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EVALUATION OF THE ROLE OF ANTIPLATELET MEDICATIONS IN CARDIOVASCULAR DISEASE

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ABSTRACT

Cardiovascular disease (CVD) and its complications are the most common causes of mortality and morbidity worldwide. It is shown that patients with myocardial infarctions (MIs) have high platelets activation and aggregation rates which lead to atherothrombosis after the rupture of an unstable atherosclerotic plaque. Therefore, antiplatelet therapy has become an important part of the secondary prevention of cardiovascular disease. To provide a review about the role of antiplatelet medications in preventing cardiovascular disease and its complications. The articles were selected in regards to the inclusion criteria, based on the incorporation of one of the following topics: antiplatelet action in cardiovascular disease. Exclusion principles were all other articles, which did not have one of these topics as their essential endpoint. PubMed database was utilized for articles selection, and the following keys were used in the mesh ((“antiplatelet"[Mesh]) AND (“cardiovascular disease” [Mesh]) OR (“DAPT"[Mesh])).
Aspirin was the first antiplatelet medicine identified, and it is still recommended as the first line of defense in the secondary prevention of cardiovascular disease. For many years, clopidogrel has been the predominant P2Y12 inhibitor in the acute context. peripheral angioplasty with stenting or Following elective percutaneous coronary intercession (PCI), the state-of-the-art dual antiplatelet treatment (DAPT) regimen includes clopidogrel plus aspirin. The appropriate DAPT length following stent implantation has been a topic of extreme controversy and considerable scientific interest. More research is necessary to determine the optimal duration that is safe and effective for post-PCI patients.

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Introduction

The most common cause of death and morbidity around the globe is cardiovascular disease. Coronary heart disease (also known as ischemic heart disease) and the leading mortality rate around the globe are strokes reported by the World Health Organization [1]. Patients with MI have increased platelet activation when compared to individuals with steady ischemic heart disease, and aggregation, leading to atherothrombosis following the rupture or fissuring of an unstable atherosclerotic plaque [2]. An increased risk of atherothrombosis can last for years after an MI, and stable ischemic heart disease patients who have had an MI are at a higher risk of major adverse cardiovascular events [3, 4].

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In the secondary prevention of CVD, pharmacological treatment is crucial. There is a lot of evidence that medications from numerous different kinds can help people live longer: examples of preventive medications are β-blockers, angiotensin receptor blockers/Angiotensin-converting enzyme inhibitors, and lipid-lowering medications [5, 6].
Nevertheless, we will focus in this study on antiplatelet medications only. Antiplatelet therapy has become a critical and an important part of the secondary prevention of cardiovascular disease [7]. We will give an overview of the currently available oral antiplatelet medications that are utilized in the treatment of cardiovascular disease, both acutely and long-term.

Materials and Methods

The articles were drafted in regards to the inclusion principles, based on the incorporation of one of the following topics: antiplatelet action in cardiovascular disease. Elimination criteria were all other articles, which did not have one of these topics as their essential endpoint.
PubMed database was utilized for articles selection, and the following keys were used in the mesh ((“antiplatelet"[Mesh]) AND (“cardiovascular disease”[Mesh]) OR (“DAPT"[Mesh])).
Around 211 publications were chosen as the most clinically relevant out of 4,376 articles indexed in the last decade, and their full texts were evaluated. A total of 42 of the 211 were included after a thorough examination. Additional research and publications were found using reference lists from the recognized and linked studies. Expert consensus recommendations and commentary were added where relevant to help practicing physicians assess cirrhosis most simply and practically possible.

Results and Discussion

Enucleated cytoplasmic remnants of megakaryocytes are platelets in the bone marrow that have a limited capability for protein synthesis. Despite the lack of DNA, platelets possess megakaryocyte mRNA, as well as protein-synthesis components and, are adequate for nuclear tasks such as pre-RNA splicing. Platelets have a 7–10 day lifetime once in circulation. Platelets' principal purpose is to prevent bleeding from vascular damage sites. This is done by involving numerous critical pro-activation mediators in the major platelet functional activities of adhesion, activation, cross-linking, and aggregation [8, 9].

