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PHARMACOLOGICAL MANAGEMENT OF THE SECOND PLAQUETARY ANTIAGREGANT IN ACUTE CORONARY SYNDROMES: AN INTEGRATIVE REVIEW OF THE LITERATURE

Paulo Fernando Andrade Vieira de Barros Souza
Afya Jaboatão dos Guararapes Medical School
Jaboatão dos Guararapes - Pernambuco
http://lattes.cnpq.br/0354187157517303

Mylena Victoria Cavalcante Rodrigues
Afya Jaboatão dos Guararapes Medical School
Jaboatão dos Guararapes - Pernambuco
http://lattes.cnpq.br/4603600276009524

Joana Carla Bezerra Martins Pérez
Afya Jaboatão dos Guararapes Medical School
Jaboatão dos Guararapes - Pernambuco
http://lattes.cnpq.br/3604111045392997

Luiz Fernando de Lima
Afya Jaboatão dos Guararapes Medical School
Jaboatão dos Guararapes - Pernambuco
https://lattes.cnpq.br/1334796323859524

Ana Paula Fernandes da Silva
Afya Jaboatão dos Guararapes Medical School
Jaboatão dos Guararapes - Pernambuco
http://lattes.cnpq.br/8969810893566749

Abstract: This is an integrative review, using articles from the PubMed and SciELO databases, from 2019 to 2024, in Portuguese and English. The aim is to clarify the importance of the use of second-choice drugs in the pharmacological management of acute coronary syndromes (ACS), with an emphasis on the use of P2Y12 inhibitors for adequate treatment of ACS. It was shown that the use of second-line platelet antiaggregants is of great importance in the treatment and prognosis of ACS. It is therefore concluded that the benefits provided by the correct choice of dual antiplatelet therapy (DAPT) are indisputable, since its proper indication can alter cardiovascular outcomes and prevent new events.
Keywords: Acute coronary syndromes, Acute myocardial infarction, Antiplatelet agents.

INTRODUCTION

Acute Coronary Syndromes (ACS) are a set of signs and symptoms common to a specific group of cardiovascular diseases. ACS encompass conditions such as unstable angina and acute myocardial infarction (AMI), which can manifest clinically as ST-segment elevation or non-ST-segment elevation ACS (Hirotoshi et al., 2019).

In unstable angina, coronary perfusion is critical. The marked reduction in coronary flow favors an intense inflammatory response in the vessel wall, leading to the formation of platelet thrombi and the deposition of atherosclerotic plaques along the perforating branches of the coronary arteries. Over time, in the absence of proper management and prolonged exposure to risk factors, there may be total occlusion of the vessel, resulting in AMI (Damluji, 2023).

The diagnosis of AMI is eminently clinical, and its early identification is extremely important, since management must be individualized for SCASSST and SCACSST. AMI is considered when there is acute myocardial damage detected by elevated troponin levels (at least one value above the 99th percentile), associated with the presence of acute myocardial ischemia, which can be evidenced by one or more of the following criteria: angina or anginal equivalents, electrocardiographic changes (pathological Q waves on the ECG), the presence of a thrombus (identified by angiography or biopsy) and loss of myocardial tissue of ischemic etiology (Zeymer, 2019).

According to the 2021 Brazilian Guideline on non-ST-segment elevation AMI (NSTEMI), the HEART Score is recommended for patients who come to the emergency department with chest pain. This score aims to quantify the risk of a major cardiac event within six weeks of the onset of symptoms (Nicolau et al., 2021).

The patient will be fit for hospital discharge if the score is less than or equal to 3, associated with negative troponin, ECG without ischemic changes and no history of coronary artery disease (Damluji, 2023).

Considering the recommendations, the level of evidence and the difficulties in accessing treatment, one of the most important pillars is dual antiplatelet therapy (DAPT). The importance of this therapeutic approach is indisputable, since the reduction in morbidity and mortality in patients who use this therapy has been scientifically proven (Bergmark, 2022).

The use of platelet antiaggregants in ACS has been consolidated over the years, mainly due to their effectiveness in preventing intracoronary thrombosis. Rupture of the atherosclerotic plaque leads to exposure of the subendothelial tissue and, consequently, to local platelet activation, culminating in the formation of thrombi. In addition to this widely proven benefit, there is already evidence demonstrating a reduction in subsequent events, such as myocardial reinfarction and ischemic strokes (Joo-Yong Hahn et al., 2019).

