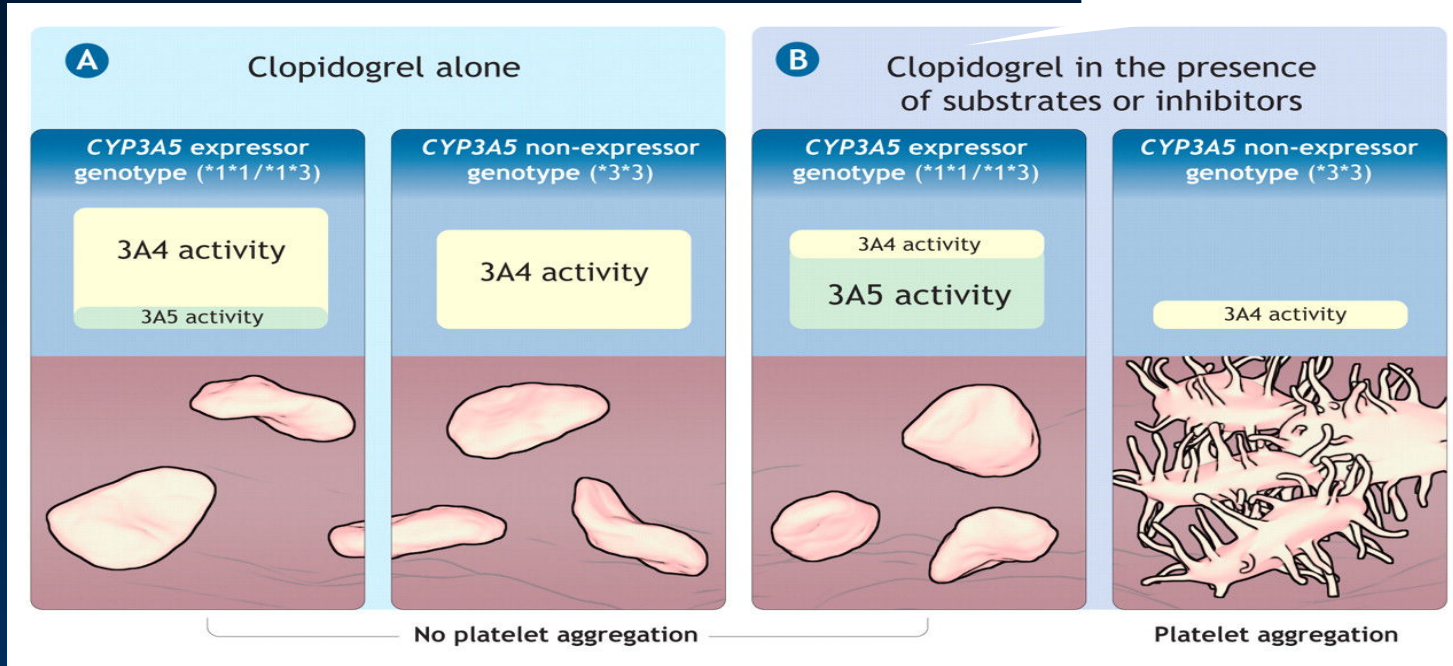
Causes of Clopidogrel Resistance

- Absorption
- Metabolism, Drug interaction
 - CYP3A4 activity (Lau WC, et al. Circulation 2004)
 - CYP3A5 polymorphism (Suh JW, et al. CMAJ 2006)
 - CYP2C19 polymorphism (Hulot JS, et al. Blood 2006)
- P2Y12 R_c polymorphism
 - Controversial
 - Pro ; Cerebrovascular ds (Ziegler S, Stroke 2005), PAD (Fontana P, Circulation 2003)
 - Cons ; CAD (Smith SM, Platelets 2006/ Angiolillo DJ, Thromb Res 2005)

