MEDDOCS Open Access Publisher

ISSN: 2637-4900

Journal of Community Medicine

Open Access | Research Article

The Role of Current Major Antiplatelet Agents in Cardiovascular Diseases

Zhiyou Zhou[1,2]; Lianfang Huang[1]; Hui Luo[1]*; Xiao Zhu[1]*

[1]The Marine Biomedical Research Institute, Guangdong Medical University, Zhanjiang, China

[2]Department of Cardiovascular Internal Medicine Department, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

***Corresponding Author(s): Xiao Zhu & Hui Luo**

The Marine Biomedical Research Institute, Guangdong Medical University, Zhanjiang, China.

Email: xzhu@gdmu.edu.cn & luohui@gdmu.edu.cn

Received: July 23, 2020

Accepted: Aug 25, 2020

Published Online: Aug 28, 2020

Journal: Journal of Community Medicine

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

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

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.

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.

Cite this article: Zhou Z, Huang L, Luo H, Zhu X. The Role of Current Major Antiplatelet Agents in Cardiovascular Diseases. J Community Med. 2020; 3(1): 1021.

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 sheer, platelets are Activated, and Aadenosine Diphosphate (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 Glycoprotein (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 antiplatelet 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 antithrombotic 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 acetylating serine 529 in the platelet COX-1enzyme, 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 of30 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 inpatients 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 antiplatelet 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 resultsare 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 Glycoprotein GPIIlb / 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 asa 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 complications [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 antiplatelet agents, isdistinct from thienopyridines and ADP analogs [44]. Besides, ticagrelor, a reversibly and orally component, 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 unrestraint 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 adenosine has been related to the selective inhibition of sodium- independente quilibrate nucleoside transporter (ENT1) at concentrations of clinical relevance [3]. (Figure 2). Distinct from the strong adenosine uptake inhibitor dipyridamole, 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 havea great impact on adenosine uptake. Comparing to ENT1 affinity, ticagrelorhas 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, ticagrel or greatly enhanced the area under the curve of Coronary Blood Flow Velocity (CBFV) versus the adenosine dose caused by placebo. Ticagrelor plasma concentrations and an increase in the area under the curve 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 cardio protection. Animals received the corresponding maintenance doses of the anti platelet 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 ticagrel or 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, ticagrel or not reduced the inflammatory cytokines level of interleukin 6 and tumor necrosis factor alpha, but also improved a diponectin 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 topotent 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 without 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 led 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 led 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 denylyl 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 occurin 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 suggests 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 cardio 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].

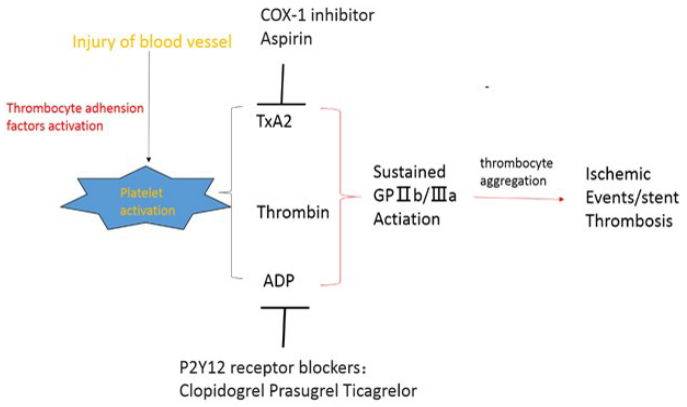

Figure 1: The targets of antiplatelet (aspirin, clopidogrel, prasugrel, ticagrelor).

