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# Aspirin and Clopidogrel Resistance in Coronary Artery Disease

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## ABSTRACT

Dual antiplatelet therapy has been proven effective to reduce recurrent cardiovascular eventin patients with coronary artery disease and recommended as standard therapy for acute coronary syndrome and patients who underwent percutaneous coronary intervention. The adverse clinical occurrence in patients who taking aspirin and clopidogrel associates with antiplatelet non responsiveness, in addition to repetitive bleeding incident in such a way that platelet reactivity and genetic polymorphisms investigation rises intense interest. Resistance to antiplatelet or antiplatelet non responsiveness means a phenomenon in which antiplatelet drug fails to deliver pharmacological target and it is determined by platelet function measurement. Recent laboratory methods have been developed to diagnose antiplatelet resistance, but none of them was considered as standard tool since its wide inter-individual variability and poor correlation between them. The mechanism of antiplatelet resistance is not fully understood, multifactorial, involving pharmaco dynamic and pharmacokinetic of the drugs. This review is aimed to comprehend the antiplatelet resistance mechanism and provide crucial information on managing patients who take dual antiplatelet treatment with adverse clinical events.

**Keywords**: antiplatelet resistance; mechanism; laboratory measurement; management

## INTISARI

Terapi antiplatelet ganda telah terbukti efektif untuk menurunkan kejadian kardiovaskular berulang pada pasien dengan penyakit arteri coroner dan direkomendasikan sebagai terapi standar untuk sindroma coroner akut dan pasien yang menjalani intervensi coroner perkutan. Kejadian klinik buruk pada pasien yang mendapatkan aspirin dan klopidogrel berhubungan dengan sifat non reponsif terhadap antiplatelet, selain adanya perdarahan berulang yang menyebabkan pengkajian tentang reaktivitas platelet dan polimorfis megenetik menjadi meningkat. Resistensi terhadap antiplatelet atau nonresponsive terhadap antiplatelet berarti suatu fenomena dimana obat antiplatelet tidak mampu mencapai target farmakologi dan hal ini ditentukan oleh pengukuran fungsi platelet. Dewasa ini, metode pengukuran laboratorium telah dikembangkan untuk mendiagnosis resistensi antiplatelet, namun belum ada yang diterima sebagai alat standar karena adanya variabilitas antar individu dan korelasi yang buruk diantara alat-alat tersebut. Mekanisme resistensi antiplatelet tidak sepenuhnya dimengerti, multifaktor, melibatkan farmako dinamik dan farmako kinetic dari obat. Tinjauan pustaka ini bertujuan untuk mengetahui mekanisme resistensi antiplatelet dan memberikan informasi penting dalam tata laksana pasien yang mendapatkan terapi antiplatelet ganda dan mengalami kejadian klinik buruk.

## INTRODUCTION

Antiplatelet drugs are widely used to reduce thrombosis process in atherosclerosis patients. There are three kinds of antiplatelet drug which have been proven their benefit to coronary artery disease (CAD), i.e. (i)cyclooxygenase (COX)-1 inhibitor such as aspirin, (ii) adenosine 5'-diphosphate (ADP) antagonist receptor

such as thienopyridine (ticlopidin, clopidogrel, prasugrel), and (iii) GPIIb/IIIa antagonist such as abciximab, eptifibatide,and tirofiban. Aspirin and thienopyridinework selectively on inhibiting platelet activation and subsequent aggregation; aspirin in thromboxan A2 production through irreversibly COX-1 inhibition, while thienopyridinedisturbed ADP pathway through thrombocyte ADP receptor blockade. The prevention of platelet's clumping result in reduction of atherothrombotic event patient with CAD.[1,2,3]

In addition to their advantages, researchers reported significant antiplatelet debilitiessuch as low responsiveness (resistance), lack of platelet inhibition ability, variation of individual response, and lengthen time to recovery. Residual platelet reactivity is correlated with increased risk of major cardiovascular events.[4] Chirumamilla et al. (2012) investigated the relationship of platelet reactivity and atherosclerotic burden in patients treated with percutaneous coronary intervention (PCI). That study suggested that an increased platelet reactivity on antiplatelet treatment was correlated with higher burden of CAD and plaque calcification.[5] Antiplatelet resistance is also associated with repetitive bleeding events in CAD patients.[6]

## *THE INCIDENCE OF ANTIPLATELET RESISTANCE*

The prevalence of antiplatelet resistance in different population with several methods of laboratory tests is various. Numerous studies report the prevalence of aspirin and clopidogrel resistance is about 5-60%, as shown on table 1 and 2. The results show a wide variation and poor consistency among those researches. Therefore, it is needed to evolve more studies to investigate the ideal laboratory test which can identify antiplatelet resistance and the patients who at risk of future adverse cardiovascular events.[7]

