¹ Seção de Angioplastia Coronária, Instituto Dante Pazzanese de Cardiologia, São Paulo, SP, Brazil.

Monotherapy with P2Y12 receptor inhibitors in patients treated by percutaneous coronary intervention

Monoterapia com inibidores dos receptores P2Y12 em pacientes tratados por meio de intervenção coronária percutânea

Luiz Fernando Leite Tanajura^{1iD}, Áurea Jacob Chaves^{1iD},
Andrea Cláudia Leão Sousa Abizaid^{1iD}, José de Ribamar da Costa Júnior^{1iD}

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ABSTRACT – Since the mid-1990s, the dual antiplatelet therapy, consisting of the association between acetylsalicylic acid and a platelet P2Y12 receptor inhibitor, is the core of thrombosis prevention after coronary stent implantation, regardless of the models used. It is also used to prevent the occurrence of atherothrombotic events in the late phase after the intervention. The clinical presentation of coronary artery disease influences the duration of dual therapy, which tends to be longer in treated cases of acute coronary syndrome (usually for one year), when compared to cases of chronic coronary disease (often for up to 6 months). After this period, the P2Y12 inhibitor is usually discontinued, and monotherapy with aspirin is maintained. However, in the last two decades, it has been observed that prolonged use of two associated antiplatelet agents predisposes treated cases to bleeding complications, with potentially severe consequences – including increased mortality. Thus, alternatives that minimize this risk have been considered and evaluated, such as early discontinuation of acetylsalicylic acid (between 1 and 3 months after discharge), or the so-called monotherapy with P2Y12 inhibitors, aiming to reduce bleeding without compromising prevention of ischemic events. In the last decade, a series of randomized clinical trials evaluated this hypothesis, generally resulting in reduced bleeding complications, although not necessarily of those classified as major, with no significant increase in the most relevant cardiovascular events. This review discusses the main results of these clinical trials and their potential clinical implications for routine cardiology practice.

Keywords: Myocardial infarction; Angina, unstable; Prasugrel hydrochloride; Ticagrelor; Clopidogrel; Percutaneous coronary intervention

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Corresponding author:

Luiz Fernando Leite Tanajura
Rua Cayowaa, 683 – Vila Pompéia
Zip code 05018-000 – São Paulo, SP, Brazil
E-mail: lftanajura@uol.com.br

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RESUMO – Desde meados da década de 1990, o esquema antiplaquetário duplo, constituído pela associação entre ácido acetilsalicílico e um inibidor dos receptores plaquetários P2Y12, constitui o cerne da prevenção das trombozes após implantes de stents coronários, independentemente dos modelos utilizados, sendo também utilizado para prevenir a ocorrência de eventos aterotrombóticos na fase tardia após a intervenção. A forma clínica de apresentação da coronariopatia influencia na duração da dupla terapia, que tende a ser mais prolongada nos casos tratados na vigência de uma síndrome coronária aguda (em geral, 1 ano), quando comparada a casos de doença coronária crônica (comumente até 6 meses). Finalizado esse período, geralmente descontinua-se o inibidor P2Y12, e mantém-se a monoterapia com aspirina. No entanto, nas duas últimas décadas, também foi observado que o uso prolongado de dois antiplaquetários associados predispõe os casos tratados às complicações hemorrágicas, com consequências potencialmente graves – inclusive o aumento da mortalidade. Dessa forma, têm sido consideradas e avaliadas alternativas que minimizem esse risco, como a interrupção precoce do ácido acetilsalicílico (entre 1 e 3 meses após a alta), constituindo a chamada monoterapia com inibidores P2Y12, opção que visaria à redução das hemorragias, sem comprometer a prevenção de eventos isquêmicos. Na última década, uma série de ensaios clínicos randomizados avaliou essa hipótese, em geral com resultado de redução das complicações hemorrágicas, embora não necessariamente das classificadas como maiores, sem aumento significativo dos eventos cardiovasculares mais relevantes. Esta revisão discute os principais resultados aferidos nestes ensaios clínicos e sua potencial implicação clínica na prática rotineira do cardiologista.

