**EDITORIAL COMMENT**

**Beta-Blockers for Atrial Fibrillation: Must We Consider Asymptomatic Arrhythmias?**

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Atrial fibrillation (AF) affects more than 5% of the U.S. population >65 years, and 10% of those >80 years of age, making it the most common arrhythmia requiring treatment. Efforts to treat with ablation or devices show promise, but to date, pharmacologic therapy represents the mainstay of AF treatment. The benefit of efforts to control the rhythm (as opposed to rate control with antiarrhythmia) is debated, and mortality benefit may be clarified by the ongoing AFFIRM trial; nevertheless, most physicians remain committed to reducing symptoms through restoration and maintenance of sinus mechanism. Generally, the agents employed to stabilize the atria are the drugs in the Vaughan Williams categories of class IA, IC and III. In this issue of the *Journal*, Külkamp et al. (1) present data that show beta-adrenergic blockade also acts to reduce the frequency of symptomatic AF.

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**PHARMACOLOGIC TREATMENT TO STABILIZE THE ATRIA**

Treatment to reduce the recurrence of AF has achieved modest success thus far. Quinidine, disopyramide, flecainide, propafenone, d,l-sotalol and amiodarone have all shown efficacy in reducing AF recurrence in patients with paroxysmal and/or persistent AF (2,3). Unfortunately, these agents are associated with serious side effects, including life-threatening proarrhythmia in the class I agents and d,l-sotalol, and noncardiac (but also potentially life-threatening) complications of amiodarone. Newer class III agents, such as dofetilide and azimilide (4,5), may be associated with similar efficacy and perhaps reduced proarrhythmia, although concerns about safety remain.

The efficacy of antiarrhythmic medications for AF has been assessed in a number of ways. Measurement of recurrence over six or 12 months provides a relatively pessimistic perspective, since AF recurs in approximately 50% no matter what kind of therapy is administered (except for amiodarone, where the recurrence rate may be slightly lower) (3). What these statistics fail to note is that occasional brief or well-tolerated recurrences may represent substantial improvement and an acceptable result of therapy. Since AF is a chronic condition, complete elimination of recurrence is unrealistic. As such, assessment of the relative reduction in frequency is best performed by generating Kaplan-Meier curves and comparing the median times to recurrence of AF between groups. A prolongation in the median time to recurrence, by at least twofold, has been used as the cutoff for efficacy in treatment of AF; by this criterion, randomized trials with flecainide (6) and propafenone (7) showed efficacy, while study with the investigational agent, bidisomid (8), did not. Of note, recently the Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee has accepted such assessment of efficacy as providing pivotal data in consideration of labeling for treatment of AF. In addition to suppression of symptomatic AF, concern has been raised about the occurrence of asymptomatic AF.

**ASYMPTOMATIC AF**

Only recently have we recognized that patients with symptomatic paroxysmal AF have substantial asymptomatic AF as well. In response to concerns that studies using transtelephonic ECG recorders (activated in response to symptoms) might be missing asymptomatic AF, we attempted to define the frequency of asymptomatic paroxysmal supraventricular arrhythmias in 22 untreated patients (9). Patients were provided transtelephonic ECG recorders for 29 days, with simultaneous 24-h continuous ambulatory ECG (Holter) monitor placed weekly (total of five 24-h recordings). Among eight patients with AF, asymptomatic AF (>30 s in duration) occurred more frequently than symptomatic AF by a ratio of 12.1 (with 62.5 asymptomatic events per 100 days per patient, as compared with just 5.2 symptomatic events; p < 0.01). In contrast, among 14 patients with paroxysmal supraventricular tachycardia, there were no episodes of asymptomatic recurrence. Although the findings for AF were collected in a relatively small, well-selected group of patients, they raise important concerns about the true recurrence rate of AF (with obvious implications with regard to anticoagulation).

