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# The Role Of Renin Angiotensin System In Atrial Fibrillation

Girish M. Nair. MBBS, MSc., FRCPC, Pablo B. Nery. MD,Calum J. Redpath. MB, ChB, PhD., MRCP, David H. Birnie. MB, ChB, MD, MRCP

*Arrhythmia Service, Division of Cardiology, University of Ottawa Heart Institute, 40 Ruskin Ave, Ottawa, Canada – K1Y 4W7.*

**Abstract**

**Atrial fibrillation (AF) is the most prevalent arrhythmia and its incidence is on the rise. AF causes significant morbidity and mortality leading to rising AF-related health care costs. There is experimental and clinical evidence from animal and human studies that suggests a role for the renin angiotensin system (RAS) in the etiopathogenesis of AF. This review appraises the current understanding of RAS antagonism, using angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB) and aldosterone antagonists (AA), for prevention of AF. RAS antagonism has proven to be effective for primary and secondary prevention of AF in subjects with heart failure and left ventricular (LV) dysfunction. However, most of the evidence for the protective effect of RAS antagonism is from clinical trials that had AF as a secondary outcome or from unspecified post-hoc analyses. The evidence for prevention in subjects without heart failure and with normal LV function is not as clear. RAS antagonism, in the absence of concomitant antiarrhythmic therapy, was not shown to reduce post cardioversion AF recurrences. RAS antagonism in subjects undergoing catheter ablation has also been ineffective in preventing AF recurrences.**

## Introduction

Atrial Fibrillation (AF) is the most commonly encountered cardiac arrhythmia and affects 1% of the North American population. The prevalence of AF increases to 8-10% in people older than 80 years.[1-4] AF independently increases the risk of heart failure, stroke, dementia and mortality. There is also a steep increase in AF related morbidity and hospital admissions with increasing age.[5-11] The rising burden of AF and related health care costs are responsible for placing a heavy economic burden on health care systems around the world.[12-16] Anti-arrhythmic medications and non-pharmacological interventions, such as catheter ablation, aimed at secondary prevention of AF have thus far been unsuccessful in curing AF.[17,18] There is a pressing need for primary and secondary prevention strategies to reduce AF related morbidity, mortality and health care costs.[2,15,19-21] This review appraises the role of the Renin-Angiotensin system (RAS) in the etiopathogenesis of AF and the evidence for therapeutic RAS blockade in primary and secondary prevention of AF.

**Key Words:**
Atrial Fibrillation, Renin Angiotensin System, Angiotensin Converting Enzyme- Inhibitors, Angiotensin Receptor Blockers, Aldosterone Antagonists, Angiotensin Converting-Enzyme Gene Polymorphism, Clinical Trials; Primary And Secondary Prevention, Review.

**Disclosures:**
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**Corresponding Author:**
Girish M. Nair. MBBS, MSc., FRCPC
H-1285 B
University of Ottawa Heart Institute
40 Ruskin Ave, Ottawa – K1Y 4W7

## The Renin Angiotensin System And Human Atrial Fibrillation

RAS is an important neuro-endocrine/paracrine system involved in the regulation of multiple cardiovascular, pulmonary and renal processes in humans.[22] Systemic hypertension and heart failure are the most important risk factors associated with the development of AF.[3,6,23,24] The activation of RAS plays an integral part in the neuro-humoral processes leading to changes seen in systemic hypertension and heart failure. There is some evidence to suggest that RAS is associated with the development of AF in subjects with systemic hypertension and heart failure.[22,25,26] In addition multiple RAS gene polymorphisms have been linked to the development of AF in subjects with known conditions that directly or indirectly result in increased left atrial pressure, such as systemic hypertension or heart failure.[27-32] Analysis of human atrial myocytes in subjects undergoing cardiac surgery has demonstrated increased tissue levels of angiotensin converting enzyme (ACE) and angiotensin II (AT-II) receptors in subjects with AF compared to those in sinus rhythm.[33] Reduced density of AT-II -type 1 receptors, responsible for atrial fibrosis subjects with AF, was also noted and this was thought to be secondary to down regulation in response to high tissue ACE levels.[34] The activation of RAS with consequent electrical and ultrastructural changes, called "atrial remodeling", is thought to play a role in the development of AF in humans.

