Sodium-hydrogen exchange inhibition by cariporide to reduce the risk of ischemic cardiac events in patients undergoing coronary artery bypass grafting: results of the EXPEDITION study.

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Sodium-Hydrogen Exchange Inhibition by Cariporide to Reduce the Risk of Ischemic Cardiac Events in Patients Undergoing Coronary Artery Bypass Grafting: Results of the EXPEDITION Study

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Background. **The EXPEDITION study addressed the efficacy and safety of inhibiting the sodium hydrogen exchanger isoform-1 (NHE-1) by cariporide in the prevention of death or myocardial infarction (MI) in patients undergoing coronary artery bypass graft surgery. The premise was that inhibition of NHE-1 limits intracellcular Na accumulation and thereby limits Na/Ca-exchanger–mediated calcium overload to reduce infarct size.**

Methods. **High-risk coronary artery bypass graft surgery patients (n = 5,761) were randomly allocated to receive either intravenous cariporide (180 mg in a 1-hour preoperative loading dose, then 40 mg per hour over 24 hours and 20 mg per hour over the subsequent 24 hours) or placebo. The primary composite endpoint of death or MI was assessed at 5 days, and patients were followed for as long as 6 months.**

Results. **At 5 days, the incidence of death or MI was reduced from 20.3% in the placebo group to 16.6% in the treatment group ($p = 0.0002$). Paradoxically, MI alone declined from 18.9% in the placebo group to 14.4% in the treatment group ($p = 0.000005$), while mortality alone increased from 1.5% in the placebo group to 2.2% with cariporide ($p = 0.02$). The increase in mortality was associated with an increase in cerebrovascular events. Unlike the salutary effects that were maintained at 6 months, the difference in mortality at 6 months was not significant.**

Conclusions. **The EXPEDITION study is the first phase III myocardial protection trial in which the primary endpoint was achieved and proof of concept demonstrated. As a result of increased mortality associated with an increase in cerebrovascular events, it is unlikely that cariporide will be used clinically. The findings suggest that sodium hydrogen exchanger isoform-1 inhibition holds promise for a new class of drugs that could significantly reduce myocardial injury associated with ischemia-reperfusion injury.**

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The EXPEDITION (for Na+/H+ Exchange inhibition to Prevent coronary Events in acute cardiac condition) study addressed the efficacy and safety of inhibiting the sodium hydrogen exchanger (NHE) by cariporide in the prevention of death or nonfatal myocardial infarction (MI) in patients undergoing coronary artery bypass grafting (CABG). The premise was that inhibition of the NHE-1 isoform (NHE-1) limits intracellular Na accumulation and thereby limits Na/Ca exchanger mediated calcium overload to reduce infarct size.

With more than 1 million interventions per year worldwide, CABG is one of the most common surgical procedures performed today [1]. The benefits of CABG are partially offset by periprocedural ischemic events manifesting themselves as myocardial stunning or myocardial necrosis and can result in significant morbidity and mortality [2, 3]. Inadequate myocardial protection and ischemia/reperfusion injury remain major problems after CABG. Despite intensive research toward the development of more effective agents, a specific drug that unequivocally reduces the incidence or magnitude of peri-

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*Investigators and centers participating in the trial are listed in the Appendix.

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operative myocardial necrosis after CABG is lacking [4]. Although many have been proposed, drugs that activate the sodium-proton exchange systems have received considerable attention.

Cariporide, a NHE-1 inhibitor, has been shown experimentally to reduce intracellular calcium overload and prevent myocardial injury associated with ischemia/reperfusion (provide reference or clarification). Ischemia/reperfusion has been shown to increase intracellcular Na concentration. This occurs in part as a result of increased Na entry through NHE-1. The increase in intracellular Na concentration contributes to a reversal of the driving force for the sodium-calcium exchanger to increase net entry of Ca through the sodium-calcium exchanger and thereby increase cytosolic calcium concentration, leading to intracellular calcium overload [5, 6]. These results served as the rationale for the GUARDIAN trail, a study performed to evaluate the efficacy of cariporide in reducing myocardial injury in patients with unstable angina and those undergoing either percutaneous coronary intervention or CABG [7]. Although it failed to meet the study endpoint, this trial did suggest the drug was safe and cardioprotective in patients undergoing CABG. The EXPEDITION trial was conducted to confirm whether treatment with cariporide could reduce the incidence of death or nonfatal MI in patients undergoing CABG.

