Effects of switching ticagrelor to clopidogrel on cardiovascular outcomes in patients with acute coronary syndrome

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Abstract

Present study was to evaluate whether switching ticagrelor to clopidogrel would impact platelet reactivity and cardiovascular outcomes in acute coronary syndrome (ACS) patients after percutaneous coronary intervention (PCI).

A total of 202 ACS patients after PCI were enrolled and prescribed ticagrelor. Before discharge, 138 (68%) patients were switched to clopidogrel. Peripheral blood was obtained before switching and at 48 hours after switching to measure platelet reactivity. Patients were followed for 30 days to evaluate cardiovascular events.

Compared to ticagrelor group, patients in clopidogrel group were more likely to be male (69.6% vs 65.6%), smokers (34.1% vs 31.3%) and had higher prevalence of hypertension (75.4% vs 71.9%). The frequency of right coronary artery lesion was significantly higher in ticagrelor group (34.4% vs 30.4%). There were no significant differences in baseline platelet reactivity (37.6 ± 5.2% vs 38.4 ± 4.9%). Forty-eight hours after switching to clopidogrel, platelet reactivity in clopidogrel group was significantly higher (46.3 ± 5.6% vs 38.1 ± 5.0%, $P < .05$). Patients in clopidogrel group had significantly higher incidence of cardiovascular events (3.6% vs 1.6%, $P < .05$). However, after further adjusted for platelet reactivity at 48 hours of switching, clopidogrel switching was not significantly associated with composite outcomes, with hazard ratio 1.08 (95% confidence interval 0.98–1.21, $P = .063$), indicating that platelet reactivity was a critical mediator between antiplatelet drug switching and cardiovascular outcomes.

ACS patients after PCI treatment, early switching ticagrelor to clopidogrel results in increased platelet reactivity and higher incidence of short-term cardiovascular events.

Abbreviations: ACS = acute coronary syndrome, CYP450 = cytochrome peptide 450, PCI = percutaneous coronary intervention.

Keywords: antiplatelet drugs, cardiovascular events, pharmacodynamics

1. Introduction

After acute coronary syndrome (ACS) or receiving percutaneous coronary intervention (PCI) treatment, patients are required to take dual antiplatelet therapy for 12 months in order to prevent recurrence of cardiovascular events and cardiovascular mortality.[1,2] Of note, aspirin combined a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) is the cornerstone of dual antiplatelet therapy, which is strongly recommended by the recent guidelines for ACS patients.[1,2]

Notably, clopidogrel is a pro-drug which requires to be metabolized into its active form via the cytochrome peptide 450 (CYP450) enzyme systems.[3,4] In contrast, ticagrelor is an active antiplatelet medication which has rapid and potent effects on

platelet inhibition compared to clopidogrel.[5] In addition, recent clinical studies have demonstrated that compared to clopidogrel, ticagrelor has better effects on reducing cardiovascular events and mortality in ACS patients after coronary artery stenting.[6]

Nevertheless, compared to clopidogrel, the expenditure for ticagrelor is much higher and physicians usually have to switch ticagrelor to clopidogrel after acute period of ACS.[7,8] Prior study indicated that in ACS patients, after switching prasugrel to clopidogrel, the on-treatment platelet reactivity was increased.[9] Interestingly, one recent study also indicated that within the first 48 hours of switching, platelet reactivity was found to rebound and be significantly higher in the clopidogrel group compared to the ticagrelor group.[10] However, whether these short-term pharmacodynamic differences would influence cardiovascular outcome is unknown. We, therefore, conducted a prospective study to evaluate whether switching ticagrelor to clopidogrel would impact platelet reactivity and cardiovascular outcomes in ACS patients after PCI treatment. Results from our present study would shed lights into the clinical relevance of the short-term pharmacodynamic changes in relation to anti-platelet drug switching.

