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VIEWPOINT
Thrombosis and antithrombotic treatment

Oral $P2Y_{12}$ inhibitor pre-treatment for percutaneous coronary intervention in non–ST-elevation acute coronary syndromes: evolving notions in ESC guidelines

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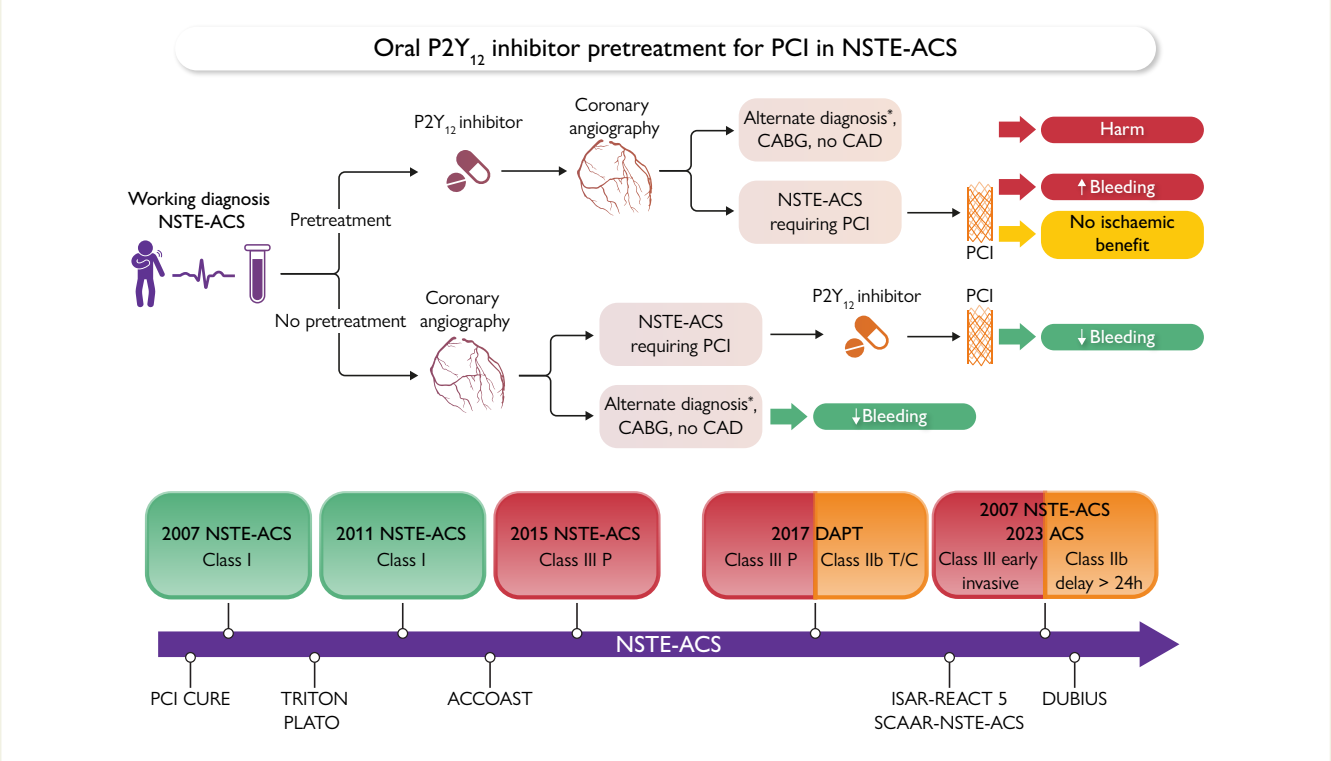
Graphical Abstract



Oral $P2Y_{12}$ inhibitor pre-treatment in non–ST-elevation acute coronary syndromes (NSTE-ACS). The upper portion summarizes the pre-treatment vs. no pre-treatment pathways. The classes of recommendation in the European Society of Cardiology guidelines as well as the acronyms of the main contributing studies are reported in the lower panel. *May include, among other, aortic dissection, pulmonary embolism, myopericarditis, and gastric ulcer. ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; NSTEMI, non–ST-elevation myocardial infarction; P, prasugrel; PCI, percutaneous coronary intervention; T, ticagrelor; C, clopidogrel.

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Oral $P2Y_{12}$ receptor inhibitor pre-treatment (simplified as 'pre-treatment' in the text) defines the systematic drug administration prior to coronary angiography, as opposed to a more selective one at the time of percutaneous coronary intervention (PCI). In the setting of suspected non–ST-elevation acute coronary syndromes (NSTE-ACS), the purpose of pre-treatment is to prevent (recurrent) myocardial infarction (MI) prior to coronary angiography as well as PCI complications. Risks of pre-treatment include peri-procedural bleeding, related or not to vascular access as well as increased bleeding and treatment delay in case of emergent/urgent coronary artery bypass surgery. In addition, pre-treatment may be deleterious in case of misdiagnosis (e.g. aortic dissection, pulmonary embolism, myopericarditis, and gastric ulcer).

