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P2Y12 inhibitor de-escalation after percutaneous coronary interventions

De-escalação de inibidores dos receptores P2Y12 após intervenção coronária percutânea

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ABSTRACT - In patients who have acute coronary syndromes and are treated with percutaneous coronary intervention, the prescription of a dual antiplatelet regimen, consisting of acetylsalicylic acid and a P2Y12 receptor inhibitor, is mandatory, contributing to the reduction of major cardiac events. However, while preventing ischemic events, this association may precipitate major bleeding complications, which is more commonly seen when more potent drugs, such as prasugrel or ticagrelor, are prescribed. These findings led to the search for therapeutic alternatives that could maintain the protection against ischemic events and, at the same time, prevent the occurrence of hemorrhages. One of the strategies being studied is de-escalation of P2Y12 inhibitors, which consists of the use of more potent drugs in an early phase after the procedure, replacing them with clopidogrel, after a period of, in general, 30 days of clinical course. Another possibility would be to simply reduce the dose of the most potent drug, which so far can only be considered with prasugrel. De-escalation can be done in a guided way, using objective measuring tests of platelet aggregation or exams to assess the genetic profile of patients, or unguided, in which the cardiologist simply replaces or reduces the dose at the end of the stipulated period, with no ancillary tests. The literature includes clinical trials with these two strategy options, which are discussed in this review. So far, no medical guideline explicitly recommends the regular use of this therapeutic alternative.

Keywords: Myocardial infarction; Angina, unstable; Prasugrel hydrochloride; Ticagrelor; Clopidogrel; Percutaneous coronary intervention; Dual anti-platelet therapy; Purinergic P2Y receptor antagonists

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RESUMO - Em pacientes que apresentam síndromes coronárias agudas e são tratados com intervenção coronária percutânea, a prescrição do esquema antiplaquetário duplo, composto de ácido acetilsalicílico e um inibidor dos receptores P2Y12, é mandatória, contribuindo para a redução de eventos cardíacos maiores. No entanto, ao mesmo tempo em que previne eventos isquêmicos, essa associação pode precipitar complicações hemorrágicas maiores, o que é mais comumente observado quando são prescritos os medicamentos mais potentes, como o prasugrel ou o ticagrelor. Essas constatações levaram à procura de alternativas terapêuticas capazes de manter a proteção contra eventos isquêmicos e, ao mesmo tempo, prevenir a ocorrência de hemorragias. Uma das estratégias que está em estudo é a de-escalação dos inibidores P2Y12, que consiste no uso dos medicamentos mais potentes numa fase precoce após o procedimento, com substituição deles pelo clopidogrel, após um período de, em geral, 30 dias de evolução; outra possibilidade seria a simples redução da dose do fármaco de maior potência, algo que, até o momento, só pode ser cogitado com o prasugrel. A de-escalação pode ser feita de forma guiada, utilizando testes de mensuração objetiva da agregação plaquetária ou exames para avaliar o perfil genético dos pacientes, ou não guiada, na qual o cardiologista simplesmente faz a substituição ou redução da dose ao fim do período estipulado, sem o auxílio de exames complementares. A literatura contempla ensaios clínicos com essas duas opções de estratégia, os quais são discutidos nesta revisão. Até o momento, nenhuma diretriz médica recomenda de forma explícita o uso regular dessa alternativa terapêutica.

