ESC European Society of Cardiology

European Heart Journal (2017) **38**, 3079–3081
doi:10.1093/eurheartj/ehx253

EDITORIAL

Clopidogrel instead of prasugrel or ticagrelor after 1 month in stabilized ACS patients: back to square one for DAPT?

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Online publish-ahead-of-print 16 May 2017

This editorial refers to 'Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study'[†], by T. Cuisset *et al.*, on page 3070.

Following an acute coronary syndrome (ACS), patients remain at risk for new ischaemic events, regardless of the type of presentation or the initial management. Although a substantial proportion of the recurrent events occur in the first months, there is a continuing accruement of new ischaemic events afterwards.[1] As a consequence, guidelines recommend a $P2Y_{12}$ inhibitor to be added to low-dose aspirin for the first year following an ACS, whether or not a percutaneous coronary intervention (PCI) is performed, and to continue low-dose aspirin alone indefinitely. The recommended duration of 1 year of dual antiplatelet therapy (DAPT) after an ACS is arbitrarily based on the treatment duration in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, the first outcome trial on DAPT in ACS.[2] Because DAPT puts ACS patients at an increased risk of bleeding complications, $P2Y_{12}$ inhibitors are often deliberately discontinued before 1 year because of the occurrence of bleeding or a perceived or real high bleeding risk. On the other hand, registries have shown, surprisingly, that in a significant proportion of ACS patients DAPT is continued beyond 1 year because neither ischaemic nor bleeding events had occurred (the 'never change a winning team' approach).[3,4]

The superiority of ticagrelor and prasugrel over clopidogrel in the first year following an ACS has been clearly established in two pivotal large international trials.[5,6] Landmark analyses of these trial data show a greater reduction in recurrent ischaemic events with these new agents throughout the year following the event, thus not only during the acute phase but also afterwards.[7,8] Ticagrelor and prasugrel (the latter with some restrictions) are hence unequivocally recommended on top of low-dose aspirin for 1 year after an ACS.[9,10] Clopidogrel only remains a recommended option for ACS patients without access to either ticagrelor or prasugrel. Still, ever since these trials, cardiologists have wondered whether tiered, step-wise approaches could be as effective and perhaps safer than the guidelines recommendations. One option among many, for instance, is switching to clopidogrel at discharge or a few weeks later instead of continuing prasugrel or ticagrelor. Issues with reimbursement or availability, or with a perceived bleeding risk are assumed to justify a switch to the less potent and cheaper $P2Y_{12}$ inhibitor clopidogrel.

In this issue of the journal, Cuisset and colleagues report the results of the Timing Of Platelet Inhibition after acute Coronary syndrome (TOPIC) study, the first randomized clinical trial investigating a switch from prasugrel or ticagrelor to clopidogrel vs. continuing either drug after a PCI for ACS.[11] A total of 646 patients with an ST-segment elevation myocardial infarction (STEMI), non-STEMI, or unstable angina who did not experience an ischaemic or bleeding event in the first 30 days after the event were then randomized to either strategy. One year after the ACS, significantly more patients who continued their more potent $P2Y_{12}$ inhibitor experienced the combined endpoint of cardiovascular death, stroke, unplanned hospitalization leading to revascularization, or a Bleeding Academic Research Consortium (BARC) bleeding category of ≥ 2 compared with those switching to clopidogrel. With very low numbers of ischaemic events or Thrombolysis In Myocardial Infarction (TIMI) major bleeding complications, not unexpectedly this difference was mainly driven by fewer non-major bleedings including the relatively innocuous BARC type 2 bleedings, i.e. harmless bleedings leading to medical attention. The number of BARC type 2 bleedings was not reported separately. There was even a non-significant numerical excess in ischaemic events in patients continuing ticagrelor or prasugrel. Most of these events were unplanned revascularizations however, and the proportion of patients who needed a new intervention because of a new spontaneous MI was not reported, nor was the

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

[†] doi: 10.1093/eurheartj/ehx175.

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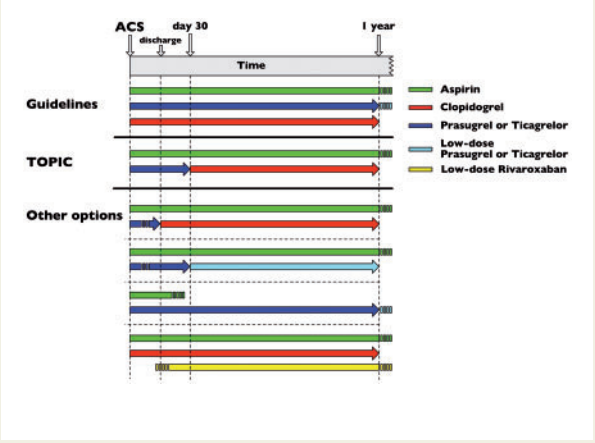

Figure 1 Options for 1-year dual antiplatelet therapy: guideline-recommended combinations, TOPIC, and selected alternative strategies to be explored in clinical trials. ACS, acute coronary syndome.

number of MIs itself. Recurrent MIs not leading to revascularization were not part of the primary endpoint as well.

