Impact of sodium-hydrogen exchange inhibition by cariporide on death or myocardial infarction in high-risk CABG surgery patients: Results of the CABG surgery cohort of the GUARDIAN study

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See related editorial on page 326.

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Objectives: To evaluate the effects of cariporide on all-cause mortality or myocardial infarction at 36 days in patients at risk of myocardial necrosis after coronary artery bypass graft surgery.

Methods: In the coronary artery bypass graft cohort of the GUARD During Ischemia Against Necrosis trial, patients ≥18 years who required urgent coronary artery bypass graft, repeat coronary artery bypass graft, or had a history of unstable angina and ≥2 risk factors (age >65 years, female gender, diabetes mellitus, ejection fraction <35%, or left main or 3-vessel disease) were randomized to placebo (n = 743) or cariporide 20 mg (n = 736), 80 mg (n = 705), or 120 mg (n = 734). A 1-hour intravenous infusion was initiated shortly before surgery and administered every 8 hours for 2 to 7 days. Patients were followed up for 6 months. A nonparametric covariance analysis was used to calculate the primary efficacy endpoint.

Results: Baseline characteristics were similar between treatment groups. The cariporide 20- and 80-mg groups had event rates similar to placebo. The endpoint of all-cause mortality or myocardial infarction at day 36 was significant with cariporide 120 mg versus placebo (event rate 12.2% vs 16.2%; $P = .027$). The risk reduction was evident on postoperative day 1 (3.3% vs 6.5%; $P = .005$) and was maintained at 6 months (event rate 15.0% vs 18.6%; $P = .033$). Cariporide was well tolerated, and most adverse events were mild and transient in this high-risk population.

Conclusions: Clinical benefit with cariporide 120 mg was observed early after treatment initiation and continued for 6 months postsurgery, suggesting that sodium-hydrogen exchange inhibition with cariporide is cardioprotective in patients undergoing high-risk coronary artery bypass graft surgery.

Refinements in coronary artery bypass graft (CABG) surgery since the first bypass procedure was performed in 1967 have led to an expected 30-day mortality of <1% in low-risk patients.[1,2] Predictive factors of increased mortality after CABG include the urgency of the operation, previous heart surgery, age >65 years, left ventricular dysfunction, female gender, and left main or 3-vessel disease.[3] The prevalence of high-risk CABG patients is increasing due to an aging population, improving survival of coronary heart disease patients, and expanding

use of percutaneous transluminal coronary angioplasty (PTCA), which may prolong the time before a patient ultimately presents for CABG.[1] Thus, a need exists for new treatment options to improve mortality and morbidity outcomes after CABG in high-risk patients.

Sodium-hydrogen exchanger (NHE) activation is associated with cell injury and necrosis in myocardial ischemia and reperfusion states.[4] NHE-1, 1 of 6 identified NHE isoforms, is the predominant isoform in cardiomyocytes.[5,6] During myocardial hypoxia and ischemia, anaerobic metabolism leads to intracellular acidosis. NHE-1 is activated to regulate the intracellular pH by extruding hydrogen in exchange for sodium.[7-9] The increase in intracellular sodium in turn activates Na^+-Ca^{2+} exchange. The resultant increase in intracellular Ca^{2+} directly mediates cell death by protease activation, cell contracture, and membrane rupture.[4,5,7,10,11] Cariporide, a novel NHE-1 inhibitor, reduces Na^+ influx and, in turn, Ca^{2+} overload during ischemia or reperfusion.[10,11] Preclinical studies have demonstrated a cardioprotective effect in animal models.[12-17] Recently, the first large-scale study, the GUARD During Ischemia Against Necrosis (GUARDIAN) trial, evaluated the effect of cariporide on the composite endpoint of all-cause mortality and myocardial infarction (MI) at day 36 in 11,590 patients in different clinical settings at risk of myocardial necrosis. Although in the overall analysis no significant reduction was achieved by any of the 3 cariporide groups,[18] a nominally significant reduction in the primary endpoint incidence was observed in the entry category of patients undergoing CABG who were treated with cariporide 120 mg, as evidenced by a 25% relative risk reduction (RRR) ($P = .027$). This observation prompted more detailed analyses of the findings in the CABG cohort of the GUARDIAN study, which are the subject of this publication.

