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Post-Reperfusion Myocardial Infarction

Long-Term Survival Improvement Using Adenosine Regulation With Acadesine

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OBJECTIVES The purpose of this study was to assess the safety and efficacy of the adenosine regulating agent (ARA) acadesine for reducing long-term mortality among patients with post-reperfusion myocardial infarction (MI).

BACKGROUND No prospectively applied therapy exists that improves long-term survival after MI associated with coronary artery bypass graft (CABG) surgery—a robust model of ischemia/reperfusion injury. Pretreatment with the purine nucleoside autocoid adenosine mitigates the extent of post-ischemic reperfusion injury in animal models. Therefore, we questioned whether use of the ARA acadesine—by increasing interstitial adenosine concentrations in ischemic tissue—would improve long-term survival after post-reperfusion MI.

METHODS At 54 institutions, 2,698 patients undergoing CABG surgery were randomized to receive placebo (n = 1,346) or acadesine (n = 1,352) by intravenous infusion (0.1 mg/kg/min; 7 h) and in cardioplegia solution (placebo or acadesine; 5 μg/ml). Myocardial infarction was prospectively defined as: 1) new Q-wave and MB isoform of creatine kinase (CK-MB) elevation (daily electrocardiography; 16 serial CK-MB measurements); or 2) autopsy evidence. Vital status was assessed over 2 years, and outcomes were adjudicated centrally.

RESULTS Perioperative MI occurred in 100 patients (3.7%), conferring a 4.2-fold increase in 2-year mortality ($p < 0.001$) compared with those not suffering MI. Acadesine treatment, however, reduced that mortality by 4.3-fold, from 27.8% (15 of 54; placebo) to 6.5% (3 of 46; acadesine) ($p = 0.006$), with the principal benefit occurring over the first 30 days after MI. The acadesine benefit was similar among diverse subsets, and multivariable analysis confirmed these findings.

CONCLUSIONS Acadesine is the first therapy proven to be effective for reducing the severity of acute post-reperfusion MI, substantially reducing the risk of dying over the 2 years after infarction. (J Am Coll Cardiol 2006;48:206–14) © 2006 by the American College of Cardiology Foundation

Reperfusion injury, occurring with restoration of blood flow to ischemic tissue, is associated with myocardial cell death and apoptosis, microvascular injury, myocardial stunning, and arrhythmias—all of which can result in mortality and morbidity, including heart failure (1,2).

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Reperfusion injury can occur after percutaneous coronary intervention (PCI) or thrombolysis for acute myocardial infarction (MI) as well as after coronary blood flow is halted for 30 min or longer during coronary artery bypass graft (CABG) surgery. Over the past three decades, the adoption of highly effective new pharmacological and mechanical reperfusion treatments has improved survival for patients who experience acute MI. Adjunctive antiplatelet and anti-coagulation therapies have produced further improvements in clinical outcomes for these patients (3–5). Although several techniques have shown promise in preclinical models, no drug or technique has been shown to reduce reperfusion injury in the medical or PCI treatment of acute MI.

In the controlled ischemia/reperfusion setting of coronary revascularization bypass graft surgery, where the myocardium must be made ischemic, an estimated 3% to 20% of patients experience MI associated with reperfusion after bypass grafting (6); however, no effective pretreatment to prevent or lessen the loss of viable myocardium has been effective.

One approach to reduce ischemia/reperfusion injury—adenosine regulation using acadesine—is particularly intriguing, given the fundamental role adenosine plays in reperfusion, preconditioning, and inflammation, especially in light of the unique safety profile of this agent, achieved through its site- and event-specific character. Therefore, we designed a long-term survival study with the in-hospital, multi-institutional, randomized trial cohort of nearly 3,000 patients, prospectively assessing post-reperfusion MI, and following all patients over the 2

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Abbreviations and Acronyms

ARA = adenosine regulating agent
CABG = coronary artery bypass graft
CK-MB = MB isoform of creatine kinase
MI = myocardial infarction
PCI = percutaneous coronary intervention

years after surgery. We hypothesized that, assessed against placebo, acadesine treatment improved 2-year survival among those patients suffering post-reperfusion MI.

METHODS

In-hospital and long-term post-infarction survival study designs. The Acadesine 1024 Trial had assessed the effects of acadesine versus placebo on MI and secondarily on the combined outcome of cardiac death, MI, or stroke assessed at 4 days after CABG surgery. This in-hospital, multi-institutional clinical trial was prospectively designed, randomized, placebo-controlled, and double-blinded. For all patients, institutional approval and patient informed consent were obtained before enrollment. The study—designed to detect a 50% or greater reduction in the primary end point—was stopped for futility, having shown a statistically insignificant 15% reduction with acadesine (22% adjusted for early stopping) in perioperative MI. Regarding safety, the number and incidence of serious adverse events was similar among groups: acadesine-treated patients experienced 506 events, with a 16.9% incidence (n = 228 of 1,351), whereas those patients administered placebo had 547 events, with a 17.9% incidence (n = 241 of 1,345) (p = 0.35). In addition, the types of serious adverse events were similar (Table 1). Additionally, the incidence of adverse events was not different between groups, (i.e., 93.6% [n = 1,264 of 1,351] in the acadesine group, and 93.4% [n = 1,256 of 1,345] in the placebo group [p = 0.82]).