In addition, studies have shown its effectiveness in preventing future occlusions triggered by invasive procedures such as angioplasty and stent implantation, which in themselves cause aggression to the coronary endothelium and can lead to platelet activation (Joo-Yong Hahn et al., 2019).

In standardized form, acetylsalicylic acid (ASA) - or aspirin - is considered the first--choice medication in identified cardiovascular events. Its action consists of the irreversible inhibition of the cyclooxygenase (COX) enzyme, in a non-selective way, affecting both COX-1 and COX-2. This inhibition promotes a reduction in the synthesis of thromboxane A2 (TXA2), a potent platelet aggregating agent derived from prostaglandins H2, which in turn are produced from arachidonic acid (Hirotoshi et al., 2019).

It is worth noting that TXA2 is a metabolite directly related to the action of COX-1, while prostacyclins are synthesized from COX-1 and COX-2. Thus, the non-selective action of acetylsalicylic acid is fully justified in its indication for inhibiting platelet aggregation (Schüpke; Menichelli, 2019).

The use of a second platelet antiaggregant arose from the realization that the thrombogenic activity of platelets is not completely suppressed by acetylsalicylic acid alone, since other mechanisms and pathways of platelet activation remain active. This finding showed that hemostasis was not totally compromised in patients using ASA therapy alone. However, the existence of these other platelet aggregation pathways also opened the door to the occurrence of unpreventable thrombogenic events (Atwood, 2022).

Faced with this need, P2Y12 receptor inhibitors such as clopidogrel, ticagrelor and prasugrel emerged. This new class of drugs was introduced after a series of clinical studies and has brought with it a number of controversies and peculiarities regarding its clinical application. Considering these peculiarities, this review aims to clarify the pharmacological management regarding the choice of the second platelet antiaggregant in the context of acute coronary syndromes (Hirotoshi et al., 2019).

Therefore, the aim of this integrative review was to highlight the importance of using a second platelet antiaggregant in the management of acute coronary syndromes, as well as to provide guidance on its appropriate choice and use in the context of these medical emergencies.

METHODOLOGY

This is an integrative literature review, developed in accordance with the following stages: (1) formulation of the topic; (2) definition of the inclusion and exclusion criteria; (3) data collection and analysis; (4) interpretation of the results; and (5) synthesis and review of the contents. The study was therefore designed to clarify and highlight the importance of the pharmacological management of the second platelet antiaggregant in acute coronary syndromes.

The searches were carried out on the National Library of Medicine and The National Institutes of Health (PubMed) and Scientific Electronic Library Online (SciELO) electronic databases. The Health Sciences Descriptors (DeCS) were used, with the Boolean operators "AND" and "OR", composing the search strategy based on the following descriptors: "Acute coronary syndromes", "Myocardial infarction", "Platelet Aggregation Inhibitors" and "Antiplatelet agents".

This study adopted specific inclusion criteria to select the materials used, prioritizing the most relevant and scientifically reliable. Included were: articles published on national and international platforms, in Portuguese and English, in the last five years; scientifically-based textbooks , available in virtual libraries; and teaching materials accessible in full that addressed the subject of this review.

The following were excluded: editorials, banners, monographs, handouts, materials that were not directly related to the topic, publications outside the proposed time frame and studies using animal models.

The data collected was organized in a file for joint analysis by the authors and the supervisor. The Excel platform was used to tabulate the data, classifying it according to title, relevance, authority of the source, year of publication and type of study, with the aim of increasing the accuracy and reliability of the information obtained.

RESULTS

A total of 371 articles with different methodologies were analyzed and jointly assessed by the authors of this study. Of these, 9 articles were selected to make up the final analysis, with the aim of providing support for this literature review, according to the inclusion criteria previously established in the methodology (Figure 1).

Table 1 summarizes the selected studies with the names of the authors, year of publication, methods and main results of each study.

