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Beneficial Effects of Ramipril on Left Ventricular End-Diastolic and End-Systolic Volume Indexes After Uncomplicated Invasive Revascularization Are Associated With a Reduction in Cardiac Events in Patients With Moderately Impaired Left Ventricular Function and No Clinical Heart Failure

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OBJECTIVES We sought to assess the effect of ramipril on left ventricular (LV) volumes, and the clinical significance thereof, in patients with moderate LV dysfunction and no clinical heart failure undergoing invasive revascularization for chronic stable angina.

BACKGROUND It is unsettled whether treatment with an angiotensin-converting enzyme inhibitor has an impact on LV volumes in this patient group, and, if so, whether this is associated with the clinical outcome.

METHODS A total of 133 patients with a left ventricular ejection fraction (LVEF) between 0.30 and 0.50 and no clinical heart failure undergoing invasive revascularization for chronic stable angina were randomized to receive ramipril 10 mg once daily or placebo and were followed for a median of 33 months with echocardiography at baseline and 3, 12 and 24 months postoperatively.

RESULTS Repeated measures analysis of all time points showed that ramipril significantly reduced the end-diastolic volume index (EDVI) ($p = 0.032$) and end-systolic volume index (ESVI) ($p = 0.006$) as compared with placebo. Ramipril also reduced the incidence of the triple composite end point of cardiac death, acute myocardial infarction or development of heart failure ($p = 0.046$). Cox regression analysis, controlling for baseline LVEF and assignment to ramipril, revealed: 1) that increases in EDVI and ESVI up to three months predicted an increasing risk of a future adverse clinical outcome; and 2) that the benefit with ramipril on clinical outcome was partly dependent on a reduction in LV volumes.

CONCLUSIONS Even in this patient group, LV dilation may supervene and lead to an adverse clinical outcome. Ramipril reduces the postoperative increase in LV volumes and may thereby improve clinical outcome. (J Am Coll Cardiol 2001;37:1214–20) © 2001 by the American College of Cardiology

In patients with ischemic heart disease, left ventricular (LV) volume and left ventricular ejection fraction (LVEF) are important predictors of prognosis (1–3). Thus, interventions that may influence these variables may alter the clinical course. After invasive revascularization, LV volume and LVEF may change due to a recovery of stunned or hibernating myocardium (4–6), due to periprocedural ischemia and the progressive nature of the disease (5) or due to a loss of pericardial strain after pericardiotomy (7).

Angiotensin-converting enzyme (ACE) inhibitor treatment has been shown to attenuate LV dilation and decrease in LVEF after acute myocardial infarction (AMI) in patients with LV dysfunction (8–12), and at least part of the clinical benefit with ACE inhibitor treatment has been attributed to this mechanism (9–11). In the Angiotensin-converting enzyme inhibition Post REvascularization Study (APRES) (13), which included patients with moderately impaired LV function and no clinical heart failure undergoing invasive revascularization for chronic stable angina pectoris, we found that ramipril, an ACE inhibitor, improved the clinical outcome with respect to cardiac death, AMI and development of heart failure.

Because the beneficial effects of ACE inhibitor treatment on LV volume and LVEF have primarily been described in patients with severe LV dysfunction (9–11) and within the first month(s) after an AMI (8,9,12), and because invasive revascularization may alter LV volume and LVEF (4–7) per se, it remains to be elucidated whether the beneficial effects of ACE inhibitor treatment on LV volume and LVEF may apply to patients with moderately impaired LV dysfunction undergoing invasive revascularization for chronic angina pectoris, and, if so, whether this effect may be associated with a beneficial effect on clinical outcome.

