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Prevention of Atrial Fibrillation by Renin-Angiotensin System Inhibition

A Meta-Analysis

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Objectives The authors reviewed published clinical trial data on the effects of renin-angiotensin system (RAS) inhibition for the prevention of atrial fibrillation (AF), aiming to define when RAS inhibition is most effective.

Background Individual studies examining the effects of RAS inhibition on AF prevention have reported controversial results.

Methods All published randomized controlled trials reporting the effects of treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the primary or secondary prevention of AF were included.

Results A total of 23 randomized controlled trials with 87,048 patients were analyzed. In primary prevention, 6 trials in hypertension, 2 trials in myocardial infarction, and 3 trials in heart failure were included (some being post-hoc analyses of randomized controlled trials). In secondary prevention, 8 trials after cardioversion and 4 trials assessing the medical prevention of recurrence were included. Overall, RAS inhibition reduced the odds ratio for AF by 33% ($p < 0.00001$), but there was substantial heterogeneity among trials. In primary prevention, RAS inhibition was effective in patients with heart failure and those with hypertension and left ventricular hypertrophy but not in post-myocardial infarction patients overall. In secondary prevention, RAS inhibition was often administered in addition to antiarrhythmic drugs, including amiodarone, further reducing the odds for AF recurrence after cardioversion by 45% ($p = 0.01$) and in patients on medical therapy by 63% ($p < 0.00001$).

Conclusions This analysis supports the concept of RAS inhibition as an emerging treatment for the primary and secondary prevention of AF but acknowledges the fact that some of the primary prevention trials were post-hoc analyses. Further areas of uncertainty include potential differences among specific RAS inhibitors and possible interactions or synergistic effects with antiarrhythmic drugs. (J Am Coll Cardiol 2010;55:2299–307) © 2010 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common cardiac arrhythmia, causing substantial cardiovascular morbidity and mortality (1,2). New approaches for the prevention and treatment of AF are needed, considering the limited efficacy and significant side effects of antiarrhythmic drugs and catheter ablation procedures. Moreover, AF is a progressive disease, becoming more difficult to treat over time in individual patients. This natural history of AF is based on structural remodeling, in particular

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Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
AF = atrial fibrillation
ARB = angiotensin receptor blocker
CI = confidence interval
ECG = electrocardiography
MI = myocardial infarction
OR = odds ratio
RAS = renin-angiotensin system
RCT = randomized controlled trial

left atrial dilation and fibrosis, and electrical remodeling, including the shortening of atrial refractoriness (3). In addition, impaired hemodynamic state, including volume changes, increased afterload states, pre-hypertension, and frank hypertensive disease, is thought to play a significant role in triggering AF (4).

More recently, there has been an interest in the potential role of renin-angiotensin system (RAS) blockade for the prevention and treatment of AF. Intriguingly, mice with cardiac-restricted angiotensin-converting enzyme expression have normally structured ventricles but exhibit severe atrial dilation and develop AF (5). In the atria of patients with chronic AF, increased expression of angiotensin-converting enzyme and the angiotensin II type 1 receptor, as well as increased angiotensin II-dependent activation of downstream signaling pathways involved in fibrogenesis, have been found (6,7). In addition to effects on structural remodeling, angiotensin II affects electrophysiological properties of the myocardium and the pulmonary veins. Recent data suggest that angiotensin II type 1 receptors are located in close proximity to potassium channels within the membrane (8) and that angiotensin II inhibits outward potassium currents thought to be involved in the pathophysiology of AF (9).

Animal models of AF have shown that RAS blockade, using either an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), has beneficial effects on electrical remodeling (9,10) and on structural remodeling, in particular left atrial fibrosis and dilation (11,12). In humans, the use of ACEIs was associated with less atrial fibrosis (13), and the blockade of angiotensin II has been shown to have beneficial effects on electrical remodeling in human atrial tissue (14). In addition, RAS inhibition has been extensively studied with regard to its blood pressure–reducing properties as well as its known afterload-reducing effects by lowering central blood pressure (15). Regarding the clinical effects of RAS inhibition, a substantial amount of human trial data have accumulated. However, the results of the individual trials are conflicting. We have therefore performed a meta-analysis and a comprehensive review of the available data, aiming to more clearly define the conditions and circumstances in which RAS blockade may be a promising preventive therapy.

