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A Review of the Role of the Antiplatelet Drug Ticagrelor in the Management of Acute Coronary Syndrome, Acute Thrombotic Disease, and Other Diseases

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCE **Luyuan Tao**
BC **Shijia Ren**
CD **Li Zhang**
CDF **Wenhua Liu**
F **Yi Zhao**
C **Changgong Chen**
B **Xiang Mao**
FG **Zili Chen**
A **Xingjian Gu**

Department of Cardiology, Taizhou First People's Hospital, Huangyan, Taizhou, Zhejiang, PR China

Corresponding Author: Xingjian Gu, e-mail: xingjian1967@sina.com

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P2Y12 inhibitors, including aspirin, are key components of dual-antiplatelet therapy (DAPT), which is the optimal therapeutic strategy for preventing arterial thrombosis in patients with acute coronary syndromes (ACS) who underwent stent implantation. Ticagrelor is a cyclopentyl-triazole pyrimidine antiplatelet drug that was the first reversible oral P2Y12 receptor antagonist. Compared with clopidogrel, ticagrelor exerts a faster onset and offset of function by reversible and selective inhibition of platelet aggregation in ACS patients, including those with coronary artery blood revascularization. Despite improvement in stent materials, stent thrombosis (ST) due to high on-treatment platelet reactivity (HPR) to clopidogrel continues to occur. In addition to antiplatelet aggregation, ticagrelor displays pleiotropic cardioprotective effects, including improving coronary blood flow, reducing myocardial necrosis after an ischemic event, and anti-inflammatory effects. The benefits of ticagrelor over clopidogrel were consistent in the PLATO results, with lower incidence of the primary endpoint. Also, in 2020, the findings from the phase 3 THALES trial (NCT03354429) showed that aspirin combined with 90 mg of ticagrelor significantly reduced the rates of stroke and death compared with aspirin alone in patients with AIS or TIA. Here, we review recent research on the superiority of ticagrelor over clopidogrel, discuss the pharmacological mechanism, and present future perspectives. This review aims to present the roles of ticagrelor in the management of acute coronary syndrome, acute thrombotic disease, and other diseases.

Keywords: **Acute Coronary Syndrome • Clopidogrel • Dual Anti-Platelet Therapy • Ticagrelor**

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Background

Acute coronary syndrome (ACS), including ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and unstable angina pectoris, is a common cardiovascular disease with high sudden death rate and serious morbidity. Dual-antiplatelet treatment (DAPT) is the cornerstone of treatment for ACS patients, regardless of whether percutaneous coronary intervention (PCI) is administered. The atherosclerotic plaque rupture activates platelet aggregation, resulting in arterial thrombosis, a pathological basis for ACS [1]. While contributing to development of thrombosis, activated platelets further trigger the release of various inflammatory factors, promoting the progression of atherosclerosis.

Aspirin is the first antiplatelet drug that was developed to irreversibly block platelet-induced cyclooxygenase (Cox)-1 enzyme for inhibiting the formation of thromboxane-A2, an effective agonist of platelet aggregation and vasoconstrictor [2]. P2Y12 receptor antagonists are another commonly used class of antiplatelet agents, including thiophene pyridine (clopidogrel and prasugrel) and non-thiophene pyridine (ticagrelor). According to the guidelines, PCI is strongly recommended in high-risk ACS patients [3]. Notably, successful PCI will enhance these benefits as well as the treatment of DAPT [4]. The P2Y12 receptor antagonist could prevent stent thrombosis or restenosis by effectively inhibiting the superimposing of platelet-rich thrombus [5]. At present, aspirin combined with a P2Y12 receptor antagonist is a fundamental treatment for patients with ACS or coronary stent implantation [6]. Since 1997, clopidogrel has been recommended by the Food and Drug Administration as a standard P2Y12 receptor antagonist. However, clinical trials have demonstrated that approximately 25-50% of patients have poor response to clopidogrel, and high platelet residual activity can still be detected in patients receiving sufficient and regular medication [7-9]. In this case, a 2- to 6-fold increase in the risk of a variety of thrombotic events has been found in patients with poor response to clopidogrel as compared to those with normal response; this phenomenon is clinically referred to as high platelet reactivity in treatment (HRP) [10-12].

