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Adenosine as an Adjunct to Thrombolytic Therapy for Acute Myocardial Infarction

Results of a Multicenter, Randomized, Placebo-Controlled Trial: The Acute Myocardial Infarction STudy of ADenosine (AMISTAD) Trial

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OBJECTIVES The Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial was designed to test the hypothesis that adenosine as an adjunct to thrombolysis would reduce myocardial infarct size.

BACKGROUND Reperfusion therapy for acute myocardial infarction (MI) has been shown to reduce mortality, but reperfusion itself also may have deleterious effects.

METHODS The AMISTAD trial was a prospective, open-label trial of thrombolysis with randomization to adenosine or placebo in 236 patients within 6 h of infarction onset. The primary end point was infarct size as determined by Tc-99 m sestamibi single-photon emission computed tomography (SPECT) imaging 6 ± 1 days after enrollment based on multivariable regression modeling to adjust for covariates. Secondary end points were myocardial salvage index and a composite of in-hospital clinical outcomes (death, reinfarction, shock, congestive heart failure or stroke).

RESULTS In all, 236 patients were enrolled. Final infarct size was assessed in 197 (83%) patients. There was a 33% relative reduction in infarct size ($p = 0.03$) with adenosine. There was a 67% relative reduction in infarct size in patients with anterior infarction (15% in the adenosine group vs. 45.5% in the placebo group) but no reduction in patients with infarcts located elsewhere (11.5% for both groups). Patients randomized to adenosine tended to reach the composite clinical end point more often than those assigned to placebo (22% vs. 16%; odds ratio, 1.43; 95% confidence interval, 0.71 to 2.89).

CONCLUSIONS Many agents thought to attenuate reperfusion injury have been unsuccessful in clinical investigation. In this study, adenosine resulted in a significant reduction in infarct size. These data support the need for a large clinical outcome trial. (J Am Coll Cardiol 1999;34:1711–20)
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Reperfusion therapy for acute myocardial infarction (MI) has been shown to reduce mortality (1). Angiographic data show that earlier and more complete reperfusion is related to improved survival (2). At the same time, reperfusion itself may result in deleterious effects, including myocyte death, microvascular injury, myocardial stunning and arrhythmias, although the clinical relevance of these phenomena is debatable (3). There is an excess of mortality in the day after thrombolytic therapy, which may in part be related to "reperfusion injury" (1). The mechanism of reperfusion injury has not been completely delineated but is thought to result from multiple processes, including production of oxygen free radicals, changes in intracellular calcium homeostasis, recruitment of neutrophils, complement activation, disturbed endothelial function, impaired cellular energetics and damage to the extracellular collagen matrix (3,4).

Adenosine has been studied extensively as a cardioprotective agent. It has been shown to replenish high-energy phosphate stores in endothelial cells and myocytes (5–9), to

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Abbreviations and Acronyms

AMISTAD = Acute Myocardial Infarction STudy of ADenosine
CORE = Collaborative Organization for RheothRx Evaluation (trial)
MI = myocardial infarction
SPECT = single-photon emission computed tomography
TIMI = Thrombolysis In Myocardial Infarction (trial)

inhibit oxygen free radical formation (10–12), to inhibit neutrophil activity and accumulation (10–14) and to improve microvascular function (15). In addition, adenosine has been shown to participate in myocardial ischemic preconditioning, which may be particularly important because MI in humans commonly is caused by dynamic coronary occlusion with intermittent periods of blood flow (16–19). In animal models of reperfusion injury, adenosine has consistently reduced infarct size, improved left ventricular function and improved coronary blood flow (15,20–26).

Despite substantial investigation of adenosine in animal models of reperfusion, only a few studies have evaluated adenosine in patients with acute coronary syndromes. Small clinical studies have shown that adenosine is associated with smaller infarcts at six-week follow-up (27) and less "no-reflow" phenomenon, congestive heart failure and Q-wave MI (28) in patients undergoing primary angioplasty for acute MI and reduced ST segment shift, lactate production, and ischemic symptoms in patients undergoing elective angioplasty (29).

The Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial was designed to test the hypothesis that adenosine would reduce the size of MI measured by single-photon emission computed tomographic (SPECT) imaging with Tc-99 m sestamibi in patients undergoing thrombolysis.

METHODS

Study organization. The AMISTAD trial was a prospective, open-label, placebo-controlled, randomized study to evaluate the safety and efficacy of adenosine as an adjunct to thrombolytic therapy in the treatment of acute MI. Patients were enrolled at 19 centers in the U.S., Argentina and Canada (see Appendix for complete list of investigators).

