Dronedarone in High-Risk Permanent Atrial Fibrillation

Stuart J. Connolly, M.D., A. John Camm, M.D., Jonathan L. Halperin, M.D., Campbell Joyner, M.D., Marco Alings, M.D., John Amerena, M.D., Dan Atar, M.D., Álvaro Avezum, M.D., Per Blomström, M.D., Martin Borggrefe, M.D., Andrzej Budaj, M.D., Shih-Ann Chen, M.D., Chi Keong Ching, M.D., Patrick Commerford, M.D., Antonio Dans, M.D., Jean-Marc Davy, M.D., Etienne Delacrétaz, M.D., Giuseppe Di Pasquale, M.D., Rafael Diaz, M.D., Paul Dorian, M.D., Greg Flaker, M.D., Sergey Golitsyn, M.D., Antonio Gonzalez-Hermosillo, M.D., Christopher B. Granger, M.D., Hein Heidbüchel, M.D., Josef Kautzner, M.D., June Soo Kim, M.D., Fernando Lanas, M.D., Basil S. Lewis, M.D., Jose L. Merino, M.D., Carlos Morillo, M.D., Jan Murin, M.D., Calambur Narasimhan, M.D., Ernesto Paolasso, M.D., Alexander Parkhomenko, M.D., Nicholas S. Peters, M.D., Kui-Hian Sim, M.D., Martin K. Stiles, M.D., Supachai Tanomsup, M.D., Lauri Toivonen, M.D., János Tomcsányi, M.D., Christian Torp-Pedersen, M.D., Hung-Fat Tse, M.D., Panos Vardas, M.D., Dragos Vinereanu, M.D., Denis Xavier, M.D., Jun Zhu, M.D., Jun-Ren Zhu, M.D., Lydie Baret-Cormel, M.D., Estelle Weinling, Pharm.D., Christoph Staiger, M.D., Salim Yusuf, M.D., Susan Chrolavicius, R.N., B.A., Rizwan Afzal, M.Sc., and Stefan H. Hohnloser, M.D., for the PALLAS Investigators*

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Connolly at the Population Health Research Institute, Hamilton Health Sciences, Hamilton, ON L8L 2X2, Canada, or at connostu@phri.ca.

*Investigators in the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) are listed in the Supplementary Appendix, available at NEJM.org.

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ABSTRACT

BACKGROUND
Dronedarone restores sinus rhythm and reduces hospitalization or death in intermittent atrial fibrillation. It also lowers heart rate and blood pressure and has antiadrenergic and potential ventricular antiarrhythmic effects. We hypothesized that dronedarone would reduce major vascular events in high-risk permanent atrial fibrillation.

METHODS
We assigned patients who were at least 65 years of age with at least a 6-month history of permanent atrial fibrillation and risk factors for major vascular events to receive dronedarone or placebo. The first coprimary outcome was stroke, myocardial infarction, systemic embolism, or death from cardiovascular causes. The second coprimary outcome was unplanned hospitalization for a cardiovascular cause or death.

RESULTS
After the enrollment of 3236 patients, the study was stopped for safety reasons. The first coprimary outcome occurred in 43 patients receiving dronedarone and 19 receiving placebo (hazard ratio, 2.29; 95% confidence interval [CI], 1.34 to 3.94; P = 0.002). There were 21 deaths from cardiovascular causes in the dronedarone group and 10 in the placebo group (hazard ratio, 2.11; 95% CI, 1.00 to 4.49; P = 0.046), including death from arrhythmia in 13 patients and 4 patients, respectively (hazard ratio, 3.26; 95% CI, 1.06 to 10.00; P = 0.03). Stroke occurred in 23 patients in the dronedarone group and 10 in the placebo group (hazard ratio, 2.32; 95% CI, 1.11 to 4.88; P = 0.02). Hospitalization for heart failure occurred in 43 patients in the dronedarone group and 24 in the placebo group (hazard ratio, 1.81; 95% CI, 1.10 to 2.99; P = 0.02).