The current long-term follow-up study was prospectively designed to investigate the effects of acadesine versus placebo on 2-year, all-cause mortality after perioperative MI (as defined in the in-hospital study protocol described herein) in the Acadesine 1024 Trial. After conclusion of the in-hospital enrollment, we designed the current study and then collected long-term data.

Table 1. Serious Adverse Events

Adverse Event (WHO Preferred Term)	Placebo (n = 1,345)	Acadesine (n = 1,351)
Cardiac failure	54 (4.0)	35 (2.6)
Infection	35 (2.6)	32 (2.4)
Respiratory insufficiency	27 (2.0)	32 (2.4)
Death	34 (2.5)	30 (2.2)
Cerebrovascular disorder	26 (1.9)	24 (1.8)
Hypotension	23 (1.7)	20 (1.5)
Atrial fibrillation	24 (1.8)	19 (1.4)
Cardiac arrest	16 (1.2)	17 (1.3)
Hemorrhage NOS	22 (1.6)	16 (1.2)
Ventricular tachycardia	13 (1.0)	16 (1.2)
Pneumonia	19 (1.4)	15 (1.1)
Ventricular fibrillation	21 (1.6)	11 (0.8)

Values are n (%).
NOS = not otherwise specified; WHO = World Health Organization.

Study drug administration and protocol. Starting approximately 15 min before induction of anesthesia, the study drug (acadesine or placebo) was administered intravenously at 0.1 mg/kg/min for 7 h continuously. Administration thus occurred during the intraoperative (pre- and post-bypass) and immediately postoperative (into the intensive care unit) periods. The trial was blinded to all clinicians, investigators, and analysis team members. In addition, if cardioplegia solution was used for myocardial protection during cardiopulmonary bypass, it contained either acadesine at a concentration of 5 μg/ml for patients randomized to receive acadesine or sterile water for injection for patients randomized to receive placebo.

Preoperatively, cardiac history and cardiac catheterization findings were recorded by investigators. Cardiovascular medications in use at the time of admission (including nitrates, beta-blocking and calcium channel-blocking drugs, aspirin) were continued until the time of surgery; however, the use of agents potentially affecting endogenous adenosine concentration (which could complicate the analysis of efficacy) was restricted: allopurinol was discontinued, dipyridamole was to be discontinued at least 48 h before surgery and not resumed until 24 h after surgery; methylxanthines were to be restricted for the 24 h before and the 48 h after surgery; and adenosine and pentoxifylline were to be restricted 12 h before and for 48 h after surgery.

During surgery, patients were monitored without restriction, according to the institution's standard practice for cardiovascular and pulmonary function. Heart rate and blood pressure were to be maintained within specific boundaries with anesthetic alterations and cardiovascular agents during the pre-bypass, bypass, and post-bypass periods. For all studies, prophylactic use of cardiovascular agents having potential anti-ischemic properties (nitrates, calcium channel blockers) was specifically excluded to avoid confounding interpretation of the data. Anesthetic techniques were prescribed. Cardiopulmonary bypass procedure and surgical technique were determined by the individual surgeon. Bypass typically was conducted with a membrane oxygenator and arterial filter with hemodilution and moderate systemic hypothermia. Neither the type nor mode of administration of cardioplegia was controlled. The use of inotropic and vasodilating agents was not controlled, but all medications administered were recorded.

Measurement of outcomes. All outcomes were prespecified, defined by protocol, and adjudicated by investigators blinded to treatment group. Post-reperfusion MI was defined prospectively by protocol. Myocardial infarction required either: 1) the presence of both a new Q-wave on electrocardiography and new post-reperfusion elevation of the MB isoform of creatine kinase (CK-MB); or 2) evidence

of infarction upon autopsy (7,8). For all patients, 12-lead electrocardiography data were collected daily, preoperatively on the day of surgery and postoperatively through postoperative day 4. New Q waves were diagnosed by central, blinded investigators with Minnesota Code criteria. The CK-MB concentrations were sampled before surgery and over 16 time-periods (9) during the first 4 postoperative days and analyzed centrally by SmithKline Beecham laboratories, with an immunoenzymetric assay (Hybritech Tandem-E CK-MB II, Hybritech Inc., San Diego, California). The pre-specified CK-MB criteria for infarction (in combination with a new Q-wave) were: 1) CK-MB concentration ≥100 ng/ml anytime after removal of the aortic cross clamp, with a bordering value of 50% or more; 2) CK-MB concentration ≥70 ng/ml anytime after 12 h after removal of the aortic cross clamp with a bordering value of 50% or more; or 3) CK-MB concentration ≥70 ng/ml anytime after 36 h after removal of the aortic cross clamp. The presence of infarction at autopsy was based on autopsy pathologic data from the respective institution and confirmed centrally by the end point committee. An independent safety and data monitoring panel reviewed all safety data on an ongoing basis and oversaw the stopping rules for the trial.

