

A CLINICAL TRIAL OF THE ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR TRANDOLAPRIL IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION AFTER MYOCARDIAL INFARCTION

LARS KØBER, M.D., CHRISTIAN TORP-PEDERSEN, M.D., PH.D., JAN E. CARLSEN, M.D., HENNING BAGGER, M.D., PH.D., PER ELIASSEN, M.D., PH.D., KJELD LYNGBORG, M.D., PH.D., JØRGEN VIDEBAEK, M.D., PH.D., DAVID S. COLE, PH.D., LAURENT AUCLERT, M.D., NANCY C. PAULY, M.D., ETIENNE ALIOT, M.D., STIG PERSSON, M.D., PH.D., AND A. JOHN CAMM, M.D., FOR THE TRANDOLAPRIL CARDIAC EVALUATION (TRACE) STUDY GROUP*

Abstract Background. Treatment with angiotensin-converting-enzyme (ACE) inhibitors reduces mortality among survivors of acute myocardial infarction, but whether to use ACE inhibitors in all patients or only in selected patients is uncertain.

Methods. We screened 6676 consecutive patients with 7001 myocardial infarctions confirmed by enzyme studies. A total of 2606 patients had echocardiographic evidence of left ventricular systolic dysfunction (ejection fraction, ≤ 35 percent). On days 3 to 7 after infarction, 1749 patients were randomly assigned to receive oral trandolapril (876 patients) or placebo (873 patients). The duration of follow-up was 24 to 50 months.

Results. During the study period, 304 patients (34.7 percent) in the trandolapril group died, as compared with 369 (42.3 percent) in the placebo group ($P=0.001$). The relative risk of death in the trandolapril group, as compared with the placebo group, was 0.78 (95 percent confidence interval, 0.67 to 0.91). Trandolapril also reduced

the risk of death from cardiovascular causes (relative risk, 0.75; 95 percent confidence interval, 0.63 to 0.89; $P=0.001$) and sudden death (relative risk, 0.76; 95 percent confidence interval, 0.59 to 0.98; $P=0.03$). Progression to severe heart failure was less frequent in the trandolapril group (relative risk, 0.71; 95 percent confidence interval, 0.56 to 0.89; $P=0.003$). In contrast, the risk of recurrent myocardial infarction (fatal or nonfatal) was not significantly reduced (relative risk, 0.86; 95 percent confidence interval, 0.66 to 1.13; $P=0.29$).

Conclusions. Long-term treatment with trandolapril in patients with reduced left ventricular function soon after myocardial infarction significantly reduced the risk of overall mortality, mortality from cardiovascular causes, sudden death, and the development of severe heart failure. That mortality was reduced in a randomized study enrolling 25 percent of consecutive patients screened should encourage the selective use of ACE inhibition after myocardial infarction. (N Engl J Med 1995;333:1670-6.)

A SERIES of clinical trials¹⁻⁷ have examined the effects of angiotensin-converting-enzyme (ACE) inhibitors on survival after acute myocardial infarction. Large studies²⁻⁴ have shown a moderate benefit of short-term ACE inhibition started early after infarction in unselected patients. Other studies, in which long-term treatment was started some days after infarction in selected patients with left ventricular dysfunction⁵ or clinical signs of heart failure,⁶ have shown a greater benefit. Because of the differences among various studies in relative benefit, timing and duration of treatment, and selection of patients, important questions about the role of ACE inhibition remain unanswered. Another problem is that in most studies the portion of the screened population randomly assigned to treatment has been either small or not fully described, and the mortality among enrolled patients has been lower than in epidemiologic studies of unselected patients with myocardial infarction.^{8,9} Thus, even though the total number of patients enrolled in previous studies is large, it is difficult to extrapolate the results of these studies to apply to the wider population of patients with myocardial infarction.

The Trandolapril Cardiac Evaluation (TRACE) study

was designed to determine whether patients who have left ventricular dysfunction soon after myocardial infarction benefit from long-term oral ACE inhibition. We used a strict procedure based on screening of consecutive patients and ensured that the majority of patients with left ventricular dysfunction would be enrolled.

METHODS

A detailed description of the study and demographic information on the screened population have been reported previously.^{10,11} In brief, TRACE was a double-blind, randomized, placebo-controlled study conducted at 27 centers in Denmark. The study was registered with the National Board of Health and the Danish Data Protection Agency and was approved by the regional ethics committees. An independent safety committee reviewed quarterly safety reports, as well as three preplanned interim analyses of mortality.

Screening and Inclusion

All participating hospitals identified all patients with myocardial infarction within their catchment areas. Consecutive patients above the age of 18 years who were hospitalized with myocardial infarction were screened between day 2 and day 6 after the onset of symptoms. The criteria for myocardial infarction were chest pain or electrocardiographic changes suggestive of infarction or ischemia, accompanied by an increase in the level of one or more cardiac enzymes to at least twice the upper limit of the normal value at the laboratory of the participating hospital.