Asymptomatic AF was further described by Wolk et al. (10), this time in patients receiving propranolol or propafenone. Although there are methodologic flaws in this study (nonrandomized, nonblinded, some patient exposure to both drugs), the findings are intriguing. In terms of short-term symptomatic relief from AF, propafenone resulted in a lack of symptoms in 26 of 35 trials (74%), while propranolol yielded suppression of symptoms in 18 of 34 trials (53%). Holter monitors were placed only in the patients without symptomatic recurrence of AF, one to four

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weeks after initiation of drug therapy, looking for asymptomatic AF (defined as >5 s while awake); asymptomatic AF was documented in 27% of the propafenone group and 22% of the patients taking propranolol. Of the total 11 patients with asymptomatic AF, the lack of symptoms was attributed to shorter duration of AF in seven; slowing of the AF was held responsible in the remaining four patients (mean 126 beats/min in AF before initiation, reduced to 82 beats/min with therapy). Data were not provided on asymptomatic AF prior to therapy, nor were data provided for those patients who experienced recurrent symptoms. Despite obvious problems with design, this trial documents frequent occurrence of asymptomatic AF in patients receiving therapy, including beta-blockade. Frequent asymptomatic AF was also documented in a recent abstract, as seen in routine daily transtelephonic ECG from patients with symptomatic paroxysmal AF (11). In addition, implanted devices with capability for automated storage of recorded arrhythmias allow long-term monitoring for asymptomatic AF; in a study using dual chamber pacemaker in 354 patients, 104 of the 179 patients who showed supraventricular arrhythmias had no symptoms (12). Finally, the neurology literature is filled with reports of patients presenting with embolic stroke and newly diagnosed asymptomatic AF.

BETA-BLOCKER THERAPY IN TREATMENT OF ATRIAL FIBRILLATION

Beta-adrenergic blockers have been an option in the control of ventricular response in AF for many years; but recently, beta-blockers, along with calcium channel blockers, have replaced digoxin as first-line therapy for AF rate control. Randomized studies have confirmed the superiority of beta-blockers in controlling the ventricular response, especially with exercise (13).

Beta-blockers generally have not been considered to be atrial stabilizing agents except in two well-defined situations. First, a small population of patients experience recurrent AF in association with stress or anxiety; these patients with adrenergically mediated AF may respond well to beta-blockade (as opposed to the opposite syndrome of vagally mediated AF, in which beta-blockers may exacerbate AF and treatment with agents possessing anticholinergic properties is desirable). Second, and more common, is the use of beta-blockers for prevention of AF in patients following cardiothoracic surgery, in which AF occurs in approximately 30% of patients (3). The benefit of beta-blockade is greatest in patients who previously have received beta-blockers, although a reduction in AF is seen also in patients not previously receiving beta-blockers. The efficacy of beta-blockers in this circumstance likely relates to the elevated sympathetic tone present postoperatively.

It is widely believed that shortening of atrial refractoriness facilitates AF and prolonging refractoriness suppresses AF. Shorter atrial refractory periods presumably shorten the wavelength (defined by [conduction velocity] × [refractory period]) and thus stabilize the multiple reentrant wavelets that perpetuate AF. In animals, rapid pacing shortens atrial refractoriness and allows sustained AF where it was previously nonsustained. Class IA and class III agents are thought to protect against AF by prolonging atrial refractoriness. Although beta-blockers are not generally regarded as membrane stabilizing agents, they may protect against AF by delaying atrial repolarization. Kuhlkamp et al. (1) speculate that beta-blockers protect against adrenergically mediated shortening of the action potential duration (APD) that is thought to help precipitate and maintain AF. Another potential mechanism for preventing AF could result from suppression of pulmonary vein ectopy that triggers AF (14).

DO BETA-BLOCKERS REDUCE THE RECURRENCE OF PERSISTENT AF?

