Clinical Impact of Pharmacogenomics of Clopidogrel in Stroke

Article, see p 21

Tabassome Simon, MD, PhD
Nicolas Danchin, MD, PhD

Despite progress in the diagnosis and treatment of stroke, it is estimated that >900 000 patients each year in the United States have a new stroke or transient ischemic attack (TIA) with an annual risk of 3% to 4% for recurrent events.[1] The incidence of stroke or TIA is even higher in some countries such as China.[2] Preventing stroke is therefore a major worldwide public health issue.

Clopidogrel, in addition to 3 weeks of aspirin therapy, has been effective in reducing the risk of recurrence at 3 months in Chinese patients with TIA or a minor acute ischemic stroke, mainly by reducing the risk of recurrent ischemic stroke.[3] To become active, clopidogrel needs to be metabolized via a 2-step oxidation process involving several hepatic cytochrome P450 isoenzymes, notably *CYP2C19*, and irreversibly binds to $P2Y_{12}$ receptors.[4] Conversion of clopidogrel to its active metabolite depends on *CYP2C19* genetic polymorphisms, with decreased platelet inhibition in carriers of 1 or 2 loss-of-function alleles (ie, intermediate or poor metabolizers).

Several studies have shown that in patients with acute coronary syndromes treated by clopidogrel, carriers of at least 1 *CYP2C19* loss-of-function allele, notably *CYP2C19*2*, were at increased risk of major cardiovascular events and stent thrombosis, with a gene-dose relationship.[5–8] Conversely, the *CYP2C19*17* variant allele has been related to enhanced levels of active clopidogrel metabolites, greater inhibition of ADP-induced platelet aggregation, and increased risk of bleeding without an impact on ischemic events.[9]

The US Food and Drug Administration boxed warning in 2010 stated that *CYP2C19* genotyping can be used as an aid in assessing the therapeutic safety and for considering alternative strategies to *CYP2C19* poor metabolizers. From a clinical standpoint, however, the added value of assessing *CYP2C19* polymorphisms depends on 3 factors: the efficacy of clopidogrel in preventing ischemic events, with a favorable risk/benefit profile, in a given population; the prevalence of *CYP2C19* genetic polymorphisms in the population considered for treatment; and the impact of nongenetic unmodifiable and modifiable factors (ie, age, diabetes mellitus, drug compliance, inadequate dose, smoking status, drug-drug interactions, among many others) on clopidogrel platelet inhibition in the target population.

The efficacy of clopidogrel alone in reducing recurrent ischemic events in patients with recent stroke or TIA has been limited (with a nonsignificant 7.3% risk reduction in the CAPRIE trial [Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events][10]), but it was substantial (with a 22% risk reduction) when used in combination with aspirin in the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events).[3] Whether these latter results are generalizable to other populations is currently being evaluated in the POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke)[11] funded by the National Institutes of Health (clinical trials.gov; unique identifier: NCT00991029). Indeed, the

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Tabassome Simon, MD, PhD, Département de Pharmacologie Clinique-URCEST, UPMC-Site Saint Antoine, 27 Rue Chaligny, 75012, Paris, France. E-mail tabassome.simon@aphp.fr

Key Words: Editorials ■ outcome assessment (health care) ■ pharmacogenetics ■ platelet aggregation inhibitors ■ stroke ■ thrombosis

prevalence of diabetes mellitus and hypertension can be higher in China. Moreover, in Caucasian populations, the frequency of *CYP2C19* loss-of-function alleles ranges up to 30%, of whom 2% to 3% are *CYP2C19* poor metabolizers. In contrast, among East Asian patients, the frequency of intermediate or poor metabolizers reaches 50% to 60%, of whom 10% to 12% are poor metabolizers.

In this issue of *Circulation*, Pan et al[12] present the results of a meta-analysis of genomic data of studies that enrolled 4762 clopidogrel-treated patients with stroke or TIA. The meta-analysis included 15 studies (3 from Europe and 12 from East Asia), of which 11 were performed in China. Most were cohort studies, and one third of the overall population is drawn from the genetic substudy of the CHANCE trial.[13] The authors looked for a relationship between the clinical response to clopidogrel, combining vascular mortality, nonfatal myocardial infarction, and stroke, and *CYP2C19* polymorphisms. They also summarized the data from all other known genetic polymorphisms that could affect the pharmacokinetic, pharmacodynamic, and clinical effects of clopidogrel and found that none of the polymorphisms were related to clinical outcomes.

In contrast, patients carrying any *CYP2C19* loss-of-function allele were at increased risk for stroke (relative risk, 1.92; 95% confidence interval, 1.57–2.35) or vascular events (relative risk, 1.51; 95% confidence interval, 1.10–2.06) compared with noncarriers, with no significant influence on the risk of bleeding. Because the deleterious effect of *CYP2C19* loss-of-function variant alleles can be partly reduced by the concomitant presence of *17, the increased risk associated with *CYP2C19* loss of function might have been even greater if patients concomitantly carrying *CYP2C19*17* had been classified as unknown metabolizers and excluded from the analysis. Of note, the increased risk of vascular events was of a magnitude similar to that observed in invasively managed patients with acute coronary syndromes with any CYPC19 loss-of-function allele.[7]

A gene-dose effect of the *CYP2C19* loss-of-function variant allele, similar to that seen in patients with acute coronary syndromes with respect to stent thrombosis,[8] was observed by Pan et al, with homozygous carriers having the highest risk of stroke compared with noncarriers (relative risk, 2.52; 95% confidence interval, 1.93–3.30 for homozygous carriers; relative risk, 1.79; 95% confidence interval, 1.45–2.22 for heterozygous carriers).

