Editorial

Restoring Platelet Function in Patients on P2Y<sub>12</sub> 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 al<sup>5</sup> present the results of the prospective open-label Antagonize P2Y<sub>12</sub> Treatment Inhibitors by Transfusion of Platelets in an Urgent or Delayed Timing After Acute Coronary Syndrome or PCI Presentation (APTTITUDE) study. Within APTITUDE study, the authors investigated the ability of platelet transfusion to restore platelet function in patients after loading with different P2Y<sub>12</sub> inhibitors (clopidogrel, 600 and 900 mg; prasugrel, 60 mg; and ticagrelor, 180 mg) in an ex vivo setting by autotransfusion (APTTITUDE-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 (APTTITUDE-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 P2Y<sub>12</sub> 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 al<sup>5</sup> are to be commended for this study and for providing important data on platelet restoration with the available P2Y<sub>12</sub> receptor inhibitors in both an ex vivo and in vivo setting.<sup>5</sup> 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 P2Y<sub>12</sub> 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.

From the Medizinische Klinik und Poliklinik I, Klinikum der Universität München, Ludwig-Maximilians-Universität München, Munich, Germany, DZHK (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany.

Correspondence to Dirk Sibbing, MD, Medizinische Klinik und Poliklinik I, Ludwig-Maximilians-Universität München, Marchioninstraße 15, 81377 Munich, Germany. E-mail dirk@sibbing.net

See Article by O’Connor et al

DOI: 10.1161/CIRCINTERVENTIONS.115.003257.

© 2015 American Heart Association, Inc.

Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org

DOI: 10.1161/CIRCINTERVENTIONS.115.003257

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
As long as this is not the case, we have to take the data coming from (in vitro) studies such as APTITUDE\(^5\) and others\(^-\)\(^\text{10}\) as the best available evidence for guidance of patient treatment. Second, the comparatively low sample size for prasugrel-treated patients precludes from drawing definite conclusions on the effectiveness of maintenance treatment with these drugs, other studies and case reports provided conflicting data.\(^6\)\(^-\)\(^\text{11}\) 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.\(^7\) Other reports provided similar results.\(^5\)\(^9\) Furthermore, for APTITUDE-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\(^\text{11}\) 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 P2Y\(_\text{12}\) 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 fragment (Fab) antidote, it successfully neutralized ticagrelor and ticagrelor’s active metabolite in a preclinical study.\(^\text{12}\) Importantly, the antidote also normalized ticagrelor-dependent bleeding in a mouse model of acute surgery.\(^\text{11}\) Interestingly, the affinity of the Fab antidote is \(\approx 100\) 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\(^\text{11}\) 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.\(^\text{13}\) 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, Daiichi Sankyo, Bayer Vital, AstraZeneca, Verum Diagnostica and Roche Diagnostics and research grants from Roche Diagnostics. The other authors report no conflicts.

**References**


**Key Words:** Editorials - acute coronary syndrome - coronary artery disease - general surgery - platelet aggregation inhibitors - platelet transfusion
Restoring Platelet Function in Patients on P2Y₁₂ Receptor Inhibitor Treatment: Still Some Issues to Be Solved!
Dirk Sibbing and Steffen Massberg

Circ Cardiovasc Interv. 2015;8:
doi: 10.1161/CIRCINTERVENTIONS.115.003257
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/8/11/e003257

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Interventions can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Interventions is online at:
http://circinterventions.ahajournals.org//subscriptions/