Patient population. Patients presenting within 6 h of the onset of chest pain (consistent with ischemia, lasting at least 20 min, and not relieved by sublingual nitroglycerin) who had ST segment elevation >0.1 mV in two contiguous leads, in whom the clinical decision was made to treat with thrombolytic therapy, were eligible for enrollment. The criteria for exclusion were age <18 years or >79 years, women known or suspected to be pregnant, lactation, dipyridamole treatment within the past 24 h, systolic blood pressure <100 mm Hg, cardiogenic shock (systolic blood pressure <90 mm Hg with rales or cardiac index <2.2 L/min/m^2), underlying condition in which hypotension may be poorly tolerated (such as severe aortic stenosis or cerebrovascular disease), history or clinical evidence of bronchospastic lung disease or prior bronchodilator therapy, second-degree or greater atrioventricular block without functional pacemaker, left bundle branch block, sustained bradycardia (<60 beats/min for >20 min), current enrollment in other investigational drug studies and patients unlikely to be available for follow-up (at four to six weeks). All patients gave informed consent for participation and the study was approved by the institutional review board at each hospital.

Trial design. Enrollment began in December, 1994 and ended in July, 1997. Eligible patients were stratified by MI location (anterior or nonanterior as assessed by the site investigator) and then randomly assigned to adenosine (Adenoscan, Fujisawa USA, Inc., Deerfield, Illinois) given by peripheral intravenous infusion at 70 μg/kg/min for 3 h or placebo (normal saline at 70 μg/kg/min for 3 h). The protocol initially specified that the primary end point was to be myocardial salvage determined from sequential (acute and 5 to 12 days later) SPECT myocardial perfusion imaging with Tc-99 m sestamibi. Because of slow enrollment related to difficulty in obtaining the acute image, the protocol was modified by an amendment in August 1995 such that the primary end point became final infarct size as determined by SPECT myocardial perfusion imaging with Tc-99 m sestamibi five to seven days after enrollment. The enrollment goal also was adjusted. Secondary end points were: 1) myocardial salvage index in patients with both acute and final images, and 2) a composite clinical end point reported by the site investigators. Myocardial salvage index was defined as: [myocardium at risk (acute image) − final infarct size (final image)]/(myocardium at risk). The composite clinical end point consisted of death, reinfarction, congestive heart failure, cardiogenic shock or stroke.

Patient recruitment and treatment. Investigators or study coordinators telephoned or faxed a 24-hour-a-day, 7-day-a-week randomization center to review the eligibility of patients and to receive treatment assignments.

By protocol, the adenosine infusion was to begin before thrombolytic therapy was given. In patients undergoing acute cardiac imaging, SPECT imaging was to be performed within 6 h after injection of Tc-99 m sestamibi (20- to 30-mCi dose), which was to be injected before thrombolytic therapy began (accelerated alteplase or streptokinase per institutional protocol).

Also by protocol, intravenous lidocaine was to be given before thrombolytic therapy began, according to individual institutional protocol, to achieve and maintain therapeutic

levels for ≥6 h. A previous study (23) had reported that adenosine was associated with reduced infarct size in dogs after coronary occlusion and reperfusion only when given with lidocaine.

Adenosine infusion rates were to be reduced by decrements of 10 μg/kg/min if side effects occurred. After resolution of any side effect, the infusion rate was to be increased in increments of 10 μg/kg/min to the maximum tolerated dose, but not to exceed 70 μg/kg/min. Other cardiac medications, diagnostic procedures, cardiac interventions or revascularization procedures were at the discretion of the physician.

The final infarct size was to be determined by Tc-99 m sestamibi SPECT image performed 6 ± 1 days after enrollment. A follow-up clinic visit or telephone contact occurred four to six weeks after hospital discharge.

Nuclear imaging technique and equipment. All imaging data were submitted to the Nuclear Core Laboratory (Mayo Clinic Foundation, Rochester, Minnesota), which was blinded to treatment assignment. Imaging equipment and image-acquisition technique at each site were validated by this core laboratory using a cardiac phantom (30). For single-headed gamma camera systems, images were acquired using either a "step-and-shoot" mode or a continuous mode and a circular orbit. Between 30 and 32 images were acquired in a 64 × 64-word mode matrix. Image time was ≥40 s. For a multihead SPECT system, acquisition was performed over 360° every 6°. Data were stored in a 64 × 64-word mode matrix. The time per image was ≥30 s. Data were sent to the laboratory on floppy diskettes and included raw planar data, the most recent 30 M count flood image and the most recent center-of-rotation study.

Statistical analysis. The target sample size of 300 patients was based on an assumption of a 35% reduction in the final infarct size associated with adenosine with a power of 80% at the alpha = 0.05 level. The prespecified primary end point was final infarct size, using multivariable regression modeling to adjust for covariates: MI location, time from enrollment to determination of the final infarct size, use of revascularization procedures, type of thrombolytic therapy, use of lidocaine, interaction between treatment and MI location and interaction between treatment and type of thrombolytic therapy. Modeling techniques used the ranks of the final infarct size data due to anticipated asymmetry in the distribution of these data. This analysis was based on an intent-to-treat strategy for patients who had a final infarct size determination. Variables with significance at the $p \leq 0.05$ were retained in the model.

Further techniques were used to compare the final infarct size between treatment groups. First, comparisons were performed based on the Wilcoxon rank-sum test. Second, imputation techniques were used to account for patients with missing final infarct size data. Patients who died before assessment of the final infarct size were assigned the largest infarct-size rank for the group defined by MI location, and patients with data missing for other reasons were assigned the median rank of the infarct size for the group defined by MI location. Categorical variables were summarized as percentages and continuous variables as medians with 25th and 75th percentiles.

