



## PERSPECTIVES IN CARDIOLOGY

# Do we need P2Y<sub>12</sub> inhibitor pretreatment in non-ST elevation acute coronary syndrome?



## Precisamos do inibidor da P2Y<sub>12</sub> como precarga na síndrome coronária aguda sem elevação do segmento ST?

Raffaele De Caterina<sup>a,b,\*</sup>, Alessia Delli Veneri<sup>c</sup>

<sup>a</sup> "G. d'Annunzio" University, Chieti-Pescara, Italy

<sup>b</sup> Fondazione "G. Monasterio", Pisa, Italy

<sup>c</sup> "La Sapienza" University, Rome, Italy

The early initiation of treatment with P2Y<sub>12</sub> inhibitors – in addition to aspirin – soon after the diagnosis of a non-ST elevation acute coronary syndrome (NSTEMI-ACS), irrespective of the management strategy, has been recommended in the past.<sup>1,2</sup> This recommendation, endorsed by the 2011 version of the European Society of Cardiology (ESC) guidelines,<sup>2</sup> was based on pathophysiological considerations and on limited clinical evidence.

From a pathophysiological standpoint, since non-occlusive mural thrombosis superimposed on a ruptured or eroded coronary plaque, with an important platelet component, is considered to be the underpinning precipitating cause in the majority of NSTEMI-ACS cases,<sup>3,4</sup> it makes sense to start dual antiplatelet treatment as early as possible, to prevent or limit irreversible cardiac damage due to bouts of intermittent ischemia occurring over time in the setting of NSTEMI-ACS. In addition, extensive experience of the acute risk of percutaneous coronary interventions (PCI), including the risk of acute stent thrombosis, supports the idea that intraprocedural levels of platelet inhibition are directly related to outcomes.<sup>2</sup>

One important caveat to this reasoning is that any decision to proceed to coronary artery bypass graft surgery (CABG) could expose pretreated patients to the risk of excessive bleeding. From a clinical standpoint, however, early experience with clopidogrel in the CURE trial<sup>5</sup> also supported the concept of pretreatment. In CURE, of the 12 562 patients recruited, 2072 underwent CABG, with a median time from randomization to CABG of 25.5 days.<sup>6</sup> The time to CABG for those undergoing the procedure during the initial hospitalization was 12 days. The primary outcome still occurred less in clopidogrel-treated (14.5%) than in placebo-treated (16.4%) patients undergoing CABG. For those undergoing surgical revascularization during hospitalization, 16.4% of placebo-treated and 13.4% of clopidogrel-treated patients experienced cardiovascular death, myocardial infarction (MI), or stroke,<sup>6</sup> findings consistent with the treatment effect observed in the entire trial.<sup>5</sup> Among patients undergoing CABG, benefits were observed mainly before the procedure. Therefore, allocation to CABG treatment, only possible after knowledge of coronary anatomy, did not nullify the benefit of clopidogrel pretreatment.

In PCI-CURE,<sup>7</sup> 2658 patients with NSTEMI-ACS undergoing PCI in the CURE study had been randomly assigned double-blind treatment with clopidogrel (n=1313) or placebo

\* Corresponding author.

E-mail address: [rdecater@unich.it](mailto:rdecater@unich.it) (R. De Caterina).

(n=1345). Patients were pretreated with aspirin and the study drug for a median of six days before PCI during the initial hospital admission, and for a median of 10 days overall. Fifty-nine (4.5%) patients in the clopidogrel group had the primary endpoint of death, MI and stroke, compared with 86 (6.4%) in the placebo group (relative risk 0.70 [95% CI 0.50-0.97],  $p=0.03$ ), further indicating the benefit associated with clopidogrel pretreatment, although the study design could not discriminate between the effect of adding clopidogrel vs. the effect of clopidogrel pretreatment vs. no pretreatment.