Descritores: Infarto do miocárdio; Angina instável; Cloridrato de prasugrel; Ticagrelor; Clopidogrel; Intervenção coronária percutânea; Terapia antiplaquetária dupla; Antagonistas do receptor purinérgico P2Y

INTRODUCTION

De-escalation is a therapeutic alternative considered in patients treated with percutaneous coronary intervention (PCI) in the presence of an acute coronary syndrome (ACS), in which, after a brief period (in general, 1 month), a more potent P2Y₁₂ receptor inhibitor antiplatelet medication (prasugrel or ticagrelor) is replaced by a less potent one (clopidogrel). The aim is to reduce the prospect of major bleeding after hospital discharge, but not compromising the ability of the prescribed therapeutic scheme to prevent major adverse cardiac events (MACE). There is also the possibility of de-escalation being performed by reducing the dose of the most potent antiplatelet medication.^{1,2}

Since it should be understood, it is based on the premise that most ischemic events would occur in the mentioned period, after which the prescription of a more potent antiplatelet medication, and, consequently, more capable of causing bleeding complications, would be less necessary, and it could be replaced by an agent with less potency, without this causing an increase in risk of ischemia.^{1,2}

In subsequent items, details related to this new therapeutic alternative are discussed.

Percutaneous coronary intervention

As a result of the development and expansion of the use of drug eluting stents, PCI is currently the main method of myocardial revascularization, regardless of the clinical presentation of the coronary disease.³⁻⁵ One of the most contemporary clinical trials, the ISAR-REACT 5, an investigation restricted to the scope of ACS, has strongly demonstrated this statement, since PCI was the definitive therapeutic option in about 85% of included cases.⁶

To ensure the procedures are safely performed, since the mid-1990's, the so-called dual antiplatelet therapy, a synergistic association composed of acetylsalicylic acid (ASA) and an inhibitor of platelet P2Y₁₂ receptors, has been used with the aim to prevent thrombosis in the stent and the occurrence of MACE. This association is maintained for variable periods, depending on a series of clinical, angiographic and procedure-related factors, but which, in most situations, are restricted to a 6-12-month period after the intervention.^{3-5,7}

Despite the efficacy of the dual therapy for the purposes described, the concomitant use of two drugs that inhibit platelet activity predisposes to bleeding complications, which can hinder patient safety and, in more serious situations, even increase mortality.^{3-5,7,8} Previous clinical studies have shown a significant increase in late morbidity and mortality in patients affected by these complications, making clear the need to investigate alternatives that could effectively prevent them.^{1,3-5,7,8}

Initially, the possibility of early discontinuation of the dual therapy was suggested, more specifically the discontinuation of the P2Y₁₂ inhibitor, in those most predisposed to developing bleeding in the late phase.^{1,3-5} More recently,

other clinical trials investigated the possibility of early discontinuation of ASA, which is implicated in the increase in bleeding from the digestive tract, and maintaining the isolated use of the P2Y₁₂ receptor inhibitor, to maintain the treated cases free of major cardiovascular events. This alternative provides, at the same time, a lower prospective of hemorrhagic complications, and is known as "monotherapy with P2Y₁₂ receptor inhibitors".^{1,5,8} Finally, another option would be "de-escalation of P2Y₁₂ inhibitors".^{1,2}

Before specifically discussing this strategy, aspects of the clinical pharmacology of this class of drugs are explained, to facilitate understanding of the bases upon which the strategy was conceived.^{1,3-5,9,10}

P2Y₁₂ receptor inhibitors

Currently, there are three drugs that can be prescribed: clopidogrel, prasugrel, and ticagrelor. Relevant differences exist among these drugs, which require knowledge and attention on the part of physicians for a proper selection, providing a better risk/benefit/cost analysis at the time of their prescription.^{1,3-5}

Clopidogrel is a compound that acts on the adenosine diphosphate (ADP) pathway of platelet aggregation, inhibiting P2Y₁₂ receptors, which are fundamental in this process. It is indicated both in cases of acute and chronic coronary insufficiency; in the latter situation, so far, its use has been restricted to cases of intolerance to ASA in secondary prevention, or to patients treated by means of PCI. Although it has proven efficacy and convenient dosage (single daily dose), facilitating patient adherence to treatment, some drawbacks were observed by clinical experience: slow onset of action; less than desired inhibition of platelet aggregation; inconsistent effect in the presence of genetic polymorphisms and/or undesired potential drug interactions (the latter are less valued at present). These limitations led to the development of new drugs, to overcome these shortcomings.^{3-5,11-16}

