Early administration of verapamil after thrombolysis in acute anterior myocardial infarction. Effect on left ventricular remodeling and clinical outcome

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Key words:
Myocardial infarction; Thrombolytic therapy; Remodeling, left ventricular; Verapamil; Controlled clinical trials.

Background. **The administration of verapamil during the reperfusion phase of acute myocardial infarction can reduce the extent and severity of microvessel damage and limit myocardial dysfunction. We aimed at investigating the effect of early verapamil administration on left ventricular remodeling and the clinical evolution after myocardial infarction.**

Methods. **Eighty-eight patients with first acute anterior myocardial infarction thrombolysed < 4 hours from symptom onset were enrolled in a multicenter, randomized, double-blind, controlled study of verapamil administration (5 mg i.v. + 2 μg/kg/min over 24 hours). Echocardiographic end-diastolic (EDV) and end-systolic (ESV) left ventricular volumes were assessed by biplane Simpson's rule.**

Results. **At 90 days, EDV in the verapamil and placebo groups was respectively 88.9 ± 27.8 and 95.8 ± 30.7 ml (p = 0.11), ESV was 52.6 ± 22.7 and 57.7 ± 25.4 ml (p = 0.18). There was no change over time in the verapamil group (day 3 vs day 90: EDV 85.0 ± 17.7 vs 88.9 ± 27.8 ml, p = NS; ESV 48.7 ± 14.1 vs 52.6 ± 22.7 ml, p = NS) while left ventricular volume increased in the placebo group (day 3 vs day 90: EDV 87.6 ± 21.1 vs 95.8 ± 30.7 ml, p = 0.03; ESV 52.0 ± 16.9 vs 57.7 ± 25.4 ml, p = 0.08). NYHA functional classes were differently distributed at 30 and 90 days (χ^2 = 0.009 and 0.07), with a lower prevalence of classes II and III in the verapamil group (p = 0.03).**

Conclusions. **The early intravenous administration of verapamil in thrombolysed patients can reduce left ventricular remodeling and NYHA functional class after acute anterior myocardial infarction.**

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Introduction

It is known that prolonged myocardial ischemia followed by myocardial reperfusion leads to ischemic damage of varying severity at the level of myocardiocytes and the coronary microcirculation. The variable degree of this damage leads to a potentially dysfunctioning but still viable myocardium of the stunned or hibernating type in the area at risk of necrosis. The presence of a viable myocardium has recently been studied as a positive prognostic factor after myocardial infarction, and as a potential therapeutic target[1-10].

Some experimental studies have shown that the administration of calcium antagonists (particularly verapamil) during the reperfusion phase is capable of reducing the extent and severity of microvessel damage and limiting myocardial dysfunction[11-17]. This effect may be favorably reflected in the postinfarct remodeling of the left ventricle, the importance of which has been widely explored in the recent literature because of the postinfarction prognostic significance of cardiac volume and the progressive dilation of the left ventricle[18-21].

The aim of this pilot study was to assess the hypothesis that verapamil administration in the early postinfarction period is capable of favorably influencing left ventricular remodeling and exerting a beneficial effect on the clinical evolution of the patients.

Methods

The Verapamil Acute Myocardial Infarction (VAMI) trial was a multicenter, randomized, double-blind, controlled study, which was conducted between March 1995

and May 1997 in the Coronary Care Units of 10 Italian Centers (see Appendix). The trial was approved by the Ethics Committees of each participating Center.

Study population. The trial population included patients who had experienced a first acute anterior myocardial infarction, had been admitted to a Coronary Care Unit within 4 hours of symptom onset, and given standard thrombolytic treatment (front-loaded tissue-type plasminogen activator - rt-PA), in Killip class I, and with technically excellent two-dimensional digital echocardiograms (defined as a stop-frame identifying Ž 85% of the endocardial border). The patients gave their written informed consent to enter the trial.

The diagnosis of acute anterior myocardial infarction was made on the basis of the following criteria: typical chest pain lasting Ž 30 min unresponsive to sublingual trinitroglycerin, with electrocardiographic signs of ongoing myocardial infarction (ST segment elevation > 0.1 mV in leads D1 and aVL and/or > 0.2 mV in two or more contiguous precordial leads from V_1 to V_6).

