

# Trandolapril Reduces the Incidence of Atrial Fibrillation After Acute Myocardial Infarction in Patients With Left Ventricular Dysfunction

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on behalf of the TRACE Study Group

**Background**—Studies have suggested that ACE inhibitors have an antiarrhythmic effect on ventricular arrhythmias. Whether they have an effect on atrial fibrillation is unknown.

**Methods and Results**—We investigated the effect of ACE inhibition with trandolapril on the incidence of atrial fibrillation in patients with reduced left ventricular function secondary to acute myocardial infarction. The patients in this study were those who qualified for inclusion into the TRAndolapril Cardiac Evaluation (TRACE) study, a randomized double-blind placebo-controlled study and who had sinus rhythm on the ECG obtained at randomization. Patients who fulfilled the criteria for inclusion were randomized to treatment with the ACE inhibitor trandolapril or placebo and were followed up for 2 to 4 years. Development and time to occurrence of atrial fibrillation in one 12-lead ECG recorded at the outpatient visits was the primary end point of this investigation. Of the 1749 patients included in the TRACE study, 1577 had sinus rhythm on the ECG recorded at randomization. Of these patients, 790 were randomized to trandolapril treatment and 787 to placebo treatment. The groups differed only slightly with respect to baseline characteristics. A total of 64 patients developed atrial fibrillation during the 2- to 4-year follow-up period. Significantly more patients developed atrial fibrillation in the placebo group than in the trandolapril group, 5.3% (n=42) versus 2.8% (n=22), respectively,  $P<0.05$ . Cox multivariable regression analysis, adjusting for important baseline characteristics, revealed that trandolapril treatment significantly reduced the risk of developing atrial fibrillation (RR, 0.45; 95% CI, 0.26 to 0.76;  $P<0.01$ ).

**Conclusions**—The results from the present study demonstrate that trandolapril treatment reduces the incidence of atrial fibrillation in patients with left ventricular dysfunction after acute myocardial infarction. (*Circulation*. 1999;100:376-380.)

**Key Words:** angiotensin ■ enzymes ■ fibrillation ■ myocardial infarction

Angiotensin-converting enzyme inhibitor drugs are not antiarrhythmic in the conventional sense, but it has been suggested that they reduce the occurrence of arrhythmias in patients with ischemic heart disease and left ventricular dysfunction.<sup>1</sup> This reduction has been reported primarily as a decrease in the occurrence of ventricular arrhythmias.<sup>2-4</sup> Although the antiarrhythmic mechanism of ACE inhibitors is not completely understood,<sup>1</sup> it is possible that they affect the tendency to develop supraventricular arrhythmias, such as atrial fibrillation. Webster et al<sup>5</sup> observed that ACE inhibition was associated with a trend toward reduction of the frequency of atrial premature beats over time in addition to a decrease in atrial pressure. In another study, Van den Berg et al<sup>6</sup> observed that pretreatment with an ACE inhibitor before DC cardioversion of atrial fibrillation caused a nonsignificant reduction of the relapse rate. These observations indicate that ACE-in-

hibitor treatment might reduce the occurrence of atrial fibrillation, an aspect that has not previously been investigated. In the present investigation, we studied whether the ACE inhibitor trandolapril had any effect on the incidence of atrial fibrillation in patients with left ventricular dysfunction after acute myocardial infarction.

## Methods

The patients in the present study are those who were included in the TRAndolapril Cardiac Evaluation (TRACE) study,<sup>7</sup> a randomized double-blind placebo-controlled study, and who had sinus rhythm at the 12-lead ECG obtained at randomization. The design of the TRACE study has previously been described in detail.<sup>8</sup> Briefly, consecutive patients >18 years old admitted to 27 centers in Denmark in the period May 1990 to June 1992 with acute myocardial infarction were screened for inclusion into the study. Patients who fulfilled the criteria for inclusion and who had impaired left

Received December 31, 1998; revision received April 12, 1999; accepted April 28, 1999.

