

toward the improvement of long-term outcomes in renal transplantation. Our study in a larger study sample did not find any such association, thus highlighting the multifactorial nature of graft failure. It is unlikely that any one gene plays an overwhelming role in the pathways that lead to graft failure.

Mira Varagunum, Ph.D.

Barts and the London School of Medicine and Dentistry
London E1 1BB, United Kingdom

Gerhard Opelz, M.D.

University of Heidelberg
D-69120 Heidelberg, Germany

Muhammad M. Yaqoob, M.D.

Barts and the London School of Medicine and Dentistry
London E1 1BB, United Kingdom
m.m.yaqoob@qmul.ac.uk

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Dronedronone in Atrial Fibrillation

TO THE EDITOR: We have two questions about the trial (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedronone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter [ATHENA]) (ClinicalTrials.gov number, NCT00174785) reported by Hohnloser et al. (Feb. 12 issue).¹ Dronedronone was designed to reduce the risk of thyroid-related and pulmonary disease associated with amiodarone, and in two previous randomized, controlled trials it was shown to be more effective than placebo in maintaining sinus rhythm and controlling the ventricular rate during recurrences of atrial fibrillation. First, why is the comparison drug in this trial not amiodarone? It would be more useful to see a head-to-head trial comparing the efficacy and safety of these two drugs. Second, why is an antiarrhythmic agent being evaluated as first-line treatment in this patient population when rate control has been shown to be the preferred treatment approach? The conclusions of a systematic review were that “pharmacological cardioversion of atrial fibrillation is not superior to rate control and that, particularly in older patients with significant comorbidity, a strategy of rate control is a highly acceptable primary strategy.”² Therefore, avoiding the issue of rate control and implying that a rhythm-control strategy should be first-line therapy may not be appropriate.

Aaron M. Tejani, Pharm.D.

Therapeutics Initiative
Vancouver, BC V6T 1Z3, Canada
aaron.tejani@fraserhealth.ca

Vivian Yih, B.Sc. (Pharm.)

Fraser Health
Burnaby, BC V5G 2X6, Canada

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dronedronone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;360:668-78.

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TO THE EDITOR: We are doubtful about the real effect of dronedronone on the primary outcome (i.e., first hospitalization or death) in the trial reported by Hohnloser et al. Dronedronone significantly reduced the incidence of first hospitalization, defined as an overnight hospital stay. In most cases, this reduction was due to a reduction in the recurrence of atrial fibrillation, which could have been treated by electrical cardioversion, with discharge from the hospital within 12 hours. Thus, the study shows only that dronedronone is better than placebo for maintenance of sinus rhythm. This observation has already been reported in a previous trial.¹ Moreover, we think that if the control group had been allowed to take class I or III antiarrhythmic drugs, the results of the study would have been different, especially with respect to clinical practice. Finally, according to Table 1 of the article, there were significantly more women in the dronedronone group than in the placebo group ($P=0.002$), and this sex imbalance could have further influenced the study results.

Mariateresa Pugliano, M.D.

University of Milan
20142 Milan, Italy

Giorgio Costantino, M.D.

Ospedale L. Sacco
20157 Milan, Italy

Gian Marco Podda, M.D.

Ospedale San Paolo
20142 Milan, Italy
gmpodda@gmail.com

for Gruppo di Autoformazione Metodologica

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James Floyd, M.D.

Public Citizen
Washington, DC 20009
jfloyd@citizen.org

TO THE EDITOR: Hohnloser et al. report a potentially important reduction in hospitalization for acute coronary syndromes in the dronedarone group in their study. Was this finding related to a reduction in heart rate or blood pressure in the dronedarone group with treatment? Was it seen both in patients who received and those who did not receive beta-blockers or statins?

Simon M. Horner, M.D., M.B., B.S.

Stockport Foundation National Health Service Trust
Stockport SK2 7JE, United Kingdom
simon.horner@zen.co.uk

Dr. Horner reports owning stock in Sanofi. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In reporting the results of the ATHENA trial, Hohnloser et al. state that there was a significant reduction in death from cardiovascular causes with the use of dronedarone, but this conclusion is problematic. As revealed at a recent advisory committee meeting of the Food and Drug Administration, outcomes were not centrally adjudicated, but instead were marked on brief and inadequate case-report forms by site investigators and then inconsistently categorized as being cardiovascular or noncardiovascular.¹ Also, the prespecified analysis of secondary outcomes was hierarchical — because all-cause mortality was not reduced with the use of dronedarone, deaths from cardiovascular causes should not have been compared between the two study groups.

The results of a substudy of symptoms of atrial fibrillation within the ATHENA trial were also revealed at the meeting of the advisory committee; these results showed no difference between the dronedarone and placebo groups. These data should have been reported. Given the modest 25% relative reduction in the rate of asymptomatic recurrence of atrial fibrillation with the use of dronedarone as compared with placebo² and the preliminary results of the DIONYSOS (Efficacy and Safety of Dronedaron versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation) study (ClinicalTrials.gov number, NCT00489736) showing that it is inferior to amiodarone with regard to the same outcome (absolute increase in risk, 22 percentage points),³ the efficacy of this new antiarrhythmic agent is brought into question.

