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EDITORIAL COMMENT

Extended antithrombotic therapy in secondary prevention: ''There is no such thing as a free lunch''

Terapêutica antitrombótica alargada em prevenção secundária: «não há almoços grátis»

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The article by Faria et al. published in this issue of the *Journal*[1] calls attention to an important issue in medicine, which is the applicability in clinical practice of the results of published randomized clinical trials (RCTs). This becomes even more complicated when there are multiple studies on the same clinical issue, but with different inclusion and exclusion criteria, which makes it difficult to put them all into perspective. For this reason, the results of these RCTs must be complemented with real-world registries, as these are likely to have broader inclusion criteria, making it easier to validate some of the therapeutic options for the many patients who would not have been included in the trials.

In the real world, the expression ''there is no such thing as a free lunch'' is once again applicable, since the reduction of ischemic events seen with extended antithrombotic therapy for secondary prevention of acute coronary syndrome is accompanied by an increase in bleeding events in all published antithrombotic trials. Hence the importance in clinical practice of determining which patients are most at risk of ischemic events without a high risk of bleeding. It must, however, be borne in mind that most patients with a higher ischemic risk also have a high bleeding risk. It is therefore not surprising that a large number of real-world patients do not meet the inclusion criteria for these clinical trials (about 50% in the study by Faria et al.). Another interesting finding in this study was the large number of patients excluded for having an indication for chronic anticoagulation (46.2% on the PEGASUS criteria and 32.1% on the COMPASS criteria), which certainly reflects the high prevalence of other clinical conditions such as atrial fibrillation among these patients at high ischemic risk.[1]

Coronary artery disease (CAD), a process of atherosclerotic plaque formation in the coronary arteries, can be stable for long periods, but can also become unstable at any time due to an acute atherothrombotic event, typically caused by plaque erosion and rupture. Patients who have had an acute coronary syndrome, especially myocardial infarction (MI), are at high risk for recurrent ischemic events, which suggests that this population may derive particular benefit from more intensive secondary prevention.[2,3]

The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin Thrombolysis In Myocardial Infarction 54) trial demonstrated that long-term dual antiplatelet therapy (DAPT) with aspirin (75-150 mg) and ticagrelor 60 or 90 mg twice daily, started in stable patients 1-3 years after MI, reduced ischemic events at the expense of more non-fatal bleeding. The rates of bleeding and dyspnea were numerically lower with 60 mg of ticagrelor than with 90 mg, resulting in a lower rate of discontinuation of the study drug and a better safety profile with the 60 mg dose.[4] Subgroup analysis demonstrated greater absolute reductions in ischemic events with long-term ticagrelor (60 mg twice daily) in higher-risk post-MI

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patients with diabetes, peripheral arterial disease, or multivessel CAD.[5–7]

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial randomized 27 395 participants with stable atherosclerotic vascular disease to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), aspirin (100 mg once daily), or placebo. Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes but more major non-fatal bleeding. The net clinical benefit outcome, defined as a composite of cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into a critical organ, was also lower with rivaroxaban plus aspirin than with aspirin alone (4.7% vs. 5.9%, p<0.001).[8]

There has been no head-to-head comparison between the two strategies, and both PEGASUS and COMPASS show that escalation of antithrombotic therapy in high-risk stable CAD patients leads to improved event rates, including numerical reductions in cardiovascular death, particularly in individuals at the highest risk. Direct comparison between drugs studied in different trials is methodologically suspect, but it should also be remembered that there were important differences between the patients included in these two trials. The proportion of subjects who had had an MI was 100% in PEGASUS but only 62% in COMPASS. In addition, the time since MI was 1-3 years in PEGASUS, but in COMPASS it could have been at any time in the previous 20 years. In addition, patients in the two trials did not necessarily have the same initial bleeding risk, and the trials used different methods to define significant bleeding, making it difficult to compare bleeding rates between them.

The current European guidelines on chronic coronary syndromes give a class IIa recommendation for extension of antithrombotic therapy by adding a second antithrombotic drug to aspirin for long-term secondary prevention (after one year) in patients with a high risk of ischemic events and without high bleeding risk.[2] Although the guidelines do not specifically recommend any of the available drugs, the risk/benefit balance appears to be better with ticagrelor 60 mg twice daily and rivaroxaban 2.5 mg twice daily than with clopidogrel or prasugrel. A meta-analysis of DAPT compared with aspirin monotherapy for secondary prevention in patients with previous MI also showed significantly better outcomes in patients with DAPT, using the same primary endpoint as the COMPASS trial, as well as in cardiovascular death, MI, and stroke individually.[9]

In a strategy of extending treatment after ACS, in which most patients are treated with aspirin plus ticagrelor and in which the risk of recurrent ischemic events is due more to the complexity of CAD and its treatment (such as diffuse multivessel disease, multiple stenting, left main involvement or coronary bifurcations), it seems most logical to opt for ticagrelor 60 mg twice daily for therapeutic extension one year after ACS, without suspending DAPT. Similarly, patients not already on DAPT, with extensive atherosclerotic disease that involves other vascular territories, may benefit more from the association of aspirin with rivaroxaban.

In all cases, patients with a history of previous stroke, recent bleeding, anemia, liver failure, extreme advanced age or frailty and severe renal failure should be excluded, regardless of the choice of drug for therapeutic extension.

In short, we need drugs to protect our patients from new ischemic episodes, such as those included in a long-term dual antithrombotic therapy strategy. This is not an option in patients whose risk of bleeding exceeds the potential benefit, regardless of the criteria used. The drugs and dosages for this therapeutic extension for which most evidence is available are ticagrelor 60 mg twice daily and rivaroxaban 2.5 mg twice daily, which can be used in similar clinical contexts. However, there are some signs that prolonged DAPT is more effective at reducing recurrent MI and stent thrombosis, as opposed to the greater efficacy of the COMPASS strategy for reducing stroke and peripheral vascular disease.

Conflicts of interest

Marco Costa has participated in advisory boards and received speaker fees from AstraZeneca and Bayer.

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