REVIEW

Inhibition of the Renin-Angiotensin System for Prevention of Atrial Fibrillation

THEODOROS ZOGRAFOS, M.D. and DEMOSTHENES G. KATRITSIS, M.D., PH.D.
From the Department of Cardiology, Athens Euroclinic, Athens, Greece

Atrial fibrillation (AF) is a source of considerable morbidity and mortality. There has been compelling evidence supporting the role of renin-angiotensin system (RAS) in the genesis and perpetuation of AF through atrial remodeling, and experimental studies have validated the utilization of RAS inhibition for AF prevention. This article reviews clinical trials on the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) for the prevention of AF. Results have been variable, depending on the clinical background of treated patients. ACEIs and ARBs appear beneficial for primary prevention of AF in patients with heart failure, whereas they are not equally effective in hypertensive patients with normal left ventricular function. Furthermore, the use of ACEIs or ARBs for secondary prevention of AF has been found beneficial only after electrical cardioversion. Additional data are needed to establish the potential clinical role of renin-angiotensin inhibition for prevention of AF. (PACE 2010; 33:1270–1285)

atrial fibrillation*, *renin*, *angiotensin

The Burden of Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and a source of considerable morbidity and mortality. The presence of AF accounts for a 50–90% increased risk for overall mortality in the Framingham Heart Study.[1] AF is also associated with significant morbidity, including a four- to fivefold increased risk for stroke,[2,3] a twofold increased risk for dementia,[4,5] and a tripling of risk for heart failure.[3] In the Framingham Study, the percentage of strokes attributable to AF increases steeply from 1.5% at 50–59 years of age to 23.5% at 80–89 years of age.[2] AF and its associated morbidity represent a significant socio-economic burden on the health-care system consuming between 0.9% and 2.4% of total National Health Service expenditure in the UK, while in the USA, total Medicare costs are 8.6–22.6% higher for patients with AF in all age-sex strata.[6,7] Additionally, the Euro Heart Survey on AF identified inpatient care and interventional procedures as the principal components of the increased economic burden posed by AF.[8] Consequently, treatment of patients with AF and, more importantly, primary or secondary prevention of AF, may yield significant benefits by reducing mortality and morbidity as well as health-care costs.

The recognition of novel risk factors for the development of AF and the fact that current antiarrhythmic drug therapy to maintain sinus rhythm is limited by inadequate efficacy and potentially serious adverse effects,[9] have increased interest in novel therapeutic approaches that target AF substrate development.[10] Among them, the inhibition of the renin-angiotensin-aldosterone system (RAAS) has been considered useful in the primary and secondary prevention of AF, particularly in patients with left ventricular hypertrophy (LVH) or heart failure.

The RAAS is a major endocrine/paracrine system involved in the regulation of several cardiovascular processes.[11] Its primary mediator, angiotensin II, is an octapeptide, formed from the liver-derived 485-aminoacid precursor angiotensinogen through a process involving the enzymatic activities of renin and angiotensin-converting enzyme (ACE).[10] Angiotensin II binds to the angiotensin II type 1 (AT1) receptor, which mediates the pathways that lead to vasoconstriction and water retention, increased renal tubular sodium reabsorption, impaired endothelial function, stimulation of connective tissue deposition, and low-density lipoprotein cholesterol transport. Angiotensin II also binds to the angiotensin II type 2 (AT2) receptor that mediates vasodilation, decreases renal tubular sodium reabsorption, improves endothelial function, and inhibits cell growth and connective tissue deposition. These opposing effects of the two receptors are believed to be regulated through

There is no conflict of interest to be disclosed.

Address for reprints: D. Katritsis, M.D., Ph.D., Athens Euroclinic, 9 Athanassiadou Street, Athens 11521, Greece. Fax: 210 6416661, e-mail: dkatritsis@euroclinic.gr

Received December 9, 2009; revised March 23, 2010; accepted May 21, 2010.

doi: 10.1111/j.1540-8159.2010.02832.x

©2010, The Authors. Journal compilation ©2010 Wiley Periodicals, Inc.

receptor expression patterns. In adults, AT1 is constitutively expressed in a wide range of tissues of the cardiovascular, renal, endocrine, and nervous system. By contrast, AT2 expression is activated during stress and is mainly restricted to the pancreas, heart, kidney, brain, adrenals, and vasculature.[12] Three classes of antihypertensive drugs that involve inhibition of the RAAS have been developed. Angiotensin receptor blockers (ARBs) modulate blood pressure by inhibiting the activation of the AT1 receptor by angiotensin II. In doing so, a feedback mechanism increases angiotensin II synthesis, which, during stress, leads to AT2 activation. ACE inhibitors (ACEIs) modulate blood pressure by inhibiting ACE-mediated production of angiotensin II. Recently, a direct renin inhibitor has been developed that blocks RAAS further upstream.[12]

A growing body of evidence implicates angiotensin II and the RAAS in the development and maintenance of AF and supports the beneficial effects of ACEIs and ARBs in AF treatment.

The Role of RAAS in the Pathogenesis of AF

Atrial Stretch and AF

Atrial arrhythmias frequently occur under conditions associated with atrial dilatation.[13] The effect of atrial pressure in atrial refractoriness was evaluated in several animal models as well as in humans.[14–16] Increased atrial pressure results in an increased susceptibility to AF that is associated with shortening of the atrial effective refractory period (AERP), possibly by opening of stretch-activated ion channels.[17] There is evidence that these changes are completely reversible after the release of the atrial stretch, resulting in prompt termination of AF.[14]

The effects of angiotensin on left atrial pressure have been long known, with angiotensin increasing left atrial systolic pressure through increased left ventricular end-diastolic pressure.[18] Immediate or sustained reduction of left atrial pressure, estimated by pulmonary capillary wedge pressure, is a well-established effect of ACEIs in patients with congestive heart failure (CHF).[19,20] Furthermore, in animal models of heart failure, direct measurements of left atrial pressure have demonstrated similar effects for ARBs.[21,22] Therefore, ACEIs and ARBs may reduce atrial susceptibility to AF by reducing atrial stretch, although there are data supporting that further mechanisms are involved in the antiarrhythmic properties of RAAS inhibition. In an animal model of ventricular tachypacing (VTP)-induced CHF, it has been shown that although a hydralazine/isosorbide mononitrate vasodilator combination may have similar effects with an ACEI in reducing left atrial pressure, ACE inhibition is more successful in reducing burst pacing-induced AF promotion.[23]

Structural Remodeling

Fibrosis plays a key role in the development of a vulnerable substrate for AF mainly by promoting conduction heterogeneity. Atrial fibrosis results from deregulated extracellular matrix metabolism with excessive fibrillar collagen deposition, generally in response to a cardiac insult.[24]

The proinflammatory and profibrotic effects of angiotensin II have been well described (Fig. 1).[25,26] *In vitro* studies of neonatal and adult rat cardiac fibroblasts have shown that angiotensin II directly stimulates cardiac fibroblast proliferation and collagen synthesis via AT1 receptors.[27–29] Angiotensin II binding to AT1 receptors induces a phosphorylation cascade that activates mitogen-activated protein kinases (MAPKs), which stimulate proliferation of fibroblasts, cellular hypertrophy, and apoptosis. In contrast, activation of the AT2 receptor can inhibit MAPK via activation of different phosphatases. Thus, activation of the AT2 receptor has antiproliferative effects.[30]

Besides these direct actions of angiotensin II, there is strong evidence that angiotensin II regulates cardiac fibroblast function indirectly as well, via specific growth factors.[31] Principal candidate mediators of angiotensin II profibrotic effects include transforming growth factor-beta 1 (TGFβ1), osteopontin (OPN), and endothelin-1 (ET-1),[31] with several studies supporting that the profibrotic effects of angiotensin II are primarily mediated by the induction of TGFβ1 production.[27,32] TGFβ1 itself is strongly profibrotic and induces cardiac fibroblast differentiation and collagen synthesis.[33] Furthermore, cardiac overexpression of TGFβ1 in transgenic mice results in selective atrial fibrosis, conduction heterogeneity, and AF propensity.[34]

In addition to its direct and indirect effects on collagen synthesis, angiotensin II has been also shown to regulate collagen degradation by modulating interstitial matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinase (TIMP) activity.[30] Imbalances between MMPs and TIMPs have been reported in atrial tissue in both clinical and animal studies of AF,[30] and can be reflected in serum concentrations of these biomarkers.[35]

The role of angiotensin II on collagen regulation is increased in AF. Studies have shown increased atrial expression of ACE and increased activation of the angiotensin II-related intracellular signal transduction pathway in fibrillating human atria.[36] In a canine model of VTP-induced CHF, CHF was shown to result in atrial overexpression of angiotensin II, which resulted in the development of an AF-promoting

