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EDITORIAL COMMENT

Atrial Fibrillation, Maybe it Is Not So Lone?*

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Although the clinical phenotype of atrial fibrillation (AF) has multiple causes, the most prevalent cause in the Western world is hypertensive heart disease caused by the high prevalence of hypertension. Change in hemodynamic status by an increase in blood pressure has many direct effects on left ventricular and atrial structure and function. Since the first report of angiotensin-converting enzyme inhibition (ACEI) in patients with acute myocardial infarction (1), there have been numerous reports that treatment with either ACEI or angiotensin receptor blockade reduces the risk of new-onset AF. This has led to 2 schools of thought: that these agents either possess antiarrhythmic properties, which some studies actually suggest, or that the primary effect of this treatment is in fact not by electrical remodeling but rather by changing and improving the hemodynamic status

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in patients at risk for AF. This has led to several currently ongoing studies looking at how treatment-induced hemodynamic improvement affects the risk of risk new-onset AF. Furthermore, studies have also investigated whether improvement of left ventricular structure (i.e., by reduced left ventricular hypertrophy) (2) and function reduces the risk of AF. Finally, a few studies have recently investigated whether reduction in left atrial structure (size) and improvement in left atrial function can reduce the risk of AF. The clinical implication has moved focus away from treating AF with beta-receptor blockers as well as conventional antiarrhythmic drugs; the latter treatment has turned out to be quite difficult because of side effects. The new approach is to utilize existing treatment known to improve patients' hemodynamic status by reducing central blood pressure, reducing left ventricular mass, improving left ventricular systolic function, reducing left atrial size, and improving left atrial function.

If one believes in this hemodynamic hypothesis, a logical consequence is that AF is in fact not lone but should be considered as target organ damage of impaired hemodynamic status, increased blood pressure, inappropriate left ventricular hypertrophy, and left atrial size as well as impaired left ventricular and atrial function. Examples of AF during changed hemodynamic status have been reported in young people on drinking sprees or during strenuous exercise, in which large volume changes occur. However, in more mature patients, episodes of AF are more likely to be caused by impaired hemodynamic status attributable to increased blood pressure, just by the a priori risk of hypertensive disease in elderly patient populations. Therefore, a clinical strategy, if we have done our best to find any other causative disease of AF, could be to conclude that blood pressure for this individual is too high and must be brought down to improve the patient's hemodynamic status.

This action could also be justified by the clinical problem of relating an individual patient's blood pressure to that of groups of normal subjects. When the clinician determines whether any given patient is hypertensive, blood pressures are most often related to so-called normal values (i.e., 140/90 mm Hg). However, in an individual patient it is always unknown whether blood pressure just precedes our definition of hypertension and blood pressure is increased for that patient. Prediction models predict that increased systolic blood pressure by 10-mm Hg increases the risk of AF independent of age, sex, and any given level of electrocardiographic left ventricular hypertrophy (3). A logical but still undocumented consequence would be that an increase of systolic blood pressure in the normal range would also increase the risk of AF. However, if AF per se were considered target organ damage, a given patient with systolic blood pressure over 120 mm Hg would by definition be considered hypertensive and treatment should be initiated at much lower values than currently recommended. The current European Society of Cardiology/European Society of hypertension Guidelines on treating hypertension (4) has already in part taken these considerations into account, as patients with an associated clinical condition (i.e., acute myocardial infarction, stroke, or renal impairment) should have antihypertensive treatment initiated if systolic blood pressure exceeds 120 mm Hg. In addition, the guidelines now suggest that systolic blood pressure between 130 and 139 mm Hg should also be treated with concomitant AF.

The study by Belluzzi et al. (5) in this issue of the *Journal* is an interesting study that in a standardized fashion evaluates whether ramipril is able to prevent recurrent episodes of so-called lone AF. The study shows that the placebo-treated patients have a more than 3-fold increased risk of recurrent lone AF compared with the active treatment with ramipril. One obvious limitation of the study is the small sample size. However, patients with lone AF, if it exists as a disease entity, are rare and few. The importance of the current study is that it suggests that improvement of

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the hemodynamic status in patients with systolic blood pressures between 130 and 139 mm Hg and normal left atrial or ventricular structure and function does reduce patients' risk of future new-onset AF. Thus, this study further supports the idea that AF is a marker of target-organ damage even with normal systolic blood pressure and substantiates the thoughts that treatment should be initiated even with normal or high-normal systolic blood pressure if AF is present. Furthermore, the fact that some patients randomized to placebo also became hypertensive during the study is also a clue indicating that AF in an individual patient just precedes our definition of hypertension and is a marker of target organ damage by reflecting an impaired hemodynamic state.

One major piece of missing information in the study by Belluzzi et al. (5) is nonavailable data on time-varying blood pressure. It would be of great interest to investigate how much additional effect the ACEI ramipril has on reducing the risk of AF beyond its blood pressure-lowering effect. This would indicate the ACEI composite efficacy of hemodynamic improvement on central blood pressure as well as direct ACEI improvement in left ventricular and left atrial structure and function. The CAFÉ (Conduit Artery Function Evaluation) study (6), a substudy from ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), showed that the combination of perindopril/amlodipine resulted in significant improvement in central blood pressure compared with the beta-blocker/diuretic combination, although the 2 treatment arms had similar brachial blood pressures. If one accepts the hemodynamic approach to treating AF and that differences in central blood pressure are essential to reducing the risk of new-onset AF, beta-blockade may not always be a natural choice (3). Although beta-blockade does reduce blood pressure and by this hemodynamic effect will reduce the risk of AF, the central blood pressure is not reduced, and as a result reoccurrences of AF are frequent. In addition, beta-blockade may also have other detrimental effects through its heart rate reducing properties in patients in sinus rhythm and normal left ventricular function treated for the prevention of paroxysmal AF. Beta-blockade also will tend to increase atrial wall stress and may thereby promote AF caused by increased left ventricular stroke volume during heart rate reduction while maintaining cardiac output.

These thoughts lead to the conclusion that AF should be considered a marker of target organ damage with impaired hemodynamics. Treating AF, whether lone or not, also includes reduction in cardiovascular risk by using treatments for known cardiovascular risk factors such as reducing blood pressure, improving central hemodynamics, and reducing left ventricular and atrial structure and function.

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Key Words: lone atrial fibrillation ■ ramipril ■ atrial remodeling ■ ACE inhibitors.