JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 24, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.09.064

EDITORIAL COMMENT

Prasugrel in NSTEMI

Loading After Seeing*

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An early invasive strategy has become the standard of care for patients with non-ST-segment elevation myocardial infarction (NSTEMI) (1,2). Atherosclerotic plaque disruption/erosion with superimposed thrombus is the underlying etiology of most cases of NSTEMI. Consequently, many patients with NSTEMI undergo percutaneous coronary intervention (PCI) and are treated with coronary stenting during the index catheterization procedure. Approximately one-third of patients are typically triaged after diagnostic angiography to cardiac procedure or treated medically. Besides early catheterization, anticoagulant/antiplatelet therapies represent the cornerstone of pharmacological strategy for NSTEMI. The role of dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor) has been shown to be critical not only as immediate treatment of the NSTEMI episode but also as maintenance therapy to prevent stent thrombosis and major adverse cardiovascular events in the long term.

Thus, it is rather remarkable that the best timing for the initiation of $P2Y_{12}$ inhibitors in patients with NSTEMI has not been clearly established. Clinical guidelines (the 2012 American College of Cardiology Foundation/American Heart Association Focused Update and 2011 European Society of Cardiology guidelines) recommend the initiation of $P2Y_{12}$ inhibitors "on presentation; as soon as possible" (i.e., before catheterization) (1,2) on the basis of clinical evidence showing that "on admission" initiation of $P2Y_{12}$ inhibitors with clopidogrel was superior to no administration of $P2Y_{12}$ inhibitors (3,4). This appeared to be a reasonable expert consensus given the delayed onset of peak antiplatelet activity with the loading dose of clopidogrel. Until the publication of the ACCOAST (A Comparison of prasugrel at the time of percutaneous Coronary intervention Or as pre-treatment At the time of diagnosis in patients with non–ST-segment elevation myocardial infarction) trial (5), no study had ever compared different timings of $P2Y_{12}$ initiation in patients with NSTEMI, making it a landmark trial. The ACCOAST trial randomized 4,033 patients with NSTEMI to pre-treatment with prasugrel (a loading dose of prasugrel 2 to 48 h before catheterization) or no pre-treatment with prasugrel (a loading dose of prasugrel after initial angiography). The primary endpoint (composite of cardiovascular death, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor bailout through day 7) was not different between groups. This result implied that a similar clinical effect with a fast-acting agent (onset within 30 min) can be achieved even if it is given after definition of the coronary anatomy when planning for PCI, thus avoiding unnecessary treatment with this agent for patients suitable for cardiac surgery procedure or medical therapy alone. The rate of bleeding events (both coronary artery bypass graft [CABG] related and non-CABG related) at 7 and 30 days was significantly higher in the prasugrel pre-treatment group than in the no prasugrel pre-treatment group.

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In this issue of the *Journal*, Montalescot et al. (6) present the results of analysis of the large subset (69%) of subjects in the ACCOAST trial who

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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underwent PCI. Concordant to the main study population, the incidence of the primary (ischemia-related) endpoint was identical (13.1%) between groups. Also, as in the overall population, the rate of all bleeding events was significantly higher in the prasugrel pre-treatment group than in the no prasugrel pre-treatment group.

Performing subgroup analyses of patients undergoing PCI in large NSTEMI trial populations has limitations. First, the PCI population was not randomized; thus, any potential unknown confounders may affect the results. Second, the composition of this subgroup is most probably affected by the study intervention. Finally, the PCI subgroup is not a clinically definable cohort (defined after angiography, and thus pre-PCI treatment is impossible to define). Despite these limitations, the analysis of a subpopulation undergoing PCI is of great value because it represents the best case scenario favoring the study drug/intervention in the mode of pre-treatment. Pre-treatment with prasugrel was supposed to result in higher platelet inhibition at the time of PCI and thus was supposed to reduce ischemic complications upon intervention. Against this reasonable assumption was the ability of prasugrel itself to quickly amass platelet inhibition even after coronary angiography. In other words, would pre-treatment with prasugrel (a few hours before the procedure) prevail over its own virtue of fast-acting, high-intensity antiplatelet action after coronary angiography? The current study of patients who had PCI definitively shows that pre-treatment with prasugrel is not needed in patients with NSTEMI.

