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THE SUCCESS OF DIFFERENT APPROACHES TO THE DEVELOPMENT TO ANTIPLATELET DRUGS

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Key words:

Platelet aggregation, antiplatelet drugs, triples antiplatelet therapy.

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ABSTRACT: The aim of this research is to precisely discuss and appraise the success of different approaches to the development to antiplatelet drugs. Platelets play a main function in haemostasis and the development of arterial thrombosis that is the final event complicating cardiovascular diseases and peripheral vascular diseases, and antiplatelet drugs improve survival of patients with these diseases. Antiplatelet drugs are aimed to avert and/or reverse platelets aggregation in arterial thrombosis, most significantly in myocardial infarction (MI), ischaemic stroke, and peripheral artery disease. The current therapeutic strategies aimed at inhibiting platelet aggregation: inhibition of cyclooxygenase, such as aspirin; inhibition of phosphodiesterases III and V and adenosine uptake by red blood cells, such as dipyridamole and cilostazol; inhibition of the platelet adenosine diphosphate (ADP) P2Y12 receptor, such as ticlopidine and clopidogrel; inhibition of glycoprotein IIb/IIIa receptors that prevent fibrinogen binding, such as abciximab; and increasing nitric oxide level, such as triflusal. A range of new drugs are currently in different phases of clinical trials, including reloading of clopidogrel, the improvement of drug efficacy, thrombin receptor inhibition, thromboxane receptor inhibition, oral glycoprotein IIb/IIIa inhibition, phosphodiesterases inhibitors, and signalling pathways inhibition are revolution in the development of antiplatelet drugs. A greater understanding of a patient response can improve the efficacy and safety of antiplatelet therapy. This can be achieved by drug dose adjustment based on functional testing, by changing drugs combination, or by developing more potent and safer drugs.

INTRODUCTION: Platelets play a main function in haemostasis and the development of arterial thrombosis that is the final event complicating cardiovascular diseases and peripheral vascular diseases, and antiplatelet drugs improve survival of patients with these diseases [1, 2, 3, 4].

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Platelets are produced and freed into the bloodstream by megakaryocytic that live within the bone marrow [5]. They lack a nucleus and do not synthesise new proteins [6]. Platelets are disc-shaped and about 2µm in diameter, and highly refractive [7, 8]. Platelets lifespan is approximately 10 days, after which they destroyed by macrophages in the spleen and liver. A normal platelet count in healthy individual is between 150,000 and 400,000 per mm^3 of blood (150-400 $X10^9$/I) [7, 9, 10].

This range changes extremely little in health, proposing that a homeostatic mechanism controls

production of thrombocytes [9]. Platelets contain contractile protein actin, myosin and thrombosthenin that can lead the platelets to contract and are therefore can cause clot retraction [11]. Platelets contain two or eight mitochondria per cell [12], which can produce adenosine-5'-triphosphate (ATP) and ADP, and can also synthesis prostaglandins and thromboxane A2 [13].

When platelets are activated, they undergo a series of reactions, which are vital for haemostasis, significant for the curing of damaged tissues, and play a part in inflammation [14]. Platelets activation involves both a change in shape of the platelets and the release of ADP that can cause more aggregation [6]. In the first reaction, platelets adhere to damaged endothelium via von Willebrand [6] [14]. The stimulation by ADP, adrenaline, and collagen causes activation of platelet membrane phospholibase A_2 (PLA_2). PLA_2 separates membrane phospholipids and releases arachidonic acid that is converted into a cyclic endoperoxide by cyclooxygenase; thromboxane synthase then converts the cyclic endoperoxide into thromboxane A_2 [6]. Calcium (Ca^{2+}) mediated contraction of actin and myosin leads to the release of granules from cells [6].

Antiplatelet drugs are aimed to avert and/or reverse platelets aggregation in arterial thrombosis, most significantly in MI, ischaemic stroke, and peripheral artery disease [15]. Platelet aggregates as haemostatic plugs at the location of vascular injury, as a result of which bleeding is partial or detained in advance of plasma coagulation; this function of platelet aggregation is crucial [15]. Too much build up of platelets at places of atherosclerotic plaque rupture is one of the main pathogenic episodes precipitating arterial thrombus formation, causing acute MI, peripheral artery disease, and ischemic stroke [16].

