Overview of the 2010 Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee Meeting Regarding Ticagrelor

Michael A. Gaglia, Jr, MD, MSc; Ron Waksman, MD

Landmark clinical trials established the benefit of the thienopyridine clopidogrel, an irreversibly binding inhibitor of the platelet P2Y<sub>12</sub> receptor, in the setting of acute coronary syndromes (ACS).<sup>1–3</sup> Clopidogrel has thus become a key component of the current standard of care for antiplatelet therapy in the setting of ACS.<sup>4,5</sup> Evidence has emerged, however, regarding the inherent limitations of clopidogrel. The concept of “clopidogrel resistance,” or the failure of clopidogrel to inhibit the target of its action,<sup>6</sup> is in part due to a wide range of variability in the antiplatelet effect of clopidogrel. Specifically, clopidogrel is a prodrug that requires metabolism by the cytochrome P450 system to generate an active metabolite,<sup>7–9</sup> as such, common variations in genes encoding enzymes that are involved in the metabolism of clopidogrel may affect the level of platelet inhibition.<sup>10</sup> Furthermore, high on-treatment platelet reactivity is an emerging risk factor in patients undergoing percutaneous coronary intervention (PCI), and increased doses of clopidogrel only partially ameliorate this difficulty.<sup>11</sup> The newly approved thienopyridine prasugrel achieves more rapid and effective platelet inhibition than clopidogrel as a result of more efficient metabolism<sup>12</sup>; in addition, the effect of prasugrel is not affected by genetic variations in cytochrome P450.<sup>13</sup> Although prasugrel appeared to reduce myocardial infarction (MI) and stent thrombosis when compared directly to clopidogrel, this came at the cost of an increase in major bleeding.<sup>14</sup>

Ticagrelor is the first of a new class of antiplatelet agents, the cyclopentyl-triazolo-pyrimidines, that also target the P2Y<sub>12</sub> receptor. Unlike the thienopyridines, however, it is a reversibly binding inhibitor with a half-life of approximately 12 hours.<sup>15,16</sup> Furthermore, it does not require metabolic activation, and it achieves greater and more consistent platelet inhibition than clopidogrel.<sup>16</sup> This drug was examined against clopidogrel in the Study of Platelet Inhibition and Patient Outcomes (PLATO), which showed a mortality benefit of the former in a broad spectrum of ACS patients.<sup>17</sup> AstraZeneca (ie, the sponsor) therefore presented efficacy and safety data regarding ticagrelor to the US Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee (CRDAC) on July 28, 2010, in Adelphi, MD. The sponsor sought approval for the indication of reduction of thrombotic events, including stent thrombosis, in patients with unstable angina, non–ST-segment MI (NSTEMI), and ST-segment elevation MI (STEMI) who are to be managed either medically or invasively (with either PCI or coronary artery bypass grafting). The FDA asked CRDAC to opine on whether the data presented by the sponsor demonstrated a reasonable level of efficacy (in regard to the end point of cardiovascular death, MI, and stroke) and safety, including the adverse events of bleeding, dyspnea, and bradycardia.

**Pharmacokinetic and Pharmacodynamic Data**

The sponsor summarized data from 4 phase II clinical pharmacology studies (Table 1).<sup>18</sup> Each trial compared ticagrelor to clopidogrel as the active control on a background of aspirin therapy. The first trial, DISPERSE (Dose-finding Investigative Study to assess the Pharmacodynamic Effects of AZD6140 in atheRoSclerotic diseasE), included 201 patients with stable coronary artery disease.<sup>16</sup> This study determined that a ticagrelor dose of 50 mg twice per day provided an inhibition of platelet aggregation similar to clopidogrel 75 mg once per day; 100- and 200-mg doses of ticagrelor, however, provided greater inhibition of platelet aggregation than clopidogrel. DISPERSE-2, which included 990 patients with non–ST-elevation ACS, was designed to compare the safety of ticagrelor 90 and 180 mg twice per day versus clopidogrel 75 mg once per day.<sup>19</sup> This study showed similar bleeding rates for all 3 regimens, but identified higher incidences of dyspnea and ventricular pauses with the ticagrelor 180-mg regimen; the 90-mg dose was determined to have the best balance of efficacy and safety. The ONSET/OFFSET study (Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Coronary Artery Disease) compared the time course of platelet inhibition in patients given ticagrelor versus clopidogrel, showing that platelet inhibition was more rapid and complete with the former; specifically, 90% of patients receiving ticagrelor versus 16% of those receiving clopidogrel achieved an inhibition of platelet aggregation >70% at only 2 hours after a loading dose (P<0.001).<sup>20</sup> Lastly, the RESPOND study (A Study of the Antiplatelet Effects Comparing AZD6140 With Clopi-
Table 1. Phase II Studies of Ticagrelor vs Clopidogrel