The exclusion criteria were: an age > 75 years; preexisting heart failure; previous myocardial infarction; coronary surgery or angioplasty in the 6 months preceding the infarction; significant valvular disease; cardiomyopathy; congenital heart diseases; admission more than 4 hours after the onset of chest pain; contraindications to treatment with thrombolytics or heparin; Killip class > 1; signs of peripheral hypoperfusion; heart rate < 60 b/min; systolic blood pressure < 100 mmHg; atrial tachyarrhythmias; sino-atrial or atrioventricular block; left bundle branch block; inability or refusal to give informed consent; chronic obstructive pulmonary disease; obesity; the presence of a pacemaker. Five patients were subsequently excluded because of trial protocol violations.

The trial was originally planned with a sample group of 264 patients, a power of 0.90 and a significance of 0.05. At the end of the trial, 90 patients had been enrolled: complete data for the final analysis were available in relation to 88 patients. It was decided to stop enrollment because the enrollment rate was much lower than that planned for the predetermined enrollment period.

Study protocol. The patients underwent a trial protocol consisting of randomization to verapamil or placebo during the first 24 hours of admission, and clinical and echocardiographic follow-up for the subsequent 90 days as shown in figure 1.

Randomization. After verifying the inclusion criteria and definitely entering the patient in the trial, the randomization procedure began. This procedure was carried out by the Trial Coordinating Center (ARC-Associazione per la Ricerca in Cardiologia) by means of a specific software program available on a computer network connecting the Coordinating Center with the participating Centers.

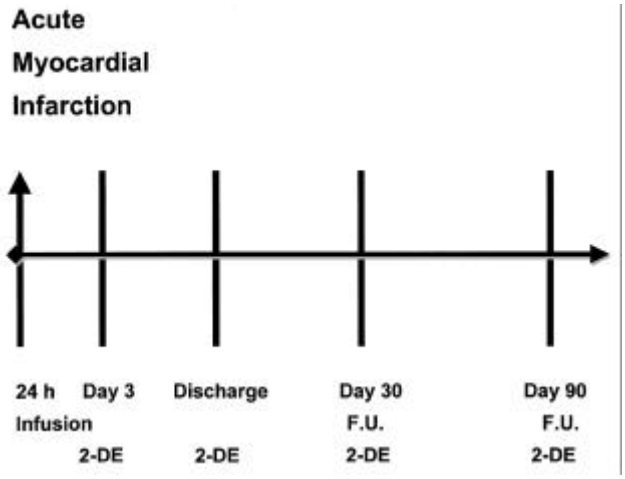

Figure 1. *VAMI study protocol. 2-DE = two-dimensional echocardiography; FU = follow-up.*

Administered drugs. Immediately after being enrolled in the trial, the patients were treated with verapamil or placebo, in addition to standard heparin and aspirin therapy administered by each individual Center as described below.

Verapamil was administered in an intravenous bolus of 5 mg, followed by an infusion of 2 μg/kg/min over the subsequent 24 hours. The treatment was administered as early as possible before beginning thrombolytic therapy, which involved the administration of rt-PA (15 mg i.v. bolus, followed by an infusion of 0.75 mg/kg body weight up to a maximum of 50 mg over 30 min, and a further infusion of 0.50 mg/kg body weight up to a maximum of 35 mg over 60 min) and heparin 5000 IU i.v. bolus, followed by an infusion of 1000 IU/hour (1200 IU/hour in patients weighing > 80 kg). Aspirin 160 mg was administered as soon as possible after admission, and then at a dose of 160-325 mg/day.

The placebo formulation was identical to the verapamil formulation.

Concomitant treatments. Any concomitant treatments capable of affecting the study results were carefully evaluated throughout the study and follow-up periods. Pharmacological treatments that may have influenced myocardial contractility, such as nitrates and antiarrhythmic agents (other than lidocaine and amiodarone) were not allowed, except in the case of unequivocably documented silent ischemia and/or angina. Beta-blockers and ACE-inhibitors were allowed as from day 4 following the infarction, according to the practice of each participating Center. Upon discharge, digitalis and diuretics were allowed only in the case of patients with cardiac decompensation, and calcium antagonists or nitrates in those with unequivocably documented silent ischemia or angina. Any beta-blocker treatment was interrupted at least 3 days before the echocardiographic examinations on day 30 and 90. In the case of the patients

who had undergone myocardial revascularization by means of angioplasty or aortocoronary bypass, only the results of the last follow-up examination carried out before revascularization were included in the statistical analysis. A routine coronary angiography was performed when clinically indicated at the discretion of the peripheral cardiologist.

