Aspirin versus P2Y12 inhibitors for secondary prevention after percutaneous coronary intervention

Ácido acetilsalicílico versus inibidores dos receptores P2Y12 para prevenção secundária em pacientes tratados por meio de intervenção coronária percutânea

Luiz Fernando Leite Tanajura1id, Aqura Jacob Chaves1id, Rafaela Penalva Freitas1id, Ana Beatriz de Andrade Rangel Barbosa1id, Kelvyn Melo Vital1id, José Henrique Herrmann Delamain1id

DOI: 10.31160/JOTCI202331A202304

ABSTRACT – Currently, percutaneous coronary intervention with a drug-eluting stent implantation is the main method of myocardial revascularization in tertiary care hospitals, regardless of the clinical presentation of coronary artery disease. It is well known that to be effective, it requires the use of a dual antiplatelet therapy, which is a combination of acetylsalicylic acid and a P2Y12 platelet receptor inhibitor, which plays a key role in preventing thromboses after endoprosthesis implantation and is also indicated to prevent atherothrombotic events in the late clinical course, regardless of the stent model used. After a variable period of time, depending on some factors, such as the clinical presentation of coronary artery disease and the type of stent implanted, this therapy is discontinued, and the current guidelines recommend interrupting the P2Y12 receptor inhibitor and maintaining acetylsalicylic acid in the long term, as one of the main pharmacological measures for secondary prevention of atherosclerosis. However, recently, due to their greater antiplatelet potency and probable lower potential for significant bleeding, especially in the digestive tract, P2Y12 inhibitors have been considered a valid and attractive option as an antiplatelet agent for long-term use; but this alternative has not been endorsed by guidelines yet. This review discusses the details related to this important decision that must be made by cardiologists when discontinuing the different antithrombotic therapies initially used after percutaneous coronary intervention. In principle, the scarcity of conclusive and normative clinical studies, especially in the population treated by percutaneous intervention, means that acetylsalicylic acid is the only antiplatelet agent with class I indication for secondary prevention of atherosclerosis.

Keywords: Myocardial infarction; Angina, unstable; Aspirin; Ticagrelor; Clopidogrel; Secondary prevention; Percutaneous coronary intervention

RESUMO – Na atualidade, as intervenções coronárias percutâneas com implante de um stent farmacológico constituem o principal método de revascularização miocárdica em centros hospitalares terciários, independentemente da forma clínica de apresentação da doença arterial coronária. É de conhecimento geral que, para sua efetivação, há necessidade do uso de um esquema antiplaquetário duplo, constituído pela associação do ácido acetilsalicílico e um inibidor dos receptores plaquetários P2Y12, que é o cerne da prevenção das tromboses após implantes das endopróteses, sendo também indicado para prevenir a ocorrência de eventos aterotrombóticos na evolução clínica tardia, qualquer que seja o modelo de stent utilizado. Após período variável de tempo, independentemente de fatores como forma clínica de apresentação da coronariopatia e do tipo de stent implantado, esse esquema é interrompido, e, na atualidade, as principais diretrizes preconizam a suspensão do inibidor dos receptores P2Y12 e a manutenção do ácido acetilsalicílico em longo prazo como uma das principais medidas farmacológicas de prevenção secundária da aterosclerose. No entanto, recentemente, em razão de sua maior potência antiplaquetária e provável menor potencial de causar hemorragias significantes, em especial no tubo digestivo, os inibidores P2Y12 têm sido considerados alternativa válida e atraente como antiplaquetário de utilização em longo prazo, alternativa ainda não referendada pelas diretrizes. Esta revisão discute os pormenores relacionados a essa importante decisão que deve ser tomada pelo cardiologista no momento da interrupção dos diferentes esquemas antitrombóticos inicialmente utilizados após uma intervenção coronária percutânea. Em princípio, a escassez de estudos clínicos conclusivos e normativos, em especial...
na população tratada por meio de uma intervenção percutânea, faz com que o ácido acetilsalicílico ainda se mantenha como o único antiagregante plaquetário com indicação classe I com a finalidade de prevenção secundária da aterosclerose.

