

Predictors of contemporary coronary artery bypass grafting outcomes

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Objectives: The study objective was to identify the predictors of outcomes in a contemporary cohort of patients from the Reduction in cardiovascular Events by acadesine in patients undergoing CABG (RED-CABG) trial. Despite the increasing risk profile of patients who undergo coronary artery bypass grafting, morbidity and mortality have remained low, and identification of the current predictors of adverse outcomes may permit new treatments to further improve outcomes.

Methods: The RED-CABG trial was a multicenter, randomized, double-blind, placebo-controlled study that determined that acadesine did not reduce adverse events in moderately high-risk patients undergoing nonemergency coronary artery bypass grafting. The primary efficacy end point was a composite of all-cause death, nonfatal stroke, or the need for mechanical support for severe left ventricular dysfunction through postoperative day 28. Logistic regression modeling with stepwise variable selection identified which prespecified baseline characteristics were associated with the primary outcome. A second logistic model included intraoperative variables as potential covariates.

Results: The 4 independent preoperative risk factors predictive of the composite end point were (1) a history of heart failure (odds ratio, 2.9); (2) increasing age (odds ratio, 1.033 per decade); (3) a history of peripheral vascular disease (odds ratio, 1.6); and (4) receiving aspirin before coronary artery bypass grafting (odds ratio, 0.5), which was protective. The duration of the cardiopulmonary bypass (odds ratio, 1.8) was the only intraoperative variable that contributed to adverse outcomes.

Conclusions: Patients who had heart failure and preserved systolic function had a similar high risk of adverse outcomes as those with low ejection fractions, and new approaches may mitigate this risk. Recognition of patients with excessive atherosclerotic burden may permit perioperative interventions to improve their outcomes. The contemporary risks of coronary artery bypass grafting have changed, and their identification may permit new methods to improve outcomes. (*J Thorac Cardiovasc Surg* 2014;148:2720-6)

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Abbreviations and Acronyms

BM	= bone marrow
CABG	= coronary artery bypass grafting
CVD	= cerebrovascular disease
EF	= ejection fraction
Hct	= hematocrit
HF	= heart failure
Hgb	= hemoglobin
MI	= myocardial infarction
PCI	= percutaneous coronary intervention
POD	= postoperative day
PVD	= peripheral vascular disease
RED-CABG	= Reduction in cardiovascular Events by acaDesine in patients undergoing CABG
SLVD	= severe left ventricular dysfunction

See related commentary on pages 2727-8.

Supplemental material is available online.

Coronary artery bypass grafting (CABG) has evolved remarkably over the last decade. Recent studies have more clearly defined the current indications for CABG distinct from percutaneous coronary interventions (PCIs).^{1,2} Because of the increasing complexity and disability of patients who are referred for CABG rather than PCI,^{3,4} the predictors of the current results of CABG must be periodically updated to account for the changes in patient characteristics and contemporary surgical techniques. To determine the predictors of current outcomes, we evaluated the results in a recently completed multicenter trial of 3080 patients undergoing CABG (Reduction in cardiovascular Events by acaDesine in patients undergoing CABG [RED-CABG] trial).⁵ The goal of this report is to identify the current predictors of CABG outcomes to target interventions to improve the results.^{6,7}

We first determined the preoperative predictors and then evaluated intraoperative variables to assess their added value to predict postoperative adverse outcomes. Innovative approaches to preoperative preparation and new intraoperative techniques may improve outcomes in the future.

METHODS**Study Design and Patient Populations**

The RED-CABG trial (clinicaltrials.gov Identifier: NCT00872001) 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 moderate- to high-risk subjects undergoing nonemergency CABG. All patients in the study underwent CABG with cardiopulmonary bypass, had an increased risk of postoperative adverse events, and met all of the criteria for trial entry. The primary results of the trial were recently reported.⁵ The baseline characteristics are provided in [Table E1](#). Patients requiring urgent, emergency, or salvage CABG were excluded. In addition, patients with preoperative renal dysfunction (serum creatinine level >2 mg/dL or 180 μ mol/L) were specifically excluded to avoid complications associated with acadesine treatment.