The aim of the present study was to assess, in this patient group, whether treatment with ramipril initiated early after invasive revascularization improves the outcome with re-

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Abbreviations and Acronyms

ACI	= angiotensin-converting enzyme
AMI	= acute myocardial infarction
APRES	= Angiotensin-converting enzyme inhibition Post REvascularization Study
CABG	= coronary artery bypass graft surgery
CI	= confidence interval
EDVI	= end-diastolic volume index
ESVI	= end-systolic volume index
LV	= left ventricular
LVEF	= left ventricular ejection fraction
PTCA	= percutaneous transluminal coronary angioplasty
RR	= relative risk
SD	= standard deviation
WMI	= wall motion index
ΔEDVI, ΔESVI, ΔLVEF	= increase from baseline in EDVI and ESVI and decrease from baseline in LVEF, respectively

spect to LV volume and LVEF, whether the serial changes in these provide independent predictive information and whether the impact of ramipril on LV volume and LVEF is associated with the clinical outcome.

METHODS

Patients. Included in this study were patients in APRES (13) in whom a baseline and at least one postoperative echocardiogram was obtained. In short, after uncomplicated invasive revascularization with coronary artery bypass graft surgery (CABG) or percutaneous transluminal balloon angioplasty (PTCA) for chronic stable angina pectoris, patients with no clinical heart failure, no need for diuretics for heart failure and LVEF between 0.30 and 0.50, as determined by ventriculography or echocardiography, were randomized to receive ramipril 10 mg once daily or placebo and were followed for a median of 33 months. The study was approved by the local Ethics Committee and the National Board of Health, and all patients gave written, informed consent.

Outcome measures. The main outcome measures were the changes from baseline to 3, 12 and 24 months postoperatively in left ventricular end-diastolic volume index (EDVI), end-systolic volume index (ESVI) and LVEF, as determined by echocardiography. The LVEF was derived from (EDVI − ESVI/EDVI). Clinical end points were the triple composite end point of cardiac death, AMI or development of heart failure, and cardiac death alone (13).

Echocardiographic methods and reproducibility. Echocardiography was performed at baseline and at 3, 12 and 24 months postoperatively. Patients undergoing CABG had baseline echocardiography performed before the operation, whereas patients undergoing PTCA had echocardiography performed after the procedure but before randomization, because of a policy of ad hoc PTCA during some of the study period. Apical two- and four-chamber recordings were obtained and digitized on-line and stored on optical discs. All recordings and analyses were done by a single observer. To prevent bias in the analysis of serial changes, recordings from separate occasions were arranged by patient side by side in a quadscreen format and in a random manner with respect to recording dates. All recordings were analyzed in a blinded manner with regard to the examination date, patient data and treatment code. Endocardial borders were traced manually in the two- and four-chamber apical views at end-diastole (defined as the frame at the beginning of the QRS complex) and at end-systole (defined as the frame before the early opening of the mitral valve). Biplane volumes were calculated by the disc summation method (modified Simpson's rule) and indexed according to body surface area at baseline. For statistical analyses, the mean results of three separate endocardial tracings and calculations were used. In a random sample of 50 patients, the biplane volume analysis was repeated. The repeatability coefficients (14) (i.e., two standard deviations [SD] of the difference of repeated analyses for ΔEDVI, ΔESVI and ΔLVEF [derived from ESVI and EDVI]) were 9.5 ml/m^2, 9.7 ml/m^2 and 0.13, respectively.

To provide an independent baseline LVEF, a nine-segment wall motion index (WMI) was determined in a separate session. This method has previously been evaluated, and an estimate of LVEF can be derived by multiplying the WMI by 0.3 (15). The mean ± SD difference between LVEF derived from the biplane volumes and LVEF derived from WMI and ventriculography was −0.03 ± 0.08 and −0.05 ± 0.09, respectively.

Statistics. The significance of a treatment effect (ramipril group vs. placebo group) on EDVI, ESVI and LVEF was determined by repeated measures analysis of covariance after adjusting for baseline values, as described by Frison and Pocock (16). The interaction of baseline variables was determined by adding these as covariates. As repeated measures analysis requires measurements of all three postoperative time points to be available, patients with missing measures (e.g., death, withdrawal, not followed for 24 months) were assigned an imputed value according to the mean value of the patients' postoperative measures. Analyses using other imputation algorithms, or simply omitting patients (25% of patients) with a missing measure from the repeated measures analysis, gave similar results. The percentage of imputed values for EDVI, ESVI and LVEF was 10.5%. Significance of change from baseline within treatment groups was tested by the paired *t* test. Basic intergroup comparisons were performed by using the unpaired *t* test for continuous variables and the chi-square test for categoric variables.