At the time of screening, an echocardiographic examination was recorded on videotape by the investigator and sent by courier to the study office, where within 24 hours, two of us calculated the wall-motion index using a nine-segment model originally described by Heger et al.¹² The scale used for the wall-motion index has been described previously, and the method validated.^{13,14} Potentially eligible patients were those with left ventricular systolic dysfunction (wall-motion index, ≤ 1.2 , corresponding to an ejection fraction ≤ 35 percent¹⁵).

Only the following exclusion criteria were used: an absolute or rel-

From the Department of Cardiology, Gentofte University Hospital (L.K., C.T.-P.), and the TRACE Study Office (J.E.C.), Copenhagen, Denmark; Esbjerg Hospital, Esbjerg, Denmark (H.B.); Slagelse Hospital, Slagelse, Denmark (P.E.); Frederiksberg Hospital, Frederiksberg, Denmark (K.L.); Bispebjerg Hospital, Copenhagen, Denmark (J.V.); the Knebworth Consultancy, Knebworth, United Kingdom (D.S.C.); Roussel-Uclaf, Romainville, France (L.A., N.C.P.); Hôpital Central, Nancy, France (E.A.); University Hospital of Malmö, Malmö, Sweden (S.P.); and St. George's Hospital Medical School, London (A.J.C.). Address reprint requests to the TRACE Study Office, Svanemøllevej 2, DK-2100 Copenhagen, Denmark.

Supported by grants from Roussel-Uclaf and Knoll.

*The members of the TRACE study group are listed in the Appendix.

ative contraindication to ACE inhibition or a definite need for ACE inhibition; severe, uncontrolled diabetes mellitus; hyponatremia (<125 mmol of sodium per liter); an elevated serum creatinine level (2.3 mg per deciliter [$200 \mu\text{mol}$ per liter]); pregnancy or lactation; acute pulmonary embolism; vascular collagen disease; nonischemic obstructive heart disease; unstable angina pectoris requiring immediate invasive therapy; severe liver disease; neutropenia; concurrent immunosuppressive or antineoplastic therapy; drug or alcohol abuse; or treatment with another investigational drug.

Eligible patients were enrolled in the study provided they gave informed consent and could tolerate a test dose of 0.5 mg of trandolapril.

Dose Titration and Duration of Treatment

Double-blind medication was started between day 3 and day 7 after the myocardial infarction. Patients were randomly assigned to receive 1 mg of trandolapril once daily or matching placebo on the basis of a computer-generated assignment scheme with randomization in blocks of four and stratification according to the center and the degree of left ventricular dysfunction (wall-motion index, <0.8 or between 0.8 and 1.2). After two days, the dose was increased to 2 mg of trandolapril once daily or matching placebo. After four weeks, the dose was again increased, to 4 mg once daily or matching placebo. If the highest dose was not tolerated, patients could continue with a dose of 2 mg or 1 mg once daily, but the drug was withdrawn if a dose of 1 mg once daily was not tolerated. Outpatient visits were scheduled one and three months after the infarction, with subsequent visits every three months. Echocardiography was repeated after 3, 6, and 12 months.

The original protocol specified that treatment would continue for at least 12 months. When the results of the Survival and Ventricular Enlargement (SAVE) study were published,³ showing no survival benefit until after almost one year of treatment with ACE inhibitors, the steering committee decided (without any knowledge of the results of the study) to extend the closing date to 24 months after the last random assignment.

End Points

A mortality end-point committee evaluated information on all deaths before the treatment code was broken. In the case of inadequate information, the cause of death was classified as "unknown." If sufficient information was available, death was judged to be due to cardiovascular or noncardiovascular causes. Among deaths from cardiovascular causes, sudden death was defined as death occurring within one hour after the onset of new symptoms. The committee determined the cause of death independently of its timing. Deaths from cardiovascular causes were further specified as due to recurrent infarction or progressive heart failure.

A reinfarction end-point committee evaluated all cases of nonfatal reinfarction reported by the investigators; again, this review was performed before the treatment code was broken. A reinfarction was defined as the onset of new symptoms or typical electrocardiographic changes accompanied by elevated cardiac enzyme levels (or both) or as the development of a new Q wave accompanied by typical symptoms.

The primary end point was death from any cause. Information on survival status was available for all patients at the end of the study. Secondary end points were death from a cardiovascular cause, sudden death, progression to severe heart failure (defined as the first of the following events: hospital admission for heart failure, death due to progressive heart failure, or heart failure necessitating the administration of open-label ACE inhibition), recurrent infarction (fatal or nonfatal), and a change in the wall-motion index.

Statistical Analysis

The calculation of the sample size has been described previously.¹⁰ Analyses of mortality were performed on an intention-to-treat basis. The final analysis of the primary end point, which took into account the interim analyses, was planned as an asymmetric, one-sided test with a significance level of 0.0225 in favor of trandolapril and 0.10 in favor of placebo. Two-sided P values are cited throughout this report.

