The Role of Current Major Antiplatelet Agents in Cardiovascular Diseases

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Abstract

Coronary Artery Disease (CAD), a primary cause of morbidity and mortality worldwide, has arrived at a prevalence because of the quick modernization of the developing countries nowadays. Moreover, coronary thrombosis is the most severe complications leading to a constant cause of cardiovascular death, myocardial infarction and ischemic stroke, which is closely associated with a platelet-rich aggregation on existent CAD. Therefore, antiplatelet agents become critical in therapy and secondary prevention to reduce the main adverse cardiovascular events (MACE). The current main antiplatelet components are of cyclooxygenase-1 (COX-1) inhibitors: Aspirin and Adenosine Diphosphate (ADP) P2Y \(^12\) receptor antagonists including clopidogrel, prasugrel, and ticagrelor, three of which belong to novel second-generation P2Y \(^12\) inhibitors. The review is to elucidate current research results about their critical roles in the therapy of cardiovascular diseases and potential pharmacological mechanisms.

Keywords: Coronary artery disease; Coronary thrombosis; Cyclooxygenase-1 inhibitors; P2Y \(^12\) receptor antagonists.

Abbreviations: AA: Arachidonic Acid; ACS: Acute Coronary Syndrome; ADP: Adenosine Diphosphate; APT: Antiplatelet Therapy; ASA: Acetylsalicylic Acid; CABS: Coronary Artery Bypass Surgery; CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease; CAS: Carotid Artery Stenting; CBFV: Coronary Blood Flow Velocity; COX-1: Cyclooxygenase-1; COX2: Cyclooxygenase-2; CPTP: Cyclopentyl-Triazolo-Pyrimidine; DAPT: Dual-Antiplatelet Therapy; ENT1: Equilibrate Nucleoside Transporter-1; Epcs: Endothelial Progenitor Cells; GP: Glycoprotein; HAPR: High On-Aspirin Platelet Reactivity; IS: Infarct Size; MACE: Main Adverse Cardiovascular Events; MI: Myocardial Infarction; NF-Kb: Nuclear Factor Kappa-B; PCI: Percutaneous Coronary Intervention; PGI2: Prostaglandin I2; PLATO: Platelet Inhibition And Patient Outcomes; TIMI, Thrombolysis In Myocardial Infarction; TRAP: Thrombin Receptor Activator Peptide; Txa2: Thromboxane-A2.

Introduction

The key role acted by platelets in thrombosis at the sites of vascular damage provides a shred of compelling evidence for interdicting their effect on a series of cerebrovascular events [1,2]. Adhering to the site of arterial damage under the force of shear, platelets are Activated, and Adenosine Diphosphatelyse (ADP) is released from dense granules; Arachidonic Acid (AA) is also produced from membrane phospholipids by the cyclooxygenase-1 (COX-1)/thromboxane synthase pathway, which leads to the activation of thrombin via the coagulation pathway on the surface of activated platelet. ADP, thromboxane-A2 (TxA2), and thrombin are of three critical G-protein-Coupled Receptors (GPCR). P2Y12 receptor, thromboxane receptor, and Protease-Activated Receptor (PAR)-1 respectively and a set of intracellular signaling events, resulting in the activation of the Glyceroprotein (GP) IIb/IIIa receptor that sticks to the dimeric fibrinogen molecule to regulate thrombocyte aggregation in the end (Figure 1). Owing to the importance of the ADP-P2Y12 and TxA2-ATP pathways in expanding platelet activation in response to multiple agonists, a P2Y 12 inhibitor in addition to aspirin is the most broadly considered as an antplatelet strategy to prevent thrombotic events in high-risk CAD patients [3,4]. In this review, we enumerate critical components of contemporary Anti Platelet Therapy (APT): aspirin, clopidogrel, prasugrel, and ticagrelor, in an individual standpoint both mechanism and the relevant evidence from which their use is supported.

