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Effect of the Angiotensin-Converting Enzyme Inhibitor Trandolapril on Mortality and Morbidity in Diabetic Patients With Left Ventricular Dysfunction After Acute Myocardial Infarction

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OBJECTIVES This study evaluated the efficacy of long-term treatment with the angiotensin-converting enzyme (ACE) inhibitor trandolapril in diabetic patients with left ventricular dysfunction after acute myocardial infarction (AMI).

BACKGROUND Patients with diabetes mellitus have a high mortality following AMI, probably due to a high risk of congestive heart failure and reinfarction. Because ACE inhibition effectively reduces progression of heart failure, it could be particularly beneficial in diabetic patients after AMI.

METHODS The study is a retrospective analysis using data from the Trandolapril Cardiac Evaluation (TRACE) study, which was a randomized, double-blind, placebo-controlled trial of trandolapril in 1,749 patients with AMI and ejection fraction ≤35%. The mean follow-up time was 26 months.

RESULTS A history of diabetes was found in 237 (14%) of the 1,749 patients. Treatment with trandolapril resulted in a relative risk (RR) of death from any cause for the diabetic group of 0.64 (95% confidence interval 0.45 to 0.91) versus 0.82 (0.69 to 0.97) for the nondiabetic group. In the diabetic group, trandolapril reduced the risk of progression to severe heart failure markedly (RR, 0.38 [0.21 to 0.67]), and no significant reduction of this end point was found in the nondiabetic group.

CONCLUSIONS The ACE inhibition after myocardial infarction complicated by left ventricular dysfunction appears to be of considerable importance in patients with diabetes mellitus by saving lives and substantially reducing the risk of progression to severe heart failure. (J Am Coll Cardiol 1999; 34:83–9) © 1999 by the American College of Cardiology

Patients with diabetes mellitus have a poor prognosis after acute myocardial infarction (AMI). In most patients studied, the mortality rate after AMI is reported to be approximately twice that of patients without diabetes (1–3). The excess mortality seems to be due to a higher risk of congestive heart failure and reinfarction (4,5).

Angiotensin-converting enzyme (ACE) inhibition attenuates progression of heart failure and reduces mortality after AMI (6–8). One important mechanism behind these effects appears to be a beneficial influence on postinfarction left ventricular remodeling (9). Other mechanisms have, however, been suggested and some of these could be of particular importance in diabetic patients. Hence, ACE inhibitors can improve fibrinolytic balance, endothelial function, sympathovagal balance and glycemic control in addition to their ability to prevent or delay deterioration of renal function in diabetic patients.

Recent studies have suggested that ACE inhibition in diabetics with AMI is associated with a larger reduction in short-term mortality and congestive heart failure compared with nondiabetic patients (10,11). Analysis of long-term benefit of ACE inhibition after AMI in a diabetic subgroup is available only from the Survival and Ventricular Enlargement (SAVE) trial. In that study there was a trend for a mortality benefit for patients without diabetes, although the power was not adequate to make conclusions (12).

We hypothesize that long-term ACE inhibition could be particularly beneficial in diabetic patients after AMI. No

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
AIRE	=	Acute Ramipril Efficacy study
AMI	=	acute myocardial infarction
CI	=	confidence interval
GISSI-3	=	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
RR	=	relative risk
SAVE	=	Survival and Ventricular Enlargement trial
TRACE	=	Trandolapril Cardiac Evaluation study
WMI	=	wall motion index

detailed analysis of long-term benefit of ACE inhibition after AMI in high-risk diabetic patients is currently available. The purpose of this study was to evaluate the effect of long-term treatment with trandolapril on mortality and morbidity in diabetic patients with left ventricular dysfunction after AMI using data from the Trandolapril Cardiac Evaluation (TRACE) study.

METHODS

Patients. The current study includes 1,749 patients from the TRACE study, which was a randomized, double-blind, placebo-controlled trial to determine whether patients with left ventricular dysfunction shortly after myocardial infarction benefit from long-term oral ACE inhibition. Details of the TRACE study design and results have been published previously (6).

