JACC: CARDIOVASCULAR INTERVENTIONS VOL. 11, NO. 2, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

CYP2C19 Genotyping in Percutaneous Coronary Intervention-Treated Patients

Ready for Prime Time?*

Dirk Sibbing, MD, Lisa Gross, MD

Dual antiplatelet treatment (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is the current mainstay of treatment for patients undergoing percutaneous coronary intervention (PCI). With respect to $P2Y_{12}$ receptor inhibitors, the in vivo bioactivation of the second-generation thienopyridine clopidogrel is significantly influenced by certain genetic variants of genes encoding for enzymes of the cytochrome P450 (CYP) system. As matters stand and in contrast to clopidogrel, the antiplatelet action of the potent $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor is not influenced by such genetic variants (1). For clopidogrel, however, the isoenzyme CYP2C19 is a major determinant for its bioactivation and a common genetic variant within the *CYP2C19* gene, the *CYP2C19*2* loss-of-function (LOF) polymorphism, was found to be associated with an attenuated response to clopidogrel (2). This observation is true for heterozygous **2* allele carriers and even more so for subjects who are homozygous carriers of the mutant **2* allele. Thus, it did not come as a surprise that a number of studies (3,4) and meta-analyses (2) could show that the mere presence of the *CYP2C19*2* allele in clopidogrel-treated patients undergoing PCI was found to be associated with a higher risk of ischemic events, including the occurrence of early stent thrombosis. Further on and in line with mechanistic data, a gene-dose effect for the LOF allele was reported, with homozygous **2* allele carriers exhibiting the highest risk of stent thrombosis (3). However, beyond the clearly established prognostic value of *CYP2C19*2* as a risk factor in PCI-treated patients receiving clopidogrel, there is little evidence at present in how far (routine) genetic testing and a genotype-guided antiplatelet therapy is feasible and effective in reducing ischemic events in PCI-treated patients receiving clopidogrel as a first-line treatment.

SEE PAGE 181

In this issue of the *JACC: Cardiovascular Interventions*, Cavallari et al. (5) provide important and interesting results on outcomes following nonrandomized clinical implementation of *CYP2C19* genotype-guided antiplatelet therapy in 1,815 patients treated with PCI for stable coronary artery disease or acute coronary syndrome (ACS). Consecutive patients from 7 institutions who underwent PCI and *CYP2C19* genotyping were part of this analysis. Intensified therapy consisting of prasugrel, ticagrelor, or high-dose clopidogrel was intended for patients with 1 or 2 LOF alleles, but the decision whether to recommend alternative therapy was left to the discretion of the treating physician. The primary endpoint of this investigation was defined as the composite of myocardial infarction, stroke, or death within 12 months following the index PCI and was compared among the 572 patients with a LOF allele in patients prescribed clopidogrel (n = 226) versus intensified antiplatelet therapy (n = 346). After Cox regression and adjusting for group differences, the authors found that the incidence of the primary study endpoint in patients with a LOF allele was significantly higher (adjusted hazard ratio [HR_{adj}] 2.26; 95% confidence interval [CI]: 1.18 to 4.32; p = 0.013) when they were

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the Department of Cardiology, LMU München, Munich, Germany; and the DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany. Dr. Sibbing has received grant support from Roche Diagnostics and from Daiichi-Sankyo; and personal fees from Bayer AG, Daiichi-Sankyo, Eli Lilly, Roche Diagnostics, Merck Sharp & Dohme, Pfizer, and AstraZeneca. Dr. Gross has reported that she has no relationships relevant to the contents of this paper to disclose.

ISSN 1936-8798/$36.00 http://dx.doi.org/10.1016/j.jcin.2017.08.041

treated with standard-dose clopidogrel (n = 226) versus alternative therapy with prasugrel (n = 222), ticagrelor (n = 116 patients), or high-dose clopidogrel (n = 8). Similar findings were observed for the large subgroup (n = 1,210) of ACS patients (HR_{adj} 2.87; 95% CI: 1.35 to 6.09; p = 0.013). Of note, there was no difference in ischemic events between patients without a LOF allele and LOF allele carriers prescribed intensified therapy (HR_{adj} 1.14; 95% CI: 0.69 to 1.88; p = 0.60). With the present study, the investigators confirm and expand prior reports (2–4) on the prognostic value of *CYP2C19* genotyping for ischemic risk prediction in clopidogrel-treated patients undergoing PCI. Cavallari et al. (5) must be commended for this very well done and first large multicenter investigation on clinical outcomes of *CYP2C19* genotype-guided personalized antiplatelet therapy in PCI patients. However, in interpreting the data, some issues and important aspects merit mentioning.

First, allocation to one of the treatment groups was not randomized and the study did not include a control group. Thus, both decisions whether to perform *CYP2C19* genotyping at all and whether to intensify antiplatelet treatment in LOF allele carriers were entirely left to the discretion of the treating physician and were obviously triggered by patients' characteristics such as age, comorbidities such as diabetes, and the presumed bleeding risk. In line with this, a comparison of baseline characteristics showed significant between-group differences for a number of variables, and it seems unlikely that a propensity score approach could fully adjust for this. Further on, point estimates of reported HRs for primary endpoint comparisons suggest a relevant selection bias, as risk reductions observed for clopidogrel versus intensified treatment in LOF allele carriers were larger than had been the case when the potent antiplatelet drugs prasugrel or ticagrelor were compared versus clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) and TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction) 38 trials (6,7).

