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REVIEW ARTICLE

Antiplatelet Agents in Acute Coronary Syndromes

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Abstract

Under balanced conditions, hemostasis is maintained by a complex interaction between endothelium, platelets, and coagulation factors. Situations involving injury and discontinuation of the endothelial lining stimulate the adhesion, activation, and aggregation of platelets, culminating in the formation of arterial or venous thrombi. In this context, antiplatelet therapy occupies a prominent role in the management of pathologies arising from this process, notably acute coronary syndromes. The increased conceptual understanding of receptors, agonists, and antagonists of the pathophysiological cascades involved in this process has allowed the development of new drugs and refinement of the current therapy, demanding a complete knowledge of the arsenal of antiplatelet agents with respect to their indication, dosage, moment of administration, and duration of treatment. The objective of this review is to define the role of antiplatelet drugs in the management of acute coronary syndrome, revisiting aspects that have been already consolidated and addressing current and still controversial topics on the subject.

Introduction

Ischemic heart disease is the single leading cause of death and loss of quality of life worldwide.[1] In Brazil, it is estimated to be related to an annual rate of approximately 55 deaths per 100,000 inhabitants.[2,3] Acute coronary syndrome (ACS), with its broad range of manifestations, takes on a leading role in these statistics, and myocardial revascularization procedures and antithrombotic pharmacotherapy are fundamental pillars of its treatment.

Hemostasis is a physiological process maintained through a complex interaction between endothelium, platelets, and coagulation factors. Under conditions of emergency and imbalance, hemostasis can lead to the formation of arterial or venous thrombi, resulting in the occurrence of acute coronary events, cerebrovascular events, or episodes of thromboembolism. In this context and along with anticoagulant therapy, antiplatelet drugs stand out in the management of these conditions.[4]

Situations involving injury and discontinuation of the endothelial lining stimulate platelet adhesion to subendothelial matrix proteins. This interaction activates intracellular signals that promote the release of adenosine diphosphate (ADP), adrenaline, serotonin, thrombin and thromboxane A2, potent agonists of platelet activation. Once platelets are activated, glycoprotein IIb-IIIa complexes bind to fibrinogen to constitute the final stage of platelet aggregation and thrombus formation.[5]

The factors activating this process and the receptors involved in it have become targets for the development of antithrombotic agents. Evidence-based medicine enabled the advent, implementation, and refinement of the current therapeutic approach. However, by increasing the population's life expectancy and the coexistence of multiple comorbidities, we often find clinical scenarios in which the risk of ischemic complications goes hand in hand with the risk of hemorrhagic complications.[6] This demands complete knowledge of the arsenal of antiplatelet agents in regards to their indication, dosage, and moment of administration.

The objective of this review is to define the role of antiplatelet drugs in the management of ACS, revisiting aspects that have been already consolidated and addressing current and still controversial topics on the subject.

Keywords

Acute Coronary Syndrome; Myocardial Infarction; Platelet Aggregation; Blood Platelets Inhibitors; Antifibrinolytic Agents.

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Development

a) Acetylsalicylic acid

Acetylsalicylic acid (ASA) at low doses selectively inhibits cyclooxygenase (COX)-1, establishing antiplatelet activity, while at high doses it inhibits COX-1 and COX-2 with anti-inflammatory and analgesic effects. This medication is rapidly absorbed, reaching a peak plasma concentration 30 minutes after intake, in the case of a regular formulation, and 4 hours after intake, in the case of an enteric release formulation.[7]

Since the gastrointestinal side effects of ASA increase in proportion to its dose, an oral loading dose of 150-325 mg (swallowed, if a regular formulation, and chewed, if an enteral one) is recommended for ACS, or 80-150 mg intravenously in locations in which this presentation is available, followed by 81-100 mg as maintenance.[8] In the pioneering study Second International Study of Infarct Survival (ISIS)-2, ASA promoted a significant 23% reduction in cardiovascular mortality compared with placebo after 5 weeks of treatment in patients with acute myocardial infarction (AMI) with ST-segment elevation, with this effect being additive and synergistic when associated with streptokinase, reducing the rate of events by 42%.[9] These benefits were corroborated by several subsequent studies and by the compilation of their data in large meta-analyses, thus becoming one of the pillars of antithrombotic pharmacotherapy in the different spectra of ACS.[10]

