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Letters

TO THE EDITOR

Pre-Hospital Ticagrelor in ST-Segment Elevation Myocardial Infarction

Should the Hypothesis Be Re-Evaluated?

We read with great interest the paper by Montalescot et al. (1) and the editorial by McDaniel (2) on the effect of pre-hospital ticagrelor during the first 24 h after primary percutaneous coronary intervention (PCI). In the ATLANTIC trial, pre-hospital loading of ticagrelor compared with loading at presentation to the hospital reduced neither major adverse cardiac events (MACEs) at 30 days nor the primary endpoints of the proportion of patients achieving ≥70% ST-segment resolution and TIMI (Thrombolysis in Myocardial Infarction) flow grade 3 in the infarct artery before primary PCI (3). Similarly, in the present post hoc analysis, pre-hospital ticagrelor also failed to reduce MACEs at 24 h and the primary endpoints, and only after the inclusion of the bailout glycoprotein IIb/IIIa inhibitor use in the MACE composite were reductions in MACEs, stent thrombosis, and myocardial infarction achieved. However, as pointed out in the editorial (2), there were more anterior myocardial infarctions and numerically less pre-PCI glycoprotein IIb/IIIa use in patients receiving pre-hospital ticagrelor.

Although these results do not lend support to the advantage of loading in the ambulance, we believe that the hypothesis should not be completely abandoned. In our opinion, besides the limited difference of only 31 minutes between the 2 arms of the study and the possible influence of morphine administration, the fact that only patients in the first 6 h of symptoms were included may have played a role in the results. In the same way that fibrinolysis works effectively in the first 3 h but is clearly inferior to primary PCI after that interval and also the demonstrated advantage of prasugrel over clopidogrel in patients with more organized thrombus, that is, in secondary PCI (4), we believe that pre-hospital loading of ticagrelor may provide advantages not only in patients with longer transfers but also in those with more evolved infarctions.

Moreover, in PLATO (Platelet Inhibition and Patient Outcomes), in 7,544 patients with ST-segment elevation myocardial infarction, ticagrelor fulfilled the secondary endpoints of total mortality, myocardial infarction, and stent thrombosis, but the p value of the primary endpoint remained 0.07, because of a moderate increase in stroke with ticagrelor (5), and in patients with more evolved infarctions, the results would probably have been better for ticagrelor. In these patients with longer delays before reperfusion, the more potent effect of ticagrelor would favor reductions in total mortality, myocardial infarction, and stent thrombosis but with an expected same rate of stroke, because this latter complication would be a consequence of the proper characteristics of the patients, independent of delays in reperfusion.

In summary, the results of ATLANTIC may be due to the short difference in the moment of administration of the drug and the influence of morphine, but an advantage of pre-hospital administration of ticagrelor cannot be ruled out for more evolved infarctions.

***Iñigo Lozano, MD, PhD**
Juan Rondan, MD, PhD
Jose M. Vegas, MD
Eduardo Segovia, MD

*Cardiología
Hospital de Cabueñes
Avda. Los Prados 395
Gijón 33203
Spain
E-mail: inigo.lozano@gmail.com

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Please note: Dr. Lozano has given lectures about ticagrelor. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Immediate Versus Delayed Invasive Intervention for Non–ST-Segment Elevation Myocardial Infarction Patients (RIDDLE-NSTEMI Study)

A Game Changer for Interventional Cardiologists?

We read with great interest the recent study published by Milosevic et al. (1) assessing clinical outcomes at 30-day and 1-year follow-up in patients with non-ST-segment elevation myocardial infarction (MI) in stable condition undergoing immediate versus delayed percutaneous coronary intervention in a single-center, prospective, randomized study (RIDDLE-NSTEMI [Randomized Study of Immediate Versus Delayed Invasive Intervention in Patients With Non ST-Segment Elevation Myocardial Infarction]). The median time from onset of chest pain to coronary angiography was 6.4 h in the immediate-intervention group and 67.5 h in the delayed-intervention group. At 30-day and 1-year follow-up, significant differences in the rates of primary (death and new MI) and secondary (death, new MI, or recurrent ischemia) outcomes were observed between the 2 treatment strategies, with differences notable mostly in the pre-catheterization period. No significant differences were seen in the time period from 31 days to 1-year follow-up.

We believe that several factors may have skewed outcomes in favor of the immediate-intervention strategy. First, the definition of new MI did not include troponin I levels, as suggested in the "reinfarction" definition outlined in the third universal definition of MI (2), if ischemic symptoms and electrocardiographic changes occurred within the first 24 h of randomization ("early new MI"). In contrast, a rise in troponin I >20% (if initial elevated values were stable or decreasing) occurring >24 h to 7 days from randomization, in the presence of symptoms and electrocardiographic changes, was defined as a "late new MI." Perhaps the investigators adopted this definition to avoid overdiagnosis of "new early MI" in patients with initially elevated cardiac troponin I, thus making it difficult to discriminate between the occurrence of new MI and the initial index event. Nevertheless, because patients randomized to the immediate-intervention arm underwent PCI <24 h from randomization, could it be possible that recurrent MIs in this early period were undiagnosed or attributed to the percutaneous coronary intervention procedure (type 4a MI) (2)?

Second, it is unclear why more patients in the delayed-intervention group were referred for coronary artery bypass grafting and had a higher proportion of GRACE (Global Registry of Acute Coronary Events) score (3) >140. This suggests that these patients had a greater coronary artery disease burden and thus were "sicker" and at higher risk than those in the immediate-intervention group. Considering that these high-risk patients were not crossed over to the immediate-intervention strategy, as recommended in the most recent European Society of Cardiology (4) and American College of Cardiology and American Heart Association (5) guidelines, one could argue that the occurrence of adverse clinical events would be expectedly higher in this patient subgroup.

This study suggests benefits of an early invasive intervention strategy in high-risk patients with non-ST-segment elevation MI, with reductions of death and new MI at 30 days and 1 year. We agree with the investigators that an investigation with larger sample size, longer clinical follow-up, and precise definitions of new MI, reinfarction, and periprocedural MI is required to assess the long-term benefits of such a strategy given its potential impact on the health care system and the delivery of care in the catheterization laboratory.

Marie-Jeanne Bertrand, MD, MSc
***Jean-François Tanguay, MD**
*Université de Montréal
Montreal Heart Institute
5000 Bélanger Street
Montreal QC H1T 1C8
Canada
E-mail: jean-francois.tanguay@icm-mhi.org

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Please note: Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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