2. Methods

2.1. Study design and participants enrolment

This was a prospective, observational and single-center study. Present study was approved by the Clinical Research Ethic Committee of The Third People's Hospital of Huizhou. Informed consent was obtained before enrolment and all participants were

treated in accordance with the Declaration of Helsinki. Participants' enrolments were conducted from October 1, 2017 to January 31, 2018 and the inclusion criteria were as follows: participants were hospitalized for ACS and had received PCI during the indexed hospitalization. Exclusion criteria were as follows: the ACS patients with complicated acute decompensated heart failure, required medical inotrope (dopamine or dobutamine), or intra-aorta balloon pump support, or the ACS patients had arrhythmias with hemodynamic unstable, had coronary artery complication (rupture or aneurysm) during indexed PCI or had major bleeding.

2.2. Data collection

Baseline characteristics including age, gender, smoking status, systolic/diastolic blood pressure (SBP/DBP), and heart rate (HR) at admission were collected by 2 investigators. Risk factors including documented hypertension, diabetes mellitus and dyslipidemia, and history of atrial fibrillation, congestive heart failure, myocardial infarction, ischemic stroke, chronic kidney disease (CKD), and prior PCI or coronary artery bypass graft (CABG) and current medication usages were extracted from electronic health record.

Fasting venous blood was drawn for assessment of low-density lipoprotein cholesterol (LDL-C), glycated hemoglobin A1c (HbA1c), serum reatinine (Scr), high sensitivity cardiac troponin-I (Hs-CTnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.

2.3. Antiplatelet medications usage and platelet reactivity evaluation

At admission, all ACS patients were prescribed a loading dose of ticagrelor (180 mg) and then continued on maintenance dose of ticagrelor (90 mg twice daily) before discharge. Blood samples were collected to evaluate baseline platelet reactivity before switching ticagrelor to clopidogrel. Patients were informed of the potential harms and benefits of medications switching, and whether acceptance of switching ticagrelor to clopidogrel was at the patient's discretion. Those switching to clopidogrel would take 300 mg loading dose of clopidogrel at 12 hours after the final dose of ticagrelor and then continues on 75 mg clopidogrel daily as a maintenance dose. Forty-eight hours later, patients were required to come back to hospital for blood sampling to evaluate platelet reactivity after switching. Platelets from peripheral blood were stimulated with adenosine diphosphate (10 μmol/L) and the absolute reduction in maximal platelet aggregation from baseline (ΔMPA)[11] were reported and compared.

