Intravenous Diltiazem in Acute Myocardial Infarction

Diltiazem as Adjunctive Therapy to Activase (DATA) Trial

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Objectives. This study was defined as a pilot investigation of the usefulness and safety of intravenous diltiazem as adjunctive therapy to tissue plasminogen activator in acute myocardial infarction, followed by oral therapy for 4 weeks.

Background. Experimental studies have documented that calcium antagonists protect the myocardial cell against the damage caused by coronary artery occlusion and reperfusion, yet no benefits have been conclusively demonstrated in acute myocardial infarction (AMI) in humans.

Methods. In this pilot study, 59 patients with an AMI treated with tissue-type plasminogen activator (t-PA) were randomized, double blinded, to intravenous diltiazem or placebo for 48 h, followed by oral therapy for 4 weeks. The primary objective was to detect an effect on indices of regional left ventricular function and perfusion. Patients were also closely monitored for clinical events, coronary artery patency and indices of infarct size and of left ventricular function.

Results. Creatine kinase elevation, Q wave score, global and regional left ventricular function and coronary artery patency at 48 h were not significantly different between the diltiazem and placebo groups. A greater improvement observed in regional perfusion and function with diltiazem was likely explained by initial larger defects. Diltiazem, compared to placebo, reduced the rate of death, reinfarction or recurrent ischemia at 35 days from 41% to 13% (p = 0.027) and prevented the need for an urgent intervention. The rate of death or myocardial infarction was reduced by 65% (p = 0.15). These benefits could not be explained by differences in baseline characteristics such as age, site and extent of infarction, time of inclusion or concomitant therapy. Heart rate and blood pressure were reduced throughout the study with active diltiazem treatment. Side effects of diltiazem were bradycardia and hypotension that required transient or permanent discontinuation of the study drug in 27% of patients, vs. 17% of patients with placebo.

Conclusions. A protective effect for clinical events related to early postinfarction ischemia and reinfarction was suggested in this study, with diltiazem administered intravenously with t-PA followed by oral therapy for 1 month, with no effect on coronary artery patency and left ventricular function and perfusion.

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Experimental data strongly support a benefit of calcium antagonists in acute myocardial infarction (AMI) (1). This pharmacologic approach can preserve high energy phosphate metabolism (2,3) and mitochondrial ultrastructure (4), prevent myocardial stunning, regional dysfunction (5,6) and neutrophil accumulation (7) and reduce infarct size in the reperfused (7–10) and nonreperfused myocardium (11–14). The effects are greater with shorter duration of ischemia (14,15) and when treatment is initiated before coronary occlusion (8,10), before reperfusion (2,7,10,14) or early during the ischemic state (14,16).

In clinical practice diltiazem is used mainly for its anti-ischemic effect. Studies performed during the evolving AMI have failed to document a benefit with the use of calcium antagonists (17–23). In most of these studies the drugs were administered outside the context of reperfusion. Two studies have described their effect in conjunction with mechanical revascularization. In one study (22), a deleterious effect of diltiazem on enzymatic infarct size and mortality was suggested. The other study (23) was a retrospective analysis of the impact on survival of medication used at the time of reperfusion and suggested no favorable influence of calcium antagonists.

The present study was undertaken to investigate the paradox of benefit in experimental settings but no clinical gain in patients with an AMI.

Methods

Inclusion and Exclusion

A total of 60 patients with an evolving AMI and ST-segment elevation were entered into the study. One patient allocated to placebo was excluded from the analysis because he rapidly developed cardiogenic shock before the study drug and

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Abbreviations and Acronyms

AMI = acute myocardial infarction
CK = creatine kinase
t-PA = tissue-type plasminogen activator

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before tissue-type plasminogen activator (t-PA) could be initiated. The entry criteria were evolving chest pain within the previous 6 h with ST-segment elevation 1 mm or more in two or more adjacent leads, the absence of a contraindication to thrombolysis or to diltiazem and a signed patient consent form. Contraindications to fibrinolysis included: uncontrolled hypertension >220 systolic and >110 diastolic, active peptic ulcer, trauma or surgery within the previous 2 weeks, stroke within the previous 3 months or a bleeding disorder. Contraindications to diltiazem administration were cardiogenic shock, pulmonary edema, congestive heart failure, atrial flutter or fibrillation and first, second or third atrioventricular block.