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 (POD) 28: all-cause death, nonfatal stroke, or the need for mechanical support for severe left ventricular dysfunction (SLVD). Nonfatal stroke was defined as an acute focal neurologic deficit of sudden onset that was not reversible within 24 hours and was not due to an identifiable nonvascular cause accompanied by clear evidence of a new stroke on brain imaging (computed tomography scan or magnetic resonance imaging). SLVD was defined as the new use of a mechanical circulatory assist device, such as an intra-aortic balloon pump or a ventricular assist device, during or after CABG for at least 1 hour for the treatment of low cardiac output.⁸ Indications for using circulatory assist devices were determined by the attending physician on the basis of his/her clinical judgment and included cardiogenic shock, difficulty 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 syndrome. All efficacy end points except all-cause death were adjudicated by an independent, blinded clinical events committee.

Secondary End Points

The key secondary efficacy end point was the first occurrence of any component of the composite end point occurring during and after CABG surgery through POD 28.

Statistical and Analytic Plans

Logistic modeling was used to assess the prognostic factors for the primary composite end point of the trial through POD 28. Candidate variables for this model were selected on the basis of clinical importance and included age, gender, ejection fraction (EF), extent of coronary artery disease, preoperative evidence of cerebrovascular disease (CVD) (prior stroke, transient ischemic attack, or other CVD; carotid stenosis; carotid endarterectomy; or PCI), history of peripheral vascular disease (PVD) (prior PVD, claudication, or peripheral arterial revascularization), previous coronary intervention (CABG or PCI), history of heart failure (HF), previous myocardial infarction (MI), hypertension, hyperlipidemia, diabetes mellitus, history of cigarette smoking, history of atrial fibrillation/flutter, anemia (hemoglobin [Hgb] <11 g/dL or hematocrit [Hct] <33% before the start of CABG), and the preoperative use of clopidogrel or aspirin. Restricted cubic splines were used to examine the conformity of continuous variables with the assumption of a linear relationship to the outcome. Principle components analysis was used in an effort to consolidate information from multiple sources (eg, for history of PVD). A simple composite indicator was found to be adequate for these categories.

Stepwise selection of covariates from the candidate list of preoperative variables was performed with model inclusion and exclusion criteria of $P = .05$. Wald chi-square P values and odds ratios with 95% confidence intervals were used to summarize the risk associated with the final model covariates. Figures of the adjusted relationship of each factor in the final preoperative model were generated by calculating the predicted probability and 95% confidence interval of each outcome, assuming the median value for all other factors.

In a second stage of the modeling process, intraoperative variables were included along with the significant preprocedure covariates previously selected as potential covariates for a parsimonious model of the primary outcome (a composite of death, SLVD, or nonfatal stroke at POD 28). Stepwise selection was used, using a selection and retention criteria of $P = .05$. The candidate covariates that were considered were age, history of PVD, history of HF, aspirin use before CABG, last Hgb and Hct measurements before CABG end, transfusion of whole blood or packed red blood cells during the CABG procedure, cardioplegia type, temperature and direction (antegrade, retrograde, or combined), number of nonarterial grafts, number of arterial grafts, duration of crossclamp (in hours), duration of CPB (in hours), and atrial fibrillation before completion of the CABG procedure from the electrocardiogram recordings. Statistical analyses were performed by the coordinating center (Duke Clinical Research Institute, Durham, NC) using SAS version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

This multicenter trial provides an overview of current techniques of CABG at multiple institutions in North America and Europe. Table E1 lists the countries where CABG cases were enrolled in this study. Neither country nor continent was predictive of adverse outcomes.

Preoperative Predictors of Outcome After Coronary Artery Bypass Grafting

From the patient’s perspective, the most important outcome of CABG is event-free survival. The primary composite end point of this trial was designed to represent this perspective. The primary composite end point of this trial included all-cause death, nonfatal stroke, or need for mechanical support for SLVD through POD 28. Table E2 outlines the factors evaluated to determine the independent predictors. The statistically significant preoperative predictors of adverse primary outcome (Table 1) included a history of HF, a history of PVD, and age, whereas aspirin use before CABG was protective.

