

Case Report

The individualized antiplatelet therapy following percutaneous coronary intervention: a case report and literature review

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Received May 23, 2017; Accepted May 24, 2018; Epub August 15, 2018; Published August 30, 2018

Abstract: Acute coronary syndrome (ACS), as a significant cardiovascular disease entity, is associated with risks of mortality and morbidity, such as heart failure, myocardial infarction, and ventricular arrhythmia et al. Current guidelines and cardiological experts recommend the antithrombotic therapy, with dual antiplatelet therapy consisting of a low-dose acetylsalicylic acid and ADP P2Y₁₂ inhibitors with clopidogrel, ticagrelor or prasugrel as the first line to reduce the recurrent ischaemic events. As another risk factor for mortality and disability from thromboembolism, atrial fibrillation (AF) brought massive health burdens of the world. The antithrombotic treatment is a particular challenge in patients who present with both AF and ACS. Clopidogrel resistance refers to the occurrence of adverse cardiovascular events despite adequate antiplatelet treatment and compliance. Studies have demonstrated that clopidogrel resistance is related to CYP2C19 gene polymorphism. In our case report, we analysis an atrial fibrillation patient with clopidogrel resistance concurrence ACS following percutaneous coronary intervention. We introduce the diagnosis clopidogrel resistance by LTA and Verifynow, and explicit the CYP2C19 loss of function allele *3 variants might be responsible for clopidogrel resistance. Furthermore, we introduce the adjustment of antiplatelet treatment and the adverse drug reaction in the patient. Finally, under the circumstance of discontinuing clopidogrel, this clopidogrel resistance patient suffered from a cerebral hemorrhage. The optimal individualized antiplatelet therapy in patients with clopidogrel resistance following PCI, especially concurrence atrial fibrillation still need further to be studied.

Keywords: Clopidogrel, VerifyNow antiplatelet assay, CYP2C19 genotype

Introduction

Clopidogrel has been widely recommended by current guidelines in patients undergoing PCI or acute coronary syndrome (ACS). It plays a key role in inhibiting platelet adhesion, activation, and aggression. With the development of clinical studies, it has been pointed out that inter-individual variability in platelet inhibitory response and high on-treatment platelet reactivity (HPR) are primarily associated with the cardiovascular composite endpoints such as death, MI, stent thrombosis, bleeding and other potential side effects. We discuss the clinical application of VerifyNow P2Y₁₂ assay in the evaluation of clopidogrel resistant or high platelet reactivity in patients undergoing PCI. We introduced the hepatic cytochromes (CYP450) enzymes

metabolic pathways of clopidogrel and the pivotal role of CYP2C19 genotype on outcome of clopidogrel therapy. Based on our case and other related clinical studies, we evaluated the composite end point events for the patients with high on-treatment platelet reactivity after stent implantation, especially patients in East Asian.

Case presentation

Clinical data

A 62-year-old coronary heart disease man who had experienced paroxysmal ischemic chest pain for fifteen years came to the cardiology department after an episode of chest pain at ten o'clock on September 12, 2016.

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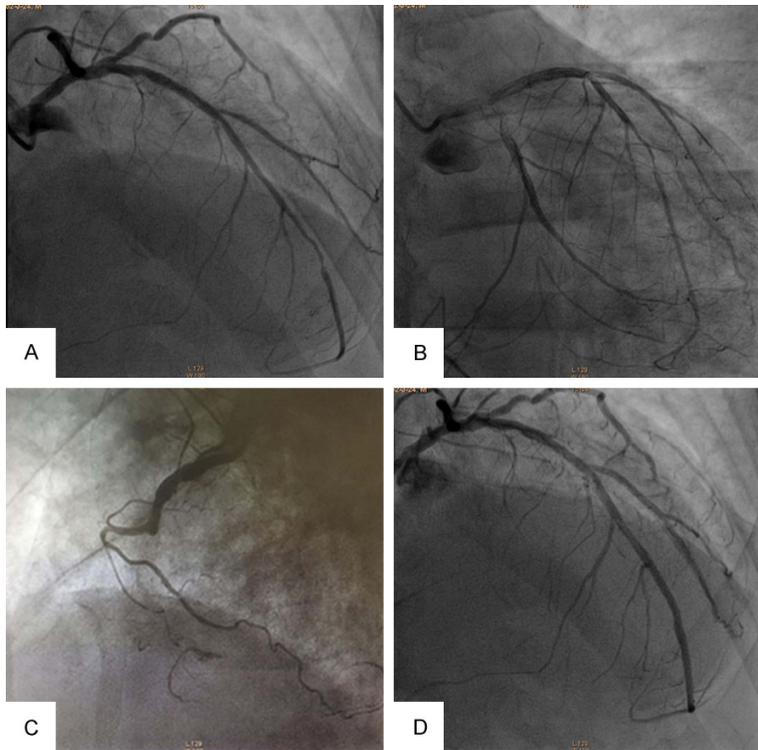