Recently, large-scale clinical trials have shown that the new P2Y12 receptor antagonists ticagrelor and prasugrel are more effective than clopidogrel in inhibiting platelet aggregation and are significantly better at reducing the incidence of ischemic events [13,14]. Ticagrelor, which was approved for use in the United States in 2011, is a non-thienopyridine, reversible inhibitor of adenosine diphosphate (ADP) receptors (P2Y 12) on platelets and is used to decrease the risk of recurrent coronary thromboses in patients who undergo interventions during an acute coronary syndrome. Ticagrelor is available in 90-mg tablets under the commercial name Brilinta. The usual maintenance dose is 90 mg twice daily in combination with daily low-dose aspirin (<100 mg). Meanwhile, studies such as the THALES trial (NCT03354429) [15], 2020 ESC Guidelines [16], Triton-TIMI 38 [17], TRILOGY-ACS Trials [17], ONSET/OFFSET [18], and PLATO [17,19] provided more evidence that ticagrelor and prasugrel are superior to clopidogrel. For patients with ACS, ticagrelor is currently recommended as a first-line antiplatelet agent [20-22]. However, 2 other large randomized controlled trials (RT) [23,24] and 2 observational trials (OBS) [25,26] found that compared with clopidogrel, ticagrelor did not significantly reduce the incidence of ischemic events. Furthermore, comprehensive meta-analyses have revealed that antagonistic effects of ticagrelor in some categories of patients, which involve many interference factors, may have some limitations, while there exist controversies regarding the safety and practical efficacy of this novel oral ADP receptor antagonist [27,28]. Based on the controversial data on the efficacy and safety of ticagrelor, the present article briefly reviews pharmacokinetics, pharmacodynamics, clinical indications, and adverse effects of P2Y12 antagonists, while presenting the latest evidence that ticagrelor is superior to clopidogrel. We also discuss various guidelines and reviews of clinical studies in which P2Y12 receptor antagonists were reasonably selected for ACS patients in dual-antiplatelet treatment. This review aims to present the roles of ticagrelor in the management of acute coronary syndrome, acute thrombotic disease, and other diseases.

Mechanisms

Ticagrelor, a cyclopentolate triazolopyridine, is thought to be a nucleoside analog with a structure similar to that of adenosine [2]. While being a new oral P2Y12 receptor antagonist with direct action and reversible binding, ticagrelor itself is an active drug with an average absolute bioavailability of 36%, which is not affected by cytochrome P450 (cytochrome P450, CYP) 2C19 genotype [29]. Compared with clopidogrel, ticagrelor displayed a faster onset of action after a loading dose with 30 min, inhibiting 88% of platelets at 2 h [2], with a half-life of 10.9-14.9 h [30]. Ticagrelor was absorbed rapidly with no effect by food, degrading to a major active metabolite. Ticagrelor and its active metabolite with high plasma protein binding rate have linear pharmacokinetics showing no clinically significant effect of body weight, sex, race, or smoking. Clopidogrel is a thiophene pyridine that irreversibly inhibits platelet adenosine diphosphate (ADP) receptors to prevent platelet aggregation induced by activated platelets-released ADP. Clopidogrel is a drug precursor that is metabolized by liver cytochrome p450 enzymes into active metabolites with irreversible binding to the p2Y12 receptor. The presence of very low plasma concentration of the original drug clopidogrel is attributed to its rapid metabolization in the liver, which leads to a peak concentration of blood levels of the drug in 1 h and a half-life of plasma clearance at 7-8 h. Compared with clopidogrel, ticagrelor exerts

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a faster and stronger inhibition of platelet aggregation, especially in cases of ACS and emergency PCI [31,32].

