Enalapril Decreases the Incidence of Atrial Fibrillation in Patients With Left Ventricular Dysfunction

Insight From the Studies Of Left Ventricular Dysfunction (SOLVD) Trials

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Background—Atrial fibrillation (AF) is frequently encountered in patients with heart failure (HF) and is also a predictor of morbidity and mortality in this population. Recent experimental studies have shown electrical and structural atrial remodeling with increased fibrosis in animals with HF and have suggested a preventive effect of ACE inhibitors (ACEi) on the development of AF. To verify the hypothesis that ACEi prevent the development of AF in patients with HF, we conducted a retrospective analysis of the patients from the Montreal Heart Institute (MHI) included in the Studies Of Left Ventricular Dysfunction (SOLVD).

Methods and Results—Clinical charts were reviewed and serial ECGs interpreted by a single cardiologist blinded to drug allocation. Patients with AF or flutter on the baseline ECG were excluded. Baseline characteristics were obtained from the SOLVD databases. The mean follow-up was 2.9±1.0 years. Of the 391 patients randomly assigned at MHI, 374 were in sinus rhythm at the time of random assignment, with 186 taking enalapril and 188 taking placebo. Baseline characteristics were similar in the two groups except for a higher incidence of previous myocardial infarction in the enalapril group. Fifty-five patients had AF during the follow-up: 10 (5.4%) in the enalapril group and 45 (24%) in the placebo group (P<0.0001). By Cox multivariate analysis, enalapril was the most powerful predictor for risk reduction of AF (hazard ratio, 0.22; 95% CI, 0.11 to 0.44; P<0.0001).

Conclusions—Treatment with the ACEi enalapril markedly reduces the risk of development of atrial fibrillation in patients with left ventricular dysfunction. (Circulation. 2003;107:2926-2931.)

Key Words: angiotensin • inhibitors • fibrillation • heart failure

Atrial fibrillation (AF) is a common finding in patients with heart failure (HF), its prevalence increasing with the severity of the disease and reaching 40% in advanced stages.1,2 AF may also cause patients with congestive HF to decompensate, as evidenced by a decline in cardiac index and peak oxygen consumption and worsening of functional class when AF occurs in these patients.3 In this population, the presence of AF is an independent predictor of morbidity and mortality,4–6 increasing the risk of death and cardiovascular hospitalization by 76%.5 AF occurring in the course of experimental HF induced by rapid ventricular pacing is accompanied by atrial electrical and structural remodeling, including atrial dilation, contractile dysfunction, and fibrosis.7,8 Recent studies have demonstrated a role for ACE inhibitors (ACEi) in the prevention of this atrial structural remodeling.9,10 Whether chronic ACEi therapy has an impact on the incidence of AF in patients with established left ventricular dysfunction remains unanswered. Accordingly, we conducted a retrospective analysis of the Montreal Heart Institute patients randomly assigned in SOLVD (Studies Of Left Ventricular Dysfunction) to assess the impact of the ACEi enalapril on the incidence of AF in this population.

Methods

Study Population
The patients of the Montreal Heart Institute who were enrolled in the SOLVD trials constituted our study population. SOLVD was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated the effect of the ACEi enalapril on survival in patients with left ventricular (LV) dysfunction (ejection fraction ≤35%).11,12 The design of the study has been reported previously.13 Briefly, from June 1986 to August 1991, 4228 patients with asymptomatic or mildly symptomatic (not requiring treatment with digitalis, diuretics, or vasodilators for heart failure at study entry) LV dysfunction (LVEF ≤0.35) were included in the prevention trial and 2569 patients with overt congestive HF in the treatment trial.13 Patients were randomly assigned to enalapril (5 to 20 mg/d) or placebo. Exclusion criteria included age<80 years, unstable angina, myocardial infarction in the previous month, severe pulmonary disease, renal insufficiency (creatinine level >177 µmol/l), current ACEi
use, or intolerance to ACEI. Follow-up visits were scheduled 2 and 6 weeks after random assignment and every 4 months until the end of the study, for a mean follow-up of 3.4 and 3.1 years for the treatment and prevention trials, respectively.

**Data Collection and Definitions**

Baseline characteristics, medical history, and drug therapy at the time of enrollment were obtained from the SOLVD databases. Serial ECGs were not collected specifically for the SOLVD trials. However, the routine clinical follow-up of patients at our institution usually included a 12-lead ECG. Thus, the medical file of each patient was carefully reviewed, and a single experienced cardiologist, blinded to treatment allocation, interpreted every ECG.