CYP3A5 SNP & Clopidogrel Drug Interaction

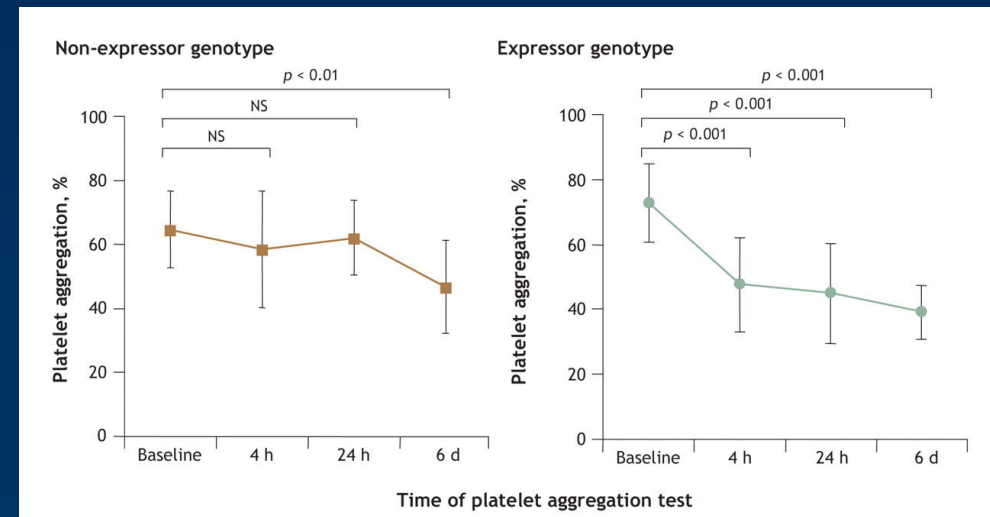
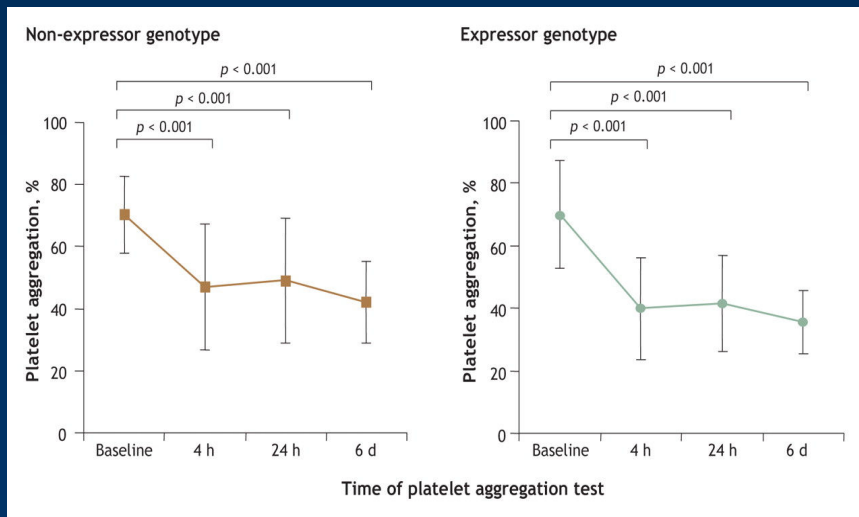
(Suh JW, et al. CMAJ 2006)

Lipophilic statin, metoprolol, diltiazem, nifedipine, losartan, cimetidine



A

B



CYP3A5 SNP & Clopidogrel Drug Interaction

(Suh JW, et al. CMAJ 2006)

Table 3: Clinical outcomes after coronary angioplasty and bare-metal stent implantation, by *CYP3A5* genotype

Outcome after stent implantation	<i>CYP3A5</i> genotype; no. of patients		<i>p</i> value
	Non-expressor <i>n</i> = 193	Expressor <i>n</i> = 155	
At 1 mo			
Sudden death			
MI (subacute thrombotic)			
Nonhemorrhagic stroke			
Total			
1-6 mo			
Sudden death	0	0	—
MI	4	0	
Nonhemorrhagic stroke	0	0	
Total	4	0	0.10
6-mo cumulative	14	3	0.023

Note: MI = myocardial infarction.

Table 4: Risk factors for atherothrombotic events after coronary angioplasty and bare-metal stent implantation among patients taking clopidogrel

Risk factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
<i>CYP3A5</i> non-expression (v. expression)	3.96 (1.12-14.0)	4.89 (1.28-18.7)
Co-administered <i>CYP3A</i> metabolizers† (every increase in no.)	2.15 (1.15-4.03)	2.22 (1.10-4.47)
Age ≥ 65 yr (v. < 65 yr)	0.98 (0.94-1.03)	0.98 (0.93-1.03)
Male sex (v. female)	1.74 (0.64-4.70)	2.08 (0.65-6.61)
Previous MI (v. no previous MI)	0.80 (0.22-2.86)	0.72 (0.17-3.10)
Diabetes mellitus (v. no diabetes)	1.52 (0.57-4.05)	1.15 (0.39-3.40)
LV systolic ejection fraction < 45% (v. > 45%)	1.12 (0.25-5.07)	1.13 (0.20-6.34)
Stent diameter ≥ 2.75 mm (v. < 2.75 mm)	0.89 (0.36-2.23)	0.66 (0.24-1.85)
Stent length ≥ 20 mm (v. < 20 mm)	0.99 (0.92-1.06)	0.98 (0.91-1.06)

Laboratory Diagnosis of Resistance

Laboratory assays of platelet function

Lab method	Pros	Cons
<u>Light transmittance aggregometry</u>	<ul style="list-style-type: none"> Considered gold standard Monitors aspirin, thienopyridines, and IIB/IIIA inhibitors 	<ul style="list-style-type: none"> Time-consuming Cannot be run at bedside Variable results depending on reagents used
Platelet Function Analyzer (PFA)-100	<ul style="list-style-type: none"> Allows for bedside analysis Easy to use and rapid Whole blood assay 	<ul style="list-style-type: none"> Depends on vWF and haematocrit Monitors only aspirin (not thienopyridines or IIB/IIIA inhibitors)
VerifyNow Rapid Platelet Function Assay	<ul style="list-style-type: none"> Allows for bedside analysis Easy to use and rapid Whole blood assay Monitors aspirin, thienopyridines,^a and IIB/IIIA inhibitors 	
<u>Urinary 11-dehydrothromboxane B2</u>	<ul style="list-style-type: none"> COX-1 dependent 	<ul style="list-style-type: none"> Indirect measure Not platelet-specific Depends on renal function Monitors only aspirin (not thienopyridines or IIB/IIIA inhibitors)

^aRapid Platelet Function Assay is now FDA approved for clopidogrel.