The TOPIC investigators need to be commended for conducting this first randomized clinical trial investigating a 'downgrading' of the DAPT regimen in stabilized ACS patients. The randomization of 646 patients in a single centre and successfully following these patients up to 1 year is a testimony of their hard work. While the results from TOPIC are certainly intriguing, they obviously need be interpreted in view of the limitations of this single-centre trial. The open-label nature of the trial, the telephone-based follow-up, the internal event adjudication, as well as an envelope system of randomization warrant a judicious interpretation. Importantly, the number of patients lost to follow-up plus the patients crossing over to the other treatment strategy arm exceeds the total number of many of the individual endpoints which also prohibits making definite conclusions.

Other 'idiosyncrasies' of TOPIC also deserve further comments. An unknown proportion of patients in this trial did not have elevated cardiac markers of necrosis at the time of their ACS but, together with non-STEMI patients, they appear to constitute the majority of patients included here (60%). In this era of high-sensitivity troponin, one can only wonder to what extent these unstable angina patients differ from stable PCI patients who are known to do very well on aspirin and clopidogrel after PCI. Also, while events with ticagrelor vs. prasugrel were not reported separately, 10 mg of prasugrel was used, without a reduced dose in the elderly (ESC guidelines do recommend using 5 mg in this population). It remains unclear how many elderly patients were on the 10 mg dose, and how many of these patients contributed to the total number of bleeding complications. Finally, the most difficult to interpret quirk of TOPIC is the occurrence of events in the first month before the randomization at day 30, despite significant ischaemic or bleeding events during this first month being exclusion criteria. Even when most events occur between day 30 and 1 year, judging from the event curves, pre-randomization events appear to disfavour the unchanged DAPT arm during the first month.

Taken together, the results of TOPIC obviously do not invalidate the superiority of ticagrelor or prasugrel over clopidogrel as observed in the much larger, double-blind, multicentre trials, and as a consequence cannot influence clinical practice and affect future guidelines. They may, however, add fuel to the debate on individualizing and optimizing post-ACS treatment. There still remain many options for long-term anti-thrombotic treatment after an ACS. Some of them have not found their way into clinical practice, such as adding a low dose of rivaroxaban to aspirin and clopidogrel in spite of a mortality reduction shown in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2-TIMI 51) trial, although this may change when the results of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial will become available. Other options are worth exploring in new outcome trials, e.g. a lower dose of ticagrelor or prasugrel after a few days or 1 month, switching to clopidogrel as done in TOPIC but in specific subgroups based for instance on age or bleeding risk or on platelet and genetic testing results, or discontinuing aspirin altogether and keeping the patient on ticagrelor or prasugrel alone (*Figure 1*). From this viewpoint, TOPIC is not a return to square one in post-ACS management, but hopefully the first square in a new board game of tailored anti-thrombotic strategies in the post-ACS setting.

Conflict of interest: P.R.S. has received speaker's fees, clinical trial fees, or small grants at an institutional level from AstraZeneca, Daiichi Sankyo, MSD, Sanofi, Boehringer Ingelheim, Pfizer, and Bayer. F.V. has received institutional grants from Boehringer Ingelheim, Sanofi, MSD, and The Medicines Company, and honoraria from AstraZeneca, Bayer, MSD, Eli-Lilly, The Medicines Company, Sanofi, and Boehringer Ingelheim.

References

1. Fox KA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, Buysschaert I, Lambrechts D, Van de Werf F. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). *Eur Heart J* 2010;**31**:2755–2764.
2. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494.
3. Bueno H, Pocock S, Danchin N, Annemans L, Gregson J, Medina J, Van de Werf F. International patterns of dual antiplatelet therapy duration after acute coronary syndromes. *Heart* 2017;**103**:132–138.
4. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Berger PB, Iakovou I, Dangas G, Waksman R, Antoniucci D, Sartori S, Krucoff MW, Hermiller JB, Shawl F, Gibson CM, Chieffo A, Alu M, Moliterno DJ, Colombo A, Pocock S. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet* 2013;**382**:1714–1722.
5. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
6. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–2015.

7. Mahaffey KW, Wojdyla DM, Carroll K, Becker RC, Storey RF, Angiolillo DJ, Held C, Cannon CP, James S, Pieper KS, Horrow J, Harrington RA, Wallentin L; PLATO Investigators. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) Trial. *Circulation* 2011;**124**:544–554.
8. Antman EM, Wiviott SD, Murphy SA, Voitk J, Hasin Y, Widimsky P, Chandna H, Macias W, McCabe CH, Braunwald E.Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol* 2008;**51**:2028–2033.
9. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J; Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
10. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;**33**:2569–2619.
11. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, Bonnet G, Fourcade L, Mouret JP, Lambert M, Verdier V, Morange PE, Alessi MC, Bonnet JL. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J* 2017;**38**:3070–3078.