Material and Methods

Inclusion and Exclusion Criteria

Patients more than 18 years of age with an indication for CABG and presenting with risk factors for perisurgical ischemic events were invited to participate in this study at 235 centers in 26 countries worldwide. Inclusion criteria was a multivessel disease, a history of recent (<4 weeks) angina at rest or minimal exercise, and at least one additional risk factor (age > 65 years, female sex, diabetes mellitus, or left ventricular ejection fraction < 35%).

The clinical study protocol and informed consent documents were reviewed and approved by the Institutional Review Board at each study center. Signed informed consent was obtained from each study participant before enrollment. The study was conducted in accordance with good clinical practice as indicated in the Declaration of Helsinki [8].

Treatment Regimen

On enrollment, central telephone randomization (ClinPhone, Princeton, New Jersey) was used to assign patients to receive either cariporide or matching placebo in a double-blind fashion. The study medication was given as a continuous intravenous infusion for a total of 49 hours, beginning 2 hours before induction of anesthesia. A 1-hour loading infusion of placebo or 180 mg cariporide was followed by a maintenance infusion over 48 hours (placebo or 40 mg/h cariporide for the first 24 hours and placebo or 20 mg/h cariporide for the second 24 hours; subjects weighing < 50 kg received placebo or 20 mg/h cariporide over the entire 48-hour period).

Study Endpoints

The primary objective of the study was to demonstrate that cariporide reduces the composite endpoint of all-cause mortality or nonfatal MI by day 5, day 30, and month 6. The safety and tolerability of cariporide was assessed descriptively by frequency of adverse events (AE), changes in laboratory variables and postsurgical functional recovery.

Study Procedures

Upon enrollment, a complete physical examination, 12-lead electrocardiogram, standard laboratory assessment, and total creatine kinase–myocardial band (CK-MB) isoenzyme measurements were performed. During the treatment and follow-up phase, electrocardiograms were performed 24, 48, and 72 hours after surgery and also on day 5, day 30, and month 6 follow-up visits. Serial serum CK-MB values were obtained 4, 8, 12, 18, 24, 36, and 48 hours after intensive care unit arrival and whenever an ischemic event was suspected. The diagnosis of Q-wave MI was determined by electrocardiogram criteria of a two-step Q-wave change as defined by the Minnesota code with the Nova-code adjustment [9]. In the absence of a new Q wave, CK-MB elevation more than tenfold the upper limits of normal (ULN) range of the investigator's local laboratory within 24 hours of CABG was considered indicative of a non–Q-wave MI. If MI was suspected more than 24 hours after CABG, a CK-MB elevation greater than two times the ULN with chest pain or an elevation greater than three times ULN was considered indicative of MI. In addition, CK-MB values and electrocardiograms from all patients were screened for the presence of previously unreported "database-identified MI."

Statistical Procedures

Efficacy analyses were performed on all randomly allocated patients. Safety analyses were performed on all patients who received any amount of cariporide. An unadjusted χ^2 statistic was used for the primary efficacy analysis. The secondary endpoint analysis used survival analysis methodology (Gehan-Wilcoxon test and Kaplan-Meier curves). Descriptive analyses are provided and p values given where appropriate. The planned sample size of 7,000 assumed a 12% primary event rate at day 5 for the placebo group and a 20% relative risk reduction in the cariporide treatment arm, a two-sided type 1 error rate of 5%, and power approximately 90%. The protocol specified rules for the conduct of the interim analyses by the Data Safety Management Board to allow stopping the study early for overwhelming evidence of efficacy or for futility [10, 11]. Rules for early termination for efficacy required a nominal significance level of 0.00001 with demonstration of reduction in risk for both components of the primary endpoint (death or nonfatal MI by day 5). The Data Safety Management Board also assessed the overall safety profile to determine study continuation,

Table 1. Baseline Characteristics of Subjects by Treatment Group (Intent to Treat Population)