Clinical events. During the follow-up, the occurrence of both major (death, reinfarction) and minor clinical events (heart failure) were evaluated. Reinfarction was defined as the presence of at least two of the following criteria[22]: 1) typical nitroglycerin-resistant chest pain lasting Ž 30 min; 2) new and persistent ST-T changes or new Q waves identified according to the criteria of the Minnesota code; 3) an increase in cardiac enzymes (particularly CPK and CK-MB) to double the maximum normal level or Ž 50% above the previous determination if this was Ž 1.5 times the maximum normal value. Alternatively, the appearance of Q waves was identified according to the criteria of the Minnesota code. Heart failure was defined as the presence of at least two of the following signs or symptoms: bi-basilar pulmonary ralings; the presence of the third tone; dyspnea; pulmonary congestion at chest X-ray[23], evaluated on the basis of a 4-point scale in which 1 = absent, 2 = mild (venous congestion), 3 = moderate (interstitial congestion), 4 = severe (pulmonary edema)[24], and defined as early or late depending on whether it appeared by or after day 4 following randomization[23]. For the purposes of evaluating the tolerability of the treatments, other minor clinical and/or ECG detectable events occurring during the study and follow-up were considered.

NYHA functional classification. The NYHA functional class[25] was established after 30 and 90 days of follow-up.

Two-dimensional digital echocardiography. The echocardiographic examinations foreseen in the trial flow-chart were performed at the following times: 3 days after admission, before discharge, and then on day 30 and 90.

The images were acquired using the digital echocardiographic equipment available at the participating Centers (PreVue, NovaMicrosonics, Allendale, NJ, USA), and sent for centralized reading to the ARC Coordinating Center by means of an image and data transmission network[26]. Each examination consisted of the acquisition of quad-screen images of four cardiac cycles of the 2- and 4-chamber apical views of the left ventricle, optimized for the study of left ventricular volumes.

Cardiac volume was evaluated by means of the software available in the ImageVue equipment (NovaMicrosonics, NJ, USA) by applying the Simpson's biplane method modified using the 2- and 4-chamber apical views of the left ventricle.

With the aim of eliminating interobserver variability from the volume measurement procedure, all of the echocardiographic readings were made by the same operator in blinded conditions.

Statistical analysis. The patients were divided into two groups (verapamil and placebo). The mean volumes of the sample were compared using an analysis of variance after verifying the normality of the distribution of the variables under study. The effects and interaction of treatment and time of the echocardiographic examination were assessed using a multifactor ANOVA with two factors. Clinical events and other suitable parameters were statistically analyzed using the χ^2 test and Fisher's exact test.

Results

The results are shown in tables I-III and figures 2 and 3.

Table I shows the distribution of the baseline clinical characteristics, coronary risk factors, and the concomitant treatments administered during hospitalization or prescribed at discharge in the two study treatment groups. There were no significant differences in any of these three criteria, although a family history of ischemic heart disease was more frequent in the placebo group. A coronary angiographic study was performed in 71 patients (verapamil group 35, placebo group 36, p = NS). In the verapamil and placebo group respectively, the infarct-related artery was found to be occluded in 6 (17.1%) and 4 patients (11.1%) (p = NS), reopened with a TIMI 1 grade in 7 (20.0%) and 4 patients (11.1%) (p = NS), TIMI 2 grade in 10 (28.6%) and 18 (50.0%) (p = 0.054), TIMI 3 grade in 12 (34.3%) and 10 patients (27.8%) (p = NS).

The trends of left ventricular end-diastolic (EDV) and end-systolic (ESV) volumes, and left ventricular ejection fraction, are shown in figure 2. After 90 days of follow-up, the mean ± SD of EDV in the verapamil and placebo groups were respectively 88.9 ± 27.8 and 95.8 ± 30.7 ml (p = 0.11), and ESV 52.6 ± 22.7 and 57.7 ± 25.4 ml (p = 0.18). There was no significant increase in EDV over time in the verapamil group, but a significant increase in the placebo group (p = 0.03, Table II). There was no significant increase in ESV over time in the verapamil group but a statistical trend towards an increase in the placebo group (p = 0.08, Table II). There was no significant variation in left ventricular ejection fraction (Table II). A more conservative statistical approach, using a multifactor ANOVA with two factors (treatment and time) to test the factor effects and their interaction, yielded: EDV: treatment p = NS, time p = 0.06, interaction p = NS; ESV, ejection fraction, systolic blood pressure and heart rate: treatment, time and interaction p = NS.