Of more concern is the significant increase in bleeding events in the prasugrel pre-treatment group, although the incidence of major bleeding was low (1.4% and 0.5% in the pre-treatment and no pre-treatment groups, respectively). Almost 40% of all major bleeding events in the prasugrel pre-treatment group occurred at the vascular access site, which is why it is remarkable that 43% of patients underwent radial access. Of the 19 major bleeding events in the prasugrel pre-treatment group, only 4 occurred in patients undergoing radial access, similar to what was observed in the no prasugrel pre-treatment group (of all 7 major bleeding events, only one occurred in a patient undergoing radial access). These data support the superiority of choosing this arterial site in preventing bleeding complications at the access site (7). The higher bleeding rates in the prasugrel pre-treatment group are not completely understood. It could be hypothesized that pre-treatment with prasugrel results in higher platelet inhibition at the time of vascular access and that this translates into an increased incidence of acute bleeding events. However, there is an unexplained increase in bleeding events in the prasugrel pre-treatment group at 30 days. Of note, between day 7 and day 30, there were 5 new major bleeding events in the prasugrel pre-treatment group compared with 2 new major bleeding events in no prasugrel pre-treatment group. Given the rapid onset of the antiplatelet effect of prasugrel, any excess bleeding a few hours after PCI is unexpected. Finally, higher rates of bleeding complications (mostly at the arterial access site) also were observed in other studies of pre-treatment with intense antiplatelet agents (8,9) as compared with selective administration immediately before PCI.

How do these results apply to the wider spectrum of acute coronary syndromes and to other clinically recommended $P2Y_{12}$ inhibitors? The results of the ATLANTIC (A 30 Day Study to Evaluate Efficacy and Safety of Pre-hospital vs. In-hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for Percutaneous Coronary Intervention [PCI]) trial of ticagrelor were very recently reported (10). This agent is also able to produce a more potent and faster-onset platelet $P2Y_{12}$ inhibition than clopidogrel. More than 1,800 patients with ST-segment elevation myocardial infarction were randomized to receive ticagrelor during ambulance transfer or at the time of PCI. Pre-treatment with ticagrelor was not associated with better surrogates of perfusion (ST-segment resolution/Thrombolysis In Myocardial Infarction [TIMI] flow) and, importantly, was not associated with any excess bleeding. Interestingly, the rate of acute stent thrombosis was numerically lower in the ticagrelor pre-treatment group, leaving room for further explorations regarding the role of pre-treatment with ticagrelor in patients with ST-segment elevation myocardial infarction.

The extrapolation of the results of the ACCOAST-PCI study to all $P2Y_{12}$ inhibitors in the context of NSTEMI requires caution. The peak of antiplatelet action of different $P2Y_{12}$ inhibitors is a critical aspect; new potent $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) have a rapid antiplatelet effect. Conversely, clopidogrel has a less rapid onset of action, and (the lower) peak of antiplatelet activity is reached 4 to 6 h after administration of the loading dose. In this regard, indirect analyses from the CREDO (Clopidogrel for the Reduction of Events During Observation) trial (11) suggested that the initiation of treatment with clopidogrel several hours before PCI resulted in a reduction of clinical events. These data show that the pre-treatment strategy depends on the $P2Y_{12}$ inhibitor used. If this is clopidogrel, it seems reasonable to adopt a pre-treatment strategy hours before

angiography; if potent, fast-acting $P2Y_{12}$ inhibition with prasugrel is chosen, a no pre-treatment strategy seems to be a better option. The latter strategy has the benefit of identifying candidates for CABG who would not be treated with $P2Y_{12}$ inhibitors and could therefore undergo surgery without delay. It also eliminates unnecessary treatment of patients directed to any type of surgery or medical therapy alone, thus affording fewer adverse effects for such patients.

What are the clinical implications of the ACCOAST trial? The recent 2014 American Heart Association/American College of Cardiology guidelines on NSTEMI (12) have been reinforced by the data from the ACCOAST trial. In these new guidelines, prasugrel is not recommended for pre-treatment in patients with NSTEMI, mostly on the basis of the ACCOAST trial. The new guidelines recommend either clopidogrel or ticagrelor in addition to aspirin (class I indication), with no description of timing of initiation. In patients who undergo an early invasive strategy, ticagrelor is the preferred option (Class IIa indication). The European Society of Cardiology guidelines recommend ticagrelor as the pre-treatment $P2Y_{12}$ or clopidogrel in patients who cannot be treated with ticagrelor. Similar to the American Heart Association/American College of Cardiology guidelines, prasugrel is recommended only after angiography (2). Given that prasugrel is not recommended as pre-treatment in both the American and European NSTEMI guidelines, these trial results are not expected to change clinical practice but confirm the robust evidence that is required to reinforce society-driven clinical practice guidelines.

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REFERENCES

1. Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e179–347.

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. 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.

4. 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.

5. 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.

6. Montalescot G, Collet J-P, 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. Rao SV, Turi ZG, Wong SC, Brener SJ, Stone GW. Radial versus femoral access. J Am Coll Cardiol 2013;62:S11–20.

8. Stone GW, Bertrand ME, Moses JW, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: The ACUITY Timing trial. JAMA 2007;297:591–602.

9. 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.

10. Montalescot G, Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014;371:1016–27.

11. Steinhubl SR, Berger PB, Brennan DM, Topol EJ. Optimal timing for the initiation of pretreatment with 300 mg clopidogrel before percutaneous coronary intervention. J Am Coll Cardiol 2006;47:939–43.

12. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139–228.

KEY WORDS acute coronary syndrome(s), antiplatelet therapy, percutaneous coronary intervention, prasugrel