## *MECHANISM OF ACTION: ASPIRIN AND CLOPIDOGREL*

Aspirin causes permanent inhibition of COX-1 by acetylating a serine residue at position 530 with the result that prevent the changes of arachidonic acid (AA) to the unstable prostaglandin (PG) which is converted to thromboxan A2 (TXA2), a platelet agonisand vasoconstrictor. Clopidogrel is an inactive prodrug derived thienopyridine, converted into active form by hepatic P450 cytochrom enzyme, acts byirreversible antagonism of $P2Y_{12}$ adenosine diphosphate (ADP) receptor. Those dual antiplatelets therapy significantly decrease thrombotic events. The action's mechanism of aspirin and clopidogrel are shown on figure 1.[8]

## *DEFINITION OF ANTIPLATELET RESISTANCE*

European Society of Cardiology (ESC) Working Group on Thrombosis states that definition of antiplatelet resistance remains unclear since the standardized platelet function test has not been established to define whether it is responders or non-responders (resistance). The terminology of antiplatelet resistance consists of two features: clinical and laboratory. A patient who receives antiplatelet drug routinely but still experiences in cardiovascular event implied as clinical resistance. While laboratory resistance is defined when antiplatelet drug does not work properly to block platelet activation on in vitroexamination.[9]

Inter individual variability concept upon any agent may be described as follows, different effect with varied intensity on different subject regardless the same agent's plasma concentration. Absorbtion, distribution, metabolism (biotransformation) and elimination, known as pharmacokinetics, each contributes on plasma concentration variation and or active metabolites in any individual who receives the same dose. Biomechanical and physiological effects of the agent and its action mechanism, created complex relations with the given concentration and the clinical effect shown, called pharmacodynamics. Both pharmacokinetics

Table 1. Prevalence of aspirin resistance based on laboratory assay[7]

**Table 2.** Summary of laboratory tests reporting Aspirin resistance.

| Study | n | Type of subjects | Aspirin dose | Platelet function test | Prevalence of resistance (%) |
|---|---|---|---|---|---|
| Gum et al[50] | 325 | Stable CAD | 325 mg | ADP and AA induced optical aggregation | 5.2 |
| Mueller et al[38] | 100 | PAD | 100 mg | Corrected whole blood aggregometry | 60 |
| Grotemeyer et al[35] | 180 | CVA | 1500 mg | Platelet reactivity | 33 |
| Chen et al[24] | 151 | Elective PCI | 80–325 mg | RPFA | 19 |
| Andersen et al[23] | 202 | Post MI | 160 mg Aspirin vs. 75 mg Apirin plus warfarin | PFA-100 | 35% in patients taking aspirin only, vs. 40% in patients taking aspirin and warfarin |
| Macchi et al[21] | 98 | Stable CAD | 160 mg | PFA-100 | 29% |
| Helgason et al[51] | 306 | CVA | 300–325 mg | ADP induced platelet aggregation | 25% |
| Hobikoglu et al[22] | 204 | ACS: 104 Stable CAD: 100 | 80–300 mg | PFA-100 | 40% in ACS<br>27% in Stable CAD |
| Grundmann et al[52] | 53 | CVA/TIA in prev 3 days 35 | 100 mg | PFA-100 | 34% in symptomatic<br>0% in asymptomatic patients |
| Alberts et al[53] | 129 | CVA | 81 mg vs. 325 mg | PFA-100 | 37% overall, with 56% in patients on 81 mg vs. 28% in those on 325 mg aspirin. |

*Source of table: Saraf et al. (2009)[7]*

Table 2. Prevalence of clopidogrel resistance based on laboratory assay[7]

**Table 3.** Summary of laboratory tests reporting clopidogrel resistance.

| Study | n | Condition studied | Loading dose clopidogrel | Maintenance dose clopidogrel | Platelet function test | Prevalence of resistance |
|---|---|---|---|---|---|---|
| Gurbel et al[54] | 92 | PCI | 300 mg | 75 mg | LTA | 31%–35% |
| Angiolillo et al[55] | 52 | Diabetes | 300 mg | 75 mg | LTA and Flow cytometry | 38% in DM, 8% in non-DM |
| Angiolillo et al[56] | 48 | PCI | 300 mg | 75 mg | LTA | 44% |
| Lepantalo et al[57] | 50 | PCI | 300 mg | 75 mg | LTA and PFA 100 | 40% |
| Jaremo et al[58] | 18 | PCI | 300 mg | 75 mg | LTA | 28% |
| Lev El et al[59] | 150 | PCI | 300 mg | – | LTA | 24% |
| Mobely et al[60] | 50 | PCI | 300 mg | 75 mg | LTA | 30% |
| Muller et al[61] | 115 | PCI | 600 mg | 75 mg | LTA | 5%–11% |
| Barragan et al[62] | 48 | ISR[16] vs no ISR[32] | | Clop 75 mg B.I.D. vs. Ticlopidine 250 mg B.I.D. | Flow cytometry | 63% (ISR) vs. 40% (no ISR) |
| Bounamici et al[32] | 804 | ISR | 600 mg | 75 mg | ADP induced platelet aggregation | 13% |
| Ajzenberg et al[63] | 32 | ISR[10] vs. no ISR[22] | 300 mg | 75 mg | Shear induced platelet aggregation (SIPA) | 41% (cases) vs. 18% (controls) at shear rate of 200/s 57% (cases) vs. 23% (controls) at shear rate of 4000/s |
| Matetzky et al[29] | 60 | STEMI | 300 mg | 75 mg | LTA | 25% |
| Dziewierz et al[64] | 31 | CAD | 300 mg | – | LTA | 23% |