The base-line characteristics of the treatment and placebo groups were compared with the Cochran–Mantel–Haenszel test.^{16,17} Frequen-

cies of adverse events were compared with the chi-square test. Differences in base-line continuous variables, as well as serial changes in the wall-motion index, were determined by an analysis of variance. Time-to-event curves were generated with the use of Kaplan–Meier estimates.¹⁸ Comparisons of mortality from all causes were made with the log-rank test, with the wall-motion index and center as stratification variables. Comparisons of time-to-event distributions for secondary end points and of the time-to-discontinuation distribution were made without stratification variables. In the analyses of end points other than mortality, data were censored at the time of the first relevant event or two weeks after withdrawal. Relative risk was calculated as a hazard ratio derived from the Cox proportional-hazards regression. For the analysis of subgroups, estimates of relative risk and the associated 95 percent confidence intervals were generated with a Cox proportional-hazards model. Calculations were performed with the SAS software (SAS Institute, Cary, N.C.).

RESULTS

Patient Selection and Demographic Data

Between May 1, 1990, and July 7, 1992, a total of 7001 consecutive episodes of myocardial infarction were evaluated in 6676 patients, with some patients undergoing screening on more than one occasion. Screening with echocardiography resulted in the identification of 2606 eligible patients with a wall-motion index less than or equal to 1.2 , corresponding to an ejection fraction less than or equal to 35 percent. A total of 3920 patients were excluded because they had a wall-motion index that was higher than 1.2 , and 475 were excluded because the wall-motion index could not be determined. As described in detail previously,¹⁴ there was an inverse relation between the wall-motion index and mortality. Among the patients with an index higher than 1.2 , 40 percent had signs of congestive heart failure,¹¹ and the overall mortality at one year was 12 percent. Among the 2606 patients who were eligible for the trial (i.e., those with a wall-motion index ≤ 1.2 , indicating severe left ventricular systolic dysfunction), 74 percent had signs of congestive heart failure, and mortality at one year was 34 percent.¹¹

Of the 2606 eligible patients, 859 were excluded because of mandatory ACE inhibition (150 patients), cardiogenic shock (101), death during screening (70), renal failure or a single kidney (65), intolerance of the test dose of trandolapril (39), lack of consent (218), or other reasons (216).

Altogether, 1749 patients (67 percent of those with a wall-motion index ≤ 1.2 , plus 2 patients erroneously enrolled even though they had an index >1.2) were included: 876 in the trandolapril group, and 873 in the placebo group. There were no important differences between the base-line characteristics of the two groups (Table 1).

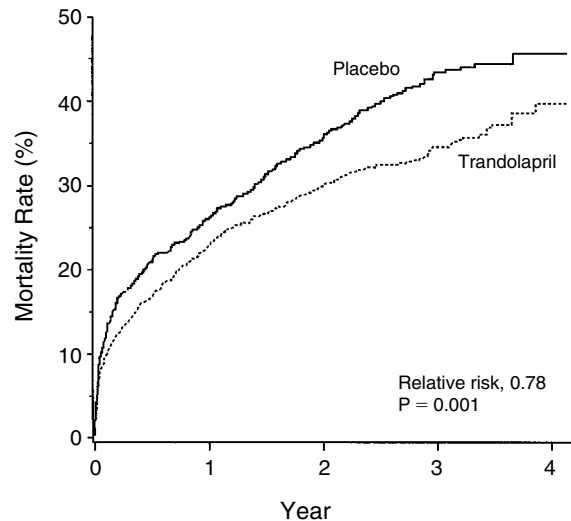
Mortality

The three preplanned interim analyses of mortality were conducted in June 1991 (with a total of 673 patients), February 1992 (with a total of 1209), and August 1993 (with a total of 1745). The outcomes were sent only to the safety committee. The criteria for stopping the study were not met, and the study continued to its planned conclusion.

The mortality from all causes at one year was 24 per-

cent. During the study period, 304 patients in the trandolapril group died (34.7 percent), as did 369 in the placebo group (42.3 percent). Mortality curves are shown in Figure 1. The relative risk of death from any cause in the trandolapril group, as compared with the placebo group, was 0.78 (95 percent confidence interval, 0.67 to 0.91; $P=0.001$). The mortality curves diverged early (Kaplan–Meier estimate of mortality at one month, 8.8 percent in the trandolapril group and 11.2 percent in the placebo group) and continued to diverge throughout the follow-up period.

The effect of trandolapril on overall mortality in subgroups of patients is shown in Table 2. In every subgroup, treatment with trandolapril was associated with a reduction in risk. Classifications of deaths according to cause by the mortality end-point committee are shown in Table 3. There were significantly fewer deaths from cardiovascular causes in the trandolapril group than in the placebo group (226 vs. 288; $P=0.001$; relative risk, 0.75; 95 percent confidence interval, 0.63 to 0.89). There were also significantly fewer sudden deaths in the trandolapril group (105 vs. 133; $P=0.03$;



No. AT Risk					
Trandolapril	876	677	613	319	20
Placebo	873	647	562	280	22

Figure 1. Cumulative Mortality from All Causes among Patients Receiving Trandolapril or Placebo.