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Ticagrelor Dose</th>
<th>Clopidogrel Dose</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISPERSE</td>
<td>201 Patients with CAD</td>
<td>75 mg MD</td>
<td>75 mg MD</td>
<td>28 d</td>
<td>Inhibition of platelet aggregation with 100 and 200 mg of ticagrelor greater than 75 mg of clopidogrel</td>
</tr>
<tr>
<td>DISPERSE-2</td>
<td>990 Patients with non-ST-</td>
<td>270 mg LD/90 or 180 mg BID MD</td>
<td>300 mg LD/75 mg MD</td>
<td>4, 8, or 12 wk</td>
<td>Bleeding similar between ticagrelor and clopidogrel</td>
</tr>
<tr>
<td>ONSET/OFFSET</td>
<td>123 Patients with CAD</td>
<td>180 mg LD/90 mg BID MD</td>
<td>600 mg LD/75 mg MD</td>
<td>6 wk</td>
<td>Faster onset and offset of inhibition of platelet aggregation with ticagrelor vs clopidogrel</td>
</tr>
<tr>
<td>RESPOND</td>
<td>98 Patients with CAD</td>
<td>180 mg LD/90 mg BID MD</td>
<td>600 mg LD/75 mg MD</td>
<td>2 wk</td>
<td>Patients nonresponsive to clopidogel were responsive to ticagrelor</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; MD, maintenance dose; BID, twice per day; and LD, loading dose.

dogrel Responders and Non-Responders) examined the effect of switching from clopidogrel to ticagrelor; “nonresponders” to clopidogrel were shown to be responsive to ticagrelor.21

**PLATO Trial Design**

Both the sponsor22 and the FDA23 presented an overview of the design of the phase III PLATO study, an international, multicenter, randomized, double-blind active controlled trial. PLATO was designed as a time-to-event superiority trial; it was thus estimated that 18 000 patients would need to be randomized to reach the required 1780 events. The study ultimately randomized 18 758 ACS patients between a 180-mg loading dose and a 90-mg twice-per-day maintenance dose of ticagrelor versus a 300-mg loading dose and 75-mg maintenance dose of clopidogrel (with an additional 300 mg permitted at the time of PCI). The primary end point, detected in 1878 patients, was a composite of cardiovascular death, MI, or stroke. The final visit for patients was at 6, 9, or 12 months, depending on the enrollment date.

Robert Harrington, MD, speaking on behalf of the sponsor, emphasized that the trial was designed to examine patients at the point of entry, “upstream,” before most decisions were made. Patients across the spectrum of ACS (unstable angina, NSTEMI, and STEMI) were thus included, as were patients who ultimately underwent PCI, coronary artery bypass grafting, or medical management. As a result, randomization occurred within 24 hours of symptom onset and at the initial presentation (i.e., before angiography). In addition, patients undergoing chronic clopidogrel therapy were included, as were patients who received up to 600 mg of clopidogrel before enrollment.

The FDA generally agreed that PLATO was well designed, and they applauded the effort to enroll patients early in their ACS presentation and in essence study a strategy in addition to a novel drug. The FDA panel, however, was somewhat perplexed by the sponsor’s presentation of missing data. Although the sponsor claimed that only 5 patients were lost to follow-up overall, panel member James Neaton, PhD, observed that 15% of patients had incomplete follow-up with regard to nonfatal cardiovascular events; specifically, these patients did not have a final clinic visit. The sponsor countered that the actual number of patients not achieving the target follow-up duration was 8.9% when phone contact was considered as a final “visit.” Furthermore, the sponsor presented results of a sensitivity analysis; even assuming 50 nonfatal cardiovascular events were “missed” in the ticagrelor group, the results of the trial would still be significant. The panel, however, expressed frustration with regard to the unnecessary confusion that accompanied the sponsor’s presentation of follow-up data and wondered whether nonfatal events were missed because of the absence of a final clinic visit in some patients. Thomas Marciniak, MD, the FDA clinical team leader, observed that such problems of incomplete follow-up are threatening the integrity of cardiovascular outcomes trials in general.