Methods

Patients presenting with unstable angina (UA) or non–Q-wave MI or undergoing high-risk coronary revascularization (PTCA or CABG) were enrolled from May 1997 to April 1999 at 382 study sites in 23 countries in this randomized, placebo-controlled, double-blind, parallel group trial.[11] The clinical study protocol and informed consent documents were reviewed and approved by an institutional review board for 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.

The study design of the GUARDIAN trial has been published.[11,18] The CABG cohort included patients ≥18 years of age who required urgent CABG, repeat CABG, or had angina at rest or with minimal exercise within the previous 4 weeks and ≥2 of the following risk criteria: age >65 years, female gender, diabetes mellitus, ejection fraction <35%, or left main or 3-vessel disease. Exclusion criteria included persistent ST elevation or new Q-wave MI, secondary causes of UA, cardiogenic shock or pulmonary edema refractory to medical treatment, permanent ventricular pacing, automated implanted cardiac defibrillator, or left bundle branch block. Other exclusion criteria included elevations in liver function tests 3 times the upper limit of normal (ULN), serum bilirubin >1.75 mg/dL (>30 μmol/L), serum creatinine >2 mg/dL (>177 μmol/L), clinically severe hepatic or renal impairment, and women who were breastfeeding or pregnant. Patients who had previous exposure to cariporide, had a history of hypersensitivity to amiloride, or who had participated in an investigational study within 30 days were also excluded.

On enrollment, patients were randomized to 4 parallel treatment groups. A 1-hour intravenous infusion of cariporide 20, 80, or 120 mg or placebo was initiated 15 minutes to 2 hours before surgery and administered every 8 hours for ≥2 days to a maximum of 7 days. The dose of cariporide was adjusted for patients with a serum creatinine of 1.5 to 2.0 mg/dL (133-177 μmol/L) at baseline or a creatinine of 1.5 to 3.0 mg/dL (133-265 μmol/L) during treatment. Cariporide was discontinued after the investigator determined that the patient was clinically stable and symptom-free for 12 to 24 hours (or 24 hours prior to discharge).

The primary endpoint was the combined incidence of all-cause mortality or MI at day 36 in patients undergoing CABG. Secondary endpoints included all-cause mortality or MI at 10 days, events related to left ventricular dysfunction (LVD) [ie, composite endpoint of cardiac-related mortality, MI, cardiogenic shock, congestive heart failure (CHF), and life-threatening arrhythmia] at day 36 and at 6 months, refractory ischemia at day 36, and peak creatine kinase with muscle and brain subunits (CK-MB) levels measured to assess the extent of infarction. The safety and tolerability of study medications were assessed throughout the trial.

Enrollment evaluations included complete physical examination, 12-lead electrocardiogram (ECG), standard laboratory assessment, and total creatine kinase (CK) and CK-MB isoenzymes. Additionally, an ECG was performed 24 to 72 hours after surgery, and serial serum CK-MB values were obtained 8, 12, 18, and 24 hours after surgery. The diagnosis of Q-wave MI was determined by ECG criteria of a 2-step Q-wave change as defined by the Minnesota code.[19] In the absence of a new Q-wave, a CK-MB elevation >100 U/L (or 100 ng/mL, if a CK-MB mass assay was used) within 24 hours of CABG was considered indicative of non–Q-wave MI. If CK-MB values continued to elevate after 24 hours without a trough value, the highest value was chosen to represent peak CK-MB elevation. Furthermore, the protocol specified that when a patient reported chest pain >20 minutes during the postoperative phase, an additional ECG should be obtained and serial CK-MBs be repeated at 4, 8, 12, and 24 hours. In this case, MI was diagnosed in patients who had a re-elevation of CK-MB occurring after a prior nadir that exceeded 2 × ULN and exhibited a typical rise and fall. After surgery, non–Q-wave MI was diagnosed as evidenced by a >2-fold increase in CK-MB in the absence of a percutaneous intervention, or >3-fold increase after percutaneous intervention. At discharge or on day 10 for patients who were still hospitalized, physical examination, ECG, and lab assessments were repeated. Follow-up evaluations were performed at day 36 and 6 months and included blood pressure, pulse, ECG, concomitant medications, and review of endpoints. In addition to MI reported by the investigators, CK-MB values and ECG from all patients were screened for presence of previously unreported "da-

