JACC Vol. 15, No. 3
March 1, 1990:708–9

Editorial Comment

New Hope in Atrial Fibrillation*

ROBERT A. BAUERNFEIND, MD, FACC,
WILLIAM J. WELCH, MD, FACC
Richmond, Virginia

Atrial fibrillation is a common arrhythmia; in fact, it may be the most common arrhythmia requiring antiarrhythmic drug therapy now that asymptomatic ventricular premature beats are thought to be inappropriate targets. Atrial fibrillation can cause unpleasant palpitation, as well as decreased cardiac output due to loss of atrial contribution to ventricular filling or inappropriate ventricular rates (1). In addition, this arrhythmia is associated with increased risk of stroke due to cerebral embolism (2). Atrial fibrillation that does not terminate spontaneously usually can be converted by direct current countershock; unfortunately, the rate of recurrence is high (3,4).

Role of class IA agents. Quinidine has been the mainstay of therapeutic attempts to prevent recurrence of atrial fibrillation. However, this therapy is far from ideal. It is frequently ineffective; in most trials only 20% to 50% of patients treated with quinidine (compared with 10% to 25% of patients given placebo) have remained in sinus rhythm for 1 year after electrical conversion of atrial fibrillation (5,6). Quinidine tends to decrease atrioventricular (AV) node refractoriness and thus to increase the ventricular rate during atrial fibrillation. In addition, it frequently causes side effects and, occasionally, serious proarrhythmia. Other class IA agents, procainamide or disopyramide, add little in terms of efficacy or tolerance (7). Thus, atrial fibrillation may be not only the most frequently treated arrhythmia, but also the most frustrating arrhythmia to treat.

Newer drugs for atrial fibrillation. In recent years a number of new antiarrhythmic agents have been introduced that may be useful in treating atrial fibrillation. Several of these agents, flecainide, encainide and propafenone, are placed in class IC, and their action in atrial muscle is primarily to slow conduction. These agents appear to have efficacy in preventing the recurrence of atrial fibrillation, even in patients who have been refractory to quinidine, and they tend to increase rather than decrease AV node refractoriness (8–12). They also are well tolerated. However, they tend to depress myocardial function and, inevitably, are associated with occasional serious proarrhythmia. Preliminary findings from the Cardiac Arrhythmia Suppression Trial (CAST) (13) suggest that with flecainide or encainide proarrhythmia frequently occurs late, long after any reasonable period of inpatient electrocardiographic monitoring. Flecainide-induced proarrhythmia, although common in cases of severe heart disease, was previously thought to be rare in relatively healthy hearts (14). However, one recent report (15) has raised questions regarding this premise.

Two newer agents, amiodarone and sotalol, are placed in class III, and in atrial muscle they primarily increase refractoriness. Both of these agents also have beta-adrenergic blocking activity. Amiodarone appears to be quite effective in preventing the recurrence of atrial fibrillation and also increases AV node refractoriness (16–18). However, this agent is associated with considerable long-term toxicity. Furthermore, it has a very long half-life, making it difficult to substitute another drug in the event of failure. Although sotalol has properties that seem ideal for treatment of atrial fibrillation, there are few reported data on its use (19).

Sequential trials of propafenone and sotalol: the present study. In this issue of the Journal, Antman et al. (20) report on their experience with sequential trials of propafenone and sotalol in a series of 109 patients with recurrent, symptomatic atrial fibrillation that had been unsuccessfully treated with one or more class IA agents. During treatment with propafenone, approximately 39% of the patients were free of recurrence for 6 months. Most of the remaining patients, in whom propafenone was either ineffective or poorly tolerated, were subsequently treated with sotalol. It is striking that during loading with sotalol, 7 of 26 patients with chronic atrial fibrillation had spontaneous conversion to sinus rhythm and that, during maintenance therapy with this drug, approximately 50% of patients were free of recurrence for 6 months. Overall, 55% of the 109 patients were considered to have been successfully treated with one drug or the other. The study confirms that propafenone has efficacy in atrial fibrillation and it provides exciting new data regarding the usefulness of sotalol in patients with this arrhythmia. It implies that with addition of the newer agents, drug-refractory atrial fibrillation may become a rare phenomenon.

Several features of the present study (20) may have caused estimates of efficacy to be inflated. First, propafenone and sotalol were frequently given multiple opportunities to prevent atrial fibrillation; often, when arrhythmia recurred during administration of one of the drugs, the dosage was increased and the trial restarted. In contrast, previous trials of class IA agents appear to have been

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Division of Cardiology, Department of Medicine, Medical College of Virginia, Richmond, Virginia.
Address for reprints: Robert A. Bauernfeind, MD, Box 53, MCV Station, Medical College of Virginia, Richmond, Virginia 23298.

0735-1097/90/$3.50

cursory. Second, the duration of follow-up was limited. Short follow-up is particularly problematic in evaluation of drug efficacy after electrical conversion of chronic atrial fibrillation (3,4). Finally, as the authors (20) point out, some recurrences of atrial fibrillation may not have produced symptoms and thus may have gone undocumented. However, even asymptomatic recurrence might cause cerebral emboli or insidious cardiac decompensation. Thus, although the results of the present study are encouraging, they probably approximate a "best case" analysis.