	Placebo n = 2,891 (% = 100.0)		Cariporide n = 2,870 (% = 100.0)	
Characteristic	Number of Patients	(%)	Number of Patients	(%)
Sex				
Male	2,108	(72.9)	2,071	(72.2)
Female	783	(27.1)	799	(27.8)
Age (years)				
<55	262	(9.1)	282	(9.8)
55 to <65	611	(21.1)	585	(20.4)
65 to <75	1,338	(46.3)	1,359	(47.4)
≥75	680	(23.5)	644	(22.4)
Race				
Caucasian	2,783	(96.3)	2,739	(95.4)
Black	51	(1.8)	56	(2.0)
Asian/Oriental	45	(1.6)	54	(1.9)
Multiracial	12	(0.4)	21	(0.7)
Smoker (past/present)	1,700	(58.8)	1,704	(59.4)
Obese (>30 kg/m^2)	856	(29.6)	900	(31.4)
Medical history				
History of myocardial infarction	1,384	(47.9)	1,435	(50.0)
Congestive heart failure	294	(10.2)	283	(9.9)
Diabetes mellitus (any)	1,141	(39.5)	1,136	(39.6)
Cerebrovascular disease	342	(11.8)	341	(11.9)
Peripheral vascular disease	476	(16.5)	492	(17.1)
Unstable angina	1,737	(60.1)	1,767	(61.6)
Prior cardiac interventions				
PCTA, no stent	174	(6.0)	192	(6.7)
PCTA, with stent	319	(11.0)	288	(10.0)
CABG	337	(11.7)	342	(11.9)

CABG = coronary artery bypass grafting surgery; PCTA = percutaneous coronary transluminal angioplasty.

modification, or termination based on evidence that cariporide conveyed undue risk.

Results

Patients were enrolled into EXPEDITION from July 24, 2001, through July 23, 2002, when the Data Safety Management Board recommended termination of the study. A total of 5,761 subjects were randomly assigned during this period. The early termination was based on the assessment of the benefits and risks on occasion of the second planned interim analysis. At that time, a marked reduction in the incidence of MI at day 5 was observed. That was offset by an increase in mortality and the number of persistent CVEs in cariporide-treated patients. Upon termination of the study, follow-up was completed and findings were reviewed. Accordingly, access to unblinded follow-up data continued to be limited until completion of month 6.

Baseline Demographics

Baseline characteristics were well balanced between the two groups (Table 1). Eighty percent of patient procedures were considered elective CABG, 11% elective repeat surgery, and 9% urgent CABG. Compliance with study drug administration was high and also balanced between the treatment groups. Main reasons for premature discontinuations were technical reasons (3% in both arms). Early death or termination due to renal insufficiency accounted for termination in less than 1% of subjects in either group. Adverse events (AEs) resulted in premature termination in 0.9% versus 1.2% of subjects in the placebo and cariporide group, respectively ($p = 0.32$).

Surgical Procedures

On-pump CABG procedures were performed on 93.7% of patients, and 5.5% of patients received off-pump CABG. Only 0.8% of patients did not have a CABG for varied reasons (Table 2). Blood cardioplegia was used in 53.5% of patients with a higher frequency of blood cardioplegia used in the United States (75%). Crystalloid cardioplegia was used in the remainder of patients who underwent on-pump CABG.

Efficacy

The study achieved its primary objective by demonstrating a decrease in the incidence of death or nonfatal MI with cariporide at day 5 from 20.3% to 16.6%, an 18.28%

Table 2. Death/Myocardial Infarction at Day 5—Subgroup Analyses

Variable	Placebo (n = 2,891)		Cariporide (n = 2,870)		*p* Value (χ^2)
	Number of Patients	(%)	Number of Patients	(%)	
CABG category					
Elective CABG	2,329	(17.6)	2,303	(14.9)	0.014
Repeat CABG	327	(33.6)	316	(28.2)	0.13
Urgent CABG	235	(28.9)	251	(17.5)	0.003
CABG type					
On pump	2,730	(20.9)	2,715	(17.0)	0.0002
Off pump	161	(11.2)	155	(12.3)	0.77
Other					
No diabetes	1,757	(22.1)	1,636	(17.0)	0.0001
Diabetes	1,134	(17.6)	1,234	(16.0)	0.31
LVEF > 35%	2,022	(20.6)	2,023	(17.1)	0.067
LVEF < 35%	267	(22.5)	271	(16.2)	0.067
LVEF n/available	602	(18.6)	576	(15.1)	0.11
One- or 2-vessel disease	359	(14.8)	379	(15.4)	0.81
Triple-vessel disease (n)	2,518	(21.1)	2,467	(16.8)	0.0001
Isolated left main disease	14	(15.4)	24	(12.5)	0.81
Type of cardioplegia					
Blood cardioplegia	1,475	(23.3)	1449	(17.5)	0.0001
Crystalloid cardioplegia	1,255	(16.8)	1266	(15.7)	0.42
None/other	161	(11.2)	155	(12.3)	0.77