Cyclooxygenase-1 inhibitors: Aspirin

Pharmacological action of aspirin

Aspirin is rapidly taken up in the upper gastrointestinal tract and has a pesticide effect of 15 to 20 minutes [5]. The anti thrombotic effect of aspirin has been on account of effective acetylation of the platelet COX-1 enzyme that generates quickly in the pre hepatic circulation after rapid absorption [6] (Table 1). Irreversibly acetylation serine 529 in the platelet COX-1 enzyme, aspirin blocks the binding of AA to the catalytic site (Tyr 385) and suppresses the synthesis of prostaglandin G2 and prostaglandin H2. Consequently, TxA2 generated by platelet thromboxane and TxA2-induced platelet tagregation is inhibited for the activity of the platelet (~ten days) [5,7]. Although a daily dose of 30 mg/day is enough to suppress COX-1 in platelets, it is recommended a 75-150 mg daily dose for long-term precaution and a 150-325 mg loading dose for quick and entire inhibition of platelets in patients with a high-risk of cardiovascular disease [6,8,9]. Aspirin has been the mainstay of APT for secondary prevention in early recurrence and severity of cerebrovascular events [10,11].

Aspirin latest research and clinical new discovery

Although aspirin has been the cornerstone for guarding against cardiovascular disease to reduce the incidence of Main Adverse Cerebro Vascular Events (MACVE), an increasing risk in gastrointestinal bleeding is keeping many patients from sticking to the daily rationale [12,14]. According to relevant evidence, a combination pill containing agents of aspirin and omeprazole, is a novel drug treatment that has the potential to enhance patient compliance with the aspirin regimen on the account of fewer gastrointestinal adverse effects, comparing to aspirin only, which could reduce effectively the incidence rate of MACVE [15]. High on-Aspirin Platelet Reactivity (HAPR) is related with increasing thrombosis, which leads to the risk of elderly patients with coronary artery syndrome [16,18]. By measuring the parameters of higher serum uric acid, low-level platelet count, hemoglobin and hematocrit corrected with HAPR, which might provide novel therapeutic targets for optimizing antplatelet therapy [15]. As for patients with Percutaneous Coronary Intervention (PCI), short or long term Dual-Antiplatelet Therapy (DAPT) has been controversial [19,20]. Owing to DAPT score <2 or score ≥2, comparing patients with high scores receiving paclitaxel-eluting stents, prolonged DAPT lead to harm in patients with low scores undergoing PCI but decrease the incidence of ischemic events. However, to patients after PCI with the Nobori Drug-Eluting Stent (DES), six months of DAPT was not so good to eighteen months. On the contrary, prolonged DAPT resulted in a risk of main bleeding events [19,21]. Clopidogrel versus aspirin better-reduced MACVE, but enhance the risk of main bleeding time in patients with CAD [22-25]. Besides, for patients with peripheral artery disease, DAPT not only reduces the MACVE, but also improve the prognosis. Comparing to aspirin, clopidogrel is cost-effective for APT [26-28]. To achieve are liable conclusion, the more emerging experimental results are needed validation in large multicenter trials.

Adenosine diphosphate (ADP) P2Y 12 receptor antagonists: Clopidogrel

Pharmacological action of clopidogrel

Clopidogrel selectively prevents ADP from binding to platelet receptor and stimulates ADP-mediated secondary Glyceroprotein GPIIb/IIIa complex activation, then inhibits platelet aggregation by biotransformation [29,30] (Table 1). Moreover, clopidogrel also blocks the amplification of platelet caused by the release of ADP, following the inhibition of the platelet aggregation [31,32]. Further research was found that clopidogrel could irreversibly modify the platelet ADP receptors [24,33].

DAPT of aspirin and clopidogrel

The utility of DAPT with aspirin and clopidogrel has been plentifully confirmed in peripheral vascular and coronary treatment to effectively decrease periprocedural thrombo embolic events [28,34-38]. Clopidogrel is often not only taken to decrease the incidence of procedure-related thrombotic ischemic complications but also as a selective P2Y12 receptor antagonist, owing to its lower cost as a general agent [39,40]. Moreover, it is often used to prevent secondary ischemia for patients undergoing Carotid Artery Stenting (CAS) or with cerebrovascular disease treated by endovascular techniques. Endovascular surgery has emerged as an effective alternative for the treatment of cerebrovascular disease. Most of the patients with neuro interventional procedures form complications of blood clots, while carotid angioplasty often is related to ischemic complicactions [41,42]. Besides, according to the American Heart Association (AHA)/American Stroke Association guidelines, it suggested mono therapy with clopidogrel as a reasonable option guarding against ischemic stroke [43]. For preventing 24 hours of a minor ischemic stroke or transient ischemic attack, DAPT with aspirin and clopidogrel is often prescribed.