Long-term survival assessment. The current long-term follow-up study was prospectively designed to investigate

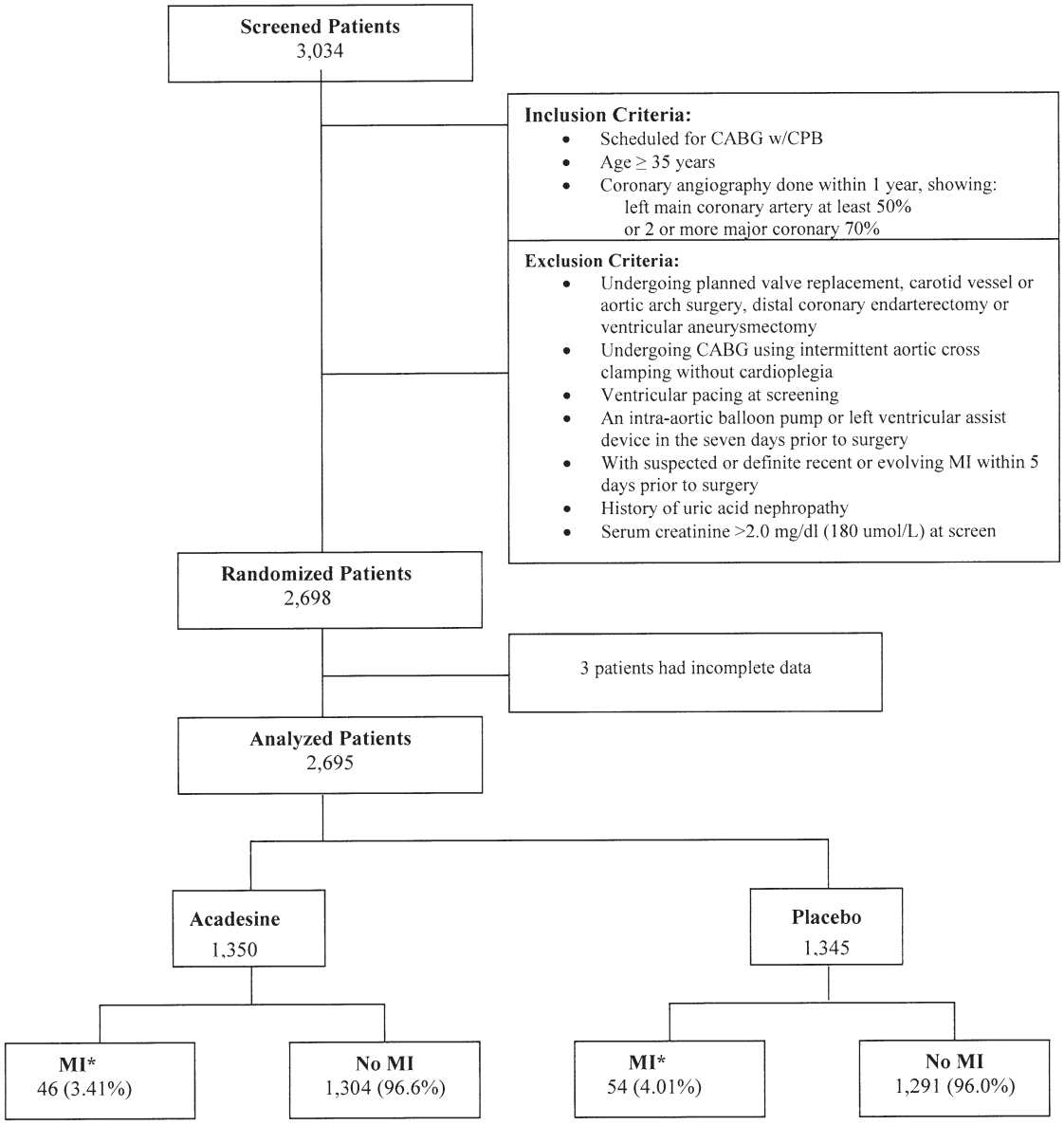

Figure 1. Consort diagram for the study patients. *Myocardial infarction (MI) indicates large, acute ST-segment elevation MI requiring either: 1) the presence of a new Q-wave on electrocardiogram and new post-reperfusion elevation of the MB isoform of creatine kinase (≥100 ng/ml anytime after removal of cross clamp, with a bordering value of 50% or more; or ≥70% ng/ml anytime after 12 h after removal of cross clamp with a bordering value of 50% or more; or ≥70 ng/ml anytime after 36 h after removal of cross clamp); or 2) the presence of autopsy evidence of infarction. CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass.

