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REVIEW ARTICLE

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Ticagrelor versus clopidogrel in the management of acute myocardial infarction

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ABSTRACT

Hypothesis: In the care of acute myocardial infarction, ticagrelor attenuates post-ischemic myocardial damage and inhibits platelet activity to a greater extent than clopidogrel.

Methods: Scholarly articles published in the last 10 years were compiled from a PubMed MeSH search focusing on acute coronary infarction and the antiplatelet therapies clopidogrel and ticagrelor. The databases used were PubMed, Google Scholar, Dynamed, and EBSCOhost. Eight articles were chosen based on subject matter related to the hypothesis, including cardioprotective effects, mortality benefits, platelet reactivity, angiographic effects, and electrocardiography changes.

Results: Evidence from randomized clinical trials demonstrates that ticagrelor reduces infarct size, prevents remodeling, and reduces mortality rate after acute myocardial infarction to a greater extent than clopidogrel. However, some angiography studies show no difference between the two treatment regimes. Two articles show that ticagrelor is more effective in treating individuals with high platelet reactivity (HPR). In addition, there is some evidence of increased dyspnea and significant bleeding with ticagrelor.

Discussion: Although there is growing evidence that ticagrelor is the better antiplatelet drug post-acute coronary infarction, more research needs to be done to determine the situations in which ticagrelor provides the optimal treatment regime in regards to cardioprotective effects, antiplatelet effects and an overall decrease in mortality.

Conclusion: Ticagrelor was found to be superior to clopidogrel in relation to cardioprotective effects, mortality, and antiplatelet activity.

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1. Introduction

Ischemic heart disease is the leading cause of death in the USA and is associated with the development of atherosclerotic plaques, leading to acute myocardial infarction (MI) [1]. One American suffers from an MI every 42 seconds; it is essential to develop treatment options in acute management and the prevention of future cardiovascular events [2]. 6.9% of individuals post-MI have a recurrent MI, and 11.7% die due to another infarction, stroke, or heart failure [3].

Post-MI complications are often associated with activation of physiological hemostatic mechanisms. Tissue damage leads to exposure of von Willebrand factor (vWF), ultimately leading to the activation of platelets and the release of granule contents including adenosine diphosphate (ADP); which binds to the $P2Y_{12}$ purinergic receptor and amplifies the process [4].

The first $P2Y_{12}$ receptor antagonist, ticlopidine, was developed to prevent this amplification but removed from the market due to aplastic anemia and agranulocytosis [5]. This led to the development of clopidogrel, an irreversible $P2Y_{12}$ receptor antagonist that requires activation by cytochrome P450 systems. Clopidogrel and aspirin became the dominant dual antiplatelet therapy in the management of individuals with an MI, particularly those who have undergone percutaneous coronary intervention (PCI) [6]. However, 20–50% of individuals developed clopidogrel resistance or non-responsiveness, leading to the development of new antiplatelet agents [4,7].

One of the newer antiplatelet agents is ticagrelor, a reversible $P2Y_{12}$ receptor antagonist that binds at an allosteric site different from the ADP binding site, and doesn't require metabolic activation [5]. Ticagrelor enhances coronary blood flow through microvascular vasodilation by inhibiting adenosine uptake by erythrocytes [4]. Adenosine offers myocardial protection against ischemia-reperfusion injury [8]. In summary, ticagrelor can be antiplatelet, vasodilatory, and cardioprotective. Compared to clopidogrel, ticagrelor has a faster onset of action and stronger platelet inhibition [4]. The Platelet Inhibition and Patient Outcomes (PLATO) study showed that ticagrelor reduces

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mortality due to a cardiovascular event and has a good safety profile [3]. The same study showed non-fatal complications such as dyspnea and arrhythmias due to ventricular pauses. There seems to be conflicting research in regards to ticagrelor having excess bleeding risks [3,9]. The PLATO trial led to ticagrelor implementation into clinical practice around the world [10].

Some experts argue that the Federal Drug Association was too fast to allow ticagrelor into the market with only one significant trial (PLATO) showing decreased mortality in treated patients [10]. The increased use of ticagrelor in antiplatelet management quantifies the need to establish whether this drug is better than the conventional dual antiplatelet therapy.