Table 1. Base-Line Characteristics of 1749 Patients Assigned to Receive Trandolapril or Placebo.*

CHARACTERISTIC	TRANDOLAPRIL (N = 876)	PLACEBO (N = 873)
Mean age (yr)	67.7	67.3
Male sex (% of patients)	72	71
Body-mass index	25.8	25.6
Clinical history (% of patients)		
Hypertension	23	23
Diabetes mellitus	13	14
Angina pectoris	47	44
Previous myocardial infarction	37	34
Heart failure	21	23
Current or previous smoker	73	75
Infarct type and location (% of patients)		
Anterior Q wave	47	47
Inferior Q wave	19	18
Non-Q wave	14	15
Other or mixed	13	11
Mean time from infarction to randomization (days)	4.5	4.5
Events between infarction and randomization (% of patients)		
Killip class ≥ 2 †	59	59
Thrombolysis	45	44
Cardiac status at randomization		
Mean wall-motion index	1.0	1.0
Killip class ≥ 2 (% of patients)	21	21
NYHA class 1 (% of patients)	42	40
Systolic pressure (mm Hg)	122	120
Diastolic pressure (mm Hg)	76	75
Heart rate (beats/min)	81	81
Medications (% of patients)		
Aspirin	92	90
Beta-blocker	17	15
Calcium antagonist	28	28
Diuretic	64	68
Nitrates	56	50
Digoxin or digitalis	26	29

*There were no significant differences in any of the characteristics, except the use of nitrates ($P<0.005$). The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. NYHA denotes New York Heart Association.

†The Killip class was the highest value recorded between infarction and randomization.

relative risk, 0.76; 95 percent confidence interval, 0.59 to 0.98). Time-to-event curves for these secondary end points are shown in Figure 2.

Other Clinical End Points

Progression to severe heart failure occurred in 125 patients in the trandolapril group and 171 in the placebo group (relative risk, 0.71; 95 percent confidence interval, 0.56 to 0.89; $P=0.003$). Heart failure developed significantly earlier in the placebo group than in the trandolapril group (Fig. 2). Eighty-two patients receiving trandolapril and 103 receiving placebo died from heart failure.

There was a trend toward a reduction in recurrent fatal or nonfatal infarction among the patients receiving trandolapril, as compared with those receiving placebo (Fig. 2). There were 99 fatal or nonfatal reinfarctions in the trandolapril group and 113 in the placebo group ($P=0.29$; relative risk, 0.86; 95 percent confidence interval, 0.66 to 1.13).

At base line and after 3, 6, and 12 months, the mean wall-motion index was 1.03, 1.12, 1.16, and 1.15, respectively, in the trandolapril group and 1.03, 1.10, 1.15, and 1.18, respectively, in the placebo group. After three months, the mean change from the base-line index was 0.09 in the trandolapril group and 0.06 in the placebo group ($P=0.03$). This statistically significant difference was absent at 6 and 12 months.

Follow-up and Withdrawal

The follow-up period was 24 to 50 months. Apart from the patients who died, 328 (37.4 percent) were withdrawn from the trandolapril group and 310 (35.5 percent) from the placebo group. The need for open-label ACE inhibition to treat heart failure was a more common reason for withdrawal in the placebo group

Table 2. Relative Risk of Death from Any Cause in Subgroups of Patients Receiving Trandolapril or Placebo.*

VARIABLE	TRANDOLAPRIL	PLACEBO	RELATIVE RISK WITH TRANDOLAPRIL (95% CI)
	(N = 876)	(N = 873)	
	<i>no. of deaths/no. of patients</i>		
Age (yr)			
≥65	247/571	278/551	0.83 (0.70–0.98)
<65	57/305	91/322	0.62 (0.45–0.86)
Sex			
Male	203/627	256/621	0.74 (0.62–0.89)
Female	101/249	113/252	0.90 (0.69–1.18)
Wall-motion index†			
<0.8 (LVEF <25%)‡	53/89	62/90	0.87 (0.60–1.26)
0.8–1.0 (LVEF 25–30%)	136/308	173/322	0.76 (0.61–0.95)
>1.0 (LVEF >30%)	115/479	134/461	0.80 (0.63–1.03)
Anterior infarction			
Yes	110/407	153/412	0.67 (0.53–0.86)
No	191/463	215/457	0.86 (0.71–1.05)
Previous infarction			
Yes	130/322	149/297	0.76 (0.60–0.97)
No	173/552	219/573	0.79 (0.65–0.97)
Killip class ≥1‡			
Yes	232/513	273/512	0.82 (0.69–0.98)
No	72/363	96/361	0.70 (0.52–0.96)
Diuretic therapy at randomization			
Yes	247/558	307/591	0.82 (0.70–0.97)
No	57/318	62/282	0.78 (0.54–1.12)
Thrombolytic therapy			
Yes	101/395	117/386	0.84 (0.64–1.09)
No	203/480	252/487	0.77 (0.64–0.92)
Use of aspirin			
Yes	271/803	318/788	0.81 (0.69–0.95)
No	33/73	51/85	0.64 (0.41–0.99)
Use of beta-blockers			
Yes	26/148	36/130	0.60 (0.36–1.00)
No	278/728	333/743	0.82 (0.70–0.96)
Residual angina			
Yes	79/211	89/193	0.82 (0.60–1.11)
No	225/665	280/680	0.78 (0.66–0.93)
Nitrate therapy			
Yes	175/489	188/434	0.82 (0.66–1.00)
No	129/387	181/439	0.75 (0.60–0.94)

*Data on anterior infarctions were missing for 10 patients, data on previous infarctions were missing for 5, and data on thrombolytic therapy were missing for 1. CI denotes confidence interval, and LVEF left ventricular ejection fraction.

