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Effect of Very Early Angiotensin-Converting Enzyme Inhibition on Left Ventricular Dilation After Myocardial Infarction in Patients Receiving Thrombolysis

Results of a Meta-analysis of 845 Patients

Pieter J. de Kam, MSc,* Adriaan A. Voors, MD, PhD,†‡ Maarten P. van den Berg, MD, PhD,* Dirk J. van Veldhuisen, MD, PhD, FACC,* Jan Brouwer, MD, PhD,* Harry J. G. M. Crijns, MD, PhD,* Claudio Borghi, MD,§ Ettore Ambrosioni, MD,§ Judith S. Hochman, MD,‖ Thierry H. LeJemtel, MD,¶ Jan-Herre Kingma, MD, PhD,† Martin St. John Sutton, MD, MBBS, FACC,# Wiek H. van Gilst, PhD,*‡ on behalf of the FAMIS, CAPTIN and CATS Investigators

Groningen and Nieuwegein, The Netherlands; Bologna, Italy; New York, New York; and Philadelphia, Pennsylvania

OBJECTIVES We sought to investigate the effect of angiotensin-converting enzyme (ACE) inhibition <9 h after myocardial infarction (MI) on left ventricular (LV) dilation in patients receiving thrombolysis.

BACKGROUND The ACE inhibitors reduce mortality after MI. Attenuation of LV dilation has been suggested as an important mechanism.

METHODS The data of 845 patients with three-month echocardiographic follow-up after MI were combined from three randomized, double-blind, placebo-controlled studies. The criteria for these studies included: 1) thrombolytic therapy; 2) ACE inhibition within 6 to 9 h; and 3) evaluation of LV dilation as the primary objective.

RESULTS The ACE inhibitor was started 3.2 ± 1.7 h after the patients' first (mainly, 85%) anterior MI. After three months, LV dilation was not significantly attenuated by very early treatment with an ACE inhibitor. The diastolic volume index was attenuated by 0.5 ml/m^2 (95% confidence interval [CI] −1.5 to 2.5, p = 0.61), and the systolic volume index by 0.5 ml/m^2 (95% CI −1.0 to 1.9, p = 0.50). Subgroup analysis demonstrated that LV dilation was significantly attenuated by ACE inhibitor treatment for patients in whom reperfusion failed. In contrast, LV dilation was almost unaffected by ACE inhibitor treatment in successfully reperfused patients.

CONCLUSIONS We could not demonstrate attenuation of LV dilation in patients receiving thrombolysis by ACE inhibitor treatment within 6 to 9 h after MI. We speculate that very early treatment with an ACE inhibitor has a beneficial effect on LV remodeling only in patients in whom reperfusion failed. Other mechanisms may be responsible for the beneficial effects of ACE inhibitors in successfully reperfused patients after MI. (J Am Coll Cardiol 2000;36:2047–53)
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The important role of angiotensin-converting enzyme (ACE) inhibitors in reducing mortality after myocardial infarction (MI) has been well established (1). The optimal timing of treatment with an ACE inhibitor after MI, as well as the exact mechanisms leading to the beneficial effects of ACE inhibitors, have not been completely resolved. Timing of ACE inhibitors after MI in large mortality trails was either late (>3 days) or early (<24 to 36 h) (1). The beneficial effects of very early (<6 h) ACE inhibitor treatment on cardiac death have only been demonstrated in one recent angiographic study (2). Because mortality is directly related to the extent of left ventricular (LV) dilation (3), an important suggested mechanism by which ACE inhibitors produce their beneficial effects is attenuation of LV dilation (4). Previously, we performed a study in 298 patients receiving thrombolysis after their first anterior wall MI, to address the effect of very early treatment with an

See page 2054

ACE inhibitor on LV dilation (5,6). In this study, only a modest beneficial effect of ACE inhibitor treatment on LV dilation was demonstrated during one year of follow-up, and it was calculated that at least 700 patients would have been needed to conclude a true effect of ACE inhibitors on ventricular dilation. Therefore, in the present study, we combined the data of 845 patients from three similar randomized, double-blind, placebo-controlled, echocardiographic studies who received thrombolysis after MI. The