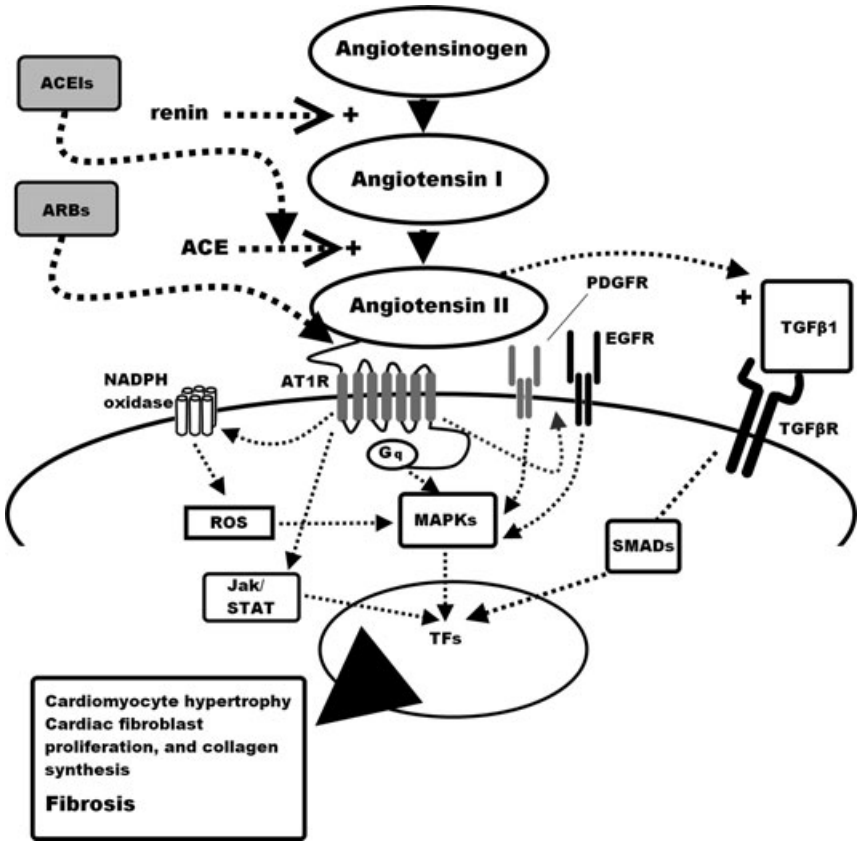

Figure 1. *Representation of the major pathways involved in structural remodeling. ACE = angiotensin-converting enzyme; ACEIs = ACE inhibitors; ARBs = angiotensin receptor blockers; PDGFR = platelet-derived growth factor receptor; EGFR = epidermal growth factor receptor; TGFβ1 = transforming growth factor-beta 1; TGFβR = transforming growth factor-beta receptor; AT1R = angiotensin II type1 receptor; MAPK = mitogen-activated protein kinase; ROS = reactive oxygen species; Jak = Janus kinase; STAT = signal transducers and activators of transcription; TF = transcription factors.*

substrate.[23,37] These effects of elevated atrial tissue angiotensin II concentration on the development of atrial fibrosis and AF have also been verified in transgenic mice with cardiac-restricted ACE overexpression.[38]

Inhibition of the RAAS results in attenuation of structural remodeling. ACE inhibition has been shown to prevent increases in tissue angiotensin II concentration and attenuate fibrosis and AF maintenance.[23,37,39,40] Similar effects on atrial fibrosis[41] and AF maintenance have been achieved by selective AT1 receptor blockade.[42]

Electrical Remodeling

Using a goat model of AF, Wijffels et al. in their seminal study have demonstrated that when AF is maintained artificially, the duration of burst pacing-induced paroxysms progressively increases until AF becomes sustained.[43] The phenomenon of "AF begets AF" is seen in clinical practice as with time it becomes more and more difficult to keep a patient with AF in sinus rhythm. Electrical remodeling refers to the development of an atrial substrate that promotes AF perpetuation and may involve alterations in ionic currents and properties of cellular excitability (Fig. 2).[11,44] Wijffels et al. have demonstrated that the increased propensity to AF is associated with shortening of the AERP in accordance with the multiple wavelet theory.[43] This tachypacing-induced shortening of the AERP was subsequently attributed to a reduction of action potential duration (APD) secondary to the progressive downregulation of the transient outward current (I_{to}) and the L-type Ca^{2+} current ($I_{Ca,L}$).[45] Effects of angiotensin II on the $I_{Ca,L}$ remain controversial, with studies reporting angiotensin II increasing, decreasing, or even having no effect on $I_{Ca,L}$.[10,46] The role of angiotensin II in I_{to} downregulation is better understood. AT1 receptor forms a complex with

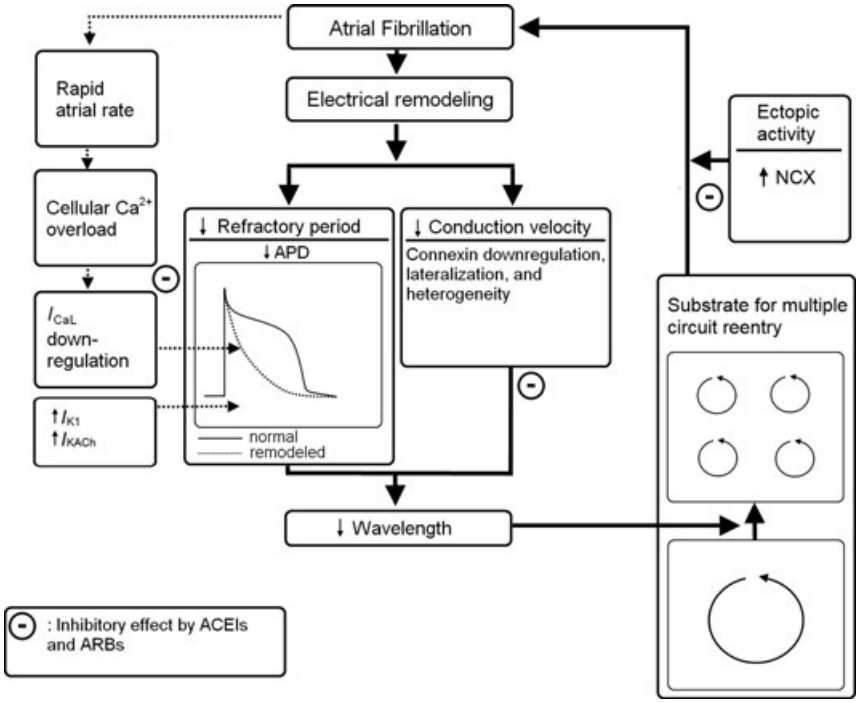

Figure 2. *Pathophysiology of electrical remodeling. During the upstroke of the action potential, the opening of the L-type Ca^{2+} channel (I_{CaL}) leads to Ca^{2+} entry in the cell and triggers further Ca^{2+} from the sarcoplasmic reticulum. Ca^{2+} overload contributes to I_{CaL} downregulation, followed by a shorter AP plateau and reduced AP duration (APD), thus promoting functional reentry. It also activates the Na^{+}/Ca^{2+} exchange pump (NCX), causing delayed afterdepolarizations and triggered activity. Inhibition of RAAS has been shown to modulate intracellular Ca^{2+} cycling and NCX activity in the pulmonary veins, although evidence is not conclusive. Changes in inward-rectifier K^{+} currents, mainly I_{K1} and I_{KACh}, have been reported in AF and they contribute to APD shortening. Reduced refractory period and conduction velocity result in reduced wavelength, thus enabling smaller functional reentry circuits to be present in the atria. This process produces a pro-arrhythmic substrate in the atria, which in combination with increased ectopic triggering activity facilitates AF perpetuation. Modified from reference 44.*

Kv4.3 (the pore-forming α-subunit underlying I_{to}) and regulates its cell-surface expression.[47] Stimulation of AT1 receptor with angiotensin II leads to internalization of the complex, resulting in I_{to} reduction. Recently, a rabbit model demonstrated that ACE inhibition increases $I_{Ca,L}$ current density but does not prevent its downregulation from tachypacing, whereas it has no influence on I_{to} current density although it can prevent its tachypacing-induced downregulation.[46]

Regardless of its specific action on ionic currents, Nakashima et al., in a canine model, have shown that ACEI or ARB treatment results in complete inhibition of the shortening of AERP normally induced by rapid atrial pacing.[48]