**Safety and Adverse Events**

The discussion of safety and adverse events focused on 3 topics: Bleeding, dyspnea, and ventricular pauses.22,23 Major bleeding in the PLATO trial, using the study definition of life-threatening bleeding, decline in hemoglobin of more than 3 g/dL, or need for transfusion of at least 2 units of red blood cells, was similar between ticagrelor and clopidogrel (11.6% versus 11.2%, P = 0.43). Rates of major bleeding did not vary significantly by any subgroup except for a borderline increase in the risk of bleeding with ticagrelor in patients with a body mass index >30 kg/m². There was also a small but statistically significant increase in fatal intracranial hemorrhages, but fewer extracranial fatal bleeds, with ticagrelor. Melanie Blank, MD, clinical reviewer for the FDA, observed that PLATO used a rather broad definition of major bleeding. Specifically, this resulted in a rather high rate of coronary artery bypass grafting-related bleeds because of “routine” transfusion during coronary artery bypass grafting. The removal of transfusion from the definition of major bleeding, however, reduced coronary artery bypass grafting-related bleeding with ticagrelor from 42% to 11%.

Dyspnea was more frequent with ticagrelor versus clopidogrel (13.8% versus 7.8%, P <0.001), as was dyspnea that led to discontinuation of study drug (0.9% versus 0.1%, P <0.001). The sponsor estimated that 9 in 1000 patients would discontinue ticagrelor because of dyspnea, although they also presented data showing that patients with cardiopulmonary disease at baseline did not have an increased relative risk of dyspnea. Furthermore, patients taking ticagrelor did not have measurable changes in pulmonary function.
Lastly, patients taking ticagrelor versus clopidogrel had more ventricular pauses that were ≥3 seconds detected by Holter monitoring during the first week of treatment (5.8% versus 3.6%, \( P=0.01 \)). These pauses, however, did not result in an increase of other arrhythmias or need for pacemaker insertion. Furthermore, the benefit of ticagrelor with regard to the primary end point was maintained in patients with such ventricular pauses. Although the mechanism for the side effects of dyspnea and ventricular pauses is still unknown, it was hypothesized that ticagrelor may inhibit adenosine re-uptake by red blood cells. The sponsor concluded that these adverse events associated with ticagrelor were clinically manageable.

### Efficacy

The primary results of the PLATO trial, as presented by the sponsor, are shown in Table 2. A total of 9.8% of patients taking ticagrelor versus 11.7% of patients taking clopidogrel experienced the end point of cardiovascular death, MI, or stroke at 1 year (hazard ratio 0.84, 95% confidence interval 0.77 to 0.92, \( P<0.001 \)). Rates of cardiovascular death, MI, and stent thrombosis individually were also lower with ticagrelor versus clopidogrel, although stroke rates were similar. Furthermore, hazard ratios were generally similar for all types of index ACS (eg, STEMI versus NSTEMI/unstable angina), in both invasively and medically managed patients (72% and 28% of patients, respectively).

Robert Fiorentino, MD, of the FDA observed that the time course of benefit with ticagrelor was rather different from the thienopyridine trials. Specifically, the Kaplan-Meier curves of ticagrelor and clopidogrel did not begin to separate until after 30 days; this is in contrast to the TRITON-TIMI 38 trial (TRial to assess Improvement in Therapeutic outcomes by Optimizing platelet inhibitionN with Prasugrel), in which the benefit of prasugrel versus clopidogrel was observed immediately.\(^\text{14}\) It was emphasized, however, that the 2 trials were quite different. Importantly, TRITON excluded patients taking clopidogrel at baseline, whereas PLATO included them, and all patients in TRITON underwent PCI versus only a majority of patients in PLATO. It was also observed that almost one third of patients in PLATO received a loading dose of clopidogrel before randomization to ticagrelor; this might also explain the delayed separation of the ticagrelor and clopidogrel curves. The FDA also drew attention to the 6 potential subgroups of patients who were studied in PLATO (Table 3), observing that there was no benefit of ticagrelor in patients with unstable angina. The question of whether there should be 6 separate indications was thus raised, although the sponsor noted that patients were randomized before the decision of invasive versus medical management was established, when the specific type of index ACS was still in question. The committee generally agreed that ticagrelor should be examined in the population studied and not by the index ACS that was established after enrollment. In other words, the population studied should be given more weight than a subgroup analysis. The majority of discussion therefore centered on the apparent lack of benefit with ticagrelor in the United States.