From the *Department of Cardiology, University Hospital, Groningen, The Netherlands; †Department of Cardiology, St. Anthonius Hospital, Nieuwegein, The Netherlands; ‡Department of Clinical Pharmacology, University of Groningen, Groningen, The Netherlands; §Department of Cardiology, University of Bologna, Bologna, Italy; ‖Department of Cardiology, St. Luke's–Roosevelt Hospital, New York, New York; ¶Division of Cardiology, Albert Einstein College of Medicine, New York, New York; and #Cardiovascular Division, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania. The three studies on which this meta-analysis was based (CATS, FAMIS and CAPTIN) were all financially supported by Bristol-Myers Squibb.

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JACC Vol. 36, No. 7, 2000
December 2000:2047–53

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
CAPTIN	= CAPtopril plus Tissue plasminogen activator following acute myocardial INfarction study
CATS	= Captopril And Thrombolysis Study
CONSENSUS-II	= COoperative New Scandinavian ENalapril SUrvival Study II
FAMIS	= Fosinopril in Acute Myocardial Infarction Study
GISSI-3	= Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-3
HOPE	= Heart Outcomes Prevention Evaluation study
LV	= left ventricular
MI	= myocardial infarction
SAVE	= Survival And Ventricular Enlargement trial

aim of the present study was to assess the effect of treatment with an ACE inhibitor within 6 to 9 h on LV dilation in patients receiving thrombolysis, mainly after their first anterior MI.

METHODS

Study design. We combined the data of 845 patients receiving thrombolysis from three multicenter, randomized, double-blind, placebo-controlled, echocardiographic studies, which initiated ACE inhibitor treatment 3.2 ± 1.70 h after the onset of mainly (85%) their first anterior MI. This resulted in a data base containing the data of all studies performed in this setting, with the primary objective being assessment of the effect of very early treatment with an ACE inhibitor on LV dilation, with at least one-month echocardiographic follow-up. The three studies included in this meta-analysis were the Captopril And Thrombolysis Study (CATS, n = 298, April 1990 to December 1992), the Fosinopril in Acute Myocardial Infarction Study (FAMIS, n = 285, January 1992 to June 1993) and the CAPtopril plus Tissue plasminogen activator following acute myocardial INfarction study (CAPTIN, n = 262, September 1990 to July 1992). Only CATS (5,6) and FAMIS (7,8) have been published as full reports. Of the 845 patients included in this meta-analysis, 421 were randomized to placebo and 424 to an ACE inhibitor; 711 patients (84%) had at least one echocardiographic assessment. Double-blind placebo or ACE inhibitor treatment was initiated either immediately on completion of thrombolytic therapy (CATS and CAPTIN) or within 3 h after thrombolysis (FAMIS). In CAPTIN, 2 to 4 mg captopril was initially administered intravenously within 6 h after MI, followed by the first oral dose of 6.25 mg 2 h after thrombolytic therapy. In CATS, administration of 6.25 mg captopril orally was started within 6 h after MI. If tolerated, both CATS and CAPTIN gradually adjusted the dose upward to 25 mg. The initial oral dose of fosinopril in FAMIS was administrated within 9 h of MI and was 5 mg for the first two days, and if tolerated, titrated upward to 20 mg. Treatment with an ACE inhibitor continued until the end of the study (one year for CATS and three months for FAMIS and CAPTIN).

Patients. The three studies were very similar in terms of patient selection criteria. Patients were considered eligible if MI was diagnosed on the basis of the presence of symptoms and at least 2-mm ST segment elevation in two or more precordial leads (V_1 to V_6). In addition, patients had to be eligible for thrombolytic therapy immediately after admission to the coronary care unit (continuous intravenous infusion of streptokinase [1,000,000 IU during 30 min] in CATS and FAMIS or recombinant tissue-type plasminogen activator [60 mg in the first hour, 20 mg in the second and third hours] in CAPTIN). Thrombolytic therapy had to be administered within 6 h (CATS and CAPTIN) or within 8 h (FAMIS) after the onset of MI symptoms. During double-blind therapy, all patients received the usual recommended therapy, including beta-blockers and aspirin.

