Editorial

Powerful P2Y12 inhibition after percutaneous coronary intervention for an acute coronary syndrome: "the times they are a changing"

Stefano Savonitto, Luca A. Ferri, Giorgio Bassanelli, Gianluca Tiberti, Luigi Piatti

Cardiovascular Department, Ospedale A. Manzoni, Lecco, Italy

Correspondence to: Dr. Stefano Savonitto. Cardiovascular Department, Manzoni Hospital, Via dell' Eremo, 9. 23900 Lecco, Italy.
Email: s.savonitto@asst-lecco.it.

Comment on: Sibbing D, Aradi D, Jacobshagen C, *et al.* Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017;390:1747-57.

Received: 05 November 2017; Accepted: 25 January 2018; Published: 08 February 2018.
doi: 10.21037/amj.2018.01.17
View this article at: http://dx.doi.org/10.21037/amj.2018.01.17

A brief history of dual antiplatelet therapy (DAPT)

DAPT using aspirin and a $P2Y_{12}$ platelet ADP receptor blocker has been established since more than 20 years as the pharmacological background of percutaneous coronary intervention (PCI) and post-acute coronary syndrome (ACS) (*Table 1*). First, the combination of aspirin and ticlopidine given for 30 days has shown superiority over aspirin and anticoagulant therapy in patients undergoing coronary artery stenting (1). Subsequently, in the landmark CURE study, DAPT using aspirin and clopidogrel (the so called 2nd generation $P2Y_{12}$ receptor blocker, devoid of the myelotoxicity of ticlopidine) given for a median duration of 9 months (maximum 12 months) has shown superiority over aspirin alone in patients with non-ST elevation ACS (2). Finally, two "3rd generation" $P2Y_{12}$ blockers, prasugrel and ticagrelor, more powerful and predictable in antiplatelet effect as compared to clopidogrel, showed superiority over clopidogrel as adjunct to aspirin across the ACS spectrum. The two trials validating these new agents had a duration of about 12 months (3,4), reinforcing (though not necessarily confirming, due to the missing aspirin-only arm) the CURE study standard. Following these studies, practice Guidelines have recommended, and maintained indefinitely, to start DAPT at the time of index ACS using the 3rd generation $P2Y_{12}$ blockers, and to continue this treatment for 12 months. However, the duration of DAPT has become matter of debate for years, and even the subject of specific Guidelines on both sides of the Atlantic (5,6).

Longer or shorter duration of DAPT?

In recent years, several important studies have tackled the CURE-derived concept of 12-month DAPT, many of them testing shorter duration, and some testing longer duration of therapy (6). This trial-based controversy has also been the subject of metanalyses (7,8). Implicit in its mode of action, there is no doubt that, compared to aspirin alone, DAPT significantly increases the risk of bleeding, particularly gastrointestinal, and especially in elderly patients. This increased risk persists indefinitely and unpredictably (9): although some bleeding risk scores have been developed and validated, they have been endorsed with moderate enthusiasm by practice Guidelines, with a grade IIb recommendation (6). Prolonging DAPT has systematically been shown to increase significantly the risk of major nonfatal bleeding (10). On the other hand, due to the well-known protective effect of antiplatelet therapy in secondary prevention of ischemic heart disease (11), prolonging DAPT has actually been shown to reduce the risk of MI and stroke, but had no effect on overall or cardiovascular mortality (10). Therefore, current guidelines are very prudent (grade IIb, LoE A) in recommending prolongation of DAPT after the 12-month standard, stating that "$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischemic and bleeding risk of the patient" (12). However, for most clinicians, and for many reasons, the real

Table 1 Generations of orally active $P2Y_{12}$ platelet ADP receptor blockers and pivotal trials in Acute Coronary Syndromes and Percutaneous Coronary Interventions

Generation, drug	Pivotal trials (ref)	Duration	Ischemic events (HR, 95% CI)*	Bleeding events (HR, 95% CI)*
1st generation, ticlopidine	ISAR (1) Ticlopidine + aspirin *vs.* VKA + aspirin	30 days	0.25, 0.06–0.77	0.00, 0.00–0.19
2nd generation, clopidogrel	CURE (2) Clopidogrel + aspirin *vs.* aspirin alone	3–12 months (median 9 months)	0.80, 0.72–0.90	1.38, 1.13–1.67
3rd generation, prasugrel	TRITON-TIMI 38 (3), Prasugrel + aspirin *vs.* Clopidogrel + aspirin	6–15 months (median 14.5 months)	0.81, 0.73–0.90	1.32, 1.03–1.68
3rd generation ticagrelor	PLATO (4) Ticagrelor + aspirin *vs.* clopidogrel + aspirin	6–15 months (median 9 months)	0.84, 0.77–0.92	1.25, 1.03–1.53

*, HR<1 favours experimental group, VKA, vitamin K antagonist.

issue has now become "how short can we make DAPT after a PCI-treated ACS?"