Table III and figure 3 show the distribution of the NYHA functional classes at 30 and 90 days, with a lower prevalence of class II and III in the verapamil group. When considering patients in NYHA class I vs patients in NYHA class II + III, it was possible to compare them

Table I. Basal features.

	N.	Placebo	N.	Verapamil	p
Basal clinical features					
Males/females	44	36/8	44	37/7	NS*
Age (years)	44	57.8 ± 10.6	44	55.8 ± 9.7	NS*
Time to treatment (min)	44	141 ± 83	44	169 ± 65	NS*
Time to thrombolysis (min)	44	153 ± 80	44	178 ± 68	NS*
Time to basal 2D-echo (days)	44	3.4 ± 0.8	44	3.4 ± 0.6	NS*
CK-MB max (IU)	44	109 ± 132	44	118 ± 146	NS*
Coronary risk factors					
Family history	39	16 (41%)	41	7 (17%)	0.02**
Hypertension	44	16 (36%)	42	15 (36%)	NS**
Diabetes	43	8 (19%)	44	12 (27%)	NS**
Smoke	43	22 (51%)	44	24 (55%)	NS**
Hypercholesterolemia	40	12 (30%)	40	8 (20%)	NS**
Preinfarct angina	44	28 (64%)	44	26 (59%)	NS**
Concomitant treatments§					
ACE-inhibitors	42	27 (64%)	40	26 (65%)	NS**
Beta-blockers	42	15 (36%)	40	9 (23%)	NS**
Calcium antagonists	42	7 (17%)	40	3 (8%)	NS**
Nitrates	42	26 (62%)	40	20 (50%)	NS**
Diuretics	42	19 (45%)	40	13 (33%)	NS**
Cortison	42	0 (0%)	40	1 (3%)	NS**

CK = creatine kinase; 2D = two-dimensional. * Student's t test; ** Fisher's exact test; § administered during hospital admission or prescribed at discharge.

Table II. Left ventricular volumes, ejection fraction, systolic blood pressure, and heart rate.

	N.	Placebo	N.	Verapamil	p
End-diastolic volume (ml)					
Day 3	43	87.6 ± 21.1	39	85.0 ± 17.7	NS
Predischarge	40	91.4 ± 26.8	40	91.6 ± 16.7	NS
Day 30	37	91.6 ± 20.3	33	92.6 ± 22.1	NS
Day 90	34	95.8 ± 30.7*	35	88.9 ± 27.8**	0.11
End-systolic volume (ml)					
Day 3	43	52.0 ± 16.9	39	48.7 ± 14.1	NS
Predischarge	40	53.9 ± 21.4	40	52.6 ± 13.1	NS
Day 30	37	53.2 ± 14.4	33	53.8 ± 17.9	NS
Day 90	34	57.7 ± 25.4***	35	52.6 ± 22.7**	0.18
Ejection fraction (%)					
Day 3	43	41.5 ± 6.8	39	43.2 ± 6.6	NS
Predischarge	40	42.3 ± 6.3	40	43.1 ± 6.1	NS
Day 30	37	42.3 ± 5.7	33	43.1 ± 6.8	NS
Day 90	34	41.4 ± 7.0**	35	42.3 ± 7.5**	NS
Systolic blood pressure (mmHg)					
Day 1	43	138.8 ± 23.9	42	145.0 ± 23.9	NS
Day 30	37	123.9 ± 13.8	36	125.1 ± 11.5	NS
Day 90	35	124.6 ± 9.0	38	123.5 ± 10.7	NS
Heart rate (b/min)					
Day 1	43	82.3 ± 13.4	42	78.7 ± 12.2	NS
Day 30	37	80.1 ± 7.0	36	76.1 ± 7.4	NS
Day 90	35	78.8 ± 4.5	38	77.9 ± 5.7	NS

Data are expressed as mean ± SD. End-diastolic volume, end-systolic volume, and ejection fraction: p variance analysis; systolic blood pressure and heart rate: p unpaired Student's t test. * p = 0.03 vs day 3; ** p = NS vs day 3; *** p = 0.08 vs day 3.

