

## New platelet aggregation inhibitors and the role of platelet function measurement

W. Toller

*University Hospital of Graz, Austria*

Acute coronary syndrome (ACS) is a life-threatening condition that has to be treated immediately in order to revascularize the jeopardized myocardium. While most patients receive a combination of a pharmacological intervention and placement of a coronary stent, 3 – 15% have to undergo a CABG procedure (1).

Typically, ACS-patients take a dual antiplatelet therapy consisting of acetylsalicylic acid and an inhibitor of the platelet P2Y<sub>12</sub>-receptor, i.e. clopidogrel, prasugrel and, more recently, ticagrelor. The rationale for such a combination is based on large RCT's that demonstrate a reduction of ischemic events when compared with patients taking aspirin alone. A typical and not unexpected side-effect of the combination of aspirin and a P2Y<sub>12</sub>-receptor antagonist is an increase in bleeding complications which is of special interest in the perioperative period. Recently, the newer P2Y<sub>12</sub>-inhibitors, prasugrel and ticagrelor, have been compared with the old and long-standing substance, clopidogrel, in this regard. Both the combination of aspirin with prasugrel (2) and the combination of aspirin with ticagrelor (3) demonstrated a 2.2 and 1.9% reduction of the composite endpoint of cardiovascular death, nonfatal myocardial infarction and stroke in comparison to patients taking aspirin and clopidogrel at the risk of increased bleeding. Post-hoc analyses of TRITON-TIMI 38 and PLATO evaluating patients undergoing CABG demonstrated as survival benefit of prasugrel and ticagrelor a compared to clopidogrel with overall increased and similar bleeding,

respectively (1). Currently, 2011 ESC guidelines therefore recommend (Class IIa/C) withdrawal of clopidogrel and ticagrelor 5 – 7 days before major surgery including CABG (4).

Remarkably, the power of this recommendation is weak due to the lack of prospective RCT's and, in parallel, partly controversial results in studies analyzing clopidogrel-associated perioperative bleeding. The reasons for these inconsistencies are unknown but may be related to varying definitions of bleeding, retrospective study designs and heterogeneous inclusion criteria of patients. In contrast, the TEG-assessed P2Y<sub>12</sub> receptor inhibition has been demonstrated to be associated with bleeding risk in 2 prospective, single center studies in patients undergoing CABG with and without cardiopulmonary bypass, indicating the usefulness of such a diagnostic approach (5, 6).

In this context, the most recent 2012 guidelines of the Society of Thoracic Surgeons (STS)(7) recommend withdrawal of P2Y<sub>12</sub> inhibitors "several days" preoperatively but with consideration of "drug responsiveness" and risk of ischemia, indicating a more individual approach when compared to the ESC guidelines. While this indicates the usefulness of preoperative P2Y<sub>12</sub> blockade measurement, no validated cutoff's for bleeding and no favor for a specific type of test exists.

In addition to drug-specific influence on bleeding complications (i.e. degree of P2Y<sub>12</sub>-receptor blockade) other factors have been demonstrated to be of importance in-

cluding triggers of transfusion, degree of hemodilution and surgeon's experience.

In conclusion, new P2Y<sub>12</sub> receptor inhibitors provide a clear 1-year survival benefit after CABG but may in parallel be associated with an increased bleeding risk. Current recommendations regarding the perioperative management of patients taking such drugs are mainly based on retrospective studies and post-hoc analyses of RCTs not controlling for perioperative confounders. The role of the preoperative assessment of platelet function is currently unclear but recent studies emphasize the efficacy and safety of individual instead of general management strategies.

## References

1. Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: Results from the PLATO (platelet inhibition and patient outcomes) trial. *J Am Coll Cardiol* 2011; 57: 672-684
2. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; 357: 2001-2015
3. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361: 1045-1057
4. Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011; 32: 2999-3054
5. Mahla E, Suarez TA, Bliden KP, et al. Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing

coronary artery bypass graft surgery: The timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. *Circ Cardiovasc Interv* 2012; 5: 261-269

6. Kwak YL, Kim JC, Choi YS, et al. Clopidogrel responsiveness regardless of the discontinuation date predicts increased blood loss and transfusion requirement after off-pump coronary artery bypass graft surgery. *J Am Coll Cardiol* 2010; 56: 1994-2002
7. Ferraris VA, Saha SP, Oestreich JH, et al. 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and non-cardiac operations. *Ann Thorac Surg* 2012; 94: 1761-1781

### *Correspondence address:*

Univ.-Prof. Dr. med. Wolfgang Toller  
Medizinische Universität Graz  
Klinische Abteilung für Anästhesie, für  
Herz- und Gefäßchirurgie und  
Intensivmedizin  
Auenbruggerplatz 29  
A-8036 Graz, Austria  
wolfgang.toller@medunigraz.at