LTA (light transmittance aggregometry)

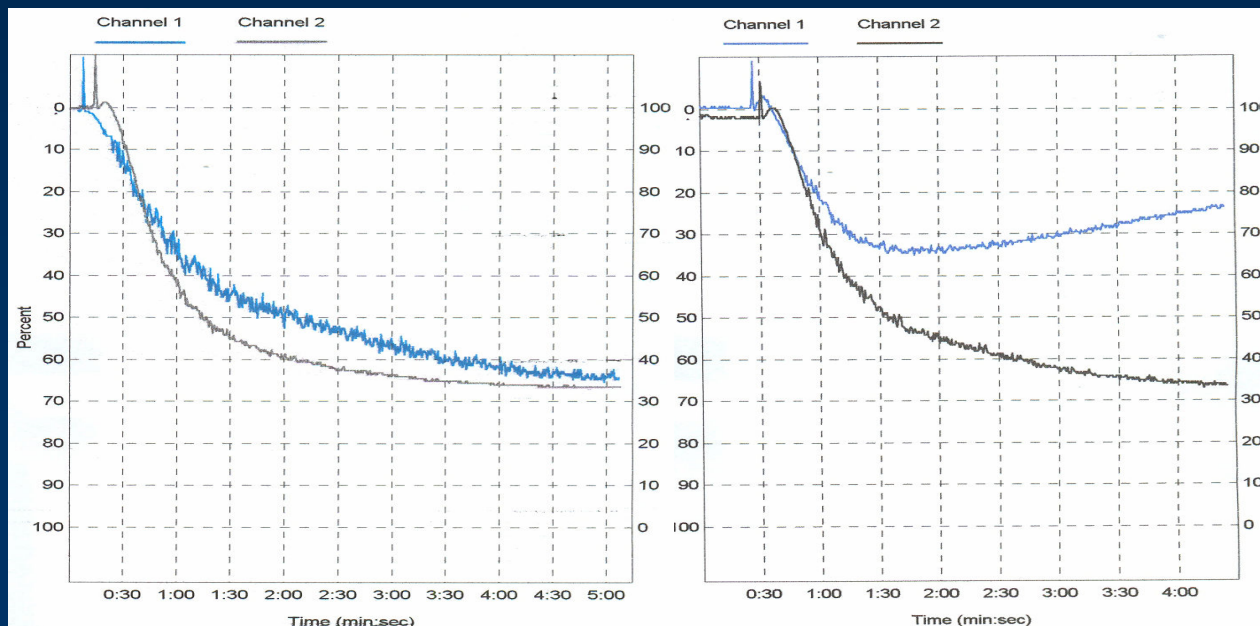
□ Platelet aggregation

- Maximal percent change in light transmittance from baseline
- Platelet rich plasma
- Chrono-log 400 series, 500 series[®]



Pre-treatment

Clopidogrel – post 1wk



*Blue – responder
Δ aggregation: 27%

*Black- nonresponder
Δ aggregation: -1%

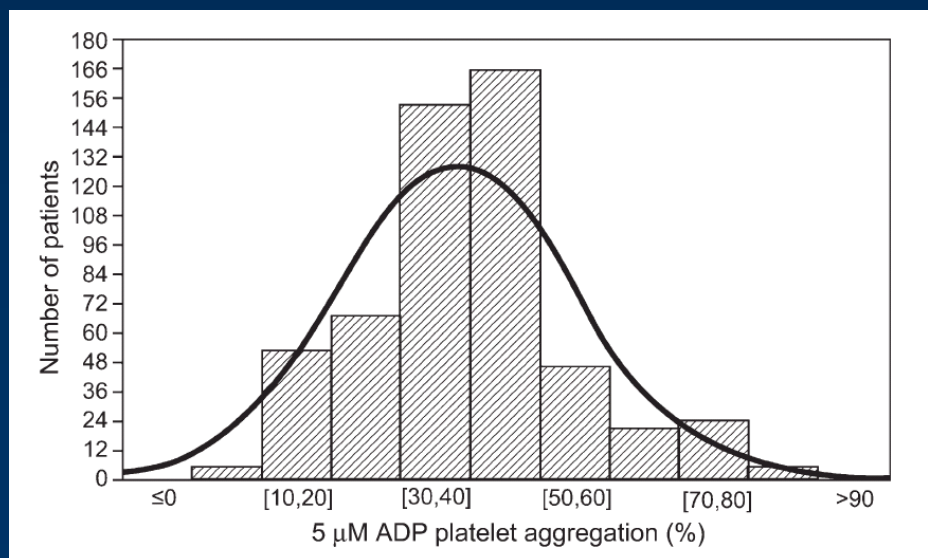
Definition of resistance

□ Aspirin resistance

- 0.5mg/mL AA-induced platelet aggregation $\geq 20\%$ and
- 5 μ M/L ADP-induced platelet aggregation $\geq 70\%$

□ Clopidogrel resistance

- Absolute difference between baseline and post-treatment aggregation (Δ aggregation) $\leq 10\%$ in response to both 5 & 20 μ M/L ADP



VerifyNow™ (Ultegra) RPFA

- ❑ VerifyNow™ Aspirin Assay
- ❑ VerifyNow™ IIb/ IIIa Assay
- ❑ VerifyNow™ Clopidogrel Assay