Methods

Study selection. A comprehensive search was conducted to identify all relevant human trials of treatment with ACEIs or ARBs, reporting on new-onset or recurrent AF. PubMed was searched using the terms "angiotensin," "angiotensin receptor blocker," and "angiotensin converting enzyme," individual names in these drug classes, and "atrial fibrillation" using Boolean operators. In addition, relevant review reports and the reference lists of retrieved reports were searched for further potentially relevant studies. Only full publications in English were considered (no abstracts). Two reviewers independently evaluated the retrieved reports, which were considered further if they reported on either ACEI or ARB treatment in comparison with placebo or alternative therapy but were excluded if none of these control groups were present (e.g., excluding the recent ONTARGET [Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial]). Any discordance between the reviewers was resolved by discussion. For the main analysis, only reports including absolute or percent rates of AF development or recurrence derived from prospective studies randomized for ACEI or ARB treatment and alternative therapy or placebo were included. In a subanalysis, we excluded those trials in which AF had not been a pre-specified end point (i.e., in which AF was analyzed post-hoc, which was the case in some of the primary prevention studies). For final sensitivity analysis of all data, the main analysis was repeated after the additional inclusion of published nonrandomized observational studies and those in which initial randomization was not for ACEI or ARB therapy (e.g., Palardy et al. [16]). Studies reporting AF rates in the context of cardiac surgery and in the context of catheter ablation procedures were not included. The last follow-up observation was entered into these analyses, and AF rates and odds ratios (ORs) were calculated based on the intention-to-treat principle. In 1 study, the data from 2 control arms were pooled (17). Two studies had separate treatment arms with ACEIs and ARBs (18,19), which were either pooled for the analysis of effects of ACEIs and ARBs combined or taken as separate strata.

Statistical analysis. Meta-analysis was performed using RevMan version 4.2 for Windows (The Nordic Cochrane Centre, Copenhagen, Denmark). Statistical heterogeneity across the various trials was tested using the Q statistic, and I^2 was calculated to quantify inconsistency among trials. A random-effects model was used to weight effect sizes by sample size to calculate weighted mean effect sizes (20). These are presented as ORs with 95% confidence intervals (CIs). A value of $p < 0.05$ (2-sided) was considered statistically significant.

Results

Of the identified studies, 23 were randomized for ACEI or ARB treatment or placebo or alternative therapy, while 5 were not randomized (21–25) and 1 was randomized for antiarrhythmic drugs but not for ACEI or ARB treatment (16). The characteristics of all trials are summarized in Table 1. Our primary analysis included only those studies randomized for ACEI or ARB treatment or placebo or alternative therapy. These included a total of 87,048 pa-