2.4. Study endpoints

Participants were followed for 30 days after discharge via phone call or at outpatient clinic. Ischemic event included non-fatal myocardial infarction, non-fatal ischemic stroke, definite stent thrombosis, and cardiovascular death. Bleeding events included intracranial hemorrhage and gastrointestinal bleeding. Study endpoints were adjudicated by 1 independent cardiologist who was unaware of the usage of antiplatelet medications. Composite
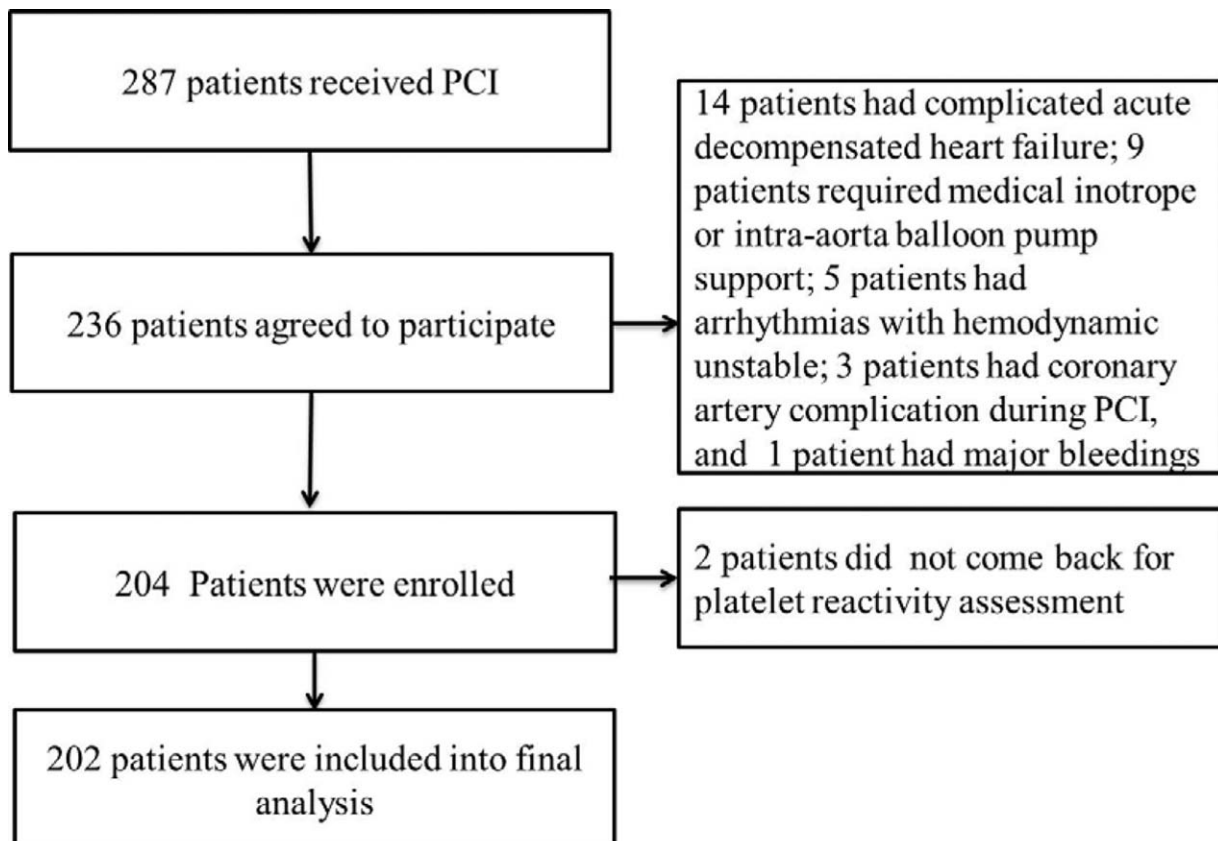

Figure 1. Research schematic.

study endpoints comprise both ischemic events and bleeding events.

2.5. Statistical analysis

Continuous variables were expressed as mean ± SD or median (interquartile ranges) and categorical variables were expressed as number and frequency of cases. Between-group differences were evaluated by the independent Student t test or the Mann–Whitney U test for continuous variables, or the Chi-square analysis or Fisher exact tests for the categorical variables as appropriate. Cox proportional hazards regression analysis was used to evaluate the association of clopidogrel switching and composite study endpoints. Statistical analysis was conducted in SPSS 23.0 (IBM). All P values were 2 sides, and statistical significance was defined as $P < .05$.

3. Results

3.1. General characteristics

A total of 287 ACS patients had received PCI in our hospital during enrolment period and 236 patients agreed to participate in our study. After exclusion of 32 patients, 204 patients were recruited. Two patients did not come back for platelet reactivity assessment after discharge and no patients were loss of follow-up. Therefore, 202 patients were included into final analysis (Fig. 1).

Among the 202 ACS patients, 138 patients (68%) were switched to clopidogrel and the others remained on ticagrelor treatment. General characteristics were compared (Table 1). Compared to the ticagrelor group, patients in the clopidogrel group were more likely to be male and current smokers and had higher prevalence of hypertension. No significant between-group differences in other general characteristics were observed. Before PCI treatment, nearly 19.6% and 20.3% of patients in both groups were taking clopidogrel and none was on ticagrelor treatment.

3.2. Baseline procedure characteristics

Baseline procedure characteristics were compared and as represented in Table 2, the frequency of right coronary artery lesion was significantly higher in the ticagrelor group compared to the clopidogrel group (34.4% vs 30.4%), and no other significant between-group differences were observed. Of note, the mean numbers of stent implantation in both groups were 1.8 versus 1.7 and most of the stents implanted were drug eluting stents.