**Descritores:** Infarto do miocárdio; Angina instável; Ácido acetilsalicílico; Ticagrelor; Clopidogrel; Prevenção secundária; Intervenção coronária percutânea

### INTRODUCTION

Due to the introduction and subsequent improvement of drug-eluting stent (DES) technology, percutaneous coronary intervention (PCI) is now the main method of myocardial revascularization, regardless of the clinical presentation of coronary artery disease (CAD). One of the most recent clinical trials, ISAR REACT 5, which compared different antiplatelet agents in the setting of an acute coronary syndrome (ACS), strongly supported this statement, since PCI was the definite therapeutic option in most cases included in the study (85%).

Recently, a large clinical study (ADAPTABLE) involving 15,076 patients with established cardiovascular atherosclerosis, compared different doses of ASA, aiming to determine whether higher daily doses (325mg/day) would be more effective than the usual doses. In 12 months of clinical course, no significant advantages of the higher dosage were observed in relation to death, acute myocardial infarction (MI) or cerebrovascular accident (stroke), supporting the usual dose option.

#### P2Y12 receptor inhibitors

Currently, there are three drugs in this class that can be prescribed: clopidogrel, prasugrel, and ticagrelor. Relevant differences exist among these drugs, which require knowledge and attention on the part of the physician for a proper selection, for a better risk/benefit/cost analysis at the time of the prescription.

Clopidogrel acts on the adenosine diphosphate (ADP) pathway of platelet aggregation, inhibiting P2Y12 receptors, which are fundamental in this process. It is indicated for both acute and chronic CAD; in the latter situation, to date, its use has been limited to cases treated with PCI or situations of intolerance to ASA. Although it has proven efficacy, dosage convenience (single daily dose), and low incidence of relevant side effects, over the course of clinical experience several worrisome drawbacks were found: slow onset of action; inhibition of platelet aggregation below the desired level, and inconsistent effect, especially in the presence of genetic polymorphisms capable of interfering with its action (present in approximately a quarter of cases). These observations led to the development of new drugs, seeking greater efficiency.

Two other drugs were then developed: prasugrel and ticagrelor. Both act on the ADP pathway of platelet aggregation, likewise inhibiting the P2Y12 receptor. As demonstrated by pharmacodynamics assays, both outperformed clopidogrel in terms of speed of action and antiplatelet potency; to date, there is no knowledge of genetic polymorphisms that limit their action. At the present time (August 2023), the routine prescription of these two antiplatelet agents is restricted to the scope of ACS.
Impact of bleeding complications after percutaneous coronary intervention

Besides their potential to inhibit platelet aggregation, the use of different antiplatelet agents must consider another factor: the risk of a major bleeding complication, which is associated with worse prognosis.1,6

A large meta-analysis of 42 clinical trials, involving more than 500 thousand patients treated with PCI, found an over three-fold increase in mortality, and a nearly four-fold increase in major cardiac events in the clinical course of patients who presented major bleedings during the index hospitalization for PCI, demonstrating the clinical relevance of these bleeding events, and, therefore, the need for effective prevention measures.6 Similarly, later bleeding complications may also significantly affect the patients’ prognosis.1,6,7

Prescription of antiplatelet agents in secondary prevention of coronary disease

At the end of the period of use of the dual therapy, one of the drugs must be discontinued. As already mentioned, the main guidelines recommend maintaining ASA as the preferred option, but this has been contested.1,4,7,13,19

The possible option of maintaining the P2Y12 inhibitor instead of ASA arises from the favorable findings of recent clinical studies, in which the possibility of preventing more major cardiovascular events in late clinical course by prescribing P2Y12 inhibitors was observed, also with less bleeding complications, especially in the digestive tract.13-15 The results of different clinical trials, older or more contemporary, are shown below. We commented only on the study results comparing the single use of the aforementioned drugs for secondary prevention of atherosclerosis, although not all samples were composed exclusively of cases treated with PCI.

CLINICAL STUDIES COMPARING ACETYLSALICYLIC ACID VERSUS P2Y12 RECEPTOR INHIBITORS IN SECONDARY PREVENTION OF ATHEROSCLEROSIS

The main studies are mentioned below.

CAPRIE

This was the first head-to-head study comparing ASA (325mg/day) versus a P2Y12 inhibitor, more specifically clopidogrel (75mg/day), in patients with established atherosclerosis, externalized by stroke in the last 6 months, acute MI in the last 35 days, or symptomatic peripheral arterial obstructive disease. Many patients had more than one inclusion criterion, denoting more extensive and potentially more severe atherosclerosis.