*Source of table: Saraf et al. (2009)[7]*

and pharmacodynamics work as the basis to understand successful rate of therapy and its side effect (figure 2).[10]

*MECHANISM OF ANTIPLATELET RESISTANCE*

When coronary artery plaques ruptur, thrombogenic substrate is released into blood circulation and result in the activation and aggregation of platelet. On PCI procedures (especially when balloon or stents are deployed), patients are at high risk of thrombotic response due to vascular injury. Aspirin and clopidogrel are proven to reduce in stent thrombosis or restenosis after drug-eluting stenting. However, antiplatelet non-responsiveness still occurs in some patients on standard dual antiplatelet therapy. The mechanism of antiplatelet resistance is not fully understood.[11] High individual response variability on antiplatelets agents involve many factors, such as non-compliance and low absorption.[4] Other mechanisms responsible to antiplatelet resistance include lowering bioavailability, genetic variations, increased platelet turnover, activation of platelet from other pathway, and individual variation (table 3).[7]

*MECHANISM OF ASPIRIN RESISTANCE*

Pharmacodynamics resistance of aspirin caused by change of aspirin target enzyme, COX-1, and increasing the dosein vitro did not significantly alter thromboxan-A2 production. This phenomenon refers to

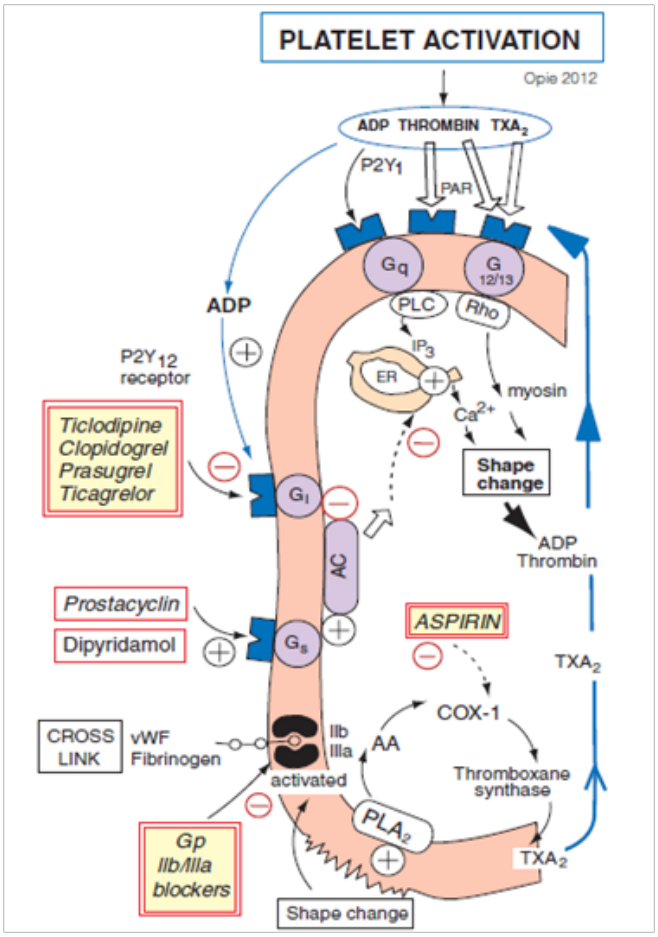


Figure 1.Antiplatelet site of action
*Source: Fox et al.(2013)[8]*

laboratory resistance which aspirin does not block properly with in vitro platelet reactivity. Pharmacokinetics resistance was a condition caused by limited supply of active agents on plasma that caused low therapeutics response (such as low dose or absorption change) that improved significantly by adding aspirin in vitro dosage.[12]