The changing landscape of ACS and PCI

Over the last 15 years, the routine coronary interventional approach to ACS, based on timely myocardial reperfusion in STEMI, and early aggressive treatment in NSTEACS, has improved outcomes across the ACS spectrum in both sexes and at all ages, including elderly patients (13,14). The increasing operator expertise in stent-lesion matching, and the continuous improvement in stent technology, raise questions about the current validity of the 15-year old standard of 12-month DAPT. Perhaps, also the ubiquitous use of high-dose statins starting from an ACS episode has also contributed to plaque stabilization and improved post-acute outcomes. A further reason for shortening DAPT duration is the increasing number of elderly patients being treated with PCI during an ACS, and the additional fact that almost 10% of the ACS population has atrial fibrillation (15), with the associated need of long-term oral anticoagulant therapy in adjunct to DAPT (6).

The concept of stage-adapted DAPT

Post-hoc analyses of the classical post-ACS DAPT studies have shown that most of the reduction in ischemic recurrences after an ACS was observed within the first four weeks of treatment (16), but major bleeding events continued to accrue throughout the year (17,18). These observations led to conceive a first phase with an elevated risk of recurrent thrombotic events, followed by a second phase where the risk of bleeding complications outweighs the ischemic risk. The ischemic phase would require a potent platelet inhibition, using 3rd generation $P2Y_{12}$ blockers, whereas, during the secondary phase, the degree of platelet inhibition could be reduced (by stepping down to clopidogrel) to optimize the balance between ischemic benefit and bleeding risk. A few studies have been completed in the last year (*Table 2*). It is remarkable that all these studies, focusing the post-acute phase of ACS, had an extremely low ischemic event rate at one year, highlighting the above mentioned current post-ACS landscape.

The TOPIC study

The single center TOPIC study (19) conducted in Marseille, France, investigated the impact of switching from aspirin plus a 3rd generation $P2Y_{12}$ blocker to a combination of aspirin and clopidogrel one month after ACS. 646 pts were enrolled over 25 months, at the remarkable pace of 26 pts per month, which means an all-comer study. Patients were enrolled across the ACS spectrum, including those with unstable angina and negative troponin. All patients had undergone PCI during index admission, and drug eluting stents were used in 91% of the cases. At discharge, 43% of the patients were on ticagrelor, and 57% on prasugrel. Randomization took place at one month in patients with no events during the first month. At 1 year, the allocated DAPT regimen was still used by 86% of 322 patients in the switched DAPT group and 75% of 323 patients in the unchanged DAPT group (P<0.01): the main reasons for drug change in both groups were ischemic or bleeding events, need for surgery or need for triple therapy, adding

Table 2 Recent trials of "stage-adapted" $P2Y_{12}$ receptor blockade in ACS-PCI

Study (ref)	Initial $P2Y_{12}$ blocker	Time of switch	Mode of switch	Ischemic events (HR, 95% CI)*	Bleeding events (HR, 95% CI)*
TOPIC (19)	Prasugrel or ticagrelor	30 days	Random	0.80, 0.50–1.29	0.30, 0.18–0.50
TROPICAL ACS (20)	Prasugrel	15 days	Based upon PFT results	0.77, 0.50–1.21	0.82, 0.59–2.13
ANTARCTIC (21)	Prasugrel 5 mg	15 days	Based upon PFT results	1.06, 0.69–1.62	1.04, 0.68–1.40

ANTARCTIC enrolled patients aged ≥75 years. *, HR<1 favours switched group. PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; PFT, platelet function testing.

an anticoagulant for atrial fibrillation. The primary aggregate endpoint of cardiovascular death, urgent coronary revascularization, stroke, and Bleeding Academic Research Consortium (BARC) episodes ≥2 at 12 months occurred in 43 (13.4%) patients in the switched DAPT group and in 85 (26.3%) patients in the unchanged DAPT (HR 0.48, 95% CI, 0.34–0.68, P<0.01). No significant differences were reported in ischemic endpoints, while BARC ≥2 bleeding occurred in 13 (4.0%) patients in the switched DAPT and in 48 (14.9%) in the unchanged DAPT group (HR, 0.30, 95% CI, 0.18–0.50, P<0.01). Although the study was not powered to discriminate individual ischemic endpoints, all of them were lower in the switching therapy group, and all relevant subgroups showed the same trend.