TABLE 1. Baseline characteristics of CABG cohort by treatment group

Characteristic	Placebo (n = 743)	Cariporide 20 mg (n = 736)	Cariporide 80 mg (n = 705)	Cariporide 120 mg (n = 734)
Gender [n (%)]				
Male	521 (70.1)	517 (70.2)	483 (68.5)	507 (69.1)
Female	222 (29.9)	219 (29.8)	222 (31.5)	227 (30.9)
Age [n (%)]				
<55 y	97 (13.1)	75 (10.2)	78 (11.1)	83 (11.3)
55-64 y	160 (21.5)	153 (20.8)	134 (19.0)	168 (22.9)
65-74 y	337 (45.4)	366 (49.7)	324 (46.0)	333 (45.4)
≥75 y	148 (19.9)	142 (19.3)	169 (24.0)	150 (20.4)
Race [n (%)]				
Caucasian	699 (94.1)	696 (94.6)	658 (93.3)	697 (95.0)
African American	28 (3.8)	31 (4.2)	29 (4.1)	24 (3.3)
Asian	11 (1.5)	4 (0.5)	9 (1.3)	5 (0.7)
Multiracial	5 (0.7)	5 (0.7)	9 (1.3)	7 (1.0)
Smoker or previous smoker [n (%)]	483 (65)	496 (67.4)	456 (64.7)	474 (64.5)
BMI (mean ± SD)	28.1 ± 4.7	28.2 ± 5.7	27.9 ± 4.7	28.1 ± 4.6
Obese (ie, >28 kg/m^2) [n (%)]	343 (46.2)	332 (45.2)	319 (45.4)	333 (45.4)
Cardiac history (%)				
History of MI	51.5	52.2	52.7	48.5
MI at study entry	5.5	4.9	6.7	4.9
CHF	9.3	10.9	9.4	9.7
Diabetes	36.9	36.9	42.3	41.7
CVD	7.8	8.7	9.1	12.9
PVD	17.4	19.3	16.9	18.1
UA	59.3	61.4	58.8	59.0
Previous cardiac interventions (n)				
Previous PTCA	18.6	20.0	18.5	18.3
Previous CABG	16.3	17.1	17.0	16.6

BMI, Body mass index; *CABG*, coronary artery bypass graft; *CHF*, congestive heart failure; *CV*, cardiovascular; *CVD*, cerebrovascular disease; *HTN*, hypertension; *MI*, myocardial infarction; *NA*, not applicable; *PTCA*, percutaneous transluminal coronary angioplasty; *PVD*, peripheral vascular disease; *SD*, standard deviation; *UA*, unstable angina; *y*, year.

tabase-identified MI" by a central ECG Core Laboratory (B. Chaitman, MD, St. Louis, Mo), which was blinded to treatment assignments throughout the study. All primary and secondary endpoints were further validated by an independent, blinded "endpoint validation committee."