3.3. Platelet reactivity assessment

The duration of patients treated with ticagrelor before baseline platelet reactivity assessment was 4.1 ± 0.3 days in clopidogrel group versus 4.2 ± 0.3 days in ticagrelor group. As shown in the Figure 2, there were no significant differences in baseline platelet reactivity in both groups (37.6 ± 5.2% versus 38.4 ± 4.9%). Forty-eight hours after switching to clopidogrel, the platelet reactivity in the clopidogrel group was increased, which was significantly higher than that in the ticagrelor group (46.3 ± 5.6% vs 38.1 ± 5.0%, $P < .05$).

3.4. Endpoints at 30 days

Patients were followed for 30 days after discharge and study endpoints were compared. As presented in the Table 3, compared to the ticagrelor group, patients in the clopidogrel group were

Table 1

General characteristic comparison.

Variables	Clopidogrel group (n = 138)	Ticagrelor group (n = 64)
Age, years	51.8 ± 12.4	50.5 ± 13.7
Male, n, %	96 (69.6)[*]	42 (65.6)
Current smoker, n, %	47 (34.1)[*]	20 (31.3)
Systolic BP, mm Hg	139 ± 24	137 ± 22
Diastolic BP, mm Hg	70 ± 18	71 ± 15
Heart rate, bpm	85 ± 16	87 ± 15
Hypertension, n, %	104 (75.4)[*]	46 (71.9)
Diabetes mellitus, n, %	50 (36.2)	23 (36)
Dyslipidemia, n, %	68 (49.3)	31 (48.4)
HbA1c, %	6.6 ± 1.4	6.6 ± 1.1
LDL-C, mmol/L	5.0 ± 0.7	4.9 ± 0.8
Creatinine, μmol/L	79.6 ± 15.8	80.8 ± 14.7
Hs-CTnI, ng/L	24.6 ± 10.3	22.5 ± 9.4
NT-proBNP, pmol/L	265.6 ± 84.6	257.3 ± 69.4
eGFR, 1.73m²/mL/min	82.5 ± 14.3	81.1 ± 13.7
h/o MI, n, %	8 (5.8)	4 (6.3)
h/o ischemic stroke, n, %	6 (4.3)	3 (4.7)
h/o PCI, n, %	13 (9.4)	7 (10.9)
h/o CABG, n, %	None	None
h/o Af, n, %	3 (2.2)	1 (1.6)
h/o CKD, n, %	8 (5.8)	3 (4.7)
Aspirin, n, %	119(86.2)	55(85.9)
Clopidogrel, n, %	27(19.6)	13(20.3)
Statins, n, %	30(46.9)	66(47.9)
Beta-blocker, n, %	90(65.2)	42(65.6)
ACEi/ARB, n, %	84(60.9)	38(59.3)
Anti-diabetes, n, %	46(33.3)	21(32.8)

[*] $P < .05$ versus ticagrelor group, ACEi/ARB = angiontensin converting enzyme inhibitor/angiotensin receptor blocker, Af = atrial fibrillation, BP = blood pressure, bpm = beat per minute, CABG = coronary artery bypass graft, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, h/o = history of, HbA1c = glycated hemoglobin, Hs-CTnI = high sensitivity cardiac troponin-I, LDL-C = low density lipoprotein-cholesterol, MI = myocardial infarction, NT-proBNP = N-terminal pro-brain natriuretic peptide, PCI = percutaneous coronary intervention.

more likely to have non-fatal myocardial infarction and definite stent thrombosis although there was no statistical significance. In the composite study endpoints, patients in the clopidogrel group had significantly higher incidence of events compared to patients in the ticagrelor group (3.6% vs 1.6%, $P < .05$). In specific, in the clopidogrel group, 3 patients had non-fatal myocardial infarction and 2 patients had stent thrombosis and no bleeding events occurred. While no ischemic events and 1 bleeding event occurred in the ticagrelor group.

