Effect of Adenosine-Regulating Agent Acadesine on Morbidity and Mortality Associated With Coronary Artery Bypass Grafting The RED-CABG Randomized Controlled Trial

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Despite improvements in myocardial protection and perioperative care, the risk of death is still substantial in the first month after coronary artery bypass graft (CABG) surgery, averaging 3.0% to 6.0%, and can be even higher in patients with poor left ventricular function. Up to 50% of these deaths have been attributed to a cardiac cause, and this percentage has remained fairly constant over time. This suggests that there are still cases in which the ischemia/reperfusion injury to the myocardium during the cross-clamp period may not be fully addressed by current techniques of myocardial protection. Several drugs with purported cardioprotective effects, particularly a sodium-proton exchange inhibitor, have been studied.

Context Ischemia/reperfusion injury remains an important cause of morbidity and mortality after coronary artery bypass graft (CABG) surgery. In a meta-analysis of randomized controlled trials, perioperative and postoperative infusion of acadesine, a first-in-class adenosine-regulating agent, was associated with a reduction in early cardiac death, myocardial infarction, and combined adverse cardiac outcomes in participants undergoing on-pump CABG surgery.

Objective To assess the efficacy and safety of acadesine administered in the perioperative period in reducing all-cause mortality, nonfatal stroke, and severe left ventricular dysfunction (SLVD) through 28 days.

Design, Setting, and Participants The Reduction in Cardiovascular Events by Acadesine in Patients Undergoing CABG (RED-CABG) trial, a randomized, double-blind, placebo-controlled, parallel-group evaluation of intermediate- to high-risk patients (median age, 66 years) undergoing nonemergency, on-pump CABG surgery at 300 sites in 7 countries. Enrollment occurred from May 6, 2009, to July 30, 2010.

Interventions Eligible participants were randomized 1:1 to receive acadesine (0.1 mg/kg per minute for 7 hours) or placebo (both also added to cardioplegic solutions) beginning just before anesthesia induction.

Main Outcome Measure Composite of all-cause mortality, nonfatal stroke, or need for mechanical support for SLVD during and following CABG surgery through postoperative day 28.

Results Because results of a prespecified futility analysis indicated a very low likelihood of a statistically significant efficacious outcome, the trial was stopped after 3080 of the originally projected 7500 study participants were randomized. The primary outcome occurred in 75 of 1493 participants (5.0%) in the placebo group and 76 of 1493 (5.1%) in the acadesine group (odds ratio, 1.01 [95% CI, 0.73-1.41]). There were no differences in key secondary end points measured.

Conclusion In this population of intermediate- to high-risk patients undergoing CABG surgery, acadesine did not reduce the composite of all-cause mortality, nonfatal stroke, or SLVD.

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a purinergic receptor antagonist, and a complement activation inhibitor, have been tested in large-scale randomized controlled trials in patients undergoing CABG surgery but failed to yield better postoperative outcomes.

One cardioprotective approach is based on the pharmacological duplication of one of the most powerful physiologic means of reducing ischemia/reperfusion injury, ischemic preconditioning. This endogenous protective process involves the release of several mediators, among which adenosine plays a key role. The administration of adenosine during CABG surgery is difficult to regulate and was not demonstrated to be beneficial. These issues led to the development of adenosine-regulating agents, of which acadesine is the first to be tested in large-scale clinical trials. By competing with adenosine for the nucleoside transmembrane transporter, acadesine increases extracellular adenosine levels by inhibiting adenosine deaminase and increases intracellular adenosine levels. Additionally, acadesine activates AMP-activated protein kinase, the central regulator of a host of intracellular enzymes involved in regulation of cellular energy and production of intracellular adenosine triphosphate.