Table 1 Characteristics of Included Studies

Study	Patient Group	Study Design	n	Follow-Up (Months)	ACEI/ARB (Type)	Comparator Drug	Outcome	End Point	How AF Diagnosed
Primary prevention									
Hypertension trials									
Hansson et al. (CAPPP), 1999 (26)	HTN	RCT	10,915	73.2	Captopril	Diuretic/BB	All AF	2° end point	Adverse event
Hansson et al. (STOP-2), 1999 (17)	HTN	RCT	6,303	60	Enalapril/lisinopril	Diuretic/BB or CCB	All AF	2° end point	Adverse event
Wachtell et al. (LIFE), 2005 (37)	HTN + LVH	RCT	8,480	57.6 ± 12	Losartan	Atenolol	New-onset AF	2° end point	Yearly ECG
Salehian et al. (HOPE), 2007 (27)	High risk ± HTN	RCT	8,335	54	Ramipril	Placebo	New-onset AF	Post-hoc	Biannual ECG
Schmieder et al. (VALUE), 2008 (30)	HTN + high risk	RCT	13,760	50.4	Valsartan	Amlodipine	New-onset AF	2° end point	Yearly ECG
Yusuf et al. (TRANSCEND), 2008 (28)	High risk ± HTN (ACE intolerant)	RCT	5,701	56	Telmisartan	Placebo	New-onset AF	2° end point	Not stated
Post-MI									
Pedersen et al. (TRACE), 1999 (32)	Post-MI	RCT	1,577	24–48	Trandolapril	Placebo	New-onset AF	Post-hoc	Regular ECG
Pizzetti et al. (GISSI-3), 2001 (31)	Post-MI	RCT	17,711	1.5	Lisinopril	Placebo	New-onset AF	Post-hoc	In-hospital ECG
Heart failure									
Vermes et al. (SOLVD), 2003 (33)	Heart failure	RCT	374	34.8 ± 12	Enalapril	Placebo	New-onset AF	Post-hoc	ECG and Holter monitoring
Ducharme et al. (CHARM), 2006 (34)	Heart failure	RCT	6,379	37.7	Candesartan	Placebo	New-onset AF	2° end point	Adverse event
Maggioni et al. (Val-HeFT), 2005 (35)	Heart failure	RCT	4,395	23	Valsartan	Placebo	New-onset AF	Post-hoc	Adverse event
Secondary prevention									
After cardioversion									
Van den Berg et al., 1995 (43)	Persistent AF + CHF	RCT	18	1.5	Lisinopril	Placebo	Recurrence	1° end point	Holter monitoring
Madrid et al., 2002 (47)	Persistent AF	RCT	154	2	Irbesartan	No irbesartan	Recurrence	1° end point	Regular ECG
Ueng et al., 2003 (49)	Persistent AF	RCT	145	9	Enalapril	No enalapril	Recurrence	1° end point	Regular ECG
Madrid et al., 2004 (48)	Lone persistent AF	RCT	60	7.3	Irbesartan	No irbesartan	Recurrence	1° end point	ECG and Holter monitoring
Grecu et al., 2007 (50)	Lone persistent AF	RCT	36	12	Perindopril	No perindopril	Recurrence	1° end point	Regular ECG
Tveit et al., 2007 (45)	Persistent AF	RCT	137	6	Candesartan	Placebo	Recurrence	1° end point	ECG
Belluzzi et al., 2009 (51)	Lone persistent AF	RCT	62	36	Ramipril	Placebo	Recurrence	1° end point	ECG and Holter monitoring
Disertori et al. (GISSI-AF), 2009 (44)	Persistent AF	RCT	1,442	12	Valsartan	Placebo	Recurrence	1° end point	Telemonitoring
Van Noord et al., 2005 (25)	*Persistent AF*	*OBS*	*107*	*1*	*ACEI*	*No ACEI*	*Recurrence*	*NA*	*Regular ECG*
Fazio et al., 2007 (21)	*Paroxysmal and persistent AF*	*OBS*	*187*	*24*	*ACEI*	*No ACEI*	*Recurrences >2*	*NA*	*ECG*
By medical therapy									
Yin et al., 2006 (19)	Lone paroxysmal AF	RCT	177	24	Losartan or perindopril	Placebo	Recurrence	1° end point	ECG and Holter monitoring
Fogari et al., 2006 (52)	Paroxysmal AF	RCT	222	12	Losartan	Amlodipine	Recurrence	1° end point	ECG
Fogari et al., 2008 (18)	Paroxysmal AF	RCT	369	12	Valsartan or ramipril	Atenolol	Recurrence	1° end point	ECG and Holter monitoring
Fogari et al., 2008 (53)	Paroxysmal AF	RCT	296	12	Valsartan	Atenolol	Recurrence	1° end point	ECG
Palardy et al., 2008 (16)	*Paroxysmal AF*	*RCT*	*401*	*15.6 ± 5*	*ACEI or ARB**	*No ACEI or ARB*	*Recurrence*	*Post-hoc*	*ECG*
Hirayama et al., 2005 (22)	*Paroxysmal AF*	*OBS*	*95*	*99.6 ± 42*	*ACEI*	*No ACEI*	*Persistent AF*	*NA*	*ECG*
Kawamura et al., 2007 (23)	*Paroxysmal and persistent AF*	*OBS*	*125*	*24*	*ACEI or ARB*	*No ACEI or ARB*	*Recurrence*	*NA*	*ECG*
Komatsu et al., 2008 (24)	*Paroxysmal AF*	*OBS*	*58*	*43 ± 18*	*Enalapril*	*No enalapril*	*Persistent AF*	*NA*	*Regular ECG*

Observational studies are in *italics*. *The study by Palardy et al. (16) was initially randomized for amiodarone versus sotalol or propafenone and retrospectively compared for ACEI or ARB versus non-ACEI and non-ARB treatment.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BB = beta-blocker; CAPPP = Captopril Prevention Project; CCB = calcium-channel blocker; CHARM = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CHF = chronic heart failure; ECG = electrocardiography; GISSI-AF = Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico–Atrial Fibrillation; GISSI-3 = Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico-3; HOPE = Heart Outcomes Prevention Evaluation; HTN = arterial hypertension; LIFE = Losartan Intervention For Endpoint Reduction in Hypertension; LVH = left ventricular hypertrophy; MI = myocardial infarction; NA = not applicable; OBS = observational; 1° = primary; RCT = randomized controlled trial; STOP-2 = Swedish Trial in Old Patients With Hypertension-2; TRACE = Trandolapril Cardiac Evaluation; TRANSCEND = Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease; 2° = secondary; Val-HeFT = Valsartan Heart Failure Trial; VALUE = Valsartan Antihypertensive Long-Term Use Evaluation.