In the Cox proportional hazards regression model 1, after adjusted for age, male gender, smoking status, hypertension, vessel lesions location, number of stent implantation and stent diameter and length, clopidogrel treatment was significantly associated with the composite endpoints, with hazard ratio 1.20 (95% confidence interval 1.14–1.48, $P = .019$). However, after further adjusted for the platelet reactivity at 48 hours of switching, clopidogrel treatment was not significantly associated with the composite endpoints, with hazard ratio 1.08 (95% confidence interval 0.98–1.21, $P = .063$), indicating that platelet reactivity was a critical mediator between antiplatelet drug switching and cardiovascular outcomes.

4. Discussion

Our current study shows that in ACS patients after coronary artery stenting, switching ticagrelor to clopidogrel results in

Table 2

Baseline procedure characteristics.

Variables	Clopidogrel group (n = 138)	Ticagrelor group (n = 64)
Lesion		
LM, n, %	3 (2.2)	1 (1.6)
LAD, n, %	66 (47.3)	30 (46.9)
LCX, n, %	31 (22.5)	14 (21.9)
RCA, n, %	42 (30.4) *	22 (34.4)
Contrast, mL	76.5 ± 15.7	75.2 ± 14.3
DES, n, %	130 (94.2)	60 (93.8)
Number of stent	1.8 ± 0.6	1.7 ± 0.5
Stent length, mm	25.4 ± 4.6	26.1 ± 5.8
Stent diameter, mm	2.7 ± 0.5	2.7 ± 0.7

* $P < .05$ versus ticagrelor group; DES = drug eluting stent, LAD = left anterior descending, LCX = left circumflex, LM = left main, RCA = right coronary artery.

platelet activity rebound which is consistent to prior reports.[9,10] In addition, our current study also indicates that the short-term pharmacodynamics change is associated with increased short-term risk of cardiovascular events. However, after adjusting for the platelet reactivity, clopidogrel switching is not significantly associated with cardiovascular outcomes, suggesting that platelet activity increase after switching ticagrelor to clopidogrel may mediate the association between clopidogrel switching and short-term cardiovascular outcomes.

Notably, dual antiplatelet therapy profoundly reduces stent thrombosis and restenosis and cardiovascular events.[12,13] In the last 2 decades, clopidogrel combined aspirin is the mainstay of dual antiplatelet therapy for ACS patients and those receiving coronary artery stenting. However, accumulating evidence has demonstrated that a substantial portion of patients is resistant to clopidogrel treatment due to their loss-of-function of CYP450 2C19 gene,[3,4,11] which plays a major role in converting

clopidogrel into its active metabolites. In recent years, 2 novel oral antiplatelet medications, namely prasugrel, and ticagrelor, have been demonstrated to be superior to clopidogrel in inhibiting platelet activity.[14,15] In addition, 2 milestone randomized clinical trials also demonstrated that both prasugrel and ticagrelor are better than clopidogrel in reducing cardiovascular events and mortality in ACS patients after PCI treatment.[6,16] Therefore, both the recent ACC/AHA and ESC guidelines have recommended prasugrel and ticagrelor as the preferred anti-platelet medications for patients with ACS.[1,2] However, the expenditure of the novel antiplatelet medications is much higher than clopidogrel and many patients have to switch to clopidogrel for chronic antiplatelet treatment.

Interestingly, in 2013, Kerneis et al [9] reported that ACS patients treated with prasugrel had low on-treatment platelet reactivity, indicating that early switching prasugrel 10 mg to clopidogrel 75 mg put the patients at increased risk of platelet reactivity rebound. In another study conducted by Franchi et al,[10] they also observed that in patients with coronary artery disease, de-escalation from ticagrelor to clopidogrel is associated with an increase in platelet reactivity. These 2 studies demonstrate that early switching potent antiplatelet medications to clopidogrel results in impaired inhibition of platelet activity. However, whether this pharmacodynamics change is related to cardiovascular outcomes is unclear. Our present study also observed that in the Chinese populations, early switching ticagrelor to clopidogrel is associated with increased platelet activity. Due to the higher prevalence of loss-of-function of CYP450 2C19 gene in the Asians compared to the Caucasians,[17,18] one may anticipate that the percentages of patients with platelet activity rebound might be even higher than that of Caucasians after switching.