This pathological process is responsible for more morbidity and mortality than any other disease process and, as a result, the platelet represents a key target for therapeutic intervention [16]. In relation to pathological effects, platelets aggregation is potentially fatal. Because in both, the pathological and the physiological, the mechanism of aggregation is similar, dividing the therapeutic from the damaging effects of antiplatelet therapy depends on exploiting differences in the pathophysiological environment where the aggregation takes place [15]. In practice, a positive balance between the beneficial and damaging effects of antiplatelet drugs can be achieved by treating patients with thrombotic risk evidently exceeds their risk of bleeding problems [17].

The aggregation process is caused by alterations in the normal haemodynamic and/or biochemical environment of circulating platelets [15]. Optical aggregometry technique was developed in 1960s to diagnose a range of obtained and inherited platelet imperfections and has been the gold standard for investigating platelet aggregation [18] [19].

Platelet aggregation can be quantified by recording the transmission of a light beam across a suspension of continually disturbed platelets in an aggregometer [20]. Optical aggregometry caused the finding of the first aggregation inhibitors, namely ATP and adenosine **Fig.1**; it has been examined first because of their close chemical association to proaggregatory ADP [21] [15]. ATP and adenosine, and other aggregation inhibitors have also been found effective in vivo, by preventing the formation and embolisation of platelet thrombi in injured arterioles and venules [22]. Inhibition of platelet aggregation has certainly become the most thrilling and extensive finding, because it established the therapeutic opportunity of preventing arterial thrombosis by antiplatelet drugs and started the era of their use for the prevention of MI and stroke [15].

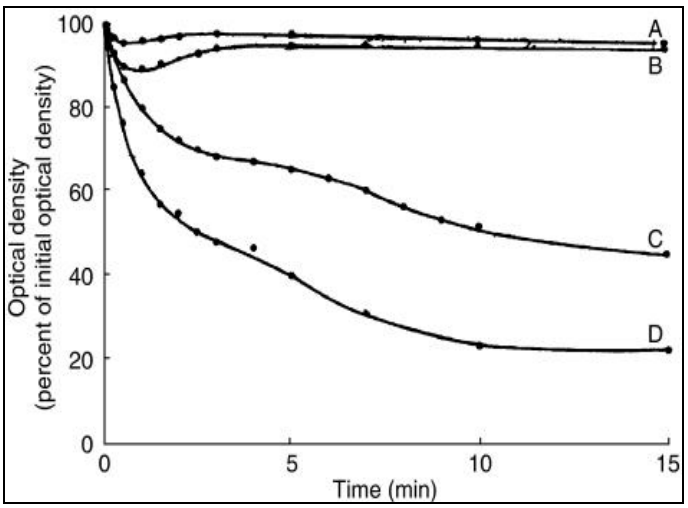

FIG. 1: PLATELET AGGREGATION WITH INCREASING CONCENTRATION OF ADP [15]

In 1965 the establishment had been made for the development of antiplatelet drugs as a new class of therapeutic agents; however it took so long until the basic principles and methodologies have been adequately known for the introduction of aspirin as the first antiplatelet drug to prevent coronary and cerebral thrombosis [15].

The current therapeutic strategies aimed at inhibiting platelet aggregation: inhibition of cyclooxygenase, such as aspirin; inhibition of phosphodiesterases III and V and adenosine uptake by red blood cells, such as dipyridamole and cilostazol; inhibition of the platelet ADP P2Y12 receptor, such as ticlopidine and clopidogrel; inhibition of glycoprotein IIb/IIIa receptors that prevent fibrinogen binding, such as abciximab; and increasing nitric oxide level, such as triflusal [23].

Aims:

The aim of this research project is to precisely discuss and appraise the success of different approaches to the development to antiplatelet drugs.

Literature review:

Development of new antiplatelet drugs:

Triple antiplatelet therapy:

Geeganage [23] found that triple antiplatelet therapy based on intravenous (IV) GPIIb/IIIa inhibitors was more effective than aspirin-based dual therapy in decreasing vascular events in patients with acute coronary syndromes (ACSs), ST elevation myocardial infarction (STEMI) and non-ST elevation acute coronary syndromes (NSTEMI). A large sample of 17,383 individuals with ischaemic heart disease was participated in twenty five completed randomised trials, using IV GP IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban), aspirin, clopidogrel and/or cilostazol [23]. In contrast to aspirin-based therapy, triple therapy using an IV GP IIb/IIIa inhibitor significantly decreased vascular events and MI in patients with non-ST elevation ACSs and STEMI [23]. Geeganage [23] observed a significant decrease in death in STEMI patients treated with GP IIb/IIIa based triple therapy. Absolute event rates for composite vascular event are exhibited in **Fig. 2**; the patients benefiting from triple antiplatelet therapy was greater than the patients experiencing major bleeding [23]. The authors also observed increased in minor bleeding between STEMI and elective percutaneous coronary intervention (PCI) patients treated with a GP IIb/IIIa based triple therapy [23].

