Pretreatment in the Setting of Non–ST-Elevated Acute Coronary Syndrome-When It Is Time to Change

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Early inhibition of thromboxane A2, adenosine diphosphate, and thrombin is the ultimate goal of antithrombotic treatments prescribed for patients with acute coronary syndrome (ACS) to prevent the extent of coronary plaque thrombosis and to avoid peri-interventional myocardial infarction (MI). Intravenous administration of aspirin and anticoagulation allows an immediate biological effect whereas the mandatory oral intake and metabolization $P2Y_{12}$ inhibitors delay their onset of action. To overcome this limitation, a strategy of pre-treatment, defined as the administration of an oral P2Y12 inhibitor with aspirin to all patients with suspected ACS irrespective of knowledge of the coronary anatomy and possible lesions of the individual patient, has been developed. Although widely adopted for ST-elevated MI undergoing primary percutaneous coronary intervention, this approach has been debated for more than 20 years in the setting of non–ST-elevated acute coronary syndrome (NSTE-ACS) and is now challenged by recent data. Indeed, a more aggressive platelet inhibition does not necessarily lead to less peri-interventional MI and has never been associated with any ischemic benefit, whereas more bleedings in patients with NSTE-ACS undergoing CABG surgery[1] or without underlying obstructive coronary artery disease has been established.[2]

The 2020 European Society of Cardiology (ESC) Guidelines on management of NSTE-ACS do not recommend any more routine pre-treatment with oral P2Y12 inhibitors as the standard of care (Class IIIA) but that it may be considered in patients who are not planned to undergo an early invasive strategy and do not have high bleeding risk (Class IIb).[3] The main concern of the pretreatment proponents is the potential occurrence of lethal arrhythmias or large MI during the unsafe waiting period from admission to angiography. However, these events are very uncommon and not prevented by pretreatment whatever is the time of the coronary angiogram within the first 48 hours of admission.[4,5] This shift on pretreatment in the 2020 ESC guidelines on NSTE-ACS vs the 2017 ESC update on dual antiplatelet therapy in acute coronary syndrome[6] was mainly based on 4 randomized trials published within a 18 years' time and a large registry of patients with ACS (ARIAM-Andalucía Registry).[7]

Each of these trials have limitations but they are consistent and in addition, supported by real life data sets.[7] Of importance, the 2020 ESC guidelines on pre-treatment in NSTE-ACS are not contradictory with the recommendation to start therapy with ticagrelor at the time point of diagnosis in patients planned for noninvasive management (IB). The Platelet Inhibition and Patient Outcomes (PLATO) study did not answer the question of pretreatment since all patients were pretreated, including those who were medically managed. However, the debate continues.[8] The open-label Downstream vs Upstream Strategy for the Administration of P2Y12 Receptor Blockers (DUBIUS) trial was obviously a missing part.[9] Its primary aim was to compare pretreatment vs no pretreatment using ticagrelor, in patients with NSTE-ACS undergoing an early invasive management. Although this trial was underpowered and stopped prematurely, similar event rates were reported with or without pretreatment, for the patients having their angiogram within the first 24 hours or between 24 and 72 hours.

It is now time to change practice as elegantly demonstrated by the systematic review and meta-analysis of Dawson et al who reviewed 7 trials, published during the last 20 years, that evaluated pretreatment with oral P2Y12 inhibitors in patients with NSTE-ACS.[10] Their key message is that the strategy of systematic pretreatment with a P2Y12 inhibitor in patients with NSTE-ACS does not

confer any ischemic benefit but may be associated with harm. Combining trials with ticagrelor, prasugrel, and clopidogrel, the Australian investigators found no reduction in major adverse cardiac events, but rather a 50% increase in the risk of major bleeding events at 30 days (OR 1.51, 95% CI 1.16-1.97). The association with harm was especially driven by the findings of the Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) trial and the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT 5) trial and was consistent irrespectively of the type of P2Y12 inhibitor and vascular access used. If interventionalists are concerned about the risk of peri-intervention MI, the use of intravenous P2Y12 inhibitor is an additional option demonstrated to be effective in naïve patients (class of recommendation IIb; level of evidence A).

The 20-year-long tale of whether pretreatment should be used in NSTE-ACS is important because it reflects on the too long process of implementation of evidence-based medicine in scientific guidelines and whether interventional cardiologists are able to update their practices. The meta-analysis by Dawson et al is an important step further: pretreatment is associated with harm and does not reduce ischemic events and it is time to change.

ARTICLE INFORMATION

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