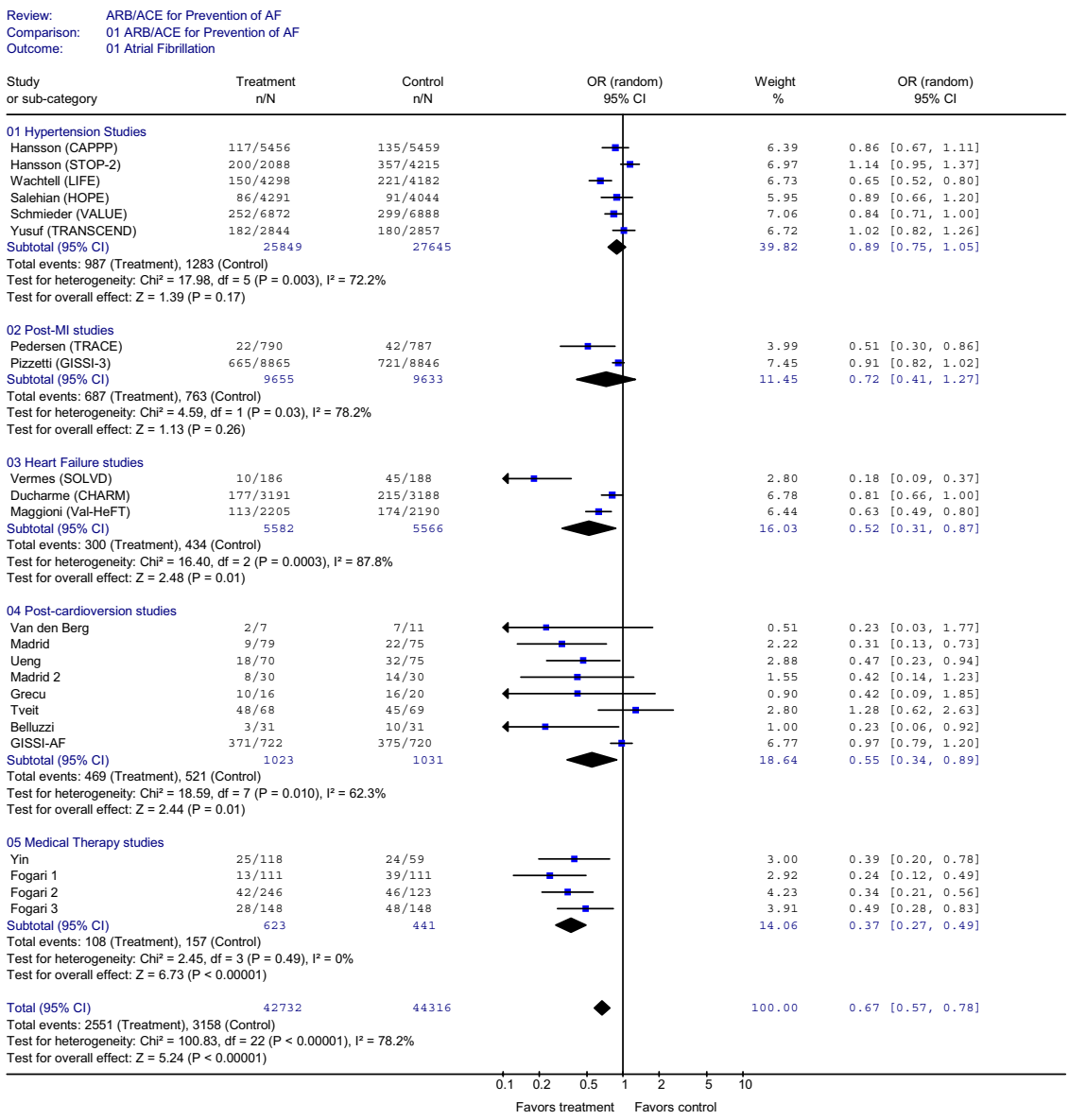

Figure 1 **Effect of RAS Inhibition on Occurrence of AF**

Effect of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) treatment on the occurrence of atrial fibrillation (AF) in primary prevention (hypertension, post-myocardial infarction [MI], and heart failure studies) and in secondary prevention (post-cardioversion and medical therapy studies). CAPPP = Captopril Prevention Project; CHARM = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CI = confidence interval; GISSI-AF = Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico–Atrial Fibrillation; GISSI-3 = Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico–3; HOPE = Heart Outcomes Prevention Evaluation; LIFE = Losartan Intervention For Endpoint Reduction in Hypertension; OR = odds ratio; RAS = renin-angiotensin system; STOP-2 = Swedish Trial in Old Patients With Hypertension-2; TRACE = Trandolapril Cardiac Evaluation; TRANSCEND = Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease; Val-HeFT = Valsartan Heart Failure Trial; VALUE = Valsartan Antihypertensive Long-Term Use Evaluation.