Novel second-generation P2Y12 inhibitors

Pharmacological mechanisms of ticagrelor

Ticagrelor, as the Cyclo Pentyl – Triazolo - Pyrimidine (CPTP) class of antplatelet agents, is distinct from thienopyridines and ADP analogs [44]. Besides, ticagrelor, a reversibly and orally active, could block ADP-induced P2Y 12 receptor signaling selectively and potently [45] (Table 1). Ticagrelor via preventing ADP binding reversibly suppresses the ADP-induced recep-
tor structural change and G-protein activation by adhering to a different domain [46,47]. These features make the receptor being in a dormant and unrestrained state, which could reactive the receptor via ADP.

**Pleiotropic effects of ticagrelor**

**The inhibition of adenosine**

Ticagrelor via P2Y12 inhibition prevents adenosine from the reuptake of erythrocytes and other cells [48]. The effect of preventing reuptake of adenosine has been related to the selective inhibition of sodium-independent quillate nucleoside transporter (ENT1) at concentrations of clinical relevance [3]. (Figure 2). Distinct from the strong adenosine uptake inhibitor dipyrindamole, ticagrelor shows up a sixteen-fold lower affinity for ENT1. However, in addition to ticagrelor, other P2Y 12 blockers like cangrelor, the activated metabolites of clopidogrel and prasugrel do not have a great impact on adenosine uptake. Comparing to ENT1 affinity, ticagrelor has more than a twenty-fold higher affinity for P2Y12. Ticagrelor has no direct impact on adenosine receptors and also is not metabolized to adenosine [3]. However, it has been reported that in blood collected from Acute Coronary Syndrome (ACS) patients treated with ticagrelor compared to clopidogrel or aspirin, there is significantly higher plasma concentration of adenosine. Besides, in vitro when incubated with serum from patients treated with ticagrelor but not clopidogrel, uptake of exogenous adenosine by erythrocytes was inhibited [3]. For a study in vitro, the anti-platelet function of ticagrelor has been partially influenced by a drug-induced increase in extracellular adenosine levels and adenosine-mediated platelet blockage by the A2A receptor [38,49-52]. Furthermore, ticagrelor is of the low-binding affinity and functional inhibition of adenosine receptors. It has been reported that ticagrelor and its primary circulating metabolites, had low affinity for each of the adenosine A1, A2A, and A2B receptors, while ticagrelor had a greater affinity for the adenosine A3 receptor. Therefore, in functional assays, the high concentrations of ticagrelor only partially suppressed adenosine-induced de polarizations in the relevant animal experiments of guinea pig and rats (by 35% and 49%, respectively) [3].

**Coronary blood flow**

According to a double-blind, placebo-controlled research forty healthy male subjects randomly taking a single dose of ticagrelor (180 mg) or placebo in a crossover fashion, ticagrelor or greatly enhanced the area under the curve of Coronary Blood Flow Velocity (CBFV) versus the adenosine dose caused by plasmoglobin, ticagrelor plasma concentrations and an increase in the area under the curve of CBFV were closely relevant. For the two groups, the adenosine-induced increase in CBFV was greatly decreased by theophylline, with no obvious change between subjects taking ticagrelor placebo (Table 2 & Figure 2). Ticagrelor dramatically enhanced the sensation of dyspnea via adenosine infusion, and the outcomes were reduced through theophylline [53]. In another perspective, single-center, single-blind, crossover study, fifty-six patients with a high risk of ACS randomly taking either ticagrelor 90 mg BID or prasugrel 10 mg OD with a 15-day the remedy, the results demonstrated that compared with prasugrel, ticagrelor significantly increased period Maximal CBFV area under the curve, with the least squares mean difference of 7.16. Moreover, by trans thoracic Doppler echocardiography, ticagrelor compared with prasugrel significantly improved Maximal CBFV/baseline CBFV ratio [54]. In conclusion, to some extent, ticagrelor could better increase CBFV than prasugrel when incremental doses of adenosine are treated (Table 2 & Figure 2).