## Postulated Mechanisms Linking The Renin Angiotensin System And Atrial Fibrillation (See Table 1)

Activation of RAS in hypertension and heart failure results in Angiotensin II mediated elevation in left atrial (LA) pressure, secondary to rise in left ventricular end diastolic pressure (LVEDPP).[35-37] Atrial dilatation is associated with stretch related alteration in ion-channels that is believed to be responsible for electrophysiological changes such as shortened refractory periods (electrical remodeling).[38-41] Prolonged activation of RAS results in high myocardial tissue levels of ACE and density of AT-II receptors triggering inflammation and fibrosis. These effects are mediated by fibroblast-derived cytokines such as transforming growth factor-β (TGF-B) and AT II receptor activated phosphorylation cascade causing release of mitogen-activated protein kinases (MAPK). Extensive atrial collagen deposition results from uncontrolled extracellular matrix metabolism and angiotensin II mediated modulation of matrix –metalloproteinases (structural remodeling). AF is considered to be one of the clinical manifestations of atrial remodeling.[22,25,42,43] Animal models of rapid atrial pacing induced AF have shown high atrial tissue levels of ACE, chymase and angiotensinogen. Increased production of tissue level AT II mediated by paracrine activation of ACE, chymase and angiotensinogen is also thought to be responsible for atrial remodeling leading to AF. The cascade of events leading up to AF has been summarized in Figure 1.

Interruption of key steps in the RAS cascade (RAS antagonism) using angiotensin converting enzyme inhibitors (ACE-I), angiotensin-II receptor blockers (ARB) and aldosterone antagonists (AA) has been shown to reverse some of the electrical and ultrastructural changes in patients with AF.[44-46] The important basic science data has been summarized in Table 1.

## The Renin Angiotensin System Gene Polymorphisms And Atrial Fibrillation

The evidence linking RAS to atrial remodeling in AF and the inherent variation among individuals with respect to the extent and consequences of RAS activation had led investigators to suspect a role for genetic polymorphisms in the ACE gene. The human

**Table 1:** Summary of studies demonstrating the role of the renin-angiotensin system (RAS) in atrial remodeling and reversal of atrial remodeling after pharmacological antagonism of RAS