Improving Coronary Blood Flow

Use of a high level of adenosine in ticagrelor treatment was hypothesized to optimize preconditioning, possibly decreasing infarct size and preventing sudden cardiac death [33]. Furthermore, human and animal studies have shown that ticagrelor reduced the contraction of the great and small arteries induced by 2-Mes-ADP, probably improving coronary vasospasm. This observation demonstrated a unique property of ticagrelor, which has not been found in the case of prasugrel or clopidogrel [34,35]. In addition to inhibiting P2Y12, ticagrelor has other biological effects on increasing coronary blood flow. It has been shown that ticagrelor enhances adenosine-induced coronary flow in a canine model [36] and normal healthy volunteers based on transthoracic Doppler echocardiography compared with placebo [37], as well as in ACS patients as compared to prasugrel [38]. Meanwhile, due to inhibition on adenosine uptake via human erythrocytes [36], ACS patients receiving ticagrelor displayed a higher endogenous adenosine plasma level (APL) than those taking clopidogrel [39,40]. It was reported that adenosine could alleviate ischemia/reperfusion injury of the peri-infarct myocardium [41]. Ticagrelor could reduce ischemia-related arrhythmic events or salvage jeopardized tissue in ACS by augmenting APL. Patients with stable CAD treated with ticagrelor exhibited augmented global coronary flow induced by adenosine compared with those receiving clopidogrel [42]. In a ticagrelor group, these benefits were present in areas with impaired myocardial blood flow reserve, achieving equal effect to both medium and high doses of adenosine [42]. Compared with placebo, ticagrelor significantly increased adenosine-induced coronary blood flow velocity (CBFV) [37]. Ticagrelor also exerts many more functions, such as improving coronary blood flow after PCI with coronary artery chronic total occlusion (CTO) [43].

Reducing Myocardial Infarction Area

Ticagrelor can reduce myocardial infarct size, whereas clopidogrel cannot. Treatment with ticagrelor leads to activation of adenosine-receptor as well as downstream upregulation of cyclooxygenase-2 (COX2) and endothelial nitric oxide synthase, exerting an important myocardial-protective effect [44]. Adenosine is a key mediator of protection against myocardial ischemia-reperfusion injury, while forming a basis for the myocardial protection via various pharmacological and ischemic preconditioning [45,46]. Statins can activate the conversion of adenosine monophosphate into adenosine induced by ecto-5' nucleotidase [47] and reduce infarct size (IS) via adenosine-receptor activation [45,46,48]. Moreover, the myocardial-protective effects of statins are dependent of the activation of cyclooxygenase-2 (COX2) [49-51]. As specific inhibitors of COX2, statins exhibit IS-limiting effects that can be abrogated by high-dose aspirin [50,52]. It was recently suggested that the potential interaction between high maintenance doses of aspirin and ticagrelor [53,54] may underlie the association between some of the myocardial benefits of ticagrelor and COX2 activity, which can be attenuated by higher doses of aspirin [55]. Patients with multivessel coronary disease undergoing PCI who received ticagrelor or prasugrel had smaller total infarct size and lower rate of microvascular obstruction (MVO) based on cardiac magnetic resonance (CMR) imaging than those receiving clopidogrel. These findings may give a reasonable explanation of clinical outcomes with the antiplatelet agents of third-generation agents compared to clopidogrel [56]. In another substudy, ticagrelor was associated with lower MVO incidence and smaller infarct size [56], and another randomized trial presented the same results [57].

Reducing High On-Treatment Platelet Reactivity

Although DAPT has achieved greater efficacy, especially in patients with stent implantation, a substantial proportion of patients receiving such therapy still experience recurrent ischemic events [58], which is attributed to the difference in pharmacodynamic response among clopidogrel-treated patients [59-61]. As a two-edged sword, the variability of pharmacodynamic response to P2Y12 receptor inhibitors has placed hyporesponsive patients at risk for thrombotic events, while creating a potential risk of bleeding in hyperresponsive patients [62]. Both Matetzky et al [59] and Bliden et al have reported a connection between low response to clopidogrel and HPR to adenosine diphosphate (ADP) in ischemic events. The relationship between HPR and thrombotic events following PCI has been well documented in several large studies. HPR related to short-term thrombotic events, such as acute and subacute stent thrombosis, has been detected in patients with stent implantation [59,63-69]. Multiple studies have demonstrated that ADP-stimulated platelet function provides significant prognostic information for patients who received clopidogrel treatment [70-74]. The PLATO substudy showed that for ACS treatment, ticagrelor displays greater activities in activation of antiplatelet in the first hours of therapy or during maintenance treatment than clopidogrel [32]. A prospective randomized study reported that, compared with clopidogrel, prasugrel and ticagrelor exert similar levels of P2Y12 inhibition and reduce HPR rates. The ONSET/OFFSET study [18] indicated that ticagrelor displays faster and greater platelet inhibition than clopidogrel. Several studies on Hispanic, Chinese, and Black patients found that during both the loading dose and maintenance dose, ticagrelor achieves a more rapid and