Beyond the pharmacodynamics changes, we also observed that antiplatelet medications switching is associated with short-term
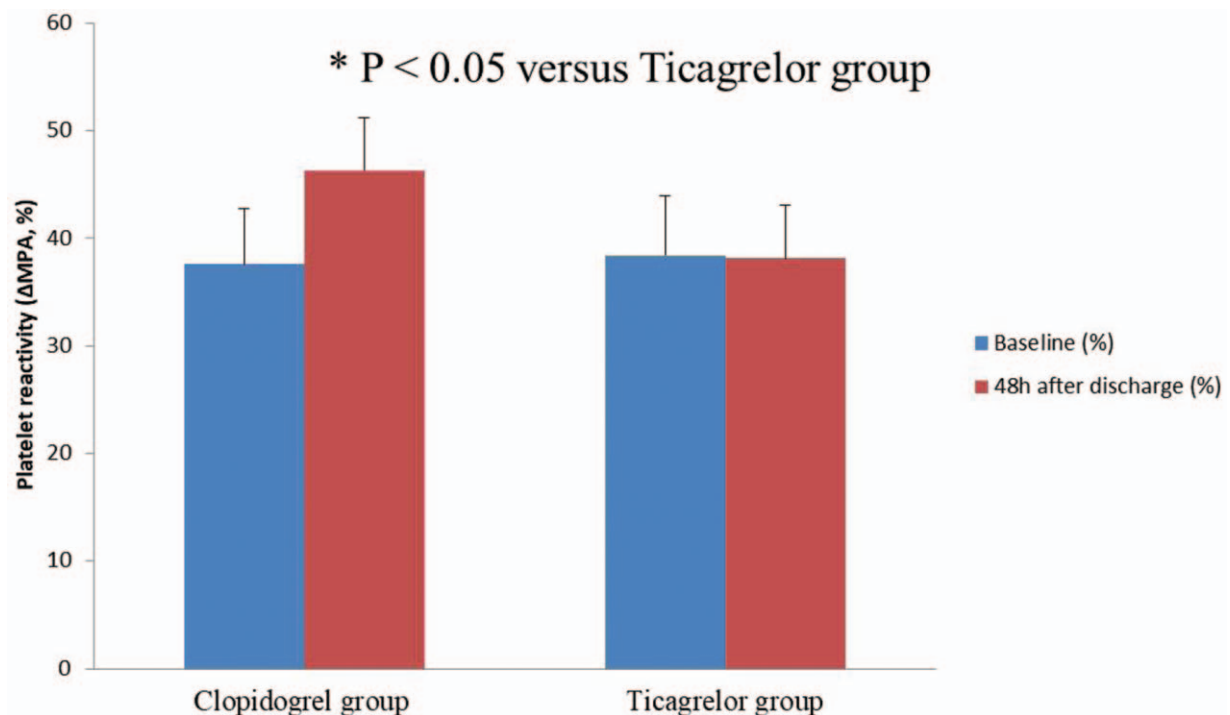

Figure 2. Comparison of platelet reactivity.

Table 3

Endpoints at 30 days.