†The LVEF represents an approximate translation from the wall-motion index, as determined according to the method of Berning et al.¹⁵

‡The Killip class was the highest value recorded between infarction and randomization.

(accounting for 75 patients) than in the trandolapril group (accounting for 48). Other important reasons for withdrawal were cough (in 39 patients in the trandolapril group and 13 in the placebo group), hypotension (in 18 and 7, respectively), and a reduction in kidney function (in 18 and 6, respectively).

Tolerance

The most frequently reported adverse events in the trandolapril and placebo group, including those that differed significantly between the two groups, are shown in Table 4. The tolerance profile of trandolapril was similar to that of other ACE inhibitors. Cough was reported frequently in both groups, probably because the patients were asked specifically about this symptom at every follow-up visit.

DISCUSSION

This study has demonstrated that survival was improved among patients with left ventricular systolic dys-

function who were selected from among consecutively screened patients with myocardial infarction and treated with the ACE inhibitor trandolapril for two to four years. The improvement in survival was observed whether or not there were clinical signs of heart failure. There was an associated reduction in deaths from cardiovascular causes and sudden deaths, as well as in the development of severe heart failure. Fatal or nonfatal reinfarctions were not significantly reduced in frequency.

Unlike other large trials of treatment after myocardial infarction, the TRACE study was performed in one small country, Denmark. This approach facilitated the screening of consecutive patients and the inclusion of a large fraction of the target population with left ventricular systolic dysfunction.^{10,11} Consequently, patients in TRACE were older than in other studies and had a higher mortality rate. Among the patients excluded because of a wall-motion index that was greater than 1.2, the mortality rate at one year was 12 percent.¹⁴ This rate is lower than that among the patients in our study with a lower wall-motion index but higher than the rates reported in most studies. We attribute these differences to systematic consecutive screening and complete regional case ascertainment without an upper age limit.

To date, the TRACE study is the only trial of ACE inhibition after myocardial infarction that has shown a significant reduction in sudden deaths. We defined sudden deaths as those occurring within one hour after the onset of symptoms. It is therefore uncertain whether our result reflects the protective effect of trandolapril against severe arrhythmias, as suggested by studies in animals,¹⁹ or a reduction in sudden deaths from nonarrhythmic causes. The importance of the concept of sudden death as an indicator of death from arrhythmic causes in patients with heart failure has been challenged.²⁰ We did not observe a reduction in recurrent infarction, as was observed in the SAVE study.⁵ Our definition of reinfarction was strict, and the overall rate of a first recurrent infarction was low. The validity of the reduction in the rate of clinical reinfarction reported in the SAVE study has been subject to criticism.²¹ No single trial using strict, predefined criteria

Table 3. Causes of Death in the Trandolapril and Placebo Groups.*

	TRANDOLAPRIL (N = 876)	PLACEBO (N = 873)
Cardiovascular	226	288
Timing		
Sudden	105	133
Not sudden	117	142
Unknown	4	13
Cause		
Heart failure	82	103
Recurrent infarction	34	47
Arrhythmia	24	36
Other	24	27
Unknown	62	75
Noncardiovascular	78	81
Total	304	369

*The classification of cardiovascular deaths according to timing and cause was performed independently. The classification of arrhythmia as the cause of death was made independently of the classification of heart failure or recurrent infarction.

