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RENIN-ANGIOTENSIN-ALDOSTERONE-SYSTEM INHIBITORS: TREATMENT AND PREVENTION OF ATRIAL FIBRILLATION

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Atrial Fibrillation (AF) is a source of significant morbidity and mortality. It is estimated that 2.2 million Americans experience paroxysmal or persistent AF. This number is expected to rise with the increasing age of the population and success of treating cardiovascular disease. AF can lead to deep vein thrombosis, worsening heart failure, stroke, and reductions in quality of life.[1]

The current treatment options available to patients with AF have been unsuccessful in finding a satisfactory balance between safety and efficacy. Current antiarrhythmic drugs like amiodarone are effective in maintaining sinus rhythm for patients with AF, but are associated with serious adverse events. Ablative therapy can restore sinus rhythm, but is an invasive procedure that puts patients at risk for procedural stroke and pulmonary vein stenosis.[1] In addition to the limitations of current therapies, there are relatively few modalities for preventing AF in the first place.

The unbalanced benefit to risk ratio in AF has lead to the idea of upstream therapy. Upstream therapy deals with altering physiologic mechanisms that produce an arrhythmogenic substrate with the hopes of preventing AF from developing. Upstream therapies are designed to prevent further damage to the heart, limiting relapses in patients with established AF. Currently, upstream therapy is focused on altering known factors in the pathogenesis of AF including neurohormonal activation, tissue inflammation, oxidative stress, and electrical remodeling.[2]

Specifically, agents that act by inhibiting the Renin-Angiotensin-Aldosterone-System (RAAS) are being examined as upstream therapy. Many large, randomized, controlled trials have shown a serendipitous benefit of preventing both AF relapses and the incidence of new-onset AF with the use of RAAS inhibitors (RAASI's). The objective of this article is to review the clinical evidence of RAASI's in the setting of AF and to discuss the potential utility of these agents in AF therapy.

MECHANISM OF RAAS INHIBITION IN AF

The mechanism of AF prevention through the use of RAASI's is a direct function of modulating the effects of angiotensin II (Ang II) on the heart. By inhibiting the effect of Ang II, RAASI's can prevent the electrical and structural remodeling that is characteristic of AF.[3]

The most frequently encountered changes that occur in AF patients include atrial muscle loss and

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atrial fibrosis. While these changes can be genetically predisposed, they can also be a consequence of disease states that induce atrial dilation. Disease states often associated with atrial dilation include valvular heart disease, hypertension, chronic heart failure (CHF), and coronary artery disease (CAD).[1]

Following atrial stretching, several molecular pathways are activated, including the RAAS. Activation of this system up-regulates the production of Ang II and transforming growth factor-beta1 (TGF-beta1), which in turn leads to increased levels of connective tissue growth factor (CTGF).[1] Patients with persistent AF have a 3-fold increase in ACE levels.[4] These changes in signaling molecules lead to production of fibrous cardiac tissue that can serve as arrhythmogenic substrates. Additionally, myocardial dilation can lead to electrical remodeling that prolongs conduction time and causes conduction abnormalities within cardiac muscle.

Ang II can cause atrial dilation indirectly via its vasoconstrictive actions. As a potent vasoconstrictor, Ang II can increase afterload and cardiac wall pressure. This increased stress on the walls of the heart leads to dilation and the development of arrhythmic substrates.[3] The RAAS can also influence the development of AF through electrical remodeling. Ang II is responsible for shortening the refractory period of the atria and increasing intracellular calcium levels. The increase in intracellular calcium along with a decrease in potassium efflux may cause a decreased refractoriness that leads to arrhythmias.[3] In an animal model, Ang II was shown to significantly decrease the atrial refractory period during rapid atrial pacing, which was reversed with candesartan and captopril.[5]

The induction of the RAAS is associated with many arrhythmia producing changes in the atria. The RAAS system tends to be up-regulated in many chronic, cardiovascular disease states including hypertension, CHF, and CAD. Therefore, the goal of upstream therapy with RAASI's is to mitigate the RAAS's arrhythmogenic influence on the heart in order to preserve atrial function and either prevent relapse of AF or prevent the initial development of AF in at-risk patients.