Two new drugs were then developed: prasugrel and ticagrelor. Like clopidogrel, both act on the ADP pathway of platelet aggregation, likewise inhibiting the P2Y₁₂ receptor. As demonstrated by pharmacodynamic assays, both outperformed clopidogrel in terms of speed of action and antiplatelet inhibitory potency, and, to date, there is no knowledge of any genetic polymorphisms that restrict their performance.^{1,3-5,9,16}

Prasugrel is a prodrug, *i.e.*, its effect depends on the action of a metabolite derived from hepatic metabolism. It is administered in a single daily dose, and its effect on platelets is irreversible.^{1,7} In contrast, ticagrelor, the first drug available in clinical practice of a new class of antiplatelet agents called cyclopentyl-triazolopyrimidines, acts directly on platelets and requires two daily doses, since it has a shorter half-life and its effect is reversible, characteristics that render essential the administration of the second daily dose.^{1,7}

To verify these advantages, two large multicentric clinical trials were conducted in patients with ACS involving the two new drugs, always in direct comparison with clopidogrel: the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction)¹⁷ and PLATO (Study of Platelet Inhibition and Patient Outcomes).¹⁸ Both demonstrated a significant advantage of contemporary drugs in the combined primary endpoint of death, acute myocardial infarction (MI) or stroke in one year of clinical course. Due to their greater potency, they were also associated with a greater probability of causing major bleeding, which is why they require more careful selection at the time of their prescription.^{1,3-5,19,20}

In addition to the greater potential for triggering hemorrhages, these two most potent drugs are more expensive than clopidogrel, restricting their long-term use, especially in our country.

Therefore, the rationale for suggesting the hypothesis of adopting de-escalation becomes clear: using a more potent medication at the most critical moment, *i.e.*, when the probability of MACE occurring is greater, replacing it with another not as potent, as this possibility decreases, which would imply the maintenance of the benefit in the prevention of ischemic complications and a lower risk of bleeding.^{1,2}

DE-ESCALATION OF P2Y12 RECEPTOR INHIBITORS

When the cardiologist chooses to adopt this therapeutic alternative, it can be performed in two ways:

- Guided: an objective test objectively measuring platelet aggregation or a genetic profile exam demonstrating the patient's responsiveness to clopidogrel is performed, allowing the substitution in a safer but more expensive and restrictive way, because these exams imply higher costs and depend on local availability for their execution.
- Unguided: the substitution is done without the support of these tests, rendering it less safe, but more pragmatic, reflecting the real-world situation and allowing more patients to be treated.^{1,2}

There are clinical trials involving both possibilities.

Clinical studies with guided de-escalation

There are four clinical studies on the subject, of which three are completed and one is in progress.²¹⁻²⁴

ANTARCTIC²¹

A French multicenter clinical trial (35 centers) involving 877 patients aged over 75 years who presented with ACS and were treated with PCI. It was a prospective, randomized, open clinical trial.

All patients were initially medicated with a combination of AAS and prasugrel at a dose of 5mg per day, with adjustments made every 2 weeks after randomization in

the patients allocated to the guided strategy (two exams in the first month), using the VerifyNow® system, an objective method of measuring platelet aggregation. Using P2Y12 reaction unit results between 85 and 208 as a reference, the patients with a value <85 were downscaled to clopidogrel, whereas those with a result >208 had their dose increased to 10mg per day. Following this premise, the cases were randomized into two groups: A total of 442 cases were allocated to the guided group; and 435 patients were treated with a fixed 5mg dose of prasugrel daily without any platelet aggregation monitoring.