CONCLUSIONS
Dronedarone increased rates of heart failure, stroke, and death from cardiovascular causes in patients with permanent atrial fibrillation who were at risk for major vascular events. Our data show that this drug should not be used in such patients. (Funded by Sanofi-Aventis; PALLAS ClinicalTrials.gov number, NCT01151137.)
Dronedarone is a new antiarrhythmic agent that is used to restore sinus rhythm and to reduce rates of hospitalization for cardiovascular causes in patients with intermittent (paroxysmal or persistent) atrial fibrillation. In ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Flutter; ClinicalTrials.gov number, NCT00174785), 4628 patients with intermittent atrial fibrillation were randomly assigned to receive either dronedarone or placebo. Dronedarone reduced the incidence of the primary outcome of unplanned hospitalization for cardiovascular causes or death. Significant reductions in rates of death from cardiovascular causes, stroke, and hospitalization for acute coronary syndrome were also seen.

We decided to evaluate dronedarone in patients with permanent atrial fibrillation because such patients are at high risk for cardiovascular events of the type that had been reduced in frequency in ATHENA. The treatment effects of dronedarone in ATHENA had been seen in most sub-groups of patients, including those in whom permanent atrial fibrillation developed during the study, which suggested that restoration of sinus rhythm may not be the only mechanism of benefit associated with this drug. Dronedarone has other effects that would be potentially beneficial in patients with permanent atrial fibrillation, including slowing of the heart rate during atrial fibrillation, blood-pressure lowering, and adrenergic blockade. In addition, dronedarone has been shown to suppress ventricular fibrillation in animal models and significantly reduced the rate of death from arrhythmia in ATHENA.

PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy) was designed to test whether dronedarone would reduce rates of major vascular events or unplanned hospitalization for cardiovascular causes in patients with permanent atrial fibrillation who were at high risk for vascular events.

METHODS

STUDY POPULATION

We enrolled patients with permanent atrial fibrillation or flutter, as documented on electrocardiography performed both within 14 days before randomization and 6 or more months beforehand, who had no evidence of intervening sinus rhythm and for whom there was no plan to restore sinus rhythm. Eligible patients were at least 65 years of age with at least one of the following risk factors: coronary artery disease; previous stroke or transient ischemic attack; symptomatic heart failure, which was defined as current New York Heart Association class II or III symptoms and admission to the hospital for heart failure in the previous year (but not in the most recent month); a left ventricular ejection fraction of 40% or less; peripheral arterial disease; or the combination of an age of 75 years or older, hypertension, and diabetes. Major exclusion criteria were paroxysmal or persistent atrial fibrillation, use of an implantable cardioverter–defibrillator, sustained daytime bradycardia of less than 50 beats per minute, or a QT interval corrected for heart rate of more than 500 msec (or >530 msec for patients with a paced ventricular rhythm). All patients provided written informed consent.

STUDY DESIGN

Eligible patients were randomly assigned to receive either dronedarone (at a dose of 400 mg twice daily) or matching placebo. Patients were seen on days 7 and 30, at 4 months, and every 4 months thereafter. Investigators were advised to use digoxin with caution and to monitor serum levels closely. The serum level of digoxin was measured on day 7. Drugs that are known to prolong the QT interval were prohibited. Liver-function tests (measurements of alanine aminotransferase and bilirubin levels) were initially performed at each study office visit; after a protocol amendment in January 2011, these tests were performed monthly in the first...
6 months and every 2 months for the remainder of the first year.

**STUDY OUTCOMES**
The first coprimary outcome was a composite of stroke, myocardial infarction, systemic embolism, or death from cardiovascular causes. The second coprimary outcome was unplanned hospitalization for a cardiovascular cause or death. Other outcomes were death from cardiovascular causes, death from arrhythmia, recurrent hospitalization for cardiovascular causes, total nights in the hospital for cardiovascular reasons, acute coronary syndrome, stroke or systemic embolism, hospitalization for heart failure or heart-failure episode without hospitalization, and death from any cause. Death from cardiovascular causes included deaths associated with arrhythmia and those caused by heart failure, stroke, and other vascular events. Deaths from arrhythmia included un witnessed deaths occurring without symptoms or previous hemodynamic decompensation. The diagnosis of myocardial infarction was based on a characteristic rise and fall in cardiac biomarkers with other evidence of myocardial ischemia. Stroke was defined as the rapid onset of a new, persistent neurologic deficit attributable to an obstruction in cerebral blood flow or hemorrhage and was classified as ischemic, hemorrhagic, or unspecified. Unplanned cardiovascular hospitalization was defined as nonelective hospitalization for a specified cardiovascular reason for at least two consecutive dates (overnight) or a prolongation of a noncardiovascular hospitalization for cardiovascular reasons. Heart-failure episodes (without hospitalization) were defined as new or worsening signs or symptoms of heart failure requiring intensification of heart-failure treatment. All primary and secondary outcomes (except heart-failure episodes) were adjudicated by an expert committee whose members were unaware of study-group assignments.