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ventricular function determined by echocardiography (wall motion index [WMI]  $\leq 1.2$ , corresponding to a left ventricular ejection fraction [LVEF]  $\leq 36\%$ ) were randomized to trandolapril treatment or placebo between days 3 and 7 after the onset of symptoms of myocardial infarction. The study drug was initially given as 1 mg/d and, if possible, was increased to 2 mg/d before discharge from hospital. Approximately 4 weeks after the myocardial infarction, the dose was increased to 4 mg/d if possible. Patients who did not tolerate the dose increase were kept on a lower dose, a minimum of 1 mg/d. The patients were followed up for 2 to 4 years after inclusion. They were seen 1 month after inclusion, after an additional 2 months, and thereafter every 3 months until the study was completed. At each of these outpatient visits, a clinical examination including blood sampling was performed and a 12-lead ECG was recorded. The blood samples were collected according to a standardized method in the morning after an overnight fast and  $\approx 24$  hours after the last dose of the trial medication. All measurements were performed in 1 central laboratory. The evaluation of the ECGs by the investigators was entered into the patient's case report form. Atrial fibrillation was defined as absence of P waves, coarse or fine fibrillatory waves, and completely irregular RR intervals. In addition, at the visits at 3 months, 6 months, and 12 months after randomization, a new echocardiographic examination was performed to determine left ventricular function. The echocardiographic method used for the screening and follow-up procedure has been described in detail.<sup>9,10</sup> In a 9-segment model of the left ventricle, WMI was calculated by use of a reverse scoring system, as described by Berning et al.<sup>10</sup> With this method, WMI multiplied by 0.3 gives a precise estimation of LVEF. In this article, we primarily report the estimated LVEF. For comparison, WMI=2.0 corresponds to LVEF=60%, WMI=1.2 corresponds to LVEF=35%, and WMI=0.6 corresponds to LVEF=18%. The ethics committee of the participating departments approved the study. Informed consent was obtained before patients were included in the study.

## Statistical Methods

Differences in baseline characteristics between the groups were examined by use of  $\chi^2$  and Mann-Whitney tests for categorical and continuous variables, respectively. Categorical data are presented as percentages, and continuous variables are presented as median values. Development and time to occurrence of atrial fibrillation in one 12-lead ECG during the follow-up was the primary end point of the study. The cumulative incidences of atrial fibrillation in the trandolapril-treated group and the placebo group were estimated by the Kaplan-Meier method and are presented in a Kaplan-Meier plot. The log-rank test was used to assess differences between the groups. Cox proportional-hazards regression analysis was used to examine the risk reduction between the groups, with adjustment for important baseline characteristics. A stepwise backward procedure was used, excluding variables above a value of  $P=0.05$ . A value of  $P<0.05$  was considered statistically significant. All statistical analyses were performed by use of the SAS statistical package (SAS Institute).

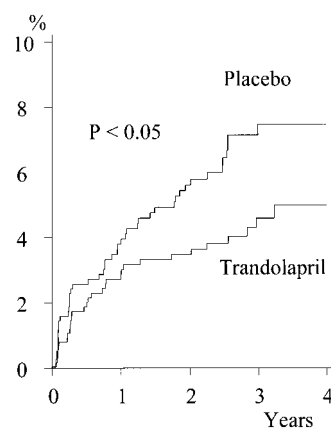
## Results

### Study Population

Of 1749 patients randomized to the TRACE study, 1577 had sinus rhythm at the time of randomization. These are the patients investigated in the present study. Of the 1577 patients with sinus rhythm, 790 were randomized to trandolapril treatment and 787 to placebo treatment.

### Development of Atrial Fibrillation

A total of 64 patients developed atrial fibrillation during the follow-up period. In the placebo group, 5.3% ( $n=42$ ) developed atrial fibrillation, whereas in the trandolapril group, 2.8% ( $n=22$ ) developed atrial fibrillation,  $P<0.05$  (Figure 1). Cox multivariable regression analysis revealed that trandola-



Kaplan-Meier plot of incidence of atrial fibrillation during a 2- to 4-year follow-up period in 1577 post-myocardial infarction patients with reduced left ventricular function and sinus rhythm at baseline randomized to trandolapril treatment or placebo.

pril treatment significantly reduced the risk of developing atrial fibrillation (RR, 0.45; 95% CI, 0.26 to 0.76;  $P<0.01$ ), with adjustment for a number of baseline characteristics.

Eighteen baseline variables were originally included in the Cox model. After the stepwise backward Cox regression procedure was performed, 6 variables remained in the model. The following factors were significantly related to development of atrial fibrillation: severe congestive heart failure at baseline, left ventricular function, male sex, use of digitalis at baseline, age, and systolic blood pressure.

### Baseline Characteristics

The distribution of the baseline characteristics between treatment groups is shown in Table 1. There were differences between the trandolapril group and the placebo group. The patients in the trandolapril group had a slightly higher diastolic blood pressure at baseline than the placebo group. Slightly more patients received nitrates, and there was a trend toward a higher prevalence of history of angina at baseline in the trandolapril group and this group was less often treated with diuretics. The differences were small, and none of the other baseline characteristics differed between the groups. Except for digoxin, very few patients—6 total—received antiarrhythmic treatment at baseline.

