Effects of Captopril on Ischemic Events After Myocardial Infarction

Results of the Survival and Ventricular Enlargement Trial

John D. Rutherford, MB, ChB; Marc A. Pfeffer, MD, PhD; Lemuel A. Moyé, MD, PhD; Barry R. Davis, MD, PhD; Greg C. Flaker, MD; Peter R. Kowey, MD; Gervasio A. Lamas, MD; Henry S. Miller, MD; Milton Packer, MD; Jean L. Rouleau, MD; Eugene Braunwald, MD, on behalf of the SAVE Investigators*

Background In the Survival and Ventricular Enlargement (SAVE) trial, recurrent myocardial infarction (MI) was the most important predictor of a poor outcome and conferred a sevenfold increase in risk of death. The purpose of this study was to determine the predictors of recurrent MI in study participants and to examine the influence of the angiotensin-converting enzyme inhibitor captopril on this and other myocardial ischemic events.

Methods and Results The 2231 patients had survived the acute phase of MI (3 to 16 days) and had a radionuclide ventricular ejection fraction ≤40%. Patients were randomly assigned to receive double-blind treatment with either placebo or captopril and were followed for an average of 42 months. The influence of captopril on recurrent MI, cardiac revascularization procedures, and hospitalization with unstable angina was examined. The likelihood of recurrent MI was greater in patients with an MI or functional disability before the index infarction and higher systolic pressure (all $P<.001$) but was not influenced by baseline left ventricular ejection fraction. Therapy with captopril reduced the risk of development of recurrent MI by 25% (95% confidence intervals, 5% to 40%; $P=.015$) and the risk of death after recurrent MI by 32% (95% confidence intervals, 4% to 51%; $P=.029$). Captopril-assigned patients were also less likely to require cardiac revascularization procedures ($P=.010$), but hospitalization for unstable angina was unaltered. When all three of these major coronary ischemic events were considered together, captopril therapy reduced the risk (14% risk reduction; 95% confidence intervals, 0% to 26%; $P=.047$).

Conclusions In post-MI patients with asymptomatic left ventricular dysfunction, long-term administration of captopril reduced recurrence of MI and the need for cardiac revascularization but had no influence on the rate of hospitalization with a discharge diagnosis of unstable angina. The finding that the recurrence of MI was independent of left ventricular ejection fraction suggests that captopril could be useful in preventing recurrent MI in patients with more preserved left ventricular function. The need for cardiac revascularization was reduced in patients receiving long-term captopril therapy, suggesting either an anti-ischemic effect or the ability of the angiotensin-converting enzyme inhibitor to modify the atherosclerotic process in survivors of MI. (***Circulation.* 1994;90: 1731-1738.**)

Key Words • myocardial infarction • angioplasty • captopril • ischemia • bypass

Survivors of myocardial infarction (MI) are at increased risk for subsequent fatal and nonfatal ischemic events.[1,2] The SAVE Trial has shown that in survivors of MI with left ventricular dysfunction but without heart failure, the long-term administration of the angiotensin-converting enzyme (ACE) inhibitor captopril is associated with an improvement in survival and reduced morbidity and mortality due to major cardiovascular events, including recurrent MI.[3] We previously reported that in the 303 patients experiencing at least one clinically reported MI, 170 occurred in the placebo group and 133 in the captopril group (a reduction in risk of 25%; 95% confidence interval, 5% to 40%; $P=.015$). In the captopril group, there was also a substantial reduction in the number of patients who had recurrent MIs and subsequently died (56 versus 80 in the placebo group; reduction in risk, 32%; 95% confidence interval, 4% to 51%; $P=.029$.[3] Long-term therapy with enalapril has also been shown to reduce the incidence of MI and hospitalization with unstable angina in patients with low ejection fractions (≤0.35) of all causes in the presence or absence of overt heart failure.[4] On the other hand, it is not clear whether ACE inhibitors influence myocardial ischemia, with some small trials of patients with coronary disease suggesting an anti-ischemic effect[5-14] but others not supporting this position.[6,15,16]

The purpose of this analysis was to elucidate the predictors of recurrent MI in a population of survivors of MI, to ascertain the impact of recurrent MI on

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From the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass (J.D.R., G.A.L., M.A.P., E.B.); the University of Missouri Health Science Center, Columbia (G.C.F.); Lankenau Hospital and Medical Research Center, Wynnewood, Pa (P.R.K.); Bowman Gray School of Medicine, Winston-Salem, NC (H.S.M.); School of Public Health, University of Texas Health Science Center at Houston (B.R.D., L.A.M.); Columbia College of Physicians and Surgeons, New York, NY (M.P.); and Hôpital du Sacré-Coeur, Montreal (J.L.R.).

Correspondence to John D. Rutherford, MB, ChB, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75235-9047.