AF was defined as rapid oscillations or fibrillatory waves that vary in size, shape, and timing, associated with an irregular, frequently rapid ventricular response. For the purpose of this study, paroxysmal AF was defined as episodes in which the patient reverted to sinus rhythm spontaneously, with medical therapy or with a single cardioversion, whereas patients who remained in AF despite changes in medical therapy and/or cardioversion were defined as having persistent AF. Episodes occurring during a 24-hour Holter monitoring were also considered. The end points were the development and time to first occurrence of AF on either one 12-lead ECG and/or a 24-hour Holter monitoring recorded during any available follow-up visits (including research, outpatient clinic, or emergency room visits). Participants with significant supraventricular arrhythmia on the baseline ECG (AF or flutter) were excluded. Participants with a history of arrhythmia (either supraventricular or ventricular) but who were in sinus rhythm on the ECG at the time of random assignment were included.

**Statistical Analysis**

The baseline characteristics of the two groups were compared by means of Student’s t test for continuous variables and χ² test for categorical variables. The incidence of AF between the two groups was compared by means of the χ² test. Time to the first occurrence of AF during the follow-up was analyzed by means of Kaplan-Meier curves and compared by means of the log-rank test. To analyze the effect of enalapril on development of AF, a Cox regression analysis was used to take into account the effect of potential confounding baseline variables (age, sex, New York Heart Association class, history of supraventricular or ventricular arrhythmia, ischemic cause, diabetes, and ejection fraction) and time-dependent variables (systolic blood pressure, diastolic blood pressure, pulse pressure, serum potassium, and drug therapy). Cox proportional-hazard models were performed for each variable with treatment (enalapril) forced in all models. Variables with a probability value ≤0.2 were included in a multivariate Cox proportional hazard model. For time-dependent variables, the last value before the occurrence of AF was taken or, if AF did not develop in the patient, the value at the last visit was used. Subgroup analysis was conducted by means of the χ² test. Preliminary assumptions were verified before all analysis. A probability value <0.05 was considered statistically significant. All analyses were performed with SAS version 8.2 (SAS Institute Inc).

**Results**

Among the 391 patients from the Montreal Heart Institute who were randomly assigned in SOLVD, 17 (4.3%) had significant arrhythmia on the baseline ECG at random assignment (16 AF and 1 flutter). The remaining 374 patients constituted our study population: 251 in the prevention arm and 123 in the treatment arm. Of these, 186 were randomly assigned to enalapril and 188 to placebo. The mean follow-up of our patients was 2.9±1.0 years.

**Baseline Characteristics**

The baseline characteristics of the two groups are presented in Table 1. The majority of patients were male, white, with severe LV dysfunction (mean LVEF=27%) of ischemic cause and with NYHA class II symptoms. Medications were well balanced between the two groups. Patients taking enalapril had a higher prevalence of previous myocardial infarction, and there was a trend toward an increase in current smoker status (P=0.072).

**Development of Atrial Fibrillation**

A total of 1491 ECGs were examined: 693 in the placebo group and 798 in the enalapril group (3.7±4.1 and 4.3±5.0 ECGs per patient, respectively, P=NS). Similarly, 43 Holter...
examinations were performed: 19 and 24 in the placebo and enalapril groups \((P=\text{NS})\). A total of 55 patients presented 1 episode of AF during the 2.9 years of follow-up: 10 (5.4%) in the enalapril group and 45 (24%) in the placebo group \((P<0.0001)\), an absolute risk reduction of 18.6%. A brief description of the episodes is provided in Table 2. The majority were paroxysmal and required hospitalization for worsening HF. Despite the new onset of AF in these patients, electrical cardioversion was only performed in a minority.

During follow-up, the probability of remaining in sinus rhythm was significantly higher with enalapril than with placebo \((P<0.0001)\), Figure 1. By Cox multivariate analysis (Table 3), allocation to enalapril was the most powerful predictor for reduction in the incidence of AF (hazard ratio \([\text{HR}]=0.22; 95\% \text{ CI}, 0.11 \text{ to } 0.44; P<0.0001\)). Although the numbers are small, the presence of an ischemic case for LV dysfunction also had an impact on the risk of development of AF \((\text{HR}=4.9; 95\% \text{ CI}, 2.32 \text{ to } 10.41; P<0.0001)\). Age, history of supraventricular arrhythmia, and diuretic use tended to increase the risk of development of AF without reaching significance in the multivariate analysis.