This was a large clinical trial, involving 19,185 patients, the majority of whom had CAD (48% had a past history consistent with this diagnosis), which compared clopidogrel or ASA as monotherapy in the prevention of acute MI, stroke, or death from cardiovascular causes during late clinical course (progression of 1 to 3 years, with a mean of 1.9 year). Using the intention-to-treat principle, the use of the P2Y12 inhibitor achieved a significant reduction in the aforementioned events by 8.7%, but with a 0.52% difference in absolute values (5.32% versus 5.84%; p=0.043), i.e., a numerically modest drop. A more pronounced reduction in the combined primary endpoint was observed in patients who had a history of acute MI associated with stroke or peripheral vascular disease (22.7%) than in that measured in the group with any acute MI (7.4%). The incidence of any bleeding complications was similar in both groups (9.27% versus 9.28%; p=NS).

Due to the not so significant decrease in events, as well as the fact that, at the time, the new drug was expensive, ASA was not replaced by clopidogrel in everyday clinical practice.14

Moreover, the pioneering trial was carried out almost 30 years ago but it has clear limitations regarding the analysis of its results regarding the topic addressed in this review: it did not inform how many of the enrolled patients had previously undergone PCI; at the time, no DES or high-potency statins were available, making it difficult to extrapolate the results measured to the current clinical practice; and a high dose of ASA was used (325mg/day), higher than what is currently recommended.1,4,12

GLOBAL LEADERS

This study involved 15,968 patients undergoing PCI during any clinical presentation of CAD, with the aim to evaluate the impact of ticagrelor as monotherapy compared to standard dual therapy. The selected patients were randomized to two strategies: the experimental group, in which the included cases received ASA and ticagrelor for 30 days, after which monotherapy with ticagrelor was maintained...
for another 23 months; the control group, in which ACS cases used ASA and ticagrelor for 12 months, followed by another 12 months using only ASA; non ACS cases were medicated with ASA and clopidogrel, also for 12 months, and on monotherapy with ASA after this period of time. The combined primary endpoint of the trial was death or non-fatal ST-segment elevation myocardial infarction during a 24-month clinical course, which did not differ among the groups –nor regarding bleeding complications.

Despite not being a clinical trial specifically evaluating secondary prevention after PCI, a post-hoc sub-analysis published in 2022 cannot go unmentioned. It covered specifically the period between the first and the second year of the clinical course in a group of 11,121 patients (70% of the original series) involved in the study, who did not have thrombotic or bleeding events in the first year of follow-up, all medicated with ASA or ticagrelor as monotherapies, according to the study randomization. 14

The cases included in the ticagrelor group showed a significant decrease in ischemic events (1.9% versus 2.6%; p=0.01), but they also showed a significant increase in bleeding complications of types 3 or 5, according to the Bleeding Academic Research Consortium (BARC; 0.5% versus 0.3%; p=0.005). In the conclusion, the authors only emphasized the result related to ischemic events. 14

Meta-analysis by Chiarito et al. 15

Published in 2020, it covered nine clinical studies that directly compared ASA and a P2Y12 inhibitor in the context of secondary prevention of cases with clinically documented atherosclerosis, involving 42,108 patients. Clinical trials of cases with CAD (five studies), cerebrovascular disease (three studies), and multiple conditions (one study, the aforementioned CAPRIE study), 12 were included.

Another relevant detail: three different P2Y12 inhibitors were used in distinct clinical trials (ticlopidine, clopidogrel, and ticagrelor). ASA was prescribed in doses ranging from 75mg to 1.3g/day; the other drugs were used at the usual maintenance doses. Due to heterogeneity of the studies, some of the main past medical histories of the patients included also varied widely, such as, stroke prior to inclusion, which ranged from 2.1 to 100%, or acute MI, from 4.1 to 100%. The period of late clinical course was also very heterogeneous, ranging from 3 to 36 months.

Cardiovascular and total mortality, as well as the occurrence of a new stroke, did not differ between the groups. A significant, albeit modest, reduction in the occurrence of MI was observed in patients treated with P2Y12 inhibitors (relative risk reduction – RRR –0.81; CI 0.66-0.99), requiring treatment of 244 patients to prevent an event. All of these results were not influenced by the type of P2Y12 inhibitor used, according to the publication.

The same limitations that made it difficult to extrapolate the CAPRIE 12 results to cases treated with PCI apply to this meta-analysis; heterogeneity that is inherent to these investigations also makes it difficult to extrapolate these findings to routine practice.

