

Heart Rhythm Disorders

Prevention of Atrial Fibrillation With Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

A Meta-Analysis

Jeff S. Healey, MD,* Adrian Baranchuk, MD,* Eugene Crystal, MD,† Carlos A. Morillo, MD,*
Michael Garfinkle, BA,† Salim Yusuf, MD, PhD,* Stuart J. Connolly, MD*

Hamilton and Toronto, Ontario, Canada

- OBJECTIVES** This study was designed to identify all randomized clinical trial data evaluating angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for the prevention of atrial fibrillation (AF), to estimate the magnitude of this effect and to identify patient subgroups most likely to benefit.
- BACKGROUND** Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce morbidity and mortality in patients with heart failure, vascular disease, and hypertension. Several reports suggest that they may also prevent the development of AF.
- METHODS** A systematic review of the literature was performed to identify all reports of the effect of ACEIs or ARBs on the development of AF. Eligible studies had to be randomized, controlled, parallel-design human trials of an ACEI or ARB that collected data on the development of AF.
- RESULTS** A total of 11 studies, which included 56,308 patients, were identified: 4 in heart failure, 3 in hypertension, 2 in patients following cardioversion for AF, and 2 in patients following myocardial infarction. Overall, ACEIs and ARBs reduced the relative risk of AF by 28% (95% confidence interval [CI] 15% to 40%, $p = 0.0002$). Reduction in AF was similar between the two classes of drugs (ACEI: 28%, $p = 0.01$; ARB: 29%, $p = 0.00002$) and was greatest in patients with heart failure (relative risk reduction [RRR] = 44%, $p = 0.007$). Overall, there was no significant reduction in AF in patients with hypertension (RRR = 12%, $p = 0.4$), although one trial found a significant 29% reduction in patients with left ventricular (LV) hypertrophy. In patients following cardioversion, there appears to be a large effect (48% RRR), but the confidence limits are wide (95% CI 21% to 65%).
- CONCLUSIONS** Both ACEIs and ARBs appear to be effective in the prevention of AF. This benefit appears to be limited to patients with systolic left ventricular dysfunction or LV hypertrophy. The use of these drugs following cardioversion appears promising but requires further study. (J Am Coll Cardiol 2005;45:1832-9) © 2005 by the American College of Cardiology Foundation

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-II receptor blockers (ARBs) reduce morbidity and mortality in patients with heart failure (HF) (1,2) or systolic dysfunction after myocardial infarction (MI) (3-5) and are effective in the treatment of hypertension (6). Retrospective analyses of some of these trials suggest that these medications may prevent the development or recurrence of atrial fibrillation (AF) (7-14). Atrial fibrillation is associated with a higher risk of stroke, death, and HF. It is therefore important to understand the effect of these agents on the occurrence of AF (15,16).

There are several potential mechanisms by which inhibition of the renin-angiotensin-aldosterone system (RAAS) with ACEIs and ARBs may reduce AF. Al-

though certain drugs may possess direct anti-arrhythmic properties (17), in animal models ACEIs and ARBs appear to prevent AF by attenuating changes in cardiac structure and function (18-22). In these studies, these drugs prevented left atrial dilation, atrial fibrosis, and conduction velocity slowing, and these changes were associated with a lower rate of AF induction with atrial pacing (18,22-24). One study demonstrated that these benefits were not seen in animals treated to identical hemodynamic targets with hydralazine and isosorbide mononitrate, suggesting that the beneficial effect is specifically related to RAAS inhibition (23).

There have been few prospectively designed clinical trials to test whether ACEIs and ARBs prevent AF (7,12). Several secondary analyses of large randomized trials suggest a benefit. A systematic review of published and unpublished data is timely and provides the best way to estimate of the effectiveness of ACEIs and ARBs and identify patient subgroups who may be most likely to benefit.

From the *Population Health Research Institute, McMaster University, and Hamilton Health Sciences, Hamilton, Ontario, Canada; and †University of Toronto, Toronto, Ontario, Canada.

Manuscript received October 8, 2004; revised manuscript received November 15, 2004, accepted November 29, 2004.