Echocardiographic measurements. In CATS, LV volume was measured by serial two-dimensional echocardiograms at 1, 3 and 10 days and 3 and 12 months; in FAMIS, within 2 days, at hospital discharge (15 days) and at 3 months; and in CAPTIN, at 3 days and 1 and 3 months after the onset of symptoms. In the three studies, the echocardiographic methods were similar, as reported previously (5,7). For each of the three studies, the echocardiograms were centrally evaluated in a single echocardiographic core laboratory. The echocardiographic analysis was performed without knowledge of the study medication and echocardiogram sequence.

Reperfusion status. Reperfusion was assessed clinically, as relief of chest pain, rapid reversal of ischemic electrocardiographic changes, rapid peak of creatine kinase (within 16 h after onset of symptoms) and typical transient arrhythmias. At least three of these four findings had to be present to conclude that reperfusion was successful after thrombolysis (7).

Statistical analysis. Analysis was performed on an intention-to-treat basis. Continuous baseline characteristics are expressed as the mean value ± SD if normally distributed, and the median value (interquartile range) if distributed skewed. The differences were tested by one-way analysis of variance or by the Kruskal-Wallis test, when appropriate. Categorical variables were described by frequencies and percentages, and the chi-square test was used.

A random-effects model for longitudinal data (SAS, version 6.12, PROC MIXED, Cary, North Carolina) (9) was used to test the attenuation of LV systolic and diastolic volume indexes by ACE inhibition. Logarithmic-transformed LV volume indexes were analyzed. Mean values and standard errors were back-transformed. The effects of ACE inhibitors on LV dilation were corrected for significant baseline characteristics and the differences be-

Table 1. Baseline Characteristics of the Patients of Studies Included in This Meta-Analysis

Characteristics	CATS (n = 298)	FAMIS (n = 285)	CAPTIN (n = 262)
Age (yrs)	59 ± 10	60 ± 10	59 ± 10
Males	224 (75%)	235 (85%)	209 (80%)
Mean arterial pressure (mm Hg)*	93 ± 14	102 ± 15	99 ± 15
Heart rate (beats/min)†	82 ± 15	78 ± 15	80 ± 15
Body surface area (m^2)*	1.90 ± 0.16	1.84 ± 0.17	1.94 ± 0.22
Killip class I	224 (75%)	227 (80%)	189 (72%)
Killip class II	72 (24%)	57 (20%)	71 (27%)
Clinical history			
Ischemic heart disease*	26 (9%)	65 (23%)	42 (16%)
Hypertension*	65 (22%)	104 (36%)	97 (37%)
Diabetes mellitus*	28 (9%)	42 (15%)	52 (20%)
Current smoker†	186 (63%)	148 (52%)	149 (57%)
Medication history			
Beta blockers*	57 (19%)	24 (8%)	38 (15%)
Calcium antagonists†	42 (14%)	50 (18%)	22 (8%)
Diuretics†	35 (12%)	12 (4%)	18 (7%)
Nitrates	30 (10%)	24 (8%)	37 (14%)
Echocardiographic measures			
Systolic volume index (ml/m^2)†	24 (18–32)	27 (20–34)	27 (20–33)
Diastolic volume index (ml/m^2)†	55 (47–62)	55 (46–64)	51 (45–61)
Ejection fraction (%)*	56 (47–62)	50 (44–57)	49 (42–55)
Peak creatine kinase (IU/1,000)*	1.36 (0.7–2.50)	1.85 (0.9–3.1)	2.28 (0.9–3.8)
Reperfusion	188 (73%)	206 (73%)	199 (76%)

*Significantly different ($p < 0.001$). †Significantly different ($0.01 < p < 0.05$). Data are presented as the mean value ± SD, number (%) of patients or median value (interquartile range).