A broad combined primary endpoint was established, consisting of death from cardiovascular causes, AMI, stroke, stent thrombosis, urgent myocardial revascularization or bleeding complications of types 2, 3 or 5, according to the Bleeding Academic Research Consortium (BARC) criteria, measured at the end of the first year of follow-up. The study hypothesis was a primary endpoint reduction in the de-escalation group.

Two thirds of the patients evolved with ACS without ST-segment elevation. Approximately 30% were diabetic, and 60% had severe multivessel disease on diagnostic coronary angiography; 90% of the procedures in both groups were performed via the radial approach.

At the end of the evaluation period, it was observed that 55% of the patients included in the guided group maintained the initially prescribed dose of prasugrel, the same occurring with 93% of the patients in the non-guided group. The most commonly observed change in the guided group was de-escalation to clopidogrel (39%).

The combined primary objective occurred in 28% of the patients in both groups, suggesting lack of effectiveness of the strategy guided by objective measurement of platelet aggregation in the elderly population aged over 75 years and initially medicated with prasugrel at a dose of 5mg a day. None of the participants, when evaluated individually, showed significantly different results, including bleeding complications, confirming this impression.

Two main observations are worth highlighting in relation to this study and its result: at no time did the authors mention a previous study that clearly established the 30-day period after PCI in the presence of an ACS as the period in which events would be most common; the observations and measured results should not be extrapolated to alternative methods of objective measurement of platelet function or genetic profile tests, as well as for patients of a younger age group and medicated with the usual doses of prasugrel or ticagrelor.

TROPICAL-ACS²²

A European clinical study involving 33 centers, randomized, prospective, and open-label. A total of 2,610 patients with ACS undergoing PCI were included, who obligatorily had to present a significant increase in myocardial injury biomarkers during the index hospitalization, with a planned dual antiplatelet treatment regimen for 1 year,

consisting of ASA and prasugrel in the usual doses (5 or 10mg/day).

The recruited cases were divided into two groups. One of them was the guided group, in which patients received prasugrel for 7 days, which was replaced by clopidogrel, at the usual maintenance dose (75mg daily), for the subsequent 7 days. At the end of this 2-week period, platelet aggregation was measured using the Multiplate® Analyzer method and, in the patients with high platelet aggregation (values above 46 units by this method), prasugrel was reintroduced, whereas in the remaining cases, de-escalation was maintained. The control group consisted of patients who maintained the use of prasugrel at the usual doses (they also had their platelet aggregation measured by the aforementioned method). The combined primary endpoint was the occurrence of cardiovascular death, AMI, stroke, or hemorrhages according to BARC criterion (subtypes 2, 3 or 5), which was measured after 1 year, with the hypothesis of non-inferiority, with the final analysis performed by the principle of intention to treat.

In most patients (approximately 55%) in both groups, the initial clinical presentation was ST-segment elevation AMI, with most interventions performed via the radial approach; drug-eluting stents were implanted in 77% of patients.

The results of the objective measurement of platelet aggregation performed on the 14th day of clinical course showed high values in 39% of the patients in the guided group, in which prasugrel was reintroduced in 99% of the cases, and in 14% of the cases allocated to the control group. Therefore, de-escalation was effectively performed in 61% of patients in the guided group.

After 1 year of follow-up, the combined primary endpoint occurred similarly in the guided and control groups (7% versus 9%; $p=0.0004$ for non-inferiority), the same occurring with MACE (3% versus 3%; $p=0.01$ for non-inferiority). Bleeding complications did not differ (5% versus 6%; $p=0.23$), including major ones (1% versus 2%; $p=0.63$). Therefore, these results demonstrate that, in the sample evaluated, the strategy of de-escalation of the P2Y12 inhibitor did not demonstrate any significant clinical disadvantage in relation to the double regimen usually prescribed.

Unlike ANTARCTIC,²¹ in the elaboration of the protocol and in the discussion of the present clinical trial, there was mention of subanalyses^{23,24} conducted in the TRITON-TIMI 38¹⁷ and PLATO¹⁸ studies, in which the occurrence of MACE was predominantly during the first month of clinical course, justifying the de-escalation at the end of this period, although in TROPICAL-ACS²² the timing of the definitive replacement of antiplatelet agents was even earlier, after 15 days.