The TROPICAL ACS study

A more complex approach has been used by the TROPICAL ACS Investigators (20) in a multicenter study enrolling 2,610 patients at 33 Centers in Europe. All patients had biomarker-positive ACS with successful PCI and a planned treatment with DAPT for 12 months. Enrolled patients were randomised to either standard treatment with prasugrel for 12 months or a stepdown regimen (1-week prasugrel followed by 1-week clopidogrel and PFT-guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge; guided de-escalation group). The Multiplate analyser (Roche Diagnostics, Rotkreuz, Switzerland) was used for testing. A status of high platelet reactivity (HPR) was defined based on the results of previous studies and the consensus documents of the Working Group on HPR as an ADP test aggregation value of 46 units or higher on the Multiplate analyser (22). In the guided de-escalation group, testing results determined the further course of treatment: patients with HPR were immediately switched back to prasugrel (511 out of 1,304 patients, 39% of the intention-to-treat population), while those without HPR continued on clopidogrel. Analysis was intention to treat but, differently from the TOPIC study, de-escalation to clopidogrel actually happened in only 61% of the experimental group. The primary endpoint was the net clinical outcome of cardiovascular death, MI, stroke or bleeding grade ≥2 according to BARC criteria at 1 year. This endpoint occurred in 95 patients (7%) in the guided de-escalation group and in 118 patients (9%) in the control group (HR, 0.81; 95% CI, 0.62–1.06; $P_{non\text{-}inferiority}$=0.0004, $P_{superiority}$=0.12). Neither the ischemic (3% *vs.* 3%), nor the bleeding events (5% *vs.* 6%) were different in the two groups.

The ANTARCTIC study in patients aged ≥75 years

A platelet function testing approach to allow safe downgrading of antiplatelet therapy was also followed in the ANTARCTIC study (21). Elderly patients have been shown to display high on-clopidogrel platelet reactivity (23), but are also at elevated risk of bleeding events. Therefore, fine tuning of of antiplatelet therapy would seem ideal. In this study done at 35 Centers in France, 877 patients aged ≥75 years, who had undergone coronary stenting for ACS, were randomly assigned to receive prasugrel 5 mg daily with dose or drug adjustment in case of inadequate response (monitoring group), or prasugrel 5 mg daily with no monitoring or treatment adjustment (conventional group). Platelet function testing was done 14 days after randomisation and repeated 14 days after treatment adjustment in patients in the monitoring group. In the monitoring group, 45% of the patients had their $P2Y_{12}$blocker adjusted based on the results of platelet function test: in those with high platelet reactivity

(≥208 $P2Y_{12}$ reaction units) the prasugrel dose was increased to 10 mg. In patients with low platelet reactivity (≤85 $P2Y_{12}$ reaction units) prasugrel 5 mg was replaced with clopidogrel 75 mg, with subsequent checks after a further 14 days. The primary endpoint (a composite of cardiovascular death, MI, stroke, stent thrombosis, urgent revascularisation, and BARC-defined bleeding types 2, 3, or 5 at 12 months) occurred in 28% of the patients in the monitoring group, and 28% in the conventional group (HR, 1.003, 95% CI, 0.78–1.29; P=0.98). No trends between groups were observed in the rates of ischemic or bleeding events.

The above mentioned three studies (*Table 2*) followed different approaches for adapting DAPT intensity to the different stages of ACS follow-up. The TOPIC study followed a lean approach to reducing $P2Y_{12}$ intensity, simply shifting from a 3rd generation blocker to clopidogrel, and showed clearcut results, at least in terms of reduced bleeding, in favor of downgrading the intensity of platelet inhibition after 1 month of powerful platelet inhibition. On the other hand, the TROPICAL ACS and the ANTARCTIC studies, led by experts in platelet function testing, made a more complicated attempt to adjust $P2Y_{12}$ therapy guided by the on-treatment platelet reactivity displayed by the patients after the downgrading (TROPICAL ACS) or after two weeks of the initial drug (ANTARCTIC). The results of these studies, if not powered to definitely reduce to one month after ACS the duration of intense platelet inhibition, should at least further discourage the clinician to use platelet function testing for adapting treatment to disease stage or patient risk.

