The Incidence of Bradyarrhythmias and Clinical Bradyarrhythmic Events in Patients With Acute Coronary Syndromes Treated With Ticagrelor or Clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) Trial

Results of the Continuous Electrocardiographic Assessment Substudy

Benjamin M. Scirica, MD, MPH,* Christopher P. Cannon, MD,* Håkan Emanuelsson, MD, PhD,† Eric L. Michelson, MD,‡ Robert A. Harrington, MD,§ Steen Husted, MD DSc,¶ Stefan James, MD, PhD, Hugo Katus, MD,# Prem Pais, MD,** Dimitar Raev, MD,†† Jindrich Spinar, MD,‡‡ Ph. Gabriel Steg, MD,§§ Robert F. Storey, MD, DM,## Lars Wallentin, MD, PhD,¶ for the PLATO Investigators

Boston, Massachusetts; Mölndal and Uppsala, Sweden; Wilmington, Delaware; Durham, North Carolina; Århus, Denmark; Heidelberg, Germany; Bangalore, India; Sofia, Bulgaria; Brno, Czech Republic; Paris, France; and Sheffield, United Kingdom

Objectives
The aim of this study was to determine whether ticagrelor increased the risk of ventricular pauses compared with clopidogrel and whether these pauses were associated with any clinical bradycardic events in patients presenting with acute coronary syndromes.

Background
Ticagrelor, an oral reversibly binding P2Y12 inhibitor, provides more potent and consistent inhibition of platelet aggregation than clopidogrel but in a phase II study was associated with increased risk for ventricular pauses. A prospective continuous electrocardiographic (cECG) assessment was therefore performed within the PLATO (Platelet Inhibition and Patient Outcomes) study comparing ticagrelor and clopidogrel in patients hospitalized with acute coronary syndromes.

Methods
Patients in the cECG assessment had planned 7-day cECG recording initiated at the time of randomization (week 1), which was within 24 h of symptom onset, and then repeated at 1 month after randomization during the convalescent phase. The principal safety endpoint was the incidence of ventricular pauses lasting at least 3 s. Investigators also reported symptomatic bradycardic adverse events during the entire study duration (median 277 days).

Results
A total of 2,908 patients were included in the cECG assessment, of whom 2,866 (98.5%) had week 1 recordings, 1,991 (68.4%) had 1-month recordings, and 1,949 (67.0%) had both. During the first week after randomization, ventricular pauses ≥3 s occurred more frequently in patients receiving ticagrelor than clopidogrel (84 [5.8%] vs. 51 [3.6%]; relative risk: 1.61; p = 0.006). At 1 month, pauses ≥3 s occurred overall less frequently and were similar between treatments (2.1% vs. 1.7%). Most were ventricular pauses, and the greatest excess associated with ticagrelor were asymptomatic, sinoatrial nodal in origin (66%), and nocturnal. There were no differences between ticagrelor and clopidogrel in the incidence of clinically reported bradycardic adverse events, including syncope, pacemaker placement, and cardiac arrest.

Conclusions
In the PLATO cECG assessment, more patients treated with ticagrelor compared with clopidogrel had ventricular pauses, which were predominantly asymptomatic, sinoatrial nodal in origin, and nocturnal and occurred most frequently in the acute phase of acute coronary syndromes. There were no apparent clinical consequences related to the excess in ventricular pauses in patients assigned to ticagrelor. (A Comparison of AZD6140 and Clopidogrel in Patients With Acute Coronary Syndrome [PLATO]; NCT00391872) (J Am Coll Cardiol 2011;57: 1908–16) © 2011 by the American College of Cardiology Foundation
Ticagrelor, an oral reversibly binding P2Y₁₂ inhibitor, provides more potent and consistent inhibition of platelet aggregation than clopidogrel. In the PLATO (Platelet Inhibition and Patient Outcomes) study of 18,624 patients with acute coronary syndromes (ACS), ticagrelor was superior to clopidogrel, significantly reducing the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke (1). In the DISPERSE-2 (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs Clopidogrel in Non-ST-Segment Elevation Myocardial Infarction 2) trial, a phase Ib dose-ranging study in patients with ACS, 2 doses of ticagrelor (90 or 180 mg twice daily) were compared with clopidogrel in 990 patients. Continuous electrocardiographic (cECG) recording started at randomization and lasting for a median of 4 days after the index hospitalization was performed with the objective of detecting recurrent ischemia. A post hoc analyses of cardiac arrhythmias revealed an unexpected increased in the incidence of predominately asymptomatic ventricular pauses in patients treated with ticagrelor compared with those treated with clopidogrel (2).