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

TABLE 1. Baseline Characteristics of the Patients in the Two Treatment Groups*

Characteristic	Placebo (N=1116)	Captopril (N=1115)
Mean age, y	59.5	59.3
Clinical history at presentation with MI, %		
Previous MI	35	36
Diabetes mellitus	23	21
Hypertension	42	44
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

MI indicates myocardial infarction.
*No significant differences were detected for any of the comparisons shown.
†As assessed by ECG.

subsequent mortality, and also to examine the influence of the ACE inhibitor captopril on coronary ischemic events (recurrent MI, need for cardiac revascularization, and hospitalization for unstable angina).

Methods

The study organization, recruitment of patients, randomization, dose titration, and follow-up in the SAVE trial have been described in detail elsewhere.[17] Briefly, 2231 MI survivors with a mean age of 59 years and a mean radionuclide left ventricular ejection fraction (LVEF) of 31% (all ≤40%) were randomized to placebo or captopril 3 to 16 days (mean, 11 days) after myocardial infarction and were followed for an average of 42 months. At the time of randomization, patients with overt heart failure requiring vasodilator therapy or evidence of ongoing uncontrolled myocardial ischemia such as typical anginal chest pain, chest pain with reversible ECG ST-T changes, or an exercise tolerance test highly suggestive of active ischemia were excluded. Recurrent ischemic discomfort 72 hours after the onset of the index infarction or a positive exercise test required that cardiac catheterization and coronary arteriography be performed. In the patients who underwent cardiac catheterization, a clinical decision for revascularization had to be implemented before randomization, or the patient was ineligible. Approximately a quarter of randomized patients underwent a revascularization procedure (8.6% coronary artery bypass graft surgery [CABG], 18.1% percutaneous transluminal coronary angioplasty [PTCA]) before randomization. Approximately 80% of the patients had experienced Q-wave MIs. One third of the patients had a history of prior MI, and one fifth of the patients had a history of diabetes mellitus (Table 1). Recurrent clinical MI was reported by investigators on a specific form (using symptoms, cardiac enzymes, and ECG changes) or as a fatality attributed to MI identified by the mortality committee. All centers submitted recurrent MI forms that were overread by observers blinded to treatment assignment for certain arbitrary but "strict" criteria. Confirmation was present if creatine kinase levels were 2 times the upper limit of normal in the absence of creatine kinase isoenzyme determinations. In the presence of the MB isoform, a creatine kinase level of 1.5 times the upper limit of normal would be sufficient for confirmation.[18] Hospitalizations for other coronary events, including unstable angina and cardiac revascularization (PTCA or CABG), were prospectively recorded during follow-up of 42±10 months (range, 24 to 60 months).

Statistical Analysis

The statistical methods used in the study have been described.[17] All probability values are two sided, and analyses involving the use of captopril are as intention to treat. The comparability of baseline characteristics in the two treatment groups was ascertained by χ^2 tests for categorical variables and standard normal *(z)* tests for continuous variables. Univariate determinations of risk factors for recurrent MI were ascertained by examination of Cox proportional-hazard models.[19] For each independent variable, a Cox proportional-hazard model was constructed, with that covariate being the only independent variable in the model. All covariates found to be significantly related in these models as well as variables with an established epidemiological relation with MI (eg, age, diabetes mellitus, hypertension) were included in the multivariate model. The relations between recurrent MI and subsequent mortality were ascertained by Cox proportional-hazard analyses with time-dependent covariates.[19] Logistic regression analysis was performed to assess the relation between patients who met the MI definitions (clinical MI, nonfatal MI) and the end point of a deterioration of at least 9 units in ejection fraction. Kaplan-Meier estimates[19] for the distributions of time from randomization to the clinical events were used to generate the life tables.

Results

After randomization, 303 patients (14%) had at least one clinically reported (fatal or nonfatal) MI, which conferred a subsequent relative risk of death of 7.1 (Table 2). Seventy-five patients (fatal recurrent MI) died within 10 days of recurrent MI, and 228 patients survived their recurrent MI for at least 10 days (nonfatal MI). These survivors of a nonfatal recurrent MI had a risk of subsequent death 3.0 times greater than nonrecurrent MI patients. Furthermore, irrespective of therapy assignment, patients who suffered clinical recurrent MIs experienced other cardiovascular end points more frequently than did patients who were free of recurrent MI—ie, cardiovascular death (42% versus 16%), congestive heart failure requiring open-label captopril (31% versus 11%) or hospitalization (33% versus 13%), and deterioration in LVEF ≥9 units (28% versus 13%, Table 2). The risk of death and of each cardiovascular event examined in the 303 patients with clinical recurrent MI and in the two subgroups that made up the group, ie, the 237 patients with confirmed recurrent MI and the 66 patients with unconfirmed recurrent MI, was significantly greater than in the reference population (Table 3).