Efficacy analyses were performed on all randomized patients (ie, intent to treat). A nonparametric covariance adjustment analysis[20] was used to calculate probability values and 98% confidence limits for the primary endpoint. Predefined covariates included age, sex, CHF diabetes, index MI, previous MI, ST-segment depression, and cerebrovascular or peripheral vascular disease. To test for homogeneity of the covariates, the Wilcoxon rank sum test was used for continuous variables, and Fisher exact test was used for categoric data. The square root of the unadjusted χ^2 statistics was calculated, and Kaplan-Meier curves were used to present time to first primary endpoint event. The same methodology, when appropriate, was used to analyze the secondary efficacy endpoints. An extended Mantel-Haenszel statistic examined the peak CK-MB scores. Safety analyses were performed on the treated population using Fisher exact tests.

Results

Baseline Demographics

Of the 11,590 patients enrolled in the GUARDIAN trial, 2918 (25.2%) were in the CABG entry cohort and were randomized to treatment with cariporide 20, 80, or 120 mg, or placebo (Table 1). Baseline characteristics were similar between treatment groups. The median time from the first cariporide infusion to anesthesia induction was 1 hour. Mean treatment duration was approximately 3 days, during which a median number of 8 infusions were administered. The number of patients requiring a dose reduction increased as the cariporide dosage increased, primarily because of elevations in serum creatinine.

Efficacy

The primary endpoint of all-cause mortality or MI at day 36 was significantly reduced in the cariporide 120-mg treatment group compared with placebo (event rate 12.2% vs 16.2%; $P = .027$) (Table 2, Figure 1). A significant reduction in event rates was apparent within 24 hours after initiating cariporide 120 mg and continued throughout the 6 months of follow-up (Table 2). The primary cause of death was cardiovascular, and no significant difference was observed between treatment groups for either cardiovascular or total death (Table 3). Thus, the reduction in risk was attributed to fewer nonfatal Q-wave and non–Q-wave MIs.

TABLE 2. Incidence and relative risk reduction of death or MI over 6 months by treatment group

Time point	Placebo (n = 743)	Cariporide 20 mg (n = 736)	Cariporide 80 mg (n = 705)	Cariporide 120 mg (n = 734)
Day 1				
Event rate (%)	6.46	7.20	6.24	3.27
RRR (%)	–	−8.41	0.47	48.92
P value	–	.676	.980	.005
Day 5				
Event rate (%)	14.16	14.41	14.49	9.56
RRR (%)	–	−0.23	−4.33	32.34
P value	–	.985	.740	.007
Day 10				
Event rate (%)	14.71	15.66	15.78	10.53
RRR (%)	–	−4.99	−9.11	28.47
P value	–	.692	.480	.016
Day 36				
Event rate (%)	16.22	17.30	17.37	12.23
RRR (%)	–	−5.00	−8.70	24.69
P value	–	.673	.474	.027
Month 6				
Crude event rate (%)	18.57	19.43	19.57	14.99
P value		.829	.658	.033

MI, Myocardial infarction; *RRR,* relative risk reduction.

There was a 32% RRR in nonfatal MIs with cariporide 120 mg compared with placebo. The cariporide 20- and 80-mg groups had event rates similar to placebo.

Infarction size was estimated according to peak CK-MB levels. The reduction in the incidence of MI in the cariporide 120-mg group was associated with fewer patients having increased peak CK-MB values compared with placebo (Table 4). To account for variations between laboratories, the ratio of the peak CK-MB value to the ULN was calculated; patients receiving cariporide 120 mg had a significant reduction in this ratio compared with patients receiving placebo (6.47 vs 8.00; $P = .021$). No significant reduction in peak CK-MB values occurred with the 20- and 80-mg treatment groups.

LVD-associated events were reduced at 6 months in the 120-mg treatment group compared with placebo (9.4% vs 13.5%, respectively) primarily because of the lower incidence of MI. Other secondary endpoints, including cardiovascular death, cardiogenic shock, overt CHF, and life-threatening arrhythmias, were not different between cariporide treatment groups or placebo at 36 days. Additionally, the frequency of refractory ischemia at 36 days and rehospitalization were comparable between treatment groups. However, the rehospitalization rate due to endpoint events was slightly lower with cariporide 120 mg compared with cariporide 20 and 80 mg and placebo (7.8% vs 11.5%, 13.2%, and 14.7%, respectively).