A newly discovered proarrhythmic effect of RAAS is modulation of gap junctions. Gap junctions provide low-resistance pathways for the propagation of impulses between cardiomyocytes, and are predominantly situated at the intercalated discs at cell poles, contributing to cardiac anisotropy.[49] They are formed by the alignment of two hemichannels, called connexons, each composed of six connexins (Cx). In the human heart, there are mainly three Cx isoforms, namely, Cx40, Cx43, and Cx45. Cx43 is expressed in all chambers of the heart, but predominantly in the ventricles, while Cx40 is mainly expressed in atrial tissue and in the conduction system. Cx45 has been detected primarily in the conduction system of the heart and during early development of the heart.[50] Several studies have indicated the importance of Cx40 for impulse conduction in the atria and have associated Cx40 gene polymorphisms with the development of nonfamilial AF[51]; however, evidence regarding the pathogenic role of Cx40 in AF is conflicting.[52] Ambiguity mostly regards Cx40 protein expression levels, while most of the available data indicate that AF is associated with heterogeneous expression

and lateralization of Cx40.[52] The effects of angiotensin II on atrial Cx40 modulation have not been fully investigated, although it was recently reported that cardiac-restricted ACE overexpression causes transcriptional downregulation and reduces protein expression of atrial Cx40.[53] Angiotensin II effects on Cx43 have been studied more extensively. Aminoacid motifs of the C-terminus of the Cx43 molecule are susceptible to phosphorylation and functional Cx43 is usually phosphorylated.[54] Conversely, dephosphorylation of Cx43 is associated with electrical uncoupling of cardiomyocytes.[11] Angiotensin II has been implicated in downward remodeling of Cx43, through dephosphorylation, whereas treatment with ACEIs or ARBs has attenuated this effect.[55–57] Although these findings may not be directly applicable to Cx40 and AF, they indicate that Cx function may be modified by RAAS inhibition and warrant further investigation.

RAAS Gene Polymorphisms and AF

In a case-control study, Gensini et al. genotyped the insertion/deletion (I/D) polymorphism of the ACE gene in patients with persistent AF and identified ACE DD genotype as a predisposing factor for persistent AF.[58] Furthermore, it was recently reported that the ACE I/D polymorphism modulates response to anti-arrhythmic drug therapy in patients with lone AF, DD genotype being associated with lowest rates of symptomatic response.[59] Polymorphisms of the angiotensinogen gene have also been associated with nonfamilial AF.[60] Recent evidence supports significant interactions between angiotensinogen gene haplotypes and ACE I/D polymorphism resulting in increased susceptibility to AF.[61,62]

Clinical Evidence

The case for a causative role of the RAAS in the development of AF is supported by clinical data. Studies on primary prevention, especially in patients with heart failure, have been promising but the benefits of using ACEIs or ARBs for the secondary prevention of AF have not been established.

Primary Prevention

Heart Failure

The effect of RAAS inhibition in reducing the incidence of new onset AF is most pronounced in populations with heart failure (Table I). Vermes et al., in a retrospective analysis of the SOLVD trial, have shown that enalapril reduces the risk of AF development in patients with various degrees of heart failure.[63] Similarly, a retrospective analysis of the Val-HeFT trial demonstrated that a reduction in the risk of AF can be achieved by blocking the RAAS further downstream using the ARB valsartan.[64] Since 92.5% of the patients in the Val-HeFT trial were receiving concomitantly ACEIs, it was demonstrated that ARBs can exert a favorable effect on AF prevention on top of current heart failure treatment. The benefit of adding an ARB to ACEI treatment was also supported by the results of the CHARM trial.[65] Patients in the CHARM trial were enrolled into three component trials based on left ventricular ejection fraction (LVEF) and ACEI treatment. CHARM-Alternative included patients with LVEF $\leq$0.40 not treated with ACEIs because of prior intolerance, CHARM-Added included patients with LVEF $\leq$0.40 treated with an ACEI, and CHARM-Preserved included patients with LVEF $>$0.40 and allowed ACEI treatment (20% in the candesartan group and 23% in the placebo group were receiving ACEIs by the end of the study). Candesartan reduced the incidence of new onset AF and there was no heterogeneity of the effect of candesartan between the three component trials, although the most pronounced effect of candesartan in reducing AF risk was observed in the CHARM-Alternative trial.[65]

According to the provided evidence, ACEI or ARB use in patients with heart failure, apart from the established favorable influence on the long-term prognosis of heart failure,[66] seems to confer additional benefits by preventing AF.

Post-MI

Available evidence from two studies regarding the use of ACEIs following MI seems contradictory. Pedersen et al. reported that patients with impaired left ventricular function secondary to acute myocardial infarction had significantly lower incidence of AF at the end of a 2- to 4-year follow-up when they were treated with trandolapril.[67] Significant data regarding the incidence and prognostic significance of AF after MI were reported by Pizzetti et al. based on the GISSI-3 trial.[68] Patients in the GISSI-3 trial were randomized within 24 hours of acute MI to receive oral lisinopril or no lisinopril and glyceryl trinitrate or no glyceryl trinitrate. The authors reported that AF occurred in 665 patients randomized to lisinopril and 721 controls, but noticed that 319 of these 1,386 patients had AF on the admission electrocardiogram, that is to say before treatment allocation. Since the subsequent treatment allocation of these 319 patients is not known, it is not possible to estimate the actual effect of lisinopril on AF development. Therefore, although according to data from the TRACE study ACEI treatment reduces the incidence of AF, further studies are needed to corroborate these findings.

Table I.

Clinical Studies of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) in Primary Prevention of Atrial Fibrillation

Study	Population	Number of Patients Analyzed	Study Drug	Follow-Up	Main Findings	Study Design
Heart failure						
Vermes et al.[63] (SOLVD) 2003	LVD, CHF	374	Enalapril vs placebo	3.4 years	Reduced new onset AF (5.4 vs 24%, $P < 0.0001$)	*Post hoc*, randomized, double-blind
Maggioni et al.[64] (Val-HeFT) 2005	CHF	4,395	Valsartan vs placebo	23 months	Reduced incidence of new onset AF (5.12 vs 7.95%, $P < 0.0002$)	*Post hoc*, randomized, double-blind
Ducharme et al.[65] (CHARM) 2006	CHF (LVD or PLVF)	6,379	Candesartan vs placebo	37.7 months	Reduced incidence of new onset AF (5.55 vs 6.74%, $P < 0.05$)	Secondary endpoint, randomized, double-blind
Post-MI						
Pedersen et al.[67] (TRACE) 1999	Post-MI, LVD	1,577	Trandolapril vs placebo	2–4 years	Reduced new onset AF (2.8 vs 5.3%, $P < 0.05$	*Post hoc*, randomized, double-blind
Pizzetti et al.[68] (GISSI-3) 2001	Within 24 hours post-MI	17,749	Lisinopril ($\pm$nitrates) vs control ($\pm$nitrates)	42 days	Patients randomized to lisinopril plus nitrates had lower incidence of AF (OR = 0.76, 95% CI = 0.65–0.89)	*Post hoc*, randomized
Hypertension						
Hansson et al.[69] (CAPPP) 1999	Hypertensive, 25–66 years old	10,985	Captopril vs β-blockers and/or diuretics	6.1 years	Nonsignificant difference in AF	Open-label, blinded endpoint
Hansson et al.[70] (STOPH2) 1999	Hypertensive, $\geq$70 years old	6,614	Enalapril or Lisinopril vs conventional antihypertensive or CCBs	5 years	Nonsignificant difference in AF frequency	Open-label, masked endpoint
L'Allier et al.[71] 2004	Hypertensive, $\geq$18 years old	10,926	ACEIs vs CCBs	4.5 years	Reduced new onset AF incidence with adjusted hazards ratio 0.85 (95% CI = 0.74–0.97)	Retrospective, longitudinal, cohort study

Continued.

Table I.

Continued

Study	Population	Number of Patients Analyzed	Study Drug	Follow-Up	Main Findings	Study Design
Wachtel et al.[72] (LIFE) 2005	Hypertensive, LVH	8,851	Losartan vs atenolol	4.8 ± 1.0 years	Reduced new onset AF (6.8 vs10.1 per 1,000 person-years	*Post hoc*, randomized, double masked
Schaer et al.[74] 2010	Hypertensive, 20–79 years old	23,303	Exclusive therapy with ACEIs or ARBs or β-blockers vs CCBs	10 years	Reduced new onset AF	Nested, case control analysis
Increased cardiovascular risk						
Salehian et al.[75] (HOPE) 2007	≥ 55 years old, high cardiovascular risk, with no known HF or LVEF<0.40	8,335	Ramipril vs placebo	4.5 years	No significant reduction in incidence of new onset AF (2.0% ramipril vs 2.2% placebo)	*Post hoc*, randomized, double-blind
Schmieder et al.[76] (VALUE) 2008	Hypertensive, ≥50 years old, high cardiovascular risk	13,760	Valsartan vs Amlodipine	5 years	Reduced incidence of new onset AF (3.67 vs 4.34%, P = 0.046)	Pre-specified secondary endpoint, randomized, double-blind
Postoperative AF						
White et al.[80] (AFIST II and III) 2007	Patients undergoing CABG surgery and/or valve surgery	338	ACEIs or ARBs vs controls	30 days	Nonsignificant reduction in postoperative AF	Observational
Ozaydin et al.[79] 2007	Patients undergoing CABG surgery and/or valve surgery	128	ACEIs plus candesartan vs ACEIs vs controls	10 days	Lower rate of postoperative AF in patients receiving ACEIs or ACEIs plus candesartan (12.2% and 10.2% vs 33.3%)	Randomized, masked endpoint

MI = myocardial infarction; LVD = left ventricular dysfunction; CHF = congestive heart failure; PLVF = preserved left ventricular function; LVH = left ventricular hypertrophy; LVEF = left ventricular ejection fraction; CABG = coronary artery bypass graft; CCB = calcium channel blocker; AF = atrial fibrillation.