Abbreviations and Acronyms

AF	= atrial fibrillation
ACEI	= angiotensin-converting enzyme inhibitor
ARB	= angiotensin-II receptor blocker
CI	= confidence interval
HF	= heart failure
LVEF	= left ventricular ejection fraction
MI	= myocardial infarction
RAAS	= renin-angiotensin-aldosterone system
RRR	= relative risk reduction

METHODS

A comprehensive search was conducted to identify all human randomized controlled trials of ACEIs or ARBs that recorded new or recurrent AF as an outcome. Medline and Embase were searched for any relevant human randomized controlled trials or reviews published since 1980, using the terms “angiotensin-converting enzyme inhibitor,” “angiotensin receptor blockers,” the individual names of all drugs in these classes, and “atrial fibrillation.” The search was limited to English-language publications. Two reviewers then independently evaluated identified titles, and manuscripts were retrieved for any publication that either reviewer felt was potentially relevant. Additional publications were sought using the reference lists of identified papers; published reviews on the topic; and a manual search of abstracts from the scientific sessions of the American College of Cardiology, the American Heart Association, the European Society of Cardiology, and the North American Society of Pacing and Electrophysiology during the past four years. Finally, a second Medline search was done without the term “atrial fibrillation” to identify additional randomized controlled trials of ACEIs and ARBs that might contain data on AF. The results sections and tables of these studies were then examined to see if data on AF were reported. Attempts were made to contact authors of ACEI or ARB trials that did not report on AF.

Two blinded reviewers re-evaluated all of the abstracts and manuscripts identified as potentially relevant, and publications were selected for this review if both reviewers felt that they met the following criteria: 1) randomized controlled human trials with parallel design, 2) comparing an ACEI or ARB to an alternative therapy, and 3) collecting data on AF during follow-up. Studies were included in this review if both authors felt they were relevant. Any discordance between reviewers was resolved by consensus.

Relevant study data were independently abstracted, in duplicate, using a standardized form. Any discrepancies during data abstraction were resolved by consensus. For studies using a factorial design, data on all patients were used in this analysis. Data analysis was performed with Review Manager 4.1 using the random-effects model. Effect sizes were weighted by the sample size to calculate a weighted mean effect size using the Dersimonian and Laird method (25), and the chi-square test was used to assess for

heterogeneity between studies. The effect of treatment was presented using the relative risk.

Identified studies. Our database search identified a total of 1,021 randomized controlled human trials of ACEIs or ARBs, 85 of which included the term “atrial fibrillation.” An additional 14 studies were identified from conference proceedings. These 99 manuscripts and abstracts were blindly reviewed by two investigators who identified 10 relevant studies: 6 from the literature search and 4 from the review of conference proceedings. There was 100% agreement between the two reviewers in the identification of studies. Next, the titles of studies identified in the database search that did not contain the term “atrial fibrillation” were reviewed, and 95 were searched for data on AF. This yielded another two relevant studies with data on AF (26,27). Authors of ACEI and ARB trials that did not present data on AF were contacted to determine if unpublished data existed. No additional available data were identified in this fashion; however, at least two large trials of ACEIs had collected data on AF but have not yet analyzed or presented the results: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (28) and Heart Outcomes Prevention Evaluation (HOPE) study (29). In total, 12 relevant publications were identified, including two reports from the Studies Of Left Ventricular Dysfunction (SOLVD), one examining the incidence of AF at a single large center (11) and the other describing hospital admissions for atrial tachyarrhythmias for the entire study population (30). Despite a smaller number of outcome events (55 of 374 vs. 158 of 6,797), the single-center data were used for this analysis because its primary outcome, the occurrence of AF, was selected as the outcome event for this meta-analysis. Hospitalization for AF, the primary outcome of the other report (30), captured too many other variables and did not directly answer the primary question of this meta-analysis. A sensitivity analysis using the data from this alternative publication (30) was performed.

RESULTS

Of the identified studies, eight were published in manuscript form and three as abstracts. The characteristics of included studies are summarized in Tables 1 and 2. Study populations and trial design were quite different. There were 56,308 patients in the identified studies: 26,403 in three hypertension trials (13,26,27), 17,711 in a trial of patients following MI (14), 1,577 in a second post-MI trial that enrolled only patients with left ventricular (LV) dysfunction (9), 10,319 in four trials of HF (8,11,28,31), and 299 in two post-AF cardioversion trials (7,12). Angiotensin-converting enzyme inhibitors were studied in seven trials and ARBs in four (Table 1). The definition of AF (new vs. all) and the methods used to document AF were different between studies (Table 2) but were similar enough to permit pooled analysis.

