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Review Article

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P2Y12 Receptor Inhibitors in ACS Management with or without ST-segment Elevation, Literature Review

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ABSTRACT

In patients suffering acute coronary syndrome, antiplatelet agents are one of the mainstays in treating and preventing lethal consequences, with or without ST-segment elevation. Large evolving trials currently are comparing the new antiplatelet P2Y12 inhibitors to the reference clopidogrel. The focus of this literature review is to analyze the standard antiplatelet to P2Y12 in patients enduring acute coronary syndrome with or without ST-segment acclivity. We searched in the PubMed database for relative articles using the following Mesh words "P2Y12 inhibitors", "Prasugrel," "clopidogrel," "Ticagrelor," and "acute coronary syndrome." Most of the available trials concluded that P2Y12 inhibitors are superior to clopidogrel in preventing acute coronary syndrome complications, such as death or stroke. In addition, P2Y12 inhibitors were not found to have more risk of major bleeding complications compared to clopidogrel. In regards to which P2Y12 inhibitors are more effective and safe to use, either ticagrelor or prasugrel, this remains an area of debate. Further clinical trials and meta-analyses are recommended to answer this question.

Key words: *P2Y12 Inhibitors, Ticagrelor, Prasugrel, Clopidogrel, Coronary artery disease, Angiography*

INTRODUCTION

Antiplatelet therapy (APT) has become a cornerstone in treating and preventing atherosclerotic events, especially those with coronary artery disease [1]. An extensive clinical trial has evolved regarding the association between APT prescription in various clinical contexts and risk vs. benefit relationships [1]. P2Y12 receptor inhibitors and aspirin are commonly utilized nowadays as double antiplatelet treatment (DAPT) in Acute Coronary Syndrome (ACS) patients, encompassing unsteady angina, non-ST-segment rise MI (NSTEMI), and STEMI [2]. These agents are mainly used in ACS patients sustaining Percutaneous Coronary Intervention (PCI) [2].

Reversible inhibitor such as Ticagrelor shows more compatible platelet inhibition with rapid onset and are also administered orally; Furthermore, in comparison to clopidogrel and prasugrel, it does not demand enzymatic activation and leads to faster, compelling, and more subtle platelet inhibition [3, 4]. Ticagrelor was found to be more effective and superior to clopidogrel in preventing ischemic events, including deaths from vascular causes, stroke, and myocardial infarction [4]. Furthermore, all death causes were found to be lesser in ticagrelor, without a Substantial increment in all-cause major bleeding, making ticagrelor use increase worldwide [3, 4]. The recommendation to utilize the ticagretor with aspirin in favor of clopidogral in patients with ACS is approved by

the newest American College of Cardiology, American Heart Association, The European Society of Cardiology, and the European Association guidelines for Cardio-thoracic Surgery [3, 4].

Third-generation thienopyridine and Prasugrel, similar to clopidogrel, is irreversibly inhibiting P2Y12 but with faster and more compatible platelet inhibition [4]. When compared to clopidogrel, prasugrel was related to reduce ischemic events in patients with ACS undergoing PCI in the Trial to Assess Improvement in Therapeutic Result by Optimizing Platelet Inhibition with Prasugrel (TRITON) [4]. Nonetheless, in non-ST-rise acute coronary disorder patients who planned for medical treatment without revascularization, prasugrel was found to have no advantage over clopidogrel [4, 5]. Nevertheless, in non-ST-elevation acute coronary syndrome patients who organized for medical therapy without revascularization, prasugrel was found to have no advantage over clopidogrel, with comparable bleeding risks were observed [4, 5]. Besides, when prasugrel as compared to clopidogrel in patients who underwent angiography, there were fewer cardiovascular deaths, myocardial infarction, or strokes [6].

MATERIALS AND METHODS

Patients with ACS in DAPT duration

Although there are many possible antiplatelet regimen combinations, the term DAPT has been utilized absolutely for antiplatelet treatment with both aspirin and P2Y12 receptor inhibitors [7]. Regarding DAPT duration following stent implantation, five RCTs have compared patients with Drug Eluted Stent (DES) implantation with shorter-duration (3 to 6 months) DAPT with 12 months DAPT [7]. These studies, including several meta-analyses, did not show an increase in the risk of stent thrombosis with shorter-duration DAPT; moreover, shorter-duration DAPT was found to be a feasible option in patients taking newer DES agents, including everolimus or zotarolimus-eluting stents, which showed to have lower MI and thrombosis rates than those with first-generation (sirolimus and paclitaxel-eluting stents) [7].

Longer-duration DAPT following stent implantation has been pondered in six RCTs, with an overall duration of 18 to 48 months, with an average of 6 to 12 months of DAPT [7]. The trial is the largest studied under patients who underwent DES with PCT implantation pursued by DAPT 12-month without bleeding or ischemic events amid the study period [7]. As a result, extended DAPT had a total fall of 0.7% in very late stent thrombosis, a 2.0% absolute reduction in MI, a 1.6% absolute reduction in major adverse cardiac events (MACE), and a 0.9% absolute increment in mild to severe bleeding [7]. Overall, longer-duration DAPT studies for an extra 18 to 36 months following DES showed an absolute decrease in late stent thrombosis and ischemic consequences of 1% to 2% and an absolute increase in bleeding consequences of 1% [7].

