Prognostic significance of elevated creatine kinase MB after coronary bypass surgery and after an acute coronary syndrome: Results from the GUARDIAN trial

Jeffrey A. Gavard, PhD,^a Bernard R. Chaitman, MD, FACC,^a Shunta Sakai, MD,^a Karen Stocke, MBA,^a Nicolas Danchin, MD, FACC,^b Leif Erhardt, MD,^c Richard Gallo, MD, FACC,^d Eric Chi, PhD,^e Andreas Jessel, MD,^e and Pierre Thérault, MD, FACC,^d for the GUARD During Ischemia Against Necrosis (GUARDIAN) Investigators*

Dr Chaitman

Objective: To determine if the correlation between magnitude of creatine kinase-myocardial band release after coronary artery bypass surgery and 6-month mortality is comparable to that of patients admitted with an acute coronary syndrome.

Methods: The GUARDIAN trial tested the efficacy of cariporide, an Na⁺/H⁺ exchange inhibitor, on reduction of myocardial ischemia or death in high-risk patients. We compared 6-month survival in a cohort of 2332 GUARDIAN patients scheduled for coronary artery bypass surgery at entry with 4233 acute coronary syndrome patients stratified by level of creatine kinase-myocardial band release. Cumulative 6-month survival by creatine kinase-myocardial band categories was performed using life table analysis, adjusting for variables known to impact prognosis using Cox regression.

Results: The 6-month mortality rates for coronary artery bypass surgery patients with peak creatine kinase-myocardial band ratios of <1, ≥1 and <5, ≥5 and <10, and ≥10 upper limits of normal (ULN) were 5.8, 2.8, 5.9, and 12.0%, respectively ($P < .0001$). The 6-month mortality rates for acute coronary syndrome patients with peak creatine kinase-myocardial band ratios of <1, ≥1 and <5, ≥5 and <10, and ≥10 ULN were 6.3, 9.8, 10.0, and 12.3%, respectively ($P < .0001$). Patients with coronary artery bypass surgery or acute coronary syndrome had similar adjusted 6-month survival estimates at normal creatine kinase-myocardial band levels and when the creatine kinase-myocardial band level was ≥10 ULN. Patients with coronary artery bypass surgery had significantly better survival at intermediate enzyme levels (≥1 and <10 ULN; $P < .001$).

Conclusions: Modest elevations of creatine kinase-myocardial band release (≥1 and <10 ULN) after coronary artery bypass surgery are not associated with adverse 6-month survival, in contrast to that seen in acute coronary syndrome patients. Routine creatine kinase-myocardial band sampling should be considered in all higher-risk patients undergoing coronary artery bypass surgery procedures to identify the sizable cohort of patients with creatine kinase-myocardial band release ≥10 ULN; these patients may benefit from postoperative angiotensin-converting enzyme inhibitor and beta-blocker therapy. Newer cardioprotective agents that reduce the number of patients with marked creatine kinase-myocardial band release are currently being tested in large randomized controlled clinical trials.

From the St Louis University School of Medicine,^a St Louis, Mo; Hôpital Européen Georges Pompidou,^b Paris, France; Malmö University Hospital,^c Malmö, Sweden; Montreal Heart Institute,^d Montreal, Quebec, Canada; and Aventis Pharmaceuticals, Inc,^e Bridgewater, NJ.

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Address for reprints: Bernard R. Chaitman, MD, St Louis University School of Medicine, Division of Cardiology (15th Floor), 3635 Vista Avenue at Grand Blvd, PO Box 15250, St Louis, MO 63110-0250 (E-mail: chaitman@slu.edu).

*A complete listing of the GUARDIAN investigators is found in *Circulation* 2002; 102:3032.

