EDITORIAL COMMENT

Angiotensin II Inhibition and Prevention of Atrial Fibrillation and Stroke*

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Atrial fibrillation (AF), the most common cardiac arrhythmia encountered in clinical practice, is a growing public health problem. Atrial fibrillation currently affects more than two million individuals in the U.S., and its age-adjusted prevalence is expected to exceed five million by the year 2050 (1,2). Patients with hypertension and heart failure are at high risk of developing AF and, in both conditions, AF increases the risk of cardiovascular morbidity and mortality, particularly the risk of fatal or nonfatal stroke (3–8).

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The development and maintenance of AF are associated with changes in cardiac structure, function, and electrical properties known as cardiac remodeling (9). Although the mechanisms leading to AF are complex and the process of cardiac remodeling is still incompletely understood, several lines of evidence accumulated over the past five years suggest that the renin-angiotensin aldosterone system (RAAS) plays a major role in the pathogenesis of AF. Both hypertension and heart failure are associated with activation of the RAAS, and in patients with heart failure, greater activation of the RAAS with increasing severity of ventricular dysfunction is associated with a greater risk of AF (4). Angiotensin II is a potent promoter of fibrosis, and atrial fibrosis, a frequent finding in patients with AF, may lead to intra-atrial conduction disturbances and to persistent susceptibility to AF (4). Increased angiotensin-converting enzyme (ACE) expression and changes in angiotensin receptor expression occur in the atria of patients with AF. In humans, angiotensin II type 1 receptor stimulation causes atrial hypertrophy and fibrosis, whereas angiotensin II type 2 receptor stimulation counteracts this effect. Patients with AF have reduced type 1 and increased type 2 angiotensin II receptor density (10). Furthermore, there is also evidence suggesting that both ACE and RAAS polymorphisms play a role in predisposing patients to AF (11,12). However, the strongest arguments for a major role of RAAS in AF come from the accumulating evidence that RAAS inhibition prevents the emergence and recurrence of AF.

Atrial fibrillation occurring during the course of experimental heart failure induced by rapid atrial pacing is accompanied by atrial electrical and structural remodeling, including atrial dilation, contractile dysfunction, and fibrosis (9). Recent data suggest that ACE inhibitors attenuate this atrial remodeling in experimental models of AF (13). At least two recent clinical studies have shown that, compared to placebo, treatment with an ACE inhibitor markedly reduces the incidence of AF in patients with left ventricular dysfunction (3,4). In the Trandolapril Cardiac Evaluation (TRACE) study, the ACE inhibitor trandolapril reduced the incidence of AF by 47% after acute myocardial infarction in patients with left ventricular dysfunction (3). In a retrospective analysis of patients from the Montreal Heart Institute included in the Studies Of Left Ventricular Dysfunction (SOLVD), the ACE inhibitor enalapril decreased the incidence of AF by 77% over a mean follow-up of 2.9 ± 1.0 years (4). Moreover, Ueng et al. (5) have reported that the addition of enalapril to amiodarone significantly decreased the rate of immediate recurrences and facilitated subsequent long-term maintenance of sinus rhythm after elective electrical cardioversion in patients with persistent AF.

More recent experimental data suggest that RAAS inhibition by angiotensin II receptor antagonists (ARBs) also prevents the promotion of AF by suppressing the development of electrical and structural cardiac remodeling (14). In addition, Madrid et al. (6) have shown that pre-treatment with the ARB irbesartan could also reduce the recurrence of AF after electrical cardioversion in amiodarone-treated patients.

In this issue of the *Journal*, two subgroup analyses of the Losartan Intervention for End point reduction in hypertension (LIFE) study extend these observations and provide further evidence, in hypertensive patients with electrocardiogram (ECG)-documented left ventricular hypertrophy, for the benefit of RAAS inhibition, compared to beta-adrenergic blockade, in the prevention of new-onset AF and in the reduction of cardiovascular morbidity and mortality associated with new-onset or persistent AF (7,8). In the subgroup of patients with a history of AF or ECG-documented AF, as compared to atenolol-based therapy, losartan-based therapy reduced the primary composite end point of the LIFE study (cardiovascular mortality, fatal or nonfatal stroke, and fatal or nonfatal myocardial infarction) by 42% and the occurrence of stroke by 45% over 4.8 ± 1.0 years of follow-up (7). In patients in sinus rhythm at entry, losartan-based therapy reduced new-onset AF by 33% and subsequent stroke by 51% compared to atenolol-based therapy, despite similar blood pressure reduction. Patients who developed new-onset AF in the losartan group had 40% fewer primary composite end points and 51% fewer strokes than those in the atenolol group (8).