The current meta-analysis does not rule out publication bias; a significant heterogeneity was found for the composite of vascular events (but not for stroke alone). The effect estimate for the composite of vascular events, however, remained significant after funnel plots and regression tests, suggesting that the results presented are robust.

How should these results be interpreted, and what are the messages for clinicians?

1. The results of this meta-analysis in acute stroke are consistent with those previously reported in patients with acute coronary syndromes, in whom the pathogenesis of recurrent events is more clearly linked to intra-arterial thrombosis. This gives further credibility to the determinant role of *CYP2C19* as a necessary step to clopidogrel transformation into its active metabolite and its association with the ischemic risk.
2. These results also give more substance to the value of clopidogrel as an efficacious antithrombotic agent in patients with acute ischemic stroke. The risk of recurrent events is twice as low in wild-type patients, suggesting that, when pharmacologically sufficiently active, clopidogrel can effectively prevent further ischemic events, in particular at the acute stage (within 24 hours of symptom onset) because a high proportion of recurrent strokes occur early. This point is important in view of the results of the CAPRIE trial, which enrolled patients with recent stroke (<6 months).
3. The added value of *CYP2C19* genotyping, however, depends also on the question, unresolved by the current meta-analysis in the absence of placebo group, of the potential efficacy of the drug among the poor/intermediate metabolizers (ie, gene-drug interaction). Clopidogrel may have no benefit in poor/intermediate metabolizers and may become efficacious only in extensive metabolizers (ie, carrying no *CYP2C19* loss-of-function allele). This hypothesis is plausible when contrasting the results of the genetic findings with those of the overall CHANCE trial, in which 41% of the patients only were extensive metabolizers.[13] The effect of clopidogrel versus placebo in the whole population would correspond to an ≈20% reduction in event rates, granting that clopidogrel reduced event rates by ≈50% in the extensive metabolizers compared with poor/intermediate metabolizers and assuming that the drug would have no effect in poor/intermediate metabolizers. This is in line with the 22% rate reduction seen in the CHANCE trial overall.[3]
4. Therefore, if one considers that the clinical efficacy of clopidogrel in poor/intermediate metabolizers is nil or at least extremely limited in patients with acute stroke or those with acute coronary syndromes treated with stenting, the value of genetic profiling before treatment depends mostly on the prevalence of the mutations. In East Asian populations, there is little question that genetic profiling would be worthwhile because it would avoid unnecessarily treating approximately half of the target population. The answer is more complex in populations such as Caucasians with a lower

prevalence of mutations and raises the issue of the cost-effectiveness of this strategy. Because genotyping costs have decreased dramatically, such a policy may be cost-effective by avoiding potential inappropriate long- term treatment in one third of the population.

5. It is possible that, in patients with an acute stroke, the ischemic/bleeding risk ratio of possible alternative antiplatelet drugs, that is, prasugrel or ticagrelor, compared with clopidogrel would be more optimal among *CYP2C19* poor/intermediate metabolizers than in unselected populations. Of note, in genetic substudies of the TRITON trial (Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel),[7,14] the benefit of prasugrel versus clopidogrel appeared largely confined to patients carrying *CYP2C19* loss-of-function alleles but not in the extensive metabolizers, who represented >70% of the overall included patients with acute coronary syndromes undergoing percutaneous coronary intervention, whereas in the PLATO trial (Platelet Inhibition and Patient Outcomes),[15] the superiority of ticagrelor compared with clopidogrel was present regardless of genetic status.

Although evidence of the clinical relevance of *CYP2C19* genotyping before prescribing clopidogrel is available, it remains, to a large extent, circumstantial. Definite proof is needed and can been provided only by prospective trials, as seen with the failure of trials trying to target an antiplatelet regimen according to in vitro platelet reactivity testing.[16,17] It might be time to consider a prospective trial of personalized medicine using *CYP2C19* genotyping in acute ischemic stroke and considering alternative medications in poor/intermediate metabolizers such as in the currently ongoing POPular (Patient Outcome After Primary PCI) genetics trial in patients with ST-segment–elevation myocardial infarction undergoing percutaneous coronary intervention.[18]

DISCLOSURES

Dr Simon reports institutional grants support from AstraZeneca, Daiichi-Sankyo, Eli-Lilly, and Sanofi, as well as board membership, speaker, or consulting fees from AstraZeneca, Lilly, and Sanofi. Dr Danchin reports speaker fees from AstraZeneca, Lilly, and Sanofi.

