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EFFECT OF CAPTOPRIL ON MORTALITY AND MORBIDITY IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION AFTER MYOCARDIAL INFARCTION

Results of the Survival and Ventricular Enlargement Trial

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Abstract *Background.* Left ventricular dilatation and dysfunction after myocardial infarction are major predictors of death. In experimental and clinical studies, long-term therapy with the angiotensin-converting–enzyme inhibitor captopril attenuated ventricular dilatation and remodeling. We investigated whether captopril could reduce morbidity and mortality in patients with left ventricular dysfunction after a myocardial infarction.

Methods. Within 3 to 16 days after myocardial infarction, 2231 patients with ejection fractions of 40 percent or less but without overt heart failure or symptoms of myocardial ischemia were randomly assigned to receive double-blind treatment with either placebo (1116 patients) or captopril (1115 patients) and were followed for an average of 42 months.

Results. Mortality from all causes was significantly reduced in the captopril group (228 deaths, or 20 percent) as compared with the placebo group (275 deaths, or 25 percent); the reduction in risk was 19 percent (95 percent confidence interval, 3 to 32 percent; P = 0.019). In addition, the incidence of both fatal and nonfatal major cardiovascular events was consistently reduced in the captopril group. The reduction in risk was 21 percent (95 percent confidence interval, 5 to 35 percent; P = 0.014) for death from cardiovascular causes, 37 percent (95 percent confidence interval, 20 to 50 percent; P<0.001) for the development of severe heart failure, 22 percent (95 percent confidence interval, 4 to 37 percent; P = 0.019) for congestive heart failure requiring hospitalization, and 25 percent (95 percent confidence interval, 5 to 40 percent; P = 0.015) for recurrent myocardial infarction.

Conclusions. In patients with asymptomatic left ventricular dysfunction after myocardial infarction, long-term administration of captopril was associated with an improvement in survival and reduced morbidity and mortality due to major cardiovascular events. These benefits were observed in patients who received thrombolytic therapy, aspirin, or beta-blockers, as well as those who did not, suggesting that treatment with captopril leads to additional improvement in outcome among selected survivors of myocardial infarction. (N Engl J Med 1992;327: 669-77.)

SURVIVORS of acute myocardial infarction are at a greatly increased risk for subsequent fatal and nonfatal cardiovascular events.[1] This heightened risk is influenced by many factors, the most important of which is the severity of left ventricular dysfunction. The degree of ventricular dysfunction correlates highly with mortality and is useful in stratifying survivors of acute myocardial infarction according to risk.[2-5]

In a rat model of myocardial infarction, progressive left ventricular dilatation has been shown to occur as a function of the size and age of the infarct.[6,7] During the early postinfarction phase, before scar formation, there is an increase in ventricular diastolic volume as a consequence of infarct expansion and an increase in filling pressure.[8,9] After the formation of a discrete scar, the left ventricle may continue to dilate as the

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*The investigators and institutions that participated in the Survival and Ventricular Enlargement (SAVE) study are listed in the Appendix.

result of remodeling of the residual viable myocardium, acting first to restore the stroke volume.[9,10] If the infarct is of sufficient size, the ventricular volume may continue to increase, leading to further deterioration in ventricular performance.[11] In the rat model, the long-term administration of the angiotensin-converting–enzyme inhibitor captopril attenuates this gradual left ventricular enlargement[12] and prolongs survival after infarction.[13]

Recently, several clinical studies have confirmed the progressive nature of left ventricular enlargement and dysfunction after a myocardial infarction.[10,14] Long-term angiotensin-converting–enzyme inhibition has also been shown to attenuate ventricular enlargement and prevent further deterioration of ventricular performance.[15,16] Although the end points in these studies (ventricular size and function) were well defined, the samples were too small for the critical issue to be addressed — i.e., the influence of therapy with angiotensin-converting–enzyme inhibitors on long-term survival and clinical outcome. On the basis of the suggestive evidence from the aforementioned experimental[12,13] and clinical[15,16] studies, we designed the Survival and Ventricular Enlargement (SAVE) trial to test the hypothesis that the long-term administration of captopril to survivors of acute myocardial infarction who had base-line left ventricular dysfunction but did not have overt heart failure requiring vasodilator therapy would reduce mortality, lessen deterioration in cardiac performance, and improve clinical outcome.[17]

Methods

Study Organization

The trial was a randomized, double-blind, placebo-controlled trial in 2231 patients with an acute myocardial infarction and left ventricular dysfunction who were enrolled at 45 centers comprising 112 participating hospitals in the United States and Canada (Appendix), in each of which the institutional review board approved the protocol. The data were collected and analyzed at an independent Data Coordinating Center at the University of Texas, Houston. All the patients provided signed, informed consent before randomization. The principal investigator of the trial at the Clinical Coordinating Center, located at Harvard Medical School and Brigham and Women's Hospital in Boston, was responsible for the overall execution of the trial, and inquiries related to the protocol or the patients were directed to either coordinating center. An independent Data and Safety Monitoring Board was responsible for decisions about the safe conduct and continuation of the trial.