Table 2. Baseline Characteristics for All Patients, Patients Suffering MI, and Patients Not Suffering MI

	All Patients			Patients With MI			Patients Without MI		
	Placebo (n = 1,345)	Acadesine (n = 1,350)	p Value	Placebo (n = 54)	Acadesine (n = 46)	p Value	Placebo (n = 1,291)	Acadesine (n = 1,304)	p Value
Age									
Mean ± SD	63.2 ± 9.5	63.1 ± 9.6		63.4 ± 8.9	62.0 ± 10.1		63.2 ± 9.6	63.1 ± 9.5	
Median	64.0	64.0	0.58	65.0	63.5	0.45	64.0	64.0	0.67
Gender: female	286 (21.3)	254 (18.8)	0.11	15 (27.8)	12 (26.1)	0.85	271 (21.0)	242 (18.6)	0.12
Medical history									
Smoking	986 (73.6)	966 (71.7)	0.28	36 (66.7)	35 (76.1)	0.30	950 (73.9)	931 (71.6)	0.19
Myocardial infarct(s)	716 (53.8)	725 (54.3)	0.81	34 (64.2)	30 (65.2)	0.91	682 (53.4)	695 (53.9)	0.80
Angina	1,269 (94.3)	1,273 (94.3)	0.95	52 (96.3)	44 (95.7)	>0.99	1,217 (94.3)	1,229 (94.2)	0.98
Arrhythmias	234 (17.5)	234 (17.4)	0.96	12 (22.2)	4 (8.70)	0.07	222 (17.3)	230 (17.7)	0.77
Congestive heart failure	182 (13.5)	169 (12.5)	0.43	8 (14.8)	5 (10.9)	0.56	174 (13.5)	164 (12.6)	0.50
Hypercholesterolemia	693 (54.7)	722 (56.1)	0.48	33 (66.0)	27 (61.4)	0.64	660 (54.2)	695 (55.9)	0.40
Hypertension	796 (59.5)	773 (57.5)	0.30	36 (66.7)	24 (53.3)	0.18	760 (59.2)	749 (57.7)	0.43
Valvular disease	85 (6.32)	80 (5.94)	0.68	4 (7.41)	2 (4.35)	0.68	81 (6.28)	78 (6.00)	0.76
CABG	108 (8.03)	95 (7.04)	0.33	13 (24.1)	5 (10.9)	0.09	95 (7.36)	90 (6.90)	0.65
PTCA	172 (12.8)	184 (13.6)	0.52	6 (11.1)	7 (15.2)	0.54	166 (12.9)	177 (13.6)	0.59
Diabetes	350 (26.0)	351 (26.0)	0.99	13 (24.1)	8 (17.4)	0.41	337 (26.1)	343 (26.3)	0.91
Stroke	115 (8.55)	102 (7.56)	0.34	6 (11.1)	5 (10.9)	0.97	109 (8.44)	97 (7.44)	0.34
Neurologic disease	286 (21.3)	292 (21.6)	0.82	14 (25.9)	13 (28.3)	0.79	272 (21.1)	279 (21.4)	0.84
Vascular disease	418 (31.1)	384 (28.4)	0.13	15 (27.8)	12 (26.1)	0.85	403 (31.2)	372 (28.5)	0.13
Preoperative medications									
Aspirin use (prior to surgery)	358 (26.6)	359 (26.6)	0.99	9 (16.7)	8 (17.4)	0.92	349 (27.0)	351 (26.9)	0.95
Beta-blockers use (prior to surgery)	765 (56.9)	774 (57.3)	0.81	33 (61.1)	31 (67.4)	0.51	732 (56.7)	743 (57.0)	0.89
Calcium channel blockers use (prior to surgery)	802 (59.6)	776 (57.5)	0.26	31 (57.4)	25 (54.3)	0.76	771 (59.7)	751 (57.6)	0.27
Lipid-lowering agents use (prior to surgery)	239 (17.8)	254 (18.8)	0.48	12 (22.2)	9 (19.6)	0.75	227 (17.6)	245 (18.8)	0.43

Values are n (%) unless indicated otherwise.
CABG = coronary artery bypass grafting; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

the effects of acadesine versus placebo on 2-year all-cause mortality after perioperative MI (as defined in the in-hospital study protocol described herein) in the Acadesine 1024 Trial. After conclusion of the in-hospital enrollment, we designed the current study and then collected long-term survival data. Patients' survival status at 2 years was determined by telephone interview, if possible; the U.S. National Death Index; Medicare claims data; or Canadian provincial death indices and registries.