Design and Objectives

This pilot study included a relatively homogeneous patient population with an evolving ST-segment elevation AMI with the objective of detecting a potential protective effect of diltiazem. Because no reliable markers of infarct size exist in humans, a variety of methods was used to evaluate the size of the area of necrosis relative to the area at risk. The objective was to detect improvement in the global contraction and perfusion score with diltiazem compared with placebo, with consistent trends observed in other parameters, and more important in clinical evolution, regrouping death, reinfarction and recurrent ischemia with ST-segment changes or the need for an urgent intervention. This latter goal was based on the well-documented antiischemic properties of the drug and on favorable effects observed in non-Q-wave AMI (24). The incidence of congestive heart failure, bradyarrhythmia and hypotension, bleeding complications and the results of the exercise tests were analyzed. All patients were carefully monitored during their hospitalization and for 4 weeks following hospital discharge. The study was divided into four study periods: an acute phase from admission to 4 h, a subacute phase from 4 to 48 h, an intermediate observation period until

Figure 1. Outline of the investigation performed during the various study periods. 99m-Tc SPECT = technetium-99m sestamibi single emission-computed tomography.

Study periods

Investigation	Acute (0-4 hrs)	Subacute (4-48 hrs)	Intermediary (48 hrs - 5 days)	Follow-up (35 days)
Clinical + ECG	√	√	√	√
Serial enzymes	√	√	√	-
Radionuclide ventriculogram	-	√	-	√
99m-Tc SPECT	√	√	-	√
Cardiac cath	-	-	√	-

hospital discharge, including coronary angiography between days 2 and 4, radionuclide studies and treadmill exercise testing between days 5 and 7 and a follow-up phase extending from hospital discharge to 35 days. Figure 1 provides the outline of the investigation performed during the various study periods.

Study Drugs and Other Medications

Patients were randomized to receive double blinded either diltiazem hydrochloride or placebo in addition to aspirin, heparin and t-PA. Diltiazem was administered as an intravenous bolus of 10 mg in 10 min followed by an infusion at a rate of 10 mg/h for 48 h. Oral therapy with diltiazem 120 mg three times a day (360 mg daily dose) or placebo was started 8 h after the discontinuation of the infusion and continued until the 4-week follow-up visit. Plasma levels of diltiazem measured by high-performance liquid chromatography on blood obtained during the steady-state intravenous infusion 24 to 36 h after the start of therapy averaged 371 ± 162 ng/ml. Tissue-type plasminogen activator (Activase, Genentech Canada, Burlington, Ontario) was initiated concomitantly with the bolus injection of the study drug as a 7 mg I.V. bolus in 3 min followed by 53 mg in 57 min, 20 mg in 1 h and 10 mg/h for 2 h. The dose of aspirin was 325 mg orally at admission and daily thereafter. An infusion of heparin was also initiated at the same time in all patients at a rate of 1,000 U/h with no initial bolus injection. An activated partial thromboplastin time was obtained after 12 h to titrate the infusion rate of heparin to two times the control values. The heparin infusion was generally discontinued after 72 h.

A methodology was designed to ensure safe and blind administration of diltiazem. A volume of 500 ml of normal saline was rapidly administered when symptomatic hypotension or heart rate below 55 beats/min was experienced by patients from either treatment group. If the hemodynamic condition was not corrected by this measure, the infusion rate of the study drug was decreased by 50%. In the absence of improvement or in the presence of more severe bradyarrhythmia such as atrioventricular dissociation or second degree atrioventricular block, the study drug was discontinued then resumed after the condition was corrected. Recurrence of the abnormal state after a second initiation of the study drugs or appearance of more severe hypotension or of congestive heart failure or cardiogenic shock during study drug administration mandated the permanent discontinuation of the study drug.

The use of cardiac medications was left to the discretion of the treating physician with the exception of calcium antagonists, which were prohibited throughout the study. During the acute and subacute phases, intravenous nitroglycerin was administered in 19 patients randomized to the diltiazem group and in 23 patients randomized to the placebo group, beta-blockers in 12 and 22 patients, respectively, and angiotensin-converting enzyme inhibitors in 6 and 12 patients.

Clinical Evaluation

Clinical events considered in addition to events related to ischemia were events related to left ventricular dysfunction including congestive heart failure, acute pulmonary edema and cardiogenic shock. The diagnosis of infarct extension required a new episode of prolonged chest pain, new electrocardiogram (ECG) changes and reelevation of plasma levels of creatine kinase (CK) and of CK MB fraction. Early ischemia was defined as a recurrence of ischemic chest pain 12 h or more after the initial infarct with documentation of transient ST-T changes or with the need for an urgent catheterization with a view to coronary artery bypass surgery or coronary angioplasty. An intervention procedure on the indication of coronary anatomy without symptoms was not considered as an end point.