A total of 7,001 AMIs occurring in 6,676 patients were screened consecutively for the TRACE study in 27 Danish coronary care units between 1990 and 1992. Patients were eligible for entry into the TRACE study if left ventricular dysfunction was present two to six days after an enzyme-verified AMI. Left ventricular systolic function was assessed by echocardiography performed locally and subsequently analyzed centrally by two members of the study group (13). The criterion for left ventricular dysfunction was wall motion index (WMI) $\leq$1.2 corresponding to an ejection fraction (EF) $\leq$35%. A total of 2,606 patients were eligible according to left ventricular systolic function, and 1,749 patients were included in the study. The most frequent reasons for exclusion were mandatory need for ACE inhibition (150 patients), cardiogenic shock (101), death during screening (70), renal failure (65) and lack of informed consent (218). Thirty-nine patients were excluded because they did not tolerate a test dose of 0.5 mg trandolapril.

Study medication was started between days 3 and 7 after the AMI. Initially the patients were given either 1 mg trandolapril once daily or matching placebo. Target dose was 4 mg administered once a day. If this dose was not tolerated, patients could continue at a dose of 2 mg or 1 mg daily; however, patients who did not tolerate 1 mg once daily were withdrawn from the study.

The mean follow-up time was 26 months, ranging from 24 to 50 months. Excluding patients who died, 37.4% in the trandolapril group and 35.5% in the placebo group were withdrawn from study medication. Details of discontinuation of the study drug have been described elsewhere (14).

The primary end point was death from any cause. Information on survival status was available for all patients at the end of the study in 1994 and also by October 1996, six years after randomization of the first patient.

Predefined secondary end points were cardiovascular death, sudden death, progression to severe/resistant heart failure, recurrent infarction (fatal or nonfatal) and change in WMI. Sudden death was defined as death within 1 h of development of new symptoms, and progression in heart failure was defined as hospital admission for heart failure, death resulting from progressive heart failure, or heart failure necessitating open-label ACE inhibition.

Information on diabetic status was obtained at screening by case history, and diabetes was classified as being treated with insulin, oral hypoglycemic agents or diet alone. If a patient received both insulin and oral hypoglycemic agents he was classified as treated with insulin.

Using data from the TRACE study the present study is a retrospective analysis of the influence of having diabetes mellitus on the efficacy of trandolapril in decreasing mortality and morbidity after myocardial infarction complicated by left ventricular dysfunction. Of the secondary end points, change in WMI is omitted in this analysis as no difference in this parameter between the treatment group and the placebo group was found in the main study.

Statistics. Baseline characteristics for patients with and without diabetes and for diabetic patients treated with trandolapril or placebo were compared using the continuity-adjusted chi-square test for discrete variables and the Wilcoxon two-sample test for continuous variables. Mortality data were analyzed on an intention-to-treat basis. Time-to-event curves were generated with the use of Kaplan-Meier estimates. Comparisons of mortality and secondary end points were made using the Cox proportional hazards models. The interaction of diabetes with the effect of ACE inhibition was analyzed using a likelihood ratio test. A p value < 0.05 was considered significant. All calculations were generated by the SAS software (SAS Institute, Cary, North Carolina).

Ethics. The TRACE study was approved by all Danish regional ethics committees. All patients gave their informed consent before inclusion in the randomized trial.

RESULTS

Clinical characteristics. A history of diabetes was found in 237 (14%) of the 1,749 randomized patients. Of these, 50 (21%) patients were treated with insulin, 118 (50%) with oral hypoglycemic agents and 69 (29%) with diet alone. Median duration of diabetes (5 to 95 percentiles) was 7 (1 to 26) years.

Baseline characteristics for patients with and without

Table 1. Baseline Characteristics of 1,749 Patients With and Without a History of Diabetes

	Diabetics (n = 237)	Nondiabetics (n = 1,512)	p-Value
Mean age (±SD), years	70 (±9)	68 (±10)	0.003
Male gender, %	60	73	0.001
Mean BMI (±SD), kg/m^2	26.2 (±4.0)	25.6 (±3.8)	0.03
Current or ex-smoker, %	35	50	0.001
Clinical history			
Previous AMI, %	46	34	0.001
Angina pectoris, %	60	43	0.001
Treated hypertension, %	34	21	0.001
Cerebrovascular disease, %	12	8	0.06
Mean SBP (±SD), mm Hg	126 (±19)	121 (±17)	<0.001
Mean DBP (±SD), mm Hg	77 (±11)	76 (±10)	0.26
Mean s-creatinine (±SD), μmol/liter	120 (±33)	117 (±35)	0.05
Mean peak CK-B (±SD), U/liter	66 (±69)	101 (±111)	<0.001
Mean WMI (±SD)	0.97 (±0.19)	1.02 (±0.18)	<0.001
Thrombolysis, %	30	48	0.001
Atrial fibrillation, %	28	25	0.48
Ventricular fibrillation, %	5	9	0.06
Killip class ≥2 at randomization, %	67	57	0.01
Medication at randomization			
Aspirin, %	88	91	0.08
Beta-blockers, %	13	16	0.17
Calcium-antagonists, %	32	27	0.13
Diuretics, %	80	63	0.001
Nitrates, %	57	52	0.14

