European Journal of Cardio-Thoracic Surgery 53 (2018) 3–4
doi:10.1093/ejcts/ezx333 Advance Access publication 26 September 2017

EDITORIAL

Cite this article as: Jeppsson A, Petricevic M, Kolh P, Valgimigli M. 2017 European Society of Cardiology (ESC) focused update on dual antiplatelet therapy in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2018;53:3–4.

2017 European Society of Cardiology (ESC) focused update on dual antiplatelet therapy in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

Anders Jeppsson[a,*], Mate Petricevic[b], Philippe Kolh[c] and Marco Valgimigli[d]

[a] Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[b] Department of Cardiac Surgery, School of Medicine, University of Zagreb, University Hospital Center Zagreb-Rebro, Zagreb, Croatia
[c] Department of Biomedical and Preclinical Sciences, University Hospital (CHU, ULg) of Liège, Liège, Belgium
[d] Department of Cardiology, Inselspital Universitätsspital Bern, Bern, Switzerland

* Corresponding author. Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 405 30 Gothenburg, Sweden. Tel: +46-31-3427515; fax: +46-31-417991; e-mail: anders.jeppsson@vgregion.se (A. Jeppsson).

Keywords: Dual antiplatelet therapy • Cardiac surgery

INTRODUCTION

Antiplatelet therapy (APT) reduces the risk for adverse ischaemic events in patients with coronary artery disease (CAD). Dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel and ticagrelor) is more effective than ASA alone and is indicated in most patients with acute coronary syndrome (ACS), i.e. myocardial infarction or unstable angina pectoris, and after percutaneous coronary interventions. In fact, DAPT has moved from a treatment discovered to prevent stent thrombosis after percutaneous coronary interventions to a treatment which is indicated well beyond stent insertion. However, APT also increases the risk for both spontaneous and perioperative bleeding complications, which may cause a problem if urgent or emergent surgery, e.g. coronary artery bypass grafting (CABG), is necessary. The bleeding risk is further increased in patients treated with DAPT, especially with the third-generation $P2Y_{12}$ inhibitors, prasugrel and ticagrelor.

Excessive perioperative bleeding in cardiac surgery is neither an uncommon nor a trivial event. Severe or massive bleeding according to the Universal Definition of Perioperative Bleeding occurred in approximately 10% of adult cardiac surgery patients and was associated with a 6-fold increase in operative mortality compared to patients with insignificant bleeding, after adjustment for other factors influencing mortality [1]. Every effort to reduce the risk for severe bleeding complications, including timely discontinuation of $P2Y_{12}$ inhibitors, needs thus to be considered preoperatively. It is not completely understood why bleeding complications are so harmful, given the possibility of blood transfusions, but the blood loss volume, organ hypoperfusion, the repeated surgical trauma during re-exploration and transfusions have all been suggested to contribute.

The bleeding in cardiac surgery patients is multifactorial. Preoperative use of APT and anticoagulants contributes but also the surgical trauma and an impaired perioperative haemostasis, due to exposure of blood to non-endothelialized surfaces, haemodilution, increased fibrinolysis, reheparinization, consumption of platelets and coagulation factors influence. In addition, patient- and procedure-related factors, such as low body mass index, preoperative anaemia, poor renal function, advanced age, previous sternotomy and acute operations, have been persistently associated with increased bleeding in different studies.

Although ongoing or recently stopped APT increases the risk for perioperative bleeding complications, it is important to balance the negative effect of APT on bleeding risk with the reduced risk for ischaemic events. Reinstitution of DAPT in ACS patients may improve outcome and is recommended also in current revascularization guidelines [2] but is often neglected after CABG [3, 4].

The knowledge about APT, including DAPT, in patients with CAD is constantly evolving, and the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) have therefore collaboratively published a new focused update on DAPT in this issue of the *European Journal of Cardio-Thoracic Surgery* [5] and in the *European Heart Journal* [6]. The update contains a review of the efficacy and safety of DAPT and new detailed guidelines for the use of DAPT in patients with stable CAD and ACS. A separate chapter contains recommendations about DAPT in cardiac surgery patients, including perioperative discontinuation and reinstitution of ASA and the different $P2Y_{12}$ inhibitors, the use of platelet function test and gaps in evidence.

Some key messages and recommendations in the update regarding cardiac surgery patients are worth mentioning. It is still recommended to continue low-dose ASA throughout the perioperative period in patients preoperatively treated with ASA (Class I, level of evidence C). In patients treated with DAPT before CABG, it is recommended to discontinue prasugrel at least 7 days, clopidogrel at least 5 days and ticagrelor at least 3 days before

surgery (Class IIa, level of evidence B) whenever possible. The recommendation for ticagrelor has changed compared to previous guidelines, where a 5-day discontinuation period was recommended. The change is based on 3 observational studies, which could not establish any increased risk for major bleeding when ticagrelor was stopped 72–120 h before surgery compared with >120 h [5]. In patients with very high risk for thrombotic events, e.g. recent stent implantation, cangrelor or a glycoprotein IIb/IIIa blocker may be considered to bridge the patients to CABG. In all ACS patients and in patients with recent coronary stent implantation, it is recommended to resume $P2Y_{12}$ inhibitor therapy as soon as deemed safe after surgery and continue with DAPT until the recommended duration of therapy is completed (Class I, level of evidence C). In patients with stable CAD, the update does not recommend DAPT after surgery. This is in contrast with the 2016 ACC/AHA guidelines, where DAPT was also recommended in patients with stable CAD to improve graft patency [7]. This present ESC/EACTS task force found the evidence for a recommendation insufficient and felt that further studies were warranted. The task force found also insufficient evidence to recommend DAPT in combination with anticoagulants ('triple treatment') in patients with indication for anticoagulation after CABG.