A univariate analysis performed to ascertain differences in the baseline characteristics of those patients who had a recurrent MI compared with those patients who did not (Table 4) revealed that the former were more likely to have a history of MI, angina pectoris, a previous revascularization, diabetes mellitus, hypertension, and a lower functional (Karnofsky) score, all preceding the SAVE MI (all $P<.001$). Patients who developed a recurrent MI also had a significantly higher systolic blood pressure at the time of randomization and were less likely to undergo revascularization by either PTCA or CABG (16% versus 26%, $P<.001$) between the index MI and randomization (Table 4). There were no other major differences in hospital management of

TABLE 2. Influence of Recurrent Clinical Myocardial Infarction on SAVE End Points

	No Recurrent MI			All Clinical MI						Nonfatal MI (10-Day Survivors)					
Events	At Risk	Events	%	At Risk	Events	%	RR	95% CI	P	At Risk	Events	%	RR	95% CI	P
Death	1928	367	19	303	136	45	7.1	5.8-8.7	<.001	228	61	27	3.0	2.2-3.9	<.001
Cardiovascular death	1928	294	15	303	128	42	9.1	7.3-11.3	<.001	228	55	24	3.6	2.7-4.8	<.001
CHF needing ACEI	1928	202	10	303	95	31	3.8	2.9-4.8	<.001	228	81	36	3.7	2.9-4.8	<.001
CHF needing hospitalization	1928	246	13	303	100	33	3.4	2.7-4.3	<.001	228	75	33	2.8	2.2-3.7	<.001
LVEF change*	1516	198	13	177	49	28	2.6	1.8-3.7	<.001	171	49	29	2.7	1.9-3.8	<.001

MI indicates myocardial infarction; RR, relative risk; CI, confidence interval; CHF, congestive heart failure; ACEI, angiotensin-converting enzyme inhibitor; and LVEF, left ventricular ejection fraction.
*Deterioration of ≥9 LVEF units.

the SAVE MI between those patients who subsequently experienced a recurrent MI and those who did not; ie, the rates of cardiac catheterization (50% versus 56%) and the use of thrombolytic (28% versus 34%), β-blocker (32% versus 36%), calcium antagonist (49% versus 41%), and aspirin (57% versus 59%) therapy were not significantly different.

Multivariate analysis revealed that a history of previous MI, greater functional disability 3 weeks before randomization, and a higher systolic blood pressure at the time of randomization were all significant predictors of recurrent MI, whereas CABG performed immediately before randomization was associated with reduced risk of MI (Table 4).

There was no statistically significant relation between LVEF and the development of recurrent MI (P=.176) or the need for revascularization (P=.123).

When the effect of therapy was introduced into the multivariate analysis, captopril therapy retained a significant influence in reducing the likelihood of recurrent MI (risk reduction, 20%; 95% confidence interval, 0 to 40%; P=.018).

Captopril also reduced the need for revascularization compared with placebo (14% versus 17%; reduction in risk, 24%; 95% confidence interval, 6% to 39%; P=.01; Fig 1) by either PTCA (5% versus 8%; reduction in risk, 33%; 95% confidence interval, 6% to 52%; P=.02) or CABG (9% versus 11%; reduction in risk, 22%; 95% confidence interval, −1% to 40%; P=.06; Fig 2).

We previously reported[20] that Canadian patients were less likely to undergo revascularization before and after randomization into the SAVE trial. In light of this difference, the cumulative event curves for first revascularization (by PTCA or CABG) were compared between patients treated in the United States and Canada. In the United States, captopril reduced the need for revascularization compared with placebo (15% versus 19%; risk reduction, 21%; 95% confidence interval, −1% to 38%; P=.06). Despite the lower cumulative event rate for revascularization procedures in Canada, captopril therapy still appeared to reduce the need for revascularization (10% versus 14%; risk reduction, 34%; 95% confidence interval, −3% to 58%; P=.07). The efficacy of captopril for reducing recurrent MI and

TABLE 3. Influence of Myocardial Infarction Confirmation on SAVE End Points

	Events				
MI Confirmation	Death	Cardiovascular Death	CHF Needing ACEI	CHF Needing Hospitalization	LVEF Change*
Clinical RMI (n=303)					
RR	7.1	9.1	3.8	3.4	2.6
95% CI	5.8-8.7	7.3-11.3	2.9-4.8	2.7-4.3	1.8-3.7
Confirmed RMI (n=237)					
RR	6.5	8.5	3.6	3.1	2.5
95% CI	5.2-8.2	6.7-10.8	2.8-4.7	2.4-4.1	1.7-3.7
Unconfirmed RMI (n=66)					
RR	7.4	8.9	4.2	4.6	2.7
95% CI	5.2-10.5	6.1-13.0	2.7-6.6	3.1-6.9	1.2-6.0

MI indicates myocardial infarction; CHF, congestive heart failure; ACEI, angiotensin-converting enzyme inhibitor; LVEF, left ventricular ejection fraction; RMI, recurrent myocardial infarction; RR, relative risk; and CI, confidence interval. Reference population is 1928 SAVE patients without clinical recurrent MI.
*Deterioration of ≥9 LVEF units.