### Important Variables During the Follow-Up Period

The serum potassium concentration was almost unchanged during follow-up and was not significantly different between the groups with and without atrial fibrillation during follow-up. In the placebo group, the serum potassium concentrations in the groups that developed/did not develop atrial fibrillation were (median values, 5th and 95th percentiles) at baseline, 4.1 (3.5 to 5.1) mmol/L versus 4.1 (3.4 to 4.8) mmol/L; at day 5, 4.4 (3.6 to 4.6) mmol/L versus 4.4 (3.7 to 5.0) mmol/L; at day 30, 4.2 (3.9 to 4.7) mmol/L versus 4.2 (3.7 to 4.9) mmol/L; and at last visit, 4.6 (3.9 to 4.9) mmol/L versus 4.4 (3.6 to 5.1) mmol/L. In the trandolapril group, the serum potassium concentrations in the groups that developed/did not develop atrial fibrillation were at baseline, 4.1 (3.2 to 5.2) mmol/L versus 4.1 (3.4 to 4.8) mmol/L; at day 5, 4.3 (3.6 to 5.3) mmol/L versus 4.3 (3.6 to 4.8) mmol/L; at day 30, 4.1

**TABLE 1. Baseline Characteristics of 1577 Post-Myocardial Infarction Patients With Sinus Rhythm Randomized to Trandolapril Treatment or Placebo Treatment**

	Trandolapril (n=790)	Placebo (n=787)	P
Clinical characteristics			
Age, y	68	68	NS
Male sex, %	72	71	NS
Smoker, %	75	75	NS
Anterior AMI, %	48	48	NS
Q-wave infarction, %	67	66	NS
LVEF, %	33	33	NS
BMI, kg/m <sup>2</sup>	26	25	NS
CKB, U/L	69	64	NS
SBP, mm Hg	120	120	NS
DBP, mm Hg	80	75	<0.01
HR, bpm	80	80	NS
Killip class 3, %	1	1	NS
Medical history, %			
Previous AMI	36	34	NS
Angina pectoris	48	43	NS
Diabetes mellitus	13	13	NS
Hypertension	22	22	NS
Pulmonary disease	12	13	NS
Treatment, %			
Aspirin	92	91	NS
Digoxin	21	23	NS
β-Blocker	17	15	NS
Calcium antagonists	26	28	NS
Nitrates	56	50	<0.05
Diuretics	62	66	NS
Thrombolysis	46	45	NS

AMI indicates acute myocardial infarction; BMI, body mass index; CKB, creatinine kinase B; SBP, systolic blood pressure; DBP, diastolic blood pressure; and HR, heart rate.

(3.6 to 5.2) mmol/L versus 4.2 (3.5 to 4.8) mmol/L; and at last visit, 4.3 (3.6 to 5.1) mmol/L versus 4.2 (3.5 to 4.9) mmol/L.

As in the main study, LVEF increased during the first year of follow-up. There was a nonsignificant trend toward a lower LVEF in the groups that developed atrial fibrillation, but when the moderate changes of LVEF obtained at 3, 6, and 12 months were included in a multivariate Cox model as a time-dependent variable, the importance of the ACE inhibitor for prevention of atrial fibrillation was not changed. In contrast, development of heart failure as a time-dependent variable in the Cox model was associated with a trend toward development of atrial fibrillation ( $P=0.08$ ), but the effect of trandolapril remained consistent ( $P<0.01$ ).

### Mortality in Patients Who Developed Atrial Fibrillation

There was a trend toward a higher mortality in patients who developed atrial fibrillation during the follow-up period (RR, 1.2; 95% CI, 0.73 to 2.06;  $P=NS$ ).

## Discussion

It has been reported that ACE inhibitors reduce the incidence of ventricular arrhythmias,<sup>2-4</sup> but the present study is the first to demonstrate that ACE-inhibitor treatment also reduces the incidence of atrial fibrillation. In patients with sinus rhythm and left ventricular dysfunction secondary to myocardial infarction, ACE-inhibitor treatment with trandolapril reduced the risk of developing atrial fibrillation by 55% during a 2- to 4-year follow-up period.

### Incidence of Atrial Fibrillation

The incidence of atrial fibrillation in our study was lower than reported in some recent post-myocardial infarction studies.<sup>11-14</sup> However, the incidences observed in those studies cannot be compared with the incidence in our study. Those studies reported the incidence during the entire hospitalization, whereas our study reports the incidence from the time of randomization, which was from day 2 to day 6 (mean, 4.5 days) after the myocardial infarction and during a 2- to 4-year follow-up period.<sup>7</sup> Importantly, patients without sinus rhythm at the time of randomization (10%) were excluded from our study. In fact, the incidence in our study was higher than the incidence in the general population recently reported from the Framingham study.<sup>15</sup>

### Characteristics

The randomized groups differed slightly with respect to a few baseline characteristics (Table 1), but it is unlikely that these differences account for the difference observed with respect to development of atrial fibrillation. Importantly, adjustment for these variables in the multivariable regression analysis did not affect the result.