**Improving remodeling after myocardial infarction:**

In a correlated animal experiment, rats underwent 30-minute ischemia then 24-hour reperfusion. According to intragastric administration containing that ticagrelor 300 mg/kg and clopidogrel 62.5 mg/kg per day versus control, after four weeks, left ventricular ejection fraction was significantly decreased in the vehicle-treated group versus sham. The group of ticagrelor not only increased left ventricular ejection fraction but also decreased fibrosis and attenuated collagen-III mRNA levels. Four weeks after ischemia/reperfusion, it is the ticagrelor that has been confirmed to decrease the infarct size (IS) in a rat perfusion model that was totally changeover by an adenosine receptor antagonist, which showed that the function is regulated by endogenous adenosine [55](Table 2 & Figure 2). Moreover, in a canine coronary thrombosis model, comparing to clopidogrel, ticagrelor greatly decreased infarct size and quickly repaired tissue perfusion when added to tissue plasminogen activator [56]. In large animal myocardial infarction (MI) model, Pigs received the following before MI induction: (1) placebo-control; (2) a loading dose of clopidogrel (600 mg); (3) a loading dose of ticagrelor (180 mg); (4) a loading dose of ticagrelor followed by an adenosine A1/A2-receptor antagonist theophylline, 4 mg/kg intravenous to determine the potential contribution of adenosine in ticagrelor-related cardiac protection. Animals received the corresponding maintenance doses of the antiplatelet agents during the following 24 hours and underwent 3T-cardiac MRI analysis. Platelet inhibition was monitored by ADP-induced platelet aggregation. The results showed that clopidogrel and ticagrelor exerted a high and consistent anti platelet effect. All groups showed comparable myocardial area at risk and cardiac worsening after MI induction. 3T-Cardiac MRI analysis revealed that animals treated by clopidogrel and ticagrelor had a significantly smaller extent of MI than placebo-control animals. Yet, ticagrelor reduced infarct size to a significantly greater extent than clopidogrel. Furthermore, in comparison with clopidogrel, ticagrelor also effectively imposes restrictions on myocardial edema [48]. The conclusion was that by reducing necrotic injury and edema formation, ticagrelor protects cardio protective effects via adenosine-dependent mechanisms (Table 2 & Figure 2).

**Decreased inflammatory reaction and improving the endothelial function**

Adenosine is a critical regulator of myocardial protection against ischemia-reperfusion damage [57]. It has been reported that in rats subjected to 30-minute coronary artery ligation followed by 24-hour reperfusion, seven-day pretreatment by ticagrelor, reduced myocardial IS. It was confirmed that it is connected with adenosine receptor activation via downstream phosphorylation of protein kinase B (Akt), endothelial NO synthase, and activation of cyclooxygenase-2 (COX2). It was also consistent with a decreased inflammatory reaction that followed reduced pro inflammatory factors, like tumor necrosis factor-α, interleukin-8, and inhibited the nuclear factor kappa-B (NF-κB) signal pathway [38,56,58-63] (Figure 2).

Besides, in an emerging study containing sixty-two patients diagnosed type 2 diabetic with a high risk of the ACS, they randomly took five weeks treatment of ticagrelor or prasugrel then followed by a direct cross over to the substitutive therapy for five additional weeks. The data demonstrated that brachial ar-
tery flow-mediated dilation was improved greater for the group of ticagrelor. Besides, compared with prasugrel, ticagrelor or not reduced the inflammatory cytokines level of interleukin 6 and tumor necrosis factor alpha, but also improved a diponecint in the follow-up for ten-week. The data also showed that both groups decreased other concerning inflammatory cytokines such as high-sensitivity C-reactive protein and soluble vascular cell adhesion molecule-1. The group of ticagrelor significantly increased absolute numbers of circulating endothelial progenitor cells (EPCs) (Figure 2). Based on above results, it confirmed that compared with prasugrel, ticagrelor effectively reduced inflammatory cytokines like interleukin 6, tumor necrosis factor alpha and increased circulating EPCs, resulted in improved arterial endothelial function for patients who were diagnosed as type 2 diabetic with the ACS [55] (Figure 2). In addition to potent antiplatelet function, pleiotropic effects of ticagrelor could result in additional clinical benefits, which reduced inflammation reaction, decreased Arterial Stiffness, improved endothelial function, and increased Circulating Endothelial Progenitor Cells in patients with the ACS [59] (Table 2 & Figure 2). However, there were also relevant data showing comparing to clopidogrel, ticagrelor did not reduce the incidence of primary cerebro vascular adverse events(cardiovascular death, myocardial infarction, ischemic stroke) and not improve prognosis in patients with peripheral artery disease [64-66].