CABG = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction.

relative risk reduction (RRR [$p = 0.0003$; Fig 1]). At day 30 and month 6, the incidence of death or nonfatal MI was decreased, respectively from 21.8% to 18.3% (RRR = 16.1%; $p = 0.0009$) and from 23.9% to 20.2% (RRR = 15.7%; $p = 0.0006$). The reduction of death or nonfatal MI occurred early and persisted throughout the 6-month follow-up period (Fig 2). When the individual components of the composite endpoint were analyzed separately, however, the findings were divergent. With respect to the incidence of nonfatal MI, cariporide treatment was associated with a decrease at day 5 from 18.9% to 14.4% (RRR = 23.8%; $p = 0.000005$), at day 30 from 18.6% to 13.9% (RRR = 25.2%; $p = 0.000002$), and at month 6 from 18.5% to 13.8% (RRR = 25.6%; $p = 0.000001$; Fig 3). Analysis of the mortality at day 5 revealed that the rate increased from 1.5% in the placebo group to 2.2% with cariporide (RRR = −53.5%; $p = 0.028$; Fig 4). At day 30 and month 6, treatment was associated with an in-

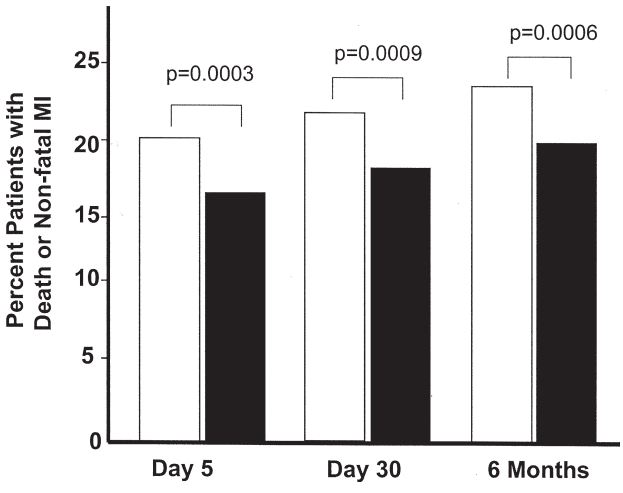

Fig 1. Proportion of patients experiencing the composite endpoint of death or nonfatal myocardial infarction (MI) in the placebo group (white bars [n = 2,891]) and cariporide-treated group (black bars [n = 2,870]). The EXPEDITION trial achieved primary endpoint by demonstrating a significant reduction in the incidence of death or nonfatal MI after coronary artery bypass graft surgery.

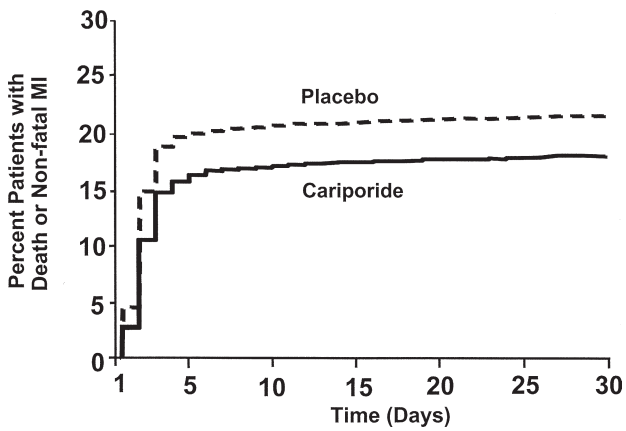

Fig 2. Time to death or nonfatal myocardial infarction (MI) in the placebo and cariporide groups. The divergence in the postoperative incidence of death/nonfatal MI occurred primarily within the first 3 days of treatment.