Recruitment of Patients

The enrollment phase of the trial began on January 27, 1987, and ended on January 28, 1990. Patients of either sex were eligible for recruitment. To be considered, they had to survive the first three days after a myocardial infarction with a left ventricular ejection fraction of 40 percent or less, as measured by radionuclide ventriculography, and be at least 21 years of age, but less than 80. The criteria for exclusion included failure to undergo randomization within 16 days after the myocardial infarction; relative contraindication to the use of an angiotensin-converting–enzyme inhibitor or the need for such an agent to treat symptomatic congestive heart failure or systemic hypertension; a serum creatinine level greater than 2.5 mg per deciliter (221 μmol per liter); other conditions believed to limit survival; unwillingness or inability to participate in a long-term trial; and an unstable course after infarction. If recurrent ischemic discomfort was present 72 hours after the onset of the index myocardial infarction or if the patient had a positive exercise test, cardiac catheterization and coronary arteriography were required, and a clinical decision was made about the need for myocardial revascularization. If it was required, revascularization had to be performed before the patient underwent randomization. A test dose of 6.25 mg of oral captopril was given to 2250 patients who did not meet the criteria for exclusion and consented to participate in the trial. This resulted in the exclusion of 3 patients for associated ischemic discomfort and of 16 patients for symptomatic hypotension, yielding a study population of 2231. The details of the screening process and of the reasons for excluding patients from enrollment have been published elsewhere.[17]

Randomization, Dose Titration, and Follow-up

Randomization to the placebo or the captopril group was achieved by computer-generated assignment and was stratified according to center. The initial dose of the blinded medication was 12.5 mg, but 6.25 mg could be administered to patients who had marked, yet asymptomatic, reductions in blood pressure with the test dose. The target dose of study medication was 25 mg three times daily by the end of the in-hospital phase; this dose was gradually increased to a maximum of 50 mg three times daily unless the physician or the patient attributed any adverse experience to the therapy. There were no specific guidelines regarding the level of blood pressure in the titration regimen. Compliance was assessed by a pill count. Outpatient visits were scheduled two weeks after randomization, at intervals of three months during the first year of follow-up, and at intervals of four months during the remainder of the trial.

During the last phase of follow-up (an average of 36 months after randomization), the surviving patients underwent repeat radionuclide ventriculography. The protocol called for a temporary (48-hour) suspension of the study medication before this repeat determination of the ejection fraction; the study medication was then resumed and continued for the remainder of the trial.

End Points

The observation period was continued through the planned completion date of January 31, 1992, by which time the last patient enrolled had finished the prespecified minimal follow-up period of two years. As prospectively specified by the Data and Safety Monitoring Committee, patients who underwent cardiac transplantation were classified with those who died of cardiovascular causes. Several prospectively defined measures of outcome served as end points: mortality from all causes; mortality from cardiovascular causes; mortality combined with a decrease in the ejection fraction of at least 9 units in surviving patients, as determined by comparing the radionuclide ventriculograms at base line and at the end of the study[17]; cardiovascular morbidity, defined as the development of severe congestive heart failure or the recurrence of a fatal or nonfatal myocardial infarction; and the combination of cardiovascular mortality and morbidity. Two end points of severe heart failure (treatment failure) were prospectively defined. The first was the development of overt heart failure that persisted despite the administration of diuretic agents and digitalis, necessitating treatment with angiotensin-converting–enzyme inhibitors. After the Clinical Coordinating Center was notified and it was confirmed that the patient could not be treated adequately by conventional therapy (dietary adjustments, diuretics, or digitalis), the study medication was discontinued so that open-label therapy with an angiotensin-converting–enzyme inhibitor could be started. The second end point was hospitalization to treat congestive heart failure. The Mortality Classification Committee assigned the causes of death on the basis of a blinded review. A myocardial infarction occurring after randomization was defined by either the clinical center or the Mortality Classification Committee. The enzyme measurements for all patients with clinically reported myocardial infarctions were independently reviewed to determine whether the creatine kinase levels

were 2 times the upper limit of normal in the absence of positive results for the myocardial isoform (MB) or 1.5 times the upper limit in the presence of the MB isoform — values specified in the protocol as criteria for myocardial infarction. The radionuclide ventriculography core laboratory evaluated 34 percent of the base-line ejection fractions.

Statistical Analysis

The statistical methods used in the study have been described elsewhere in detail.[17] All analyses were performed on an intention-to-treat basis, and P values were two-sided. The comparability of base-line characteristics in the two treatment groups was ascertained by chi-square tests for categorical variables and standard normal (z) tests for continuous variables. Kaplan–Meier estimates[18] for the distributions of time from randomization to the clinical events of interest were computed. For the comparisons of the captopril and placebo groups with respect to end points, we determined reductions in risk, P values, and confidence intervals by proportional-hazards analyses, except for end points pertaining to ejection fractions, which were analyzed with a chi-square test. A proportional-hazards regression model with time-dependent covariates was used to assess the relative risk of death for patients who had heart failure and who required open-label therapy with an angiotensin-converting–enzyme inhibitor or hospitalization. Two degrees of heart failure were considered: one that required hospitalization and a second that required therapy with an open-label angiotensin-converting–enzyme inhibitor. Patients were included in the relevant category of heart failure beginning with the date of the first occurrence of heart failure.

Results

Of the 2231 patients enrolled in the trial, the survivors were followed for an average (±SD) of 42±10 months (range, 24 to 60). At the completion of this period, the vital status of six patients (four in the placebo group and two in the captopril group) had not yet been ascertained. There were no significant differences before randomization in the characteristics of the patients in the two treatment groups (Table 1). Blood pressure increased in both groups from base line to three months, albeit to differing extents, so that systolic and diastolic pressures were both significantly higher in the placebo group than in the captopril group at three months. This difference was maintained during follow-up (values at the one-year visit, 125±18/77±10 mm Hg for placebo and 119±18/74±10 mm Hg for captopril; $P<0.001$ for both systolic and diastolic pressures). The mean heart rate for both groups was 72 beats per minute.