The predictive information provided by the changes in EDVI, ESVI and LVEF was ascertained by first adding

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Table 1. Number of Patients in Echocardiographic Study at Each Time Point

	No. of Patients at Time Point	Reason for Lacking Echocardiogram	No. of Patients in Each Treatment Group at Time Point (Ramipril/Placebo)
Randomized	159	No baseline echocardiogram obtained (n = 6) Insufficient quality of echocardiogram (n = 7)	80/79
Echocardiogram at baseline	146	Died (n = 3) Withdrawal of consent (n = 6) Lost to follow-up (n = 4) Echocardiogram not obtained (n = 2)	73/73
Echocardiogram at 3 months	131	Died (n = 4) Excluded (endocarditis) (n = 1) Withdrawal of consent (n = 2) Echocardiogram not obtained (n = 1)	66/65
Echocardiogram at 12 months*	125	Died (n = 1) Not followed for 24 months (n = 17) Echocardiogram not obtained (n = 6)	62/63
Echocardiogram at 24 months	101		48/53

*Two patients in whom an echocardiogram was not obtained at three months had an echocardiogram at 12 months. Thus, 133 patients had a baseline and at least one follow-up echocardiogram.

these as single predictors in a Cox regression proportional hazards model, with time to clinical event as the dependent measure. Significant univariate predictors were then added individually to a Cox regression model, which was constructed from baseline variables that were independent predictors of outcome. Among the continuous variables, age was entered by decade, baseline WMI <1.4 ($\sim$LVEF ≤ 0.40) and, for the remaining variables, after categorization into four groups, according to median values and quartiles. Time dependency of predictor variables was determined and controlled for if required. Significant changes in EDVI and ESVI were defined as a postoperative increase larger than the repeatability coefficient; and a significant change in LVEF was defined as a decrease larger than the repeatability coefficient.

The interaction between treatment with ramipril and the serial changes in LV measures on predictive information was ascertained by forcing the treatment code into the Cox regression model, together with the relevant LV measure.

Statistical analyses were performed using Statistica for Windows, version 5.1 (StatSoft Inc., Tulsa, Oklahoma), and a significance level of 5% was adapted.

RESULTS

Among the 159 randomized patients (130 after CABG and 29 after PTCA), 133 patients (108 after CABG and 25 after PTCA) had a baseline and at least one follow-up echocardiogram (Table 1). The baseline variables for these patients were comparable with the baseline variables of the entire

Table 2. Baseline Characteristics of the Two Treatment Groups

Characteristics	Ramipril Group (n = 67)	Placebo Group (n = 66)
Mean age (yrs)	61	61
Male gender (%)	91	89
Hypertension (%)	22	29
Diabetes mellitus (%)	6	11
Previous AMI (%)	76	80
Median interval since last AMI (months)	15	16
Electrocardiogram		
Anterolateral Q-waves (%)	31	42
Inferoposterior Q-waves (%)	57	50
Left branch bundle block (%)	3	3
Median interval since debut of clinical ischemic heart disease (months)	41	30
Frequency of single-, double- or triple-vessel disease (%)	15/25/60	15/41/44
Left ventricular ejection fraction (mean/median value)		
Ventriculography	0.45/0.45	0.45/0.45
Wall motion index	0.41/0.42	0.43/0.42
Biplane volumes	0.38/0.39	0.40/0.40
End-diastolic volume index (ml/m^2, mean/median value)	75.5/76.2	71.6/69.1
End-systolic volume index (ml/m^2, mean/median value)	47.3/44.9	43.1/42.4

There were no significant differences between the treatment groups for any baseline variable.
AMI = acute myocardial infarction.