To date, 5 studies of acadesine in participants undergoing CABG surgery have been conducted. Outcomes of these studies, which included a total of 4043 participants, were examined in a 1997 meta-analysis. In that meta-analysis, the use of acadesine was correlated with significant reductions in the occurrence of 3 end points: a 27% reduction in perioperative myocardial infarction (odds ratio [OR], 0.69 [95% CI, 0.51-0.95]; P = .02), a 50% reduction in cardiac death through postoperative day 4 (OR, 0.52 [95% CI, 0.27-0.98]; P = .04), and a 26% reduction in a composite of cardiac death, stroke, and myocardial infarction (OR, 0.73 [95% CI, 0.57-0.93]; P = .01). These significant associations persisted when examined in a random-effects model. The meta-analysis results prompted implementation of the current trial, designed to more definitely test whether acadesine could reduce the composite of all-cause mortality, nonfatal stroke, or need for mechanical support for severe left ventricular dysfunction (SLVD) occurring during and after CABG surgery through postoperative day 28.

### METHODS

#### Study Design and Population

**The Reduction in Cardiovascular Events by Acadesine in Patients Undergoing CABG (RED-CABG) trial** was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the ability of acadesine to reduce the incidence of ischemia/reperfusion injury in high-risk participants undergoing nonemergency CABG surgery. Study participants were patients undergoing CABG surgery with cardiopulmonary bypass who were at high risk of postoperative adverse events and who met all of the inclusion criteria and none of the exclusion criteria (eTable 1). The study was open to both sexes, and race/ethnicity was self-reported by participants. Enrollment was projected for 7500 patients at 300 sites in 7 countries (see “Statistical Analysis”). Enrollment occurred from May 6, 2009, to July 30, 2010. Each investigative site received institutional review board or ethics committee approval of the protocol, and all participants provided written informed consent.

Standard local procedures for CABG surgery or associated preoperative and postoperative care were followed. The study intervention was intravenous infusion of study drug or placebo before, during, and immediately after CABG surgery, which exposed the myocardium to a sufficient amount of study drug. The cardioplegic solution and cardiopulmonary bypass priming solution were also supplemented with either blinded study drug or placebo.

After the screening phase and within 14 days before surgery, participants were randomized by a central randomization service via an interactive voice/web response system in a 1:1 fashion to receive either acadesine or placebo. Randomization was stratified by sex. The dose of acadesine, consistent with previous trials, was 42 mg/kg diluted in 500 mL of normal saline, delivered as an intravenous infusion over approximately 7 hours commencing within approximately 30 minutes before induction of anesthesia, at a rate of 0.1 mg/kg per minute (1.2 mL/min for a 500-mL solution).

In addition, either saline (placebo) or acadesine solution was added to the cardioplegia solution for patients randomized to receive placebo or acadesine (5 µg/mL cardioplegia solution of acadesine), respectively. The choice and technique of preparation and delivery of standard cardioplegia and priming solutions and the volume required were determined by the attending physician.

#### Primary End Point

The primary efficacy end point was a composite of the occurrence of any of the following during surgery or through postoperative day 28: all-cause mortality, nonfatal stroke, or need for mechanical support for SLVD (defined as new use of mechanical circulatory assist devices, such as intra-aortic balloon pump or ventricular assist device, during or after CABG surgery for 1 hour or longer for treatment of low cardiac output). Indications for using circulatory assist devices were determined by the attending physician based on clinical judgment and included cardiogenic shock, difficulty in weaning from cardiopulmonary bypass, refractory left ventricular failure, refractory ventricular arrhythmias, and other indications that the investigators deemed necessary for treatment of low cardiac output. All efficacy end points (except all-cause mortality) were adjudicated by an independent, blinded clinical events committee (CEC). Cardiovascular mortality was also adjudicated by the CEC.

#### Secondary End Points

The key secondary efficacy end point was the first occurrence of any component of the composite of cardiovascular mortality, nonfatal stroke, or need for mechanical support for SLVD occurring during and after CABG surgery through postoperative day 28.
**Exploratory End Points**

Potential mechanisms of protective effects and other associated measurable clinical benefits of improved myocardial function by attenuation of ischemia/reperfusion injury were evaluated by creatine kinase MB (CK-MB) or troponin I and T levels and the incidence of myocardial infarction within 24 hours after surgery. The duration of mechanical ventilation (time from intubation to extubation); length of intensive care unit stay; length of hospitalization; prevalence of new, clinically significant atrial fibrillation within 96 hours after surgery; and estimated health state using the EuroQol 5-dimension instrument were also assessed. Perioperative myocardial infarction and clinically significant atrial fibrillation were adjudicated by the CEC.