Since the baseline characteristics suggested a trend toward a higher prevalence of supraventricular arrhythmia before random assignment in the placebo group (7.5% versus 3.8%, \(P=0.121\)), we repeated the same analysis of the effect of enalapril on AF incidence after excluding patients \((n=21)\) with a history of supraventricular arrhythmia at baseline. Results remained unchanged, with significantly fewer patients having development of AF with enalapril (8 patients, 4.5%) than with placebo (40 patients, 23%; \(P<0.0001)\).

We further stratified the analysis according to baseline functional status by analyzing the effect of enalapril on the incidence of AF in the two trial arms (prevention and treatment) separately. The beneficial effect of enalapril on the development of AF seemed more marked in the less symptomatic patients: in the SOLVD prevention arm, 4 patients (3.2%) had AF in the enalapril group versus 31 patients (24.6%) in the placebo group \((P<0.0001)\), whereas in the treatment arm, 6 patients (9.8%) had AF with enalapril versus 14 (22.6%) with placebo \((P=0.055)\). Kaplan-Meier curves for time to occurrence of AF in the two trial arms are shown in Figures 2 and 3.

### Discussion

We have shown that chronic ACEi therapy with enalapril markedly reduces the risk of development of AF in patients with LV dysfunction. Our findings extend the numerous beneficial effects of ACEi in patients with HF to the prevention of AF. This study is, to our knowledge, the first to demonstrate a reduction in the incidence of AF with ACEi in a CHF population. Pedersen and coworkers\(^{15}\) have shown a reduction in the occurrence of AF with trandolapril (versus placebo) shortly after an acute myocardial infarction (3 to 7 days). Although LV function was depressed in their patients \((\text{mean } \text{LVEF}=33\%)\), treatment was started at the time when structural myocardial changes were occurring, and this may not reflect the CHF situation in which elevated left atrial pressure has been present for a prolonged period of time; this can at least partly explain the small absolute risk reduction (2.5%) on the incidence of AF observed during the 2 to 4 years of follow-up in TRACE \((\text{TRAndolapril Cardiac Evaluation})\). Furthermore, it is not clear whether these findings reflect a direct effect on atrial structural remodeling or are the result of the attenuation by ACEi of the LV remodeling that occurs after an acute myocardial infarction.\(^{16}\)

The mechanisms by which ACE inhibition exerts its protective effect against AF development in HF are not completely understood. One potential explanation may reside...
in the inhibition of the neurohormonal activation that occurs in congestive heart failure and parallels the severity of the disease. The renin-angiotensin-aldosterone system is involved in many events that could promote AF. Angiotensin II is a potent promoter of fibrosis, leading to cardiac fibroblast proliferation and reduced collagenase activity. Among the underlying effectors through which angiotensin II exerts its action, mitogen-activated protein kinases (MAPKs) and specifically extracellular signal-regulated kinase (ERK) seem to play a major role. Increased atrial expression of ACE and ERK have been demonstrated in experimental HF and in the atrial tissue of patients with a history of AF, together with AT$_1$ receptor downregulation and AT$_2$ upregulation. When these patients were treated with ACEi, the amount of activated ERK2 was reduced, which suggests a causal relation. Experimentally, the atrial structural changes in HF induced by rapid ventricular pacing are attenuated when the ACEi enalapril is given at the onset of pacing and the animals followed for 5 weeks. This is accompanied by a significant reduction in atrial fibrosis and decreased vulnerability of these animals to AF. Whether this represents a direct effect of ACEi on the atrial fibrotic process or is just a consequence of decreased left atrial pressure induced by enalapril is unclear. Angiotensin II causes an increase in atrial pressure, and increased levels of atrial AT$_1$ receptors mRNA have also been demonstrated in response to elevated atrial pressure. Atrial stretch induced by increased atrial pressure may be involved in the initiation and pathogenesis of AF through shortening of refractory period and lengthening of intra-atrial conduction time. Because ACEi cause a decline in both left atrial and LV end-diastolic pressures in patients with HF, it is possible that these agents may decrease the susceptibility to AF simply by lowering atrial pressure and wall stress and consequently by attenuating left atrial enlargement. This hypothesis, however, seems less probable, since Li and colleagues have shown experimentally a reduction in atrial fibrosis only with enalapril despite a similar decrease in left atrial pressure with hydralazine/isosorbide.

