REVIEW

DUAL ANTIPLATELET THERAPY FOR PREVENTION OF COMPLICATIONS IN PERIPHERAL ARTERY DISEASE

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ABSTRACT

Peripheral Artery Disease is a frequent pathology, leading to severe cardiovascular and limb complications. The use of dual antiplatelet therapy, tough potentially beneficial for these patients, is still controversial and needs more attentive consideration. This review analyses its use in both mild and more severe stages of the disease, aiming to reveal its safety and efficacy through the meticulous analysis of the current research available on the topic. After and advanced search on PubMed and a thorough selection of the retrieved results, 12 articles were included. Dual antiplatelet therapy with Aspirin and Clopidogrel fails to prove its efficacy when used in patients with asymptomatic or mild peripheral artery disease, with its use being much more beneficial for patients with advanced forms of it. Similar results describe the use of Ticagrelor in addition to Aspirin. Vorapaxar is a novel medication potentially beneficial as part of dual antiplatelet therapy. In patients who underwent endovascular revascularization, 12 months of dual antiplatelet therapy reduce mortality compared to 6 months only. For patients who underwent surgical revascularization, dual antiplatelet therapy fails to provide significant improvements compared to Aspirin only. Dual antiplatelet therapy has a positive impact for patients suffering from moderate or severe peripheral artery disease and also in patients treated endovascularly for its complications. Less satisfactory findings were found for patients undergoing surgical revascularization. However, there is need for more research in the field.

KEYWORDS: *dual antiplatelet therapy, peripheral artery disease, major adverse cardiovascular events, major adverse limb events*

INTRODUCTION

Peripheral Artery Disease (PAD) represents the third most encountered manifestation of atherosclerosis, after disease involving the coronary and cerebrovascular arteries [1], [2]. Ischemia leads to complications which can be divided into major adverse cardiovascular events (MACE), such as myocardial infarction, stroke and major adverse limb events (MALE), such as acute limb ischemia (ALI), peripheral revascularization and limb amputation. These complications explain the need for prophylactic measures, which include risk factor control, antithrombotic and lipid control therapies [3].

When it comes to the use of antiplatelet therapy as a preventive measure, the current guidelines provide different or opposing recommendations, some supporting the use of antiplatelet monotherapy, while others emphasize the use of dual antiplatelet therapy (DAPT). However, there is not a consensus regarding the use of DAPT. There is a need for more consistent recommendations regarding DAPT for the prevention of PAD complications [4], [5].

The aim of this review is to analyze the use of dual antiplatelet therapy for preventing cardiovascular adverse outcomes in PAD, focusing on the most used combinations, their efficacy and safety.

MATERIALS AND METHOD

The search was conducted on PubMed. The key words used for the advanced search were Prevent*, Prophylaxis* in order to find preventive measures. The following were used for complications: Complicate*, Major Adverse Cardiac Events, MACE, Major Adverse Limb Events, MALE. The key words used so as to refer to the disease were Peripheral Artery Disease, PAD, Peripheral Arterial Occlusive Disease, PAOD, Lower Extremity Artery Disease, LEAD. Only articles published in the last 10 years, related to Humans were included. After an attentive evaluation of the generated results, we chose the articles that were the most suitable for the scope of this paper, represented by a total of 12 articles.

DISCUSSION

The combination of Acetylsalicylic Acid, known as Aspirin and Clopidogrel, a thienopyridine is a widely used one. It was investigated in CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance), which included a subgroup of patients diagnosed with asymptomatic or moderate PAD. They found a reduction of Myocardial Infarction and a decreased chance of hospitalization for ischemic complications in the DAPT group compared to those using Aspirin monotherapy. No important decrease in MACE was observed between the 2 groups. This means that the study cannot completely support the use of DAPT for patients with stable disease [2], [4]. However, a more significant reduction in MACE was found in studies, which, unlike Charisma, included patients with advanced PAD, or even with Acute Limb [6]. Taking these findings into account, it can be concluded that the benefits of DAPT with Aspirin and Clopidogrel are more representative for patients with moderate, severe PAD, even with ALI, rather than for patients with mild stages of the disease. Further on, DAPT with Aspirin and another antiplatelet, Ticagrelor, needs careful consideration.

Ticagrelor is an antagonist of the P2Y12 receptor, which can be used in combination with Aspirin for DAPT. The PEGASUS trial provided results regarding DAPT with Ticagrelor and Aspirin in patients diagnosed with PAD, but also suffering from a previous myocardial infarction. In a small subgroup, Ticagrelor and Aspirin lowered the risk of MACE. Both reduction in MALE and bleeding as an adverse effect failed to reach statistical significance. These conclusions can be partly explained since the study population was small [7], [8]. Similar results were displayed by PLATO trial in patients with Myocardial Infarction. Ticagrelor and Aspirin reduced MALE, but without statistical power [2]. Thus, these results underline the need to consider DAPT in patients with PAD, although they are unable to statistically prove its importance, just like in the case of CHARISMA.

But data proves more relevant when analyzing the results of DAPT with Aspirin and Ticagrelor on patients diagnosed with PAD who suffer not only from coronary artery disease, but also from type 2 diabetes mellitus. In such cases, of patients with other significant comorbidities, DAPT does have a major reduction effect on MALE. This comes at the cost of increasing major bleeding as an adverse reaction. Therefore, there is a need for more research to establish the right balance between advantages and disadvantages of using this combination [3]. These were common types of medication, but there are others, not so frequently used, such as Vorapaxar, which should also be considered.