RESULTS

Baseline characteristics. A total of 236 patients were enrolled. The baseline clinical and historical characteristics were similar between treatment groups (Table 1). The study drug was given to 93% of patients in the adenosine group and 94% of placebo patients. Table 2 shows the time to thrombolytic treatment and details of study drug infusion. The median duration of study drug infusion was similar between the two groups. For patients assigned adenosine, the median (25th, 75th) ratio of total dose received to the total expected dose based on body weight was 1 (0.93, 1.01). The study drug was started before thrombolytic therapy in 39% of patients in both treatment groups. Lidocaine was given to 74% of adenosine patients and 68% of placebo patients. Patients assigned adenosine therapy tended to receive thrombolysis later after symptom onset than patients assigned placebo (200 min vs. 172 min) reflecting a later arrival at the hospital after symptom onset and not a delay in treatment after arrival (Table 2).

Data completeness. The numbers of patients with determination of myocardium at risk, final infarct size or both are shown in Table 3. A total of 197 (83%) patients had assessment of final infarct size (Fig. 1). The number of days to final infarct size assessment was similar between the two groups; six (5,7) days for adenosine versus six (6,7) days for placebo. Of the 39 patients with missing final infarct size data, 11 patients had died and 28 were missing data for other reasons: refusal by the patient or physician (7 patients), unacceptable image quality (3 patients) or technical problems with data acquisition during imaging (18 patients). Missing data were not associated with MI location, thrombolytic agent or treatment assignment.

Infarct size. Table 4 shows the results of the multivariable regression modeling for all patients with known final infarct size, with and without imputation of missing infarct size data. There was a statistically significant treatment benefit with adenosine therapy ($p = 0.03$). There also was a significant interaction between treatment and MI location ($p = 0.03$), indicating that the treatment effect was significantly greater in patients with anterior MI. After imputing the missing final infarct sizes, the p value for the treatment effect of adenosine was 0.07.

Final infarct size, myocardium at risk and myocardial salvage index data are shown in Table 5 and Figures 2 and 3. For all patients, there was 33% relative reduction in final infarct size in patients assigned adenosine compared with the placebo group ($p = 0.085$ by Wilcoxon rank-sum test). Moreover, patients with anterior MI assigned to adenosine

Table 1. Baseline Clinical and Historical Characteristics

	Anterior		Nonanterior		Total	
	Adenosine (n = 47)	Placebo (n = 45)	Adenosine (n = 72)	Placebo (n = 72)	Adenosine (n = 119)	Placebo (n = 117)
Age (yr)	60 (50, 70)	58 (47.5, 67.5)	55 (49, 67)	57 (48, 63)	58 (49, 69)	57 (48, 65)
Female gender	12 (26%)	9 (20%)	20 (28%)	16 (22%)	32 (27%)	25 (21%)
Caucasian	37 (79%)	40 (89%)	59 (82%)	58 (81%)	96 (81%)	98 (84%)
Weight (kg)	78 (69, 91)	77 (70, 86)	82 (73.5, 94)	82 (68, 97.5)	80 (70, 91)	77 (70, 91)
Heart rate (bpm)	82 (68, 92)	77 (69, 87)	76 (67, 84)	74 (65, 84)	80 (68, 88)	75 (66, 84.5)
Systolic BP (mm Hg)	140 (127, 156)	139 (119, 152.5)	141 (121, 160)	140 (123, 152.5)	140 (125, 160)	140 (120, 152.5)
Diastolic BP (mm Hg)	80 (73, 94)	80 (70, 91)	80 (68.5, 100)	80 (71, 90.5)	80 (70, 98)	80 (70.5, 90.5)
Killip class						
I	41 (87%)	39 (87%)	66 (92%)	67 (93%)	107 (90%)	106 (91%)
II	6 (13%)	5 (11%)	5 (7%)	5 (7%)	11 (9%)	10 (9%)
III	0	0	1 (1%)	0	1 (1%)	0
IV	0	0	0	0	0	0
Thrombolytic therapy						
Alteplase	29 (62%)	25 (56%)	45 (62.5%)	48 (67%)	74 (62%)	73 (62%)
Streptokinase	18 (38%)	20 (44%)	27 (38%)	24 (33%)	45 (38%)	44 (38%)
Hypertension	24 (51%)	18 (40%)	35 (49%)	36 (50%)	59 (50%)	54 (46%)
Hypercholesterolemia	14 (30%)	12 (27%)	33 (46%)	32 (44%)	47 (39%)	44 (38%)
Diabetes mellitus	7 (15%)	11 (24%)	12 (17%)	13 (18%)	19 (16%)	24 (21%)
Prior CVD	2 (4%)	1 (2%)	3 (4%)	2 (3%)	5 (4%)	3 (3%)
Prior infarction	3 (6%)	5 (11%)	10 (14%)	14 (19%)	13 (11%)	19 (16%)
Prior bypass	0	0	2 (3%)	4 (6%)	2 (2%)	4 (3%)
Prior angioplasty	2 (4%)	4 (9%)	4 (6%)	15 (21%)	6 (5%)	19 (16%)
Prior angina	19 (40%)	23 (51%)	26 (36%)	44 (61%)	45 (38%)	67 (57%)
Angina <24 h preceding	14 (30%)	14 (31%)	20 (28%)	22 (31%)	34 (29%)	36 (31%)
Prior heart failure	3 (6%)	0	2 (3%)	2 (3%)	5 (4%)	2 (2%)
History of smoking	34 (72%)	37 (82%)	59 (82%)	61 (85%)	93 (78%)	98 (84%)