POPular Genetics²⁵

Another possibility to guide the de-escalation of P2Y12 inhibitor antiplatelet agents is the evaluation of the patients' genetic profile. It is known that approximately one

third of treated cases have total or partial loss of function of the alleles responsible for clopidogrel metabolism, and, in these cases, the effectiveness of this drug is lower, predisposing these patients to more MACE after discharge. However, in the patients who do not present this polymorphism, it can be prescribed, and this strategy may avoid ischemic events and, at the same time, prevent hemorrhagic complications.

The clinical study in question was an investigator-initiated, multicenter (10 European centers), prospective, randomized, open-label study involving 2,488 patients with ST-segment elevation AMI who were reperfused by primary PCI with a stent. In the first 48 hours of clinical course, they were randomized to one of the following strategies: guided (1,242 patients), in which the patients underwent an examination to assess their genetic profile with regard to clopidogrel metabolism, preferably using a device called Spartan RX; in those demonstrating loss of function, ticagrelor or prasugrel was maintained at usual doses for 1 year. In the patients who did not demonstrate this finding, it was replaced by clopidogrel, also at the usual doses, with or without a loading dose (at the discretion of each investigator), and also maintained for 12 months. The second strategy was standard or unguided (1,246 cases), in which all patients were medicated with ticagrelor or prasugrel, at usual doses, for 1 year. AAS was prescribed to all patients, regardless of the adopted strategy. The publication does not distinguish the exact moment of the de-escalation (the text describes it as occurring "as soon as possible").

Two primary outcomes were established, assessed after 1 year of clinical course: a clinical outcome, defined by the occurrence of death from any cause, AMI, stroke, definitive stent thrombosis or major bleeding according to the PLATO criteria; and a hemorrhagic outcome, defined by the observation of any hemorrhages using the aforementioned criteria. The study hypothesis was non-inferiority of the guided strategy.

After randomization and without specifying exactly in how many patients the de-escalation actually occurred, 61% of the cases in the guided group were medicated with clopidogrel – the same was done to 7% of the patients in the standard group. Prasugrel or ticagrelor were prescribed to 39% of patients in the guided group, and to 93% of those allocated to the standard group (91% with ticagrelor).

The clinical combined primary endpoint occurred in 5.1% of cases in the guided group, and in 5.9% of cases in the standard group ($p<0.001$ for non-inferiority and $p=0.40$ for superiority). Bleeding complications were observed in 9.8% of guided strategy cases, and in 12.5% of unguided strategy cases ($p=0.04$), although major complications occurred in identical percentages (2.3% in each group; 95%CI 0.58-1.63), demonstrating that the superiority observed in the guided group was essentially due to the prevention of less severe cases.

Finally, a secondary endpoint was also evaluated, which contemplated the primary variables, but replacing death

from any cause with cardiovascular causes and excluding hemorrhagic complications, which also occurred similarly between groups (2.7% *versus* 3.3%; 95%CI 0.53-1.31).

GUARANTEE²⁶

Asian clinical trial not yet completed, which will involve 4,009 patients undergoing PCI, both in the presence of ACS and chronic CAD. They will be randomized into two strategy groups: the first is guided by genetic tests, as described in the latter study, and the patients with loss of function will receive ticagrelor in the usual doses (90mg in two daily intakes), while those without loss of function will be medicated with 75mg clopidogrel a day; the second group is standard, or unguided, in which the allocated cases will be treated with clopidogrel (chronic cases) or ticagrelor (ACS), following the recommendations of the guidelines.

The combined primary endpoint will consist of death from any cause, AMI, stroke or revascularization guided by ischemia, assessed after a 1-year follow-up. Results are expected to be released in 2023.