Vorapaxar is a very potent antagonist of the PAR-1 receptor, acting as an inhibitor of platelet activation related to thrombin [9]. This is a novel approach for PAD. Vorapaxar can also be used as part of DAPT, associated with Aspirin, a

thienopyridine and even both. This results in a reduction in MALE, without having an impact on MACE. The downside of its use is moderate or severe hemorrhage. This explains why it is rarely used by clinicians, in spite of its good preventive MALE ability. Nevertheless, this medication could still prove beneficial in combination with another antiplatelet medication for patients at major risk of ALI [2], [3], [7], [8].

As encountered above, more severe forms of PAD require further analysis, especially the postinterventional care of patients benefiting from revascularization. There is a great likelihood of thrombosis in such patients due to the delay in the curative process of the endothelium. DAPT, frequently including Aspirin and an antagonist of the P2Y12 receptor is better at reducing stent thrombosis then using antiplatelet monotherapy with Aspirin [4]. Certain aspects of this area should also be carefully analyzed. To begin with, the topic of DAPT duration in such patients should be addressed.

Regarding the optimal duration of DAPT in patients who undergone Percutaneous Coronary Interventions, the PRODIGY trial proved that a duration of 24 months of treatment reduces MACE in this type of patients compared to only 6 months. This information should be interpreted cautiously owing to the small number of patients involved. The results also call for further investigation since they found no significant bleeding between the two time periods of DAPT use [2], [7], [10].

A contradictory finding though was also published. An increase in both MALE and MACE occurred in patients receiving DAPT after revascularization of the infrainguinal arteries for more than 3 months compared to those who received DAPT for less than 3 months. This can be explained since those who received DAPT for prolonged periods also had more important cardiovascular comorbidities such as Myocardial infarction or Coronary Disease. Thus, this data must also be interpreted cautiously and its reliability is slightly doubtful [4]. After discussing the topic of duration of DAPT in patients who underwent endovascular revascularization, the focus shall fall next on the efficacy and safety of DAPT in this category of patients.

When it comes to the efficacy and safety of DAPT in patients after endovascular revascularization, the MIRROR study brought some insightful information. It compared DAPT with Clopidogrel and Aspirin or Aspirin alone in patients who underwent endovascular revascularization. At 6 months, the DAPT group displayed lower risk of complications, such as Target Lesion Revascularization (TLR) and decreased mortality than the group using only Aspirin. After these first 6 months, the DAPT group stopped using Clopidogrel. At 12 months, there was no longer any difference regarding the need for TLR in the 2 groups. In spite of this, the DAPT group still presented lower mortality. Overall, the use of DAPT after endovascular revascularization for a period of 6 months proves encouraging results. But with certainty, there is a need for more convincing data [2], [4]. Furtherly, more supporting findings have also emerged. In an observational cohort DAPT had remarkable results in patients who underwent endovascular treatment. At 36 moths follow up, those who received DAPT had a reduction in MACE, limb amputation and overall mortality than those on Aspirin alone. No significant influence on MALE was observed [6]. However, the study of the literature also revealed some contrasting results. In an observational study MALE was decreased, but MACE increased at 12 months follow up in patients after endovascular revascularization of the infrainguinal arteries. In such case, the other comorbidities of the patients and the way they influence the results need an attentive [11]. Further in time, using DAPT after endovascular intervention rather than just Aspirin led to higher survival chance at 5 years [4], [12].

Since this part outlined DAPT in patients after endovascular revascularization, there is a need for emphasis of DAPT use in surgical revascularization.

As formerly described, the need for peripheral revascularization is also a complication of PAD. The DAPT use shall be also considered in patients who undergone surgical procedures for this in order to further prevent complications of PAD. In patients benefiting from surgical treatment in the form of open bypass, there were no outstanding results in either DAPT or Monotherapy with Aspirin, Clopidogrel regarding postsurgical bleeding. The

antiplatelet therapy was given to the patients at 48 hours prior to the surgery [4]. The CASPAR trial looked into the effects of using DAPT with Aspirin and Clopidogrel or Aspirin alone in patients who underwent bypass procedures inferior to the knee. There were no significant outcomes between the two groups. These referred to graft occlusion, the need for revascularization, amputation or mortality. As expected, the DAPT group has an increased bleeding risk [2]. Thus, we can conclude that DAPT therapy has limited benefits for this category of patients.

Lastly, the aspects discussed in this review have shed some light on the use of DAPT with a more general focus. It referred to DAPT for a wide variety of patients, starting with those with asymptomatic PAD and ending with those in need of endovascular or surgical revascularization. It also looked into important characteristics of DAPT, such as efficacy of certain combination, their duration. These are strong points of this review, the fact that it brought together different data and thoroughly analyzed it in order to provide an overview on the use of DAPT as a preventive measure for complications of PAD. However, there are limitations which need to be considered. Although the last 10 years brought results based on clinical research of DAPT, we are still confronted with a lack of information. This field still needs more research in the future. This is the reason why certain findings cannot be considered definitive. The conclusions made still need data in order to be decisive in the clinical setting.

CONCLUSION

This review confirms that dual antiplatelet therapy does have a significant importance for prevention of complications in Peripheral Artery Disease. Clopidogrel and Aspirin are effective at reducing MACE especially if they are used for severe PAD. DAPT including Aspirin and Ticagrelor provides a statistically significant reduction in MALE only for patients who associate other important comorbidities. Vorapaxar is a new potentially beneficial antiplatelet for DAPT. In patients who have already undergone reperfusion, DAPT is efficient for those benefiting from endovascular revascularization for 6 months. The information included in this review provides valuable new insights into the use of DAPT in PAD, with rather a general focus, looking into both mild and severe forms of PAD.

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