Overall, the use of ACEIs or ARBs reduced the relative risk of developing AF by 28% (95% confidence interval [CI]

Table 1. Characteristics of Included Studies

Author/Study, Date	Patient Group	Drug	No. Randomized	Mean Follow-Up	Mean LVEF	% HTN	Rate of AF in Control Group
ACEI trials							
Van den Burg, 1995	AF, CHF	Lisinopril	30	84 days	n/a	n/a	64%
Ueng, 2003	AF	Enalapril	145	270 days (61-575)	51	32	43%
Vermes (SOLVD), 2003	LVD, CHF, NSR	Enalapril	374	3.3 yrs	27	20	24%
Pizetti (GISSI), 2001	Post-MI, NSR	Lisinopril	17,711	42 days	n/a	30	8%
Pedersen (TRACE), 1999	Post-MI, LVD, NSR	Trandolapril	1,577	2-4 yrs	33	22	5%
STOP-H2, 1999	HTN	Enalapril	10,985	5.0 yrs	n/a	100	8%
CAPP, 1999	HTN	Captopril	6,614	6.1 yrs	n/a	100	2%
ARB trials							
CHARM, 2003*	CHF, NSR	Candesartan	5,518	3.2 yrs	39	55	8%
Madrid, 2002	AF	Irbesartan	154	254 days (60-710)	64	42	29%
ValHeFT, 2003*	CHF, NSR	Valsartan	4,409	2 yrs	28	7	8%
Wachtell (LIFE), 2003*	HTN, LVH, NSR	Losartan	9,193	4.9 yrs	n/a	100	6%

*Abstract only.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CHF = congestive heart failure; HTN = hypertension; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NSR = sinus rhythm; Post-MI = post-myocardial infarction.

15% to 40%, $p = 0.0002$). There were similar benefits seen with ACEIs (relative risk reduction [RRR] = 28%, 95% CI 7% to 44%, $p = 0.01$) and ARBs (RRR = 29%, 95% CI 16% to 40%, $p = 0.0002$). However, there were significant differences in treatment effect between individual trials, as indicated by the statistical test for heterogeneity ($p < 0.00001$) (Fig. 1). Patients with the highest rate of AF appeared to benefit the most (Table 1); however, the variability between studies was not explained by this factor alone. Further exploratory analyses determined that differences in study populations accounted for much of this heterogeneity and that the class of drug employed did not (Figs. 1 and 2). The

effect of ACE inhibitors and ARBs in different patient populations is displayed in Figure 2 and is summarized below.

Post-MI. Two studies examining the use of ACEIs following MI came to different conclusions regarding their utility in preventing AF. The Effects of Lisinopril and Transdermal Glycerol Trinitrate Singly and Together on 6-week Mortality and Ventricular Function after AMI (GISSI-3) found no significant reduction in AF with 6 weeks of ACEI therapy initiated within 24 h of MI (14), whereas the Trandolapril Cardiac Evaluation (TRACE) trial found a 48% relative risk reduction (95% CI 13% to 69%) in patients treated with trandolapril, starting 3 to 7

Table 2. Design of Included Studies

Author/Study, Date	Placebo-Controlled	Blinded	Definition of AF	How AF Diagnosed	Outcome Assessment
Van den Berg, 1995	Yes	Yes	Recurrent AF	24-h Holter at 6 and 12-weeks	Blinded investigator
Pedersen (TRACE), 1999	Yes	Yes	New AF	ECG at month 1, 2, and then Q-3 months	Blinded local investigator
Pizetti (GISSI), 2001	Yes	Yes	In hospital AF, not present on admission ECG	All in-hospital ECG	Blinded local investigator
Madrid, 2002	No	No	Recurrent AF	24-h Holter at 1, 6, 12 months Weekly ECG \times 4, then at 2, 3, 6, 12 months or if symptoms	Blinded investigator
Vermes (SOLVD), 2003	Yes	Yes	New AF	All available clinical ECG No routine ECG	Blinded investigator
Ueng, 2003	No	No	Recurrent AF >10 min	Event recorder daily \times 90 s 24 h Holter at 1, 6, 12 months ECG weekly \times 4, then monthly and with symptoms	Investigator
Wachtell (LIFE), 2003*	ACTIVE control	Yes	New AF	Yearly ECG	Blinded investigator
ValHeFT, 2003*	Yes	Yes	New AF	Recorded as study adverse event	Blinded local investigator
CHARM, 2003*	Yes	Yes	New AF	Assessed at last patient visit and with symptoms	Local investigator
STOP-H2, 1999	ACTIVE control	No	All AF	Yearly ECG and if symptoms	Events committee
CAPP, 1999	ACTIVE control	No	New AF	Not stated	Most by committee

*Abstract only.