The update also recommends that platelet function testing should be considered to guide decisions on the timing of cardiac surgery in patients who have recently received $P2Y_{12}$ inhibitors (Class IIa, level of evidence B). Originally, platelet function testing was developed to identify CAD patients with insufficient platelet inhibition after a coronary event. More recent studies have shown that platelet function testing may also have a role in timing of surgery in patients with ongoing or recently stopped DAPT [5]. Several studies have shown a significant association between adenodiphosphate (ADP)-dependent platelet aggregation preoperatively and the risk for perioperative bleeding complications in CABG patients with ongoing or recently stopped DAPT [5]. The studies in CABG patients have generally demonstrated low or moderate positive predictive values (23–63%) but high negative predictive values (85–95%). Subsequently, the tests better identify patients who are not at risk for increased bleeding due to sufficient platelet function rather than identifying which patient is at increased risk for bleeding due to poor platelet function. The high negative predictive value indicates that platelet function testing may be used to potentially shorten the waiting period following drug discontinuation. This was also demonstrated in a randomized controlled trial (RCT) demonstrating shorter waiting times in clopidogrel-treated CABG patients when preoperative platelet function testing was applied [8]. It should, however, be noted that no randomized study with bleeding-related end points have directly compared time-based and platelet function testing-based discontinuation of $P2Y_{12}$ inhibitors as yet. Furthermore, there is still no standardized use of preoperative platelet function testing. Consensus on the standardization of preanalytical handling of the blood samples and cut-off levels for the different devices is most likely needed to further improve testing.

The update contains also some more universal recommendations of interest for surgeons. The general use of proton inhibitors in patients on DAPT is recommended to minimize the risk for gastrointestinal bleeding (Class 1, level of evidence B), and similar type and duration of DAPT are recommended in male and female patients (Class I, level of evidence A). There are also still some apparent gaps in evidence related to APT in cardiac surgery patients. The recommendation of resuming DAPT after CABG in ACS patients is based on subgroup analyses from RCTs and observational studies of variable quality. An RCT in ACS patients, comparing DAPT with ASA only, which is still the standard of care at many institutions [2, 3], undergoing CABG is warranted. Similarly, the role of DAPT in patients with stable coronary disease remains unclear, and the use of platelet function testing before surgery needs to be standardized. Finally, it is unclear how an incomplete response or inadequate antiplatelet effect of ASA and or $P2Y_{12}$ inhibitors ('high on-treatment reactivity') after CABG should be addressed.

CONCLUSION

In conclusion, DAPT has become a cornerstone in the treatment of patients with CAD. This update defines the present understanding and the role of DAPT in CAD, but the field is likely to continue to evolve over the coming years. It is already evident that the 'one-size-fits-all' concept is not applicable for antiplatelet therapy. A personalized approach, when it comes to the choice of drug(s), discontinuation in the event of urgent surgery and length of the treatment period, is necessary to maintain the efficacy of the treatment and reduce the risk for bleeding complications. New data from RCTs and large observational studies will be essential to further improve DAPT.

Conflict of interest: Anders Jeppsson has received speaker's fee and/or advisory board fees from AstraZeneca, CSL Behring and Octapharma. Institutional research grants from AstraZeneca and XVIVO. Philippe Kolh has received speaker's fee and/or advisory board fee from AstraZeneca and B. Braun. Marco Valgimigli has received speaker's fee and/or advisory board fees from AstraZeneca, Terumo Inc, Abbot Vascular, Sinomed, Bayer, Correvio. Institutional research grants from AstraZeneca, Medicure, Terumo Inc, The Medicines Company. Mate Petricevic has nothing to declare.

REFERENCES

[1] Dyke C, Aronson S, Dietrich W, Hofmann A, Karkouti K, Levi M *et al*. Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg 2014;147:1458–63.

[2] Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V *et al*. 2014 ESC/EACTS guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2014;46:517–92.

[3] SWEDEHEART Annual report 2015. http://www.ucr.uu.se/swedeheart/dokument-sh/arsrapporter (15 July 2017, date last accessed).

[4] Yanagawa B, Ruel M, Bonneau C, Lee MM, Chung J, Al Shouli S *et al*. Dual antiplatelet therapy use by Canadian cardiac surgeons. J Thorac Cardiovasc Surg 2015;150:1548–54.

[5] Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2018;53:34–78.

[6] Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2017; doi: 10.1093/eurheartj/ehx419.

[7] Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA *et al*. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082–115.

[8] Mahla E, Suarez TA, Bliden KP, Rehak P, Metzler H, Sequeira AJ *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. Circulation Cardiovasc Interv 2012;5:261–9.