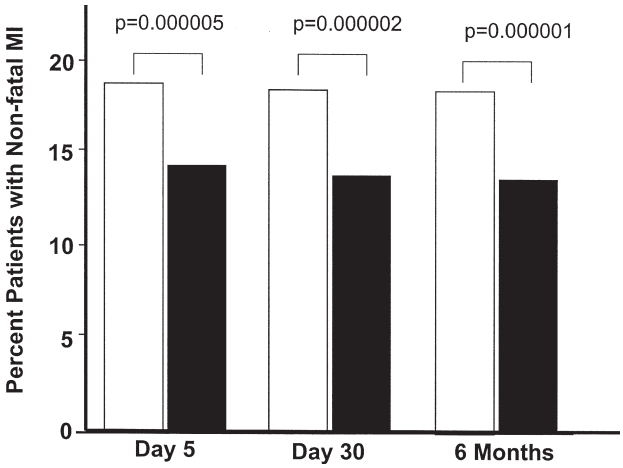

Fig 3. Cariporide treatment and incidence of nonfatal myocardial infarction (MI) after coronary artery bypass graft surgery. (White bars = placebo [n = 2,891]; black bars = cariporide-treated group [n = 2,870]). Inhibition of the sodium hydrogen exchanger (NHE) was associated with a markedly significant reduction in MI after coronary artery bypass graft surgery.

crease in mortality from 3.2% to 4.4% (RRR = −36.5%; $p = 0.020$), and 5.4% to 6.4% (RRR = −18.2; $p = 0.11$), respectively. The difference in mortality at 6 months was not significant.

Although a reduction in the composite endpoint was observed in virtually all subgroups, the imbalance in mortality against cariporide was also present in those subgroups (data not shown). In the subgroup findings, cariporide treatment was associated with a lower incidence of death or nonfatal MI in nondiabetic patients versus diabetic patients at day 5, 22.1% in the placebo group versus 17.0% in the cariporide group. Additionally, lower incidence of death or nonfatal MI was observed in patients receiving blood cardioplegia versus crystalloid cardioplegia as well as patients receiving on-pump versus off-pump strategies (Table 2). It should be noted that assignment to the different cardioplegic and on pump strategies was not randomized, and thus data should be interpreted with caution.

Regarding the effect on MI, a reduction in both Q-wave MI (RRR = 23.5%; $p = 0.013$) and non–Q-wave MI (RRR = 20.6%; $p = 0.002$) was observed (Table 3). It is noteworthy that in this population at increased risk of myocardial injury, the incidence of Q-wave MI at day 5 in the placebo group was quite high, 6.5%. As a measure of the extent of the infarction, the peak CK-MB ratio was assessed in prespecified categories and confirmed a smaller extent of injury in cariporide-treated patients ($p = 0.027$). Patients in the cariporide group had a higher incidence of no or minor myocardial injury (CK-MB ≤ ULN, or as high as five times ULN, respectively), and fewer large infarcts. Patients with cardiovascular death were captured as a separate group in the analysis and demonstrated the imbalance against the cariporide group already noted for the overall population.

Of the 5,761 patients randomized, all patients treated with cariporide were analyzed for safety. Mean duration of treatment showed no clinically relevant differences between treatment groups. The frequency of drug discontinuation due to AEs was similar in the two treatment arms. Patients in both arms had high overall frequency of AEs; the majority occurred during the treatment (Table 4).

To facilitate a uniform analysis of AEs, AEs were grouped according to "AEs of special interest at 6 months" (SAE [Table 4]). Cardiac arrhythmia, both in respect to overall AE and SAE, was balanced between the treatment groups. The incidence of atrial fibrillation/flutter was 28.5% with placebo compared with 26.7% with cariporide (data not shown). Acute renal failure AEs were more frequently observed in the cariporide group(13.1%) than in the placebo group (11.4%), and SAEs of acute renal failure were also slightly more frequent (4.4% versus 3.1%). The majority of renal SAEs in both groups either resolved completely or persisted but no further follow-up was required. Twelve of 89 patients (13.5%) with renal failure in the placebo group died compared with 18 of 124 (14.5%) in the cariporide group. Events associated with liver toxicity were observed with similar frequency in both groups. In contrast, the patients in the cariporide group experienced a higher incidence of both nonserious and serious altered mental status. The overall incidence of AEs was 12.7% in the placebo group versus 17.7% in the cariporide group, for an overall incidence of SAEs of 0.9% in the placebo versus 1.7% in the cariporide group. A marked increase was observed in the overall incidence of CVEs, specifically, 86 events (3.0%) were observed in the placebo group compared with 146 (5.2%) in the cariporide group. The vast majority of events in both groups were reported as SAEs.