In the clinical practice, nonadherence is probably the most frequent cause of aspirin nonresponsiveness. The lack of aspirin effect is due to the patient not taking the drug regularly or prematurely discontinue it. Aspirin discontinuation may not improve efficacy, but may raise bleeding risk and correlated with threefold increase in adverse cardiovascular events.[12,13] Enteric coated aspirin is considered as a culprit of lower effectivity especially on obese patients because its tendency of low bioavaibility and bad absorption due to high-pH condition in the small intestine.[12,13,14,15] The reducing bioavailibility of aspirin by gastrointestinal mucosal esterases may also occur when it takes together with proton pump inhibitor.[12] Competition with other NSAIDs connected with Ser 530 enzim COX-1, in advanced causing irreversible acethylation and enzyme inactivation. It is caused by location of binding site both aspirin and NSAIDs are within a hydrophobic channel in COX enzyme.[13,14.]

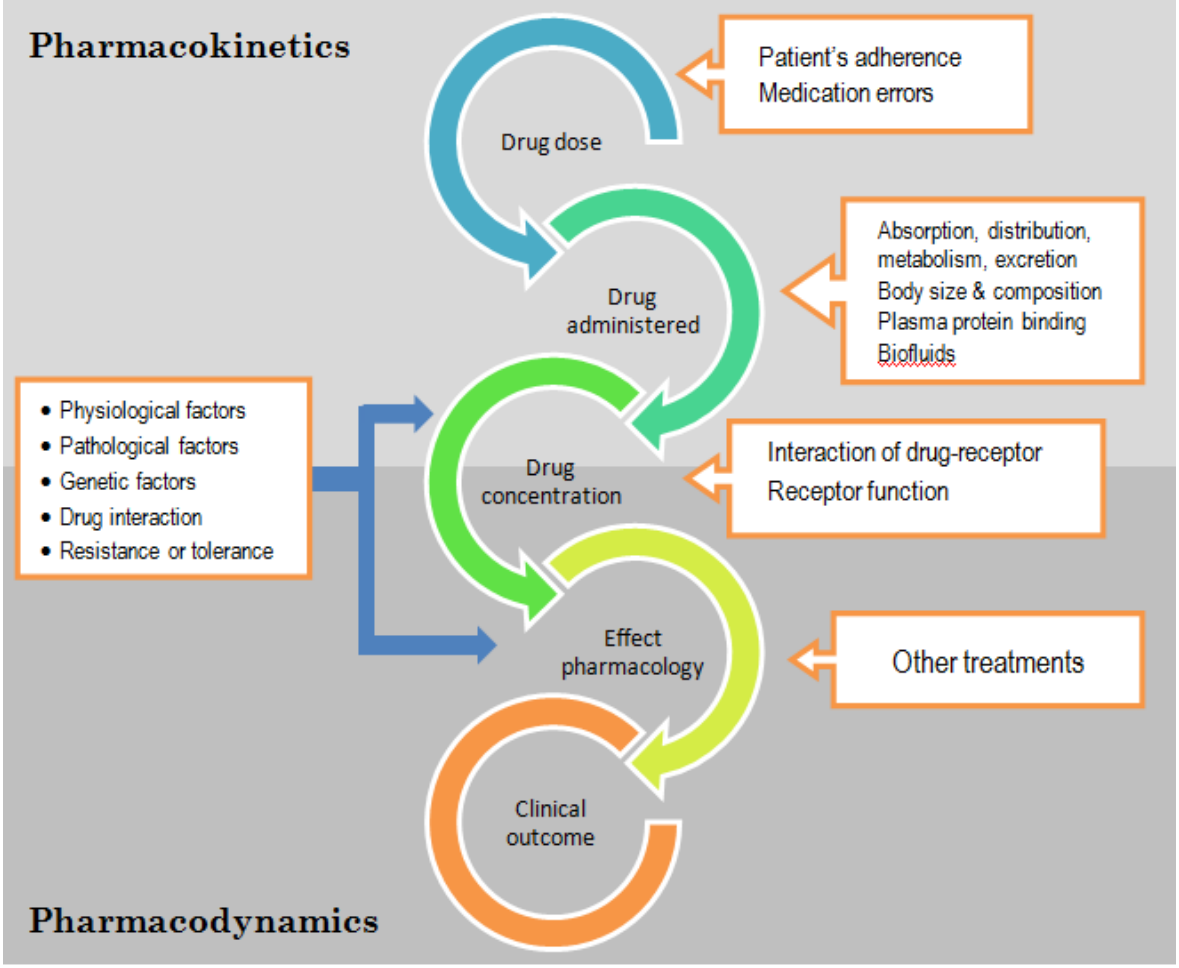


Figure 2. Pharmacokinetics and pharmacodynacis which influenced drug clinical outcome. This figure is modified from Rocca and Petrucci (2012)[10.]

