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EDITORIAL

Breaking Resistance: Is There Still a Reason for Clopidogrel in Acute STEMI?

Editorial to: "Prasugrel Versus High Dose Clopidogrel to Overcome Early High on Clopidogrel Platelet Reactivity in Patients with ST Elevation Myocardial Infarction" by D. Alexopoulos et al.

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Acute ST-elevation myocardial infarction (STEMI) is the sudden and life-threatening manifestation of coronary artery disease (CAD) leading to occlusion of a major coronary artery. Current guidelines favor primary percutaneous coronary intervention (PCI) for STEMI treatment [1, 2]. Dual antiplatelet treatment with acetylsalicylic acid and a $P2Y_{12}$ receptor blocker is the standard of care following PCI. The guideline recommendation that "clopidogrel should be given as soon as possible to all patients with STEMI undergoing PCI" at the earliest possible time by a loading dose of at least 300 mg or 600 mg has led to ambulance-based clopidogrel loading in STEMI patients in some countries [1]. However, during the acute STEMI state nausea, vomiting and stress as well as pharmacological interventions such as morphine-based analgesia might impede enteral absorption of clopidogrel and, thereby, its activation to the active metabolite. Following absorption, 85 % of the inactive prodrug clopidogrel is already hydrolyzed by circulating blood esterases to an inactive metabolite before the remaining 15 % undergoes hepatic metabolization by cytochrome P450 isoenzymes to generate the active metabolite [3]. When impaired responsiveness, which by consensus is currently denominated "high on-treatment platelet reactivity" [4], is defined based on the risk for potential stent thrombosis, a high proportion of patients in a real-world setting are suboptimal responders to clopidogrel in daily practice [5]. Only rare data are available regarding clopidogrel metabolism in STEMI patients, and those available indicate slower and less efficient metabolism as in stable patients/volunteers [6]. These considerations might be of particular importance as only oral $P2Y_{12}$ blockers are currently clinically available.

In this issue of *Cardiovascular Drugs and Therapy*, Alexopoulos et al. assessed $P2Y_{12}$ reactivity 2 h following a 600 mg loading dose of clopidogrel in STEMI patients [7]. Interestingly, this is the exact time frame that the ESC guidelines (irrespective of the lack of data to support the assumption) state as "optimal" for clopidogrel. The 2 h loading time was initially based on the fact that after such loading the glycoprotein IIb/IIIa antagonist abciximab did not provide a reduction in major cardiovascular events in elective PCI [8]. However, once patients had an acute coronary syndrome and were troponine-positive, this loading regime was not able to completely substitute for glycoprotein IIb/IIIa antagonism [9].

In the current study, the majority of STEMI patients had high on-treatment platelet reactivity 2 h after clopidogrel loading. They were, therefore, randomized to receive either an increased clopidogrel maintenance dose or were switched to prasugrel including a loading dose of 60 mg. Those on higher clopidogrel maintenance dose also missed to achieve a significant difference in the measurement compared to the time of randomization within the next 2 h. In contrast, those randomized to prasugrel rapidly achieved sufficient platelet inhibition. 24 h after randomization, the majority of patients in the clopidogrel group were still in a state of high on-treatment platelet reactivity, whereas all but one prasugrel-treated patient showed sufficient platelet inhibition. The data clearly show that clopidogrel fails to provide sufficient platelet inhibition in the early phase of STEMI. The 2010 ESC guidelines on myocardial revascularization have put clopidogrel loading for STEMI patients into perspective with the newer and more potent $P2Y_{12}$ blockers by stating that clopidogrel only "should be used primarily if the more

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effective ADP receptor blockers are contraindicated or unavailable" [10].

In particular, STEMI patients show a weaker response to clopidogrel loading than stable CAD patients undergoing PCI [11]. Previously, Heestermans et al. demonstrated that compared to healthy controls STEMI patients achieve lower maximal plasma levels of clopidogrel and its active metabolite, require longer time to reach maximal plasma levels, and have decreased exposition to the active clopidogrel metabolite [6]. Therefore, all the kinetic data derived from stable patients or even healthy volunteers might not be easily transferable to the STEMI population. Prasugrel, when compared to clopidogrel, achieves more rapid and consistently sufficient platelet inhibition as demonstrated in the phase II study PRINCIPLE-TIMI 44 [12] and in patients with acute coronary syndromes in a sub-study of the phase III TRITON trial [13].

In conclusion, the current study by Alexopoulos et al. documents that clopidogrel is no option for rapid and efficient $P2Y_{12}$ antagonism in STEMI patients. It underlines, that more efficient platelet inhibition by prasugrel achieves potent $P2Y_{12}$ inhibition more rapidly and more effectively than clopidogrel.

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