Higher Atherothrombotic Risk for the clopidogrel and Management, Ischemic Stabilization and Avoidance (CHARISM) trial established atherosclerosis for the selected patients or at high-risk atherosclerotic disease to either DAPT (with clopidgrel) or aspirin monotherapy, with DAPT [8]. The conclusion showed no significant reduction was found in ischemic effects at a median follow-up of 28 months, although there was a 0.4% absolute increment in the risk of severe bleeding [8]. Further analysis of enrolled patients with prior MI found a 1.7% absolute reduction in the compound endpoint of cardiovascular death, MI, or stroke events with DAPT, with no advantage in those with coronary artery disease (CAD) without prior MI [8, 9].

Ticagrelor vs. prasugrel in acute coronary syndrome

While an increasing number of NSTEMI cases have been noticed [10], the number of STEMI cases are slightly decreased among many communities [10, 11]. The mortality rate during the acute phase of NSTEMI is lower than STEMI (vs1) but with similar long-term mortality [12]. However, in a study comparing prasugrel with ticagrelor among NSTEMI patients who managed with revascularization, prasugrel was found to be more significant in reducing the risk of death, MI, and stroke 1-year follow-up [12]. Besides, prasugrel was not correlated with an increased risk of bleeding (vs4). Among patients who benefited from prasugrel, male patients, patients weighing >60 kg, and non-diabetic patients were the most [12].

The reason behind thought to be related to the irretrievable P2Y12 inhibition by prasugrel may be additional beneficial than the fickle blocking by ticagrelor (vs4). Additionally, the lack of early loading advantage of ticagrelor compared to prasugrel loading post coronary angiography makes prasugrel a better option [12].

The ponder showed that prasugrel was preferable to ticagrelor in preventing the key endpoint, including death, MI, or stroke 1-year following randomization after invasive evaluation [13]; to clarify, the essential endpoint in the prasugrel group was primarily driven by fewer myocardial infarctions compared to the ticagrelor group with no increased risk of bleeding [13]. Similarly, a multicenter, randomized, open-label trial compared prasugrel with

ticagrelor in ACS patients with or without ST-segment elevation [13]. Based on the PLATO trial that compares ticagrelor with clopidogrel in ACS patients, it was thought that ticagrelor has more benefits compared to other antiplatelet agents [14]. On the other hand, in another trial, pretreatment with prasugrel was not superior in ACS patients without ST-segment elevation, and further, it was associated with a more significant risk of major bleeding complications [13]. A more robust platelet inhibition hypothesis at the time of PCI reduces periprocedural thrombotic risks favors ticagrelor over prasugrel [13]. But, the prasugrel-based strategy with deferred loading in patients with ACS without ST-segment elevation favors prasugrel over ticagrelor [13].

Safety and adverse outcome

The outpatient use of ticagrelor has a lower risk of MACE and unadjusted death rates than clopidogrel in unadjusted analyses [15]. However, there have been no reported differences in ACS hospitalization, coronary revascularization, or the composite of death, ACS, or ischemic stroke [10]. Yet, it is an area of controversy, particularly after multivariable adjustment [15].

In unadjusted analyses, ticagrelor was found with no statistical significance in the major bleeding risk compared to clopidogrel [15]. Nonetheless, after a fully adjusted model, ticagrelor had a higher major bleeding risk than clopidogrel [15]. The more reported bleeding complications are gastrointestinal hemorrhage and pulmonary hemorrhage [10]. Besides, dyspnea is considered to be a higher risk related to ticagrelor after completely adjusted demonstrate [15]. However, a multicenter, prospective, accessible-label randomized clinical trial showed that commencing 12 months of ticagrelor monotherapy after 12 months of aspirin with ticagrelor has significantly lower risks of bleeding [16]. The latest trial regimen was compared to the reference regimen, a combination of ticagrelor and aspirin for 12 months charted by aspirin as a monotherapy for other 12 months, and still, ticagrelor was safer [16]. In regards to the difference between revascularized patients and non-revascularized, the risk of all-cause of death was higher in revascularized than those who were non-revascularized [16].

A multicenter, double-blind, randomized trial compared ticagrelor with clopidogrel to prevent adverse cardiovascular events following acute coronary syndrome [14]. As a result, there were no major changes between the two agents concerning the risk of significant bleeding [14]. Dyspnea was commonly presented in patients taking ticagrelor, which resulted in omitting the study by a small group of patients [17].

Further, the ticagrelor group was at higher risk for ventricular pauses in the first week than the clopidogrel group [14]. Omitting the study auxiliary to frequent adverse effects was detailed more in the ticagrelor group compared to the clopidogrel group [14]. Uric acid levels and Creatinine were higher amid the therapy duration in the ticagrelor group compared with the clopidogrel group [14].

CONCLUSION

Antiplatelet agents nowadays in acute coronary disorder patients with or without ST-segment rise are commonly utilized for the P2Y12 inhibitors, including ticagretor and prasugrel. It has more potent and faster inhibition than the standard agent, resulting in more profound platelet inhibition. Consequently, it reduces the risk of all-cause of deaths, including stroke and myocardial infarction, without increment of the bleeding danger. Current guidelines recommended the use of P2Y12 inhibitors over clopidogrel. Yet, which agent is more effective and safe is still questionable and presents an area of controversy. We suggested meta-analyses of the current articles to answer this question.

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