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Percutaneous coronary intervention in the patient at high risk of bleeding

Intervenção coronária percutânea no paciente com alto risco de hemorragia

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ABSTRACT - Currently, percutaneous coronary interventions account for more than 80% of myocardial revascularization procedures. This result was enabled by two major advances: the development of effective and safe drug-eluting stents, in addition to a potent and effective antithrombotic pharmacotherapy in the prevention of atherothrombotic events, which, in general, should be maintained for about 6 to 12 months after the index intervention. However, a significant number of cases (up to 20% of treated patients according to literature) are at risk for developing significant bleeding, which can have a serious impact on prognosis. Therefore, this population requires a series of care measures related to indication, performance of the procedure, and late follow-up. The process begins with the identification of the most predisposed cases, which, in most situations, is simple, and there are risk scores that help the cardiologist. Next, the indication of the procedure should be done appropriately. Care begins with the preferential prescription of clopidogrel instead of other P2Y12 inhibitors; at the time of the procedure, whenever feasible, the option for the radial access is advantageous, especially in acute coronary syndromes. The use of a drug-eluting stent is also recommended in these cases, since contemporary stents are safe enough to safely shorten the duration of use of the dual antiplatelet regimen. Finally, more recently, monotherapy with P2Y12 receptor inhibitors has been discussed, in which early withdrawal of acetylsalicylic acid would not compromise safety and, at the same time, it would be able to prevent major bleeding events.

Keywords: Drug-eluting stents; Bleeding; Prasugrel hydrochloride; Ticagrelor; Clopidogrel; Percutaneous coronary intervention

RESUMO - Na atualidade, as intervenções coronárias percutâneas são responsáveis por mais de 80% dos procedimentos de revascularização miocárdica. Esse resultado é possível por dois grandes avanços: o desenvolvimento de stents farmacológicos eficazes e seguros, somado a uma farmacoterapia antitrombótica potente e efetiva na prevenção de eventos aterotrombóticos, a qual, em geral, deve ser mantida por cerca de 6 a 12 meses após a intervenção índice. No entanto, expressivo contingente de casos, que a literatura situa em até 20% dos pacientes tratados, apresenta risco para desenvolver hemorragias significantes, que podem ter grave impacto no prognóstico. Assim, essa população requer uma série de cuidados relacionados com a indicação, a realização e o acompanhamento tardio. O processo se inicia pela identificação dos casos mais predispostos, que, na maior parte das situações, é simples, havendo inclusive escores de risco que auxiliam o cardiologista. Na sequência, a indicação do procedimento deve ser feita com propriedade. Os cuidados são iniciados pela prescrição preferencial do clopidogrel ao invés dos demais inibidores da P2Y12; no momento do procedimento, sempre que viável, a opção pela via radial é vantajosa, em especial em síndromes coronárias agudas. O uso de um modelo de stent com liberação de medicamentos também é recomendado nesses casos, pois os stents contemporâneos são seguros a ponto de permitirem a abreviação com segurança do tempo de uso do esquema antiplaquetário duplo. Por fim, mais recentemente, tem sido discutida a monoterapia com inibidores do receptor P2Y12, na qual a suspensão precoce do ácido acetilsalicílico não comprometeria a segurança e, ao mesmo tempo, seria capaz de prevenir eventos hemorrágicos de vulto.

Descritores: Stents farmacológicos; Hemorragia; Cloridrato de prasugrel; Ticagrelor; Clopidogrel; Intervenção coronária percutânea

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INTRODUCTION

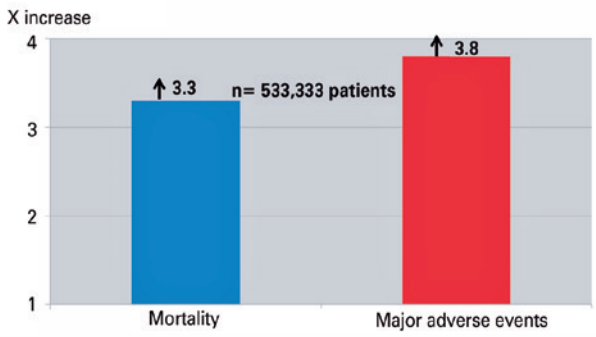
The indications for percutaneous coronary interventions (PCI) have sharply increased since their introduction, and as now is the most used method.[1,2] Currently, patients with any clinical presentation of coronary artery disease (CAD) are routinely treated using this procedure, with high success rates, and the same applies to patients with lesions with the most varied degrees of angiographic complexity.[1,2]