AF = atrial fibrillation; ECG = electrocardiogram.

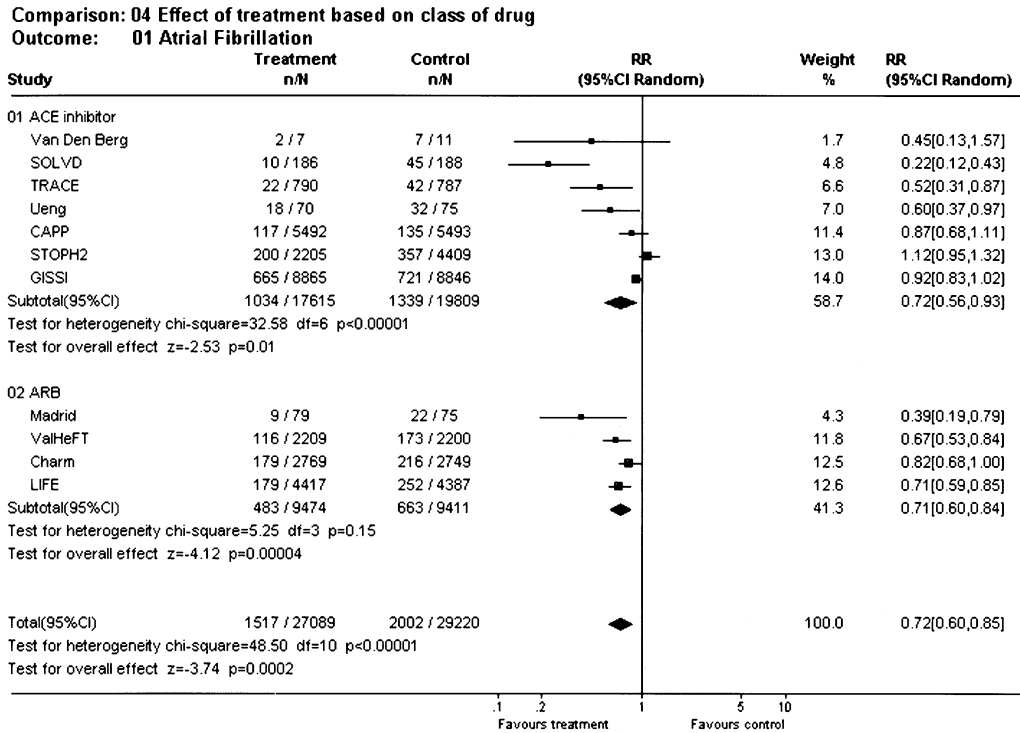


Figure 1. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). CI = confidence interval; RR = relative risk.

days following MI and followed for up to 4 years (9). The incidence of AF was higher in GISSI-3 (Table 1), and, given its much larger size, the number of patients with AF was more than 20 times that seen in the TRACE study. In addition to differences in follow-up periods, the TRACE study enrolled only patients with LV dysfunction, whereas in the GISSI-3 trial 84% of patients had no evidence of HF at the time of MI (14) (Table 1).

Heart failure. In four trials studying ACEIs or ARBs in patients with HF (8,10,11,31), there was an overall 44% relative risk reduction in the development of AF ($p = 0.007$, 95% CI 15% to 63%). All trials demonstrated a significant reduction in AF, although there was still considerable heterogeneity between trials ($p = 0.002$) (Fig. 2). Both ACEIs and ARBs reduced AF, despite the fact that many patients in the ARB trials were already receiving ACEIs. There appeared to be a relationship between the relative risk reduction and LV ejection fraction. Patients in the SOLVD substudy had the most severely impaired LV function (mean left ventricular ejection fraction [LVEF] = 26.7%) and the largest reduction in AF (RRR = 78%). As mean LVEF in HF studies increased, the RRR with therapy decreased (Valsartan Heart Failure Trial [ValHeFT]: mean LVEF = 28%, RRR = 23%; Candesartan in Heart Failure [CHARM]: mean LVEF = 39%, RRR = 18%). However, the CHARM program, which enrolled patients with normal and impaired LV function into distinct studies, found a consistent reduction in AF in both groups (31). No individual study reported on the relationship between ejection

fraction and the reduction in AF seen with RAAS inhibition.