Step 1

An assay device is inserted in the VerifyNow System



Step 2

A blood sample is inserted into the assay device



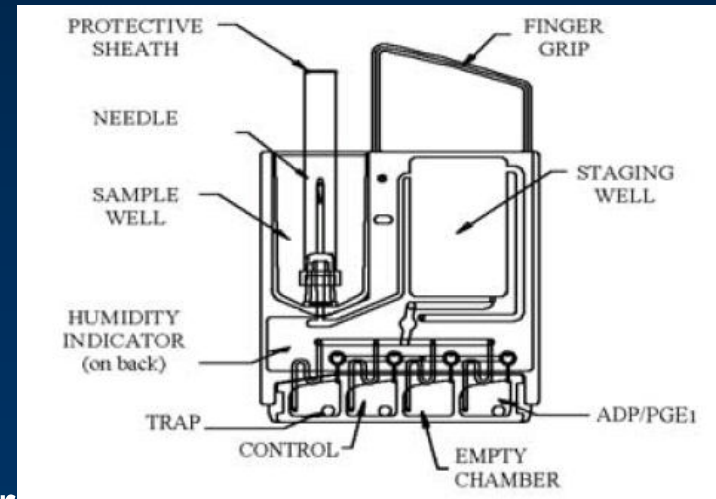
Step 3

A result is displayed

VerifyNow
ASPIRIN

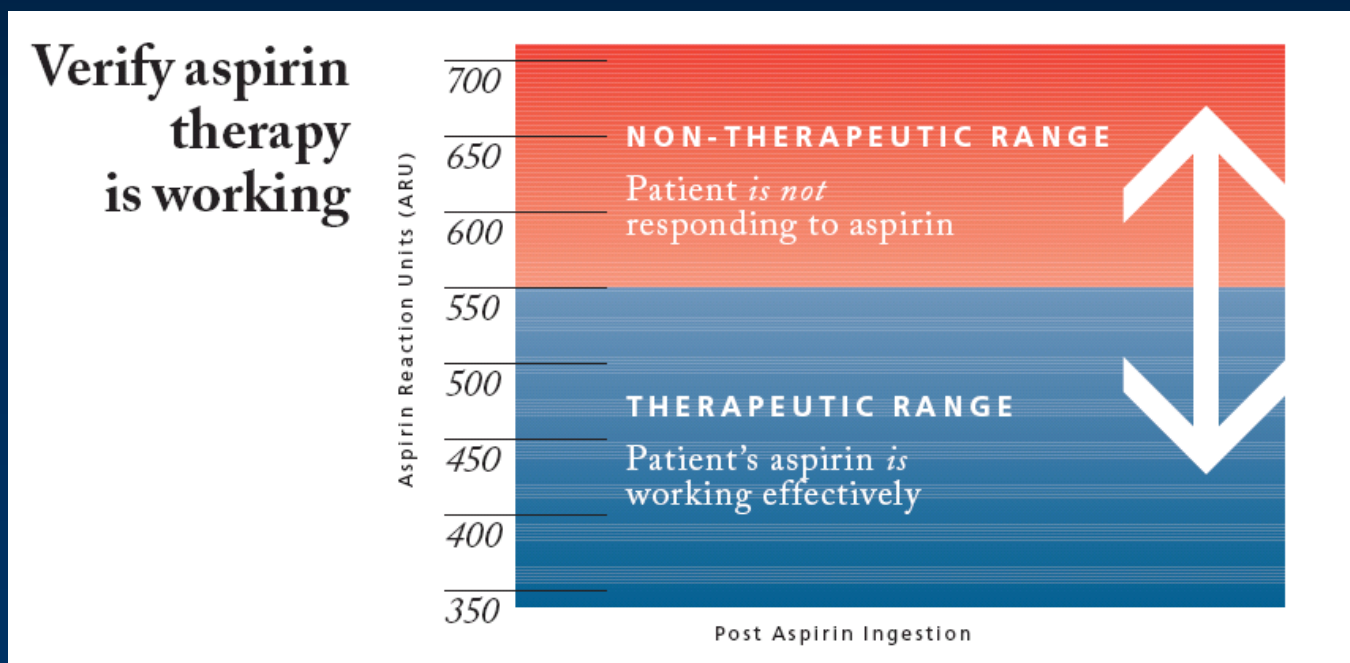
VerifyNow™ (Ultegra) RPFA

- ❑ Turbidometry-based optical detection system
- ❑ Assay device
 - Lyophilized preparation of human fibrinogen-coated beads
 - Platelet agonist
 - Preservative and buffer
- ❑ Blood sample
 - 3.2% citrated whole blood
 - No handling required by the user