Hypertension

The evidence on using ACEIs or ARBs for the primary prevention of AF in hypertensive patients with normal left ventricular function is rather inconclusive. In the CAPPP and the STOP-H2 trials, ACEIs were compared with other antihypertensive regiments for a mean follow-up time of 6.1 and 5 years, respectively. In both trials, treatment with ACEIs did not reduce the incidence of new-onset AF.[69,70] In contrast, L'Allier et al. in a retrospective, longitudinal, cohort study comparing ACEIs with calcium channel blockers, concluded that ACEIs were associated with a reduced adjusted hazards ratio for new onset AF and reduced AF-related hospitalizations.[71] A *post hoc* analysis of the LIFE trial, which compared the ARB losartan with the β-blocker atenolol, produced similar results. Patients receiving losartan had significantly lower incidence of new-onset AF and associated stroke.[72] However, the LIFE trial was different from the other above-mentioned hypertension trials in that it used an ARB rather than an ACEI, and it enrolled patients with LVH who would supposedly have more advanced hemodynamic abnormalities and higher activation of the RAAS than patients in other hypertension trials.[73] Using methodology similar to L'Allier et al., a recent nested case-control study provided some evidence that long-term antihypertensive treatment with ACEIs, ARBs, or β-blockers may decrease the risk of new-onset AF compared with treatment with calcium channel blockers.[74] However, both studies were observational and could be confounded by treatment selection bias, while AF diagnosis could not be validated.

Increased Cardiovascular Risks

Two reports with contradicting results have analyzed data regarding AF prevention in patients with increased cardiovascular risk.[75,76] Salehian et al. analyzed data from the HOPE clinical trial and reported that treatment with ramipril did not reduce the rate of new onset AF compared to placebo.[75] Conversely, Schmieder et al. reported that valsartan-based antihypertensive treatment reduced the development of new-onset AF compared to amlodipine, using data from the VALUE trial.[76] A possible explanation for the apparent discrepancy is that all patients in the VALUE trial had hypertension and approximately one-fourth had electrocardiographic evidence of LVH, whereas only half of the participants in HOPE had hypertension with approximately 8.5% of them having LVH.[77] This is probably reflected in the low incidence of new AF in HOPE, which was reported to be 2.1%.

In conclusion, evidence regarding the efficacy of RAAS inhibition as primary prevention of AF in hypertensive patients or patients with increased cardiovascular risk is at best equivocal. Patients with the highest probability of an increased activation of the RAAS seem to benefit the most from ACEIs or ARBs.

Postoperative AF

The effects of RAAS inhibition on the prevention of postoperative AF have been examined in a multicenter, prospective, observational analysis of 4,657 patients undergoing coronary artery bypass graft surgery. Among several risk factors identified, postoperative use of ACEIs was associated with reduced incidence of new-onset AF.[78] A randomized trial in 128 patients undergoing cardiac surgery has, also, shown that ACEIs or the combination of ACEIs and candesartan can reduce the rate of postoperative AF.[79] Contradictory results were reported in a *post hoc* cohort evaluation of patients who were enrolled in the AFIST II and III clinical trials. In the 338 patients who had undergone cardiac surgery, ACEIs and ARBs were associated with reduced odds of developing postoperative AF, albeit not statistically significant.[80]

Secondary Prevention

Clinical studies of ACEIs and ARBs in secondary prevention of AF are summarized in Table II.

Prevention after Cardioversion

The first clinical trial investigating a potential role of RAAS inhibition in the prevention of AF recurrence after electrical cardioversion (ECV) was published in 1995 by van den Berg et al. The researchers compared CHF patients receiving lisinopril 6 weeks before and 6 weeks after cardioversion with CHF patients receiving placebo but did not observe a statistically significant decrease in recurrent AF. It should be noted that maintenance of sinus rhythm in the lisinopril group compared to the control group was approximately double (71% vs 36%); however, small sample size (n = 30) did not allow for statistical significance.[81] Several other trials have also assessed the effect of ACEIs or ARBs in secondary prevention after cardioversion. In a small, nonrandomized, *post hoc* analysis, Van Noord et al. did not observe an effect of ACEI pretreatment on sinus rhythm maintenance following ECV.[82] Similarly, Dagres et al. did not find a benefit of irbesartan in reducing the risk of AF recurrence. Besides small sample size, the short duration of irbesartan treatment prior to ECV, which is evident in the lack of difference in blood pressure before and after ECV between patients

Table II.

Clinical Studies of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) in Secondary Prevention of Atrial Fibrillation

Study	Population	Number of Patients Analyzed	Study Drug	Follow-Up	Main Findings	Study Design
Prevention after cardioversion						
Van den Berg et al.[81] 1995	Permanent AF, CHF, undergoing cardioversion	30	Lisinopril vs placebo	12 weeks	Nonsignificant decrease in recurrent AF after cardioversion	Randomized, double-blind
Van Noord et al.[82] 2005	Persistent AF	107	ACEI pre-treatment vs controls	1 month	Nonsignificant difference in SR maintenance (49% vs 50%)	*Post hoc*, nonrandomized
Dagres et al.[83] 2006	Persistent AF undergoing cardioversion	50	Irbesartan vs controls	4 weeks	No significant difference in AF recurrence (48% vs 44%, $P = 0.78$)	Prospective, not randomized
Tveit et al.[84] (CAPRAF) 2007	Persistent AF undergoing cardioversion	171	Candesartan vs placebo	6 months	No significant difference in AF recurrence (71% vs 65%, $P = 0.42$)	Randomized, double-blind
Madrid et al.[88] 2002	Persistent AF, undergoing cardioversion	154	Irbesartan plus amiodarone vs amiodarone	254 days	Improved sinus rhythm maintenance (79.52% vs 55.91%, $P = 0.007$)	Randomized, open-label
Ueng et al.[89] 2003	Persistent AF, undergoing cardioversion	145	Enalapril plus amiodarone vs amiodarone	270 days	Improved sinus rhythm maintenance (74.3% vs 57.3%, $P = 0.021$)	Randomized, open-label
Madrid et al.[90] 2004	Persistent, lone AF	90	Irbesartan (300 mg or 150 mg) plus amiodarone vs amiodarone	220 days	Irbesartan plus amiodarone improved SR maintenance in a dose dependent manner	Randomized, open label
Belluzzi et al.[86] 2009	First episode of lone AF after cardioversion	62	Ramipril vs placebo	3 years	Ramipril reduced AF recurrences (9.7% vs 32.3%, $P < 0.03$)	Randomized, double-blind
Prevention after catheter ablation						
Richter et al.[91] 2007	Persistent or paroxysmal AF	234	Statins or ACEIs/ARBs or Statins plus ACEIs/ARBs	12.7 months	No effect on incidence of AF recurrences	Retrospective

Continued.

Table II.

Continued

Study	Population	Number of Patients Analyzed	Study Drug	Follow-Up	Main Findings	Study Design
Al Chekakie et al.[92] 2007	Persistent or paroxysmal AF	177	Statins or ACEIs/ARBs	13.8 ± 8.6 months	No effect on incidence of AF recurrences	Retrospective
Park et al.[93] 2009	Persistent or paroxysmal AF	152	ACEIs or ARBs vs controls	18 ± 14 months	Significantly reduced recurrences of AF in the ACEIs/ARBs group	Retrospective
Zheng et al.[94] 2009	Persistent AF	139	ACEIs or ARBs vs controls	14.6 ± 8.9 months	No effect on incidence of AF recurrences	Retrospective
Patel et al.[95] 2010	Persistent or paroxysmal AF, postmenopausal women	372	Statins or ACEIs/ARBs vs controls	24 ± 8.3 months	No effect on incidence of AF recurrences	Retrospective
Prevention of Paroxysmal AF						
Murray et al.[100] (AFFIRM) 2004	≥ 65 years old, SR, history of AF	1,153	ACEIs/ARBs vs control	3.5 years	Nonsignificant difference in AF recurrence (HR = 0.91, 95% CI = 0.77–1.09)	*Post hoc*, randomized
Palardy et al.[101] (CTAF) 2008	Episode of ECG-documented sustained symptomatic AF in past 6 months	403	RAAS inhibitors plus amiodarone vs RAAS inhibitors plus sotalol/propafenone vs amiodarone vs sotalol/propafenone	468 ± 150 days	No significant difference in AF recurrence	*Post hoc*, randomized, open label
Disertori et al.[102] GISSI-AF 2009	≥ 40 years old, history of recent AF, SR	1,442	Valsartan vs placebo	1 year	No significant reduction in AF recurrence (51.4% vs 52.1%, P = 0.73)	Randomized, double-blind
Yin et al.[97] 2006	History of paroxysmal, lone AF, SR	177	Losartan plus amiodarone vs perindopril pus amiodarone vs amiodarone	24 months	Losartan or perindopril with amiodarone improved SR maintenance	Randomized, open-label
Fogari et al.[98] 2006	History of recent paroxysmal AF, SR	222	Losartan plus amiodarone vs amlodipine plus amiodarone	299 days	Improved SR maintenance (13% vs 39%, P < 0.01)	Randomized, double-blind
Komatsu et al.[99] 2008	Paroxysmal and persistent AF	58	Enalapril plus amiodarone vs amiodarone	24 months	Reduced AF recurrences (36% vs 70%, P < 0.05)	Retrospective

