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ATRIAL FIBRILLATION AND HYPERTENSION: MECHANISTIC, EPIDEMIOLOGIC, AND TREATMENT PARALLELS

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Abstract

Atrial fibrillation (AF) is an increasingly prevalent condition and the most common sustained arrhythmia encountered in ambulatory and hospital practice. Several clinical risk factors for AF include age, sex, valvular heart disease, obesity, sleep apnea, heart failure, and hypertension (HTN). Of all the risk factors, HTN is the most commonly encountered condition in patients with incident AF. Hypertension is associated with a 1.8-fold increase in the risk of developing new-onset AF and a 1.5-fold increase in the risk of progression to permanent AF. Hypertension predisposes to cardiac structural changes that influence the development of AF such as atrial remodeling. The renin angiotensin aldosterone system has been demonstrated to be a common mechanistic link in the pathogenesis of HTN and AF. Importantly, HTN is one of the few modifiable AF risk factors, and guideline-directed management of HTN may reduce the incidence of AF.

Introduction

Atrial fibrillation (AF) is a major clinical and public health problem in the United States and worldwide. It is estimated that up to 2% of the U.S. adult population suffers from AF.[1] Its prevalence is on the rise and expected to double over the next 25 years with the aging of populations in industrialized nations.[1-4] Through its association with heart failure and stroke, AF exerts a profound negative impact on the quality and quantity of life of millions.[5-8] Hospitalizations and related treatment costs from AF have increased significantly, with more than $2.1 billion spent on AF care in the U.S. alone on an annual basis.[9]

Although antiarrhythmic drugs and ablative therapies reduce AF burden and improve symptoms, no cure exists. This has led many to search for "upstream" or preventative therapies to delay the onset of AF.[10] Our understanding of AF and its causes has improved markedly, with structural and electrical remodeling of the left atrium being increasingly recognized as a process that precedes and contributes to AF vulnerability. Since elevated systemic pressures influence the size and function of the left atrium, uncontrolled hypertension (HTN) is a key contributor to the generation of a substrate vulnerable to AF (Table 1). Hence, antihypertensive therapies may reduce atrial remodeling and hold promise as "upstream" therapies for AF.

Epidemiologic studies have shown that HTN is associated with a 1.8-fold increased risk of developing new-onset AF and a 1.5-fold increased risk of progression to permanent AF.[2,11] Although no randomized studies to date have shown that antihypertensive therapy reduces AF burden, studies suggest that effective treatment of HTN, particularly with renin-angiotensin aldosterone system (RAAS) antagonists, may reduce the likelihood of developing AF by preventing atrial stretch from elevated ventricular filling pressures, atrial fibrosis, and extracellular collagen deposition as well as through several other important mechanisms.[12-16]

Epidemiologic Parallels Between HTN and AF

HTN is the most common cardiovascular disorder and AF is the most common clinically significant arrhythmia. Both conditions are associated with aging and often coexist.[17-20] In some studies, up to 90% of AF patients are observed to be hypertensive (Figure 1).[21-23] Beyond the direct relations between AF and HTN, HTN is also associated with other cardiovascular comorbidities that increase risk for AF, including coronary artery disease, heart failure, metabolic syndrome, chronic kidney disease, and sleep apnea.[24-27]

Higher pulse pressure has also been shown to increase the risk of developing AF.[28] In a prospective study involving Framingham

1.	Hypertension is the most common cardiovascular comorbidity among patients with atrial fibrillation.
2.	Hypertension leads to electrical and structural alterations to the left atrium that predispose to atrial fibrillation.
3.	Both hypertension and atrial fibrillation are associated with autonomic dysfunction and renin-angiotensin-aldosterone-system up-regulation.
4.	Hypertension is a potent risk factor for stroke in patients with atrial fibrillation.
5.	Hypertension is a potent risk factor for bleeding among patients with atrial fibrillation who are treated with anticoagulants.

Table 1. Clinical links between atrial fibrillation and hypertension.

