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THE COMPARISON OF EFFICACY AND SAFETY OF TICAGRELOR VERSUS CLOPIDOGREL IN THE MANAGEMENT OF ACUTE CORONARY SYNDROME: A SYSTEMATIC REVIEW

Sami Ullah[1], Hammad Sharif [2], Madeeha Khaleeque [3], Muhammad Hassan Jan [4], Atif Ahmed [5], Muhammad Abdur Rauf [6], Irfan Ali khan[7]

[1]Medical Officer, Tehsil Headquarter Hospital, Malakand (dr_sami1989@yahoo.com)
[2]Resident Cardiology, Hayatabad Medical Complex, Peshawar, (hammadsharif_4221@yahoo.com)
[3]Resident Physician, Khyber Teaching Hospital, Peshawar (madeehakhaleeque19@gmail.com)
[4]Resident Physician, Hayatabad Medical Complex, Peshawar (hassanjan.cck18@hotmail.com)
[5]Resident Physician, Khyber Teaching Hospital, Peshawar (atifahmed.ktk@gmail.com)
[6]Assistant Professor Peshawar Medical college, Kuwait teaching Hospital.
[7]Peshawar institute of cardiology

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Abstract:

Dual antiplatelet therapy (DAPT) forms the main pillar of the medical management of acute coronary syndrome (ACS). Historically clopidogrel has been in use as part of DAPT but recent evidence has shown that it has a slow onset of action and less potent antiplatelet efficacy which has lead to cases of myocardial infarction and stent thrombosis. As a consequence, it has lead to the development of newer P2Y12 receptor antagonists like ticagrelor and prasugrel. Ticagrelor has a rapid onset of action and more potent platelet inhibition quality which has resulted in better cardiovascular outcomes in patients of ACS. We have conducted a systematic review to retrieve clinical evidence regarding the efficacy and safety profile of ticagrelor versus clopidogrel and it has shown that ticagrelor has demonstrated superiority in terms of its efficacy and safety profile as compared to clopidogrel. Such an analysis has got great clinical implications on the future of management of ACS patients as stent thrombosis and myocardial infarction, which occurs due to inadequate platelet inhibition, form the major morbidity and mortality in patients experiencing an episode of ACS. Hence the choice of a drug that has got potent antiplatelet activity, not at the expense of major bleeding, will drastically improve the prognosis of ACS patients.

Keywords: *Ticagrelor, Clopidogrel. Acute Coronary Syndrome, Bleeding, Efficacy, Cardiovascular outcomes*

Corresponding author:

Sami Ullah,
Medical Officer,
Tehsil Headquarter Hospital,
Malakand (dr_sami1989@yahoo.com)

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INTRODUCTION:

Acute coronary syndrome (ACS) is a life-threatening condition that occurs due to decreased blood flow in the coronary arteries. There is a relationship between the development of ACS and platelet aggregation, so the use of dual antiplatelet therapy (DAPT) forms the cornerstone of the medical therapy of ACS. The most commonly used antiplatelet drugs in the management of ACS are aspirin, clopidogrel, ticagrelor, and prasugrel. We will confine our discussion to clopidogrel and ticagrelor.

Clopidogrel, a P2Y12 receptor antagonist, is a worldwide known antiplatelet drug and has been in use in the management of ACS for a long time. It is a prodrug so it requires hepatic metabolism for the formation of active metabolites which then results in the antiplatelet activity of the drug [1]. There is data available that around one-third of the individuals using clopidogrel show minimal antiplatelet activity and they have been termed as "clopidogrel non-responders" [2]. Moreover, major bleeding risk, myocardial infarction (MI), stent thrombosis, and inadequate response in treating ACS patients with the use of clopidogrel shows the limitation of its effects as a good antiplatelet drug [3,4].

Ticagrelor is a P2Y12-adenosine diphosphate (ADP) receptor blocker, an oral antagonist which does not require activation of a reactive metabolite and hence shows the more rapid and potent antiplatelet activity as compared to clopidogrel [5,6]. Ticagrelor has more beneficial results in reversible long-term P2Y12 inhibition than clopidogrel and its use has resulted in a decrease in total mortality, better cardiovascular prevention, fewer cases of stent thrombosis as well as myocardial infarction, and in return, it has not lead to an increase in the incidence of major bleeding episodes [7].