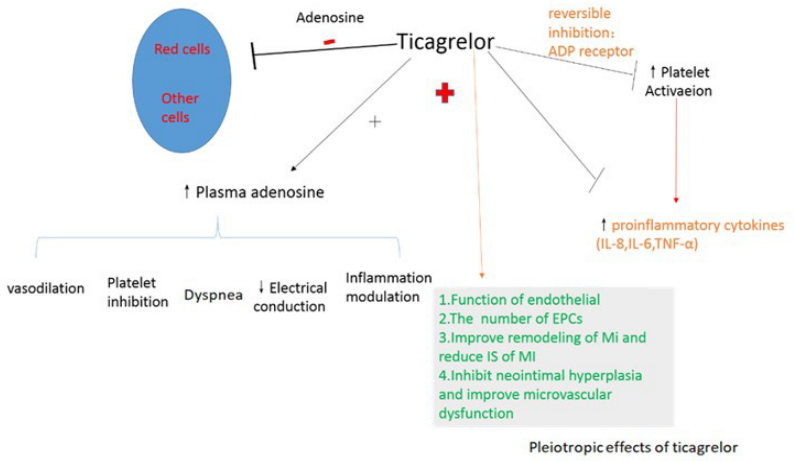

Figure 2: Pleiotropic effects of ticagrelor. Ticagrelor reduces vascular inflammation by inhibiting the activation of the P2Y 12 receptor pathway, thereby reducing the proinflammatory factors. In addition, ticagrelor augments extracellular adenosine concentrations by inhibiting the absorption of red cell and other cells, leading to multiple potential positive or adverse effects and additional clinical beneficial effects.

Table 1: Pharmacological action of antiplatelet agents.

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

Table 2: The effects of ticagrelor and adenosine.

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

Discussion

Aspirin has been recognized as the cornerstone of APT to treat a therothrombotic 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 anti platelet 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 P2Y 12 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 anti platelet 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 inhibitCOX-2 mediated production of the vasodilator prost acyclin 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 anti platelet 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 anti platelet 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 anti platelet strategies might be modified. Moreover, novel agents should have been developed, including intravenous P2Y 12 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 anti platelet strategies and controversies associated with anti platelet therapy also need to be further explored and warranted.

References

1. Goli RR, Contractor MM, Nathan A, Tuteja S, Kobayashi T, et al: Antiplatelet Therapy for Secondary Prevention of Vascular Disease Complications. Curr Atheroscler. 2017: 19: 56.
2. Vogtle T, Cherpokova D, Bender M, Nieswandt B: Targeting platelet receptors in thrombotic and thrombo-inflammatory disorders. Hamostaseologie. 2015; 35: 235-243.
3. Wittfeldt A, Emanuelsson H, Brandrup-Wognsen G, van Giezen JJ, Jonasson J, et al: Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans. J Am Coll Cardiol. 2013; 61: 723-727.
4. Serebruany VL: Mortality benefit in PLATO cannot be explained by antiplatelet properties of ticagrelor. Cardiology. 2010; 117: 231-233.
5. Loll PJ, Picot D, Garavito RM: The structural basis of aspirin activity inferred from the crystal structure of inactivated prostaglandin H2 synthase. Nat Struct Biol 1995; 2: 637-643.
6. Luscher TF, Steffel J: Individualized antithrombotic therapy. Hamostaseologie. 2016; 36: 26-32.
7. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J: Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008; 133: 844S-886S.
8. Prech M, Bartela E, Janus M, Jeremicz I, Araszkiewicz A, Urbanska L, et al: Effect of a combination of antiplatelet and antithrombotic pretreatment on myocardial perfusion in patients with an acute ST-segment elevation myocardial infarction undergoing a primary percutaneous coronary intervention. Coron Artery Dis. 2016; 27: 580-585.
9. Becker RC, Meade TW, Berger PB, Ezekowitz M, O'Connor CM, et al: The primary and secondary prevention of coronary artery disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133: 776S-814S.
10. Vogel B, Baber U: Antiplatelet treatments: recent evidence from randomized controlled trials. Curr Opin Cardiol. 2017; 32: 356-362.
11. Myat A, Tantry US, Kubica J, Gurbel PA: Current controversies in the use of aspirin and ticagrelor for the treatment of thrombotic events. Expert Rev Cardiovasc Ther. 2016; 14: 1361-1370.
12. Duffy D, Rooney B, Adams S, Whellan DJ: PA32540 for the secondary prevention of cardiovascular disease in patients at risk for aspirin-associated gastric ulcers. Expert Rev Cardiovasc Ther. 2014; 12: 1251-1260.
13. Kagolanu D, Sayedy N, Haseeb S, Shah S, Lam P, et al: Usefulness of PA32540 in Protecting the Gastric Layer While Providing Secondary Prevention for Coronary Artery Disease. Am J Cardiol. 2017; 120: 1118-1121.
14. Zhang JW, Liu WW, McCaffrey TA, He XQ, Liang WY, et al: Predictors of high on-aspirin platelet reactivity in elderly patients with coronary artery disease. Clin Interv Aging. 2017; 12: 1271-1279.
15. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Harmsze AM, et al: High on-treatment platelet reactivity to both aspirin and clopidogrel is associated with the highest risk of adverse events following percutaneous coronary intervention. Heart. 2011; 97: 983-990.
16. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ten Berg JM, et al: High on-aspirin platelet reactivity as measured with aggregation-based, cyclooxygenase-1 inhibition sensitive platelet function tests is associated with the occurrence of atherothrombotic events. J Thromb Haemost. 2010; 8: 2140-2148.