**Statistical Analysis**

The population for the efficacy analyses was the intention-to-treat (ITT) population, which included all randomized participants who had completed primary outcome follow-up, regardless of whether they received the assigned treatment or underwent CABG surgery. The as-treated population included all randomized participants who received any amount of study drug (acadesine or placebo). Safety analyses were performed in this as-treated population. General and CABG-specific safety end points were monitored, with attention given to renal function and risk of hyperuricemia and gout. All statistical tests were 2-sided.

The CEC adjudicated each suspected end point event except all-cause mortality. An independent data and safety monitoring board (DSMB) monitored aggregated and blinded efficacy end points and other safety data to ensure the safety of participants in the trial. Using the event estimation worksheet from the American College of Cardiology/American Heart Association guidelines for high-risk individuals undergoing CABG surgery who fulfilled the enrollment criteria of this study, the estimated incidence of the primary composite efficacy end point was 10%. Based on data from previous acadesine trials, a relative reduction of approximately 25% in this end point was projected. Thus, the projected sample size of 7500 participants (3750 participants per treatment group) would have approximately 85% power to detect a 20% reduction in the primary efficacy end point among participants receiving acadesine vs placebo, assuming a primary end point event rate of 10% in participants receiving placebo and a 2-sided P value of .05. A staged futility analysis with increasing futility thresholds was planned once 30% and 40% of planned participants completed postoperative day 28.

The statistical methodology used to assess futility was based on a Bayesian posterior probability approach at the interim assessment to determine the probability of observing a statistically significant result at the end of the trial. For the first futility analysis, the decision was that the trial would continue if the interim results indicated at least a 20% probability to reject the null hypothesis at the end of the study. For the second futility analysis, the trial would continue if the interim results indicated that there was at least a 65% chance to reject the null hypothesis at the end of the study. The DSMB could recommend termination of the trial for a stipulated futility.

The primary hypothesis was that in patients undergoing CABG surgery with the use of cardiopulmonary bypass, the incidence of the primary composite end point would be significantly lower with acadesine compared with placebo. This hypothesis was evaluated using Cochran-Mantel-Haenszel testing that adjusted for the stratification factor (sex). Point estimates and associated 95% CIs for treatment differences are provided. Each participant contributed only 1 efficacy end point in the composite (ie, participants with multiple component events of a composite end point were counted only once for that composite). The key secondary hypothesis (administration of acadesine compared with placebo will reduce the incidence of the primary composite end point) was evaluated using methods similar to those specified for the primary efficacy end point.

To account for missing data, Kaplan-Meier estimates for the primary and key secondary end points were calculated and log-rank testing performed. In these analyses, participants were treated as censored as of the point when the data became unavailable. Other analyses included evaluating the clinical benefits of acadesine with respect to the secondary and exploratory end points previously described. The key secondary end point was not to be tested unless the primary end point was significant at the .05 level (2-sided test). The other secondary end points and the exploratory efficacy end points were supportive only, and no adjustment for multiplicity to these end points was applied. All statistical analyses were performed using SAS version 9 (SAS Institute Inc).

To evaluate the drug effects at different levels of mortality risk, the Society of Thoracic Surgeons (STS) risk stratification score was calculated. In the RED-CABG trial, 2934 of the 3080 randomized participants received CABG surgery. Of these, 55 had mitral valve repair and were excluded from this analysis. Thus, 2879 patients were eligible for application of the STS risk score for isolated CABG. The model coefficients were applied to their corresponding covariates in the data, and a predicted probability of 30-day mortality was calculated for each participant.

**RESULTS**

The trial was stopped early at the 30% futility analysis (after 3080 study participants were randomized), based on the recommendation of the DSMB. FIGURE I outlines the assignments and reasons for continuation in the study, resulting in a final sample size of 2986 patients in the ITT analysis. Figure 1 also outlines follow-up through postoperative day 28.

