Is Ticagrelor the Antiplatelet Therapy Panacea?

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Ticagrelor is a reversibly binding P2Y12 receptor antagonist that has undergone phase 3 clinical trials and is currently under Food and Drug Administration (FDA) review. Ticagrelor has proposed benefits over clopidogrel in that it has a faster onset of action, greater platelet inhibitory potency, and less interpatient variability in pharmacodynamic response. Unlike clopidogrel, ticagrelor does not require bioactivation to an active metabolite by cytochrome P450 2C19 (CYP2C19) and, therefore, is not expected to be influenced by CYP2C19 genetic polymorphisms.

The differential effect of CYP2C19 on treatment response in clopidogrel versus ticagrelor would be strengthened by mechanistic data demonstrating a differential effect on intermediate phenotypes, such as platelet function testing or active metabolite concentrations. In this issue of Circulation: Cardiovascular Genetics, a study by Tantry and colleagues4 investigated the effects of the CYP2C19 genotype on ex vivo platelet reactivity in ticagrelor- versus clopidogrel-treated patients from the ONSET/OFFSET (Multi-Centre Randomized, Double-Blind, Double-Dummy Parallel Group Study of the Onset and Offset of Antiplatelet Effects of AZD6140 Compared With Clopidogrel and Placebo With Aspirin as Background Therapy in Patients With Stable Coronary Artery Disease) and RESPOND (Randomized, Double-Blind, Outpatient, Crossover Study of the Anti-Platelet Effects of AZD6140 Compared With Clopidogrel in Patients With Stable Coronary Artery Disease Previously Identified as Clopidogrel Non-Responders or Responders) studies. These studies were phase 2 trials designed to assess the onset and offset of platelet inhibition of ticagrelor 180-mg load and 90-mg twice daily maintenance dose versus clopidogrel 600-mg load and 75-mg daily maintenance dose, the effects of ticagrelor in clopidogrel nonresponders, and the effect of switching patients between clopidogrel and ticagrelor.5,6 As expected, the antiplatelet effects of ticagrelor were not influenced by CYP2C19 genotype. Consistent with the genetic substudy of PLATO, ticagrelor showed superior antiplatelet effects compared with clopidogrel irrespective of CYP2C19 genotype.

Ticagrelor-induced antiplatelet effect was superior to clopidogrel even among CYP2C19 extensive metabolizers and gain-of-function allele carriers, suggesting that this agent is a more-active drug than clopidogrel even in persons who presumably make the clopidogrel active metabolite. There were no *17/*17 homozygous individuals (ie, ultrarapid metabolizers) treated with clopidogrel to compare to ticagrelor-treated individuals. Consistent with most studies to date, CYP2C19 genotype significantly influenced antiplatelet activity of clopidogrel. The findings were most significant when platelet reactivity was measured using the VerifyNow assay and during maintenance therapy. The study did not replicate previous associations between ABCB1 genotype and clopidogrel response or findings of enhanced antiplatelet effects among CYP2C19*17 carriers.

What do we know about the pharmacology of ticagrelor that can explain the findings in the present analysis and previous findings from the PLATO genetic substudy? First, the ticagrelor parent compound is able to inhibit the P2Y12 receptor without need for conversion to an active metabolite by CYP450 enzymes.7 In contrast, clopidogrel requires a 2-step hepatic activation involving multiple CYP450 enzymes, including CYP2C19. This difference is important in that the multiple steps required to activate clopidogrel make

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Ticagrelor has been compared with clopidogrel in 18,624 patients with acute coronary syndromes in the Study of Platelet Inhibition and Patient Outcomes (PLATO).1 It was found to be superior to clopidogrel, with the primary outcome of death from vascular causes, myocardial infarction, or stroke occurring in 9.8% of patients receiving ticagrelor compared to 11.7% of those receiving clopidogrel (hazard ratio [HR], 0.84; 95% CI, 0.77 to 0.92; P<0.001). This leads to the question of whether the superiority of ticagrelor over clopidogrel in this acute coronary syndromes population is driven by the known diminished clinical effectiveness of clopidogrel in genetically defined subsets of patients who cannot efficiently produce the active metabolite of clopidogrel to achieve adequate inhibition of platelet aggregation (ie, CYP2C19 poor and intermediate metabolizers). This question was investigated, in part, in a previously published pharmacogenetic substudy of PLATO that demonstrated improved outcomes with ticagrelor compared to clopidogrel in both patients with CYP2C19 loss-of-function alleles (HR, 0.77; 95% CI, 0.60 to 0.99; P=0.038) and those without loss-of-function alleles (HR, 0.86; 95% CI, 0.74 to 1.01; P=0.0608).3 Further, consistent with many other published reports, in clopidogrel-treated patients, the event rates were higher among those with loss-of-function alleles than those without (5.7% versus 3.8%; P=0.028). In response to a body of data showing diminished clopidogrel response among those with loss-of-function alleles, the FDA added a boxed warning to the clopidogrel label describing the reduced efficacy of clopidogrel among CYP2C19 poor metabolizers.3
it prone to drug interactions and being influenced by genetic polymorphisms. Second, a related important difference in the pharmacology of these agents that may account for the greater improvement in outcomes with ticagrelor over clopidogrel is that ticagrelor has a faster onset of action than clopidogrel. We know that early initiation of antiplatelet therapy and achievement of adequate platelet inhibition is important from numerous clinical trials demonstrating differences between therapies very early in the treatment period.\textsuperscript{1,8,9} Third, ticagrelor provides more-complete inhibition of the P2Y\textsubscript{12} receptor, with 75% to 80% inhibition of aggregation to ADP compared to only \(\approx 30\%\) with clopidogrel.\textsuperscript{10} A summary of the pharmacological differences between ticagrelor and clopidogrel is shown in Table.

