

Awareness of antiplatelet resistance in patient with repeated episodes of thrombotic events

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Abstract. Antiplatelet has been the cornerstones management of acute coronary syndrome. However, numbers of patients on these agents had episodes of adverse cardiovascular events. A 65-year-old woman post cardiac coronary bypass surgery on dual antiplatelet therapy, Aspirin, and Clopidogrel underwent several episodes of thrombotic events despite good adhered to the daily antiplatelet regimen. These recurrent events had led to clinical suspicious of antiplatelet resistance. Platelet function test was performed which indicates a poor platelet response to Clopidogrel. Clopidogrel was discontinued and Ticagrelor was prescribed together with Aspirin. During two months of follow up, there is no episode of chest discomfort.

1. Introduction

Antiplatelet therapy has been the cornerstone management of acute coronary syndrome and other atherosclerosis vascular disease.[1] The most widely used antiplatelet agents nowadays are Aspirin and Clopidogrel due to low cost and drug availability.[1] However, recurrent ischemic events continue to occur despite combination used of these agents.[2] There has been a concern about the development of resistance to one or both these agents that have emerged from numerous trials conducted over the past decades.[3] This case report describes a case with repeated episodes of thrombotic events in post-cardiac coronary bypass surgery patient on dual antiplatelet therapy (DAPT).

2. Case Presentation

A 65-year-old woman with hypertension was admitted due to exertional angina. Coronary angiography revealed as 80% stenosis in the left main stem, 70-90% diffuse stenosis in distal ostial left anterior descending artery, 80% multiple stenosis in ostio proximal left circumflex artery and 70-90% multiple stenosis in proximal to mid right coronary artery. She successfully underwent cardiac coronary bypass surgery and discharged on DAPT, Aspirin (80 mg daily) and Clopidogrel (75 mg daily) together with antihypertension drug and statin.

Four months later, the patient was readmitted due to acute chest pain. Coronary angiography showed subtotal stenosis in proximal and distal anastomosis saphenous vein graft right coronary artery (SVG-RCA). The patient was considered as unstable angina pectoris and received heparin and DAPT during hospitalization. The patient showed good clinical improvement, DAPT continued and arranged for angioplasty. One month later, she developed another episode of typical angina and underwent



balloon angioplasty. Symptom reduced after intervention and patient continue to receive Aspirin (160 mg daily) and Clopidogrel (75 mg daily).

Despite patient's good adhered to the daily antiplatelet regimen, one year later she developed another episode of acute chest pain, and 2.25x28 mm drug-eluting stent was in SVG-RCA. Two month later, the patient was readmitted due to chest discomfort, and she was anxious about having another episode of the acute coronary syndrome. Electrocardiography showed antero-septal old myocardial infarct, but cardiac enzymes were not elevated (figure 1).