Platelet Adhesion and Activation
The tethering of circulating platelets to a region of vascular damage initiates platelet adhesion. The platelet activation intact endothelium that usually limited by serving as a physical barrier to underlying thrombogenic chemicals (such as tissue factor, von Willebrand factor, and collagen,) and by releasing mediators that suppress platelet activation. All Pathways involved in this are the arachidonic acid- the L- endothelium ecto-adenosine diphosphatase (Ecto-ADPase), arginine nitric oxide pathway, and prostacyclin pathway [10].
Mechanism presumed to be mediated by protein kinase A in platelet activation decrease and raise platelet intracellular cAMP concentrations, (such as prostaglandin I2 (PGI2)), converting arachidonic acid to prostacyclin metabolites are Endothelial Cyclo-oxygenases I and II (COX-I and II) [11]. Endothelial cells create nitric oxide, which diffuses passively into platelets, activates cGMP-dependent protein kinases, and increase cytosolic cyclic guanine monophosphate (cGMP) levels, causing an intracellular calcium reduction [12].
Endothelial cells that surface the protein is Ecto-ADPase, when activated, restricts the platelet recruitment phase by lowering plasma concentrations of nucleotides, especially ADP [13]. Circulating platelets following endothelial damage are susceptible to subendothelial matrix proteins such as fibrinogen, von Willebrand factor, and collagen or susceptible to an active or impairment endothelium. These ligands can bind to receptors on inactivated platelets and anchor them to the area where the endothelial injury is at high shear rates. Platelet adhesion initiates platelet activation, which ends in the activation of the GPIIb/IIIa receptor, which allows it to bind soluble fibrinogen and von Wille brand factor, leading to solid platelet adhesion to the endothelium [14].

Mediators of Platelet Activation and ‘Outside-In’ Signaling
Platelets can be activated by a variety of non-chemical triggers. Hypothermia, trauma, and changes in acid-base balance are among them. Endogenous substances, operating via autocrine and paracrine processes, mediate most platelet activation in both the healthy and pathological settings. Collagen, thrombin, adenosine diphosphate, adrenaline, and thromboxane A2 are the most significant.

Thrombin and Collagen
The most powerful platelet stimulators are collagen and thrombin. Collagen binds precisely to GPVI and integrin 2 or GPIA/IIa are essential for platelet anchoring to vascular damage sites. Collagen linked to von Willebrand factor binds to other integrin receptors. Protein phosphorylation and, as a result, platelet activation occurs because of intracellular signaling mechanisms that occur after interaction [15]. The intrinsic, tissue factor-driven route of the coagulation cascade produces thrombin from its precursor prothrombin at areas of vascular damage.
Platelets appear to show a serious aspect in all phases of the vascular pathophysiology of the disease, especially atherosclerosis. Recently, evidence has shown that atherosclerosis is caused by the process of an active inflammatory kind than a benign

collection of intraluminal lipids. Through the release of mediators and the facilitation of interactions of platelets with other inflammatory cells, play a most important role in the formation and growth of atherosclerotic plaques. Interruption of blood flow that causes distal ischemia damage in atherosclerotic plaques that are unstable or vulnerable to rupture, localized platelet activation, and aggregation effect in an occlusive platelet thrombus. This process underpins MI and acute coronary syndromes (ACSs), and it illustrates why antiplatelet drugs are so helpful in treating and preventing these illnesses [16]. β-3 integrins on endothelial cells connect with the fibrinogen-bound GPIIb/IIIa receptor on platelets and gets activated over the surface of the active endothelium, and solid attachment can occur when Platelets get strongly attached and can attract other platelets to the location of endothelial damage once activated [17].

Platelet activation inhibition was shown to decrease atherosclerosis development, such as reduction of activity or COX-1 dependent thromboxane A2 synthesis [18]. Platelets are well-known for their participation in the formation of a thrombus following the rupture of a susceptible plaque's thin fibrous cap. The highly thrombogenic lipid core is exposed to the circulation when the thin fibrous cap is disrupted, generally in the adjacent shoulder area, causing activation and thrombosis of a platelet cascade. However, the amount of platelets that cooperate with an entrenched susceptible plaque before it ruptures clinically is unknown. The efficacy of antiplatelet medications in lowering ischemia episodes strongly suggests it [19]. Subclinical plaque rupture is common, with burst fibrous caps found in 9% of autopsies on people who did not die from myocardial infarction (22% in patients with cardiovascular risk factors). This shows that, rather than every plaque rupture causing an ischemic event, the thrombotic response to plaque disruption in individuals with ACS is likely to be dynamic, with thrombosis and thrombolysis occurring at the same time. As a result, a rupture-prone plaque's fibrous cap may be disrupted regularly, resulting in continuing interactions with activated platelets [20].