| Mechanism | Author | Experimental Model | Main Findings |
|---|---|---|---|
| Electrical Remodeling | Wijffels MC, et al.[96] | Goat; Artificial AF maintenance using pacemaker | AERP shortening; increase in rate, inducibility and stability of AF |
| Electrical and Structural Remodeling | Sakabe M, et al.[97] | Canine; Pacing induced AF; Placebo vs. Enalapril | Enalapril prevented AF and tachycardia-mediated cardiomyopathy by suppressing interstitial fibrosis, connexin 43 over-expression and conduction delay |
| Electrical Remodeling | Laszlo R, et al.[98] | Rabbit; Rapid pacing induced atrial remodeling; Enalapril Pretreatment | Increases iCa,L current density, no effect on Ito current density. Beneficial in preventing early remodeling in AF model |
| Electrical Remodeling | Doronin SV, et al.[99] | Canine and Human Cell Lines | AT-II type 1 receptor complex associates with Kv4.3 alpha subunit. AT-II stimulation raises the activation voltage threshold to more positive values |
| Electrical Remodeling | Nakashima H, et al. [100] | Canine; Rapid atrial pacing; control, candesartan, captopril and AT- II | AERP unchanged with candesartan and captopril pretreatment. AT-II linked to electrical remodeling |
| Electrical and Structural Remodeling | Kumagai K, et al.[101] | Canine; Rapid atrial pacing; Candesartan pretreatment compared to control | AERP unaltered; Lesser interstitial fibrosis and shorter intra-atrial conduction time in candesartan treated animals |
| Structural Remodeling | Milliez P, et al.[102] | Rat; Post MI- Heart Failure model; spironolactone, lisinopril or atenolol | Atrial fibrosis reduced by spironolactone |
| Electrical Remodeling | Tillmann HC, et al.[103] | Human; Action potential duration before and after aldosterone infusion | Aldosterone increases monophasic action potential duration |
| Electrical Remodeling | Cheng CC, et al.[104] | Rabbit pulmonary vein cardiomyocytes, whole cell patch clamp; heat stress | Heat stress attenuated the electrophysiological effects of AT-II |
| Electrical and Structural Remodeling | Reil JC, et al.[26] | Rat; Aldosterone infusion | Increase in p-wave duration, total right atrial activation time, increase in atrial fibroblasts and interstitial collagen, atrial myocyte hypertrophy |
| Structural Remodeling | Crabos M, et al.[105] | Rat adult cardiac fibroblast culture | AT-II, via AT-II- Type 1 receptors, mediates cardiac fibroblast growth and increases collagen synthesis in cardiac tissue |
| Structural Remodeling | Lee AA, et al.[106] | Rat adult cardiac fibroblast culture | AT-II effects on myocardium mediated by production and release of TGF-beta 1 by cardiac fibroblasts |
| Structural Remodeling | Kallergis EM, et al. | Human; serum markers of collagen type I turnover | Markers of collagen synthesis and breakdown were increased in subjects with AF compared to those in sinus rhythm. Subjects with higher burden of AF had more intense evidence of increased collagen synthesis and breakdown. |
| Structural Remodeling | Goette A, et al.[33] | Human; Atrial tissue samples from open heart surgery subjects | ACE and extracellular signal related kinase (Erk1/Erk2) increased in subjects with AF and may be responsible for atrial fibrosis |
| Structural Remodeling | Goette A, et al.[34] | Human; Atrial tissue samples from open heart surgery subjects | AT-II Type 1 and 2 (AT1 and AT2) receptors were analysed. AT1 receptor density was reduced and AT2 receptor density was increased in subjects with AF. This was associated with increased interstitial fibrosis. |
| Structural Remodeling | Dahl JS, et al.[107] | Human; Subjects with aortic valve replacement treated with Candesartan; Placebo controlled prospective study | Candesartan treatment resulted in greater LV mass index reduction, improvement in LV systolic function and greater reduction in LA volume |
| Electrical and Structural Remodeling; Arrhythmogenesis | Xiao HD, et al.[108] | Mouse; ACE 8/8 with 4.3 fold increased levels of cardiac angiotensin II levels | Atrial fibrosis, morphological changes resulting in atrial fibrillation and conduction block |

AERP: Atrial effective refractory period; AF: Atrial fibrillation; iCaL: long acting L-type calcium ion channel; AT-II: Angiotensin II; MI: Myocardial infarction; TGF: Transforming growth factor