Hypertension. Three trials compared ACEIs (26,27) or ARBs (13) to other agents in the treatment of hypertension (Fig. 2). Overall, there was no significant reduction in AF (RR = 0.88, 95% CI 0.66 to 1.19, $p = 0.4$). However, the results from hypertension trials are statistically heterogeneous (chi-square test, $p = 0.001$) despite similar follow-up periods (Table 1). Only the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial demonstrated a significant reduction in AF (13). The LIFE trial was also the only one of the three studies to use an ARB, and it was the only one to enroll only patients with evidence of LV hypertrophy (13). The CAPP and Swedish Trial in Old Patients with Hypertension-2 (STOP-H-2) trials studied general hypertensive populations (26,27). In the Captopril Prevention Project (CAPP) and STOP-H-2, there was no reduction in AF with ACEIs compared to beta-blockers, calcium channel antagonists, and diuretics (26,27).

Secondary prevention of AF following cardioversion. Two randomized trials were designed to test whether an ACEI (12) or an ARB (7) would reduce the recurrence of AF in patients following electrical cardioversion (Fig. 2). Most patients in these trials had hypertension with preserved LV function (Table 1). Both studies showed a significant reduction in AF with treatment (Fig. 2), which was apparent within weeks of the cardioversion. Both studies were small, had a short follow-up period, and, although randomized, were not placebo controlled (Table 2).

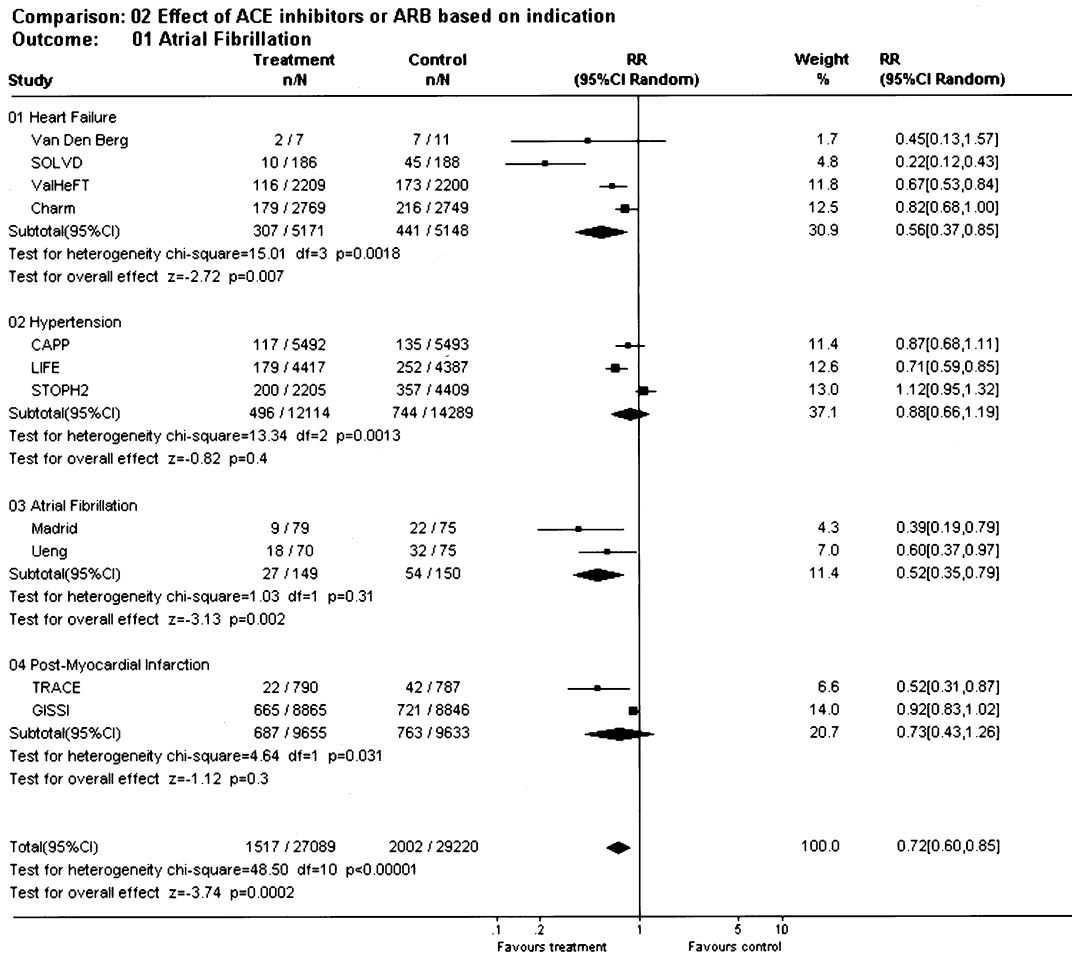


Figure 2. Prevention of atrial fibrillation in various patient populations. Abbreviations as in Figure 1.

