Atrial fibrillation and hypertension are 2 prevalent, and often coexistent, conditions in the North American population. Their incidence increases with advancing age, and they are responsible for considerable morbidity and mortality. Although the relation between the 2 conditions has long been known, the treatment of hypertension is not currently a focus in the clinical management of atrial fibrillation. Hypertension is associated with left ventricular hypertrophy, impaired ventricular filling, left atrial enlargement, and slowing of atrial conduction velocity. These changes in cardiac structure and physiology favor the development of atrial fibrillation, and they increase the risk of thromboembolic complications. Conventional therapy of atrial fibrillation has focused on interventions to control heart rate and rhythm and the prevention of stroke through the use of anticoagulant medications. In patients with atrial fibrillation, aggressive treatment of hypertension may reverse the structural changes in the heart, reduce thromboembolic complications, and retard or prevent the occurrence of atrial fibrillation. Specific pharmacotherapy could potentially play a major role in the primary and secondary prevention of atrial fibrillation and its complications.

HYPERTENSION AS A COMPOUNDING RISK FACTOR FOR STROKE

Atrial fibrillation is responsible for 15% of strokes overall and 25% of strokes in persons >80 years of age (Figure 2).9 In patients with atrial fibrillation, 70% of strokes are thought to be cardioembolic in origin.9,10 In addition to its role as a major risk factor for the development of atrial fibrillation, the presence of hypertension increases the risk of stroke in patients with atrial fibrillation. Patients with atrial fibrillation have a 3- to 6-fold increase in stroke risk compared with the general population.9,11–13 In patients with atrial fibrillation, hypertension worsens the stroke rate by an additional 2- to 3-fold.14,15 Among individuals with atrial fibrillation, the relative risk for stroke associated with hypertension is inversely proportional to age, decreasing from 3.5 in patients aged 50 to 59 to 1.7 in those aged 80 to 89.14 Finally, changes in cardiac structure seen with hypertension have been identified as risk factors for stroke. Among 568 patients in the Stroke Prevention in Atrial Fibrillation study (which prospectively compared warfarin, aspirin, and placebo for the prevention of stroke), left ventricular dysfunction and left atrial enlargement were associated with an increased risk of stroke in patients with atrial fibrillation.15

Hypertension is associated with structural changes in the left atrium that are associated with atrial fibril-
lation. They include left atrial enlargement, changes in left atrial mechanical function, altered left atrial electrophysiology, and increased atrial ectopic activity.

### LEFT VENTRICULAR HYPERTROPHY

One effect of hypertension on the heart that is greatly studied is hypertrophy of the left ventricle. Left ventricular hypertrophy (LVH), detected by electrocardiography or echocardiography, is an important risk factor for atrial fibrillation. In the Framingham cohort, patients with an electrocardiographically determined diagnosis of LVH had a 3- to 3.8-fold increased risk of developing atrial fibrillation. The risk of developing atrial fibrillation also increases by 28% for each 4-mm increase in echocardiographically measured left ventricular thickness.

### LEFT ATRIAL ENLARGEMENT

Left atrial enlargement may develop early in patients with hypertension, before any evidence of ventricular hypertrophy or atrial arrhythmia. Findings in another study showed that 21% of hypertensive patients without electrocardiographic evidence of LVH had left atrial enlargement of \(>4\) cm. This finding suggests that left atrial enlargement develops earlier than LVH or, alternatively, that echocardiography is more sensitive for diagnosis of atrial enlargement than of ventricular hypertrophy. Once patients develop LVH that can be detected by electrocardiography, the prevalence of left atrial enlargement is high: 56% in women and 38% in men. Most studies have reported that the magnitude of atrial enlargement correlates with the degree of hypertension. Left atrial enlargement in hypertensive patients may be the result of elevated left ventricular filling pressures and impairment of left ventricular diastolic function.

Enlargement of the left atrium is an important step in the progression from hypertension to atrial fibrillation. Cross-sectional studies have demonstrated that hypertensive patients with a history of paroxysmal...
atrial fibrillation have larger left atria than do patients without a history of paroxysmal atrial fibrillation.\textsuperscript{18,27} Other support for left atrial enlargement as a causal risk factor for atrial fibrillation comes from cohort studies that use enlargement of the left atrium as a prospective predictor of the occurrence of atrial fibrillation and show that the risk of atrial fibrillation is correlated with the severity of atrial enlargement. Among 4,731 patients in the Framingham study who underwent baseline echocardiography, the risk of developing atrial fibrillation increased by 39\% for each 5-mm increment increase in left atrial size, after adjustment for other risk factors.\textsuperscript{4} In 2 other prospective studies, it was confirmed that atrial enlargement predicts the development of atrial fibrillation, and in both cases it was a better predictor than the presence of LVH.\textsuperscript{3,8}

The electrocardiographic assessment of left atrial size typically involves the measurement of the anteroposterior diameter. However, newer, more precise measures of left atrial size have been developed. In a retrospective cohort of 1,655 randomly chosen adults without a history of atrial fibrillation, Tsang et al\textsuperscript{28} found that an increase in left atrial volume, measured echocardiographically using a biplane area-length method, was highly predictive of the onset of atrial fibrillation, independent of clinical variables. In this cohort, a 30\% increase in left atrial volume was correlated with a 43\% increased risk of atrial fibrillation, and left atrial volume was a more sensitive marker for this risk than conventional left atrial diameter.