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greater antiplatelet effect in patients with ACS or stable coronary artery disease than does clopidogrel [75-78]. Ticagrelor exerts highly effective platelet inhibition and overcomes HPR in high-risk coronary patients who have HPR with clopidogrel treatment [79]. Compared with clopidogrel, ticagrelor causes more prompt and potent inhibition of platelets, as well as lower HPR rates in low-risk ACS patients undergoing PCI [80]. In a Chinese study of 102 patients with acute myocardial infarction [81], 48 patients with HPR were randomly assigned to either a ticagrelor group or a high-dose clopidogrel group for 24 h, and the ticagrelor group had lower platelet reactivity than the high-dose clopidogrel group. Two other studies [82,83] have shown that tailored DAPT can ameliorate the antiplatelet response in patients with HPR, possibly reducing thrombotic events and causing no increased risk of bleeding.

Reducing Ischemia-Reperfusion Injury and Improving Cardiac Function

Studies on animal models revealed that compared with clopidogrel, ticagrelor can better protect against myocardium reperfusion injury and improve myocardial remodeling. In the pig models [84], pigs underwent different treatments such as ticagrelor (180 mg; 90 mg/bid), clopidogrel (600 mg; 75 mg/qd), and placebo-control. Compared with the control group, the 2 P2Y12 antagonists reduced infarct size at day 3 after treatment, and there was a further 5% reduction in the ticagrelor group ($P<0.05$ vs clopidogrel). Notably, a reduction of edema (≈23%) associated with smaller scar size was evident in the ticagrelor group at day 42 after treatment. The ejection fraction (EF) of the left ventricular was increased in the ticagrelor group 3 days after MI, and high EF lasted up to day 42. There was extensive and severe abnormal wall motion in the control and clopidogrel groups, as well as reduced myocardial viability in the jeopardized myocardium due to lower myocardial AMPK and Akt/PKB activation with decreased aquaporin-4 levels, but these abnormalities were absent in the ticagrelor group. Similarly, another study [85] reported that ticagrelor reduced the infarct size in a dose-dependent manner by decreasing apoptosis and increasing myocardial levels of adenosine, endothelial NO synthase, phosphorylated Akt, and ERK 1/2, while clopidogrel had no such effects. In addition, ticagrelor improved EF 4 weeks after ischemia/reperfusion by attenuating fibrosis and decreasing the mRNA level of collagen-III, but clopidogrel did not. Moreover, ticagrelor decreased the levels of interleukin-1β, proinflammatory tumor necrosis factor-α, and interleukin-18, while increasing the levels of anti-inflammatory 15-epi-lipoxin-A4 [85], in agreement with other research [86]. To date, there has been no large randomized, double-blind, and multicenter research to investigate whether ticagrelor can improve myocardial remodeling after myocardial infarction. A trial [87] that is being conducted at 10 sites in Korea might provide a satisfactory answer.

Clinical Research

STEMI Patients

The PLATO study of a STEMI subgroup enrolled 8430 STEMI patients, including 4201 in the ticagrelor group and 4229 in the clopidogrel group; most of the patients underwent reperfusion therapy. The study showed that patients treated with ticagrelor had a lower risk of cardiovascular primary composite endpoints than those administered clopidogrel (9.3% vs 11.0%, $P=0.02$), consistent with the overall PLATO results [88]. The ATLANTIC study suggested that early pre-hospital administration of ticagrelor significantly reduced the risk of stent thrombosis of PCI compared with in-hospital administration [89]. Patients undergoing ambulance administration of ticagrelor had a lower probability of stent thrombosis after PCI than those receiving in-hospital administration of ticagrelor. Ticagrelor and prasugrel were associated with similar rates of stent thrombosis [90]. A recent trial from Canada (TOTAL) [91] recruited 9932 patients at hospital discharge, who were divided into clopidogrel, prasugrel, and ticagrelor groups. After adjustment, ticagrelor was associated with a lower risk of cardiovascular complications than clopidogrel. Three real-world studies on STEMI patients with PCI revealed that, compared with clopidogrel, ticagrelor improved 1-year survival [92], and was associated with lower adjusted 12-month mortality [93] and all-cause mortality rates [94].