Data presented are median (25th, 75th percentiles) or number (%) of patients. BP = blood pressure; CVD = cerebrovascular disease.

had a 67% relative reduction in final infarct size (p = 0.014 by Wilcoxon rank-sum test). There was no reduction in the final infarct size observed in patients with nonanterior MI (p = 0.96 by Wilcoxon rank-sum test). Among the 62 (26%) patients with an acute sestamibi image, the myocardium at risk was similar between treatment groups. There was also a nonsignificant improvement in myocardial salvage index for patients assigned adenosine versus control (0.49 vs. 0.17, p = 0.098 by Wilcoxon rank-sum test). There was a significantly higher myocardial salvage index in the patients with anterior MI assigned adenosine compared with placebo patients (0.62 vs. 0.15, p = 0.015 by Wilcoxon rank-sum test). The effect of adenosine on final infarct size was similar among patients treated with alteplase versus streptokinase and patients with and without lidocaine use.

Clinical outcomes and adverse events. Table 6 shows the secondary end point data for the composite in-hospital end

Table 2. Treatment Details

	Anterior		Nonanterior		Total	
	Adenosine	Placebo	Adenosine	Placebo	Adenosine	Placebo
Time from study drug initiation to start of thrombolysis (min)	0 (−8, 5)	0 (−5, 5)	0 (−5, 3)	0 (−6, 6)	0 (−6, 5)	0 (−6, 5)
Duration of drug infusion (min)	180 (180, 180)	180 (180, 186)	180 (175, 182)	180 (180, 185)	180 (180, 180)	180 (180, 185)
Time from symptom onset to start of thrombolysis (min)	195 (135, 295)	165 (113, 215)	206 (140, 275)	175 (110, 230)	200 (136, 285)	172 (110, 228)
Time from symptom onset to hospital arrival (min)	94 (44, 173)	80 (43, 150)	120 (74, 168)	91 (51, 146)	111 (60, 170)	90 (47, 150)
Time from hospital arrival to start of thrombolysis (min)	74 (50, 125)	71 (53, 107)	67 (46, 86)	65 (43, 90)	68 (47, 108)	70 (43, 93)

Data presented are median (25th, 75th percentiles).

Table 3. Number and Percent of Patients With Assessment of Myocardium at Risk and Final Infarct Size

	Anterior		Nonanterior		Total	
	Adenosine (n = 47)	Placebo (n = 45)	Adenosine (n = 72)	Placebo (n = 72)	Adenosine (n = 119)	Placebo (n = 117)
Acute image	12 (25%)	9 (20%)	28 (39%)	19 (26%)	40 (34%)	28 (24%)
Final image	39 (83%)	38 (84%)	62 (86%)	58 (81%)	101 (85%)	96 (82%)
Acute and final image	12 (25%)	8 (18%)	25 (35%)	17 (24%)	37 (31%)	25 (21%)

Data presented are number (%) of patients.

point. There was no significant difference in clinical outcomes between treatment groups, and the overall number of events was small. However, there was a nonsignificant excess of deaths (10 vs. 6), reinfarctions (7 vs. 3), congestive heart failure (13 vs. 8) and cardiogenic shock (6 vs. 4) in the adenosine patients. The composite end point was reached in 22 patients in the adenosine group compared with 16 in the placebo group (odds ratio 1.43, 95% confidence intervals 0.71 to 2.89). There was a tendency toward a greater excess of adverse events with adenosine in the nonanterior MI group.

Additional in-hospital cardiovascular events are shown in Table 7. There was slightly more bradycardia, heart block, hypotension and ventricular arrhythmias in the adenosine patients, especially those with nonanterior MI. There was no observed difference in the number of adverse events by type of thrombolytic therapy or use of lidocaine.

DISCUSSION

The principal finding of this study was that a 3-h adenosine infusion resulted in a significant reduction in infarct size determined by SPECT cardiac imaging ($p = 0.03$ after adjustment for covariates of infarct size). In patients with anterior MI, there was a striking 67% ($p = 0.014$ by Wilcoxon rank-sum test) reduction in infarct size in patients assigned adenosine therapy versus placebo. No reduction in infarct sizes in patients with nonanterior MI was shown.

Despite the reduction in left ventricular infarct size in the adenosine group, in-hospital clinical outcomes were similar between the two treatment groups. However, there was a tendency toward more adverse clinical events in the patients assigned adenosine compared with placebo although the overall number of events was small.