17. Bulluck H, Kwok CS, Ryding AD, Loke YK: Safety of short-term dual antiplatelet therapy after drug-eluting stents: An updated meta-analysis with direct and adjusted indirect comparison of randomized control trials. Int J Cardiol. 2015; 181: 331-339.

18. Washam JB, Dolor RJ, Jones WS, Halim SA, Hasselblad V, et al: Dual antiplatelet therapy with or without oral anticoagulation in the postdischarge management of acute coronary syndrome patients with an indication for long term anticoagulation: a systematic review. J Thromb Thrombolysis. 2014; 38: 285-98.

19. Mulukutla SR, Marroquin OC, Vlachos HA, Selzer F, Toma C, Kip KE, et al: Benefit of long-term dual anti-platelet therapy in patients treated with drug-eluting stents: from the NHLBI dynamic registry. Am J Cardiol. 2013; 111: 486-92.

20. Ebrahimi R, Gupta S, Carr BM, Bishawi M, Bakaeen FG, Almassi GH, et al: Comparison of Outcomes and Costs Associated With Aspirin +/- Clopidogrel After Coronary Artery Bypass Grafting. Am J Cardiol. 2018; 121: 709-714.

21. Yeh RW, Kereiakes DJ, Steg PG, Cutlip DE, Croce KJ, et al: Lesion Complexity and Outcomes of Extended Dual Antiplatelet Therapy After Percutaneous Coronary Intervention. J Am Coll Cardiol. 2017; 70: 2213-2223.

22. Hahn JY, Song YB, Oh JH, Cho DK, Lee JB, et al: 6-month versus 12- month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. Lancet. 2018; 391: 1274-1284.

23. Alrifai A, Soud M, Kabach A, Jobanputra Y, Masrani A, et al: Dual antiplatelet therapy versus single antiplatelet therapy after transaortic valve replacement: Meta-analysis. Cardiovasc Revasc Med. 2018; 19: 47-52.

24. Secemsky EA, Yeh RW, Kereiakes DJ, Cutlip DE, Steg PG, Massaro JM, et al: Extended Duration Dual Antiplatelet Therapy After Coronary Stenting Among Patients With Peripheral Arterial Disease: A Subanalysis of the Dual Antiplatelet Therapy Study. JACC Cardiovasc Interv. 2017; 10:942-954.

25. Yin D, Matsumura M, Rundback J, Yoho JA, Witzenbichler B, Stone GW, et al: Comparison of plaque morphology between peripheral and coronary artery disease (from the CLARITY and ADAPT-DES IVUS substudies). Coron Artery Dis. 2017; 28:369-375.

26. Lemesle G, Lamblin N, Meurice T, Tricot O, Lallemant R, Nugue O, et al: Dual antiplatelet therapy in patients with stable coronary artery disease in modern practice: prevalence, correlates, and impact on prognosis (from the Suivi d'une cohorte de patients COROnariens stables en region NORd-Pas-de-Calais study). Am Heart J. 2014; 168: 479-486.

27. Hassan AE, Zacharatos H, Suri MF, Qureshi AI: Drug evaluation of clopidogrel in patients with ischemic stroke. Expert Opin Pharmacother. 2007; 8: 2825-2838.

28. Savi P, Herbert JM: Clopidogrel and ticlopidine: P2Y12 adenosine diphosphate-receptor antagonists for the prevention of atherothrombosis. Semin Thromb Hemost. 2005; 31: 174-183.

29. Dash D: Current Status of Antiplatelet Therapy in Acute Coronary Syndrome. Cardiovasc Hematol Agents Med Chem. 2015; 13: 40-49.