Effects of study size, methodology, publication bias, and study selection. The five trials showing the largest effect of treatment (7–9,11,12) were also the five smallest, and together accounted for <5% of patients in this analysis. This systematic review did not find any corresponding small negative trials, and thus there is suggestion of publication bias. Although publication bias could result in an overestimation of treatment effect, this would not likely produce a qualitative change in the results of this analysis, given the relatively large number of patients in this analysis. Indeed, a sensitivity analysis, which excluded all reports of <1,000 patients, still found a significant reduction in AF with ACEIs or ARBs, but the apparent treatment effect was considerably smaller, with a relative risk reduction of 18% (95% CI 5% to 29%, $p = 0.01$).

Overall, the duration of follow-up in individual trials did not appear to influence the effect of therapy (Table 1, Fig. 1). However, the methods used to document AF may have had an impact. Most trials used only periodic electrocardiograms to document AF, usually no more than once per year (Table 2). However, the two post-cardioversion trials (7,12) and two of the HF trials (8,9) performed extensive investigations to document AF (Table 2), and, in these four trials, the benefit seen with ACEIs or ARBs was greater than all

but one of the other trials in this analysis (Fig. 1). This may simply suggest that the benefit of ACEIs and ARBs is more apparent if one uses more sensitive techniques to document AF. Alternatively, these drugs may have a lesser effect on the development of sustained AF that is more likely to be documented on infrequent electrocardiograms.

There were two reports from the SOLVD study regarding AF (11,30); the one used for this meta-analysis reported episodes of AF from a single site (11), the other reported hospitalizations for atrial arrhythmias for the entire SOLVD study population (30). A sensitivity analysis was done using data from the second publication, which found that hospitalizations for atrial arrhythmias occurred in 68 of 3,401 patients randomized to enalapril and 90 of 3,396 randomized to placebo. The use of these data instead of the single-center publication lowered the apparent effect from a relative risk reduction of 29% to a relative risk reduction of 22% (95% CI 11% to 33%, $p = 0.0004$).

DISCUSSION

This meta-analysis, based on 11 randomized controlled trials, indicates that both ACEIs and ARBs are effective at preventing the development of AF. This effect appears to be

most clearly seen in patients with systolic LV dysfunction and clinical HF (9,11). In patients treated for hypertension, a reduction in AF was seen only in one trial evaluating subjects with established LV hypertrophy (13,26,27). Limited data suggests that ACEIs and ARBs reduce AF following cardioversion (7,12).

There are several possible biologic mechanisms by which ACEIs and ARBs might reduce the development of AF. One ARB agent has been reported to possess direct antiarrhythmic properties (17). However, the greater effectiveness of these agents in patients with HF and LV dysfunction and a greater reduction in AF among patients with more severely impaired ejection fraction suggests that their benefit may be related to an improvement in cardiac hemodynamics and a reduction in LV and left atrial wall stress.

The hypertension trials (13,26,27) did not demonstrate a consistent reduction in AF with ACEIs and ARBs. The overall apparent lack of AF prevention in the hypertension trials may reflect the less severe hemodynamic abnormalities in these patients, or, alternatively, result from the use of alternative antihypertensive agents in the control groups of these trials. The hypertension trials were the only trials in this systematic review to use an active therapy in their control groups; therefore, assuming that AF prevention is the result of blood pressure lowering, it is possible that antihypertensive therapy in the control group may also have prevented AF, thereby obscuring any benefit of ACEIs. Indeed, there is some evidence to suggest that other antihypertensive agents, such as calcium channel blockers, may also prevent AF (32). These explanations are consistent with the reduction in AF observed in the LIFE trial (13), the only hypertension trial to show a reduction in AF with RAAS inhibition. This study enrolled only patients with LV hypertrophy, a group of hypertensive patients with more advanced hemodynamic abnormalities. As well, the comparative treatment in the LIFE trial was beta-blockers, a class of agents that is less effective at reducing LV hypertrophy (33) and possibly less effective at preventing AF.