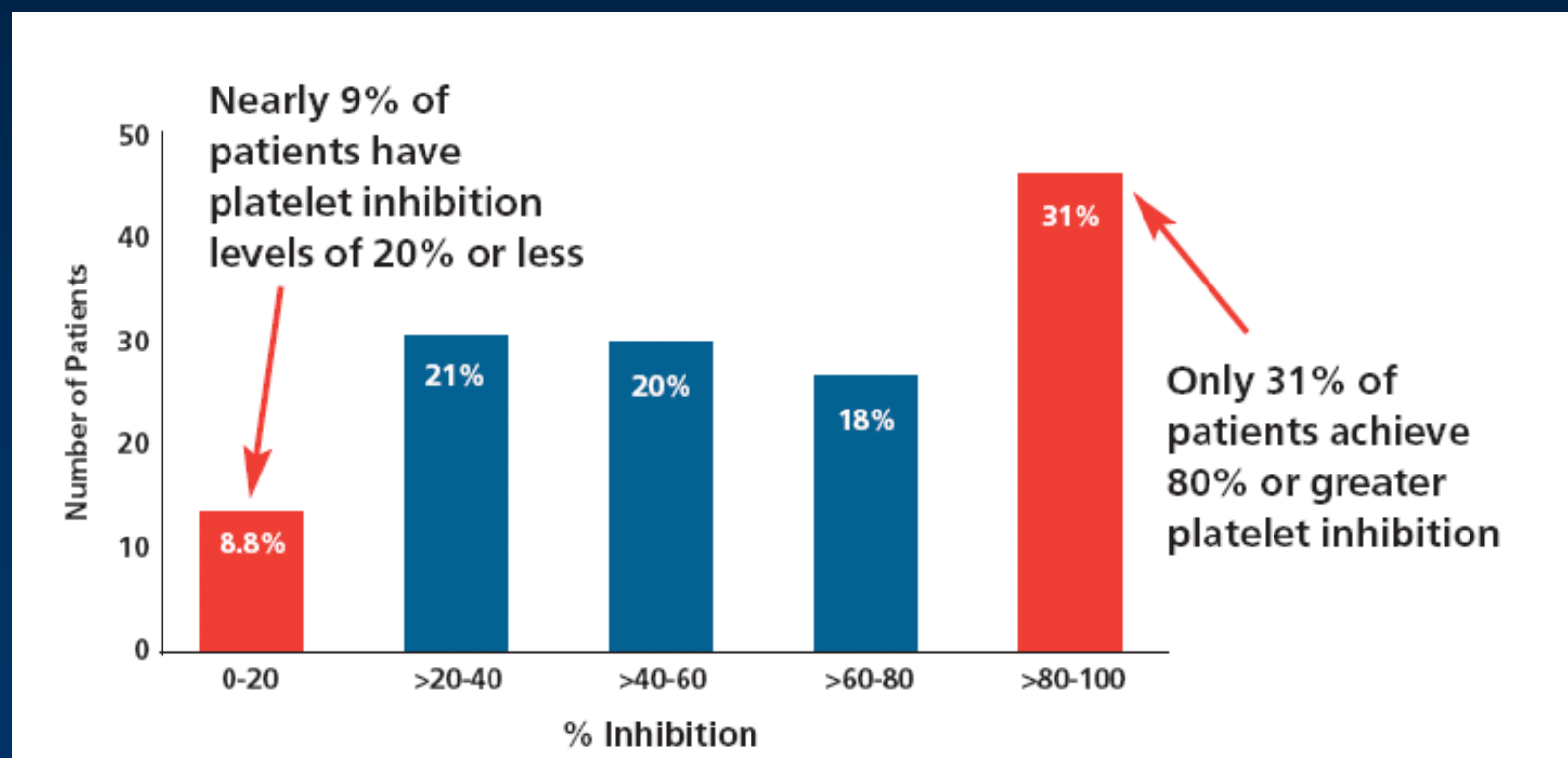
Definition of resistance

- Aspirin
 - Aspirin reaction unit (ARU) ≥ 550
 - inadequate platelet inhibition by Aspirin



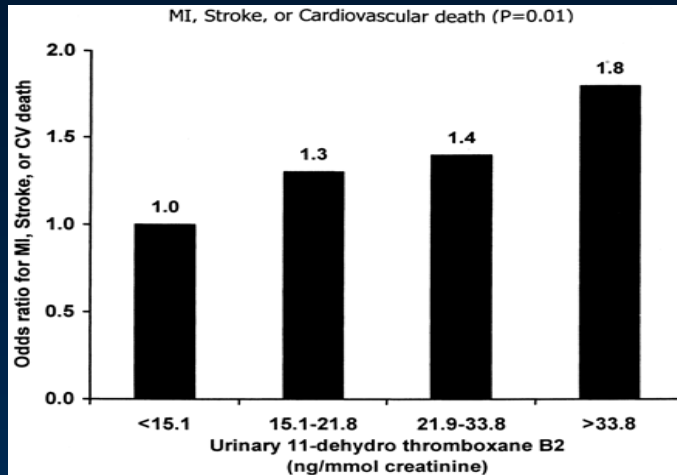
Definition of resistance ; P2Y12

Monitoring platelet inhibition after clopidogrel with the VerifyNow-P2Y12[®] rapid analyzer: The VERIfy Thrombosis risk ASsessment (VERITAS) study

