Antiplatelet therapy at the time of coronary artery surgery: can a personalized approach improve outcomes?

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We read with great interest the recently published multicentre cohort study by Kremke et al. [1]. Patients exposed to antiplatelet therapy (APT) at the time of coronary artery surgery (CAS) had greater postoperative bleeding volumes and greater transfusion requirements [1]. Exposure to clopidogrel, but not aspirin, was associated with greater reoperation rates and was an independent risk factor for severe postoperative bleeding, although mean bleeding volumes were not significantly different in the aspirin and clopidogrel subgroups [1].

Despite current guidelines, it is apparent that many patients are proceeding with CAS without the 5-day delay off clopidogrel. The efficacy of platelet inhibition with clopidogrel varies widely among patients, from intensive platelet inhibition to poor platelet response [2], and these variations could, to some degree, explain the non-significant differences in mean bleeding volumes in the aspirin and clopidogrel subgroups [1]. The effect of clopidogrel on bleeding mainly depends on two factors: (i) observed platelet inhibition, which depends on inherent platelet activity prior to clopidogrel administration and platelet inhibitory response to clopidogrel and (ii) newborn platelets ability to restore normal aggregation after clopidogrel discontinuation. Therefore, the use of suitable point-of-care platelet function tests seems to be reasonable in this field. Recently, we found aspirin- (P = 0.014) and clopidogrel- (P = 0.003) sensitive platelet function tests to be predictive of excessive postoperative bleeding in patients following CAS [2]. Of note, 76.3% patients were transfused with no significant differences among the groups with regard to the preoperative APT administration regimen (P = 0.636) [2]. However, transfused patients had significantly lower values of aspirin-sensitive platelet function tests (P = 0.002) [2].

In our opinion, the study cohort is somehow heterogeneous. Eligible procedures were either isolated CAS or CAS combined with aortic valve replacement (AVR) [1]. AVR certainly extends the duration of cardiopulmonary bypass, which was recently described as a predictor of transfusion requirements [3]. After matching, authors reported a slightly greater use of antifibrinolytic drugs in the APT group [1]. Both on-pump and off-pump procedures were included [1]. Authors reported that off-pump surgery and perioperative use of tranexamic acid were associated with a lower risk of severe postoperative bleeding [1]. The use of antifibrinolytic drugs should be equally balanced since there is evidence that antifibrinolytic therapy reduces bleeding and transfusion outcomes [4]. It would be interesting to see if exclusion of CAS + AVR and off-pump CAS patients would bring different results.

During the study period, thromboelastometry-guided blood component therapy became available at two of three participating centres [1]. At the same time, multivariate analysis revealed that surgery at one of the participating centres was one of independent risk factors for severe postoperative bleeding [1]. Spiess et al. [5] reported thromboelastography-guided haemostatic management to have significantly reduced the incidence of overall transfusion and mediastinal re-exploration due to excessive bleeding. Thus, perhaps one could assume that one centre, which was found to be independent risk factor for severe postoperative bleeding, was in fact the one without thromboelastometry guided transfusion therapy available.

The largest extent of chest tube output together with the greatest transfusion rates, was observed in the subgroup of patients exposed to dual APT [1]. Those results are in line with the results recently published by Miceli et al. [6]. Further incremental platelet inhibition may be observed in the group of patients receiving dual APT. Therefore, the role of aspirin and clopidogrel administration management should be separately assessed by drug-specific platelet function tests, thus facilitating an individual therapeutic approach for discontinuation management of each antiplatelet agent preoperatively.

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REFERENCES


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We agree that newer platelet function tests have the potential to change the management of bleeding complications after cardiac surgery. These tests may indicate the presence of platelet dysfunction, either caused by exposure to antiplatelet drugs or the use of cardiopulmonary bypass [3]. Unfortunately, randomized trials evaluating their prognostic value are rare [4].

Preoperatively, platelet function tests may allow for earlier elective surgery, when normal platelet function is shown despite recent exposure to antiplatelet drugs. However, this approach is not likely to alter the outcome after cardiac surgery, as elective patients with a low risk of ischaemic events can safely withhold platelet inhibitors according to existing guidelines.

In patients with recent exposure to antiplatelet drugs and increased risk of ischaemia, platelet function tests have a questionable value. Surgeons might delay coronary bypass grafting (CABG) in patients with platelet dysfunction, with potentially fatal consequences. Even though preoperative clopidogrel exposure is associated with an increased risk of severe postoperative bleeding, we could not demonstrate an independent effect on postoperative mortality [2].

Petricevic et al. noticed that patients from one participating centre had a greater risk of severe postoperative bleeding (>1000 ml). We believe that this was due to the longer delay until the bleeding patient was reoperated at this hospital: bleeding volumes were significantly different between the participating centres (ranging from 712 to 984 ml in the matched cohort), while there were inverse differences in the frequency of reoperation due to bleeding (ranging from 6.2 to 3.0%).

Petricevic et al. argued that the study groups were heterogeneous with regard to the type of surgery (CABG only vs combined CABG and aortic valve replacement). Actually, there were fewer patients undergoing combined surgery in the matched antiplatelet group. Nonetheless, bleeding volumes were greater in this group. The observed heterogeneity is therefore not likely to have an influence on outcomes. Besides, off-pump surgery was also a matching factor.

Petricevic et al. commented that antifibrinolytic use was slightly different in the matched control and antiplatelet therapy (APT) (aprotinin 1.5 vs 1.8%; tranexamic acid 83.1 vs 90.7%; \( P < 0.0001 \)). Again, it was patients in the matched antiplatelet group who received antifibrinolytics more frequently. Nonetheless, they bled more and received more blood products.

The use of antifibrinolytics is a well-known factor influencing postoperative bleeding. Therefore, we included it in the logistic regression analysis. There, it had, like the factors mentioned above, no impact on severe bleeding.

An analysis of matched patients including only stand-alone CABG, on-pump surgery and perioperative tranexamic acid use revealed almost identical bleeding volumes as in the total cohort, being 756 ml (control), 848 ml (aspirin), 1016 ml (clopidogrel) and 1128 ml (dual APT subgroup). Furthermore, these subgroups were significantly different from each other (\( P < 0.001 \); analysis of variance).

Therefore, eliminating the confounders mentioned by Petricevic et al. did not change our finding that continued antiplatelet therapy is associated with increased postoperative bleeding and greater transfusion requirements after CABG.

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