There has been much debate as to whether clopidogrel or ticagrelor will offer improved clinical outcomes in the management of ACS without leading to major bleeding episodes. Therefore, we provide this article review to provide conclusive clinical evidence concerning the efficacy and safety profile of ticagrelor versus clopidogrel in patients.

MATERIALS AND METHODS:

The PubMed database was searched for publications with the medical subject heading "ticagrelor" and keywords "acute coronary syndromes" or "clopidogrel and ticagrelor" or "clopidogrel and ticagrelor and acute coronary syndromes" or "clopidogrel and ticagrelor and safety and efficacy". Our inclusion criteria were the English language, cardio-vascular relevance, time frame of the last twenty years (2001-2021) and only peer-reviewed publications. Our exclusion criteria was non-medical relevance and languages other than English. 20 publications were initially identified and subsequently 11 publications were included in our study.

Review

A multicenter, double-blind, randomized PHILO trial compared the safety and efficacy of ticagrelor vs. clopidogrel in 801 patients with ACS. All patients were planned to go under Percutaneous Coronary Intervention (PCI) within 24 hours of the onset of symptoms. The primary efficacy endpoint was the occurrence of myocardial infarction, stroke, or death from vascular outcomes and the primary safety outcome was the occurrence of any major bleeding episode. At the end of a 12 month follow up period, the primary efficacy endpoint occurred in 9.0% of patients treated with ticagrelor and in 6.3% of patients treated with clopidogrel, respectively (HR, 1.47; 95% CI: 0.88-2.44) while overall major bleeding occurred in 10.3% of patients treated with ticagrelor and 6.8% of patients treated with clopidogrel (hazard ratio (HR), 1.54; 95% confidence interval (CI): 0.94-2.53) [8]. The trial showed the superior efficacy of ticagrelor versus clopidogrel but also resulted in increased bleeding incidence.

A randomized clinical trial, PLATO trial, was conducted to compare the efficacy and safety profile of ticagrelor with clopidogrel. The efficacy endpoint was the decrease in the occurrence of myocardial infarction and cardiovascular death whereas the safety endpoint was the occurrence of a major bleeding episode. The primary endpoint was noted to be reduced with ticagrelor versus clopidogrel [10.0 vs. 12.3%; hazard ratio (HR) 0.83; 95% confidence interval (CI) = 0.74-0.93] while major bleeding rate was remain similar between treatment groups (13.4 vs. 12.6%; HR 1.07; 95% CI = 0.95-1.19), but ticagrelor was noted to be associated with an increase in non-CABG major bleeding (4.8 vs. 3.8%; HR 1.28; 95% CI = 1.05-1.56) [9]. Hence shows that the use of ticagrelor will reduce cardiovascular mortality as compared to clopidogrel without increasing the risk of major bleeding.

Michalis Hamilos et al conducted the MIRTOS trial to verify the efficacy versus the safety of ticagrelor and clopidogrel in STEMI patients treated with thrombolysis. They recruited 335 thrombolysis-eligible STEMI patients under the age of 75, of which 167 were randomized to receive clopidogrel and 168 to receive ticagrelor with thrombolysis.

Clinical events were then followed up over 3 months and no clinically significant difference was found between the two groups. Also, there was no difference for an episode of major bleeding in the ticagrelor and clopidogrel groups [10]. Hence the trial was not able to show the superiority of ticagrelor over clopidogrel in terms of efficacy but it also shows that the use of ticagrelor will not result in any significant bleeding incidence as compared to clopidogrel.

Xin-Yun Li et al conducted a randomized controlled trial on the efficacy of switching ticagrelor to clopidogrel in patients with ST-segment elevation myocardial infarction (STEMI) who underwent percutaneous coronary intervention (PCI) successfully. . A total of 653 patients were assigned randomly, who received a loading dose of either clopidogrel or ticagrelor before PCI followed by maintenance dose over 12months. The primary outcome of efficacy was major adverse cardiac events (MACE), including non-fatal myocardial infarction, cardiovascular death, and ischemic stroke. Secondary efficacy outcome was thrombosis of the stent, unstable angina, and coronary revascularization while the safety outcome was bleeding. There is significant reduction of secondary ischemic events in ticagrelor as compared to de-escalation group (15.1% vs 5.6%, P = 0.008) but lower than that in clopidogrel group (15.1% vs 24.6%, P = 0.03). No significant differences were noted in MACE in all three groups (P= 0.16). Also, no major significant differences in rate of major bleeding were noted among de-escalation, ticagrelor, and clopidogrel groups respectively [11].