tients: 53,494 in 6 hypertension trials (primary prevention), 19,288 in 2 trials after myocardial infarction (MI) (primary prevention), 11,148 in 3 heart failure trials (primary prevention), 2,054 in 8 studies after cardioversion (secondary prevention), and 1,064 patients in 4 studies of medical therapy for AF (secondary prevention). The effects of ACEIs were studied in 45,841 patients and the effects of ARBs in 41,389 patients.

Overall, treatment with an ACEI or an ARB reduced the OR of developing AF (primary and secondary prevention) by 33% (OR: 0.67; 95% CI: 22% to 43%; $p < 0.00001$) (Fig. 1). Similar benefits were observed when separately considering ACEIs (OR: 0.64; 95% CI: 19% to 50%; $p = 0.0003$) or ARBs (OR: 0.64; 95% CI: 22% to 48%; $p < 0.0001$). However, treatment effects were different among individual trials, as evidenced by a significant test for

heterogeneity ($p < 0.00001$). We therefore analyzed the effect of ACEI or ARB treatment separately in different treatment populations, to more clearly define the clinical conditions in which RAS inhibition is most effective.

Primary prevention. HYPERTENSION. Six trials compared ACEIs or ARBs with other agents for the treatment of arterial hypertension. Overall, no significant reduction in the OR for AF was detectable (OR: 0.89; 95% CI: 0.75 to 1.05; $p = 0.17$). However, there was significant heterogeneity among trials (chi-square test, $p = 0.003$). CAPPP (Captopril Prevention Project) (26), STOP-2 (Swedish Trial in Old Patients With Hypertension-2) (17), the HOPE (Heart Outcomes Prevention Evaluation) study (27), and the recent TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease) (28) did not detect any effect of treatment with an ACEI or an ARB. In contrast, the LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) (29) and the VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) (30) trials, both testing the effect of ARBs, detected significant reductions in the rates of new-onset AF.

POST-MI. Two studies examined the effect of RAS inhibition on the development of AF after MI, both using ACEIs. When combining the evidence from these 2 studies, no beneficial effect of ACEI treatment was detectable overall (OR: 0.72; 95% CI: 0.41 to 1.27; $p = 0.26$). However, these 2 studies came to disparate conclusions, also indicated by a significant test for heterogeneity (chi-square test, $p = 0.03$). In the larger study, the GISSI-3 (Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico-3) study (31), no significant reductions in AF rates were found over a follow-up period of 6 weeks by lisinopril treatment starting within the first 24 h after MI. Of note, most patients (84%) had no evidence of heart failure at the time of MI. In the smaller TRACE (Trandolapril Cardiac Evaluation) study (32), only subjects with evidence of heart failure were included, and the follow-up period was much longer (2 to 4 years). This study detected a significant and large reduction of 49% in the OR for new-onset AF after MI.

HEART FAILURE. Three studies examined the effect of RAS inhibition on AF in patients with heart failure. In the smallest, SOLVD (Studies Of Left Ventricular Dysfunction) (33), the effect of the ACEI enalapril was examined, whereas CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) (34) and Val-HeFT (Valsartan Heart Failure Trial) (35) studied the effects of the ARBs candesartan and valsartan, respectively. Overall, there was a significant beneficial effect of RAS inhibition (OR: 0.52; 95% CI: 0.31 to 0.87; $p = 0.01$). All 3 individual trials demonstrated significant reductions in new-onset AF rates, although there was significant heterogeneity among the studies (chi-square test, $p = 0.0003$). SOLVD, including patients with the most severely impaired left ventricular systolic function among the 3 trials, showed the largest reduction in AF rates (OR: 0.18), whereas reductions in AF rates were more modest in CHARM (OR: 0.81) and Val-HeFT (OR: 0.63).

Secondary prevention. AFTER CARDIOVERSION. Eight trials investigated the effects of RAS inhibition on the recurrence of AF after electrical or chemical cardioversion. Overall, there was a significant reduction in the risk for AF recurrence after cardioversion with the use of ACEIs or ARBs (OR: 0.55; 95% CI: 0.34 to 0.89; $p = 0.01$). The majority of individual trials demonstrated beneficial effects. The recently published GISSI-AF (Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico–Atrial Fibrillation) trial did not detect any effect of treatment with valsartan on the recurrence of AF, which largely accounts for the heterogeneity among studies in this particular patient population (chi-square test, $p = 0.01$).