This remarkable expansion of the scope of the method was enabled by the introduction and development of coronary stents, especially from the broader use of drug-eluting stents (DES), which account for expressive reductions in the rates of restenosis and additional revascularizations that occurred in the late phase, also making it possible to obtain complete revascularization more frequently. At the same time, there were also important changes in the adjunctive drug therapy, which also contributed to further reduction in the most relevant ischemic clinical events during the late clinical course.[1,2]

However, the implantation of any model of coronary stent is accompanied by the need to use the so-called dual antiplatelet treatment (DAPT), composed of acetylsalicylic acid (ASA) and a P2Y12 receptor inhibitor, for longer periods of time, usually for 6 (elective cases) to 12 months (acute coronary syndromes; ACS), or even longer, which, on the one hand reduces the occurrence of later major cardiac events and stent thrombosis, and on the other hand predisposes to more bleeding complications.[1,2]

The occurrence of a major bleeding complication markedly affects the late prognosis of the patient treated with PCI. As we can see in Figure 1, the deleterious impact of this type of complication is very serious. The main causes of problems caused by bleeding, including higher mortality, are the consequences of the bleeding itself and its treatment, which may require invasive interventions, including surgery,[3] and partial or complete interruption of prescribed antithrombotic drugs, predisposing to stent thrombosis, which is a serious complication, with high morbidity and mortality and which, in the absolute majority of cases, occurs outside the hospital environment.[3]

As the number of patients at high risk of developing bleeding when undergoing PCI is increasing, we prepared this review, identifying more precisely the cases and discussing the current guidelines to minimize the highest risks.[1,2,4,5]



Source: adapted from Kwok CS, Rao SV, Myint PK, Keavney B, Nolan J, Ludman PF, et al. Major bleeding after percutaneous coronary intervention and risk of subsequent mortality: a systematic review and meta-analysis. Open Heart. 2014;1(1):e000021. https://doi.org/10.1136/openhrt-2013-000021.[3]

Figure 1. Adverse impact on late clinical outcomes after major bleeding complication in patients undergoing percutaneous coronary intervention.

IDENTIFICATION OF CASES MOST PRONE TO BLEEDING

These are situations commonly seen in clinical practice, with reports citing numbers around 20% of treated cases.[4-6] In routine practice, these would include patients aged >75 years, those who need chronic use of oral anticoagulants or anti-inflammatory drugs, those with invasive procedures planned within the first year after PCI, those with a history of bleeding or stroke, those with anemia or renal failure, those with severe liver disease, those with cancer and other less frequent conditions, such as thrombocytopenia (platelet count <100,0000/mm^3) and, in some countries, such as Brazil, those with conditions like dengue fever.[1,4,5] In addition to being common, many of these conditions coexist, increasing even more the risk.

Although not always necessary, because the mentioned situations, when present, render other assessments superfluous, there are scores[4,5] specifically developed to identify this type of patients, which are undoubtedly useful when the diagnosis is not clear. Let's focus on two, perhaps the most relevant scores at the moment.

PRECISE-DAPT score[4]

A tool developed from clinical trials involving 14,963 patients treated with PCI for varied clinical presentations of CAD, rendering it attractive and, perhaps, more specific for this population. In addition, as it is easily accessed through internet tools, it is extremely practical.

There are five pieces of information that allows its calculation, all of which are easily accessible: hemoglobin level, age in years, leukocyte count, estimated plasma creatinine clearance rate, and presence or absence of a history of bleeding. When these data are entered into the tool, the physician is immediately informed of the value of the score, which, when it is equal to or greater than 25, denotes a patient at a higher risk of developing bleeding, which automatically means that the clinician can take the necessary measures to minimize the risk or, eventually, opt for other forms of treatment.

An interesting subanalysis of the SMART-DATE clinical study,[6] which compared 6 *versus* 12 months of DAPT in patients treated for ACS, performed by Choi et al., showed the practical value of applying the score in this sub-

group of patients, by demonstrating in those with a high PRECISE-DAPT score (≥25) that the shorter DAPT time reduced major bleeding, without significantly interfering with the occurrence of ischemic events.

In short, it is a simple, effective and easily accessible option, whose use, when necessary, may prove to be relevant. It should be noted, however, that it lacks unquestionable evidence regarding its effectiveness, as there are no prospective clinical trials that support its routine use.

ARC-HBR score[5]

It was developed by an international group of specialists, called Academic Research Consortium, which had already given their collaboration in the field of Interventional Cardiology by creating a classification of stent thrombosis.