Patients with Non-ST Elevated Acute Coronary Syndrome

Patients with non-ST elevated acute coronary syndrome include unstable angina pectoris and NSTEMI, both of which have similar pathogenesis and clinical manifestations, but with different severity [95]. For these patients, risk stratification should be carried out early, while relevant treatment strategies should be selected according to the degree of risk. Clinical application recommendations are as follows: (1) For patients with early invasive treatment of ischemic high-risk programs, ticagrelor is administered at a loading dose of 180 mg followed by a maintenance dose of 90 mg twice per day; (2) For patients with early conservative treatment, ticagrelor is recommended; and (3) Ticagrelor should be used in combination with aspirin for at least 12 months. The PLATO study enrolled 11 080 patients with non-ST elevated acute coronary syndrome. Among all the patients, 74%, 46%, and 5% underwent coronary angiography, PCI treatment, and coronary artery bypass grafting, respectively, within the first 10 days, while 5366 (48.4%) did not receive revascularization. Compared with clopidogrel, ticagrelor significantly decreased the rate of cardiovascular event complex endpoints and all-cause mortality, as well as rates of cardiovascular mortality and myocardial infarction. Ticagrelor and clopidogrel displayed the same benefits in reducing ischemic events and total mortality in patients with non-ST elevated acute coronary syndrome as those in the PLATO whole

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test, and these benefits occurred irrespective of whether revascularization was performed during the first 10 days [96].

ACS Patients Undergoing CABG

About 10% of patients in the PLATO study were randomly grouped to receive CABG treatment; among these patients, 1261 stopped the study drug for no more than 7 days before surgery. According to the study protocol, these patients should stop ticagrelor 1-3 days before surgery or clopidogrel 5 days before surgery. Compared with the clopidogrel group, the rates of cardiovascular death and all-cause death in the ticagrelor group were significantly lower, while the bleeding risk was similar. Ticagrelor reduces the risk of death after CABG, and this reduction may be associated with the effect of ticagrelor on decreasing death from cardiovascular disease, bleeding, and infection [97]. A study on CABG patients in China [98] found that the ticagrelor group exhibited a greater inhibition of platelet aggregation 2 h after the first drug administration than the clopidogrel group (34.2% vs 5.3%, $P<.001$). Moreover, the maximum mean inhibition rate of platelet aggregation within 2-24 h in the ticagrelor group remained higher than that in the clopidogrel group, but there was no associated increased risk of bleeding or major adverse cardiac events.

Stable Coronary Heart Disease

Regarding non-revascularization patients, the PEGASUS-TIMI54 research project [99] enrolled patients with a history of myocardial infarction for more than 1 year as well as more than 1 of the following risk factors: older than 65 years of age, diabetes, renal insufficiency, multiple lesions, and over 2 myocardial infarctions. In the study, 90 mg/day and 60 mg/day groups of ticagrelor on aspirin displayed lower major therapeutic end-events (7.85% and 7.77%, respectively) than the placebo group (9.04%), and the risk of cardiovascular death was lower in the ticagrelor groups. Moreover, prolonged treatment with ticagrelor plus aspirin for 30 months decreased MACEs without increasing fatal bleeding in patients with MI. The ONSET/OFFSET study [18] has shown that greater IPA (platelet inhibition) occurred in patients treated with ticagrelor versus clopidogrel. The rate of patients who achieved >50% IPA and >70% IPA was higher in the ticagrelor group 2 h after receiving the loading dose.