Because of the increased incidence of ventricular pauses observed in DISPERSE-2, the PLATO study included a prospectively designed cECG assessment, with the goal of including 3,000 patients who would have 7-day cECG recording initiated at the time of randomization during their hospitalization for ACS (visit 1 or week 1). Two thousand of these patients were then to have another 7-day cECG assessment during the ambulatory convalescent phase, 1 month after randomization (visit 2 or 1 month) (3). The objectives of the cECG assessment were to determine whether ticagrelor increased the risk of ventricular pauses and whether these pauses were associated with any clinical bradycardic events.

**Methods**

**Study design.** The details of the PLATO study design have been published previously (1,3). In brief, patients were eligible if they were hospitalized for ACS, with or without ST-segment elevation, with an onset of symptoms during the previous 24 h. A broad population of patients were included with intention for primary interventional or medical treatment. For patients who had ACS without ST-segment elevation, at least 2 of the following 3 criteria had to be met: ST-segment changes on electrocardiography, indicating ischemia; a positive biomarker test result, indicating myocardial necrosis; or 1 of several risk factors (age ≥60 years; previous myocardial infarction or coronary artery bypass grafting; coronary artery disease with stenosis of ≥50% in at least 2 vessels; previous ischemic stroke, transient ischemic attack, carotid stenosis of at least 50%, or cerebral revascularization; diabetes mellitus; peripheral artery disease; or chronic renal dysfunction, defined as creatinine clearance <60 ml/min/1.73 m²). For patients who had ACS with ST-segment elevation, the following 2 inclusion criteria had to be met: persistent ST-segment elevation of at least 0.1 mV in at least 2 contiguous leads or a new left bundle branch block and the intention to perform primary percutaneous coronary intervention. Major exclusion criteria were any contraindication against the use of clopidogrel, fibrinolytic therapy within 24 h before randomization, a need for oral anticoagulation therapy, and concomitant therapy with a strong cytochrome P450 3A inhibitor or inducer. Patients at increased risk for a bradycardic event were also excluded (e.g., known sick sinus syndrome, second- or third-degree atrioventricular (AV) conduction block, or previously documented syncope suspected to be due to bradycardia unless treated with a pacemaker). Patients received, in a double-blind, double-dummy design, either ticagrelor, given in a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily, or an appropriate loading dose of clopidogrel followed by a maintenance dose of 75 mg/day. Treatment continued for up to 1 year, with median follow-up of 277 days.

**cECG assessment.** cECG recordings (digital, 3-lead recordings on a memory chip; Lifecard CF, DelMar Reynolds/Spacelabs Healthcare, Issaquah, Washington) were to be initiated at or shortly after the administration of first dose of study drug and continued for up to 7 days after randomization. Any patient who completed the baseline cECG assessment was also to have a second 7-day recording performed 1 month after randomization. The target enrollment originally was 3,000 patients with baseline cECG recording to achieve 2,000 patients with both week 1 and 1-month cECG recording. A total of 2,908 patients were included in the cECG analysis of whom 2,866 (98.5%) had week 1 recordings, 1,991 (68.4%) had 1-month recordings, and 1,949 (67.0%) had both week 1 and 1-month recordings. The full patient flow diagram is presented in Figure 1. Only 13 patients (5 patients in the ticagrelor group and 8 in the clopidogrel group) were excluded
from the cECG substudy population because their cECG recordings were not interpretable.

All cECG recordings were analyzed at the TIMI (Thrombolysis In Myocardial Infarction) Electrocadio-
graphic Core Laboratory (Boston, Massachusetts). Arr-
rhythmias were identified using a commercially available arrhythmia software program (Pathfinder, Spacelabs
Healthcare) that uses a combined automated and interactive
detection technique. All ventricular pauses lasting at least
2.5 s were reviewed and confirmed by analysts and cardiol-
gists blinded to treatment assignment or outcome and
categorized as due to sinoatrial (SA) node dysfunction, AV
node dysfunction, or other cause. The TIMI Electrocadio-
graphic Core Laboratory analyzed the recordings as they
received them. The PLATO Data Safety Monitoring Board
reviewed visit 1 and 2 cECG data on a monthly basis.