Subgroup analyses were performed on the endpoints of all-cause mortality or MI at 36 days to clarify the risk reduction in patients treated with cariporide 120 mg (Table 5). The reduction in event rates was maintained with cariporide 120 mg compared with placebo in patients with UA and 2 or more risk factors (11.6% vs 15.2%), or 3 or more risk factors (14.1% vs 16.8%) and in patients undergoing repeat CABG (18.4% vs 27.2%). The only exception was for the small group of patients requiring urgent CABG (<10% of the total cohort), in whom the event rate was 14.2% with cariporide vs 10.8% with placebo. The duration of CABG surgery was also assessed regarding its potential influence on treatment effects. The percentage of event rates for cariporide 120 mg was lower than for the other treatments during short (<4.2 hours), medium (4.2-4.9 hours), and long (>4.9 hours) procedures. The difference in event rates was most pronounced in the one third of patients with the longest duration of surgery (>4.9 hours), and with the longest aortic crossclamp time >105 minutes, where the event rates were 18.1% and 19.8% with cariporide 120 mg, respectively, and 25.3% with placebo. A reduction in the event rate was observed irrespective of whether the patients received blood cardioplegia (14.0% vs 18.5%) or crystalloid cardioplegia (9.0% vs 14.1%). (Note: Since patients were not randomly assigned to receive either blood or crystalloid cardioplegia, overall event rates for the different cardioplegia strategies are not comparable). Event rates were somewhat higher for patients treated in the United States/Canada (12.8% with cariporide 120 mg vs 16.1% with placebo) compared with Europe/rest of world (11.0% vs 16.2%) but again similar risk reductions were observed between treatment groups in both geographic regions.

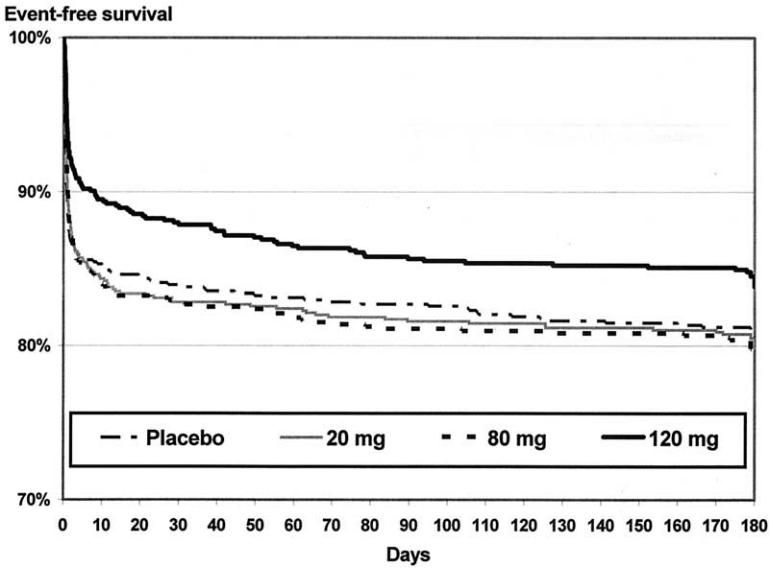

Figure 1. Event-free survival up to 6 months by treatment group. $P = .0334$.