Similar to Jones' criteria for the diagnosis of rheumatic fever, those responsible for developing the new score subdivided the characteristics found into major and minor; the finding of one major variable or two minor variables at the time of PCI classified the patient as having high risk of bleeding. By definition, a patient is considered high risk if the bleeding risk by Bleeding Academic Research Consortium (BARC) grade 3 or 5 is estimated to occur at a rate of >4% at 1 year, or the risk of intracranial bleeding is >1% at 1 year.

The major criteria listed are long-term use of oral anticoagulants; severe chronic renal failure, with creatinine clearance rate <30 mL/minute; hemoglobin level <11 g/dL; spontaneous bleeding in the last 6 months that required intervention or that occurred at any time, if recurrent; moderate or severe thrombocytopenia (<100x10^9/L); chronic bleeding diathesis; liver cirrhosis with portal hypertension; malignant neoplasm in the last year, except non-melanoma skin cancer; previous hemorrhagic stroke at any time of the clinical course or ischemic stroke, of moderate or severe degree, in the last 6 months; unavoidable major surgeries that would be performed using DAPT; history of major surgery or major trauma in the 30 days prior to PCI.

The minor criteria include age ≥75 years; moderate chronic renal dysfunction (creatinine clearance between 30 and 59mL/minute); hemoglobin level between 11 and 12.9g/dL for men, or between 11 and 11.9g/dL for women; spontaneous bleeding requiring hospitalization or transfusion in the last 12 months, not classified within the major criteria; need for chronic use of hormonal or non-hormonal anti-inflammatory drugs; any ischemic stroke in the clinical course of the patient not classified within the major criteria.

As mentioned in relation to the PRECISE-DAPT score, there is also a lack of specific clinical trials using this tool to definitively corroborate its effectiveness.

PRE-PERCUTANEOUS CORONARY INTERVENTION CARE

In the pre-PCI clinical evaluation, when a patient is identified as fitting the described profile, the cardiologist must pay attention to a series of pertinent details, which are discussed below.

Appropriateness of indication[1,2]

Due to the higher risk of bleeding in the clinical course, the indication for the intervention must be correctly justified. Therefore, details such as severity and refractoriness of anginal symptoms to drug treatment, as well as limitations imposed on the patient's usual routine of life, high ischemic burden in functional tests, denoting a marked amount of myocardial area at risk, should guide the decision-making process.[1,2]

Consultation with experts from other areas[1,2]

When patients have non-cardiac conditions that predispose them to bleeding, contacting other specialists is essential to determine, by common agreement, safer procedures. The procedure should only be scheduled when all possible doubts have been clarified and the inconveniences remedied, except in emergency situations. A clear example are patients who report having scheduled non-cardiac surgeries, which may or may not be urgent, for this influences the decision-making of when and how to perform the PCI.

Choice of P2Y12 receptor inhibitor[1,2,4,5,7]

Three drugs of this class are available for clinical use: clopidogrel, prasugrel and ticagrelor. The latter two drugs are more potent than the former and, as a consequence, they can reduce major cardiac events in patients treated for ACS. However, precisely because of their greater antiplatelet potency, they may cause more major bleeding complications. For this reason, in patients more prone to bleeding, the preferred option should be clopidogrel. It should be reinforced the concept that, at least in the hospital phase and in the first months of the late clinical course, the association with ASA is, in general, mandatory.

The preferred option for clopidogrel in these patients, suggested by the guidelines,[1,2] was supported by the results of a Dutch clinical study involving 12 centers, called POPular AGE,[8] in which patients over 70 years of age who developed non-ST segment elevation ACS were included in an open, prospective and randomized trial, being subdivided into a group that used clopidogrel compared to another in which prasugrel or ticagrelor was used, at the usual loading and maintenance doses. The primary endpoint was the observation of any bleeding by the PLATO criterion; the co-primary endpoint involved bleeding complications associated with death, acute myocardial infarction (MI) or stroke. This was a non-inferiority trial, with an intention-to-treat analysis.

At the end of 12 months of follow-up, bleeding was observed in 18% of patients in the clopidogrel group, and in 24% of patients receiving the most contemporary drugs (p=0.002 for superiority). The co-primary endpoint occurred in 28% of patients who received clopidogrel; the same was observed in 32% of those included in the other group (p=0.03 for non-inferiority).

According to the authors, clopidogrel proved to be a safer and equally effective alternative in this relevant subgroup of patients, still underrepresented in large randomized clinical trials on ACS plaque passivation, and may be considered a valid alternative in situations that include a higher risk for bleeding.