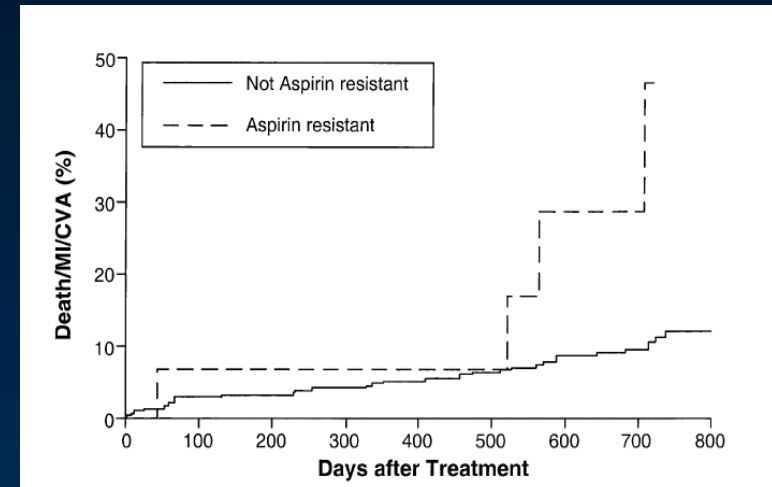


Implication of Resistance

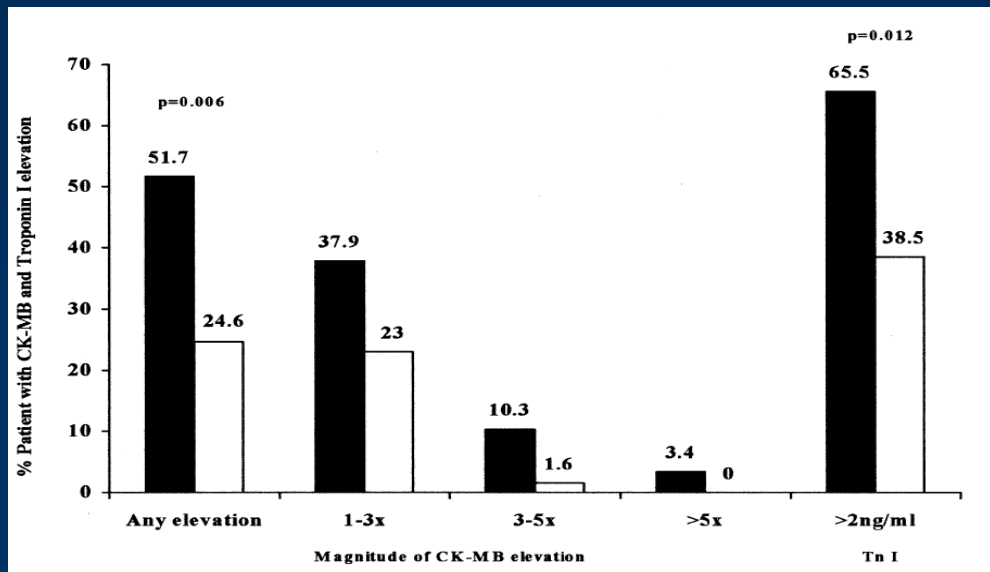
Implication of Aspirin Resistance



Eikelbloom JW, et al. *Circulation* 2002



Gum PA, et al. *JACC* 2003



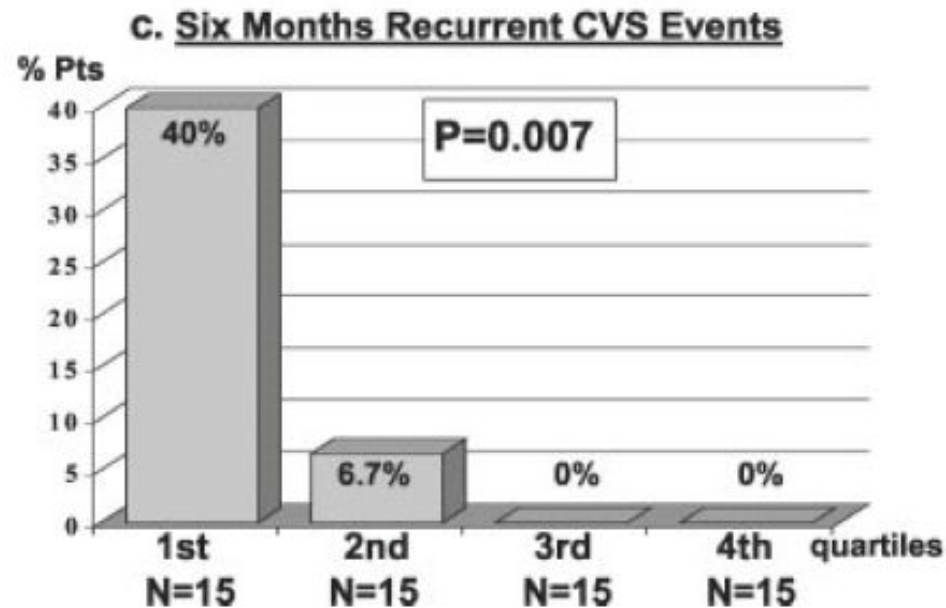
Chen WH, et al. *JACC* 2004

Implication of Clopidogrel Resistance

Circulation 2004;109:3064-7

Clopidogrel Resistance Is Associated With Increased Risk of Recurrent Atherothrombotic Events in Patients With Acute Myocardial Infarction

Shlomi Matetzky, MD; Boris Shenkman, MD, PhD; Victor Guetta, MD; Michael Shechter, MD; Roy Bienart, MD; Ilan Goldenberg, MD; Ilya Novikov, PhD; Hanna Pres, MSc; Naphtali Savion, PhD; David Varon, MD; Hanoch Hod, MD



What can we do for 'resistant' patients?

