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„Adenosine di-phosphate receptor antagonist discontinuation management prior to coronary artery surgery “

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We read with great interest the recently published meta-analysis by Morici et al [1]. The authors included any observational and experimental study that compared any early discontinuation of adenosine di-phosphate receptor antagonists (ADPRA) drugs to later discontinuation treatment or no discontinuation for patients with acute coronary syndrome (ACS) referred to coronary artery bypass graft (CABG) surgery[1].

Expected inhibition of platelet function after ADPRA administration varies widely among patients, from pronounced platelet inhibition to high level of residual platelet reactivity. The effect of ADPRA discontinuation management on bleeding and ischemic events mainly depends on two factors: (1) observed platelet inhibition, which is depending on inherent platelet activity prior to ADPRA administration and platelet inhibitory response to ADPRA, and (2) newborn platelets ability to restore normal aggregation after ADPRA discontinuation. This results in individual widespread variability in adenosine – diphosphate (ADP) platelet receptors activity which consequently reflects similar variability in proclivity to excessive bleeding and/or adverse ischemic events. Therefore, when assessing influence of preoperative ADPRA administration management on postoperative mortality (<30 days) and re-operation due to bleeding, objective quantification of platelet activity should inextricably be included into considerations.

Up to date, the risk versus benefit of ADPRA discontinuation in ACS patients undergoing CABG remains unclear. In present meta-analysis [1] the prediction interval also suggests that further studies are likely to confirm that longer time of discontinuation is safer than later discontinuation[1]. Price et al[2] investigated recovery of platelet function after discontinuation of ADPRA's. The initial magnitude of platelet inhibition at discontinuation was an independent predictor of the time to recovery[2]. Although most patients in the study[2] returned to baseline platelet reactivity after 5 and 7 days of clopidogrel and prasugrel discontinuation, respectively,

patients in both groups displayed residual effects beyond these waiting periods[2]. Unique recommendation for ADPRA's discontinuation should be made according to ADP specific platelet function test values, rather than number of days, in the light of the introduction of novel, more potent P2Y12 ADP-receptor antagonists with more delayed platelet function recovery[2] where the recommended 5-day wash-out period might not be sufficient. Of more importance, too early cessation of ADPRA may be associated with a “rebound” effect that is pro-thrombotic (increase in platelet reactivity to a level that exceeds what it was at baseline prior to the initiation of ADPRA therapy) and pro-inflamatory, thus, probably contributing for adverse clinical events[3].

There is evidence that ADPRA also interferes with arachidonic acid (AA) – mediated platelet stimulation [4] potentiating the effect of aspirin. This would manifest as an apparent reduction in the response of an individual patient to aspirin when clopidogrel is stopped as assessed by AA-induced platelet reactivity[3]. In our recent study, we found 31.3% of patients scheduled to CABG to have residual platelet reactivity at 100 mg aspirin daily therapy[5]. It would mean that patients who are relatively hyporesponsive to aspirin would be at particular risk of adverse events when clopidogrel is discontinued. In present meta-analysis the control group was defined as any other antiplatelet treatment during 2-7 days preceding CABG, such as aspirin or no treatment[1]. There is evidence that certain patients have an accentuated response to the usual doses of preoperative aspirin that may result in increased perioperative blood loss[6, 7]. In our opinion, the control group is somehow heterogenous, and has possibility for creating bias since profound platelet inhibition after aspirin administration might influence the secondary outcome (re-operation due to bleeding).

Benefits and risks of ADPRA discontinuation before CABG should be individually assessed according to drug specific platelet function tests and role of aspirin should inevitably be included into considerations since aspirin influences both primary as well as secondary outcome evaluated in present meta-analysis[1]. For patients receiving dual antiplatelet therapy (APT) (aspirin + ADPRA) prior to CABG, the influence of aspirin on bleeding and ischemic adverse events should separately be examined using aspirin sensitive platelet function test. Evaluation of APT (aspirin and/or clopidogrel) effect on both bleeding and ischemic events should be based on platelet function assessment with subsequent distinction of patients with high residual platelet activity, thus proclivity to ischemic events, or enhanced platelet inhibition, thus proclivity to excessive bleeding. The group of patients with pronounced platelet inhibition observed during APT could benefit from early preoperative APT withdrawal in terms of excessive bleeding prevention. Patients with residual platelet reactivity after aspirin and/or clopidogrel administration could benefit from APT late discontinuation. Such a strategy may help to prevent pre- and early postoperative onset of "rebound effect" that is pro-thrombotic or pro-inflammatory, therefore risk factor for adverse ischemic events. Further studies are required in order to provide precise and comprehensive view on the relationship between APT administration management and both, bleeding and ischemic events, through achieved platelet inhibition, quantified by platelet function tests, aiming to create a „safety window" defined with range of drug specific platelet function test values between thrombotic burden and bleeding threat. However, such an approach requires prospective multicentre study that will delineate „safety window" of drug specific platelet function test values. Clinical judgement should direct conduct, by taking into account both thrombotic burden and bleeding threat in individual patients, to offer therapy best tailored to the needs of each individual patient according to drug specific platelet function test values.

Data concerning transfusion requirements and chest tube drainage were not included in present meta-analysis[1]. Red blood cell transfusion increases platelet activation and aggregation, mediated through the P2Y12 activation pathway[8],thus influences adverse events onset. Dixon et al reported chest tube output (CTO) as the strongest independent predictor of mortality[9] which is in line with findings recently obtained by our working group[10]. Therefore, inclusion of these data (transfusion requirements and chest tube output) should inevitably be considered in further trials.

Finally, we call for both pre- and postoperative platelet function assessment since they could influence primary, as well as secondary outcome in present meta-analysis[1]. Recently we found platelets to be prone to development of postoperative hyperactivity [5] in early post-CABG period. Together with possible "rebound phenomenon" following too early preoperative APT discontinuation, that could influence the incidence of 30 day mortality regardless of preoperative APT administration/discontinuation management.

A uniform strategy of a 5-day waiting period after clopidogrel could expose patients with marginal response to thrombotic risk, while exposing "hyper-responders" to an increased surgical bleeding risk. Platelet function testing could help guide surgical timing in thienopyridine-treated patients to minimize bleeding complications, although the evidence supporting such an approach is requires definition of firm cutoff for drug specific platelet function tests values that predict bleeding and/or ischemic events.

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