The influence of age on the primary outcome is depicted in Figure 1, assuming the median value of history of HF or PVD (both no) and use of aspirin before CABG (yes). Increasing age was associated with an increased risk of the composite outcome. The estimated composite event rate for patients with and without a history of HF is presented in Figure 2, assuming an age of 66 years, no history of PVD, and aspirin before CABG. HF increased the risk of the composite outcome (Figure 2). Similar results were seen in the adjusted bar graph of patients with and without PVD (Figure 3) and those not receiving aspirin before CABG (Figure 4).

A history of HF was a more powerful predictor of the composite end point than EF. Among the 404 patients with HF, 260 had an EF of 30% or greater, and among the 298 patients with an EF less than 30%, 154 did not have a history of HF. The patients with HF with an EF of 30% or greater had a greater incidence of diabetes mellitus and hypertension than patients with no HF or patients with

TABLE 1. Composite of death, severe left ventricular dysfunction, or nonfatal stroke to postoperative day 28: Independent predictors of the primary composite outcome: All-cause death, need for mechanical support for severe left ventricular dysfunction, or nonfatal stroke to postoperative day 28

Analysis of maximum likelihood estimates				
Parameter	Odds ratio	95% Wald		P value
		confidence limits		
History of HF	2.905	2.006	4.208	<.0001
Age (per 10-y increase)	1.033	1.013	1.053	.0011
History of PVD	1.621	1.115	2.357	.0115
Aspirin before CABG	0.501	0.328	0.766	.0014

CABG, Coronary artery bypass grafting; HF, heart failure; PVD, peripheral vascular disease.

HF and an EF less than 30%, suggesting that these patients may have had diastolic dysfunction. The patients with a low EF who did not have HF had the lowest incidence of diabetes and PVD.

PVD may have contributed to adverse outcomes because of an increased atherosclerotic burden. The majority of patients with PVD (355/483 [73%]) had claudication or previous vascular interventions. Patients with PVD were more likely to be smokers (79%) than patients without PVD (59%).

The rate of the composite outcome was approximately twice as high among patients not receiving aspirin (8.72%) compared with patients receiving aspirin (4.58%) preoperatively. More of the patients taking aspirin preoperatively also were receiving clopidogrel (40% vs 23%), and fewer of the patients taking aspirin were anemic (Hgb <11 or Hct <33) before surgery (16% vs 18%). Clopidogrel was considered as a potential covariate in our model but was not found to be statistically significant

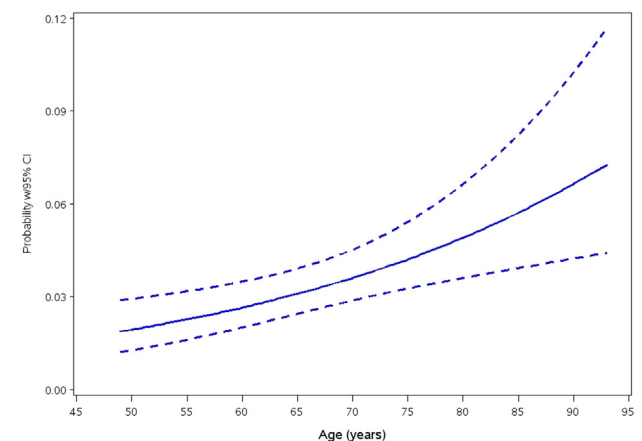


FIGURE 1. Adjusted association between age and primary composite end point. The figure plots increasing age against the estimated event rates for the primary composite outcome, assuming the median value of history of HF (no) and history of PVD (no) and use of aspirin before CABG (yes). Increasing age was associated with an increased risk of the composite outcome. CI, Confidence interval.

