

Which strategy should be used for postinfarct treatment?

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The renin-angiotensin-aldosterone system (RAAS) is both a trophic factor and an apoptotic trigger in postinfarct ventricular remodeling. Its cardiac paracrine impact on endothelium, small vessel tone, and fluid-electrolyte balance hastens the heart failure syndrome. Although the current consensus, based largely on first year follow-up data, favors modulating the RAAS with a combination of angiotensin-converting enzyme (ACE) inhibitors and β -blockers, studies to date may have overestimated the degree of longer-term benefit. Meta-analysis of post-infarct trials shows that survival curves in patients with and without ACE-inhibitor therapy become roughly parallel after the initial 1 to 2 years. Thus, the RAAS may eventually become refractory to ACE inhibitor blockade. Ongoing trials aim to determine whether angiotensin II receptor blockade will prove more effective, in isolation or in combination with ACEI.

Keywords: myocardial infarction; renin-angiotensin system; ventricular remodeling; heart failure; ACE inhibition

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EFFECT OF ACE INHIBITION EARLY AFTER MYOCARDIAL INFARCTION

An acute myocardial infarct can induce a dynamic process of changes in the architecture, shape, and size of the left ventricle, which can lead to severely compromised left ventricular function. This process—whether at the acute or chronic stage—involves both the infarcted area and more distant areas of the heart, modifying the ventricular structure, causing the ventricle to dilate and become more spherical and compromising diastolic and systolic function. This process is not homogeneous, and is, to some extent, unpredictable even in apparently similar patients. An echocardiographic substudy of the Gruppo Italiano per lo Studio della Soprav-

vivenza nell'Infarto miocardico III (GISSI 3) trial¹ enrolled 614 subjects in whom a series of 4 echocardiograms were carried out: one within 48 hours of the onset of the symptoms, one at discharge from hospital, one after 6 weeks, and the last after 6 months of follow-up. Profoundly different sequences of ventricular remodeling were observed. In short, about one fifth of the subjects had pronounced left ventricular dilatation while they were in hospital, but, unexpectedly, subsequently remained stable without further geometric changes in the ventricular chamber. In contrast, about one fifth of the subjects developed no left ventricular size changes during their stay in hospital, but subsequently developed marked ventricular remodeling with progressive dilatation of the left ventricle. Of note, 92% of the patients with severe (>20%) early left ventricular dilata-

SELECTED ABBREVIATIONS AND ACRONYMS

| | |
|---------------------|---|
| CAPTIN | Captopril Plus Tissue plasminogen activator following acute myocardial INfarction |
| CATS | Captopril And Thrombolysis Study |
| CONSENSUS II | COoperative North Scandinavian ENalapril SUrvival Study II |
| FAMIS | Fosinopril in Acute Myocardial Infarction Study |
| GISSI 3 | Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico III |
| RAAS | renin-angiotensin-aldosterone system |
| SAVE | Survival And Ventricular Enlargement |
| SOLVD | Studies Of Left Ventricular Dysfunction |

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tion did not show any further dilatation at 6 months, and 91% of patients with severe late dilatation did not have in-hospital dilatation. While the initial left ventricular dilatation developed in parallel with a recovery of ejection fraction, the delayed dilatation was associated with a reduction in ejection fraction and thus compromised systolic ventricular function. All patients were randomized to treatment with lisinopril, which was maintained for 6 weeks and then stopped in patients with preserved left ventricular systolic function. Multivariate analysis showed that this treatment was not an independent factor correlated with the evolution of ventricular remodeling.

Large randomized placebo-controlled studies have examined the effects of angiotensin-converting enzyme (ACE) inhibition on left ventricular remodeling following an acute myocardial infarction: the most relevant are the Survival And Ventricular Enlargement (SAVE), COoperative North Scandinavian ENalapril SURvival Study II (CONSENSUS II), and GISSI 3 trials.

An echocardiographic substudy of the SAVE trial² was carried out in 512 patients with acute myocardial infarction. The patients were randomized to treatment with captopril or placebo. The 420 patients having survived for more than 1 year underwent echocardiographic follow-up, which disclosed that the left ventricular end-systolic and end-diastolic areas in the patients treated with captopril for 1 year were about 3 cm² smaller than in the patients who had received the placebo.