Situations that constitute a clear contraindication to ASA are rare, and include mainly active digestive bleeding and known hypersensitivity (urticaria, bronchospasm, or anaphylaxis), although different desensitization protocols have been described allowing the chronic use of this medication with proven efficacy and safety.[11]

B) $P2Y_{12}$ platelet receptor antagonists

The association between ASA and a $P2Y_{12}$ receptor antagonist, known as dual antiplatelet therapy, is the treatment foundation of patients with ACS and those undergoing percutaneous coronary intervention (PCI). Ticlopidine is a first generation thienopyridine derivative that, despite its efficacy and due to its hematological (thrombocytopenia, aplastic anemia, thrombotic thrombocytopenic purpura, neutropenia) and gastrointestinal side effects, has been rapidly replaced by clopidogrel.[12]

b.1) Clopidogrel

Clopidogrel is a thienopyridine agent that irreversibly blocks the $P2Y_{12}$ receptor. The steady-state inhibition of platelet function with clopidogrel is achieved with a maintenance dose of 75 mg after 5-7 days from treatment initiation, whereas with the administration of 300 mg and 600 mg loading doses, this effect is reached in 6 and 2 hours, respectively, a relevant aspect in the context of medical emergencies.[13]

In the landmark clinical trial Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE), 12,562 patients with non-ST elevation AMI treated with ASA were randomized to receive clopidogrel or placebo for 3 to 12 months.[14] The clopidogrel group exhibited a significant 20% reduction in the risk of cardiovascular death, reinfarction, or stroke when compared with the placebo group, with benefits already apparent in the first hours after initiation of therapy and independent of invasive stratification. In the scenario of AMI with ST-segment elevation, two important studies validated clopidogrel as an effective adjuvant therapy. Among 3,491 patients randomized to 300 mg of clopidogrel and 75 mg of clopidogrel maintenance *versus* placebo in the clinical trial Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28, of whom 99.7% underwent thrombolysis, a 36% reduction was observed in the risk of death, recurrent AMI, or occluded infarct-related artery by the time of angiography.[15] In contrast, in the study, Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), among 45,852 randomized patients, with 50% undergoing thrombolysis, the administration of a daily dose of 75 mg clopidogrel over a mean period of 28 days resulted in a 9% reduction in the rates of death, reinfarction, or stroke compared with placebo.[16]

Thus, supported by the results of randomized controlled trials in ACS and by the pharmacodynamic and pharmacokinetic characteristics of clopidogrel, a loading dose of 600 mg is recommended for patients in whom invasive risk stratification is predicted or who are referred for primary PCI, and 300 mg for patients undergoing fibrinolytic therapy. An exception should be made to patients with a history of thrombolysis who are aged ≥ 75 years, in whom the loading dose should be omitted. In the absence of a clear benefit from maintaining clopidogrel at a double dose (150 mg), the dose should be 75 mg.[8]

However, clopidogrel exhibits unmet limitations and needs, partly explained by its properties, such as slow

onset and withdrawal and limited platelet inhibition potential. The interindividual variability of the drug's action is large, with the percentage of patients exhibiting inadequate therapeutic response estimated at up to 35%.[17] The mechanisms involved are multifactorial and include drug interactions (*e.g.*, proton pump inhibitors such as omeprazole and esomeprazole), the environment and clinical comorbidities (*e.g.*, adherence to therapy, smoking, diabetes mellitus, obesity, ACS), in addition to genetic polymorphisms, with emphasis on the alleles that determine a loss of CYP2C19 function.[18] It is known that patients with these variants are at increased risk of stent thrombosis, AMI recurrence, and death.[19] However, although the subject is still under scrutiny in ongoing studies, the evidence currently available does not endorse the individualization of therapy based on the results of genetic tests or the measurement of platelet function.[20,21] With that, a vast field of research has opened up with different treatment proposals, new $P2Y_{12}$ receptor antagonists, and blockade of new targets on the surface of the platelets.