Table 1. Base-Line Characteristics of the Patients in the Two Treatment Groups.*

Characteristic	Placebo (N = 1116)	Captopril (N = 1115)
Mean age (yr)	59.5	59.3
Age >70 yr (%)	15	15
Sex ratio, M/F (%)	82/18	83/17
Clinical history at presentation with MI (%)		
Previous MI	35	36
Diabetes mellitus	23	21
Hypertension	42	44
Current smoker	53	53
Mean days to randomization	11	11
Events between MI and randomization		
Highest serum creatine kinase†	13.6	13.8
Killip class I (%)	59	60
Thrombolytic therapy (%)	32	34
Cardiac catheterization (%)	54	57
PTCA (%)	17	17
Coronary-artery bypass surgery (%)	8	10
Infarct type and location (%)‡		
Anterolateral Q wave	54	56
Inferoposterior Q wave	17	18
Both	12	11
Non–Q wave	10	10
Other	7	5
Mean radionuclide ejection fraction (%)	31	31
Medication use within 24 hr of randomization (%)		
Antiarrhythmic drugs	11	14
Anticoagulant agents	28	28
Aspirin	59	59
Other antiplatelet agents	14	14
Beta-blockers	36	35
Calcium-channel blockers	42	42
Digitalis	27	25
Diuretics	35	35
Nitrates	53	50
Mean blood pressure (mm Hg)		
Systolic	113	112
Diastolic	70	70
Mean heart rate (beats/min)	78	78

*No significant differences were detected for any of the comparisons shown. MI denotes myocardial infarction, and PTCA percutaneous transluminal coronary angioplasty.

†Expressed as a multiple of the upper limit of normal.

‡As assessed by electrocardiography.

Mortality

There were 503 deaths during the study: 275 of the 1116 patients (25 percent) in the placebo group and 228 of 1115 (20 percent) in the captopril group; the reduction in the risk of death from all causes was 19 percent (95 percent confidence interval, 3 to 32 percent; P = 0.019) (Fig. 1).

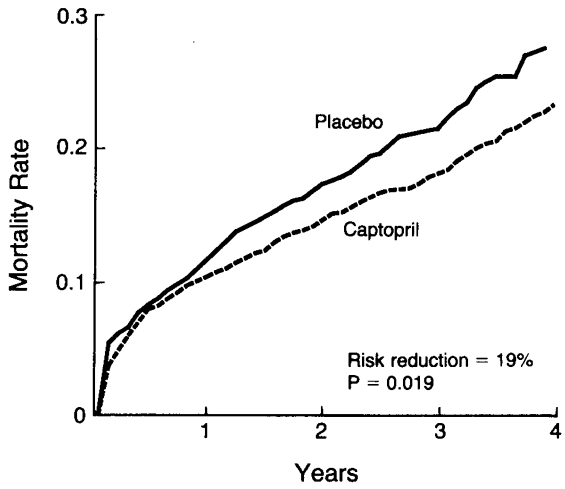
Of the deaths, 84 percent (422 of 503) were due to cardiovascular causes (234 in the placebo group vs. 188 in the captopril group); the reduction in risk was 21 percent (95 percent confidence interval, 5 to 35 percent; P = 0.014) (Table 2). Within this category, there was a marked reduction in mortality due to progressive heart failure in the captopril group as compared with the placebo group (38 vs. 58 deaths, respectively). These 96 deaths included the 12 patients who underwent cardiac transplantation (7 assigned to placebo and 5 to captopril); the reduction in the risk of progressive heart failure was 36 percent (95 percent confidence interval, 4 to 58 percent; P = 0.032). Deaths due to noncardiovascular causes (16 percent) were distributed evenly between the two treatment groups (Table 2). There were no differences between the two groups with regard to deaths due to cancer, including gastrointestinal cancer.

Repeat ejection fractions were obtained in 96 percent of the surviving patients randomly assigned to placebo (806 of 841) and in 95 percent of those assigned to captopril (838 of 887) toward the end of the observation period, and a deterioration of 9 or more units was noted in 16 percent of the surviving patients in the placebo group (125 of 806) and 13 percent of

those in the captopril group (110 of 838) (P = 0.168). When this measure of progressive left ventricular dysfunction was combined with mortality from all causes, this prospectively defined end point was reached in 36 percent of the patients assigned to placebo (400 of 1116) and 30 percent of the patients assigned to captopril (338 of 1115); the reduction in risk was 15 percent (95 percent confidence interval, 5 to 25 percent; P = 0.006).

Morbidity Due to Cardiovascular Causes

The failure of digitalis and diuretic agents to control congestive heart failure and the subsequent need for open-label therapy with an angiotensin-converting–enzyme inhibitor became more frequent over time, with 13 percent of the overall population (297 of 2231) having this degree of heart failure. Regardless of therapy assignment, the need for open-label therapy with an angiotensin-converting–enzyme inhibitor was associated with an increased risk of death: 37 percent of patients with this degree of heart failure died during the trial (110 of 297), whereas only 20 percent of patients who did not require an angiotensin-converting–enzyme inhibitor died (393 of 1934) (relative risk, 4.5; 95 percent confidence interval, 3.6 to 5.6; P<0.001). However, the patients randomly assigned to receive captopril were significantly less likely to have this form of treatment failure than those assigned to placebo (118 of 1115 [11 percent] vs. 179 of 1116 [16 percent], respectively; reduction in risk, 37 percent; 95 percent confidence interval, 20 to 50 percent; P<0.001) (Fig. 2). The group randomly assigned to captopril therapy also had a considerable reduction in the number of patients who died after starting open-label therapy with an angiotensin-converting–enzyme inhibitor (39 patients vs. 71 in the placebo group; reduction in risk, 47 percent; 95 percent confidence interval, 21 to 64 percent; P = 0.002) (Fig. 3).