Data and statistical analyses. Among patients suffering a post-reperfusion MI, the risk of all-cause death at 2 years for patients randomized to acadesine versus placebo (primary hypothesis) was compared with the chi-square test and adjusted sequential analysis. Odds ratios and

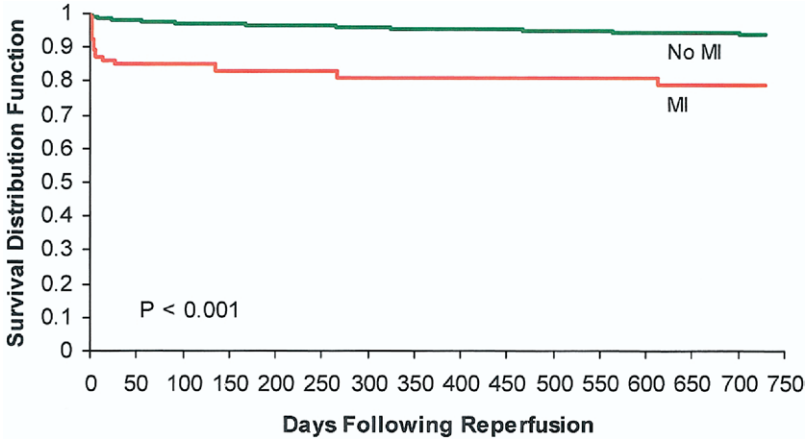

Figure 2. Kaplan-Meier analysis of 2-year survival according to with or without postoperative myocardial infarction (MI) among the 2,698 study patients.

their 95% confidence intervals are presented with associated p values. For the survival data analyses, the Kaplan-Meier product-limit method was used to compare the two (acadesine vs. placebo) survival distributions. Secondarily, we performed multivariate analyses to confirm the point-estimate and survival findings. Predictor variables significant at two-tailed nominal p values <0.2 in univariate analyses were entered into two multivariable logistic models for 2-year mortality (acadesine- and placebo-treated patients). Stepwise logistic regression was performed, retaining variables significant at two-tailed nominal p values <0.05. The occurrence of MI then was forced into both models to assess differential effects. Two approaches were taken. In the first, we performed logistic regression within the placebo population, assessing perioperative factors, including post-reperfusion MI, for association with 2-year mortality, and in parallel, performed the same analysis for acadesine patients. In the second, we performed logistic regression for all patients, testing the interaction between treatment and MI for 2-year mortality. All statistical analyses were performed with SAS version 8.12 software (SAS Institute, Cary, North Carolina).

RESULTS

A total of 2,698 patients were randomized. Three patients had incomplete data, leaving 1,345 receiving placebo and 1,350 receiving acadesine, or a total of 2,695 patients (Fig. 1). Generally, for all patients and for patients with and without postoperative MI, placebo- and acadesine-treated patients had similar cardiac medical histories and preoperative medications (Table 2); furthermore, the groups were similar for preoperative cardiac catheterization findings, cardioplegia types, and mean durations of placebo and acadesine infusions (see subsequent section regarding CABG incidence difference for patients with versus without MI).

Post-reperfusion MI. Myocardial infarction occurred in 100 of the 2,695 patients enrolled (3.7%). Although acadesine reduced the incidence of MI (placebo, 4.01% [54 of 1,345]; acadesine, 3.41% [46 of 1,350]), the reduction was not statistically significant (p = 0.24).

Post-reperfusion MI, long-term survival, and treatment. The occurrence of a perioperative MI conferred a 4.2-fold increased risk in 2-year mortality. Among the 2,595 patients not suffering infarction, 2-year mortality was 4.28%, versus