HOST-EXAM 16

A more recent randomized, prospective and open clinical trial, published in 2021 (with cases included between 2014 and 2018), carried out in 37 South Korean centers, involving 5,438 patients treated with PCI using DES (of second generation in 97% of cases), was the first study that truly evaluated the context discussed in this review. This study evaluated whether monotherapy with clopidogrel (75mg/day) was superior to monotherapy with ASA (100mg/day) as a chronic maintenance therapy (secondary prevention tool for atherosclerosis), after the end of the established period of use of the dual antiplatelet therapy. Percutaneous procedures were performed between six and 18 months before inclusion in the study. Patients who had major cardiovascular or bleeding events in the period between PCI and the time of randomization were excluded. The stipulated late follow-up period was 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. Half of the patients included had multivessel coronary disease on diagnostic coronary angiography.

A broad combined primary endpoint was established, consisting of death, acute MI, stroke, readmission due to a new ACS, or BARC types 3 to 5 bleeding. After a 2-year clinical course, more than 98% of participants were able to have the combined endpoint of the trial evaluated, with a significant advantage in the clopidogrel group (Figure 1). A significant reduction was also observed in the monotherapy with P2Y12 receptor inhibitor when both thrombotic (3.7% versus 5.5%; p=0.003) and bleeding events (2.3% versus 3.3%; p=0.03) were individualized, demonstrating its potential superiority as a maintenance therapy after the

![Graph](image)

Source: Koo et al. 16

RRR: relative risk reduction; ASA: acetylsalicylic acid.

**Figure 1.** Combined primary endpoint of the HOST-EXAM clinical trial (death, myocardial infarction, stroke, readmission for new acute coronary syndrome, or bleeding types 3 to 5 as per BARC criteria).
end of the dual antiplatelet therapy period, in cases treated with revascularization by percutaneous coronary intervention. Regarding the individual analysis of the three main late atherothrombotic events, mortality and the occurrence of acute MI did not differ between the groups, but stroke was significantly less observed in patients randomized to the clopidogrel group (0.7% versus 1.6%; p=0.002).

In the publication, it was observed that a separation in the clinical course curves occurred between the ninth and tenth months after randomization, i.e., still in the first year after discontinuation of the dual therapy.

Meta-analysis by Aggarwal et al.17

Recently released, it included 61,623 cases involved in nine clinical trials comparing ASA and P2Y12 inhibitors in secondary prevention of atherosclerosis (five used clopidogrel, and four used ticagrelor). Compared to the article by Chiarito et al.,15 additional clinical trials on the topic were added.

A significant reduction in major cardiac events was observed in patients treated with a P2Y12 inhibitor (RRR 0.89; CI 0.84-0.95), especially due to the reduction in MI (RRR 0.81; CI 0.71-0.92); both results were obtained regardless of the type of P2Y inhibitor used. The incidence of bleeding complications did not differ between groups.

As mentioned in the evaluation of the meta-analysis by Chiarito et al., the main limitation on the results, regarding the population treated with PCI, is the fact that this meta-analysis also included cases not submitted to percutaneous revascularization (approximately two thirds of the sample did not undergo PCI).

HOST-EXAM Extended16

Since it is the only clinical trial published to date comparing ASA versus clopidogrel specifically in secondary prevention after PCI, the HOST-EXAM16 investigators deemed it relevant to extend the period of late clinical evaluation, foreseen for 2 years by the protocol, to provide additional information to the data collected in that period.

In January 2023, the results of the longer clinical course, called HOST-EXAM Extended,18 were released, comprising 4,717 patients, or 87% of the cases of the original publication. The analysis of the results was carried out according to the initial randomization, although after the end of the clinical course period stipulated by the HOST-EXAM16 protocol, the prescription of one or another drug was decided by the attending physician. The reasons for excluding 721 patients from the original trial were: nine withdrew consent, 94 could not be located for late assessment, and 618 changed the medication assigned by randomization. The remaining patients comprised the cases of the new clinical trial and were followed up for an average period of 5.8 years (4.7 to 6.2 years).

Discontinuation of the drug assigned by randomization was higher in the ASA group (13.5% versus 8.0%; p<0.001), and the most common reason was decision made by the attending physician.