AF = atrial fibrillation; CHF = congestive heart failure; SR = sinus rhythm; ECG = electrocardiogram; RAAS = renin-angiotensin-aldosterone system; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers.

and controls, may be responsible for this result. Nevertheless, this study demonstrated that treatment with irbesartan attenuates left atrial stunning after cardioversion.[83] A similar lack of effect on the recurrence rate of AF for candesartan treatment was reported in the CAPRAF trial.[84] The authors attributed these results in the relatively short time of candesartan treatment before ECV (median time: 29 days) which is manifested in the absence of significant differences in blood pressure between the treatment and placebo groups. Although this time was adequate for an effect on electrical remodeling, as reported by a *post hoc* subset analysis of the CAPRAF trial,[85] the authors hypothesized that longer treatment and possibly a higher dosage would be needed for an effect on structural remodeling. Recently, the results of a trial aiming to verify ACEI effectiveness in preventing relapses of lone AF after cardioversion were reported.[86] At the end of a 3-year follow-up, ramipril treatment succeeded in reducing AF recurrences and preventing left atrium enlargement, which has been demonstrated to occur in the natural history of lone AF.[87]

Three trials have estimated the effects of combinations of amiodarone with an ACEI or an ARB in preventing AF recurrences after cardioversion and compared them with amiodarone alone.[88–90] The addition of an ACEI or an ARB to amiodarone improved significantly sinus rhythm maintenance and there is evidence that this anti-arrhythmic effect is dose-dependent, at least for irbesartan.[90]

The above-mentioned data support a beneficial role of ACEIs or ARBs in sinus rhythm maintenance after cardioversion, primarily when RAAS inhibition is used as an adjunct to amiodarone.

Prevention after Catheter Ablation

The potential of ACEIs or ARBs for improving the outcome after catheter ablation has been assessed in several retrospective studies (Table II).[91–95] A common finding in all but one of them is that RAAS inhibition did not reduce the incidence of AF recurrences after the procedure. Evidence from these studies raises the question whether ACEIs or ARBs have the potential to invert atrial remodeling in patients with drug-refractory AF. Another issue arising is whether the use of agents known to prevent fibrosis may as well reduce scar formation, thereby reducing the efficacy of the ablation.[96]

Prevention in the Setting of Paroxysmal AF

Considerable research has also been conducted for the prophylactic use of ACEIs and ARBs against recurrences of paroxysmal AF. Two clinical trials have compared the long-term efficacy of the losartan-amiodarone or perindopril-amiodarone combination with amiodarone alone or combined with amlodipine.[97,98] In both cases, the use of losartan or perindopril was associated with improved sinus rhythm maintenance. Similarly, in a retrospective analysis of patients with predominantly paroxysmal AF, the combination of enalapril with amiodarone compared with amiodarone monotherapy was proven to enhance sinus rhythm maintenance and prevent the development of atrial structural remodeling.[99] Conducting a *post hoc* analysis, Murray et al. identified the patients who were randomized to the rhythm-control arm of the AFFIRM trial and compared AF recurrence with exposure to ACEIs or ARBs.[100] They observed no beneficial role for RAAS inhibition in the overall study population; however, subgroup analysis revealed that ACEIs and ARBs reduced the risk of AF recurrence in patients with a history of CHF or impaired left ventricular function. Data from the CTAF trial also did not support an additional benefit of RAAS inhibition against AF recurrence in patients treated with conventional antiarrhythmic treatment.[101] Recently, results from GISSI-AF, a well-designed large, randomized trial, were reported.[102] A total of 1,442 enrolled patients with a history of recent AF were randomly assigned to receive valsartan or placebo and were followed up for a year. The rate of AF recurrences in the valsartan group was not significantly lower than in the placebo group. A possible limitation of this study is that patients in the valsartan group had a significantly higher prevalence of coronary artery disease and peripheral artery disease. This may confer a higher risk of AF to these patients, even though cardiovascular risk factors associated with AF were evenly distributed between valsartan and placebo groups. In addition, it may also explain the unexpected finding of increased thromboembolic events in the valsartan group. Another potential limitation could be that 58% of the patients in the valsartan group and 56% of the placebo group were receiving concomitant ACEI treatment; thus, the RAAS was already inhibited in these patients. Therefore, the GISSI-AF trial did not address the question whether RAAS inhibition is important in AF prevention, but the clinically more significant question if there is an additional benefit by adding ARBs to ACEIs. Such a benefit was supported by Val-HeFT and CHARM trials,[64,65] although this was not the case with GISSI-AF.[102]

Meta-Analyses and Future Trials

A common limitation of most of clinical studies regarding primary prevention of AF with RAAS inhibition is that they were conducted *post*

Table III.

Relative Risk of Atrial Fibrillation in Published Meta-Analyses

Meta-Analysis	Total Effect ACEIs and ARBs	ACEIs	ARBs	Heart Failure	Hypertension	Post-MI	Secondary Prevention after ECV
Madrid et al.[107] 2004	0.57 [0.39–0.82]*	–	–	–	–	–	–
Healey et al.[108] 2005	0.72 [0.60–0.85]	0.72 [0.56–0.93]	0.71 [0.60–0.84]	0.56 [0.37–0.85]	0.88 [0.66–1.19]	0.73 [0.43–1.26]	0.52 [0.35–0.79]
Anand et al.[109] 2006	0.82 [0.70–0.97]	0.75 [0.57–0.99]	0.81 [0.62–1.06]	0.57 [0.37–0.89]	0.94 [0.72–1.23]	0.73 [0.43–1.26]	–
Kalus et al.[110] 2006	0.51 [0.36–0.72]	0.31 [0.11–0.86]	0.64 [0.54–0.75]	–	–	–	0.39 [0.20–0.75]
Salehian et al.[75] 2007	0.73 [0.62–0.86]	0.75 [0.60–0.94]	0.70 [0.59–0.83]	0.55 [0.39–0.79]‡	0.88 [0.66–1.19]†	–	0.52 [0.35–0.79]
Jibrini et al.[111] 2008	0.81 [0.76–0.87]*	0.87 [0.80–0.94]*	0.70 [0.62–0.79]*	0.68 [0.59–0.79]	0.77 [0.69–0.86]	0.90 [0.81–0.99]	0.49 [0.33–0.72]

*No distinction between primary and secondary prevention trials.
†Patients with left ventricular dysfunction were excluded.
‡Left ventricular dysfunction trials.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MI = myocardial infarction; ECV = electrical cardioversion.
Data are presented as relative risk (RR) and 95% confidence interval.

hoc and they used annual electrocardiograms or patient-reported symptoms for the detection of AF, thus under detecting asymptomatic short-lasting AF. However, it is now well known from catheter ablation studies that patients with AF may not provide reliable data on the frequency and duration of their paroxysms.[103,104] Up to 50% of AF episodes may escape detection and diagnosis following AF ablation.[105,106] This also applies to secondary prevention trials, especially for paroxysmal AF. Clinical trials of RAAS inhibition in secondary prevention of AF usually employ frequent electrocardiographic monitoring; however, they are hampered by small sample sizes. Thus, a relative uncertainty about results is a common feature of all AF trials.