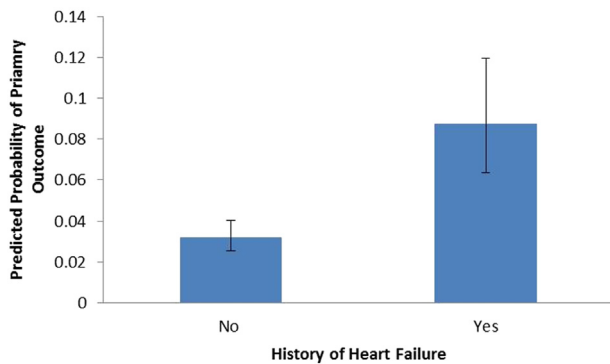


FIGURE 2. Adjusted association between HF and primary composite end point. Estimated event rates for patients with and without a history of HF, assuming an age of 66 years, no history of PVD, and aspirin before CABG. The risk of the composite outcome was greater in patients with HF.

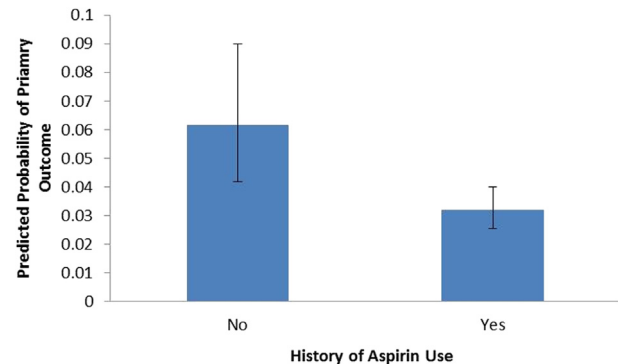


FIGURE 4. Adjusted association between preoperative aspirin and primary composite end point. The estimated event rates for patients with and without preoperative aspirin treatment, assuming an age of 66 years and no history of HF or PVD. The risk of the composite outcome was lower for those who were taking aspirin preoperatively.

unadjusted or after adjustment for other covariates, including aspirin use.

Tables 2-4 summarize the performance of the preoperative predictors of the composite end point when applied to the individual components of death, stroke, and SLVD, respectively. The 4 preoperative predictors of the composite outcome selected by stepwise methods also were significant in modeling early (28-day) mortality. When applied to the stroke component, only the covariates age and a history of PVD were significant. Of note, PVD was more predictive than a history of CVD.

Preoperative and Intraoperative Predictors of Coronary Artery Bypass Grafting Outcome

Although preoperative predictors can be used to counsel patients and their relatives about the risks of surgery, intraoperative predictors may influence decisions about postoperative surveillance and treatments. Therefore, we evaluated candidate predictors considering both

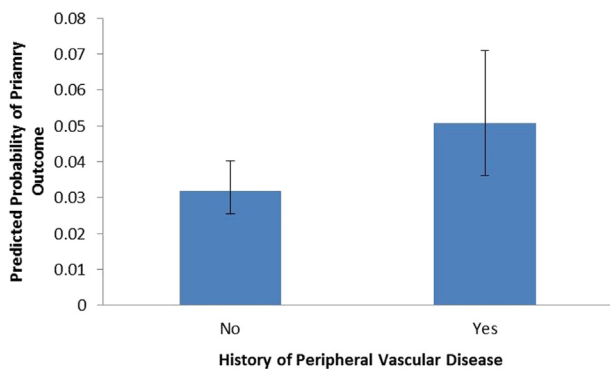


FIGURE 3. Adjusted association between PVD and primary composite end point. The estimated event rates for patients with and without a history of PVD are presented, assuming an age of 66 years, no history of HF, and aspirin before CABG. The risk of the composite outcome was greater in patients with PVD.

preoperative variables previously identified as significant predictors and intraoperative variables, which are listed in Table E2. The results of this analysis are presented in Table 5. In addition to the 4 factors identified as preoperative predictors, the intraoperative factor identified was the duration of the cardiopulmonary bypass.

Factors Not Predictive in the Multivariable Model

Many factors that were previously predictive of CABG outcomes were no longer predictive in this recent cohort (Table E3). Previous PCI was not a univariate predictor of the composite end point ($P = .634$), but previous CABG was a univariate predictor ($P = .036$). Neither previous PCI nor previous CABG was an independent predictor.