Table 3. Clinical Outcome by Treatment Group Among Patients With Paired Echocardiograms

	Ramipril Group (n = 67)	Placebo Group (n = 66)	p Value
Death/cardiac death			
At 3 months	0/0	0/0	
At 12 months	1/0	4/3	
End of study	1/0	4/3	>0.20*
Cardiac death, AMI or heart failure			
At 3 months	0	3	
At 12 months	3	6	
End of study	5	13	0.046*

*By the log-rank test.
AMI = acute myocardial infarction.

randomized study group (13) (Table 2). The clinical outcomes of the patients who entered the echocardiographic study are presented in Table 3.

The mean changes from baseline to 3, 12 and 24 months postoperatively in EDVI, ESVI and LVEF in the two treatment groups are depicted in Figures 1 through 3. Repeated measures analysis of all time points showed significant differences in the changes in EDVI ($p = 0.032$) and ESVI ($p = 0.006$) between the ramipril and placebo groups, but not for LVEF derived from EDVI and ESVI ($p = 0.15$). These effects resulted from an increase in EDVI (71.6 to 74.7 ml/m^2; $p = 0.07$) and ESVI (43.1 to 47.9 ml/m^2; $p < 0.001$) and a decrease in LVEF (0.40 to 0.37; $p < 0.001$) in the placebo group; and preserved EDVI (75.5 to 72.8 ml/m^2; $p = 0.10$), ESVI (47.3 to 46.8 ml/m^2; $p = 0.68$) and LVEF (0.38 to 0.37; $p = 0.32$) in the ramipril group. The significance of the difference in the treatment response between the groups was consistent when baseline WMI <1.4 (LVEF ≤0.40), triple-vessel disease, anterolateral Q-waves on the electrocardiogram, use of anti-schemic drugs and CABG versus PTCA were added as covariates, individually or together. With all covariates added, $p = 0.021$ for ΔEDVI, $p = 0.003$ for ΔESVI and $p = 0.11$ for ΔLVEF. The p values for a difference in the mean change

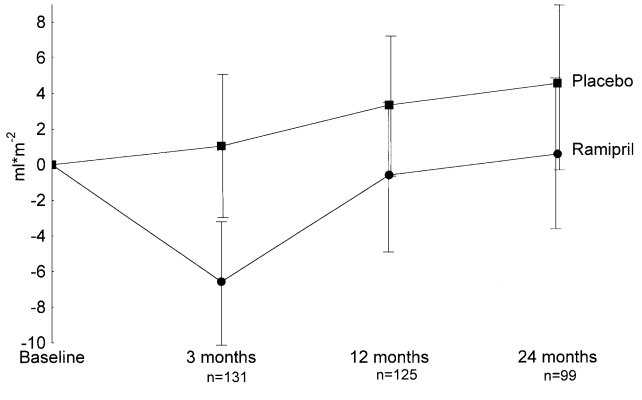

Figure 1. Mean change from baseline (with 95% confidence interval) in left ventricular end-diastolic volume index in the two treatment groups. By repeated measures analysis of all time points, $p = 0.032$ for the difference in change in left ventricular end-diastolic volume index between the treatment groups.

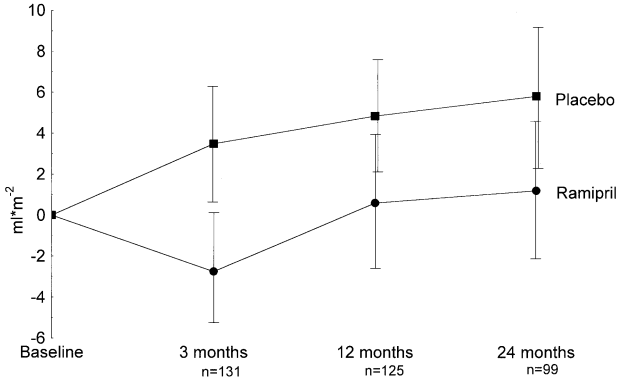

Figure 2. Mean change from baseline (with 95% confidence interval) in left ventricular end-systolic volume index in the two treatment groups. By repeated measures analysis of all time points, $p = 0.006$ for the difference in change in left ventricular end-diastolic volume index between the treatment groups.

from baseline to the specific time points of 3, 12 and 24 months between treatment groups were 0.005, 0.16 and 0.20 for ΔEDVI; 0.002, 0.048 and 0.058 for ΔESVI; and 0.18, 0.059 and 0.086 for ΔLVEF, respectively.