AMI = acute myocardial infarction; BMI = body mass index; CK-B = creatine kinase B; DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation; WMI = wall motion index.

diabetes are presented in Table 1. As expected, the two groups differed in many ways. Diabetic patients were slightly older, more often females, had a higher body mass index (BMI) and were less often smokers. The diabetic patients had a higher frequency of previous myocardial infarction (MI), angina pectoris and arterial hypertension. At randomization, patients with diabetes had higher systolic blood pressure, slightly lower WMI and higher prevalence of heart failure. A smaller proportion of the diabetic patients received thrombolytic therapy. More diabetics were treated with diuretics, whereas similar proportions of diabetics and nondiabetics were treated with aspirin, beta-blockers, calcium antagonists and nitrates at randomization. Treatment with trandolapril was evenly distributed in the two groups. In the diabetic group of 237 patients, 114 (48.1%) received trandolapril, corresponding to 762 (50.4%) of the 1,512 nondiabetic patients ($p = 0.56$). The target dose of 4 mg trandolapril was tolerated by 85% in both groups, excluding 54 patients in the diabetic group and 288 in the nondiabetic group, which did not survive the drug titration period.

Baseline characteristics were similar in the trandolapril-treated and placebo-treated diabetic patients (Table 2). This was also true for patients without diabetes but with two exceptions: Compared with patients randomized to placebo, patients randomized to trandolapril had a slightly higher diastolic blood pressure ($p = 0.02$) and a slightly higher frequency of history of hypertension ($p = 0.04$) (data not shown).

Mortality. During follow-up, 126 patients (53%) in the diabetic group died versus 547 (36%) in the nondiabetic group. Fifty-one (45%) of the diabetic patients randomized to trandolapril died versus 75 (61%) of the diabetics randomized to placebo, resulting in a relative risk (RR) of death from any cause in diabetic patients treated with trandolapril of 0.64 (95% confidence interval [CI] 0.45 to 0.91). In the nondiabetic group, 253 (33%) patients treated with trandolapril died versus 294 (39%) of patients treated with placebo, the relative risk (RR) of death being 0.82 (95% CI 0.69 to 0.97) (Fig. 1). The number needed to treat for saving one life in 26 months was 6 in the diabetic group and 17 in the nondiabetic group. The interaction between benefit on mortality from treatment with trandolapril and a history of diabetes was not significant ($p = 0.3$).

Similar results were obtained using a multivariate comparison including age, gender, BMI, smoking, previous MI, hypertension, atrial fibrillation, ventricular fibrillation, congestive heart failure, residual angina and WMI as covariates: In the patients with diabetes, trandolapril was associated with a risk reduction of 0.72 (95% CI 0.53 to 0.98), whereas

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Table 2. Baseline Characteristics of Diabetic Patients Randomized to Placebo or Trandolapril

	Placebo (n = 123)	Trandolapril (n = 114)	p-Value
Mean age (±SD), years	70 (±10)	69 (±9)	0.37
Male gender, %	54	67	0.07
Previous AMI, %	43	49	0.42
History of AP, %	62	58	0.63
Treated hypertension, %	33	35	0.78
Mean SBP (±SD), mm Hg	125 (±19)	127 (±20)	0.86
Mean DBP (±SD), mm Hg	76 (±11)	77 (±11)	0.39
Mean WMI (±SD)	0.97 (±0.20)	0.98 (±0.19)	0.74
Thrombolysis	25	35	0.13
Killip class ≥2 at randomization, %	66	68	0.89

AMI = acute myocardial infarction; AP = angina pectoris; DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation; WMI = wall motion index.

in patients without diabetes the risk reduction was 0.89 (95% CI 0.78 to 1.02).

Two years after the end of the study period, four to six years after randomization, the survival gain in diabetic patients was maintained, RR of death in diabetic patients treated with trandolapril being 0.68 (95% CI 0.50 to 0.91). The corresponding RR for the nondiabetic patients was 0.88 (95% CI 0.77 to 1.02).