Activated platelets may thus be linked with unstable plaques at any given moment, probably in a quantity and frequency proportionate to the degree of plaque instability, in addition to their function in acute plaque rupture. The detection of active platelets may allow for the early diagnosis of unstable plaques before they rupture [21].

Antiplatelet Medications

Aspirin

Aspirin was the first antiplatelet medicine identified and recommended as the first line of defense in the prevention of auxiliary cardiovascular disease [7]. Irreversible inhibition of COX-1 is mediated by the entire antiplatelet impact that is already apparent at a low dose of 75–100 mg/day, resulting in prostaglandin G2 and H2 production drop, and leads to reduced thromboxane A2 levels [22, 23]. The Veterans experiment, a double-blind, placebo-controlled multicenter trial including 1,266 male patients who received either a daily dosage of 324 mg aspirin or a placebo for 12 weeks, was the first to show that aspirin was effective in individuals suffering from ACS. The primary outcome was mortality or acute MI. Aspirin reduced the chance of a nonfatal MI by 51%. Furthermore, the group that received aspirin had a decreased overall mortality rate [24].

The Second International Study of Infarct Survival (ISIS-2) included 17187 patients with acute MI from 417 hospitals. Randomly Patients assign to one of four groups and given either:

1. An intravenous streptokinase infusion of 1.5 million International Units.
2. One month of a daily dosage of 160 mg aspirin.
3. Both therapies
4. None of them.

Mortality of 5-week alone reduced Aspirin while aspirin with streptokinase lowered 5-week mortality even more. Aspirin alone decreased the risk of reinfarction and non-fatal stroke. Nevertheless, it was not linked to an increase in transfusion-related bleeding or intracerebral hemorrhage [25]. In a multicenter trial, aspirin was found to have a beneficial impact, the participant consist of 555 patients with wobbly angina, and the Research group on volatility in coronary artery disease trial involved 796 males with wobbly angina or non-Q wave myocardial infarction, [25, 26]. When compared to low dosage aspirin, high dose aspirin did not lower the incidence of ischemic events, confirming the existing prescription of a daily dose of 75 to 100 mg of aspirin in patients with established cardiovascular disease [27].

The study found that commonly prescribed analgesics reduce aspirin-mediated platelet inhibition when a problem of low aspirin receptivity was initially documented in 2001. Suggesting that aspirin's antiplatelet effectiveness was reduced because the administration of ibuprofen and aspirin was linked to greater levels of serum thromboxane B2 and residual platelet aggregation [7, 28]. Catella-Lawson *et al*. demonstrated their results by nonsteroidal anti-inflammatory medications competing for access to the acetylation site of platelet COX-1 (NSAID) [28]. Primarily, a key issue that may be to blame for the absence of inhibitory effects is aspirin non-compliance. Other variables, aside from treatment with particular NSAIDs, may explain the increment of platelet reactivity despite aspirin therapy. Moreover, platelets from aspirin-treated individuals can still be activated through routes that are unaffected by the drug. Furthermore, increased platelet turnover has been proposed as a cause of inadequate aspirin-mediated platelet inhibition on several occasions [29, 30].

Insufficient platelet-aggregation suppression evidence in up to 80% of individuals who are treated with low-dose aspirin with essential thrombocytopenia. This difficulty may be solved by taking aspirin twice a day (2 x 100 mg), however, it is worth emphasizing that the dosage interval, not the amount, is also important [31]. Increased platelet activation and a reduced response to antiplatelet medication in patients with chronic kidney disease (CKD) may explain worse long-term outcomes following PCI compared to non-CKD patients [32]. Non-response to aspirin, defined as the inability to block its

pharmacological target, thromboxane A2 production, is a relatively unusual occurrence. However, the degree of aspirin-mediated platelet inhibition differs from patient to patient. Aspirin resistance is a term used to explain the behavior mentioned above. However, because the underlying processes are so varied, there is no widely agreed definition of "aspirin resistance," and the phrase "aspirin treatment failure" could be a better fit.
Recent guidelines advocate low-dose aspirin for secondary prevention of atherothrombotic events in CVD but advise its use for primary prevention owing to the increased risk of bleeding [7, 33].