**STATISTICAL ANALYSIS**
Assuming an event rate of 4.5% in the control group for the first coprimary outcome at 1 year, we estimated that an enrollment of 10,800 patients during a 2-year period with 1 year of additional follow-up would result in the occurrence of 844 events. We calculated that this sample size would provide a power of 90% to detect a relative reduction of 20% in the rate of the first coprimary outcome. The primary analysis was based on a log-rank test with a two-sided alpha level of 0.05. A Holm’s procedure was planned to control for multiple statistical comparisons. Student’s t-test and the chi-square test were used for the evaluation of continuous and categorical variables, respectively. For patients receiving anticoagulation therapy, we calculated the time in the therapeutic range using linear interpolation of values for the international normalized ratio (INR) over time. A data monitoring committee was charged with recommending termination of the study for safety reasons in the case of clear, consistent, and persistent evidence of net harm that overwhelmed benefit. One scheduled interim analysis for efficacy was planned when 50% of expected events had occurred, on the basis of a modified Haybittle–Peto boundary of 4 SD.

**RESULTS**

**PATIENTS AND FOLLOW-UP**
Study enrollment began on July 19, 2010. The data monitoring committee recommended on July 5, 2011, that the study be terminated for safety reasons. A date of July 15, 2011, was specified for the end of follow-up. A total of 3236 patients had undergone randomization with median follow-up of 3.5 months. There were two patients without vital-status assessment at the end of the study. The two study groups were well balanced with respect to demographic and clinical characteristics (Table 1). Patients had a mean age of 75 years, and 69% had more than a 2-year history of permanent atrial fibrillation or flutter. About two thirds of the patients had a history of heart failure. A total of 88% of the patients were receiving rate-control medication, one third were receiving digoxin, and 84% were receiving a vitamin K antagonist (Table 1 in the Supplementary Appendix, available at NEJM.org).

In the intention-to-treat population, the baseline electrocardiogram showed atrial fibrillation in 98% of the patients and atrial flutter in 2%. At the planned 4-month visit, sinus rhythm was present in 23 of 621 patients (3.7%) in the dronedarone group and in 9 of 638 patients (1.4%) in the placebo group (P=0.01). Cardioversion was attempted in 4 patients (0.2%) in the dronedarone group and 2 patients (0.1%) in the placebo group.

The mean (±SD) baseline heart rate was 77±16 beats per minute in the dronedarone group and 78±16 beats per minute in the placebo group. At
the planned 1-month visit, the mean heart rate was reduced by 7.6±14.5 beats per minute in the dronedarone group and was increased by 0.1±14.0 beats per minute in the placebo group (P<0.001). The baseline systolic blood pressure was 133±17 mm Hg in the two study groups. At 1 month, the mean reduction in systolic blood pressure was 3.5±16.1 mm Hg in the dronedarone group and 1.7±16.1 mm Hg in the placebo group (P=0.003). The mean corrected QT interval (Bazett’s formula) was 426±40 msec in the dronedarone group and 425±40 msec in the placebo group at baseline; at 1 month, the mean increase was 8±40 msec in the dronedarone group and 2±38 msec in the placebo group (P<0.001).