AFFILIATIONS

From French Alliance for Cardiovascular Trials, an F-CRIN Network, DHU FIRE, Paris, France (T.S., N.C.); INSERM U1148, Paris, France (T.S.); Department of Clinical Pharmacology, Unité de Recherche Clinique de l'Est Parisien (URC-EST), Assistance Publique-Hôpitaux de Paris, Paris, France (T.S.); Université Pierre et Marie Curie, Paris, France (T.S.); Université René Descartes, Paris, France (N.D.); and Assistance Publique-Hôpitaux de Paris, Department of Cardiology, Hopital Georges Pompidou, Paris, France (N.D.).

FOOTNOTES

Circulation is available at http://circ.ahajournals.org.

REFERENCES

1. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236. doi: 10.1161/STR.0000000000000024.
2. Zhao D, Liu J, Wang W, Zeng Z, Cheng J, Liu J, Sun J, Wu Z. Epidemiological transition of stroke in China: twenty-one-year observational study from the Sino-MONICA-Beijing Project. *Stroke*. 2008;39:1668–1674. doi: 10.1161/STROKEAHA.107.502807.
3. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, Jia J, Dong Q, Xu A, Zeng J, Li Y, Wang Z, Xia H, Johnston SC; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. doi: 10.1056/NEJMoa1215340.
4. Mega JL, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. *Lancet*. 2015;386:281–291. doi: 10.1016/S0140-6736(15)60243-4.
5. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, Steg PG, Ferrières J, Danchin N, Becquemont L; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009;360:363–375. doi: 10.1056/NEJMoa0808227.
6. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, Payot L, Brugier D, Cayla G, Beygui F, Bensimon G, Funck-Brentano C, Montalescot G. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet*. 2009;373:309–317. doi: 10.1016/S0140-6736(08)61845-0.
7. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009;360:354–362. doi: 10.1056/NEJMoa0809171.
8. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, Cannon CP, Danchin N, Giusti B, Gurbel P, Horne BD, Hulot JS, Kastrati A, Montalescot G, Neumann FJ, Shen L, Sibbing D, Steg PG, Trenk D, Wiviott SD, Sabatine MS. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA*. 2010;304:1821–1830. doi: 10.1001/jama.2010.1543.
9. Sibbing D, Koch W, Gebhard D, Schuster T, Braun S, Stegherr J, Morath T, Schömig A, von Beckerath N, Kastrati A. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation*. 2010;121:512–518. doi: 10.1161/CIRCULATIONAHA.109.885194.
10. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339. doi: http://dx.doi.org/10.1016/S0140-6736(96)09457-3.

11. Johnston SC, Easton JD, Farrant M, Barsan W, Battenhouse H, Conwit R, Dillon C, Elm J, Lindblad A, Morgenstern L, Poisson SN, Palesch Y. Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial: rationale and design. *Int J Stroke*. 2013;8:479–483. doi: 10.1111/ijs.12129.
12. Pan Y, Chen W, Xu Y, Yi X, Han Y, Yang Q, Li X, Huang L, Johnston SC, Zhao X, Liu L, Zhang Q, Wang G, Wang Y, Wang Y. Genetic polymorphisms and clopidogrel efficacy for acute ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Circulation*. 2017;135:21–33. doi: 10.1161/CIRCULATIONAHA.116.024913.
13. Wang Y, Zhao X, Lin J, Li H, Johnston SC, Lin Y, Pan Y, Liu L, Wang D, Wang C, Meng X, Xu J, Wang Y; CHANCE Investigators. Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. *JAMA*. 2016;316:70–78. doi: 10.1001/jama.2016.8662.
14. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias WL, Braunwald E, Sabatine MS. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation*. 2009;119:2553–2560. doi: 10.1161/CIRCULATIONAHA.109.851949.
15. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, Husted S, Katus H, Steg PG, Shah SH, Becker RC; PLATO Investigators. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet*. 2010;376:1320–1328. doi: 10.1016/S0140-6736(10)61274-3.
16. Collet JP, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrié D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthélémy O, Beygui F, Silvain J, Vicaut E, Montalescot G; ARCTIC Investigators. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med*. 2012;367:2100–2109. doi: 10.1056/NEJMoa1209979.
17. Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Stillabower ME, Stillablower ME, Aragon JR, Kandzari DE, Stinis CT, Lee MS, Manoukian SV, Cannon CP, Schork NJ, Topol EJ; GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA*. 2011;305:1097–1105. doi: 10.1001/jama.2011.290.
18. Bergmeijer TO, Janssen PW, Schipper JC, Qaderdan K, Ishak M, Ruitenbeek RS, Asselbergs FW, van 't Hof AW, Dewilde WJ, Spanó F, Herrman JP, Kelder JC, Postma MJ, de Boer A, Deneer VH, ten Berg JM. 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. doi: 10.1016/j.ahj.2014.03.006.

Clinical Impact of Pharmacogenomics of Clopidogrel in Stroke

Tabassome Simon and Nicolas Danchin

Circulation. 2017;135:34-37
doi: 10.1161/CIRCULATIONAHA.116.025198
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539