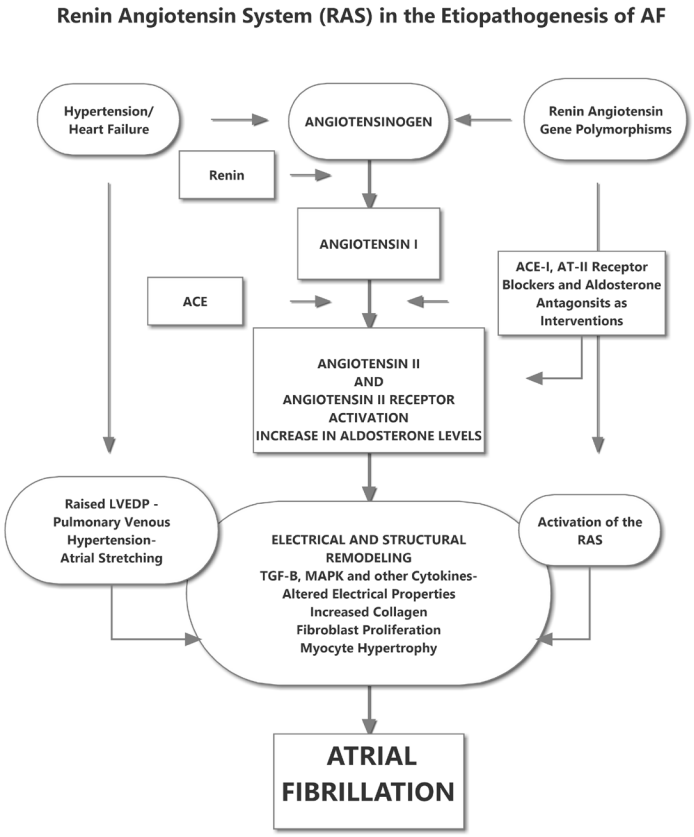


**Figure 1:** Figure summarizing the role of RAS in the etiopathogenesis of AF

RAS: Renin angiotensin system; LVEDP: Left Ventricular End Diastolic Pressure; TGF: Transforming growth factor; MAPK: Mitogen-activated protein kinase; ACE-I: Angiotensin converting enzyme; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker

ACE gene is situated in chromosome 17q23.3 and demonstrates a polymorphism consisting of insertion (1) or deletion (D) in the intron.[16] Consequently three genotypes are encountered in human populations- homozygous D/D and I/I and heterozygous I/D. ACE I/D polymorphism accounts for half of the variance noticed in ACE levels in humans, with the D/D alleles manifesting highest levels of the enzyme.[47] The I/D heterozygous polymorphism has been associated with cardiovascular diseases including left ventricular hypertrophy, essential hypertension, dilated cardiomyopathy and myocardial infarction.[48] ACE I/D polymorphism has been shown to increase the risk for development of AF in case-control studies.[27,49] ACE D/D polymorphism has been shown to be associated with poor response to anti-arrhythmic medications in subjects with AF.[28] ACE I/D polymorphisms have also been identified in certain cases of nonfamilial AF.[27] A recent meta-analysis of case-control studies failed to demonstrate a significant association between the ACE I/D polymorphism and AF risk. However, there was a significant association noted between the I/D polymorphism and AF risk in subjects with hypertension.[31] Another prospective study evaluating 238 consecutive subjects with paroxysmal or persistent AF undergoing catheter ablation found that the ACE D/D homozygous gene variant to be associated with an increased risk of post ablation AF recurrence.[50]

The aldosterone synthase (CYP11B2) T-344C gene polymorphism and resultant raised aldosterone levels have been independently linked to an increased risk of AF in subjects with symptomatic heart failure (left ventricular ejection fraction <40%).[29] A more recent case-control study in 620 Chinese subjects showed that the aldosterone synthase (CYP11B2) T-344C gene polymorphism (the CC homozygous allele) was associated with echocardiographic markers of atrial remodeling in hypertensive subjects. However, the distribution of the different alleles of this gene (TT/TC/CC) did not differ among hypertensive and normotensive subjects.[30]

## Renin Angiotensin System Antagonism And Primary Prevention Of Atrial Fibrillation (Table 2)

### Heart Failure Trials

A Retrospective, sub-group analyses from multiple large trials evaluating the role of RAS antagonism in subjects with heart failure and LV systolic dysfunction have found a lower incidence of new-onset AF.[51-54] Systematic reviews of these studies have demonstrated a 21-50% risk-reduction for new-onset AF in heart failure subjects receiving RAS antagonists.[55-64] However, RAS antagonism in subjects with heart failure and preserved LV systolic function has not shown benefit in preventing new onset AF.[65]

### Systemic Hypertension Trials

Systematic review of hypertension trials found a 25% reduction in new-onset AF. This was principally due to a 33% reduction noted in one trial evaluating losartan for AF prevention.[66-71]

### Post Myocardial Infarction Trials

Two trials have evaluated the incidence of new-onset AF in subjects treated with RAS antagonists following myocardial infarction (MI). Subjects with impaired LV function following MI had lower incidence of AF after treatment with trandolapril. The GISSI-3 trial reported a lower incidence of new-onset AF in post MI subjects treated with lisinopril. However, about a third of subjects showed AF on their admission EKG bringing into question whether this study truly evaluated RAS antagonism for primary prevention of AF.[64,72]

