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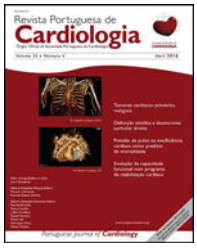

EDITORIAL COMMENT

Pretreatment with $P2Y_{12}$ inhibitors in ST-elevation myocardial infarction: Should we keep doing it?

Dose de carga de inibidor P2Y12 o mais cedo possível no contexto de enfarte agudo do miocárdio com supradesnivelamento do segmento ST: fazer ou não fazer, eis a questão

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Dual antiplatelet therapy is an established and essential treatment in acute coronary syndrome (ACS) patients, with a class I recommendation in the European and American guidelines. Current practice in many centers still mandates an upfront loading dose with a $P2Y_{12}$ inhibitor as soon as possible, before percutaneous coronary intervention (PCI). However, the evidence is scarce and conflicting, and benefits from routine pretreatment before arrival at the cath lab remain uncertain. This is true for non-ST-elevation myocardial infarction and even more so for ST-elevation myocardial infarction (STEMI) patients.

What is the rationale of pretreatment?

One of the main arguments is biological plausibility.[1] Since ACS most frequently results from occlusion of an artery by a platelet-rich thrombus, it is logical to assume that early administration of aspirin and a $P2Y_{12}$ inhibitor should provide greater benefit, enabling the highest level of platelet inhibition in the shortest possible time. For clopidogrel, still the most frequently used $P2Y_{12}$ inhibitor, its pharmacokinetic characteristics are relevant, given its very slow onset of action. However, various studies and meta-analyses suggest that pretreatment with clopidogrel in patients with STEMI reduces the rate of ischemic events without excess bleeding.[2,3] Regarding ticagrelor, although it does not require metabolic activation to exert its antiplatelet action, it is still extensively metabolized; its only active metabolite, AR-C124910XX, is as potent as ticagrelor itself. In the setting of ACS, intestinal uptake of ticagrelor may be significantly delayed, especially in patients administered morphine and in those with STEMI.[4]

Besides these reasonable arguments, a possible psychological effect should be borne in mind, arising from the comfort some physicians may feel from doing something that is thought of as being biologically important for the patient, especially since the same drug is used in both pretreatment and in cath lab loading. We live in an era of widely used and safer radial access, and the number of patients who require urgent bypass surgery in this context is very small. Add the well-known fact that times from first medical contact to reperfusion are much longer than recommended in many centers and the question ''why not do it sooner?'' begins to look logical. Unfortunately, as in many other clinical contexts, biological and pathophysiological plausibility does not necessarily mean clinical efficacy. When tested with good methodology, plausible treatments may even prove harmful.

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What does the most robust evidence available tell us?

The Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial,[5] published in 2014, was an international multicenter double-blind trial that recruited 1862 patients with STEMI (<6 hours duration) and randomized them to ticagrelor given prehospital (in the ambulance) or in the cath lab. The coprimary endpoints were the proportion of patients who did not achieve a 70% or greater resolution of ST-segment elevation before PCI and the proportion of patients who did not have Thrombolysis in Myocardial Infarction flow grade 3 in the infarct-related artery at initial angiography. Secondary end points included the rates of major adverse cardiovascular events and definite stent thrombosis at 30 days. The take-home message of this trial was that compared to in-hospital administration, prehospital administration of ticagrelor appears to be safe and may offer a small benefit in preventing stent thrombosis without any difference in major bleeding, but does not improve pre-PCI coronary reperfusion. The time difference between the two arms was only 31 minutes, a small difference that may have played a role in the end result.

More recently, using data from the Swedish Coronary Angiography and Angioplasty Registry,[6,7] Redfors et al.[6] studied 44 804 patients admitted with STEMI between 2005 and 2016, investigating the association between pretreatment with $P2Y_{12}$ inhibitors (58.3% clopidogrel, 35.3% ticagrelor and 5.3% prasugrel) and the risk of adverse outcomes using a propensity score to account for clustering of patients within hospitals. The primary endpoint was all-cause mortality at 30 days. Secondary endpoints were infarct-related artery occlusion, 30-day stent thrombosis, in-hospital bleeding, neurological complications and cardiogenic shock. The majority of patients (85%) were pretreated. The authors found no statistically significant association between prehospital treatment and lower in-hospital mortality, improved infarct artery patency, lower stent thrombosis, or higher bleeding rates. However, confidence intervals were wide, ranging from real benefit to harm, which make firm conclusions impossible.

In this issue of the *Journal*, Guedes and coworkers[8] return to this open and still unanswered question. They looked at a series of 4123 STEMI patients admitted between 2010 and 2017 and compared those receiving a $P2Y_{12}$ loading dose before or in the cath lab. The main efficacy endpoint was major adverse events (MAE) and the main safety endpoint was a composite of major bleeding, hemoglobin drop >2 g/dl and need for transfusion. As in the Swedish series, most patients received a clopidogrel loading dose prior to arrival at the cath lab. Their conclusion is that this strategy does not appear to provide any benefit regarding mortality or MAE. Furthermore, there was an increased bleeding risk, raising concerns about safety.[8]

The authors deserve commendation for addressing this issue and their work provides yet another piece of evidence that should be taken into account by physicians when deciding the best timing to administer a $P2Y_{12}$ loading dose. However, the limitations of this study should be kept in mind: it is retrospective, the two groups were very heterogeneous, and the time difference between the groups in antiplatelet therapy administration, a critical piece of information, is not provided.

There is thus still no definitive answer at this time. Unfortunately, trials testing a strategy of very rapid onset and high level of $P2Y_{12}$ receptor inhibition at the time of PCI using intravenous cangrelor did not address this question, providing only indirect evidence suggesting a reduction in ischemic risk.[9]

So what should be done?

As stated in the current European Society of Cardiology STEMI guidelines,[10] earlier administration may be preferable to achieve early efficacy, particularly when there are long delays, which are unfortunately still very common. However, in cases in which a STEMI diagnosis is not clear, the patient has a high bleeding risk or a significant probability of undergoing surgical coronary revascularization or whenever other etiologies that may require urgent surgical treatment cannot be ruled out, delaying $P2Y_{12}$ inhibitor loading must be considered.

Conflicts of interest

The author has no conflicts of interest to declare.

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