b.2) Prasugrel

Similar to clopidogrel, prasugrel is a second-generation thienopyridine that is a prodrug and requires biotransformation to become an active metabolite. However, it has an earlier onset of action, about 30 minutes after the administration of a 60 mg loading dose, in addition to a more predictable response, due to its broad absorption, a need for a single oxidation step mediated by CYP3A4 and CYP2B6, conferring greater bioavailability, higher levels of platelet inhibition, and less variability of response among patients.[22]

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON)-TIMI 38 clinical trial, 13,608 patients admitted for ACS with or without ST-segment elevation undergoing PCI were randomized to receive a 60 mg loading dose of prasugrel and 10 mg maintenance dose, or a 300 mg loading dose of clopidogrel and 75 mg maintenance dose for up to 15 months.[23] Prasugrel treatment was shown to be superior with a significant 19% reduction in the risk of cardiovascular death, AMI, or nonfatal stroke, with a reduction of infarction of 24% and stent thrombosis of 52%, with an even greater benefit among patients with diabetes.

Consistent with the increased antiplatelet potency of prasugrel, the study found a significant 32% increase in the risk of severe bleeding, including fatal and life-threatening bleeding. In some patients' profiles, the net clinical benefit, which considers anti-ischemic efficacy and safety, was unfavorable to prasugrel, including patients with a prior stroke or transient ischemic attack (TIA), aged ≥ 75 years, and with a body weight < 60 kg. In the latter two situations, in case there is a need to prescribe the drug and a lack of therapeutic alternatives, a maintenance dose of 5 mg is recommended.[24] There are no indications to date in terms of prescribing prasugrel to ACS patients who did not undergo PCI, or in a time frame other than after the knowledge of the coronary anatomy and the realization of the interventional procedure. In patients with an indication for myocardial revascularization surgery, prasugrel should ideally be discontinued for 7 days.

b.3) Ticagrelor

The first clinically available representative of the cyclopentyltriazolopyrimidine class, ticagrelor is a reversible $P2Y_{12}$ receptor antagonist, exerting its inhibitory effect through a noncovalent attachment to a different platelet binding site than ADP. Unlike thienopyridine agents, ticagrelor is not a prodrug and acts immediately after oral absorption. It exhibits, thus, a rapid onset of action following the ingestion of a loading dose of 180 mg and a peak action in 2 hours. With a plasma half-life of 8-12 hours, ticagrelor requires a maintenance dose of 90 mg every 12 hours, and because it binds to the receptor in a reversible fashion, it has an earlier termination of action, around 2-3 days, even though the package insert recommends its suspension for 5 days before a surgical intervention. Since the metabolism of ticagrelor is mediated by CYP3A4 or CYP3A45, concomitant administration of strong inducers or CYP3A4 inhibitors during its use should be avoided.[25]

In the clinical trial Platelet Inhibition and Patient Outcomes (PLATO), 18,624 patients featuring all ACS manifestations (with the exception of those with AMI with ST-segment elevation who underwent thrombolysis) were randomized to receive ticagrelor or clopidogrel for 12 months.[26] In the ticagrelor arm, there was a significant 16% reduction in the risk of cardiovascular death, AMI or stroke. In a prespecified hierarchical analysis, ticagrelor alone reduced the occurrence of cardiovascular death (21%), AMI (16%), and definitive stent thrombosis (33%), with no difference in the rate of severe or fatal bleeding. Despite the consistency of the results obtained among the different subgroups analyzed, there was an interaction between patients treated in North America and the rest of the world, without a clear benefit of ticagrelor in the first group.