Baseline characteristics (TABLE 1) are typical of an intermediate- to high-risk population of patients undergoing CABG surgery and reflect the in-
There was no significant difference between the placebo and acadesine groups, with incidence rates of 5.0% and 5.1%, respectively (OR, 1.01 [95% CI, 0.73-1.41]; P = .94). TABLE 2 lists the primary and key secondary end points and individual components of the ITT population with complete follow-up and CEC-adjudicated end points. FIGURE 2, a Kaplan-Meier curve of the ITT analysis of the primary outcome, demonstrates the lack of effect of acadesine treatment on the composite end point. An exploratory post hoc analysis was performed to assess the effects of the patient risk profile on treatment efficacy. Using the STS risk stratification score, participants were categorized into quintiles. As shown in FIGURE 3 and eTable 4, a comparison of the primary end point across these quintiles did not show any statistical differences across the various risk groups.

Of the secondary end points, none reached or approached statistical significance at 28 days, including all-cause mortality, nonfatal stroke, need for mechanical support for SLVD, and the other secondary composite end points (eTable 5). Cardiovascular mortality through postoperative day 4 was numerically lower in acadesine-treated participants, but this was not statistically significant and was not evident through postoperative day 28. Additional exploratory efficacy end points, including length of mechanical ventilation and intensive care unit and hospital stay, are listed in eTable 6 and eTable 7. None of these exploratory secondary end points, including peak cardiac enzyme level and quality of life (eTable 8 and eTable 9), reached statistical significance.

Consistent with previous trials, adverse events were not significantly different between the treatment and placebo groups, with the exception of an increased incidence of hyperuricemia and elevated uric acid levels in the treatment group. Safety end points of special interest are included in eTable 10 and eTable 11.

**COMMENT**

In this population of intermediate- to high-risk patients undergoing CABG surgery, acadesine had no effect on the composite end point of all-cause mortality, nonfatal stroke, and SLVD requiring mechanical support through postoperative day 28. The incidence of the primary composite end point in the overall study population (including the placebo group) was substantially below that projected from the previous studies and historical data. The lower-than-predicted incidence is consistent with results from recent perioperative CABG trials in which advances in clinical practice appeared to reduce morbidity and mortality. A large portion of the lower event rate was attributable to a lower-than-predicted incidence of SLVD requiring mechanical support, which also indicates an improved degree of myocardial protection in a high-risk population. There was no trend toward a benefit in the overall study, resulting in the recommendation by the DSMB that the study be terminated based on predefined stopping rules.
These findings illustrate inherent risks of using promising meta-analysis results to plan “confirmatory” clinical trials. There are several potential explanations for the negative results we observed. One consideration is the decision around study eligibility criteria and the overall primary end point of the trial. The eligibility criteria were based on previous studies of acadesine that showed a greater benefit in higher-risk patients, especially women. However, based on analysis of the risk profile of the patients enrolled, the overall mortality risk based on STS criteria was lower than originally projected, resulting in the study participants being at lower risk than anticipated. Although a comparison of the primary end point by treatment group across quintiles of STS risk stratification did not show any statistically significant differences, we cannot exclude the possibility that a more favorable result might have been obtained in patients deemed to be at higher risk of intraoperative ischemic events, such as those undergoing long and complex combined valve and coronary procedures (Figure 3). Moreover, where these robust national databases exist, the inclusion of major outcome-linked variables in the case report forms of major clinical trials enables this kind of risk profile comparison to be made.

Lack of benefit of acadesine may be related to the dosing regimen used. Previous studies have indicated that sufficient concentrations of the drug in the ischemic myocardium are needed before application of the aortic cross

