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EDITORIAL COMMENT

Efficacy and Safety of Amiodarone in Patients With Atrial Fibrillation in the Era of Target-Specific Anticoagulants*

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In patients with atrial fibrillation (AF), loss of organized atrial contraction and accelerated ventricular rate can have both immediate and long-term adverse consequences, including deterioration of hemodynamics, progressive atrial and ventricular dysfunction, and an ongoing risk of ischemic stroke and systemic embolic events (SEEs). The principal goals of therapy are control of symptoms and prevention of thromboembolism.

The AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial and other studies demonstrated that both rate control and rhythm control strategies improve symptoms in patients with AF, but neither of these strategies is associated with better survival or a lower risk of ischemic stroke than the other (1). Patients with AF and additional risk factors for thromboembolism require long-term anticoagulation, even after sinus rhythm has been restored. The 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society AF guidelines recommend antiarrhythmic drug therapy to reduce the frequency and duration of episodes and improve quality of life in patients with paroxysmal or persistent AF (2). The class III antiarrhythmic drug, amiodarone, is currently the most effective available agent. Amiodarone is recommended for patients with frequent, symptomatic recurrences, especially in older patients with structural heart disease.

The clinical utility of amiodarone is limited by its potential toxicity, including cutaneous, ocular, thyroid, hepatic, neurological, and pulmonary side effects, some of which are dose-related, and by a possible association with an increased risk of neoplasia. Pharmacokinetic interactions with other drugs further complicate therapy. Amiodarone inhibits the clearance of warfarin, and 1 of its metabolites, monodesethylamiodarone, is a potent CYP2C9 inhibitor, potentiating the anticoagulant effect (3).

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In this issue of the *Journal*, Flaker et al. (4) report the outcomes associated with amiodarone among patients participating in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, which compared an oral Factor Xa inhibitor with warfarin for stroke prevention. The exploratory post hoc analysis provided insights into contemporary patterns of amiodarone use and compared the incidence of thromboembolism and bleeding in patients treated concurrently with amiodarone and either warfarin or apixaban.

As in most anticoagulation trials, patients with paroxysmal AF represented only approximately one third of the population enrolled in ARISTOTLE. Amiodarone therapy was not randomized, but 11% of patients were taking the drug at entry. There was considerable geographic variation, with amiodarone being used most frequently in Latin America (17.9%) and Europe (12%) and used less frequently in Asian Pacific countries (9.5%) and North America (6.6%). As catheter ablation procedures for rhythm control become more widely adopted, one might speculate

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that long-term amiodarone therapy may be prescribed less often.

Patients treated concurrently with warfarin had a lower average time in the therapeutic range than those not on amiodarone (56.6% vs. 63.0%; $p < 0.0001$). Although mortality and major bleeding rates were not significantly different between patients managed with or without amiodarone, the combined stroke or SEE rate was significantly higher in patients taking amiodarone. Analysis of interaction found no significant influence of amiodarone on the superior efficacy of apixaban seen in the trial as a whole compared with warfarin. Patients taking amiodarone experienced major bleeding more frequently with concomitant warfarin than with apixaban.

Although the analysis did not permit exact understanding of the mechanisms leading to a higher burden of stroke and SEEs in patients treated with amiodarone, the lower time in the therapeutic range in the subgroup on amiodarone and warfarin might explain the trend. Because the reasons for therapy were not known, those prescribed amiodarone could have been at a higher intrinsic risk. It is tempting to conclude that patients treated with amiodarone to control AF might have better outcomes when anticoagulated with apixaban, and by extension, perhaps one of the other target-specific oral anticoagulants (e.g., the direct thrombin inhibitor dabigatran [RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial], or the Factor Xa inhibitors, rivaroxaban [ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)] or edoxaban [ENGAGE-AF- TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial]), rather than warfarin.

Although initially developed as an antianginal drug, clinicians have used amiodarone for >3 decades to manage patients with AF, despite concerns about potential side effects associated with long-term use. In the CTAF (Canadian Trial of Atrial Fibrillation), 403 patients who had at least 1 episode of AF within 6 months were randomized to treatment with sotalol, propafenone, or low-dose amiodarone. In CTAF, there were no differences in mortality during a mean follow-up of 16 months, but there was a trend toward more frequent side effects with amiodarone, leading to discontinuation of therapy (5). Amiodarone was not associated with a higher risk of treatment-ending side effects than sotalol in the AFFIRM trial (1). In SAFE-T (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) (6), the only difference in adverse effects was a slight increase in minor bleeding in patients treated with amiodarone. Mortality was not significantly greater with amiodarone and sotalol than with placebo.

In the report by Flaker et al. (4), a trend toward greater mortality in patients who received amiodarone did not reach statistical significance, which added to the uncertainty raised by conflicting reports of mortality (including noncardiovascular death) associated with amiodarone. Considering that 2 prospective trials of dronedarone (a less effective, but chemically-related drug), in which mortality was part of the primary composite endpoint, yielded divergent results, it is possible that the mortality signal arising from the 2,051 patients treated with amiodarone in ARISTOTLE could dissipate if tested in a randomized format.

In this analysis from ARISTOTLE on the utilization of amiodarone, a few limitations are worth highlighting. Patients with permanent AF are not generally considered candidates for antiarrhythmic therapy, yet most patients who entered ARISTOTLE, including those treated with amiodarone, were classified as having persistent or permanent AF; the investigators did not distinguish these patterns from one another. The duration of amiodarone treatment was not specified and neither was information about its efficacy in maintaining sinus rhythm, which could have implications for clinical outcomes and whether these might differ in patients with recent-onset versus long-standing AF. The analyses were not adjusted for left ventricular ejection fraction or for hepatic or renal disease, which could have contributed to the risks of thromboembolism and bleeding that are difficult to predict.

The challenges of amiodarone therapy are compounded in patients with AF who receive warfarin because of interactions that increase the risks of complications of anticoagulation. The ARISTOTLE investigators provided the first report that assessed the safety and efficacy of this powerful antiarrhythmic drug in patients who received apixaban as an alternative anticoagulant. Similar analyses of outcomes among patients with AF in trials of other target-specific anticoagulants could enhance our understanding of the safety and efficacy of amiodarone therapy in particular, and antiarrhythmic therapy in general, without the encumbrances of warfarin.

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