Electrocardiography

Infarcts were classified as inferior or anterior based on leads with ST-segment elevation on the 12-lead ECG, and on the location of the culprit lesion and wall motion abnormality on the angiograms. An index of infarct size developed by Selvester et al. (25) and Wagner et al. (26) was calculated. This score correlates with postmortem infarct size: $r = 0.80$ for anterior infarcts (26), 0.74 for inferior infarcts (27) and 0.72 for posterolateral infarcts (28). The score considers the duration and magnitude of each deflection of the QRS complex. The sum of ST-segment elevation was calculated on the ECG performed before initiation of treatment and the Q wave score on subsequent ECGs as indices of area at risk and of area of necrosis, respectively (29–33).

A treadmill exercise test using the Naughton protocol, limited to a workload of 5 mets or to 80% of maximal age-predicted heart rate, was also performed before hospital discharge in the 49 patients with no contraindications. The criterion for a positive test was ST-segment depression 1 mm or more compared to baseline.

Radionuclide Ventriculography

Equilibrium radionuclide ventriculography was performed using in vivo red blood cell labeling with 1 GBq (27 mCi) of technetium-99m (Tc-99m) pertechnetate. Segmental wall motion was assessed visually in five sectors in three standard views (left anterior oblique-best septal, anterior, and left lateral) and graded: 0 = hyperkinesis, 1 = normal, 2 = mild hypokinesis, 3 = moderate hypokinesis, 4 = severe hypokinesis, 5 = akinesis and 6 = dyskinesis. A wall motion score of the infarct zone was calculated by averaging the scores for the sectors involved in the acute infarct area on the initial angiogram and by following the same zone on subsequent examinations. A global score was calculated by adding the 15 individual scores for each of the patients.

Technetium-99m Sestamibi Single Photon Emission Computed Tomography (SPECT)

SPECT studies were obtained 2 to 4 h after injections of 1 GBq (27 mCi) Tc-99m sestamibi at the time thrombolytic therapy was initiated, 16 to 36 h later and before hospital discharge (after 5 to 7 days). Sixty-four projections were acquired over a 360° variable elliptic orbit on a $64 \times 64 \times 16$-byte matrix with a zoom of 1.44. Processing and image analyses were performed by a methodology already described (34,35). In summary, 25 regions of interest of equal size were automatically drawn on the polar bidimensional map of each patient. The relative uptake in each of these sectors was determined and normalized to the sector with maximal value. Values were compared to those of rest Tc-99m sestamibi SPECT studies obtained from normal volunteers. A sector was considered abnormal when normalized counts were more than two standard deviations below the normal mean. Defect size was calculated as the ratio of the number of abnormal sectors to the total number of sectors. Defect intensity was defined as the ratio of the average normalized counts in the abnormal sectors to the corresponding normal means. A global defect score index was calculated as the product of defect size and defect intensity. These analyses were performed excluding perfusion defects that were clearly distinct from the AMI related to a previously well-documented myocardial infarction.

Statistical Analysis

The study was unblinded only after final adjudication of all events and validation of the database. Results were analyzed by the intention-to-treat principle. Per protocol, the patient who rapidly developed cardiogenic shock before the initiation of the study drug and of t-PA was excluded. The sample size in this pilot study was estimated at 30 patients per group to detect with 90% power a 50% greater improvement in the global contraction and perfusion score with diltiazem vs. placebo.

Comparisons of baseline characteristics between the two study groups were performed with the unpaired Student t test and chi-square statistics. These tests were also used to compare clinical and laboratory data. An analysis of variance was performed when more than two sets of data were compared for the evaluation of heart rate and blood pressures and of markers of left ventricular function and perfusion. Odd ratios and 95% confidence interval (CI) were calculated for the clinical event rates. A Kaplan–Meier survival curve was constructed to compare survival without myocardial infarction and without recurrent ischemia and analyzed by the log-rank statistic. A proportional hazard regression with the Cox model was also performed for potential confounding effects of age and sex, site and extent of ST-segment elevation, size of the perfusion defect at admission, time to thrombolysis and other drugs used. Correlations were also made between the ECG findings and the radionuclide data at admission and 1 and 4 weeks later in the two study groups. Nominal p values of less than 0.05 were considered statistically significant. Values are

Table 1. Baseline Characteristics

	Diltiazem (n = 30)	Placebo (n = 29)	p Value
Age (yr)	57 ± 11	60 ± 9	NS
Male patients (%)	25 (83%)	24 (83%)	NS
Smokers	16 (52%)	13 (45%)	NS
Diabetes mellitus	2 (6%)	3 (10%)	NS
Previous HBP	6 (19%)	6 (21)	NS
Previous CAD	10 (33%)	10 (34%)	NS
Site of AMI			
Anterior	12 (40)	13 (45)	
Inferior	18 (60)	16 (55)	NS
Time from onset of pain to thrombolysis (min)	175 ± 64	151 ± 48	0.12

CAD = coronary artery disease; HBP = high blood pressure.

means and standard deviations except when otherwise specified.