Special Groups

Patients with Chronic Kidney Disease (CKD)

Ticagrelor has a very low rate of metabolism and is excreted through the kidneys, while the recovery of ticagrelor and its active metabolites in the urine is less than 1% of the dose. There were no significant differences in pharmacodynamics, pharmacokinetics, and safety data between patients with severe renal failure (creatinine clearance <30%) versus those with normal renal function [100]. Compared with clopidogrel, ticagrelor remarkably reduced the risk of active endpoint events (17.3% vs 22%, $P<0.05$) and all-cause mortality (10.0% vs 14.0%, $P<0.05$) in the CKD subgroup [101]. Moreover, ticagrelor displayed a higher rate of platelet inhibition and faster inhibitory effect in dialysis patients and patients with impaired renal function compared to clopidogrel [102-104]. Recent studies have revealed that in comparison with clopidogrel, ticagrelor markedly reduced hospitalization and 1-year cardiovascular events without increasing the risk of bleeding in patients with acute myocardial infarction and end-stage renal failure [105].

Patients with Complex Coronary Artery Lesions

The PLATO study included a total of 4646 patients with complex coronary lesions. Compared with clopidogrel, ticagrelor significantly reduced cardiovascular complex endpoints (14.9% vs 17.6% $P<0.05$) [106].

Diabetes

Diabetes is a strong independent predictor of short-term and long-term recurrent ischemic events in patients with coronary heart disease [107,108]. Compared with patients without diabetes, the risk of cardiovascular death was 1.8 times higher in ACS patients with diabetes and 1.4 times higher in patients with MI [109]. Abnormal regulation of platelets in diabetic patients via multiple signaling pathways, including receptors and intracellular and downstream pathways, leads to increased platelet reactivity [110,111]. Although aspirin combined with clopidogrel improves the prognosis of ACS patients, patients with diabetes remain at high risk of adverse events during follow-up [112]. The PLATO study, involving 4662 diabetic patients, revealed that the absolute risk of endpoint events and all-cause mortality were both decreased in the ticagrelor group, but there was no increase in major bleeding [113]. The PLATO study on a prespecified subgroup of diabetic patients identified an additional benefit of ticagrelor treatment in reducing cardiovascular accident over a 12-month follow-up. Another study found that, compared with clopidogrel, ticagrelor significantly reduced the incidence of thrombus formation in CAD patients [114]. A Chinese group [115] investigated 200 ACS patients with diabetes and found better outcomes for angina and lower stent thrombosis and all-cause mortality one month after PCI in the ticagrelor group versus the clopidogrel group. Compared with clopidogrel, ticagrelor reduced platelet resistance [116] and vascular inflammatory response, while improving vascular endothelial function [117] and vascular blood flow [118] in patients with coronary heart disease and diabetes.

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Elderly Patients

The risk of recurrent ischemic events and death is high in elderly ACS patients with catheter-based complications. The PLATO trial found relationships between the primary composite outcome and age, as well as major bleeding. The composite of cardiovascular death, stroke, myocardial infarction, cardiovascular death, definite stent thrombosis, and all-cause mortality was not significantly different between patients aged ≥75 and those <75 years of age and both groups showed the clinical benefit of ticagrelor over clopidogrel. No increase in PLATO-defined major bleeding was found with ticagrelor versus clopidogrel in patients aged ≥75 years. Ticagrelor treatment led to the common adverse events of dyspnea and ventricular pauses, which were not related to age. It has been demonstrated that the overall safety and significant clinical benefit of ticagrelor versus clopidogrel in ACS patients of the PLATO study were not dependent on age [119].

