



## Središnja medicinska knjižnica

**Petričević M., Biočina B., Zrno Mihaljević M., Boban M., Samardžić J.,  
Konosić S., Ivančan V. (2015) *Preoperative prasugrel discontinuation  
management in coronary artery surgery. Thoracic and Cardiovascular  
Surgeon, 63 (1). pp. 36-7. ISSN 0171-6425***

<http://www.thieme.de/thoracic>

<http://dx.doi.org/10.1055/s-0034-1390156>

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## **„Preoperative Prasugrel Discontinuation Management in Coronary Artery Surgery“**

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Keywords: prasugrel; clopidogrel; coronary surgery; platelet function; hemorrhage; transfusion

We read with great interest the recently published study by Drews et al[1]. Authors compared transfusion and bleeding outcomes among patients undergoing coronary artery surgery (CAS) with respect to preoperative exposure to either prasugrel or clopidogrel[1]. Patients pretreated with prasugrel more often needed perioperative platelet transfusions and had a higher rate of surgical reexploration due to bleeding complications[1]. Logistic regression revealed that preoperative exposure to prasugrel and urgent/emergent surgery were predictors for the composite endpoint defined as “need for perioperative platelet transfusion and/or surgical reexploration for bleeding complications”[1].

Study by Drews et al[1] certainly adds to the current knowledge, however some methodological considerations should inevitably be addressed.

The proportion of patients undergoing urgent/emergent CAS was higher in patients pretreated with prasugrel compared with those on clopidogrel pretreatment[1]. This may be considered as a bias since patient groups were not balanced for “urgent/emergent CAS” parameter, found to be predictor of observed clinical endpoints. Therefore, it would be interesting to see if the results would remain the same if two groups would be balanced for “urgent/emergent CAS” parameter using propensity matching.

Furthermore, in such a type of studies, clinical endpoints should be carefully defined. In present study, patients in “prasugrel” group have had significantly higher rate of reexplorations for excessive bleeding[1]. At the same time, “prasugrel” patients have had significantly higher rate of platelet concentrate used[1]. Hypothetically, these outcomes should be inversely related in optimal hemostatic management protocol, as it is expected that higher rate of platelet concentrate used should prevent or at least reduce occurrence of reexploration for bleeding. The role of

platelet concentrate transfusion is even more important considering the fact that in present study, diffuse bleeding was found in all cases of reoperation for excessive bleeding[1]. Therefore, different way in defining clinical endpoints would be desirable. The fact is that the optimal definition of perioperative bleeding remains to be challenging issue. However, International Initiative for Hemostasis in Cardiac Surgery recently proposed universal, multistage definition of perioperative bleeding in cardiac surgery[2]. This definition presents composite endpoint that is consisted of all variables relevant for assessment of bleeding outcome and provides grading of bleeding severity[2]. In our opinion, this definition should be used for further similar studies as does provide the most reliable estimation of the relationship between preoperative exposure to different antiplatelet drugs and occurrence of mild, moderate, severe and massive bleeding, respectively[2]. Hypothetically, using this approach, further studies could provide better understanding of the possible risks of bleeding inherent to antiplatelet drugs, and expected severity of bleeding which in turn could advise preferred preoperative antiplatelet discontinuation management as well as timing of surgery.

Finally, when assessing influence of preoperative antiplatelet drugs administration management on bleeding and transfusion outcomes[3], objective quantification of platelet activity using point-of-care devices should inextricably be included into considerations[3] as it may provide more clear pharmacodynamic insight. Our working group recently found that platelet ADP activity varies widely among patients exposed to clopidogrel, and corresponds to the extent of postoperative bleeding[3,4]. The effect of ADP receptor blockers depends on (1) baseline, inherent platelet ADP receptor activity, (2) platelet inhibitory response to antiplatelet drug, as well as on (3) recovery rate of platelet function after drug discontinuation. The initial magnitude of platelet inhibition at discontinuation has been described as an independent predictor of time to

recover platelet function[5]. Patients experiencing “on clopidogrel” pronounced platelet inhibition may have the same risk for bleeding as the patients exposed to more potent drug such as prasugrel as they may reach the same level of ADP inhibition as those exposed to prasugrel. This observation, along with widespread variability in platelet inhibitory response to clopidogrel, suggests that assessment of platelet function using drug specific reagents should inextricably be included in studies evaluating relationship between antiplatelet drugs and clinical endpoints such as bleeding outcome[3]. According to predefined ADP test value cutoff’s (uniformly applicable to patients exposed to either clopidogrel or prasugrel)[4] it would be possible to stratify patients in regard to bleeding risk. In addition to, recovery of platelet function following drug discontinuation could be quantified by serial platelet function testing and once platelet function outgrows predefined cutoff value that delineates bleeding tendency it would be safe to proceed with surgery regardless the number of days following drug cessation. This personalized approach may shorten waiting time and optimize bleeding and transfusion outcomes at the same time.

Notably, for patients receiving dual antiplatelet therapy preoperatively, the role of aspirin should not be underestimated as it is well known that dual antiplatelet therapy provides more potent aspirin inhibitory effect[6], which in turn enhances the risk of bleeding attributable to aspirin effect[7]. Therefore, it seems reasonable to perform drugs specific platelets function testing using both ADP as well as arachidonic acid induced platelet function agonists.

We congratulate authors for timely and elegant study. Further studies evaluating the relationship between preoperative antiplatelet therapy management and bleeding outcomes should use standardized way in defining clinical endpoints[2] and should inevitably include drug specific platelet function testing as it may provide better understanding on the platelet inhibitory effect of the drugs and dynamics of platelets recovery after drugs discontinuation.

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