For patients receiving digoxin, the mean serum digoxin concentration on day 7 was 1.2±0.8 ng per milliliter for 447 patients in the dronedarone group and 0.9±0.6 ng per milliliter for 438 patients in the placebo group (P<0.001). Study medication was permanently discontinued prematurely in 348 patients (21%) in the dronedarone group and in 178 patients (11%) in the placebo group (P<0.001). For patients receiving a vitamin K antagonist, the mean time in the therapeutic range (INR, 2.0 to 3.0) was 55.6% in the dronedarone group and 52.5% in the placebo group (P=0.003). The mean time in the therapeutic range (INR, 2.0 to 3.0) was 55.6% in the dronedarone group and 52.5% in the placebo group (P=0.003). The mean time in the therapeutic range (INR, 2.0 to 3.0) was 55.6% in the dronedarone group and 52.5% in the placebo group (P=0.003). The mean time in the therapeutic range (INR, 2.0 to 3.0) was 55.6% in the dronedarone group and 52.5% in the placebo group (P=0.003). The mean time in the therapeutic range (INR, 2.0 to 3.0) was 55.6% in the dronedarone group and 52.5% in the placebo group (P=0.003). The mean time in the therapeutic range (INR, 2.0 to 3.0) was 55.6% in the dronedarone group and 52.5% in the placebo group (P=0.003). The mean time in the therapeutic range (INR, 2.0 to 3.0) was 55.6% in the dronedarone group and 52.5% in the placebo group (P=0.003). The mean time in the therapeutic range (INR, 2.0 to 3.0) was 55.6% in the dronedarone group and 52.5% in the placebo group (P=0.003). The mean time in the therapeutic range (INR, 2.0 to 3.0) was 55.6% in the dronedarone group and 52.5% in the placebo group (P=0.003). The mean time in the therapeutic range (INR, 2.0 to 3.0) was 55.6% in the dronedarone group and 52.5% in the placebo group (P=0.003). The mean time in the therapeutic range (INR, 2.0 to 3.0) was 55.6% in the dronedarone group and 52.5% in the placebo group (P=0.003).

**OUTCOMES**

The first coprimary outcome occurred in 43 patients receiving dronedarone and 19 patients receiving placebo (hazard ratio in the dronedarone group, 2.29; 95% confidence interval [CI], 1.34 to 3.94; P=0.002) (Table 2 and Fig. 1). The second coprimary outcome occurred in 127 patients receiving dronedarone and 67 patients receiving placebo (hazard ratio, 1.95; 95% CI, 1.45 to 2.62; P<0.001) (Fig. 2). There were 25 deaths in the dronedarone group and 13 in the placebo group (hazard ratio, 1.94; 95% CI, 0.99 to 3.79; P=0.049). There were 21 deaths from cardiovascular causes in the dronedarone group and 10 in the placebo group (hazard ratio, 2.11; 95% CI, 1.00 to 4.49; P=0.046), including those associated with arrhythmia in 13 patients receiving dronedarone and 4 patients receiving placebo (hazard ratio, 3.26; 95% CI, 1.06 to 10.00; P=0.03). Stroke occurred in 23 patients in the dronedarone group and 10 in the placebo group (hazard ratio, 2.32; 95% CI, 1.11 to 4.88; P=0.02).

Unplanned hospitalization for cardiovascular causes occurred in 113 patients receiving dronedarone and 59 patients receiving placebo (hazard ratio, 1.97; 95% CI, 1.44 to 2.70; P<0.001). Hospitalization for heart failure occurred in 43 patients in the dronedarone group and 24 in the placebo group (hazard ratio, 1.81; 95% CI, 1.10 to 2.99;
Hospitalization for heart failure or a heart-failure episode occurred in 115 patients receiving dronedarone and 55 receiving placebo (hazard ratio, 2.16; 95% CI, 1.57 to 2.98; P<0.001).

ADVERSE EVENTS
The most common adverse events were diarrhea, asthenic condition, nausea and vomiting, dizziness, dyspnea, and bradycardia. An elevation of alanine aminotransferase of more than three times the upper limit of the normal range occurred in 23 of 1574 (1.5%) patients receiving dronedarone and in 9 of 1589 (0.6%) receiving placebo (P = 0.013) (Table 3).