CAPTIN = CAPtopril plus Tissue plasminogen activator following acute myocardial INfarction study; CATS = Captopril And Thrombolysis Study; FAMIS = Fosinopril in Acute Myocardial Infarction Study.

tween trials. All p values were two-sided; $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics. Although the patient selection criteria for the three studies were similar, there were some differences in baseline characteristics (Table 1). The CAPTIN study included patients with larger infarctions, as compared with FAMIS and CATS. In CATS, there were fewer patients with hypertension and preexisting ischemic heart disease, and the mean arterial pressure was lower. Despite these differences, owing to the random assignment to the two treatment groups (placebo and ACE inhibitor), the baseline characteristics of the groups were comparable (Table 2). The overall successful reperfusion rate was 74%. During the first 10 days after MI, 4.9% of patients, and during the first three months, 7.7% of patients initially randomized to placebo, crossed over to active treatment.

Left ventricular dilation. Except for the baseline assessment in the CAPTIN study, for each of the three studies, the mean LV volume indexes were comparable between the two groups (Table 3). When combining the studies, the patients receiving placebo and those treated with an ACE inhibitor showed very comparable LV diastolic and systolic dilation (Fig. 1). Treatment with an ACE inhibitor did not significantly attenuate the LV diastolic volume index at three months by 0.5 ml/m^2 (95% CI −1.5 to 2.5) and also did not significantly attenuate the LV systolic volume index by 0.5 ml/m^2 (95% CI −1.0 to 1.9). However, at three months after MI, LV systolic and diastolic volume indexes were significantly increased as compared with baseline, for both the ACE inhibitor and placebo groups. The diastolic volume index increased for the ACE inhibitor group by 3.9 ml/m^2 (95% CI 2.5 to 5.3), and for the placebo group by 4.3 ml/m^2 (95% CI 3.0 to 5.6). The systolic volume index increased for the ACE inhibitor group by 1.4 ml/m^2 (95% CI 0.4 to 2.4), and for the placebo group by 1.9 ml/m^2 (95% CI 0.9 to 2.8). The lack of an effect of ACE inhibitor therapy on LV diastolic and systolic dilation was consistently found among the subgroups (Fig. 2). However, treatment with an ACE inhibitor in the subgroup of patients in whom reperfusion failed resulted in significant attenuation of both LV diastolic and systolic dilation after thrombolytic therapy, as compared with placebo (Fig. 3). In contrast, LV dilation was almost unaffected by treatment with an ACE inhibitor in successfully reperfused patients. For patients in whom reperfusion failed, ACE inhibitor treatment resulted in attenuation of the LV diastolic volume index by 4.9 ml/m^2 (95% CI 0.7 to 8.8), as well as attenuation of the LV systolic volume index by 4.0 ml/m^2 (95% CI 1.2 to 6.4), both at three months. Furthermore, both LV systolic and diastolic dilations were significantly more pronounced for patients in whom reperfusion failed, as compared with successfully reperfused patients (Fig. 4). The additional increase in the LV diastolic volume index of patients in whom reperfusion failed over that of successfully

JACC Vol. 36, No. 7, 2000
December 2000:2047–53

Table 2. Baseline Characteristics of the Patients Randomly Allocated to Placebo and Angiotensin-Converting Enzyme Inhibitor Treatment