In relation to stroke events, they could not recognise significant trends, and inadequate data occurred for patients employed into trials on the basis of stroke or peripheral vascular disease [23].

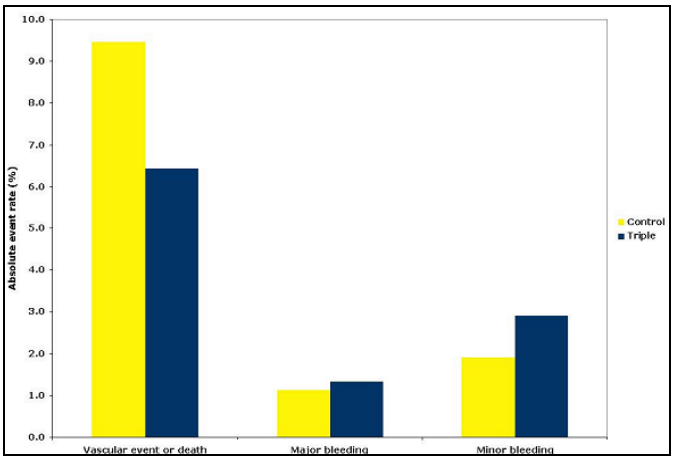

FIG. 2: ABSOLUTE EVENT RATES FOR VASCULAR EVENTS OR DEATH (EVENT/TOTAL: CONTROL =6/3891, TRIPLE =37/3969) AND BLEEDING (MAJOR, CONTROL =67/5926, TRIPLE =88/5988 AND MINOR, CONTROL =175/5733, TRIPLE =110/5796) IN TRIPLE ANTIPLATELET THERAPY (NSTE-ACS: GP IIb/IIIa, STEMI: GP IIb/IIIa, elective PCI: GP IIb/IIIa, cilostazol and clopidogrel) [23]

Yang [24] examined whether triple antiplatelet therapy can be maintained in diabetic patients, where platelet reactivity is raised and the stent thrombosis risk is higher. In this research study, 55 type-2 diabetic patients who underwent drug eluting stent (DES) implantation and chronic antiplatelet therapy (more than 1 month) were classified as stated by the status of antiplatelet therapy [24]. Optical aggregometry between dual (aspirin + clopidogrel, n=34) and triple therapy (aspirin, clopidogrel + cilostazol, n=21) had been used to compare platelet after ADP (10µmol/L and 20µmol/L) stimulation [24].

They found that the two groups had similar clinical and procedural characteristics; maximum ADP stimulated platelet aggregation was significantly lower in the triple therapy group compared with the dual therapy group, however there was no dissimilarities in diabetic treatment (oral hypoglycaemic drug vs. insulin) or diabetic control (haemoglobin A1c <7 vs. haemoglobin >7) [24].

Yang [24] concluded that triple antiplatelet therapy demonstrated more potent inhibition of maximum ADP stimulated platelet aggregation in patients with type-2 diabetes receiving chronic antiplatelet therapy. They also stated that this finding proposes that triple antiplatelet therapy might be more efficient for preventing thrombotic complication after DES implantation in patients with type-2 diabetes [24].

Reloading of clopidogrel:

This is aimed at improving effectiveness, and in consideration of the observed variable response to clopidogrel, the improved laboratory response was reported on increasing the loading dose from 300mg to 600mg and increasing the maintenance dose from 75mg/day to 150mg/day [25]. Matetzky *et al* [26] research study found that clopidogrel reloading and increased maintenance dose might overcome clopidogrel non-responsiveness in patients with acute MI. In this study, 30 patients had ADP stimulated platelet aggregation using optical aggregometry and were considered clopidogrel non-responders; non-responders were reloaded with clopidogrel 600mg, followed by 150mg/day for four weeks; a 75 mg/day dose was restarted afterward [26]. ADP stimulated platelet aggregation was assessed again four hours after reloading and every two weeks for ten weeks. Flow cytometry had been used to decide platelet P-selectin expression and fibrinogen binding before and four hours after reloading.