**DOPPLER AND ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT ATRIAL FUNCTION**

Doppler assessment of mitral and pulmonary venous flow can be used to evaluate left atrial and left ventricular function. In patients with hypertension, Doppler is a very sensitive method for detecting changes in cardiac function, and abnormalities of flow patterns often precede the development of LVH.\textsuperscript{27,29,30} In hypertensive patients who go on to develop atrial fibrillation, Doppler studies have documented impaired left atrial function compared with hypertensive patients who remain in sinus rhythm.\textsuperscript{8,27} Other methods of assessing left atrial function, such as measuring left atrial fractional shortening, have confirmed this observation.\textsuperscript{27} Impaired contractile function of the left atrium has also been shown to predict the development of atrial fibrillation in patients with heart failure.\textsuperscript{31}

Atenuating the impairment of left atrial function may prevent further structural deterioration of the atrium and could reduce the incidence of atrial fibrillation. In a dog model of pacing-induced congestive heart failure, Shi et al\textsuperscript{12} demonstrated that atrial dilatation, impairment of atrial function, and the development of atrial fibrosis were minimized in animals that were pretreated with the angiotensin-converting enzyme (ACE) inhibitor enalapril. This group also found that the duration of atrial fibrillation was decreased in treated animals and concluded that the renin–angiotensin system played a vital role in arrhythmogenic atrial remodeling.\textsuperscript{32}

**CHANGES IN ATRIAL ELECTROPHYSIOLOGY**

Changes in atrial electrical properties occur early in hypertensive heart disease, preceding the appearance of left ventricular and left atrial enlargement.\textsuperscript{33} There have been 2 distinct abnormalities that have been studied: the prolongation of atrial conduction velocity as assessed by the signal-averaged p-wave duration and the decrease in atrial refractoriness. Both of these substrate changes are associated with the development and maintenance of atrial fibrillation.\textsuperscript{34–36} In a study of 234 control subjects and 84 patients with hypertension, but without LVH or left atrial enlargement, prolongation of the signal-averaged p-wave duration was prolonged in these hypertensive patients, who did not have any history of atrial fibrillation.\textsuperscript{33} The prolongation of p-wave duration varied directly with the severity of hypertension.\textsuperscript{33} As the signal-averaged p-wave duration also increases in patients with a history of paroxysmal atrial fibrillation,\textsuperscript{34,35,37} it is reasonable to postulate that slowing of atrial conduction velocity is a mechanism by which hypertension predisposes individuals to atrial fibrillation.

Another electrophysiologic change seen in patients with atrial fibrillation is the heterogeneous decrease in atrial effective refractory periods. Although no studies have examined the effects of hypertension on atrial refractoriness, animal studies have shown that increased dispersion of atrial refractoriness and shortened effective refractory period are associated with elevations in left atrial pressure\textsuperscript{36} and can be induced by balloon dilatation of the left atrium.\textsuperscript{38} Similar results were also seen in the Langendorff-perfused rabbit heart, where increasing the atrial pressure by up to 15 cm H\textsubscript{2}O resulted in shortening of atrial effective refractory period and monophasic action potential duration. It also increased the inducibility of atrial fibrillation from 0\% to 100\%.\textsuperscript{39} Because increases in left atrial size and pressure do occur in the later stages of hypertensive heart disease, it is possible that this type of electrical remodeling is important for the development of atrial fibrillation in patients with hypertension. In both animals and humans, the shortening of the atrial effective refractory period and the loss of its normal rate adaptation are associated with an increase in the duration of episodes of atrial fibrillation.\textsuperscript{40,41}

**PREMATURE ATRIAL CONTRACTIONS**

Atrial fibrillation is now known to be frequently initiated by atrial premature beats arising from within the pulmonary veins.\textsuperscript{42} In some patients, atrial fibrillation can be eliminated with catheter ablation of these pulmonary vein sites.\textsuperscript{42} At present, there is a lack of...
data on the link between hypertension and atrial fibrillation that incorporates this new finding. Studies of the association between hypertension and atrial premature beats are scant, and the risk factors for the development of pulmonary venous ectopy are unclear. Pulmonary veins may undergo hypertensive remodeling as the left atrium does because up to 70% of the circumference of a pulmonary vein is left atrial tissue.\textsuperscript{43,44}

Hypertension is associated with an increased frequency of premature atrial contractions. However, the site of origin for these contractions was not determined.\textsuperscript{45} In a study of 85 patients with essential hypertension, patients with LVH had an increase in the number of atrial premature beats compared with hypertensive patients without LVH.\textsuperscript{45} Both groups had more atrial premature beats than an age-matched control group. Antihypertensive therapy with β-blockers or calcium antagonists resulted in a decreased frequency of premature atrial contractions.\textsuperscript{45} Further study in this area is required to determine the effects of hypertension on the development of premature atrial contractions and, specifically, on the structure and electrophysiology of the pulmonary veins.