Effects on peripheral arteriopathy and cardiopathy

Peripheral artery disease is closely related to adverse cardiovascular and ischemia limb events [67]. Previous evidence has indicated that patients taking clopidogrel or ticagrelor mono therapy had a minor rate of adverse cardiovascular events, but the underlying mechanism is still elusive. Compared with diabetes, patients with diabetes have a higher rate of peripheral artery disease, which account for the micro vascular complications from the diabetes [59]. Ticagrelor could have better effect on peripheral arteriopathy by mitigating low-shear blood viscosity and improving microcirculation via property of the increasing adenosine. Besides, ticagrelor could improve peripheral revascularization, endovascular revascularization, and reduce lower baseline ankle-brachial index [68]. To patients with transient ischemic attack in patients with peripheral artery disease, ticagrelor could lead to a lower adjusted rate of ischemic and all-cause stroke (cardiovascular death, myocardial infarction, or ischemic stroke) [51,69-72]. Although clopidogrel monotherapy had decreased the rate of cardiovascular events than those taking aspirin in patients with symptomatic peripheral artery disease, ticagrelor was not more beneficial to clopidogrel. Moreover, at similar rates occurred major bleeding that could lead to ischemia stroke [59,73]. Besides, utility of ticagrelor in Peripheral Artery Disease could decrease a composite of MACE via enhancing endovascular revascularization and improving low-shear blood viscosity [74-76]. Data was shown that the peripheral artery disease of patients underwent previous revascularization were associated with higher risk of myocardial infarction and acute limb ischemia, stroke, while ticagrelor could reduce the rate of cardiovascular or acute limb events. In conclusion, ticagrelor is beneficial to adverse cardiovascular events caused by peripheral artery disease.

Ticagrelor and aspirin

A P2Y12 inhibitor plus aspirin is the most broadly considered as an anti-platelet strategy to reduce the incidence of adverse cerebrovascular events in the setting of a therothrombotic vascular disease [77]. Ticagrelor, as a reversibly binding oral P2Y12 receptor blocker, mediates potent inhibition of adenosine diphosphate-induced platelet function (Table 1). It is more effective than clopidogrel in preventing thrombotic events in acute coronary syndrome patients. In the North American sub group of the Platelets inhibition and patient Outcomes (PLATO) due to the lack of use raction for ticagrelor versus clopidogrel, the PLATO trial has given rise to a higher concomitant aspirin dose [78].

Ticagrelor was not only confirmed to decrease mortality in patients undergoing Coronary Artery Bypass Grafting (CABG) but also has a beneficial effect on graft patency [79]. In a randomized trial, to explore the medication within seventy-two hours after CABG, compared ticagrelor versus placebo for 3 months added to aspirin, aspirin was begun in twelve hours. The results indicated that graft occlusion took place lower on ticagrelor than on placebo. Major bleeding events did not occur, but minor bleeding was higher in ticagrelor [80]. In conclusion, the above data showed that compared to aspirin, ticagrelor not only decreased graft occlusion but also had an important influence on multivariable analysis.

It has been reported that the ADP-P2Y 12 signal path is not critical for the generation of TxA2, but for the non reciprocal aggregation related with ATP receptor activation [81-84]. Comparing to a high concentration of ticagrelor in vitro, aspirin might not offer significantly anti-aggregatory effects in response to ADP, AA, epinephrine, and Thrombin Receptor activator peptide (TRAP) [82]. In vitro, the influence of aspirin on platelet function, it showed that the doses of aspirin were closely related to anti-platelet reaction [85]. It has been confirmed that P2Y 12 inhibitors decreased TxA2-induced platelet aggregation and TxA2 production and sensitize platelets to the anti-aggregatory effects of prostaglandin by inhibiting P2Y 12 receptor, which results in inhibiting the a denyl cyclase. Therefore, it showed that in the presence of potential P2Y12 obstruction triggered by ticagrelor, a high dose of aspirin might decrease the production of prostaglandin I2 (PGI2) and change the effect of aspirin toward prothrombosis [82].