ADP stimulated platelet aggregation significantly reduced four hours after reloading. The reduction in platelet aggregation was maintained throughout the four weeks doubled maintenance dose [26]. After restarting a maintenance dose of 75mg/day, ADP stimulated platelet aggregation returned to 66+/-12%, and 5 patients (17%) had ADP stimulated platelet aggregation. Flow cytometry demonstrated a significantly reduce in P-selectin expression and fibrinogen binding in ADP induced platelet four hours after reloading [26].

Bonello *et al* [27] study evaluated the clinical effect of adjusting the loading dose of clopidogrel as indicated by vasodilator-stimulated phosphoprotein (VASP) index in patients with clopidogrel resistance undergoing PCI. 162 patients were participated in this randomised, multicentre study. Eight significant adverse cardiac events (5%) were recorded during the 1 month follow up, with a significantly lower rates in the VASP guided group compared to the control group [27]. The authors proposed that adjusting the clopidogrel loading dose as indicated by platelet monitoring using the VASP index is safe and might significantly improve the clinical result after PCI in patients with clopidogrel resistance regardless of the first 600mg loading dose [27].

A recent study stated that antiplatelet treatment using aspirin and clopidogrel is of significant importance after coronary stent [28]. This study found that the prevalence of clopidogrel or aspirin low response can be significantly decreased and the risk of insufficient dual antiplatelet therapy reduced [28]. Therefore, a person tailored therapy can significantly improve the effect of antiplatelet therapy in a greater number of patients after coronary stent and eradicate resistance to antiplatelet. In this study, platelet function testing using whole blood aggregometry was carried out 48 hours after coronary stent on 504 patients [28]. Of the total 504 patients, 30.8% clopidogrel low-responders and 19.4% aspirin low-responders had been detected. The antiplatelet treatment contained a loading dose of 600mg clopidogrel and 500mg aspirin, followed by 75mg clopidogrel and 100mg aspirin one a day [28].

The improvement of drug efficacy:

Different approaches have been used by the pharmaceutical industries aimed at improving the effect of thienopyridines derivatives [25]. The example of this drug is the prasugrel that was established to be more potent than clopidogrel, because of its higher rate change into active metabolite [29]. Additionally, by contrast to clopidogrel, prasugrel was not found to be affected by genetic variation in cytochrome P450 [30]. Wiviott *et al.*, [31] clinical trial compared the effect of prasugrel, a new thienopyridine to clopidogrel in ACS patients. 13,608 patients randomly participated in this trial. They found that in patients with ACSs with scheduled PCI, prasugrel therapy was linked to significantly decreased rates of ischemic events, and stent thrombosis, however with an increased risk of major bleeding, as well as

fatal bleeding; there was no significant difference in overall mortality between treatment groups [31].

In a group of patients with diabetes, the overall benefit of prasugrel was more significant, with an improved efficacy and a lower rate of major bleeding [32]. The Wiviott *et al.* [31] finding is in conformity with resistance of platelet drug observed in patients with diabetes, proposing more effectively potent drug in diabetic patients as compared to nondiabetic patients with ACS.

There are several other new P2Y12 inhibitors, which are presently at different phases of clinical development, including P2Y12 inhibitors that reversibly inhibit the P2Y12 receptor, such as ticagrelor, which is orally administered [25]. The study of platelet inhibition and patients outcomes (PLATO) trial in patients with an ACSs shown ameliorated CV outcomes, including decrease MI and vascular events using ticagrelor as compared to clopidogrel with comparable rates of major bleeding [33]. However, a mystifying finding from PLATO trial was the absence of benefit with ticagrelor in patients registered from the USA that had led to ticagrelor disapproval at USA [32].

Nawarskas *et al.*[33] concluded that ticagrelor is a new oral antiplatelet drug that is in final phases of clinical development; ticagrelor have many advantageous characteristics in contrast to thienopyridines clopidogrel and ticlopidine in relations to rapid, predictable, and reversible antiplatelet effects and clinical efficacy superior to clopidogrel without excessive bleeding, different from prasugrel; the major adverse effects of ticagrelor in clinical trials was dyspnoea that is of unidentified aetiology, however only rarely has led to drug been stopped. Extra benefits of ticagrelor are its efficacy in patients not responding to clopidogrel and absence of interaction with proton-pump inhibitors [32].