Endpoints. The principal safety endpoint for this assess-
ment was the incidence of ventricular pauses lasting at least
3 s, which was chosen on the basis of guidelines that
recommend consideration of pacemaker placement for
symptomatic patients with evidence of 3 s pauses (4). Other
endpoints included the incidence of ventricular pauses
lasting at least 5 s (4) and the incidence of ventricular
tachycardia (5) and supraventricular tachycardia (any epi-
ode at >100 beats/min lasting at least 4 beats), and other
bradyarrhythmias such as sinus bradycardia (at least 4 beats
\( \leq 45 \) beats/min) or dropped beats (no ventricular beat
within 180% of the previous RR interval).

In PLATO, a pre-specified list of preferred adverse event
(AE) terms was chosen to identify any other potential AEs
that could be related to a bradycardic event (Online Table 1).

Investigators in the PLATO study reported symptomatic
AEs that were possibly bradycardic in nature (e.g., AV
block, sinus pauses, sick sinus syndrome, syncope, unex-
plained accidents, and sudden death) as AEs of special
interest using a dedicated case report form for possible
bradycardic events. All pacemaker use (permanent and
temporary) was recorded. Information about the suspected
etiology of syncope AEs (including results of diagnostic
investigations) and the reasons for pacemaker insertion
(including results of diagnostic investigations) were also
collected on the bradycardic event page.

Statistical analyses. Ventricular pauses were summarized
by length of pause (\( \geq 3 \) and \( \geq 5 \) s). The difference in the
incidence of episodes of ventricular pauses \( \geq 3 \) s detected on
cECG assessment between treatment groups was described
using risk ratios and 95% confidence intervals (CIs). The
differences in the incidence of clinically reported bradycardic
events detected on cECG assessment between treatment
groups were described as relative risks (RRs) and 95% CIs
calculated using chi-square tests.

Results

The median duration of cECG monitoring was 6.2 days
during week 1 after randomization and 6.8 days at 1 month.
Baseline characteristics of patients included in the cECG
assessment are presented in Table 1. Overall, there were no
important differences between patients assigned to ticagre-
lor versus clopidogrel in terms of baseline characteristics,
index diagnosis, planned invasive therapy, and the concom-
itant use of drugs known to potentially adversely affect SA

Figure 1 cECG Assessment Patient CONSORT Diagram

AE = adverse event; cECG = continuous electrocardiographic; CONSORT = Consolidated Standards of Reporting Trials. Figure illustration by Craig Skaggs.
Bradyarrhythmias by treatment. During the first week after randomization, ventricular pauses ≥3 s in length occurred more frequently in patients assigned to ticagrelor than clopidogrel (84 [5.8%] vs. 51 [3.6%]; RR: 1.61; 95% CI: 1.14 to 2.26). This was due primarily to an excess in SA node pauses (63 [4.3%] vs. 31 [2.2%]; RR: 1.98; 95% CI: 1.32 to 3.61), with no difference in AV node pauses (20 [1.4%] vs. 17 [1.2%]). The pattern was similar for longer pauses lasting ≥5 s (Table 2).

The incidence of ventricular pauses did not vary significantly by index diagnosis, although the proportion of patients with ventricular pauses during the first-week event was numerically larger in patients treated with ticagrelor compared with clopidogrel with unstable angina compared to non–ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction (7.3% vs. 3.1%, RR: 2.34, 95% CI: 0.97 to 5.63 in unstable angina; 5.7% vs. 3.8%, RR: 1.50, 95% CI: 0.94 to 2.39 in non–ST-segment elevation myocardial infarction; and 5.0% vs. 3.9%, RR: 1.29, 95% CI: 0.69 to 2.43 in ST-segment elevation myocardial infarction).

There were numerically more patients with pauses lasting at least 3 s during the first 48 h of the visit 1 recordings compared with later time periods (66 patients [2.3%] within 48 h from randomization, 47 patients [1.6%] between 48 and 96 h, and 48 patients [1.7%] >96 h after randomization). During each time period, ticagrelor was associated with a greater risk for pauses (odds ratio: 1.42, 95% CI: 0.87 to 2.33, p = 0.12 for <48 h; odds ratio: 1.58, 95% CI: 0.88 to 2.85, p = 0.13 for 48 to 96 h; and odds ratio: 2.67, 95% CI: 0.44 to 4.94, p < 0.001 for >96 h).