30. Tcheng JE, Mackay SM: Prasugrel versus clopidogrel antiplatelet therapy after acute coronary syndrome: matching treatments with patients. Am J Cardiovasc Drugs. 2012; 12: 83-91.

31. Marsousi N, Daali Y, Fontana P, Reny JL, Ancrenaz-Sirot V, Calmy A, et al: Impact of Boosted Antiretroviral Therapy on the Pharmacokinetics and Efficacy of Clopidogrel and Prasugrel Active Metabolites. Clin Pharmacokinet. 2018; 57: 1347-1354.

32. Hernandez-Suarez DF, Nunez-Medina H, Scott SA, Lopez-Candales A, Wiley JM, Garcia MJ, et al: Effect of cilostazol on platelet reactivity among patients with peripheral artery disease on clopidogrel therapy. Drug Metab Pers Ther. 2018; 33: 49-55.

33. Brown SA, Pereira N: Pharmacogenomic Impact of CYP2C19 Variation on Clopidogrel Therapy in Precision Cardiovascular Medicine. J Pers Med 8,.2018.

34. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al: Special article 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Rev Esp Cardiol (Engl Ed); 2018; 71: 42.

35. Bernlochner I, Byrne RA, Kastrati A, Sibbing D: The future of platelet function testing to guide therapy in clopidogrel low and enhanced responders. Expert Rev Cardiovasc Ther 2011; 9: 999-1014

36. Wei Z, Huang L, Cui L, Zhu X: Mannose: Good player and assister in pharmacotherapy. Biomed Pharmacother. 2020; 129: 110420.

37. Liang X, Li D, Leng S, Zhu X: RNA-based pharmacotherapy for tumors: From bench to clinic and back. Biomed Pharmacother.2020; 125: 109997.

38. Liang B, Ding H, Huang L, Luo H, Zhu X: GWAS in cancer: progress and challenges. Mol Genet Genomics. 2020; 295: 537-561.

39. Salzler GG, Farber A, Rybin DV, Doros G, Siracuse JJ, Eslami MH: The association of Carotid Revascularization Endarterectomy versus Stent Trial (CREST) and Centers for Medicare and Medicaid Services Carotid Guideline Publication on utilization and outcomes of carotid stenting among "high-risk" patients. J Vasc Surg. 2017; 66: 104-111 e1.

40. Lal BK, Meschia JF, Brott TG: Clinical need, design, and goals for the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis trial. Semin Vasc Surg. 2017; 30: 2-7.

41. Wu Y, Zhou Y, Pan Y, Zhao X, Liu L, Wang D, et al: Impact of CYP2C19 polymorphism in prognosis of minor stroke or TIA patients with declined eGFR on dual antiplatelet therapy: CHANCE substudy. Pharmacogenomics J. 2018; 18:713-720.

42. JJ VANG, Nilsson L, Berntsson P, Wissing BM, Giordanetto F, Tomlinson W, et al: Ticagrelor binds to human P2Y(12) independently from ADP but antagonizes ADP-induced receptor signaling and platelet aggregation. J Thromb Haemost . 2009; 7: 1556-65.

43. Danielak D, Karazniewicz-Lada M, Glowka F: Ticagrelor in modern cardiology – an up-to-date review of most important aspects of ticagrelor pharmacotherapy. Expert Opin Pharmacother. 2018; 19: 103-112.

44. Capodanno D, Dharmashankar K, Angiolillo DJ: Mechanism of action and clinical development of ticagrelor, a novel platelet ADP P2Y12 receptor antagonist. Expert Rev Cardiovasc Ther. 2010; 8: 151-158.

45. Vilahur G, Gutierrez M, Casani L, Varela L, Capdevila A, Pons-Llado G, et al: Protective Effects of Ticagrelor on Myocardial Injury After Infarction. Circulation. 2016; 134: 1708-1719.

46. Cattaneo M, Schulz R, Nylander S: Adenosine-mediated effects of ticagrelor: Evidence and potential clinical relevance. J Am Coll Cardiol. 2014; 63: 2503-2509.

47. Armstrong D, Summers C, Ewart L, Nylander S, Sidaway JE, van Giezen JJ: Characterization of the adenosine pharmacology of ticagrelor reveals therapeutically relevant inhibition of equili-

brative nucleoside transporter 1. J Cardiovasc Pharmacol Ther. 2014; 19: 209-219.