Descritores: Infarto do miocárdio; Angina instável; Cloridrato de prasugrel; Ticagrelor; Clopidogrel; Intervenção coronária percutânea

INTRODUCTION

The introduction and subsequent advances of coronary stents, more specifically with the development and expanded use of drug-eluting models, have made percutaneous coronary intervention (PCI) the main method of myocardial revascularization today, regardless of the clinical presentation of the disease.¹ One of the most contemporary clinical trials is the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment).⁵ It compared different antiplatelet agents in the setting of an acute coronary syndrome (ACS), conclusively demonstrating this assertion, since PCI was the definitive therapeutic option in approximately 85% of cases included.²

Since the mid-1990s, the so-called dual antiplatelet therapy, composed of acetylsalicylic acid (ASA) and a P2Y₁₂ platelet receptor inhibitor, has been used by the main centers that perform PCI, aiming to prevent stent thrombosis and the occurrence of late atherothrombotic events. This association is maintained for variable periods, depending on a series of clinical, angiographic, and procedure-related factors. However, in most situations, it is limited to the period of 6 to 12 months after the intervention.¹⁻⁵

Despite the efficacy of the dual therapy for the purposes mentioned, concomitant use of two drugs that inhibit the action of platelets predisposes to bleeding complications. These may compromise the patient's safety and, in extreme situations, even increase mortality.⁶ Currently, factors such as clinical presentation, number of vessels treated, extension of the segment covered by the stents, and presence of predisposing factors for development of hemorrhages have led cardiologists to maintain the dual therapy for different periods, with a clear tendency to shorten the time of concomitant use of the two antiplatelet agents. Moreover, in general, once the dual antiplatelet therapy period is over, the choice is to maintain the use of ASA (less potent) and discontinue the use of the P2Y₁₂ inhibitor (more potent).¹⁻⁵

More recently, some clinical trials have investigated the possibility of early withdrawal of ASA, implicated in increased bleeding, especially in the digestive tract. They maintained the isolated use of the P2Y₁₂ receptor inhibitor to preserve treated cases free of major cardiovascular events, and simultaneously provide a lower perspective of bleeding complications.⁷⁻¹¹ This alternative, called "antiplatelet monotherapy with P2Y₁₂", is not yet consensual, but, since the results of specific clinical trials on the subject are already available, its analysis may anticipate future changes in guideline recommendations.⁷⁻¹¹

Before discussing the studies, we will discuss aspects of the clinical pharmacology of P2Y₁₂ receptor inhibitors currently available for clinical use, and the potential conse-

quences that a significant bleeding complication could have on prognosis of patients undergoing PCI.^{3,6,12,13}

P2Y₁₂ RECEPTOR INHIBITORS

Currently, both in our country and abroad, we have three prescription drugs available: clopidogrel, prasugrel, and ticagrelor. These three drugs have relevant differences among them, requiring knowledge and attention from the physician for their proper selection, and providing better risk/benefit/cost evaluation.^{1,3-5}

Clopidogrel is a compound that acts on the adenosine diphosphate (ADP) pathway of platelet aggregation, inhibiting the P2Y₁₂ receptors, which are fundamental in this process. It is indicated both in cases of acute and chronic coronary insufficiency. Until now, in the latter situation, its use is restricted to cases of intolerance to ASA in secondary prevention, or to those treated by PCI. Although its efficacy has been proven and it is convenient to use (a single daily dose), with the course of clinical experience it was found this drug had relevant drawbacks: slow onset of action; inhibition of platelet aggregation lower than desired; inconsistent effect, especially in the presence of genetic polymorphisms; and/or unwanted drug interactions (the latter are less valued today). These restrictions have led to the development of new drugs, aiming to overcome the limitations.^{3,14-19}

Two new drugs have been developed: prasugrel and ticagrelor. Like clopidogrel, they act on the ADP pathway of platelet aggregation, also by inhibiting the P2Y₁₂ receptor. As shown by pharmacodynamic tests, both have outperformed clopidogrel in speed of action and antiplatelet inhibitory potency, and to date, there is no knowledge of genetic polymorphisms that restrict their action.^{1-5,12,13,19}

Prasugrel is a prodrug, i.e., its performance 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.^{13,15-17} On the other hand, ticagrelor, the first drug available in clinical practice of a new class of antiplatelet agents called cyclopentyl-triazolopyrimidines, acts directly on platelets, requiring two daily doses, since it has a shorter half-life and its effect is reversible - details that make the administration of the second daily dose essential.^{1-5,12,13,19}