Univariate regression on triple composite end point of cardiac death, AMI or development of clinical heart failure. Increases in EDVI and ESVI and a significant decrease in LVEF up to 12 months were associated with an increasing risk of an adverse clinical outcome (Table 4). Increases in EDVI and ESVI from baseline to three months and a significant increase in ESVI or a decrease in LVEF up to 12 months were associated with an increasing risk of a future adverse outcome (Table 4, right columns).

Multivariate regression analysis on triple composite end point. As for the main study (13), among the baseline variables, assignment to ramipril (relative risk [RR] 0.35, 95% confidence interval [CI] 0.12 to 0.98) and WMI <1.4 (RR 3.23, 95% CI 1.25 to 8.38) were the only independent predictors of an adverse outcome with respect to the triple composite end point of cardiac death, AMI or heart failure. Age, gender, hypertension, diabetes mellitus, use of beta-blockers, use of calcium antagonists, anterolateral Q-waves

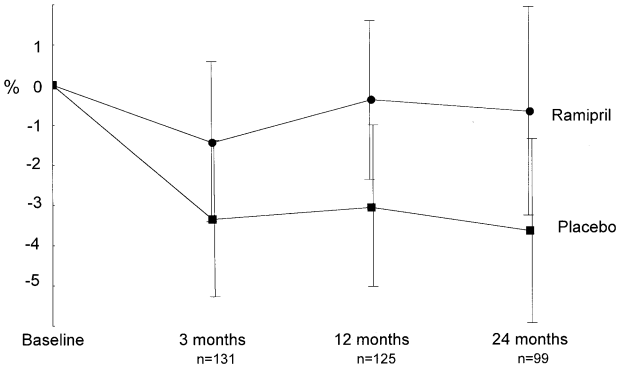

Figure 3. Mean change from baseline (with 95% confidence interval) in left ventricular ejection fraction in the two treatment groups. By repeated measures analysis of all time points, $p = 0.15$ for the difference in change in left ventricular end-diastolic volume index between the treatment groups.

Table 4. Predictive Information of Changes From Baseline Left Ventricular End-Diastolic Volume, End-Systolic Volume and Ejection Fraction in Univariate Regression Model for Triple Composite End Point of Cardiac Death, Acute Myocardial Infarction or Development of Heart Failure

	All Patients			Patients Free of Triple Composite End Point at 3 Months (n = 128) and 12 Months (n = 118)		
	RR	95% CI	p Value	RR	95% CI	p Value
ΔEDVI at 3 months	2.12	1.29–3.50	0.003	2.11	1.22–3.63	0.007
Significant ΔEDVI at 3 months	4.09	1.58–10.56	0.004	3.30	1.13–9.67	0.030
ΔESVI at 3 months	2.24	1.32–3.80	0.003	2.25	1.26–4.02	0.006
Significant ΔESVI at 3 months	2.75	1.01–7.43	0.047	2.00	0.67–6.7	0.23
ΔLVEF at 3 months	1.12	0.64–1.95	0.692	1.20	0.64–2.27	0.565
Significant ΔLVEF at 3 months	1.25	0.29–5.44	0.769	1.51	0.34–6.67	0.587
ΔEDVI at 12 months	1.58	0.99–2.52	0.057	1.32	0.73–2.38	0.357
Significant ΔEDVI at 12 months	2.80	1.05–7.50	0.040	1.40	0.35–5.65	0.637
ΔESVI at 12 months	2.32	1.33–4.04	0.003	1.91	0.97–3.76	0.062
Significant ΔESVI at 12 months	7.07	2.55–19.59	< 0.001	5.68	1.51–21.41	0.010
ΔLVEF at 12 months	1.40	0.89–2.19	0.144	1.20	0.68–2.13	0.525
Significant ΔLVEF at 12 months	3.83	1.33–11.02	0.013	6.80	1.82–25.39	0.004