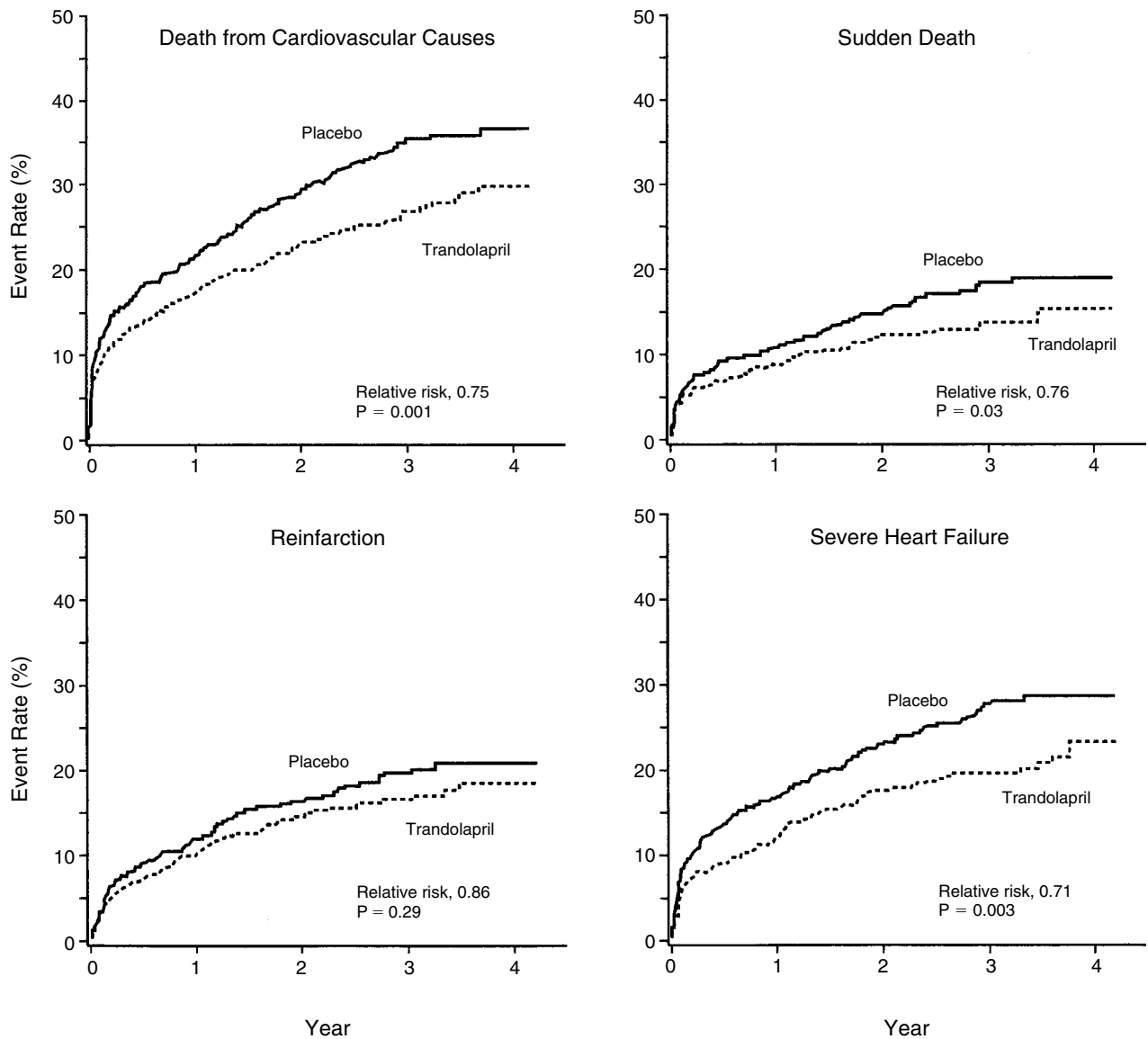


Figure 2. Event Rates for the Secondary End Points of Death from Cardiovascular Causes, Sudden Death, Reinfarction, and Severe or Resistant Heart Failure among Patients Receiving Trandolapril or Placebo.

for reinfarction has shown that long-term ACE inhibition has a clear-cut benefit with respect to recurrent infarction.

Like the SAVE study,⁵ the TRACE study included patients with left ventricular systolic dysfunction, but there are important differences between the two trials. In the SAVE study, left ventricular function was measured by radionuclide cardiography an average of 11 days after infarction. Patients with overt heart failure or active ischemia were specifically excluded from the SAVE study, whereas the TRACE study was designed to include the majority of patients with left ventricular systolic dysfunction.

The Acute Infarction Ramipril Efficacy (AIRE)⁶ study differed from the SAVE and TRACE studies. In the AIRE study, a 27 percent reduction in mortality was observed among patients treated with ramipril who had clinical signs of heart failure after infarction. The AIRE

substudy of left ventricular function²² indicates that in a substantial fraction of patients, left ventricular function was preserved. On the other hand, patients with left ventricular dysfunction but without signs of heart failure would have been excluded from the AIRE study. In comparison, 40 percent of the patients excluded from the TRACE study because of a wall-motion index higher than 1.2 had clinical signs of heart failure, and 24 percent of the enrolled patients did not have signs of heart failure.

Because similar degrees of reduction in mortality were observed in all three studies, it appears likely that patients with clinical signs of heart failure and preserved left ventricular systolic function will benefit from ACE inhibition. In the TRACE study, the benefit of trandolapril appeared to be similar whether or not there were clinical signs of heart failure. This finding indicates that an assessment of left ventricular function is

Table 4. Incidence of Adverse Events.

EVENT	TRANDOLAPRIL (N = 876)	PLACEBO (N = 873)	P VALUE
	% of patients		
Angina pectoris	36.4	38.1	0.49
Chest pain	3.8	4.2	0.62
Hypertension	3.3	6.8	0.001
Pneumonia	9.9	15.0	0.001
Bronchitis	4.5	6.0	0.16
Dyspnea	3.9	5.3	0.17
Lung disorder	2.2	3.7	0.06
Cough	33.9	21.0	<0.001
Hypotension	31.1	22.2	<0.001
Renal dysfunction	13.7	10.8	0.06
Cerebrovascular accident	5.8	5.7	0.93
Peripheral vascular disorder	3.8	1.8	0.01
Hyperkalemia	4.9	2.6	0.01
Myalgia	4.1	2.9	0.16
Rash	2.7	1.9	0.27
Dyspepsia	5.4	4.5	0.39
Thrombocytopenia	2.4	1.6	0.24
Atrial fibrillation	6.6	8.7	0.10
Atrial flutter	1.8	0.7	0.03
Ventricular fibrilla- tion	2.9	4.8	0.03
Ventricular tachy- cardia	4.3	3.9	0.64

necessary to identify all patients who will benefit from long-term ACE inhibition.