The hypothesis says that the addition of ticagrelor in the care of acute MI patients, STEMI and NSTEMI, reduces post-ischemic myocardial damage and platelet reactivity more than clopidogrel. This research literature review analysis aims to evaluate the current research on the cardioprotective effects and antiplatelet effects of $P2Y_{12}$ inhibitors post infarction and to determine if ticagrelor is the better drug to be utilized in this situation. The randomized controlled trials are associated with conflicting results, particularly the USA sub-population of the PLATO trial and the Asian sub-population of a more recent trial [3,11]. Considering the variation between different studies, it is essential to examine the research and weigh the evidence.

2. Methods

2.1. Selection criteria

The following filters narrowed selection: clinical study, clinical trial, controlled clinical trial, multicenter study, observational study, randomized controlled trial, within ten years, English language, and only humans. One article included a third drug, prasugrel, in its comparison, but only the data comparing clopidogrel and ticagrelor was analyzed.

Exclusion criteria: Further inspection and review of the abstracts eliminated articles that were not relevant to the hypothesis, that is, a comparison of the two drugs. Articles were excluded if they focused on another population, such as diabetes, pregnancy, or pre-hospital trials.

Inclusion criteria: Primary literature and journal articles that compared Clopidogrel with Ticagrelor.

3. Results

3.1. Articles comparing mortality

The PLATO trial compared mortality between ticagrelor and clopidogrel in ACI and showed ticagrelor to reduce the risk of MI, stroke, and death from vascular causes, without an overall increase in bleeding complications [3]. PLATO demonstrated that the ticagrelor group reached the primary endpoint of death from any vascular reason at a significantly lower rate than clopidogrel and had lower secondary endpoint rates. The clopidogrel group had less hemorrhagic strokes, and stent thrombosis rates were lower in the ticagrelor group than in the clopidogrel group.

Three subgroups did not display ticagrelor benefits over clopidogrel. One of these included all participants enrolled in North America, where 11.9% of the ticagrelor group reached the primary endpoint, vs. 9.6% of the clopidogrel group. This result was opposite to that of the trial overall. PLATO demonstrated that ticagrelor reduced the rate of vascular-related deaths compared to clopidogrel, despite the adverse effects of ticagrelor, which included dyspnea, ventricular pauses, and major bleeding [3].

The PHILO study demonstrated contradictory findings to the PLATO trial that are consistent with the North American subset of PLATO, showing ticagrelor had a higher incidence of primary endpoints compared to clopidogrel [11]. The authors followed the methods of PLATO, with the addition of a matching placebo in each arm of a randomized Asian population. They utilized the same efficacy, primary and safety endpoints as the PLATO study [3]. In this trial, clopidogrel was shown to have fewer incidences of primary endpoints. Similar to PLATO, the ticagrelor group had more dyspnea compared to the clopidogrel group. Goto et al. [11] demonstrated that ticagrelor had increased primary endpoints and increased major and minor bleeding compared to clopidogrel in the Asian population.

Berwanger et al. researched the bleeding safety of ticagrelor in patients with ST-elevation myocardial infarction treated with fibrinolytic therapy and found that in patients younger than 75 years with ST-segment elevation MI, delayed administration of ticagrelor after fibrinolytic treatment was noninferior to clopidogrel for thrombus in myocardial infarction (TIMI) classification of major bleeding at 30 days [12,13].

3.2. Articles comparing drug effects

Di Vito et al. conducted a post-hoc trial on high thrombus ladened STEMI patients, enrolled in the COCTAIL II Trial, who underwent primary PCI [14,15]. They quantified residual intra-stent burden, utilizing optical coherence tomography findings, and calculated thrombus volume and reperfusion indexes and ultimately, showed that neither drug reduced thrombus size or reperfusion index in individuals with STEMI.