Figure 1. The image of coronary angiography and percutaneous coronary intervention. A. The patency of the stent was on the proximal left anterior descending (LAD), while 90% stenosis of the distal LAD. There is about 90% obstruction of the first diagonal branch of the LAD. B. The stent patency was in the proximal left circumflex coronary artery. There was the complete occlusion in the distal of the left circumflex coronary artery. C. There was restenosis after implantation in the right coronary artery, non-calcified and mixed plaques. There was the complete occlusion in the middle of right coronary artery. D. We implanted a Giwei stent (2.5*28 mm) on the distal left anterior descending (LAD). Angiography revealed a good result at the site of stent deployment. The lesion of the first diagonal branch of LAD were successful crossed with Fielder FC guide wire, and MINI TRED balloon (2.0*15 mm) was performed at the lesion. Angiography revealed a good result at the site of the balloon.

Past history

He had three stents implanted in 2001, three stents implanted in 2008, and one stent implanted in 2014. He was with no history of hypertension and diabetes mellitus. He was without hepatitis and tuberculosis.

Personal history

No history of smoking or drinking.

Course of analysis

His blood pressure at presentation was 100/70 mmHg, heart rate 70 bpm, afebrile, oxygen saturation (SaO₂ 99%). Heart sounds are inten-

sively and no splitting with the rate of 80 bpm. Cardiac rhythm is irregular. No pathological murmurs. His bed side Electrocardiogram (ECG) showed atrial fibrillation. A hemogram showed a high D-dimer 3.46 mg/L and fibrinogen 5.35 g/L. Biochemistry test results revealed renal insufficiency (creatinine 180.9 umol/L), and high total cholesterol 5.22 mmol/L. Creatine kinase-MB (CK-MB) 11 U/L and B-natriuretic peptide (BNP) 2516 pg/ml were also present. He was treated with oxygen, aspirin, beta-blocker, clopidogrel, an intravenous nitrate, et al.

On hospital day 2, the patient underwent coronary angiography on September 13, 2016. The imaging showed (Figure 1) that the patency after left main coronary artery stenting, the patency of the stent of the proximal left anterior descending (LAD), while 90% stenosis of the distal LAD. There is about 90% obstruction of the first diagonal branch of the LAD. The stent patency was in the proximal left circumflex coronary artery. There was the complete occlusion in the distal of the

left circumflex coronary artery. Restenosis after stent implantation was in the right coronary artery with non-calcified and mixed plaques, and the complete occlusion of the middle of right coronary artery. We implanted a Giwei stent (2.5*28 mm) on the distal left anterior descending (LAD). Angiography revealed a good result at the site of stent deployment.

The postoperative patient was given standardization of low molecular weight heparin and followed by antiplatelet therapy with aspirin, clopidogrel and platelet glycoprotein IIb/IIIa inhibitors (tirofiban). We tested the platelet aggregation with the PFA-100 platelet function analyzer in hospital outpatient department (2016-

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10-16). The results showed that ACA 8.6% (55.0-90.0%) and ADP 53.1% (55.0-90.0%). The blood routine examination showed PLT: $240 \times 10^9/L$. According to the severity of coronary artery disease, the incidence of chest distress recently, and the platelet function monitoring by PFA-100 platelet function analyzer, we adjust his antiplatelet therapy using aspirin 100 mg QD + ticagrelor 90 mg BID and other routine treatment (2016-10-16).