An echocardiographic substudy was also carried out in the CONSENSUS II trial.³ This trial was prematurely halted because of the lack of clinical benefits in the group of pa-

tients treated with enalapril. Nevertheless, in the echocardiographic substudy, at 6 months, the patients treated with ACE inhibitors had a smaller left ventricular end diastolic volume than those given a placebo. The absolute difference was about 3 mL/m².

By far the largest study on the effects of ACE inhibition on left ventricular remodeling following a myocardial infarction is GISSI 3.⁴ In the GISSI 3 trial, the effects of lisinopril, transdermal nitrate, combined therapy with both, and no treatment were tested with a 2×2 factorial design. The treatments were assigned randomly to 19 394 eligible patients who were admitted to hospital with a diagnosis of myocardial infarct within 24 hours of the onset of their symptoms. The aim was to establish whether, and if so by how much, short-term treatment (6 weeks) was effective in modifying the patients' subsequent outcome. In the absence of specific indications for continuing the treatment, this was stopped after 6 weeks and the patients were followed up for 6 months. The GISSI 3 protocol included an echocardiographic examination in all patients 6 weeks and 6 months after the acute myocardial infarct in order to measure the combined end point of mortality and severe ventricular dysfunction. A two-dimensional echocardiogram was also performed at discharge from hospital. Overall, the echocardiographic database consisted of 8619 echocardiograms carried out at discharge, 12 125 echocardiograms at the 6-week follow-up, and 10 726 echocardiograms at the 6 month follow-up, in 50.8%, 72.6%, and 73.3%, respectively, of all the patients with a confirmed infarct and a legible echocardiogram.

Interestingly, use of an algorithm to predict left ventricular dilatation at 6 months in 7842 patients with a

predischarge echocardiogram enabled left ventricular systolic and diastolic volumes to be predicted with $r=0.72$ and $r=0.65$, respectively.⁵ Patients predicted to be at risk for long-term left ventricular dilatation had an increased risk of mortality (relative risk [RR] 1.87, 95% confidence interval [CI] 1.48 to 2.36) and an increased risk of heart failure at 6 months (RR 2.59, 95% CI 2.04 to 3.28), but no increased risk of reinfarction. The variables included in the algorithm were gender, peak creatine phosphokinase (CPK) release (as a marker of infarct size and its evolution), and echocardiographic left ventricular volumes. If the accuracy of this prediction model of postinfarct left ventricular dilatation is confirmed, it should contribute to more efficient risk stratification early after myocardial infarction and facilitate decision-making on the therapeutic strategies in postinfarct patients.

The subpopulation of 6405 GISSI 3 patients with the full series of 3 legible echocardiograms was used to evaluate changes in left ventricular remodeling over time and the effect of lisinopril on this process. The left ventricular end diastolic and end systolic volumes and the ejection fraction measured at discharge were independent predictors of mortality and incidence of nonfatal heart failure at 6 months (*Figure 1*).⁶ The patients in whom left ventricular asynergy exceeded 27% of the whole ventricular wall developed left ventricular enlargement over time. Treatment with lisinopril reduced the ventricular dilatation (*Figure 2*).⁶ The difference in end-diastolic ventricular volumes between patients treated with lisinopril and those not treated was statistically significant in patients with the most extensive infarcts (asynergy $\geq 27\%$) while ventricular remodeling was not evident during follow-up in pa-

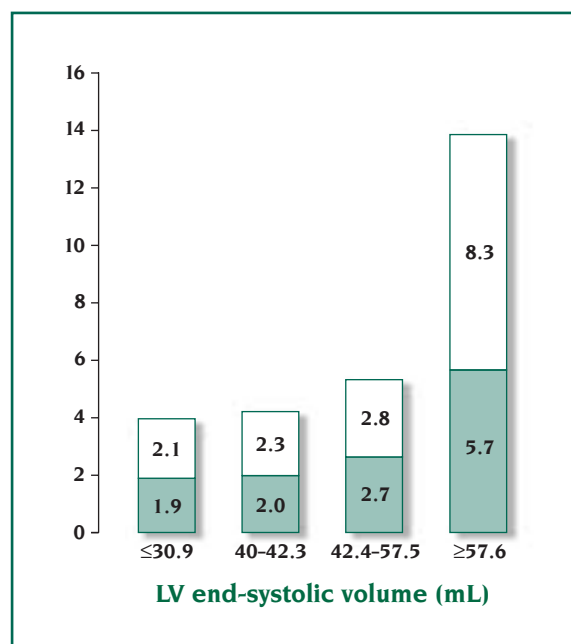


Figure 1. Predischarge echocardiographic variables in quartiles vs 6-month mortality (■) plus nonfatal late congestive heart failure (CHF) (□). Data refer to 8606 myocardial infarction patients discharged alive.

