Research and Therapeutic Nihilisms in Chronic Kidney Disease.

Marc Laine, Stéphane Burtey, Etienne Puymirat, Gilles Lemesle, Laurent Bonello

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We congratulate Baber et al. (1) for their new analysis of the PROMETHEUS registry. Large real-life registries are critical to confirm the efficacy and safety of new drugs and provide data for key subgroups of patients who are under-represented in clinical trials (CT). Although patients with chronic kidney disease (CKD) compose between 20% and 40% of acute coronary syndromes, they were under-represented in the PLATO (Study of Platelet Inhibition and Patient Out-comes) and TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) trials. In the present study, Baber et al. (1) investigated the real-life outcome of prasugrel compared with clopidogrel in acute coronary syndromes undergoing percutaneous coronary inter-vention based on kidney function. They identified a lower use of prasugrel in this high ischemic risk pop-ulation. This is related to therapeutic nihilism, which is well recognized in patients with CKD. Another key result is the lack of significant difference in outcomes after adjustments between prasugrel and clopidogrel (1). However, it should be acknowledged that this lack of significant difference does not imply a lack of benefit of new P2Y12-ADP receptor antagonists given the limited power of the analysis and the methodology.

The present study raises critical issues regarding the current trend in CT. In fact, for safety reasons, CT investigating new drugs or interventions often exclude the most severely diseased patients. This not only limits the ability of the intervention to demon-strate superiority but also prevents those who would derive most benefit from these improvements to be eligible for them. Accordingly, CKD remains a cumbersome population with high ischemic and mor-tality rates (2). In addition, in patients with CKD high on-treatment platelet reactivity is not only associated with ischemic events but also with mortality (3).The biologic efficacy of prasugrel and ticagrelor in these patients has been confirmed (4).Ofimportance, a subgroup analysis of PLATO suggested that patients with CKD under ticagrelor had a superior absolute risk reduction than patients without CKD, including a near 30% mortality benefit, without safety issue (2).Un-fortunately, this subgroup analysis only enrolled a limited number of patients and none with stage 5 CKD.

Therefore, despite the potential of these new P2Y12-ADP receptor antagonists in CKD, clopidogrel remains largely used in clinical practice. New forms of CT including registry-based CT or large pragmatic trials may help to resolve the issue of therapeutic nihilism in research. The TROUPER (TicagRelor Or Clopidogrel in severe and terminal chronic kidney disease patients Undergoing PERcutaneous coronary intervention for an acute coronary syndrome) trial, which will start recruiting in 2017, aims to provide the benefit/risk ratio of ticagrelor 90 mg twice daily compared with clopidogrel 75 mg in patients with stage 4 and 5 CKD undergoing percutaneous coronary intervention for an acute coronary syndrome.

Marc Laine, MD
Stephane Burtey, MD, PhD
Etienne Puymirat, MD, PhD
Gilles Lemesle, MD, PhD
* Laurent Bonello, MD, PhD
* Service de Cardiologie
Centre Hospitalier Universitaire de Marseille INSERM UMRS 1076
Aix-Marseille Université
Chemin des Bourrely
Marseille 13015
France

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