The combined primary endpoint, identical to that used in the HOST-EXAM study,16 also demonstrated a significant reduction in the group assigned to use clopidogrel (12.8% versus 16.9%; p<0.001). The same occurred when the ischemic (7.9% versus 11.9%; p<0.001) and the bleeding (4.5% versus 6.1%; p=0.016) components were individually evaluated. Mortality was similar between groups (6.2% versus 6.0%; p=NS).

The analysis of the different subgroups confirmed the main findings of the study, demonstrating significant advantages for patients who used clopidogrel; for example, in patients aged over or under 65 years, in diabetics, in patients with chronic renal dysfunction, and in patients with significant multiple vessel disease, among others. Table 1 shows the percentages of reduction in events measured in the subgroups of greatest interest using clopidogrel.

A new evaluation is planned when patients complete a 10-year follow-up.

Meta-analysis by Gragnano et al.19

The so-called PANTHER Collaboration was released very recently, involving 24,325 patients from seven clinical trials, all with established coronary artery disease. Despite the study profile mentioned by the authors, the investigation included the CAPRIE12 study in the analysis, whose sample comprised not only patients with coronary artery disease; it excluded GLOBAL LEADERS,13 which included only patients with CAD, and strangely included a pre-specified sub-analysis of the latter study, named GLASSY23 (7,065 cases included, 44% of study sample), whose results included cases with events measured since the moment of the PCI, that is, while using the dual antiplatelet therapy for purposes other than secondary prevention.

### Table 1. Main results of analysis of subgroups in HOST-EXAM Extended clinical trial

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>RRR with clopidogrel (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>20</td>
<td>0.01</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>29</td>
<td>0.004</td>
</tr>
<tr>
<td>CRF</td>
<td>33</td>
<td>0.009</td>
</tr>
<tr>
<td>MVD</td>
<td>31</td>
<td>0.002</td>
</tr>
<tr>
<td>ACS</td>
<td>28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HRB</td>
<td>29</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Source: Kang et al.18

RRR: relative risk reduction; CRF: chronic renal failure; MVD: multivessel disease; ACS: acute coronary syndromes; HRB: high risk of bleeding.
The primary endpoint established was the occurrence of major cardiovascular events within 24 months of clinical course. The most prescribed P2Y12 inhibitor was clopidogrel (62% of patients using this class of antiplatelet drugs).

After a mean clinical course of 2 years, a significant reduction in the combined endpoint by 12% was observed in cases treated with P2Y12 inhibitor, due to a considerable 23% drop in cases of MI (p<0.001). These outcomes occurred in several of the subgroups evaluated and regardless of using clopidogrel or ticagrelor. Total and cardiovascular mortality, as well as cases of stroke or major bleeding complications, did not differ between the groups.

FINAL CONSIDERATIONS

From the results of the literature review on the topic discussed, we found that:
- To date, ASA remains the only antiplatelet agent with a class I recommendation in secondary prevention of patients with clinically evidenced atherosclerosis, including the population undergoing PCI, regardless of the presence of any other factors;\(^{1,7,9,24,25}\) the European guideline on prevention of cardiovascular diseases also discusses clopidogrel as class I, but only in cases of intolerance to ASA.\(^9\)
- The only randomized clinical trial that evaluated ASA compared to P2Y12 receptor inhibitors in patients treated with PCI demonstrated a significant advantage of the latter group of drugs, at different moments of late clinical course.\(^{16,18}\)
- The meta-analyses included heterogeneous studies, with a broad clinical scope, not limited to patients with CAD.\(^{15,17,19}\)
- Currently, the initial option for a P2Y12 inhibitor is recommended only in cases with restrictions on the prescription of ASA.\(^{1,7,9,24,25}\)
- There is no information on the use of prasugrel for secondary prevention of atherosclerosis.\(^{1,7,9,24,25}\)
- Finally, the latest American guideline on chronic CAD only mentions the acronym SAPT (single antiplatelet therapy) as a class I recommendation after the end of the dual antiplatelet therapy in cases treated by PCI, not specifying one type of drug over the other, which may open room for prescription of clopidogrel in these cases.\(^9\)

SOURCE OF FINANCING

None.

CONFLICTS OF INTEREST

LFLT wrote medical texts for the companies Daiichi Sankyo Brazil and Terumo in the past 2 years. The other authors reported no conflicts of interest.

CONTRIBUTION OF AUTHORS

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

REFERENCES

Acetylsalicylic acid versus P2Y12 inhibitors for secondary prevention after percutaneous coronary intervention