An analysis of focal persistent CVE occurring during the observation period was reviewed by a blinded panel of neurologic and cardiac surgery experts (Table 5). Nearly all of these CVEs were of an ischemic nature. A higher frequency of embolic strokes occurred in the cariporide group (41 versus 21 events). However, in about

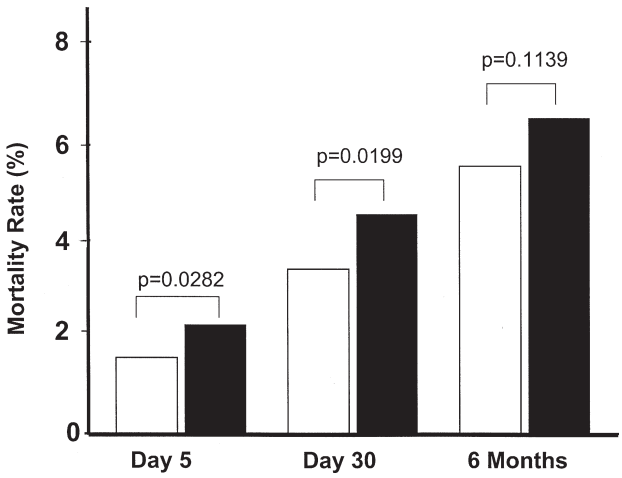

Fig 4. Cariporide treatment and effect on mortality after coronary artery bypass graft surgery. (White bars = placebo [n = 2,891]; black bars = cariporide-treated group [n = 2,870]).

Table 3. Details of Myocardial Infarction

Variable	Placebo n = 2,891 (% = 100.0) Number of Patients	(%)	Cariporide n = 2,870 (% = 100.0) Number of Patients	(%)	Relative Risk (95% CI)	*p* Value (χ^2)
All MI by day 5	562	(19.4)	439	(15.3)	21.31	0.0001
Q-wave MI	187	(6.5)	142	(4.9)	23.51	0.013
Non–Q-wave MI	369	(12.8)	291	(10.1)	20.56	0.002
Peak CK-MB ratio[a]						
Number with data	2,862	(99.0)	2,820	(98.3)	—	—
CK-MB ≤ ULN	142	(4.9)	167	(5.8)	—	—
>ULN to ≤5 × ULN	1,659	(57.4)	1,704	(59.4)	—	—
5 × ULN to ≤10 × ULN	539	(18.6)	509	(17.7)	—	—
10 × ULN to ≤15 × ULN	185	(6.4)	140	(4.9)	—	—
15 × ULN to ≤20 × ULN	67	(2.3)	65	(2.3)	—	—
20 × ULN	160	(5.5)	105	(3.7)	—	—

[a] Cochran-Mantel-Haenszel test (*p* value = 0.03).

CI = confidence interval; CK-MB = creatine kinase–myocardial band; MI = myocardial infarction; ULN = upper limit of normal.

half of the cases, a pathoanatomical classification was not possible owing to limited information.

Investigators were requested to assess the clinical outcome of focal persistent CVE patients utilizing the Rankin scale [12, 13]. The assessment occurred at least 6 months after enrollment. Outcomes were quite similar with the exception of death (34 in the cariporide group versus 18 in the placebo).

In total, there were 152 deaths reported in the placebo group and 185 in the cariporide group (Table 6). All deaths were reported on a "death" endpoint form and were centrally adjudicated by the Endpoint Validation Committee. Additionally, any death possibly related to the study treatment was documented as a SAE. The central classification by the Endpoint Validation Committee demonstrated that the imbalance in the death in the cariporide group appeared to be mainly due to an increase in "noncardiovascular death" (1.7% in the placebo versus 2.3% in the cariporide). The most common primary cause of death was cardiac. Deaths due to ischemic, arrhythmic, and pump failures were slightly higher in the cariporide group. Shock, sepsis, or multiorgan failures were overall infrequent, yet observed twice as often in the cariporide-treated group (14 versus

Table 4. Safety: Adverse Events (AE) and Serious AE (SAE) of Special Interest by Month 6