Characteristics	Placebo (n = 421)	Ace Inhibitor (n = 424)
Age (years)	60 ± 10	59 ± 10
Males	343 (81%)	325 (77%)
Mean arterial pressure (mm Hg)	98 ± 15	98 ± 15
Heart rate (beats/min)	80 ± 14	80 ± 15
Body surface area (m^2)	1.90 ± 0.18	1.89 ± 0.19
Killip class I	317 (75%)	323 (76%)
Killip class II	103 (25%)	97 (24%)
Clinical history		
Ischemic heart disease	55 (13%)	78 (18%)
Hypertension	114 (27%)	152 (36%)
Diabetes mellitus	53 (13%)	69 (16%)
Current smoker	226 (54%)	257 (61%)
Medication history		
Beta-blockers	54 (13%)	65 (15%)
Calcium antagonists	57 (14%)	57 (13%)
Diuretics	29 (7%)	36 (8%)
Nitrates	41 (10%)	50 (12%)
Echocardiographic measures		
Systolic volume index (ml/m^2)	26 (20–32)	26 (20–34)
Diastolic volume index (ml/m^2)	54 (46–61)	54 (46–63)
Ejection fraction (%)	54 (46–61)	54 (46–63)
Peak creatine kinase (IU/1,000)	1.80 (0.8–3.1)	1.70 (0.9–3.1)
Reperfusion	312 (77%)	281 (70%)

Data are presented as the mean value ± SD, number (%) of patients or median value (interquartile range).
ACE = angiotensin-converting enzyme.

reperfused patients was 4.0 ml/m^2 (95% CI 0.7 to 5.3), and the additional increase in the LV systolic volume index was 3.1 ml/m^2 (95% CI 0.7 to 5.3), both at three months.

DISCUSSION

This meta-analysis of 845 patients receiving thrombolysis in three prospective, randomized, double-blind, placebo-controlled studies shows that LV dilation at three months is not significantly attenuated by treatment with an ACE inhibitor within 6 to 9 h after the patients' first (mainly) anterior MI (Fig. 1). Subgroup analysis, however, suggests a beneficial effect of ACE inhibition on LV dilation for patients in whom thrombolytic therapy failed to establish reperfusion (Fig. 3). In contrast, subgroup analysis showed no effect of ACE inhibition on LV dilation in reperfused patients. In accordance with previous studies (10,11), subgroup analysis in the present study showed significant prevention of LV dilation after successful reperfusion after MI (Fig. 4). There are three major differences between the present study and most other echocardiographic studies. First, in the present study, all patients were treated with thrombolytic therapy at arrival in the coronary care unit. Second, patients were not selected on the basis of ventricular dysfunction. Third, ACE inhibitor treatment was started very early (i.e., within 6 to 9 h) after MI. These differences may explain the result of no significant attenuation of LV dilation by treatment with an ACE inhibitor as compared with placebo.

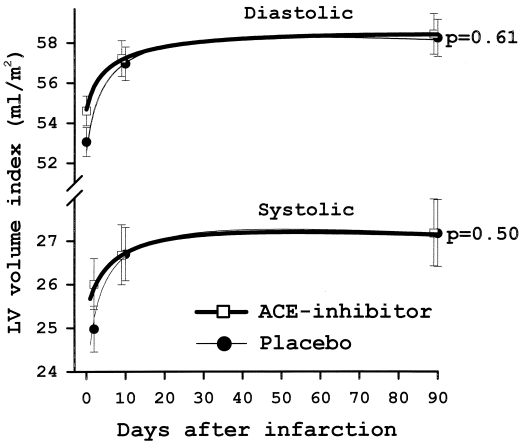

Figure 1. The effect of ACE inhibitor treatment within 6 to 9 h on LV dilation in patients receiving thrombolysis (n = 845) after MI. Data are presented as the mean value ± SEM.

Thrombolytic therapy. The first possible reason for our finding of no significant attenuation of LV dilation may be the administration of thrombolytic therapy. The first evidence of attenuation of LV dilation produced by ACE inhibition as compared with placebo was obtained from experimental studies of occluded arteries (12). Some small echocardiographic studies showed large effects of ACE inhibition on LV dilation, but they were conducted in

Table 3. Mean Ventricular Volume Indexes for Each of the Studies Separately (CATS, FAMIS and CAPTIN)