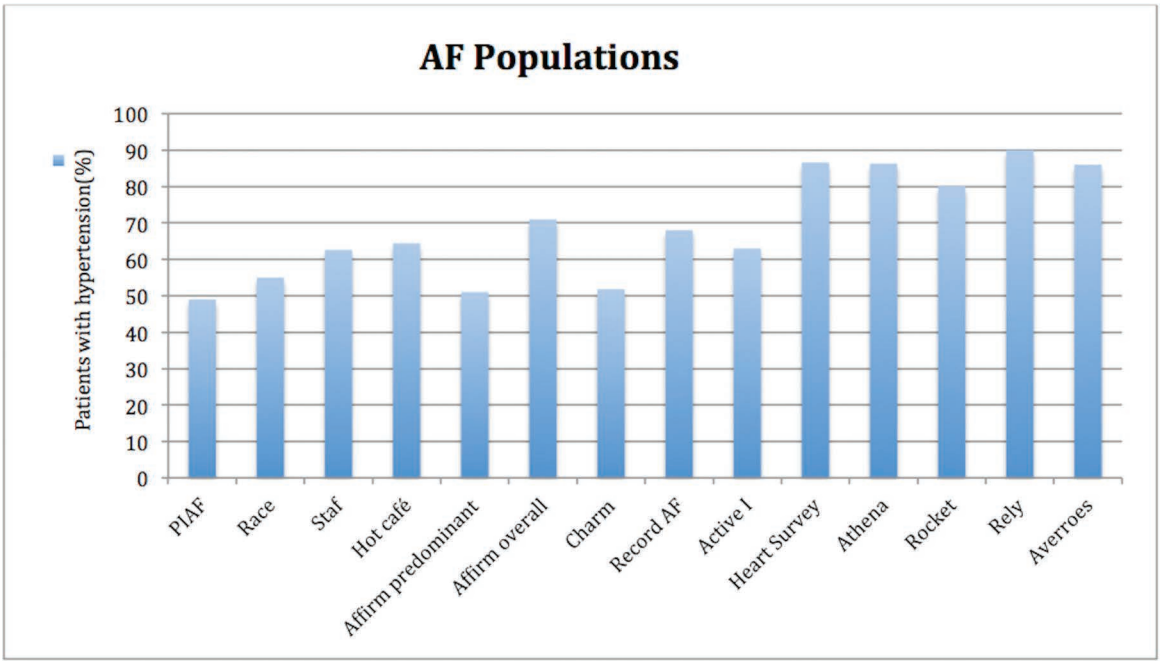

Figure 1. Prevalence of hypertension in atrial fibrillation trials. AF: atrial fibrillation. Adapted with permission from Manolis et al. J Hypertens; 2012;30:239-52.[16]

Heart Study and Offspring participants, each 20 mm Hg increase in pulse pressure was associated with a 24% increased risk of AF over a 20-year follow-up. Notably, models were adjusted for mean blood pressure and other clinical risk factors for both AF and HTN. This suggests that increased pulse pressure may be an independent predictor of arterial stiffness and capture an additional modifiable AF risk element distinct from systolic hypertension.[28]

The relationship between increased left atrial size and AF is well established, with HTN being a potential intermediate causal factor.[29] In a longitudinal follow-up of the Framingham study participants, higher systolic blood pressure and antihypertensive treatment were associated with higher baseline left atrial size and, just as importantly, greater left atrial enlargement over adulthood.[30] Higher pulsatile load on the left atrium promotes dilatation, which in turn leads to a larger tissue area vulnerable to reentry and AF. Therefore, markers of left atrial structural remodeling, including echocardiographic left atrial size or volume, MRI, or CT-based measures of left atrial volume or fibrosis all represent intermediate phenotypes connecting the primary exposure, HTN, to the end-stage phenotype, AF.[30] Notably, there appear to be interactions between HTN and other modifiable AF risk factors, such as body mass, with both exerting a synergistic effect and accelerating atrial remodeling over adulthood.