Table 3 .Underlying mechanisms of antiplatelet resistance[7]

| | |
|---|---|
| Bioavailabilitasdecrement | • Incompliance<br>• Inadequate dosage<br>• Low absorption (*enteric coated* aspirin)<br>• Increased metabolism<br>• Other drug interaction (involving P-450 CYP3A4 cytochrome system for conversion onto active metabolyte)<br>• Other drug interaction (NSAIDs) |
| Genetics Variations | • Gene COX1 mutation<br>• Gene COX1, glycoprotein(GP) Ia/IIa, GP IIIa, P2Y1 or P2Y12 polymorphism<br>• Gene P-450 CYP3A polymorphism (for clopidogreland any other prodrug that metabolised with the system)<br>• Platelet glycoprotein receptor polymorphism<br>• Platelets and endothel cell's COX 2 overexpression |
| Enhanced platelet turnover | • Increment of bone marrow's platelet production<br>• Unexposed aspirin and clopidogrel new platelets (case example, tranfusion)<br>• Platelet activation induced by cigars.<br>• Platelet activation induced by erythrocyte increment. |
| Platelet activation from alternative pathway | • TXA2 synthesis induced by cytokines, oxidative stress or nucleated cells<br>• Platelet activation induced by cathecolamine caused by exaggerated physical or mental stress.<br>• High incidencee of shear stress, collagen, thrombin and other platelet activation pathway. |
| Individual variation | • Diabetes or insulinresistance<br>• Hypercholesterolaemia<br>• Hypertension<br>• Old age<br>• Obesity<br>• Sex |

*Source of table: Saraf et al. (2009)[7]*

In pharmacodynamics perspective, production of residual thromboxan by COX-1 and COX-2 is thought to be responsible for aspirin resistance. Furthermore, enhanced platelet turnover (primary or secondary) or high interaction between platelet and vessel wall (such as diabetes) may cause more relevant to COX-1 activity than aspirin effectiveness. COX-2 overexpressionson platelet, megakaryosites and its upregulations on monocytes, macrophages and vascular endothel cells (as seen in diabetes, hyperlipidemia, smoking, and heart failure) may cause biosynthesis thromboxan elongation, which later could contribute to aspirin resistance. This conditions may be caused by overproduction of prostaglandin-like compound which relate with oxygen free-radicals nonenzymatic acidarachidonic lipid peroxidation.[12] Genetic factors also correlate with aspirin resistance. Its includes genetic polymorphisms of thromboxan synthesis, P1A1/A2 (encoded gene of platelet membrane's GPIIIa), COX-1 and platelet collagen-receptor's GPIa/IIa, and polymorphisms which cause overexpression of COX-2 mRNA in platelets and endothelial cells.[12]

*MECHANISM OF CLOPIDOGREL RESISTANCE*

There are multiple etiologies which contribute the nonresponsiveness to clopidogrel. Its proposed mechanisms include bioavailability, cellular factors, genetic polymorphism, and other factors such as body mass index, diabetes, hypercholesterolemia, and smoking (table 4).[11,13] The lack of clopidogrelbio availibility

Table 4. Factors influence variability of clopidogrel response[7]

| | |
|---|---|
| Bioavailability | • Nonadherence patient<br>• Drug interaction (lipophilic statins, omeprazole)<br>• Poor absorption<br>• Underdosing |
| Cellular factor | • Enhanced platelet turnover<br>• Increased platelet sensitivity to ADP and collagen<br>• Reduced activity CYP3A<br>• Increased exposure ADP<br>• Upregulation of P2Y12 pathways<br>• Upregulation of P2Y-independent pathways: collagen, thrombin, epinephrin, TXA2 |
| Genetic factor | • Polymorphisms of P450(CYP2C19681G>A[*2,*3,*4, and *5]<br>• Polymorphisms of P2Y1<br>• Polymorphism of P2Y12<br>• Polymorphism GPIa<br>• Polymorphism GP IIIa |
| Other factors | • Increased body mass index<br>• Diabetes<br>• Hiperinsulinemia<br>• Hypercholesterolemia<br>• Smoking |

*Source of table: Saraf et al. (2009)*[7]

commonly due to non adherence patients, underdosing, and lowering prodrug intestinal absorption. Clopidogrel may interact with lipophilic statin, calcium-channel blocker, and omeprazole result in changes in hepatic cytochrome P450 isoenzymes activity and responsible on interfering clopidogrel action.[13] Interaction with benzodiazepine and selective serotonin reuptake inhibitor (SSRI) are also able to decrease clopidogrel biovailability.[17]

The genetic factors which affect the clopidogrel response are polymorphisms of cytochrom P450, variations in $P2Y_{12}$ receptor density, andcarriers of disabled CYP2C19681G>A*2.[13] Hulot et al (2006) conducted pharmacogenetic study to figure out the mechanism of clopidogrel hyporesponsiveness which related to genetic variation.