Placebo	1116	987	915	609	262
Captopril	1115	1000	938	614	288

Figure 1. Cumulative Mortality from All Causes in the Study Groups.
The number of patients at risk at the beginning of each year is shown at the bottom.

Table 2. Causes of Death in the Study Patients.*

Cause of Death	Placebo	Captopril	Risk Reduction (95% CI)	P Value
	no. of deaths		*percent*	
Cardiovascular	234	188	21 (5–35)	0.014
Atherosclerotic heart disease	222	174	23 (6–37)	0.009
Progressive heart failure†	58	38	36 (4–58)	0.032
Sudden, with preceding symptoms	50	43	—	NS
Sudden, unexpected	75	62	—	NS
Acute myocardial infarction	25	24	—	NS
Cardiac procedure	9	5	—	NS
Other cardiac	5	2	—	NS
Vascular	12	14	—	NS
Noncardiovascular	41	40	—	NS
Cancer	20	14	—	NS
Infection or gastrointestinal bleeding	18	16	—	NS
Traumatic or unknown	3	10	—	NS
All	275	228	19 (3–32)	0.019

*CI denotes confidence interval, and NS not significant.

†Death was attributed to progressive heart failure if it occurred during a hospitalization for management of heart failure or if it was preceded by a recent deterioration in clinical status attributed to heart failure.

Treatment failure that resulted in the need for hospitalization to treat congestive heart failure was an even worse prognostic sign. Regardless of therapy assignment, such hospitalizations, which occurred in 15 percent of the study population (346 of 2231), were associated with a markedly increased risk of death. Among the patients with this degree of heart failure, 47 percent (164 of 346) died during the trial, whereas among the patients not hospitalized for heart failure, 18 percent (339 of 1885) died (relative risk, 6.4; 95 percent confidence interval, 5.3 to 7.8; P<0.001). With captopril therapy, the proportion of patients who required hospitalization for congestive heart failure was reduced (to 14 percent, or 154 of 1115 patients, vs. 17 percent, or 192 of 1116 patients, with placebo; risk reduction, 22 percent; 95 percent confidence interval, 4 to 37 percent; P = 0.019) (Fig. 2). The captopril group also had significantly fewer patients who were hospitalized for congestive heart failure and who later died (64 patients vs. 100 in the placebo group; reduction in risk, 38 percent; 95 percent confidence interval, 15 to 54 percent; P = 0.003) (Fig. 3).

After randomization, 303 patients had at least one clinically reported (fatal or nonfatal) myocardial infarction (170 patients in the placebo group and 133 in the captopril group; reduction in risk, 25 percent; 95 percent confidence interval, 5 to 40 percent; P = 0.015) (Fig. 2). Of these patients, 129 assigned to placebo and 108 assigned to captopril had the specified levels of creatine kinase or were designated as having a fatal myocardial infarction by the Mortality Classification Committee (reduction in risk, 19 percent; 95 percent confidence interval, −4 to 37 percent; P = 0.102). In the captopril group, there was also a

substantial reduction in the number of patients who had recurrent clinical myocardial infarctions and subequently died (56 vs. 80 in the placebo group; reduction in risk, 32 percent; 95 percent confidence interval, 4 to 51 percent; P = 0.029) (Fig. 3).

The number of patients who either died of cardiovascular causes or had major nonfatal events (heart failure requiring angiotensin-converting–enzyme therapy, heart failure requiring hospitalization, or recurrent myocardial infarction) was reduced with captopril therapy (from 448 of 1116 patients [40 percent] in the placebo group to 359 of 1115 patients [32 percent] in the captopril group; risk reduction, 24 percent; 95 percent confidence interval, 13 to 34 percent; P<0.001) (Fig. 2).

The effect on mortality from all causes and on cardiovascular mortality and morbidity of major, prospectively specified, prerandomization characteristics known to influence survival after myocardial infarction was as anticipated; that is, regardless of treatment assignment, advanced age, history of myocardial infarction, lower left ventricular ejection fraction, and higher Killip classification were each associated with a higher incidence of adverse events. When these subgroups were analyzed, captopril therapy showed a consistent benefit, although to varying degrees, in reducing both mortality from all causes and mortality and morbidity from cardiovascular causes (Table 3). The effect of the drug on risk reduction within subgroups was essentially uniform. The efficacy of captopril was of particular note in patients in Killip class I — i.e., those who did not have even transient pulmonary congestion at the time of their acute myocardial infarction. A proportional-hazards model for mortality from all causes demonstrated a significant influence of captopril in reducing mortality independently of age, ejection fraction, history of myocardial infarction, sex, base-line arterial blood pressure, and use of thrombolytic therapy, aspirin, or beta-blockers (P = 0.013).