Patients with a history of preoperative CVD (35% of the population) had a trend toward a higher incidence of the composite end point (5.91%) compared with those who did not have CVD (4.41%, $P = .063$ by univariate analysis). However, a history of CVD was not as predictive as PVD and was not statistically significant in the multivariable model of the composite end point. Histories of hypertension, hyperlipidemia, diabetes, and smoking were frequent in this CABG population, but did not contribute

TABLE 2. Death at postoperative day 28: Independent predictors of all-cause mortality to day 28

Analysis of maximum likelihood estimates				
Parameter	Odds ratio	95% Wald confidence limits		P value
History of HF	1.929	1.022	3.641	.0428
Age (per 10-y increase)	1.034	1.002	1.067	.0353
History of PVD	1.724	0.954	3.118	.0714
Aspirin before CABG	0.316	0.176	0.566	.0001

CABG, Coronary artery bypass grafting; HF, heart failure; PVD, peripheral vascular disease.

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TABLE 3. Stroke at postoperative day 28: Independent predictors of stroke to day 28

Analysis of maximum likelihood estimates				
Parameter	Odds ratio	95% Wald confidence limits		P value
History of HF	1.288	0.621	2.672	.4966
Age (per 10-y increase)	1.036	1.003	1.070	.0308
History of PVD	1.926	1.058	3.504	.0320
Aspirin before CABG	0.855	0.382	1.915	.7032

CABG, Coronary artery bypass grafting; HF, heart failure; PVD, peripheral vascular disease.

significantly to the final model. Preoperative atrial fibrillation was more common among patients who experienced the composite outcome (13%) compared with those who did not (8%, $P = .018$), but that history was not an independent predictor. In some patients, atrial fibrillation may have been a late manifestation of HF with cardiac dilatation. Preoperative anemia (Hgb <11 or Hct <33) was found in 16% of the patients, and the anemic patients had a higher proportion of the composite outcome, 7.4% (33/445 patients) compared with 4.6% for the nonanemic patients (118/2297, $P = .016$).

Potentially important predictors of outcome that were not in the final models included not only preoperative anemia but also intraoperative Hgb concentrations and transfusions (Table E3), and none were independently predictive of outcomes. A variety of myocardial protection techniques were used, but none of the alternative approaches independently influenced the outcomes.

DISCUSSION

This report documents the risk factors predictive of adverse events in a large contemporary multinational series of patients undergoing CABG from the RED-CABG trial. The 4 independent preoperative predictors of the composite end point (at 28 days: death, nonfatal stroke, and SLVD) were (1) a history of HF; (2) age; (3) a history of PVD; and (4) not receiving aspirin before CABG. Many of the risk factors that were important in previous eras of CABG surgery were no longer significant in this contemporary report. A remarkable finding was the low rates of mortality

TABLE 4. Severe left ventricular dysfunction at postoperative day 28: Independent predictors of need for mechanical support for severe left ventricular dysfunction to day 28

Parameter	Odds ratio	95% Wald confidence limits		P value
History of HF	6.470	3.969	10.547	<.0001
Age (per 10-y increase)	1.013	0.985	1.041	.3731
History of PVD	1.043	0.577	1.883	.8903
Aspirin before CABG	0.478	0.260	0.881	.0181

CABG, Coronary artery bypass grafting; HF, heart failure; PVD, peripheral vascular disease.

TABLE 5. Independent predictors of composite outcome including preoperative and intraoperative variables

Analysis of maximum likelihood estimates				
Parameter	Odds ratio	95% Wald confidence limits		P value
History of HF	2.731	1.871	3.986	<.0001
Duration of CPB	1.774	1.460	2.156	<.0001
Age (per 10-y increase)	1.039	1.019	1.059	.0001
Aspirin before CABG	0.445	0.288	0.686	.0002
History of PVD	1.677	1.147	2.451	.0076

CABG, Coronary artery bypass grafting; HF, heart failure; PVD, peripheral vascular disease; CPB, cardiopulmonary bypass.

and morbid events, which were consistent across the contributing sites. Careful attention to these preoperative risk factors may identify methods to further reduce the risks of CABG. Awareness of these risk factors may alter perioperative approaches, such as ensuring that nearly all patients receive preoperative aspirin. We also evaluated intraoperative variables and found that prolonged bypass time was predictive of more postoperative complications. Efforts to avoid complications that extend bypass duration may improve outcomes.