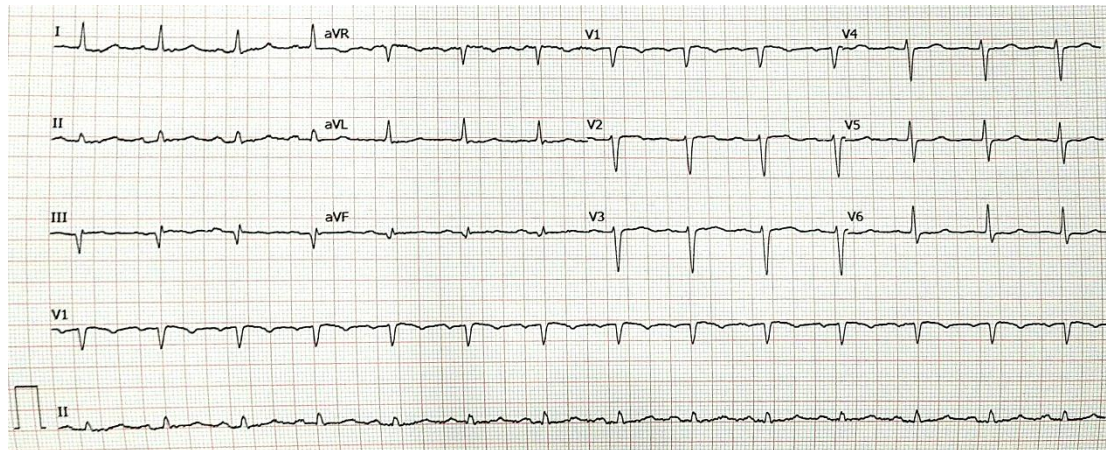


Figure 1. Electrocardiography is on the latest hospital admission.

Repeated episodes of thrombotic events in this patient had led to clinical suspicion of antiplatelet resistance. Platelet function test was with the VerifyNow system (Accumetrics, San Diego, CA, USA). It showed 417 Aspirin reaction unit (ARU) which demonstrate good Aspirin response. While platelet function test for Clopidogrel revealed, 267 P2Y₁₂ reaction units (PRU) indicate a poor platelet response. Thus, it appeared that high residual platelet reactivity was due to Clopidogrel resistance. Therefore, Clopidogrel was discontinued, and Ticagrelor (90 mg BID) was prescribed together with Aspirin. After two months of follow up, the patient did not report any episodes of chest discomfort.

3. Discussions

Thrombosis and restenosis of the coronary stent can manifest as recurrent angina-like symptoms. Several drugs used to prevent these events including Aspirin, Thienopyridines such as Clopidogrel, Prasugrel, Ticagrelor, Ticlopidine or glycoprotein IIb/IIIa inhibitor such as Eptifibatide[2]. However, Aspirin and Clopidogrel are both the most common antiplatelet agents used due to effectiveness, lower cost and drug availability.[4]

The term Aspirin resistance denotes the drug's inability to effectively suppress cyclooxygenase-1 dependent thromboxane A (TxA₂) production.[5] Aspirin resistance is a failure to act on its pharmacologic target originates from variable enteral absorption, cyclooxygenase-1 gene mutation, drug-drug interactions, patient noncompliance, accelerated post cardiopulmonary bypass platelet turn over, and TxA₂-independent platelet activation pathways.[4] The prevalence of Aspirin resistance varies widely in the literature because of variable platelet agonist used in testing and different Aspirin related platelet function descriptors.[4]

Prevalence of Clopidogrel resistance is also various between 5-44%.[6] Clopidogrel is an inactive prodrug that undergoes extensive conversion into a short-lived active metabolite by hepatic cytochrome P450 enzymes (CYP3A4, CYP3A5, and CYP2C19).[4] The active metabolite of Clopidogrel acts by permanently inhibits the P2Y₁₂ adenosine diphosphate (ADP) receptor which is one of the pivotal routes of platelet activation.[3] It also inhibits collagen and thrombin-induced platelet aggregation which can be overcome by increased concentration of these agonists.[6] Thus,

Clopidogrel resistance is the failure of this molecule to inhibit the target of actions.[6] Several mechanisms responsible for Clopidogrel resistance is differences in intestinal absorption, hepatic conversion of active metabolite by cytochrome CYP2C19, and platelet receptor polymorphisms.[6] Clopidogrel resistance should be suspected especially in high risk acute coronary syndrome patients, e.g., diabetic, renal impairment, prior stroke or transient ischemic attack.[4]

