

cific interventions. A better understanding of what is driving these improvements is needed.

Joe V. Selby, M.D.

Kaiser Permanente Northern California  
Oakland, CA 94612  
joe.selby@kp.org

Carol M. Mangione, M.D.

University of California Los Angeles School of Medicine  
Los Angeles, CA 90095

Robert B. Gerzoff, M.S.

Centers for Disease Control and Prevention  
Atlanta, GA 30341

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**THE AUTHORS REPLY:** Both Sadof and Rosenbaum suggest that we might have observed improvements in intermediate outcomes, given more time. Conceptually, we agree that, to the extent that outcomes of care are directly related to process interventions, more time than the period of our study might be needed to observe meaningful improvements in clinical outcomes such as mortality or the incidence of acute myocardial infarction. There is no reason to expect, however, that the intermediate outcomes we assessed (e.g., control of glycated hemoglobin and control of hypertension) would require such a lag. In addition, as we state, the 1-year postintervention assessment period began 1 year after the

completion of the intervention, a timing consistent with that suggested by Sadof.

Smolkin argues that improvements in the processes of care are meaningless if they are not accompanied by improvements in outcomes. With the exception of asthma, the intermediate outcomes we assessed examine the control of important risk factors. Given the required time frame and sample size, we could not assess clinical outcomes such as the incidence of cardiovascular disease or mortality, but we would expect that these outcomes would ultimately be affected by improvements in the processes of care. Moreover, many of the process measures we examined are strongly linked to these meaningful clinical outcomes (e.g., daily aspirin use) but are not directly related to the intermediate outcomes we assessed. Selby and colleagues studied the association between various care-management techniques and the quality of care of patients with diabetes and reported results similar to ours.<sup>1</sup> We agree with their suggestion that quality-improvement efforts should focus on evidence-based processes of care that have been rigorously linked to important clinical outcomes.

Finally, Rosenbaum provides important information on the broad policy context and the challenges facing community health centers. We agree that such centers are an important cornerstone of efforts to provide a safety net for millions of Americans and that every effort should be made to provide adequate funding to meet the needs of the underserved populations they care for.

Bruce E. Landon, M.D., M.B.A.

LeRoi S. Hicks, M.D., M.P.H.

Edward Guadagnoli, Ph.D.

Harvard Medical School  
Boston, MA 02115  
landon@hcp.med.harvard.edu

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## Amiodarone for Atrial Fibrillation

**TO THE EDITOR:** In his review article on amiodarone for atrial fibrillation, Zimetbaum (March 1 issue)<sup>1</sup> did not mention that there are two forms of amiodarone-induced thyrotoxicosis (AIT) — an important distinction that has a major influence on subsequent management. In type I AIT, patients usually have preexisting thyroid abnormalities,

such as nodular goiter, an autonomous thyroid nodule, or latent Graves' disease. This syndrome is thought to be due to the Jod-Basedow phenomenon. In type II AIT, the thyroid gland is normal, and thyrotoxicosis results from subacute destructive thyroiditis with the release of preformed thyroid hormone. The uptake of radioactive iodine is

normal or high in type I AIT but low or absent in type II AIT. Moreover, parenchymal blood flow as seen on color-flow Doppler is present in type I AIT but absent in type II AIT.<sup>2</sup> The treatment of type I AIT involves thionamides, potassium perchlorate, or lithium and discontinuation of amiodarone, whereas the treatment of type II AIT involves glucocorticoids.<sup>3</sup>

Habib ur Rehman, F.R.C.P.C.

Regina Qu'Appelle Health Region  
Regina, SK S4P 3X15, Canada  
habib31@sasktel.net

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**TO THE EDITOR:** Zimetbaum discusses the difficulties in recognizing the onset of AIT, which is often associated with only mild clinical signs and symptoms. Many patients receiving amiodarone are also treated with warfarin. Thyroid function affects the pharmacodynamics of warfarin: hyperthyroidism potentiates the anticoagulant effect of warfarin, whereas hypothyroidism attenuates the anticoagulant effect.<sup>1</sup> Therefore, an otherwise unexplained rise in the international normalized ratio in such patients can be a valuable clue to the onset of AIT even before the manifestation of other clinical symptoms<sup>2</sup> and should prompt laboratory assessment of thyroid function.

Daniel Kurnik, M.D.

Vanderbilt University Medical School  
Nashville, TN 37232  
daniel.kurnik@vanderbilt.edu

Ronen Loebstein, M.D.

David Olchovsky, M.D.

Chaim Sheba Medical Center  
52621 Tel Hashomer, Israel

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**TO THE EDITOR:** Zimetbaum reports that "amiodarone is an excellent choice for use in patients with structural heart disease or congestive heart failure." However, the cited Congestive Heart

Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT)<sup>1</sup> enrolled a small population, lasted only 2 years, and lacked an on-treatment analysis despite its significant dropout rate.