Several meta-analyses of the available trials have been conducted.[75,107–111] A beneficial effect of ACEIs and ARBs against AF development has been a consistent finding in all (Table III). This effect was more pronounced in patients with heart failure,[75,107–109,111] while in two of these meta-analyses it was completely abrogated when considering patients with hypertension and normal left ventricular function.[75,108] When secondary prevention trials were pooled, meta-analyses showed a significant relative risk reduction in AF recurrences after cardioversion by both ACEIs and ARBs.[108,110,111] A recent meta-analysis, incorporating data from GISSI-AF and the recent paper by Belluzzi et al.,[86] reached similar conclusions regarding the beneficial effects of RAAS inhibition in secondary prevention of AF. Analyzing primary prevention trials, this meta-analysis observed no effects of RAAS inhibition in reducing AF incidence in populations other than heart failure patients.[112] A common finding in most of these meta-analyses is the comparable effect of both ACEIs and ARBs against AF development.[108,111] This finding is corroborated by the recently reported data from the ONTARGET and TRANSCEND trials.[113] In ONTARGET, new-onset AF was documented in 6.9% of the patients receiving ramipril and 6.7% of the patients receiving telmisartan, supporting similar effects of both interventions. Furthermore, data from TRANSCEND show that telmisartan did not reduce the incidence of new-onset AF when compared with placebo. The ONTARGET/TRANSCEND results further support that RAAS blockade reduces the risk of AF mainly in patients with heart failure and LVH. The lack of beneficial effects should be attributed to the exclusion of patients with heart failure from ONTARGET/TRANSCEND and the relatively small proportion of patients with LVH.[113]

Forthcoming trials are expected to further elucidate the efficacy of ACEIs and ARBs in primary and secondary prevention of AF. The

J-RHYTHM II and the ANTIPAF trials are designed to evaluate the use of ARBs in reducing the recurrence rate of paroxysmal AF and their results are eagerly awaited.[114,115] Other studies of the anti-arrhythmic effects of RAAS inhibition on patients undergoing cardiac surgery [NCT00141778], or patients with hypertension and permanent pacemakers [NCT00225667], are also underway.

Conclusions

There has been compelling evidence supporting the role of RAAS in the genesis and perpetuation of AF. Experimental studies have demonstrated the beneficial effects of ACEIs and ARBs on AF prevention; however, clinical studies on the efficacy of such therapeutic interventions have produced variable results depending on the clinical background of treated patients. In patients with heart failure, ACEIs and ARBs appear particularly useful for primary prevention of AF. Meta-analyses of secondary prevention trials also suggest significant risk reduction after cardioversion with the use of ACEIs and ARBs. Additional data are needed to further elucidate the clinical role of RAAS inhibition for primary and secondary prevention of AF.

References

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation 1998; 98:946–952.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. Stroke 1991; 22:983–988.
3. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: Incidence, risk factors, and prognosis in the Manitoba Follow-up Study. Am J Med 1995; 98:476–484.
4. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study: The Rotterdam Study. Stroke 1997; 28:316–321.
5. Miyasaka Y, Barnes ME, Petersen RC, Cha SS, Bailey KR, Gersh BJ, Casaclang-Verzosa G, et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: Data from a community-based cohort. Eur Heart J 2007; 28:1962–1967.
6. Stewart S, Murphy NF, Walker A, McGuire A, McMurray JJ. Cost of an emerging epidemic: An economic analysis of atrial fibrillation in the UK. Heart 2004; 90:286–292.
7. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. Arch Intern Med 1998; 158:229–234.
8. Ringborg A, Nieuwlaat R, Lindgren P, Jonsson B, Fidan D, Maggioni AP, Lopez-Sendon J, et al. Costs of atrial fibrillation in five European countries: Results from the Euro Heart Survey on atrial fibrillation. Europace 2008; 10:403–411.
9. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Mahe I, Bergmann JF. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: A systematic review of randomized controlled trials. Arch Intern Med 2006; 166:719–728.
10. Ehrlich JR, Hohnloser SH, Nattel S. Role of angiotensin system and effects of its inhibition in atrial fibrillation: Clinical and experimental evidence. Eur Heart J 2006; 27:512–518.
11. Iravanian S, Dudley SC, Jr. The renin-angiotensin-aldosterone system (RAAS) and cardiac arrhythmias. Heart Rhythm 2008; 5:S12–S17.
12. Ram CV. Angiotensin receptor blockers: Current status and future prospects. Am J Med 2008; 121:656–663.
13. Murgatroyd FD, Camm AJ. Atrial arrhythmias. Lancet 1993; 341:1317–1322.
14. Ravelli F, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. Circulation 1997; 96:1686–1695.
15. Solti F, Vecsey T, Kekesi V, Juhasz-Nagy A. The effect of atrial dilatation on the genesis of atrial arrhythmias. Cardiovasc Res 1989; 23:882–886.
16. Calkins H, el-Atassi R, Kalbfleisch S, Langberg J, Morady F. Effects of an acute increase in atrial pressure on atrial refractoriness in humans. Pacing Clin Electrophysiol 1992; 15:1674–1680.
17. Bode F, Sachs F, Franz MR. Tarantula peptide inhibits atrial fibrillation. Nature 2001; 409:35–36.
18. Matsuda Y, Toma Y, Matsuzaki M, Moritani K, Satoh A, Shiomi K, Ohtani N, et al. Change of left atrial systolic pressure waveform in relation to left ventricular end-diastolic pressure. Circulation 1990; 82:1659–1667.
19. Chatterjee K, Parmley WW, Cohn JN, Levine TB, Awan NA, Mason DT, Faxon DP, et al. A cooperative multicenter study of captopril in congestive heart failure: Hemodynamic effects and long-term response. Am Heart J 1985; 110:439–447.
20. de Graeff PA, Kingma JH, Dunselman PH, Wesseling H, Lie KI. Acute hemodynamic and hormonal effects of ramipril in chronic congestive heart failure and comparison with captopril. Am J Cardiol 1987; 59:164D–170D.
21. Fitzpatrick MA, Rademaker MT, Charles CJ, Yandle TG, Espiner EA, Ikram H. Angiotensin II receptor antagonism in ovine heart failure: Acute hemodynamic, hormonal, and renal effects. Am J Physiol 1992; 263:H250–H256.
22. Rademaker MT, Charles CJ, Espiner EA, Frampton CM, Nicholls MG, Richards AM. Combined inhibition of angiotensin II and endothelin suppresses the brain natriuretic peptide response to developing heart failure. Clin Sci (Lond) 2004; 106:569–576.
23. Li D, Shinagawa K, Pang L, Leung TK, Cardin S, Wang Z, Nattel S. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. Circulation 2001; 104:2608–2614.
24. Burstein B, Nattel S. Atrial structural remodeling as an antiarrhythmic target. J Cardiovasc Pharmacol 2008; 52:4–10.
25. Burstein B, Nattel S. Atrial fibrosis: Mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol 2008; 51:802–809.
26. Corradi D, Callegari S, Maestri R, Benussi S, Alfieri O. Structural remodeling in atrial fibrillation. Nat Clin Pract Cardiovasc Med 2008; 5:782–796.
27. Sadoshima J, Izumo S. Molecular characterization of angiotensin II–induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts. Critical role of the AT1 receptor subtype. Circ Res 1993; 73:413–423.
28. Crabos M, Roth M, Hahn AW, Erne P. Characterization of angiotensin II receptors in cultured adult rat cardiac fibroblasts. Coupling to signaling systems and gene expression. J Clin Invest 1994; 93:2372–2378.
29. Zhou G, Kandala JC, Tyagi SC, Katwa LC, Weber KT. Effects of angiotensin II and aldosterone on collagen gene expression and protein turnover in cardiac fibroblasts. Mol Cell Biochem 1996; 154:171–178.
30. Lin CS, Pan CH. Regulatory mechanisms of atrial fibrotic remodeling in atrial fibrillation. Cell Mol Life Sci 2008; 65:1489–1508.
31. Dostal DE. Regulation of cardiac collagen: Angiotensin and cross-talk with local growth factors. Hypertension 2001; 37:841–844.
32. Lee AA, Dillmann WH, McCulloch AD, Villarreal FJ. Angiotensin II stimulates the autocrine production of transforming growth factor-beta 1 in adult rat cardiac fibroblasts. J Mol Cell Cardiol 1995; 27:2347–2357.
33. Lijnen PJ, Petrov VV, Fagard RH. Induction of cardiac fibrosis by transforming growth factor-beta(1). Mol Genet Metab 2000; 71:418–435.
34. Nakajima H, Nakajima HO, Salcher O, Dittie AS, Dembowsky K, Jing S, Field LJ. Atrial but not ventricular fibrosis in mice expressing a mutant transforming growth factor-beta(1) transgene in the heart. Circ Res 2000; 86:571–579.