TABLE 4. Analysis for Differences in Baseline Characteristics of Patients With Recurrent Myocardial Infarction and Those Without

Characteristic	Univariate Analysis for Predictors of Recurrent MI			Multivariate Analysis for Predictors of Recurrent MI		
	Relative Risk	95% CI	*P*	Relative Risk	95% CI	*P*
Age	1.3	1.1-1.4	.001	1.1	0.9-1.2	NS
Sex	0.9	0.7-1.2	NS	1.0	0.7-1.4	NS
Clinical history at presentation with MI						
Previous MI	1.8	1.4-2.2	.001	1.4	1.0-1.8	.016
Diabetes mellitus	1.7	1.3-2.2	.001	1.1	0.7-1.6	NS
Hypertension	1.5	1.2-1.9	.001	1.2	0.9-1.5	NS
Previous revascularization	1.7	1.3-2.2	.001	1.3	0.9-1.7	NS
Functional status 3 wk before randomization						
Clinical angina	1.7	1.4-2.2	.001	1.2	0.9-1.6	NS
Karnofsky score	0.8	0.7-0.8	.001	0.9	0.8-1.0	.004
Medication use 24 h before randomization						
Aspirin	0.9	0.7-1.2	NS	1.1	0.9-1.4	NS
Diuretics	1.6	1.3-2.0	.001	1.2	1.0-1.6	NS
Nitrates	1.5	1.2-1.9	.001	1.1	0.9-1.4	NS
Oral hypoglycemic	1.6	1.2-2.3	.004	1.3	0.8-2.0	NS
Insulin	1.8	1.2-2.5	.002	1.4	0.9-2.3	NS
Calcium blocker	1.3	1.0-1.6	.048	1.1	0.8-1.3	NS
β-Blocker	0.8	0.6-1.0	NS	0.9	0.7-1.2	NS
Hospital status immediately before randomization						
Thrombolysis	0.8	0.6-1.0	.053	1.1	0.8-1.4	NS
PTCA performed	0.7	0.5-0.9	.015	0.8	0.5-1.1	NS
CABG performed	0.4	0.2-0.7	.001	0.3	0.2-0.5	.001
Baseline Killip class	1.2	1.0-1.4	.016	1.1	0.9-1.3	NS
Higher blood pressure*						
Systolic	1.2	1.1-1.3	.001	1.1	1.0-1.2	.005
Diastolic	1.1	1.0-1.2	NS	0.9	0.8-1.1	NS
Captopril therapy	0.8	0.6-0.9	.015	0.8	0.6-1.0	.018

MI indicates myocardial infarction; CI, confidence interval; PTCA, percutaneous transluminal coronary angioplasty; and CABG, coronary artery bypass graft surgery.
*Relative risk for a change in 10 units.

the need for revascularization was similar for the groups with LVEFs above and below the median.

The incidences of hospitalization for unstable angina pectoris were similar in the placebo and treatment groups (Table 5). When all three coronary ischemic outcomes, ie, recurrent MI, revascularization, and hospitalization for unstable angina, were considered together, there was a 14% risk reduction by captopril (95% confidence interval, 0% to 26%; $P=.047$; Table 5).

Discussion

A number of small trials have demonstrated a modest anti-ischemic effect of ACE inhibitors in patients with chronic stable angina. During exercise testing of such patients, these drugs have been shown to delay the development of angina[6-8]; delay the onset[9,10] and reduce the extent of ST-segment depression[11,12]; increase exer-

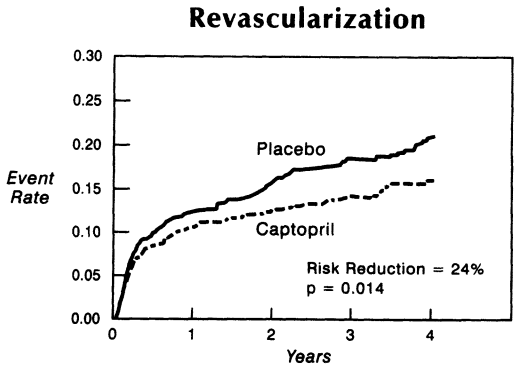

FIG 1. Life table of cumulative need for revascularization (by either percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery) after randomization. For this combined analysis, the time to first event was used.