Subgrouping the diabetics according to their antidiabetic treatment regimen indicated that the group treated with oral hypoglycemic agents had the greatest survival benefit of ACE inhibition. In fact, there was a significant interaction between treatment with trandolapril and diabetes treated with tablets with respect to mortality ($p = 0.04$). However, the numbers of insulin-treated and diet-treated diabetics were limited and therefore the power of this analysis was not adequate to draw definite conclusions.

Other clinical end points. Table 3 offers analyses of the influence of treatment with trandolapril on the occurrence of secondary end points in patients with and without diabetes. Treatment with trandolapril reduced all secondary endpoints by approximately 50% for the diabetic group, though not significantly with regard to reinfarction ($p = 0.08$). For the nondiabetic group only cardiovascular death was reduced significantly (RR, 0.79 [0.66 to 0.96], $p = 0.02$).

In the diabetic group, trandolapril reduced progression to severe heart failure in particular (RR, 0.38 [0.21 to 0.67], $p < 0.001$). The interaction between benefit from treatment with trandolapril and diabetes was significant with regard to this end point ($p = 0.03$). Figure 2 shows that the rate of progression in heart failure was much higher in the diabetic group than in the nondiabetic group, which means that the reduction in absolute risk of progression in heart failure was substantial (21%) in the diabetic group compared with the nondiabetic group (4%).

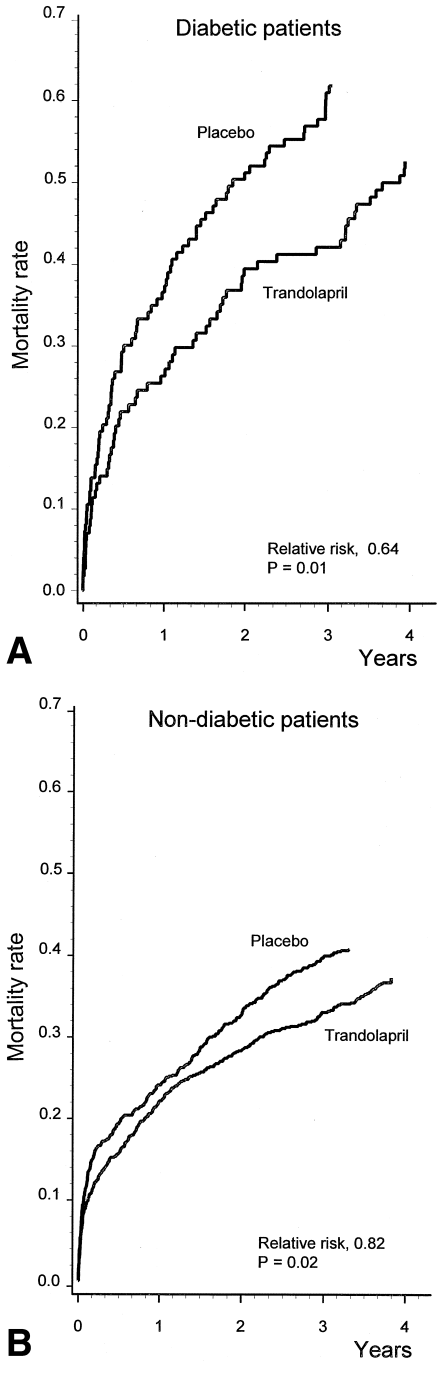

Figure 1. Cumulative mortality from all causes for patients with **(A)** and without **(B)** diabetes receiving trandolapril or placebo.

Adverse events. Serum(s)-creatinine decreased slightly (1.3 μmol/liter) from baseline to one month after randomization in the diabetic group with no statistical difference between the decrease in s-creatinine seen in the placebo-treated and the trandolapril-treated patients. For nondiabetic patients treated with trandolapril, s-creatinine in-

Table 3. Influence of Treatment With Trandolapril on the Occurrence of Secondary End Points in Patients With and Without Diabetes

	Diabetics		Nondiabetics		Interaction
End Point	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**	**p**
Cardiovascular death	0.56 (0.37–0.85)	0.01	0.79 (0.66–0.96)	0.02	0.17
Sudden death	0.46 (0.25–0.85)	0.01	0.84 (0.63–1.12)	0.23	0.09
Reinfarction	0.55 (0.29–1.07)	0.08	0.93 (0.69–1.26)	0.65	0.15
Progression in HF	0.38 (0.21–0.67)	<0.001	0.81 (0.63–1.04)	0.10	0.03

CI = confidence interval; HF = heart failure; RR = relative risk.

creased marginally (0.7 μmol/liter), while it decreased (2.3 μmol/liter) for nondiabetic patients treated with placebo ($p = 0.02$).

