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EDITORIAL COMMENT

Non-ST-Segment Elevation Acute Coronary Syndrome

The Last Nail in the Coffin of Pre-Treatment*

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Pre-treatment with an oral $P2Y_{12}$ receptor inhibitor in addition to aspirin is defined by its administration to every patient before coronary angiography, which will (or not) confirm the diagnosis of non-ST-segment elevation acute coronary syndromes (NSTE-ACS) and indicate (or not) whether percutaneous coronary intervention (PCI) can be performed. Both confirmation of the diagnosis and PCI treatment occur in only 65% of patients carefully selected in randomized clinical trials and in even less patients represented in real-life registries. Intuitively, pre-treatment is appealing for these 65% of patients, as early administration would guarantee enough time for these oral antiplatelet agents to achieve optimal antiplatelet effect during and immediately after PCI and would thereby possibly provide better protection against PCI-related thrombotic complications. The other 35% heading to the catheterization laboratory may expect harm more than benefit, as they would be overtreated in case of misdiagnosis (aortic dissection, myopericarditis, heart failure, hypertension, gastric ulcer, pulmonary embolism, and so on) or be exposed unnecessarily to a risk of perioperative bleeding when heading to the operating room for an emergent CABG. We are looking back on 20 years of debate on the issue of pre-treatment in NSTE-ACS, and it is probably time to turn this page; however, first, let us answer the key questions for the clinicians.

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DOES PRE-TREATMENT REALLY BENEFIT NSTE-ACS PATIENTS UNDERGOING PCI?

Four randomized PCI studies have now evaluated, one way or the other, this question with all 3 $P2Y_{12}$ antagonists (clopidogrel, prasugrel, and ticagrelor) (1–5), including the study by Tarantini et al. (4) in this issue of the *Journal*. These studies have different designs, endpoints, and populations (but all include NSTE-ACS patients). None of them showed a benefit of pre-treatment over no pre-treatment. Even the CREDO (Clopidogrel for the Reduction of Events During Observation) study, in which pre-treatment was defined as the administration of clopidogrel before PCI but after coronary angiography (not real pre-treatment), did not significantly reduce ischemic events at 28 days, and only a subgroup analysis showed that patients who had received clopidogrel more than 6 h before PCI experienced a significant reduction of death, myocardial infarction, or stroke. ACCOAST (A Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST-Elevation Myocardial Infarction), the largest and only double-blind study in NSTE-ACS, was unable to show any benefit of prasugrel pre-treatment in the subgroup of patients undergoing PCI (6). This finding is very similar to the older experience with glycoprotein IIb/IIIa inhibitors (GPI), when no difference was observed between a selective use of eptifibatide after the coronary angiogram versus a systematic pre-treatment in NSTE-ACS (7). At that time, these data contradicted the previous evidence from large phase 3 studies, drug labels, practice, and guidelines. It seems that history is repeating itself, and globally, intense

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antiplatelet therapy started before the coronary angiogram does not reduce the global ischemic risk of NSTE-ACS populations.

DOES PRE-TREATMENT REALLY HARM NSTE-ACS PATIENTS NOT UNDERGOING PCI?

The answer to this question is simply yes. Double antiplatelet therapy, whatever the agent, combined with aspirin has systematically been associated with more bleeding complications in patients who are medically treated, in those undergoing CABG surgery, as well as in those pre-treated before PCI (6,8).

WHAT IS THE ISCHEMIC RISK OF WAITING WITHOUT PRE-TREATMENT?

The time from admission to coronary angiography has shortened considerably from 10 days in CURE to a few hours in the most recent trials. The risk of developing dynamic ST-segment changes or hemodynamic or arrhythmic instability during the waiting period is around 2% in clinical trials. The effect of pre-treatment on these early events has been evaluated in a blinded fashion, and pre-treatment did not prevent these events whatever the time of the coronary angiogram within the first 48 h (9). The open-label DUBIUS (Downstream Versus Upstream Strategy for the Administration of $P2Y_{12}$ Receptor Blockers) study seems to confirm with similar event rates, with or without pre-treatment, for the patients having their angiogram within the first 24 h or between 24 and 72 h (4).

WHAT DOES THE DUBIUS STUDY ADD TO THE CURRENT KNOWLEDGE?

DUBIUS was an ambitious trial in NSTE-ACS patients undergoing an invasive management, and its first aim was to compare pre-treatment versus no pre-treatment using ticagrelor, a missing piece of the pre-treatment puzzle (4). The second aim, which was to compare prasugrel with ticagrelor after PCI in non-pre-treated patients, limits this comparison to the 70% of patients undergoing PCI in one-half of the enrolled population (~500 patients). The study has other limitations: early interruption for futility after 5 years of recruitment, open-label design, unusually low event rates compared with other contemporary trials, one-third of the size of ACCOAST (A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non–ST Segment-Elevation Myocardial Infarction) or ISAR-REACT-5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5), short follow-up, and finally, a serious lack of power for every analysis. Nevertheless, it confirms that the diagnosis of NSTE-ACS is difficult, with 1 in 10 patients having the diagnosis refuted after the angiogram, while one in three patients did not undergo PCI but rather CABG or medical treatment. All of these patients were illegitimately exposed to the iatrogenic bleeding risk of pre-treatment. For those with confirmed NSTE-ACS and a PCI performed, no hint of a benefit, even numerically speaking, was observed with ticagrelor pre-treatment.

ARE REAL-LIFE DATA DIFFERENT?