Patients were categorized and assigned a rank (1 to 4) according to quartiles of ΔEDVI and ΔESVI and ΔLVEF, and relative risk was calculated according to one step in rank (i.e., for increases in EDVI and ESVI and for decreases in LVEF). The right columns (patients free of end point at 3 months and 12 months, respectively) indicate risk of future event.

CI = confidence interval; ΔEDVI, ΔESVI and ΔLVEF = increases from baseline in end-diastolic volume index, end-systolic volume index and left ventricular ejection fraction, respectively; RR = relative risk; significant ΔEDVI, ΔESVI and ΔLVEF = increases in EDVI and ESVI or decrease in LVEF greater than the repeatability coefficient, respectively.

on the baseline electrocardiogram, triple-vessel disease and CABG versus PTCA were not significantly associated with the outcome. In the multivariate regression model controlling for assignment to ramipril and WMI <1.4, the univariate predictors, with few exceptions, remained as the independent predictors (Table 5). Increases in EDVI and ESVI from baseline to three months and a significant increase in ESVI or a decrease in LVEF up to 12 months were independent predictors of an increasing risk of a future adverse outcome (Table 5, right columns). Similar results were obtained when age, hypertension, diabetes mellitus and gender were forced into the multivariate model or when LVEF ≤0.40 was determined by ventriculography or echocardiography.

The multivariate model also revealed that when the change from baseline in EDVI, ESVI and LVEF were added as predictors, assignment to ramipril was no longer an independent predictor (Table 5). This points to a link between the beneficial effect of ramipril on LV volumes and LVEF and the beneficial effect of ramipril on clinical outcome.

Cardiac death. The number of patients who had a cardiac death and who had sequential echocardiograms was too low (n = 3) to allow for detailed statistical analysis. However, the available data suggest an excellent survival rate for patients without significant LV dilation up to three months. The frequency of cardiac death for patients who did not have a significant increase in EDVI up to three months was 1 (0.9%) in 111 (95% CI 0% to 2.7%), and the frequency for patients without a significant increase in ESVI up to three months was 1 (0.9%) in 107 (95% CI 0% to 2.7%). For patients who had a significant increase in EDVI and ESVI up to three months, the frequencies were 2 (10%) in 20 (95% CI −3.1% to 23.1%) and 2 (8.3%) in 24 (95% CI −2.7% to 19.3%), respectively.

DISCUSSION

Left ventricular volumes and LVEF are important prognostic predictors for patients with AMI (9,17) and for patients undergoing invasive revascularization (1–3). After AMI, subsequent LV dilation and a decrease in LVEF can further identify patients at high risk (9,18); this patient group, in particular, seems to benefit from attenuation of LV dilation by treatment with ACE inhibitors (9). In contrast, the clinical significance of changes in LV volume and LVEF after invasive revascularization and that of drug treatments that might further modify these measures have not been clarified.

The main findings in this study are that: 1) ramipril reduced LV end-diastolic and end-systolic volumes, as compared with placebo; 2) postoperative increases in EDVI and ESVI were associated with an increasing risk of sustaining the triple composite end point of cardiac death, AMI or development of clinical heart failure; 3) the level of increase in EDVI and ESVI from baseline up to three months postoperatively provided independent, predictive information with respect to future clinical outcome; and 4) there was an association between the effect of ramipril on EDVI and ESVI and the clinical benefit with ramipril.

