Dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ receptor inhibitor is the current mainstay of pharmacological treatment in both patients with stable coronary artery disease and acute coronary syndrome managed invasively by percutaneous coronary intervention (PCI). The primary goal of DAPT is to reduce the risk of ischemic events including (re-)infarction and stent thrombosis. Contrary, this well-recognized ischemic benefit of DAPT is cut down by an increased on-treatment bleeding risk including major and fatal bleeding in both a nonoperative and operative setting like coronary artery bypass grafting (CABG). Bleeding risks differ for the currently available oral P2Y₁₂ receptor inhibitors. On the basis of the results of large-scale clinical trials and the clinical experience in recent years, we considered that the risk of bleeding to be modest for the second-generation thienopyridine clopidogrel, whereas more potent platelet inhibition, such as it is delivered by the third-generation thienopyridine prasugrel or the cyclo-pentyl-triazolo-pyrimidine ticagrelor, comes along with a substantially higher risk of bleeding. Immediate and sustained restoration of platelet function in patients on DAPT may become mandatory in a nonoperative setting like coronary artery bypass grafting. Bleeding risks differ for the irreversibly acting P2Y₁₂ receptor inhibitors. Hence, the currently available oral P2Y₁₂ receptor inhibitors (clopidogrel, 600 and 900 mg; prasugrel, 60 mg; and ticagrelor, 180 mg) in an ex vivo setting by autotransfusion (APTITUDE-Acute Coronary Syndrome (ACS)) and in an in vivo setting with allogeneic platelet transfusion in cardiac surgery patients on DAPT who had excessive bleeding during surgery (APTITUDE-CABG). As a key result of the APTITUDE-ACS study (n=59 patients), the authors were able to show that the level of restoration of platelet function by ex vivo administration of autologous platelet-rich plasma significantly decreased with increasing potency of the antiplatelet agent. In clopidogrel-treated patients, platelet function restoration was highest, whereas restoration was lower in prasugrel-treated subjects and by comparison lowest in the subgroup of ticagrelor-treated patients. In APTITUDE-CABG (n=52 patients), platelet transfusion resulted in a significant 23% relative increase (42.2±23.6% platelet reactivity index [PRI] before transfusion versus 56.6±23.6% PRI after transfusion; P=0.008) of the VASP PRI and the primary study end point was met. Of note, for the merged subgroup of patients (n=9) treated with potent P2Y₁₂ inhibitors (n=6 prasugrel patients and n=3 ticagrelor patients), there was also a relative increase of 24% in platelet reactivity but this did not reach a level of statistical significance (28.1±15.3% PRI versus 34.9±15.3% PRI; P=0.22).

O’Connor et al⁶ are to be commended for this study and for providing important data on platelet restoration with the available P2Y₁₂ receptor inhibitors in both an ex vivo and in vivo setting. However, in interpreting the data, some issues and important aspects merit mentioning: First, in APTITUDE, various platelet function profiles were used as surrogate end points to assess the pharmacological characteristics of the currently available oral P2Y₁₂ receptor inhibitors in a setting of platelet transfusion for platelet function restoration. Although platelet function markers for this study were wisely chosen, the interplay of blood platelets, various signaling cascades, and the entire coagulation system to achieve hemostasis is complex and can hardly be explored entirely by ex vivo testing. Thus, adequately powered and larger clinical trials with bleeding outcome assessment would be required here before definite conclusions can be drawn. It remains doubtful—in terms of feasibility—if such trials will ever be conducted in an adequate setting and with a critical quantity of enrolled patients.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Editorial

Restoring Platelet Function in Patients on P2Y₁₂ Receptor Inhibitor Treatment
Still Some Issues to Be Solved!

Dirk Sibbing, MD; Steffen Massberg, MD

In this issue of Circulation: Cardiovascular Interventions, O’Connor et al⁶ present the results of the prospective open-label Antagonize P2Y₁₂ Treatment Inhibitors by Transfusion of Platelets in an Urgent or Delayed Timing After Acute Coronary Syndrome or PCI Presentation (APTITUDE) study. Within APTITUDE study, the authors investigated the ability of platelet transfusion to restore platelet function in patients after loading with different P2Y₁₂ inhibitors (clopidogrel, 600 and 900 mg; prasugrel, 60 mg; and ticagrelor, 180 mg) in an ex vivo setting by autotransfusion (APTITUDE-Acute Coronary Syndrome (ACS)) and in an in vivo setting with allogeneic platelet transfusion in cardiac surgery patients on DAPT who had excessive bleeding during surgery (APTITUDE-CABG). As a key result of the APTITUDE-ACS study (n=59 patients), the authors were able to show that the level of restoration of platelet function by ex vivo administration of autologous platelet-rich plasma significantly decreased with increasing potency of the antiplatelet agent. In clopidogrel-treated patients, platelet function restoration was highest, whereas restoration was lower in prasugrel-treated subjects and by comparison lowest in the subgroup of ticagrelor-treated patients. In APTITUDE-CABG (n=52 patients), platelet transfusion resulted in a significant 23% relative increase (42.2±23.6% platelet reactivity index [PRI] before transfusion versus 56.6±23.6% PRI after transfusion; P=0.008) of the VASP PRI and the primary study end point was met. Of note, for the merged subgroup of patients (n=9) treated with potent P2Y₁₂ inhibitors (n=6 prasugrel patients and n=3 ticagrelor patients), there was also a relative increase of 24% in platelet reactivity but this did not reach a level of statistical significance (28.1±15.3% PRI versus 34.9±15.3% PRI; P=0.22).