35. Kallergis EM, Manios EG, Kanoupakis EM, Mavrakis HE, Arfanakis DA, Maliaraki NE, Lathourakis CE, et al. Extracellular matrix alterations in patients with paroxysmal and persistent atrial fibrillation: Biochemical assessment of collagen type-I turnover. J Am Coll Cardiol 2008; 52:211–215.
36. Goette A, Staack T, Rocken C, Arndt M, Geller JC, Huth C, Ansorge S, et al. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. J Am Coll Cardiol 2000; 35:1669–1677.
37. Cardin S, Li D, Thorin-Trescases N, Leung TK, Thorin E, Nattel S. Evolution of the atrial fibrillation substrate in experimental congestive heart failure: Angiotensin-dependent and -independent pathways. Cardiovasc Res 2003; 60:315–325.
38. Xiao HD, Fuchs S, Campbell DJ, Lewis W, Dudley SC, Jr., Kasi VS, Hoit BD, et al. Mice with cardiac-restricted angiotensin-converting enzyme (ACE) have atrial enlargement, cardiac arrhythmia, and sudden death. Am J Pathol 2004; 165:1019–1032.
39. Sakabe M, Fujiki A, Nishida K, Sugao M, Nagasawa H, Tsuneda T, Mizumaki K, et al. Enalapril prevents perpetuation of atrial fibrillation by suppressing atrial fibrosis and over-expression of connexin43 in a canine model of atrial pacing-induced left ventricular dysfunction. J Cardiovasc Pharmacol 2004; 43:851–859.
40. Li Y, Li W, Yang B, Han W, Dong D, Xue J, Li B, et al. Effects of Cilazapril on atrial electrical, structural and functional remodeling in atrial fibrillation dogs. J Electrocardiol 2007; 40:100e1–100e6.
41. Okazaki H, Minamino T, Tsukamoto O, Kim J, Okada K, Myoishi M, Wakeno M, et al. Angiotensin II type 1 receptor blocker prevents atrial structural remodeling in rats with hypertension induced by chronic nitric oxide inhibition. Hypertens Res 2006; 29:277–284.
42. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. J Am Coll Cardiol 2003; 41:2197–2204.
43. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995; 92:1954–1968.
44. Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodeling in the heart: Heart failure, myocardial infarction, and atrial fibrillation. Physiol Rev 2007; 87:425–456.
45. Yue L, Feng J, Gaspo R, Li GR, Wang Z, Nattel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circ Res 1997; 81:512–525.
46. Laszlo R, Eick C, Rueb N, Weretka S, Weig HJ, Schreieck J, Bosch RF. Inhibition of the renin-angiotensin system: Effects on tachycardia-induced early electrical remodelling in rabbit atrium. J Renin Angiotensin Aldosterone Syst 2008; 9:125–132.
47. Doronin SV, Potapova IA, Lu Z, Cohen IS. Angiotensin receptor type 1 forms a complex with the transient outward potassium channel Kv4.3 and regulates its gating properties and intracellular localization. J Biol Chem 2004; 279:48231–48237.
48. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. Circulation 2000; 101:2612–2617.
49. Valderrabano M. Influence of anisotropic conduction properties in the propagation of the cardiac action potential. Prog Biophys Mol Biol 2007; 94:144–168.
50. Jongsma HJ, Wilders R. Gap junctions in cardiovascular disease. Circ Res 2000; 86:1193–1197.
51. Tsai CT, Lai LP, Hwang JJ, Lin JL, Chiang FT. Molecular genetics of atrial fibrillation. J Am Coll Cardiol 2008; 52:241–250.
52. Chaldoupi SM, Loh P, Hauer RN, de Bakker JM, van Rijen HV. The role of connexin40 in atrial fibrillation. Cardiovasc Res 2009; 84:15–23.
53. Kasi VS, Xiao HD, Shang LL, Iravanian S, Langberg J, Witham EA, Jiao Z, et al. Cardiac-restricted angiotensin-converting enzyme overexpression causes conduction defects and connexin dysregulation. Am J Physiol Heart Circ Physiol 2007; 293:H182–H192.
54. Imanaga I. Pathological remodeling of cardiac gap junction connexin 43-With special reference to arrhythmogenesis. Pathophysiology 2010; 17:73–81.
55. Emdad L, Uzzaman M, Takagishi Y, Honjo H, Uchida T, Severs NJ, Kodama I, et al. Gap junction remodeling in hypertrophied left ventricles of aortic-banded rats: Prevention by angiotensin II type 1 receptor blockade. J Mol Cell Cardiol 2001; 33:219–231.
56. Fischer R, Dechend R, Gapelyuk A, Shagdarsuren E, Gruner K, Gruner A, Gratze P, et al. Angiotensin II-induced sudden arrhythmic death and electrical remodeling. Am J Physiol Heart Circ Physiol 2007; 293:H1242–H1253.
57. Mayama T, Matsumura K, Lin H, Ogawa K, Imanaga I. Remodelling of cardiac gap junction connexin 43 and arrhythmogenesis. Exp Clin Cardiol 2007; 12:67–76.
58. Gensini F, Padeletti L, Fatini C, Sticchi E, Gensini GF, Michelucci A. Angiotensin-converting enzyme and endothelial nitric oxide synthase polymorphisms in patients with atrial fibrillation. Pacing Clin Electrophysiol 2003; 26:295–298.
59. Darbar D, Motsinger AA, Ritchie MD, Gainer JV, Roden DM. Polymorphism modulates symptomatic response to antiarrhythmic drug therapy in patients with lone atrial fibrillation. Heart Rhythm 2007; 4:743–749.
60. Tsai CT, Lai LP, Lin JL, Chiang FT, Hwang JJ, Ritchie MD, Moore JH, et al. Renin-angiotensin system gene polymorphisms and atrial fibrillation. Circulation 2004; 109:1640–1646.
61. Ravn LS, Benn M, Nordestgaard BG, Sethi AA, Agerholm-Larsen B, Jensen GB, Tybjaerg-Hansen A. Angiotensinogen and ACE gene polymorphisms and risk of atrial fibrillation in the general population. Pharmacogenet Genomics 2008; 18:525–533.
62. Tsai CT, Hwang JJ, Chiang FT, Wang YC, Tseng CD, Tseng YZ, Lin JL. Renin-angiotensin system gene polymorphisms and atrial fibrillation: A regression approach for the detection of gene-gene interactions in a large hospitalized population. Cardiology 2008; 111:1–7.
63. Vermes E, Tardif JC, Bourassa MG, Racine N, Levesque S, White M, Guerra PG, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: Insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. Circulation 2003; 107:2926–2931.
64. Maggioni AP, Latini R, Carson PE, Singh SN, Barlera S, Glazer R, Masson S, et al. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: Results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 2005; 149:548–557.
65. Ducharme A, Swedberg K, Pfeffer MA, Cohen-Solal A, Granger CB, Maggioni AP, Michelson EL, et al. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Am Heart J 2006; 152:86–92.
66. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119:e391–e479.
67. Pedersen OD, Bagger H, Kober L, Torp-Pedersen C. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. Circulation 1999; 100:376–380.
68. Pizzetti F, Turazza FM, Franzosi MG, Barlera S, Ledda A, Maggioni AP, Santoro L, et al. Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: The GISSI-3 data. Heart 2001; 86:527–532.
69. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmaki K, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999; 353:611–616.
70. Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten B, Wester PO, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: Cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999; 354:1751–1756.
71. L'Allier PL, Ducharme A, Keller PF, Yu H, Guertin MC, Tardif JC. Angiotensin-converting enzyme inhibition in hypertensive patients is associated with a reduction in the occurrence of atrial fibrillation. J Am Coll Cardiol 2004; 44:159–164.
72. Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlof B, Ibsen H, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: The Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005; 45:712–719.
73. Velagaleti RS, Gona P, Levy D, Aragam J, Larson MG, Tofler GH, Lieb W, et al. Relations of biomarkers representing distinct