The use of high maintenance doses of ASA (≥ 200 mg) is believed to be a probable justification for this finding, prompting an alert for the prescription of doses < 200 mg in chronic use.[27]

Ticagrelor exhibits pleiotropic effects not mediated by its blocking of the $P2Y_{12}$ receptor, including the inhibition of adenosine uptake by erythrocytes, which increases the circulating levels of adenosine.[28] Adenosine is known to have several properties, including coronary vasodilation, reduction of ischemia and reperfusion injury, inhibition of inflammatory responses to stress conditions, negative chronotropic and dromotropic effect, reduction of glomerular filtration rate, and stimulation of vagal C fibers in the lungs. These effects are still under investigation and would justify, among the users of ticagrelor, a higher prevalence of dyspnea without alteration of pulmonary function tests, ventricular pauses without clinical impact or requirement of a definitive pacemaker, elevated serum creatinine and uric acid levels, as well as greater electrical stability and a reduction of sudden arrhythmic deaths, the latter still under speculation.[29,30]

Table 1 provides a compilation of the main indications, dosages, and recommendations regarding the prescription of $P2Y_{12}$ receptor antagonists in ACSs.

c) Glycoprotein IIb-IIIa inhibitors

The glycoprotein IIb-IIIa inhibitors approved for clinical use – abciximab, tirofiban and eptifibatide – are potent platelet antagonists of parenteral administration, of which only the first two are commercially available in Brazil. The pharmacological characteristics of these agents are summarized in Table 2.

Table 1 – Indications of the P2Y12 receptor antagonists in acute coronary syndromes

Drug	Indication	Loading dose	Maintenance dose	Duration of treatment	Suspension for surgery
Clopidogrel	AMI with post-thrombolysis ST elevation	300 mg*	75 mg/day	1 year	5 days
Clopidogrel	ACS without ST elevation Primary PCI	300-600 mg	75 mg/day	1 year	5 days
Prasugrel	ACS treated with PCI	60 mg	10 mg/day†	1 year	7 days
Ticagrelor	ACS (except post-thrombolysis)	180 mg	90 mg every 12 hours	1 year	3-5 days

*AMI: acute myocardial infarction; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention. * The loading dose is omitted if aged ≥ 75 years. † Maintenance dose of 5 mg if weight < 60 kg or age ≥ 75 years.*

Table 2 – Pharmacological properties of glycoprotein IIb-IIIa inhibitors

	Abciximab	Tirofiban
Structure	Monoclonal antibody	Nonpeptide antagonist
Molecular weight	48 kDa	< 1 kDa
Onset	Rapid	Rapid
Reversibility	Slow (12 hours)	Fast (2 hours)
Half-life	10-30 minutes	2 hours
Excretion	Unknown	Renal (40-70%) and biliary
Loading dose	0.25 mg/kg	25 μg/kg
Maintenance dose	0.125 μg/kg/min for 12 hours	0.15 μg/kg/min for 18 hours
Dose adjustment	No	↓ 50% if clearance ≤ 30 mL/min

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Abciximab is a monoclonal antibody with a high affinity for glycoprotein IIb-IIIa receptors. Following a loading dose of 0.25 mg/kg, more than 80% of the receptors are blocked, with a reduction of platelet aggregation in response to ADP stimulation to less than 20% of the baseline value. This inhibition is maintained by a continuous infusion of abciximab at a dose of 0.125 μg/kg/min, up to a maximum of 10 μg/min. Thrombocytopenia is reported in 1-4% of the patients treated with the drug, commonly detected within the first 24 hours and up to 2 hours after the initiation of its administration. This is believed to be an antibody-mediated complication, with a reversal in most cases after its suspension and an occasional requirement of platelet transfusion.[31]

