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Prasugrel versus ticagrelor in acute coronary syndromes

Prasugrel versus ticagrelor nas síndromes coronárias agudas

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ABSTRACT – Acute coronary syndromes are common situations in medical practice, with high morbidity and mortality. Consequent to its relevance, its clinical management has always been subject of discussion and controversy. Since the past decade, the dual antiplatelet regimen has been the main therapeutic option used in its passivation, whereas percutaneous interventions have become the most common therapeutic option. Clopidogrel, the drug initially used in combination with aspirin, is effective and safe; however, it has disadvantages that led to the development of a new generation of more efficient antiplatelet drugs, such as prasugrel and ticagrelor. In large comparative clinical trials, these two drugs proved superior to clopidogrel in reducing major combined cardiac events. Hence the main guidelines currently support the two new agents, which are considered first-line drugs. Due to the clear differences between the protocols of clinical trials corroborating their inclusion in clinical practice, it is not possible to make direct comparison without the risk of generating hasty impressions. More recently, a large prospective, randomized clinical trial provided an appropriate head-to-head comparison between prasugrel and ticagrelor in cases of acute coronary disease, in a population submitted to invasive treatment. The study demonstrated a significant advantage of prasugrel. In this review, we discuss the primary details of these more contemporary drugs and the most relevant clinical trials related to them, identifying the advantages and disadvantages of each agent. At the end, we state our view on their current prescription.

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

RESUMO – As síndromes coronárias agudas são situações comuns na prática médica, apresentando elevada morbimortalidade. Por sua relevância, seu manejo clínico sempre foi alvo de discussão e controvérsia. Desde a década passada, o esquema antiplaquetário duplo é a principal opção terapêutica utilizada em sua passivação; paralelamente, as intervenções percutâneas tornaram-se a opção terapêutica definitiva mais comum. O fármaco inicialmente utilizado em associação com a aspirina, o clopidogrel, apesar de eficaz e seguro, apresenta inconvenientes que levaram ao desenvolvimento de uma nova geração de antiplaquetários mais eficientes, o prasugrel e o ticagrelor, que, em grandes ensaios clínicos comparativos, mostraram-se superiores a ele na redução de eventos cardíacos maiores combinados na evolução. Em razão disso, os dois novos medicamentos obtiveram respaldo das principais diretrizes, sendo tidos na atualidade como preferenciais. Pelas diferenças claras entre os protocolos dos ensaios clínicos que ratificaram sua incorporação na prática clínica, não havia como compará-los diretamente, sem o risco de gerar impressões precipitadas. Mais recentemente, um grande ensaio clínico prospectivo e randomizado proporcionou uma comparação adequada “cabeça a cabeça” entre prasugrel e ticagrelor, no âmbito da doença coronária aguda, em uma população submetida à estratégia invasiva, que demonstrou vantagem significativa do prasugrel. Nesta revisão, discorremos acerca dos principais detalhes desses fármacos mais contemporâneos e dos estudos clínicos mais relevantes a eles relacionados, identificando as vantagens e as desvantagens de cada um. Ao final, expõe-se nossa visão sobre sua prescrição na atualidade.

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

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INTRODUCTION

Acute coronary syndromes (ACS) are a huge problem in public health in the Western world. Recent North American data have clearly demonstrated their relevance:

one myocardial infarction (MI) occurs at every 40 seconds, totaling up more than one million per year, of which one third is recurrent. In 2016, there were 635,260 deaths due to cardiac causes, and although there are no specific figures for the impact of ACS on such events, it seems obvious to presume that a large amount of them is consequent to ACS. Therefore, interventions that minimize the risk of these cases have great clinical and economic relevance, justifying dedicated investigation.¹ More updated statistics have confirmed the relevance and severity of the situation.^{2,3}

At the beginning of the past decade, the results of the CURE⁴ trial and its substudy on percutaneous coronary intervention (PCI), PCI CURE⁵, demonstrated the dual antiplatelet therapy, exclusively *per oris*, was better than the isolated prescription of acetylsalicylic acid (ASA), in passivation of ACS. The P2Y₁₂-receptor inhibitor used, clopidogrel, was quickly supported by the main guidelines, since it enabled replacing high-cost drugs (glycoprotein IIb/IIIa inhibitors) by a simple tablet used in the daily routine, simplifying and facilitating medical prescription.⁶⁻⁸

Clopidogrel is a thienopyridine drug that acts on the adenosine diphosphate (ADP) pathway of platelet aggregation, inhibiting the P2Y₁₂ receptor, which is essential in this process.⁶⁻¹⁰ It is indicated for both acute and chronic cases; in the latter situation, its use is restricted to cases of intolerance to ASA, or those treated by PCI.⁶⁻⁸