biological pathways to left ventricular geometry. Circulation 2008; 118:2252–2258.
74. Schaer BA, Schneider C, Jick SS, Conen D, Osswald S, Meier CR. Risk for incident atrial fibrillation in patients who receive antihypertensive drugs: A nested case-control study. Ann Intern Med 2010; 152:78–84.
75. Salehian O, Healey J, Stambler B, Alnemer K, Almerri K, Grover J, Bata I, et al. Impact of ramipril on the incidence of atrial fibrillation: Results of the Heart Outcomes Prevention Evaluation study. Am Heart J 2007; 154:448–453.
76. Schmieder RE, Kjeldsen SE, Julius S, McInnes GT, Zanchetti A, Hua TA. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: The VALUE trial. J Hypertens 2008; 26:403–411.
77. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342:145–153.
78. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004; 291:1720–1729.
79. Ozaydin M, Dede O, Varol E, Kapan S, Turker Y, Peker O, Duver H, et al. Effect of renin-angiotensin aldosteron system blockers on postoperative atrial fibrillation. Int J Cardiol 2008; 127:362–367.
80. White CM, Kluger J, Lertsburapa K, Faheem O, Coleman CI. Effect of preoperative angiotensin converting enzyme inhibitor or angiotensin receptor blocker use on the frequency of atrial fibrillation after cardiac surgery: A cohort study from the atrial fibrillation suppression trials II and III. Eur J Cardiothorac Surg 2007; 31:817–820.
81. Van Den Berg MP, Crijns HJ, Van Veldhuisen DJ, Griep N, De Kam PJ, Lie KI. Effects of lisinopril in patients with heart failure and chronic atrial fibrillation. J Card Fail 1995; 1:355–363.
82. Van Noord T, Crijns HJ, Van Den Berg MP, Van Veldhuisen DJ, Van Gelder IC. Pretreatment with ACE inhibitors improves acute outcome of electrical cardioversion in patients with persistent atrial fibrillation. BMC Cardiovasc Disord 2005; 5:3.
83. Dagres N, Karatasakis G, Panou F, Athanassopoulos G, Maounis T, Tsougos E, Kourea K, et al. Pre-treatment with Irbesartan attenuates left atrial stunning after electrical cardioversion of atrial fibrillation. Eur Heart J 2006; 27:2062–2068.
84. Tveit A, Grundvold I, Olufsen M, Seljeflot I, Abdelnoor M, Arnesen H, Smith P. Candesartan in the prevention of relapsing atrial fibrillation. Int J Cardiol 2007; 120:85–91.
85. Bollmann A, Tveit A, Husser D, Stridh M, Sornmo L, Smith P, Olsson SB. Fibrillatory rate response to candesartan in persistent atrial fibrillation. Europace 2008; 10:1138–1144.
86. Belluzzi F, Sernesi L, Preti P, Salinaro F, Fonte ML, Perlini S. Prevention of recurrent lone atrial fibrillation by the angiotensin-II converting enzyme inhibitor ramipril in normotensive patients. J Am Coll Cardiol 2009; 53:24–29.
87. Katritsis DG, Toumpoulis IK, Giazitzoglou E, Korovesis S, Karabinos I, Paxinos G, Zambartas C, et al. Latent arterial hypertension in apparently lone atrial fibrillation. J Interv Card Electrophysiol 2005; 13:203–207.
88. Madrid AH, Bueno MG, Rebollo JM, Marin I, Pena G, Bernal E, Rodriguez A, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: A prospective and randomized study. Circulation 2002; 106:331–336.
89. Ueng KC, Tsai TP, Yu WC, Tsai CF, Lin MC, Chan KC, Chen CY, et al. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation. Results of a prospective and controlled study. Eur Heart J 2003; 24:2090–2098.
90. Madrid AH, Marin IM, Cervantes CE, Morell EB, Estevez JE, Moreno G, Parajon JR, et al. Prevention of recurrences in patients with lone atrial fibrillation. The dose-dependent effect of angiotensin II receptor blockers. J Renin Angiotensin Aldosterone Syst 2004; 5:114–120.
91. Richter B, Derntl M, Marx M, Lercher P, Gossinger HD. Therapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and statins: No effect on ablation outcome after ablation of atrial fibrillation. Am Heart J 2007; 153:113–119.
92. Al Chekakie MO, Akar JG, Wang F, Al Muradi H, Wu J, Santucci P, Varma N, et al. The effects of statins and renin-angiotensin system blockers on atrial fibrillation recurrence following antral pulmonary vein isolation. J Cardiovasc Electrophysiol 2007; 18:942–946.
93. Park JH, Oh YS, Kim JH, Chung WB, Oh SS, Lee DH, Choi YS, et al. Effect of angiotensin converting enzyme inhibitors and angiotensin receptor blockers on patients following ablation of atrial fibrillation. Korean Circ J 2009; 39:185–189.
94. Zheng B, Kang J, Tian Y, Tang R, Long D, Yu R, He H, et al. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have no beneficial effect on ablation outcome in chronic persistent atrial fibrillation. Acta Cardiol 2009; 64:335–340.
95. Patel D, Mohanty P, Di Biase L, Wang Y, Shaheen MH, Sanchez JE, Horton RP, et al. The impact of statins and renin-angiotensin-aldosterone system blockers on pulmonary vein antrum isolation outcomes in post-menopausal females. Europace 2010; 12:322–330.
96. Folkeringa RJ, Crijns HJ. Do non-antiarrhythmic drugs have enough pleiotropic power to reduce atrial fibrillation? Europace 2010; 12:299–300.
97. Yin Y, Dalal D, Liu Z, Wu J, Liu D, Lan X, Dai Y, et al. Prospective randomized study comparing amiodarone vs. amiodarone plus losartan vs. amiodarone plus perindopril for the prevention of atrial fibrillation recurrence in patients with lone paroxysmal atrial fibrillation. Eur Heart J 2006; 27:1841–1846.
98. Fogari R, Mugellini A, Destro M, Corradi L, Zoppi A, Fogari E, Rinaldi A. Losartan and prevention of atrial fibrillation recurrence in hypertensive patients. J Cardiovasc Pharmacol 2006; 47:46–50.
99. Komatsu T, Ozawa M, Tachibana H, Sato Y, Orii M, Kunugida F, Nakamura M. Combination therapy with amiodarone and enalapril in patients with paroxysmal atrial fibrillation prevents the development of structural atrial remodeling. Int Heart J 2008; 49:435–447.
100. Murray KT, Rottman JN, Arbogast PG, Shemanski L, Primm RK, Campbell WB, Solomon AJ, et al. Inhibition of angiotensin II signaling and recurrence of atrial fibrillation in AFFIRM. Heart Rhythm 2004; 1:669–675.
101. Palardy M, Ducharme A, Nattel S, Tardif JC, White M, Racine N, Tetreault K, et al. Absence of protective effect of renin-angiotensin system inhibitors on atrial fibrillation development: Insights from the Canadian Trial of Atrial Fibrillation (CTAF). Can J Cardiol 2008; 24:709–713.
102. Disertori M, Latini R, Barlera S, Franzosi MG, Staszewsky L, Maggioni AP, Lucci D, et al. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med 2009; 360:1606–1617.
103. Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li JH, Carbucicchio C, Kottkamp H. Perception of atrial fibrillation before and after radiofrequency catheter ablation: Relevance of asymptomatic arrhythmia recurrence. Circulation 2005; 112:307–313.
104. Verma A, Minor S, Kilicaslan F, Patel D, Hao S, Beheiry S, Lakkireddy D, et al. Incidence of atrial arrhythmias detected by permanent pacemakers (PPM) post-pulmonary vein antrum isolation (PVAI) for atrial fibrillation (AF): Correlation with symptomatic recurrence. J Cardiovasc Electrophysiol 2007; 18:601–606.
105. Hohnloser SH, Capucci A, Fain E, Gold MR, van Gelder IC, Healey J, Israel CW, et al. ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial (ASSERT). Am Heart J 2006; 152:442–447.
106. Klemm HU, Ventura R, Rostock T, Brandstrup B, Risius T, Meinertz T, Willems S. Correlation of symptoms to ECG diagnosis following atrial fibrillation ablation. J Cardiovasc Electrophysiol 2006; 17:146–150.
107. Madrid AH, Peng J, Zamora J, Marin I, Bernal E, Escobar C, Munos-Tinoco C, et al. The role of angiotensin receptor blockers and/or angiotensin converting enzyme inhibitors in the prevention of atrial fibrillation in patients with cardiovascular diseases: Meta-analysis of randomized controlled clinical trials. Pacing Clin Electrophysiol 2004; 27:1405–1410.
108. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: A meta-analysis. J Am Coll Cardiol 2005; 45:1832–1839.
109. Anand K, Mooss AN, Hee TT, Mohiuddin SM. Meta-analysis: Inhibition of renin-angiotensin system prevents new-onset atrial fibrillation. Am Heart J 2006; 152:217–222.

110. Kalus JS, Coleman CI, White CM. The impact of suppressing the renin-angiotensin system on atrial fibrillation. J Clin Pharmacol 2006; 46:21–28.
111. Jibrini MB, Molnar J, Arora RR. Prevention of atrial fibrillation by way of abrogation of the renin-angiotensin system: A systematic review and meta-analysis. Am J Ther 2008; 15:36–43.
112. Schneider MP, Hua TA, Böhm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by renin-angiotensin system inhibition: A meta-analysis. J Am Coll Cardiol 2010; 55:2299–2307.
113. Kintscher U. ONTARGET, TRANSCEND, and PRoFESS: New-onset diabetes, atrial fibrillation, and left ventricular hypertrophy. J Hypertens 2009; 27(Suppl 2):S36–S39.
114. Goette A, Breithardt G, Fetsch T, Hanrath P, Klein HU, Lehmacher W, Steinbeck G, et al. Angiotensin II antagonist in paroxysmal atrial fibrillation (ANTIPAF) trial: Rationale and study design. Clin Drug Investig 2007; 27:697–705.
115. Yamashita T, Ogawa S, Aizawa Y, Atarashi H, Inoue H, Ohe T, Okumura K, et al. Randomized study of angiotensin II type 1 receptor blocker vs dihydropiridine calcium antagonist for the treatment of paroxysmal atrial fibrillation in patients with hypertension. Circ J 2006; 70:1318–1321.