Choice of oral anticoagulant[9]

When there is an absolute need to use this type of drug, as in patients with atrial fibrillation, it is possible to prescribe warfarin or one of the so-called direct-acting oral anticoagulants (DOAC), which have a fixed-dosing regimen, do not require periodic control with laboratory tests; do not have relevant drug interactions and a shorter residual effect when discontinued. For these reasons, they lead to a significant reduction in mortality and more severe bleeding, such as intracranial bleeding, when compared to warfarin. Therefore, when their use is clinically and economically viable, they are the first-choice medications in these circumstances.[9]

Once these steps are over and the PCI indication is confirmed, it is up to the clinical cardiologist to contact the interventional cardiologist, expose the patient's higher risk of developing bleeding complications and, together, plan the intervention.

CARE DURING PERCUTANEOUS CORONARY INTERVENTION

There are also details on the timing of the PCI that should be carefully considered when the intervention involves this subgroup of patients.

Use of heparins[1,2]

This is always required at the time of PCI. If the patient presents with ACS and is using this medication, crossover between low molecular weight and unfractionated heparin or vice versa should be avoided as much as possible, because this is accompanied by an increase in bleeding complications.[1,8] Although not available in Brazil, the use of bivalirudin seems to be superior to unfractionated heparin, the substance most used during PCI, in the prevention of bleeding complications during primary intervention in acute MI.[1,2]

Access route[1,2,10]

When feasible, the radial access should be the preferred choice, since it is associated with less bleeding, especially in ACS settings, in which multiple antithrombotic drugs are used in its passivation.

The results of the RIVAL clinical trial,[10] involving 7,021 patients treated for non-ST-segment or ST-segment elevation ACS, who were randomized to be treated by radial or femoral approach, clearly demonstrated this. At 30 days of clinical follow-up, bleeding unrelated to coronary artery bypass graft (CABG) surgery were significantly less observed in those approached by radial route, both in the scenario with ST-segment elevation (51% reduction; p=0.009) and in those without this electrocardiographic change (59% reduction; p<0.001).

A meta-analysis recently published by Chiarito et al.[11] encompassing the main randomized studies, which evaluated 30,096 patients recruited in 31 clinical trials, confirmed these impressions, demonstrating a significant reduction by 47% in major bleeding with the use of the radial access, a similar trend occurring with vascular complications and mortality.

IIb/IIIa glycoprotein inhibitors[1,2]

They are potent intravenously administered antiplatelet drugs, which, due to their greater potency, predispose treated patients to higher rates of bleeding complications. Their prescription, currently, has fallen exponentially in all settings; in the situation being discussed, it should only be considered in an unplanned manner.

Choice of stent model[1,2,12,13]

Today, practically all PCIs are performed with implantation of intracoronary prostheses. Exclusive balloon interventions practically have no more space, with very rare exceptions of specific indications.

Due to its greater effectiveness in preventing recurrences, DES are always the first choice option, but the need for prolonged use of DAPT was considered a restriction for its use in patients most prone to bleeding. Therefore, until recently, patients that could not wait this longer period to stop DAPT, or when the cardiologist judged that the prolonged use of two antiplatelet agents was too risky, invariably received a bare metal stent (BMS), which is safe, because it allows clopidogrel to be discontinued after 30 days, but is less effective.[1,2,12,13]

In the mid-2010s, the results of the prospective randomized LEADERS FREE study were published,[12] in which a new model of non-polymeric DES, developed to provide faster and more effective reendothelization, allowing the interruption of DAPT at 30 days, was evaluated in a population of 2,466 patients at high risk for bleeding, and compared with a BMS. All patients, regardless of the model used, discontinued DAPT at the end of the first month.

At 1-year-follow-up, those treated with DES had a significant 29% reduction in the combined primary endpoint of death, acute MI, or ischemia-guided target vessel revascularization. Additional revascularizations were reduced by almost 50% with this biolimus A9-eluting stent (5.1% *versus* 9.8%; p<0.001). Stent thromboses also did not differ. An interesting subanalysis involving only the 659 cases treated for ACS demonstrated a similar effect, which is a clinically relevant outcome, for the reasons explained in the preceding items.