Comparisons and dissimilarities with other studies. It is well documented that ACE inhibitor treatment, as compared with placebo, reduces LV volume in patients with AMI and LV dysfunction (8,9,12). The effect of LV remodeling after AMI seems most explicit in the first months(s) after AMI (8,12); therefore, it might be questionable whether the effect of ACE inhibitors on LV

Table 5. Predictive Information of Changes From Baseline in Left Ventricular End-Diastolic Volume, End-Systolic Volume and Ejection Fraction in Multivariate Regression Model for Triple Composite End Point of Cardiac Death, Acute Myocardial Infarction or Development of Heart Failure

	All Patients			Patients Free of Triple Composite End Point at 3 Months (n = 128) and 12 Months (n = 118)		
	RR	95% CI	p Value	RR	95% CI	p Value
ΔEDVI at 3 months	1.87	1.14–3.07	0.013	1.91	1.11–3.27	0.019
WMI <1.4	2.80	1.08–7.30	0.035	2.76	0.97–7.83	0.057
Ramipril assignment	0.47	0.16–1.34	0.156	0.60	0.20–1.80	0.363
Significant ΔEDVI at 3 months	3.00	1.09–8.23	0.033	2.61	0.84–8.17	0.098
WMI <1.4	2.82	1.08–7.39	0.035	2.88	1.01–8.21	0.047
Ramipril assignment	0.47	0.16–1.39	0.172	0.57	0.18–1.78	0.335
ΔESVI at 3 months	2.03	1.18–3.48	0.010	2.09	1.16–3.75	0.014
WMI <1.4	2.83	1.09–7.36	0.033	2.81	0.99–7.97	0.052
Ramipril assignment	0.50	0.18–1.43	0.199	0.65	0.22–1.94	0.443
Significant ΔESVI at 3 months	1.97	0.71–5.49	0.196	1.52	0.46–4.98	0.492
WMI <1.4	2.80	1.06–7.41	0.038	2.91	1.01–8.37	0.048
Ramipril assignment	0.38	0.13–1.08	0.070	0.47	0.16–1.40	0.177
ΔESVI at 12 months	1.81	1.03–3.16	0.038	1.65	0.79–3.45	0.185
WMI <1.4	3.14	1.03–9.54	0.044	1.25	0.30–5.19	0.762
Ramipril assignment	0.60	0.20–1.77	0.351	0.36	0.07–1.81	0.216
Significant ΔESVI at 12 months	4.41	1.43–13.66	0.010	4.66	1.02–21.38	0.048
WMI <1.4	2.65	0.85–8.26	0.092	0.93	0.21–4.07	0.920
Ramipril assignment	0.63	0.21–1.91	0.416	0.40	0.08–2.02	0.266
Significant ΔLVEF at 12 months	3.56	1.19–10.64	0.023	5.45	1.39–21.47	0.015
WMI <1.4	4.62	1.60–13.31	0.005	1.77	0.47–6.63	0.394
Ramipril assignment	0.50	0.17–1.48	0.213	0.39	0.08–2.00	0.260

Among the baseline variables, assignment to ramipril (relative risk [RR] 0.35, 95% confidence interval [CI] 0.12 to 0.98) and wall motion index (WMI) <1.4 (RR 3.23, 95% CI 1.25 to 8.38) were the single independent predictors at multivariate analysis. WMI = 1.4 for the study group median; WMI <1.4; ~LVEF ≤0.40.

For other abbreviations, refer to Table 4 footnote.

volume applies to patients without AMI. However, results from the Studies Of Left Ventricular Dysfunction (SOLVD) show that it may (10,11), at least in patients with more severe LV dysfunction. In the present study, the patients had no AMI and had less LV systolic dysfunction as compared with the patients in the large ACE inhibitor trials (9–11). Nevertheless, we found an effect of ramipril on LV volume.

Although some previous studies may have suggested an effect of ACE inhibitors on LV volume in patients with lesser degrees of systolic dysfunction (8,12), our findings are novel in that: 1) our patients had no recent AMI; 2) they had just undergone invasive revascularization, an intervention that may improve outcome and alter LV function and dimensions; and 3) we were able to demonstrate a clinical importance of the effect of ramipril on LV volume. Thus, our results indicate that the beneficial effect of ACE inhibitor treatment on LV volume extends beyond patients with AMI, severe LV dysfunction or clinical heart failure and may add to the benefit of invasive revascularization.