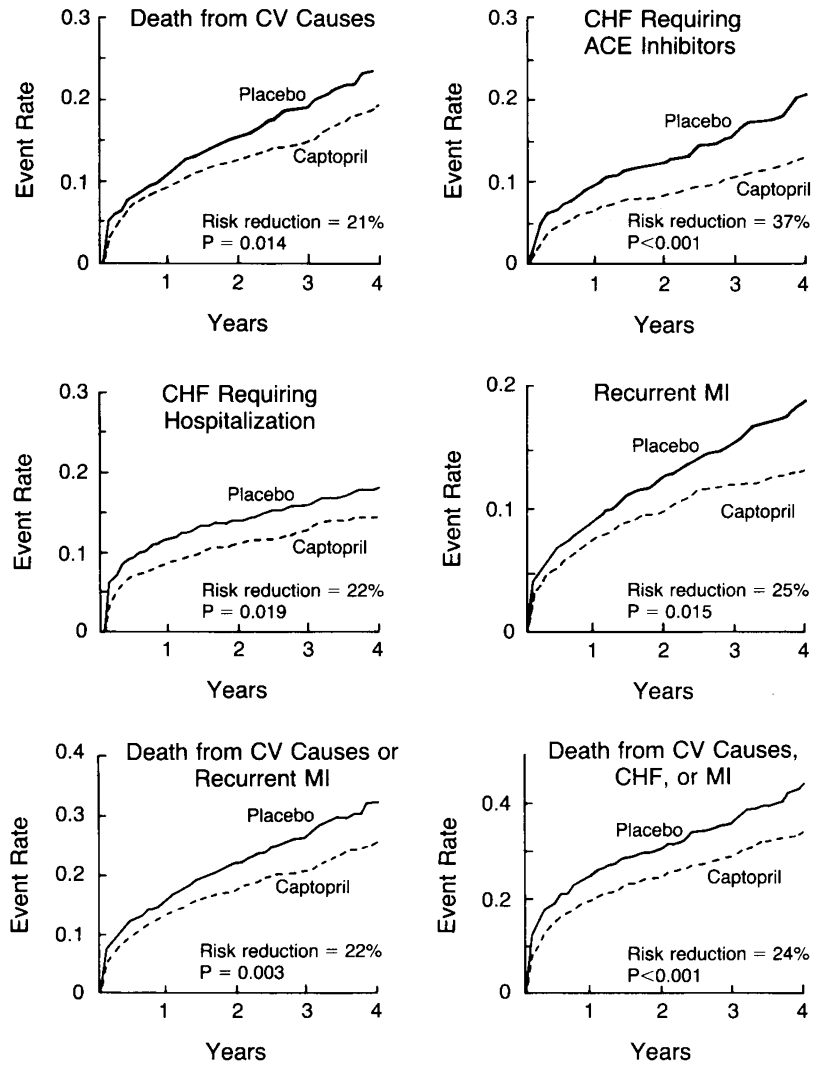


Figure 2. Life Tables for Cumulative Fatal and Nonfatal Cardiovascular Events. CV denotes cardiovascular, CHF congestive heart failure, and MI myocardial infarction. The bottom right panel shows the following events: death from cardiovascular causes, severe heart failure requiring angiotensin-converting–enzyme inhibitors or hospitalization, or recurrent myocardial infarction. For all the combined analyses, only the time to the first event was used.

Compliance with Treatment and Adverse Events

The number of patients taking their assigned study medication at one year was similar in the placebo group (808 of 985, or 82 percent) and the captopril group (787 of 1001, or 79 percent). At the last study visit, 73 percent of the surviving patients in the placebo group (612 of 841) and 70 percent of those in the captopril group (619 of 887) were still taking the study drug (P not significant). Of these patients, 90 percent of those in the placebo group (549 of 612) and 79 percent of those in the captopril group (486 of 619) reached the target dose of 150 mg per day after randomization. The use of beta-blockers, aspirin, digitalis, and nitrates was similar in the two groups. There was, however, more use of diuretic therapy among the patients taking placebo (38 percent vs. 32 percent for captopril, P = 0.002), a finding consistent with the higher incidence of symptomatic heart failure in this group.

The following symptoms were reported significantly

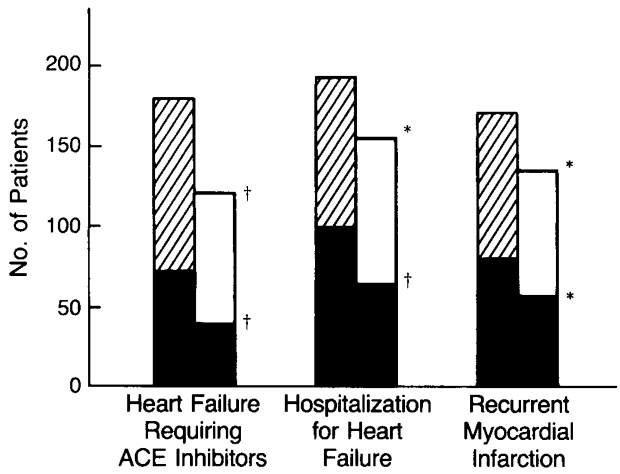


Figure 3. Cardiovascular Morbidity and Mortality in the Study Groups.

In each pair of bars, the bar at left (with hatching) represents the placebo group, and the bar at right the captopril group. Each bar as a whole represents the number of patients in the group who had the event, and the solid portion of the bar the number of these patients who subsequently died. The upper symbols indicate significant reductions in the incidence of the event among the captopril-treated patients, and the lower symbols significant reductions in mortality among the captopril-treated patients who had the event; asterisks denote $P<0.05$, and daggers $P<0.005$. ACE denotes angiotensin-converting enzyme.

more often by the captopril-treated patients (i.e., the uncorrected z score for the excess over placebo was higher than 1.96): dizziness (5 percent), alteration in taste (2 percent), cough (6 percent), and diarrhea (2 percent). The following numbers of patients discontinued the study medication at the time of these adverse events: 25 in the placebo group and 32 in the captopril group who had dizziness (P not significant); 5 and 9, respectively, who had taste alteration (P not significant); 9 and 27 with cough ($P = 0.003$); and none with diarrhea.