To prove these advantages, two large multicenter clinical trials in patients with ACS were conducted involving the two new drugs, always in direct comparison with clopidogrel: TRITON TIMI 38²⁰ and PLATO.²¹ Both showed a significant advantage of the contemporary drugs in the primary combined endpoint of death, acute myocardial infarction (MI), or stroke in one year of follow-up. Because of their greater potency, they were also associated with a greater likelihood of causing major bleeding, which is why

they require more precise and careful selection at the time of prescription.^{20,21}

IMPACT OF BLEEDING COMPLICATIONS AFTER PERCUTANEOUS CORONARY INTERVENTION

The occurrence of a major bleeding complication in patients treated by PCI is associated with a worse prognosis, and may lead to a significant increase in in-hospital and late mortality.¹⁻⁶

A large meta-analysis involving 42 clinical trials and more than 500 thousand treated cases, reported a more than three-fold increase in mortality and almost a four-fold rise in major cardiac event in those who presented with major bleeding during the index hospitalization for PCI. This demonstrated the undeniable clinical relevance of these events and, consequently, the need to adopt effective measures for their prevention.⁶ Similarly, late bleeding complications may also significantly compromise the prognosis of patients, because they have a deleterious potential proportional to the benefit of avoiding an acute MI in the progress.^{1,6}

The reasons that explain these findings are well defined: the consequences of the hemorrhage itself, such as hypovolemia, hypotension, hypoxemia, the need for blood transfusions and, not rarely, surgical repair of the access route, as well as the fact that they determine that the cardiologist discontinue or, at least, reduce the different antithrombotic drug regimens, predisposing patients to stent thrombosis, a severe complication with high morbidity and mortality, especially if it occurs outside the hospital environment.¹⁻¹¹

Thus, possible strategies that prove capable of protecting the patient from the occurrence of a late major event and that, at the same time, are effective in preventing bleeding would be clinically relevant, justifying large clinical trials exploring these alternatives.⁷⁻¹¹

RATIONALE FOR P2Y12 RECEPTOR INHIBITOR MONOTHERAPY

The main guidelines recommend the associated use of ASA and a P2Y12 inhibitor for variable periods, after which the rule is that the P2Y12 inhibitor is discontinued and ASA is maintained indefinitely. In recent years, in patients with high hemorrhagic risk, an increasingly common population in tertiary care hospitals, the period for use of the dual antiplatelet therapy has been shortened.^{1,4,5,7-11,16}

The possibility of discontinuing ASA instead of the P2Y12 inhibitor has been raised by observations of markedly reduced rates of stent thrombosis with last generation drug-eluting stents, and with this, the hypothesis has been put forward that monotherapy with more potent antiplatelet agents could prevent major cardio-

vascular events in the late clinical course. On the other hand, discontinuing ASA could lead to fewer bleeding complications – especially those occurring in the digestive tract.⁷⁻¹¹ Clinical trials evaluating patients treated in the presence of atrial fibrillation, who, in addition to antiplatelet agents, had to use oral anticoagulants continuously, corroborated this impression.^{7-11,22}

Since the studies that involved the largest sample sizes evaluated ticagrelor, it is interesting to explain the hypothesis suggested for using this drug: pharmacodynamic studies have demonstrated its greater potency in relation to clopidogrel by a wide margin. Thus, ticagrelor monotherapy could be equal to or even superior to the combination of ASA and clopidogrel in preventing major ischemic events in the late phase. On the other hand, when compared to concomitant use with ASA, ticagrelor monotherapy could maintain this protective effect and not predispose to further bleeding complications.^{7,10,11,13}

The results of the clinical trials already conducted involving the different drugs are summarized in the following topic.

CLINICAL STUDIES OF P2Y12 RECEPTOR INHIBITOR MONOTHERAPY

Until August 2021, the main clinical studies were as described below.