The sum of these factors undermines the value of the asserted neutral effect of amiodarone on mortality. Furthermore, the recent Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)<sup>2</sup> showed no difference in outcome according to the cause of disease, negating the concept from CHF-STAT that amiodarone is potentially beneficial in non-ischemic congestive heart failure; the study also revealed a worrisome reduction in survival among patients in New York Heart Association class III. Cause for concern also arose from the Antiarrhythmic Trial with Dronedronarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA),<sup>3</sup> in which dronedronarone, an iodine-free amiodarone derivative, was associated with an increase in mortality in a population with a reduced ejection fraction. Several mechanisms through which amiodarone may have an adverse effect on the course of congestive heart failure have been described.<sup>4</sup> After consideration of all these facts, it would be prudent to recommend against amiodarone therapy when atrial fibrillation coexists with congestive heart failure.

Michele Coceani, M.D.

Institute of Clinical Physiology  
56124 Pisa, Italy  
michecoc@ifc.cnr.it

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**TO THE EDITOR:** Zimetbaum leaves out an important piece of data for deciding whether antiarrhythmic therapy should be recommended for a patient with atrial fibrillation — data on mortality. The results of the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T),<sup>1</sup> which showed a decrease in recurrence of atrial fibrillation in the antiarrhythmic-therapy groups as compared with placebo, also showed that patients who received the study drug had a mortality ratio of 2.0 (P=0.11

for the comparison of amiodarone and placebo). An increase in mortality has been remarkably consistent in numerous studies, none of which have been powered to look at mortality. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial<sup>2</sup> enrolled 4060 patients and at 5 years showed a hazard ratio for mortality of 1.15 (P=0.08) for treatment with antiarrhythmic drugs. The Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial<sup>3</sup> randomly assigned 522 patients with atrial fibrillation to receive either antiarrhythmic therapy or rate control and showed more primary end points, including deaths, in the group undergoing antiarrhythmic therapy. The information on mortality from numerous studies is important to consider as a consistent and troubling signal.

Neil Skolnik, M.D.

Abington Memorial Hospital  
Abington, PA 19046

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**TO THE EDITOR:** Zimetbaum states that neurologic side effects may occur in up to 30% of patients receiving amiodarone therapy and may be more common in the elderly. Treatment-emergent parkinsonism has been reported with amiodarone use<sup>1,2</sup> but is underrecognized and difficult to treat. The drug's half-life is long and variable, averaging 58 days.<sup>3</sup> Consequently, if parkinsonism is recognized late, several months may elapse before reversal can be expected. Moreover, I have encountered an instance in which use of amiodarone in a patient with preexisting Parkinson's disease was associated with aggravation of muscular rigidity. This previously ambulatory patient became frozen and virtually immobile within 2 months after the initiation of treatment with amiodarone. Since his family could no longer care for him, he had to be moved to a nursing home. Explicit enumeration of parkinsonism among the treatment-emergent neurologic side effects of amiodarone may promote an earlier rec-

ognition of this condition. Use of amiodarone is probably inadvisable in patients with preexisting Parkinson's disease.

Carmel Armon, M.D., M.H.S.

Baystate Medical Center  
Springfield, MA 01199  
carmel.armon@bhs.org

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**THE AUTHOR REPLIES:** Rehman and Kurnik et al. raise important issues related to amiodarone and its interaction with the thyroid. Mention of these issues was omitted from my article owing to word constraints, but the correspondents' discussion of these interactions is very welcome.

Coceani and Skolnik both raise appropriate concerns about the safety and possible increase in mortality associated with the use of amiodarone, particularly among patients with congestive heart failure. It is quite clear from numerous studies they mention that amiodarone does not reduce the rate of death from all causes or from arrhythmia in any population, particularly in patients with congestive heart failure. There may be a trend toward increased mortality in this latter population, but it has not been shown to be significant. Furthermore, implantable cardioverter-defibrillators are increasingly used in this population, which potentially limits the adverse cardiovascular outcomes associated with amiodarone (e.g., bradycardia and torsades de pointes). I believe there are insufficient data and justification to accept Coceani's recommendation that amiodarone should be avoided in patients with atrial fibrillation and congestive heart failure.

Armon mentions the potential for exacerbation of parkinsonism associated with amiodarone. This phenomenon is infrequent and has been described in case reports only; however, it is worrisome and clearly warrants a more systematic evaluation.

Peter Zimetbaum, M.D.

Beth Israel Deaconess Medical Center  
Boston, MA 02215  
pzimetba@bidmc.harvard.edu