Discussion

The prognosis of survivors of acute myocardial infarction is related to complex interactions involving a number of characteristics, such as age, coexisting conditions, the extent of coronary artery disease, propensity toward arrhythmias, and most important, the degree of left ventricular dysfunction.[2,3,5,19] The treatment of survivors of myocardial infarction has been advanced considerably by therapeutic approaches designed to reduce both the progression of coronary artery disease and the potential for coronary reocclusion. Interventions that address the management of coronary artery disease, such as the modification of risk factors and the administration of beta-adrenergic–blocking agents, aspirin, and anticoagulants, and in suitable patients coronary revascularization, reduce the risk of adverse cardiovascular events after myocardial infarction.[20-24] The objective of the present study was to determine whether a further improvement in survival after myocardial infarction could be achieved by the early initiation and long-term administration of treatment with an angiotensin-converting–enzyme inhibitor, a therapy designed to attenuate progressive left ventricular dysfunction, the most important prognostic factor for survival.

Using a randomized, controlled, double-blind design, we demonstrated in this study that long-term therapy with captopril in survivors of acute myocardial infarction with depressed left ventricular ejection fractions but without overt heart failure resulted in reductions in both total and cardiovascular mortality, in the frequency of severe congestive heart failure and recurrent myocardial infarction, and in the proportion of patients who either died or survived with marked deterioration in left ventricular ejection fraction. These beneficial effects support the study hypothesis that a therapeutic intervention directed at the attenuation of progressive left ventricular dilatation and dysfunction would result in an improved clinical outcome. The selection of patients with objective evidence of left ventricular dysfunction (ejection fraction, ≤40 percent) was based on the finding in previous clinical studies[15,16] that captopril attenuated ventricular dilatation in such patients. The exclusion from this trial of patients with symptomatic heart failure who required vasodilator agents was based on the demonstrated efficacy of this therapy for the treatment of heart failure.[25-27] In the present study, the efficacy of captopril therapy in reducing mortality and the incidence of major adverse cardiovascular events was apparent only with more protracted follow-up (Fig. 1 and 2), underscoring the value of this agent as preventive therapy in patients with left ventricular dysfunction but without overt heart failure after a myocardial infarction.

Survivors of acute myocardial infarction are at high risk for the development of symptomatic heart failure. In the Framingham Study, the risk of this condition in patients with a myocardial infarction was 7 to 10 times higher than that in a matched normal population,[28] and the incidence of symptomatic heart failure increased progressively in the years after myocardial infarction.[1] As is the case for mortality, the risk of overt heart failure is also related to the severity of left ventricular dysfunction — i.e., patients with left ventricular ejection fractions of less than 40 percent who have had an infarction have a higher likelihood of overt heart failure.[29,30] The present study demonstrates that the long-term administration of captopril to this high-risk population resulted in a reduction not only in the incidence of symptomatic heart failure, but also in the number of subsequent deaths.

The initial rationale for our study was the hypothesis that the attenuation of ventricular enlargement would result in clinical benefit. A quantitative echocardiographic study in a subgroup of the study patients was designed to determine whether the proposed benefit of captopril therapy in terms of clinical outcome could be attributed to such an attenuation. Ventricular size, quantitated as the echocardiographi-

Table 3. Effect of Captopril on Major Clinical End Points in Subgroups Defined by Characteristics Known to Have an Important Influence on Survival after Myocardial Infarction.*