GLOBAL LEADERS⁷

A mega-study involving 15,968 patients undergoing PCI in the presence of acute or chronic coronary artery disease (the latter represented about half of the sample), had two clear objectives: to evaluate the impact of ticagrelor monotherapy compared with standard dual therapy, and the possibility of this drug proving to be a valid alternative in situations of stable angina. The selected patients were randomized to two strategies: experimental group, in which the included cases would receive ASA and ticagrelor for 30 days, after which they would maintain monotherapy with ticagrelor for another 23 months; and control group, in which ACS cases would use ASA and ticagrelor for 12 months, followed by another 12 months using only ASA. Chronic cases were treated with ASA and clopidogrel again for 12 months, also followed by ASA monotherapy. The primary endpoint of the combined trial was death or nonfatal Q-wave infarction in the 24-month course. The secondary endpoint involved bleeding complications types 3 and 5 of the Bleeding Academic Research Consortium (BARC) criteria during the same period.

At the end of 2 years, ticagrelor monotherapy was unable to significantly reduce the combined primary endpoint (3.8% versus 4.3%; $p=0.07$), or the bleeding complications (2.0 versus 2.1%; $p=0.77$), demonstrating, in this series with few exclusion criteria, not to be superior to standard treatment.

SMART CHOICE⁸

An Asian study was done involving 2,993 patients, most of whom (58%) were treated in the setting of ACS with implantation of different drug-eluting stents of newer generations. The trial was randomized, open-label, non-inferiority proposition of an antiplatelet regimen consisting of ASA in association with a P2Y12 receptor inhibitor for 3 months, followed by monotherapy with the latter drug for another 9 months, compared to standard treatment with both drugs given for 12 months. The majority of cases in both groups used clopidogrel (77%). At the end of the 1-year period, the combined target of death from any cause, MI or stroke was similar in the groups evaluated (2.9% *versus* 2.5%; $p=0.007$ for non-inferiority). Bleeding complications classified as BARC 2 to 5 were significantly less frequent in the P2Y12 inhibitor monotherapy group (2.0% *versus* 3.4%; $p=0.02$), although major bleedings (BARC 3 to 5) occurred in a similar fashion (0.8% *versus* 1.0%; $p=0.87$).

STOP DAPT 2⁹

A study was conducted in Japan, involving 3,045 cases treated by PCI in acute (about 60% of sample) or chronic coronary artery disease. Compared to the previous study, this clinical trial had two differences: the dual antiplatelet therapy was maintained for 30 days instead of 3 months, and after the mentioned period, patients were randomized to monotherapy with a P2Y12 receptor inhibitor or to maintenance of the standard dual antiplatelet therapy for 12 months. Only one drug-eluting stent was used, an everolimus-releasing chrome-cobalt stent. Another detail that should be mentioned is for approximately 40% of cases in both groups were prescribed an unusual dose of prasugrel – 3.75mg, which is not available for prescription in almost all countries. Finally, this was a trial characterized by target lesions of low angiographic complexity, and using intracoronary ultrasound in more than 90% of interventions. These findings make it difficult to extrapolate the measured results to the real-world PCI scenario.

The primary endpoint consisted of combined cardiovascular events (death, infarction, stroke, or stent thrombosis) and bleeding events (any bleeding by Thrombolysis In Myocardial Infarction – TIMI criteria), and it was significantly lower in those allocated to P2Y12 inhibitor monotherapy (2.4% *versus* 3.7%; $p<0.001$ for superiority), at the expense of fewer bleeding complications (0.4% *versus* 1.5%; $p=0.004$ for superiority). The isolated set of cardiovascular events was not modified with monotherapy (2.0% *versus* 2.5%; $p=0.005$ for non-inferiority and $p=0.34$ for superiority).

An interesting *post hoc* analysis identified 509 study patients as high-risk PCI cases (three vessels treated, three or more stents implanted, three or more lesions addressed, bifurcations with two stents implanted, length of metal-covered segment greater than 60mm, or interventions in

chronic total occlusions), whose evolution was compared to that of the remaining 2,500 cases. The results of the primary and secondary endpoints already described did not differ from the observations of the clinical trial as a whole.²³