Ticagrelor and clopidogrel

In the PLATO study, patients who underwent coronary artery bypass grafting CABG and after PCI, compared to clopidogrel, ticagrelor was related with fewer deaths from Main Cardiovascular Adverse Events (MCAE). Besides, using APT with ticagrelor in combination with Acetyl Salicylic Acid (ASA) versus a combination of clopidogrel and ASA in patients with ACS following Coronary Artery Bypass Surgery (CABS), ticagrelor plus ASA ensures resource savings to treat ACS patients undergoing CABS as compared with a regimen including a combination of clopidogrel and ASA. Based on pharmaco-dynamics’ studies, in low-risk ACS patients undergoing PCI, compared with clopidogrel, ticagrelor provides more rapid and potential platelet inhibition [86,87]. Rapid reperfusion treatment regains well-balanced epi cardial bleeding flow, while micro vascular dysfunction may occur in some patients with the ACS. Due to myocardial reperfusion injury caused by intraluminal platelets, fibrin thrombi, and neutrophil plugging, antiplatelet drugs act as a critical role by guarding against thrombus micro embolization. Further exploration, owing to the potential anti-platelet function and pleiotropic properties regulated by the increasing adenosine, it has been reported that ticagrelor compared with clopidogrel might decrease the micro vascular dysfunction in patients with ACS [88].
However, emerging clinical trials demonstrated that for East-Asian patients with ACS, ticagrelor, and clopidogrel displayed similar effects and treatment of ticagrelor also showed some negative effects including an increased risk of main bleeding events [59,64]. Moreover, although Dual Anti Platelet Therapy (DAPT) is beneficial to reduce the incidence of main cardiovascular adverse events and ischemic stroke, the comparison of ticagrelor to clopidogrel is no difference in patients with peripheral artery disease [89,90].

Prasugrel

Inhibiting the P2Y 12 receptor, prasugrel gains activation to its active metabolite. Comparing to clopidogrel, prasugrel is a prodrug, which is more readily translated to its active metabolite. The metabolism is dependent on hepatic coenzymes as well as intestinal carboxylesterases [91] (Table 1). Therefore, it has a more prompt onset of action and blocks platelet aggregation. Moreover, pharma codynamics document that the level of platelet inhibition can be achieved within 30 min with prasugrel [92].

Ticagrelor and prasugrel

As novel potent second-generation ADP receptor inhibitor comparing to prasugrel, ticagrelor could reversibly block P2Y12 receptor, which is also called off-target properties [93]. Although compared to clopidogrel, both could improve the clinical prognosis and decrease the rate of MACE in ACS patients with coronary stenting, coronary artery pass by grafting or micro vascular function after MI, there was no significant difference between ticagrelor and prasugrel [94,95,96]. However, given that the sole off-target properties including in creased adenosine plasma levels, comparing to clopidogrel or prasugrel, ticagrelor has pleiotropic effects according to the emerging data (Figure 2). (1) improving the endothelial function and other circulating biomarkers and increasing the absolute number of endothelial progenitor cells in humans trials and animal experiments [45,53,58,97,98]; (2) inhibiting the neointimal hyperplasia and protecting the endothelial function in a porcine coronary stent restenosis model [58,99,100]; (3) improving remodeling of MI, myocardial size and reperfusion injury by reducing necrotic injury and edema formation in myocardial infarction model of rats or pigs [101,102]; (4) decreasing microvascular dysfunction in revascularized patients with ST-segment elevation myocardial infarction [103]; (5) inhibiting ADP-induced vascular smooth muscle cell contraction [102]. Although compared with clopidogrel, prasugrel/ticagrelor, the new oral P2Y12 inhibitors, have more beneficial to patients with ACS, but to patients with creatinine clearance <60 ml/min/1.73 m, hypertension, underwent a trans-femoral approach and diagnosed as NSTEMI, they did not decrease the composite rate of CVD, recurrent MI or stroke, however, increasingly enhance major bleeding events [104]. Besides, to patients with AMI, co-administration of morphine with P2Y12 inhibitors (prasugrel or ticagrelor) probably reduce their function in platelet inhibition, which increase the risk of thrombosis [105]. An emerging evidence was showed that compared with prasugrel, ticagrelor decreased the rate of recurrent nonfatal CVD events and major and minor bleeding events [106]. However, to further confirm beneficial effects, additional and particularly designed clinical studies are imperatively needed in the future following randomized, controlled and double-blind trials.