Efficacy was proved, but over the course of clinical experience, it was found that this drug had significant inconvenience: delayed onset of action; less platelet aggregation inhibition than desired, and inconsistent effect, especially in genetic polymorphisms and/or unwanted drug interactions. To overcome these restrictions, two new drugs were developed: prasugrel and ticagrelor.^{6,7,11-13} Like clopidogrel, they act in the ADP pathway of platelet aggregation, inhibiting the P2Y₁₂ receptor. As shown by pharmacodynamic studies, both outperformed clopidogrel in rapid onset of action and in the inhibitory capacity for platelet aggregation. As of the time this paper was written, we are not aware of genetic polymorphisms that restrict their performance.¹⁴⁻²⁰

Prasugrel is a prodrug, that is, the active drug is a metabolite from its hepatic metabolism. It is administered in a single daily dose, and its effect is irreversible.^{13,15-17} On the contrary, ticagrelor, the first drug of a new class of antiplatelet drugs called cyclopentyl-triazole-pyrimidine, available in clinical practice, acts directly on platelets, requiring two daily doses, since it has a shorter half-life and reversible effect, details that render the administration of the second daily dose essential.^{13-15,18-20}

To prove these advantages in clinical practice, two large multicenter clinical trials were carried out with patients with ACS, including the two new drugs, always in direct

comparison with clopidogrel: TRITON TIMI 38²¹ and PLATO.²²

TRITON TIMI 38 AND OTHER CLINICAL TRIALS WITH PRASUGREL

TRITON TIMI 38²¹ published the results first, and the population of ST-segment elevation ACS and non-ST-segment elevation ACS patients (stratified as moderate or high risk), always using ASA, was randomized to receive prasugrel or clopidogrel. In this study, prasugrel was administered with a loading dose of 60mg, followed by maintenance dose of 10mg daily. The protocol recommended all patients included to undergo invasive strategy and subsequent PCI, receiving dual antiplatelet regimen for one year. At the end of this period, the combined primary endpoint of death, acute MI or stroke was significantly reduced by 19% with prasugrel, demonstrating its superiority (Figure 1), especially by reducing MI (5.8% *versus* 9.5%; $p < 0.001$); the 11% reduction in mortality was not significant. Due to its higher potency, the cases treated with this medication, as expected, presented an excess of major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) score: 2.4% *versus* 1.8% ($p = 0.03$). An unfavorable result was also noted in those who had a history of cerebrovascular events,

Source: Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al.; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357(20):2001-15. <https://doi.org/10.1056/NEJMoa0706482>. Table 2, Major efficacy end points in the overall cohort at 15 months; $p = 0.008$.⁽²¹⁾ Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al.; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361(11):1045-57. <https://doi.org/10.1056/NEJMoa0904327>. Table 3, Major efficacy end points at 12 months; $p = 1.052$.⁽²²⁾

Figure 1. Results of the combined primary endpoint in the TRITON TIMI 38²¹ and PLATO²² clinical trials.

which is why, today, this is still an absolute restriction for the use of prasugrel.

Regarding the sub-analyses, diabetic patients had greater benefit as compared to those with no diabetes.²³ Two other relevant sub-analyses refer to subgroups whose results were neutral: the elderly aged over 75 years and those under 60kg, that is, groups that demonstrated to be more predisposed to develop major bleeding complications.²¹ As a result, a new 5-mg presentation of the drug was developed, specifically indicated for these patients.²⁴

In the clinical pharmacodynamic trial GENERATIONS, focused on the objective measurement of platelet aggregation, this new presentation proved to be not inferior to the 10mg dose in patients aged under 65 years, and superior to clopidogrel in cases of older subjects, in a cohort of 155 patients with stable coronary disease, assessed by three different methods of measuring platelet aggregation. Although no major clinical experience has been reported, this presentation is available for clinical use.²⁴

There was no specific evaluation of prasugrel in patients with ACS not submitted to revascularization in the TRITON TIMI 38.²¹ The pharmaceutical industries responsible for its marketing conducted another prospective, double-blind clinical trial called TRILOGY ACS,²⁵ aimed to evaluate the impact of the drug in this subgroup. A total of 7,243 patients with non-ST-segment elevation ACS and aged 60 years or older, up to 10 days since the onset of the index event and no indication of revascularization by any methods, were recruited. They were randomized to receive prasugrel or clopidogrel at the usual doses, being followed up for an average period of 17 months.²⁵