TWILIGHT¹⁰

This study was designed with the predetermined objective of seeking options to prevent bleeding complications after PCI, specifically using ticagrelor monotherapy. It included 9,006 patients treated by PCI using ASA and ticagrelor, who had to present at least one clinical or angiographic factor that made them at high-risk for major cardiac or bleeding events in their evolution. Cases of ST-segment elevation ACS, those complicated by cardiogenic shock, and those requiring regular use of oral anticoagulants were excluded. The 7,119 cases that had no cardiovascular events or bleeding in the subsequent 3 months, two-thirds of whom were treated for ACS during the index procedure, were then randomized to two regimens for the following 12 months: ticagrelor monotherapy, or maintenance of the originally prescribed dual antiplatelet therapy. The primary endpoint was the occurrence of bleeding BARC 2, 3, or 5. At the end of the follow-up, the cases randomized to ticagrelor monotherapy showed a significant reduction in bleeding complications (4.0% *versus* 7.1%; $p<0.001$), even when only major bleedings were quantified (1.0% *versus* 2.0%; $p=0.0006$). The combined occurrence of death, MI or stroke was similar in both groups (3.9% in both groups; $p<0.001$ for non-inferiority).

TICO¹¹

This is a Korean clinical trial involving 3,056 patients, similar in design to TWILIGHT.¹⁰ It used only ticagrelor as a P2Y12 inhibitor, but with clinical presentation restricted to cases of ACS. Thus, after 3 months of follow-up, in one group ASA was discontinued, and in the other, the standard dual antiplatelet therapy was maintained until 12 months were completed. The combined primary endpoint of major bleeding by TIMI criteria, death, MI, stroke, stent thrombosis, or target-vessel revascularization was significantly reduced in the ticagrelor monotherapy group (3.9% *versus* 5.9%; $p=0.01$), at the expense of a significant reduction in bleeding complications (1.7% *versus* 3.0%; $p=0.02$). Major cardiac and cerebrovascular events were similarly observed (2.3% *versus* 3.4%; $p=0.09$).

In early 2021, a pre-specified subanalysis of the study, called TICO-STEMI,²⁴ restricted to the 1,103 patients included after ST elevation ACS (36.1% of included cases), was published. The outcome was similar to that observed in the main trial, with a significant reduction in major bleedings (0.9% *versus* 2.9%; $p=0.02$) in the P2Y12 inhibitor

monotherapy group, and no impact on major cardiac and cerebrovascular events (2.7% *versus* 2.5%; $p=0.81$).

HOST-EXAM²⁵

A more contemporary, randomized, prospective, open-label clinical trial conducted at 37 South Korean centers involving 5,438 patients treated by PCI using drug-eluting stents, evaluated whether clopidogrel monotherapy was superior to ASA monotherapy as chronic maintenance therapy after the end of the established period of dual antiplatelet therapy. Thus, the major difference with the previously discriminated clinical trials is that there was no control group treated with the standard dual antiplatelet therapy, because the percutaneous procedures had been performed between 6 and 18 months prior to study inclusion. Those who had experienced major cardiovascular or bleeding events in the period between PCI and the time of study inclusion were excluded. After randomization, patients were followed up for 24 months.

About three-quarters of patients in both groups had ACS at the time of PCI; the predominant dual therapy (81% of cases) at the time of randomization was the combination of ASA and clopidogrel.

A broad combined primary endpoint was established, consisting of death, acute MI, stroke, readmission for new ACS, or bleeding BARC 3 to 5. At the end of the two-year follow-up, more than 98% of participants were able to have the combined endpoint of the trial evaluated, which was significantly lower in the clopidogrel monotherapy group

(5.7% *versus* 7.7%; $p=0.003$). A significant reduction was also seen with P2Y12 receptor inhibitor monotherapy when both thrombotic (3.7% *versus* 5.5%; $p=0.003$) and bleeding events were individualized (2.3% *versus* 3.3%; $p=0.03$), demonstrating its potential superiority as maintenance therapy after the end of the dual antiplatelet therapy period.

META-ANALYSIS OF THE MAIN STUDIES²⁶

It was published in 2020, and included all the major clinical trials discussed previously, with the exception of TICO¹¹ and, as expected, HOST-EXAM.²⁵ A total of 29,089 patients were included, mean age of 66 years, and approximately a quarter were female. Major bleeding complications or bleeding requiring closer medical evaluation occurred less commonly in the P2Y12 monotherapy group (39% reduction; $p=0.03$); however, analyzing major bleedings alone, there was no significant reduction, despite a clear decrease in these events (37% less; $p=0.08$). The 8% decline in major cardiovascular events was also not significant. Similarly, no significant reductions were observed when individualizing the different ischemic components of the combined primary endpoint. Importantly, these observations were independent of ASA use for 1 or 3 months before randomization.