Tirofiban is a nonpeptide tyrosine derivative that acts through a reversible and selective blockade of the glycoprotein IIb-IIIa receptor, preventing its binding to fibrinogen and to the von Willebrand factor. With renal and bile excretion, tirofiban has a plasma half-life of 1.5-2 hours, with a requirement for dose adjustment in patients with renal insufficiency and creatinine clearance ≤ 30 mL/min, but not in cases of liver disease. When administered at a loading dose of 25 μg/kg, tirofiban exhibits similar efficacy to that of abciximab. Cases of severe thrombocytopenia, although rare and reversible, have also been reported. The occurrence of severe thrombocytopenia is attributed to an immune-mediated phenomenon, since the binding of tirofiban promotes a conformational change in the receptor, with generation of antibodies against the new exposed epitope.[32]

The evidence that has validated the use of glycoprotein (GPIs) IIb-IIIa inhibitors in PCI, given the ability of these agents to reduce periprocedural AMI and the need for emergency revascularization, originated mainly from clinical studies conducted prior to the advent of thienopyridine agents and routine stent implantation. In the contemporary era of interventional cardiology, meta-analyses have been performed to evaluate the actual role played by these agents as adjunctive therapy for PCI.

In the treatment of non-ST–elevation ACS, a meta-analysis involving 31,402 patients demonstrated a mild but significant benefit in the reduction of death and AMI at 30 days, favoring the use of glycoprotein IIb-IIIa inhibitors, especially among patients considered to be at high risk (*e.g.*, patients with positive myocardial necrosis markers, increased thrombotic load, or complex lesions).[33] A meta-analysis involving seven randomized trials and 19,929 patients evaluated the most appropriate timing for administration of glycoprotein IIb-IIIa inhibitors.[34] A strategy of early infusion prior to the admission of the patient to the catheterization laboratory was unable to reduce the incidence of mortality at 30 days or recurrent AMI. However, it was associated with a higher rate of severe bleeding.

Although primary PCI reduces mortality compared with fibrinolysis, suboptimal reperfusion is observed in a non-negligible proportion of patients, with distal embolization playing a central role in the genesis of this phenomenon. In this sense, there has been great interest in the role of glycoprotein IIb-IIIa inhibitors in this clinical scenario. A meta-analysis including large contemporary clinical trials conducted during pretreatment with clopidogrel and including 10,085 patients, assessed the efficacy and safety of glycoprotein IIb-IIIa inhibitors as adjunctive therapy for primary PCI in AMI with ST-segment elevation.[35] No reduction was observed in mortality at 30 days with the use of these inhibitors or recurrence of AMI, but there was an increased rate of severe bleeding. However, a meta-regression analysis observed a benefit favoring glycoprotein IIb-IIIa inhibitors among patients at higher risk (age ≥ 65 years, hemodynamic instability, anterior AMI, diabetics).

Based on the hypothesis that an increased local concentration of abciximab would enhance its antiplatelet, antithrombotic, and anti-inflammatory effects, intracoronary bolus administration of this drug has been tested during primary PCI. A meta-analysis including six randomized trials and 1,246 patients concluded that compared with intravenous infusion, intracoronary administration of abciximab resulted in a significant reduction of 57% in mortality and 43% in the need for target vessel revascularization at 30 days, without an increase in severe bleeding rate, although these findings were not subsequently confirmed in a large randomized study involving 2,065 patients.[36,37]

Thus, glycoprotein IIb-IIIa inhibitors play an important role as adjunctive therapy in PCI, but the prescription of these agents is restricted to non-programmed situations, especially in the catheterization laboratory, with emphasis on patients with high-risk non-ST–segment elevation ACS and without previous treatment with $P2Y_{12}$ receptor inhibitors, from the presence of thrombotic complications during PCI (abrupt vessel occlusion, slow epicardial flow, coronary dissection, lateral branch occlusion) to AMI with ST-segment elevation in high-risk patients or in the presence of an increased thrombotic load. Upon consideration of these agents, the risk profile of the patients should be considered in regard to the

occurrence of hemorrhagic events, which are known promoters of increased morbidity and mortality.