DISCUSSION
In this study, among patients with permanent atrial fibrillation and additional cardiovascular risk factors who received dronedarone, we found a highly significant doubling in the rate of the first composite coprimary outcome (stroke, myocardial infarction, systemic embolism, or death from cardiovascular causes) across subgroups. For the second coprimary outcome of unplanned hospitalization for cardiovascular causes or death, there was one significant interaction: as compared with patients without diabetes, there was a relatively greater risk associated with dronedarone in patients with diabetes (P=0.03 for interaction). The risk associated with dronedarone was consistent for both primary outcomes and for hospitalization for heart failure, regardless of whether the left ventricular ejection fraction was 40% or lower or above 40% or whether patients had New York Heart Association class II or III symptoms.
diovascular causes). This increase was driven by increased rates of stroke and death from cardiovascular causes, with myocardial infarction and systemic embolism occurring at very low rates. We also found an increase in rates of heart failure in the dronedarone group. The increased rates of stroke, death from cardiovascular causes, and heart failure explain, to a considerable extent, the highly significant near doubling in the rate of the second coprimary outcome (unplanned hospitalization for cardiovascular causes or death).

The early trial termination markedly reduced the statistical power of the study. Early termination also increases uncertainty about the interpretation of the P values, and the point estimate of the hazard ratio is potentially biased away from the null. Despite these limitations, however, the assessment of net harm from dronedarone in patients with permanent atrial fibrillation who are at high risk appears to be sound.

In our study after 1 month, patients receiving dronedarone had significant net reductions of 8 beats per minute in heart rate and reductions of 3.5 mm Hg in systolic blood pressure. These physiological effects did not translate into reductions in rates of heart failure and other events, either because the changes were too small or because there were other effects that concurrently increased the risk. In dogs with healed myocardial infarction, dronedarone did not reduce measures of myocardial contractile function, nor did it reduce the left ventricular ejection fraction in patients with compensated heart failure and an ejection fraction of less than 30%. However, dronedarone affects the inward sodium channels in the cardiac-cell membrane, and other drugs with this property do reduce left ventricular contractility. In ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease, NCT00543699) involving 627 patients with heart failure and severe left ventricular systolic dysfunction, dronedarone increased mortality, an effect that was largely attributed to heart failure and that suggested a negative inotropic effect of dronedarone. However, in ATHENA, there was a consistent decrease in rates of hospitalization for heart failure in patients with heart failure.

In our study, the increased risk of stroke in patients receiving dronedarone is unexplained. In ATHENA, there was a reduction in the rate of stroke among patients receiving dronedarone, a finding that could be related to the prevention of recurrence of atrial fibrillation. Dronedarone interacts minimally with vitamin K antagonists, and in our study, the time in the therapeutic INR range was significantly lower among patients receiving dronedarone. However, this effect appears to be too small to explain the large increase in the rate of stroke.

The increase in the rate of death from cardiovascular causes was mostly due to a substantial increase in the rate of death associated with ar-
rhythmia. This finding was surprising, since dronedarone had not been associated with proarhythmic toxic effects in previous studies in animals,\textsuperscript{10,11} and in ATHENA, dronedarone significantly reduced the tertiary outcome of death from arrhythmia by 45%.\textsuperscript{2} However, dronedarone is a cardiac multiple ion-channel blocker,\textsuperscript{14,15} and other cardiac ion-channel-blocking antiarrhythmic drugs have been shown to increase rates of death associated with arrhythmia.\textsuperscript{20,21}

Dronedarone increases the serum digoxin level through a P-glycoprotein interaction,\textsuperscript{19} and digoxin toxicity is associated with life-threatening ventricular arrhythmia and conduction block.\textsuperscript{22} In our study, almost one third of patients were receiving digoxin, and in these patients, dronedarone increased digoxin serum levels by 33%, from 0.9 to 1.2 ng per milliliter. A post hoc analysis of the Digitalis Investigation Group (DIG) trial (NCT00000476)\textsuperscript{23} reported that a serum digoxin level of more than 1.2 ng per milliliter was associated with a significant increase in death from cardiovascular causes not related to heart failure. It is therefore possible that digoxin toxicity induced by dronedarone played a role in the increased cardiovascular mortality.