DISCUSSION

Acute Coronary Syndromes (ACS) represent a spectrum of urgent cardiac conditions, from unstable angina to acute myocardial infarction (AMI). These critical conditions are based on coronary atherosclerosis, which manifests itself with a sudden reduction or blockage of blood flow in the coronary arteries, resulting in ischemia or myocardial damage (Bergmark, 2022).

The pathophysiology of ACS is directly linked to atherosclerosis, where the accumulation of plaques in the coronary arteries can cause them to rupture, thus triggering an inflammatory response, thrombosis and arterial obstruction. This resulting ischemia can manifest as unstable angina or, in more severe cases, as AMI (Bergmark, 2022).

The diagnosis of ACS involves an assessment of the patient's clinical history, as well as exploring the classic symptoms and risk factors, while the physical examination focuses on signs of cardiac injury. The electrocardiogram (ECG) plays a crucial role, with the identification of heart rate patterns and signs of ST-segment changes indicating STEMI when ST-segment elevation and STEMI when ST-segment absence or depression. To aid diagnosis, cardiac markers, including the most common such as troponins and CK-MB, confirm myocardial damage (Zeymer, 2019).

Pharmacological management of Acute Coronary Syndromes (ACS) is crucial for relieving symptoms, limiting damage to the myocardium and improving patient survival. Initially, among the stabilization measures implemented, we have support with oxygen supply to optimize availability to the myocardium, followed by symptomatic drugs, especially for the management of pain and nausea, which together make up the main symptoms, and medications that increase survival, such as DAPT and statins, and finally prophylactic drugs, mainly those for gastric protection (Damluji, 2023).

Antiplatelet agents play a crucial role and prevent thrombotic events as well as exacerbated platelet activation. Beta-blockers are used to reduce the heart rate and thus the heart's oxygen demand, while statins, which like DAPT come in both attack and maintenance doses, are one of the main agents in prolonging survival, acting in various ways to prevent new events. Finally, full anticoagulation for its direct action on existing plaque and angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), which are used to optimize cardiac function and reduce mortality (Atwood, 2022).

Invasive interventions, such as coronary angioplasty with stenting (PCI), can be performed to restore coronary blood flow in ca-