In this study, HF but not EF was an independent risk factor for adverse outcomes. Patients with HF but preserved systolic function are increasingly recognized as high risk for morbidity and mortality with revascularization,^{9,10} but the influence of this condition on the outcomes of CABG has been infrequently described. Hypertensive and diabetic patients have a greater prevalence of HF despite preservation of systolic function, and dyspnea or fatigue may result from left ventricular diastolic dysfunction.¹⁰ Therefore, cardiac surgeons should pay particular attention to patients with HF with preserved systolic function. Careful preoperative assessment may identify the underlying cardiac diastolic dysfunction and pulmonary, endocrine, or renal abnormalities that would permit interventions to mitigate this important risk factor. Attention to meticulous myocardial protection and expeditious operations may improve outcomes in this population. Reducing the intraoperative crystalloid load may reduce early postoperative cardiac edema and improve outcomes in these patients.^{11,12} Incomplete protection and prolonged procedures increase postoperative cardiac edema,^{11,12} which could exacerbate diastolic dysfunction and increase the risks of postoperative adverse events.

The increasing age of those presenting for CABG^{3,7} mirrors the aging population, which is anticipated to continue to increase in the next decade. The reasons for the increased risk in older patients have not been fully elucidated, but stem cell dysfunction in older patients undergoing CABG may contribute to their limited healing capacity.^{13,14} The recent National Institutes of Health Effectiveness of Stem Cell Treatment for Adults With

Ischemic Cardiomyopathy (the FOCUS Study) by the Cardiovascular Cell Therapy Research Network (CCTR) trial¹⁵ documented the bone marrow (BM) stem cell dysfunction in older patients with poor ventricular function after an MI. The number of patients with active BM stem cells was found to decrease with increasing age, but some elderly patients had active BM stem cells and some younger patients did not.^{16,17} In the near future, we may be able to identify patients who have stem cell dysfunction and rejuvenate their BM stem cells to restore their reparative capacity.^{13,14,16,17}

The increased risk in those who did not receive aspirin preoperatively has been reported. In a prospective placebo-controlled randomized trial of preoperative aspirin, Deja and colleagues¹⁸ followed patients for up to 6 years after CABG and found that preoperative aspirin decreased both the risk of a major cardiac events (MI or repeated revascularization, $P = .046$) and the composite of death, MI, or revascularization ($P = .06$). Bybee and colleagues¹⁹ retrospectively reviewed 1636 patients undergoing primary CABG and reported that preoperative aspirin reduced the hospital mortality ($P = .007$) without increasing the risk of bleeding. Mangano²⁰ reported that aspirin administration before or within 48 hours after revascularization surgery was associated with a 68% reduction in overall mortality and substantially reduced the rates of ischemic complications in the heart (44% reduction in fatal and nonfatal MI or congestive HF), the brain (62% reduction in fatal and nonfatal stroke or encephalopathy), the kidneys (60% reduction in renal dysfunction or failure), and the intestines (70% reduction in ischemia or infarction). Therefore, the benefits of preoperative and early postoperative aspirin are well supported.

Previous studies documented the detrimental influence of PVD on CABG outcomes. Both the Syntax Trial²¹ and the study by Algarni and colleagues³ found that PVD was an independent predictor of adverse long-term outcomes after CABG. In addition to mortality, patients with an extensive atherosclerotic burden have an increased risk of stroke, perhaps because aortic atherosclerosis is a source for cerebral emboli.²² PVD, and not a history of CVD, was an independent determinant of stroke, perhaps because patients with CVD had preoperative interventions (eg, carotid stenting or carotid endarterectomy surgery) or received careful intraoperative monitoring (including increased perfusion pressures on bypass), which may have reduced their risk of stroke with CABG.²³ However, patients with extensive aortic atherosclerosis have an increased risk of stroke with any surgical approach that requires aortic manipulation.²²

Prolonged CPB time has been reported to correlate with adverse outcomes.^{3,7} Reasons for prolonged CPB times include operator facility, intraoperative problems with diffuse coronary disease that may strain the capability of

myocardial protection, bleeding due to tissue disruption, or early ventricular dysfunction requiring multiple interventions before separation from the bypass circuit. Extended efforts to control bleeding or repair disrupted friable tissues may be associated with adverse outcomes. Awareness of the adverse influence of prolonged CPB duration may permit surgical teams to avoid time-consuming complications.