BY MEDICAL THERAPY. Four studies examined the effects of treatment with ACEIs or ARBs on the recurrence of AF in patients with paroxysmal AF. Overall, there was a significant reduction in the recurrence of AF with ACEI or ARB treatment (OR: 0.37; 95% CI: 0.27 to 0.49; $p < 0.001$). In contrast to the other subgroups, the 4 included studies were homogeneous (chi-square test, $p = 0.49$), and all 4 studies documented large and significant reductions in the risk for AF by RAS inhibition.

SUBANALYSIS EXCLUDING POST-HOC DATA. In secondary prevention, all included trials in the primary analysis had AF pre-specified as their primary end point (Table 1). In some of the primary prevention trials, however, AF had not been a pre-specified outcome parameter. Excluding these trials, the overall result in the hypertension group would still be negative, with an OR of 0.89 ($p = 0.23$), including all studies except HOPE. The hypertension studies then included would remain highly heterogeneous, with no effect in the older studies CAPPP and STOP-2 (AF pre-specified but detected only as an adverse event), no effect in TRANSCEND (AF pre-specified but the method of AF detection not reported), and positive results in LIFE and VALUE (AF pre-specified and detected by yearly electrocardiography [ECG] at core laboratories). No studies would remain in the post-MI group, and 1 study would remain in the heart failure group (CHARM, with a beneficial effect of RAS inhibition; OR: 0.85; $p = 0.05$). Excluding these trials with AF not being a pre-specified end point would not affect the overall results of the meta-analysis, as the overall reduction in the OR for AF would remain at 33% ($p < 0.00001$), although with a slightly wider CI (95% CI: 19% to 44%).

PUBLICATION BIAS AND STUDY SELECTION. We refrained from using funnel plots, which can be misleading when there is a real difference in effect sizes between studies with high precision and those with low precision (36). In our case, except for the GISSI-AF trial, most studies with high

precision were primary prevention trials, whereas studies with low precision were secondary prevention trials, and different treatment effect sizes between these populations are likely. From the 5 trials showing the largest beneficial effect of RAS inhibition, 3 belonged to the group of the 5 smallest trials. Nonetheless, excluding these 5 trials from the analysis still resulted in a significant effect of RAS inhibition on AF rates (OR: 0.77; 95% CI: 0.67 to 0.87; $p < 0.0001$). Finally, for analysis of sensitivity, we repeated the meta-analysis after additional inclusion of the 6 studies not fulfilling the criteria for the primary analysis. After including these studies, the overall reduction in the OR for AF was 35% (OR: 0.65; 95% CI: 0.56 to 0.76; $p < 0.00001$). Thus, including these studies did not diminish the beneficial effect of RAS inhibition in our analysis.

Discussion

The results of the present meta-analysis based on 23 randomized controlled trials (RCTs) indicate that RAS inhibition with either ACEIs or ARBs is effective in the primary and secondary prevention of AF. Our analysis further suggests that in the context of primary prevention, patients with left ventricular hypertrophy and/or heart failure benefit most from RAS inhibition. In secondary prevention after cardioversion of persistent AF or medical therapy for paroxysmal AF, RAS inhibition is overall beneficial.