Data on oral $P2Y_{12}$ inhibitor pre-treatment in non–ST-elevation acute coronary syndromes

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study randomized, between 1999 and 2000, 12 562 NSTE-ACS patients to clopidogrel for 3–12 months or placebo on top of aspirin and established the benefit of dual antiplatelet therapy (DAPT) in the medical management of NSTE-ACS.[1] Among the 2658 patients who underwent PCI, those allocated to clopidogrel derived a significant benefit in terms of cardiovascular (CV) death, MI, or urgent target vessel revascularization at 30 days [risk ratio 0.70; 95% confidence interval (CI) 0.50–0.97; $P = .03$; PCI-CURE].[2] However, those results can hardly be interpreted in favour of $P2Y_{12}$ pre-treatment in current practice because coronary angiography and revascularization were strongly discouraged in the trial, revascularization occurred after a median of 10 days from randomization, and clopidogrel is no more the drug of choice in ACS.

The Platelet Inhibition and Patient Outcomes (PLATO) study, which showed the superiority of ticagrelor as compared with clopidogrel on top of aspirin in over 18 000 ACS patients, is frequently mentioned to justify pre-treatment.[3] However, as all the patients received a $P2Y_{12}$ inhibitor at the time of diagnosis, no conclusion can be drawn on the efficacy or safety of the pre-treatment. In addition, the Kaplan–Meier curves depicting ischaemic events in NSTE-ACS patients undergoing revascularization allocated to ticagrelor or clopidogrel remained superimposed during the first 60 days, suggesting the lack of benefit of pre-treatment with a potent $P2Y_{12}$ inhibitor as compared with a weaker one.

The Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pre-treatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) study is the only large-scale randomized trial which addressed the value of pre-treatment in NSTE-ACS.[4] A total of 4033 patients with NSTEMI scheduled for an early invasive strategy were randomized to prasugrel 30 mg at the time of diagnosis or placebo. Patients undergoing PCI (69% of the population) received additional 30 mg of the drug at the time of the procedure if they were in the pre-treatment group, while the corresponding dose for the placebo arm was 60 mg. While the calculated sample size was 4100 patients, the trial was prematurely stopped because of safety concerns. The primary endpoint of CV death, MI, stroke, urgent revascularization, and glycoprotein IIb/IIIa receptor inhibitor bailout at 7 days was no different between groups [hazard ratio (HR) 1.0], while prasugrel pre-treatment was associated with a significant increase in major bleeding, both in the total population and in the PCI subgroup (HR 2.7 in the latter). While the time window between prasugrel pre-treatment and coronary angiography was short (< 4.5 h), the excess of bleeding and the lack of ischaemic benefit were consistent across the quartiles of pre-treatment duration.[5] While 57% of the PCI patients were treated by femoral access, the safety hazard of pre-treatment was comparable in the transradial group. Those findings were confirmed in a subsequent meta-analysis.[6]

The early indefectible confidence in pre-treatment is documented in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), in which over 90% of the almost 65 000 NSTE-ACS patients undergoing PCI between 2010 and 2018 were pre-treated.[7] In an adjusted analysis, pre-treatment was not associated with improved survival at 30 days [odds ratio (OR) 1.17; 95% CI 0.66–2.11; $P = .58$] or at 1 year (OR 1.34; 95% CI 0.77–2.34; $P = .30$) or decreased stent thrombosis rates (OR 0.81; 95% CI 0.42–1.55; $P = .52$), while it was associated with increased risk of in-hospital bleeding (OR 1.49; 95% CI 1.06–2.12; $P = .02$). Propensity score matching confirmed the findings.

The Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial randomized ACS patients undergoing PCI to a ticagrelor-based or a prasugrel-based strategy.[8] Patients allocated to the ticagrelor arm were all pre-treated, while in the prasugrel arm, STEMI patients were pre-treated and NSTE-ACS patients received prasugrel at the time of PCI. In the NSTE-ACS population ($n = 2365$), a strategy based on ticagrelor pre-treatment was associated with a significant increase in the primary endpoint of death, MI, or stroke at 1 year (HR 1.41, 95% CI 1.04–1.90) as compared with a strategy based on prasugrel administration at the time of PCI, with no difference in bleeding.[9] Although the delay of administration between ticagrelor and prasugrel was <1 h, the significant increase in ischaemic events associated with ticagrelor pre-treatment makes it unlikely that a longer time window would have changed the outcomes. In the Downstream Versus Upstream Strategy for the Administration of $P2Y_{12}$ Receptor Blockers In Non-ST Elevated Acute Coronary Syndromes With Initial Invasive Indication (DUBIUS) trial, NSTE-ACS patients scheduled for PCI were randomized to ticagrelor at the time of diagnosis vs. at the time of PCI.[10] The study was terminated after enrolment of 57% of the 2520 patients planned because of lower than predicted event rates and futility. The rate of the primary endpoint, a composite of CV death, MI, and stroke, and Bleeding Academic Research Consortium (BARC) type 3–5 bleeding at 30 days did not differ between the groups. Acknowledging that the study was underpowered, no signal in favour of pre-treatment was detected.

Recommendation for oral $P2Y_{12}$ inhibitor pre-treatment in non–ST-elevation acute coronary syndrome in the ESC guidelines: from Class I to a Class III

The 2007 and 2011 NSTE-ACS guidelines, solely based on the CURE/PCI-CURE data, recommended (Class I) an immediate administration of clopidogrel at the time of diagnosis for all patients. Following the ACCOAST trial, the safety and efficacy of pre-treatment in NSTE-ACS became source of heated debates.[11,12] The 2015 NSTE-ACS guidelines

stated that 'as the optimal timing of ticagrelor or clopidogrel administration in NSTE-ACS patients scheduled for an invasive strategy has not been adequately investigated, no recommendation for or against pre-treatment with these agents can be formulated. Based on ACCOAST results pre-treatment with prasugrel is not recommended' (Class III).[13] The 2017 DAPT-focused update gave a Class IIa recommendation for ticagrelor (or clopidogrel if ticagrelor was not an option) pre-treatment while maintaining the Class III recommendation for prasugrel.[14] However, the level of evidence for the recommendation for ticagrelor and clopidogrel was C, i.e. based solely on an expert consensus. The divergence in the recommendations may seem awkward. According to the DAPT-focused update task force, the adverse effects observed in ACCOAST with prasugrel could not be applied 1:1 to ticagrelor (no class effect), and the administration of ticagrelor at the time of PCI could not be recommended, as the drug was not administered that way in PLATO. The 2020 NSTE-ACS guidelines extended the Class III recommendation against pre-treatment to all $P2Y_{12}$ inhibitors.[15] This was based on the assumption of a class effect for all $P2Y_{12}$ inhibitors regarding the ACCOAST findings, on the SCAAR pre-treatment analysis as well as on the ISAR-REACT 5 results. However, the guidelines opened the door for ticagrelor (or clopidogrel) pre-treatment on a case-by-case decision in patients expected to undergo invasive strategy beyond 24 h who were not at high bleeding risk (recommendation Class IIb), while acknowledging the lack of data for that recommendation (level of evidence C). In the 2023 ACS guidelines, the recommendations on $P2Y_{12}$ inhibitor pre-treatment remained unchanged, comforted by the lack of benefit of ticagrelor pre-treatment observed in DUBIUS.[16]

Conclusions

Despite limited data, $P2Y_{12}$ inhibitor pre-treatment in NSTE-ACS patients undergoing PCI has been enthusiastically embraced by the community and since 2007 was backed by ESC guidelines. This affected the design of the PLATO trial, which mandated $P2Y_{12}$ inhibitor administration (ticagrelor vs. clopidogrel) at the time of ACS diagnosis and *de facto* pre-treatment for all patients undergoing PCI. Despite the harm associated with prasugrel pre-treatment in ACCOAST, pre-treatment with ticagrelor or clopidogrel in NSTE-ACS continued to be widely practiced, and it took almost 15 years for the ESC guidelines to reverse an undue Class I recommendation. From 2020 on, ESC guidelines took position against routine $P2Y_{12}$ inhibitor pre-treatment for NSTE-ACS patients undergoing early invasive strategy, position that we fully embrace, while leaving the door open for pre-treatment on a case-by-case basis if coronary angiography is delayed (*Graphical Abstract*). While an adequately powered randomized trial comparing pre-treatment vs. no pre-treatment with ticagrelor in a broad spectrum of delays to coronary angiography—now allowed according the ESC guidelines—is warranted, it is unlikely that this will happen following the premature termination of DUBIUS.

In memoriam

Professor Jean-Philippe Collet left us way too early. He was a great person and friend as well as a remarkable clinician, scientist, and teacher. Among his many scientific interests, $P2Y_{12}$ inhibitor pre-treatment in acute coronary syndromes was very close to his heart. He has been instrumental in the ACCOAST trial and chaired the 2020 ESC NSTE-ACS guidelines.

Declarations

Disclosure of Interest

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