Risk of bleeding in patients with the treatment of antiplatelet

Given that ticagrelor is an efficient reversible P2Y12 receptor blocker, there was an increased risk of bleeding in patients treated with ticagrelor that might have an influence on its compliance. According to a recent analysis of major trials of high dose clopidogrel, prasugrel, and ticagrelor, it was reported that compared to 300 mg clopidogrel strategy, 600 mg clopidogrel, prasugrel or ticagrelor in addition to aspirin was related with a great reduction in MACE at thirty days, but it causes an increased risk of Thrombolysis In Myocardial Infarction (TIMI) major bleeding with all the above strategies. Due to higher cost and potential interaction with high dose aspirin associated with ticagrelor therapy, a twice-daily dose may be a critical concern for compliance in a real-life scenario [103].

The emerging evidence of antiplatelet agents on animal research

Via establishing a novel porcine model of thrombotic myocardial infarction, the emerging evidence illustrates that dual anti platelet therapy (aspirin and prasugrel) is more beneficial than the control in aspects of platelet aggregation, myocardial infarction volume and cardiac function [107]. Additionally, caspase-1 inhibitor VX-765 plus P2Y12 receptor antagonist ameliorated the IS and cardiac dysfunction prior to the ischemic-reperfusion injury, which benefits from mitigating pyroptosis of the myocardium and sustaining mitochondrial membrane integrity in rats [108]. However, some documents indicated that cardiac protection offered by P2Y12 receptor antagonist would clinically diminish after ischemic post conditioning in acute myocardial infarction. Inflammation plays a vital role in ischemic reperfusion, which could lead to severe myocardial injury. An emerging experiment demonstrated that ticagrelor could partly down regulate the expression of galectin-3, a known inflammatory cytokine near the infarct area involved positively in ischemia-induced inflammation, to reduce IS and improve cardiac function in ischemia-reperfusion model of rats [109]. Moreover, the small molecule MERTK inhibitor UNC2025 in combination with P2Y12 receptor antagonist ameliorates platelet activation and prevents thrombosis. Interestingly, ticagrelor has a protective effect on a mouse model of ischemic stroke mainly via promoting the phosphorylation of endothelial nitric oxide synthase and extracellular signal-regulated kinase 1/2, which suggests that ticagrelor has additionally neuroprotective effects via other mechanisms other than its anti platelet action [110]. In summary, the above experiments in combination with others in animal models obviously indicate that the inhibition of platelet aggregation with DAPT has clinically protective effect on patients with ACS [111].

![Figure 1: The targets of antiplatelet (aspirin, clopidogrel, prasugrel, ticagrelor)](image-url)
Figure 2: Pleiotropic effects of ticagrelor. Ticagrelor reduces vascular inflammation by inhibiting the activation of the P2Y_12 receptor pathway, thereby reducing the proinflammatory factors. In addition, ticagrelor augments extracellular adenosine concentrations by inhibiting the absorption of red cell and other cells, leading to multiple potential positive or adverse effects and additional clinical beneficial effects.

Table 1: Pharmacological action of antiplatelet agents.

<table>
<thead>
<tr>
<th>Agents</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological efficiency</td>
<td>&gt;90</td>
<td>&gt;55</td>
<td>&gt;85</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Main Metabolic organ</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic+ intestinal tract</td>
<td>Hepatic</td>
</tr>
<tr>
<td>The half time of the agents</td>
<td>About 2-3 h</td>
<td>7-8 h</td>
<td>7-9h</td>
<td>6-9h</td>
</tr>
<tr>
<td>The major mode of excretion</td>
<td>Urine</td>
<td>Urine +choler</td>
<td>Urine +shit</td>
<td>Choler</td>
</tr>
<tr>
<td>Major action and platelet inhibition</td>
<td>The inhibition of COX-1, irreversible</td>
<td>The inhibition of ADP P2Y_{12}, Irreversible</td>
<td>The inhibition of ADP P2Y_{12}, Irreversible</td>
<td>The inhibition of ADP P2Y_{12}, reversible</td>
</tr>
</tbody>
</table>

Table 2: The effects of ticagrelor and adenosine.