Compliance

- ❑ Aspirin resistance & compliance (*Schwartz KA et al. AJC 2005*)
 - LTA assay after usual dose of daily aspirin 325mg
→ aspirin resistance in 9%
 - LTA assay at 2hrs after direct observed ingestion of aspirin
→ aspirin resistance in <1%

Compliance as a critical consideration in patients who appear to be resistant to aspirin after healing of myocardial infarction. (Am J Cardiol. 2005;15:973-5)

- ❑ Premature discontinuation of clopidogrel
 - Most important risk factor of stent thrombosis
 - **HR 89.78** (C.I 29.9-269.60, $p < 0.001$, *JAMA 2006*)

Control of Co-morbidities

- Hyperglycemia
- Hyper-TG
- Active inflammation
- Congestive heart failure
- Catecholamine surge

Drug interaction

□ Aspirin

- Omeprazole
- NSAIDs ; Ibuprofen, Indomethacin

□ Clopidogrel ; *via CYP3A*

Substrates	Diltiazem ,Verapamil, Nifedipine, Losartan, Atorvastatin, metoprolol, Benzodiazepine, Cyclosporine
Inducers	Rifampin, Alcohol, Phenobarbital, Phenytoin sodium Carbamazepine
Inhibitors	Ketoconazole, Itraconazole, Grapefruit juice Clarithromycin, Erythromycin, Cimetidine, Nefazodone Protease inhibitors, Verapamil

Dose up

□ Aspirin ; controversial

■ BRAVO-2, CURE ; Major bleeding risk ↑

- *BRAVO (Blockage of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion)*
- *CURE (The Clopidogrel in Unstable Angina to Prevent Recurrent Events)*

□ Clopidogrel

■ Increase of loading dose upto 600mg

→ Superior to 300mg

■ ARMYDA-2, ALBION, ISAR-CHOICE

- *ARMYDA-2 (The Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty)*
- *ALBION (the Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation, and Ongoing Necrosis)*
- *ISAR-CHOICE (Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect Trial)*

Another antiplatelet agent

- Clopidogrel in aspirin resistance
 - CAPRIE ; Clopidogrel > Aspirin
 - CAPRIE (*The Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events*)
 - Resistance to aspirin *in vitro* is associated with increased platelet sensitivity to ADP (*Throm Res 2002*)

- Cilostazol
 - PDE inhibitor ; cAMP in platelet ↑
 - Aspirin+Clopidogrel+Cilostazol > Aspirin+Clopidogrel in pts undergoing PCI (*Lee SW, et al. JACC 2005*)

Another antiplatelet agent

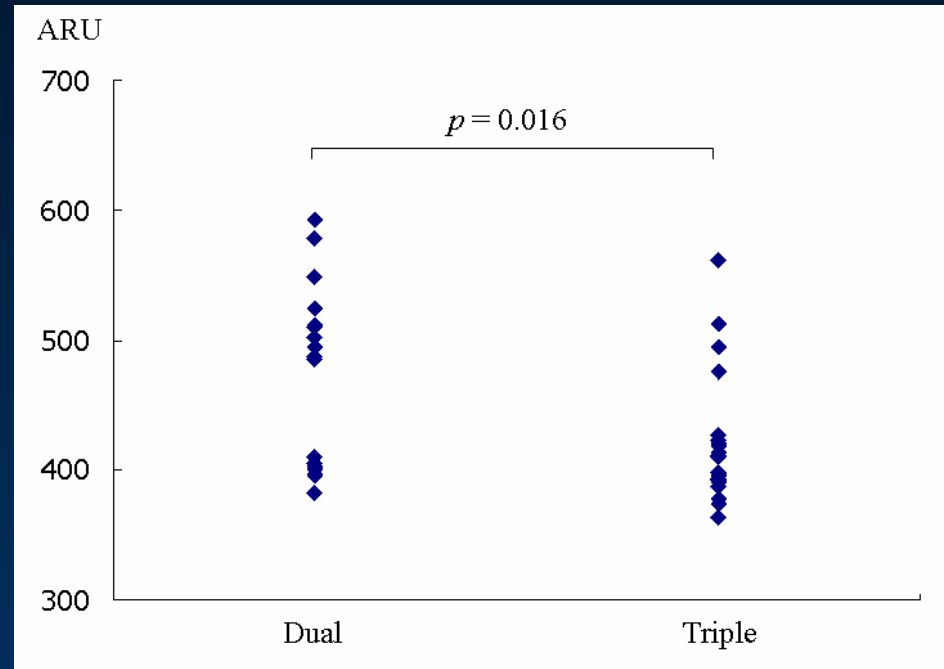
□ Triflusal

- COX-1 / COX-2 inhibition
- NO production

Suh JW, et al. *Clin Ther.* *in press*

□ Gp IIb /IIIa inhibitor

- RESISTOR Study
- Ultegra RPFA ; Responder vs. nonresponder
- Eptifibatide + heparin vs. heparin