Previous clinical studies. In addition to a large amount of experimental evidence to support adenosine as a cardioprotective agent, two small randomized trials have suggested a benefit from adenosine in patients with acute MI or in patients undergoing elective angioplasty. Intracoronary adenosine in patients undergoing primary angioplasty for acute MI was associated with a higher postprocedure Thrombolysis In Myocardial Infarction (TIMI) flow grade (2.18 ± 1.25 vs. 2.7 ± 0.4, $p < 0.01$), less no-reflow phenomenon (0 patients vs. 6 patients), fewer Q-wave MIs (50% vs. 80%, $p = 0.047$), and less congestive heart failure (0% vs. 20%, $p = 0.035$) (28). Intracoronary adenosine during elective angioplasty was associated with significantly fewer ST segment changes, lower chest pain scores and less lactate production (29). The adenosine A_1 receptor mediates ischemic preconditioning (16), and adenosine has been shown to reduce the effects of later ischemia both in animal models (16–18) and in human coronary angioplasty (29). However, a study in patients with acute MI treated with primary angioplasty and intravenous adenosine showed no

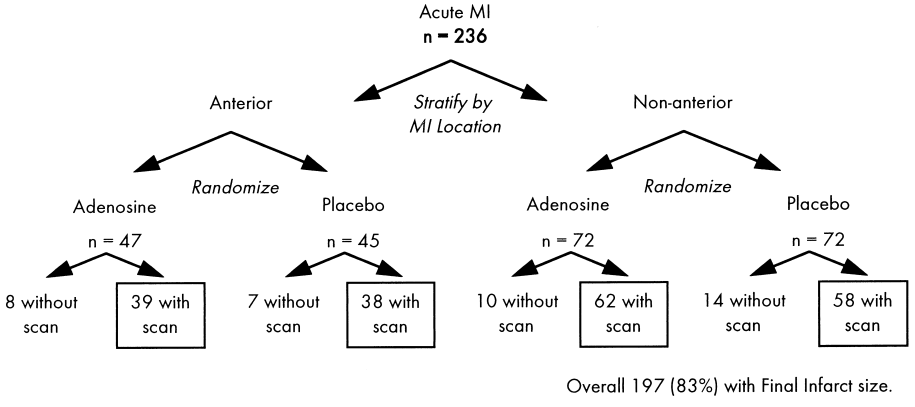

Figure 1. Stratification and randomization scheme showing the number of patients in each treatment arm and number of patients with determination of final infarct size.

Table 4. Multivariable Regression Modeling*

	p
Model excluding patients with missing final infarct-size data*	
Infarct location (anterior vs. nonanterior)	< 0.001
Adenosine effect	0.03
Treatment × infarct location interaction	0.03
Model with imputation of missing data†	
Infarct location (anterior vs. nonanterior)	< 0.001
Adenosine effect	0.07
Treatment × infarct location interaction	0.05

*Candidate variables included treatment, infarct location, type of thrombolytic (streptokinase vs. alteplase) interaction of treatment and infarct location, interaction of treatment and type of thrombolytic, use of lidocaine, days from enrollment to infarct size determination and use of cardiac procedures (bypass or angioplasty); †Patients missing data because of death were assigned the maximum rank for infarct size of the group defined by infarct location. Patients missing data for other reasons were assigned the median rank for infarct size for the group defined by infarct location.

improved myocardial salvage by discharge versus historical controls (27).

Adenosine as a coronary vasodilator. Adenosine is widely used as a safe pharmacological stress agent for detection of coronary artery disease (31–48). Adenosine may be detrimental in patients with acute coronary occlusion due to coronary steal, bradyarrhythmias and negative inotropic effects. The incidence of bradycardia, hypotension and atrioventricular block were relatively low in the current study but tended to be higher in patients with nonanterior MI, perhaps due to the higher vagal tone in this population. Despite these concerns, patients with acute MI treated with adenosine in this study had a significant reduction in infarct size. Theoretically, more specific targeting of adenosine receptor subtypes could be advantageous in maintaining myocardial protection while limiting potential side effects.

Other reperfusion injury agents. Clinical trials of other agents that have shown promise in reducing infarct size have been disappointing when studied more rigorously in larger cohorts. Such agents have included prostacyclin (49), fluosol (50), magnesium (51), poloxamer 188 (RheothRx) (52) and trametazidine (53). Of particular importance in RheothRx, which in an early clinical study of 114 patients resulted in improved left ventricular function, reduced infarct size, fewer reinfarctions and no safety concerns (54). The larger Collaborative Organization for RheothRx Evaluation (CORE) trial (52) of over 3,000 patients found a trend towards worse outcome with RheothRx in the composite outcome of death, cardiogenic shock or reinfarction at 35 days (13.6% vs. 12.7%). There was a significant increase in renal dysfunction associated with RheothRx and higher rates of sinus tachycardia, atrial flutter, atrial fibrillation and heart failure.

Infarct location. Patients were stratified by MI location at enrollment to ensure balance in baseline characteristics known to be strongly related to final infarct size (55). That infarctions were larger among patients with anterior MI was expected to result in a larger absolute reduction in infarct size with adenosine, but the finding of a statistically significant difference in the treatment effect according to MI location was unexpected.