The initial report of this trial indicated that the majority of patients were within the highest 3 quintiles of the Society of Thoracic Surgeons risk score. This report provides additional risk prediction to that achieved with the Society of Thoracic Surgeons calculator.

Predictors of CABG outcomes that were previously important were not significant in this study because of the limited power of the study or changes to current surgical techniques. Preoperative anemia was previously reported to increase the risk of CABG.²⁴ This trial excluded patients undergoing urgent CABG or within 5 days of an MI, and these patients contributed to many of the anemic patients in previous reports. In this series of mostly elective but moderately high-risk patients, preoperative anemia, intraoperative anemia, and the need for blood transfusions were not independently predictive of outcomes.

A recent meta-analysis found that blood was superior to crystalloid cardioplegia and that tepid was better than warm blood cardioplegia in most randomized clinical trials.²⁵ However, although bypass time was an independent predictor, the type of myocardial protection was not significantly associated with adverse outcomes. Either this study lacks sufficient power to distinguish among the various cardioplegic combinations or cardiac surgeons have optimized their approaches to myocardial protection and developed permutations of temperature, composition, and delivery to meet the needs of each individual patient, such that none of the individual approaches are no longer predictive of outcomes. We were surprised to find little regional variation in the primary outcomes of the trial, and region was not a univariable or multivariable predictor of any of the outcomes studied. In addition, we did not find that diabetes mellitus added to the early risk of adverse outcomes, similar to the report of the FREEDOM Trial.⁴ Consistent with recent reports, hypertension, hyperlipidemia, smoking, and a history of atrial fibrillation did not influence early outcomes of CABG, although these factors will have an effect on intermediate- and long-term outcomes.¹⁻⁴ Left main stenosis, reoperative CABG, and previous PCI have not been important predictors for many years.^{1-4,26}

Study Limitations

A major limitation of this report is that the trial was intended to evaluate the effects of acadesine and not to determine the predictors of adverse outcomes. However, the investigators initiated this substudy to use the extensive

data collected in this large trial. Another limitation of the current study is the lack of inclusion of patient populations commonly seen by cardiac surgeons, including those undergoing combined valve and CABG surgery, and those with recent MI. However, the uniform patient characteristics and large multinational patient population provide current predictors and permit the identification of interventions to modify adverse outcomes.

CONCLUSIONS

This study provides a snapshot of the predictors of adverse outcomes in a large contemporary cohort of patients undergoing CABG. The independent preoperative predictors of adverse outcome were preexisting HF, PVD, advancing age, and no preoperative aspirin. As anticipated, age and PVD predicted stroke, whereas a history of HF predicted SLVD. This information identifies new targets for quality improvement that may further reduce the risks of CABG surgery.

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ROLE OF THE SPONSOR

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TABLE E1. Baseline characteristics

Characteristic	N = 3080
Age, y	
Mean (SD)	66.5 (8.6)
Median (IQR)	66.0 (60.0-73.0)
Sex, no. (%)	
Women	1042 (33.8)
Men	2038 (66.2)
Race/ethnicity, no. (%)	
White	2687 (91.8)
Nonwhite	240 (8.2)
Body weight, kg	
Mean (SD)	86.5 (19.5)
Median (IQR)	85.0 (73.0-98.0)
Country of enrollment, no. (%)	
Canada	303 (9.8)
France	152 (4.9)
Germany	446 (14.5)
Italy	105 (3.4)
The Netherlands	13 (0.4)
Spain	75 (2.4)
United States	1986 (64.5)
Cardiovascular history, no. (%)	
Hypertension	2727 (88.6)
History of cigarette smoking	1916 (62.3)
Hyperlipidemia	2656 (86.3)
Diabetes mellitus	1866 (60.6)
Family history of CAD	1143 (49.0)
Prior MI	1487 (48.4)
Prior angina	1696 (55.1)
Prior stroke	302 (9.8)
Prior transient ischemic attack	186 (6.0)
Prior known carotid stenosis $\geq 50\%$	373 (12.1)
Other CVD	53 (1.7)
Prior PVD	483 (15.7)
Claudication	278 (9.0)
HF	408 (13.3)
History/presence of AF or atrial flutter	251 (8.2)
Prior PCI	803 (26.1)
Prior CABG surgery	153 (5.0)
Prior percutaneous carotid intervention	43 (1.4)
Prior carotid endarterectomy	123 (4.0)
Peripheral arterial revascularization (noncoronary, noncerebral)	150 (4.9)