Atrial Fibrillation and Hypertension: Pathophysiologic Considerations

Hypertension Begets Atrial Fibrillation

AF is a product of electrical and structural atrial remodeling, autonomic perturbations, impaired myocardial mechanics, and metabolism as well as other environmental and heritable factors (Figure 2). Disturbances of atrial architecture result in an increase in susceptibility to AF.[31,32] Renin-angiotensin-aldosterone system activation and HTN are closely linked, as illustrated by the fact that high circulating levels of angiotensin II are seen in hypertensive patients and through the therapeutic effects of RAAS inhibition on systemic pressures.[33] Likewise, components of the RAAS promote AF through direct arrhythmogenic effects of angiotensin II.[34-36] Angiotensin II also promotes AF through direct effects on ion channel structure, function, and distribution (particularly potassium channels) and through proinflammatory mechanisms. Higher angiotensin II and angiotensin converting enzyme (ACE) levels are observed in patients with AF.[34-36]

High circulating aldosterone levels and overexpression of cardiac mineralocorticoid receptors have been documented in human and animal models of AF.[37-39] Aldosterone is therefore another component of the RAAS thought to play a key role in the development of AF through local effects on the myocardium and the cardiac interstitial milieu. Aldosterone exerts its profibrillatory effects by promoting fibrosis through upregulation of matrix metalloproteinases and possibly through direct effects on ion channel function and distribution.[37-39] The contribution of aldosterone to AF independent of its effects on systemic blood pressure is evidenced by the fact that incidence of AF is 12-fold higher in patients with primary hyperaldosteronism compared to matched counterparts with essential HTN.[37] The presence of a strong correlation between RAAS activation, HTN, and AF has led some to promote the use of target-specific agents such as ACE inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) as "upstream therapies" to prevent occurrence and recurrence of AF.[12]

Atrial Fibrillation and Hypertension: Preventive and Therapeutic Implications

The concept of "upstream therapy" in the prevention of incident (primary prevention) and recurrent (secondary prevention) AF is garnering increased attention.[12] Clinical evidence suggests that it may be possible to leverage the potentially beneficial antiarrhythmic properties of antihypertensive medications to prevent or treat AF (Table 2). This concept is theoretically appealing on several levels. First, many patients with or at risk for AF have HTN. Second, neither ablation nor typical antiarrhythmic drug therapies are particularly effective once AF is manifest, and they often have narrow therapeutic-to-toxic indices. Therefore, novel therapies are needed, with attention increasingly shifting to prevention in lieu of treatment. To date, antihypertensive drugs studied in patients with AF include ACEIs, ARBs, and aldosterone receptor antagonists. It is important to note