Reproduced from reference 6: Nicolosi GL, Latini R, Marino P, et al. The prognostic value of predischarge quantitative two-dimensional echocardiographic measurements and the effects of early lisinopril treatment on left ventricular structure and function after acute myocardial infarction in the GISSI-3 Trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Eur Heart J. 1996;17:1646-1656. Copyright © 1996, The European Society of Cardiology.

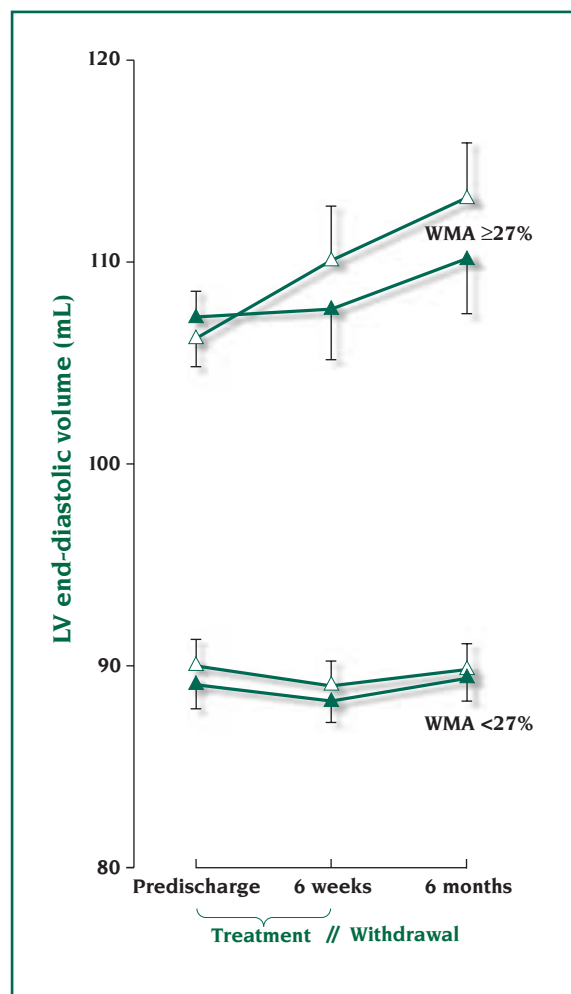


Figure 2. Left ventricular (LV) end-diastolic volume in lisinopril (▲) and no lisinopril (△) patients with wall motion asynergy (WMA) <27% and with wall motion asynergy ≥27% (n=6405). Sample sizes were as follows: Wall motion asynergy ≥27%; lisinopril=909, no lisinopril=903. Wall motion asynergy <27%; lisinopril=2277, no lisinopril=2316.

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tients with smaller infarcts (asynergy <27%), in both study groups. This finding is in accordance with previous studies in which ventricular remodeling was observed only in patients with moderately sized or large infarcts. A similar trend over time was observed for the end-systolic volume, although the difference in this parameter between patients treated or not treated with lisinopril did not reach a statistically significant level. Given the large number of centers participating in this study and the lack of strict selection criteria for enrolling the patients, the GISSI 3 population can be considered a representative sample of the general population of patients with acute myocardial infarction in the thrombolytic era.

A meta-analysis of the effects of ACE inhibition during the acute phase of a myocardial infarct on ventricular remodeling has recently been published.⁷ Data from 845 subjects, collected in three randomized studies, were analyzed. The three studies were the Captopril And Thrombolysis Study (CATS), Captopril Plus Tissue plasminogen activator following acute myocardial infarction (CAPTIN), and Fosinopril in Acute Myocardial Infarction Study (FAMIS) in which the patients received thrombolytic therapy and were randomized to captopril (CATS, CAPTIN) or to fosinopril (FAMIS vs placebo within 6 to 9 hours of the onset of symptoms), and underwent echocardiographic follow-up for 3 months. Left ventricular dilatation was the primary measurement outcome of the study. Eighty-five percent of the patients had had an anterior acute myocardial infarct. The analysis did not demonstrate any significant effect of ACE inhibition on left ventricular dilatation. End-diastolic and end-systolic ventricular volume both decreased by 0.5 mL/m² (P=0.05 and 0.061, respectively). Left ven-

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tricular dilatation was significantly reduced only in a small subgroup, which included the 26% of patients in whom, on the basis of indirect criteria, thrombolysis was considered not to have been successful and in whom reperfusion of the infarcted area had not, therefore, been achieved.

promptness of administration of these drugs during acute myocardial infarction.