Ventricular pauses occurred less frequently at 1 month, with absolute rates less than one-half the rates at week 1. There were still numerically more patients with ventricular pauses ≥3 or ≥5 s in the ticagrelor group than with clopidogrel, although the differences were small and not statistically significant (Table 2). A large proportion of patients in both treatment groups had at least 1 bradycardia detected on the cECG assessment, and this was observed during both week 1 and at 1 month. More patients in the ticagrelor group than in the clopidogrel group had at least 1 bradycardia recorded, and this was observed during both cECG periods. Part of this difference was related to the difference in proportion of patients with ventricular pauses ≥3 s, but other cECG findings also contributed, such as bradycardia (Table 2). However, there was no difference between treatment groups in mean heart rates during either week 1 or at 1 month (Table 2).

Patients with paired recordings. Among patients with both week 1 and 1-month recordings, the pattern was similar, with more patients assigned to ticagrelor having ventricular pauses, in particular SA node pauses, compared with patients assigned to clopidogrel (Online Table 2). Online Table 3 presents a “shift” analysis of the incidence of ventricular pauses at both week 1 and 1 month in patients with paired readings. Pauses were less frequent at 30 days. Among the 58 patients assigned to ticagrelor who had

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ticagrelor 90 mg Twice Daily (n = 1,472)</th>
<th>Clopidogrel 75 mg/day (n = 1,436)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63.1 ± 11.49</td>
<td>63.0 ± 11.34</td>
</tr>
<tr>
<td>Men</td>
<td>1,065 (73.7%)</td>
<td>1,052 (73.3%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.4 ± 16.63</td>
<td>80.6 ± 16.74</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.9 ± 4.96</td>
<td>27.7 ± 5.00</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>514 (34.9%)</td>
<td>515 (35.9%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>439 (29.8%)</td>
<td>405 (28.2%)</td>
</tr>
<tr>
<td>Habitual smoker</td>
<td>519 (35.3%)</td>
<td>516 (35.9%)</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>23 (1.6%)</td>
<td>19 (1.3%)</td>
</tr>
<tr>
<td>Final diagnosis of index ACS event by intended treatment approach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive treatment approach at randomization</td>
<td>1,045</td>
<td>997</td>
</tr>
<tr>
<td>UA</td>
<td>96 (9.2%)</td>
<td>121 (12.1%)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>511 (48.9%)</td>
<td>473 (47.4%)</td>
</tr>
<tr>
<td>STEMI</td>
<td>402 (38.5%)</td>
<td>382 (38.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (3.4%)</td>
<td>21 (2.1%)</td>
</tr>
<tr>
<td>Medically managed treatment approach at randomization</td>
<td>427</td>
<td>439</td>
</tr>
<tr>
<td>UA</td>
<td>111 (26.0%)</td>
<td>107 (24.4%)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>261 (61.1%)</td>
<td>281 (64.0%)</td>
</tr>
<tr>
<td>STEMI</td>
<td>47 (11.0%)</td>
<td>41 (9.3%)</td>
</tr>
<tr>
<td>Use of selected concomitant medications affecting SA and/or AV nodal function during cECG recording</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with at least 1 nodal agent*</td>
<td>1,387 (94.2%)</td>
<td>1,364 (95.0%)</td>
</tr>
<tr>
<td>Patients with more than 1 nodal agent</td>
<td>395 (26.8%)</td>
<td>356 (24.5%)</td>
</tr>
<tr>
<td>Beta-blockers (including sotalol)</td>
<td>1,325 (90.0%)</td>
<td>1,314 (91.5%)</td>
</tr>
<tr>
<td>Other antiarrhythmic drugs</td>
<td>225 (15.3%)</td>
<td>206 (14.3%)</td>
</tr>
<tr>
<td>Calcium-channel blockers (excluding dihydropyridine agents)</td>
<td>150 (10.2%)</td>
<td>132 (9.2%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>94 (6.4%)</td>
<td>68 (4.7%)</td>
</tr>
<tr>
<td>Digoxin (or other digitalis glycoside agents)</td>
<td>38 (2.6%)</td>
<td>34 (2.4%)</td>
</tr>
<tr>
<td>Adenosine (or adenosine analogues)</td>
<td>26 (1.8%)</td>
<td>33 (2.3%)</td>
</tr>
<tr>
<td>Dipyridamole (IV or oral)</td>
<td>9 (0.6%)</td>
<td>8 (0.6%)</td>
</tr>
<tr>
<td>Ibudravine</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Use of CYP 3A4 inhibitors or inducers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate inhibitors (amiodarone, verapamil, or diltiazem)</td>
<td>235 (16.0%)</td>
<td>190 (13.2%)</td>
</tr>
<tr>
<td>Strong inhibitors (clarithromycin, erythromycin, ketoconazole)</td>
<td>10 (0.7%)</td>
<td>6 (0.4%)</td>
</tr>
<tr>
<td>Strong inducers (carbamazepine, phenytoin, rifampin)</td>
<td>5 (0.3%)</td>
<td>6 (0.3%)</td>
</tr>
<tr>
<td>Any proton pump inhibitor use</td>
<td>714 (48.5%)</td>
<td>664 (45.1%)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or as n (%). *Concomitant medications include medications taken from start of visit 1 cECG recording (or randomization) to end of last cECG recording.