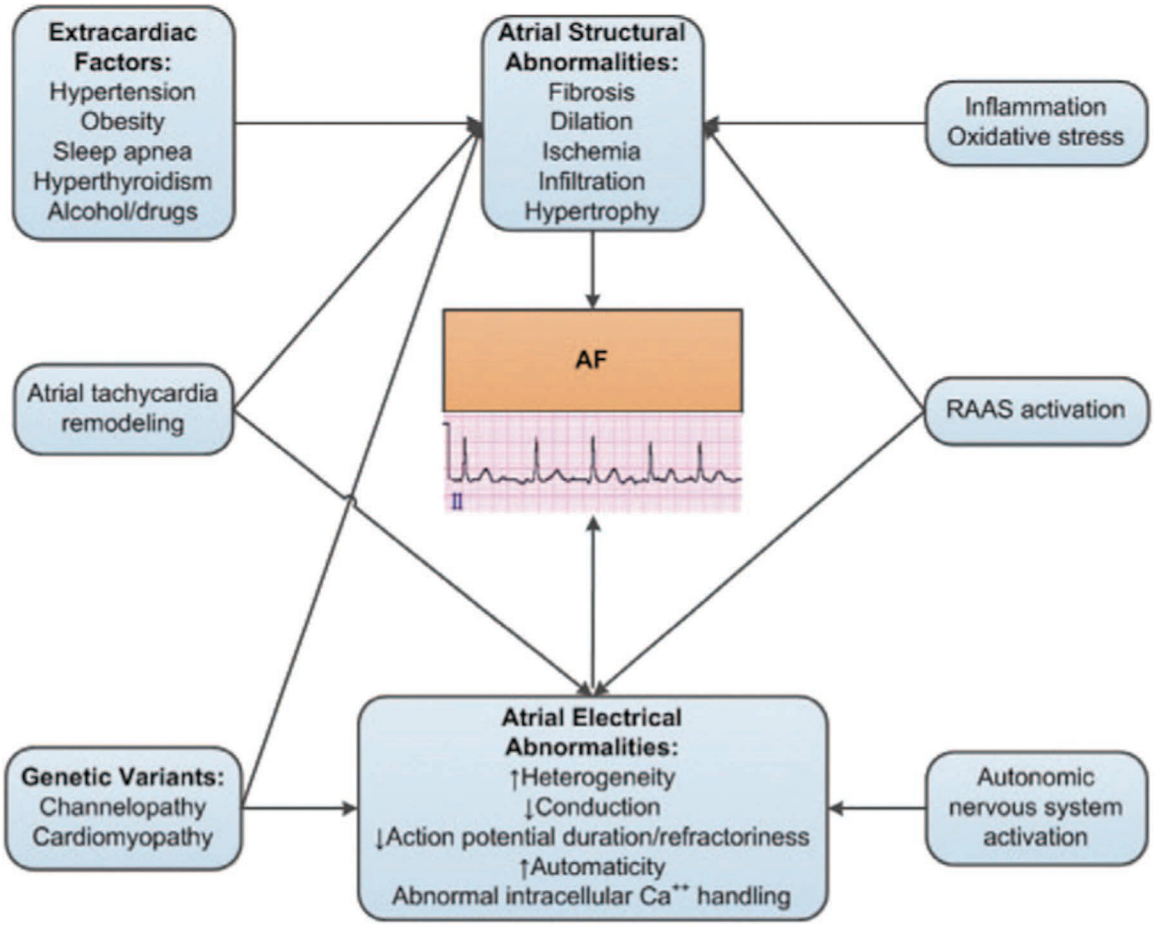

Figure 2. Mechanisms of atrial fibrillation. AF: atrial fibrillation; Ca++: ionized calcium; RAAS: renin-angiotensin-aldosterone system. Adapted with permission from January et al. J Am Coll Cardiol; 2014;64:2305-7.[3]

that most of the studies conducted to date are secondary analyses of trial data. Despite great need, there have been remarkably few prospective randomized clinical studies for AF prevention.[3,12,16]

Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Four meta-analyses have been conducted to summarize the impact of ACEIs and ARBs on the incidence of AF in study participants enrolled in clinical HTN trials.[13,14,40,41] Although the overall trend observed across these trials suggests a benefit in using RAAS inhibitors for AF prevention, only one of the meta-analyses showed a statistically significant risk reduction in the incidence of AF among RAAS-treated patients.[40] In this one and only study showing a significant benefit of RAAS antagonists, a total of 11 randomized controlled clinical trials were analyzed to evaluate the effect of ACEIs and ARBs on AF development. The authors observed that randomization to receive either an ACEI or an ARB was associated with a 23% lower risk for AF (RR = 0.77, 95% CI 0.69-0.86). In another meta-analysis performed by Schneider et al., a 30% lower incidence of AF was observed in ACEI- or ARB-treated patients.[14] In a third meta-analysis by Kalus et al., patients with AF and HTN who were randomized to receive an ACEI or ARB had between 35% and 72% lower rates of incident AF, respectively.[15] Notably, most of the antiarrhythmic benefits derived from ACEIs and ARBs are seen in patients with HTN who have left ventricular hypertrophy or left ventricular dysfunction.[12,42,16]