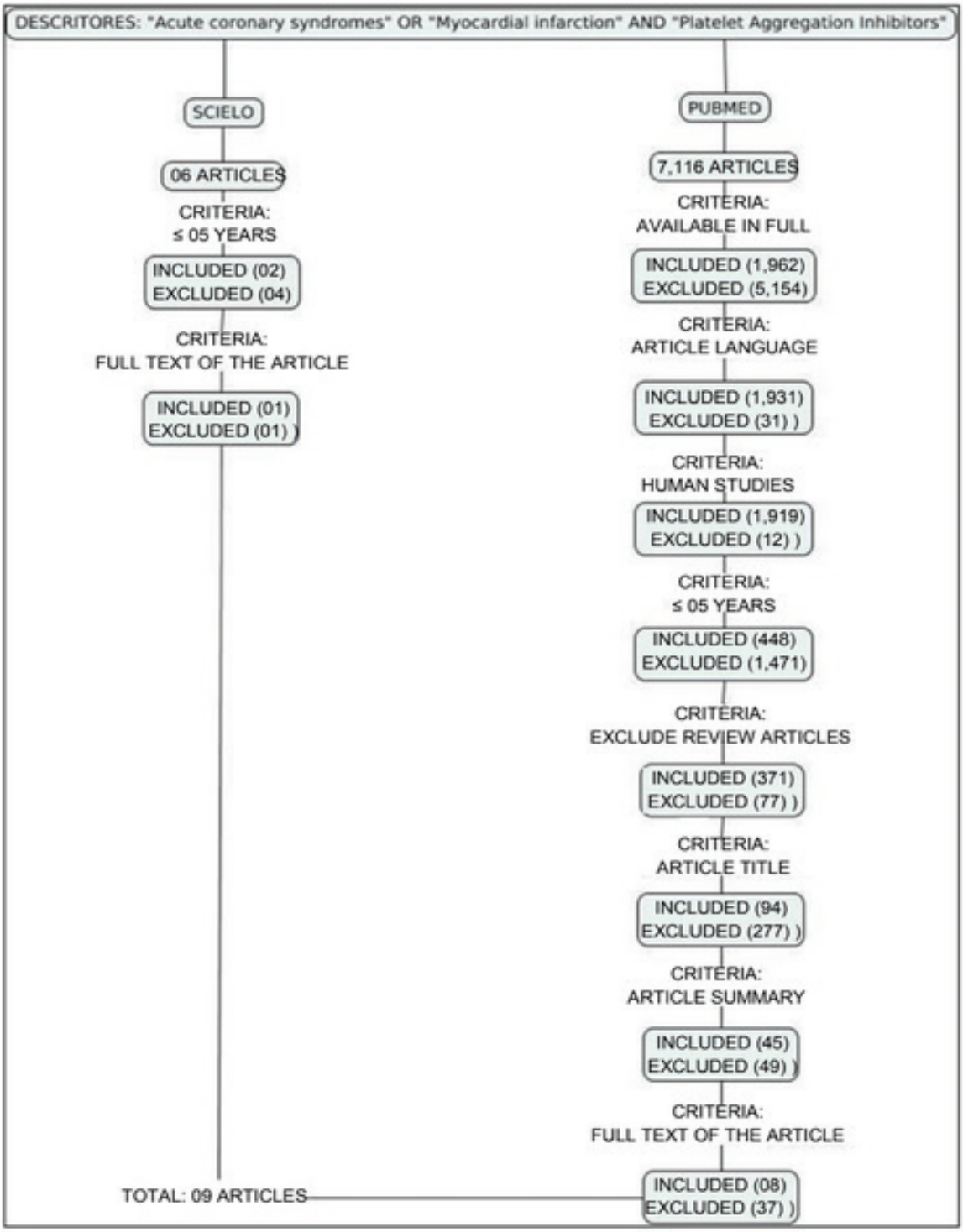

Figure 1. Flowchart for selecting articles for this integrative review.

Source: Authors (2024).

Author, year and country	Methodology	Results
Bularga et al., 2021, United Kingdom	Several databases were analyzed with the aim of identifying randomized clinical trials comparing long-acting dual antiplatelet therapy with short-acting or very short-acting antiplatelet therapy in patients with acute coronary syndromes.	Short-term dual antiplatelet therapy tended to reduce all-cause mortality and had a lower incidence of bleeding compared to long-term therapy. The efficacy between the regimens did not differ significantly. In subgroups, the short-term approach reduced the risk of bleeding in both acute and chronic coronary syndromes, but increased the risk of stent thrombosis in acute coronary syndrome.
Garmendia et al., 2021, Argentina	This is a pre-specified sub-analysis of the BUENOS AIRES I registry, which included patients divided according to the use of P2Y12 inhibitors before the coronary anatomy was known ("pre-treatment") or after its definition ("in--room treatment"). The analysis considered the incidence of clinical events according to the use of clopidogrel or ticagrelor in each of these strategies.	The average age of the patients was 65, with a predominance of males. The majority of patients received a P2Y12 inhibitor, most of them on a pre-treatment regimen. The pre-treated patients were younger and had a higher incidence of acute myocardial infarction compared to those treated after anatomical definition. After six months, there was no significant difference in the occurrence of major cardiovascular events or bleeding between the two administration times. The use of ticagrelor was associated with fewer cardiovascular events compared to clopidogrel, with no increase in bleeding. There was no difference in the efficacy of ticagrelor between the pre-treatment and in-room treatment strategies.
Kim et al., 2020, South Korea	After percutaneous coronary intervention, patients were randomized in equal proportions to receive ticagrelor monotherapy after three months of dual antiplatelet therapy (DAPT) or to maintain ticagrelor-based DAPT for twelve months. When necessary, loading doses of aspirin and ticagrelor were administered. During the first three months, all patients used aspirin and ticagrelor. After this period, aspirin was discontinued in the patients allocated to monotherapy, while it was maintained in those who continued with DAPT. The use of other antiplatelet agents or anticoagulants was prohibited, and the other treatments were left to medical discretion, with a strong recommendation to follow clinical guidelines.	Of the patients included in the study, the majority completed follow-up. Monotherapy with ticagrelor after three months of DAPT showed a lower occurrence of the primary endpoint compared to maintenance DAPT for twelve months. Most of the secondary endpoints showed no significant difference between the groups. The monotherapy group had fewer episodes of major bleeding. The incidence of adverse cardiac and cerebrovascular events was similar between the strategies.
Lahu et al., 2022, Germany	Patients with acute coronary syndrome who were candidates for an invasive strategy and randomized to receive ticagrelor or prasugrel in the ISAR-REACT 5 study were included. The primary endpoint was a composite of all-cause death, myocardial infarction or stroke at one year. The secondary safety endpoint considered major bleeding, classified as type 3 to 5 by the Academic Bleeding Research Consortium, also over one year.	Patients with acute coronary syndrome and previous infarction have a higher risk of recurrent ischemic events, but not of bleeding. In these cases, prasugrel has been shown to be superior to ticagrelor in reducing ischemic events, without increasing the risk of bleeding, regardless of previous history of infarction.
Lee et al., 2021, South Korea	Three-month dual antiplatelet therapy (DAPT) followed by P2Y12 inhibitor monotherapy was compared to 12-month DAPT in patients undergoing percutaneous coronary intervention. A platelet function test was performed in 833 patients who were on clopidogrel-based therapy.	In the study, a small percentage of patients had a non-adherence reaction to the use of clopidogrel. Patients with a history of previous heart attacks had a significantly higher rate of major adverse cardiovascular events compared to those without this history. Regarding the effect of treatment with clopidogrel monotherapy for adverse events after twelve months, there was no significant difference when compared to dual antiplatelet therapy between patients with and without a history of infarction.