A standardized method to evaluate in vivo platelet response is still lacking and not freely available. Aggregometry can evaluate platelet function, flow cytometer or vasodilator-stimulated phosphoprotein phosphorylation test.[2] Light transmission aggregometry (LTA) is considered as the “gold standard” method and has been used in many prospective studies to evaluate response to Clopidogrel and predict cardiovascular events.[7] However, LTA requires equipment and technicians that both time and cost are consuming.[7] VerifyNow system (Accumetrics, Inc., San Diego, CA, USA) is a fully automated, point of care test which is easy to use and can measure platelet response to Clopidogrel in a few minutes. Trials have shown that this assay has a good correlation with LTA and is probably the optimal assay for platelet measurement in a clinical setting because of its potential availability even in catheterization laboratories.[7] Although no definite guidelines are providing a clinical definition of Aspirin and Clopidogrel resistance, it has suggested that Aspirin resistance unit (ARU) level >550 indicates clinically important hyporesponsiveness and this level has been shown to predict post-percutaneous coronary intervention myonecrosis.[1] While suggesting a clinically relevant cut off point of Clopidogrel resistance to predict subsequent negative clinical events based on two recent studies are P2Y₁₂ reaction unit (PRU) 235 or 240.[1]

The assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) registry evaluated the effect of high on-treatment reactivity on clinical outcomes. In patients who received Aspirin and Clopidogrel after drug-eluting stent implantation and showed that Clopidogrel resistance was strongly related to stent thrombosis and myocardial infarction and was inversely related to bleeding.[8] However, this registry demonstrated that high platelet reactivity on Aspirin was not with stent thrombosis, but Aspirin resistance has been reported to depend on drug adherence strongly. In this case, self-reported adherence was good, suggesting that Aspirin resistance was not related to stent thrombosis.

Despite the ability to evaluate platelet functions, there is still no current consensus on how to manage patient's risk of recurrent ischemic events. However, there is increasing evidence of some solution to overcome this situation. The first solution is to increase doses in every patient which provide higher degrees of platelet inhibition.[7] In the Escalating Clopidogrel by Involving a Genetic Strategy (ELEVATE TIMI-56) study, each 75 mg increase in Clopidogrel doses lead to 8-9% absolute reduction in platelet reactivity index.[3] The second solution is to provide either a tailored therapy based on a platelet function test with repeated loading doses of Clopidogrel 600 mg or the use of glycoprotein IIb/IIIa antagonist. The third solution is to use new drugs, which are more potent and have less inter-individual variability.[7] Platelet inhibition can be obtained by inhibiting several platelet receptors, but the P2Y₁₂ receptor has proven to be a key target for the prevention of complication. New drugs which are available are Prasugrel, Elinogrel, Ticagrelor, and Cangrelor but unfortunately, all these alternative agents are expensive.[3] Ticagrelor was the third drug used after Aspirin in the Second International Study of Infarct Survival (ISIS-2) trial and Clopidogrel in the Clopidogrel and Metoprolol in Myocardial Infarction (COMMIT) trial that demonstrate a significant absolute reduction regarding mortality in acute coronary syndrome patients.[7]

The mechanisms of underlying thrombosis are multifactorial include patient-related factors (diabetes mellitus, renal failure), procedural factors (the complexity of the lesion, bifurcating lesions and poor stent expansion and opposition to vessel wall) and post-procedural factors (type and duration of antiplatelet therapy).[8] Insufficient antiplatelet treatment and mechanical problem have two cardinal risk factors for stent thrombosis.

In the case described here, a post-cardiac coronary bypass surgery patient underwent several episodes of recurrent angina-like symptoms that represent repeated thrombosis events. The patient had no history of diabetes or renal impairment and had admitted having good adherence to DAPT. This

condition should alert to the possibility of antiplatelet resistance, and therefore platelet function test should be evaluated. The result from VerifyNow showed insufficient Clopidogrel inhibition suggesting that the absence of P2Y₁₂ inhibitory effect played a crucial role in these thrombotic events. Platelet function test is only available in the limited laboratory in our country, and it might have been the cause of delay to evaluate platelet function test in this patient because this assay still not routinely conducted. Clopidogrel was switched to Ticagrelor as management of Clopidogrel resistance and during two months of follow up no angina-like symptom was reported.

4. Conclusions

This case illustrates the importance to suspect antiplatelet resistance in patients on antiplatelet agents who have repetitive episodes of thrombotic events. Platelet function test should be checked and antiplatelet agent doses tailored or switched accordingly.

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