TABLE 3. Components of primary endpoint at 36 days

Event	Placebo (n = 743) n (%)	Cariporide 20 mg (n = 736) n (%)	Cariporide 80 mg (n = 705) n (%)	Cariporide 120 mg (n = 734) n (%)
Total subjects with endpoints	120 (16.2)	127 (17.3)	122 (17.3)	89 (12.1)
Total deaths	31 (4.2)	37 (5.0)	30 (4.3)	37 (5.0)
Cardiovascular	28 (3.8)	35 (4.8)	29 (4.1)	33 (4.5)
Sudden death	6	4	0	6
Circulatory failure	18	24	20	22
Other	4	7	9	5
Noncardiovascular	3 (0.4)	2 (0.3)	1 (0.1)	4 (0.5)
MI				
Q wave	36 (4.8)	37 (5.0)	39 (5.5)	24 (3.3)
Non-Q wave	53 (7.1)	53 (7.2)	53 (7.5)	28 (3.8)

MI, Myocardial infarction.

Safety

Approximately 94% of the CABG cohort experienced an adverse event, reflecting the severity of the underlying disease and surgical intervention. Differences between treatment groups were small. The frequency of adverse events considered possibly related to treatment was 21.8% in cariporide patients and 20.0% in placebo patients (Table 6). Small differences between treatment groups were mainly due to dose-dependent increases in the incidence of confusion and abnormal liver function tests. Confusion tended to occur early, and no increase was observed at later time points in the cariporide groups compared with placebo. Arrhythmias were slightly more common with cariporide than placebo because of an increase in nonserious adverse events of atrial fibrillation. However, the incidence of episodes of atrial fibrillation qualifying as serious adverse events was similar across treatment groups (Table 6). Other adverse events showing a trend toward more reports in cariporide-treated patients included dizziness, dyspnea, hemorrhage, fever, urinary tract infection, and peripheral edema. Most were considered mild to moderate in severity. Changes observed in blood pressure, pulse, ECG parameters, and laboratory evaluations that included hematology, electrolytes, and metabolism were not considered clinically relevant.

Predefined serious adverse events that occurred more frequently with cariporide than placebo included altered mental status (1.4% in placebo patients vs 2.1% in 120-mg patients), and renal (2.1% placebo vs 2.3% in 120-mg patients) and hepatic dysfunction (0.0% placebo vs 0.4% in 120-mg patients). The former event, altered mental status, presented primarily as confusion, while the latter events

TABLE 4. Peak CK-MB levels by treatment group

Score (CK-MB value)	Placebo (n = 743) n (%)	Cariporide 20 mg (n = 736) n (%)	Cariporide 80 mg (n = 705) n (%)	Cariporide 120 mg (n = 734) n (%)
Unclassified	25 (3.4)	22 (3.0)	20 (2.8)	28 (3.8)
0 (≤60 U/L)	562 (75.6)	567 (77.0)	538 (76.3)	582 (79.3)
1 (>60-≤100 U/L)	54 (7.3)	45 (6.1)	52 (7.4)	48 (6.5)
2 (>100-≤200 U/L)	43 (5.8)	47 (6.4)	50 (7.1)	29 (4.0)
3 (>200-≤300 U/L)	19 (2.6)	8 (1.1)	5 (0.7)	8 (1.1)
4 (>300 U/L or cardiac death)	40 (5.4)	47 (6.4)	40 (5.7)	39 (5.3)

CK-MB, Creatine kinase with muscle and brain subunits.