### Subjects With Multiple Cardiovascular Risk Factors

RAS antagonism (ramipril and telmisartan) for prevention of major adverse cardiac events in patients with multiple cardiovascular risk factors has not shown a reduction in the incidence of AF.[73,74]

### Post-Cardiac Surgery Trials

A prospective, multicenter analysis of subjects who had undergone coronary artery bypass graft (CABG) surgery found that postoperative use of ACE-I was associated with reduction in new-onset AF.[75] A randomized trial in subjects undergoing cardiac surgery demonstrated that the use of ACE-I or the combination of ACE-I and candesartan reduced postoperative AF. However, this trial enrolled a relatively small number of subjects (N= 60) and was not adequately powered to answer the primary hypothesis that RAS antagonism was capable of reducing the incidence of AF post cardiac surgery[76] Subgroup analyses from two large retrospective observational studies in patients undergoing cardiac surgery failed to demonstrate a protective effect for RAS antagonism.[77,78]

## Renin Angiotensin System Antagonism And Secondary Prevention Of Atrial Fibrillation (Table 3)

### Prevention Of Paroxysmal And Recurrent Persistent AF

The GISSI-AF trial did not demonstrate an additional benefit for adding ARB (Valsartan) to ACE-I therapy for prevention of AF recurrence.[79] Three recent trials evaluating the role of RAS antagonism (J-RHYTHMII, Fogari et al. and ANTIPAF) showed conflicting results, with two of the trials (J-RHYTHM II and ANTIPAF) failing to show any benefit of RAS antagonism for

**Table 2:** Summary of clinical studies evaluating RAS antagonism for primary prevention of AF

| Patient Population | Author | Subjects Enrolled | Study Interventions | Study Interventions | Principal Findings |
|---|---|---|---|---|---|
| Post – MI; Heart Failure | Pedersen OD, et al.[64] | 1,577 | Trandolapril vs. Placebo | RCT; AF primary outcome of trial | Reduced AF incidence |
| Subjects with multiple CV risk factors; Intolerant to ACE-I | Yusuf S, et al.[74] | 5,926 | Telmisartan vs. Placebo | RCT; AF primary outcome of trial | No effect on AF incidence |
| Post Cardiac Surgery | Ozaydin M, et al.[76] | 128 | ACE-I with Candesartan vs. ACE-I vs. controls | RCT; Small sample size and not adequately powered | Reduced AF incidence |
| Post - MI | Pizzetti F, et al.[72] | 17,944 | Lisinopril vs. Placebo | Post-hoc analysis of RCT | Reduced AF incidence |
| Hypertension | Hansson L, et al. [66] | 6,614 | Enalapril or Lisinopril vs. older AHT medications | Post-hoc analysis of RCT | No effect on AF incidence |
| Hypertension | Hansson L, et al.[67] | 10,985 | Captopril vs. BB or diuretics | Post-hoc analysis of RCT | No effect on AF incidence |
| Hypertension | Wachtell K, et al.[69] | 8,851 | Losartan vs. BB | Post-hoc analysis of RCT | Reduced AF incidence |
| Hypertension | Schmieder RE, et al.[71] | 15,245 | Valsartan vs. Amlodipine | Post-hoc analysis of RCT | Reduced AF incidence |
| Heart Failure | Vermes E, et al.[51] | 374 | Enalapril vs. Placebo | Post-hoc analysis of RCT | Reduced AF incidence |
| Heart Failure | Maggioni AP, et al.[52] | 4,395 | Valsartan vs. Placebo | Post-hoc analysis of RCT | Reduced AF incidence |
| Heart Failure | Ducharme A, et al.[65] | 6,379 | Candesartan vs. Placebo | Post-hoc analysis of RCT | Reduced AF incidence |
| Heart Failure | Swedberg K, et al.[54] | 1,794 | Eplerenone | Post-hoc analysis of RCT | Reduced AF incidence |
| Subjects with multiple CV risk factors | Salehian O, et al.[73] | 8,335 | Ramipril vs. Placebo | Post-hoc analysis of RCT | No effect on AF incidence |
| Post Cardiac Surgery | Mathew JP, et al.[75] | 4,657 | ACE-I | Prospective, observational study | Reduced AF incidence |
| Hypertension | L'Allier PL, et al.[68] | 10,926 | ACE-I vs. CCB | Retrospective, longitudinal, cohort analysis | Reduced AF incidence |
| Hypertension | Schaer BA, et al.[70] | 23,303 | ACE-I or ARB vs. BB vs. CCB | Nested Case-control | Reduced AF incidence |
| Post Cardiac Surgery | White CM, et al.[77] | 338 | ACE-I or ARB vs. controls | Observational study | No effect on AF incidence |
| Post Cardiac Surgery | Rader F, et al.[78] | 6744 | ACE-I or ARB vs. controls | Observational study; propensity matched | No effect on AF incidence |