### Mechanisms

Several possible mechanisms exist by which ACE inhibitors may have antiarrhythmic activity. These include decrease of wall stress, modulation of refractoriness, interference with ion currents, β-blocking properties, modification of sympathetic tone, and stabilization of electrolyte concentrations.<sup>16-21</sup>

### Serum Potassium

It is believed that ACE inhibition stabilizes the serum potassium concentration and that this may prevent the development of arrhythmias.<sup>20</sup> The serum potassium concentration remained virtually unchanged during the follow-up in the groups that developed atrial fibrillation and not different from the groups that did not develop atrial fibrillation. Thus, it is unlikely that the difference in development of atrial fibrillation was caused by changes in the extracellular potassium concentration.

### Ventricular Function and Heart Failure

The difference in incidence of atrial fibrillation cannot be explained by differences in left ventricular systolic function (Table 2). Deterioration of left ventricular function and development of clinical heart failure are expected to precipitate development of atrial fibrillation. Although the observed difference in development of atrial fibrillation could not be explained by differences in left ventricular function, it may be

**TABLE 2. LVEF in 1577 Post-Myocardial Infarction Patients Within the First 12 Months After Randomization to Trandolapril Treatment or Placebo Treatment**

	LVEF, %			
	Trandolapril		Placebo	
	AF	No AF	AF	No AF
Baseline	30 (18–36)	33 (21–36)	30 (18–36)	33 (21–36)
Month 3	30 (24–39)	35 (24–45)	33 (18–45)	33 (21–42)
Month 6	33 (21–42)	36 (24–48)	33 (18–48)	36 (21–48)
Month 12	33 (27–42)	36 (24–48)	35 (18–42)	36 (24–51)

The treatment groups are separated into those who did (AF) or did not (no AF) develop atrial fibrillation during the 2- to 4-year follow-up period. Median values and 5th and 95th percentiles are indicated.

related to the increased development of heart failure observed in the placebo group. In our analysis, there was a trend toward an association with development of severe heart failure, but the effect of ACE inhibition remained consistent.

### Atrial Stretch

We have no data to explain the underlying mechanism of the finding in our study. However, increasing evidence suggests that atrial stretch induced by increased atrial pressure may precipitate atrial fibrillation through an effect on atrial refractoriness.<sup>21,22</sup> Interestingly, it is known that ACE inhibitors decrease atrial pressure,<sup>5</sup> and in patients with chronic mitral regurgitation, ACE inhibitors reduce regurgitation.<sup>23</sup> Therefore, it is possible that ACE-inhibitor treatment minimizes the susceptibility to develop atrial fibrillation by lowering atrial pressure and reducing left atrial enlargement. Whether this is the mechanism of the present finding remains to be demonstrated.

### Mortality

It has recently been reported that development of atrial fibrillation in the general population is associated with increased mortality.<sup>15</sup> Accordingly, we found a trend toward an increased mortality in those patients who developed atrial fibrillation after acute myocardial infarction. We had much shorter follow-up than Benjamin et al<sup>15</sup> and fewer patients who developed atrial fibrillation. A longer follow-up period might have resulted in a significant result. Whether prevention of development of atrial fibrillation also reduces mortality remains unanswered.

In the main TRACE study, trandolapril, in addition to reducing all-cause mortality, also reduced sudden cardiac death, and in the present study, the incidence of atrial fibrillation is reduced. ACE inhibitors attenuate left ventricular enlargement after acute myocardial infarction.<sup>24</sup> Therefore, it might be possible that these findings are all a result of an optimal treatment of the underlying heart disease.

### Limitations

There are limitations of this study. The present analysis was not a prespecified end point in the TRACE study. However, the 12-lead ECGs, which are the basis of the analysis, were

prospectively recorded and evaluated. Therefore, only the statistical analysis was done retrospectively.

The end point of this study was the time to the first occurrence of atrial fibrillation on one 12-lead ECG recorded at the routine follow-up visits in the 2- to 4-year follow-up period. This may not reflect the true burden of atrial fibrillation, and it remains unanswered whether Holter monitoring every 3 months would have captured more cases of atrial fibrillation. It is also important to mention that we did not record episodes that occurred outside the planned routine visits. These limitations may have influenced the registration of atrial fibrillation, but this was similar for the 2 groups. It also means that we did not differentiate between development of paroxysmal and persistent/permanent atrial fibrillation.

### Acknowledgment

The TRACE study was supported by a grant from Roussel Uclaf, Romainville, France, and Knoll, Ludwigshafen, Germany.

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*Circulation*. 1999;100:376-380  
doi: 10.1161/01.CIR.100.4.376

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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