Results

Study Population and Study Groups

The mean age of the population was 58 years old (range 34 to 74) with 10 women and 49 men. Twenty-nine patients were current smokers and five had treated diabetes mellitus. A previous history of coronary disease was present in 20 patients. The thrombolytic treatment was initiated an average of 163 ± 58 min (range 56 to 370 min) after the onset of chest pain, slightly later in the diltiazem group (NS). The baseline characteristics were otherwise evenly distributed in the two study groups (Table 1). The distribution of anterior vs. inferior infarcts was also similar. The amount of ST-segment elevation was nonsignificantly greater in the diltiazem group, particularly in anterior infarcts 19.8 ± 11 mm vs. 14.7 ± 9 mm (Table 2). This corresponded in anterior AMI to more extensive perfusion defect in patients at the SPECT study, 24.2 ± 9 vs. 11.3 ± 7 in the placebo group (p < 0.002), and to a greater regional contraction score at the radionuclide angiogram, 4.3 ± 0.6 vs. 3.4 ± 1.5 (Table 3).

Cross-correlation Between Various Parameters

The correlation matrix observed between the various measurements at baseline and at various periods of the study showed a significant correlation between most parameters. Exceptions were: 1) ejection fraction at 24 h and sum of ST-segment elevation at admission and QRS scores at 24 h and 7 days and 2) 7-day perfusion defect score and sum of Q wave at 24 h and 7 days. The best correlation coefficients were between admission sum of ST-segment elevation and subsequent Q-wave and contraction scores (p = 0.0001), between admission perfusion defect, peak CK elevation and final contraction score (p = 0.0001) and between the final contraction score, Q-wave score and ejection fraction (p = 0.0001). The sequential changes observed with each investigation method also correlated well.

Table 2. Clinical and Electrocardiographic Findings

	Diltiazem (n = 30)	Placebo (n = 29)	p Value
Time to pain relief (min)	41 ± 65	51 ± 70	
Peak CK, IU/L	2,751 ± 2,007	2,336 ± 1,950	NS
Peak CK-MB, IU/L	315 ± 230	249 ± 161	NS
Time to peak CK-MB (h)	13 ± 5	12 ± 6	NS
Concomitant therapy			
Aspirin	30	29	NS
Heparin	30	29	NS
Nitroglycerin	19	23	NS
ACE inhibitors	6	11	0.08
Beta-blockers	11	20	0.02
ECG			
Admission			
Σ ST (mm)	13.9 ± 10	12.5 ± 8	NS
Anterior MI	19.8 ± 11	14.7 ± 9	NS
Inferior MI	9.7 ± 7	10.9 ± 8	NS
24 h			
Σ Q, mm	15.4 ± 18	14.8 ± 17	NS
Wagner score	4.5 ± 3.3	4.1 ± 3.4	NS
Anterior MI	5.2 ± 3.7	4.8 ± 3.5	NS
Inferior MI	3.9 ± 3.0	3.5 ± 3.4	NS
7 days			
Σ Q, mm	15.3 ± 19	11.1 ± 24	NS
Wagner score	4.4 ± 3.3	3.4 ± 3.2	NS
Anterior MI	5.2 ± 3.1	4.3 ± 3.1	NS
Inferior MI	3.9 ± 3.4	2.7 ± 2.0	NS

ACE = angiotensin-converting enzyme; Σ = sum.