When considering new-onset AF in patients with arterial hypertension, our analysis of 6 large clinical trials failed to demonstrate any overall effect. These trials, however, were highly heterogeneous. In the 2 oldest trials, CAPPP (26) and STOP-2 (17), sensitivity and accuracy for the detection of new-onset AF may have suffered from AF being ascertained merely as an adverse event. HOPE (27) and TRANSCEND (28) were not "pure" hypertension trials but rather included subjects at high cardiovascular risk, with hypertension being 1 of several qualifying risk factors. Nonetheless, these 2 trials included large numbers of patients with hypertension (>50% in HOPE, >70% in TRANSCEND) but failed to detect any beneficial effects of RAS inhibition. In VALUE (30), hypertension was required as an inclusion criterion, and this study detected a modest but significant reduction in new-onset AF from 4.34% with amlodipine to 3.67% with valsartan. However, this was at odds with blood pressure lowering per se, as the blood pressure reduction was slightly greater in amlodipine-treated patients than in valsartan-treated patients, suggesting that mechanisms beyond blood pressure control may have contributed to the beneficial effects of valsartan. The largest reduction of new-onset AF was found in the LIFE study, from 5.28% in the atenolol group to 2.49% in the losartan group, which was associated with a reduced risk for cardiovascular morbidity and mortality, stroke, and hospitalization for heart failure for similar blood pressure reduction (37). The lower incidence of AF during treatment with losartan was associated with greater regression of left ventricular hypertrophy and greater reduction of left atrial size compared to treatment with atenolol (38,39). Both left ventricular hypertrophy and left atrial volume are known to be strong predictors of AF development (40,41). Although peripheral blood pressure lowering was similar with losartan and atenolol, recent studies suggest that central blood pressure lowering might be inadequate with atenolol because of unfavorable effects on arterial wave reflection (15). Thus, central hemodynamic factors could have contributed to the disparate AF rates in the LIFE study. Also of note is that yearly ECG was performed only in the 2 studies with positive results. Less frequent ECG and in particular analyses based on adverse event rates may give dramatically different results as opposed to those based on yearly ECG: in VALUE, no effect of valsartan on AF rates would be detected if this analysis were based merely on adverse event rates (42). Of final note, impaired detection of AF as an end point, as particularly the case in the older trials, most likely contributed to a more conservative estimate of the efficacy of ACEIs and ARBs (i.e., assuming the baseline randomization process worked, not detecting an end point tends to lead to type II error, resulting in no or less difference between active treatment and control, even though it is biologically present). We believe that all available data should be used for the current analysis, but we also note that the power to detect larger differences is low. However, more sophisticated methods of detecting AF, such as telemonitoring or implantable loop recorders, can overcome this in future studies.

The impression gained from the hypertension trials that patients with structural and/or functional cardiac abnormalities derive the greatest benefit from RAS inhibition is further strengthened by the results of the 2 post-MI studies and the 3 heart failure trials. Of the 2 post-MI studies, only TRACE, which included patients with signs of heart failure at the time of MI, detected a benefit of RAS inhibition with trandolapril (32), whereas GISSI-3 failed to detect a beneficial effect of lisinopril in post-MI patients without heart failure (31). Furthermore, all 3 individual trials in patients with heart failure were able to demonstrate a beneficial effect of RAS inhibition on new-onset AF rates (33–35). Further supporting the link between left ventricular dysfunction and benefit from RAS inhibition, the effect was greatest in SOLVD (33), in which patients were randomized to either enalapril or placebo and in which patients had the most severely impaired left ventricular function among the 3 heart failure trials. However, it should also be noted that the lesser effect of additional therapy with an ARB seen in the more recent CHARM and Val-HeFT trials was most likely also caused by the fact that a large number of patients were already receiving ACEIs as their standard therapy for heart failure.

As a main inclusion criterion of our analysis, all data, including those on primary prevention, were derived from RCTs. However, as a potential limitation of our analysis,

some of the reports on primary prevention were post hoc analyses, and AF was not a pre-specified end point. Because of the large number of patients included in all identified RCTs, we believe that all RCTs should be considered in our analysis, not just those in which AF was a pre-specified end point and, as alluded to earlier, not just those with higher accuracy for the detection of AF. We hope that in the future, more primary prevention studies will be published with AF as a pre-specified end point and with more accurate methods for AF ascertainment. Of note, all of the studies included on secondary prevention, as discussed in the following text, pre-specified AF as their primary end point.

In the recurrence of AF after cardioversion, our meta-analysis showed a beneficial effect of RAS inhibition overall but with significant heterogeneity among individual studies. The first report in post-cardioversion patients, from Van den Berg et al. (43), demonstrated a beneficial effect of lisinopril, but this study was unique in that only patients with concurrent chronic heart failure were included. In the remaining 7 trials, 5 demonstrated beneficial effects and 2 no effect. A potential cause for the lack of an effect of RAS inhibition in these 2 post-cardioversion studies might be the low rates of concomitant use of antiarrhythmic drugs, in particular amiodarone (44,45). Also, in GISSI-AF, the high rate of concurrent ACEI use (57% of subjects) may have obscured any potential effect of valsartan, as pointed out in an editorial accompanying this study (46). Among the 5 trials in which a beneficial effect of RAS inhibition was documented, 3 used amiodarone as concomitant treatment (47–49). Grecu et al. (50) used propafenone instead and detected a beneficial effect of perindopril. In the most recent study by Belluzzi et al. (51), cardioversion was achieved chemically with propafenone. Even though antiarrhythmic drugs were not used after cardioversion, a beneficial effect of RAS inhibition was detected, perhaps because the included patients with lone AF were comparably healthy, and recurrence rates in the placebo group were relatively low (32%).