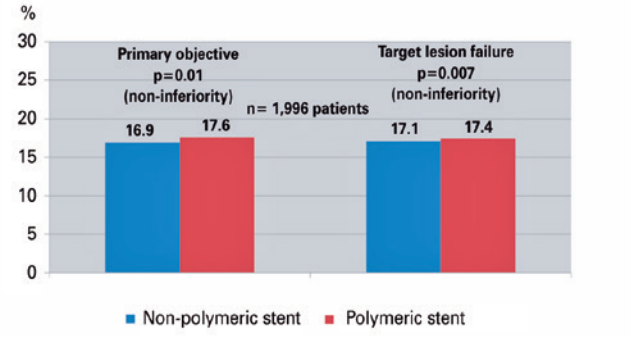
This result was undoubtedly clinically relevant, but there were fears that the indication would be restricted to only a specific model of DES. Subsequently, the results of a new clinical trial, ONYX ONE,[13] demystified this impression. In this new prospective randomized study, a population of 1,996 patients at high risk of bleeding, selected by the same criteria as the LEADERS FREE trial,[12] were randomized to receive the same type of non-polymeric DES used in that study, or a polymeric zotarolimus-eluting model. All cases received DAPT only for 30 days. At 1 year of clinical course, the combined primary endpoint of death from any cause, acute MI or stent thrombosis was similar in both groups (Figure 2).

The results of the ONYX ONE study[13] demonstrated that, in the population more prone to bleeding complications, in which the use of DAPT was restricted to a shorter period of time (1 month), different models of DES, polymeric or not, could be used, with no impact on the safety and effectiveness of PCI.

CARE AFTER HOSPITAL DISCHARGE

At hospital discharge, the cardiologist should advise the patient about care measures, such as adherence to treatment and lifestyle changes, with the aim to reduce the occurrence of later major events and prevent the progression of atherosclerosis, as well as to establish the duration and composition of the antithrombotic regimen to be used.[1,2]

In this latter aspect, details related to two different settings should be discussed: patients who use oral anticoagulants chronically and the moment of discontinuing DAPT specifically in patients more prone to bleeding.



Source: adapted from Windecker S, Latib A, Kedhi E, Kirtane AJ, Kandzari DE, Mehran R, et al.; ONYX ONE Investigators. Polymer-based or polymer-free stents in patients at high bleeding risk. N Engl J Med. 2020;382(13):1208-18. https://doi.org/10.1056/NEJMoa1910021.[13]

Figure 2. ONYX ONE clinical trial primary and secondary outcomes

Chronic prescription of oral anticoagulants[1,2,9,14]

Until the middle of the last decade, these patients were discharged from hospital using three antithrombotic drugs, more specifically DAPT associated with an oral anticoagulant. Despite being effective in preventing major cardiac events and systemic-pulmonary thromboembolisms, the so-called triple regimen had always been associated with higher rates of major bleeding complications in the clinical course.

As a result, alternatives capable of minimizing bleeding complications were sought without affecting the patient safety, *i.e.*, without predisposing them to higher rates of stent thrombosis or other late atherothrombotic events. The most successful option to date (June 2022) is the short-term use of ASA, which is discontinued at the time of hospital discharge or up to 15 days after PCI, maintaining an anticoagulant associated with a P2Y12 inhibitor, preferably clopidogrel, due to its lower potential to trigger major bleeding complications.[1,2,9,14] A recent meta-analysis[9] involving the main clinical trials on the subject demonstrated the feasibility and greater safety of this alternative, significantly associated with lower percentages of severe bleeding, without significantly interfering with later major ischemic events, which could possibly have been more frequent due to the early discontinuation of ASA. In the meta-analysis subgroup considered the best option, which involved the prescription of a P2Y12 inhibitor, usually clopidogrel, associated with a DOAC, at hospital discharge, there was a 48% reduction in major bleeding by Thrombolysis in Myocardial Infarction (TIMI) criterion, and a 66% reduction in intracranial bleedings.

An interesting clinical trial that has been recently published, the AUGUSTUS study,[14] granted access to a series of specific information on the most common subgroup of individuals who chronically use oral anticoagulants: patients with atrial fibrillation. In the study, patients with this arrhythmia treated for ACS or requiring PCI were randomized in a two-by-two factorial way using a DOAC (apixaban) or warfarin, and a comparison of ASA *versus* placebo was also evaluated at 6 months of clinical course. The primary endpoint of the study was the occurrence of major or clinically significant bleeding.

A total of 4,614 cases were recruited, in 33 countries. When compared with warfarin, apixaban provided a significant 31% reduction in bleeding complications (10.5% *versus* 14.7%, $p<0.001$ for both non-inferiority and superiority), also demonstrating a significant 17% reduction in death or need for new hospitalization. On the other hand, the prescription of ASA was associated with a significant increase by 89% in bleeding (16.1% *versus* 9.0%; $p<0.001$), with no benefit regarding the occurrence of other clinical events. Therefore, the prescription of a DOAC instead of warfarin, without the concomitant use of ASA, was associated with lower rates of bleeding and ischemic events, confirming the safety of not prescribing the latter drug in this subgroup of patients.