### Lack of Benefit in the United States

It was somewhat surprising that ticagrelor did not show a benefit in the subgroup of US patients, or in North America for that matter. Indeed, the trend actually favored clopidogrel in such patients, with no overlap of the 95% confidence intervals in US versus non-US patients (hazard ratio 1.27, 95% confidence interval 0.92 to 1.75 versus hazard ratio 0.81, 95% confidence interval 0.74 to 0.90, respectively). The sponsor went to great lengths in an attempt to explain the apparent lack of benefit observed with ticagrelor in US patients. This was because, in the words of Robert Temple, MD, of the FDA, the panel was being asked to approve ticagrelor in a country where it did not show a benefit. The sponsor posited 3 possible explanations for the observations in the US population: Systematic issues in trial conduct at US sites; the play of chance; or differences in baseline characteristics or clinical management between US and non-US populations.

The sponsor ruled out systematic issues in trial conduct, including mislabeled drug or quality issues at US sites. The play of chance, however, was thought to be a plausible explanation, in part because the treatment-by-region interaction was the only 1 of 31 prespecified subgroup analyses that

### Table 2. Efficacy Results of Ticagrelor vs Clopidogrel at 1 Year in the PLATO Trial\(^\text{17}\)

<table>
<thead>
<tr>
<th>Event</th>
<th>Ticagrelor, %</th>
<th>Clopidogrel, %</th>
<th>Hazard Ratio for Ticagrelor (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, MI, or stroke</td>
<td>9.8</td>
<td>11.7</td>
<td>0.84 (0.77–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>4.0</td>
<td>5.1</td>
<td>0.79 (0.69–0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause death</td>
<td>4.5</td>
<td>5.9</td>
<td>0.78 (0.69–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI</td>
<td>5.8</td>
<td>6.9</td>
<td>0.84 (0.75–0.95)</td>
<td>0.005</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.5</td>
<td>1.3</td>
<td>1.17 (0.91–1.52)</td>
<td>0.22</td>
</tr>
<tr>
<td>Stent thrombosis (definite)</td>
<td>1.3</td>
<td>1.9</td>
<td>0.67 (0.50–0.91)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

\(CI\) indicates confidence interval; \(MI\), myocardial infarction.

### Table 3. Hazard Ratios (Ticagrelor vs Clopidogrel) for Primary End Point by Planned Treatment Approach and Index ACS Event\(^\text{23}\)

<table>
<thead>
<tr>
<th>Event</th>
<th>Medical Management</th>
<th>Invasive Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>0.73 (0.46–1.16)</td>
<td>0.86 (0.72–1.01)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>0.85 (0.70–1.02)</td>
<td>0.82 (0.70–0.97)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0.97 (0.69–1.37)</td>
<td>0.95 (0.67–1.35)</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; STEMI, ST-elevation myocardial infarction; and NSTEMI, non–ST-elevation myocardial infarction.
The sponsor therefore searched for a factor that had both a strong qualitative interaction with randomized treatment for the primary end point and was also strongly imbalanced between US and non-US sites. There were a number of factors that appeared more frequent in US patients, including diabetes mellitus, index event of NSTEMI, planned invasive management, and higher aspirin maintenance dose. None of these factors was associated with a lesser treatment effect of ticagrelor in US patients versus non-US patients except for higher median aspirin maintenance dose. It is notable that half of US patients received an aspirin maintenance dose of 325 mg, whereas the majority of non-US patients received 75 or 100 mg. Specifically, higher maintenance-dose aspirin was associated with relatively unfavorable outcomes with ticagrelor; this was true for both US and non-US patients (Figure). The sponsor therefore concluded that when ticagrelor was administered with low-dose aspirin, a positive treatment effect was observed in both US and non-US regions.

The sponsor also presented data to support the biological plausibility of this effect of high-dose aspirin. They started from the hypothesis that the antplatelet effect of high-dose aspirin varies based on the degree of P2Y₁₂ receptor blockade. In a setting of modest P2Y₁₂ inhibition (ie, clopidogrel), high-dose aspirin would add an antplatelet benefit through inhibition of platelet cyclooxygenase pathways; in a setting of more complete P2Y₁₂ inhibition (ie, ticagrelor), high-dose aspirin would add little antplatelet benefit but might increase vascular resistance through inhibition of cyclooxygenase enzymes within blood vessels. This hypothesis was studied in a dog model, which showed an increase in vascular resistance with high-dose aspirin, as well as with human platelets in vitro, which showed little inhibition with ticagrelor but more inhibition with clopidogrel in the presence of high-dose aspirin.