Although the reason for the lack of treatment effect of adenosine in nonanterior MI is unknown, the trend towards more adverse events in this group is consistent with the hypothesis that an adverse effect related to more hypotension, bradycardia or ventricular arrhythmias may reduce the effectiveness of either thrombolysis or adenosine in reducing infarct size. Another possible explanation relates to collateral circulation. Collateral flow is an independent predictor of infarct size, and the impact of collateral flow is greater in patients with anterior MI (56,57). Since one of the proposed mechanisms of adenosine as a cardioprotective agent is through effects on the microvasculature (15), particularly collateral circulation, the lack of observed benefit in nonanterior MI in our study may relate to differences in collateral flow. Finally, the lack of benefit in the patients with nonanterior MI may simply have been due to chance.

The use of final infarct size carries the risk of imbalances in baseline myocardium at risk according to treatment group. Use of myocardial salvage index rather than the final infarct size has the advantage of allowing patients to act as their own controls (to account for heterogeneity in baseline characteristics such as previous MI). This is of particular concern in small trials. In our population, the numbers of patients with prior MI were similar between treatment groups. Although acute images were obtained in only 25% of patients, baseline images showed that myocardium at risk

Table 5. Final Infarct Size, Myocardium at Risk and Myocardial Salvage Index

	Anterior			Nonanterior			Total		
	Adenosine	Placebo	p	Adenosine	Placebo	p	Adenosine	Placebo	p
Final infarct size (% of LV)	15 (6, 39)	45.5 (11, 55)	0.014	11.5 (4, 21)	11.5 (1, 24)	NS	13 (4, 23)	19.5 (3.5, 42)	0.085
Myocardium at risk (% of LV)	49.5 (43, 63.5)	51 (47, 67)	NS	19 (8, 30)	22 (10, 30)	NS	26 (10, 47.5)	26 (10, 50)	NS
Myocardial salvage index*	0.62 (0.39, 0.75)	0.15 (0.04, 0.23)	0.015	0.19 (0.00, 0.83)	0.20 (0.07, 0.38)	NS	0.49 (0.07, 0.79)	0.17 (0.07, 0.30)	0.098

*(myocardium at risk − final infarct size)/(myocardium at risk). Data presented are median (25th, 75th percentiles). LV = left ventricle.

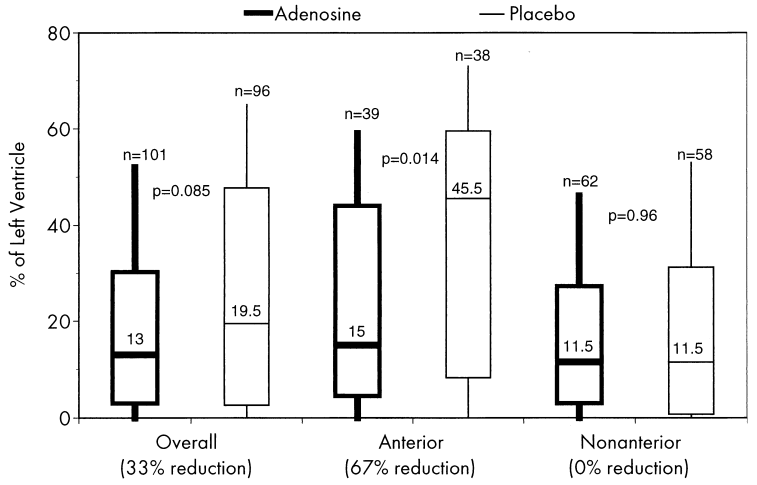

Figure 2. Box-and-whisker plots of the final infarct size as a percentage of the left ventricle by treatment group and infarct location. The **boxes** represent the 25th and 75th interquartile ranges; **vertical lines** represent the 5th and 95th percentiles. The median values are shown above the **horizontal lines**.

was equal between treatment groups according to MI location. Similarly, if the final infarct size in placebo-treated patients with anterior MI was higher than usual due to chance, this could explain a larger-than-expected apparent treatment effect of adenosine. Compared with other studies of reperfusion therapy, the infarct size in anterior MIs was similar to that observed in the CORE trial (52), which used the same core laboratory and enrolled patients with similar baseline clinical characteristics (S. Yusuf, personal communication, 1999).

Lidocaine. Lidocaine was included in the study based on findings that adenosine reduced infarct size in a dog model of reperfusion injury only when given in conjunction with lidocaine (23). Moreover, most animal studies of adenosine for reperfusion injury have included lidocaine infusions (15,20–22). Although most patients did receive lidocaine as mandated by the protocol in this study, 26% did not, and there was no difference in the treatment effect of adenosine by lidocaine use. These data suggest that lidocaine need not be given in conjunction with adenosine.