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The clinical significance of an elevation in cardiac serum markers on long-term survival is not as well established after coronary artery bypass surgery (CABG) as after a percutaneous coronary intervention (PCI). Creatine kinase-myocardial band (CK-MB) isoenzyme elevation occurs in 20% to 30% of patients after PCI, and the magnitude of CK-MB elevation directly correlates with long-term survival.¹⁻⁵ CK-MB elevation occurs in 90% of patients after CABG.⁵⁻⁹ Several

authors have reported a reduced survival when CK-MB release after CABG exceeds 10 times the upper limits of normal (ULN).^{5,6} There are no data that compare the survival of patients after CABG with patients with an acute coronary syndrome (ACS) matched for similar levels of CK-MB release.

The GUARDIAN trial was a randomized multicenter clinical trial that tested the efficacy of cariporide, an Na^+/H^+ exchange inhibitor, on reduction of death or myocardial infarction in 11,590 patients at clinically high risk of developing myocardial necrosis.¹⁰⁻¹² We examined data from a subset of the GUARDIAN patients to determine if 6-month survival after CABG were comparable to those observed in patients with an ACS matched for similar levels of CK-MB release.

Methods

Study Design

The GUARDIAN trial enrolled 5233 patients with an ACS at entry, 3439 patients scheduled for high-risk PCI, and 2918 clinically high-risk patients for CABG between May 1997 and November 1998.¹¹ Inclusion/exclusion criteria have been previously described.¹⁰ The protocol was approved by the Institutional Review Board at each participating institution and each patient consented to be enrolled in the study. The CABG cohort required urgent intervention (as following a failed PCI) or repeat CABG, or had a history of angina at rest or on minimal exercise within 4 weeks prior to randomization, with 2 or more of the following risk factors: age >65 years, female gender, diabetes mellitus, left ventricular ejection fraction <35%, or left main or 3-vessel coronary artery disease. The ACS cohort required repetitive or prolonged angina pain at rest or on minimal exercise within 12 hours prior to randomization with ST-T changes (ST segment shift >1 mm in ≥ 2 contiguous leads or T wave inversion >1.5 mm in ≥ 3 contiguous leads) or elevation of cardiac serum markers [serum creatinine kinase or CK-MB >1.5 $\times$ upper normal limits or troponin I >2 ug/L or troponin T >0.15 ug/L]. Patients with rest angina 12 hours to 4 weeks after an acute myocardial infarction (MI) also were eligible. Patients with new ST segment elevation MI, significant hepatic or renal impairment, or secondary causes of unstable angina, such as anemia or hyperthyroidism, were excluded.

Demographic information, medical/surgical history, 12-lead electrocardiogram (ECG), and CK-MB enzymes were collected at baseline before randomization. CK-MB enzymes also were collected at 4, 8, 12, and 24 hours after randomization for ACS patients and at 8, 12, 16, and 24 hours after the procedure for CABG patients. Peak CK-MB ratio was determined by dividing the peak CK-MB value by the ULN for that laboratory because the ULN for CK-MB and type of assay used varied across laboratories.

Patient Population

Six-month vital status was known for 2891 of the 2918 patients initially entered into the GUARDIAN CABG group. After exclusion of operative deaths, MI at study entry, incomplete CK-MB, or ECG data and patients who underwent concomitant valve replacement surgery, the CABG study population in this report consisted

of 2332 patients, 119 of whom died during the 6-month follow-up period.

Six-month vital status was known for all 5233 patients initially entered into the GUARDIAN ACS group. Patients were excluded if they did not have sufficient CK-MB or ECG information either at entry or in the immediate postrandomization phase. Thus, the ACS study population in this report consisted of 4233 patients, 348 of whom died during the 6-month follow-up period.