Clinical and Electrocardiographic Data

Figure 2 illustrates the serial changes in heart rate and blood pressure during treatment and Table 2 describes the clinical and electrocardiographic data. Diltiazem reduced heart rate and systolic and diastolic blood pressures at all times, and consequently the pressure rate product. Peak total CK and CK-MB elevations, time to peak elevation and time to relief of pain were all similar between the two groups. Beta-blockers and converting-enzyme inhibitors were used less frequently in the diltiazem-treated patients. The sum of ST-segment elevation was slightly greater at baseline in the diltiazem group, more specifically in anterior infarcts (19.8 ± 11 vs. 14.7 ± 9); the sum of Q and the Wagner scores at 24 h and at 1 week were, however, the same in the two study groups. The sum of ST-segment elevation correlated with the Wagner score at 24 h (1.897 ± 0.18) and at 1 week (1.668 ± 0.175). This correlation was similar in diltiazem (1.73 ± 0.198) and placebo patients (2.155 ± 0.153), considering all infarcts and also anterior infarcts alone (0.684 ± 0.226 and −0.113 ± 0.303, respectively).

Myocardial Perfusion

The size and score of the perfusion defect decreased in the two study groups between admission and 24 h and again between 24 h and 7 days, suggesting a decreasing infarct size relative to the area at risk (Table 3). The magnitude of the

Table 3. Radionuclide Studies

	Diltiazem	Placebo	p Value
Radionuclide ventriculogram			
24 h			
Ejection fraction (%)	50.2 ± 11	49.8 ± 14	NS
Contraction score			
Global	15.3 ± 13	15.9 ± 13	NS
Infarct zone	3.6 ± 1.3	3.1 ± 1.6	NS
7 days			
Ejection fraction (%)	46.2 ± 12	48.1 ± 14	NS
Contraction score			
Global	11.5 ± 13.3	12.7 ± 12.5	NS
Infarct zone	3.0 ± 1.4	2.6 ± 1.4	
6 weeks			
Ejection fraction	47.3 ± 11	47.7 ± 15	NS
Contraction score			
Global	14.9 ± 13	14.5 ± 13	NS
Infarct zone	3.1 ± 1.5	2.9 ± 1.6	NS
Δ Ejection fraction (24 h–35 days)	−2.9 ± 0.8	−2.9 ± 0.9	NS
Δ Contraction score (24 h–35 days)			
Global	−0.4 ± 0.7	−1.2 ± 0.9	NS
Infarct zone	0.51 ± 0.9	0.18 ± 1.1	NS
Tc-99m SPECT studies			
Score at entry	18.0 ± 8	13.0 ± 6	0.02
Score 24 h	13.1 ± 8	10.1 ± 6	NS
Score 7 days	9.6 ± 7	7.2 ± 6	NS
Δ Score entry (7 days)	−8.3 ± 5	−5.6 ± 4	0.04
Anterior AMI	−12.4 ± 3	−5.9 ± 4	0.002
Inferior AMI	−6.5 ± 4	−5.4 ± 5	NS

Δ = difference.

Figure 2. Heart rate and systolic and diastolic blood pressures before and after the intravenous administration of diltiazem or placebo. The standard errors are shown here. bpm = beats per minute. *p < 0.05, †p < 0.01, ‡p < 0.001.

decrease was significantly greater with diltiazem (p = 0.04 for all and 0.002 for anterior infarcts). The significance of this finding, however, may be confounded by a greater initial defect in the diltiazem group compared to placebo and a positive correlation between the initial defect and subsequent improvement (change in score = −1.6 − 0.346 × initial score, p = 0.001).

Left Ventricular Function

Table 3 shows the results of the serial radionuclide angiograms obtained at 24 h, 7 days and 35 days. The analysis of variance demonstrated no significant changes with time in ejection fraction and in global and infarct zone contraction scores between diltiazem and placebo-treated patients. In anterior AMI, the ejection fraction at 24 h was 45.8 ± 13% with diltiazem and 44.3 ± 13% with placebo, and at 6 weeks, 46.2 ± 16% and 44.7 ± 14%, respectively (NS).

