Guided antiplatelet therapy in patients undergoing percutaneous coronary intervention

Marco Cattaneo

Fondazione Arianna Anticoagulazione, Bologna, Italy

Patients undergoing percutaneous coronary intervention (PCI) are treated with dual antiplatelet therapy (DAPT) with aspirin plus an antagonist of the P2Y12 platelet receptor to reduce the risk of major adverse cardiovascular events (MACE).[1] Clopidogrel, which is a pro-drug and the most commonly used P2Y12 antagonist, does not adequately inhibit platelet function in about 1/3 of treated patients, who display high on-treatment platelet reactivity (HTPR) and are insufficiently protected from MACE.[2,3] Mutations of cytochrome-P450 (CYP) isoforms, which are responsible for the generation of the active metabolite, are associated with response variability to clopidogrel, in combination with other variables.[2] Two alternative oral anti-P2Y12 drugs, prasugrel and ticagrelor, display more favorable pharmacokinetics than clopidogrel, conferring more consistent inhibition of platelet function and efficient prevention of thrombotic events, albeit at the expense of higher incidence of bleeding complications.[3]

Correspondence: Marco Cattaneo, Fondazione Arianna Anticoagulazione, via Paolo Fabbri 1/3, 40138 Bologna, Italy
E-mail: marco.natale.cattaneo@gmail.com

Citation: Cattaneo M. Guided antiplatelet therapy in patients undergoing percutaneous coronary intervention. Bleeding, Thrombosis, and Vascular Biology 2023;2:86.

Key words: P2Y12, antiplatelet therapy, cardiovascular diseases, monitoring, genotype, platelet function tests.

Conflict of interest: the author declares no potential conflict of interest.

Funding: none.

Received: 31 May 2023.
Accepted: 5 June 2023.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Bleeding, Thrombosis and Vascular Biology 2023; 2:86
doi:10.4081/btvb.2023.86

It has been hypothesized that tailoring anti-P2Y12 treatment to individual patients would increase the clinical benefit of DAPT.[2] Randomized controlled trials (RCTs) have been performed to test the safety and efficacy of guided therapy (GT) based on the results of patient genotyping (genotype-GT) or platelet function tests (PFT-GT). Typically, patients were randomized to GT or unguided therapy and the incidence of MACE and bleeding events was recorded during pre-defined follow-up periods. Some RCTs, however, had a different design from the above: all clopidogrel-treated patients underwent PFT and only those with HTPR were randomized to continue on clopidogrel or switch to alternative drugs: these RCTs (HTPR-therapy), therefore, did not test the safety and efficacy of GT, but those of alternative therapies for patients with HTPR.

Meta-analyses of published studies gave contrasting results, likely due to the heterogeneity of the included studies. Some meta-analyses lumped together RCTs, non-randomized intervention studies and observational studies. Meta-analyses that considered RCTs only, or analyzed the results of RCTs separately, included both studies on PFT-GT and HTPR-therapy,[4] genotype-GT and PFT-GT,[5] genotype-GT, PFT-GT and HTPR-therapy.[6] One meta-analysis included genotype-GT only,[7] while none analyzed PFT-GT studies only. Additional meta-analyses of homogenous studies are necessary in order to evaluate the safety and efficacy of different GT strategies. To this aim, Birocchi *et al.* recently elected to perform 3 separate systematic reviews and meta-analyses, each one for each of the 3 different study designs of RCTs.[8]

According to the meta-analysis by Birocchi *et al*.,[8] genotype-GT did not affect the incidence of bleeding events, but reduced the incidence of MACE. However, most of the evidence of protective effects of genotyping stemmed from RCTs that had been performed in China, because those performed elsewhere failed to show statistically significant benefit. This finding is compatible with the marginal role of CYP2C19 mutations in the response to clopidogrel among non-asiatic populations,[9] while they bear greater influence among patients from East/South Asia, among whom their prevalence is very high.[9] The meta-analysis of the overall published RCTs on genotype-GT by Birocchi *et al.*[8] sub-

Abbreviations
PCI, percutaneous coronary intervention
DAPT, dual antiplatelet therapy
MACE, major adverse cardiovascular events
HTPR, high on-treatment platelet reactivity
LTPR, low-on-treatment platelet reactivity
GT, guided therapy
PFT-GT, platelet function tests-guided therapy
RCT, randomized controlled trial

stantially confirmed the results of a previous meta-analysis,[7] which, however, failed to differentiate between RCTs performed in East-Asia and elsewhere.