A randomized control trial by Zhu et al. [16] focused on the efficacy and safety of ticagrelor and clopidogrel in

individuals with ACI undergoing PCI treatment. The study was designed to demonstrate if ticagrelor is better than clopidogrel due to clopidogrels' slower onset, irreversible effects resulting in more extended time to restoration of platelet function, and resistance. Analysis of platelet aggregation rate (PAR) demonstrated no difference before treatment between the two, but ticagrelor was more effective at platelet inhibition at 24 hours. The ticagrelor group had no recurrence of MI compared to the clopidogrel group, who displayed significantly more mucosal bleeding and vomiting than the ticagrelor group. Zhu et al. [16] ultimately showed that ticagrelor was more effective at platelet inhibition at 24 hours and had fewer adverse reactions compared to the clopidogrel group.

Alexopoulos et al. [17] conducted a prospective, randomized, parallel design, 3 center study to determine the effects of ticagrelor and clopidogrel on the treatment of HPR in individuals undergoing fibrinolysis. The PLATO trial excluded any individuals who underwent fibrinolysis, and some studies show that fibrinolysis can lead to a pro-thrombotic state with increased platelet activity [18]. This study hypothesized that despite an increased bleeding risk in the administration of an antiplatelet post-fibrinolysis, there might be a balance found between the pro-thrombotic and antiplatelet effects. Ticagrelor had significantly lower platelet reactivity compared to clopidogrel at hour 2 and 24 and a higher percentage of platelet inhibition. There was no significant difference pre-discharge between the two drugs. In summary, this study showed that ticagrelor had decreased platelet reactivity and increased platelet inhibition compared to clopidogrel, in STEMI patients undergoing fibrinolysis.

Another study comparing HPR was performed by Li et al. [19], this time in patients who had coronary artery in-stent restenosis (ISR) and MI. This single-center, single-blind, randomized prospective controlled trial took STEMI, NSTEMI and ISR patients who had HPR and showed that ticagrelor was able to reduce the platelet reactivating unit (PRU) levels in individuals with HPR who were refractory to clopidogrel treatment [19].

Winter et al. did an open-label randomized study on the effects of ticagrelor and clopidogrel on angiographic findings in patients with STEMI [20]. This study was done because little data existed on the impact of the two drugs on myocardial reperfusion. Randomization occurred in the emergency department, and patients were given a LD of either clopidogrel or ticagrelor before primary angioplasty. The primary endpoint in this experiment was the correct TIMI frame count (cTFC), after PCI in patients treated with the drugs prior to the procedure [20]. Secondary endpoints were cTFC before PCI, myocardial brush grade (MBG), the percentage of ST resolution, and TIMI flow grade. All experimental techniques will be discussed in supplement.

Before PCI, cTFC was significantly lower in ticagrelor. However, no difference observed in TIMI flow grade, cTFC, or MBG percentages between the ticagrelor and clopidogrel groups. No difference in ST resolution was observed between ticagrelor and clopidogrel. In summary, Winter et al. found that ticagrelor showed no superiority over clopidogrel when examining angiographic and ECG changes after angioplasty [20].

4. Discussion

Antiplatelet management post-ACI is crucial to the prevention of further vascular complications. Clopidogrel, the previous drug of choice, requires hepatic metabolism, resulting in delayed onset and longer duration. Its hepatic metabolism might contribute to known resistance [4]. This resistance led to the development of ticagrelor as a reversible antiplatelet agent with adenosine-mediated vasoactive activity.

