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EDITORIAL COMMENT

Antithrombotics without intracoronary thrombus. The case of Takotsubo Syndrome

Antitrombóticos sem trombo intracoronário. O exemplo da Síndrome de Takotsubo

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The paper by Pereyra et al.[1] published in this issue of the Journal, based on the RETAKO Registry (Registry on Takotsubo Syndrome),[2] studies a topic of major controversy and for which scientific evidence is scarce.

The question to be answered is nothing more than discovering the impact of antiplatelet therapy (APT) after acute coronary syndrome (ACS) in patients diagnosed with Takotsubo Syndrome (TTS), which is, by definition without significant obstructive coronary lesions, possibly with atherosclerotic plaques, but with a lumen reduction of <50%.

The authors analyzed a series of 544 TTS survivors, 321 of whom were discharged on APT (aspirin and/or P2Y12 inhibitors) and 221 did not receive these drugs. Patients were followed for a mean time of 10.6 months, this period being 13.2 months in the group with APT and 7.2 months in the group without APT.

The group on APT was the clinically less severe group and probably for this reason also had a shorter hospital stay.

Total mortality in an unadjusted analysis was lower in the APT group (hazard ratio (HR) 0.325; 95% confidence interval (CI) 0.146-0.880, p=0.025) and after multivariate adjustment that benefit remains (HR 0.315; 95% CI 0.106-0.943, p=0.039).

The effect on hospital readmissions was also positive in an unadjusted analysis (HR 0.439; 95% CI 0.211-0.915, p=0.028), however, this benefit was lost after adjustment for potential confounders (HR 0.486; 95% CI 0.227-1.041, p=0.064).

Finally, the composite of death and hospital readmissions showed favorable behavior, both in unadjusted analysis (HR 0.39; 95% CI 0.215-0.705, p=0.002) and in adjusted multivariate analysis (HR 0.318; 95% CI 0.164-0.619), p=0.001).

The scientific evidence supporting the use of APT in patients after ACS without obstructive coronary disease, is very scarce and has no support based on clinical trials. To complicate matters, we found contradictory results in the literature.

While some small studies show some benefit, a meta-analysis was published showing results in the opposite direction, giving a good idea of the controversy that this topic generates.

In the aforementioned meta-analysis, Francesca Rizzetto et al.[3] analyzed six studies with 1997 patients, the vast majority of whom had long-term follow-up information.

The analysis revealed a higher incidence of events either in the composite endpoint of multiple events (OR: 1.54;

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95% CI 1.09-2.17; p=0.014), or in isolated events, especially total death (OR 1.72; 95% CI 1.07-2.77; p=0.027). It did not show any significant difference in TTS recurrence, or in the occurrence of stroke/transient ischemic attack, myocardial infarction, or worsening of coronary artery disease when comparing groups with or without any form of APT.

In 2021, Jinhai Lin et al.[4] published (in the BMJ Open) the intention of performing a meta-analysis focusing only on the long-term results of the exclusive use of aspirin, but to my knowledge the results have not yet been published.

The use of APT in patients with acute coronary disease without obstructive coronary artery disease is also a matter of debate in relation to patients diagnosed with myocardial infarction without obstructive coronary arteries (MINOCA).

In this domain, we ourselves have devoted some attention. Based on data from the National Registry of Acute Coronary Syndromes of the Portuguese Society of Cardiology, Fernando Sá, at the time a collaborator in our group, published a paper analyzing the role of dual APT in patients identified as MINOCA.[5]

In a series of 709 patients, representing 4.4% of the total number of patients included in the registry, the authors found that 390 (55%) were discharged from hospital medicated with dual APT.

In a multivariate analysis to identify independent predictors, male gender (OR=1.67, CI 95 [1.05-2.38], p=0.027); active smoking (OR=1.82, CI 95 [1.05-3.16], p=0.033); a previous percutaneous coronary intervention (OR=3.18, CI 95 [1.48-6.81], p=0.003); presentation with ST elevation (OR=2.70, CI 95 [1.59-4.76], p<0.001); the presence of sinus rhythm on admission (OR=3.94, CI 95 [2.07-7.48], p<0.001); all were identified.

Analyzing these predictors, one is left with the impression that at the origin of the decision to prescribe double APT in patients without obstructive coronary disease, there is a clinical environment favorable to the occurrence of thrombotic phenomena, thus conditioning the therapeutic decision.

The rationale for the use of antithrombotic agent and especially APT in patients with TTS has been explored by some investigators. Blood hyperviscosity and endothelial dysfunction have been identified in patients with TTS, somehow supporting the use of those drugs, although intra-coronary ultrasound studies have not identified the presence of plaque rupture or the presence of intra-lumen thrombus.[6–8]

In the study by Cecchi et al.,[6] 17 women with TTS underwent adrenergic stimulation with a cold pressor test and hemorrheologic parameters were studied. They concluded that changes in the erythrocyte membrane and endothelial integrity can determine a microvascular hypoperfusion favoring the occurrence of characteristic ventricular ballooning.

The relative predominance of TTS in postmenopausal women may further suggest that estrogen deprivation plays a role, probably mediated, once again, by endothelial dysfunction.[9]

In summary, everything we can say about antithrombotic therapy in patients with TTS is speculative in the absence of adequate clinical trials. Despite this, the rationale for this therapy seems to exist, but the decision will always be and even with better evidence, taken on a case-by-case basis.

The absence of obstructive plaques in the coronary lumen is not enough to give reassurance, either in patients with TTS or MINOCAs. The clinical profile of the patient must weigh in on the decision, which will always be individualized. If, at the time of admission of patients with TTS, the therapeutic approach is the one that is standardized in the guidelines for patients with SCA,[10] including mandatory dual APT, at the time of discharge or at the first follow-up visit, it must be reviewed.

In the absence of evidence for the maintenance of dual APT, single APT therapy should be considered based on the patient atherothrombotic risk profile. According to age, the presence of co-morbidities, especially type 2 diabetes, in menopausal women, as well as in other concomitant manifestations of atherosclerotic disease, APT should be considered in the final decision.

Conflicts of interest

The author has no conflicts of interest to declare.

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