Although the use of glycoprotein IIb-IIIa inhibitors has no influenced on the efficacy of the new oral antiplatelet drugs (ticagrelor, prasugrel) in the treatment of ACS, further research is required regarding their use in patients treated with the new $P2Y_{12}$ receptor inhibitors, or those with CYP2C19 genetic variants or low clopidogrel response, or regarding the option of reducing or suppressing its maintenance dose.

d) Pretreatment with $P2Y_{12}$ receptor antagonists

In the acute phase of ACS, a scenario characterized by a prothrombotic status and intense platelet activation, dual antiplatelet agglutination represents an important therapeutic step, and it is intuitive to assume that a potent and early pharmacological action is capable of conferring anti-ischemic efficacy, reducing thrombotic events (periprocedural infarction, stent thrombosis, coronary reocclusion), especially among patients undergoing invasive risk stratification and PCI. However, counterpoints to pretreatment with $P2Y_{12}$ receptor antagonists include the increased prevalence of hemorrhagic complications with antithrombotic therapy, as well as a possible delay in implementing surgical treatment in patients with multivessel disease and indication of revascularization, prolonging the hospitalization duration and increasing the risk of bleeding related to surgery. Still, there is scarce evidence from randomized clinical trials with adequate casuistry and statistical power for a clear and definitive response to this topic.

The trial Clopidogrel for the Reduction of Events During Observation (CREDO) is one of the pioneer studies suggesting a benefit from early dual antiplatelet therapy initiated immediately after diagnosis. This trial randomized 2,116 patients, including 66% diagnosed with ACS.[38] The objective of the trial was to evaluate the benefit of a loading dose of 300 mg of clopidogrel 3-24 hours prior to PCI and maintenance of the dual therapy for 12 months. Pretreatment with clopidogrel was associated with a nonsignificant reduction of 18% in the risk of death, AMI, or emergency revascularization at 28 days. However, in a prespecified subgroup analysis, a significant reduction of 38.6% in the primary outcome was observed in patients whose therapy was initiated 6 hours before PCI, the conceptual basis for the adoption of this strategy.

In the era of new and potent $P2Y_{12}$ receptor inhibitors, the study Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST–Elevation Myocardial Infarction (ACCOAST) randomized 4,033 patients with non-ST–segment elevation ACS to receive a 30 mg dose of prasugrel at the time of diagnosis (pretreatment) plus 30 mg in case of PCI, compared with 60 mg immediately prior to the procedure.[39] The primary efficacy endpoint, composed of cardiovascular death, AMI, stroke, urgent revascularization, or unplanned use of glycoprotein IIb-IIIa inhibitors at 7 days did not differ between groups, whereas the safety outcome, severe bleeding occurrence by TIMI classification, was almost double among those pretreated with prasugrel, with its use in such circumstances being discouraged.

Even though ticagrelor was administered early in the PLATO study, prior to invasive stratification, the study did not evaluate pretreatment or not with the drug. In contrast, the study Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) randomized 1,862 patients with ST-segment elevation AMI to ticagrelor at a dose of 180 mg, prior to transfer to primary PCI, including prehospital transport, against a loading dose administered in the catheterization laboratory.[40] The ≥ 70% resolution of ST-segment elevation or TIMI 3 flow in the infarct-related artery at angiography, surrogate endpoints that comprised the investigation hypothesis of the study, did not differ between the strategies. The authors observed a highly significant interaction related to the use of prehospital morphine, evidencing a benefit in the primary objective among patients who did not use the opioid derivative. Ongoing studies are evaluating the effects of morphine on the pharmacokinetic and pharmacodynamic properties of $P2Y_{12}$ receptor inhibitors.[41] An interesting finding in one of the study's secondary endpoints, concerning the occurrence of definite stent thrombosis at 30 days, consisted of a significant reduction of this complication favoring pretreatment, despite a difference of only 31 minutes between administration of the drug in the two groups. Despite generating a hypothesis, this evidence supports the early onset of the double antiaggregation.