Other trials have evaluated the use of short-term ACE inhibition after acute myocardial infarction in unselected patients. The Fourth International Study of Infarct Survival (ISIS-4)² and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3)³ recruited very large numbers of patients. Both studies found a moderate reduction in short-term mortality among patients treated with captopril for five weeks or lisinopril for six weeks, beginning within 24 hours after infarction. It is likely that the greater benefits of ACE inhibition observed in the more selective trials are also present in the less selective trials but are diluted because of the many patients who did not have a benefit. In the TRACE study, 24 lives were saved after one month of treating 1000 patients. Since 25 percent of consecutive patients with acute myocardial infarction were randomly assigned to treatment and on the assumption that none of the other 75 percent would have benefited from treatment, roughly six lives would have been saved if all the patients had been treated — an outcome very similar to that in the less selective trials — suggesting that the 25 percent of patients who were selected from the screened population account for the entire benefit. The populations screened for the various studies, however, may not have been similar.

In conclusion, the results of our study indicate that at least two thirds of patients who have echocardiographic signs of left ventricular systolic dysfunction three to seven days after a myocardial infarction are candidates for long-term treatment with trandolapril and

that such treatment improves survival and reduces cardiovascular morbidity.

APPENDIX

The TRACE study group included the following members: *Steering Committee:* A.J. Camm, United Kingdom; H. Bagger, P. Eliassen, K. Lyngborg, J. Videbæk, L. Køber, and C. Torp-Pedersen, Denmark; E. Aliot, France; S. Persson, Sweden; N. Pauly, France; and D. Cole, United Kingdom. *Safety Committee:* J.R. Hampton and A. Skene, United Kingdom; and P. Bloch Thomsen, Denmark. *Mortality End-Point Committee:* J. Fischer Hansen, E. Kjølner, and K. Skagen, Denmark. *Reinfarction End-Point Committee:* P. Hildebrandt, S. Rasmussen, and R. Videbæk, Denmark. *Publication Working Group:* L. Auclert, France; D. Cole, United Kingdom; and J. Carlsen, L. Køber, and C. Torp-Pedersen, Denmark. *Echocardiography:* L. Køber, C. Torp-Pedersen, H. Egeblad, and R. Videbæk, Denmark. *Study Office:* J. Carlsen, A. Hansen, N. Carlsen, K. Houe, D. Hansen, L. Agerholm, H. Tveskov, I. Andersen, and C. Deela, Denmark. *Data Management and Statistical Analyses:* Pharmaceutical Research Associates, Charlottesville, Va. — K. Troyer, K. Arthur, A. Brown, D. Handelsman, J. Lien, and S. O'Dell. *Investigators:* Bispebjerg Hospital — J. Videbæk, S. Høiberg, H. Weil, and I. Andersen; Esbjerg Centralsygehus — H. Bagger, O. Pedersen, J. Nørby, B. Bengtsson, and K. Poulsen; Fakse Amtssygehus — K. Kølendorf, N. Krogsgaard, and J. Rolighed; Frederiksberg Hospital — K. Lyngborg, B. Sonne, L. Køber, M. Snøgaard, and D. Raae; Frederikshavn Sygehus — J. Kjærgaard, S. Løvschall, E. Diernaes, T. Hansen, E. Korup, and L. Nielsen; Helsingør Sygehus — J. Petersen, O. Wiemann, E. Agner, and L. Hornum; Herning Centralsygehus — E. Klarholt, H. Vejby-Christensen, S. Nielsen, A. Raft, H. Sauer, I. Højriis, K. Rønne, and A. Henriksen; Hjørring Sygehus — E. La Cour Petersen, E. Madsen, P. Sørensen, H. Sejersen, B. Grønlund, L. Breuning, J. Christiansen, H. Hansen, H. Mørk, and B. Grønhøj; Hvidovre Hospital — I. Christiansen, E. Gyemose, H. Janiche, J. Madsen, S. Stabel, S. Rasmussen, K. Meier, and N. Skov; Hørsholm Sygehus — O. Faber, H. Nielsen, P. Nielsen, N. Ralfskjær, B. Holmgaard, and D. Bustoft; Kalundborg Sygehus — I. Lindbjerg, S. Rasmussen, J. Bing, M. Westergaard, and J. Jacobsen; Kjellerup Sygehus — M. Scheibel, V. Haahr, A. Raft, L. Mansfeld, and A. Fenger; Kolding Sygehus — M. Asklund, C. Olesen, N. Gyldenkerne, B. Severinsen, G. Løwenstein, and I. Metais; Skt. Lukas Stiftelsen — O. Dietrichson, R. Ackermann, B. Hundborg, and L. Koch; Roskilde Amtssygehus i Køge — K. Garde, H. Burchardt, S. Rasmussen, M. Winthereik, H. Luggin, K. Vennervald, I. Christensen, L. Agerholm, and I. Børgesen; Middelfart Sygehus — M. Felsby, C. Clausen, O. May, and P. Glesner; Slagelse Centralsygehus — P. Eliassen, M. Lessing, J. Lomholt, and L. Kjølner-Hansen; Tønder Sygehus — E. La Cour Petersen, M. Brøns, J. Andersen, S. Sækmose, E. Albrechtsen, and M. Lauridsen; Varde Sygehus — B. Dorff, L. Petersen, and K. Poulsen; Gentofte Amtssygehus — P. Fritz-Hansen, C. Torp-Pedersen, P. Hildebrandt, K. Wensell, and U. Jørgensen; Holbæk Centralsygehus — E. Madsen and M. Ottesen; Herlev Amtssygehus — K. Skagen, U. Høst, F. Nielsen, and A. Therkelsen; Ålborg Sygehus — E. Steinmetz, K. Rasmussen, E. Korup, and G. Mikkelsen; Skt. Elisabeth Hospital — E. Kjølner, S. Jørgensen, and O. Østergaard; Sønderborg Sygehus — J. Juul, I. Rasmussen, G. Sørensen, C. Hansen, and N. Tougaard; Århus Amtssygehus — K. Thygesen, P. Søggaard, A. Nørgaard, and L. Pedersen; and Odense Sygehus — B. Nielsen, J. Nielsen, and C. Tveskov.

