JAFIB
Editorial
Journal of Atrial Fibrillation
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Angiotensin Receptor Blockers for the Prevention of Atrial Fibrillation Recurrences: Unending Hot Debate

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Introduction

How angiotensin inhibition might protect against AF is not completely known. There is a plausible scientific basis for the notion that inhibition of the renin-angiotensin system can reduce the incidence of AF.[1] To best of our knowledge, angiotensin receptor blockers (ARBs) have been shown to be effective in the prevention of AF despite the fact that this essential benefit appears to be limited to patients with systolic left ventricular (LV) dysfunction or LV hypertrophy associated with hypertension.[2] Three mechanisms have been suggested to explain antiarrhytmic actions of ARBs in AF. First; improved LV-hemodynamics and reduced atrial stretch. Second; supressed angiotensin-II induced fibrosis and third, direct modulation of ion-channel function.[1] Both animal and human studies suggest that angiotensin II is involved in electrical and atrial myocardial remodeling.[3,4] In an animal model, inhibition of angiotensin II with captopril or candesartan prevented shortening of the atrial effective refractory period and atrial electrical remodeling during rapid atrial pacing,[3] while atrial tissue obtained during open heart surgery from patients with AF revealed downregulation of AT1 receptor proteins and upregulation of AT2 receptor.[4]

Post hoc analyses of randomized trials and nonrandomized observations suggested that angiotensin converting enzyme (ACE) inhibitors and ARBs reduce the incidence of new AF in a variety of settings including the treatment of left ventricular dysfunction and hypertension, and after coronary artery bypass graft surgery. The possible efficacy of angiotensin inhibition for the prevention of AF was addressed in a meta-analysis of 11 trials with over 56,000 patients.[2] In that meta-analysis almost all of data involved new onset rather than recurrent AF. ACE inhibitors and ARBs significantly reduced the risk of the development of AF (relative risk reduction [RRR] 28 %); the benefit was equivalent with the 2 classes of drugs. The benefit was greatest in patients with heart failure (RRR 44%), and was not significant in hypertension (RRR 12%). There was a significant reduction in the risk of AF recurrence when used after cardioversion (RRR 48%). However most of the data in the meta-analysis were derived from subset analyses of trials performed for reasons other than prevention of AF (eg, heart failure, post-MI, or hypertension). In addition, heterogeneity and the likely presence of publication or ascertainment bias lessen the strength of the evidence. On the other hand in GISSI-AF trial, 1442 patients in sinus rhythm and a history of symptomatic AF were assigned to receive either valsartan or placebo.[5] All patients had underlying cardiovascu-

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lar disease, diabetes, or left atrial enlargement. In contrast to the earlier data, GISSI-AF found that valsartan did not prevent recurrent AF. At 1 year follow-up, there was no significant difference between valsartan or placebo in the proportion of patients who had more than 1 episode of AF or in the median time from randomization to the first recurrence of AF. Although 57 % of patients were taking an ACE inhibitor and 70% were taking arrhythmic drugs at baseline that were continued throughout the trial and might have confounded the results, the outcomes in subgroup analysis were similar in the patients who were or were not being treated with such agents. Another possible contributor to the lack of benefit in GISSI-AF was a low prevalence of heart failure/left ventricular dysfunction (8%), since the meta-analysis cited above found that the benefit was greatest in patients with these conditions.[2]

There are currently seven commercially available ARBs, with telmisartan offering unique pharmacologic features compared with the other agents of its class. Telmisartan displays insurmountable, but reversible binding to the AT1 receptor, and it has the highest binding affinity for this receptor among commercially available ARBs.[6] Telmisartan modulates peroxisome proliferator-activated receptor γ (PPARγ), an established therapeutic target in the treatment of insulin resistance, diabetes, and metabolic syndrome.[7] A recent report on the ONTARGET study[8] indicated that 80 mg of telmisartan daily was equivalent to the ACE inhibitor ramipril, and was effective in preventing relapses of lone AF.[9] In this issue of the Journal of Atrial Fibrillation Maeda and his associates investigated the dose-dependent effects of telmisartan on the prevention of AF in patients associated with risk factors.[10] One hundred hypertensive patients were randomized to take 40 mg or 80 mg of telmisartan for 24 months. At the end of the follow-up, the incidence of AF was lower in the high-dose group than in the low-dose group. Moreover, the proportion of AF recurrences in the patients with a past history of paroxysmal AF was lower in the high-dose group than in the low-dose group. Concordantly our group has recently showed that telmisartan significantly lowered P-wave dispersion values, indicative of nonhomogenous conduction in the left atrium and AF frequency in patients with hypertension after 6-month treatment.[11]

In conclusion although there is a plausible scientific basis for the notion that inhibition of the renin-angiotensin system can reduce the incidence of AF the greatest benefit was seen in patients with heart failure/left ventricular dysfunction in whom therapy with an ACE inhibitor or ARB is probably already indicated. A number of initial studies suggested that ACE inhibitors and ARBs might prevent new onset and recurrent AF. However, the available data do not support the use of these drugs solely for the prevention of AF. I believe that additional prospective definitive trials are needed to clarify the role of ARBs in the prevention of AF recurrence.

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