Forty days after his discharge (2016-10-24), the patient returned with chest congestion and dyspnea. His blood pressure at presentation was 110/70 mmHg, heart rate 78 bpm, afebrile, oxygen saturation (SpO_2 99%). Respiratory movement is bilaterally symmetric with the frequency of 22/min. No wheezes and no rales were heard. Heart sounds are intensively and no splitting with the rate of 90 bpm. Cardiac rhythm is irregular. No pathological murmurs. There is no articular swelling. We performed a complete echocardiographic examination identifying the patient with left ventricular ejection fraction (EF) about 39% and diffuse hypokinetic left ventricular wall motion and the result was similar with previous one. He discharged from our hospital in 2016-10-27. We thought that dyspnea might be due to the side effect of ticagrelor, so we adjust the antiplatelet agents once again, using aspirin 100 mg QD and clopidogrel 75 mg QD. We tested the platelet function with the VerifyNow antiplatelet assay (2016-11-09). Results showed that P2Y₁₂ reaction unit (PRU) value of 330 (reference range for PRU from 95 to 208 PRU), with the rate of inhibition of 0%, and baseline 329 PRU. The result of VerifyNow platelet-function testing showed the patient with high on-clopidogrel platelet reactivity, which means the patient with clopidogrel resistance. We detected CYP2C19 genotyping for clopidogrel in 2016-11-11, with the result of genetic testing CYP2C19*3/*3 (636AA, 681 GG). We readjusted his antiplatelet therapy using aspirin 100 mg QD + Clopidogrel 75 mg QD + Cilostazol 100 mg BID after discharge from the hospital. We did telephone follow-up after discharge and got feedback that the patient occurred chest distress and fatigue once in a while, without severe chest pains and dyspnoea. The patient came to subsequent visit in 2016-11-21. After the routine assessment, we did the platelet function with the VerifyNow antiplatelet assay (2016-11-

09). Results showed that P2Y₁₂ reaction unit (PRU) value of 276 PRU, with the rate of inhibition of 8%, and baseline 299 PRU. The ECG revealed atrial fibrillation and ST-T change. The patient was instructed in the use of aspirin 100 mg QD + Clopidogrel 75 mg QD + Cilostazol 100 mg BID. We informed him to contact us if he felt discomfort immediately. However, he didn't follow the doctor's advice due to personal reason, stopping Cilostazol and taking clopidogrel irregularly.

He was admitted to our department with an outbreak of dizziness and vomiting for 1 hour in 2017-01-14. The patient said that he felt dizzy and then vomited gastric content after defecation. Physical examination at admission revealed an irregular heart rate of 75 beats/min (bpm), blood pressure 168/80 mmHg, respiratory rate 20 per min. He was conscious. The lungs were clear to auscultation, and heart sounds were intensively and no splitting with the rate of 84 bpm. Bilateral muscle strength is asymmetry and the right side of the limb was graded as grade 4. Bilateral pathological signs were negative. The ECG revealed atrial fibrillation and ST-T change. Cranial CT (2017-01-14): left thalamic hemorrhage breaking into ventricular, left frontal lobe encephalomalacia and brain atrophy. Lung CT: bilateral interstitial pneumonia, upper lobe bronchiectasis, and bilateral pleural effusion. A hemogram showed a high D-dimer 8.26 mg/L and fibrinogen 6.32 g/L. Biochemistry test results revealed renal insufficiency (creatinine 439.9 μ mol/L), and total cholesterol 2.42 mmol/L. Creatine kinase-MB (CK-MB) 14 U/L were also present. After acute consultant, the patient was transferred to the department of neurology for further treatment. He was discharged from neurology department after the specialized treatment.

Diagnosis

The final diagnosis was coronary atherosclerotic heart disease and unstable angina after percutaneous coronary stents placement, with class III systolic heart failure, atrial fibrillation, cerebral hemorrhage, and chronic renal failure.

Discussion

The patient has been treated in our department for several times since 2014. He had

eight stents implanted totally, without a history of hypertension and diabetes mellitus. We did platelet function analysis by LTA and Verifynow after his last percutaneous coronary intervention with stenting. The results showed clopidogrel resistance in this patient. Furthermore, we explicit the CYP2C19 loss of function allele *3 variants might be responsible for clopidogrel resistance. We weight the risk of bleeding and ischemic event by the platelet function analysis and CHA2DS2-VASC/HAS-BLED score. Based on these results, we did adjust the antiplatelet therapy with aspirin + ticagrelor or aspirin + clopidogrel + cilostazol. However, the patient was intolerable to the changes. Due to personal reasons, he did not follow the doctor's advice, stopping Cilostazole and taking clopidogrel irregularly. Finally, this patient with clopidogrel resistance suffered a cerebral hemorrhage.

Recently, we did an observational research about the relationship between platelet reactivity and clinical outcomes in patients following PCI in our cardiology department [ChiCTR-IOR-17013665]. Till now, we included about 100 patients with coronary heart disease undergoing PCI. The preliminary statistical analysis showed that about 30% patients are clopidogrel resistance. In the clopidogrel resistance group, patients are treated with clopidogrel 75 mg QD or ticagrelor 90 mg BID. We evaluated the primary endpoints of aspirin plus clopidogrel and aspirin plus ticagrelor among patients with clopidogrel resistance following PCI. The results showed there was no major bleeding, MACE (defined as death, acute coronary syndrome, stent thrombosis, revascularization et al.) stroke with clopidogrel treatment. It has been accepted that patients in East Asian exist the higher level of platelet reactivity as compared with Westerners. However, the former might has similar rates or lower rates of ischemic outcomes when compared with the later.

