# News and Views From the Literature

## Antiplatelet Therapy

### Ticagrelor in Acute Coronary Syndrome: A New Frontier in Platelet Inhibition

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Dual antiplatelet therapy with aspirin and the thienopyridine clopidogrel has resulted in major reductions in cardiovascular events in patients with acute coronary syndrome (ACS),[1-4] and is recommended by the current clinical practice guidelines for the treatment of patients with ACS with and without ST-segment elevation.[5-9] Despite its proven efficacy, clopidogrel has several limitations. It is a prodrug that requires hepatic conversion to an active metabolite, resulting in delayed onset of action and wide interindividual variability in antiplatelet effects.[10,11] At steady state, mean levels of inhibition of adenosine diphosphate (ADP)-induced platelet aggregation achieved with clopidogrel are modest (30%-40%), and up to one-third of patients exhibit minimal platelet inhibition, so-called clopidogrel resistance, that is associated with an increased risk of adverse clinical outcomes.[12-14] Additionally, the active metabolite of clopidogrel binds irreversibly to $P2Y_{12}$ receptors prohibiting the recovery of platelet function. Some of these drawbacks have been overcome with a new thienopyridine agent, prasugrel, which is more efficiently metabolized to its active form and has a more consistent and pronounced inhibitory effect on platelets.[15,16] Compared with clopidogrel, prasugrel significantly reduced the rates of ischemic events, including myocardial infarction (MI) and stent thrombosis, in moderate- to high-risk patients with ACS scheduled for percutaneous coronary intervention, but increased the risk of major bleeding as well.[17]

*Ticagrelor (AZD6140) is the first reversible oral $P2Y_{12}$ receptor antagonist (half-life of approximately 12 hours) that belongs to a new chemical class of antiplatelet agents termed* cyclopentyl-triazolo-pyrimidines.

Ticagrelor (AZD6140) is the first reversible oral $P2Y_{12}$ receptor antagonist (half-life of approximately 12 hours) that belongs to a new chemical class of antiplatelet agents termed *cyclopentyl-triazolo-pyrimidines*.[18-20] It has the potential to address many of the inherent limitations of thienopyridine therapy; for example, it is not a prodrug and therefore does not require metabolic conversion to an active form, it has a rapid and reversible concentration-dependent direct inhibitory effect on the $P2Y_{12}$ receptor, and it nearly completely inhibits ADP-induced platelet aggregation. Properties of all current $P2Y_{12}$ inhibitors are listed in Table 1.

## Phase II Studies: DISPERSE and DISPERSE-2

The Dose-finding Investigative Study to Assess the Pharmacodynamic Effects of AZD6140 in Atherosclerotic Disease (DISPERSE) trial randomized 200 patients with stable atherosclerotic disease to 1 of 4 different dose regimens of ticagrelor (50, 100, or 200 mg twice daily, or 400 mg once daily) or to clopidogrel (75 mg once daily) for 28 days along with aspirin (75-100 mg once daily).[19] ADP-induced platelet aggregation was rapidly and nearly completely inhibited by the 3 higher doses of ticagrelor (100 and 200 mg twice daily, 400 mg once daily) on day 1 with peak final-extent inhibition of platelet aggregation (IPA) observed at 2 to 4 hours postdose, whereas there was minimal inhibition of platelet aggregation with clopidogrel on day 1 (mean IPA $<$ 20% at all time points). The final-extent mean percentage IPA achieved with the 3 higher doses of ticagrelor at 4 hours postdose at steady state was comparable ($\sim$ 90%-95%), which was higher than that achieved with ticagrelor, 50 mg twice daily, or clopidogrel ($\sim$ 60%). Ticagrelor was generally well tolerated with all bleeding events (except 1 in a patient receiving 400 mg once daily) being minor and of mild-to-moderate severity. Dyspnea was more commonly reported with ticagrelor and the incidence appeared to increase with increasing dose, though none of the episodes were considered serious.

The Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 Versus Clopidogrel in Non–ST-Segment Elevation Myocardial Infarction (DISPERSE-2) trial randomized 990 patients with non–ST-segment elevation ACS, treated with aspirin and other standard therapy for ACS, in a 1:1:1 double-blind fashion to ticagrelor, 90 mg twice daily or 180 mg twice daily, or clopidogrel, 300-mg loading dose, followed by 75 mg once daily for up to 12 weeks.[21] The Kaplan-Meier rate of the primary endpoint (protocol-defined major or minor bleeding at 4 weeks) was 8.1% in the clopidogrel group, 9.8% in the ticagrelor 90-mg group, and 8.0% in the ticagrelor 180-mg group ($P$ = .43 and $P$ = .96, respectively, vs clopidogrel). Encouraging trends were seen in the Kaplan-Meier rates of MI in the ticagrelor groups at 12 weeks, although they did not reach statistical significance (5.6%, 3.8%, and 2.5%, respectively; $P$ = .41 and $P$ = .06, respectively, vs clopidogrel). In a post hoc analysis, a greater frequency of mostly asymptomatic ventricular pauses $>$ 2.5 seconds

**Table 1**
**Properties of Current $P2Y_{12}$ Inhibitors**

| | Ticlopidine Hydrochloride | Clopidogrel Bisulfate | Prasugrel Hydrochloride | Ticagrelor (not FDA approved) |
|---|---|---|---|---|
| **US brand name** | Ticlid® | Plavix® | Effient® | Brilinta® (proposed) |
| **Loading/maintenance dose** | 500 mg/250 mg twice daily | 300-600 mg/75 mg once daily | 60 mg/10 mg once daily | 180 mg/90 mg twice daily |
| **Metabolism** | Prodrug | Prodrug | Prodrug | Active drug |
| **Mechanism of action** | Irreversible | Irreversible | Irreversible | Reversible |
| **Elimination half-life** | 13 hours (active metabolite) | 8 hours (active metabolite) | 7 hours (active metabolite) | 12 hours (parent compound) |
| **Duration of action** | 5-7 days | 5-7 days | 5-9 days | 3-5 days |

FDA, US Food and Drug Administration.
Brilinta is manufactured by AstraZeneca, Wilmington, DE.
Effient is manufactured by Eli Lilly and Co., Indianapolis, IN.
Plavix is manufactured by Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Bridgewater, NJ.
Ticlid is manufactured by Roche Laboratories, Nutley, NJ.

was detected during continuous electrocardiogram monitoring among patients receiving ticagrelor, especially those receiving the higher dose (4.3%, 5.5%, and 9.9%, respectively; $P = .58$ and $P = .01$, respectively, vs clopidogrel). Dyspnea was more common in the ticagrelor groups and appeared to be dose related (6.4%, 10.5%, and 15.8%, respectively; $P = .07$ and $P < .0002$, respectively, vs clopidogrel). Importantly, none of the episodes were severe or associated with congestive heart failure or bronchospasm, were often self-limited, and infrequently led to drug discontinuation. A pharmacodynamics substudy of DISPERSE-2 found that platelet aggregation was inhibited to a greater extent (in a dose-dependent manner) by ticagrelor, compared with a standard regimen of clopidogrel in patients with non–ST-segment elevation ACS, and there was a further suppression of platelet aggregation with ticagrelor in clopidogrel-pretreated patients.[22]