\begin{table}[h]
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\caption{Pharmacological Characteristics of Ticagrelor and Clopidogrel}
\begin{tabular}{|l|l|}
\hline
                        & Ticagrelor            & Clopidogrel          \\
\hline
Onset of action (t\textsubscript{onset}) & 1.5 h                  & 4 h                  \\
Offset of action       & 1–2 d                  & 5 d                  \\
P2Y\textsubscript{12} receptor binding & Reversible            & Irreversible         \\
Dosing interval        & Twice daily            & Once daily           \\
Metabolism             & Active parent drug     & Prodrug; requires 2-step activation by multiple CYP450s; esterase inactivation \\
                        & converted to active metabolite by CYP3A4/5 & \\
Adverse effects        & Bleeding (major and minor-14.6\%), dyspnea (~14\% of patients), ventricular pauses, increase in serum uric acid and creatinine & Bleeding (major and minor-16.1\%), dyspnea (~8\% of patients), interpatient variability \\
\hline
\end{tabular}
\end{table}

The study by Tantry and colleagues\textsuperscript{4} advances our knowledge in the field of P2Y\textsubscript{12} antagonist pharmacogenetics and raises several interesting questions. For example, the method used to measure antiplatelet response does seem to influence the strength of the pharmacogenetic findings. Although ticagrelor provided greater reduction in platelet reactivity using all methods of measurement, whether the association between clopidogrel response and genotype was found differed depending on whether ADP-induced platelet aggregation using light transmittance aggregometry, VerifyNow, or vasodilator-stimulated phosphoprotein phosphorylation (VASP-P) was used to measure the phenotype. It is unclear why VerifyNow would provide the strongest signals for the association between CYP2C19 and clopidogrel response, although a previous study found stronger correlations between plasma levels of the clopidogrel active metabolite and platelet reactivity measured using VerifyNow and VASP-P than with 5 \(\mu\)mol/L ADP-induced aggregation.\textsuperscript{11} It is also possible that the labor-intensive nature of light transmittance aggregometry and VASP-P could have resulted in greater noise and, therefore, less-significant results. In addition, the study found that the influence of CYP2C19 on platelet reactivity was most notable during clopidogrel maintenance therapy compared to post-loading dose. This finding is important for future strategies aimed at implementing personalized antiplatelet therapy in that it may help to better define the timing in which platelet reactivity studies should be conducted to help guide treatment decisions.

Issues that are yet to be clarified from a pharmacogenetics standpoint include whether the CYP2C19*17 allele is indeed associated with improved clopidogrel response and increased risk of bleeding because the present study did not have any *17/*17 individuals treated with clopidogrel to evaluate, and these are potentially the patients who would have had the greatest response to clopidogrel. However, the relatively small number of patients expected to carry this genotype might limit the clinical relevance of findings regardless of whether the analysis could have been conducted. Regarding the association between ABCB1 genotype and clopidogrel response, 2 recent studies have reported conflicting associations with the C3435T polymorphism. In the PLATO study, CC individuals treated with clopidogrel had an increase in events, whereas in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) study, TT individuals had an increase in events.\textsuperscript{2,12} In the present study, there was no association with clopidogrel antiplatelet effects and ABCB1 genotype. Therefore, given the contradictory data regarding the effects of this polymorphism on P-glycoprotein expression and on clopidogrel treatment outcomes, it does not seem likely that it plays an important role in clopidogrel response.\textsuperscript{2,12–14}

The main finding of Tantry and colleagues\textsuperscript{4} is that in confirmation of previous outcomes findings of the PLATO pharmacogenetics substudy,\textsuperscript{2} ticagrelor-induced antiplatelet effects are indeed superior to those of clopidogrel irrespective of CYP2C19 genotype. That being said, the world of personalized antiplatelet therapy for patients with coronary artery disease is still very much in flux. Clopidogrel will be coming off patent soon, so cost will be a factor for payers in determining which antiplatelet therapies to cover. Ticagrelor has yet to obtain FDA approval, and the issue of its failure to demonstrate a benefit among North American study participants was raised at the advisory committee meeting. Further, in patients in whom adherence is an issue, clopidogrel or prasugrel may be more-appropriate choices given the shorter duration of action of ticagrelor and, hence, requirement for twice-daily dosing. Similarly, ticagrelor had a higher incidence of several adverse effects, including increases in uric acid and creatinine, dyspnea, and ventricular pauses.\textsuperscript{1} Therefore, whether certain subpopulations who might be most susceptible to these adverse effects would gain greater benefit from alternative agents is unknown. Finally, clopidogrel is approved for some indications in which ticagrelor has not yet been studied, such as stroke and peripheral arterial disease. Taken together, there likely will be patients in whom clopidogrel remains indicated and in whom it will be useful to understand factors associated with and methods for overcoming nonresponse.

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Disclosures

None.

References


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