The antithrombotic treatment is a well-known challenge for patients who present with atrial fibrillation (AF) and acute coronary syndrome, especially in those who underwent coronary percutaneous intervention with stents (PCIS). Up to now, there is a shortage of randomized trials comparing the safety and efficacy of the antithrombotic treatment triple oral antithrombotic therapy (TOAT: aspirin, clopidogrel, and

warfarin) and dual antiplatelet therapy (DAPT: aspirin and clopidogrel). After searching from the Medline, Embase databases and Cochrane, we found that nine observational trials investigated the effects of DAPT and TOAT among patients with AF concurrent to PCIS [1-9] (**Table 1**).

It is accepted that platelet activation and aggregation play a pivotal role in the pathogenesis of thrombosis and atherosclerotic process. Platelet activation and aggregation may induce not only acute coronary syndrome (ACS) but also major adverse cardiac events (MACE) in patients following coronary angioplasty. Several international guidelines have already recommended dual use of aspirin and clopidogrel for the prevention of ACS and MACE after percutaneous coronary intervention (PCI) [10-13]. It is well known that clopidogrel has a wide variability in platelet responsive. Thought antiplatelet treatment of clopidogrel correctly, there still exists 5-10% of patients experience thrombosis events after percutaneous coronary intervention [14, 15].

In general, clopidogrel resistance refers to the occurrence of adverse cardiovascular events despite adequate antiplatelet treatment and compliance [16, 17]. Clopidogrel resistance also call nonresponsiveness. It has been published several definitions for clopidogrel resistance based on light transmission aggregometry (LTA) assay: <10% absolute decrease in LTA-ADP max from the baseline, or LTA-ADP max value >50% during treatment [18, 19]. Recently, the Verifynow-P2Y12 assay is considered to be a reliable, accurate, sensitive device for clinical monitoring platelet inhibition with clopidogrel [20, 21].

Clopidogrel, a thienopyridine, is a prodrug. In liver, about 15% absorbed clopidogrel is metabolized to an active metabolite by hepatic cytochromes (CYP450) enzymes in a 2-step process. It has been proven that CYP2C19, CYP1A2, CYP2B6 isoenzymes have a critical role in the first step, and CYP2C19, CYP3A4, CYP2C9 play a crucial role for the second step. By irreversibly binding of the P2Y12 ADP receptor on platelet surface, Clopidogrel inhibits the platelet activation and aggregation [22]. Various factors have been implicated in clopidogrel resistance, for example, clinical, cellular, and genetic factors et al. [23, 24]. First, Because of patient noncompliance, clopidogrel treat-

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Table 1. Design and baseline characteristics of the selected clinical trials

Author year	DAPT		TOAT		Clinical Outcome	Median Follow-up years
	Events no.	Total patients no.	Events no.	Total patients no.		
Choi HI, 2017	112	629	16	75	The primary outcome was a composite of cardiovascular mortality, nonfatal MI or nonfatal stroke (from any cause).	6.2
Lamberts M, 2012	725	3,144	269	1,495	The primary outcome was nonfatal or fatal bleeding.	8.0
Kang DO, 2015	42	236	29	131	The primary end point was a 2-year net clinical outcome: A composite of major bleeding and major adverse cardiac and cerebral events.	2.0
Gao F, 2010	67	334	12	136	The primary end point was defined as the occurrence of MACE, including mortality, MI, target vessel revascularization, stent thrombosis or stroke at 12 months.	1.0
Fosbol EL, 2012	922	2,841	187	731	The primary outcome was a major cardiac event within 1 year defined as a composite end point of mortality, hospitalization for recurrent MI or hospital for ischemic stroke.	1.0
Manzano-Fernández, 2008	0	38	2	49	The primary end point was defined as the occurrence of major bleeding complications.	1.0
Maegdefessel L, 2008	18	103	1	14	A combined end point comprised of severe bleeding events, myocardial infarctions, strokes and cardiovascular death.	1.4
Hansen ML, 2010	94	2,859	64	1,261	The primary end point was bleeding. Bleeding was defined as an admission to a Danish hospital with a bleeding diagnosis (primary or secondary), a nonfatal bleeding episode or a diagnosis of bleeding as the cause of mortality.	3.3
Hess CN, 2015	1,173	3,589	446	1,370	The primary outcome was 2-year MACE comprising of mortality, readmission for MI or stroke.	2.0