Antagonists of P2Y12
ADP that binds P2Y12 is a G-protein-coupled receptor that improves prolonged platelet aggregation by enhancing the affinity for its primary ligand, soluble fibrinogen, through intracellular signaling and conformational modifications of the GPIIb/IIIa receptor. The thienopyridines, such as ticlopidine, clopidogrel, and prasugrel, and the nucleoside–nucleotide compounds, such as ticagrelor and cangrelor, are the two types of P2Y12 inhibitors now accessible [34]. Before permanently attaching to the P2Y12 receptor, all thienopyridines must be transformed into active metabolites by the hepatic cytochrome (CYP) P450 enzyme system. Due to its numerous negative effects, ticlopidine is rarely used in clinical practice and is not recommended in current guidelines [35].
Following elective PCI or peripheral angioplasty with stenting, the state-of-the-art DAPT regimen includes clopidogrel plus aspirin [35, 36]. Furthermore, for many years, clopidogrel has been the predominant P2Y12 inhibitor in the acute context. However, high-on- residual platelet reactivity therapy, also known as high-on-treatment residual platelet reactivity, delayed initiation of action is characterized, large response changeability, and inadequate antithrombotic effectiveness in certain individuals [8, 34]. Because of these qualities, more effective and dependable medicines targeting the P2Y12 receptor have been developed: prasugrel, the third thienopyridine, has higher bioavailability, a supplementary robust antiplatelet action, and less inter-individual response changeability than clopidogrel. Furthermore, it was superior to clopidogrel in lowering ischemic outcomes in patients with ACS who had PCI, but not in patients with ACS who were medically treated [37].
In individuals with ACS, recent results show that prasugrel is better than the fourth P2Y12 inhibitor, ticagrelor. The nucleoside–nucleotide antagonists ticagrelor and cangrelor, unlike the thienopyridines, do not require CYP450-mediated biotransformation to reversibly bind to the P2Y12 receptor and block ADP-induced platelet aggregation [38]. When compared to clopidogrel, ticagrelor has a higher bioavailability and reduced response variability, similar to prasugrel. Furthermore, ticagrelor outperformed clopidogrel in both medically managed and PCI-treated patients with ACS [8, 39]. The only P2Y12 inhibitor available intravenously is cangrelor, an adenosine triphosphate (ATP) analogue. It has a quick start of action of 2 minutes and a short half-life of 3 to 5 minutes, blocking P2Y12 receptors directly and reversibly.
Cangrelor in combination with aspirin is authorized for individuals with PCI who have not previously been treated with a P2Y12 inhibitor [8, 35].

Glycoprotein IIb/IIIa Inhibitors
GPIIb/IIIa receptor antagonists are ligand-mimetic compounds that reduce platelet aggregation by preventing fibrinogen from binding to activated platelets. Abciximab, tirofiban, and eptifibatide are the three GPIIb/IIIa inhibitors currently on the market. Abciximab is a mouse monoclonal antibody that has humanized antigen-binding fragments. Eptifibatide is a cyclic heptapeptide, while tirofiban is a nonpeptidic small molecule that both mimic the GPIIb/IIIa fibrinogen-binding sequence [8]. All three medications are administered intravenously, and their clinical application is limited to patients with ACS with a significant thrombus load or no-reflow syndrome following PCI due to their substantial bleeding risk.

Protease-Activated Receptor 1 Antagonists
The key thrombin binding site on human platelets is a Protease-activated receptor 1 (PAR-1), indulgent for powerful and long-lasting platelet activation. Vorapaxar is a viable PAR-1 antagonist that is administered in addition to ordinary antiplatelet medication in individuals with symptomatic peripheral arterial disease or a history of MI to prevent ischemic episodes. Vorapaxar repudiates in individuals with a transient ischemic attack or history of stroke since it has been linked to an increase in cerebral hemorrhagic accidents in two most important phase 3 clinical studies [40, 41].

DAPT
One of the most widely given medications in cardiovascular medicine is a combination of aspirin and a P2Y12 inhibitor. The proper DAPT length of the following stent implantation has been a topic of extreme controversy and considerable scientific interest. While we appreciate the significant achievements in transcatheter treatments methods and technology in this 5th decade of Interventional Cardiology, the ideal duration of DAPT remains uncertain. Recent transatlantic recommendations have emphasized the individualization of DAPT by requiring a full assessment of ischemia and bleeding risks [42, 43].