The results from the randomized studies were largely confirmed by several meta-analyses and registries from different countries. The absence of ischemic benefit associated with an excess of bleeding complications were consistently found with different $P2Y_{12}$ inhibitors including ticagrelor, for example, in the large Swedish Coronary Angiography and Angioplasty Registry and the Spanish Ariam-Andalucia Registry (10,11). The current utilization of upstream dual-antiplatelet therapy varies enormously from country to country, with this practice being dominant, up to 92%, in Sweden, for example (10). However, practice is now changing fast with the accumulation of consistent information and the changeover of the European guidelines.

WHAT DO THE GUIDELINES SAY?

The guidelines from the American College of Cardiology and American Heart Association have been very cautious through the years, without recommending or mentioning pre-treatment for NSTE-ACS patients. By contrast, the European Society of Cardiology has always recommended pre-treatment in all of the different sets of guidelines dealing with NSTE-ACS and in all the updates, also after 2013, which validated a Class III indication for the sole use of prasugrel on the basis of the ACCOAST study. These guidelines were probably dazzled by the extremely positive results of the PLATO (Platelet Inhibition and Patient Outcomes) study, which, however, did not answer the question of pre-treatment since all patients were pre-treated (and sometimes twice by clopidogrel and ticagrelor). Wisdom has reached the ESC guidelines in 2020 (12) with a new recommendation stating that “It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned” (Class III, Level of Evidence: A), a totally identical recommendation to that for GPI (10).

WHAT SHALL WE DO?

A patient admitted with a working diagnosis of NSTE-ACS should receive aspirin and anticoagulation (unless the diagnosis is very uncertain) and be scheduled for a coronary angiography, if possible on the next day or next Monday (if on a weekend). If not possible (lack of facilities or transfer needed), catheterization should be performed within 48 to 72 h. If not possible or if a conservative strategy is decided, this would typically correspond to a "CURE-study-situation," and ticagrelor or clopidogrel should be initiated unless contraindicated. We will educate our fellows to understand that a proactive strategy with systematic pre-treatment is harmful in NSTE-ACS (it is a different story in ST-segment elevation myocardial infarction). In the catheterization laboratory, after the coronary angiogram, a loading dose of a $P2Y_{12}$ inhibitor, preferably crushed prasugrel or orodispersible ticagrelor, should be administered as soon as ad hoc PCI is decided. As shown in an important ISAR-REACT-5 substudy, also published in this issue of the *Journal*, the superior efficacy of prasugrel over ticagrelor relates to different levels of platelet inhibition reached with the loading doses of the 2 drugs (13). The higher potency of the prasugrel loading dose (vs. ticagrelor loading dose) has been known for years and has even led to the use of half loading doses of prasugrel (30 mg) in large trials, for safety reasons (6,14). The improved efficacy is less a question of drug than a question of dose in a given patient with a given level of platelet reactivity (13). In case of high-risk PCI (usually associated with high platelet reactivity), intravenous cangrelor or GPI may also be used for an immediate and more potent antiplatelet effect.

Thus, the time has come for a definite change in recommendations and practice about pre-treatment in NSTE-ACS. There is nothing dubious about it, pre-treatment is not effective and potentially harmful, and this is a class effect. We shall be better safe than sorry with our patients.

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REFERENCES

1. Steinhubl SR, Berger PB, Mann JT, et al. for the CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial [published correction in JAMA 2003;289:987]. JAMA 2002;288:2411–20.

2. Widimsky P, Motovska Z, Simek S, et al. Clopidogrel pre-treatment in stable angina: for all patients > 6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8. Eur Heart J 2008;29:1495–503.

3. Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med 2013;369:999–1010.

4. Tarantini G, Mojoli M, Varbella F, et al. Timing of oral P2Y12 inhibitor administration in patients with non-ST-segment elevation acute coronary syndrome. J Am Coll Cardiol 2020;76:2450–9.

5. Valina C, Neumann F-J, Menichelli M, et al. Ticagrelor or prasugrel in patients with non-ST-segment elevation acute coronary syndromes. J Am Coll Cardiol 2020;76:2436–46.

6. Montalescot G, Collet JP, Ecollan P, et al. Effect of prasugrel pre-treatment strategy in patients undergoing percutaneous coronary intervention for NSTEMI: the ACCOAST-PCI study. J Am Coll Cardiol 2014;64:2563–71.

7. Giugliano RP, White JA, Bode C, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. N Engl J Med 2009;360:2176–90.

8. Dudek D, Dziewierz A, Widimsky P, et al. Impact of prasugrel pretreatment and timing of coronary artery bypass grafting on clinical outcomes of patients with non-ST-segment elevation myocardial infarction: from the A Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST-Elevation Myocardial Infarction (ACCOAST) study. Am Heart J 2015;170:1025–32.

9. Silvain J, Rakowski T, Lattuca, et al. Interval from initiation of prasugrel to coronary angiography in patients with non-ST-segment elevation myocardial infarction. J Am Coll Cardiol 2019;73:906–14.

10. Dworeck C, Redfors B, Angerås O, et al. Association of pretreatment with P2Y12 receptor antagonists preceding percutaneous coronary intervention in non-ST-segment elevation acute coronary syndromes with outcomes. JAMA Netw Open 2020;3:e2018735.

11. Almendro-Delia M, Gonzalez-Torres L, Garcia-Alcantara A, et al. Prognostic impact of clopidogrel pretreatment in patients with acute coronary syndrome managed invasively. Am J Cardiol 2015;115:1019–26.

12. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2020 Aug 29 [E-pub ahead of print].

13. Mayer K, Bongiovanni D, Karschin V, et al. Ticagrelor or prasugrel for platelet inhibition in acute coronary syndrome patients: the ISAR-REACT 5 pharmacodynamic substudy. J Am Coll Cardiol 2020;76:2569–71.

14. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012;367:1297–309.

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