ACS = acute coronary syndrome; AV = atrioventricular; BMI = body mass index; cECG = continuous electrocardiographic; CYP = cytochrome P450; IV = intravenous; NSTEMI = non-ST-segment elevation myocardial infarction; PLATO = Platelet Inhibition and Patient Outcomes; SA = sinoatrial; STEMI = STE-segment elevation myocardial infarction; UA = unstable angina.
asymptomatic ventricular pauses ≥3 s at randomization, 16 (28%; 1.7% of all patients with cECG recordings) also had pauses at 1 month, compared to 6 (18%; 0.6% of all patients with cECG recordings) of the 34 patients assigned to clopidogrel who had pauses during week 1 (RR: 1.56; 95% CI: 0.63 to 5.06; p = 0.04). There was similarly no difference in the incidence of ventricular pauses by treatment group according to the time of day. There seemed to be a nocturnal excess of pauses among patients assigned to ticagrelor, with a peak in the frequency of ventricular pauses at night that was less evident in patients assigned to clopidogrel.

**Multiple ventricular pauses.** Among patients who had any ventricular pauses ≥3 s during week 1, 70 patients (3.2% of all patients) experienced only 1 pause, while 20 (0.6%) had more than 4 pauses. At 1 month, only 9 patients (0.05%) had a single pause, while 17 patients (0.8%) experienced more than 4 pauses. The largest relative excess in ventricular pauses in patients assigned to ticagrelor was observed in patients who experienced multiple pauses (Fig. 2).

**Nocturnal pauses.** Figure 3 presents the incidence of ventricular pauses by treatment group according to the time of day. There seemed to be a nocturnal excess of pauses among patients assigned to ticagrelor, with a peak in the frequency of ventricular pauses at night that was less evident in patients assigned to clopidogrel.

**Clinical bradycardic events.** The rates of clinical bradycardic events were much lower than the rates of ventricular pauses on cECG recordings. For example, during the cECG monitoring periods, syncope occurred in 5 patients (0.3%) in the ticagrelor group and 2 (0.1%) in the clopidogrel group, heart block in 6 (0.4%) and 15 (1.0%) patients, and pacemaker placement in 7 (0.5%) and 14 (1.0%) patients, respectively (Table 3). A similarly low rate was seen over the duration of the entire PLATO study in this subset of patients with cECG recordings with respect to syncope in 21 patients (1.4%) assigned to ticagrelor and 18 patients (1.3%) assigned to clopidogrel, heart block in 11 (0.7%) and 20 (1.4%) patients, and pacemaker placement in 13 (0.9%) and 17 (1.2%) patients, respectively (Online Table 5).

Patients with at least 1 ventricular pause on cECG assessment were more likely to have clinical arrhythmic events compared with patients with no ventricular pauses detected on cECG monitoring, regardless of treatment assignment. However, during the cECG monitoring period, there were no apparent differences in the incidence of clinical arrhythmic AEs of interest between ticagrelor and clopidogrel groups among all patients in the cECG assessment (148 [10.1%] vs. 126 [8.8%]), patients with at least 1 pause ≥3 s (23 [25.8%] vs. 16 [25.8%], or patients with at least 1 pause ≥5 s (10 [31.3%] vs. 8 [40.0%]) (Table 3). To further investigate any potential relationship between ventricular pauses detected on cECG monitoring and clinical events, the incidence of bradyarrhythmia AEs of interest that occurred on the same day as ventricular pauses was examined. Although overall, a few more patients had asymptomatic bradycardia or bradyarrhythmia reported on ticagrelor than on clopidogrel, there were no differences in the numbers of patients with symptomatic AEs occurring
on the same day as the ventricular pauses between treatment groups (Online Table 4). In addition, there were similar proportions of patients with arrhythmic AEs of interest in each treatment group over the entire PLATO study duration (Online Table 5).