In the secondary prevention of AF by medical therapy, the included studies were homogenous, with all individual studies finding beneficial effects of RAS inhibition. The study by Yin et al. (19) in lone AF demonstrated that combinations of amiodarone with losartan or perindopril were more effective in preventing recurrence of AF compared with amiodarone alone, with no difference between perindopril and losartan. Perhaps the potent antiarrhythmic effects of amiodarone combine very favorably with the beneficial effect of ACEIs and ARBs on atrial fibrosis and conduction, but further experimental studies are required to confirm this. The unique aspect of this study was that left atrial diameters were also assessed, demonstrating that the addition of losartan or perindopril to amiodarone significantly attenuated the increase in left atrial diameter compared with amiodarone alone. The 3 studies by Fogari et al. (18,52,53) focused on patients with arterial hypertension and used active comparator drugs. The first trial demonstrated that recurrence rates are lower with losartan and amiodarone than with amlodipine and amiodarone (52). The second compared the effects of valsartan, ramipril, and amlodipine without concurrent treatment with amiodarone (18). A lower recurrence rate of AF was found with both RAS inhibitors compared with amlodipine despite similar blood pressure lowering, again suggesting beneficial effects of RAS inhibition beyond blood pressure control. Interestingly, the beneficial effect was greater in patients receiving valsartan compared with ramipril, which was associated with more favorable effects on P-wave dispersion. The third study, in patients with hypertension and type 2 diabetes, demonstrated that valsartan or amlodipine is superior to atenolol or amlodipine, despite similar effects on peripheral blood pressure (53). Again, this might not be true for central blood pressure (15). Furthermore, this study showed that the beneficial effects of valsartan or amlodipine were more pronounced in those patients concurrently treated with amiodarone or propafenone compared with those treated with disopyramide or flecainide. More data in this group will be available after reporting of the ANTIPAF (Angiotensin II Antagonist in Paroxysmal Atrial Fibrillation) trial, examining the efficacy of olmesartan versus placebo in patients with paroxysmal AF. The ANTIPAF trial will provide the first placebo-controlled data in the absence of concomitant therapy with antiarrhythmic drugs, and the detection of AF in this study is being performed by telemonitoring (54).

Our analysis also demonstrates similar benefits of ACEIs and ARBs overall, but analyses in specific subgroups were precluded by too few data when separating ACEI and ARB studies. The hemodynamic effects of these drugs are very similar, and it might well be that ACEIs and ARBs also have similar effects on depolarization, fibrosis, and so on, and therefore similar overall efficacy in preventing AF. There is, however, some evidence for disparate, direct antiarrhythmic effects among specific compounds, even within drug classes. As an example, specific antiarrhythmic effects were found for the losartan metabolite EXP3174 but not for losartan itself or for captopril (55). Furthermore, the previously mentioned study by Yin et al. (19) seems to hint at a slightly greater effect of perindopril over losartan on left atrial remodeling. Clearly, further research is needed in this area. We have already mentioned the issue of pre-defined end points, but considerable improvement is also needed in the detection of AF in future clinical trials. Many episodes of AF are clinically asymptomatic (56), and correspondingly, AF-like symptoms correlate very poorly with true episodes of AF (57). For the assessment of true AF burden, new approaches, including telemetry and implantable loop recorders, are clearly superior to any assessment based on clinical symptoms (adverse event rates) or on more or less frequent ECG. Last but not least, we would like to point out that previous data from the LIFE trial (58) and first results from ACTIVE-I (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) indicate that RAS inhibition reduces cardiovascular mor-

bidity and mortality in patients with persistent AF. RAS inhibition may therefore be effective across the full continuum of AF, from prevention of AF to reducing the consequences in those in whom sinus rhythm can no longer be restored.

Conclusions

Our meta-analysis demonstrates substantial benefits from RAS inhibition in the primary and secondary prevention of AF, supporting the concept of RAS inhibition as an emerging treatment option for the prevention of AF. In primary prevention, benefits were greatest in patients with left ventricular hypertrophy and/or heart failure, but it must be acknowledged that some reports were based on post hoc analyses. In secondary prevention, the data suggest a beneficial effect of RAS inhibition after the cardioversion of persistent AF and in the medical prevention of paroxysmal AF. In secondary prevention, it also appears that RAS inhibition was most effective when patients also received amiodarone. We also need more information on the effects of ACEIs and ARBs on AF in the absence of concomitant antiarrhythmic therapy.

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