Variable	Placebo n = 2,839 (% = 100.0) Number of Patient	(%)	Cariporide n = 2,870 (% = 100.0) Number of Patients	(%)	*p* Value (χ^2)
Arrhythmia					
Any AE	1,129	(39.8)	1,061	(37.8)	0.032
SAE	127	(4.5)	109	(3.9)	0.224
Acute renal failure					
Any AE	323	(11.4)	368	(13.1)	0.102
SAE	89	(3.1)	124	(4.4)	0.022
Liver toxicity					
Any AE	252	(8.9)	248	(8.8)	0.789
SAE	68	(2.4)	66	(2.4)	0.880
Altered mental status[a]					
Any AE	361	(12.7)	496	(17.7)	<0.0001
SAE	26	(0.9)	48	(1.7)	0.016
Cerebrovascular events					
Any AE	86	(3.0)	146	(5.2)	0.0001
SAE	78	(2.7)	136	(4.8)	<0.0001
Focal persistent CVE	71	(2.5)	126	(4.5)	0.0001

[a] Altered mental status is defined as any perioperative confusion syndrome.

CVE = cerebrovascular event.

Table 5. Focal Persistent Cerebrovascular Events (CVEs) at Month 6

Variable	Placebo n = 71 (% = 100.0) Number of Patients	(%)	Cariporide n = 126 (% = 100.0) Number of Patients	(%)
Type of stroke				
Ischemic	67	(94.4)	124	(98.4)
Embolic	21	(29.6)	41	(32.5)
Large artery (thrombotic)	2	(2.8)	4	(3.2)
Watershed infarction	3	(4.2)	2	(1.6)
Lacunar	4	(5.6)	1	(0.8)
Unable to classify	37	(52.1)	76	(60.3)
Hemorrhagic	4	(5.6)	2	(1.6)
Clinical outcome (Rankin scale)				
No symptoms	9	(12.7)	20	(15.9)
No significant disability	15	(21.1)	24	(19.0)
Slight disability	13	(18.3)	17	(13.5)
Moderate disability	2	(2.8)	13	(10.3)
Moderate to severe disability	8	(11.3)	10	(7.9)
Severe disability	2	(2.8)	5	(4.0)
Death	18	(25.4)	34	(27.0)
Not available	4	(5.6)	3	(2.4)

28 deaths). Other causes of death were rare and equally distributed among both treatment groups. This analysis included deaths that occurred after the 6-month observation periods; thus, the number of events cannot be directly compared with those given at 6 months.

Comment

Myocardial infarction and stunning are significant postoperative complications that limit survival after heart surgery. In high-risk CABG patients, mortality may exceed 10% to 15%. While there are many causes, ischemia/reperfusion injury and the lack of optimal myocardial protection are important contributing factors that are amenable to improvement. The EXPEDITION study is an important, large, drug intervention study that tested the hypothesis that targeting an ischemia/reperfusion injury mechanism can result in a reduction in the incidence of MI after CABG.

The results of EXPEDITION revealed (1) compelling evidence that the incidence of intraoperative myocardial necrosis in patients undergoing CABG occurs more frequently than previously appreciated; (2) a reduction in the primary endpoint of all-cause death or nonfatal MI was achieved with cariporide; and (3) the reduction in the primary endpoint was due almost exclusively to a reduction in nonfatal MI; however, this benefit was offset by a higher incidence of CVEs ad mortality in patients receiving cariporide.

The finding that incidence of myocardial necrosis after CABG is greater than generally appreciated may be due in part to the lack of consensus regarding the definition of a postoperative MI and the assumption that it is not necessary to perform routine postoperative CK-MB measurements as modest elevations are not associated with increased mortality rates. Clearly, myocardial damage associated with heart surgery can be induced by different mechanisms. With respect to CK-MB levels, there have been different thresholds for identifying MI after CABG [14]. By utilizing these definitions or modifications, the findings in EXPEDITION are consistent with observations that incidence of any MI after CABG ranged between 12% and 19% [7, 15, 16].

The observation that CK-MB release after CABG is greater than generally accepted is particularly important because there is increasing evidence the CK-MB release exceeding 10 times ULN is associated with reduced survival over time. Thus, there is considerable evidence that even mild to moderate elevations of CK-MB release levels after CABG are associated with decreased survival over time [17–19]. Based on these findings, one might expect that the reduction in the incidence and magnitude of MI observed with cariporide treatment in EXPEDITION would have resulted in an improvement in the 6-month survival. Possibly, the 6-month follow-up was too short to appreciate fully the impact of varying degrees of myocardial necrosis on mortality.