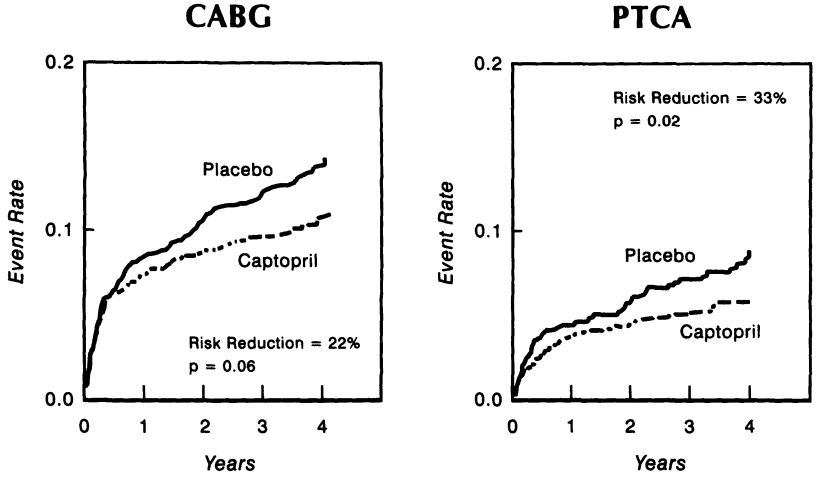

FIG 2. Life table of cumulative need for revascularization by coronary artery bypass graft surgery (CABG) and percutaneous transluminal coronary angioplasty (PTCA) after randomization.

cise duration[6,8,12,14]; and reduce the severity, number, and duration of ischemic episodes during ambulatory ECG monitoring.[21] However, these results have not been uniform, with some small trials reporting exacerbation of angina[6,15] and another showing no influence of ACE inhibitors on exercise-induced ischemia.[16]

Enalapril therapy has been shown to reduce the incidence of MI or unstable angina in patients with low ejection fractions in the presence or absence of overt heart failure.[4] Both the SAVE Trial[3] and Søgaard et al[5] demonstrated an anti-ischemic effect of captopril in infarct survivors. In the AIRE Study of infarct survivors with clinical evidence of heart failure, ramipril therapy administered 3 to 10 days after infarction improved survival and reduced the occurrence of the first validated adverse event (death, heart failure, MI, or stroke) during an average follow-up period of 15 months.[22] In CONSENSUS II, patients were treated with intravenous (and later oral) enalapril within 24 hours of the onset of MI. The trial was terminated after 6 months of follow-up. Although this trial demonstrated that patients receiving enalapril were less likely to require a change in therapy for treatment of heart failure, no improvement in survival or reduction in the rate of recurrent MI was demonstrated.[23] In SAVE,[3] in which the therapy was administered 3 to 16 days after acute MI and the average follow-up was 42 months, captopril-treated patients had a 25% reduction in recurrent MI compared with placebo-treated patients. This was an important finding, since we found that recurrent MI conferred a sevenfold increase in the risk of dying that was even greater than the risk of death in patients who developed severe heart failure. It has been demonstrated previously that in postinfarction patients, recurrent nonfatal MI is an important independent predictor of cardiac mortality.[24] Furthermore, compared with event-free patients, the patients who suffer a recurrent MI are more likely to have had prior cardiac-related symptoms or a prior MI.[2,25-27] Interestingly, we also found that prior hypertension or a higher blood pressure in the course of the index infarct appeared to be associated with a greater likelihood of recurrent MI (Table 4).

The SOLVD investigators also demonstrated in patients with low LVEFs (with and without overt heart failure) that recurrent MI conferred a relative risk of death at 1 year of 7.8, and even after deaths within 7 days of MI were excluded, the relative risk was 3.5. They also noted that the reduction in occurrence of MI and unstable angina with enalapril treatment seemed greater in patients with angina at the time of randomization.[4] Other drugs have also been studied in postinfarction populations.[28] It is well known that β-blockers reduce not only mortality[27-29] but also the reinfarction rate.[27] Although calcium antagonists have not altered mortality,[28,30] diltiazem has been shown to reduce the frequency of early reinfarction in patients with non–Q-wave infarction.[31] It is noteworthy that in the SAVE trial, captopril exerted a beneficial influence on mortality and morbidity (including MI) in the presence of

TABLE 5. Effect of Captopril on Ischemic and Morbid Events

Event	No. With Event (%)		Risk Reduction, % (95% CI)	*P*
	Captopril (n=1115)	Placebo (n=1116)		
Clinical MI	133 (12)	170 (15)	25 (5-40)	.015
Clinical MI followed by death	56	80	32 (4-51)	.029
Fatal MI (died within 10 days of MI)	32	43	28 (−14-54)	.159
Revascularization	154 (14)	195 (17)	24 (6-39)	.010
Hospitalization for unstable angina	135 (12)	133 (12)	0 (−26-22)	.930
Any of above	327 (29)	363 (33)	14 (0-26)	.047

CI indicates confidence interval; MI, myocardial infarction.