SUPPORT FOR RAAS INHIBITION IN AF

Much of the evidence supporting RAAS inhibition in AF is derived from post hoc analyses of large, randomized, controlled trials. Since using these agents as upstream therapy is a relatively new concept, there are few trials prospectively designed to study this effect. Until more large scale trials are published, it is difficult to define a true cause and effect relationship with these agents in AF. There is also the question of whether the benefits seen in the post hoc analyses are due to preventing damage and remodeling of the atria or if RAAS inhibition has a direct antiarrhythmic effect on the heart.

PREVENTION OF NEW-ONSET AF

One of the first trials to look at the use of angiotensin converting enzyme inhibitors (ACEI) in the prevention of AF was the Trandolapril Cardiac Evaluation (TRACE) study.[6] In this study, trandolapril was compared to placebo in patients who had a myocardial infarction (MI) with a left ventricular ejection fraction (LVEF) $\leq$ 36%. The primary endpoint was ECG confirmed development of AF. During the 2-4 year follow-up period, patients receiving trandolapril had a significantly reduced risk of developing AF (RR of 0.45; 95% CI 0.26-0.76; $p < 0.01$). When controlling for baseline characteristics between groups, CHF, left ventricular function, male sex, use of digitalis, age, and systolic blood pressure were all significantly related to the development of AF. This study was one of the first large, randomized controlled trials to suggest that ACEI's may have a significant impact on the incidence of AF in patients with left ventricular impairment.[6]

In a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trials, ACEI use was associated with a lower incidence of AF.[8] This study examined patients with a reduced LVEF ($\leq$ 35%) that were randomized to placebo or enalapril 5-20 mg/day. Treatment with enalapril was associated with an absolute risk reduction in the incidence of AF by 18.6% (5.4% of patients in the enalapril group vs. 24% in the placebo treated group; $p < 0.0001$). Even after excluding patients with a history of supraventricular arrhythmias, enalapril demonstrated a close association with a decreased incidence of AF vs. placebo (4.5% vs. 23%, respectively; $p < 0.0001$). The investigators felt that the risk reduction observed in SOLVD was greater than the TRACE study since SOLVD data came from patients with established myocardial dysfunction. In the TRACE study, patients were studied immediately after an MI when atrial remodeling may not yet have occurred.[7] The

Table 1. RAAS inhibition for primary prevention of AF.

STUDY	DESIGN	POPULATION	TREATMENT	MAIN FINDINGS
TRACE[6] (1999)	Post hoc analysis	AMI and reduced LV function	• Trandolapril (n=790) • placebo (n=787)	New-onset AF: trandolapril 5.3% vs. placebo 2.8% (p<0.05)
SOLVD[7] (2003)	Post hoc analysis	Asymptomatic to overt CHF with LVEF ≤ 35%	• Enalapril (n=186) • placebo (n=188)	New-onset AF: enalapril 5.4% vs. placebo 24% (p<0.0001)
SOLVD[8] (2004)	Post hoc analysis	Asymptomatic to overt CHF with LVEF ≤ 35%	• Enalapril (n=3396) • placebo (n=3401)	RR of hospitalization due to AF in enalapril group (patients without AF at study entry): 0.64 (95% CI: 0.46-0.88; p=0.004)
Val-HeFT[9] (2005)	Post hoc analysis	CHF and LVEF ≤ 40%	• Valsartan (n=2205) • placebo (n=2190)	AF occurrences: valsartan 5.12% vs. placebo 7.95% (p<0.0001)
CHARM[10] (2006)	Prescpecified secondary endpoint	CHF and reduced or preserved LVEF	• Candesartan (n=3191) • placebo (n=3188)	New-onset AF: candesartan 5.55% vs. 6.74% (p=0.048)
VALUE[15] (2008)	Prespecified secondary analysis	Aged ≥ 50 y and HTN with at least one CV risk factor	• Valsartan (n=7649) • amlodipine (n=7596)	New-onset AF: valsartan 3.7% vs. amlodipine 4.3% (HR 0.843; 95% CI: 0.713-0.997)
L'Allier et al.[16] (2004)	Retrospective, longitudinal cohort study	Aged ≥ 18 y with HTN (At baseline: AF=2.4%; CHF=3.7%)	• ACEI (n=5463) • CCB (n=5463)	HR for new-onset AF: ACEI 0.85 (95% CI: 0.62-0.89) Incidence ratio of AF related hospitalizations with ACEI 0.74 (95% CI: 0.62-0.89)
LIFE[14] (2005)	Prespecified secondary analysis	Aged 55-80 y with HTN, LVH and no AF	• Losartan (n=4298) • atenolol (n=4182)	New-onset AF: losartan 3.5% vs. atenolol 5.3%: RR 0.67 (95% CI: 0.55-0.83); p<0.001
CAPPP[12] (1999)	Prespecified secondary endpoint	Aged 25-66 y with HTN (At baseline: < 1% with AF or CHF)	• Captopril (n=5492) • diuretic, BB, or both (n=5493)	New-onset AF: captopril 2.1% vs. control 2.5% (NS)
STOP-2[13] (1999)	Prespecified secondary endpoint	Aged 70-84 y with HTN (At baseline: AF=4.7%; CHF=1.9%)	• ACE inhibitors (n=2205) • CCB (n=2196) • diuretic, BB, or both (n=2213)	New-onset AF: No significant difference between groups
HOPE[17] (2007)	Post hoc analysis	Aged ≥ 55 y, high CV risk, and preserved LVEF	• Ramipril (n=4645) • placebo (n=4652)	New-onset AF: Ramipril 2.0% vs. placebo 2.2% (NS)

ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; AMI = acute myocardial infarction; BB = beta blocker; CHF = chronic heart failure; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; HTN = hypertension; LV = left ventricular; LVEF = left ventricular ejection fraction; NSR = normal sinus rhythm: RR = relative risk; SR = sinus rhythm.

SOLVD data also showed that treatment of patients with reduced LVEF had a lower rate of hospitalizations due to AF when treated with enalapril than with placebo.[8]

The reduced incidence of new-onset AF is also seen in patients treated with angiotensin II receptor blockers (ARB's). In the Valsartan Heart Failure (Val-HeFT) trial, the occurrence of AF was examined in patients with CHF who were in normal sinus rhythm at study entry. The valsartan group had a significantly decreased occurrence of AF vs. placebo (5.12% vs. 7.95% p = 0.0001)[9]. Unfortunately, this study did not differentiate between patients with or without a past history of AF so it is unknown if valsartan is associated with a prevention of AF relapse or prevention of new-onset AF. The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study included a planned secondary analysis designed to observe the development of newly diagnosed AF. Across the arms of the CHARM study (preserved ejection fraction of > 40%, and low ejection fraction), candesartan was as-

sociated with a significant decrease in the occurrence of newly diagnosed AF (OR of 0.81; 95% CI 0.66-0.99) vs. placebo. This effect was maintained in the subset of data from the two low ejection fraction studies (OR of 0.78; 95% CI 0.61-0.99). Interestingly, candesartan did not reduce new-onset AF in those patients with a preserved ejection fraction.[10] This finding was later confirmed in the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) Study.[11]

These studies suggest a significant association between a reduced incidence of AF and the use of RAASI's in patients with CHF or decreased ejection fraction. Since RAASI's are associated with improved morbidity and mortality in patients with CHF, post-MI, and reduced LVEF, this data adds another reason for clinicians to evaluate their patients as potential RAASI candidates.

Several studies have evaluated RAASI's in the prevention of new-onset AF in patients without CHF or other structural heart disease. In the Captopril Prevention Project (CAPPP) and Swedish Trial in Old Patients with Hypertension-2 (STOP-2) studies, patients with hypertension were treated with ACEI's or placebo. The difference in the incidence of AF between groups failed to achieve significance.[12,13]

In contrast, the Losartan for End Point Reduction (LIFE) study was a randomized, controlled trial that compared patients with hypertension and no history of AF to losartan or atenolol.[14] Those subjects in the losartan treatment arm were significantly less likely to develop new-onset AF than patients taking atenolol (RR of 0.67; 95% CI 0.55-0.83; $p < 0.001$). Patients treated with losartan were also significantly less likely to experience stroke (HR of 0.49; 95% CI 0.29-0.86; $p = 0.01$) and the overall composite endpoint (HR of 0.60; 95% CI 0.38-0.94; $p = 0.03$).[14] The available evidence seems to support the use of RAASI's in patients with hypertension to help prevent the occurrence of AF (Table 1).