When the associated prescribing period of an anticoagulant and a P2Y12 inhibitor has expired, guidelines[1,2] suggest that the patient be maintained on only the first medication.

Moment of discontinuation of dual antiplatelet treatment[1,2]

In patients prone to bleeding and who are not using oral anticoagulants, the guidelines recommend shorter periods of use of DAPT. The recommendation is, in general, 3 months in cases of stable CAD, and 6 months in patients with ACS, *i.e.*, the time of use is reduced to half of what was routinely indicated.

However, evidence-based medicine always provides new information to physicians from clinical trials that may suggest different approaches. Recently, a large prospective randomized clinical trial demonstrated the possibility of an even greater reduction in these periods.[15]

The acronym of the study is MASTER DAPT.[15] It is a prospective, multicenter (140 recruiting centers, distributed by 30 countries) and randomized clinical trial, in which all 4,434 patients recruited were prone to bleeding complications, all of whom were treated with PCI using a state-of-the-art sirolimus-eluting stent. After 30 days of clinical course with no death, MI, stroke, major adverse cardiovascular events (MACE) or active bleeding, randomization was performed, and in one group, DAPT was discontinued at this time (short-term group, DAPT administered for only 1 month) and, in the other, DAPT was maintained for at least 2 more months (standard group). The study objectives, evaluated at the end of the first year of clinical course, were: net adverse clinical events (NACE); MACE; major or clinically relevant bleeding. The first two objectives were evaluated with the hypothesis of non-inferiority, and the last one, under the prism of superiority.

Patients with any form of DAC presentation could be included, requiring successful PCI. The main criteria to characterize a patient as high risk for bleeding were chronic use of oral anticoagulants (most cases with atrial fibrillation), presence of documented anemia, proven history of significant bleeding in the last year, and a PRECISE-DAPT score greater than or equal to 25. About half of the cases were randomized as ACS.

After a mean period of late clinical course of 335 days, the occurrence of NACE was similar between the groups (short-term group 7.5% *versus* standard group 7.7%; p=0.001 for non-inferiority), the same occurring with MACE (short-term group 6.1% *versus* standard group 5.9%; p=0.001 for non-inferiority). It is important to note that these results were independent of the presence or absence of a history of previous infarction, a characteristic that, in general, increases the severity profile of patients, according to the authors. Major bleeding was significantly more common in the standard group (9.4% *versus* 6.5%; p<0.001 for superiority of the short-term regimen).

Therefore, in this population highly prone to bleeding complications and treated by implanting a state-of-the-art DES with low thrombogenicity, the short-term DAPT administration for only 30 days was non-inferior to the longer standard prescription. In addition, it had lower rates of hemorrhagic complications with clinical repercussions, which renders this strategy attractive and clinically viable for the aforementioned population.

Besides the timing of discontinuation of DAPT, comments on how to do it are also necessary. The main guidelines[1,2] are not clear or precise so far on whether the medication to be discontinued should be ASA or the P2Y12 inhibitor. As a result, a series of clinical studies on what is conventionally called "monotherapy with P2Y12 receptor inhibitors"[16] was carried out, whose protocols and results are shown below.

MONOTHERAPY WITH P2Y12 INHIBITORS

A therapeutic alternative whose title is self-explanatory and which has a series of clinical trials that discuss its clinical applicability.

GLOBAL LEADERS[17]

It involved 15,968 patients undergoing PCI for acute or chronic CAD (chronic CAD represented about half of the sample), with two objectives: to evaluate the impact of ticagrelor monotherapy compared to standard dual therapy, and the possibility of this drug be a valid alternative in a stable angina scenario. The selected patients were randomized to two therapeutic alternatives: experimental group, in which the included cases received ASA and ticagrelor for 30 days, after which only ticagrelor was maintained for another 23 months; control group, in which ACS cases used ASA and ticagrelor for 12 months, followed by another 12 months using only ASA; the chronic cases were medicated with ASA and clopidogrel, also for 12 months, and also by monotherapy with ASA afterwards. The combined primary endpoint of the trial was the occurrence of death or nonfatal ST-segment elevation infarction during the 24-month follow-up; the secondary endpoint involved BARC criteria types 3 and 5 bleeding complications, in the same period.