ment can't continue. Second, Studies have demonstrated that clopidogrel resistance is related to gene polymorphism [25, 26]. Concerning clopidogrel metabolism in health individuals, carriers of a reduced-function allele of CYP2C19 had 30% lower levels of the active clopidogrel metabolite and a 25% relative reduction in platelet inhibition *ex vivo* [27]. It maybe point out that CYP2C19 does affect the pharmacodynamics of clopidogrel in patients as well. In clinical research, patients with acute MI on clinical who sustained subsequent cardiovascular events were more likely to carry CYP2C19 loss-of-function alleles compared to control group, showing an increased effect particularly in patients who underwent PCI [28]. In another study including patients treated with clopidogrel, carriers of a reduced-function CYP2C19 allele had significantly lower levels of the active metabolite of clopidogrel with diminished platelet inhibition and a higher rate of MACE (major adverse cardiovascular events) [29]. The percentage of poor CYP2C19 metabolizer subjects is about 2-4.8% worldwide, with a particularly high incidence of 22.5% among East Asians [30, 31]. Furthermore, the interaction between drug-drug many is associated with the variability in the absorption of clopidogrel. Concerns have been raised about the adverse cardiovascular effects of proton pump inhibitors (PPIs) especially omeprazole in patients receiving clopidogrel [32, 33].

The Verifynow is superior to the conventional platelet assay, for the specific inhibition the platelet aggregation via the ADP-induced P2Y₁ receptor on its surface. As previous recommendation, value >208 P2Y₁₂ receptor units (PRU) was defined as clopidogrel resistance or high on-treatment platelet reactivity [34]. The level of on-treatment high platelet reactivity according to the ADP-P2Y₁₂ assay is related to long-term cardiovascular events in patients following PCI, such as death, MI, and stent thrombosis. It has been accepted recently that a PRU value >208 can well predict death, myocardial infarction or stent thrombosis [35]. It has been indicated that CYP2C19 polymorphism plays a pivotal role in clopidogrel pharmacodynamics and pharmacokinetics. Patients can be divided into four categories based on this clopidogrel metabolism genotype [36, 37]. The first kind is normal metabolizer, which is also called extensive metabolizers (EMs: wild-type for the CYP-

2C19 polymorphisms). The second kind is poor metabolizers (PMs: homozygous or compound heterozygous genotypes for the LOF CYP2C19 polymorphisms). The third is intermediate metabolizers (IMs: heterozygous genotype for the LOF CYP2C19 polymorphisms and wild type of the CYP2C19). The fourth is ultra-rapid metabolizer (UM: heterozygous or homozygous genotype for the CYP2C19*17 and wild type of CYP2C19).

It has been reported that the clopidogrel resistance with CYP2C19-loss-of-function allele may not be overcome through high loading doses and maintenance dose [38-41]. It has been recommended that patients with poor metabolizers should take the new type P2Y₁₂ receptor inhibitor or triple antiplatelet treatment. It is known to all that ticagrelor could interfere with adenosine metabolism, leading to increased adenosine plasma concentration [42, 43]. An increase in adenosine concentration is the reason for dyspnea. Though ticagrelor has been widely used nowadays, we should pay attention to its side effect, especially dyspnoea. The clinical outcome of the patient reminds that East Asian patients might have the different risk profiles for both thromboembolism and hemorrhagic tendency compared with white patients [44, 45]. Though East Asian patients have a higher level of on-treatment platelet reactivity, clinical data signified that the clinical ischemic events with East Asian patients are similar to white patients after PCI [46]. Perhaps, there might be a different 'therapeutic window' of on-treatment platelet reactivity in East Asian patients. It has been reported that increased bleeding risk in patients with impaired renal function [47]. We also speculate that the impaired renal function in this patient with clopidogrel resistance may also contribute to the cerebral hemorrhage.

Finally, with the development of clinical research, we should undertake the evidence-based review to assess the risk of embolism and bleeding, before we determine the race-tailored antiplatelet treatment strategies in patients following PCI or ACS.

Acknowledgements

This study was supported by the Science Fund for Distinguished Young Scholars from the Fourth Affiliated Hospital of Harbin Medical

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University (No:HYDSYJQ201504). The funders had no role in this study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure of conflict of interest

None.

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