Preoperative Fibrinogen and Morbidity in Patients With Residual Platelet Inhibition Undergoing Off-Pump Coronary Artery Bypass Grafting

– Cause or Effect? –

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The package insert for clopidogrel recommends withholding the drug at least 5 days prior to any elective surgery, including coronary artery bypass grafting (CABG). Indeed, bleeding varied markedly compared with placebo in patients undergoing CABG in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial according to whether clopidogrel was stopped for ≤5 days or >5 days before surgery. However, discontinuation of antiplatelet therapy (DAPT) before surgery may come at the expense of an increased risk of ischemic events in the perioperative period. Irrespective of any bleeding consideration, increased residual antiplatelet effects were shown to be associated with a significant reduction in the risk of early mortality in patients treated with more potent antiplatelet agents than clopidogrel (ie, prasugrel and ticagrelor), mirroring similar prior observations with clopidogrel and abciximab.

To maximize the tradeoff of continuing DAPT in proximity to CABG, off-pump techniques have been introduced to attenuate postoperative bleeding and transfusion requirements, but whether off-pump CABG is associated with less bleeding in patients who maintain clopidogrel within a few days from the operation remains controversial and possibly subject to undefined underlying factors that distinguish patients at high or low risk. Fibrinogen, a soluble plasma glycoprotein that is converted by thrombin into fibrin as part of the process of blood clot formation and stabilization, could be one of those factors. Indeed, a pro-inflammatory role for fibrinogen that extends beyond its traditional function in the acute hemostatic cascade has been advocated in several disease conditions, but whether fibrinogen levels correlate with bleeding at the lower end, or ischemic complications at the higher end, is poorly explored in the setting of CABG, particularly when performed off-pump.

In this issue of the Journal, Kim et al report on the clinical effect of preoperative fibrinogen levels in 538 patients who were still on DAPT with aspirin and clopidogrel in proximity (<5 days) to off-pump CABG for multivessel coronary artery disease. Perioperative blood loss and various morbidity endpoints were examined after stratification by tertile of baseline fibrinogen concentration. Patients in the highest tertile presented with the worst clinical risk profile and were at higher risk of postoperative myocardial infarction and a composite morbidity endpoint. High preoperative fibrinogen concentration independently predicted the primary ischemic endpoint. Conversely, patients in the lowest tertile suffered from larger blood loss, but preoperative fibrinogen lost any significance for this endpoint after adjustment for potential confounders.

Overall, the results of the study support pre-procedural risk stratification by fibrinogen level to predict morbidity (2-fold increased risk for the highest tertile) but low fibrinogen levels were not found to anticipate more bleeding, a finding in contrast with previous literature. The authors speculate that this might be specific to off-pump CABG, where previous studies suggested postoperative fibrinogen levels to be higher on average than those described after on-pump CABG. Another potential explanation is that stratification by tertile might not entirely capture the complex, and possibly nonlinear, interplay between fibrinogen levels and bleeding. Replication of the study findings using a more conventional threshold for the lower end (ie, <200 mg/dl) would have better clarified this issue.

On the other hand, the relationship between higher fibrinogen levels and ischemic cardiac events is biologically plausible and comes as no surprise, but raises additional questions. Fibrinogen plays important roles in platelet activation and promotes the cross-linking of platelets by means of glycoprotein IIb/IIIa receptors. The third tertile of the study population, defined as fibrinogen between 370 and 854 mg/dl, resembled the values normally indicated by most laboratories. This may have overshadowed the putative relationship between low fibrinogen and bleeding. Replication of the study findings using a more conventional threshold for the lower end (ie, <200 mg/dl) would have better clarified this issue.
on DAPT in the proximity to surgery might be attenuated in patients with high fibrinogen levels. It should be noted that being on dual antiplatelet therapy within 5 days from CABG is not a default choice by many surgeons, so it is likely that patients included in the study were at high baseline risk of ischemic events per se, with some selection bias possibly at play. Consequently, the results are not generalizable to all patients undergoing off-pump CABG, and the lack of a control group of patients who stopped antiplatelet therapy >5 days from surgery does not allow us to fully elucidate the potential interaction between high fibrinogen levels and residual platelet reactivity. Similarly, the study does not give insight to platelet function profiles, which may vary significantly in proximity to surgery even after discontinuation of clopidogrel. Under these circumstances, whether a high fibrinogen concentration represents the cause of postoperative ischemic events or is merely a marker of the underlying thrombotic risk remains unknown. If fibrinogen truly plays a primary role (ie, by making platelets more prone to activation), this would encourage broader implementation of bridging protocols with fast-acting intravenous antiplatelet agents (Figure), particularly those targeting the glycoprotein IIb/IIIa receptor.

**Disclosures**

Advisory Board/Speaker’s honoraria: Eli-Lilly/Daiichi Sankyo, AstraZeneca.

**References**


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