PREVENTION OF AF RELAPSE

Another potential use for RAASI's is the prevention of AF relapse. Since patients with AF are more likely to have some degree of atrial remodeling and structural heart damage, RAASI's may remove some of the burden from the RAAS and help prevent further remodeling.

In 2002, Madrid et al. evaluated patients with recurrent, persistent AF who were either treated with amiodarone or amiodarone in combination with irbesartan.[18] They demonstrated that patients on irbesartan and amiodarone had a 2 month probability of maintaining sinus rhythm after successful cardioversion of 84.79% compared to the 63.16% probability with amiodarone alone ($p = 0.008$). Even after controlling for various patients factors including history of diabetes, irbesartan demonstrated an 81% reduction in the risk of relapsing into AF vs. amiodarone alone (RR of 0.19; 95% CI 0.04-0.86; $p = 0.031$).[18]

A subanalysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial investigated whether treatment with RAASI's prevented AF relapses in patients in the rhythm control arm of the trial.[19] Patients exposed to RAASI's were significantly more likely to have hypertension, history of CHF, CAD, diabetes, and reduced LVEF (defined as less than < 40%). Initially, no significant difference in AF relapse between the groups was found (HR of 0.91; 95% CI 0.77-1.09; $p = 0.31$). However, when patients with a history of CHF or those with moderate to severe left ventricular dysfunction were compared separately, RAASI use was associated with a significantly reduced risk of AF recurrence (HR of 0.63; $p = 0.02$ for CHF and HR of 0.48; $p = 0.04$ for left ventricular dysfunction).[19]

Yin et al. prospectively compared paroxysmal AF recurrence rates in patients taking amiodarone, amiodarone plus losartan, or amiodarone plus perindopril.[20] All patients had preserved LVEF and after co-

Table 2. Changes in echocardiographic findings.[21]

	RAMIPRIL BASELINE	PLACEBO BASELINE	RAMIPRIL FOLLOW-UP	PLACEBO FOLLOW-UP
Left Atrium SI (cm)	4.1 ± 0.3	4.3 ± 0.4	4.0 ± 0.3	4.5± 0.4*
Left Atrium ML (cm)	3.4 ± 0.4	3.6 ± 0.3	3.3 ± 0.3	4.2 ± 0.5*†
Left Atrium area (cm^2)	14.0 ± 2.1	14.9 ± 2.1	13.2 ± 2.0	16.8 ± 1.9*†
LVEF (%)	66 ± 7	65 ± 7	67 ± 6	63 ± 7
LVEDV (mL)	44 ± 5	47 ± 5	43 ± 5	46 ± 7

LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; ML = mediolateral atrial diameter; SI = superoinferior atrial diameter.
* = $p < 0.05$ vs. respective ramipril.
† = $p < 0.05$ vs. respective baseline.

Table 3. RAAS inhibition for prevention of AF relapse.