THE AUTHORS REPLY: With regard to the comments of Tejani and Yih: the use of an active comparison drug in clinical trials is appropriate when this comparison drug has proven efficacy. Amiodarone, however, has never been shown to reduce hospitalizations due to cardiovascular events or deaths in patients with atrial fibrillation. Trials of rate control versus rhythm control suggest that there is little to choose between these strategies. However, ATHENA showed that a rhythm-control drug (with additional rate-control properties) reduced the incidence of hospitalization due to cardiovascular events or death. These results may cause a reevaluation of the rate-control versus rhythm-control question.

In response to Pugliano et al.: dronedarone significantly reduced the incidence of hospitalization due to cardiovascular events, whether or not the primary diagnosis was atrial fibrillation. The majority of cardioversions in ATHENA were performed in an outpatient setting (70%), indicating that dronedarone's effect on the primary outcome was not driven by cardioversion. Much of the benefit of dronedarone appears to be due to a reduction in the consequences of atrial fibrillation for conditions such as stroke, angina, and heart failure. There were slightly more women in the dronedarone group; however, dronedarone's effects were similar in both sexes for all end points.

In response to Horner: dronedarone reduced blood pressure and heart rate, which probably played a role in the reduced incidence of hospitalization for an acute coronary syndrome. This reduction was consistently observed with dronedarone use, regardless of status with respect to baseline beta-blocker or statin use.

In response to Floyd: it is correct to say that

hospitalizations due to cardiovascular events were not adjudicated; it is not correct that the case-report forms were inadequate or that the designation of hospitalizations as being due to cardiovascular or noncardiovascular causes was inconsistent. The investigators were unaware of assignment to study groups, and they defined the primary cause of hospitalization according to a prespecified list of causes. The cause of death was adjudicated, with few differences between the investigators and the committee, which was also unaware of study-group assignments. The primary outcome of ATHENA was significantly reduced with the use of dronedarone. We agree that the outcomes of death due to cardiovascular events and arrhythmia are secondary outcomes and that the reductions seen are “hypothesis generating,” requiring confirmation in subsequent studies. In ATHENA, symptom questionnaires, designed and validated

for longitudinal studies, were collected only once, at 12 or 18 months, and took into account only the preceding 4 weeks. Although these results give a very limited picture, the reduction of hospitalizations due to cardiovascular events undoubtedly has a profoundly positive impact on quality of life. Although amiodarone is more potent than dronedarone in maintaining sinus rhythm, it has many side effects that limit its usefulness.

Stefan H. Hohnloser, M.D.

J.W. Goethe University
60590 Frankfurt, Germany
hohnloser@em.uni-frankfurt.de

Martin van Eickels, M.D.

Sanofi-Aventis
60590 Frankfurt, Germany

Stuart J. Connolly, M.D.

McMaster University
Hamilton, ON L8S 4L8, Canada

Case 4-2009: A Pregnant Woman with Fever after a Trip to Africa

TO THE EDITOR: Duff et al. (Jan. 29 issue)¹ report a case of a 39-year-old pregnant woman with a fever after two trips to Africa less than a year apart. The authors state that the patient “took mefloquine daily during each trip and for 3 weeks after returning from each trip.” It is important that travelers take medications for malaria prophylaxis properly.

Prophylactic administration of mefloquine should begin at least 1 week before arrival in a area where malaria is endemic. Subsequent weekly doses should be taken regularly, always on the same day of each week, preferably after a full meal. To reduce the risk of malaria after leaving an endemic area, prophylaxis should be continued for 4 additional weeks to ensure suppressive blood levels of the drug when merozoites emerge from the liver.

Marc Itskowitz, M.D.

Allegheny General Hospital
Pittsburgh, PA 15212
mitskowi@wpahs.org

1. Case Records of the Massachusetts General Hospital (Case 4-2009). *N Engl J Med* 2009;360:508-16.

recent of two visits to East Africa, implying a disease with a long incubation period. A differential diagnosis is offered, but several important disease possibilities are omitted. Although intestinal parasites were ruled out because of a negative stool test for ova and parasites, tissue parasites, including visceral leishmaniasis¹ and toxocariasis,² remained possibilities. There was no discussion of the elevated eosinophil count. Schistosomiasis was apparently ruled out because of the negative stool analysis and antibody test. However, eggs may be excreted sporadically or in small numbers, making stool analysis less useful. A negative schistosoma antibody is reported, but the sensitivity of the test of enzyme immuno units for species other than *Schistosoma mansoni* is reduced.³ Reference is made to hepatitis A, B, and C, and the associated serologic tests were negative. However, there is no reference to hepatitis E, which is found in East Africa and represents a special risk to pregnant women.⁴

Jeffrey G. Jones, M.D., M.P.H.

St. Francis Traveler's Health Center
Indianapolis, IN 46203
jjones3054@aol.com

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TO THE EDITOR: Duff et al. report the case of a pregnant woman with fever and hepatic dysfunction, which developed 3 months after the most