Clinical studies with unguided de-escalation

There is also a more pragmatic and comprehensive alternative, which is de-escalating independently of any assessments to guide decision-making. Despite being a more feasible and attractive strategy, as it would bring greater agility and lower cost to the process, the replacement of a more potent drug by another less potent one, which may be less effective, undoubtedly brings fears to the cardiologist. Next, we will discuss the clinical trials that evaluated this possibility.²⁷⁻²⁹

TOPIC²⁷

A French unicentric, prospective, randomized and open study, in which 646 patients with ACS and treated with PCI were evaluated, initially medicated with prasugrel or ticagrelor, and who, at the end of the first month of clinical course, were divided into two groups (323 cases allocated in each): one group maintained the medication currently in use, and the other had it replaced by clopidogrel. Both groups maintained the medications for 1 year.

The absolute majority of PCIs were performed via the radial approach (approximately 95% in both groups). Drug-eluting stents were implanted in 91% of patients. Prasugrel was the most commonly prescribed drug at first (57%).

At the end of the aforementioned period, adherence to treatment was significantly more frequent in the de-escalation group (86.0% *versus* 74.9%; $p < 0.01$). Although there is no specific comment in the publication about the cause of this finding, it is fair to assume that it must have been motivated by side effects, more commonly present, in general, with the prescription of ticagrelor.^{18,19}

The combined primary endpoint of the study consisted of death from cardiovascular causes, urgent CABG, stroke, or grade ≥ 2 hemorrhages according to the BARC criteria.

After 12 months of clinical course, the primary endpoint occurred more frequently in the non-de-escalated group (26.3% *versus* 13.4%; 95%CI 0.34-0.68; $p < 0.001$). When the different components were discriminated, a significant reduction in bleeding complications was verified (4.0% *versus* 14.9%; 95%CI 0.18-0.50; $p < 0.01$), which was not observed with the set of ischemic components (9.3% *versus* 11.5%; 95%CI 0.50-1.29). However, there was no significant difference with regard to hemorrhages classified as major.

HOST-REDUCE-POLYTECH-ACS²⁸

A clinical study carried out in South Korea, involving 2,338 patients recruited from 35 hospital centers, who evolved with ACS and were treated with PCI. As already mentioned, it was a prospective, randomized and open-label study. After 30 days of follow-up and regular use of the combination of AAS and prasugrel at a dose of 10mg/day, the included cases were randomized into two strategies: de-escalation by reducing the dose of prasugrel to 5mg/day (1,170 cases included); standard care, maintaining the drug at the usual dose (1,168 patients allocated). Both groups maintained the dual regimen for 12 months.

The combined primary endpoint assessed at one year included death from any cause, AMI, stroke, stent thrombosis, new CABG, or any hemorrhages scored as 2 or more by the BARC criteria. The hypothesis of the study was the non-inferiority of the de-escalation strategy. The secondary endpoints consisted of an individualized evaluation of the clinical and hemorrhagic events described.

In most patients in both groups, the predominant clinical presentation was unstable angina (60% in both groups). All recruited patients received drug-eluting stents, and procedure success exceeded 99% in both groups.

The combined primary endpoint was significantly reduced in cases allocated to the de-escalation strategy (7.2% *versus* 10.1%; $p = 0.01$ for non-inferiority). Regarding the secondary endpoints, the clinical picture did not differ (1.4% *versus* 1.8%; $p = 0.40$), but hemorrhage was significantly more observed in the standard group (2.9% *versus* 5.9%; $p < 0.0007$), although there was no difference regarding major bleeding complications (0.8% *versus* 0.7%; $p = 0.82$).

Therefore, the result demonstrated the feasibility of the non-guided de-escalation strategy by means of reducing the dose of the P2Y12 inhibitor, instead of changing it to a less potent medication, which did not result in more ischemic events in the follow-up and avoided an excess of hemorrhages, most of which were classified as minor.