REFERENCE	DESIGN	POPULATION	TREATMENT	MAIN FINDINGS
Madrid et al.[18] (2002)	R, OL	History of persistent AF > 7 days	• Irbesartan + amiodarone (n=79) • amiodarone (n=75)	AF recurrence: Irbesartan + amiodarone 15.2% vs. 36.8 % amiodarone (p=0.008)
Ueng et al.[23] (2003)	R, OL	Chronic AF > 3 months	• Enalapril + amiodarone (n=70) • amiodarone (n=75)	Patients remaining in SR: enalapril + amiodarone 74.3% vs. amiodarone 57.3%; p=0.021
Madrid et al.[24] (2004)	R, OL	Normotensive with persistent AF > 7 days	• Irbesartan 300mg + amiodarone (n=30) • irbesartan 150mg + amiodarone (n=30) • amiodarone (n=30)	Time to recurrence of AF: both irbesartan groups were significantly more likely to stay in SR
Yin et al.[20] (2006)	R, OL	Lone paroxysmal AF	• Losartan + amiodarone • perindopril + amiodarone • Amiodarone	Relapse of AF: losartan + amiodarone 19% vs. perindopril + amiodarone 24% vs. amiodarone 41% (both groups were significant against amiodarone monotherapy)
Belluzzi et al.[21] (2009)	R, DB	Normotensive with single episode of AF without structural heart abnormalities	• Ramipril (n=31) • placebo (n=31)	AF relapse: ramipril 3 patients vs. placebo 10 patients (p<0.03)
GISSI-AF[22] (2009)	R, DB	NSR with a history of AF and ≥ 1 CV disease risk factor	• Valsartan (n=722) • placebo (n=720)	AF relapse: valsartan 51.4% vs. placebo 52.1% (NS)
AFFIRM[19] (2004)	Retrospective analysis	NSR in the rhythm control arm of AFFIRM	• ACEI or ARB (n=421) • control (n=732)	AF recurrence: patients with history of CHF or LV dysfunction had significantly lower AF recurrence with ACEI or ARB than without

R = randomized; OL = open-label; DB = double-blind; ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; AMI = acute myocardial infarction; BB = beta blocker; CHF = chronic heart failure; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; HTN = hypertension; LV = left ventricular; LVEF = left ventricular ejection fraction; NSR = normal sinus rhythm; RR = relative risk; SR = sinus rhythm.

variate adjustment, amiodarone alone was associated with a significantly higher probability of relapse into AF than those patients treated with amiodarone plus losartan or perindopril ($p = 0.02$). There was no significant difference between losartan and perindopril ($p = 0.47$).[20]

A question that remains is whether RAASI's have a direct antiarrhythmic effect or if they simply reduce the atrial remodeling that increases a patient's risk for AF recurrence. In 2009, Belluzzi et al. studied normotensive patients with no structural heart abnormalities (based on echocardiogram) with ramipril 5 mg daily.[21] Included patients had one episode of lone AF that was cardioverted with propafenone. Patients were randomized to ramipril 5 mg daily or placebo. After a 3 year follow up period, patients taking ramipril had significantly fewer relapses of AF than placebo (3 cases vs. 10 cases, respectively; $p < 0.03$). In addition, patients treated with ramipril had no significant increases in left atrial size, whereas the opposite was true in those treated with placebo ($p < 0.05$) (Table 2). This suggests that RAASI's may prevent relapses of AF in normotensive patients, and by preventing atrial enlargement, may prevent proarrhythmic substrates from forming.[21]

In April, 2009, the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico – Atrial Fibrillation (GISSI-AF) trial were published.[22] This large scale randomized, controlled trial enrolled 1,442 patients with a history of AF and underlying cardiovascular disease, diabetes, or left atrial enlargement. In this study, valsartan was compared to placebo in the prevention of AF relapse. After a mean follow-up of 1 year, no significant differences were observed in AF relapse between groups (51.4% in the valsartan group and 52.1% in the placebo group; $p = 0.73$).[22] One limitation of this study

is the relatively short follow-up; other studies have observed patients for up to 3 years. This may be important given the uncertainty surrounding the length of time necessary to realize RAASI-associated prevention of AF relapse (Table 3).

SUMMARY

The rationale for RAASI therapy in the treatment and prevention of AF is thought to be due to a mitigation of the RAAS's effect on the heart. By inhibiting the RAAS, which is often up-regulated in patients with established heart disease, RAASI's prevent the formation and further development of arrhythmogenic substrates. Studies show conflicting data regarding RASSI's ability to prevent new-onset and relapse of existing AF. Overall, it appears that patients with a history of structural heart disease with lower LVEF achieve the greatest benefit whether they have established AF or not. While further investigation through prospective, large scale trials is needed, clinicians can feel confident in knowing that patients who were already candidates for RAASI therapy may derive an additional benefit from these medications.

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