At the end of this assessment, the combined primary endpoint of cardiovascular death, MI or stroke did not differ between the groups (prasugrel 13.9% *versus* clopidogrel 16.0%; $p=0.21$), the same occurring with major bleeding by the TIMI score (prasugrel 1.1% *versus* clopidogrel 0.8%; $p=0.27$), including intracranial bleeding. Therefore, the indication for use of prasugrel remained unchanged, with no precise indication to this date for its prescription in non-revascularized cases.²⁵

The last clinical trial that seemed relevant to include was the ACCOAST, designed to assess the impact of the use of prasugrel before diagnostic coronary angiography in patients with non-ST-segment elevation ACS and with troponin elevation. A total of 4,033 cases with this diagnosis and indication of invasive strategy were included and randomized to two therapeutic regimens. The pre-treatment group received an initial dose of 30mg of the medication before coronary angiography, followed by an additional 30mg in the case of indication of PCI after coronary angiography. The control group received the usual loading dose of 60mg after diagnostic angiography. The combined primary endpoint of cardiovascular death, MI, stroke, need

for urgent revascularization procedures or rescue therapy with glycoprotein IIb/IIIa inhibitors did not differ between the groups after 7 days, (10.0% *versus* 9.8%; $p=0.81$), including those effectively treated by means of PCI (69% of sample). Major bleeding according to the TIMI score was significantly more frequent in the pre-treated group (2.6% *versus* 1.4%; $p=0.006$), which resulted in the maintenance of the initial proposal made by the TRITON TIMI 38²¹ trial related to the prasugrel prescription. According to this trial, administration in cases with non-ST-segment elevation should occur only after diagnostic coronary angiography and subsequent indication of PCI.²⁶

PLATO²² TRIAL AND OTHER CLINICAL TRIALS WITH TICAGRELOR

Shortly thereafter, the results of the PLATO study were released, which had a population similar to that of TRITON TIMI 38²¹ and compared ticagrelor (loading dose of 180mg, followed by maintenance with 90mg every 12 hours) and clopidogrel, also prescribed for one year. The protocol did not provide for a mandatory invasive strategy (approximately 20% of cases in both groups were not submitted to diagnostic catheterization), and roughly 25% of patients were not revascularized. Ticagrelor also significantly reduced (16%) the same primary endpoint of death, MI or stroke (Figure 1), including significant reductions of 21% in mortality and 16% in MI. According to the TIMI score, there was no excess of major bleeding with ticagrelor (7.9% *versus* 7.7%; $p=\text{not significant}$). However, in the sub-analysis including only cases that were not surgically revascularized (90% of sample), those who received ticagrelor had a significant increase in major bleeding by the TIMI score (2.8% *versus* 2.2%; $p=0.03$).

The advantage of ticagrelor occurred both in patients submitted to invasive strategy and in those maintained in conservative treatment, making its prescription spectrum broader than that of prasugrel.^{6,7,22}

The new drug had more side effects during the study than clopidogrel, especially dyspnea, which affected about 14% of those who used the drug, often requiring discontinuation. It should be mentioned that the latter finding, associated with the need for two daily doses, made the prospect of compliance to chronic use of ticagrelor more problematic.²²

Some relevant subgroup analyses showed consistent benefit from ticagrelor,^{27,28} including in patients with history of stroke, which is an absolute restriction for prescription of prasugrel.²⁸

Although not clearly associated with the objective of reducing bleeding events, the pharmaceutical industry that holds the patent for ticagrelor subsequently evaluated a lower dosage presentation (60mg). In the study PEGASUS

TIMI 54, a population of more than 21 thousand patients with previous infarction, between 1 and 3 years before inclusion in the study, was randomized to three treatment options: ticagrelor in the usual dose, ticagrelor 60mg every 12 hours, and placebo. In 36-month follow-up, the two doses of ticagrelor proved to be significantly better than placebo in preventing death, MI or stroke, however at the expense of an equally significant increase in major bleeding by 2.5-fold, as compared to placebo (2.7-fold with the 90mg dose and 2.3-fold the 60mg dose). Currently, this new 60mg presentation is not yet available for clinical use.²⁹