Current therapy of atrial fibrillation. It is clear that several of the newer antiarrhythmic agents have efficacy in preventing recurrence of atrial fibrillation. Given the shortcomings of quinidine, it is reasonable to ask whether any of these agents should replace quinidine as the first-line therapy. Caution is in order in this regard. There are few data to suggest that any of the new agents (except perhaps amiodarone) are more effective than quinidine (9,10). Occasional efficacy in patients who have not responded to quinidine is consistent with the premise that different patients respond to different drugs, or it may simply reflect random variability of frequency of arrhythmia recurrence or selective reporting of favorable results. Ultimately, randomized clinical trials will be needed to determine the relative effectiveness, and safety, of the various agents.

In the meantime, how should one treat atrial fibrillation? In patients with severe underlying heart disease it seems wise to start (and perhaps stop) with quinidine or procainamide. In these patients the risk of proarrhythmia, particularly late proarrhythmia, with class IC agents may be prohibitive (13). Furthermore, class IC agents or sotalol can aggravate heart failure. These concerns are less relevant in patients with little or no heart disease (14). In these patients class IA agents, class IC agents and, if available, sotalol seem to be reasonable alternatives. Agents from different classes can be used in sequential trials, in any order. However, because of its toxicity and long half-life, amiodarone should generally be used last, and only in patients with severe symptoms or those at exceptional risk for cerebral embolism. In any case, the present list of therapeutic options is a refreshing sight after so many years of meager offerings.

References

1. Lipkin DP, Frenneaux M, Stewart R, Joshi J, Lowe T, McKenna WJ. Delayed improvement in exercise capacity after cardioversion of atrial fibrillation to sinus rhythm. Br Heart J 1988;59:572–7.
2. Wolf PA, Dawber TR, Thomas HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham Study. Neurology 1978;28:973–7.
3. Morris JJ, Peter RH, McIntosh HD. Electrical conversion of atrial fibrillation: immediate and long-term results and selection of patients. Ann Intern Med 1966;65:216–31.
4. Waris E, Kreus K-E, Salokannel J. Factors influencing persistence of sinus rhythm after DC shock treatment of atrial fibrillation. Acta Med Scand 1971;189:161–6.
5. Hillestad L, Bjerkelund C, Dale J, Maltau J, Storstein O. Quinidine in maintenance of sinus rhythm after electroconversion of chronic atrial fibrillation: a controlled clinical study. Br Heart J 1971;33:518–21.
6. Sodermark T, Jonsson B, Olsson A, et al. Effect of quinidine on maintaining sinus rhythm after conversion of atrial fibrillation or flutter: a multicentre study from Stockholm. Br Heart J 1975;37:486–92.
7. Szekely P, Sideris DA, Batson GA. Maintenance of sinus rhythm after atrial defibrillation. Br Heart J 1970;32:741–6.
8. Berns E, Rinkenberger RL, Jeang MK, et al. Efficacy and safety of flecainide acetate for atrial tachycardia or fibrillation. Am J Cardiol 1987;59:1337–41.
9. van Wijk LM, den Heijer P, Crijns HJ, van Gilst WH, Lie KI. Flecainide versus quinidine in the prevention of paroxysms of atrial fibrillation. J Cardiovasc Pharmacol 1989;13:32–6.
10. Makynen PJ, Koskinen PJ, Saaristo TE, Liisanantti RK. Comparison of encainide and quinidine for supraventricular tachyarrhythmias. Am J Cardiol 1988;62:55L–9L.
11. Porterfield JG, Porterfield LM. Therapeutic efficacy and safety of oral propafenone for atrial fibrillation. Am J Cardiol 1989;63:114–6.
12. Connolly SJ, Hoffert DL. Usefulness of propafenone for recurrent paroxysmal atrial fibrillation. Am J Cardiol 1989;63:817–9.
13. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406–12.
14. Morganroth J, Anderson JL, Gentzkow GD. Classification by type of ventricular arrhythmia predicts frequency of adverse cardiac events from flecainide. J Am Coll Cardiol 1986;8:607–15.
15. Falk RH. Flecainide-induced ventricular tachycardia and fibrillation in patients treated for atrial fibrillation. Ann Intern Med 1989;111:107–11.
16. Horowitz LN, Spielman SR, Greenspan AM, et al. Use of amiodarone in the treatment of persistent and paroxysmal atrial fibrillation resistant to quinidine therapy. J Am Coll Cardiol 1985;6:1402–7.
17. Gold RL, Haffajee CI, Charos G, Sloan K, Baker S, Alpert J. Amiodarone for refractory atrial fibrillation. Am J Cardiol 1986;57:124–7.
18. Brodsky MA, Allen BJ, Walker CJ, Casey TP, Luckett CR, Henry WL. Amiodarone for maintenance of sinus rhythm after conversion of atrial fibrillation in the setting of a dilated left atrium. Am J Cardiol 1987;60:572–5.
19. Singh BN, Nademanee K. Sotalol: a beta blocker with unique antiarrhythmic properties. Am Heart J 1987;114:121–39.
20. Antman EM, Beamer AD, Cantillon C, McGowan N, Friedman PL. Therapy of refractory symptomatic atrial fibrillation and atrial flutter: a staged care approach with new antiarrhythmic drugs. J Am Coll Cardiol 1990;15:698–707.