48. Nardin M, Verdoia M, Pergolini P, Rolla R, Barbieri L, Marino P, et al: Impact of adenosine A2a receptor polymorphism rs5751876 on platelet reactivity in ticagrelor treated patients. Pharmacol Res. 2018; 129: 27-33.

49. Alexopoulos D, Moulias A, Koutsogiannis N, Xanthopoulou I, Kakkavas A, Mavronasiou E, et al: Differential effect of ticagrelor versus prasugrel on coronary blood flow velocity in patients with non-ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention: an exploratory study. Circ Cardiovasc Interv. 2013; 6: 277-283.

50. Yao D, Huang L, Ke J, Zhang M, Xiao Q, et al: Bone metabolism regulation: Implications for the treatment of bone diseases. Biomedicine & Pharmacotherapy.2020; 129.

51. Liang G, Fan W, Luo H, Zhu X: The emerging roles of artificial intelligence in cancer drug development and precision therapy. Biomed Pharmacother. 2020; 128:110255.

52. Li K, Luo H, Huang L, Luo H, Zhu X: Microsatellite instability: a review of what the oncologist should know. Cancer Cell Int. 2020; 20:16.

53. Ye Y, Birnbaum GD, Perez-Polo JR, Nanhwan MK, Nylander S, Birnbaum Y: Ticagrelor protects the heart against reperfusion injury and improves remodeling after myocardial infarction. Arterioscler Thromb Vasc Biol. 2015; 35: 1805-1814.

54. van Giezen JJ, Sidaway J, Glaves P, Kirk I, Bjorkman JA: Ticagrelor inhibits adenosine uptake in vitro and enhances adenosine-mediated hyperemia responses in a canine model. J Cardiovasc Pharmacol Ther. 2012; 17: 2164-2172.

55. Vyas FS, Nelson CP, Dickenson JM: Role of transglutaminase 2 in A1 adenosine receptor- and beta2-adrenoceptor-mediated pharmacological pre- and post-conditioning against hypoxia-reoxygenation-induced cell death in H9c2 cells. Eur J Pharmacol. 2018; 819: 144-160.

56. Babiker FA, Al-Jarallah A, Joseph S: Understanding pacing post-conditioning-mediated cardiac protection: a role of oxidative stress and a synergistic effect of adenosine. J Physiol Biochem. 2017; 73: 175-185.

57. Djerada Z, Feliu C, Richard V, Millart H: Current knowledge on the role of P2Y receptors in cardioprotection against ischemia-reperfusion. Pharmacol Res. 2017; 118: 5-18.

58. Jeong HS, Hong SJ, Cho SA, Kim JH, Cho JY, et al: Comparison of Ticagrelor Versus Prasugrel for Inflammation, Vascular Function, and Circulating Endothelial Progenitor Cells in Diabetic Patients With Non-ST-Segment Elevation Acute Coronary Syndrome Requiring Coronary Stenting: A Prospective, Randomized, Crossover Trial. JACC Cardiovasc Interv. 2017; 10: 1646-1658.

59. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, et al: Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. N Engl J Med. 2017; 376: 32-40.

60. Guo B, Li D, Du L, Zhu X: piRNAs: biogenesis and their potential roles in cancer. Cancer Metastasis Rev. 2020; 39: 567-575.

61. Tang X, Huang Y, Lei J, Luo H, Zhu X: The single-cell sequencing: new developments and medical applications. Cell Biosci. 2019; 9: 53.

62. Tang J, Xu Z, Huang L, Luo H, Zhu X: Transcriptional regulation in model organisms: recent progress and clinical implications. Open Biol 9:190183, 2019

63. Liu J, Li D, Luo H, Zhu X: Circular RNAs: The star molecules in cancer. Mol Aspects Med. 2019; 70: 141-152.

64. Jones WS, Baumgartner I, Hiatt WR, Heizer G, Conte MS, White CJ, et al: Ticagrelor Compared With Clopidogrel in Patients With Prior Lower Extremity Revascularization for Peripheral Artery Disease. Circulation. 2017; 135: 241-250.