		Baseline		Discharge		3-Month Follow-Up	
		Placebo	ACE Inhibitor	Placebo	ACE Inhibitor	Placebo	ACE Inhibitor
Mean	CATS	24.2 ± 0.84	23.6 ± 0.89	26.7 ± 0.97	24.3 ± 0.98	26.9 ± 1.25	25.3 ± 1.25
LVESVI	FAMIS	25.6 ± 0.93	26.8 ± 0.97	26.9 ± 1.08	28.6 ± 1.12	26.8 ± 1.33	28.0 ± 1.14
(± SEM)	CAPTIN	25.1 ± 0.97*	28.4 ± 1.16	26.5 ± 1.18	27.8 ± 1.58	27.8 ± 1.15	29.0 ± 1.58
	Total	25.0 ± 0.53	26.0 ± 0.58	26.7 ± 0.61	26.7 ± 0.69	27.2 ± 0.72	27.2 ± 0.77
Mean	CATS	54.9 ± 1.26	54.3 ± 1.26	58.7 ± 1.33	57.3 ± 1.34	60.5 ± 1.64	59.1 ± 1.71
LVEDVI	FAMIS	53.4 ± 1.32	54.7 ± 1.49	57.7 ± 1.49	58.8 ± 1.69	58.8 ± 1.69	59.1 ± 1.56
(± SEM)	CAPTIN	50.8 ± 1.14*	54.9 ± 1.46	53.7 ± 1.53	54.9 ± 1.96	55.2 ± 1.45	56.8 ± 2.04
	Total	53.1 ± 0.72	54.6 ± 0.74	57.0 ± 0.84	57.2 ± 0.90	58.3 ± 0.93	58.5 ± 1.02

*$p < 0.05$ for placebo vs. ACE inhibitor.
ACE = angiotensin-converting enzyme; LVESVI = left ventricular end-systolic volume index; LVEDVI = left ventricular end-diastolic volume index; other abbreviations as in Table 1.

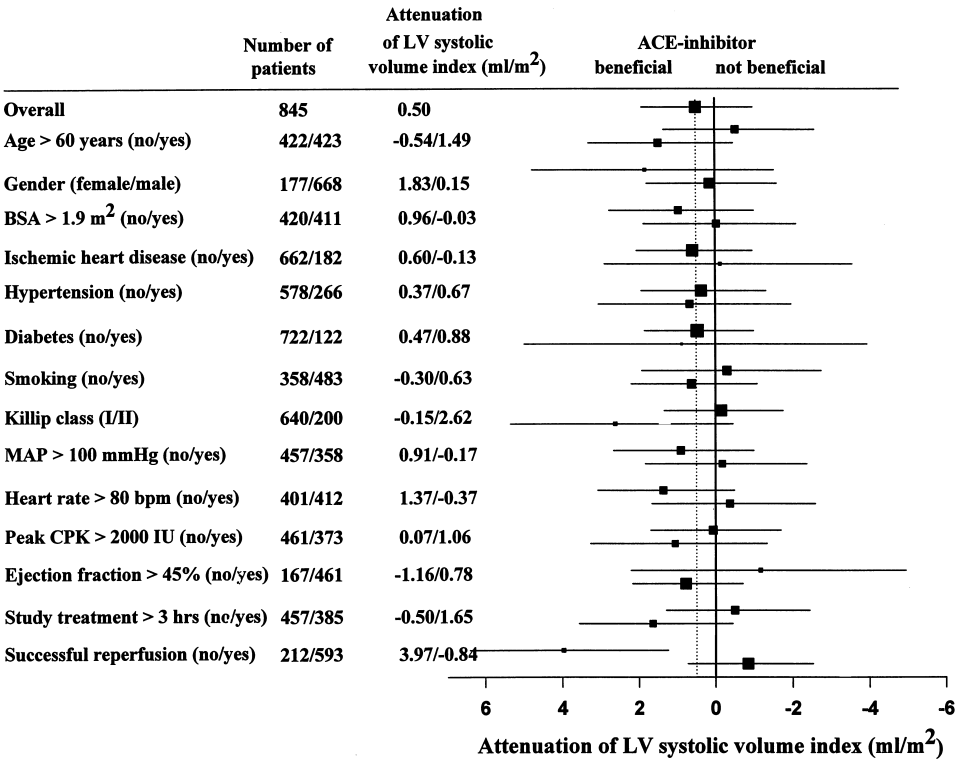

Figure 2. The effect of ACE inhibitor treatment within 6 to 9 h on LV dilation after MI in various subgroups. Data are presented as the mean value and 95% CI. BSA = body surface area; CPK = creatine phosphokinase; MAP = mean arterial pressure.