There is some data available on the role of antiplatelets in diabetic patients having acute coronary syndrome (ACS). The clinical effects of aspirin are different in diabetic patients as compared to other patients having ACS. According to a meta-analysis done by De Berardis G et al, the clinical benefit of aspirin is very limited in patients having diabetes mellitus and it explains the rapid recovery of platelet reactivity in diabetic patients [12]. A meta-analysis done by Qiutong Tan et al showed that ticagrelor could reduce the incidence of a composite endpoint of myocardial infarction, cardiovascular death, and stroke as well as platelet reactivity in diabetic patients with ACS, with no increased risk of bleeding [13].

Weiran Dai et al conducted a meta-analysis to evaluate the effects of the preoperative loading dose of clopidogrel and ticagrelor in ST-segment elevation myocardial infarction (STEMI) patients who underwent primary percutaneous coronary intervention (PPCI). In his meta-analysis, 14 randomized clinical trials were included and there were a total of 4162 patients. The results of his meta-analysis showed that as compared to the loading dose of clopidogrel, the loading dose of ticagrelor reduced the incidence of no-reflow during primary PCI and also reduced the incidence of major cardiovascular events in patients having STEMI treated with primary PCI. Furthermore, it also showed that there was no clinically significant difference in the occurrence of increased bleeding risk between the two groups as well [14].

There is a controversy on the risk of bleeding in patients treated with ticagrelor versus clopidogrel who underwent coronary artery bypass grafting (CABG). Mohammad Saifur Rohman et al performed a meta-analysis to clarify the bleeding risk of ticagrelor versus clopidogrel in patients treated with CABG. Their meta-analysis showed that there was no statistical difference between the bleeding risk of pre-CABG and post-CABG patient sub-groups [15]. Ticagrelor decreases the adverse cardiovascular outcomes in patients of ACS particularly due to its strong antiplatelet action but some of its mortality benefits might be due to a certain non-antiplatelet effect as well. A randomized double-blinded cross-over study showed that ticagrelor potentiates adenosine-induced myocardial blood flow (MBF) in patients of stable coronary artery disease as compared to the patients using clopidogrel [16].

A prospective, open-label, randomized, multicenter, parallel-group, phase IV PD study was conducted on patients having low risk acute coronary syndrome (ACS) receiving pre-treatment with ticagrelor versus clopidogrel undergoing percutaneous coronary intervention (PCI). 100 patients were randomized to receive either ticagrelor 180 mg LD or clopidogrel 600 mg LD. Platelet reactivity (PRU) was then seen and compared and it was found that the patients receiving a loading dose of ticagrelor had a much reduced PRU as compared to those using clopidogrel. Hence in low-risk ACS patients, a loading dose of ticagrelor will provide more prompt and potent platelet inhibition as compared to clopidogrel and hence gives better cardiovascular outcomes [17].

Patients having concomitant stable coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD) are at increased risk of cardiovascular mortality due to the process of chronic inflammation that results in endothelial dysfunction. A randomized clinical trial was done to compare the efficacy of ticagrelor versus clopidogrel in improving

endothelial function in patients having stable CAD and COPD. Following parameters were evaluated at baseline and at one month; a) rate of apoptosis and b) nitric oxide (NO) levels in endothelial cells of human umbilical vein c) levels of reactive oxygen species (ROS) in peripheral blood mononuclear cell. The results of this trial showed that ticagrelor was better than clopidogrel in improving surrogate markers of endothelial function and as a result had mortality benefit in patients with cardiovascular disease [18].

CONCLUSION:

Dual antiplatelet therapy forms the cornerstone of the management of the acute coronary syndrome. There has been a debate regarding the efficacy and safety profile of ticagrelor versus clopidogrel. It is clear from this review article that ticagrelor has better efficacy than clopidogrel and leads to more prompt and potent inhibition of platelet activity which leads to better cardiovascular outcomes. The use of ticagrelor over clopidogrel will lead to a decrease in the incidence of myocardial infarction, stroke, and other vascular outcomes. The only negative aspect of the use of ticagrelor over clopidogrel was the increase in the incidence of major bleeding episodes. However, this aspect was not observed uniformly in all the clinical trials and perhaps it will require more clinical data to completely elucidate the fact. Our article shows that ticagrelor is showing promising results as a component of dual antiplatelet therapy in the management of the acute coronary syndrome.

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