Is Ticagrelor the Antiplatelet Therapy Panacea?

Amber L. Beitelshees, PharmD, MPH

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 enzymes, including CYP2C19. This difference is important in that the multiple steps required to activate clopidogrel make it has a slower onset and less consistent platelet inhibitory effect compared to ticagrelor. 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 colleagues 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. 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 *CYP2C19* 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. 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...
Table. Pharmacological Characteristics of Ticagrelor and Clopidogrel

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action (t_{on})</td>
<td>1.5 h</td>
<td>4 h</td>
</tr>
<tr>
<td>Offset of action</td>
<td>1–2 d</td>
<td>5 d</td>
</tr>
<tr>
<td>P2Y12 receptor binding</td>
<td>Reversible</td>
<td>Irreversible</td>
</tr>
<tr>
<td>Dosing interval</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Active parent drug converted to active metabolite by CYP3A4/5</td>
<td>Prodrug; requires 2-step activation by multiple CYP450s; esterase inactivation</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Bleeding (major and minor-14.6%), dyspnea (≈14% of patients), ventricular pauses, increase in serum uric acid and creatinine</td>
<td>Bleeding (major and minor-16.1%), dyspnea (≈8% of patients), interpatient variability</td>
</tr>
</tbody>
</table>

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.1,8,9 Third, ticagrelor provides more-complete inhibition of the P2Y12 receptor, with 75% to 80% inhibition of aggregation to ADP compared to only ≈30% with clopidogrel.10 A summary of the pharmacological differences between ticagrelor and clopidogrel is shown in Table.

The main finding of Tantry and colleagues4 is that in confirmation of previous outcomes findings of the PLATO pharmacogenetics substudy, 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.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.

Sources of Funding
Dr Beitelshes is supported by National Institutes of Health grants K23HL091120, U01HL105198, and U01GM074492.
Disclosures

None.

References


Key Words: Editorials ■ clonidogrel ■ genetics ■ genotype ■ platelet function tests ■ AZD6140 —
Is Ticagrelor the Antiplatelet Therapy Panacea?
Amber L. Beitelshees

Circ Cardiovasc Genet. published online November 15, 2010;
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue,
Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1942-325X. Online ISSN: 1942-3268

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circgenetics.ahajournals.org/content/early/2010/11/15/CIRCGENETICS.110.958611

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Genetics can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Genetics is online at:
http://circgenetics.ahajournals.org//subscriptions/