The ACEIs and ARBs likely prevent AF by reversing changes in cardiac structure and function. Left ventricular hypertrophy and left atrial enlargement are elements of cardiac remodeling that are frequent complications of hypertension and HF and have a strong association with the development of clinical AF (34-36). Enlargement of the left atrium and increased atrial pressure may promote the development and maintenance of AF by triggering premature atrial beats (37), slowing atrial conduction velocity, and providing a greater area for re-entry (19-22,38). In animal models of HF, ACEIs and ARBs reduce aspects of cardiac remodeling such as left atrial dilation, dysfunction, fibrosis, and shortening of the atrial effective refractory period (18,22-24); which should, in turn, lead to a reduction in AF (19-21). In one study, enalapril reduced atrial structural and electrical remodeling and AF to a greater extent than hydralazine and isosorbide mononitrate (18), suggesting

that ACEIs may also prevent remodeling and AF by additional mechanisms beyond improved hemodynamics.

Study limitations. The majority of trials included in this analysis were post-hoc reports of randomized trials designed to assess outcomes other than AF. Thus, these data may be prone to multiple-testing error and data-derived emphasis biases. As well, at least 4 additional large trials (HOPE [29], ALLHAT [28], European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease [EUROPA] [39], and Valsartan Antihypertensive Long-Term Use Evaluation [VALUE] [40]), with a collective total of approximately 70,000 patients, have not yet reported any results on AF, and could potentially affect the results of this analysis. Assuming a 5% incidence of AF, which would be similar to the rate of AF in the hypertension trials already in this analysis, 3,500 events are likely to have occurred in these trials. However, even if the results of all of these trials were neutral (RR = 1.0), a significant reduction in AF with ACEIs or ARBs would still be seen (RRR = 18%, $p = 0.001$, 95% CI 8% to 28%).

Trial methodology may also have had an impact on the estimate of treatment effect. The two post-cardioversion trials both showed a large treatment effect; however, neither was placebo-controlled, only one trial clearly reported that AF was assessed in a blinded fashion (7), and only one trial followed the intention-to-treat principle (7). All of these design issues could inflate the apparent effect of treatment.

Recommendations for clinical practice. It is premature to recommend an ACEI or ARB solely for the prevention or treatment of AF, but these data raise the possibility of an added benefit in patients receiving either agent for HF or hypertension. This benefit underscores the importance of using ACEIs and ARBs in patients with established indications.

Need for a definitive trial. Additional prospective research is required to determine the impact of empiric use of ACEIs or ARBs in patients with AF and to clarify the mechanisms responsible for any reduction in AF recurrence or cardiovascular events. The irbesartan arm of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-I) trial will randomize 9,000 patients with a history of AF, with or without a history of hypertension, to receive an ARB, irbesartan, or placebo. The mean follow-up is three years, and the primary outcome is the composite of stroke, MI, and vascular death. Substudies of ACTIVE-I will examine the effects of irbesartan on the recurrence of paroxysmal AF and on the development of structural cardiac remodeling. As well, additional large trials of ARBs (such as Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment in ACE Intolerant Subjects with Cardiovascular Disease [ONTARGET/TRANSCEND]) are prospectively assessing the effects of ARBs on AF as a secondary outcome (41). Finally, a similar analysis examining the development of AF in trials of beta-blockers or aldosterone antagonists in HF would be

useful to help determine if the reduction in AF is specific to RAAS inhibiting agents; however, such an analysis was not feasible as part of this study, as there are currently no published manuscripts with data on AF incidence from these trials. Once available, these results will expand our current understanding of the role of ACEI or ARB therapy.

Conclusions. A clinically significant reduction in AF is seen in patients treated with either ACEIs or ARBs. There is substantial heterogeneity between the trials included in this analysis, which is partially explained by differences in patient population and LV function. The reduction in AF with ACEIs and ARBs appears to be related, in part, to the hemodynamic effects of these drugs, although these two classes of agents may also possess specific properties that help prevent AF. Ongoing research will help clarify these issues.

Reprint requests and correspondence: Dr. Jeff S. Healey, McMaster University-General Site, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada. E-mail: healeyj@hhsc.ca.