Despite the importance of hypertension in the development of atrial fibrillation and its complications, the recent American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) guidelines for the management of atrial fibrillation include <1 sentence about the treatment of hypertension.\textsuperscript{46} The aggressive treatment of hypertension in patients with atrial fibrillation is important for several reasons. Antihypertensive therapy has been shown to reverse some of the structural cardiac changes caused by hypertension, including LVH and left atrial enlargement.\textsuperscript{47,48} Also, emerging data suggest that the use of ACE inhibitors or angiotensin receptor blockers may directly reduce the recurrence of atrial fibrillation. Finally, the appropriate treatment of hypertension, even without atrial fibrillation, results in a significant reduction in mortality and stroke.\textsuperscript{49–51}

**EFFECTS OF ANTIHYPERTENSIVE THERAPY ON CARDIAC STRUCTURE AND PHYSIOLOGY**

There is growing evidence that many of the structural and functional changes that lead to atrial fibrillation can be attenuated or reversed through treatment with specific antihypertensive therapy.

In patients with hypertension, lowering blood pressure with a variety of agents results in regression of ventricular hypertrophy.\textsuperscript{47,52,53} Certain agents, such as calcium antagonists and ACE inhibitors, result in more regression, independent of the magnitude of blood pressure reduction.\textsuperscript{47,52–55} In a randomized study comparing verapamil and atenolol in a group of elderly hypertensive patients, verapamil resulted in a decrease in left ventricular mass and improved ventricular filling, whereas atenolol did not, despite similar reductions in blood pressure.\textsuperscript{54} In 2 large meta-analyses, findings suggest that ACE inhibitors and possibly calcium antagonists are superior to β-blockers, diuretics, and α-blockers for the regression of LVH.\textsuperscript{57,53} Even in hypertensive patients with normal left ventricular mass, 8 to 12 months of aggressive blood pressure reduction with a calcium antagonist resulted in improved peak ventricular filling rates, decreased wall thickness, and decreased left ventricular mass.\textsuperscript{56} It is not known how these changes affected the risk of atrial fibrillation.

Left atrial enlargement can also be reversed by antihypertensive therapy. In patients with hypertension, therapy with hydrochlorothiazide reduced left atrial size better than did any other class of antihypertensive agents. In the subgroup of patients with left atrial enlargement, clonidine, atenolol, and diltiazem also decreased left atrial size, whereas prazosin and captopril did not, despite similar reductions in blood pressure.\textsuperscript{48} In the same study, there was a similar reduction in left ventricular mass with hydrochlorothiazide, captopril, and atenolol, as well as an increase in mass with prazosin. The changes in left atrial size were independent of changes in blood pressure and baseline left ventricular mass.\textsuperscript{48} Other studies have shown variable reduction in left atrial size with verapamil\textsuperscript{55,57} or labetalol,\textsuperscript{58} despite reduction in left ventricular mass or wall thickness.

Thus, lowering blood pressure reduces LVH and left atrial enlargement, although certain classes of antihypertensive agents are more effective. None of these studies examined the effect of the lowering of blood pressure on the incidence of atrial fibrillation.

**ANTIHYPERTENSIVE THERAPY TO PREVENT ATRIAL FIBRILLATION**

In 2 recent studies, investigators evaluated antihypertensive therapy in patients with, or at risk of developing, atrial fibrillation. In patients after acute myocardial infarction who had left ventricular dysfunction and a mean blood pressure of 120/78 mm Hg, treatment with the ACE inhibitor trandolapril was associated with a decreased incidence of atrial fibrillation from 5.3% to 2.8% (p <0.01 over a 2- to 4-year follow-up period; Figure 3).\textsuperscript{59} More recently, Madrid et al\textsuperscript{60} examined the use of irbesartan, an angiotensin I receptor blocking agent, to reduce the recurrence of atrial fibrillation after elective electrical cardioversion.\textsuperscript{60} Approximately 40% of patients had a history of hypertension, and all patients were treated with long-term amiodarone. Irbesartan resulted in improved maintenance of sinus rhythm after a mean follow-up time of 254 days (79.5% vs 55.9%, p = 0.007). Irbesartan did not significantly lower blood pressure.\textsuperscript{60} An earlier study using lisinopril had shown a nonsignificant reduction in recurrence rate of atrial fibrillation after direct current cardioversion.\textsuperscript{61} These 2 studies suggest that blocking the renin–angiotensin system may reduce atrial fibrillation independent of changes in blood pressure.
Program, is needed to determine the effect of specific antihypertensive therapies in patients with atrial fibrillation.