Recently, the possibility of reducing the duration of the dual antiplatelet regimen in patients treated with ticagrelor has been evaluated with the predetermined objective of trying to prevent bleeding. The TWILIGHT study included a cohort of 9,006 patients treated by PCI who used ASA and ticagrelor. The patients should have at least one clinical or angiographic factor that would put them at high risk for major cardiac or bleeding events. The 7,119 cases that did not present any events in the following 3 months - two thirds of which were treated with ACS during the index procedure - were then randomized to two therapeutic schedules for the subsequent 12 months: ticagrelor in monotherapy, and maintenance of the original dual regimen prescribed. The primary endpoint was bleeding grades 2, 3 or 5 by the Bleeding Academic Research Consortium Definition of Bleeding (BARC) criteria. At the end of the late follow-up, cases randomized for monotherapy with ticagrelor had a significant reduction in bleeding complications (4.0% *versus* 7.1%; $p < 0.001$). The combined occurrence of death, infarction or stroke was similar in both groups (3.9% in both groups; $p < 0.001$ for non-inferiority). According to these results, ticagrelor in monotherapy after 3 months of dual regimen could be considered as an alternative in this set of patients.³⁰

RECOMMENDATIONS OF GUIDELINES

The main guidelines now support prasugrel and ticagrelor over clopidogrel, with a class I of recommendation, in cases of ACS, thanks to the superiority shown by both. The prescription of prasugrel was restricted to cases with known coronary anatomy and PCI proposed, whereas the use of ticagrelor was broader, not requiring diagnostic catheterization or the indication of revascularization procedures.^{6,7}

Another distinction was related to the time of administration of the initial dose. Both drugs could be prescribed as soon as possible in cases of ST-segment elevation. However, in situations with non-ST-segment elevation, ticagrelor could be immediately administered, whereas prasugrel could only be started after diagnostic coronary angiography and indication of PCI.^{6,7,31-33} Despite the difference in the spectrum of indication between prasugrel and ticagrelor, it was

obvious that there were two treatments with the same purpose. The clear differences between the protocols of the two studies^{21,22} already mentioned prevented an accurate direct comparison between them, which generated doubts, divided opinions, and demonstrated the need to develop other clinical trials that would promote an effective direct comparison between both, to establish if one of them was superior to the other.

PRAGUE 18 STUDY

It was the first relevant randomized study that directly compared the two new drugs, with a population of 1,230 patients with ST-segment elevation MI and non-ST-segment elevation MI, who underwent primary PCI, and used prospective and randomized prasugrel or ticagrelor for one year.³⁴ In the publication, the authors stated that there were plans to include 2,500 cases in the study, however only 1,230 cases were included. The inclusion was interrupted with no clear cause (the authors themselves attributed "futility" to the interruption). Even though, the results were analyzed and, using a broad combined primary endpoint (death, reinfarction, urgent target vessel revascularization, stroke or major bleeding), no significant differences were seen between the treatments. The same was noted when the different components mentioned were separately analyzed.

Since this study was not able to make an adequate comparison between the two antiplatelet drugs, attention was drawn to the clinical trial ISAR REACT 5,³⁵ which was recently published.

ISAR REACT 5 TRIAL

This is the best scientific evidence available to date to compare the drugs in focus.³⁵ It is a prospective, multicenter, randomized, investigator-led clinical trial, with the objective of comparing the drugs in the scenario of ACS. Due to the differences in the number of daily doses taken between the drugs evaluated, it was not a double-blind trial.

Cases of ST-segment elevation or non-ST-segment elevation ACS with indication of invasive strategy were included. Those with active bleeding, need for chronic use of oral anticoagulants, history of stroke or transient ischemic attack, on dialysis, and cases with significant liver dysfunction were excluded.

Prasugrel was prescribed with a loading dose of 60mg (six tablets), followed by a maintenance dose of 10mg daily. Those aged over 75 years and/or weight below 60kg maintained 5mg per day. Ticagrelor was used with a loading dose of 180mg (two tablets), with a maintenance dose of 90mg every 12 hours. Both should be taken for 1 year.

As determined by the guidelines,^{6,7} in cases with ST-segment-elevation, the loading dose of the two drugs should be administered just after randomization. In situations with non-ST-segment elevation, ticagrelor could be immediately administered, whereas prasugrel could only be used after diagnostic coronary angiography. In cases of exclusive drug therapy after diagnostic angiography, both treatments should be maintained in accordance with that indicated by randomization.

The combined primary endpoint was death, MI or stroke in one year. The secondary endpoint included definitive or probable stent thrombosis, the individual results of the components of the primary endpoint, and bleeding grades 3, 4 or 5, according to the BARC criteria measured at the end of the one-year period. Specifically for bleeding complications, the patients must have received at least one dose of the designated medication. Late follow-up could be done by telephone, face-to-face medical visits or by mail.

The sample size was calculated with the presumption of superiority of ticagrelor over prasugrel, expecting a reduction by 22.5% of primary endpoint, with a two-tailed test. Therefore, at least 1,895 patients should be included in each group. Due to the natural losses during follow-up, it was decided to include 4,000 patients in the study. The analyses were conducted using the intention-to-treat principle.