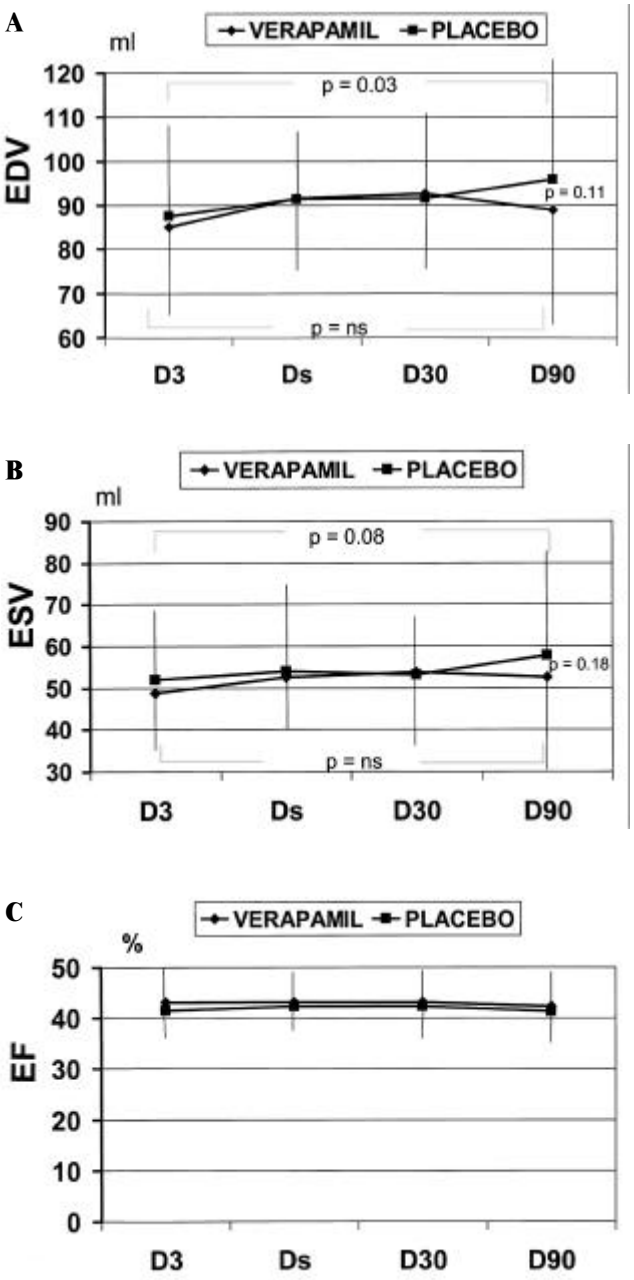

Figure 2. *A: left ventricular end-diastolic volume (EDV) at the time of the basal evaluation (D3), at discharge (Ds), on day 30 (D30) and on day 90 (D90) of the follow-up period. B: left ventricular end-systolic volume (ESV) at the time of the basal evaluation (D3), at discharge (Ds), on day 30 (D30) and on day 90 (D90) of the follow-up period. C: value of left ventricular ejection fraction (EF) at the time of the basal evaluation (D3), at discharge (Ds), on day 30 (D30) and on day 90 (D90) of the follow-up period. Values are expressed as mean ± SD.*

using a Fisher's exact test (day 30: p = 0.002, day 90: p = 0.03) (Fig. 3). The χ^2 analysis yielded a significant difference at day 30 (p = 0.009) and a statistical trend at day 90 (p = 0.07).

The distribution of major clinical events was not significantly different between the verapamil and placebo groups: 1 vs 0 deaths during hospitalization (p = NS); 0 vs 2 reinfarctions (1 during hospitalization and 1 at 90 days) (p = NS). There was likewise no significant difference in terms of heart failure: 9 patients in the verapamil group (all during hospitalization) vs 12 in the placebo group (11 during hospitalization, 1 on day 30) (p = NS).

The frequency distribution of adverse events (taken as an index of treatment tolerability) was also not statistically different between the verapamil and the placebo group: 1 vs 2 cases of pulmonary edema (p = NS), 1 vs 0 cases of cardiogenic shock (p = NS), 0 vs 1 case of ventricular fibrillation (p = NS), 2 vs 0 cases of ventricular tachycardia (p = NS), 2 vs 2 cases of atrial flutter and/or fibrillation (p = NS), 0 vs 1 case of neurological complications (p = NS). There were no cases of asystole or grade II or III atrioventricular block in any of the patients of either group.

Table III. Distribution of NYHA functional classes at 30 and 90 days of follow-up.