MI: Myocardial infarction; RCT: Randomized controlled trial; AF: Atrial fibrillation; AHT: Anti hypertensive treatment; BB: Beta blockers; CCB: Calcium channel blockers; ACE-I: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker

secondary prevention of AF.[80-82] RAS antagonism does not seem to be effective for secondary prevention of AF in subjects without structural heart disease or LV dysfunction.

**Prevention Of Recurrent AF After Catheter Or Surgical AF Ablation**

RAS antagonism following catheter ablation has not proven to be effective in reducing AF recurrence.[83-85] In contrast a recent study in subjects undergoing minimally invasive surgical ablation for AF showed that Irbesartan reduced the incidence of AF recurrence.[86]

**Prevention Of Paroxysmal And Recurrent Persistent AF**

Multiple small prospective, randomized trials have demonstrated the benefit of RAS antagonism for preventing post cardioversion recurrence, in subjects with persistent AF. The benefit of RAS antagonism in this setting is complementary to concomitant antiarrhythmic medications, usually with amiodarone.[87-93] A well-designed prospective, randomized- controlled trial (CAPRAF) failed to demonstrate the efficacy of candesartan for prevention of post cardioversion AF recurrence. In contrast to the previously mentioned trials patients in the CAPRAF trial did not receive concomitant antiarrhythmic medications before and after cardioversion.[94,95]

## Conclusions:

There is experimental and clinical evidence from animal and human studies that suggests a role for RAS in the etiopathogenesis of AF. Genetic polymorphisms of the ACE and aldosterone synthase genes have been linked to the development of AF in subjects with pre-existent risk factors for AF such as systemic hypertension and heart failure. RAS antagonism has shown to reduce the incidence of AF in subjects with heart failure and left ventricular (LV) dysfunction. However, most of the evidence for the protective effect of RAS antagonism is from clinical trials that had AF as a secondary outcome or from unspecified post-hoc analyses. The evidence for prevention in subjects without heart failure and normal LV function is not as clear. RAS antagonism, in the absence of concomitant antiarrhythmic therapy, was not shown to reduce post cardioversion AF recurrences. RAS antagonism in subjects undergoing catheter ablation has also been ineffective in preventing AF recurrences. There is need for ongoing research to identify novel targets for intervention and develop effective therapeutic agents to combat the rising burden of AF.

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**Table 3: Summary of clinical studies evaluating RAS antagonism for secondary prevention of AF**