Although not explicitly stated in the publication, the assumption of advantage of ticagrelor was probably based on the possibility that cases with non-ST-segment elevation randomized for this drug would receive the medication earlier. In the potential absence of advantage of prasugrel in cases that would be maintained with no revascularization, and in the perspective of ticagrelor causing a greater reduction in mortality, without the counterpart of generating more major bleeding. The possibility of less adhesion to this medication, for the reasons discussed above, was probably not considered.

The main baseline clinical characteristics did not show significant differences between the groups. Diabetic patients accounted to 20% to 25% of cases; history of infarction was observed in 15%, and the predominant clinical presentation was non-ST-segment elevation MI (46% of cases). Practically all patients were submitted to the invasive strategy provided by the protocol. After diagnostic angiography, the majority of patients in both groups were treated by PCI, followed by medications (Figure 2).

In relation to the study medications, in situations with non-ST-segment elevation, the recommended loading dose was administered to 98.7% of those allocated to receive ticagrelor and to 86.1% of those randomized to prasugrel. At the time of hospital discharge, roughly 81% of cases in both groups were using the medication determined by randomization. At the end of the one-year course, discontinued use of the trial medications was significantly more frequent in the ticagrelor group (15.2% *versus* 12.5%; $p=0.03$).

Source: Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, et al.; ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med*. 2019;381(16):1524-34. <https://doi.org/10.1056/NEJMoa1908973>. Table 1, Characteristics of the Patients at Baseline; p. 1.530.⁽³⁵⁾

PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; NS: not significant.

Figure 2. Description of definitive treatment after invasive strategy in the ISAR REACT 5 study³⁵.

Contrary to the hypothesis initially formulated by the researchers, the prasugrel group showed a significant reduction in the combined primary endpoint. When the individual results of the different components were described, there was a significant reduction in cases of MI in this group, while the other two items (mortality and stroke) did not differ significantly (Table 1).

Table 1. Results for combined primary endpoint and its individual components in the ISAR REACT 5 trial³⁵

	Ticagrelor (n=2,012)	Prasugrel (n=2,006)	Relative risk (95%CI)	p-value
Primary endpoint (death, MI, stroke)	9.3	6.9	1.35 (1.09-1.70)	0.006
Death	4.5	3.7	1.23 (0.91-1.68)	
MI	4.8	3.0	1.63 (1.18-2.25)	
Stroke	1.1	1.0	1.17 (0.63-2.15)	

Results expressed as %.
MI: myocardial infarction.

In the prasugrel and ticagrelor groups, respectively, stent thrombosis classified as definitive or probable (1.0% *versus* 1.3%; $p=NS$), and bleeding complications (4.8% *versus* 5.4%; $p=NS$) were also found to be similar. Finally, in non-revascularized cases, the two drugs also showed a similar result.

Despite the possible limitations, to date, the ISAR REACT 5³⁵ study is the best evidence available to directly compare prasugrel and ticagrelor in cases of ACS, with

a formal proposal of stratification by invasive strategy. Significant reduction in the primary combined endpoint of death, MI or stroke was found with the use of prasugrel, with similar rates of major bleeding. The editorial commenting on the results of the study corroborated these impressions.³⁶

Finally, the results of the ISAR REACT 5 trial have already caused changes in the guidelines that guide the management of ACS, as shown in the latest update of the European guideline for non-ST-segment elevation ACS, which suggested the preferential use of prasugrel over ticagrelor, with class IIa of recommendation.³⁷

CONCLUSION

In the presence of acute coronary syndrome, it seems possible to state that in patients undergoing percutaneous coronary intervention, prasugrel would be the drug of choice, regardless of the presence or absence of ST-segment elevation, respecting the contraindications to its prescription; in non-revascularized cases and in the subgroup with history of stroke, ticagrelor would be the best alternative; specifically in the cases more likely to present bleeding complications, the maintenance dose of prasugrel 5mg per day, or ticagrelor in monotherapy after 3 months of dual antiplatelet therapy, would be valid alternatives. There is still room for prescribing clopidogrel, particularly in patients who are at higher risk for bleeding, as well as when there is cost constraint. The recommendations of the next guidelines to be released will corroborate or not such impressions.

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DECLARATION OF CONFLICTS OF INTEREST

In the past two years, Luiz Fernando Leite Tanajura has participated in events and prepared medical texts for the company Daiichi Sankyo Brasil. The other authors declared having no conflicts of interest.

CONTRIBUTION OF AUTHORS

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

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