It is interesting to note that in the LIFE study, rates of myocardial infarction and hospitalization for angina pectoris were similar in patients treated with losartan and in those receiving atenolol, suggesting that RAAS inhibition is perhaps

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as effective as beta-blockade in the prevention of acute coronary syndromes. Such a hypothesis requires further study. On the other hand, hospitalization for heart failure was less frequent, and there was a trend for fewer sudden cardiac deaths, with the atenolol versus the losartan regimen, indicating that both treatment modalities are complementary, not mutually exclusive, in hypertensive patients.

This novel approach has considerable clinical relevance, in view of the high risk associated with AF and of the tremendous burden that it places on our health care resources. Reduction of blood pressure and reverse cardiac remodeling following ACE inhibition and angiotensin receptor blockade may not have been the only or the principal mechanism of action in these recent studies (3–8), since AF prevention occurred despite the presence of a normal mean blood pressure in the TRACE study (3), and despite similar blood pressure reduction with both treatment regimens in the LIFE study (7,8). Thus, more experimental data are needed to establish the role of RAAS inhibition on cardiac remodeling and AF prevention. Additional clinical data are also needed to compare the relative efficacy of ACE inhibitors and ARBs on the reduction of the incidence of AF in patients with hypertension and heart failure who are at increased risk of developing new-onset AF, and on the maintenance of sinus rhythm following electrical cardioversion in patients with long-standing, persistent AF. The role of RAAS inhibition in AF caused by conditions other than hypertension and heart failure, as well as "lone" AF, needs further study. Finally, the knowledge that AF can be prevented opens new and previously unsuspected avenues of intervention, such as increased intake of long-chain n-3 polyunsaturated fatty acids through fish consumption (15) and use of anti-inflammatory drugs (16).

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REFERENCES

1. American Heart Association. Heart and Stroke Statistical Update. Dallas, TX: American Heart Association, 2003:1–52.
2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulant and Risk Factors in Atrial Fibrillation (ATRIA) study. JAMA 2001;285:2370–5.
3. Pederson OD, Bagger H, Kober L, Torp-Pederson C. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. Circulation 1999;100:376–80.
4. Vermes E, Tardif JC, Bourassa MG, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction. Insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. Circulation 2003;107:2926–31.
5. Ueng KC, Tsai TP, Yu WC, et al. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation. Results of a prospective and controlled study. Eur Heart J 2003;24:2090–8.
6. Madrid AH, Bueno MG, Rebollo JMG, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation. Circulation 2002;106:331–6.
7. Wachtell K, Hornestam B, Lehto M, et al. Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005;45:705–11.
8. Wachtell K, Letho M, Gerdts E, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005;45:712–9.
9. Shi Y, Ducharme A, Li D, et al. Remodeling of atrial dimensions and emptying function in canine models of atrial fibrillation. Cardiovasc Res 2001;52:217–25.
10. Goette A, Arndt M, Rocken C, et al. Regulation of angiotensin II receptor subtypes during atrial fibrillation in humans. Circulation 2000;101:2678–81.
11. Gensini F, Padeletti L, Fatini G, Sticchi E, Gensini GF, Michelucci A. Angiotensin-converting enzyme and endothelial nitric oxide synthase polymorphisms in patients with atrial fibrillation. Pacing Clin Electrophysiol 2003;26:295–8.
12. Tsai CT, Lai LP, Lin JL, et al. Renin-angiotensin system gene polymorphisms and atrial fibrillation. Circulation 2004;109:1640–6.
13. Li D, Shinagawa K, Pang L, et al. Effects of angiotensin-converting enzyme inhibition on the development of atrial fibrillation substrate in dogs with ventricular tachycardia-induced congestive heart failure. Circulation 2001;104:2608–14.
14. Kumagai K, Nakashima H, Urata H, et al. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. J Am Coll Cardiol 2003;41:2197–204.
15. Mozaffarian D, Psaty BM, Rimm EB, et al. Fish intake and risk of incident atrial fibrillation. Circulation 2004;110:368–73.
16. Dernellis J, Panaretou M. Relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrent atrial fibrillation. Eur Heart J 2004;25:1100–7.