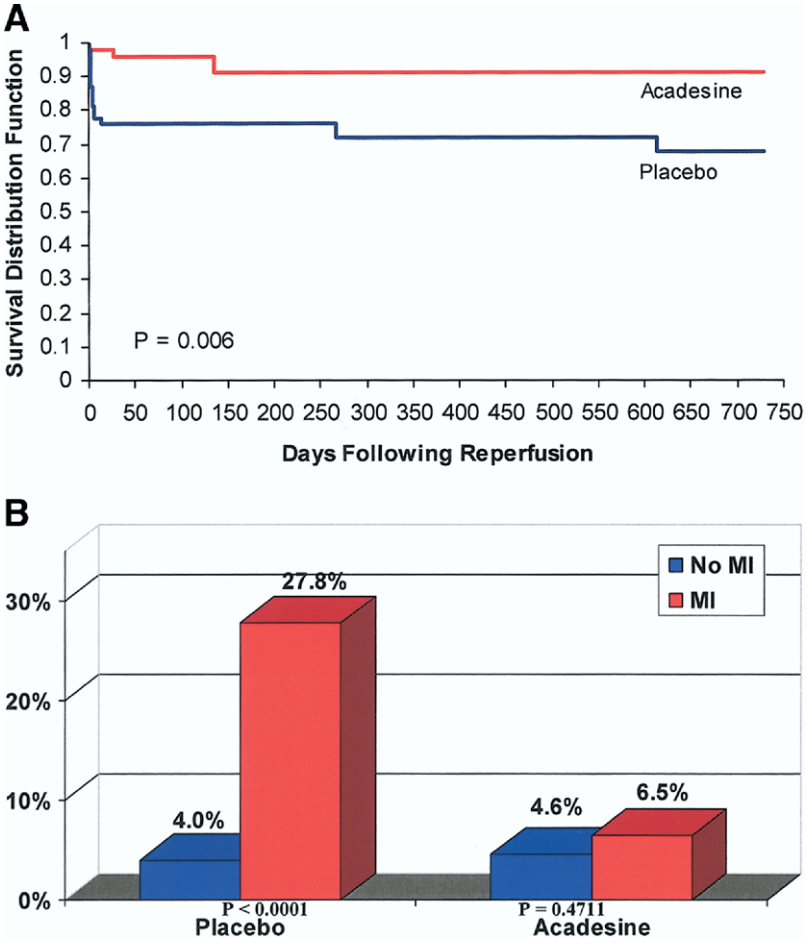

Figure 3. (A) Kaplan-Meier analysis of 2-year survival according to the use or non-use of acadesine among the 100 study patients who sustained post-reperfusion myocardial infarction (MI). **(B)** Two-year mortality by-MI and by-treatment.

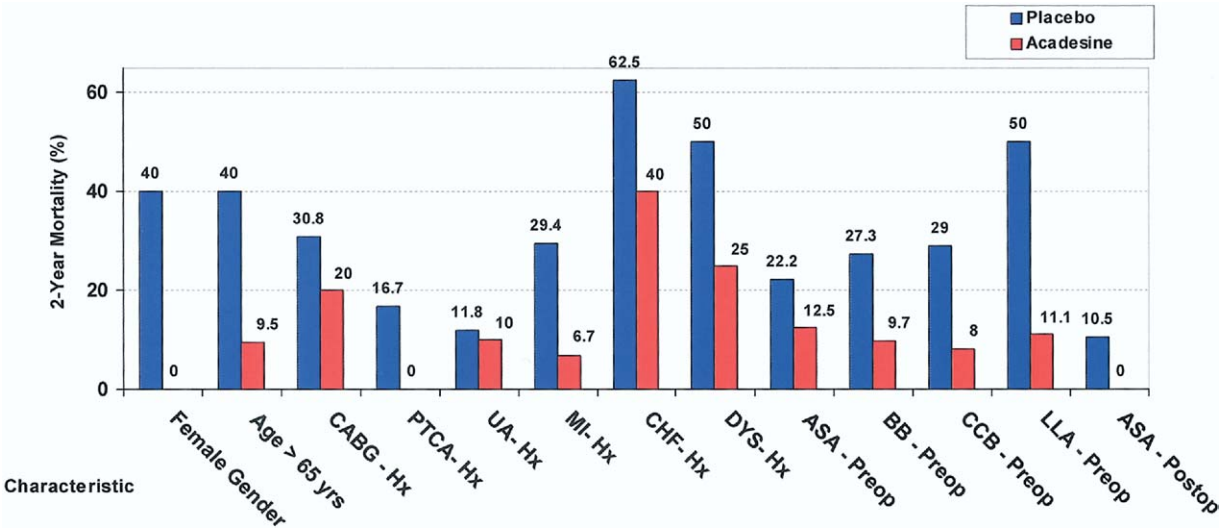

Figure 4. Two-year mortality: acadesine versus placebo by patient characteristic. ASA = acetylsalicylic acid; BB = beta-blocker; CABG = coronary artery bypass graft; CCB = calcium channel blocker; CHF = congestive heart failure; DYS = dysrhythmia; HX = history of; LLA = lipid-lowering agents; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; UA = unstable angina.

18.0% among the 100 patients suffering infarction ($p < 0.001$). The primary mortality effect appeared over the first 30 days after infarction (Fig. 2). Nine placebo-treated patients had MI diagnosed at autopsy versus one acadesine-treated patient.

The impact of acadesine treatment on post-infarction survival was significant. Acadesine treatment was associated with a 4.3-fold reduction in 2-year mortality from 27.78% (15 of 54; placebo) to 6.52% (3 of 46; acadesine) ($p = 0.006$) with the principal benefit occurring over the first 30 days after MI (Figs. 3A and 3B).

The acadesine benefit was similar among diverse subsets, including gender, race, age, disease acuity, and insurance-type (Fig. 4).

Multivariable analyses for long-term survival. Multivariable analyses for the placebo-treated patients (Table 3) demonstrated the independent effect of MI on 2-year mortality, whereas the occurrence of MI in acadesine-treated patients (Table 4) annulled the effect of post-reperfusion MI on mortality. The interaction between treatment and MI for 2-year mortality was sustained over the entire population and was independent of other perioperative covariates, including prior CABG (Table 5). Historical and perioperative factors that were independently associated with mortality were not unexpected, nor was the similarity between covariates for the placebo-patient analysis (Table 3) versus the acadesine-patient analysis (Table 4). Most impressive was the effectiveness of acadesine in reducing the placebo-MI odds from 12.4 ($p < 0.001$) to 0.8 ($p = 0.69$).