The impressive antiarrhythmic effects of ARBs observed in the Losartan Intervention for End Point Reduction in HTN (LIFE) study mainly drive the results of the meta-analyses described above.[43] In the LIFE study, new-onset AF occurred in only 150 losartan-treated patients compared to 221 atenolol-treated

1.	Hypertension should be considered in calculating stroke and bleeding risk in patients with atrial fibrillation.
2.	Although as yet unproven in large clinical trials, hypertension remains a therapeutic target of promise in the prevention of atrial fibrillation.
3.	Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is evidence-based in patients with atrial fibrillation and left ventricular systolic dysfunction.
4.	Randomized trials suggest renin-angiotensin-aldosterone system antagonists may have class-specific benefits in preventing atrial fibrillation.
5.	Beta blockers are evidence-based treatments for rate control in atrial fibrillation and are also useful in the treatment of concomitant hypertension.

Table 2. Therapeutic implications of associations between atrial fibrillation and hypertension.

patients (6.8 vs. 10.1 per 1,000 person-years; RR 0.67, 95% CI 0.55-0.83). Furthermore, patients on losartan who had pre-existing AF remained free from recurrences at rates higher than those randomized to receive atenolol. These results were observed despite the fact that losartan and atenolol had similar effects on mean systemic blood pressure, suggesting a RAAS-specific effect. Observations from the LIFE study have been replicated in studies of other RAAS antagonists. For example, a significant effect of trandolapril treatment was observed in the Trandolapril Cardiac Evaluation (TRACE) study on AF prevention.[44] A subanalysis of Studies of Left Ventricular Dysfunction (SOLVD) data also demonstrated 78% lower rates of new-onset AF among enalapril-treated patients.[45]

Despite these promising findings, not all clinical trials have shown a benefit to RAAS blockade with respect to reductions in incident or recurrent AF. For example, in the Japanese Rhythm Management Trial II for Atrial Fibrillation (J-RHYTHM II), patients randomized to treatment with candesartan did not have lower rates of recurrent AF compared to patients treated with amlodipine.[46] However, this study had important limitations, including higher rates of antiarrhythmic drug use in the amlodipine arm compared to the candesartan group, which might have influenced the observed findings. Another important consideration when interpreting the findings of this study is that mechanisms underlying AF, and therefore response to upstream therapies, may vary by racial group just as they do with rates of AF.

The American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines for management of AF recommends the use of ACEIs or ARBs for AF prevention in patients with heart failure and left ventricular dysfunction or HTN (class IIa recommendation in HF patients with left ventricular dysfunction and class IIb recommendation in patients with HTN).[3]

Aldosterone Antagonists

Although the level of evidence supporting routine use of aldosterone receptor antagonists for AF prevention is lower than that for ACEIs or ARBs, several studies suggest a benefit.[37] In animal models of AF, treatment with eplerenone or spironolactone reduced atrial fibrosis, had beneficial effects on atrial ion channel function, and reduced AF inducibility.[47-49] In the Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure (EMPHASIS-HF) clinical trial, eplerenone reduced the incidence of new-onset AF or flutter compared to placebo (HR 0.58, 95% CI 0.35-0.96; $P = 0.034$).[50] Taken in sum, these studies show a clear signal of potential benefit of aldosterone-receptor antagonism as a vehicle for AF prevention in certain high-risk subgroups, such as those with heart failure and reduced systolic function.

Beta Blockers

Although the use of beta blockers is indicated for acute and chronic rate control in AF patients as well as for prevention of sudden cardiac death in patients with AF and HF, beta blockers are generally not considered first-line therapies for most patients with HTN. However, in a systematic review of roughly 12,000 patients with HF, the incidence of new AF was noted to be significantly lower in patients who received beta blockers compared to placebo, with a relative risk reduction of 27% (95% CI 14-38, $P < 0.001$).[51] The findings of the LIFE study, however, suggest a superiority of RAAS antagonists as compared to beta blockers with respect to AF prevention. More data are needed to evaluate the antiarrhythmic properties of beta blockers among patients treated with these agents for HTN. Since stimulation of the sympathetic nervous system from other diseases (e.g., hyperthyroidism) or clinical scenarios (e.g., post-operative state) may precipitate HTN, tachycardia, and AF, beta blockers warrant evaluation in secondary AF.