Our findings regarding the effects of dronedarone among patients with atrial fibrillation differed starkly from the results in ATHENA. In that trial, there was a highly significant reduction in the primary outcome of unplanned hospitalization for cardiovascular causes or death and significant

Table 3. Adverse Events and Abnormalities on Laboratory Testing.$^*$

<table>
<thead>
<tr>
<th>Event</th>
<th>Dronedarone (N = 1614) number (percent)</th>
<th>Placebo (N = 1609) number (percent)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>797 (49.4)</td>
<td>600 (37.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>113 (7.0)</td>
<td>77 (4.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Any adverse event leading to treatment discontinuation</td>
<td>212 (13.1)</td>
<td>80 (5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any reported liver-function abnormality</td>
<td>61 (3.8)</td>
<td>28 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthenic conditions (asthenia, fatigue)</td>
<td>89 (5.5)</td>
<td>46 (2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breathing abnormalities (dyspnea)</td>
<td>75 (4.6)</td>
<td>36 (2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>101 (6.3)</td>
<td>38 (2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Electrocardiographic investigations (QT prolonged)</td>
<td>33 (2.0)</td>
<td>16 (1.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Edema (peripheral edema)</td>
<td>60 (3.7)</td>
<td>29 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal or abdominal pain</td>
<td>33 (2.0)</td>
<td>15 (0.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Increased creatinine level</td>
<td>49 (3.0)</td>
<td>11 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lower respiratory tract or lung infection</td>
<td>40 (2.5)</td>
<td>42 (2.6)</td>
<td>0.81</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>76 (4.7)</td>
<td>28 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neurologic signs or symptoms (dizziness)</td>
<td>76 (4.7)</td>
<td>39 (2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rate and rhythm disorders (bradycardia)</td>
<td>67 (4.2)</td>
<td>19 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal failure or impairment</td>
<td>35 (2.2)</td>
<td>12 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>34 (2.1)</td>
<td>35 (2.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>Alanine aminotransferase and bilirubin†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase &gt;3× ULN</td>
<td>23 (1.5)</td>
<td>9 (0.6)</td>
<td>0.013</td>
</tr>
<tr>
<td>Alanine aminotransferase &gt;3× ULN and bilirubin &gt;2× ULN</td>
<td>1 (&lt;0.1)‡</td>
<td>0 NA</td>
<td></td>
</tr>
</tbody>
</table>

* Listed are adverse events and serious adverse events that occurred in patients receiving at least one dose of a study drug with a reported frequency of 2% or more in each study group. The preferred term is provided for explanatory purposes in parentheses when one preferred term predominated. NA denotes not applicable, and ULN upper limit of the normal range. †Alanine aminotransferase was measured in 1574 patients in the dronedarone group and in 1589 in the placebo group; the combination of alanine aminotransferase and bilirubin was measured in 1571 patients in the dronedarone group and in 1589 in the placebo group. ‡One patient received the diagnosis of biliary stasis that was not considered to be related to dronedarone.
reductions in the rates of death from cardiovascular causes and stroke, without a significant increase in the rate of heart failure.\(^2\) There are important differences between our study and ATHENA. Patients in our study were older and were more likely to have a history of heart failure, coronary artery disease, or stroke. Dronedarone also increased cardiovascular mortality in patients enrolled in ANDROMEDA\(^2\) who were also at high risk for vascular events owing to severe systolic dysfunction and recent hospitalization for heart failure. However, there were some high-risk patients in ATHENA, and subgroup analyses in that study did not indicate a hazard for dronedarone in those patients.\(^2\) Moreover, subgroup analyses in our study did not suggest that the risks associated with dronedarone were concentrated among high-risk patients. Nonetheless, it is reasonable to conclude that dronedarone should be avoided in patients with heart failure and other advanced cardiovascular disease, particularly when they also have permanent atrial fibrillation.