They concluded that CYP2C19*2 loss-of-function allele was correlated with poor antiplatelet responsiveness of clopidogrel in young healthy male volunteers. The capability of clopidogrel to impede ADP-induced platelet aggregation demonstrates a wide individual variabiality.[18,19] Different platelet response to ADP which not increased by clopidogrel administration is also accounted as individual variability.[20]

## *LABORATORY MEASUREMENT OF ANTIPLATELET RESISTANCE*

Guidelines of myocardial revascularization (2014) published by ESC states that platelet function test or genetics is considered on high risk conditions such as stent thrombosis history, incompliance, resistance suspicion, and high risk bleeding (class recommendation IIb), though routine examination before and after stent implantation is not recommended.[21]

In vivo (bleeding time) and in vitro (light transmission aggregometry/LTA, PFA-100 system, ultegrarapidplatelet function assay-ASA) platelet function are not always reflecting drug ability to reach its pharmacology target.[22] Various methods is developed to obtain the most appropriate measurement of platelet function in clinical practice.[23]

Table 5. Various methodes of platelet function assessment [23]

| Method | Sample | Method application | Method principle |
|---|---|---|---|
| Bleeding time | Native WB | Screening test (obsolete) | In vivo measurement of bleeding block |
| **Tests based on platelet aggregation** | | | |
| Light transmission platelet aggregation (LTA) | Citrated PRP | Screening test for bleeding tendency<br>Diagnostic for platelet defects<br>Monitoring antiplatelet treatment effect | Photo-optical measurement of light transmission increase in relation to agonist-induced platelet aggregation |
| Impedance platelet aggregation | Citrated WB | Screening test for bleeding tendency<br>Diagnostic for platelet defects<br>Monitoring antiplatelet treatment effect | Measurement of electrical impedance increase in relation to agonist-induced platelet aggregation |
| Lumiaggregometry | Citrated WB | Detection of storage/release disorders | LTA or WB aggregometry combined with luminescence |
| Plateletworks | Citrated WB | Monitoring of the platelet response to antiplatelet agents | Platelet counting pre- and postactivation in whole blood |
| **Tests based on platelet adhesion under shear stress** | | | |
| PFA-100; Innovance PFA-200 | Citrated WB | Assessment of bleeding risk and drug effects<br>Searching severe platelet dysfunctions, revealing of VWD | Time evaluation of high shear WB flow blocked by platelet plug into a hole in activated surface |
| Impact; Cone and Plate(let) Analyzer | Citrated WB | Screening of primary hemostasis | Shear-induced platelet adhesion–aggregation upon specific surface |
| Global thrombosis test (GTT) | Native WB | Evaluation of platelet function and thrombolysis | Measurement of time cessation of WB flow by high shear-dependent platelet plug formation |
| **Platelet function methods combined with viscoelastic test** | | | |
| TEG/platelet mapping system | Citrated WB | Assessment of global hemostasis plus monitoring antiplatelet treatments effect | Evaluation of rate of clot formation based on low shear-induced and agonist addition |
| ROTEM platelet | Citrated WB | Assessment of global hemostasis plus diagnostic of platelet defects plus monitoring antiplatelet treatments effect | Measurement of electrical impedance increase in relation to agonist-induced platelet aggregation |
| **Platelet analysis based on flow cytometry** | | | |
| Flow cytometry | Citrated WB, PRP, W-Plt | Cell counting, detection platelet activation by extent of expression of surface and/or cytoplasmic biomarkers | Engineering laser-based detection of suspending fluorescent label platelets in a flowing solution |
| **Evaluation of Thromboxane metabolites** | | | |
| Radio- or enzyme-linked immune assays | Serum, urine, citrated Pls | Measurement of TxA2 metabolites (and Beta-TG, PF4, soluble P-selectine)* | Ligand-binding assays |

***Abbreviations:*** *Beta-TG, beta-thromboglobulin; Pls, plasma; PRP, platelet-rich-plasma; ROTEM, rotational thromboelastometry; TEG, thromboelastography; TxA2, thromboxane A2; WB, whole blood; W-Plt, washed platelets; VWD, Von Willebrand disease.*
*Source of table: Saraf et al. (2009)[7]*

The gold standard of antiplatelet resistanceassay is LTA or turbidometricaggregometry, which based on platelet aggregation measurement between the agent and its agonis, as AA and ADP for aspirin, or ADP only for clopidogrel, prasugrel, or ticagrelor. Recently, Verify Now®and vasodilator stimulated phosphoprotein (VASP) phosphorylationassay is considered as more practically for clinical interest, due to LTAhas a low reproducibility, interindividual variability on ADP induced platelets aggregation baseline, and the logistical condition make a difficulty to use in daily practice.[24]