Second, the authors focus their reporting on ischemic outcomes and a comprehensive analysis on minimal, minor, and major bleeding events was not included in this study. However, a detailed reporting on bleeding and the net clinical benefit of tailored and intensified antiplatelet treatment seems mandatory. Future studies on personalized antiplatelet treatment should include a detailed reporting on bleeding events that reflects contemporary standards on outcome reporting like the use of the Bleeding Academic Research Consortium classification (8) for categorizing the entire spectrum of bleeds ranging from minimal to fatal bleeding events.

Finally, the follow-up for patients in this investigation was inhomogeneous and rather short in many of the patients, with a median follow-up of 4.8 months (interquartile range: 0.6 to 9.9 months). It seems likely that the lack of standardized follow-up procedures, such as is the case in randomized controlled trials, might have led to an underreporting of clinical events in this study population. In this respect, it merits mentioning that events in this study were taken from electronic health records only and events were not adjudicated by an independent event adjudication committee.

The previously mentioned limitations of this interesting study clearly emphasize the need for randomized controlled trials with structured and standardized study protocols. In fact, 2 larger randomized clinical trials including *CYP2C19* genotyping are ongoing and will provide important results in the near future. The TAILOR-PCI (Tailored Antiplatelet Initiation to Lesson Outcomes Due to Decreased Clopidogrel Response after Percutaneous Coronary Intervention) trial (NCT01742117) with a planned enrollment of >5,000 PCI patients randomizes patients to a conventional arm versus a *CYP2C19* genotype-based antiplatelet therapy approach with application of ticagrelor in LOF allele carriers. Therefore, similar to prior studies that used platelet function testing (PFT) for guidance of treatment (9,10), the TAILOR-PCI trial aims at escalating treatment based on genotyping results by switching patients from clopidogrel to ticagrelor. Of note, prior concepts in trials of tailored and individualized treatment implying escalation of DAPT (i.e., switching from clopidogrel to potent antiplatelet drugs) in PCI-treated patients provided neutral results (9,10). A different approach for tailoring DAPT could be to follow a concept of a stage-adapted treatment with DAPT de-escalation (i.e., switching from potent antiplatelet drugs to clopidogrel) when using the information derived from genotyping (*CYP2C19*) or phenotyping (PFT). Indeed, DAPT regimens implying de-escalation from potent $P2Y_{12}$ receptor inhibitors to the less potent and off-patent clopidogrel look appealing and are already common practice despite very limited evidence on their safety (11). However, the benefits are obvious, from both a conceptual perspective (early ischemic risk vs. late bleeding risk) and from a clinical or economic point of view. The recently published TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes) trial (NCT01959451) (12) focused on a PFT-guided de-escalation of DAPT (switch from prasugrel

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 11, NO. 2, 2018
JANUARY 22, 2018:192–4

to clopidogrel) in the early maintenance phase after successful PCI in ACS patients. The study met its primary endpoint and thereby demonstrated that a guided de-escalation of antiplatelet treatment was safe (in terms of ischemia) and noninferior (in terms of net clinical benefit) to standard treatment with prasugrel at 1 year after PCI and thus can be considered as an alternative treatment strategy in ACS patients managed with PCI.

Similarly, but using genotyping for guidance of treatment, the ongoing POPGenetics (Patient Outcome after primary PCI Genetics) trial (NCT01761786) (13) aims at randomizing 2,700 STEMI patients to a *CYP2C19* genotype-guided therapy versus conventional therapy (13). This trial strictly follows the approach of DAPT de-escalation as STEMI patients without *CYP2C19* LOF allele carriage are kept on clopidogrel treatment.

In concert with published data upcoming results of the ongoing randomized trials may help to establish novel and individualized treatment concepts that aim at optimizing antiplatelet treatment by utilizing genetic or nongenetic variables for clinical decision making. It may well be that a 1-size-fits-all strategy for DAPT will be left behind in the near future and individualized treatment concepts become reality. However, only with convincing results from future studies, genotyping in PCI-treated patients will be ready for prime time. Based on the available evidence so far, this is not the case now and further evidence is urgently needed.

ADDRESS FOR CORRESPONDENCE: Dr. Dirk Sibbing, Department of Cardiology, LMU München, Marchioninistraße 15, 81377 Munich, Germany. E-mail: dirk.sibbing@med.uni-muenchen.de.

REFERENCES

1. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009;119:2553–60.

2. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA 2010;304:1821–30.

3. Sibbing D, Stegherr J, Latz W, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J 2009;30:916–22.

4. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354–62.

5. Cavallari LH, Lee CR, Beitelshees AL, et al. Multisite investigation of outcomes with implementation of *CYP2C19* genotype-guided antiplatelet therapy after percutaneous coronary intervention. J Am Coll Cardiol Intv 2018;11:181–91.

6. 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.

7. 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.

8. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

9. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA 2011;305:1097–105.

10. Collet JP, Cuisset T, Range G, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012;367:2100–9.

11. Zettler ME, Peterson ED, McCoy LA, et al. Switching of adenosine diphosphate receptor inhibitor after hospital discharge among myocardial infarction patients: insights from the Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) observational study. Am Heart J 2017;183:62–8.

12. 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.

13. Bergmeijer TO, Janssen PW, Schipper JC, et al. CYP2C19 genotype-guided antiplatelet therapy in ST-segment elevation myocardial infarction patients-Rationale and design of the Patient Outcome after primary PCI (POPular) Genetics study. Am Heart J 2014;168:16–22.e1.

KEY WORDS CYP2C19, genetics, genotyping, PCI