Table 3. Results of Multivariable Logistic Regression for 2-Year Mortality Among the Placebo-Treated Patients

Risk Factor	Odds Ratio (95% CI)	p Value
Previous CABG surgery	2.61 (1.29–5.28)	0.008
Medical history of congestive heart failure	2.96 (1.62–5.41)	<0.001
Medical history of hypercholesterolemia	0.56 (0.32–0.97)	0.04
Medical history of vascular disease	2.60 (1.49–4.52)	<0.001
Aspirin use after reperfusion	0.52 (0.29–0.92)	0.02
Post-reperfusion stroke	8.11 (2.88–22.86)	<0.001
Post-reperfusion MI	12.38 (5.82–26.34)	<0.001

CI = confidence interval; other abbreviations as in Table 2.

DISCUSSION

The objective of the current study was to assess the effects of post-reperfusion MI on 2-year survival and, if substantial, to determine whether treatment with acadesine mitigates those effects compared with placebo (that is, improves 2-year survival after post-reperfusion MI). With the Acadesine 1024 Trial—which involved 54 centers and 2,695 patients with complete data—our prospectively designed, long-term study found that post-reperfusion MI conferred a four-fold increased risk of long-term mortality. Importantly, acadesine treatment was associated with a four-fold reduction in 2-year mortality after perioperative post-reperfusion, acute MI. Both of these findings were statistically significant. Additionally, the primary point-estimate end point findings of this trial were cross-validated with several multivariable analyses that clearly indicated that for placebo-treated patients, post-reperfusion MI was associated with substantial risk for death over the 2 years after surgery (Table 3); however, that substantial risk was entirely annulled by treatment with acadesine (Table 4). The critical interaction between treatment and MI for 2-year mortality proved highly significant and independent of other prominent covariates, including prior CABG; differences between acadesine-MI and placebo-MI groups proved inconsequential (Table 5). Given our prior meta-analysis findings

Table 4. Results of Multivariable Logistic Regression for 2-Year Mortality Among the Acadesine-Treated Patients

Risk Factor	Odds Ratio (95% CI)	p Value
Age > 65 yrs	3.22 (1.69–6.14)	<0.001
Medical history of hypercholesterolemia	0.48 (0.26–0.86)	0.01
Medical history of stroke	2.46 (1.18–5.15)	0.02
Medical history of vascular disease	3.02 (1.69–5.42)	<0.001
Return to CPB	2.78 (1.19–6.51)	0.02
Aspirin use after reperfusion	0.47 (0.25–0.87)	0.02
Inotropes/vasoconstrictors use on remaining day of reperfusion	2.51 (1.37–4.58)	0.003
Post-reperfusion stroke	10.6 (3.64–30.9)	<0.001
Post-reperfusion renal failure	4.54 (1.40–14.76)	0.01
Post-reperfusion MI	0.76 (0.19–2.99)	0.69

CPB = cardiopulmonary bypass; other abbreviations as in Tables 2 and 3.

indicating a statistically significant short-term cardioprotective effect of acadesine (7), the present results indicate that the immediate benefit of acadesine is sustained for 2 years. It is the first trial of this size to demonstrate an important reduction in mortality associated with reperfusion-induced MI in any setting of clinical revascularization and the first to show a sustained benefit over the long term.

Numerous studies evaluating the use of pharmacologic and mechanical therapies to mitigate reperfusion injury have proven unsuccessful not only in CABG surgery but in PCI as well. These approaches have focused on oxygen free radicals (9,10), neutrophil accumulation and activation (8,11), intracellular Ca^{2+} overload via sodium-hydrogen exchange (NHE) inhibition (12,13), complement activation (14–16), hypothermia (17,18), hyperbaric oxygenation (19,20), and distal embolic protection devices (21). In each of these approaches, specific mechanisms of reperfusion injury were targeted. Their disappointing results might reflect the inherent limitations of therapies that target specific mechanisms or cell types involved in the pathophysiology of reperfusion injury, perhaps because they fail to address the full spectrum of its complexity.

Adenosine targets a broader spectrum of the pathophysiology of ischemia/reperfusion injury. It has been shown to improve post-ischemic ventricular function and reduce neutrophil accumulation and activation and myocardial necrosis and apoptosis (22). Adenosine directly inhibits neutrophil function. Most importantly, adenosine has been shown to be a powerful inducer of ischemic preconditioning (24). Preconditioning has offered the most potent approach to reducing infarct size in ischemia/reperfusion animal models. A major mechanism for this effect appears to be the reduction of post-reperfusion apoptosis of myocytes (23). The current results support this mechanism of action in human subjects. The iatrogenic ischemia of coronary bypass is a well-controlled ischemia/reperfusion event in man. The apparent reduction in post-MI mortality suggests a preconditioning mechanism to decrease infarct size. Thus, presumably smaller infarctions in ARA-treated patients resulted in lower mortality. This finding was confirmed by the multivariable logistic regression for the two groups.