It is interesting to note that a spontaneous reduction in left ventricular asynergy was observed throughout the follow-up of GISSI-3 patients, independently of the treatment giv-

ventricular dysfunction were carefully studied in the SOLVD trials. About 70% of the patients enrolled had a history of previous myocardial infarction. Two small longitudinal substudies, one echocardiographic, the other angiographic, were carried out in subgroups of patients in both the Treatment arm (left ventricular ejection fraction <35% and clinical signs of heart failure) and the Prevention arm (ejection fraction <35% without clinical signs of heart failure).⁸⁻¹⁰ The patients underwent double-blind treatment with enalapril or placebo and were followed-up for 3 years. Invasive left ventricular function studies were performed at baseline and after 1 year of treatment in a small subgroup of patients. Overall, both end-diastolic and end-systolic left ventricular volumes increased in the group treated with placebo, but not in the group treated with enalapril; the difference in response to the two treatments was statistically significant. Similarly, left ventricular mass increased in patients given placebo while it tended to decrease in those treated with enalapril. It is important to note that this occurred in patients who had long-standing left ventricular hypertrophy and dilatation, which demonstrates both the chronic progressive nature of ventricular remodeling and the efficacy of treatment even when considerable structural changes in the left ventricle have already occurred. *Figure 3*¹¹ illustrates the mean left ventricular pressure-volume curves of the symptomatic patients enrolled in the Treatment arm and the asymptomatic ones enrolled in the Prevention arm. The fundamental difference in the functional characteristics of the left ventricle between both groups of patients, symptomatic and asymptomatic, was not the pressure in the ventricle during diastole, in particular the end-diastolic pressure (a parameter used to evaluate the

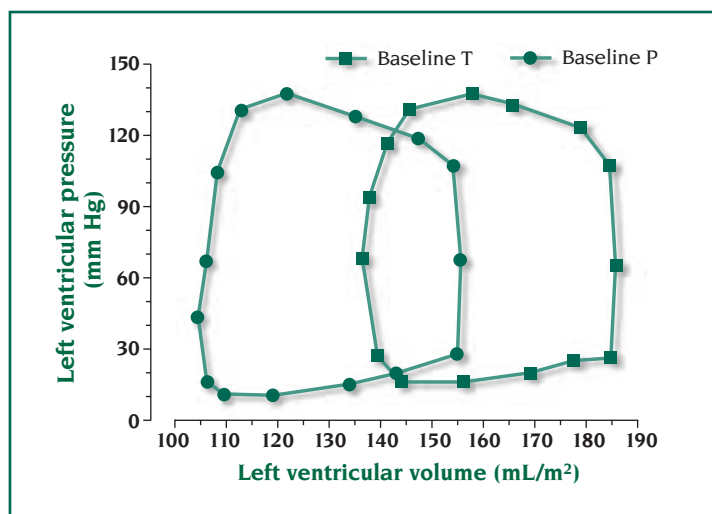


Figure 3. Averaged left ventricular pressure-volume loops of 16 congestive heart failure patients (treatment, T) and 49 asymptomatic patients (prevention, P) before their randomization in the Studies Of Left Ventricular Dysfunction.

Reproduced from reference 11: Pouleur H, Rousseau MF, van Eyll C, Melin J, Youngblood M, Yusuf S, for the SOLVD Investigators. Cardiac mechanics during development of heart failure. *Circulation*. 1993;87(5 suppl IV):IV114-IV20. Copyright © 1993, American Heart Association.

Taken together, these studies demonstrate that treatment with ACE inhibitors, when started early after an acute myocardial infarct, is able to mitigate left ventricular dilatation, but not prevent it. Overall, the extent of the effect of ACE inhibition on left ventricular remodeling is limited, and certainly less substantial than that expected after the very encouraging results obtained in the small group of patients studied invasively in the Studies Of Left Ventricular Dysfunction (SOLVD) (see below).

Moreover, the available data have not shown a correlation between the effectiveness of ACE inhibition in ventricular remodeling and the

en.⁴ These results suggest that a spontaneous, late recovery of the myocardium damaged during an infarct not only can occur, but indeed normally does so, and that this process can last months. This implies that considerable caution should be used in interpreting the extent of a myocardial infarct and the effect of drugs on ventricular remodeling in the early postinfarct period.