O’Connor et al⁶ are to be commended for this study and for providing important data on platelet restoration with the available P2Y₁₂ receptor inhibitors in both an ex vivo and in vivo setting. However, in interpreting the data, some issues and important aspects merit mentioning: First, in APTITUDE, various platelet function profiles were used as surrogate end points to assess the pharmacological characteristics of the currently available oral P2Y₁₂ receptor inhibitors in a setting of platelet transfusion for platelet function restoration. Although platelet function markers for this study were wisely chosen, the interplay of blood platelets, various signaling cascades, and the entire coagulation system to achieve hemostasis is complex and can hardly be explored entirely by ex vivo testing. Thus, adequately powered and larger clinical trials with bleeding outcome assessment would be required here before definite conclusions can be drawn. It remains doubtful—in terms of feasibility—if such trials will ever be conducted in an adequate setting and with a critical quantity of enrolled patients.
As long as this is not the case, we have to take the data coming from (in vitro) studies such as APPTITUDE and others as the best available evidence for guidance of patient treatment. Second, the comparatively low sample size for prasugrel-treated patients (n=6) and ticagrelor-treated patients (n=3) in the APPTITUDE-CABG cohort precludes from drawing definite conclusions on the feasibility of immediate and sustained platelet restoration after platelet transfusion with these 2 agents. Although the authors observed a partial restoration of platelet aggregation in patients on maintenance treatment with these drugs, other studies and case reports provided conflicting data.

The complete inefficacy of platelet transfusions to reverse the antiplatelet action of ticagrelor was nicely highlighted in a case report of a patient with intracranial hemorrhage, where platelet reactivity levels remained virtually unchanged despite transfusion of 17 U of platelets. Other reports provided similar results. Furthermore, for APPTITUDE-CABG, the authors merged prasugrel- and ticagrelor-treated patients into 1 group within their study. Such an approach, however, is debatable because it was shown in previous studies that their properties in terms of platelet function recovery may differ because of their specific pharmacological properties. In an animal model, Sugidachi et al compared pharmacological profiles of prasugrel and ticagrelor. This study showed that in the prasugrel group, platelet transfusion shortened bleeding time, whereas this was not the case for the ticagrelor group under the experimental conditions used. Third, current treatment options for patients with severe bleeding on P2Y₁₂ receptor inhibitors are limited to platelet transfusions and best supportive care. Hence, specific antidotes would be desirable to allow for an immediate offset of the antiplatelet action of the drugs under discussion here. One such antidote (MEDI2452) for ticagrelor is currently under development with initial results being auspicious. As an antigen-binding Fab antidote, it successfully neutralized ticagrelor and ticagrelor’s active metabolite in a preclinical study. Importantly, the antidote also normalized ticagrelor-dependent bleeding in a mouse model of acute surgery. Interestingly, the affinity of the Fab antidote is 100 times stronger than the affinity of ticagrelor for its target receptor, which may at least, in part, explain the convincing results reported to date. Although published result is promising for this agent, further preclinical and clinical investigations are necessary and ongoing.

Finally, besides platelet transfusion, best supportive care and the future use of a specific antidote for ticagrelor, a more individualized approach toward the duration of DAPT post PCI may also provide a solution for on-treatment bleeding events and their management in a nonoperative and operative setting. Indeed, shorter DAPT durations of 3 to 6 months may be feasible after elective PCI procedures and when newest-generation drug-eluting stents are implanted. Also, in a scenario where DAPT must be combined with oral anticoagulation (triple treatment regimen), all efforts should be made to shorten the DAPT duration to a minimum whenever possible. Such approaches may prove useful for avoiding a substantial proportion of (major) bleeding complications, making a challenging bleeding management unnecessary.

Disclosures
Dr Sibbing reports having received speaker fees and honoraria for consulting from Eli Lilly, MSD, Daiicht Sankyo, Bayer Vital, Astra Zeneca, Verum Diagnostica and Roche Diagnostics and research grants from Roche Diagnostics. The other authors report no conflicts.

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