The analysis of all published RCTs of PFT-GT revealed that it had no statistically significant effect on the incidence of both major bleedings and MACE.[8] However, a sub-analysis showed that PFT-GT significantly reduced the incidence of MACE in Chinese patients but not in non-asiatic patients.[8] The explanation for this difference is the same already given for the discrepancy observed in these populations for genotype-GT. Overall, the data suggested that PFT-GT is less effective than genotype-GT both among Chinese patients and patients from other countries, likely as a consequence of the unsatisfactory diagnostic accuracy of PFTs and the lability of the platelet reactivity phenotype, which may switch from HTPR to normal platelet reactivity or low-on treatment platelet reactivity (LTPR) and back to HTPR over time in a high proportion of patients,[2] in contrast to the stability of the CYP genotype.

The above interpretation is supported also by the results of the third meta-analysis by Birocchi *et al*., which focused on RCTs exploring the safety and efficacy of alternative treatment in patients with HTPR on clopidogrel (HTPR-therapy).[8] These RCTs showed that alternative antiplatelet regimens significantly decreased the risk of MACE in patients with HTPR, thus implying that failure of PFT-GT is not accounted for by failure of alternative regimens to reduce MACE, but rather by inadequate diagnostic accuracy of PFTs to identify patients with HTPR. RCTs of HTPR-therapy enrolled only patients with HTPR: all of them who had been randomized to the experimental arm could benefit from the administration of more effective anti-P2Y12 drugs, such as ticagrelor or prasugrel. Therefore, these RCTs simply confirm that prasugrel and ticagrelor are more effective than clopidogrel, as it had been previously shown by *ad hoc* RCTs.[3] In contrast, only a minority of enrolled patients in RCTs on PFT-GT were treated with these drugs, as patients with LTPR continued on clopidogrel. Misdiagnosis of HTPR in poor responders to clopidogrel in the experimental arm would preclude them from being treated with more efficient regimens and, consequently, lead to underestimation of the clinical benefit for the overall patient population. This interpretation is also supported by the observation that, at variance with genotype-GT and PFT-GT RCTs, the point estimates for relative risk of MACE were similar in HTPR-Therapy RCTs performed in China and elsewhere.[8]

The 2022 Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel recommends CYP2C19 genotyping of patients undergoing PCI,[10] principally based on the results of a meta-analysis,[5] which, however, analyzed together genotype-GT and PFT-GT, and did not differentiate between studies performed in China and those performed elsewhere. Based on the results of the meta-analysis by Birocchi *et al.,*[8] it is possible to conclude that most of the evidence of genotype-GT efficacy stems from RCTs in Chinese patients, in whom PFT guidance also proved effective. Evidence from the meta-analysis by Birocchi *et al*. indicates that, in patients from countries outside East/South Asia, genotype guidance is of dubious efficacy and PFT guidance is ineffective.

References

1. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation 2022;145:e18-114.
2. Cattaneo M. Response variability to clopidogrel: is tailored treatment, based on laboratory testing, the right solution? J Thromb Haemost 2012;10:327-36.
3. Cattaneo M. New P2Y(12) inhibitors. Circulation 2010;121:171-9.
4. Aluvilu A, Ferro A. Role of platelet function testing in acute coronary syndromes: a meta-analysis. Open Heart 2022;9:e002129.
5. Galli M, Benenati S, Capodanno D, et al. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. Lancet 2021;397:1470-83.
6. Yamani N, Unzek S, Mankani MH, et al. Does individualized guided selection of antiplatelet therapy improve outcomes after percutaneous coronary intervention? A systematic review and meta-analysis. Ann Med Surg (Lond) 2022;79:103964.
7. Tang B, Wang X, Wang X, et al. Genotype-guided antiplatelet therapy versus standard therapy for patients with coronary artery disease: an updated systematic review and meta-analysis. J Pharm Pharm Sci 2022;25:9-23.
8. Birocchi S, Rocchetti M, Minardi A, et al. Guided antiplatelet therapy with P2Y12 antagonists in patients undergoing percutaneous coronary intervention: 3 systematic reviews with meta−analyses of randomized controlled trials with homogeneous design. medRxiv preprint doi: https://doi.org/10.1101/2023.05.25.23290520; May 29, 2023.
9. Fricke-Galindo I, Céspedes-Garro C, Rodrigues-Soares F, et al. Interethnic variation of CYP2C19 alleles, predicted phenotypes and measured metabolic phenotypes across world populations. Pharmacogenomics J 2016;16:113-23.
10. Lee CR, Luzum JA, Sangkuhl K, et al. Clinical pharmacogenetics implementation consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update. Clin Pharmacol Ther 2022;112:959-67.