65. Patel MR, Becker RC, Wojdyla DM, Emanuelsson H, Hiatt WR, Horrow J, et al: Cardiovascular events in acute coronary syndrome patients with peripheral arterial disease treated with ticagrelor compared with clopidogrel: Data from the PLATO Trial. Eur J Prev Cardiol. 2015; 22: 734-742.

66. Pelletier-Galarneau M, Hunter C, Ascah KJ, Beanlands RSB, Dwivedi G, deKemp RA, et al: Randomized Trial Comparing the Effects of Ticagrelor Versus Clopidogrel on Myocardial Perfusion in Patients With Coronary Artery Disease. J Am Heart Assoc. 2017; 6.

67. Olinic DM, Tataru DA, Homorodean C, Spinu M, Olinic M: Antithrombotic treatment in peripheral artery disease. Vasa. 2018; 47: 99-108.

68. Hess CN, Huang Z, Patel MR, Baumgartner I, Berger JS, Blomster JI, et al: Acute Limb Ischemia in Peripheral Artery Disease: Insights from EUCLID. Circulation. 2019.

69. Kolls BJ, Sapp S, Rockhold FW, Jordan JD, Dombrowski KE, Fowkes FGR, et al: Stroke in Patients With Peripheral Artery Disease. Stroke. 2019; 50: 1356-1363.

70. Nastasi DR, Smith JR, Moxon JV, Trollope A, Golledge J: Prescription of Pharmacotherapy and the Incidence of Stroke in Patients With Symptoms of Peripheral Artery Disease. Stroke. 2018; 49: 2953-2960.

71. Song C, Kong Y, Huang L, Luo H, Zhu X: Big data-driven precision medicine: Starting the custom-made era of iatrology. Biomed Pharmacother 129:110445, 2020

72. Li Y, Tao T, Du L, Zhu X: Three-dimensional genome: developmental technologies and applications in precision medicine. J Hum Genet. 2020; 65:497-511.

73. Berger JS, Abramson BL, Lopes RD, Heizer G, Rockhold FW, Baumgartner I, et al: Ticagrelor versus clopidogrel in patients with symptomatic peripheral artery disease and prior coronary artery disease: Insights from the EUCLID trial. Vasc Med. 2018; 23: 523-530.

74. Low Wang CC, Blomster JI, Heizer G, Berger JS, Baumgartner I, Fowkes FGR, et al: Cardiovascular and Limb Outcomes in Patients With Diabetes and Peripheral Artery Disease: The EUCLID Trial. J Am Coll Cardiol. 2018; 72: 3274-3284.

75. Olivier CB, Mulder H, Hiatt WR, Jones WS, Fowkes FGR, Rockhold FW, et al: Incidence, Characteristics, and Outcomes of Myocardial Infarction in Patients With Peripheral Artery Disease: Insights From the EUCLID Trial. JAMA Cardiol; 4: 7-15.

76. Ghibes P, Partovi S, Grozinger G, Martirosian P, Schick F, Nikolaou K, et al: Reliability and Accuracy of Peri-Interventional Stenosis Grading in Peripheral Artery Disease Using Color-Coded Quantitative Fluoroscopy: A Phantom Study Comparing a Clinical and Scientific Postprocessing Software. Biomed Res Int. 2018; 2018: 6180138.

77. Saw J, Wong GC, Mayo J, Bernstein V, Mancini GB, Ye J, et al: Ticagrelor and aspirin for the prevention of cardiovascular events after coronary artery bypass graft surgery. Heart. 2016; 102: 763-769.

78. Bhavaraju K, Georgakis A, Jin J, Gartner TK, Tomiyama Y, Nurden A, et al: Antagonism of P2Y(1)(2) reduces physiological thromboxane levels. Platelets. 2010; 21: 604-609.

79. Paul BZ, Jin J, Kunapuli SP: Molecular mechanism of thromboxane A(2)-induced platelet aggregation. Essential role for p2t(ac) and alpha(2a) receptors. J Biol Chem. 1999; 274: 29108-29114.

80. Zhao Q, Zhu Y, Xu Z, Cheng Z, Mei J, Chen X, et al: Effect of Ticagrelor Plus Aspirin, Ticagrelor Alone, or Aspirin Alone on Saphenous Vein Graft Patency 1 Year After Coronary Artery Bypass Grafting: A Randomized Clinical Trial. JAMA. 2018; 319: 1677-1686.

