

Platelet Function or Genetic Testing for Guiding De-Escalation of Anti-Platelet Therapy: The Jury is Still Out

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Dual anti-platelet therapy with aspirin and a P2Y₁₂ inhibitor plays a key role in reducing ischaemic complications in patients with acute coronary syndromes (ACSs) undergoing percutaneous coronary interventions (PCIs).^{1,2} Three oral P2Y₁₂ inhibitors (clopidogrel, prasugrel and ticagrelor) are available for clinical use and approved for this indication. The enhanced reduction in ischaemic events, including stent thrombosis, associated with the use of the newer generation P2Y₁₂ inhibitors prasugrel and ticagrelor compared with clopidogrel make these the recommended agents in ACS patients undergoing PCI.^{1,2} However, while the enhanced potency of the newer P2Y₁₂ inhibitors are responsible for achieving a greater magnitude of ischaemic benefit over clopidogrel, this also explains their higher risk of bleeding complications.^{1,2} Importantly, experiencing a major bleeding complication carries prognostic implications, including increased mortality.^{1,2} These observations underscore the need to define strategies that reduce the risk of bleeding complications while preserving efficacy. In light of the better safety profiles of newer generation stent technologies, strategies that have emerged to reach these goals include shortening the duration of dual anti-platelet therapy, withdrawal of aspirin therapy and de-escalation of P2Y₁₂ inhibiting therapy.^{3–5}

The term 'de-escalation' refers to switching from a more potent to a less potent P2Y₁₂ inhibitor.⁵ The rationale surrounding de-escalation is that the magnitude of the ischaemic benefit, including reduction of stent thrombosis, with the more potent P2Y₁₂ inhibitors is mostly early, while the risk of bleeding complications accrues with the duration of treatment.^{1,2,5} Thus, a strategy of tailoring anti-platelet therapy to consider a more potent agent early after the index event followed by the use of a less potent agent once the ischaemic burden has hampered is indeed an attractive strategy to optimize clinical outcomes (ischaemic and bleed-

ing). The main concerns surrounding de-escalation are largely attributed to the well-known notion that the pharmacodynamic (PD) effects of clopidogrel are subject to broad inter-individual variability with a considerable number of subjects presenting with high on-treatment platelet reactivity (HPR), a well-known marker of thrombotic complications.⁶ Thus, a strategy of de-escalation with the goal of reducing bleeding complications has been associated with concerns surrounding the potential for thrombotic complications raising the question on whether this should be guided or not by assessments (platelet function or genetic testing) that can provide insights to the PD effects of clopidogrel. While a strategy of non-guided de-escalation was associated with a significant reduction in adverse outcomes, largely driven by a reduction in bleeding, when conducted 30 days after the index event, an enhanced risk of adverse events was observed when de-escalation occurred early after the index event.^{7,8} These observations urge caution when using a strategy of de-escalation particularly when conducted early after the index event and without knowledge of the PD response to clopidogrel. Moreover, concerns surrounding a potential drug–drug interaction, leading to a marked increase in platelet reactivity and HPR rates, when de-escalating from ticagrelor to clopidogrel should also be considered.^{9,10} A drug–drug interaction does not appear to occur when de-escalating from prasugrel to clopidogrel likely due to the fact that the agents are of the same class.¹⁰

The TROPICAL-ACS trial is the first prospective, randomized study to test a phenotype-guided de-escalation (PGDE) in ACS patients undergoing PCI ($n = 2,610$).¹¹ In brief, patients were randomized to either standard treatment with prasugrel for 12 months or a PGDE regimen (1 week prasugrel followed by 1 week clopidogrel and platelet function testing guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge).