Head-to-head comparisons between ticagrelor and prasugrel are necessary. A randomized study evaluating the occurrence of ischemic or hemorrhagic complications in 1,230 patients diagnosed with AMI who underwent PCI showed no difference between

the drugs and was prematurely interrupted because of futility.[42] Designed to access the superiority of ticagrelor *versus* prasugrel in 4,000 patients with ACS and invasive stratification planning, the Rapid Early Action for Coronary Treatment (ISAR-REACT) 5, with greater statistical robustness, will contribute to the definition of future regulations.[43] On the other hand, the comparison between pretreatment and no pretreatment with dual antiplatelet aggregation will be investigated in the currently ongoing clinical trial Downstream Versus Upstream Strategy for the Administration of $P2Y_{12}$ Receptor Blockers (DUBIUS), which plans to include 2,520 patients with non-ST–segment elevation ACS undergoing an early invasive strategy (NCT02618837).

e) Optimal duration of dual antiplatelet therapy

Dual platelet inhibition for a period of 1 year is recommended for patients diagnosed with ACS, especially those who underwent percutaneous myocardial revascularization, regardless of the type of stent; this recommendation is based on the results of randomized clinical trials such as CURE and, more recently, TRITON-TIMI 38 and PLATO, indicating an early and continuous benefit of dual antiplatelet therapy over 12 months of treatment.[44,45]

A recent topic of discussion is the maintenance of dual antiplatelet therapy for more than 12 months among individuals undergoing PCI. A meta-analysis encompassing six randomized clinical trials and 33,435 patients with a previous history of AMI showed that extending the dual antiaggregation after 1 year promotes a significant reduction of combined cardiovascular events compared with monotherapy with ASA, demonstrating an isolated reduction of cardiovascular death, AMI, stroke, and stent thrombosis at the expense of an increased occurrence of severe bleeding.[46]

Thus, the prescription of dual antiplatelet therapy for more than 12 months in patients undergoing PCI in the presence of an ACS can be considered.[47] Such a decision should be based on a risk and benefit analysis, offering this option to patients predisposed to recurrence of ischemic events (*e.g.*, previous AMI; diabetes mellitus; left ventricular dysfunction; type, diameter, and extent of implanted stent; chronic renal failure; peripheral arterial disease) but without a high risk of bleeding. The adoption of risk scores is an auxiliary tool in the decision-making process, and a judicious clinical judgment should prevail, especially the individualization of behaviors. Other speculative topics of interest and under current investigation consist of long-term monotherapy with an antiplatelet agent of higher inhibitory potency, such as ticagrelor (NCT01813435; NCT02270242), as well as the association between a $P2Y_{12}$ inhibitor and factor Xa inhibitors, in detriment to ASA, in the management of patients with ACS.[48]

f) Patients requiring oral anticoagulation

Patients with atrial fibrillation, a recent episode of venous thromboembolism, and those with mechanical valve prostheses may require PCI in the occurrence of an ACS. In this scenario, the treatment involves triple therapy, consisting of an anticoagulant agent and two antiplatelet drugs, including ASA, a situation that exponentially increases the risk of hemorrhagic complications.[49] Considering the increased potency and current absence of scientific evidence, the use of prasugrel or ticagrelor should be avoided, with clopidogrel being the $P2Y_{12}$ antagonist of choice in this situation. Reducing the duration of triple therapy would add greater safety to the treatment, with the discontinuation of an antiplatelet therapy as early as possible.[50] Although there are proposed flowcharts by expert consensus (Figure 1), the issue is still controversial and ongoing research evaluating the efficacy and safety of new oral anticoagulants associated with clopidogrel or ticagrelor will influence future standards on the subject.