REFERENCES

- Swedberg K, Held P, Kjekshus J, Rasmussen K, Rydén L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction: results of the Cooperative New Scandinavian Enalapril Survival Study (Consensus II). *N Engl J Med* 1992;327:678-84.
- ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;345:669-85.
- Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;343:1115-22.

4. Chinese Cardiac Study Collaborative Group. Oral captopril versus placebo among 13 634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet* 1995;345:686-7.
5. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;327:669-77.
6. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821-8.
7. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995;332:80-5.
8. Emanuelsson H, Karlson BW, Herlitz J. Characteristics and prognosis of patients with acute myocardial infarction in relation to occurrence of congestive heart failure. *Eur Heart J* 1994;15:761-8.
9. Stevenson R, Ranjadayalan K, Wilkinson P, Roberts R, Timmis AD. Short and long term prognosis of acute myocardial infarction since introduction of thrombolysis. *BMJ* 1993;307:349-53. [Erratum, *BMJ* 1993; 307:909.]
10. The TRACE Study Group. The TRAndolapril Cardiac Evaluation (TRACE) study: rationale, design, and baseline characteristics of the screened population. *Am J Cardiol* 1994;73:44C-50C.
11. Køber L, Torp-Pedersen C. Clinical characteristics and mortality of patients screened for entry into the Trandolapril Cardiac Evaluation (TRACE) study. *Am J Cardiol* 1995;76:1-5.
12. Heger JJ, Weyman AE, Wann LS, Rogers EW, Dillon JC, Feigenbaum H. Cross-sectional echocardiographic analysis of the extent of left ventricular asynergy in acute myocardial infarction. *Circulation* 1980;61:1113-8.
13. Berning J, Steensgaard-Hansen F. Early estimation of risk by echocardiographic determination of wall motion index in an unselected population with acute myocardial infarction. *Am J Cardiol* 1990;65:567-76.
14. Køber L, Torp-Pedersen C, Carlsen J, Videbæk R, Egeblad H. An echocardiographic method for selecting high risk patients shortly after acute myocardial infarction, for inclusion in multi-centre studies (as used in the TRACE study). *Eur Heart J* 1994;15:1616-20.
15. Berning J, Rokkedal-Nielsen J, Launbjerg J, Fogh J, Mickley H, Andersen PE. Rapid estimation of left ventricular ejection fraction in acute myocardial infarction by echocardiographic wall motion analysis. *Cardiology* 1992; 80:257-66.
16. Cochran WG. Some methods for strengthening the common χ^2 tests. *Biometrics* 1954;10:417-51.
17. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-48.
18. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley, 1980.
19. Muller CA, Opie LH, Peisach M, Pineda CA. Chronic oral pretreatment with the angiotensin converting enzyme inhibitor, trandolapril decreases ventricular fibrillation in acute ischaemia and reperfusion. *Eur Heart J* 1994;15:988-96.
20. Packer M. Lack of relation between ventricular arrhythmias and sudden death in patients with chronic heart failure. *Circulation* 1992;85:Suppl 1: I-50-I-56.
21. More on the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1993;329:1204-6.
22. Ball SG, Hall AS, Murray GD. Angiotensin-converting enzyme inhibitors after myocardial infarction: indications and timing. *J Am Coll Cardiol* 1995; 25:Suppl:42S-46S.

IMAGES IN CLINICAL MEDICINE

Images in Clinical Medicine, a weekly *Journal* feature, presents clinically important visual images, emphasizing those a doctor might encounter in an average day at the office, the emergency department, or the hospital. If you have an original unpublished, high-quality color or black-and-white photograph representing such a typical image that you would like considered for publication, send it with a descriptive legend to Kim Eagle, M.D., University of Michigan Medical Center, Division of Cardiology, 3910 Taubman Center, Box 0366, 1500 East Medical Center Drive, Ann Arbor, MI 48109. For details about the size and labeling of the photographs, the requirements for the legend, and authorship, please contact Dr. Eagle at 313-936-5275 (phone) or 313-936-5256 (fax), or the *New England Journal of Medicine* at images@edit.nejm.org (e-mail).