TALOS-AMI²⁹

Also South Korean, a prospective, randomized, and open-label investigation, involving 2,697 patients with AMI, with or without ST-segment elevation, percutaneously revascularized, included in 32 tertiary hospital centers, who were medicated with the association of AAS and ticagrelor for the 30 first days of clinical course; if there were no re-

levant ischemic or hemorrhagic complications during this period, they were then randomized into two strategies: de-escalation from ticagrelor to clopidogrel, at a dose of 75mg daily (1,349 cases); maintenance of the drugs initially prescribed (1,348 patients).

The combined primary endpoint of the investigation, assessed at the end of the first year of follow-up, included death from cardiovascular causes, AMI, stroke, and hemorrhagic complications of types 2, 3 or 5 of the BARC classification. The hypothesis of the study was non-inferiority.

Half of the interventions were performed via the femoral artery, and a little over 50% of the patients in each group had ST-segment elevation. Significant left ventricular dysfunction (according to the authors, left ventricular ejection fraction below 40% on the echocardiogram) was observed in approximately 7% of cases in both groups.

After one-year follow-up, the combined primary endpoint occurred in 4.6% of cases in the de-escalation group, and in 8.2% of the so-called active group ($p < 0.001$ for non-inferiority; $p = 0.0001$ for superiority). When an individual analysis of the ischemic components was carried out, no significant difference was observed between the groups (2.1% versus 3.1%; $p = 0.15$), contrary to hemorrhagic complications, which were more frequent in the active group (3.0% versus 5.6%; $p = 0.001$), even when only hemorrhages classified as major were cataloged (1.2% versus 2.3%; $p = 0.04$).

Meta-analyses of the clinical studies

The medical literature records two investigations of this type, published in 2021, with substantial differences between them, and it is essential to discuss such discrepancies to clearly understand what the cardiologist can learn from the results of each one of them.^{30,31}

The first meta-analysis, by Shoji et al., which involved 15 clinical trials and 55,798 patients with ACS, clearly states the term “de-escalation” in the title and conclusion, but included only two of the clinical trials mentioned above; moreover, it erroneously attributed to studies such as TRITON-TIMI 38¹⁷ and PLATO¹⁸ the evaluation of the topic addressed in this review, when, in fact, these clinical trials analyzed, respectively, prasugrel and ticagrelor in compari-

son with clopidogrel in the passivation of ACS, *i.e.*, in some studies included in the meta-analysis, there was no de-escalation from a more potent medication to a less potent one, but a direct comparison of one against the other. Therefore, despite the fact that the conclusion explicitly mentions the de-escalation of P2Y12 inhibitors as valid and effective, there is no way to support this statement due to the potential errors made.³⁰

The second meta-analysis, also published in 2021, involved, in fact, only clinical studies on de-escalation, analyzing the results of five of the six clinical trials already published on the subject, whose results were individually discriminated in the previous items of this review (only ANTARCTIC²¹ was not included). With the de-escalation strategy, a significant reduction of 43% (95%CI 0.42-0.78) was observed in hemorrhages classified as type 2 or higher by the BARC criterion, also demonstrating an equally significant superiority in the occurrence of MACE in the patients allocated to that alternative (23% reduction; 95%CI 0.62-0.96).³¹ As it included specific clinical trials on the subject, this result is more credible, although it did not lead to any explicit recommendation in favor of its adoption in the only guideline⁵ released after its publication.

DISCREPANCIES AND SIMILARITIES BETWEEN CLINICAL STUDIES

Tables 1 and 2 summarize the details of the different protocols and the most relevant results of the previously discussed clinical trials, noting a series of discrepancies in the designs and in the main findings, which potentially restrict the routine adoption of the de-escalation strategy.