Study limitations. The relatively small sample size of this study limits the ability to assess the impact of adenosine on clinical outcomes. The 95% confidence intervals are wide and include a 25% increase in the composite clinical end point. Surrogate markers, such as infarct size, are useful for evaluating new therapies but also have limitations (58). Although infarct size might be expected to translate into clinical benefit, the negative results of the CORE trial (52,54) highlight the need for large, randomized trials to adequately assess the treatment effect on clinical outcomes.

This study does not provide insight into the optimal timing and dosing of adenosine. In the study, 50% of

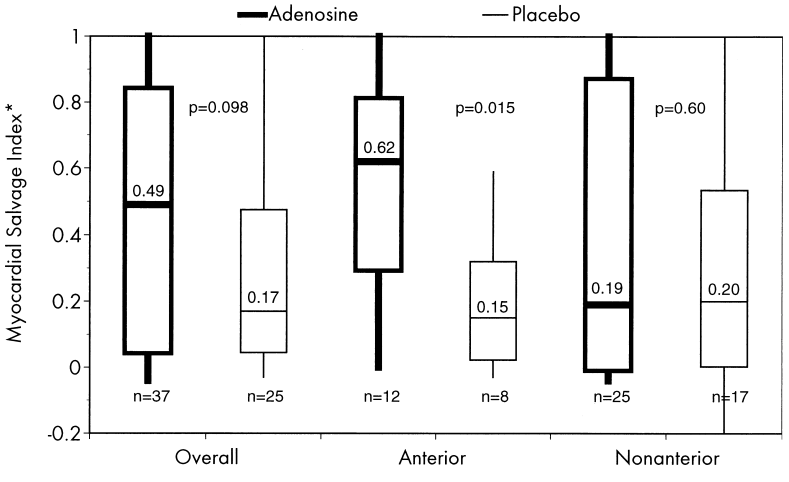

Figure 3. Myocardial salvage index = (myocardium at risk − final infarct size)/(final infarct size). See Figure 2 for description of box-and-whisker plots.

Table 6. Secondary End Point Clinical Outcome Events

	Anterior		Nonanterior		Total	
	Adenosine (n = 47)	Placebo (n = 45)	Adenosine (n = 72)	Placebo (n = 72)	Adenosine (n = 119)	Placebo (n = 117)
Death	4 (9%)	3 (7%)	6 (8%)	3 (4%)	10 (8%)	6 (5%)
Reinfarction	2 (4%)	0	5 (7%)	3 (4%)	7 (6%)	3 (3%)
Stroke	1 (2%)	0	0	2 (3%)	1 (1%)	2 (2%)
Intracranial hemorrhage	1 (2%)	0	0	0	1 (1%)	0
Cerebral infarction	0	0	0	1 (1%)	0	1 (1%)
Unknown	0	0	0	1 (1%)	0	1 (1%)
Congestive heart failure	4 (9%)	4 (9%)	9 (12.5%)	4 (6%)	13 (11%)	8 (7%)
Cardiogenic shock	1 (2%)	2 (4%)	5 (7%)	2 (3%)	6 (5%)	4 (3%)
Composite*	8 (17%)	7 (16%)	14 (19%)	9 (12.5%)	22 (18%)	16 (14%)

*Death, reinfarction, stroke, congestive heart failure or shock. Data presented are number (%) of patients.

patients did not receive the study drug before thrombolytic therapy began. However, 75% of patients began treatment either before or within 5 min after thrombolysis began. To achieve maximum benefits of treatment, the drug theoretically should be started as early as possible but definitely before reperfusion, which typically does not occur immediately after thrombolytic therapy is started.

Patients assigned to adenosine showed a trend toward more adverse events, but the potential impact of a higher or lower dose is unknown. Whether adenosine has a greater or lesser benefit among later-presenting patients also is unknown. Animal models suggest that the benefit of adenosine may be time-dependent. Adenosine reduced infarct size when given (before reperfusion) after coronary occlusion for 40 to 90 min but not after occlusion for 180 min (15,20–22). Alternatively, in humans, prevention of reperfusion injury by adenosine could extend the period during which reperfusion therapy could have a net benefit.

Potential biases are inherent in open-label study designs such as that used in AMISTAD. However, the final infarct size was determined by an independent nuclear core laboratory that was blinded to treatment. As with any study that measures a surrogate end point, missing data also could have biased the results. The 39 patients (17%) who did not have final infarct size determination were unlikely to have biased the results, however, as the treatment effect persisted when these values were imputed.

Conclusions. Attempts to prevent reperfusion injury in acute MI infarction have been marked by a series of disappointments. However, the reduction of infarct size in this study is encouraging and perhaps relates to the unique ability of adenosine to modify the cellular responses to