EFFECT OF ACE INHIBITION LATE AFTER MYOCARDIAL INFARCTION

The effects of ACE-inhibitor therapy on left ventricular structure and function in patients with chronic



overall function of the left ventricle), nor the capacity of the ventricle to generate tension during systole (measured by the peak pressure reached during systole or, better, the peak wall stress reached during systole), nor yet the stroke volume (ie, the difference between end-diastolic volume and end-systolic volume), which were similar in the two groups of patients, but rather the ventricular volumes, which were much larger in the symptomatic patients. In brief, the finding that characterized these patients was the left ventricle's exaggerated ability to distend during diastole, in other words an excess of ventricular compliance (rather than a reduction, as diastolic dysfunction is classically interpreted). It should be noted that in the SOLVD study, as in the other studies, ventricular dilatation did not appear to be dependent on changes in ventricular filling pressure: quite the contrary, the ventricle appeared to be able to distend more at every pressure. In other words, the entire pressure-volume curve was shifted to the right. These observations support the concept that the changes in volume, shape, and architecture that characterize ventricular remodeling are a cause rather than a consequence of the failing pump function seen during the process that leads from ventricular dysfunction to heart failure. The involvement of the renin-angiotensin-aldosterone

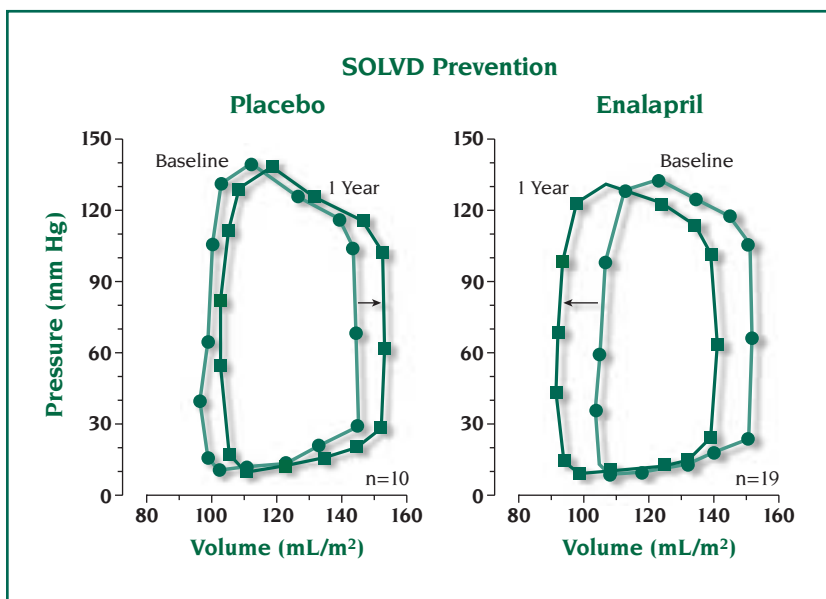


Figure 4. Mean left ventricular pressure-volume loops at baseline and 1 year in patients randomized to placebo and to enalapril. At 1 year, the entire curve was shifted to the right for the placebo group and to the left for the enalapril group.

Reproduced from reference 9: Konstam MA, Kronenberg MW, Rousseau MF, et al. Effects of the angiotensin-converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. *Circulation*. 1993;88(5 pt 1):2277-2283. Copyright © 1993, American Heart Association.

system (RAAS) in this process was convincingly demonstrated precisely by the SOLVD study. Figure 4⁹ shows the pressure/volume curves of the group of patients enrolled in the Prevention arm while Figure 5⁸

Figure 5 shows the pressure-volume loops at baseline and 1 year in patients randomized to placebo and to enalapril. At 1 year, the entire curve was shifted to the right for the placebo group and to the left for the enalapril group.