At the end of 2 years, ticagrelor monotherapy was not able to significantly reduce the combined primary endpoint (3.8% *versus* 4.3%, p=0.07) or bleeding complications (2.0 *versus* 2.1 %; p=0.77), demonstrating non-superiority to the standard treatment.

SMART CHOICE[18]

A trial that recruited 2,993 patients, most of whom (58%) were treated for ACS, with implantation of different DES of more recent generations. It was a randomized,

open-label, non-inferiority proposition of an antiplatelet regimen composed of ASA in combination with a P2Y12 receptor inhibitor for 3 months, followed by monotherapy with the latter drug for an additional 9 months, compared with standard treatment with both drugs administered for 12 months. Most cases used clopidogrel (77%). At the end of the 1-year period, the combined objective of death from any cause, MI or stroke was similar in the evaluated groups (2.9% *versus* 2.5%; p=0.007 for non-inferiority). BARC types 2 to 5 bleeding complications were significantly less frequent in the P2Y12 receptor inhibitor monotherapy group (2.0% *versus* 3.4%, p=0.02), although the major bleedings themselves (BARC types 3 to 5) have manifested themselves in a similar way (0.8% *versus* 1.0%; p=0.87). These results also did not clearly favor the proposed new strategy.

STOPDAPT-2[19]

An Asian study involving 3,045 patients treated with PCI for ACS (about 60% of sample) or chronic CAD. Compared to the previous study, this clinical trial had two clear differences: the DAPT was maintained for 30 days instead of 3 months after the mentioned period, patients were randomized to monotherapy with a P2Y12 receptor inhibitor or the standard prescription of DAPT for 12 months; only one DES model was used, a cobalt-chrome everolimus eluting stent. This was a clinical trial characterized by target lesions of low angiographic complexity and using intracoronary ultrasound in more than 90% of interventions, which renders it difficult extrapolating the results measured to the real-world scenario of PCI.

The primary endpoint consisted of a combination of cardiovascular (death, infarction, stroke, or stent thrombosis) and hemorrhagic (any TIMI bleedings) events, which was significantly lower in those assigned 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). If accepted as reliable, these results could favor the adoption of P2Y12 monotherapy in the subgroup most prone to bleeding.

However, in the second half of 2021, the results of another clinical study prepared by the same group, called STOPDAPT-2 ACS,[20] with a design similar to that described in the two previous paragraphs, but with inclusion restricted to patients with ACS (4,169 patients, of which 1,161 were from the ACS subgroup included in the STOPDAPT-2 study).[19] The clopidogrel monotherapy group maintained a significant advantage in terms of reducing any bleeding, but at the expense of a significant increase in MI in the 1-year follow-up – undoubtedly a relevant and disturbing piece of information.[1,3-5,9,20]

TWILIGHT[21]

It was designed with the predetermined goal of looking for options to prevent bleeding complications after PCI, more specifically using ticagrelor monotherapy. It included 9,006 patients treated with PCI using ASA and ticagrelor, who had at least one clinical or angiographic factor that characterized them as high risk for major or hemorrhagic cardiac events in the clinical course. The ST-segment elevation ACS cases, those complicated by cardiogenic shock, and those requiring regular use of oral anticoagulants were excluded. The 7,119 cases that did not experience any cardiovascular events or bleeding in the subsequent 3 months, two-thirds of which were treated for ACS during the index procedure, were randomized into two regimens for the next 12 months: ticagrelor monotherapy and maintenance of the original prescription of DAPT. The primary object was the occurrence of type 2, 3 or 5 bleeding by BARC criteria. At the end of the late clinical course, 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). As in the previous clinical trial, the results were favorable to the monotherapy strategy in those classified as more prone to bleeding.

TICO[22]

A Korean clinical trial involving 3,056 patients, similar in design to TWILIGHT,[21] *i.e.*, using only ticagrelor as P2Y12 inhibitor, but with clinical presentation restricted to ACS. Thus, after 3 months post-PCI, in one group the use of ASA was discontinued and, in the other, the standard DAPT was maintained until completing 12 months. The combined primary endpoint of TIMI major bleeding, 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 was published, called TICO-STEMI,[23] restricted to the 1,103 patients enrolled after an ST-elevation ACS (36.1% of included cases). The result was similar to that observed in the complete series, with a significant reduction in major bleeding (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-EXAM[24]

A more recent, randomized, prospective, open-label clinical trial conducted in 37 South Korean centers, involving

5,438 patients treated by PCI using DES. It assessed whether clopidogrel monotherapy was superior to ASA monotherapy as a chronic maintenance therapy after the end of the established period of DAPT use. Therefore, the major difference with the previously mentioned clinical trials is that there was no control group treated with the standard DAPT, since the percutaneous procedures had been performed between 6 and 18 months before inclusion in the study. Those who had major cardiovascular or hemorrhagic events in the period between PCI and the time of inclusion in the study 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 DAPT in 81% of cases at the time of randomization was an association of ASA and clopidogrel.