AF, Atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVD, cerebrovascular disease; HF, heart failure; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation.

TABLE E2. Intraoperative univariate predictors of the composite end point and each component

Variable name	28-day composite	28-day death	28-day NF-stroke	28-day SLVD
Last Hct before CABG end	0.0172	0.2709	0.0187	0.9012
Last Hgb before CABG end	0.0217	0.0301	0.3501	0.4591
Transfusion	0.0723	0.3065	0.1469	0.0002
Cardioplegia type	0.2771	0.4315	0.8504	0.7492
Cardioplegia temperature	0.2232	0.7941	0.2543	0.1638
Cardioplegia delivery method	0.2975	0.5373	0.9139	0.0262
No. of venous grafts	0.9651	0.4408	0.4583	0.0455
No. of arterial grafts	0.5038	0.9096	0.8060	0.0732
Duration of crossclamp (h)	0.1890	0.1172	0.5542	0.0139
Duration of CPB (h)	<0.0001	<0.0001	0.6084	<0.0001
Atrial fibrillation before CABG end, per ECG	0.0112	0.1199	0.4285	0.2348

The final model included 5 covariates and had a C-index of $C = 0.696$ (better than the preoperative model, which had a C-Index of 0.66) based on $N = 2897$ observations. The Hosmer-Lemeshow test for lack of fit was nonsignificant (chi-square = 4.98, $P = .76$). CABG, Coronary artery bypass grafting; CPB, cardiopulmonary bypass; ECG, electrocardiogram; Hct, hematocrit; Hgb, hemoglobin; NF, nonfatal; SLVD, severe left ventricular dysfunction.

TABLE E3. Univariate predictors of the composite end point and each component

Variable name	28-day composite	28-day death	28-day NF-stroke	28-day SLVD
Age at randomization	0.0005	0.0219	0.0237	0.2605
Male gender	0.0352	0.0220	0.8985	0.3458
EF	0.0001	0.0512	0.7071	<0.0001
No. of diseased vessels	0.3767	0.6327	0.7616	0.0398
LMT >50% stenosis	0.4494	0.2920	0.5172	0.2027
Evidence of preoperative CVD	0.0639	0.1760	0.0168	0.6818
History of PVD	0.0022	0.0425	0.0216	0.4597
Prior PCI	0.6341	0.1901	0.6108	0.9869
Prior CABG	0.0390	0.1778	0.7037	0.0030
Prior HF	<0.0001	0.0321	0.3919	<0.0001
Prior MI	0.6951	0.8119	0.6302	0.1111
Hypertension	0.5646	0.3165	0.4013	0.4131
Hyperlipidemia	0.7015	0.0366	0.6724	0.9032
Diabetes	0.8224	0.9903	0.1234	0.2254
Smoking	0.3052	0.0576	0.9178	0.6262
Prior atrial fibrillation	0.0201	0.0352	0.1622	0.8653
Aspirin before CABG	0.0012	<0.0001	0.6592	0.0230
Clopidogrel before CABG	0.6031	0.6161	0.3835	0.7100
Anemia before CABG	0.0168	0.0893	0.2377	0.3693

The final preoperative model had a C-index of 0.66, and the discrimination slope for the model was 0.029. Hosmer-Lemeshow chi-square = 7.78, $P = .46$. CABG, Coronary artery bypass grafting; CVD, cerebrovascular disease; EF, ejection fraction; HF, heart failure; LMT, left main trunk; MI, myocardial infarction; NF, nonfatal; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SLVD, severe left ventricular dysfunction.