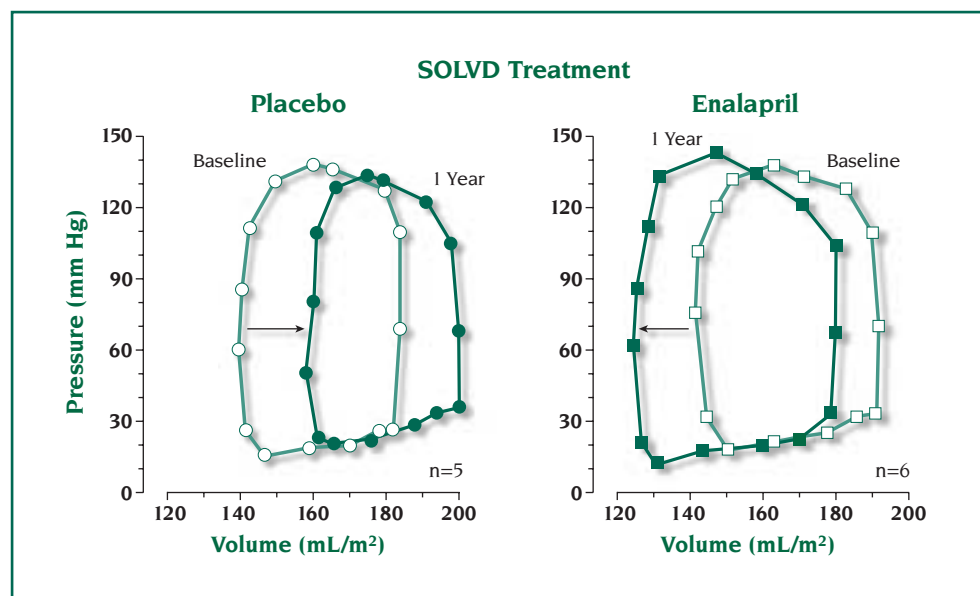


Figure 5. Mean left ventricular pressure-volume loops at baseline and 1 year in patients randomized to placebo and to enalapril. At 1 year, the entire curve was shifted to the right for the placebo group and to the left for the enalapril group.

Reproduced from reference 8: Konstam MA, Rousseau MF, Kronenberg MW, et al. Effects of the angiotensin converting-enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. *Circulation*. 1992; 86:431-438. Copyright © 1992, American Heart Association.

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shows the same curves for the group of patients enrolled in the Treatment arm, recorded at the time of enrollment and again 1 year later both in the patients given placebo and in those treated with enalapril. The process of ventricular dilatation continued in the patients who received placebo. In both symptomatic and asymptomatic patients, the evolution of the disease led to progressive ventricular dilatation without substantial changes in ventricular systolic function (once again suggesting that the latter is not the cause of the former). The process was inverted in the patients treated with enalapril: ventricular dilatation was halted and the size of the left ventricle tended to decrease. There was a process of inverse remodeling, a reduction in the structural changes of the ventricle. These beneficial effects of ACE inhibitors on ventricular remodeling, invasively recorded in this small substudy, were confirmed in a further substudy of the SOLVD trial, carried out with echocardiography.¹⁰ Thirty-one patients were enrolled and followed-up with echo-Doppler evaluations performed at the time of enrollment and after 4 and 12 months of therapy. Results showed an increase in end-diastolic and end-systolic volumes, as well as left ventricular mass, in the placebo group, but not in the group treated with enalapril. The difference in the response between the two groups was statistically significant.

CONCLUSION

The message from these studies is the proof of the pathophysiologic relevance of the RAAS in the process of postinfarct ventricular remodeling and the potential benefit that

can be achieved through modulation of RAAS hyperactivity. The size of benefit cannot be evaluated in these small studies and may have been overestimated. In fact, the long-term data of the SAVE trial show a progression of ventricular remodeling, which is roughly similar after the first year postinfarct both in the patients given captopril and in the untreated patients.¹² Similarly, a meta-analysis of postinfarct trials showed a definitely lower mortality rate in patients treated with ACE inhibitors than in the control groups during the first 1 to 2 years postinfarct, then the survival curves almost became parallel.¹³ In the long run, the RAAS may well escape, at least partially, the ACE blockade.

In conclusion, the RAAS is now firmly established as playing a key role both as a trophic factor and an apoptotic trigger in the ventricular remodeling process after a myocardial infarction, mainly through its cardiac paracrine activity. Subsequently, this results in unfavorable effects on the endothelium, small vessel tone, and fluid-electrolyte balance, and becomes a determinant of the heart failure syndrome. Many studies have demonstrated that modulation of the RAAS can modify the process of ventricular remodeling, thereby preventing or delaying the onset of heart failure. Current guidelines unanimously recommend the prescription of ACE inhibitors, in combination with β -blocker drugs, after a myocardial infarction with left ventricular dysfunction. Whether or not it may be possible to achieve more with the blockade of angiotensin II receptors in isolation or in combination with ACE inhibitors is a question that is now being tested in several ongoing trials.

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