In the failing human heart, neurohormonal activation, LV remodeling, elevated left atrial pressure, and atrial fibrosis probably interact to provide a pathophysiologic substrate for AF, which can thus be, at least partially, reversible with ACEi therapy.

Among other potentially beneficial mechanisms, a direct antiarrhythmic effect of ACEi on AF development cannot be excluded. Angiotensin II appears to contribute directly to atrial electrical remodeling, even in the absence of HF. The shortening of the atrial refractory period that occurs during rapid atrial pacing becomes more marked in the presence of angiotensin II but was prevented by treatment with candesartan or captopril. In patients with persistent AF, a beneficial effect of irbesartan on AF recurrence was observed when it was started 3 weeks before electrical cardioversion and combined with amiodarone. Most of the benefit of the AT$_1$ receptor blocker occurred during the first 2 months after conversion, suggesting a role for irbesartan on the atrial electrical remodeling process occurring after cardioversion. The rapidly diverging Kaplan-Meier curves in our study also suggest that enalapril acted in part through functional changes. Finally, enalapril appeared to be more effective in preventing AF in the least symptomatic population. Whether these differences reflect atrial structural changes that are potentially still reversible in the least symptomatic patients or are simply caused by chance (because of the small number of patients involved) remains unknown. Taken together, these experimental and clinical studies suggest that treatment interfering with the renin-angiotensin system (with either ACEi or angiotensin II receptors blockers) have protective effects against AF development, acting through various potential mechanisms in patients with HF.

**Clinical Implications**

Heart failure promotes AF, and the latter increases the risk of thromboembolism, compromises cardiac function, and in-

### TABLE 3. Univariate and Multivariate Analysis of Variables Influencing AF Development

<table>
<thead>
<tr>
<th>Variables</th>
<th>P</th>
<th>Hazard Ratio</th>
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<td><strong>At baseline analysis</strong></td>
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<tr>
<td>Age</td>
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<tr>
<td>Sex</td>
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<td>NYHA class</td>
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<td>Diabetes</td>
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<td>...</td>
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<tr>
<td>EF</td>
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<tr>
<td><strong>Time-dependent</strong></td>
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<td>Calcium channel blockers</td>
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<tr>
<td><strong>Multivariate analysis</strong></td>
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<td>Diuretics</td>
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<td>1.749</td>
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SV indicates supraventricular; EF, ejection fraction; ΔEF, EF at baseline — EF at the end of the study; SBP, systolic blood pressure; ΔSBP, SBP at baseline — SBP at the end of the study; DBP, diastolic blood pressure; and ΔDBP, DBP at baseline — DBP at the end of the study.
creases mortality rates in patients with concomitant HF. Preventing AF with ACEi may thus improve the short- and long-term prognosis of patients with CHF, by breaking this vicious cycle and avoiding the potential risk of antiarrhythmic agents. We can also speculate that the stroke prevention effect of ramipril obtained in the HOPE (Heart Outcomes Prevention Evaluation) study may be due at least partly to reduction in the incidence of AF in their high-risk population.29 With an absolute risk reduction of 18.6% when enalapril is given to patients with HF, 5 patients with congestive HF would need to be treated for 2.9 years to prevent 1 episode of AF.

Limitations of the Study
This study is a retrospective analysis of SOLVD, and the ECGs and Holter monitoring were not collected as an integral part of the studies. Nevertheless, all the available data, regardless of the settings in which they were obtained (during hospitalizations, clinical, research or emergency room visits), were analyzed prospectively and interpreted carefully by a single experienced cardiologist, blinded to treatment allocation.

Conclusions
ACE inhibition with enalapril markedly reduces the risk of development of AF in patients with LV systolic dysfunction.

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Figure 2. Kaplan-Meier curves for time to first occurrence of AF in subgroup of 251 patients of prevention arm randomly assigned to enalapril (solid line) or placebo (dotted line) \( P<0.0001 \), including patients with LVEF ≤0.35 and no history of overt HF requiring treatment at entry in the trial.

Figure 3. Kaplan-Meier curves for time to first occurrence of AF in subgroup of 123 patients of treatment arm randomly assigned to enalapril (solid line) or placebo (dotted line) \( P=0.062 \), including patients with a history of overt HF requiring treatment for symptomatic relief.
References


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