Editorial

Is Treatment of ST-Segment–Elevation Myocardial Infarction Patients With Ticagrelor or Other $P2Y_{12}$ Inhibitors Before Primary Percutaneous Coronary Intervention a Strategy Without Benefit?

Kurt Huber, MD

Based on well-investigated pathomechanisms and the hypothesis that an optimal antithrombotic milieu at time of primary percutaneous coronary intervention (pPCI) is mandatory, former and recent guidelines recommend pretreatment on transfer to the catheter laboratory (cath laboratory) with intravenous anticoagulants, intravenous or buccal aspirin, and perioral P2Y12 inhibitors, whereby the stronger agents prasugrel or ticagrelor should be preferred over clopidogrel.[1] The available scientific data, however, do not strongly support these recommendations because respective data for timely pre-treatment in patients with ST-Segment–Elevation Myocardial Infarction (STEMI) do not exist—prasugrel pre-treatment was not specifically tested in patients with STEMI but was ineffective in non ST-elevation acute coronary syndromes patients with more in-hospital bleeding hazards[2]—and ticagrelor pre-treatment was neutral compared with its administration in the catheter laboratory with the only advantage that definitive stent thrombosis rates were statistically lower at 30 days in pretreated patients (ATLANTIC trial [Administration of Ticagrelor in the Catheterization Laboratory or in the Ambulance for New ST-Elevation Myocardial Infarction to Open the Coronary Artery]).[3] Finally, clopidogrel pre-treatment seems to be beneficial, which takes no wonder as clopidogrel has a delayed action because of its inactive structure and the necessity of metabolic activation.[4,5]

See Article by Koul et al

In this issue of *Circulation: Cardiovascular Interventions*, Koul et al[6] present real-world data of ticagrelor-pretreated STEMI patients (n=5438) versus patients receiving ticagrelor in the cath laboratory (n=1995) with a similar outcome as in the ATLANTIC study: The 30-day composite end point of all-cause death, myocardial infarction, and stent thrombosis was neutral between ticagrelor-pretreated and not pretreated patients as were the single secondary end points of the composite end point. Moreover, severe in-hospital bleeding complications were comparable, and only the rate of patients arriving in shock was slightly lower in ticagrelor-pretreated patients.

Based on this result, it has to be questioned again (after ATLANTIC) whether administration of ticagrelor should be delayed after coronary anatomy is known and after potential differential diagnoses have been excluded, disease states for which full antiplatelet action is deleterious or not necessary (eg, aortic dissection, Takotsubo syndrome), or when acute coronary artery bypass grafting might be a better option than PCI.

Potential Reasons for the Missing Benefit of Early Ticagrelor Administration

Since first publications about the importance of well-organized and functioning STEMI networks,[7–9] such systems of care have been implemented worldwide with the consequence that guideline-recommended time delays from first medical contact until pPCI could be offered to a majority of patients (a maximum of 120 minutes after first medical contact until pPCI is recommended with shorter times for specific subgroups of patients). In patients with STEMI, reabsorption of the stronger oral P2Y12 inhibitors prasugrel and ticagrelor is delayed up to 4 hours, and only a minority of patients exhibits a complete platelet inhibition during pPCI.[10] This can be explained either by hemodynamic compromise in patients with STEMI or by the frequent use of morphine or morphine derivatives or both. Interestingly, morphine use had no impact on long-term clinical outcome despite its impact on gastrointestinal drug reabsorption.[11] The consequence of a delayed reabsorption is that the full antiplatelet action of oral P2Y12 inhibitors occurs frequently only 2 to 3 hours after the intervention and might help to reduce

early stent thrombosis as seen in ATLANTIC. In contrast, this could not be confirmed by the present study in which data about morphine use and the exact timing of ticagrelor intake before cath laboratory are not known. Indirect data analysis suggests that ≈60% of patients received ticagrelor within 1 hour before pPCI.[6] Whether the relatively low in-hospital

bleeding rate might be explained by an increase in radial versus femoral approach has also not been investigated in the current study.

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Is the Hypothesis Wrong That an Optimal Platelet Inhibition During pPCI Is a Prerequisite for a Beneficial Outcome?

This question sounds revolutionary but can be partially underlined by the fact that fast-acting intravenous antiplatelet agents, such as glycoprotein IIb/IIIa blockers, were not in general successful in patients with STEMI when used pre-hospital: In the prospective randomized FINESSE study (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events-Angiographic), pre-treatment with abciximab had no effect on ischemic outcomes but led to more periprocedural bleeding.[12] In contrast, in the On-TIME-2 trial (Ongoing Tirofiban in Myocardial Evaluation 2) with tirofiban pre-treatment, the positive outcome was seen especially in patients with STEMI of short duration.[13]

The intravenous fast-acting P2Y12 inhibitor cangrelor was tested in stable and unstable patients[14] and offers a treatment strategy in P2Y12 inhibitor naive patients with STEMI. Based on pharmacodynamics, it is also possible to add cangrelor in the cath laboratory to ticagrelor-pretreated STEMI patients,[15] which might optimize platelet inhibition during PCI and confirm the hypothesis that optimal platelet inhibition during pPCI is mandatory. Such strategy has, however, not been sufficiently investigated to date for efficacy and safety.

All STEMIs Are Not Alike

Because it is difficult to discard a long-term accepted hypothesis one must search for other potential explanations, the missing benefit of early ticagrelor administration in 2 studies might have its reason in the inhomogeneous character of STEMIs: Don't we know that pre-hospital glycoprotein IIb/IIIa administration is best in the early hours of high-risk STEMI patients (On-TIME-2, APEX-AMI [Assessment of Pexelizumab in Acute Myocardial Infarction], EuroTransfer studies)[16–18] when a huge part of myocardium can be saved? Accordingly, an optimal antiplatelet action of ticagrelor by early administration might mainly help high-risk patients with STEMI of short duration and longer transfer times.

Unfortunately, data about STEMI duration at time of pPCI have not been shown in the elegant paper of Koul et al,[6]and a potential association of infarct duration and success or failure of ticagrelor pre-treatment cannot be proven.

Should Pre-Treatment of STEMI Patients With Ticagrelor Be Avoided?

Although 2 studies have not shown the expected effect, it cannot be excluded that a specific subgroup of patients (eg, high-risk, short duration of STEMI) might benefit from early P2Y12 inhibitor administration. Moreover, it cannot be foreseen for the individual situation whether a transfer to the cath laboratory can be performed without longer delay.

Accordingly, the current American College of Cardiology/American Heart Association and European Society of Cardiology guideline recommendations[1,19] should not be neglected until more information is available.

Future studies of optimal timing of ticagrelor and other strong and fast-acting antiplatelet agents should focus on high-risk patients (risk stratification based on anatomy and comorbidities) and infarctions of short duration (within 2–3 hours from onset of pain) in which a beneficial outcome is more likely. Planned studies with a new subcutaneous fast-acting P2Y12 inhibitor (ACT 246475; NCT03384966) administered early after symptom onset might provide new answers.

Disclosures

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