PCI and DAPT Beginning
DAPT with aspirin and a P2Y12 inhibitor has been the standard of care for the past few 2 decades, after coronary stent implantation. The use of a first-generation DES seemed to increase the risk of LST, hence DAPT was extended to 12 months. After DES implantation, DAPT for up to 12 months was the most popular method for the next >10 years, despite the lack of dedicated research to back up this suggestion. A thorough review of PCI's history reveals key details about DAPT's

development. Because artery closure owing to recoil, dissections, and restenosis limited the initial excitement for angioplasty, stents were developed to provide luminal integrity without sacrificing safety [44]. Apart from early stent thrombosis (EST; 30 days), bare-metal stents were afflicted by restenosis, requiring recurrent revascularization in up to one-third of the patients [45]. Drug-eluting stents (DES) outperformed balloon angioplasty stents in terms of lowering restenosis and recurrent revascularizations [46]. In the first-generation DES, late stent thrombosis (LST) has a tendency toward increment (1 year, >30 days) and followed by, second-generation DES with greater biocompatibility and thinner platforms facilitated vessel repair after very late stent thrombosis (VLST) (>1 year). Comparing Everolimus eluting stents (second-generation DES) to Paclitaxel eluting stents (first-generation DES), a substantial reduction in-stent thrombosis (ST) was shown in the meta-analysis [47].

DAPT Duration

While it is well accepted that patients who have had an ischemic cardiovascular accident require lifetime antiplatelet medication with one antiplatelet drug, such as aspirin or clopidogrel, the optimum duration of DAPT following an ACS and/or PCI with stent placement is less well-established. In ACS patients having PCI with stenting, current recommendations advocate DAPT with aspirin and clopidogrel for 6 months after elective PCI with stent implantation and DAPT with aspirin and prasugrel or ticagrelor for 12 months. If one of the two newer ADP P2Y12 inhibitors cannot treat the patient, clopidogrel should be given instead of prasugrel or ticagrelor. For 12 months after the acute incident, medically treated ACS patients should take DAPT with aspirin and ticagrelor, or clopidogrel if there is a higher risk of bleeding [48, 49].

However, multiple clinical investigations have lately cast doubt on the duration of DAPT in the above-mentioned patient categories. In the DAPT trial, 9961 patients who had a PCI with a drug-eluting stent and were treated with aspirin plus clopidogrel or prasugrel for 12 months were randomly allocated to receive thienopyridine therapy or placebo in conjunction with aspirin for additional 18 months. Stent thrombosis and a composite of MI, stroke, or death during a 12- to 30-month period were the co-primary efficacy objectives. Moderate or severe bleeding was the key safety objective. The findings revealed that continuous thienopyridine therapy considerably lowered both coprimary efficacy outcomes in their patient cohort at the cost of an increased risk of moderate or severe bleeding [49]. In the ACS subgroup, the effects of longer-term DAPT were more apparent [50].

Ticagrelor 60 mg twice every day, or placebo, and followed for a middle of 33 months, 54 trials of RCT were conducted, 21162 aspirin-treated patients who had a MI 1 to 3 years before were allotted a double-blind 1:1:1 proportion to ticagrelor 90 mg twice periodically. Thrombolysis in Myocardial Infarction (TIMI) extensive bleeding was the essential safety endpoint whereas, the combination of MI, stroke, or cardiovascular death was the vital effectiveness goal. The primary effectiveness objective was dramatically lowered in both ticagrelor regimens, whereas the incidence of TIMI severe bleeding increased (without increasing the risk of cerebral bleeding or fatal bleeding) [50].

Conclusion

Aspirin was the first antiplatelet medicine identified, and it is still recommended as the first line of defense in the secondary prevention of cardiovascular disease. For many years, clopidogrel has been the predominant P2Y12 inhibitor in the acute context. Peripheral angioplasty with stenting Followed by elective percutaneous coronary intercession (PCI), the state-of-the-art dual antiplatelet treatment (DAPT) regimen includes clopidogrel plus aspirin. The DAPT proper length followed by stent implantation has been a topic of extreme controversy and significant scientific interest. More research is necessary to determine the optimal duration that is safe and effective for post-PCI patients.

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