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Platelet function testing using the Multiplate analyzer identified HPR status after de-escalating to clopidogrel in 40% of patients in the PDGE arm who then 'escalated' back to prasugrel therapy. The primary endpoint was net clinical benefit (cardiovascular death, myocardial infarction, stroke or bleeding grade 2 or higher according to the Bleeding Academic Research Consortium criteria) 1 year after randomization (non-inferiority hypothesis). TROPICAL-ACS showed that a PDGE approach of anti-platelet treatment was non-inferior to standard treatment with prasugrel at 1 year after PCI in terms of the primary endpoint of net clinical benefit.¹¹ A PDGE was not associated with any increase in ischaemic events, while there was a trend towards reduced bleeding (secondary endpoints). The lack of statistical significance on reduction of bleeding may be attributed to the fact that the benefit of de-escalating to clopidogrel could have been offset by the non-negligible number of patients who required to escalate back to prasugrel. Notably, a subsequent analysis of the trial identified an interaction on the net outcomes driven by a significant reduction in bleeding according to age, in which younger patients benefited most from a PDGE strategy.¹²

A concern that has merged from a PDGE approach as utilized in TROPICAL ACS is that patients may require multiple switches in anti-platelet therapy to define the P2Y₁₂ inhibitor of choice and that such approach may not always be feasible in real-world practice.¹³ However, the encouraging findings from the TROPICAL ACS trial, which in addition to being clinically relevant may also have cost-saving implications in light of the reduced costs associated with long-term clopidogrel use compared with the newer generation P2Y₁₂ inhibitors, has opened avenues to define alternative strategies of guided de-escalation. In particular, the use of genetic testing represents an emerging approach. In fact, genotypes of genetic polymorphisms of CYP2C19, the enzyme responsible for converting clopidogrel into its active metabolite, are associated with different degrees of enzyme activity.^{1,14} In particular, CYP2C19 *2 and *3, also referred to a loss-of-function (LOF) alleles are single-nucleotide polymorphisms associated with lack of enzyme activity which lead to reduced conversion of clopidogrel into its active metabolite, reduced clopidogrel-induced platelet inhibition, higher rates of HPR and increased incidence of thrombotic complications. Conversely, CYP2C19 *17 is associated with increased enzyme activity (gain-of-function [GOF]) with enhanced conversion of clopidogrel into its active metabolite, enhanced clopidogrel-induced platelet inhibition and increased incidence of bleeding complications. Importantly, the availability of rapid genetic testing assays, such as Spartan RX, allows for implementing genetic testing with timely results (within 1 hour) in real-world clinical practice.^{14,15}

In this issue of *Thrombosis and Haemostasis*, Gross et al report the results of a pre-defined analysis of the TROPICAL ACS trial in which genetic testing using Spartan RX was utilized in 603 patients.¹⁶ The authors observed that on-treatment platelet reactivity in subjects treated with clopidogrel varies significantly according to genotypes, while this

was not observed for patients treated with prasugrel. Accordingly, a LOF genotype was associated with a higher prevalence of HPR among clopidogrel-treated patients. These observations are in line with prior investigations in the field.¹⁴ However, in this investigation LOF and GOF genotypes were not associated with risk of ischaemic or bleeding complications, respectively.

The findings from the genetic analysis of the TROPICAL ACS trial, while not apparently encouraging for the field of genotype-guided therapy based on the clinical outcomes of the study, need to be interpreted in the correct context. First, the study was conducted in a sub-group (23% of the overall trial population) which was not powered for clinical events. Moreover, after randomization, patients in the guided arm were stratified according to results of platelet function testing. Thus, the lack of association between genetic information and clinical outcomes of the study need to be interpreted with caution. Nevertheless, the study provides encouraging data that raises hopes for using genetic testing as a strategy to define the choice of P2Y₁₂ inhibitor in clinical practice. In fact, the study supports the feasibility of using rapid genetic testing in a population, which while enrolled in a clinical trial, were representative of a real-world population based on the clinical characteristics and complexity of PCI procedures. Importantly, the clear association between specific genotypes and PD profiles are hopeful for studies of tailored therapies using the results of genetic testing. In fact, while preliminary results of genotype-guided approach have been encouraging, results of several randomized trials currently on-going will ultimately define the clinical value of such strategy.¹⁴ Indeed, the benefit of genetic testing over platelet function testing is that the results of the former remain unchanged while the results of the latter are subject to intra- and inter-individual variability. Indeed, it may be argued that 'PD phenotype' may be more predictive of future events given that it more directly correlates with the 'clinical phenotype', while genetic results represents just a 'piece of the puzzle' contributing to the PD response. However, the potential simplicity of a genotype-guided approach which would not require multiple switching and conducted at the time of PCI are indeed hopeful attributes that may favour the uptake of a genotype-guided de-escalation approach pending the results of currently on-going, adequately designed clinical trials.

