Letters to the Editor

Angiotensin-Converting Enzyme Inhibitors and Outcome Among Patients With Heart Failure and Renal Insufficiency: Need for a Prospective Study

Ezekowitz et al. (1) recently reported lack of benefit of angiotensin-converting enzyme (ACE) inhibitors on mortality in patients with chronic heart failure (CHF) in whom estimated creatinine clearance was below 60 ml/min, as opposed to a beneficial effect in those with creatinine clearance above 60 ml/min. The researchers attribute this lack of benefit to a possible interaction between aspirin and ACE inhibitor use, suggesting that aspirin might blunt the effects of ACE inhibitors. Whereas this might be true, in our opinion another explanation should be considered as well, namely prescription bias. In CHF, ACE inhibition should be prescribed to all patients, especially those with severe CHF. Regrettably, this is not always true in daily practice.

In the cohort studied by Ezekowitz et al. (1), only 60% were using ACE inhibitors. It has been reported that physicians are reluctant to prescribe ACE inhibitors in the presence of severe renal dysfunction (2). Physicians are more willing to prescribe ACE inhibitors to CHF patients if such patients are more symptomatic (3). In CHF, renal function impairment can elicit a clinically more unstable condition—for instance, by fluid retention. Accordingly, in the present study by Ezekowitz et al. (1), confounding by prescription may have occurred among the patients with renal function impairment, with ACE inhibitors being preferentially prescribed to subjects with a more unstable cardiac condition and a worse prognosis.

In view of the prognostic importance of renal function in subjects with CHF, it might be relevant that, in subjects with primary renal disease and severely impaired renal function, ACE inhibition protects against further worsening of renal function (4). Whether this might be of benefit in CHF patients has not been studied so far. Taken together, the data by Ezekowitz et al. (1) argue for prospective studies into the role of ACE inhibitors in CHF subjects with renal function impairment.

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Beta-Blockers Versus Digoxin to Control Ventricular Rate During Atrial Fibrillation

The recent study of Olshansky et al. (1) investigated the approaches used to control rate, the effectiveness of rate control, and changeovers from one drug class to another in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Comparing the cumulative achievement of adequate ventricular rate control and the time to discontinuation of rate-control therapy, the investigators concluded that beta-blockers were the most effective drugs. We believe the superiority of beta-blockers over other therapeutic options, particularly over digoxin, must be interpreted with caution.

Adequate ventricular rate control was cumulatively obtained in a similar proportion of patients taking beta-blockers alone and digoxin alone (59% vs. 58%, respectively), a result that was confirmed both during rest (68% for both therapies) and with exertion (72% vs. 70%, respectively). Afterwards, the researchers considered beta-blockers more effective, observing that, over time, more patients taking digoxin or a calcium channel blocker were changed to another drug (p < 0.0001). However, in this comparison, the group of patients using beta-blockers and calcium channel antagonists included those taking digoxin concomitantly, whereas the digoxin group included only individuals using this drug alone. It is possible to observe that, in patients using beta-blockers, the association of digoxin increased the proportion of adequate rate control from 59% to 70%, and this increment may have led to the observed superiority with beta-blocker therapy. Randomized studies have already demonstrated that the association of digoxin with beta-blockers is more effective than beta-blockers alone in this setting (2,3).

In their discussion, the investigators (1) stated that “because no placebo control was used in this trial, it is possible that no medication would have worked as well as digoxin did to control the rate.” Because the randomization of the AFFIRM trial was not performed to compare drugs to control ventricular rate, this observation should not be restricted to digoxin. The concept that oral digoxin is efficient in controlling ventricular rate during atrial fibrillation is well accepted (4), despite being supported more by studies that demonstrated the reduction of ventricular rate after the initiation of the therapy (5) than by the sparse number of randomized placebo-controlled trials (6).

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In conclusion, we do believe that the report by Olshansky et al. (1) from the AFFIRM study does not allow the conclusion that “beta-blockers were the most effective drugs” in controlling ventricular rate during atrial fibrillation. In their study, the efficacy of beta-blockers and digoxin, both used alone, was equivalent. Our opinion, in accordance with current guidelines for the management of atrial fibrillation, is that digoxin is still a first-line alternative to control ventricular rate in patients with atrial fibrillation, particularly in cases with congestive heart failure and left ventricular systolic dysfunction (4).

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REPLY

We appreciate the interest of Drs. Veloso and de Paola and their comments about our study (1).

We did not specifically recommend beta-blockers as the first-line approach to rate control of atrial fibrillation in all patients. Other therapeutic options, such as digoxin, may indeed be a more appropriate first step in individual circumstances.

In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, more patients were switched to beta-blockers than to other drug classes. Often, combination therapy was needed. The question “is there one best approach?” cannot be answered definitively from our data for several reasons:

1. Rate control can be difficult. Drugs had to be changed in about one-third of patients in the AFFIRM study. Effective rate control may require open-mindedness to all rate-control options; there may be no one best approach for all patients.

2. Our study did not randomize the rate-control strategies. Some patients required a beta-blocker or digoxin for other clinical reasons. Beta-blockers may be necessary if the patient has certain conditions, such as coronary artery disease, whereas digoxin may be a first-line alternative when congestive heart failure and left ventricular systolic dysfunction are present.

3. Rate control is difficult to define. The need for a specific rate may vary by patient, by disease, and by drug. It is possible that AFFIRM’s approach to rate control was too stringent or was not targeting the correct rate.

4. Rate control might not be the only important end point in managing atrial fibrillation with rate-controlling drugs. These drugs may increase or decrease symptoms despite proper rate control, influence mortality, affect total costs, influence hospitalization rates, or influence the return to sinus rhythm. These factors, not explored in our report, must be considered for any patient requiring therapy for rate control, and drug classes may differ in this regard.

5. We could not analyze the combination of beta-blockers and digoxin because start and stop dates for drug use were not recorded in the AFFIRM study. Although it was possible to determine whether neither drug was used, it was not possible to determine whether both drugs were used concurrently.

The success of achieving rate control in the AFFIRM study may have hinged on the flexibility of the investigators to use more than one drug class. Over the long run, more patients were switched to beta-blockers than to the other drug classes. Beta-blockers tended to be used more commonly over time, and fewer patients abandoned this drug class. Of importance, rate control was possible for the majority of patients without the need for atrioventricular junctional ablation and a pacemaker, and rate control appeared to improve over time.

We do not necessarily advocate a beta-blocker as first-line therapy for rate control for all patients. Digoxin may be reasonable as first-line therapy in some patients, especially sedentary elderly patients.

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