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EDITORIAL COMMENT

Pre-treatment with $P2Y_{12}$ inhibitors: Old habits die hard

Pré-tratamento com P2Y12 – é difícil perder velhos hábitos?

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Unlike the clearly demonstrated and proven beneficial management strategy for ST-segment elevation myocardial infarction (STEMI),[1] two major issues persist regarding the treatment of non-ST-segment elevation acute coronary syndrome (NSTE-ACS): the timing for an invasive strategy and the need for potent antithrombotic therapy in the meantime, as well as the benefit of both combined.

Higher-risk NSTE-ACS patients benefit from undergoing coronary angiography (CA) and revascularization within 24 hours of presentation,[2] but this group comprises several different clinical scenarios, for some of which robust evidence for this timing recommendation is lacking, particularly an established diagnosis of non-STEMI, which effectively means a rise and fall in troponin levels over time. Beyond patient choice, hard endpoint benefits have to date been lacking regarding the recommended timing for CA. A recent meta-analysis[3] of eight large randomized controlled trials (including TIMACS and VEREDICT, as well as the more recent EARLY and OPTIMA-2) concluded that, regardless of the clinical risk involved, major outcomes (all-cause mortality, myocardial infarction [MI], admission for heart failure, and repeat revascularization) were not improved by an early invasive strategy, and only recurrent ischemia (not clearly defined in most cases) and hospital length of stay were improved. As such, CA timing in NSTE-ACS, rather than its indication, is still under debate.

The article by Almeida et al. published in this issue of the *Journal*[4] adds an extra dimension to this already controversial topic. After the 2020 European NSTE-ACS guidelines[2] recommended withholding pre-treatment with a $P2Y_{12}$ inhibitor, should we be more cautious when deciding on a delayed CA strategy? Should using less antithrombotic therapy make us rush the patient into the cath lab? Based on Almeida et al.'s results, delaying CA without $P2Y_{12}$ inhibitor loading appears to have no major impact on in-hospital and one-year clinical outcomes, regardless of CA timing. Despite this apparent absence of harm, larger and more up-to-date studies will be required to support their conclusions, when the recommendations on pre-treatment become widespread. From 2015 to 2019, pre-treatment was advised for all acute coronary syndromes (ACS) regardless of electrocardiographic (ECG) pattern,[1,2] and so the population analyzed by Almeida et al. was probably either at low ischemic risk (as reflected by a median GRACE score of 121±31 in the early strategy group and 122±31 in the delayed strategy group), or considered by their attending physician to be at high bleeding risk, but this is not included in the data gathered in the Portuguese Registry of Acute Coronary Syndromes (ProACS).

No single randomized controlled trial is available to date that clearly elucidates this additional step in clinical decision-making. Studies in which pre-treatment did

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not prove to be beneficial had a short time to CA (under five hours in the ACCOAST trial[5] and one hour in ISAR-REACT-5[6]), while benefit was proven for NSTE-ACS patients who underwent delayed PCI (an average of 10 days after randomization) in the CURE trial.[7] On the other hand, in studies in which early CA was not superior to a delayed strategy, patients were under dual antiplatelet therapy at the time of delayed CA,[3] possibly reducing ischemic events (particularly reinfarction), preventing pump failure by improving coronary thrombosis and flow, and improving survival overall.

So far, despite class I recommendations for urgent (<2 hours) or early (<24 hours) CA in high-risk patients,[2] real-world NSTE-ACS data still show that such timings are not being achieved. Between 2002 and 2013, despite a significant increase in the proportion of NSTE-ACS patients treated by an invasive strategy, the proportion of patients in Portugal undergoing early CA was still less than 50%,[8] probably reflecting clinicians' doubts about the benefit of early CA for NSTE-ACS patients. Moreover, in the era of high-sensitivity troponins, complying with said recommendations would require restructuring cath labs, teams, and timetables to respond to an overwhelming number of NSTE-ACS cases with changing troponin levels. The benefit of early CA for these patients, as well as for those with dynamic or presumably new contiguous ST/T-segment changes, has not been consistently shown across trials, despite a class IA recommendation.[2] If CA timing has not been proved robustly superior to a delayed strategy and has not been widely adopted, should we stop giving $P2Y_{12}$ inhibitor pre-loading by default?

A related subject in ACS management is the simple dichotomization between STEMI and NSTE-ACS according to ECG patterns, which has been shown to miss around 40% of acute coronary artery occlusion MIs,[9] for whom urgent CA and potent $P2Y_{12}$ inhibitor pre-treatment is warranted. If withholding $P2Y_{12}$ inhibitor pre-treatment becomes the rule, some patients with acute occlusion MI who are misclassified as NSTE-ACS according to the ECG pattern might have worse outcomes. Such diagnostic errors are certainly responsible for additional morbidity and mortality in ACS, which has been reduced in recent years by guideline-recommended implementation of routine CA in NSTE-ACS, but might again become a source of worse outcomes if $P2Y_{12}$ inhibitor pre-treatment becomes the exception. International guidelines clearly state the diagnostic criteria for STEMI, but old-school analysis of ECG patterns, supported by recent evidence,[10] shows that deciding each patient's future based on ST-segment elevation alone might be oversimplistic. Antithrombotic therapy in NSTE-ACS should not be downgraded without keeping specific settings in mind, especially those with additional high-risk clinical features (ongoing chest pain, hemodynamic or electric instability) and certain ECG patterns.

All things considered, if some patients benefit from early CA and revascularization that improve in-hospital ischemic complications, heart failure and survival, one might wonder whether they would not also benefit from $P2Y_{12}$ inhibitor pre-treatment and thrombotic burden reduction if it is decided to delay CA. Should there be a specific setting of NSTE-ACS patients for whom an urgent or early invasive strategy should be not paired with $P2Y_{12}$ inhibitor pre-treatment, while an urgent or early $P2Y_{12}$ inhibitor pre-treatment strategy should be adopted when early CA is not possible or desirable?

Overall, the results of Almeida et al.[4] represent a subset of patients for whom withholding $P2Y_{12}$ inhibitor pre-treatment had no major impact on in-hospital and one-year clinical outcomes, regardless of CA timing. These findings, as well as the recommendations of the 2020 NSTE-ACS guidelines, are worthy of careful consideration. Further studies dedicated to high ischemic risk subsets, and analysis from real-world settings in which delayed CA is more frequent, should clarify whether $P2Y_{12}$ inhibitor pre-treatment will be lost for good.

Conflicts of interest

The author has no conflicts of interest to declare.

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