Right here waiting...?

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No surgeon in this world likes bleeding. Yet perioperative blood loss is impossible to avoid when conducting an “ultra major” cardiovascular operation, such as coronary artery bypass grafting (CABG). Every member of a “heart team” treats this common complication very seriously, simply because it has important prognostic implications for patients.¹ Because even outstanding surgical skill and meticulous perioperative management are insufficient to eliminate perioperative bleeding, prevention is the only real option.

In this regard, the meta-analysis of Cao and colleagues² in this issue of the *Journal* is both timely and of utmost importance. On the basis of a comprehensive review of the literature, Cao and colleagues² identified 5 appropriate clinical studies of 6385 patients with acute coronary syndrome (ACS) who had subsequently undergone CABG. The data for 2632 patients who received preoperative clopidogrel were compared with the data for patients who did not receive this medication, and the beneficial effect of dual antiplatelet therapy was once again confirmed. Importantly, a lower incidence of the combined end point of reoperation, major bleeding, mortality, and myocardial infarction was observed in 873 patients who underwent clopidogrel washout for more than 5 days before CABG. Cao and colleagues² concluded that dual antiplatelet therapy including clopidogrel is favorable for patients with ACS. If CABG is indicated, however, whenever feasible, clopidogrel intake should cease for at least 5 days before the cut-and-sew.

Clearly, this clinical recommendation is relevant to everyone involved in the care of patients with ACS, such as surgeons, cardiologists, anesthesiologists, and intensive-care specialists. Indeed, the guidelines provided in 2011 by both the European Society of Cardiology³ and the American Heart Association⁴ supported the proposal made by Cao and colleagues² that clopidogrel be withdrawn for 5 days before CABG. It appears questionable in 2014, however, whether we should simply adapt this 5-day waiting policy to every

patient with ACS. On top of the fact that Cao and colleagues' meta-analysis² was based on a rather more limited data set than that available today, some additional issues should not be overlooked. For instance, it is now well known that the platelet-inhibitory effect of clopidogrel varies significantly among patients. High levels of platelet reactivity have been observed in 30% to 40% of clopidogrel-treated patients, particularly those with proton-pump inhibitors.⁵ The uniform guidelines for clopidogrel discontinuation before CABG are thus unlikely to be relevant to “clopidogrel-nonresponder” patients. Moreover, the recommended 5-day duration of clopidogrel washout is also debatable, because in some patients platelet reactivity may take much less time to return to a normal level. The results of a recent prospective single-center study showed that using thromboelastography to measure platelet function can shorten the recommended 5-day preoperative waiting period for clopidogrel-treated patients by an average of 46% (2.7 days) without increasing CABG-related bleeding.⁶ Logically, the updated guidelines released by the Society of Thoracic Surgeons in 2012 gave a class IIa endorsement to the use of platelet-function tests to make decisions about the timing of CABG, rather than the uniform use of an arbitrarily specified preoperative period of withdrawal of dual antiplatelet therapy involving P2Y₁₂-receptor inhibitors such as clopidogrel.⁷

It is also worth noting that more potent P2Y₁₂-receptor inhibitors, such as prasugrel and ticagrelor, are now available. Compared with clopidogrel, these inhibitors produce less interindividual variation in treatment outcomes and better clinical results for patients with ACS. They have therefore been recommended as replacements for clopidogrel in the ACS setting.⁵ More potent drugs may also increase the incidence of bleeding, however, with particularly negative implications for the success of surgery if CABG is urgently needed. Interestingly, it has recently been proposed that during preoperative discontinuation of P2Y₁₂-receptor inhibitors and the subsequent gradual recovery of platelet function, a “therapeutic window” balancing the risk of bleeding and ischemia can be identified by appropriate platelet-function tests.⁸ This may help to determine the safer period for CABG. Such concerns highlight the increasing importance of validated platelet-function tests.

Despite a growing body of evidence supporting the use of platelet-function monitoring to tailor therapy to patients receiving irreversible P2Y₁₂-receptor blocker treatment, no large-scale randomized trial to date has defined the best assay and assay-specific bleeding cutoffs. Moreover, it has long been recognized that a wide variety of factors are involved in the complex interactions causing

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perioperative coagulopathy.⁹ Among these factors are exposure to the cardiopulmonary bypass circuit, with resultant contact activation, hemodilution, hypothermia, anticoagulation with heparin and the subsequent reaction with protamine, and fibrinolysis, whereas platelet activation and the resulting dysfunction play only partial roles in this complex chain of inflammatory events.⁹ Point-of-care testing may therefore be particularly important, because it provides a comprehensive view of blood coagulation.

We may therefore regard the systematic review conducted by Cao and colleagues² as a summary of “the end of the beginning,” which will certainly inspire further scientific exploration and more bench-to-bedside investigation. Ultimately, it is up to the surgeon to decide whether it is in the best interests of the patient to remain “right here waiting” or to take further action.

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