Clopidogrel Alternative ; under investigation

□ Prasugrel

- Oral thienopyridine
- JUMBO-TIMI 26 ; phase 2 study (*Circulation* 2005)
- More rapid, potent action
- Less bleeding than clopidogrel

□ AZD6140

- Oral antagonist of P2Y12 Rc
- Potency, no liver metabolism

□ Cangrelor

- IV form, direct antagonist of P2Y12 Rc
- No liver metabolism, potent, short action
- Facilitated PCI

Summary

Summary

□ Antiplatelet therapy

; Cornerstone of atherosclerosis treatment

□ Resistance to antiplatelet agents

- Emerging clinical entity under active investigation
- Association with grave prognosis
- No consensus on definition and method yet

□ Correction of reversible cause

- Compliance
- Drug interaction
- Glucose, cholesterol control

Prospective

- Ongoing large randomized trials
 - CHARISMA (ASA +/- Plavix for 1, 2 prevention)
 - CHARISMA substudies (SNPs, urinary 11-DHTXB₂)
 - TRITON-TIMI 38 (Prasugrel vs Plavix in ACS pts/PCI)
 - DISPERSE2 (AZD90, 180, Plavix in NSTEMI pts)
 - RESISTOR (eptifibatide vs placebo in nonresponders to ASA/Plavix in PCI)

- Routine measurement of anti-platelet drug response assay like BP, cholesterol measurement

- Tailored medicine by drug response assay & genotype

Aspirin & clopidogrel resistance

Cardiovascular Center, SNUH
Hyo-Soo Kim & Jung-Won Seo

서울대학교병원 심혈관센터
김효수, 서정원



Thank you for your attention !!

Cardiovascular Center, Seoul National University Hospital

Implication of Clopidogrel Resistance

Gurbel PA, et al. J Am Coll Cardiol 2005;46:1827–32.

Clopidogrel Effect on Platelet REactivity in Patients With Stent Thrombosis

Results of the CREST Study

Paul A. Gurbel, MD, FACC, Kevin P. Bliden, BS, Waiel Samara, MD Jason A. Yoho, MD,
Kevin Hayes, MD, Mulugeta Z. Fissha, MD, Udaya S. Tantry, PHD

Baltimore, Maryland

	SAT (n = 20)	No SAT (n = 100)	p Value
LTA (5 $\mu\text{mol/l}$ ADP) (%)	49 \pm 4	33 \pm 2	<0.001
LTA (20 $\mu\text{mol/l}$ ADP) (%)	65 \pm 3	51 \pm 2	<0.001
LTA (1 mmol/l arachidonic acid)	1 non-responder	0 non-responders	
P2Y ₁₂ reactivity ratio (%)	69 \pm 5	46 \pm 9	0.03
GP IIb/IIIa (MFI)			
Unstimulated	9 \pm 1	15 \pm 3	NS
Stimulated	138 \pm 19	42 \pm 4	<0.001

Clopidogrel vs. Ticlopidine

Effectiveness of Ticlopidine and Aspirin Versus Clopidogrel and Aspirin in Preventing Stent Thrombosis

After Coronary Stent Implantation (*Moussa I et al. Circulation 1999*)

TABLE 2. Incidence of Stent Thrombosis, Major Adverse Cardiac Events, and Drug Side Effects at 1-Month Follow-Up

Patients	TA Group (n=1390)	CA Group (n=281)	P
Stent thrombosis	21 (1.5)	4 (1.4)	1.0
Myocardial infarction	25 (1.8)	2 (0.7)	0.29
Non-Q-wave	18 (1.3)	2 (0.7)	
Q-wave	7 (0.5)	0 (0)	
Coronary artery bypass surgery	5 (0.4)	2 (0.7)	0.33
Death	12 (0.9)	3 (1)	0.73
Drug side effects			
Neutropenia	4 (0.3)	0 (0)	1.0
Diarrhea	61 (4.4)	9 (3.2)	0.5
Rash	82 (6)	6 (2)	0.008
Any side effect	147 (10.6)	15 (5.3)	0.006

Values are n (%). A value of $P < 0.05$ is considered significant.

Dual Drug Resistance

J Am Coll Cardiol 2006;47:27-33.

Aspirin and Clopidogrel Drug Response in Patients Undergoing Percutaneous Coronary Intervention The Role of Dual Drug Resistance

Eli I. Lev, MD,* Rajnikant T. Patel, MD,* Kelly J. Maresh, RN, BSN,* Sasidhar Guthikonda, MD,* Juan Granada, MD,* Timothy DeLao, MLT,* Paul F. Bray, MD,† Neal S. Kleiman, MD*

Table 1. Rates of Clopidogrel Resistance in Aspirin-Resistant Versus Aspirin-Sensitive Patients

Aspirin Resistance Definition	ASA-Resistant Patients (n)	Clopidogrel Resistance Among ASA-Resistant Patients	ASA-Sensitive Patients (n)	Clopidogrel Resistance Among ASA-Sensitive Patients	p Value
At least 2 of the 3 criteria	19	9 (47.4%)	131	27 (20.6%)	0.01
AA aggregation \geq 20% and ADP aggregation \geq 70%*	14	7 (50%)	136	29 (21.3%)	0.02
RPFA-ASA ARU \geq 50	23	11 (47.8%)	127	25 (19.7%)	0.01