Ultegra Rapid Platelet Function Assay (RPFA)-Verify Now® is a simple, rapid (less than 5 minutes), user-friendly, high reproducibility, and point-of-care assessment which use AA or propylgallate to measure aspirin effects and ADP

to find out the effect of $P2Y_{12}$ inhibitor.[24] Platelet function is assessed from the ability of activated platelet to bind fibrinogen which is detected by turbidimetric-based optical. Using light source, blood specimens is added to mixing chamber (cartridge) which contains fibrinogen-coated beads and a specific agonist. Clotting of functional platelets will raise the light transmission and the amount of fibrinogen binding by the activated platelets is determined. Three different assays are available to verify the inhibition of platelet function by anti-platelet drugs (GPIIb/IIIa inhibitor, aspirin, and clopidogrel). The result of aspirin and P2Y12 test is reported as Aspirin Reaction Unit (ARU) and P2Y12 Reaction Unit (PRU), respectively.[23,25] The cutt-off value of aspirin and clopidogrel resistance are ≥ 550 ARU and ≥ 240 PRU.[6]

## *MANAGEMENT OF ANTIPLATELET RESISTANCE*

Experts recommend three strategies to overcome antiplatelet resistance: increasing the dosage, adding other agent (such as gylcoprotein IIb/IIIa inhibitor, cilostazol), or substituting with more potent agent (such as prasugrel, ticagrelor).[6] Alegria-Barrero et al (2010) convey an algorithm on overcoming antiplatelet resistance in patient undergo PCI (figure 3). After PCI procedure, patient receives dual antiplatelet drug (aspirin 100 mg and clopidogrel 75 mg). When aspirin or clopidogrel resistance is indicated, increase aspirin dosage up to 325 mg or clopidogrel 150 mg, respectively. It may also be switched with trifusal for aspirin resistance or prasugrel/ticagrelor/prasugrel for clopidogrel resistance.[26]

Neubauer*et al.* (2011) investigate 504 patients following PCI in single center study whoreceived 500 mg aspirin (loading dose), continued with 100 mg per 24 hour and 600 mg clopidogrel (loading dose), continued with 75 mg per 24 hour. All participants undergo whole blood aggregometry examination > 48 hours

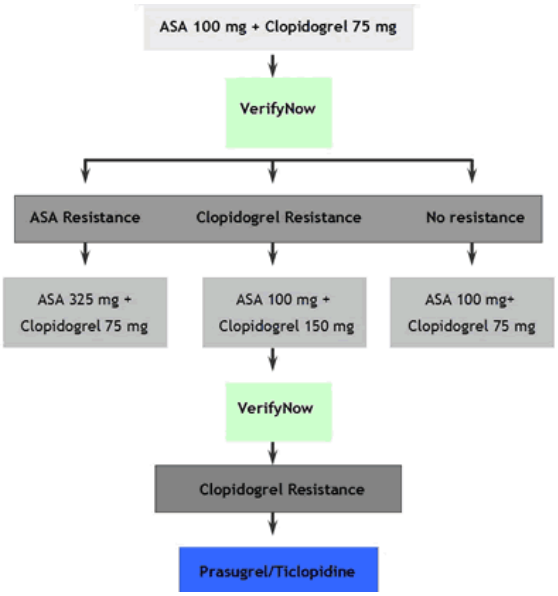


Figure 3. Algorithm of antiplatelet resistance mangement.
Reprinted with permission from Alegria-Barrero (2010)[26]

(no more than 72 hour) after stent implantation. The researcher applies the tailored algorithm on managing antiplatelet resistance which called “The Bochum clopidogrel and aspirin plan (BOCLA-Plan)”. Study result identified 30,8% clopidogrel low-responders (CLR) and 19,4% aspirin low-responders (ALR). Aspirin dosage adjustment gradually at 300 mg/day, then 500 mg/day, resulted on 5,4% residual ALR. This means aspirin maintenance dose modification is adequately success for ALR. Meanwhile, 69%CLR patients are successfully treated with increased dosage of clopidogrel (150 mg/24 hour). The remaining 12.7% CLR who is contraindicated with prasugrel or inavailability of prasugrel, show adequate response with ticlopidine.Other CLR patients given prasugrel has not shown residual properties yet.This algorithm implementation decreasing the CLR prevalence by 86.6%.[27]

The former research, Aspirin Induced Platelet Effect (ASPECT) research on stable coronary artery disease, showed ALR decrement

by increasing aspirin up to 325 mg/24 hour.[28] Practice guideline for PCI from ACC/AHA/SCAI (2005) states that patients in whom subacute thrombosis may be fatal (such as unprotected left main, bifurcating left main, or last patent coronary vessels), platelet aggregation assessment may be considered and if it reveales inhibition of platelet agregation < 50%, clopidogrel dosage should be increased up to 150 mg/24 hour (class IIb, LoE : C).[29]