Patients with Thrombolysis

Early fibrinolysis can provide timely and effective myocardial reperfusion [120-123] for STEMI patients who cannot receive timely treatment of primary PCI. If primary PCI treatment is delayed by 2 h or longer, fibrinolytic therapy causes similar mortality rates as PCI [124,125]. When primary PCI cannot be performed within 2 h after diagnosis of STEMI, medication is recommended, including immediate fibrinolytic therapy associated with rescue PCI [126,127]. It was reported that ticagrelor is better than clopidogrel in fibrinolytic treatment of STEMI patients undergoing early PCI [128]. Patients treated with ticagrelor undergoing PCI within 24 h in treatment of tenecteplase (TNK) who received ticagrelor after PCI had significantly lower PRU (platelet reactivity units) compared with clopidogrel. A good endpoint was observed in 87.8% of patients treated with ticagrelor and 57.6% of patients receiving the treatment of clopidogrel. Consistently, another study on STEMI patients undergoing fibrinolytic treatment and early PCI [129] provided evidence that patients receiving ticagrelor displayed a significantly higher rate of adequate platelet inhibition (platelet reactivity units PRU <208) on long-term follow-up than those treated with clopidogrel (clopidogrel, 82.6% vs ticagrelor, 100.0%; *P*=0.038). It has been shown that while post-fibrinolysis HPR is common in STEMI patients, lower HPR was observed in patients treated with ticagrelor versus high-dose clopidogrel [130]. There were no differences in major, fatal, and intracranial bleeding in ticagrelor and clopidogrel groups associated with a significantly lower frequency of cardiovascular events in the ticagrelor-treated group in a trial [131] of 3799 patients with STEMI undergoing fibrinolytic therapy.

Antiplatelet Therapy Under the Guidance of Genotypes

Several studies have found that clopidogrel did not effectively inhibit platelet aggregation in some patients. This phenomenon is known as "clopidogrel low response", which could be an important predictor of coronary ischemic events. Meanwhile, some patients were prone to significant bleeding reactions; this observation may be related to polymorphisms in the CYP2C19 gene. The ONSET/OFFSET and RESPOND genotype studies [132] first introduced genotypes such as cyp2c19 (*1,*2,*3,*4,*5,*6,*7,*8,*17), which were associated with clopidogrel low response and cardiovascular events. According to the manifestations of different CYP2C19 genotypes, polymorphisms in *CYP2C19* including loss-of-function (LOF) and increased function alleles could be categorized into ultrafast, rapid, intermediate (IM), and poor metabolizers (PM) [133]. Approximately 18% to 45% and 2% to 15% of the clinical population were classified as clopidogrel IM and PM, respectively, both of which were associated with clopidogrel low reactivity [134]. The proportion of patients with IM (about 50%) and PM (about 13~23%) in an Asian population was much higher than that in European and American populations [134]. Cytochrome P4502C19 (CYP2C19) plays a key role in metabolic transformation of clopidogrel. The CYP2C19*17 gain-of-function allele reduced platelet reactivity by increasing the bioavailability of clopidogrel's active metabolites. Loss-of-function alleles CYP2C19*2 and CYP2C19*3 decreased activity of the metabolites by affecting functional metabolites of the enzyme, leading to a high platelet response. Patients with CYP2C19*17 [29] and CYP4F2 T alleles [135] were at higher risk of bleeding. The PLATO study found that ticagrelor was superior to clopidogrel in reducing cardiovascular composite endpoints in all CYP2C19 genotypes. On the contrary, the incidence of 30d cardiovascular events in the clopidogrel treatment group was significantly higher among allelic carriers of CYP2C19 loss-of-function alleles, and the risk of bleeding was markedly higher in the clopidogrel treatment group. A study on Chinese patients [136] withor without CYP2C19 genotype measured ADP-induced platelet aggregation using thromboelastography (TEG) and found that TEGADP was significantly higher in non-carriers, while the level of TEGADP was similar between non-carriers and carriers in the ticagrelor group. A study of PCI in China reported a significantly lower risk of MACE in patients receiving genotype-guided therapy versus conventional therapy [137]. Finally, a study in the Netherlands with elective PCI reported that prasugrel displayed a lower risk of MACE in PM compared with clopidogrel [138]. A trial [139] of patients with stent implantation showed that carriers of loss-of-function alleles *CYP2C19**2 or *CYP2C19**3 receiving ticagrelor or prasugrel achieved more favorable results without increased bleeding outcome than the corresponding non-carriers treated with clopidogrel. In a study involving 1815 patients from 7 institutions, genetic testing of *CYP2C19* was available for clinical use in PCI patients, and prasugrel or ticagrelor was recommended in IM/PM [140]. Compared with alternative therapies, clopidogrel treatment was associated with a significantly higher risk of MACE in IM/PM during 12-month follow-up.