Coronary Angiography

Thirteen diltiazem patients and 16 placebo patients had multivessel disease. A Thrombolysis in Myocardial Infarction trial grade 3 flow was present in 86% of diltiazem patients and in 83% of placebo patients. The percent lumen diameter reductions of the culprit coronary artery lesion were 74 ± 18% and 73 ± 17%, respectively (p = NS).
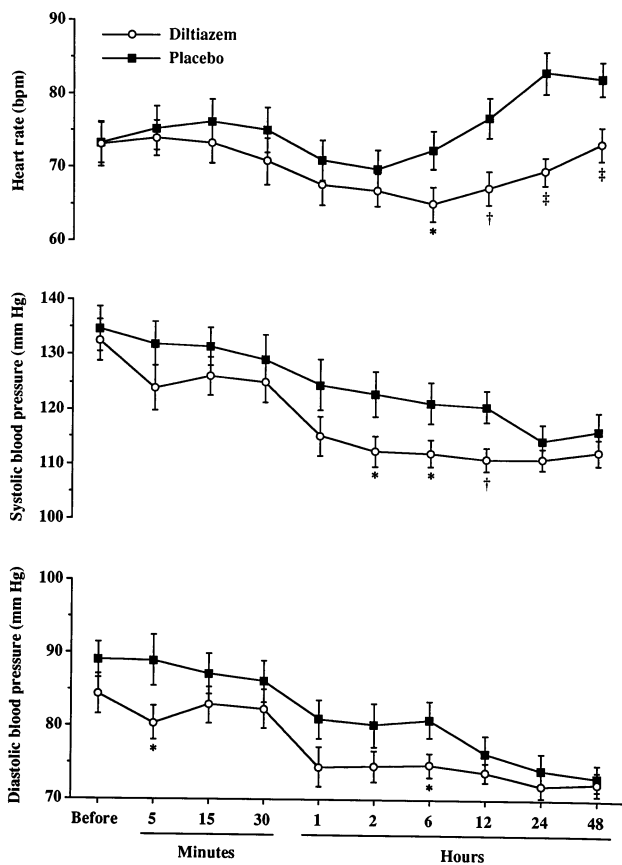
Clinical Evolution

Table 4 gives the clinical evolution in the two study groups. Death occurred in three patients, all in the placebo group; two of these patients were receiving a beta-blocker. The causes of death were cardiac rupture 21 h after randomization in one patient, progressive congestive heart failure, refractory ventricular arrhythmia and cardiogenic shock at day 3 in another and recurrent pulmonary edema after 3 weeks in the third patient. Extension of the infarction was diagnosed in three patients randomized to diltiazem and in four randomized to placebo (one in each study group receiving a beta-blocker) and recurrent ischemia in, respectively, one (on a beta-blocker) and seven patients (five of them on a beta-blocker). None of the diltiazem patients required urgent intervention compared to six (four on a beta-blocker) of the placebo patients (angioplasty in two and bypass surgery in four). Overall, balloon angioplasty or bypass surgery, including elective indications, were performed in 9 diltiazem and 16 placebo patients. Cardiac failure was observed in one diltiazem patient and in two placebo patients. Mean heart rates achieved on the limited treadmill exercise test performed before hospital discharge were 109 ± 13 beats/min with diltiazem and 111 ± 12 with placebo and a workload of 4.5 ± 1.3 and 4.1 ± 1.1. ST-segment depression was

Table 4. Clinical Outcome Events

|	Diltiazem	Placebo	Odds Ratio (95% CI)	p Value
Death	0	3	—	—
MI	3	4	—	—
Recurrent ischemia	1	7	0.11 (0.02–0.97)	0.02
Urgent intervention	0	6	0.00 (0.00–0.74)	0.009
Death/MI	3	7	0.35 (0.05–1.79)	0.15
Death/MI/recurrent ischemia	4	12	0.22 (0.05–0.90)	0.027
Death/MI/urgent intervention	3	13	0.14 (0.02–0.62)	0.003
All interventions	9	16	0.35 (0.10–1.15)	0.052

MI = myocardial infarction extension, CI = 95% confidence interval.

observed in eight and five patients, respectively. Figure 3 shows the Kaplan–Meier curves without myocardial infarction and without recurrent ischemia. The two curves diverged in the first 24 h and kept diverging during follow-up, favoring diltiazem (log-rank statistics = 0.027). The stepwise Cox regression model documented no predictive value of age, sex, anterior site of the infarction, time to thrombolysis, defect score and sum of ST-segment elevation at admission and concomitant medication used. The odds ratio for survival without myocardial infarction was 0.35 with diltiazem (95% CI 0.05 to 1.79, p = 0.15); for survival without infarction and without recurrent ischemia the odds ratio was 0.22 (95% CI 0.05 to 0.90, p = 0.015).