A broad combined primary endpoint was established, consisting of death, MI, stroke, readmission due to a new ACS or BARC type 3 to 5 bleeding. At the end of the 2-year follow-up, more than 98% of participants were assessed regarding the combined endpoint, which occurred significantly less in the clopidogrel monotherapy group (5.7% *versus* 7.7%; p=0.003). A significant reduction was also observed with monotherapy with P2Y12 receptor inhibitor when both thrombotic (3.7% *versus* 5.5%; p=0.003) and hemorrhagic events (2.3% *versus* 3.3%; p=0.03) were individualized, demonstrating its potential superiority over ASA as maintenance therapy after the end of the dual antiplatelet therapy period.

Meta-analysis of the main studies[25]

Published in 2020, it covered most of the main clinical trials discussed in the previous item, with the exception of TICO,[22] HOST-EXAM,[24] and STOPDAPT-2 ACS.[20] A total of 29,089 patients were included, with a mean age of 66 years, and a quarter of them were women. Major bleeding complications or patients requiring closer medical evaluation occurred less commonly in the P2Y12 monotherapy group (39% reduction; p=0.03). However, analyzing exclusively major bleeding, no significant reduction was observed, despite a clear reduction in these events (37% less; p=0.08). There was also no significant drop in major cardiovascular events (8% less), either as a whole or in terms of the different events considered individually.

DE-ESCALATION

It is the exchange, after a certain period of clinical course (generally 1 month after the index procedure), of a more potent P2Y12 inhibitor (prasugrel/ticagrelor) with a less potent one (clopidogrel), aiming to prevent bleeding events without impairing effectiveness, *i.e.*, the prevention of MACE. It is based on the assumption that most ischemic events occur in this earlier phase of clinical course post-PCI. It would be especially indicated in cases of ACS, which are the ones that benefit from the prescription of the most potent antiplatelet drugs.[26]

There are two possibilities to perform de-escalation: guided by objective measurement of platelet aggregation and/or by genetic tests; without the aid of these tests. Although in theory the first alternative is more effective, a recent meta-analysis has suggested that both may be effective.[27]

Despite the existence of studies specifically addressing this therapeutic alternative, it still does not have clear support for routine use, as the results of these clinical trials were not able to change clinical practice.[26] For example, the latest American guideline on myocardial revascularization does not include this alternative in the list of possibilities that may be considered to prevent bleeding complications, *i.e.*, it is an alternative without a clearly defined role.[2]

SUMMARY OF LISTED INFORMATION

Although there are still gaps to be filled, a careful evaluation of the listed information indicates the following:

- This is a subgroup of patients that are frequently present in the series of PCI and have higher clinical risk.[2,26]
- There is no great difficulty for the cardiologist in identifying these cases, and there are scores that can be used when in doubt.[2,26]
- Due to the inherent risks of the use of DAPT, indispensable in patients treated with PCI, the clinical indication for the intervention must be precise.[2,26]
- Among the possibilities of prescribing a P2Y12 inhibitor, the preferred option should be clopidogrel; if the cardiologist's choice is to prescribe one of the other P2Y12 inhibitors, the preferred one should be ticagrelor, as experience with prasugrel in these situations to date is limited. When there is a need for regular use of an oral anticoagulant after hospital discharge, DOACs are also preferred.[2,16,26]
- Whenever feasible, the radial access should be used, especially in patients with ACS.[2,26]
- When available, implantation of a DES is the first-choice option.[2,26]
- At the time of hospital discharge, in patients requiring chronic use of an anticoagulant, the current trend is for the early discontinuation of ASA, maintaining the anticoagulant and a P2Y12 receptor inhibitor.[2,26]
- The duration of DAPT use should be reduced individually, especially distinguishing ACS cases and chronic ones; monotherapy with a P2Y12 receptor inhibitor is an option to be considered, but with caution in patients treated for ACS, especially if the only P2Y12 inhibitor available for prescription is clopidogrel.[2,26]

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Luiz Fernando Leite Tanajura prepared medical texts for the companies Daiichi Sankyo Co. and Terumo in the past 2 years. Other authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

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

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