VARIABLE	DEATH FROM ALL CAUSES			CARDIOVASCULAR DEATH AND MORBIDITY		
	PLACEBO	CAPTOPRIL	RISK REDUCTION (95% CI)	PLACEBO	CAPTOPRIL	RISK REDUCTION (95% CI)
	no. of events/no. of patients (%)		%	*no. of events/no. of patients (%)*		%
Age (yr)						
≤55	54/365 (14.8)	52/375 (13.9)	8 (−34 to 37)	104/365 (28.5)	97/375 (25.9)	10 (−18 to 32)
56–64	77/352 (21.9)	69/356 (19.4)	13 (−21 to 37)	152/352 (43.2)	112/356 (31.5)	34 (16 to 48)
>64	144/399 (36.1)	107/384 (27.9)	25 (4 to 42)	192/399 (48.1)	150/384 (39.1)	25 (5 to 38)
Sex						
Male	234/912 (25.7)	191/929 (20.6)	22 (6 to 36)	367/912 (40.2)	288/929 (31.0)	28 (16 to 38)
Female	41/204 (20.1)	37/186 (19.9)	2 (−53 to 37)	81/204 (39.7)	71/186 (38.2)	4 (−32 to 30)
Previous myocardial infarction						
No	144/721 (20.0)	115/718 (16.0)	22 (0 to 39)	228/721 (31.6)	186/718 (25.9)	21 (4 to 35)
Yes	131/395 (33.2)	113/397 (28.5)	16 (−8 to 35)	220/395 (55.7)	173/397 (43.6)	29 (13 to 42)
Ejection fraction (%)†						
>32	77/517 (14.9)	75/531 (14.1)	6 (−29 to 32)	155/517 (30.0)	124/531 (23.4)	27 (7 to 42)
≤32	198/599 (33.1)	153/584 (26.2)	24 (6 to 38)	293/599 (48.9)	235/584 (40.2)	22 (7 to 34)
Killip class						
I	140/672 (20.8)	109/676 (16.1)	25 (4 to 42)	225/672 (33.5)	179/676 (26.5)	25 (8 to 38)
≥II	135/444 (30.4)	119/439 (27.1)	11 (−14 to 31)	223/444 (50.2)	180/439 (41.0)	23 (7 to 37)
Type of infarction‡						
Anterior Q wave	117/605 (19.3)	112/624 (17.9)	9 (−19 to 29)	198/605 (32.7)	177/624 (28.4)	16 (−3 to 31)
Inferior Q wave	41/193 (21.2)	36/201 (17.9)	16 (−32 to 46)	76/193 (39.4)	61/201 (30.3)	28 (−1 to 49)
Both	48/135 (35.6)	30/126 (23.8)	38 (2 to 60)	75/135 (55.6)	50/126 (39.7)	35 (7 to 55)
Non–Q wave	34/110 (30.9)	22/106 (20.8)	36 (−10 to 62)	51/110 (46.4)	38/106 (35.8)	31 (−5 to 55)
Other	35/73 (47.9)	28/58 (48.3)	−2 (−69 to 38)	48/73 (65.8)	33/58 (56.9)	20 (−25 to 49)
Thrombolytic therapy						
Yes	58/355 (16.3)	48/376 (12.8)	22 (−14 to 47)	117/355 (33.0)	99/376 (26.3)	23 (−1 to 41)
No	217/761 (28.5)	180/739 (24.4)	17 (−1 to 32)	331/761 (43.5)	260/739 (35.2)	24 (11 to 36)
Use of beta-blockers						
Yes	76/398 (19.1)	52/391 (13.3)	33 (4 to 53)	132/398 (33.2)	103/391 (26.3)	26 (4 to 43)
No	199/718 (27.7)	176/724 (24.3)	14 (−5 to 30)	316/718 (44.0)	256/724 (35.4)	23 (10 to 35)
Use of aspirin						
Yes	140/653 (21.4)	109/657 (16.6)	24 (2 to 41)	239/653 (36.6)	203/657 (30.9)	20 (3 to 33)
No	135/463 (29.2)	119/458 (26.0)	14 (−10 to 33)	209/463 (45.1)	156/458 (34.1)	29 (13 to 43)
All patients	275/1116 (24.6)	228/1115 (20.4)	19 (3 to 32)	448/1116 (40.1)	359/1115 (32.2)	24 (13 to 34)

*Cardiovascular death and morbidity includes both deaths classified as having a cardiovascular origin and the development of any of the following conditions: congestive heart failure requiring treatment with an open-label angiotensin-converting–enzyme inhibitor, heart failure requiring hospital admission, and recurrent myocardial infarction. In this time-dependent analysis, a patient could have only the first of these major cardiovascular events. CI denotes confidence interval.

†Denotes the radionuclide left ventricular ejection fraction measured at base line.

‡As classified by electrocardiography.

cally determined area of the chamber in either systole or diastole, at base line, was indeed the most powerful independent predictor of adverse cardiovascular outcome.[31] Greater increases in chamber size occurred in the patients who subsequently died or in whom heart failure developed during the follow-up period.[32] It remains to be determined whether these changes in left ventricular size are related to cardiovascular events in the two treatment groups and whether the beneficial effects of captopril therapy are associated with the attenuation of ventricular enlargement.

The beneficial actions of captopril may also result in part from the direct inhibition of the proposed deleterious effects of neurohumoral activation.[33] The renin–angiotensin system can be activated after an acute myocardial infarction.[34] In patients with severe chronic heart failure, the degree of activation is a powerful determinant of survival.[33] A recent experimental study demonstrated that the myocytolysis produced by endogenous angiotensin II could be prevented by captopril therapy.[35] These purported mechanisms by which captopril exerts its beneficial effects (i.e., the attenuation of ventricular remodeling and the inhibition of neurohumoral activation) are not mutually exclusive. Indeed, in this study the combination of ventricular enlargement and elevated plasma levels of neurohormones at base line was associated with a higher risk of death than that found for either of these adverse prognostic indicators alone.[36] In addition, other anti-ischemic mechanisms of captopril may also account for the reduced incidence of recurrent myocardial infarction. Increased plasma renin activity has been shown to be an independent marker for an augmented risk of myocardial infarction in patients with mild hypertension.[37] Approximately one quarter of the patients in our study had increased plasma renin activity at base line; this level was independent of left ventricular size and function.[34] The observation of a reduction in recurrent myocardial infarction with long-term captopril therapy suggests that an improvement in clinical outcome may also be achieved in a broader patient population.

We conclude that the early and continued administration of captopril to patients with asymptomatic left ventricular dysfunction after myocardial infarction improved survival and reduced mortality and morbid-

ity from major cardiovascular events. These benefits were also observed in patients treated with thrombolytic agents, aspirin, or beta-blockers, suggesting that this new use of captopril leads to additional improvements in clinical outcome among selected survivors of myocardial infarction.

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Appendix

The following persons and study centers participated in the SAVE study (names of participating hospitals located in the same area as the study center are given in parentheses).