TABLE 5. Findings in subgroups of patients

	Placebo	Cariporide 20 mg	Cariporide 80 mg	Cariporide 120 mg
Risks factors at study entry				
≥2 Risk factors* (n)	566	580	557	591
Death/MI, d 36 (%)	15.2	14.9	14.0	11.6
≥3 Risk factors* (n)	197	208	217	214
Death/MI, d 36 (%)	16.8	18.8	15.7	14.1
Repeat CABG* (n)	129	130	124	115
Death/MI, d 36 (%)	27.2	26.9	30.7	18.4
Urgent CABG* (n)	74	57	57	57
Death/MI, d 36 (%)	10.8	15.9	19.3	14.2
Duration of surgery				
<4.2 h (n)	288	272	278	282
Death/MI, d 36 (%)	8.0	9.2	14.1	7.9
4.2-4.9 h (n)	143	151	141	132
Death/MI, d 36 (%)	15.5	13.2	15.1	9.1
>4.9 h (n)	289	293	266	296
Death/MI, d 36 (%)	25.3	26.7	21.5	18.1
Type of cardioplegia				
Blood cardioplegia (n)	287	294	284	300
Death/MI, d 36 (%)	18.5	19.1	16.2	14.0
Crystalloid cardioplegia (n)	184	194	172	179
Death/MI, d 36 (%)	14.1	17.5	17.5	9.0
Regional distribution				
USA/Canada (n)	514	501	49	506
Death/MI, d 36 (%)	16.1	17.4	17.8	12.8
EUR/rest of world (n)	229	235	236	228
Death/MI, d 36 (%)	16.2	17.0	16.6	11.0

CABG, Coronary artery bypass graft; *Eur*, Europe; *MI*, myocardial infarction.
*Patients could be in several categories.

were manifested mainly by abnormal liver and kidney function tests. Differences between treatment groups were very small, with no evidence of a clear dose-response relationship. Stroke and transient ischemic attacks occurred in 2.7% of cariporide 120-mg patients and 2.3% of placebo patients, but no dose response was observed. In addition, the frequency of these events was comparable between cariporide and placebo groups in the UA/non–Q-wave MI and PTCA cohorts. Therefore, the increase observed in the CABG cohort is likely due to chance. No difference was observed regarding the occurrence of cardiogenic shock, cardiac ischemia, or CHF. Overall, the incidence of serious adverse events reflected disease severity. No major treatment imbalances were observed. Adverse events led to treatment discontinuation in 9.5% of cariporide patients and 6.6% of placebo patients, mainly for cardiovascular and nervous system reasons.

Discussion

In the large high-risk CABG cohort of the GUARDIAN study, a significant 25% RRR in the primary endpoint of all-cause death or MI at day 36 was observed with cariporide 120 mg administered every 8 hours for an average of 3 days. This observation was also supported by generally

TABLE 6. Safety

	Placebo (n = 729)	Cariporide 20 mg (n = 729)	Cariporide 80 mg (n = 697)	Cariporide 120 mg (n = 729)
Most frequent AEs possibly related to treatment (%)				
Total subjects with related AEs	20.0	21.5	21.8	21.8
Liver function test abnormal	2.6	3.3	3.3	4.4
Nausea	2.3	2.9	1.9	2.1
Confusion	1.2	2.1	1.4	2.2
Hypotension	1.9	1.8	2.2	1.0
Kidney function abnormal	1.1	1.6	1.4	1.1
Creatinine increased	0.4	1.1	0.7	1.0
GGT increased	0.4	0.4	0.9	1.1
Laboratory test abnormal	0.7	0.7	0.1	1.2
Hypertension	1.0	0.3	0.7	1.1
Vomiting	1.0	0.8	0.3	0.8
Serious AEs of special interest				
Altered mental status	1.4	1.4	1.9	2.1
Renal dysfunction	2.1	1.9	1.6	2.3
Liver dysfunction	0.0	0.4	0.4	0.4
Stroke/TIA	2.3	3.3	4.3	2.7
Hemorrhage	4.1	4.3	3.7	3.7
Allergic reaction	0.5	0.1	0.1	0.4
Atrial fibrillation	6.7	5.9	5.5	5.8
Premature discontinuation of study drug				
Any discontinuation	10.2	12.2	11.8	15.0
Death	1.3	2.3	1.8	2.2
AEs resulting in drug discontinuation	6.6	8.9	9.5	9.5
Cardiac events	1.9	1.5	1.0	1.6
Kidney disorders	1.4	0.4	1.4	2.5
Hepatic disorders	0.1	0.7	0.0	0.1
CNS events	0.8	1.5	1.4	1.2

AE, Adverse event; *CNS,* central nervous system; *GGT,* γ-glutamyl transpeptidase; *TIA,* transient ischemic attack.