β-blocker therapy, suggesting an independent therapeutic effect.[3]

During the interval between the index MI and randomization into the SAVE Trial, patients who had evidence of recurrent ischemia or who had a positive exercise test were required by protocol to undergo coronary arteriography. If the treating physician felt that revascularization by either PTCA or CABG was required, it was performed before the patient was randomized into the SAVE Trial. We found that patients who subsequently experienced a recurrent MI were less likely to have been revascularized during this period than were event-free patients. Although selection bias is not excluded, this finding suggests that, in addition to captopril, revascularization soon after MI might reduce the incidence of reinfarction. This suggestion is supported by the findings in the CASS registry, in which surgical revascularization appeared to reduce the risk of subsequent MI in high-risk patients,[32] and the Veterans Administration Co-operative Study group, who found that the risk of death after recurrent MI appeared to be reduced in patients randomized to surgical treatment.[33]

In the SAVE Trial, depressed LVEF was a powerful predictor of cardiovascular mortality and the development of severe heart failure[3] but was not a significant predictor of subsequent recurrent MI. This observation suggests that captopril might be useful in preventing recurrent MI not only in patients with depressed ejection fractions but also in those with more preserved ventricular function.

To explore other evidence for an anti-ischemic action of captopril in the SAVE Trial, we examined the need for revascularization (by PTCA or CABG) and hospitalization for unstable angina. Despite substantial differences in the availability of resources and indications for procedures in the United States and Canada, the requirement for revascularization by either of these procedures was reduced by captopril in the trial as a whole and in each country. This suggests a continuing anti-ischemic influence of captopril after MI.

In contrast to the SOLVD investigators,[4] we found that the number of reported episodes of unstable angina requiring hospitalization were similar in placebo- and captopril-treated patients. However, these results are difficult to interpret, since no standardized criteria for this diagnosis were established.

Therefore, in a population of survivors of predominantly Q-wave MIs without overt evidence of ongoing myocardial ischemia or heart failure and with LVEFs of ≤40%, the occurrence of recurrent MI substantially increased the risk of death. As might have been anticipated, recurrent MI was more likely to occur in the patients with greater functional disability and angina before the index infarction. However, recurrent MI appears to be independent of the baseline LVEF. The observation of a favorable effect of the ACE inhibitor on the need for revascularization suggests that in addition to favorable influences on ventricular remodeling, captopril therapy potentially has another major role, ie, reducing fatal and morbid ischemic events in MI survivors with left ventricular dysfunction.

There are several potential mechanisms by which ACE inhibitors may exert anti-ischemic actions. These drugs have the capacity to alter hemodynamics favorably in patients surviving MIs by reducing blood pressure and altering remodeling of the left ventricle, thereby reducing wall stress. We found that patients with a higher systolic blood pressure at the time of randomization were more likely to have a recurrent MI, and the SOLVD investigators noted a trend toward larger reductions in morbid events among those patients with greater blood pressure reductions in response to a test dose of enalapril,[4] suggesting an important influence of the response of the patients to therapy. We are not aware of any major study in a normotensive post-MI population demonstrating that ACE inhibitors reduce the heart rate–blood pressure product. The study most relevant to our observations is by Søgaard et al,[5] in which captopril-treated patients with left ventricular dysfunction after MI gradually developed reductions in the number of spontaneous episodes of ST-segment depression and were also less likely to develop exercise-related ST-segment depression at the end of the study despite a greater increase in both maximal heart rate–blood pressure product and a higher product at onset of 0.1-mV ST depression during testing. In a hypertensive population[34] but not in a predominantly normotensive population,[35] abnormal plasma renin profiles were associated as a risk factor for MI. If activation of the renin-angiotensin system either systemically or locally is confirmed as a risk factor for MI, then ACE inhibitors would be reducing this risk.

The observed reductions in recurrent MI of a similar magnitude and with a similar time course in two differing patient populations, ie, the SAVE population of acute MI survivors with left ventricular dysfunction but without overt heart failure and the SOLVD population of patients with low LVEF (in the presence or absence of overt heart failure) who used two different ACE inhibitors (ie, captopril and enalapril, respectively) raise the possibility that angiotensin II may be involved in the thrombotic process. Plasminogen activator inhibitor-1 (PAI-1) is the most important inhibitor of tissue-type plasminogen activator (TPA) in plasma,[36,37] and elevated PAI-1 levels may be involved in the pathogenesis of thrombotic events.[38] Recent observations in patients link thrombotic risk to the renin-angiotensin system by demonstrating that angiotensin II infusions significantly increased the levels of PAI-1 antigen[39] but not of TPA. This suggests that angiotensin II may contribute to a prothrombotic state by opposing the activity of the endogenous fibrinolytic system. The observed reductions in recurrent MI and revascularization with captopril may be related to other actions of these drugs as well.