81. Kirkby NS, Leadbeater PD, Chan MV, Nylander S, Mitchell JA, Warner TD: Antiplatelet effects of aspirin vary with level of P2Y(1)(2) receptor blockade supplied by either ticagrelor or prasugrel. J Thromb Haemost. 2011; 9: 2103-2105.

82. Gurbel PA, Bliden KP, DiChiara J, Newcomer J, Weng W, Neerchal NK, et al: Evaluation of dose-related effects of aspirin on platelet function: results from the Aspirin-Induced Platelet Effect (ASPECT) study. Circulation. 2007; 115: 3156-64.

83. Zhu X, Luo H, Xu Y: Transcriptome analysis reveals an important candidate gene involved in both nodal metastasis and prognosis in lung adenocarcinoma. Cell Biosci. 2019; 9: 92.

84. Zou Z, Tao T, Li H, Zhu X: mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges. Cell Biosci. 2020; 10: 31.

85. Park SD, Baek YS, Woo SI, Kim SH, Shin SH, Kim DH, et al: Comparing the effect of clopidogrel versus ticagrelor on coronary microvascular dysfunction in acute coronary syndrome patients (TIME trial): study protocol for a randomized controlled trial. Trials. 2014; 15: 151.

86. Wu B, Lin H, Tobe RG, Zhang L, He B: Ticagrelor versus clopidogrel in East-Asian patients with acute coronary syndromes: a meta-analysis of randomized trials. J Comp Eff Res. 2018; 7: 281-291.

87. Xiao Q, Yu H, Zhu X: The associations of hub gene polymorphisms in PI3K/AKT/mTOR pathway and Schistosomiasis Japonica infection and hepatic fibrosis. Infect Genet Evol. 2020; 85: 104423.

88. Kang HJ, Clare RM, Gao R, Held C, Himmelmann A, James SK, et al: Ticagrelor versus clopidogrel in Asian patients with acute coronary syndrome: A retrospective analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. Am Heart J. 2015; 169: 899-905 e1.

89. Brandt JT, Payne CD, Wiviott SD, Weerakkody G, Farid NA, Small DS, et al: A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. Am Heart J. 2007; 153: 66 e9-16, 2007.

90. Jakubowski JA, Winters KJ, Naganuma H, Wallentin L: Prasugrel: a novel thienopyridine antiplatelet agent. A review of preclinical and clinical studies and the mechanistic basis for its distinct antiplatelet profile. Cardiovasc Drug Rev. 2007; 25: 357-374.

91. Sumaya W, Storey RF: Ticagrelor: Effects Beyond the P2Y12 Receptor. Interv Cardiol Clin. 2017; 6: 49-55.

92. Motovska Z, Hlinomaz O, Kala P, Hromadka M, Knot J, Varvarovsky I, et al: 1-Year Outcomes of Patients Undergoing Primary Angioplasty for Myocardial Infarction Treated With Prasugrel Versus Ticagrelor. J Am Coll Cardiol. 2018; 71:371-381.

93. Bundhun PK, Shi JX, Huang F: Head to head comparison of Prasugrel versus Ticagrelor in patients with acute coronary syndrome: a systematic review and meta-analysis of randomized trials. BMC Pharmacol Toxicol. 2017; 18: 80.

94. Savarese G, Lund LH: Ticagrelor versus prasugrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention: An unresolved issue. Int J Cardiol. 2017; 249: 77-78.

95. Song C, Sukul D, Seth M, Dupree JM, Khandelwal A, Dixon SR, et al: Ninety-Day Readmission and Long-Term Mortality in Medicare Patients (>/=65 Years) Treated With Ticagrelor Versus Prasugrel After Percutaneous Coronary Intervention (from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium). Am J Cardiol. 2017; 120: 1926-1932.

96. Ariotti S, van Leeuwen M, Brugaletta S, Leonardi S, Akkerhuis KM, Rexhaj E, et al: Rationale and design of the Hunting for the off-target propertIes of Ticagrelor on Endothelial function and other Circulating biomarkers in Humans (HI-TECH) trial. Am Heart J. 2017; 189: 128-136.

97. Kim HK, Jeong MH, Lim KS, Kim JH, Lim HC, Kim MC, et al: Effects of ticagrelor on neointimal hyperplasia and endothelial function, compared with clopidogrel and prasugrel, in a porcine coronary stent restenosis model. Int J Cardiol. 2017; 240: 326-331.