There is a large body of experimental and clinical evidence that NHE inhibition can be cerebroprotective [20–29]. The challenge is to reconcile these studies with the findings in EXPEDITION. Because NHE-1 inhibition may limit cells ability to regulate intracellular pH in response to acidification, the timing and duration of administration of NHE inhibitors such as cariporide may be critical. It is well known that severe acidosis is associated with worsening of cerebral infarction whereas milder acidosis can be protective. Conversely, the absence of acidosis may exaggerate mechanisms of ischemic injury [22]. The timing and duration of administration of certain NHE inhibitors such as cariporide may be critical. Alternatively, it may be that the CVEs observed in EXPEDITION were unique to the specific molecular structure of cariporide and are not characteristic of NHE-1 inhibitors in general.

The increase in thromboembolic strokes with cariporide could indicate that the agent has a procoagulant effect. That seems unlikely because NHE-1 contributes to the platelet activation process through coupling with calcium influx after stimulation of platelets by various agonists, and inhibition of platelet NHE-1 can inhibit platelet aggregation [30, 31]. Possibly, an abrupt withdrawal of cariporide could lead to a rebound effect and result in rapid activation of the exchanger and platelet hyperactivity. Alternatively, prolonged NHE-1 blockade in the brain could result in NHE-1 upregulation. In this setting, cessation of cariporide administration could result in the brain being more susceptible to ischemic injury [32].

The variability in the literature regarding the stroke rate after CABG is due partly to reliance on registry data,

Table 6. Fatal Outcomes Over 6 Months

Variable	Placebo n = 2,839 (% = 100.0)		Cariporide n = 2,805 (% = 100.0)	
	Number of Patients	(%)	Number of Patients	(%)
All death observed[a]	152	(5.4)	185	(6.6)
All death reported as endpoint event[a]	152	(5.4)	180	(6.4)
EVC classification of death				
Cardiac death	92	(3.2)	98	(3.5)
Other cardiovascular death	10	(0.4)	17	(0.6)
Noncardiovascular death	49	(1.7)	64	(2.3)
Missing	1	(0.0)	—	—
Primary cause of death (investigator assessed)				
Cardiac, ischemic	22	—	29	—
Cardiac arrhythmia	15	—	21	—
Cardiac, pump failure	33	—	35	—
Shock, sepsis, multiorgan failure	14	—	28	—
Central nervous system events	12	—	18	—
Pulmonary events	16	—	16	—
Thrombotic events	5	—	4	—
Haemorrhagic events	7	—	9	—
Other events	16	—	14	—
Unknown	11	—	7	—

[a] Five deaths reported after the 180-day observation period not counted as endpoint event.

EVC = Endpoint Validation Committee.

definition of serious CVE, and coexisting risk factors such as renal insufficiency, recent MI, carotid artery disease, hypertension, diabetes mellitus, age greater than 75 years, severe left ventricular dysfunction, low cardiac output, and atrial fibrillation [26, 27, 32]. For these reasons, it is important that any clinical study that evaluates the risk of stroke after an intervention demonstrate that (1) the patient population under investigation has the same risk profiles; (2) the study is adequately powered and conducted in a double-blind, randomized fashion; and (3) the neurologic outcomes are evaluated in the context of both the degree of disability and death. Because EXPEDITION met these criteria, it was able to detect the small neurologic consequences of the cariporide treatment.

On the basis of EXPEDITION, it is unlikely that cariporide will be used clinically because the treatment was associated with an unanticipated higher mortality rate and incidence of CVEs. However, the importance of this study should not be underestimated; EXPEDITION clearly demonstrated that the incidence of myocardial necrosis after CABG is high and targeted pharmacologic interventions can be effective in reducing MI. In this regard, the use of NHE inhibitors could lead to significant improvement in medium- and long-term survival among patients undergoing heart surgery as well as those at risk of MI at any time. The challenge becomes to elucidate the mechanisms underlying the neurologic toxic effects associated with cariporide and to ascertain whether the phenomenon is unique to cariporide or NHE inhibition in general. The next step will be to pharmacologically dissociate the central nervous system adverse event of cariporide from its demonstrated cardioprotective properties or develop an NHE-1 inhibitor that does not exhibit neurotoxicity.

In summary, EXPEDITION demonstrated that pharmacologically induced myocardial protection designed to reduce the incidence of myocardial necrosis after CABG is feasible and that this class of agents holds considerable promise in the quest to identify a drug treatment that will reduce the overall incidence of myocardial necrosis in patients at risk of ischemia/reperfusion injury.

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