Li et al., 2023, China	This meta-analysis was conducted in accordance with the PRISMA statement, which guides the preparation of systematic reviews and meta-analyses. PubMed and Cochrane databases were extensively searched on July 14, 2022 to identify studies on non-compliance with P2Y12 inhibitors and their effects in patients with acute coronary syndrome (ACS). The inclusion criteria for the studies were: (1) patients with ACS, (2) comparison of the incidence of ischemic events between the periods 0 to 90 days and 90 to 180 or 90 to 360 days after P2Y12 inhibitor non-compliance, and (3) studies published in English.	After effect size analysis, a significantly higher incidence of death and myocardial infarction was observed in the period from 0 to 90 days after non-compliance with clopidogrel, compared to the periods from 90 to 180 or 90 to 360 days. The risk of events was higher in the first period. In patients undergoing percutaneous coronary intervention, including a study with saphenous vein grafting, the risk of death or myocardial infarction was also significantly higher in the first 90 days after non-compliance with clopidogrel compared to subsequent periods.
Orban et al., 2021, Germany	The designs and results of the IABP-SHOCK II and CULPRIT-SHOCK studies have already been published. Both were prospective, randomized, open, multicenter, controlled trials conducted with patients with ST elevation myocardial infarction (STEMI) or non-STEMI, complicated by cardiogenic shock , with the intention of undergoing early revascularization (percutaneous coronary intervention or, in the case of the IABP-SHOCK II study, bypass surgery). The IABP-SHOCK II study included 600 patients with infarction and cardiogenic shock, randomized to receive IABP or no IABP treatment. In the CULPRIT-SHOCK study, 686 patients were randomized to percutaneous coronary intervention only in the culprit lesion, with possible staged revascularization, or to immediate multivessel percutaneous coronary intervention.	All-cause mortality at one year was lowest in the prasugrel group, followed by ticagrelor, and highest in the clopidogrel group. There was also lower all-cause mortality at 30 days in the prasugrel group, followed by ticagrelor and with a higher rate in the clopidogrel group. The incidence of repeated myocardial infarction and ischemic stroke showed no significant differences between the three groups. With regard to moderate or severe bleeding events during the one-year follow-up, ticagrelor was associated with a significantly lower risk compared to clopidogrel and prasugrel. There was no significant difference in the risk of bleeding between prasugrel and clopidogrel.
Valina et al., 2020, Germany	The ISAR-REACT 5 randomized study combined the pre-specified subgroups of unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI), involving 1,179 patients assigned to ticagrelor and 1,186 to prasugrel. Ticagrelor was started immediately after randomization, while prasugrel was administered after coronary angiography. The primary endpoint was a composite of death, myocardial infarction (AMI) or stroke during the one-year follow-up, and the safety endpoint was classified according to Bleeding Academic Research Consortium class 3-5.	The primary endpoint was reached in more patients in the ticagrelor group compared to the prasugrel group, with a higher risk ratio for ticagrelor. Analysis of all-cause death and myocardial infarction (MI) showed a similar risk ratio between the two groups, with a favorable trend for prasugrel. The safety endpoint showed a small difference between the groups, with no statistically significant difference in the risk of bleeding. The historical analysis indicated that prasugrel maintained an efficacy advantage after the first month of treatment.
Watanabe et al., 2022, Japan	Patients were randomized to receive 1 to 2 months of dual antiplatelet therapy (DAPT) followed by monotherapy with clopidogrel, or to 12 months of DAPT with aspirin and clopidogrel. The group receiving clopidogrel monotherapy included 2,078 patients, while the DAPT with aspirin and clopidogrel group included 2,091 patients.	Among the randomized patients, a small number withdrew their consent. The majority of patients were included in the study, with a considerable distribution of women and cases of ST-segment elevation and non-ST-segment elevation myocardial infarction. Most completed the one-year follow-up. The group that received 1 to 2 months of dual antiplatelet therapy (DAPT) was not inferior to the group that received 12 months of DAPT for the primary endpoint, with a small difference in the event rate between the two groups. The secondary cardiovascular endpoint was more frequent in the 1-2 month DAPT group, while the risk of secondary bleeding was significantly lower in this group, indicating a reduction in the risk of bleeding.