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### Phase III PLATO Trial

The Study of Platelet Inhibition and Patient Outcomes (PLATO) was a multicenter, double-blind, randomized trial that compared ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) to clopidogrel (300-600 mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in 18,624 patients admitted to the hospital with ACS, with or without ST-segment elevation.[23] The primary endpoint of the composite of cardiovascular death, MI, or stroke was significantly reduced at 12 months among patients who received ticagrelor compared with those who received clopidogrel (9.8% vs 11.7%; hazard ratio [HR] 0.84; 95% confidence interval [CI], 0.77-0.92; $P < .001$). Ticagrelor significantly reduced the rates of other composite endpoints, as well as MI alone (5.8% vs 6.9% in the clopidogrel group; $P = .005$) and death from cardiovascular causes (4.0% vs 5.1%; $P = .001$), but not stroke alone (1.5% vs 1.3%; $P = .22$). Total mortality was also significantly reduced from 5.9% with clopidogrel to 4.5% with ticagrelor (HR 0.78; 95% CI, 0.69–0.89; $P < .001$). In the 13,408 patients for whom invasive management was planned at randomization, a lower rate of the primary endpoint was seen with ticagrelor versus clopidogrel (8.9% vs 10.6%, respectively; $P = .003$). The rate of definite stent thrombosis was reduced as well with ticagrelor (1.3% vs 1.9% with clopidogrel; $P = .009$). The ticagrelor and clopidogrel groups did not differ significantly with respect to the rates of major bleeding (11.6% and 11.2%, respectively; $P = .43$). The rate of major noncoronary artery bypass graft surgery bleeding was, however, increased with ticagrelor (4.5% vs 3.8% with clopidogrel; $P = .03$). Dyspnea occurred in a higher proportion of patients receiving ticagrelor (13.8% vs 7.8% for clopidogrel; $P < .001$), although this symptom rarely led to discontinuation of the study drug. Ventricular pauses on Holter monitoring were more common among patients receiving ticagrelor than among those receiving clopidogrel during the first week of therapy, but this difference did not persist at 30 days follow-up. Ticagrelor increased the levels of creatinine and uric acid slightly more than clopidogrel did. Overall, more patients in the ticagrelor group discontinued the study medication because of adverse events (7.4% vs 6.0% for clopidogrel; $P < .001$).

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### ONSET/OFFSET Study

The ONSET/OFFSET study (A Multi-Centre Randomised, 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) was designed to assess the onset and offset of platelet inhibition with ticagrelor, 180 mg loading dose, followed by 90 mg twice daily (as studied in PLATO) versus clopidogrel, 600 mg (high loading dose), followed by 75 mg once daily.[24] A total of 123 patients with stable coronary artery disease on background aspirin therapy were randomized in a double-blind fashion to ticagrelor, clopidogrel, or placebo for 6 weeks. Ticagrelor produced greater IPA than clopidogrel at 0.5, 1, 2, 4, 8, and 24 hours after loading and at 6 weeks ($P < .0001$ for all). The proportion of patients who achieved $> 50\%$ IPA and $> 70\%$ IPA at 2 hours

after loading was higher with ticagrelor versus clopidogrel (> 50% IPA: 98% vs 31%; and > 70% IPA: 90% vs 16%, respectively, with ticagrelor vs clopidogrel; $P <$ .0001). The offset of IPA was faster with ticagrelor than with clopidogrel (4-72 h slope [% IPA/h] −1.04 vs −0.48; $P <$ .0001). Mean IPA at 24 hours after the last dose was 58% for ticagrelor versus 52% for clopidogrel, and mean IPA for ticagrelor on day 3 was equivalent to clopidogrel at day 5.

## Conclusions

In patients with ACS with or without ST-segment elevation, treatment with ticagrelor, as compared with clopidogrel, significantly reduced the rate of the composite of cardiovascular death, MI, or stroke without an increase in the rate of overall major bleeding. The reversible binding of ticagrelor to the $P2Y_{12}$ receptor offers the potential for flexibility with respect to carrying out coronary bypass and other surgical procedures sooner after discontinuation of the drug. With the overall reduction in cardiovascular events, stent thrombosis, and total mortality, without an increase in overall major bleeding, ticagrelor seems to be a better option than clopidogrel for patients with acute coronary syndromes. ■

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