patients who did not receive thrombolytic therapy (13–16). In the most frequently cited clinical echocardiographic study showing a beneficial effect of ACE inhibition on LV dilation, only 17% of the patients underwent percutaneous transluminal coronary angioplasty or thrombolytic therapy (4). With the increase in the number of patients receiving thrombolytic therapy, however, the effect of ACE inhibition on LV dilation seemed to decrease. The echocardiographic substudy of the Survival And Ventricular Enlargement study (SAVE) showed only 3% diastolic and 5% systolic volume attenuation after one year of treatment in 512 patients, 45% of whom received thrombolytic therapy (17). In the echocardiographic substudy of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-3 (GISSI-3), 74% of the patients received reperfusion therapy (18). In this substudy, attenuation of LV dilation at six months was <1%. The survival benefit of the ACE inhibitor lisinopril could therefore not be explained by the small effect on ventricular dilation (19). In the Healing and Early Afterload Reducing Therapy (HEART) trial, reperfusion therapy was either thrombolysis or percutaneous transluminal coronary angioplasty (20). After two weeks, no significant effect on echocardiographic end points of both low and

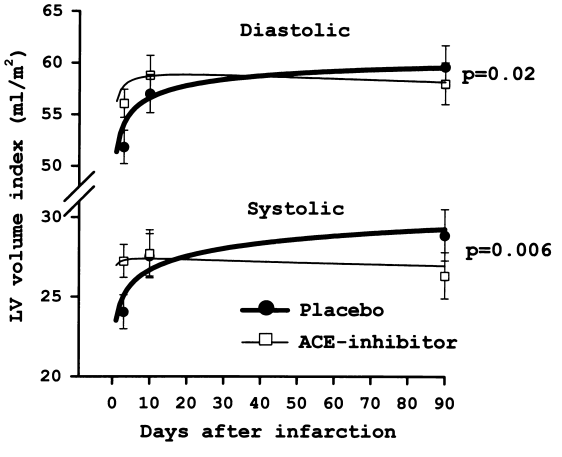

Figure 3. The effect of ACE inhibitor treatment within 6 to 9 h on LV dilation for patients in whom reperfusion therapy failed (n = 212) after MI. Data are presented as the mean value ± SEM.

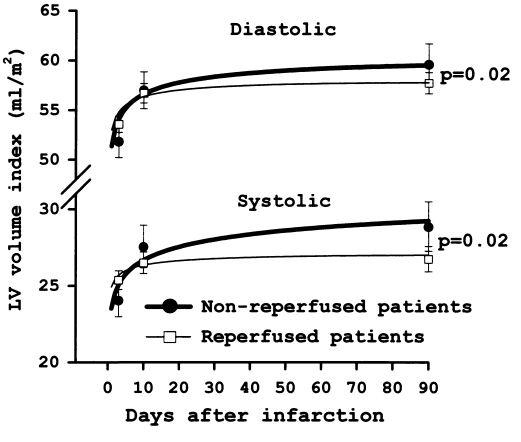

Figure 4. The effect of successful reperfusion after thrombolysis on LV dilation for the placebo group (n = 421) after MI. Data are presented as the mean value ± SEM.

high dose ramipril, as compared with placebo, was found. Only four other randomized, double-blind, placebo-controlled studies using ACE inhibition and at least one echocardiographic assessment after MI have been published, in which all patients received reperfusion therapy (2,21–23). Two small, explorative studies with one to two weeks of echocardiographic follow-up showed significant attenuation of LV dilation by ACE inhibitor as compared with placebo (21,22). In contrast, in two larger studies including ~500 patients, LV volumes were substantially unchanged (2,24).

