The Unknown Effect of Clopidogrel Resistance in Dual Antiplatelet Therapies After Coronary Artery Bypass Grafting

We read with great interest the article of Sørensen et al. (1) that reported the efficacy of post-operative clopidogrel treatment in a large patient cohort revascularized with coronary artery bypass graft surgery (CABG) after myocardial infarction. Notwithstanding the criterion of preoperative myocardial infarction, it remains interesting that this result is contrary to the CASCADE (Clopidogrel After Surgery for Coronary Artery Disease) trial, where addition of clopidogrel to aspirin revealed no changes on the post-operative outcomes (survival, 1-year intimal hyperplasia) (2). A possible explanation could be the different rates of aspirin and/or clopidogrel resistance between the 2 populations.

Aspirin resistance after cardiac surgery varies between 7% and 54% (depending on the platelet assay) (3). In contrast, clopidogrel response in patients undergoing CABG remains unknown due to the fact that aspirin is the drug of first choice after CABG, and clopidogrel administration (in addition to aspirin) is recommended mainly in patients with acute coronary syndrome (1). However, previous reports indicate that the clopidogrel resistance rate in coronary stent patients varies between 5% and 56% (4). Besides, carriers of defective alleles for CYP2C19 and CYP3A4, respectively, are at risk of clopidogrel resistance as well (5).

Certainly, the considerably high prevalence of clopidogrel resistance in noncardiac surgery patients creates the necessity for assessment of clopidogrel nonresponders undergoing CABG. Otherwise, it remains unknown in dual antiplatelet therapies whether the response to clopidogrel covers a possible aspirin resistance or vice versa. Finally, we congratulate the authors for this excellent and well-defined study and for their contribution to the optimization of the clinical outcomes in patients undergoing CABG after myocardial revascularization.

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Reply

We read with interest the letters by Drs. Kulik and Ruel and by Dr. Bisdas and colleagues commenting on our study about the efficacy of clopidogrel treatment in patients with myocardial infarction (MI) treated with coronary artery bypass graft surgery (CABG) (1).

Our study was a nationwide cohort study based on exact information from nationwide registers of claimed prescriptions and hospitalizations in Denmark. Although these registers include comprehensive data, some details are not listed, for example, on-pump/off-pump, whereas platelet function tests are currently not recommended for routine use (2). Including these variables might have increased the accuracy of our models, but we do not believe it would have changed the results substantially. Importantly, we found reduced mortality among patients receiving clopidogrel after CABG. This finding was consistent in the propensity-matched subgroup analysis. We did not find reduced recurrent MIs. However, contrary to the statement by Drs. Kulik and Ruel, we found reduced cardiovascular death among the
patients receiving clopidogrel (1). This difference persisted across the propensity-matched subgroups, but was nonsignificant ($p = 0.19$) due to the low number of patients. A discussion of this was presented in the paper (1). In our study, all patients had severe ischemic heart disease, and the lack of effect on recurrent MI might be explained by the fact that a recurrent event in these patients often is fatal, a statement supported by data from the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) (3) and PLATO (Platelet Inhibition and Patient Outcomes) (4) trials. We stated that clopidogrel was underused because only 27% received clopidogrel after CABG, even though guidelines clearly recommend 9 to 12 months of treatment. We acknowledge that the evidence behind this recommendation is weak (5), which was one reason we performed our study. We also recognize the effort of providing data on graft patency in the CASCADE (Clopidogrel After Surgery for Coronary Artery Disease) trial, but we are not confident of the conclusions due to the low number of patients (6). Furthermore, graft patency is a surrogate endpoint that does not necessarily reflect clinical events. Finally, the favorable effect of clopidogrel in our study may indicate that clopidogrel resistance is less important in this clinical setting. In summary, an adequately powered randomized trial is needed to clarify the efficacy and safety of clopidogrel treatment in MI patients undergoing CABG. Until then, we recommend following current guidelines and continue clopidogrel 9 to 12 months after MI.

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