During follow-up, the incidence of uremia was 1.9% in the nondiabetic group and 3.4% in the diabetic group. In both groups approximately 60% of the cases were seen in patients receiving trandolapril.

Reasons for discontinuation of study medication were the same in the diabetic group and the nondiabetic group.

DISCUSSION

This post hoc subgroup analysis of the TRACE data indicates that patients with diabetes mellitus who have suffered an AMI complicated by left ventricular dysfunction have a substantial benefit from long-term ACE inhibition. Mortality and, in particular, the secondary end point progression to severe heart failure were reduced markedly. Indeed, the data revealed an interaction between diabetes and the benefit from treatment with regard to progression to severe heart failure.

The data material used in this analysis is unique because two-thirds of consecutive patients with AMI and with left ventricular dysfunction were included in the TRACE study. Thus, the results are expected to be representative of infarct patients with left ventricular dysfunction.

The diabetic population was 14%, which is close to the 12% (240 patients) in the Acute Ramipril Efficacy (AIRE) study (8) but somewhat less than the 22% (492 patients) in the SAVE study (7). The TRACE study and the AIRE study were performed mostly in Europe, whereas the SAVE study was performed in the U.S., where the frequency of diabetes is higher (15,16). Baseline characteristics for the diabetic patients resemble those of other infarct studies (1,3,10). In both the diabetic group and the nondiabetic group, baseline characteristics were well balanced between placebo-treated and trandolapril-treated patients.

Mortality. The TRACE study, like other investigations in the thrombolytic era, demonstrates that diabetic patients comprise a high-risk population. The long-term mortality (26 months) was 53% for the diabetic group, which is 47% higher than for the nondiabetic group. Thus, it is important to optimize the treatment strategies in this high-risk population.

In a retrospective univariate analysis of the large diabetic population in the GISSI-3 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) study (2,790 patients) it was found that early treatment with lisinopril after AMI was associated with a 30% reduction in six-week mortality (10). The present TRACE data demonstrate a 36% reduction in 26-month mortality for diabetic patients treated with trandolapril, a reduction that was maintained two years after completion of the study. Possibly, the benefit with regard to mortality is greater for the diabetic patients than for the nondiabetic patients, but because of a relatively small number of diabetic patients, the power to detect a statistical significant interaction was not adequate.

Due to the high mortality of the diabetic patients, the absolute reduction in mortality in this group becomes substantial. For the diabetic group, the absolute mortality reduction over two years was 16%, equivalent to a number needed to treat of six patients for saving one life. The corresponding figures for the nondiabetic group were 6% and 17 patients.

Secondary end points. In addition to reduction in mortality, treatment with trandolapril resulted in an impressive reduction in morbidity after AMI in the diabetic group. There was a trend toward a substantial reduction in reinfarction for the diabetic patients. Progression to severe heart failure was reduced significantly, by more than 60%. The reduction in progression to severe heart failure was significantly higher for the patients with diabetes than for the patients without diabetes. Because the rate of progression to severe heart failure was also higher for diabetic patients, the absolute reduction in this secondary end point becomes even greater compared with nondiabetic patients.

Mechanisms for the effect of ACE inhibitors. The mechanism behind the effect of treatment with trandolapril in diabetic patients with left ventricular dysfunction after AMI is not simple nor fully understood. Because of structural, functional and metabolic myocardial factors related to diabetes, the diabetic patient with AMI has a higher risk of left ventricular remodeling, which is associated with a poor prognosis (17,18). When adjusted for size of infarction, patients with diabetes develop more congestive heart failure than do patients without diabetes (19). Diabetic patients with AMI generally have more extensive coronary artery