Aspirin resistance might be suppressed by minimalizing thromboxan production and activity or any other platelet activation pathway. Stop smoking, body weight reduction and routine physical training are mentioned to increase platelet function. Other clinical condition as hyperlipidemia, diabetes mellitus, hypertension, cardiac failure, and inflammation disturbances also disrupt aspirin activity. Incompliance, avoidance of agents interfere with aspirin absorption as proton pump inhibitor and enteric coated aspirin, agent decrease pharmacokinetics as NSAID, has its benefit on reducing resistance.[12]

Higher platelet exchange increase the dose needed for aspirin, as American Diabetes Association recommended. Dose 75-162 mg/ 24 hour on diabetic patient with cardiovascular risk increased (as primary prevention) such as male > 50 yo, female > 60 yo with minimal 1 risk factor of atherosclerotics, or secondary prevention for those already diagnosed with atherosclerotic vascular disease.[24] The proposed algorithm on handling aspirin resistance is shown on figure 4.

## CONCLUSION

Resistance to antiplatelet means a phenomenon in which antiplatelet drug fail to deliver pharmacological target and it is determined by platelet function measurement. Antiplatelet resistance is associated with recurrent adverse cardiovascular events, higher burden of CAD, plaque calcification, and repetitive bleedingoccurences. Studies develop various laboratory methods to recognize antiplatelet resistance, but none of them is considered as standard tool since its wide inter-individual variability and poor correlation between them. The published guidelines does not recommend to check the platelet function test routinely in periprocedural of PCI, unless the patient on high risk situation in

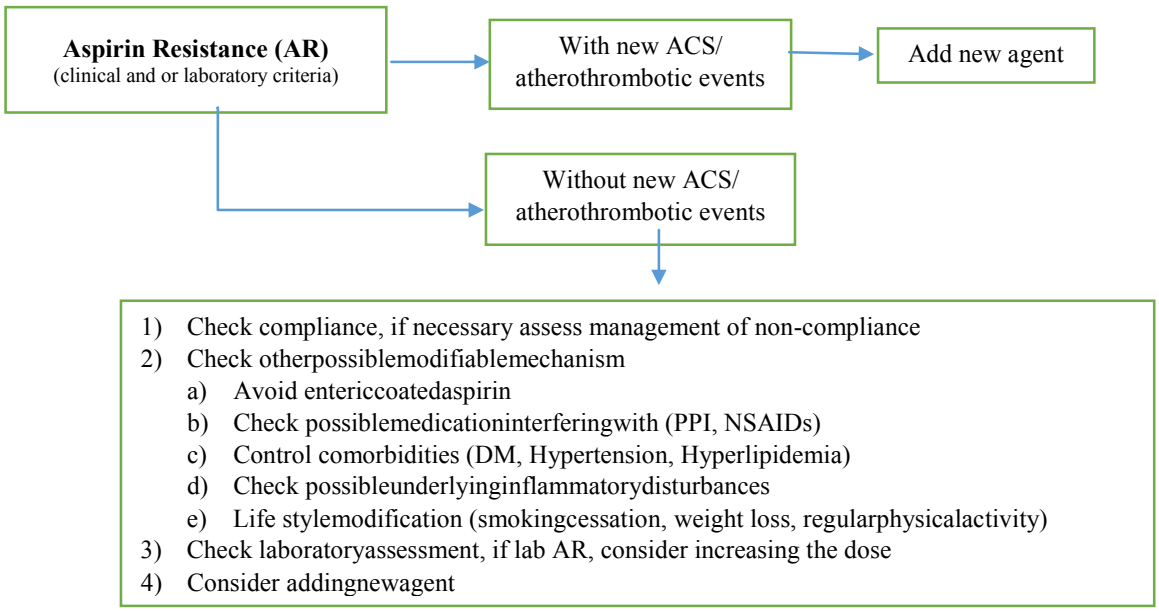


Figure 4. Proposed algorithm of managing aspirin resistance on coronary artery disease.

whom subacute thrombosis may be fatal.

The mechanism of antiplatelet resistance is involving pharmacodynamic and pharmacokinetic of the drugs, include incompliance, low absorption, high individual response variability, genetic variations, increased platelet turnover, and activation of platelet from other pathway. Experts recommend tailored strategies to overcome antiplatelet resistance: increasing the dosage, adding (such as gylcoproteinIIb/IIIa inhibitor, cilostazol) or substituting with other agent (such as trifusal for aspirin resistance; prasugrel or ticagrelor for clopidogrel resistance), and control the other possible modifiable mechanisms.

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