The CREDO trial<sup>8</sup> also corroborated the benefit of pretreatment. In CREDO, 2116 patients undergoing elective PCI were randomly allocated to clopidogrel loading (300 mg) or placebo 3-24 hours before PCI, then all received clopidogrel 75 mg/day through day 28. Clopidogrel pretreatment did not significantly reduce the combined risk of death, MI, or urgent target vessel revascularization at 28 days. However, in a prespecified subgroup analysis, patients who received clopidogrel at least six hours before PCI experienced a relative risk reduction of 38.6% for this endpoint compared with no reduction with treatment less than six hours before PCI, with a non-significant increase in the risk of major bleeding. Although performed in elective PCI, these data support the view that some intraprocedural inhibition of the P2Y<sub>12</sub> receptor is opportune, in addition to aspirin.

Supporting evidence for pretreatment with a P2Y<sub>12</sub> inhibitor also comes from experience with the intravenous P2Y<sub>12</sub> inhibitor cangrelor in the setting of the CHAMPION PHOENIX trial, in 11 145 patients who were undergoing either urgent or elective PCI.<sup>9</sup> These patients were randomly allocated to receive a bolus and infusion of cangrelor or to receive a loading dose of 600 mg or 300 mg of clopidogrel, the latter associated with considerably delayed effective P2Y<sub>12</sub> inhibition. Cangrelor significantly reduced the rate of ischemic events, including stent thrombosis,<sup>9</sup> during PCI, with no significant increase in severe bleeding. All these data indicate that pretreatment, defined as administration of P2Y<sub>12</sub> inhibitors as early as possible in patients scheduled for an invasive approach, both in an elective setting and for ACS, is associated with a net clinical benefit compared with no pretreatment.

Subsequent to this body of evidence, the results of the only ad-hoc randomized controlled trial on P2Y<sub>12</sub> inhibitor pretreatment in NSTEMI-ACS, the ACCOAST trial, were published.<sup>10</sup> ACCOAST compared pretreatment with prasugrel 30 mg and a further 30 mg dose prior to PCI with a regimen of prasugrel 60 mg after diagnostic angiography but prior to PCI among 4033 patients with NSTEMI scheduled for an early invasive strategy. The median duration of pretreatment was 4.3 hours. Sixty-nine per cent of the patients underwent PCI, 6% required surgical revascularization and the remainder were treated conservatively. At seven days, patients randomized to the pretreatment arm experienced no reduction in the primary endpoint (cardiovascular death, recurrent MI, stroke, urgent revascularization and bailout use of glycoprotein IIb/IIIa inhibitors) (hazard ratio 1.02 [95% CI 0.84-1.25],  $p=0.81$ ), and no benefits emerged at 30 days. TIMI major bleeds were significantly increased in the pretreatment group at seven days (pretreatment 2.6% vs. no pretreatment 1.4%; HR 1.90 [95% CI 1.19, 3.02],  $p=0.006$ ). It has therefore been argued that pretreatment with any

P2Y<sub>12</sub> inhibitor is harmful (because of excess bleeding) and is not associated with any benefit in efficacy endpoints.<sup>11</sup> The latest ESC guidelines on NSTEMI-ACS<sup>12</sup> do not recommend pretreatment with prasugrel, based on ACCOAST,<sup>11</sup> and for the other two available oral P2Y<sub>12</sub> inhibitors, clopidogrel and ticagrelor, advocate the cautionary position of no recommendation: "As the optimal timing of ticagrelor or clopidogrel administration in NSTEMI-ACS patients scheduled for an invasive strategy has not been adequately investigated, no recommendation for or against pretreatment with these agents can be formulated. Based on the ACCOAST results, pretreatment with prasugrel is not recommended. In NSTEMI-ACS patients planned for conservative management, P2Y<sub>12</sub> inhibition (preferably with ticagrelor) is recommended, in the absence of contraindications, as soon as the diagnosis is confirmed."<sup>12</sup>

Although we recognize the lack of a specific ad-hoc trial with clopidogrel or ticagrelor, we consider that the weight of evidence for clopidogrel or ticagrelor still favors pretreatment.