CLINICAL IMPLICATIONS

A critical analysis of what has been exposed in the preceding items shows the clinical implications on the subject:

- The de-escalation of P2Y12 inhibitors is an attractive strategy, due to the possibility of fewer bleeding complications, maintaining the prevention of MACE in the late phase, and with lower costs, however, so far, it does

Table 1. Design characteristics of different clinical trials on de-escalation

	Clinical studies					
	ANTARCTIC	TROPICAL-ACS	POPular-GEN	TOPIC	HOST-REDUCE	TALOS-AMI
Patients	877	2,610	2,488	646	2,338	2,697
Guided DE	Yes	Yes	Yes	No	No	No
PA test	Yes	Yes	No	NA	NA	NA
GEN test	No	No	Yes	NA	NA	NA
DE timing	30 days	15 days	?	30 days	30 days	30 days
DE drug	Clopidogrel	Clopidogrel	Clopidogrel	Clopidogrel	Prasugrel 5mg	Clopidogrel
Type of ACS	All	All	With STE	All	All	All

DE: de-escalation; PA: platelet aggregation; NA: not applicable; GEN: genetic; ?: uncertain; ACS: acute coronary syndrome; STE: ST elevation.

Table 2. Summaries of key clinical trial outcomes

	Clinical studies					
	ANTARCTIC	TROPICAL-ACS	POPular-GEN	TOPIC	HOST-REDUCE	TALOS-AMI
Primary endpoint achieved	No	Yes	Yes	Yes	Yes	Yes
Reduction of clinical events*	No	No	No	No	No	No
Reduction of bleeding*	No	No	Yes	Yes	Yes	Yes
Reduction of major bleeding*	No	No	No	No	No	Yes

*Significant.

not have the support of any medical guideline, possibly due to the fact that no clinical study has been considered capable of modifying clinical practice.^{1,3-5,32,33}

- Most of the results of the clinical trials discussed showed an advantage only in preventing less relevant bleeding complications, not significantly interfering with the really significant ones.^{1,21-23,25-27,33}
- No study was carried out that directly compared the two methods of performing guided de-escalation, *i.e.*, there is no way to determine which guide method should be adopted as preferred.^{1,2,33}
- In theory, guided de-escalation would be preferred, as it would offer more security when replacing the P2Y12 inhibitor, however, as clinical studies carried out without the aid of complementary tests (non-guided strategy) have shown clinical results similar to those that were guided, there is also no way to clearly determine whether, in everyday practice, one strategy is superior to the other.^{1,33}
- Another uncertainty is the universe of patients for whom it should be considered, whether for all cases of ACS treated by PCI or only for those more predisposed to develop bleeding complications.^{1,2,33}
- The exact composition of the drug regimen to be prescribed is also controversial, since, although most clinical studies opted for replacing a more potent medication with clopidogrel, in others a reduction in the maintenance dose of prasugrel was chosen, it is not possible to determine, at the moment, whether one alternative is equivalent to the other. In addition, at the moment, a maintenance dose of 5mg prasugrel a day is indicated for patients aged over 75 years or weighing <60kg, and clinical experience with this regimen in other subgroups is still very limited. The precise timing for the effectiveness of the de-escalation is also not established.^{1,2,19,32,33}
- Finally, there are alternatives to the de-escalation strategy, such as the pure and simple reduction in the time of use of the dual scheme or monotherapy with P2Y12 inhibitors, and there is no clinical trial published to date that has compared these different alternatives, making it impossible to recommend one over the other.^{1,3-5,7}

CONFLICTS OF INTEREST

Luiz Fernando Leite Tanajura wrote two medical texts for the companies Daiichi Sankyo and Terumo in the past 2 years. The other authors have no conflicts of interest to disclose.

CONTRIBUTION OF AUTHORS

Conception and design of the study: LFLT; data collection: LFLT e JRCJ; data interpretation: LFLT e AJC; text writing: LFLT, AJC e RPF; approval of the final version to be published: LFLT, AJC, RPF e JRCJ.

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