ACE inhibitors may also decrease coronary vasoconstrictor influences[40] by inhibiting the production of angiotensin II and by inhibiting the breakdown of the vasodilator bradykinin[41]; they may secondarily increase the production of endothelium-derived relaxing factor, prostacyclin, and TPA and thereby retard the atherogenic process.[42] It would now be highly desirable to carry out prospective trials of ACE inhibitors on patients with ischemic heart disease with no or only minor impairment of left ventricular function. This would permit ascertainment of whether the favorable effect of captopril on the development of recurrent MI and revascularization reported here and the favorable effect on the development of MI and unstable angina reported

with enalapril by the SOLVD investigators can be extended to a broader population.

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Appendix

Participants in the SAVE Study

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

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

References

1. Kannel WB, Sorlie P, McNamara PM. Prognosis after initial myocardial infarction: the Framingham study. *Am J Cardiol.* 1979;44: 53-59.
2. Moss AJ, Benhorin J. Prognosis and management after a first myocardial infarction. *N Engl J Med.* 1990;322:743-753.
3. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford JD, Wertheimer JH, Hawkins CM on behalf of the SAVE Investigators. 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;327:669-677.
4. Yusuf S, Pepine CJ, Garces C, Pouleur H, Salem D, Kostis J, Benedict C, Rousseau M, Bourassa M, Pitt B. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet.* 1992;340:1173-1178.
5. Søgaard P, Gotzsche C, Ravkilde J, Thygesen K. Effects of captopril on ischemia and dysfunction of the left ventricle after myocardial infarction. *Circulation.* 1993;87:1093-1099.
6. Gibbs JSR, Crean PA, Mockus L, Wright C, Sutton GC, Fox KM. The variable effects of angiotensin converting enzyme inhibition on myocardial ischemia in chronic stable angina. *Br Heart J.* 1989;62: 112-117.
7. Ikram H, Low CJ, Shirlaw T, Webb CM, Richards AM, Crozier IG. Antianginal, hemodynamic and coronary vascular effects of captopril in stable angina pectoris. *Am J Cardiol.* 1990;66:164-167.
8. Klein WW, Khurmi NS, Eber B, Dusleag J. Effects of benazepril and metoprolol OROS alone and in combination on myocardial ischemia in patients with chronic stable angina. *J Am Coll Cardiol.* 1990;16:948-956.