Drug Tolerance

Hypotension (blood pressure less than 100 mm Hg, or rapidly falling by 20 mm Hg or more) and/or bradycardia and

Figure 3. Percent cumulative survival without myocardial infarction and without recurrent ischemia **(top),** and percent cumulative survival without myocardial infarction **(bottom)** in patients randomized to diltiazem or to placebo.
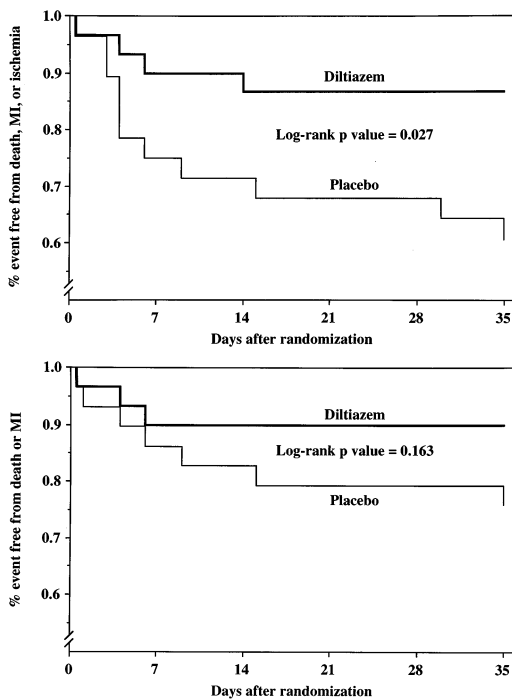
supraventricular block with heart rate less than 55 beats/min were recorded in 20 patients with diltiazem and required temporary reduction (by 50%) or discontinuation of the infusion in six patients and permanent discontinuation in two. It was observed in 11 patients during the acute phase, in six during the subacute phase and in four during the intermediate phase. Hypotension was more frequent early and bradycardia late. In the placebo group, six patients experienced hypotension during the acute phase and one during the subacute phase; two other patients had bradyarrhythmia. The infusion rate of placebo was reduced in four patients and discontinued in one. Nausea was experienced by 12 diltiazem and 8 placebo patients. Diltiazem patients more frequently developed a hematoma at the site of femoral puncture (five vs. no patients with placebo). Gastrointestinal bleeding occurred in two patients in each of the study groups and no patient had intracranial bleeding. Only one patient required blood transfusion. During the follow-up of 4 weeks after hospital discharge, one patient discontinued oral therapy with diltiazem because of gastric intolerance.

Discussion

This study was designed as a pilot study on the basis of conflicting results observed between clinical and experimental studies with calcium antagonists in AMI. The results showed that intravenous diltiazem used as adjunctive therapy to t-PA in AMI and followed by oral treatment significantly reduced the recurrence of ischemic events at 35 days. Treatment, however, had no detectable effects on the indices of ischemic area, infarct size and left ventricular function (regional and global).

Recurrent Ischemia and Recurrent Myocardial Infarction

Recurrent ischemia, before the thrombolytic era, was observed in 18% to 30% of patients and resulted in infarction extension in 28% of patients (24,36). Thrombolytic therapy has not improved these figures. Recurrent ischemia still occurs in 19% of patients and carries a risk of death or myocardial infarction of 28%; the risk is 4% in patients without ischemia (37). Reocclusion, observed in 15% to 30% of patients following successful thrombolysis and myocardial infarction in 5% to

10% of patients, is associated with an impaired short- and long-term prognosis with an event rate at 1 year approaching 70% (38,39).

In the present study, 48 h of diltiazem therapy initiated with t-PA and followed by oral therapy reduced the odds of death, myocardial infarction or recurrent ischemia at 35 days by 78%. The small number of deaths and myocardial infarction prevents any meaningful conclusion on the effect of the drug on these events. Refractory ischemia was significantly less frequent with diltiazem, and the drug prevented the need for urgent intervention procedures. The survival curves diverged early during hospitalization and further during the follow-up at 4 weeks. Consistent with the benefits to prevent recurrent ischemia, patients who received diltiazem had less symptom-based or elective intervention procedures and required less intensive medical therapy with nitroglycerin, beta blockers and an inhibitor of the angiotensin-converting enzyme.

Some imbalances were observed between the two study groups, with larger infarcts in the diltiazem group as evaluated at baseline by a greater amount of ST-segment elevation and a larger perfusion defect score (40). These imbalances could have had a negative impact on subsequent event rates with diltiazem.

Effects of Diltiazem

The exact mechanisms by which diltiazem prevents recurrent ischemia are not explained by the present study. They may be related to some effects on the complex interactions involving the underlying thrombogenic process, vascular reactivity and shear stress at the site of the residual stenosis. Heart rate and blood pressures were lower with treatment at all phases of the study, and could have resulted in more favorable hemodynamic conditions. The angiographic patency at 48 h, severity of the residual stenoses, kinetics of CK and CK-MB and regional and global left ventricular function early and late were not influenced. The significantly greater gain in regional perfusion and function observed with diltiazem may suggest better regional perfusion and viability, but should be interpreted with caution because it was associated with a larger initial defect, which is one of the main determinants of the extent of recovery (40).