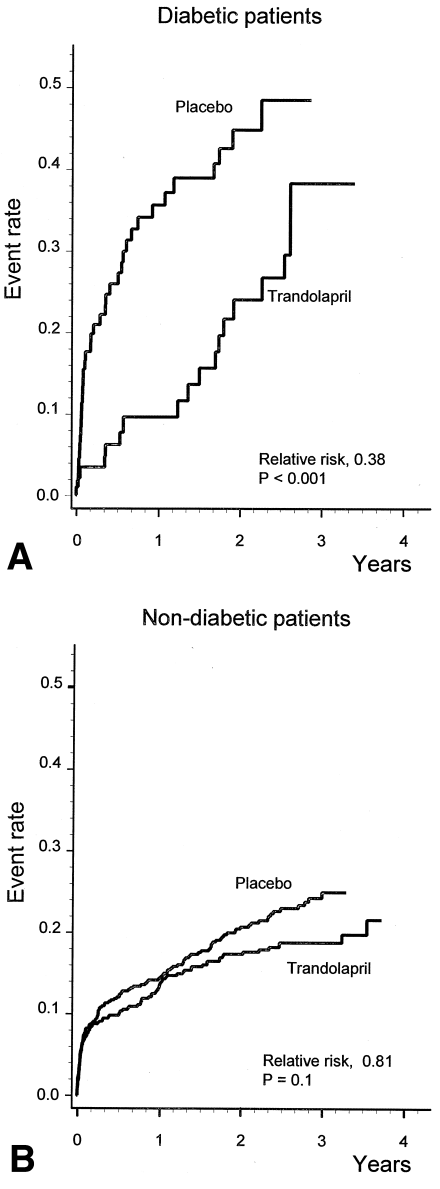

Figure 2. Rate of progression to severe or resistant heart failure for patients with **(A)** and without **(B)** diabetes receiving trandolapril or placebo.

disease and a higher frequency of previous silent infarction (3,20,21). A likely coexistence of diabetic cardiomyopathy or hypertension can possibly worsen myocardial damage. It has previously been suggested that hypertensives with AMI and left ventricular dysfunction may derive particular benefit from ACE inhibition (22), and in the present study the diabetic patients have a higher frequency of arterial hypertension. During ischemia the diabetic patient experiences decreased myocardial glucose uptake leading to suppressed adenosine triphosphate (ATP) production and myocardial contractile dysfunction (23). Because diabetic patients may be particularly prone to ventricular remodeling, ACE inhibitors may prevent death and progression in heart failure by attenuating this deleterious alteration in cardiac geometry.

In addition, ACE inhibitors counteract many of the established and putative mechanisms resulting in increased mortality of diabetic patients with AMI. Fibrinolytic balance can be improved by ACE inhibition in patients with AMI (24). Endothelial dysfunction can be attenuated by ACE inhibition in patients with coronary artery disease (25). For type 2 diabetics, ACE inhibitors have been shown to improve insulin sensitivity and glycemic control (26). Finally, it has been demonstrated that baroreflex sensitivity and heart rate variability reflecting cardiac autonomic control can be favorably modified by ACE inhibitors in patients with AMI (27,28). Autonomic imbalance, which is a complication of diabetes mellitus, is associated with an increased risk for sudden death (29), a mode of death that tends to be reduced mostly for the diabetic patients in the present study.

The beneficial effect of trandolapril in the diabetic group was not counteracted by a higher frequency of renal adverse events. Diabetic patients did not experience a higher incidence of uremia as a result of treatment with trandolapril compared with nondiabetic patients. Initial change in s-creatinine from baseline to one month after randomization was similar for patients with and without diabetes.

Study limitations. No prospective analysis of the benefit of ACE inhibition in diabetics with AMI exists, and such a study is not likely to be conducted. The main limitation of this study was the fact that it was retrospective and based on subgroup analysis. The results must therefore be interpreted with caution (30). The magnitude of the benefit from treatment with trandolapril in the diabetic subgroup, however, was striking and, indeed, clinically relevant. Furthermore, as discussed previously, the results can be explained by plausible underlying mechanisms.

Because this study was not predefined, the diagnosis of diabetes was based on history obtained at screening, and no laboratory values on glycemic status were available. The diabetic patients were not classified according to the type of diabetes, but at least 80% must have had type 2 diabetes according to their treatment mode. Owing to the relatively low number of diabetics and the lack of classification according to type, the diabetics were pooled in one group. Among the nondiabetic patients a proportion with unrecognized diabetes must be present. In a previous study, an overall prevalence of undiagnosed diabetes mellitus of 5.3% in patients with MI was estimated (31). If such patients in our study had been classified correctly, they might have tended to increase the difference in benefit observed between diabetics and nondiabetics. Conversely, some of the diabetic patients treated with diet only may not have fulfilled the diagnosis of diabetes.

Conclusions. Bearing the limitations of the study in mind, we conclude that long-term treatment with trandolapril after myocardial infarction complicated by left ventricular dysfunction appears to be of considerable importance in

patients with diabetes mellitus by saving lives and substantially reducing the risk of progression to severe heart failure.

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