Calcium Channel Blockers

Like beta blockers, nondihydropyridine calcium channel blockers such as diltiazem and verapamil are used in clinical practice to slow the ventricular response in AF and rapid ventricular rate. Also like beta blockers, such agents are rarely used as antihypertensives. In contrast, dihydropyridine calcium channel blockers such as amlodipine are common and highly effective antihypertensive drugs. Because they effectively reduce pulse pressure, one might imagine a potential benefit for AF prevention. However, studies comparing ACEIs and ARBs to calcium channel blockers have consistently shown superiority of ACEIs and ARBs for AF prevention.[52,53] In a large, longitudinal, matched cohort study including approximately 11,000 patients with HTN, treatment with ACEIs was compared to treatment with calcium channel blockers. New-onset AF as well as AF-related hospitalizations were significantly lower in patients treated with ACEIs compared to those treated with calcium channel blockers.[52] These findings were reproduced in a nested case-control study of 4,661 patients with AF from the United Kingdom's General Practice Research Database.[53] The authors concluded that the use of ACEIs, ARBs, or beta blockers was associated with a lower risk for AF when compared to calcium channel blockers.

Atrial Fibrillation and Hypertension – A Complex Interplay between Thromboembolic and Bleeding Risks

Hypertension and Risk for Thromboembolism in Atrial Fibrillation

The importance of HTN as a stroke risk factor is reflected by its inclusion in all contemporary stroke risk assessment tools, including the CHA2DS2-VASc score.[54] In a cross-sectional longitudinal analysis of data from the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials, there was a significantly higher risk for stroke and systemic embolization among AF patients with more severe HTN compared to individuals with less-severe or no HTN.[55] Looking at it from another perspective but confirming the strong association between HTN, AF, and embolic stroke, a recent population-based study showed that patients with AF and stroke had a 4-fold higher odds of having a history of HTN (OR = 4.5; 95% CI = 1.3-15.6).[56] Further analysis showed that history of HTN was the most important clinical risk factor when predicting future ischemic events in patients with AF (OR 7.1).[56] One topic of current controversy is whether or not aggressive treatment of HTN among therapeutically anticoagulated patients further reduces stroke risk. Another area of uncertainty is whether or not the initiation of anticoagulation in patients with HTN who are at high risk for AF and stroke might prove beneficial.

Hypertension and Risk for Major Bleeding

Hypertension is also a primary risk factor for major hemorrhagic events, including intracranial and fatal bleeding, in patients with AF who are treated with anticoagulation, and it is included in three of the four major bleeding risk scores.[57-59] In fact, HTN has been observed to increase the risk of bleeding by 1.7- to 2.8-fold among anticoagulated patients.[59] While control of systemic HTN is critical to reduce the risk of intracranial hemorrhage, bleeding may occur despite good HTN care since chronic

hypertension may promote vascular fragility and vulnerability to intracranial bleeds.

Conclusion

As the population ages, the burden of HTN and AF will continue to rise. Systemic HTN is the most common and modifiable risk factor for development of AF. Hypertension throughout adulthood leads to cardiac structural and electrical remodeling that predisposes to AF. Antihypertensive medications, including those that block the RAAS pathway, may decrease the risk of incident and recurrent AF. Early treatment of HTN represents a potential opportunity for AF prevention. Large-scale randomized studies are needed to establish a definitive role for antihypertensive therapies in reducing the risk of AF and to evaluate whether or not early initiation of anticoagulation in HTN patients at high risk for AF improves outcomes. Guideline-directed use of RAAS antagonists among high-risk subgroups, including patients with heart failure or diabetes, is strongly recommended as per the American Heart Association's Get with the Guidelines AF campaign.

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Keywords: nonvalvular atrial fibrillation, benign essential hypertension, RAAS pathway, arrhythmias, ACE inhibitors

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