| Patient Population | Author | Subjects Enrolled | Study Interventions | Study Design | Principal Findings |
|---|---|---|---|---|---|
| Paroxysmal AF | Gissi-AF Disertori M, et al.[79] | 1,442 | Valsartan vs. Placebo | RCT; AF primary outcome of trial | No effect on AF recurrence |
| Lone Paroxysmal AF | Yin Y, et al.[111] | 177 | Losartan with Amiodarone vs. Perindopril with Amiodarone vs. Amiodarone | RCT; AF primary outcome of trial | ACE-I and ARB with Amiodarone reduced AF recurrence |
| Paroxysmal AF; Hypertension | Fogari R, et al.[112] | 222 | Losartan with Amiodarone vs. Amlodipine with Amiodarone | RCT; AF primary outcome of trial | ARB with Amiodarone reduced AF incidence |
| Paroxysmal AF; Hypertension | Fogari R, et al.[113] | 369 | Valsartan vs. Ramipril vs. Amlodipine | RCT; AF primary outcome of trial | ACE-I and ARB reduced AF recurrence |
| Paroxysmal AF; Hypertension | Yamashita T, et al.[80] | 318 | Candesartan vs. Amlodipine | RCT; AF primary outcome of trial | No effect on AF recurrence |
| Paroxysmal AF; Hypertension and metabolic syndrome | Fogari R, et al.[81] | 391 | Telmisartan vs. Ramipril vs. Amlodipine | RCT; AF primary outcome of trial | Telmisartan more effective than Ramipril in reducing AF recurrence |
| Paroxysmal AF | Goette A, et al.[82] | 430 | Olmesartan vs. Placebo | RCT; AF primary outcome of trial | No effect on AF recurrence |
| Post-Surgical Ablation | Wang JG, et al.[86] | 83 | Irbesartan vs. Control | RCT; AF primary outcome of trial | Reduced AF recurrence |
| Post-Cardioversion | Tveit A, et al.[94] | 171 | Candesartan vs. Placebo | RCT; AF primary outcome of trial | No effect on AF recurrence |
| Post-Cardioversion | Madrid AH, et al.[88] | 154 | Irbesartan with Amiodarone vs. Amiodarone | RCT; AF primary outcome of trial | ARB with Amiodarone reduced AF recurrence |
| Post-Cardioversion (Lone AF) | Madrid AH, et al.[90] | 90 | Irbesartan (150 or 300 mg) with Amiodarone vs. Amiodarone | RCT; AF primary outcome of trial | ARB with Amiodarone reduced AF recurrence in a dose dependent fashion |
| Post-Cardioversion | Ueng KC, et al.[89] | 145 | Enalapril with Amiodarone vs. Amiodarone | RCT; AF primary outcome of trial | ACE-I with Amiodarone reduced AF recurrence |
| Post-Cardioversion | Belluzzi F, et al.[93] | 62 | Ramipril vs. Placebo | RCT; AF primary outcome of trial | Reduced AF recurrencee |
| Chronic AF with Congestive Heart Failure | Van den Berg MP, et al.[87] | 30 | Lisinopril vs. Placebo | RCT; AF not primary outcome, exercise capacity primary outcome | Non-significant decrease in AF recurrence |
| Paroxysmal AF | Murray KT, et al.[109] | 1,153 | ACE-I/ARB vs. control | Post-hoc RCT | No effect on AF recurrence |
| Paroxysmal AF | Palardy M, et al.[110] | 403 | ACE-I/ARB with Amiodarone vs ACE-I/ ARB with Sotalol/Propafenone vs. Sotalol/ Propafenone vs. Amiodarone | Post-hoc RCT | No effect on AF recurrence |
| Paroxysmal AF | Komatsu T, et al.[114] | 58 | Enalapril with Amiodarone vs. Amiodarone | Retrospective analysis | ACE-I with Amiodarone reduced AF recurrence |
| Post-Catheter Ablation | Richter B, et al.[115] | 234 | ACE-I or ARB vs. Statins vs. combination Statin with ACE-I or ARB | Prospective non-RCT | No effect on AF recurrence |
| Post-Catheter Ablation | Al Chekakie MO, et al.[83] | 177 | ACE-I or ARB vs. Statins | Retrospective analysis | No effect on AF recurrence |
| Post-Catheter Ablation | Zheng B, et al.(84) | 139 | ACE-I or ARB vs. Control | Retrospective analysis | No effect on AF recurrence |
| Post-Catheter Ablation | Patel D, et al.(85) | 372 | ACE-I or ARB with Statins vs. Control | Retrospective analysis | No effect on AF recurrence |

MI: Myocardial infarction; RCT: Randomized controlled trial; AF: Atrial fibrillation; AHT: Anti hypertensive treatment; BB: Beta blockers; CCB: Calcium channel blockers; ACE-I: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker

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