Variables	Clopidogrel group (n = 138)	Ticagrelor group (n = 64)
non-fatal MI, n, %	3 (2.2)	0
non-fatal ischemic stroke, n, %	0	0
Stent thrombosis, n, %	2 (1.4)	0
Cardiovascular death, n, %	0	0
Intracranial hemorrhage, n, %	0	0
Gastrointestinal bleeding	0	1 (1.6)
Composite study endpoints	5 (3.6)[*]	1 (1.6)

[*] $P < .05$ versus ticagrelor group; MI = myocardial infarction.

cardiovascular outcomes. We found that compared to the ticagrelor group, patients in the clopidogrel group have higher incidence of non-fatal MI and stent thrombosis. In the Cox proportional hazards regression model, before adjusted for platelet reactivity, clopidogrel switching is independently associated with 20% higher risk of composite cardiovascular outcomes. However, after adjusted for platelet reactivity, the associated is attenuated to statistical insignificance. These findings suggest that insufficient inhibition of platelet activity after switching is associated with increased risk of cardiovascular events, and short-term pharmacodynamics changes may translate into significant impact on cardiovascular outcomes. One patient in the ticagrelor group has gastrointestinal bleeding which was due to duodenal ulceration and treated with proton pump inhibitor without interruption of ticagrelor treatment.

The prospective design and follow-up for cardiovascular outcomes are the strengths of our present study. However, there are some limitations should be addressed. First, the inherent biases related to the non-randomized and open-label design could influence the association of medication switching and cardiovascular outcomes. Although we have extensively adjusted for potential biases, undetected and unmeasured biases could still exist and future randomized double-blind trials are warranted to corroborate our findings. Second, the relatively small sample size and short-term follow-up could not allow us to observe more cardiovascular events, and whether the pharmacodynamics changes could impact long-term cardiovascular outcomes is unknown. Last but not the least, results from Chinese populations may not be extrapolated to other population group due to the difference in prevalence of loss-of-function of CYP450 2C19 gene.

5. Conclusion

In summary, our study indicates that in ACS patients after coronary artery stenting, early switching ticagrelor to clopidogrel results in increased platelet reactivity and higher incidence of short-term cardiovascular events.

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Resources: Sigan Zhong.
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Writing – original draft: Lin Liu.
Writing – review & editing: Chun Xiao.

References

[1] Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 2016;134:e123–55.

[2] Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213–60.

[3] Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009;119:2553–60.

[4] Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009;302:849–57.

[5] Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol 2015;12:30–47.

[6] Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.

[7] Kohli P, Cannon CP. Acute coronary syndromes in 2011: Walking the tightrope between efficacy and bleeding. Nat Rev Cardiol 2011;9:69–71.

[8] Nikolic E, Janzon M, Hauch O, et al. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. Eur Heart J 2013;34:220–8.

[9] Kerneis M, Silvain J, Abtan J, et al. Switching acute coronary syndrome patients from prasugrel to clopidogrel. JACC Cardiovasc Interv 2013;6:158–65.

[10] Franchi F, Rollini F, Rivas RJ, et al. Pharmacodynamic effects of switching from ticagrelor to clopidogrel in patients with coronary artery disease: results of the SWAP-4 study. Circulation 2018;137:2450–62.

[11] Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354–62.

[12] Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation 2007;116:745–54.

[13] Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62:2261–73.

[14] Saucedo JF, Angiolillo DJ, DeRaad R, et al. Decrease in high on-treatment platelet reactivity (HPR) prevalence on switching from clopidogrel to prasugrel: insights from the switching anti-platelet (SWAP) study. Thromb Haemost 2013;109:347–55.

[15] De Luca L, Leonardi S, Cavallini C, et al. Contemporary antithrombotic strategies in patients with acute coronary syndrome admitted to cardiac

care units in Italy: The EYESHOT Study. Eur Heart J Acute Cardiovasc Care 2015;4:441–52.

[16] Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

[17] Jeong YH, Tantry US, Kim IS, et al. Effect of CYP2C19*2 and *3 loss-of-function alleles on platelet reactivity and adverse clinical events in East Asian acute myocardial infarction survivors treated with clopidogrel and aspirin. Circ Cardiovasc Interv 2011;4:585–94.

[18] Tang XF, Wang J, Zhang JH, et al. Effect of the CYP2C19 2 and 3 genotypes, ABCB1 C3435T and PON1 Q192R alleles on the pharmacodynamics and adverse clinical events of clopidogrel in Chinese people after percutaneous coronary intervention. Eur J Clin Pharmacol 2013;69:1103–12.