The absence of benefits of diltiazem on infarct size contrasts with the results of experimental studies that have shown a protective effect on the ischemic and reperfused myocardium (1–14). However, when calcium antagonists were administered late following coronary occlusion and during reperfusion, as in this study and as in most clinical situations, the benefits observed were less evident (2,7,10,14–16).

Limitations of the Study

This study was a pilot study and the small sample size precludes any firm conclusions of the results. The findings could be a chance effect and/or be explained by unrecognized different baseline characteristics of the study population. The

event rate in the placebo group was high, but in the expected range, with 10% mortality, 14% reinfarction, 24% recurrent ischemia and 41% combined event rate. The methods of investigation also lack sensitivity to detect modest effects of an intervention. Strong correlation was, however, observed between the various enzymatic, electrocardiographic and radio-nuclide markers of area at risk, infarct size and left ventricular function. Diltiazem had neutral effects on these markers. Recombinant t-PA was not used optimally and the more effective accelerated regimen of administration could have slightly improved the results, but very likely in a symmetrical way in both study groups. Finally, the use of medical treatment other than calcium antagonists (aspirin and heparin) was not controlled, and more patients in the placebo group used beta-blockers and angiotensin-converting enzyme inhibitors. The benefits of diltiazem were additive, however, to those of nitroglycerin administered in 71% and to those of beta-blockers administered in 53% of patients. Less frequent use of these drugs, or use of a smaller dose or a reduction of the doses of diltiazem in their presence could possibly have amplified the benefits of the drug, whereas it reduced the observed frequency of bradyarrhythmia and hypotension.

Clinical Relevance

Diltiazem was relatively well tolerated in this study with no more frequent congestive heart failure than placebo; the complications associated with its use could be relatively easily managed. The entry criteria were, however, strict, excluding patients with clinically overt signs of left ventricular dysfunction or with an atrioventricular block. The deleterious effects of diltiazem administration in patients with pulmonary edema and congestive failure have been well documented in previous clinical trials (41). Patients were also closely monitored in-hospital with strict bedside orders to correct any eventual bradycardia or hypotension. These side effects occurred frequently, in two-third of the patients; they were considered severe enough to require temporary reduction in dose in 20% of patients and permanent discontinuation in 6.7%. Bleeding risk could also be of concern. The five patients who developed a hematoma at the site of femoral arterial puncture were in the diltiazem group; this finding could be by chance or favored by the antiplatelet effect of calcium antagonists. One retrospective analysis of factors predisposing to intracerebral hemorrhage with t-PA identified an association between the risk and use of calcium antagonists at the time of myocardial infarction (42).

The antiischemic effects were striking, resulting at 35 days in a 14% reduction in the absolute risk of death, myocardial infarction or refractory ischemia. Recurrent ischemia was the only component of this composite endpoint that occurred frequently enough to allow meaningful conclusions. The absolute reduction in this end point exceeded 20%. The need for an urgent intervention procedure was prevented and the total number of interventions performed was reduced by 25% as antianginal drugs were prescribed also less frequently. The use

of diltiazem cannot be recommended based on the results of our pilot study. The findings, however, shed some perspective on the benefits to be expected from the use of calcium antagonists in AMI and more specifically from diltiazem. These findings may help orient future research such as benefits to be expected, doses and methods of administration to evaluate and on the investigation of better therapeutic strategies for cell protection to improve the success of thrombolysis. Some of the previous disappointment with these drugs may have been due to excessive expectation on their potential benefit, beyond their antiischemic effects, and also from assuming that the effects of the various calcium antagonists are class-specific rather than drug-specific. This study and others have not shown a clear benefit on infarct size. The protection observed acutely with diltiazem against recurrent ischemia and infarction was observed in trials of secondary prevention after myocardial infarction with diltiazem and with verapamil (24,43,44) outside of the context of thrombolysis. It was also more recently described in a randomized double-blind trial of intravenous diltiazem compared to intravenous glyceryl trinitrate during the acute phase of unstable angina (45). In that study, diltiazem reduced the risk of refractory angina and myocardial infarction during the infusion by 62%. It would therefore appear that the intravenous use of diltiazem might be protective against the ongoing coronary pathophysiologic processes involved with ischemia in acute coronary syndromes. It cannot be extrapolated from our results, however, that the benefits observed during the acute phase of myocardial infarction will extend beyond 36 days in long-term secondary prevention.

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