Supraventricular and ventricular tachyarrhythmias. In the cECG substudy, there was also no increased risk for either supraventricular or ventricular tachyarrhythmias observed with the use of ticagrelor compared with clopidogrel (Table 2). Importantly, and similar to the entire PLATO study, total mortality was lower in this cohort in the ticagrelor group compared with clopidogrel (36 [2.4%] vs. 56 [3.9%]; RR: 0.63; 95% CI: 0.41 to 0.94) over the duration of the PLATO trial.

**Discussion**

In this study of more than 2,900 patients admitted with ACS, we found that ticagrelor, a novel P2Y<sub>12</sub> inhibitor, increased the frequency and incidence of predominately asymptomatic ventricular pauses compared with clopidogrel. Most ventricular pauses, and most of the excess associated with ticagrelor, were due to SA node dysfunction, were nocturnal, and occurred during the first week after...
Table 3
AEs of Interest During cECG Recording Period by Ventricular Pause Duration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients in the cECG Analysis Set</th>
<th>Patients With Pauses ≥ 3 s</th>
<th>Patients With Pauses ≥ 5 s</th>
<th>Patients Without Pauses ≥ 3 s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ticagrelor 90 mg Twice Daily Clopidogrel 75 mg/day</td>
<td>Ticagrelor 90 mg Twice Daily Clopidogrel 75 mg/day</td>
<td>Ticagrelor 90 mg Twice Daily Clopidogrel 75 mg/day</td>
<td>Ticagrelor 90 mg Twice Daily Clopidogrel 75 mg/day</td>
</tr>
<tr>
<td>Number of patients</td>
<td>1,472 1,436</td>
<td>89 62</td>
<td>32 20</td>
<td>1,383 1,374</td>
</tr>
<tr>
<td>Patients with no arrhythmia AE of interest</td>
<td>1,324 (99.9%) 1,310 (91.2%)</td>
<td>66 (74.2%) 46 (74.2%)</td>
<td>22 (68.6%) 12 (60.0%)</td>
<td>1,258 (91.0%) 1,264 (92.0%)</td>
</tr>
<tr>
<td>Patients with at least 1 arrhythmia AE of interest*</td>
<td>148 (10.1%) 126 (8.8%)</td>
<td>23 (25.8%) 16 (25.8%)</td>
<td>10 (31.3%) 8 (40.0%)</td>
<td>125 (9.0%) 110 (8.0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>38 (2.6%) 41 (2.9%)</td>
<td>1 (1.1%) 2 (3.2%)</td>
<td>0 5 (0.0%)</td>
<td>37 (2.7%) 39 (2.8%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>51 (3.5%) 37 (2.6%)</td>
<td>3 (3.4%) 5 (8.1%)</td>
<td>1 (3.1%) 2 (10.0%)</td>
<td>48 (3.5%) 32 (2.3%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>61 (4.1%) 36 (2.5%)</td>
<td>16 (18.0%) 7 (13.3%)</td>
<td>7 (21.9%) 4 (20.0%)</td>
<td>45 (3.3%) 29 (2.1%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>5 (0.3%) 2 (0.1%)</td>
<td>1 (1.1%) 1 (1.6%)</td>
<td>1 (3.1%) 1 (5.0%)</td>
<td>4 (0.3%) 1.0 (1.0%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>3 (0.2%) 6 (0.4%)</td>
<td>2 (2.2%) 3 (3.2%)</td>
<td>1 (3.1%) 1 (5.0%)</td>
<td>1 (0.1%) 4 (0.3%)</td>
</tr>
<tr>
<td>Heart block</td>
<td>6 (0.4%) 15 (1.0%)</td>
<td>3 (3.4%) 5 (8.1%)</td>
<td>1 (3.1%) 1 (5.0%)</td>
<td>3 (0.2%) 10 (0.7%)</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>0 2 (0.1%)</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Pacemaker placement†</td>
<td>7 (0.5%) 14 (1.0%)</td>
<td>5 (5.6%) 5 (8.1%)</td>
<td>3 (9.4%) 2 (10.0%)</td>
<td>2 (0.1%) 9 (0.7%)</td>
</tr>
<tr>
<td>Pre-syncpe</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Vasovagal syncope</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
</tbody>
</table>

* Patients could report in more than 1 AE category. † Patients could be counted in both temporary and permanent pacemaker placement categories, but each patient was counted only once for “pacemaker placement.” Pacemaker placement included not only those pacemakers reported as AEs but also those counted on the bradycardic events page.