Concerns about the safety of any pretreatment are mostly based on the risk of bleeding with pretreatment in association with CABG. However in ACCOAST, the key safety endpoint of CABG- or non-CABG-related TIMI major bleeding showed an excess of 25 bleeding events in the pretreatment group, with a number needed to harm of around 83.<sup>13</sup> A pretreatment strategy based on either clopidogrel or ticagrelor, with less intense or more reversible antiplatelet effects, respectively, might have dramatically reduced the bleeding hazard of pretreatment in the surgical cohort. This category of patients is now rarely treated urgently with CABG without the possibility of some degree of reversal of platelet inhibition through partial discontinuation of antiplatelet treatment. The now preferentially used radial approach, associated with less periprocedural bleeding in PCI, might also have reduced the bleeding risk in the non-surgical cohort.

As to the lack of efficacy of pretreatment with prasugrel in ACCOAST, this may well have resulted from the small differences in time of P2Y<sub>12</sub> exposure in the two treatment arms. The median pretreatment time was 4.3 hours, possibly too short an interval to allow detection of a difference in outcomes. Considering that NSTEMI-ACS patients sometimes wait 24-48 hours or more before diagnostic angiography, applying the results of ACCOAST to longer preprocedural times appears unwarranted. Differences in the definition of MI in ACCOAST compared with other trials may also account for the apparent (and quite surprising) numerically higher rates of MI in the pretreatment vs. no pretreatment arms of the trial.<sup>13</sup> Significant pharmacokinetic and pharmacodynamic differences between the various P2Y<sub>12</sub> inhibitors may also mean that labeling all their clinical effects as "class effects" is unwarranted.<sup>13</sup> Finally, the non-harmful and overall favorable results with ticagrelor pretreatment in STEMI in the setting of the ATLANTIC trial, in which ticagrelor pretreatment, with only a 31-minute difference between the pretreatment and no-pretreatment arms of the study, was associated with a significantly lower rate of stent thrombosis (0% vs. 0.8% in the first 24 hours; 0.2% vs. 1.2% at 30 days),<sup>14</sup> also continues to support – in our opinion – the view that clopidogrel or ticagrelor pretreatment is also a wiser option compared with no pretreatment in the setting

of NSTEMI-ACS, especially when PCI is performed with a delay of hours and sometimes days after the clinical presentation.

In conclusion, on the basis of the ACCOAST study,<sup>10</sup> unlike clopidogrel and ticagrelor, prasugrel should be now confined to patients undergoing PCI, and this therapy should be implemented only immediately before PCI. For the time being, the lack of ischemic benefit noted with prasugrel pretreatment should not undermine the better-established value of early dual platelet inhibition in general in ACS patients or the value of other P2Y<sub>12</sub> inhibitors in this setting. More studies in contemporary practice scenarios would however certainly be welcome.

## Conflicts of interest

The authors have no conflicts of interest to declare.

## References

1. Bellemain-Appaix A, Brieger D, Beygui F, et al. New P2Y<sub>12</sub> inhibitors versus clopidogrel in percutaneous coronary intervention: a meta-analysis. *J Am Coll Cardiol.* 2010;56:1542–51.
2. Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:2999–3054.
3. Badimon L, Padro T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. *Eur Heart J Acute Cardiovasc Care.* 2012;1:60–74.
4. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med.* 2013;368:2004–13.
5. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001;345:494–502.
6. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable Angina to prevent Recurrent Ischemic Events (CURE) Trial. *Circulation.* 2004;110:1202–8.
7. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet.* 2001;358:527–33.
8. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA.* 2002;288:2411–20.
9. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med.* 2013;368:1303–13.
10. 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.
11. Collet JP, Silvain J, Bellemain-Appaix A, et al. Pretreatment with P2Y<sub>12</sub> inhibitors in non-ST-segment-elevation acute coronary syndrome: an outdated and harmful strategy. *Circulation.* 2014;130:1904–14 [discussion 1914].
12. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2016;37:267–315.
13. Valgimigli M. Pretreatment with P2Y<sub>12</sub> inhibitors in non-ST-segment-elevation acute coronary syndrome is clinically justified. *Circulation.* 2014;130:1891–903 [discussion 1903].
14. Montalescot G, van't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med.* 2014;371:1016–27.