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Tolerability and Safety

Bleeding

In the PLATO study, no significant differences in major bleeding were found between ticagrelor and clopidogrel [141]. However, non-CABG (coronary artery bypass grafting)-related hemorrhages and non-surgical-related bleeding were more common in the ticagrelor group, especially after 30 days of treatment, compared with clopidogrel. Likewise, several studies have shown that the incidence of bleeding is higher in ticagrelor-treated patients compared with those treated with prasugrel, especially during long-term treatment [142, 143]. There has been no antidote for reversal of ticagrelor, which cannot be cleared by dialysis. In case of bleeding, appropriate supportive treatment with particular emphasis on local hemostasis is needed. Anti-fibrinolytic therapy (aminoacetic acid or carbamic acid) and/or recombinant factor VIIa may enhance hemostatic effects. Ticagrelor can be reused after the cause of the bleeding is determined and the bleeding is controlled [144-146].

Dyspnea

Dyspnea is a common adverse reaction of ticagrelor and may be associated with increased plasma adenosine concentration. The rates of mild-to-moderate dyspnea are dose-related, which is probably associated with the drug's mechanism of activity [147]. Studies on healthy volunteers have demonstrated that intravenously injected adenosine can increase ventilation and heart rate, while inducing dyspnea [148,149]. Some clinical studies revealed that the percentage of patients with dyspnea after ticagrelor treatment was 10-15%, which was significantly higher than with other P2Y12 inhibitors. Notably, other trials found that nearly 40% of patients had this adverse reaction [23,150,151]. Although shortness of breath is often reported, lung function (pulmonary volume, spirometry, and pulse oximetry) of patients treated with either ticagrelor or clopidogrel was not affected [151,152]. Also, dyspnea was not related to patient age, and the efficacy and overall safety of ticagrelor were not associated with this adverse reaction [119,150]. In the PLATO study, the incidence of dyspnea in the ticagrelor group was 14.5%; among these cases, most were mild to moderate, while only 0.4% were severe. Dyspnea mostly occurred in the early stages (the median time: 23days in ticagrelor group and 43 days in the clopidogrel group, $P<0.0001$), and resolved without treatment in most cases. Approximately 0.9% of the patients decided to stop the treatment because of dyspnea [150].

Hyperuricemia

In the PLATO study, a higher increase in serum uric acid levels in the first and twelfth months of treatment was found in the ticagrelor group compared with the clopidogrel group with no statistically significant difference between the 2 groups at 1 month after ceasing treatment [13]. Butler and Teng [153] conducted a randomized, cross-over, placebo-controlled study, and found that ticagrelor elevated hypoxanthine and xanthine levels in serum, resulting in increased levels of serum uric acids. Ticagrelor-associated hyperuricemia is usually mild and reversible, and it may be related to adenosine pathways. However, a single-center study found no difference in the baseline uric acid and creatinine levels between patients treated with clopidogrel versus ticagrelor for a period of 30-90 days [154]. Another trial [155] revealed that in patients treated with DAPT, uric acid level did not affect response of platelet reactivity to ticagrelor, clopidogrel, and aspirin.

Arrhythmia

Ticagrelor has been found to increase the incidence of bradyarrhythmias, including ventricular pauses detected by Holter [156]. A Holter substudy conducted continuous electrographic analysis on 2908 patients. In the first week, patients receiving ticagrelor had a higher frequency of ventricular pauses ≥3 s than those treated with clopidogrel. A month later, the pauses ≥3 s occurred less frequently overall, and the frequency was similar between the 2 groups of patients. Most were ventricular pauses, and the largest portion associated with ticagrelor were asymptomatic, sinoatrial nodal in origin (66%), and nocturnal. There were no differences in the occurrence of clinically reported bradycardic adverse events, such as syncope, cardiac arrest, and pacemaker placement between ticagrelor versus clopidogrel groups.

Conclusions

This review has presented the current status of regulatory approvals for the use of ticagrelor in the management of acute coronary syndrome, and acute thrombotic disease when combined with aspirin, and its superiority to clopidogrel. Further controlled clinical trials are needed to determine the role of ticagrelor in the management of other diseases.

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