98. Bonello L, Frere C, Cointe S, Laine M, Mancini J, Thuny F, et al: Ticagrelor increases endothelial progenitor cell level compared to clopidogrel in acute coronary syndromes: A prospective randomized study. Int J Cardiol. 2015; 187: 502-507.

99. Liang B, Yu H, Huang L, Luo H, Zhu X: A prognostic model guides surgical resection in cervical squamous cell carcinoma. Translational Cancer Research. 2020; 9: 1711-1731.

100. Li H, He Y, Huang L, Luo H, Zhu X: The Nomogram Model Predicting Overall Survival and Guiding Clinical Decision in Patients With Glioblastoma Based on the SEER Database. Frontiers in Oncology. 2020; 10.

101. Janssens GN, van Leeuwen MA, van der Hoeven NW, de Waard GA, Nijveldt R, Diletti R, et al: Reducing Microvascular Dysfunction in Revascularized Patients with ST-Elevation Myocardial Infarction by Off-Target Properties of Ticagrelor versus Prasugrel. Rationale and Design of the REDUCE-MVI Study. J Cardiovasc Transl Res. 2016; 9: 249-256.

102. Grzesk G, Kozinski M, Navarese EP, Krzyzanowski M, Grzesk E, Kubica A, et al: Ticagrelor, but not clopidogrel and prasugrel, prevents ADP-induced vascular smooth muscle cell contraction: a placebo-controlled study in rats. Thromb Res . 2012; 130: 65-69.

103. Nijjer SS, Davies JE, Francis DP: Quantitative comparison of clopidogrel 600 mg, prasugrel and ticagrelor, against clopidogrel 300 mg on major adverse cardiovascular events and bleeding in coronary stenting: synthesis of CURRENT-OASIS-7, TRITON-TIMI-38 and PLATO. Int J Cardiol. 2012; 158: 181-185.

104. Ahn KT, Seong SW, Choi UL, Jin SA, Kim JH, Lee JH, et al: Comparison of 1-year clinical outcomes between prasugrel and ticagrelor versus clopidogrel in type 2 diabetes patients with acute myocardial infarction underwent successful percutaneous coronary intervention. Medicine (Baltimore). 2019; 98: e14833.

105. Vaidya GN, Khan A, Ghafghazi S: Effect of morphine use on oral P2Y12 platelet inhibitors in acute myocardial infarction: Meta-analysis. Indian Heart J. 2019; 71: 126-135.

106. Dawwas GK, Dietrich E, Winchester D, Winterstein AG, Segal R, Park H: Comparative Effectiveness and Safety of Ticagrelor versus Prasugrel in Patients with Acute Coronary Syndrome: A Retrospective Cohort Analysis. Pharmacotherapy, 2019.

107. Mizuno M, Ito Y, Sugidachi A: A novel porcine model of thrombotic myocardial infarction with cardiac dysfunction sensitive to dual antiplatelet therapy. Eur J Pharmacol. 2018; 834: 103-108.

108. Audia JP, Yang XM, Crockett ES, Housley N, Haq EU, O'Donnell K, et al: Caspase-1 inhibition by VX-765 administered at reper-

fusion in P2Y12 receptor antagonist-treated rats provides long-term reduction in myocardial infarct size and preservation of ventricular function. Basic Res Cardiol. 2018; 113: 32.

109. Liu X, Gu Y, Liu Y, Zhang M, Wang Y, Hu L: Ticagrelor attenuates myocardial ischaemia-reperfusion injury possibly through downregulating galectin-3 expression in the infarct area of rats. Br J Clin Pharmacol. 2018; 84: 1180-1186.

110. Branchford BR, Stalker TJ, Law L, Acevedo G, Sather S, Brzezinski C, et al: The small-molecule MERTK inhibitor UNC2025 decreases platelet activation and prevents thrombosis. J Thromb Haemost. 2018; 16: 352-363.

111. Kumar M, Kasala ER, Bodduluru LN, Dahiya V, Sharma D, Kumar V, et al: Animal models of myocardial infarction: Mainstay in clinical translation. Regul Toxicol Pharmacol. 2016; 76: 221-30.