Figure 1 illustrates a summary of bleeding complications reported in the clinical trials that comprised the meta-analysis cases and methods.

* BARC: Bleeding Academic Research Consortium; † TIMI: Thrombolysis in Myocardial Infarction.

Figure 1. Major bleeding complications from clinical trials with early (1 to 3 months) discontinuation of acetylsalicylic acid and monotherapy with P2Y12 receptor inhibitors.

ONGOING CLINICAL STUDIES

We identified two clinical trials that have not yet been finalized, the results of which should be known in the next few years.

NEO-MINDSET²⁷

A prospective, multicenter, randomized Brazilian study in which 3,400 ACS patients treated by PCI will be randomized to two therapeutic regimens. In the experimental group, the enrolled cases would be treated initially with the dual antiplatelet therapy composed of ASA associated with prasugrel or ticagrelor at the usual doses, with ASA discontinued no later than the fourth post-PCI day, followed by monotherapy with one of the P2Y12 inhibitors cited for 12 months. In the control group, they would use the standard dual antiplatelet therapy with ASA in association with prasugrel or ticagrelor, also for 12 months. Inclusions predict cases seen within 24 hours of symptom onset, with PCI covering all target lesions (culprit or not), implantation of last generation drug-eluting stents, and hospitalization for 4 days, at most. The combined primary endpoint will include death, acute MI, stroke, or urgent target-vessel revascularization, with a non-inferiority assumption of the experimental scheme.

IVUS-ACS/ ULTIMATE-DAPT²⁸

It will involve 3,486 cases of ACS patients treated by PCI with drug-eluting stents, with two distinct evaluations planned. First, whether intravascular ultrasound-guided implantation will influence late clinical outcomes, reducing the percentages of target-vessel failure (IVUS-ACS). Second, the impact of monotherapy with ticagrelor after 30 days of use associated with ASA and maintained until 12 months of evolution, when compared to the concomitant use of both for 1 year (ULTIMATE-DAPT). The hypothesis for the ticagrelor monotherapy arm is that it is superior in preventing bleeding complications and not inferior with respect to late ischemic events. Randomization will occur 30 days after the index PCI, and will be restricted to involved patients not experiencing ischemic or hemorrhagic events during this period.

CURRENT CLINICAL IMPLICATIONS

By analyzing the results of the discussed clinical studies, heterogeneous in both design and results, it is observed that monotherapy with P2Y12 inhibitors after PCI is still a subject without a definitive clinical applicability or incontestable indication.⁷⁻¹¹

The first time that this possibility of pharmacologic treatment was suggested, with the caveat that it should not be exclusively after PCI, was in the early days of the introduction of clopidogrel in medical practice, with

the CAPRIE study. It was a large clinical trial, involving 19,185 patients, most of whom had chronic coronary artery disease, which compared clopidogrel or ASA as monotherapy in prevention of acute MI, stroke, or death in the late clinical course. The use of P2Y12 inhibitor achieved a significant reduction in the events mentioned by 8.7%, but with a difference in absolute numbers by 0.51%, i.e., a modest reduction.²⁹ Because of this, as well as the fact that, at the time, the new drug was very expensive, in daily clinical practice, ASA has not been replaced by clopidogrel, except in cases of intolerance.^{1,4,5,16}

Later, with the objective of preventing stent thrombosis and, subsequently, also in the passivation of ACS cases, P2Y12 receptor inhibitors started to be commonly prescribed, but always in association with ASA. Moreover, when the established period for associated use was over, the P2Y12 inhibitor was the medication discontinued in most situations.^{1,3-5,7-11,14,16}

As of the last decade, in addition to efficacy, cardiologists began to value even more safety of the drugs prescribed, with emphasis not only on the duration of the dual antiplatelet therapy, but also on its composition, because the longer the period of associated use, the greater the probability of a severe hemorrhagic event occurring, with the consequences already exposed.^{1,3-5,7-11,14,16}

We can subdivide the discussion into two parts: the earlier discontinuation of ASA, usually between the first and third month after PCI,⁷⁻¹¹ and its replacement by P2Y12 receptor inhibitors at a later stage.²⁵

