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EDITORIAL COMMENT

Pre-Hospital Ticagrelor in ST-Segment Elevation Myocardial Infarction?

Probably Not*

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Potent early antiplatelet therapy is important in patients presenting with ST-segment elevation myocardial infarction (STEMI). At present, the American College of Cardiology Foundation/American Heart Association STEMI guidelines recommend oral $P2Y_{12}$ antagonists be given "as early as possible or at the time of percutaneous coronary intervention (PCI)" (1). However, moving the administration of these agents to pre-hospital delivery does not appear to improve outcomes compared with loading at presentation to the hospital. In the previously published ATLANTIC (Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery) trial, pre-hospital loading with ticagrelor failed to improve reperfusion of the culprit artery as measured by the proportion of patients achieving ≥70% resolution of ST-segment elevation and Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in the infarct artery before PCI (2). In addition, there was no improvement in the composite of major cardiovascular events (MACE) (death, myocardial infarction, definite stent thrombosis, stroke, or urgent revascularization) at 30 days with pre-hospital administration of ticagrelor. This finding was likely due to the unexpectedly brief time difference of only 31 min between pre-hospital ticagrelor loading and in-hospital delivery due to rapid emergency medical services transport times.

As the short interval between drug delivery and angiography may have not allowed enough time for the benefits of pre-hospital loading to take effect, an exploratory post hoc analysis was conducted evaluating outcomes in the first 24 h after primary PCI. In this ATLANTIC-H^{24} study (3) reported in this issue of *JACC: Cardiovascular Interventions*, again there was no significant difference in MACE at 24 h with pre-hospital loading compared with in-hospital loading (1.3% vs. 2.0%; $p = 0.212$). In addition, there were no significant differences in the proportion of patients achieving post-PCI TIMI flow grade 3 or ≥70% ST-segment elevation resolution. However, when bail-out glycoprotein IIb/IIIa inhibitor (GPI) use was added to the MACE composite, there were fewer MACE at 24 h with pre-hospital ticagrelor (10.4% vs. 13.7%; $p = 0.039$). In addition, lower rates were noted of the individual components of definite stent thrombosis (0% vs. 1.0%; $p = 0.008$) and new acute myocardial infarction (0% vs. 0.7%; $p = 0.031$). On the basis of these exploratory post hoc results, it was suggested that the effects of pre-hospital ticagrelor may become apparent after PCI.

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Although some of these secondary endpoints raise the possibility of benefit for pre-hospital ticagrelor use in STEMI, we should be cautious in concluding that there is little downside to pre-hospital ticagrelor loading in this population. First, this study was conducted outside the United States, and the diagnosis of STEMI was made by ambulance medical personnel required to have >6 months training in infarct diagnosis (4). Furthermore, some ambulances had physician providers; when only paramedics were present, electrocardiogram transmission to a physician at a PCI center was encouraged. As such, there was a low false-positive diagnosis rate demonstrated by the fact 87.5% of patients randomized in the study ended up undergoing PCI. However, in many countries like the United States, emergency medical services personnel

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may not have the same degree of experience in acute infarct diagnosis. In settings with higher rates of "false positive" diagnoses, the indiscriminate use of more potent pre-hospital antiplatelet agents could have a significant adverse effects. Second, the benefit for MACE was largely driven by bail-out GPI use, which may be more related to physician preferences and unrecognized differences between groups. In support of this, there were more anterior myocardial infarctions and numerically fewer pre-PCI GPI use in patients receiving in-hospital ticagrelor, which may also contribute to the higher bail-out GPI use. Moreover, physician decision was the most common reason listed for bail-out GPI use, suggesting individual preferences most influence this outcome. Third, it should be noted that there was significantly greater mortality (hazard ratio: 4.7; 95% confidence interval: 1.01% to 21.73%) noted in the pre-hospital ticagrelor group (1.1% vs. 0.2%; p = 0.048). The authors state that the immediate mortality effect of pre-hospital ticagrelor is not very plausible, with only a 31-min difference in ticagrelor delivery between the 2 treatment groups. Although this conclusion is likely correct, this same reasoning probably also applies to the other underpowered findings of less acute stent thrombosis and acute myocardial infarction. Given the very small differences in loading time between groups, differences in any of these underpowered secondary endpoints are more likely the play of chance or unrecognized imbalance between the treatment arms.

The findings of ATLANTIC-H^{24} do suggest that the early hours after PCI are a vulnerable period, and there may still be role for rapid intravenous antiplatelet agents during this time until the full effect of oral P2Y$_{12}$ antagonists has been realized. Indeed, pharmacodynamic studies have shown that inadequate platelet inhibition can occur in up to 60% of patients with STEMI at 2 h and 35% of patients at 4 h after ticagrelor loading (5). Furthermore, morphine use, which is frequently used in STEMI, has been associated with further impairment in antiplatelet effect likely due to delayed drug absorption (6). Interestingly, in the ATLANTIC-H^{24}, ~43% of patients received GPIs either before PCI or as a bail-out strategy. Moreover, 5 of 6 of the new myocardial infarctions and 7 of 8 of the acute stent thrombosis events occurred in patients without any GPI use, and there were trends toward less definite stent thrombosis in patients receiving GPIs before PCI (0.0% vs. 0.7%; p = 0.061) (Online Tables 2 and 3 [3]). Although underpowered for definitive conclusions, these data suggest that there may be a role for selected GPI use in STEMI, especially with radial access where bleeding complications are attenuated. Indeed, analysis of 970,865 patients with acute coronary syndromes from the National Cardiovascular Data Registry demonstrated a 33% relative reduction in mortality in patients with STEMI treated with GPIs (7). This finding is in line with a meta-analysis of 7,414 patients with STEMI from 20 randomized trials in which GPIs reduced 30-day mortality risk by 25% (8). In both studies, the benefits were noted despite significantly increased risk in major bleeding complications and limited because femoral access was used in the vast majority of patients.

In conclusion, the results of the ATLANTIC-H^{24} exploratory analysis reported in this issue of *JACC: Cardiovascular Interventions* does not support the use of pre-hospital ticagrelor in most patients with STEMI when transport times are relatively short. Because several hours are required to achieve effective platelet inhibition in STEMI with ticagrelor, moving this oral loading up by only 30 min probably has little clinical impact on patient outcomes. However, the ATLANTIC-H^{24} trial leaves open the possibility of improved outcomes with pre-hospital ticagrelor when longer transport times are required. Finally, these findings suggest that there may still be a role for rapid intravenous antiplatelet therapy in STEMI, particularly in higher risk patients with radial access, but further studies are warranted to investigate this strategy.

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