9. Akhras F, Jackson G. Captopril as monotherapy for stable angina and hypertension. *Eur Heart J.* 1988;9(suppl 1):2. Abstract.
10. Strozzi C, Portaluppi F, Cocco G, Urso L. Ergometric evaluation of the effects of enalapril maleate in normotensive patients with stable angina. *Clin Cardiol.* 1988;11:246-249.
11. Strozzi C, Cocco G, Portaluppi F, Urso L, Alfiero R, Tasini MT, Montanari L, Yassini KA, Rizzo A. Effects of captopril on the physical work capacity of normotensive patients with stable effort angina pectoris. *Cardiology.* 1987;74:226-228.
12. Bussmann WD, Wittig RA, Brunner I, Bahrmann H. The angiotensin-converting enzyme inhibitor in the treatment of angina pectoris. *Dtsch Med Wochenschr.* 1992;117:603-606.
13. Schneeweiss A, Marmor AT, Rettig-Sturmer G. Anti-ischemic effects of cilazapril in patients with both hypertension and angina pectoris. *Cardiology.* 1991;79:46-48.
14. Daly P, Mettauer B, Rouleau J-L, Cousineau D, Burgess JH. Lack of reflex increase in myocardial sympathetic tone after captopril: potential antianginal effect. *Circulation.* 1985;71:317-325.
15. Cleland JGF, Henderson E, McLenachan J, Findlay IN, Dargie HJ. Effect of captopril, an angiotensin-converting enzyme inhibitor, in patients with angina pectoris and heart failure. *J Am Coll Cardiol.* 1991;17:733-779.
16. Thurmann P, Odenthal HJ, Rietbrock N. Converting enzyme inhibition in coronary artery disease: a randomized, placebo-controlled trial with benazepril. *J Cardiovasc Pharmacol.* 1991;17: 718-723.
17. Moyé LA, Pfeffer MA, Braunwald E. Rationale, design and baseline characteristics of the survival and ventricular enlargement trial. *Am J Cardiol.* 1991;68:70D-79D.
18. Pfeffer MA, Moyé LA, Rutherford JD, Braunwald E. More on the Survival and Ventricular Enlargement Trial: reply to correspondence. *N Engl J Med.* 1993;329:1205-1206.
19. Kalbfleish JD, Prentice RL. *The Statistical Analysis of Failure Time Data.* New York, NY: John Wiley & Sons; 1980.
20. Rouleau JL, Moyé LA, Pfeffer MA, Arnold JMO, Bernstein V, Cuddy TE, Dagenais GR, Geltman EM, Goldman S, Gordon D, Hamm P, Klein M, Lamas GA, McCans J, McEwan P, Menapace FJ, Parker JO, Sesteir F, Sussex B, Braunwald E for the SAVE Investigators. A comparison of management patterns after acute myocardial infarction in Canada and the United States. *N Engl J Med.* 1993;328:779-784.
21. Lai C, Alberti D, Onnis E, Orani E, Soro A, Pirisi R, Cadeddu M, Lai G, Cherchi A. Effects of benazepril, a new ACE inhibitor, in effort angina. *Cardiologia.* 1991;36:785-792.
22. 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;342:821-828.
23. Swedberg K, Held P, Kjekshus J, Rasmussen K, Ryden L, Wedel H on behalf of the CONSENSUS II Study Group. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction: results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med.* 1992;327:678-684.
24. Benhorin J, Moss AJ, Oakes D. Prognostic significance of nonfatal myocardial reinfarction. *J Am Coll Cardiol.* 1990;15:253-258.
25. Vedin A, Wilhelmsson C, Elmfeldt D, Save-Soderbergh J, Tibbib G, Wilhelmsen L. Deaths and non-fatal reinfarctions during two years' follow-up after myocardial infarction: a follow-up study of 440 men and women discharged alive from hospital. *Acta Med Scand.* 1975;198:353-364.
26. Luria MH, Knoke JD, Wachs JS, Luria MA. Survival after recovery from acute myocardial infarction: two and five year prognostic indices. *Am J Med.* 1979;67:7-14.
27. The Norwegian Multicenter Study Group. Timolol-induced reinfarction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med.* 1981;304:801-807.
28. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease, I: treatments following myocardial infarction. *JAMA.* 1988;260:2088-2095.
29. Goldstein S, the BHAT Research Group. Propranolol therapy in patients with acute myocardial infarction: the Beta Blocker Heart Attack Trial. *Circulation.* 1983;67:53-56.
30. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med.* 1988;319:385-392.
31. Gibson RS, Boden WE, Theroux P, Strauss HD, Pratt CM, Gheorghiade M, Capone RJ, Crawford MH, Schlant RC, Kleiger RE, Young PM, Schechtman K, Perryman B, Roberts R and the Diltiazem Reinfarction Study Group. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction: results of double-blind, randomized, multicenter trial. *N Engl J Med.* 1986;315: 423-429.
32. Myers WO, Schaff HV, Fisher LD, Gersh BJ, Mock MB, Holmes DR, Gillispie S, Ryan TJ, Kaiser GC and CASS Investigators. Time to first new myocardial infarction in patients with severe angina and three-vessel disease comparing medical and early surgical therapy: a CASS registry study of survival. *J Thorac Cardiovasc Surg.* 1988;95:382-389.
33. Peduzzi P, Detre K, Murphy ML, Thomsen J, Hultgren H, Takaro T and the Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Ten-year incidence of myocardial infarction and prognosis after infarction: Department of Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery. *Circulation.* 1991;83:747-755.
34. Alderman MH, Madhaven SH, Ooi WL, Cohen H, Sealey JE, Laragh JH. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. *N Engl J Med.* 1991;324:1098-1104.
35. Meade TW, Cooper JA, Peart WS. Plasma renin activity and ischemic heart disease. *N Engl J Med.* 1993;329:616-619.
36. Luskutoff DJ, Sawdey M, Mimuro J. Type 1 plasminogen activator inhibitor. *Prog Hemost Thromb.* 1989;9:87-115.
37. Sprengers ED, Kluft C. Plasminogen activator inhibitors. *Blood.* 1987;69:381-387.
38. Ridker PM. An epidemiologic assessment of thrombotic risk factors for cardiovascular disease. *Curr Opin Lipid.* 1992;3:285-290.
39. Ridker PM, Gaboury CL, Conlin PR, Seely EW, Williams GH, Vaughan DE. Stimulation of plasminogen activator inhibitor in vivo by infusion of angiotensin II. *Circulation.* 1993;87:1969-1973.
40. Perondi R, Saino A, Tio RA, Pomidossi G, Gregorini L, Alessio P, Morganti A, Zanchetti A, Mancia G. ACE inhibition attenuates sympathetic coronary vasoconstriction in patients with coronary artery disease. *Circulation.* 1992;85:2004-2013.
41. Williams GH, Hollenberg NK. Accentuated vascular and endocrine response to SQ20,881 in hypertension. *N Engl J Med.* 1977;297: 194-201.
42. Powell JS, Clozel J-P, Muller RKM, Kuhn H, Hefti F, Hosang M, Baumgartner HR. Inhibitors of angiotensin-converting enzyme prevent myointimal proliferation after vascular injury. *Science.* 1989;245:186-188.

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J D Rutherford, M A Pfeffer, L A Moyé, B R Davis, G C Flaker, P R Kowey, G A Lamas, H S Miller, M Packer and J L Rouleau

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