**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 in 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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**REFERENCES**


**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).