REFERENCES

- Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995;273:1450-6.
- Granger CB, McMurray J, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative Trial. *Lancet* 2003;362:772-6.
- Cleland JG, Erhardt L, Murray G, Hall AS, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE study Investigators. *Eur Heart J* 1997;18:41-51.
- Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril or both in myocardial infarction complicated by heart failure, left ventricular dysfunction or both. *N Engl J Med* 2003;349:1893-906.
- Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin converting enzyme inhibitor Trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333:1670-76.
- Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:995-1003.
- Madrid AH, Bueno MG, Rebollo JMG, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation. *Circulation* 2002;106:331-6.
- Van den Berg MP, Crijns HJGM, van Veldhuisen DJ, Griep M, De Kam PJ, Lie KI. Effects of lisinopril in patients with heart failure and chronic atrial fibrillation. *J Card Fail* 1995;1:355-63.
- 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;100:376-80.
- Val-HeFT. Post-hoc analysis suggests valsartan reduces new AF in patients with heart failure. Presented at: ESC Congress 2003, Clinical Trial Update II: Heart Failure, Presentation #2457; August 30 to September 3, 2003; Vienna, Austria.
- Vermes E, Tardif J-C, Bourassa MG, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction. *Circulation* 2003;107:2926.
- Ueng KC, Tsai TP, Yu WC, 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;24:2090-8.
- Wachtell K, Lehto M, Gerds T, 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;45:712-9.
- Pizzetti F, Turazza FM, Franzosi MG, et al. Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: the GISSI-3 data. *Heart* 2001;86:527-32.
- Kannel WB, Wolf PA, Benjamin EJ. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;82:2N-9N.
- Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. *J Am Coll Cardiol* 2001;37:371-8.
- Moreno I, Caballero R, Gonzalez T. Efectos del irbesartan sobre los canales de potasio responsables de la repolarizacion cardiaca humana. *Rev Esp Cardiol* 2002;55:148.
- Shi Y, Tardif J-C, Nattel S. Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure. *Cardiovasc Res* 2002;54:456-61.
- Morillo CA, Klein GJ, Jones DL, Guiradon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. *Circulation* 1995;91:1588-95.
- Ravelli F, Alessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. *Circulation* 1997;96:1686-95.
- Wijffels MC, Kirchhof CJ, Dorland R, Alessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* 1995;92:1954-68.
- Shi Y, Ducharme A, Li D, Gaspo R, Nattel S, Tardif JC. Remodeling of atrial dimensions and emptying function in canine models of atrial fibrillation. *Cardiovasc Res* 2001;52:217-25.
- Li D, 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;104:2608-14.
- Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. *Circulation* 2000;101:2612-7.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
- Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPP) randomised trial. *Lancet* 1999;353:611-6.
- Hansson L, Lindholm LH, Ekblom T, 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;354:1751-6.
- The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. *JAMA* 2002;288:2981-97.
- The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145-53.
- Alsheikh-Ali AA, Wang PJ, Rand W, et al. Enalapril treatment and hospitalization for atrial tachyarrhythmias in patients with left ventricular dysfunction. *Am Heart J* 2004;147:1061-5.
- Swedberg K, Pfeffer M, Coen-Solal A, et al. Prevention of atrial fibrillation in symptomatic chronic heart failure by candesartan: results from the CHARM study (abstr). *J Am Coll Cardiol* 2004;43 Suppl A:222A.
- De Simone A, De Pasquale M, De Matteis C, et al. Verapamil Plus Antiarrhythmic Drugs Reduce Atrial Fibrillation Recurrences After an Electrical Cardioversion (VEPARAF study). *Eur Heart J* 2003;24:1425-9.
- Schmieder RE, Schlaich MP, Klingbeil AU, Martus P. Update on reversal of left ventricular hypertrophy in essential hypertension (a meta-analysis of all randomized double-blind studies until December 1996). *Nephrol Dial Transplant* 1998;13:564-9.
- Tsang TS, Barnes ME, Bailey KR, et al. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. *Mayo Clin Proc* 2001;76:467-75.

35. Benjamin EJ. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994; 271:840-44.
36. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation: the Framingham Heart Study. *Circulation* 1994;89:724-30.
37. Kalifa J, Jalife J, Zaitsev AV, et al. Intra-atrial pressure increases rate and organization of waves emanating from the superior pulmonary veins during atrial fibrillation. *Circulation* 2003;108:668-71.
38. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation* 1999;100:87-95.
39. Fox KM, for the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of Perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-8.
40. Weber MA, Julius S, Kjeldsen SE, et al. Blood pressure dependent and independent effects of anti-hypertensive treatment on clinical events in the VALUE trial. *Lancet* 2004;363:2049-51.
41. Teo K, Yusuf S, Anderson C, et al. Rationale, design, and baseline characteristics of 2 large, simple randomized trials evaluating telmisartan, ramipril and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND). *Am Heart J* 2004;148:52-61.