The study by Kuhlkamp et al. (1) represents an important contribution to the literature. In this study, patients with persistent AF were randomized to metoprolol CR/XL or matching placebo. Most patients had been converted with DC shock, although 17.5% converted after a class I antiarrhythmic medication was administered (drug and route of delivery not defined). Patients were followed up for six months or until documentation of recurrent AF or atrial flutter (as assessed by ECGs obtained in response to symptoms or at one week or one, three or six months). Using a log-rank analysis for the primary end point, a significant treatment effect of metoprolol was observed (p = 0.005), with 59.9% having recurrent AF in the placebo group, compared with 48.7% in the metoprolol group. The median time to recurrence was 7.5 days for placebo versus 13.0 days for metoprolol (ratio of 1.7). The heart rate in sinus rhythm was reduced 10 beats per minute with metoprolol, vs a reduction of 2 beats/min with placebo. With recurrence of AF, the ventricular response was reduced, at 107 beats/min with metoprolol, compared with 98 beats/min for placebo. Evaluation of safety and tolerability showed the expected adverse events associated with beta-blocker use, including dizziness, atrioventricular (AV) block, bradycardia, dyspnea and fatigue. All three deaths occurred in the metoprolol group, with one sudden death. The sample is small and clearly this finding does not meet statistical significance. In addition, there are abundant data to support a reduction of mortality associated with beta-blockers, thus negating this apparent lopsidedness in deaths. These mortality findings underscore the importance of designing trials with adequate power when evaluating drugs with potential for proarrhythmia.

Before attempting to answer the question of beta-blockers’ reduction in AF recurrence, we must examine the population studied in the report by Kuhlkamp et al. (1), and consider the potential asymptomatic AF. The authors state that no patients had a history of documented paroxysmal (or self-terminating) AF. Only 10% had previously undergone
cardioversion, so we can assume that this represented the first episode of documented AF in the vast majority of the patients enrolled. Of the patients with duration of AF documented, one half had AF lasting >30 days. Thus, a relatively homogenous population with “persistent” AF was enrolled. Persistent AF has been defined as that which sustains >48 h or until cardioversion is performed (15). This is contrasted with “paroxysmal” AF, characterized by recurrences of AF alternating with sinus mechanism, in which most of the episodes of AF terminate spontaneously within 48 h. Obviously there is potential for overlap between the persistent and paroxysmal AF groups, as acknowledged by those who created the definitions (15). Kühlkamp et al. (1) state that patients with known paroxysmal AF were not enrolled, but the potential for prior asymptomatic AF is not defined.

If the data regarding asymptomatic events are scant for paroxysmal AF, they are nonexistent for persistent AF. This raises the question, should we be concerned about asymptomatic AF in patients such as those studied by Kühlkamp et al. (1), with “persistent” AF? I think we must. As above, in the absence of nodal blockade, the distinction between persistent and paroxysmal AF is often unclear; in the presence of AV nodal blockade, the distinction may be even more obscure. Recurrent AF that previously was symptomatic and “persistent” may become so well-tolerated that it is allowed to spontaneously revert to sinus mechanism before symptoms are noted (even over a period of days).

The question of whether drugs with AV nodal blocking properties might simply be converting symptomatic to asymptomatic AF is not new. Concerns were raised at a recent Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee meeting that d,l-sotalol (a racemic mixture that has both beta-blocking and class III properties) might, in part, be reducing symptomatic recurrence of AF by slowing the ventricular response and making recurrences asymptomatic (16). Only after the majority of committee members became convinced that d,l-sotalol indeed reduced symptomatic recurrence of AF to a greater degree than simply that of a beta-blocker was the drug recommended for approval for the prevention of symptomatic AF.