Regarding the first aspect, the impression is that the option of monotherapy with a P2Y12, regardless of the drug to be prescribed, should be considered in situations in which the main concern of the cardiologist is the prevention of bleeding. In other cases, the current recommendations of the main guidelines should be followed, with maintenance of the dual antiplatelet therapy for 6 to 12 months.^{1,3,4,5,16}

Another issue that was investigated in the GLOBAL LEADERS study⁷ was the possible advantage of prescribing ticagrelor instead of clopidogrel in cases of stable coronary artery disease, which also was not proven; thus, at least until new evidence emerges, this drug should be restricted to cases of ACS.^{1,3-5,16}

With regard to prasugrel, there are still no clinical trials specifically aimed to test it as monotherapy. A significant percentage of cases treated in STOP-DAPT 2 received a dose of prasugrel that is unusual and not available in most countries, because it is restricted to Japan, which is why, for the time being, its prescription should be maintained at the usual doses of 5 or 10mg per day, directed to cases of ACS, always in association with ASA, as recommended by the guidelines as well.^{1,3-5,9,16,30}

Finalizing this first topic or first aspect, and clearly exposing the complexity of the theme, on August 31, 2021, the unpublished results of STOP DAPT 2-ACS were

released.³¹ It is a study with a design similar to that of an almost identical acronym,⁹ but with inclusion restricted to ACS patients (there were 4,169 patients, of whom 1,161 were from the ACS subgroup that was included in STOP DAPT 2).⁹ The clopidogrel monotherapy group maintained a significant advantage with respect to reduction of any bleeding, but with an equally significant increase in acute MI at one-year follow-up. These results demonstrate that extreme caution should be exercised before making drastic changes in current clinical practice.^{1,3-5,9,16,30}

The second approach would be to replace ASA with clopidogrel at a later stage, as investigated by HOST-EXAM.²⁵ This demonstrated a significant advantage of clopidogrel monotherapy in the combined target of ischemic or hemorrhagic events in the progression after discontinuing dual antiplatelet therapy. It was the only trial of those cited that demonstrated an advantage of monotherapy with P2Y12, in both ischemic and hemorrhagic events. Another detail, at the same time relevant and intriguing, is that both reductions occurred with similar percentages (roughly 30%) - something perhaps unexpected or even exaggerated. Despite these results and the pragmatic nature of the study, until now, more robust clinical trials with the same conclusion appear, any radical change in paradigms based on what was observed seems premature, although it does not seem wrong to consider prescribing clopidogrel instead of ASA in cases with a greater propensity to develop late atherothrombotic events, based on these results.²⁵

P2Y12 INHIBITOR MONOTHERAPY IN PATIENTS WITH ATRIAL FIBRILLATION UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

Although it is a scenario different from the one dealt with in this review, since patients on regular use of oral anticoagulants were excluded from the clinical trials addressed,^{7-11,25} it seems necessary to make brief considerations about this theme, since it also involves the issues discussed: antiplatelet monotherapy with P2Y12 inhibitors and bleeding prevention.

Until recently, patients with this arrhythmia, who, in most cases, use oral anticoagulants continuously, when in need of PCI, were treated with ASA, a P2Y12 inhibitor, and the anticoagulant, which compose the so-called triple antithrombotic regimen or triple therapy. This association, generally maintained for 30 days after hospital discharge, was accompanied by a higher incidence of major bleeding complications, whose impact on late clinical progress has already been discussed. For this reason, alternatives to this practice have been sought.^{1,3-5,16,22,32}

The most successful option so far has been shortening the period of use of ASA, discontinued at hospital discharge or, eventually, after a short period, maintaining the patient on the anticoagulant and monotherapy with a P2Y12

inhibitor, with the preferred option falling on clopidogrel, for its lower potential to trigger bleeding complications.^{4,5,22} A recent meta-analysis involving the main clinical trials on the subject demonstrated feasibility and greater safety of this alternative, significantly associated with lower rates of major bleeding, without interfering in late ischemic events that could be accentuated by very early withdrawal of ASA. In the subgroup of the meta-analysis assessed as the best option, which included a discharge prescription of a P2Y12 inhibitor associated with a direct anticoagulant, there was a 48% reduction in major bleedings by TIMI criteria, and 66% reduction in intracranial bleedings. These figures undoubtedly impress and draw attention of physicians.³²

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CONTRIBUTION OF AUTHORS

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

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