The FDA and panel were particularly skeptical of the sponsor’s explanation for the possible interaction between ticagrelor and aspirin. Although the panel acknowledged that the optimal maintenance dose of aspirin is yet to be established and that US and European guidelines differ pointedly in this regard, their consensus was that the lack of benefit in the United States was not adequately explained by this factor. It was also posited that aspirin maintenance dose may merely be a marker for sicker patients or different practice patterns in the United States. The FDA’s statistical reviewer, Julie Zhang, PhD, examined other covariates and could not find an alternative explanation for the difference between US and non-US patients. This reviewer, however, cautioned that the statistical robustness of this explanation was questionable, in part because very few subjects in non-US regions had higher maintenance doses of aspirin. Sanjay Kaul, MD, panel chair, perhaps summarized the consensus best. He observed that the qualitative nature (ie, the direction) of the effect of ticagrelor in the US was opposite that of the overall trial; such a scenario indicates a spurious observation is most likely. He also added that the aspirin interaction alone was an unpersuasive argument and concluded, “Certain questions are unresolvable, and this would be one.”

High- Versus Low-Dose Aspirin

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Panel Recommendations

The panel originally intended to examine the indications of STEMI managed invasively, NSTEMI/unstable angina managed invasively, and NSTEMI/unstable angina managed medically separately. It was agreed, however, to combine all patients with ACS; because the PLATO trial was one of strategy in a population of “all-comers,” the panel thought it would be inappropriate to “break apart” indications. The committee therefore voted on the following 2 questions: Should ticagrelor be approved for the reduction of thrombotic events in patients with (1) non–ST-elevation and ST-elevation ACS intended to be managed by PCI and (2) ACS intended to be managed medically? In both instances, the committee voted 7 to 1 in favor of approval; Mori Krantz, MD, was the lone dissenter. Dr Krantz found it discomforting that the direction of the effect of ticagrelor was the opposite of that expected in the United States, and he believed there should be further studies before approval. Although voting in favor of approval, Sanjay Kaul, MD, also thought there should be postapproval studies of ticagrelor in the United States that examined unstable angina, NSTEMI, and STEMI separately.

The panel also commented on the indication for reduction of stent thrombosis, although this was a nonvoting question. The consensus was that such an indication would be reasonable, in part because prasugrel had obtained a similar indication. The panel did not endorse any specific limitations for the use of ticagrelor in ACS patients and agreed that the indication sought for “reduction in thrombotic events” was reasonable. It was also agreed, however, that the US results showing no benefit of ticagrelor should be described specifically in any labeling. Furthermore, despite the overall skepticism of the panel toward the sponsor’s hypothesis regarding aspirin, the panel thought labeling should also mention the potential interaction with high-dose aspirin. James Neaton, PhD, commented, “At least the public should be aware of the post hoc findings … and make a decision for themselves” (Table 4).
Table 4. Recommendations of the FDA CRDAC Committee Regarding Ticagrelor

- Ticagrelor should be approved for the reduction of thrombotic events in patients with non–ST-elevation and ST-elevation ACS intended to be managed with percutaneous coronary intervention.
- Ticagrelor should be approved for the reduction of thrombotic events in patients with non–ST-elevation and ST-elevation ACS intended to be managed medically.
- Lack of benefit with ticagrelor in the United States should be included in product labeling.
- Consideration of low (75–100 mg) aspirin maintenance dose, and potential interaction of high-dose aspirin and ticagrelor, should be included in product labeling.

FDA CRDAC indicates Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee; ACS, acute coronary syndrome.

The committee in general believed that the adverse events (eg, dyspnea, ventricular pauses) associated with ticagrelor were addressed adequately. Although there was no consensus regarding a possible increased risk of intracranial hemorrhage with ticagrelor, the panel was satisfied with the sponsor’s presentation of overall bleeding data.

Conclusions

The sponsor was able to convincingly demonstrate to the CRDAC that ticagrelor, compared with clopidogrel, reduces thrombotic events in a broad range of ACS patients without an increase in overall bleeding. This was despite perplexing data showing a lack of benefit in US patients and a lengthy but ultimately unconvinced presentation by the sponsor regarding a potential adverse effect of high-dose maintenance aspirin in the ticagrelor arm. The results were driven not only by a reduction in MI but also by an impressive reduction in cardiovascular mortality. Future studies of ticagrelor are planned in non-ACS patients, but there is no pending trial or consensus on the definition of high on-treatment platelet reactivity to adenosine diphosphate.

Disclosures

None.

References


**KEY WORDS:** Food and Drug Administration ■ pharmacology ■ ticagrelor ■ antiplatelet drugs
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