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 1544)</th>
<th>Acadesine (n = 1536)</th>
<th>Total (N = 3080)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>66.7 (8.7)</td>
<td>66.2 (8.5)</td>
<td>66.5 (8.6)</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median (IQR)</strong>*</td>
<td>66.0 (60.0-73.0)</td>
<td>66.0 (60.0-73.0)</td>
<td>66.0 (60.0-73.0)</td>
</tr>
<tr>
<td><strong>Sex, No. (%)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong>*</td>
<td>523 (33.9)</td>
<td>519 (33.8)</td>
<td>1042 (33.8)</td>
</tr>
<tr>
<td><strong>Men</strong>*</td>
<td>1021 (66.1)</td>
<td>1071 (66.2)</td>
<td>2092 (66.2)</td>
</tr>
<tr>
<td><strong>Race/ethnicity, No. (%)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>White</strong>*</td>
<td>1347 (82.0)</td>
<td>1340 (81.6)</td>
<td>2687 (81.8)</td>
</tr>
<tr>
<td><strong>Nonwhite</strong>*</td>
<td>117 (7.0)</td>
<td>123 (8.4)</td>
<td>240 (8.2)</td>
</tr>
<tr>
<td><strong>Body weight, kg</strong>*</td>
<td>86.0 (19.2)</td>
<td>86.9 (19.8)</td>
<td>86.5 (19.5)</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median (IQR)</strong>*</td>
<td>84.1 (72.6-97.6)</td>
<td>85.2 (73.2-98.2)</td>
<td>85.0 (73.0-98.0)</td>
</tr>
<tr>
<td><strong>Country of enrollment, No. (%)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Canada</strong>*</td>
<td>160 (10.4)</td>
<td>143 (9.3)</td>
<td>303 (9.8)</td>
</tr>
<tr>
<td><strong>France</strong>*</td>
<td>79 (5.1)</td>
<td>73 (4.8)</td>
<td>152 (4.9)</td>
</tr>
<tr>
<td><strong>Germany</strong>*</td>
<td>231 (15.0)</td>
<td>215 (14.0)</td>
<td>446 (14.5)</td>
</tr>
<tr>
<td><strong>Italy</strong>*</td>
<td>48 (3.1)</td>
<td>57 (3.7)</td>
<td>105 (3.4)</td>
</tr>
<tr>
<td><strong>The Netherlands</strong>*</td>
<td>8 (0.5)</td>
<td>5 (0.3)</td>
<td>13 (0.4)</td>
</tr>
<tr>
<td><strong>Spain</strong>*</td>
<td>35 (2.3)</td>
<td>40 (2.6)</td>
<td>75 (2.4)</td>
</tr>
<tr>
<td><strong>United States</strong>*</td>
<td>983 (63.7)</td>
<td>1003 (65.3)</td>
<td>1986 (64.5)</td>
</tr>
<tr>
<td><strong>Cardiovascular history, No. (%)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong>*</td>
<td>1361 (88.3)</td>
<td>1366 (89.0)</td>
<td>2727 (88.6)</td>
</tr>
<tr>
<td><strong>History of cigarette smoking</strong>*</td>
<td>940 (61.0)</td>
<td>976 (63.6)</td>
<td>1916 (62.3)</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong>*</td>
<td>1337 (86.7)</td>
<td>1319 (85.9)</td>
<td>2656 (86.3)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong>*</td>
<td>929 (60.2)</td>
<td>937 (61.0)</td>
<td>1866 (60.6)</td>
</tr>
<tr>
<td><strong>Family history of CAD</strong>*</td>
<td>571 (48.8)</td>
<td>572 (49.1)</td>
<td>1143 (49.0)</td>
</tr>
<tr>
<td><strong>Prior myocardial infarction</strong>*</td>
<td>727 (47.2)</td>
<td>760 (49.6)</td>
<td>1487 (48.4)</td>
</tr>
<tr>
<td><strong>Prior angina</strong>*</td>
<td>829 (53.8)</td>
<td>867 (56.3)</td>
<td>1796 (55.1)</td>
</tr>
<tr>
<td><strong>Prior stroke</strong>*</td>
<td>150 (9.7)</td>
<td>152 (9.9)</td>
<td>302 (9.8)</td>
</tr>
<tr>
<td><strong>Prior transient ischemic attack</strong>*</td>
<td>86 (5.7)</td>
<td>98 (6.4)</td>
<td>186 (6.0)</td>
</tr>
<tr>
<td><strong>Prior known carotid stenosis ≥50%</strong>*</td>
<td>167 (10.8)</td>
<td>206 (13.4)</td>
<td>373 (12.1)</td>
</tr>
<tr>
<td><strong>Other cerebrovascular disease</strong>*</td>
<td>27 (1.8)</td>
<td>26 (1.7)</td>
<td>53 (1.7)</td>
</tr>
<tr>
<td><strong>Prior PVD</strong>*</td>
<td>240 (15.6)</td>
<td>243 (15.8)</td>
<td>483 (15.7)</td>
</tr>
<tr>
<td><strong>Claudication</strong>*</td>
<td>137 (8.9)</td>
<td>141 (9.2)</td>
<td>278 (9.0)</td>
</tr>
<tr>
<td><strong>Heart failure</strong>*</td>
<td>207 (13.4)</td>
<td>201 (13.1)</td>
<td>408 (13.3)</td>
</tr>
<tr>
<td><strong>History/presence of AF or atrial flutter</strong>*</td>
<td>119 (7.7)</td>
<td>132 (8.6)</td>
<td>251 (8.2)</td>
</tr>
<tr>
<td><strong>Prior PCI</strong>*</td>
<td>379 (24.5)</td>
<td>425 (27.7)</td>
<td>804 (26.1)</td>
</tr>
<tr>
<td><strong>Prior CABG surgery</strong>*</td>
<td>84 (5.4)</td>
<td>69 (4.5)</td>
<td>153 (5.0)</td>
</tr>
<tr>
<td><strong>Prior percutaneous carotid intervention</strong>*</td>
<td>14 (0.9)</td>
<td>29 (1.9)</td>
<td>43 (1.4)</td>
</tr>
<tr>
<td><strong>Prior carotid endarterectomy</strong>*</td>
<td>57 (3.7)</td>
<td>66 (4.3)</td>
<td>123 (4.0)</td>
</tr>
<tr>
<td><strong>Peripheral arterial revascularization</strong>* (noncoronary, noncerebral)***</td>
<td>72 (4.7)</td>
<td>78 (5.1)</td>
<td>150 (4.9)</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass graft; CAD, coronary artery disease; IQR, interquartile range; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