Different targets for antiplatelet therapy:

Thrombin receptor inhibitors:

Blockade of the higher affinity protease activated receptor-1 (PAR-1) is a new target for antiplatelet agents [25]. Becker *et al.* [33] study determined the tolerability and safety of vorapaxar, the oral PAR-1 antagonist. 257 patients aged 45 years or older and undergoing no urgent PCI or coronary angiography with planned PCI to an oral vorapaxar (10mg, 20mg, 40mg loading dose) or matching placebo in a 3:1 ratio were participated in a multicentre randomised clinical trial [34]. Becker *et al.* [33] found that oral vorapaxar was usually well tolerated and did not increase thrombolysis in myocardial infarction bleeding, even when given concomitantly with aspirin and clopidogrel. However, they stated that more examining in phase III trials to precisely state the safety and efficacy of vorapaxar is warranted [34].

Thromboxane receptor inhibition:

Thromboxane receptor inhibitors have defined pharmacological benefits over aspirin: as well to inhibiting the effect of TxA2 on platelets, they also block other thromboxane receptor ligands, such as endoperoxides, prostanoids and isoprostances [25]. Gaussem *et al.* [35] carried out a randomised multicentre double blinded pharmacokinetic and pharmacodynamic trial of a new oral thromboxane receptor antagonist S18886 in 30 patients with peripheral artery disease. The findings of this trial assist recognise the minimum efficient plasma concentration of S18886 needed for potent antiplatelet efficacy in patients with stable peripheral arterial disease [35].

Oral glycoprotein IIb/IIIa inhibition:

Many clinical trials have founded the advantages of IV glycoprotein IIb/IIIa inhibition in the management of coronary artery disease. By contrast, a very large, placebo controlled, randomised trials of the oral glycoprotein IIb/IIIa antagonists were unsuccessful in providing proportionate decrease in late composite ischemic end point in spite of potent inhibition of platelet aggregation [36]. In this study, the authors calculated and combined the odd ratios for death, MI, urgent revascularisation, and major bleeding from the four large samples, placebo controlled, randomised trials with oral glycoprotein IIb/IIIa inhibitors [36]. Chew *et al.* [36] found a high significant excess in mortality constant across the four clinical trials with three different oral glycoprotein IIb/IIIa inhibitors drugs, this was linked to a decrease in the required for urgent revascularisation and no increase in MI.

Blue *et al.* [37] study aimed at identifying $\alpha_{IIb}\beta3$ antagonists with novel structures. This low molecular weight compound target the αIIb unit and not β3 unit, when exposed to purified $\alpha_{IIb}\beta3$; it selectively blocks the αIIbβ3 receptor, with the absence of receptor priming and increased binding [25 37]. Derivative of this compound with potential higher affinity is under development; this compound can possibly permit chronic application of glycoprotein IIb/IIIa inhibitors [25].

Phosphodiesterases inhibitors:

Cilostazol, an oral phosphodiesterases III inhibitor with pleiotropic effect, as well to its antiplatelet effect, it was also shown to inhibit neointimal hyperplasia [38]. Biondi-Zoccai *et al.* [38] systematically reviewed 23 randomised clinical trials (5428 patients) on the angiographic and clinical effect of cilostazol after PCI. They concluded that cilostazol appears effective and safe in reducing the risk of restenosis and repeat revascularisation after PCI; however they stated that the available evidence has been limited by the effects of small studies [38].

Other double blind randomised clinical trial demonstrated that cilostazol appears to be no lesser, and may be greater, to aspirin for prevention of stroke after an ischaemic stroke, and was linked to less haemorrhagic events [39]. Thus, cilostazol might be used for prevention of stroke in patients with non-cardioembolic stroke [39]. 2757 patients were participated in this randomised clinical trial. 1379 patients have received cilostazol and 1378 have received aspirin, and 1337 patients were on cilostazol and 1335 were on aspirin [39]. The result showed that haemorrhagic events are fewer in patients on cilostazol than on aspirin [39].

Signalling pathways inhibition:

Having more knowledge about platelet signalling pathways opened new prospect for antiplatelet therapy [25]. The clinical usefulness of antagonists of the P2Y12 receptor for ADP proposes that other Platelet G protein coupled receptors and their intracellular signalling pathways might represent viable targets for novel antiplatelet drugs [40]. Interaction of the $\alpha_{IIb}\beta3$ integrin (fibrinogen receptor) with particular regulatory protein during $\alpha_{IIb}\beta3$ signalling might also give new targets for antiplatelet agent development [41]. In Smyth *et al.* [40] study, a β3(Δ760-762) knock-in mouse was produced that lacked the 3 C-terminal β3 residues (arginine-glycine-threonine [RGT]) essential for αIIbβ3 interaction with c-Src, but retained β3 residues essential for talin-dependent fibrinogen binding. Different from control mice, β3 (Δ760-762) mice were protected from carotid artery thrombosis after the injury of vessel with FeCI3. Some β3 (Δ760-762) mice showed long-lasting tail bleeding times; but, none showed spontaneous bleeding, surplus bleeding after surgery, faecal blood loss, or anaemia [40]. Fibrinogen binding to β3 (Δ760-762) platelets was normal in response to saturating concentration of protease-activated receptor-4 or glycoprotein VI agonists, however responses to adenosine diphosphate were damaged [40]. Therefore, deletion of β3 RGT disrupts c-Src–mediated $\alpha_{IIb}\beta3$ signalling and bestows protection from arterial thrombosis. As a result, targeting $\alpha_{IIb}\beta3$ signalling may represent a suitable antithrombotic strategy [40].

The defects of integrin signalling in the level of the β3 cytoplasmic domain may also affect αV β3 function in endothelia cells, and other cells; this should be examined in animal model in the future [40]. This development can be translated to a new class of antiplatelet drugs [25]. Wang *et al.* [42] study data proposed that β-nitrostyrenes might represent a new class of tyrosine kinase blockers with potent antiplatelet activities. β-nitrostyrenes derivatives blocked thrombin stimulated human platelet aggregation, ATP secretion, GPIIb/IIIa activation and protein tyrosine phosphorylation; new β-nitrostyrenes derivatives are now under development [42].

DISCUSSION: Dual antiplatelet treatment with aspirin and clopidogrel has been for many years the antiplatelet therapy of choice for patient with acute coronary syndrome and undergoing PCI. But despite the advantage of the combination between aspirin and clopidogrel, a substantial percentage of patients still present recurrent atherothrombetic events, causing the development of newer and more potent antiplatelet drugs, some of which have already been approved for clinical use, such as prasugrel and ticagrelor [43, 44, 45]. The recent approval of the first protease-activated receptor 1

(PAR1) antagonist as a novel antiplatelet drug by the Food and Drug Administration represents a potentially significant breakthrough in the treatment of thrombotic cardiovascular events and marks the long path from receptor discovery to clinical use [46].

The findings of the literature review indicated that triple antiplatelet therapy appears to be more effective to dual antiplatelet therapy in patients with ST-segment elevation myocardial infarction undergoing primary PCI with DESs. These findings might give the rationale for the use of triple antiplatelet therapy in these patients [47]. The findings also indicated that clopidogrel reloading research studies set the stage for the next step where increasing the dose, or altering the drug combination based on person laboratory response, is assessed for its potential beneficial effect on clinical result [25].

In relations to improving drug efficacy, the observation of improved efficacy attained by applying more potent P2Y12 inhibitors caused the start of many clinical trials intending to make a comparison between clinical results in ACS patients under standard combination therapy of aspirin and clopidogrel, and patients under adjusted higher dose of clopidogrel based on point of care functional testing [48]. The successful of vorapaxar, the PAR-1 inhibitor has now been moved into phase III clinical trials after demonstrating a better safety profile, even when added to the combination of aspirin and clopidogrel [34]. However, Becker *et al.*[34] state that the presently data should be carefully looked on because of the possible bias effect of small studies.

Thromboxane receptor inhibitors have defined pharmacological benefits over aspirin, and numerous thromboxane receptor inhibitors have been developed; however, not many have progressed into phase III trials due to safety issues [40]. Several clinical trials have stated the benefits of IV glycoprotein IIb/IIIa inhibition in the management of coronary artery disease. The derivatives of a new low molecular weight with unique characteristic have recently been developed [37]. Biondi-Zoccai *et al.* [38] systemic review showed that the oral phosphodiesterases III inhibitor, cilostazol appears effective and safe in reducing the risk of restenosis and repeat revascularisation after PCI; however they stated that the available evidence has been limited by the effects of small studies [38]. Having more knowledge about platelet signalling pathways opened new prospect for antiplatelet therapy [25]. The clinical usefulness of antagonists of the P2Y12 receptor for ADP proposes that other Platelet G protein coupled receptors and their intracellular signalling pathways might represent viable targets for novel antiplatelet drugs [40].

CONCLUSION: A greater understanding of a patient response can improve the efficacy and safety of antiplatelet therapy. This can be achieved by drug dose adjustment based on functional testing, by changing drugs combination, or by developing more potent and safer drugs.

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