In the study What is the Optimal antiplatElet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary StenTing (WOEST), 573 patients using oral anticoagulation with warfarin undergoing PCI, including approximately 30% during an ACS, were randomized to receive clopidogrel alone or in combination with ASA.[51] At the end of 1 year of follow-up, triple therapy promoted a significant increase in the risk of bleeding, including severe manifestations, with no benefit in reducing death, AMI, stroke, revascularization of the target vessel, or stent thrombosis. Based on this research hypothesis, the Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) trial demonstrated that the association between rivaroxaban 15 mg and a $P2Y_{12}$ inhibitor, as well as rivaroxaban 2.5 mg twice daily

and dual antiplatelet therapy, reduced the occurrence of clinically significant bleeding when compared with triple therapy with warfarin, in addition to general or recurrent hospitalization due to adverse events.[52,53]

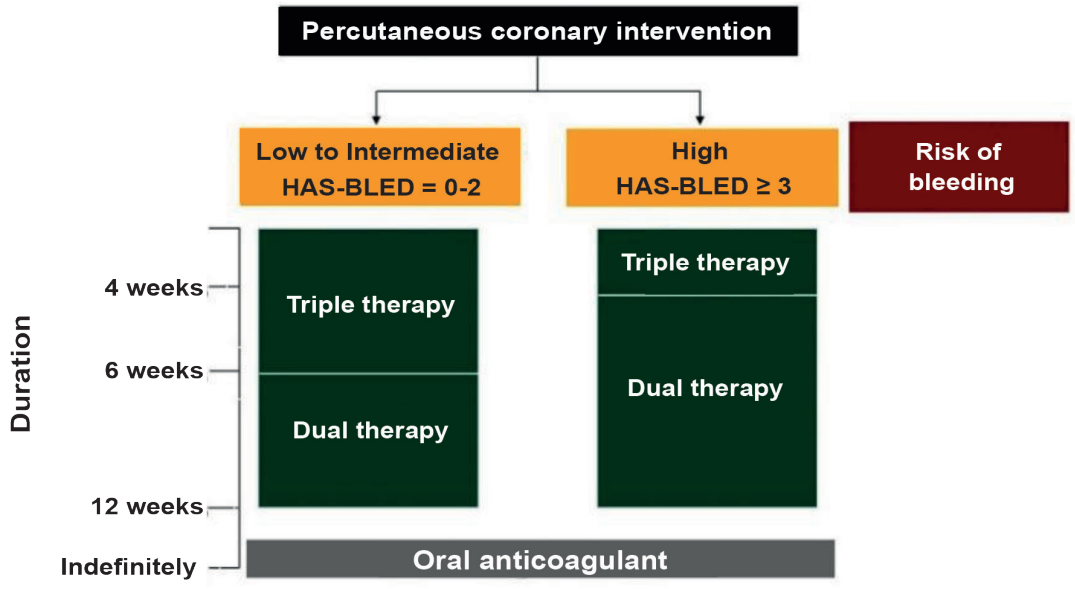

Figure 1 – *Triple therapy, after percutaneous coronary intervention in acute coronary syndrome, in patients requiring oral anticoagulation. Source: Adapted from Roffi et al.[44]*

Conclusion

Antiplatelet pharmacotherapy plays a decisive role in the clinical and invasive management of ACS. The greater knowledge of the pathophysiology of the cascades involved in this process has allowed the advent of more effective types of treatment, often associated with an increased risk of bleeding. However, the safety of any prescription is paramount in contemporary practice, since hemorrhagic complications carry a high risk of morbidity and mortality. Many ongoing research studies keep this topic current, controversial, and subject to constant regulatory changes. Thus, by always guiding ourselves by common sense, individualized approaches, and estimation of risks and benefits, we can directly interfere in the patients' prognosis and evolution.

Author contributions

Conception and design of the research: Andrade PB, Borges LSR. Acquisition of data: Andrade PB, Borges LSR. Analysis and interpretation of the data: Andrade PB, Borges LSR. Statistical analysis: Andrade PB, Borges LSR. Writing of the manuscript: Andrade PB, Borges LSR. Critical revision of the manuscript for intellectual content: Andrade PB, Borges LSR.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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