Conflict of Interest

Dr. Dominick J. Angiolillo reports receiving payments as an individual for: (1) Consulting fee or honorarium from Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Janssen, Merck, PLx Pharma, Pfizer, Sanofi and The Medicines Company; (2) Participation in review activities from Celonova and St. Jude Medical. Institutional payments for grants from Amgen, AstraZeneca, Bayer, Biosensors, Celonova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical and Renal Guard Solutions; in

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References

- 1 Sibbing D, Angiolillo DJ, Huber K. Antithrombotic therapy for acute coronary syndrome: past, present and future. *Thromb Haemost* 2017;117(07):1240–1248
- 2 Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol* 2015;12(01):30–47
- 3 Moon JY, Franchi F, Rollini F, Angiolillo DJ. Evolution of coronary stent technology and implications for duration of dual antiplatelet therapy. *Prog Cardiovasc Dis* 2018;60(4-5):478–490
- 4 Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol* 2018;15(08):480–496
- 5 Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet P2Y₁₂ receptor-inhibiting therapies. *Circulation* 2017;136(20):1955–1975
- 6 Aradi D, Kirtane A, Bonello L, et al. Bleeding and stent thrombosis on P2Y₁₂-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J* 2015;36(27):1762–1771
- 7 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(41):3070–3078
- 8 De Luca L, D'Ascenzo F, Musumeci G, et al. Incidence and outcome of switching of oral platelet P2Y₁₂ receptor inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: the SCOPE registry. *EuroIntervention* 2017;13(04):459–466
- 9 Franchi F, Rollini F, Rivas Rios J, et al. Pharmacodynamic effects of switching from ticagrelor to clopidogrel in patients with coronary artery disease: results of the SWAP-4 study. *Circulation* 2018;137(23):2450–2462
- 10 Rollini F, Franchi F, Angiolillo DJ. Switching P2Y₁₂-receptor inhibitors in patients with coronary artery disease. *Nat Rev Cardiol* 2016;13(01):11–27
- 11 Sibbing D, Aradi D, Jacobshagen C, et al; 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(10104):1747–1757
- 12 Sibbing D, Gross L, Trenk D, et al. TROPICAL-ACS Investigators. Age and outcomes following guided de-escalation of antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: results from the randomized TROPICAL-ACS trial. *Eur Heart J* 2018. Doi: 10.1093/eurheartj/ehy332
- 13 Angiolillo DJ. Dual antiplatelet therapy guided by platelet function testing. *Lancet* 2017;390(10104):1718–1720
- 14 Moon JY, Franchi F, Rollini F, et al. Role of genetic testing in patients undergoing percutaneous coronary intervention. *Expert Rev Clin Pharmacol* 2018;11(02):151–164
- 15 Cavallari LH, Franchi F, Rollini F, et al. Clinical implementation of rapid CYP2C19 genotyping to guide antiplatelet therapy after percutaneous coronary intervention. *J Transl Med* 2018;16(01):92
- 16 Gross L, Trenk D, Jacobshagen C, et al TROPICAL-ACS Investigators. Genotype-phenotype association and impact on outcomes following guided de-escalation of antiplatelet treatment in ACS patients. *Thromb Haemost* 2018;118(08). Doi: 10.1055/s-0038-1667337