consistent event rate reductions across subgroups, including CABG indication, cardioplegia type, and geographic region. The reduction in risk was observed within 24 hours of starting treatment and was maintained throughout the 6-month trial. It was primarily driven by a significant (32%) reduction in the number of nonfatal MIs, both Q-wave and non-Q-wave, although the mortality rate was similar between placebo and active treatment. This was associated with a reduction in infarct size, as shown by reduced peak CK-MB values. As previously reported, when examining the CK-MB levels in all 2918 patients enrolled in the CABG cohort of the GUARDIAN trial, a significant correlation was found between peak enzyme levels and medium-term (6 months) prognosis.[21] Therefore, the observed MI benefit in the 120-mg group may translate to an improved mortality benefit when examining longer-term survival data in a larger cohort of patients.

The observation of an apparent treatment benefit in the CABG cohort of the GUARDIAN study, which contrasts with the overall study findings, may be explained by several factors. First, patients undergoing CABG had a higher risk of global myocardial ischemia at baseline than UA/non–Q-wave MI or PTCA patients and, thus, this cohort was most likely to demonstrate a benefit. The CABG population also experienced the longest duration of ischemia. The CABG cohort had complete myocardial reperfusion while receiving cariporide, whereas immediate coronary reperfusion was not specified by the study protocol for the other cohorts. Finally, the other cohorts experienced an increased number of events after the end of study treatment, while in the CABG cohort, the period of risk of myocardial injury was predominantly during and shortly after surgery. Thus, pronounced differences in the amount of myocardium at risk, the longer duration of myocardial ischemia, reperfusion in the presence of cariporide, and the occurrence of endpoint events after the end of treatment may underlie the apparent benefit seen in the CABG cohort. This is supported by preclinical data that demonstrate that activity of NHE-1 is self-limited during ischemia but is intensified on reperfusion.[10,14,18] The reduction in death or MI observed at 36 days was limited to the cariporide 120-mg group. Lower doses of cariporide were ineffective, suggesting that cariporide may have been undertitrated. A subsequent concentration-efficacy analysis employing population pharmacoki-

netic-modeling techniques identified a minimum mean cariporide plasma concentration for efficacy of approximately 550 ng/mL.[22] This mean concentration was achieved in none of the patients in the 20-mg group, in 31% of the 80-mg group, and in 76% of the 120-mg group. Thus, a modified treatment regimen that increases exposure of patients to cariporide above this putative threshold concentration might be associated with increased efficacy. Cariporide, generally well tolerated compared with placebo, was associated with a slight increase in nervous system effects (mainly transient confusion) and liver and kidney effects, manifested as isolated elevations in lab tests. No major treatment imbalances with respect to adverse events were observed.

Conclusions

The GUARDIAN trial investigated a novel pharmacologic approach for direct myocardial cell protection. Although no benefit was observed with any dose of cariporide in the overall study population, a 25% RRR in all-cause death or MI was observed with cariporide 120 mg in the CABG cohort. This statistical positivity is dependent exclusively on a dramatic reduction in MI. Clinical benefit occurred early after treatment initiation and continued for 6 months. The reduction may have been due to the optimal timing of cariporide administration before global ischemia and during subsequent reperfusion. The consistent event rate reductions observed across different CABG subgroups and the heterogeneity of the different GUARDIAN cohorts suggest that cariporide may be effective in patients undergoing high-risk CABG surgery. The major limitation of this subanalysis is that the cariporide 120-mg group of CABG patients represents only 1 of 3 dosage groups among the 3 cohorts; therefore the benefit observed may be due to chance. However, the clinical and pathophysiologic differences between the entry cohorts and the consistent and persistent risk reduction seen in the CABG analysis suggest that cariporide 120 mg may be cardioprotective in high-risk patients undergoing CABG. Further investigation of this promising treatment principle in cardiac surgery is warranted.

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