An important difference between the two studies is that atrial fibrillation was permanent in our study and paroxysmal or persistent in ATHENA. Once permanent atrial fibrillation becomes longstanding, it is unlikely to revert to sinus rhythm. We observed a very low rate of conversion to sinus rhythm among patients receiving dronedarone (a net difference of 2% of patients at 4 months). On the other hand, in ATHENA, dronedarone significantly reduced the median time to recurrence of atrial fibrillation by 25% and reduced the need for electrical cardioversion by 32%.\(^24\) Maintenance of sinus rhythm could partly underlie reductions in stroke and in other vascular events observed in ATHENA. We can hypothesize that for high-risk patients with permanent atrial fibrillation, direct and indirect toxic effects of dronedarone are not offset by the benefit of maintaining sinus rhythm, and any benefits that might occur from heart-rate slowing, blood-pressure reduction, antiadrenergic action, and suppression of ventricular arrhythmia were either small or nonexistent.

In summary, dronedarone increased the rates of stroke, heart failure, and death from cardiovascular causes in patients with permanent atrial fibrillation and risk factors for vascular events. Our data show that dronedarone is hazardous in such patients.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors’ affiliations are as follows: the Population Health Research Institute, Hamilton, ON, Canada (S.I.C., C.M., S.Y., S.C., R.A.); St. George’s University, London (A.J.C.); Mount Sinai Medical Center, New York (J.L.H.); Sunnybrook Health Sciences Center, Toronto (C.); Amphia Hospital, Breda, the Netherlands (M.A.); Kardinia House, Geelong, VIC, Australia (J.A.); Oslo University Hospital, Oslo (D.A.); Estudios Clínicos Latinoamérica, São Paulo (A.A.); University Hospital Uppsala, Uppsala, Sweden (P.B.); University Medical Center Mannheim, Mannheim, Germany (M.B.); Grochowski Hospital, Warsaw, Poland (A.B.); Veterans General Hospital–Taipei, Taipei, Taiwan (S.-A.C.); National Heart Center, Singapore (C.K.C.); University of Cape Town, Cape Town, South Africa (P.C.); Philippine General Hospital, Manila (A.D.); Centre Hospitalier Universitaire de Montpellier–Hôpital Arnaud de Villeneuve, Montpellier, France (J.-M.D.); Universitätsklinik, Inselspital, Bern, Switzerland (E.D.); Maggiore Hospital, Bologna, Italy (G.D.P.); Estudios Clínicos Latino America, Rosario, Argentina (R.D.); St. Michael’s Hospital, Toronto (P.D.); University of Missouri, Columbia (G.F.); Russian Cardiological Research and Production Center, Moscow (S.G.); Instituto Nacional de Cardiología Ignacio Chavez, Mexico City (A.G.-H.); Duke University Medical Center, Durham, NC (C.R.G.); UZ Gasthuisberg, Leuven, Belgium (H.H.); Institute for Clinical and Experimental Medicine, Prague, Czech Republic (J.K.); Samsung Medical Center, Seoul, South Korea (J.S.K.); Universidad de La Frontera, Temuco, Chile (E.L.); Lady Davis Carmel Medical Center, Haifa, Israel (B.S.L.); Universitario La Paz, Madrid (J.L.M.); University Hospital Bratislava, Bratislava, Slovakia (J.M.); CARE Hospitals, Hyderabad, India (C.N.); Instituto de Investigaciones Clínicas de Rosario, Rosario, Argentina (E.P.); Institute of Cardiology, Kiev, Ukraine (A.P.); Imperial College, London (N.S.P.); Sarawak General Hospital, Kuching, Malaysia (K.-H.S.); Waikato Hospital and the University of Auckland, New Zealand (M.K.S.); Ramathibodi Hospital, Bangkok, Thailand (S.T.); Helsinki University Central Hospital, Helsinki (L.T.); St. John’s Health Hospital, Budapest, Hungary (J.T.); University of Copenhagen, Hellerup, Denmark (C.T.-P.); Queen Mary Hospital, Hong Kong (H.-F.T.); Medical School University of Crete, Heraklion, Greece (P.V.); Emergency Clinical University Hospital, Bucharest, Romania (D.V.); St. John’s Medical College, Bangalore, India (D.X.); Xicheng District, Beijing (J.Z.); Zhongshan Hospital, Shanghai, China (J.-R.Z.); Sanofi-Aventis, Chilly-Mazarin, France (L.B.-C., E.W., C.S.); and J.W. Goethe University, Frankfurt, Germany (S.H.H.).

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