Table 1. Characterization of the methods and main results of studies on pharmacological management and acute coronary syndromes (2019-2024).

Source: Authors (2024).

ses of STEMI. In more complex situations, coronary artery bypass grafting (CABG) can be considered (Gulati, 2020).

Platelet antiaggregants play a central role in the management of Acute Coronary Syndromes (ACS), contributing to the prevention of thrombotic events and reducing the risk of cardiovascular complications. These drugs act by inhibiting platelet aggregation, a crucial process in the formation of blood clots that can lead to acute cardiovascular events (Zeymer, 2019).

Acetylsalicylic acid is the first choice of antiplatelet for the management of ACS and is indicated for all forms of ACS. Its contraindications are severe allergy or intolerance, active bleeding and active peptic ulcer. A loading dose of 200 to 300 mg is recommended, followed by 100 mg for continuous use (Zeymer, 2019).

The second class of choice is the P2Y12 inhibitors, whose mechanism basically works by inhibiting the ADP P2Y12 receptor on the surface of platelets and also helps to reduce platelet aggregation. The use of dual antiplatelet agents is currently the rule for the initial and maintenance treatment of STEMI, and has been proven to be superior to the use of aspirin alone (Dauerman, 2021).

The criteria for choosing the representative of the P2Y12 inhibitors is much debated, although the clinical outcomes are varied, the most accurate studies indicate that although clopidogrel is the most widely available, it has a higher prevalence of bleeding than ticagrelor and prasugrel (Orban, Martin et al. 2021).

Prasugrel, on the other hand, is the drug with the best scientific evidence both in terms of survival and new events. Its limitations are still financial, since it costs more and requires prior coronary angiography for its potential to be fully utilized. It is also worth noting that it has unfavorable outcomes in those under 60 kg and over 75 years of age, which further limits its use. (Orban, Martin et al. 2021.)

Ticagrelor, on the other hand, is the drug of choice in patients who are unable to undergo coronary angiography, as it acts more uniformly on the coronary arteries (Kim, Byeong-Keuk et al. 2020).

CONCLUSION

The correct management of antiplatelet agents is an important pillar in the treatment of ACS. The presentation, dosage and drug of choice for each patient profile makes all the difference to the clinical outcomes that are consistent with the survival and morbidity and mortality presented in this review.

Therefore, the challenges for health professionals are numerous and range from the availability of medication to patient adherence. It is necessary to avoid misprescribing due to the high potential for adverse effects, while ensuring patient safety so that they do not suffer the consequences of poor adherence. Management must be aligned according to the patient's ACS, their needs, limitations and associated complications so that they benefit fully from the drugs chosen.

Finally, the correct choice of the second platelet antiaggregant is a huge step forward in terms of the benefits provided to the patient, both in terms of potential survival and the prevention of new events.

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