Table 7. In-hospital Cardiovascular Events

	Anterior		Nonanterior		Total	
	Adenosine (n = 47)	Placebo (n = 45)	Adenosine (n = 72)	Placebo (n = 72)	Adenosine (n = 119)	Placebo (n = 117)
Bradycardia	6 (13%)	3 (7%)	13 (18%)	9 (12.5%)	19 (16%)	12 (10%)
Heart block						
Second-degree (Mobitz I)	1 (2%)	0	1 (1%)	0	2 (2%)	0
Second-degree (Mobitz II)	0	0	2 (3%)	0	2 (2%)	0
Third-degree	0	0	5 (7%)	2 (3%)	5 (4%)	2 (2%)
Atrial fibrillation/flutter	8 (17%)	3 (7%)	7 (10%)	6 (8%)	15 (13%)	9 (8%)
Ventricular tachycardia (>30 s)	4 (9%)	0	5 (7%)	0	9 (8%)	0
Ventricular tachycardia (<30 s)	6 (13%)	9 (20%)	12 (17%)	14 (19%)	18 (15%)	23 (20%)
Ventricular fibrillation	2 (4%)	3 (7%)	6 (8%)	1 (1%)	8 (7%)	4 (4%)
Hypotension	13 (28%)	13 (29%)	31 (43%)	23 (32%)	44 (37%)	36 (31%)
Recurrent angina	21 (45%)	18 (40%)	30 (42%)	33 (46%)	51 (43%)	51 (44%)
Mild bleeding	17 (36%)	11 (24%)	28 (39%)	24 (33%)	45 (38%)	35 (30%)
Moderate/severe bleeding	6 (13%)	5 (11%)	6 (8%)	8 (11%)	12 (10%)	13 (11%)
Pacemaker	1 (2%)	3 (7%)	3 (4%)	5 (7%)	4 (3%)	8 (7%)
IABP	3 (6%)	3 (7%)	5 (7%)	3 (4%)	8 (7%)	6 (5%)
Defibrillation	5 (11%)	1 (2%)	3 (4%)	2 (3%)	8 (7%)	3 (3%)

Data presented are number (%) of patients. IABP = intraaortic balloon pump.

injury and to participate in ischemic preconditioning. The results of the AMISTAD trial, including the reduction in infarct size in anterior infarctions as well as the lack of an observed trend towards clinical benefit, support the need for a trial designed specifically to assess clinical outcomes.

APPENDIX

The following centers and investigators collaborated in this study: *Principal Investigators:* Christopher B. Granger, Kenneth W. Mahaffey, Joseph A. Puma, Robert M. Califf. *Coordinating Center:* Duke Clinical Research Institute, Durham, North Carolina. *Consortia: DUCCS;* Joseph A. Puma, Galen S. Wagner; *Favaloro Foundation:* Alejandro Barbagelata, Luis D. Suarez, Graciela Mo, Silvia Galante, Abraham Chownik. *Nuclear Core Laboratory:* Raymond J. Gibbons, Michael K. O'Connor, Tammy Hudson. *ECG Core Laboratory:* Galen S. Wagner, Kathy Gates, Stephen Starr. *Statisticians:* A. Cecilia Casas, Sandra Stinnett. *Project Manager:* Lindsay R. Lambe. *Investigators (number enrolled):* J. Puma, D. Small, L. Jones, Galax, Virginia (46); A. Barbagelata, B. Mautner, D. Agranatti, E. Oqueli, Buenos Aires, Argentina (34); M. DiCarli, S. Jerome, S. Korba, Detroit, Michigan (24); S. Ramee, T. Collins, S. Jenkins, M. Prechac, New Orleans, Louisiana (20); M. Fortunato, S. Nusdeo, Buenos Aires, Argentina (18): C. Granger, K. Mahaffey, R. Califf, E. Berrios, C. Martz, P. Gottlieb, K. Quintero, Durham, North Carolina (13): N. Vijay, M. Washam, Denver, Colorado (12); T. Sacchi, R. Pereira, I. Dor, A. Major, Brooklyn, New York (11); M. Leesar, R. Bolli, T. Shahab, J. Lanter, Louisville, Kentucky (11): L. Simkins, R. Schneider, L. Orihuela, M. McLaughlin, W. Schneider, Margate, Florida (10); H. Iparraguirre, H. Grancelli, M. Rodriguez, Buenos Aires, Argentina (10); K. Browne, M. Roy, Lakeland, Florida (8); S. Hegde, J. Tallet, F. Pitman, Lumberton, North Carolina (5); P. Eisenberg, R. Gropler, J. Faszholz, St. Louis, Missouri (4); G. Lane, K. Doucette, Jacksonville, Florida (3); A. Riba, S. Dabbous, C. Draus, Dearborn, Michigan (2); V. Pearson, J. Sherman, W. Pitts, Rome, Georgia (2); P. Cohen, J. Imrie, K. Woo, R. Moore, Vancouver, British Columbia (2); R. Valentine, D. Brindley, S. Scott, Indianapolis, Indiana (1); R. Taillefer, A. Gagnon, Montreal, Quebec, Canada (0); D. Vorchheimer, M. Henzlova, I. Guzman, New York, New York (0); G. Heller, F. Kiernan, D. Fram, A. Ahlberg, Hartford, Connecticut (0); R. Jesse, C. Roberts, Richmond, Virginia (0); V. Lowe, M. Wittry, J. Fletcher, S. Purnell, St. Louis, Missouri (0); S. Stowers, T. Hilton, T. Abuan, Jacksonville, Florida (0). *Sponsors:* Medco Research, Inc. and Fujisawa USA, Inc.

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