	Placebo	Verapamil	p
Day 30	n = 37	n = 37	
NYHA I	23 (62.2%)	34 (91.9%)	
NYHA II	13 (35.1%)	3 (8.1%)	0.009§, 0.002§§
NYHA III	1 (2.7%)	0 (0%)	
Day 90	n = 35	n = 37	
NYHA I	23 (65.7%)	32 (84.2%)	
NYHA II	12 (34.3%)	5 (13.2%)	0.07§, 0.03§§
NYHA III	0 (0%)*	0 (0%)	

* two data were unavailable for analysis; § χ^2 test; §§ a Fisher's exact test was applied considering the NYHA class I vs NYHA class II + III groups.

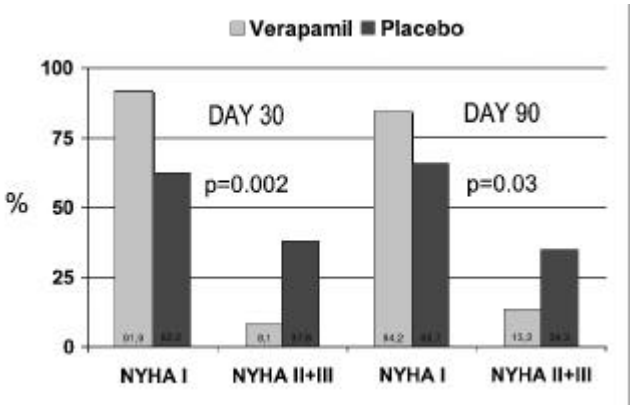

Figure 3. NYHA functional class distribution on day 30 and 90 of the follow-up period. p value assessed by Fisher's exact test.

Discussion

The ischemic damage induced by prolonged myocardial ischemia followed by myocardial reperfusion at the level of myocardiocytes and coronary microcirculation may be modified by a number of pharmacological interventions currently under investigation[10,18]. This improvement may lead to a reduction in the infarcted and

more generally dysfunctioning area, and a consequent benefit in terms of long-term left ventricular function. Ventricular remodeling depends on the extension of the infarcted area and other determinants that can be pharmacologically influenced with the aim of improving postinfarction left ventricular volume and function.

A number of experimental studies have shown that the administration of verapamil during the course of reperfusion is capable of reducing the extent and severity of microvessel damage and limiting myocardial dysfunction[11-13]. It is therefore reasonable to think that the administration of verapamil during the early postinfarction phase (before reperfusion is complete, when it is therefore still possible to obtain a protective effect on the microcirculation) may be capable of favorably influencing left ventricular remodeling and exerting a beneficial effect on the clinical evolution of the patient. On the basis of this hypothesis, we studied the effect of the early postinfarction administration of verapamil, immediately before the initiation of thrombolytic therapy, in patients who had experienced acute anterior myocardial infarction. Our somewhat arbitrary time limit of 4 hours from symptom onset was considered for patient inclusion in order to maximize the presence of myocardial viability and the hypothesized protective effect of the drug on the viable myocardium.

The data obtained from the present study provide some useful indications concerning the effect of verapamil administration in a very early phase of infarction insofar as they show that it is not associated with any postinfarction deterioration in left ventricular function, but may favorably influence left ventricular remodeling 90 days after the occurrence of the infarction. Importantly, patients in the two study groups were well compared for baseline clinical features (except family history), infarct size as determined by peak CK-MB level (Table I), status of the infarct-related artery (except a statistical trend for higher TIMI 2 grade reopening in the placebo group), and baseline left ventricular volumes (Table II). At 90 days of follow-up, EDV and ESV were tendentially lower in the verapamil-treated patients than in those receiving placebo. The lack of statistical significance is probably due to the fewer than planned number of analyzed patients. This problem also affects the interpretation of the multifactor ANOVA findings: the absence of statistical significance for the effects of either the treatment or the time on left ventricular volumes can be due to inadequate statistical power, the effects of time having been clearly demonstrated in the majority of studies of postinfarct left ventricular remodeling.

Furthermore, verapamil administration can improve the functional capacity of patients experiencing a first acute anterior myocardial infarction, as is shown by the more favorable distribution of NYHA functional classes on day 30 and 90 in the verapamil group. The attribution of this effect to the administration of verapamil is supported by the similar distribution of the baseline characteristics of the two groups (including risk factors), as well as by the similar distribution of concomitant treatments potentially capable of influencing left ventricular remodeling and NYHA functional class.