Table 2. Primary and Key Secondary End Points, Intention-to-Treat Population

<table>
<thead>
<tr>
<th>End Point</th>
<th>Total (N = 3080)</th>
<th>Placebo (n = 1544)</th>
<th>Acadesine (n = 1536)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite</strong></td>
<td>151 (5.1)</td>
<td>75 (5.0)</td>
<td>76 (5.1)</td>
<td>1.01 (0.73-1.41)</td>
<td>.94</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>56 (1.8)</td>
<td>27 (1.8)</td>
<td>29 (1.9)</td>
<td>1.08 (0.63-1.83)</td>
<td>.78</td>
</tr>
<tr>
<td><strong>Nonfatal stroke</strong></td>
<td>52 (1.7)</td>
<td>26 (1.7)</td>
<td>26 (1.7)</td>
<td>0.97 (0.54-1.72)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td><strong>Need for mechanical support for SLVD</strong></td>
<td>69 (2.3)</td>
<td>35 (2.3)</td>
<td>34 (2.3)</td>
<td>0.97 (0.60-1.56)</td>
<td>.90</td>
</tr>
<tr>
<td><strong>Key secondary composite</strong></td>
<td>147 (4.9)</td>
<td>73 (4.9)</td>
<td>74 (5.0)</td>
<td>1.01 (0.73-1.41)</td>
<td>.94</td>
</tr>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td>50 (1.6)</td>
<td>24 (1.6)</td>
<td>26 (1.7)</td>
<td>1.09 (0.62-1.90)</td>
<td>.77</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; SLVD, severe left ventricular dysfunction.