Support of this finding may be found in recent studies of patients with chronic atherosclerotic disease and no severe LV dysfunction or heart failure. Thus, in the Prevention of Atherosclerosis with Ramipril Trial (19), ramipril reduced the end-diastolic dimension and cardiovascular death, and in the Heart Outcomes Prevention Evaluation (HOPE) study (20), ramipril, in addition to reducing cardiovascular death, prevented development of heart failure.

Compared with patients with a first AMI, the patients in the present study may, due to the long duration of ischemic heart disease and a process of late remodeling, at a given ejection fraction, have more right-shifted and steeper parts of volume-pressure loops. A further increase in LV volume may then be more prone to produce symptoms in these patients. This notion may be supported by the findings of Hamer et al. (3) of the relative importance of LV volume as compared with LVEF for the prognosis for patients without a recent myocardial infarction undergoing invasive revascularization.

Similar to previous studies (8,10–12), the effect of ACE inhibitor treatment on LV volume seems most explicit in the early months after initiation of therapy. Thereafter, the rate of change apparently parallels between the treatment groups. Since we did not perform a withdrawal study, it remains unsettled whether the impact of ramipril on LV volume represents a "true" remodeling or a "resetting" of the LV. The strong prognostic significance of the changes in EDVI and ESVI from baseline up to three months is nevertheless indicative of the importance of unloading the LV soon after invasive revascularization in the present patient group.

Comparisons with main study. The baseline characteristics and the effect of ramipril on the triple composite end point were comparable with the findings in the main study. However, fewer patients who had a cardiac death were included in this echocardiographic study as compared with the main study. Therefore, this echocardiographic study

may have had a bias toward demonstrating the mechanisms behind preventing heart failure in preference to cardiac death. Thus, the findings in the present study do not exclude a possible role for the potential effects of ACE inhibitor treatment on plaque vulnerability, the fibrinolytic system and neurohormonal modulation (21) in the prevention of cardiac and sudden death found in the main study (13).

Study limitations. The fact that the baseline measures of EDVI, ESVI and LVEF were obtained before CABG but after PTCA, as well as the possible altered position and systolic motion of the heart after CABG, may limit the comparison between baseline and postoperative measures. However, first the study primarily aimed to compare the difference in the treatment response between the ramipril and placebo groups and the clinical significance thereof. It is not likely that the aforementioned conditions should have influenced systematically different in the two treatment groups. Second, the significance of the difference in the treatment response in EDVI and ESVI between the ramipril and placebo groups was consistent when PTCA versus CABG was added as a covariate. Finally, the prognostic importance of the measured changes from baseline in LV volume and LVEF suggests that the measured changes actually may reflect "true" changes.

A concern may be raised about the lower LVEF derived from EDVI and ESVI, as compared with LVEF obtained at ventriculography or from WMI. However, according to the design of the study (analyzing echocardiograms from separate occasions side by side and blinded to the recording sequence) and the statistical analyses used, the study patients served as their own control subjects. Thereby, the echocardiographic outcome measures were more dependent on precision than on accuracy. The reproducibility analysis and the association between our echocardiographic outcome measures and the patients' clinical outcomes suggest that our precision was adequate for achieving the study goals.

Conclusions. Despite the clinical benefit of invasive revascularization in patients with moderate LV dysfunction and chronic stable angina pectoris, LV dilation may supervene and lead to an adverse outcome. Treatment with ramipril reduces the postoperative increase in LV volumes, and this effect is associated with a reduction in future cardiac events. This finding may partly explain the outcome in APRES (13). Thus, it appears that the benefit of LV unloading with ACE inhibitor treatment may be extended to apply to patients with only moderately impaired LV function and no clinical heart failure undergoing invasive revascularization for chronic angina pectoris.

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