The recently published VISOR study[27], a double-blind placebo-controlled postinfarct clinical trial of verapamil, was not able to show a significant effect of verapamil on left ventricular remodeling in patients with acute anterior myocardial infarction, while a beneficial effect of the drug was found on left ventricular diastolic function. Notwithstanding the similarity of the VISOR study population and design to ours, a number of relevant differences must be considered in order to explain partially conflicting results. The VISOR study included 70 patients with acute anterior myocardial infarction, admitted within 6 hours of symptom onset, with left ventricular ejection fraction > 45%, and who had received thrombolytic treatment within 12 hours before verapamil, the drug having been administered intravenously for 24 hours and orally for 6 months. In the present study we enrolled 88 patients with anterior myocardial infarction without heart failure and no left ventricular ejection fraction threshold, admitted within 4 hours of symptom onset, and who had received verapamil starting immediately before the thrombolytic treatment; verapamil had been administered intravenously for 24 hours, then stopped. Thus, we considered patients with an earlier admission timing, who had more probability of myocardial viability and functional recovery, and, more importantly, with verapamil having been delivered to the ischemic myocardium during thrombolytic pharmacological reperfusion for optimizing its beneficial effects on reperfusion damage; our patients did not undergo the 6-month exposure to verapamil effects, either beneficial or negative for left ventricular remodeling. As a matter of fact, the differences in findings between the two studies on left ventricular remodeling may partially be due to the differences in patient population, study design for number of patients and treatment administration protocol. The limitations of the VISOR study for the remodeling data are clearly acknowledged by the authors in the discussion of their paper[27]. The placebo-controlled nature of both clinical trials (the placebo being a routine therapy of myocardial infarction including drugs with proved antiremodeling effects) (Table I), well explains the relevant difficulty of demonstrating beneficial effects of new drugs, which can only display, on the quantitative side, their limited additive effects on the left ventricular remodeling in the presence of effective routine therapy.

A useful comparison of our results can be made with the findings of the recently published paper of Taniyama et al.[28]. Although involving considerably fewer patients than VAMI, they found that the administration of verapamil led to a significantly favorable effect in terms of recovery of the asynergic area, a reduction in the "low-reflow zone"' evaluated by means

of myocardial contrast echocardiography, and (like us) a reduction in ventricular volumes. These findings also suggest a useful working hypothesis for identifying the mechanism underlying the efficacy of verapamil in reducing postinfarction ventricular remodeling.

The distribution of clinical events (which were also considered in terms of evaluating tolerability) was similar in the two groups, although the number of studied patients was much lower than that necessary for an appropriate statistical evaluation. These findings are similar to the safety results obtained in the VISOR study[27].

Study limitations. The main limitation of this trial is that the number of enrolled patients was lower than planned. However, this limitation should be reflected in a potential β error, with a consequent underestimation of the volumetric differences between the sample and the population, and the completion of the planned enrollment would probably have made these differences even more marked and statistically significant. Although our results appear to be in line with the data published in the literature, and agree with the results of recent studies such as that of Taniyama et al.[28], the limited number of patients involved means that they should be confirmed by a larger study that should also include patients whose clinical characteristics are different from those of the patients selected for the present trial. In this respect, some of the different selection criteria to be explored are: 1) the site of infarction by including patients who had experienced non-anterior infarctions (it is hypothetically possible that the safety and effect of verapamil on atrioventricular conduction may be different); and 2) the inclusion of patients with less than optimum quality echocardiograms, a category that includes a number of clinically significant subgroups in whom the echocardiographic window usable for the recording of echocardiograms is less than optimal, such as patients with chronic obstructive pulmonary disease, pulmonary emphysema, and other conditions. A larger population is also necessary to evaluate the clinical safety of verapamil administration used in this trial.

Clinical implications of our results. Despite the limitations indicated above, it is possible to hypothesize that the use of the proposed protocol for the early postinfarction administration of verapamil in patients who had experienced an acute anterior myocardial infarction may be clinically useful. Such an approach seems to be feasible and does not involve any substantial changes in the therapeutic strategies that are routinely used when treating infarcted patients.

In conclusion, in the light of the results obtained, we believe that verapamil administration during the first postinfarction hours in patients with acute myocardial infarction undergoing thrombolytic treatment has the potential of reducing left ventricular dilation and therefore of limiting left ventricular remodeling. In addition, it can favorably affect the NYHA functional class after acute myocardial infarction.

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Appendix

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