*Primary composite is all-cause mortality, nonfatal stroke, or need for mechanical support for SLVD through postoperative day 28.
*Key secondary composite is cardiovascular mortality, nonfatal stroke, or need for mechanical support for SLVD through postoperative day 28.
clamp to prevent ischemic injury. In addition, the agent needs to be present during reperfusion to ensure adequate recovery of the myocardium. The delivery technique may not have provided sufficient concentrations of the agent in the myocardium to alter the recovery from ischemia. However, dosing in our study was identical to that used in previous studies included in the meta-analysis that showed benefit for this drug.27

Recent large analyses of cardiac surgery databases have demonstrated a correlation between enzyme elevations occurring after cardiac surgery and later mortality. In the current study, there was no difference in peak enzyme elevations or the incidence of enzyme elevations 5 times greater than the upper limit of normal between acadesine and placebo. This contrasts with previous trials of acadesine that indicated differences in early mortality and perioperative myocardial infarction within the first 4 postoperative days. The incidence of perioperative myocardial infarction was defined in this trial as an elevation of CK-MB, troponin I, or troponin T level greater than 5 times the upper limit of normal and the presence of new Q-wave myocardial infarction on electrocardiogram. Because of this stricter definition, the overall rate of perioperative myocardial infarction was much lower than that reported in earlier studies (0.6% with placebo and 1.0% with acadesine), and the overall incidence of perioperative myocardial infarction was not significantly different between the 2 groups. Myocardial infarction was an exploratory outcome of the trial, and enzyme levels were only collected through 24 hours. Because of the strict criteria and shorter period of surveillance, the lower incidence is not surprising. In each of the different enzymes assessed (CK-MB, troponin I, or troponin T), there was no significant difference in peak level or the incidence of patients with enzyme level elevations greater than 5 times the upper limit of normal by treatment group (eTable 8).

The results of CABG surgery have continued to improve, as reflected in the excellent outcomes found in this trial. Recent trends in the treatment of coronary artery disease have increased the risks of patients presenting for CABG surgery, without substantial associated increase in morbidity or mortality.32 Observed causes for improvement in postoperative morbidity and mortality are likely multifactorial and may include better preoperative selection and preparation, intraoperative treatment, and postoperative recovery. However, the period of cardiopulmonary arrest is an opportunity to condition the heart and prevent or reverse ischemic/reperfusion injury. Current methods of myocardial protection have markedly improved, but pharmacological additives have not been demonstrated to be beneficial.

Despite the lack of effect of acadesine in this population, the study allowed the evaluation of quality of life after CABG surgery in a large population across many geographical regions. A consistent finding was a preservation of quality of life measured by
the EuroQol 5-dimension instrument at 28 days. There was also substantial improvement in several domains of quality of life (eTable 9). These findings, despite documented complications and the earlier-than-normal period of assessment, suggest that quality of life improves after cardiac surgery—results consistent with previous smaller studies.3,14

CONCLUSIONS

The RED-CABG study demonstrates that among intermediate- to high-risk patients undergoing CABG surgery, acadesine did not reduce all-cause mortality, nonfatal stroke, or need for mechanical support for SLVD through postoperative day 28. The incidence of the primary composite end point was 5%, indicating the need for continued investigation into therapies to reduce perioperative morbidity and mortality. However, effective therapies remain elusive.

Author Contributions: Dr Newman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Newman, Ferguson, Ambrosio, Nussmeier, Pearl, Pitt, Wechsler, Weisel, Reece, Lira, Harrington.

Acquisition of data: Newman, Ferguson, Ambrosio, Nussmeier, Pearl, Pitt, Wechsler, Weisel, Reece, Lira, Harrington.

Analysis and interpretation of data: Newman, Ferguson, White, Ambrosio, Nussmeier, Weisel, Harrington.

Drafting of the manuscript: Newman, Ferguson, Pearl.

Critical revision of the manuscript for important intellectual content: Newman, White, Ambrosio, Koglin, Nussmeier, Pearl, Pitt, Wechsler, Weisel, Reece, Lira, Harrington.

Statistical analysis: White.

Obtained funding: Koglin, Harrington.

Administrative, technical, or material support: Newman, Ferguson, Koglin, Reece, Lira, Harrington.

Study supervision: Newman, Ferguson, Ambrosio, Koglin, Pearl, Harrington.

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Additional Contributions: The RED-CABG Steering Committee and Investigators: A complete list of the RED-CABG site investigators is provided in the eAppendix available at http://jama.jamanetwork.com.

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