Conclusions

The so far recommended 12-month course of DAPT after an ACS, explicitly using the powerful 3rd generation $P2Y_{12}$ receptor blockers reflects a time of ACS treatment which is more than 10 years old. As described in the present editorial, a lot has changed in recent years with regard to PCI safety and patient population being treated with PCI in the acute phase. Shorter or stage-adapted DAPT has clearly shown benefit in terms of reduced bleeding. Larger studies powered to clearly establish the safety of early de-escalation in terms of ischemic events would be welcome. It is unlikely that such studies will be funded by the pharmaceutical industry.

Acknowledgements

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xiaoyan Wang (Department of cardiovascular medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2018.01.17). Dr. Savonitto reports grants from NOVARTIS, grants from ELI LILLY, grants from CORREVIO, personal fees from Astra Zeneca, personal fees from Bayer, personal fees from Bristol Meyer Sqibb, personal fees from Pfizer, outside the submitted work; Dr. Piatti reports personal fees from Volcano Europe, outside the submitted work. The other authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084-9.
2. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromed without ST-segment elevation. N Engl J Med 2001;345:494-502.
3. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
4. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N

Engl J Med 2009;361:1045-57.
5. Levine GN, Bates ER, Bittl JA, 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: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 ACC/AHA guideline for the management of patients with non–ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 2016;134:e123-55.
6. Valgimigli M, Bueno H, Byrne RA, et al. ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213-60.
7. Palmerini T, Benedetto U, Bacchi-Reggiani L, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. Lancet 2015;385:2371-82.
8. Palmerini T, Della Riva D, Benedetto U, et al. Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. Eur Heart J 2017;38:1034-43.
9. Berger PB, Bhatt DL, Fuster V, et al. Bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. Circulation 2010;121;2575-83.
10. Savarese G, Savonitto S, Lund LH, et al. Efficacy and safety of prolonged dual antiplatelet therapy. A metanalysis of 18 randomized trials enrolling 85,265 patients. Eur Heart J Cardiovasc Pharmacother 2016;2:218-28.
11. Patrono C, Morais J, Baigent C, et al. Antiplatelet agents for the treatment and prevention of coronary atherothrombosis. J Am Coll Cardiol 2017;70:1760-76.
12. Roffi M, Patrono C, Collet JP, et al. 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.
13. De Luca L, Olivari Z, Bolognese L, et al. A decade of changes in clinical characteristics and management of elderly patients with non-ST-elevation myocardial infarction admitted in Italian cardiac care units. Open Heart 2014;1:e000148.
14. De Luca L, Marini M, Gonzini L, et al. Contemporary trends and age-specific sex differences in management and outcome for patients with st-segment elevation myocardial infarction. J Am Heart Assoc 2016;5. pii: e004202.
15. De Luca L, Casella G, Rubboli A, et al. Recent trends in management and outcome of patients with acute coronary syndromes and atrial fibrillation. Int J Cardiol 2017;248:369-75.
16. Wilson SJ, Newby DE, Dawson D, et al. Duration of dual antiplatelet therapy in acute coronary syndrome. Heart 2017;103:573-80.
17. Antman EM, Wiviott SD, Murphy SA, et al. 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;51:2028-33.
18. Becker RC, Bassand JP, Budaj A, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 2011;32:2933-44.
19. Cuisset T, Deharo P, Quilici J, et al. 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;38:3070-8.
20. Sibbing D, Aradi D, Jacobshagen C, et al, on behalf of the TROPICAL-ACS Investigators. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017;390:1747-57.
21. Cayla G, Cuisset T, Silvain J, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet 2016;388:2015-22.
22. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62:2261-73.
23. Silvain J, Cayla G, Hulot JS, et al. High on-thienopyridine platelet reactivity in elderly coronary patients: the SENIOR-PLATELET study. Eur Heart J 2012;33:1241-9.

doi: 10.21037/amj.2018.01.17
Cite this article as: Savonitto S, Ferri LA, Bassanelli G, Tiberti G, Piatti L. Powerful P2Y12 inhibition after percutaneous coronary intervention for an acute coronary syndrome: "the times they are a changing". AME Med J 2018;3:25.