4.1. Ticagrelor may be superior to clopidogrel in reducing post-ACI mortality, but more research is needed

Two studies compared long-term mortality in patients taking ticagrelor and clopidogrel: PLATO and PHILO. The results of the two trials conflicted, with PLATO showing decreased mortality with ticagrelor (except in the US subpopulation, which had the same results as PHILO with clopidogrel showing reduced mortality). Also, the PLATO trial backed by numerous pharmaceutical companies, and their North American sub-population data was opposite from the rest of the trial. More research needs to be done in this population to investigate both the North American discrepancy in PLATO and the discrepancy between the PHILO and PLATO trials. Steiner et al. believed that mortality with clopidogrel was higher in the PLATO trial than in previous trials on clopidogrel, and this was refuted by the PLATO investigators [9,21]. One difference between the PHILO and PLATO trials was that PHILO was not designed to obtain the statistical power to detect differences in the trial but to explore the effects of ticagrelor in the Asian population for the approval of the drug in Japan. The analysis of results in PHILO determined that 62% of their primary endpoints were associated with peri-procedural MI, so they did a post-hoc analysis using spontaneous MI, stroke, or CV death [11]. Also, their ticagrelor population had a larger number of individuals over the age of 75 compared to the clopidogrel group and smaller sample size. This makes it difficult to compare the two trials, suggesting that more research needs to be done to determine if ticagrelor does, in fact, reduce mortality in ACI patients and if there are sub-populations that may have some resistance to the effects of the drug.

4.2. Ticagrelor as a possible alternative to clopidogrel in certain patients

Several different articles compared the antiplatelet effects of the two drugs, focusing on examining the degree of platelet reactivity. Zhu et al. demonstrated decreased PAR in the ticagrelor group compared to the clopidogrel group at 24 hours, showing that ticagrelor was able to reduce the aggregation of platelets [16]. They did not analyze longer-term decreases of PAR between the two drugs. Other limitations of the study by Zhu et al. [16] were the small sample size and the non-uniformity of PAR measurement in China. This non-uniform measurement could decrease the credibility of the study, as there are no experiments that compare their measurements to standardized measurements. A new trial would be needed with more subjects and another method to measure and verify PAR.

Another trial monitoring the antiplatelet effects of the two drugs was reported by Li et al. [19], who showed that ticagrelor achieved a greater decrease in PRU compared to clopidogrel. This study was done in patients who were already being treated for HPR with clopidogrel and examined the difference between a higher dose of clopidogrel and ticagrelor. While the higher dose of clopidogrel did achieve a decreased PRU in the patients who were refractory to the lower treatment, a greater decrease was achieved with ticagrelor, showing that ticagrelor can be used in individuals who have clopidogrel-refractive HPR and need a different drug.

Another trial compared the drugs in individuals with HPR, this time in individuals who had undergone fibrinolysis [17]. They demonstrated that ticagrelor decreased platelet reactivity and increased platelet inhibition more, compared to clopidogrel in STEMI patients who had undergone fibrinolysis. These results suggest that ticagrelor effects are more enhanced in individuals who have a greater thrombus burden.

Di Vito et al. [14] were the first to examine the effects of the two drugs on residual thrombus and reperfusion indexes including MBG and demonstrated that no differences existed in these parameters between the two drugs. Winter et al. [20] also demonstrated no difference in MBG and showed no difference in ST-segment changes, cTFC, or TIMI flow rate between the two groups. A possible explanation for the lack of a significant difference between the two drugs could be that the two antiplatelet agents have little role in the immediate resolution of thrombosis post-MI and play a more influential role in the prevention of subsequent thrombus. Also, PCI may cause mechanical trauma, creating distal debris and inflammation that can create an occlusion in microvessels, decreasing the interpretability of results [4]. The Winter et al. [4] study also had a significant difference in age between the two treatment arms, with the clopidogrel group being older, which could have impacted the results. Both trials showed no significant difference between the two drugs, but based on limitations, both experiments should be verified using a larger sample group to determine if there is no difference.

5. Conclusion

According to the results compiled from the studies above, ticagrelor is superior to clopidogrel in the management of antiplatelet activity and prevention of HPR in patients who are refractory to clopidogrel or have a high thrombus burden. There appears to be no significant difference between the drugs concerning thrombus size reduction and angiography parameters. Ticagrelor reduces mortality more than clopidogrel after MI, with the caveat of both the PLATO North American cohort and PHILO study demonstrating further research is needed to compare the two treatment regimens and to ensure optimal antiplatelet activity is being achieved in each patient undergoing therapy. In summary, this paper supports the hypothesis, but further research should be done to strengthen this support by addressing the discrepancies between the populations and the lack of difference in thrombus size reduction and angiography parameters.

Disclosure statement

No potential conflict of interest was reported by the authors.

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