<table>
<thead>
<tr>
<th>Organs or tissues</th>
<th>Ticagrelor</th>
<th>Adenosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery or blood vessels</td>
<td>• Increasing the coronary flow caused by adenosine-induced&lt;br&gt;• Impairing the artery injury by improving endothelial function</td>
<td>• Increasing the vasodilation&lt;br&gt;• Increased the absolute endothelial progenitor cells(EPC)&lt;br&gt;• Improving the migration, pipe formation and differen-tion of EPCs</td>
</tr>
<tr>
<td>Cardiac tissue</td>
<td>• Decreasing the incidence of MACE&lt;br&gt;• Reducing the infarction size and fibrosis&lt;br&gt;• Enhance the ejection fraction of the left ventricle</td>
<td>• Decreasing Ischemic /reperfusion injurey induced caused by pharmacological precondition&lt;br&gt;• Reducing the incidence of electrical conduction</td>
</tr>
<tr>
<td>Blood platelet</td>
<td>• Inhibiting the platelet-aggregation caused by adenosine-induced&lt;br&gt;• Reducing the rate of morbidity and mortality by anti-platelet</td>
<td>• Decreasing the inflammatory reaction and cytokines by inhibiting the release of platelet</td>
</tr>
<tr>
<td>Kidney</td>
<td>• Decreasing the creatinine levels&lt;br&gt;• Increased glomerular filtration rate</td>
<td>• Increased the vasodilation of kidney artery&lt;br&gt;• Increased creatinine clearance rate</td>
</tr>
<tr>
<td>Lung</td>
<td>• Enhancing the rate of dyspnea with acute coronary syndrome</td>
<td>• Increased the incidence of dyspnea</td>
</tr>
</tbody>
</table>
Discussion

Aspirin has been recognized as the cornerstone of APT to treat a thrombotic vascular disease for several decades. Although used worldwide, there is short of robust evidence with regard to an optimal dose of aspirin. It is wished that the adaptable study will offer a definitive answer regarding the optimal dose. Direct gastrointestinal toxicity, ineffectiveness in high-risk patients and interactions with other antiplatelet drugs like clopidogrel, prasugrel and ticagrelor are main concerns connected with aspirin treatment for secondary prevention. To patients with ACS and coronary stenting, DAPT with aspirin and a P2Y12 inhibitor is broadly considered as the first clinical trial. Any treatment rationale that strongly blocks platelet function will enhance the risk of bleeding. With the emerging consensus that bleeding is a key cause of morbidity and mortality, it is expected to minimize the risk of bleeding whenever possible. More potent second-generation P2Y12 inhibitors such as prasugrel, ticagrelor provide strong P2Y12 platelet receptor blockade in relation to clopidogrel. It would seem plausible that ticagrelor would gain significantly less from the addition of aspirin as compared to clopidogrel in a DAPT strategy. Furthermore, the minute gain in protection from ischemic events provided by aspirin to ticagrelor could be denied by the increased bleeding risk, particularly with respect to gastrointestinal toxicity. According to some trials in the setting of ST-segment elevation myocardial infarction, it has been reported that crushed ticagrelor may be absorbed more rapidly and have a stronger antiplatelet effect within the first-hour post administration, when compared with consumption of the intact tablet. However, whether or not this will translate to a reduction in adverse events remains to be further confirmed. Furthermore, the pre-specified study of the PLATO trial affords the activation for the ticagrelor-aspirin hypothesis to be recognized as a likely pharmacotherapeutic phenomenon. It seems confused that the higher level of aspirin could inhibit COX-2 mediated production of the vasodilator prostacyclin leading to vasoconstriction, but that would only manifest under the background of ticagrelor therapy.

Conclusion

For recent decades, aspirin and clopidogrel have been still considered as the bedrock of therapy for ACS. However, prasugrel and ticagrelor have a more consistent and more potential antiplatelet function than clopidogrel, which could improve clinical prognosis and reduce the relevant incidence of MACV, although at the cost of increased bleeding risk. However, in spite of current antiplatelet therapies, some patients still undergo cardiovascular events. It is likely that platelet activation may occur via other pathways not blocked by these agents. Thus, the present antiplatelet strategies might be modified. Moreover, novel agents should have been developed, including intravenous P2Y12 antagonists and oral antagonist targeting the protease-activated receptor-1 platelet activation pathway triggered by thrombin. Although the current animal models have strongly supported the idea that the DAPT has a positive protective effect on patients with ACS, more experiments still should take into consideration to elucidate the novel mechanism. In the end, current and novel antiplatelet strategies and controversies associated with antiplatelet therapy also need to be further explored and warranted.

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