Albany Medical Center: T. Biddle and J. Sacco; Albert Einstein Medical Center: J. Wertheimer and C. Strauss; Bowman Gray School of Medicine: H. Miller, Jr.; Brigham and Women's Hospital: L. Hartley and G. Mitchell; B. Heller, R. Bevivino, and R. Zickl (Norwood Hospital); R. Rimmer, F. Hubbard, G. Gaughan, and P. Boinay (Carney Hospital); M. Hession and C. Gaughan (South Shore Hospital); S. Gabbay (Waltham Hospital); Geisinger Medical Center: F. Menapace , Jr., R. Butcher, and T. Modesto; Hôpital du Sacré-Coeur, Montreal: J. Rouleau, M. Klein, and R. Lebeau; Hôpital Notre Dame, Montreal: F. Sestier, D. Savard, P. Laramee, and J. Lenis; L. Belanjer (Pierre Boucher Centre Hospitalier); Hospital of the Medical College of Pennsylvania: P. Kowey, S. Rials, and R. Marinchak; Howard University Hospital: O. Randall; Iowa Heart Center: D. Gordon and W. Wickemeyer; Jackson Clinic Foundation: D. Farnham, J. Morledge, and P. Hinderaker; G. Musser (Meriter–Madison General Hospital); Jewish General Hospital: J. McCans and D. Langleben; C. Maranda (Queen Elizabeth Hospital); Kingston General Hospital: J. Parker; Laval Hospital/Quebec Heart Institute: G. Dagenais and J. Rouleau; C. Nadeau (Enfant-Jesus Hospital); F. DeLage (Levis Hospital); Lutheran General Hospital: R. Sorkin; Maine Medical Center: C. Lambrew; Massachusetts General Hospital: R. Zusman; Mayo Clinic: D. Hayes, B. Gersh, and I. Clements; Memorial University of Newfoundland: B. Sussex; M. Furey (St. Clare's Mercy Hospital); B. Josephson (Salvation Army Grace General Hospital); Mount Sinai Medical Center, Cleveland: D. Adler; Mount Sinai School of Medicine–Winthrop University Hospital, New York and Mineola, N.Y.: M. Packer, M. Kukin, G. Neuberg, P. Wilson, D. Pinsky, M. Abittan, and Z. Neuwirth (Mount Sinai Hospital); R. Steingart, N. Kantrowitz, and S. Zeldis (Winthrop University); W. Schwartz and R. Darawhat (Elmhurst General Hospital); J. Strain (Beth Israel Medical Center); E. Lichstein and S. Charlap (Maimonides Hospital); K. Chadda and G. Friedman (Long Island Jewish Medical Center); Oregon Heart Institute: S. Lewis; Sacred Heart Hospital: K. Jacobson, L. Barlow, M. Heerema, and F. Littell; Sharp Hospital: S. Smith, Jr., and P. Hoagland; State University of New York: E. Brown, Jr., and M. Zema; R. Joseph (Huntington General Hospital); F. Mazzucchi (Nassau County Medical Center); Tulsa Heart Center: L. Basta, A. Hagan, and G. Gershony; University of Arizona–Veterans Affairs (VA) Medical Center, Tucson: S. Goldman, T. Raya, C. Appleton, and R. Lee; H. Richter, F. Cardello, and A. Cooper (Phoenix VA Medical Center); University of Arkansas–VA Medical Center, Little Rock: H. Dinh, J. Bissett, B. Baker, and M. Murphy; M. Kahn (VA Medical Center, Fayetteville); University of British Columbia: V. Bernstein and C. Nath; University of California–Davis: E. Amsterdam and R. Martschinske; University of Connecticut Health Center: W. Hager; A. Riba (Mount Sinai Hospital); M. Sands, Jr. (New Britain General Hospital); M. Radford (Newington VA Hospital); B. Clark (St. Francis Hospital); University of Louisville: J. Kupersmith and S. Wagner; University of Manitoba: T. Cuddy and A. Morris; R. Hoeschen and M. Frais (St. Boniface General Hospital); R. Kaufman (Victoria Hospital); University of Maryland School of Medicine: S. Gottlieb; M. Effron (Sinai Hospital); University of Massachusetts: J. Alpert, J. Gore, J. Greenberg, and J. Tumulo; University of Missouri: G. Flaker, R. Weber, and W. Wright; University of New Mexico: J. Abrams; University of South Florida: S. Glasser; D. Schocken (Tampa General Hospital); U. Shettigar and A. Hakki (Bay Pines VA Medical Center); University of Tennessee, Memphis: B. Hackman, E. Shick, Jr., J. Sullivan, D. Mirvis, and J. Insel; University of Texas, Galveston: J. Wallace and R. Bhalla; University of Toronto: P. McEwan and Z. Sasson; C. Lefkowitz (Toronto General Hospital); P. Daly (Toronto Western Hospital); B. Gilbert (Mount Sinai Hospital); University of Wisconsin, Madison: N. Bittar; Victoria Hospital: M. Arnold, J. Imrie, M. Weingert, L. Melenday, G. Hurwitz, and K. Finnie; Wadsworth VA Hospital: B. Singh, K. Nademanee, and M. Josephson; Washington University School of Medicine: E. Geltman, A. Jaffe, and J. Perez; D. Bauwens and S. Brodarick (St. Luke's Hospital); T. Martin (St. Elizabeth's Hospital).

Principal Investigator: M. Pfeffer; *Steering Committee:* E. Braunwald (chairman); *Data and Safety Monitoring Committee:* R. Gorlin (chairman), W. Parmley, J. Ware, and K. Weber; *Data Coordinating Center:* University of Texas Health Science Center, Houston — B. Davis, P. Hamm, C. Hawkins, and L. Moyé; *Clinical Coordinating Center:* Brigham and Women's Hospital, Boston — G. Lamas, J. Rutherford, L. Hartley, and K. Connors; *Core Directors and Committee Chairmen:* G. Lamas (catheterization), M. St. John Sutton (echocardiography), F. Wackers (radionuclide ventriculography), J. Rutherford (electrocardiography), M. Packer (mortality and end points), and E. Geltman (ancillary trials publications).

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