AE = adverse event; cECG = continuous electrocardiographic.

The adenosine-related hypothesis may explain the predominance of ticagrelor-associated nocturnal pauses due to increased local adenosine concentration that further exacerbates vagal-mediated nocturnal bradycardia, which has been postulated to be cardioprotective during ischemia (10). Proposed mechanisms include increased local adenosine concentrations that may directly affect cardiac automaticity or conduction, and increased bradycardia observed in the PLATO study will require further studies. The possibility that increased bradycardic events observed in DIPSERSE-2 and the increased bradycardic events observed in the PLATO (2) study may explain the adenosine-related hypothesis may also explain the predominance of nocturnal bradycardia due to increased adenosine concentration that further reinforces the adenosine-related hypothesis (8,9). It is possible that the increased bradycardic events observed in the PLATO study will require further studies. The possibility that increased bradycardic events observed in the PLATO study will require further studies.
bility that increased levels of adenosine may increase the risk for bradyarrhythmias is also consistent with the observation of an overall greater incidence of ventricular pauses observed during the acute phase of ACS, when burden of ischemia is large, thus augmenting local tissue levels of adenosine. The reduced ischemic stimuli at day 30 may therefore explain why the overall incidence of ventricular pauses and relative differences between treatment groups were much smaller compared with visit 1 at randomization.

Few studies have examined the incidence of ventricular pauses in large ACS cohorts. The MDPIT (Multicenter Diltiazem Postinfarction Trial) enrolled 2,466 patients 3 to 15 days after a myocardial infarction and performed a baseline 24-h cECG recording, followed by a repeat 24-h cECG recording at 3 months. The incidence of pauses >2 s was greater for diltiazem than for placebo at baseline (6% vs. 3%), with a similar difference at 3 months (6.5% vs. 2.5%) (11). However, the increased incidence of pauses with diltiazem did not result in any significant clinical consequences for patients, so there are no restrictions on its use related to ventricular pauses. In the almost 6,400 patients with non–ST-segment elevation ACS in the MERLIN (Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome)–TIMI 36 trial comparing ranolazine versus placebo, ventricular pauses ≥3 s detected on 7-day cECG monitoring at the time of the index event occurred in 4.3% of the patients who received placebo (12). Thus, the incidence of ventricular pauses in PLATO is consistent with other contemporary trials of ACS.

It should be noted that the cECG recordings in the PLATO study were used as an investigative tool, not as part of standard clinical care. Consequently, despite the finding of more, mostly asymptomatic, ventricular pauses in the ticagrelor group compared with the clopidogrel group, the absence of increased risk for adverse bradyarrhythmic events in patients assigned to ticagrelor and the clear evidence of clinical benefit consistent with the overall PLATO trial results provide important safety information regarding both the potential risks and benefits of ticagrelor in this population.

**Study limitations.** Because of the increased frequency of ventricular pauses in the post-hoc analysis of cECG data in the DISPERSE-2 study, the PLATO study excluded patients at markedly increased risk for symptomatic bradyarrhythmias, including those with histories of sick sinus syndrome or high-grade AV conduction block or syncope due to a bradyarrhythmia without a pacemaker. Because the risk or benefit in such patients has not been studied, clinicians should therefore use caution in treating these patients with ticagrelor.

**Conclusions**

Ticagrelor compared with clopidogrel increased the incidence of ventricular pauses on cECG monitoring, predominantly via SA node suppression, during the first week after hospitalization for ACS. However, most of these ventricular pauses were asymptomatic and transient, and ticagrelor treatment was not associated with an increased occurrence of clinical manifestations of bradycardia.

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Reprint requests and correspondence: Dr. Benjamin M. Scirica, TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital, 350 Longwood Avenue, 1st Floor, Boston, Massachusetts 02215. E-mail:bscirica@partners.org.

REFERENCES


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