Patient selection. The second possible reason for our finding of no significant attenuation of LV dilation may be that patients included in this meta-analysis were not selected on the basis of ventricular dysfunction. Most studies investigated the effect of ACE inhibition on LV dilation in patients with a depressed ejection fraction (<40% to 45%) (25). These studies all showed a positive effect of ACE inhibition on LV dilation. In the present study, only 13% of the patients had an ejection fraction <40%, probably caused by the widespread use of thrombolysis, beta-blockers and aspirin, which considerably increases the proportion of patients with small, aborted MIs and normal LV function. The effects of ACE inhibitors in patients with normal LV function have not been extensively studied. Very recently, however, the Heart Outcomes Prevention Evaluation (HOPE) study clearly demonstrated reductions in mortality and morbidity by treatment with an ACE inhibitor in patients at high risk for cardiovascular events, but without LV dysfunction or heart failure (26). Therefore, mechanisms other than attenuation of LV dilation may be more important in explaining the beneficial effect of ACE inhibitors in patients with normal LV function. These mechanisms may include direct vasodilatory effects, antiproliferative effects on smooth muscle cells, protection from plaque rupture, improved vascular endothelial function and enhanced fibrinolysis (27).

Timing of ACE inhibition. The third possible reason for our finding of no significant attenuation of LV dilation may be the very early start of ACE inhibitor treatment (i.e., within 6 to 9 h) after MI. A possible disadvantage of early ACE inhibition after MI is early hypotension, which may have been an important reason for the absence of survival benefit in COoperative New Scandinavian ENalapril SUrvival Study II (CONSENSUS-II) (28). Only few studies investigated the effect of very early treatment of ACE inhibition on LV dilation. An experimental study in rats showed a favorable effect on LV dilation with delayed treatment rather than immediate ACE inhibitor treatment (29). A small, explorative clinical study showed significant attenuation of LV dilation, after one week of echocardiographic follow-up, in which ACE inhibitor treatment was given within 6 h after MI (21). The present meta-analysis, however, could not confirm this finding. Whether the ACE inhibitors were started too early after the onset of MI could not be answered in this study. Subgroup analysis, however, showed no significant effect on LV dilation, either in patients treated with ACE inhibition within 3 h or patients treated >3 h after MI (Fig. 2).

Study limitations. It must be underlined that a potential limitation of this study is that it is a meta-analysis, which may result in biased conclusions. To avoid this bias, we systematically included the data of randomized, double-blind, placebo-controlled studies (published and unpublished data) that administered ACE inhibitors within 6 to 9 h after MI in patients receiving thrombolysis. Furthermore, these studies were the only confirmative studies ever performed in this setting, with the primary end point being evaluation of the effect of ACE inhibition on LV dilation. Finally, the patient selection criteria and echocardiographic methods were comparable, mainly because the studies were conducted almost simultaneously, and the principal investigators communicated during the design and conduct of each of the studies. Another important limitation of the present study is that we assessed reperfusion by using clinical variables instead of performing coronary angiography. Also, a small proportion of patients crossed over from the placebo group to the ACE inhibitor group, and it cannot be ruled out that this may have diluted a possible drug effect.

Conclusions. Attenuation of LV dilation by treatment with an ACE inhibitor has mainly been investigated late after MI in small, selected patient groups without the widespread use of thrombolytic therapy. In this meta-analysis involving 845 patients receiving thrombolysis, we could not demonstrate attenuation of LV dilation by treatment with an ACE inhibitor within 6 to 9 h after the patients' first (mainly) anterior MI. We speculate that very early treatment with an ACE inhibitor has beneficial effects on LV remodeling in patients in whom reperfusion failed. Other mechanisms may be responsible for the beneficial effects of ACE inhibitors in successfully reperfused patients after MI.

Reprint requests and correspondence: Dr. D. J. van Veldhuisen, Department of Cardiology/Thoraxcenter, University Hospital Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. E-mail: d.j.van.veldhuisen@thorax.azg.nl.

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