In considering metoprolol for prevention of symptomatic AF, we should review some of the data regarding d,l-sotalol. Kühlkamp et al. (1) reference a recent article that suggested d,l-sotalol (80 mg twice daily) was not better than atenolol (50 mg daily) in reducing recurrent AF (17). In patients with paroxysmal AF, atenolol and d,l-sotalol demonstrated similar reduction of paroxysmal AF, as assessed by 72-h ambulatory monitoring. This study used d,l-sotalol in a dosage range where beta-blocking characteristics typically overshadow class III activity, so it was essentially a comparison of two beta-blockers. The continuous nature of the monitoring periods allowed collection of all episodes of AF (both symptomatic and asymptomatic), and similar reductions of AF, compared with placebo, were seen for both atenolol and d,l-sotalol. Although distinction between symptomatic and asymptomatic AF was not made, this article was reassuring in that the true frequency of AF was evaluated, and improvement resulted from both drugs.

Is the action of d,l-sotalol on AF essentially that of beta-blockade? Most likely, the answer is no. When higher doses of d,l-sotalol (up to 160 mg twice daily) were compared with placebo and d-sotalol (the stereoisomer with only class III effects and no beta-blockade), in patients following electrical cardioversion, d,l-sotalol reduced recurrence from 68% to 50% (18). Clearly the beta-blocker effect contributed to the results, since d-sotalol alone was associated with a recurrence rate intermediate between placebo and the racemic mixture (60% recurrence).

SHOULD METOPROLOL BECOME THE “TREATMENT OF FIRST CHOICE” FOR AF?

Kühlkamp et al. (1) suggest that metoprolol CR/XL may become the treatment of first choice for those “who require drug therapy to maintain sinus rhythm.” I cannot agree with this statement on the basis of two concerns. First, the reduction in recurrence of symptomatic AF with metoprolol is modest—less than the twofold increase in median time to recurrence prospectively required for efficacy in other trials. Thus, metoprolol cannot be considered to be an atrial stabilizing agent in the same league as the commonly used agents, quinidine, disopyramide, propafenone, flecainide, d,l-sotalol and amiodarone. Second, when one considers possible asymptomatic AF, it is not clear that metoprolol truly stabilizes the atrium (despite a modest reduction of symptomatic recurrence).

However, beta-blockers have an excellent safety profile, so reduced efficacy might be acceptable in a first-line agent when the lack of proarhythmia and serious side effects are considered. In addition, beta-blockers are a good first choice in therapy for the control of the ventricular response in AF, since they control the ventricular response better than digoxin should AF recur. One must keep in mind that this heart rate control may be responsible for reducing symptoms of AF, making it even more important to continue anticoagulation.

TREATMENT OF SYMPTOMATIC AF: ISSUES OF ANTIICOAGULATION

The goal of atrial stabilizing therapy, as correctly stated by Kühlkamp et al. (1), is to prolong the time to recurrence of symptomatic AF. How important is asymptomatic AF? The answer depends on whether one is considering changes in anticoagulant therapy based on the apparent reduction in AF. Warfarin (Coumadin), and perhaps to a much lesser degree, aspirin, are the only therapies demonstrated to reduce the risk of embolic complications of AF. Based on the data cited above regarding asymptomatic AF, we should assume that patients with AF are having more events than
anyone recognizes, a situation exacerbated perhaps by drugs that block the AV node. Our group is most comfortable continuing warfarin therapy indefinitely after cardioversion of AF. Maintenance of anticoagulation provides protection from thromboembolic complications of recurrent AF (whether symptomatic or asymptomatic) and allows prompt conversion of sinus mechanism when recurrent AF is recognized (obviating the otherwise mandatory three weeks of warfarin or transesophageal echocardiogram for recurrences >48 h in duration).

If anticoagulation is ever discontinued, we advocate that two steps be considered prior to the drug change. First, a Holter monitor should be placed to evaluate for asymptomatic AF; obviously if AF is seen, discontinuation of anticoagulation should be avoided. Second, one should consider discontinuing treatment with any agents likely to reduce symptoms (such as AV nodal blocking drugs). This may seem paradoxical, but allowing a higher rate, when AF does recur, allows the best possible “warning system” for recurrent AF. Finally, although the data are not strong for its use in AF (19), in the absence of warfarin, aspirin, 325 mg daily, should be prescribed.

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