Systemic adenosine has been most recently studied in the AMISTAD-II (Acute Myocardial Infarction Study of Adenosine-II) trial, which set out to determine the effect of

Table 5. Results of Multivariable Logistic Regression for 2-Year Mortality Among All Patients

Risk Factor	Odds Ratio (95% CI)	p Value
Age > 65 yrs	2.12 (1.40–3.23)	<0.001
Female gender	1.64 (1.05–2.57)	0.03
Medical history of angina	0.44 (0.22–0.91)	0.03
Medical history of congestive heart failure	1.98 (1.25–3.13)	0.003
Medical history of hypercholesterolemia	0.52 (0.34–0.78)	0.002
Medical history of vascular disease	2.81 (1.88–4.20)	<0.001
Previous CABG surgery	2.45 (1.41–4.27)	0.002
Inotrope* use on remaining day of reperfusion	2.43 (1.62–3.64)	<0.001
Post-reperfusion renal failure	3.18 (1.38–7.35)	0.007
Post-reperfusion stroke	8.48 (4.04–17.78)	<0.001
Aspirin use (post surgery)	0.51 (0.33–0.77)	0.002
Post-reperfusion MI vs. no MI: placebo-treated patients	11.92 (5.48–25.95)	<0.001
Post-reperfusion MI vs. no MI: acadesine-treated patients	0.95 (0.26–3.52)	0.94
Acadesine vs. placebo: patients with post-reperfusion MI	0.10 (0.02–0.41)	0.002
Acadesine vs. placebo: patients without post-reperfusion MI	1.21 (0.79–1.83)	0.38

*Inotrope: epinephrine, norepinephrine, amrinone, milrinone, and enoximone.
Abbreviations as in Tables 2 and 3.

intravenous adenosine on clinical outcomes and infarct size in ST-segment elevation MI patients (25). Although adenosine did not show an overall reduction in adverse clinical events in the primary end point (death or heart failure), the treated arm did demonstrate a positive trend toward a smaller median infarct size; however, in this setting of adenosine administration well after onset of ischemia, myocardial concentration would be predicted to be much lower than with ARAs, owing to the very short intravascular half-life of adenosine (~1 s). The trend toward smaller infarct size is consistent with results seen in the AMISTAD-I trial as well as in a small study on intracoronary administration of adenosine in patients undergoing angioplasty (26,27). Clinical utility of systemic adenosine, however, is limited, owing to adenosine's undesirable peripheral hemodynamic side effects.

Study limitations. We believe the current study's methodology was robust (including prospectively defined hypotheses, data collection and analysis, all executed before unblinding). This study was a scientific product of the Ischemia Research and Education Foundation (IREF), which received no support for the long-term study. Yet, an inherent bias exists. In 2000, the primary investigator (D.T.M.) was granted a sublicense to the intellectual property rights of acadesine (from the University of California and Metabasis Therapeutics, San Diego, California), and he continues to hold such license. Nonetheless, the prospective nature of the design and analyses was designed to eliminate any effect of such conflict on the methods, analyses, and results of the current study (see the Methods and Results sections). Second, measures of infarct size would have allowed insight into mechanisms for acadesine's beneficial long-term effects on mortality, but such assessment was not straightforward here. For example, in 10 placebo patients versus 1 acadesine patient, death occurred very early after MI (which itself might indicate an effect on "MI size"); however, few of these very early deaths had sufficient cardiac enzyme measurements to allow accurate estimation of MI size (e.g., area-under-the-curve of CK-MB or troponin concentration)—that is, for the most serious MIs (those that resulted in early death), sizing of MI could not be accomplished. Finally, we have noted a difference among MI patients for history of CABG surgery; however, this difference proven in multiple analyses does not confound the findings.

Conclusions. Our results support the hypothesis that the therapeutic approach of safely increasing endogenous adenosine at the site of ischemia enables reduction of reperfusion injury and post-infarction mortality. Acadesine represents the prototype of a new class of ARAs that substantially increase endogenous adenosine, but importantly, only in ischemic tissue and only under conditions of adenosine triphosphate catabolism, imparting a unique safety profile observed in this study. Preventative treatment with acadesine is safe and useful for reduction of long-term mortality among patients suffering post-reperfusion, perioperative MI. Additional studies will be required to determine the usefulness of acadesine or other ARAs in other settings of ischemia/reperfusion injury.

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APPENDIX

For a list of participants in the Multicenter Study of Perioperative Ischemia (McSPI) Research Group and Acadesine 1024 Trial, please see the online version of this article.