Statistical Analysis

Differences in baseline demographic, medical/surgical history, and health characteristics between patients who died during follow-up and those who survived were assessed using chi-square test for categorical variables. The nonparametric Kolmogorov-Smirnov test was used for all continuous variables.¹³ Four categories were examined to facilitate comparison of the CABG and ACS groups: <1, ≥ 1 and <5, ≥ 5 and <10, and ≥ 10 ULN. Mortality was expressed per 100 patients (%). Cumulative 6-month survival by CK-MB categories was performed using life table analysis according to 10-day increments post-CABG for CABG patients and 10-day increments postrandomization for ACS patients.¹⁴ The 6-month survival experience was contrasted between CABG and ACS patients for each category of peak CK-MB ratio, adjusting for variables known to impact prognosis using Cox regression.^{15,16} The GUARDIAN trial in the dosage and drug regimen tested did not demonstrate a treatment difference in mortality for either the ACS or CABG groups.¹¹ Therefore, for the purposes of this paper, the treatment and control groups were pooled.

Results

Demographic and Medical/Surgical History

Baseline characteristics of the study population are illustrated in Tables 1 and 2. Ninety-three percent of the study population was white. Left ventricular ejection fraction <35%, and history of MI, congestive heart failure, cerebrovascular disease, peripheral vascular disease, and cardiac arrhythmias were more common in both CABG and ACS patients who died during the 6-month follow-up than in their respective survivors (Tables 1 and 2).

Relationship of Cardiac Enzymes with 6-Month Mortality

Findings for the CABG cohort indicated that patients without an increase in CK-MB (<1 ULN) had a significantly lower 6-month mortality when compared with the ≥ 10 ULN group (5.8 vs 12.0%, $P < .05$). The lack of significance in other comparisons may be partly attributed to the small sample size in the <1 ULN category ($n = 141$). The test for trend was significant ($\chi^2 = 38.39$ at 1 df, $P < .00001$). The number of deaths occurring in the first 30 days after CABG was 64/119 (53.8%), while the number occurring between 30 days and 6 months was 55/119 (46.2%). Cumulative 6-month survival was inversely related to peak CK-MB ratio ($P < .0001$, Figure 1).

The 6-month mortality rates for ACS patients with peak CK-MB ratios of <1, ≥ 1 and <5, ≥ 5 and <10, and ≥ 10

TABLE 1. Baseline demographic and medical history information of 2332 CABG patients

Characteristic	Patients deceased during 6-month follow-up (n = 119)		Patients alive at 6-month follow-up (n = 2213)		P value
	n	%	n	%	
Median age (year)	69.0		68.0		.26
Male	79	66.4	1545	69.8	.49
Median body mass index (kg/m ²)	27.1		27.6		.48
Smoking history					
Current smoker	14	11.8	332	15.0	.13
Former smoker	71	59.7	1110	50.2	
Never smoked	34	28.6	767	34.7	
Ejection fraction (%)					
<35	33	40.2	236	15.7	<.001
≥35	49	59.8	1263	84.3	
Angina	111	93.3	2104	95.1	.51
Myocardial infarction	81	68.1	1215	54.9	<.01
Congestive heart failure	40	33.6	327	14.8	<.001
Cerebrovascular disease	31	26.1	323	14.6	<.001
Peripheral vascular disease	39	32.8	368	16.6	<.001
Cardiac arrhythmias	45	37.8	439	19.8	<.001
Diabetes mellitus	51	42.9	860	38.9	.44
Prior CABG	23	19.3	373	16.9	.57
Baseline ST depression abnormality	37	31.9	486	22.6	<.05

Ejection fraction was unknown for 37 patients who died; baseline ST depression was unknown for 3 patients who died. Smoking history was unknown for 4 patients who survived; body mass index was unknown for 2 patients who survived; ejection fraction was unknown for 714 patients who survived; baseline ST depression was unknown for 65 patients who survived.

ULN were 6.3, 9.8, 10.0, and 12.3%, respectively ($P < .0001$). The test for trend was significant ($\chi^2 = 20.51$ at 1 df, $P < .00001$). The respective number of deaths occurring in the first 30 days after randomization for the <1, ≥1 and <5, ≥5 and <10, and ≥10 ULN groups was 66/113 (58.4%), 80/143 (55.9%), 23/38 (60.5%), and 33/54 (61.1%). The total number of deaths occurring in the first 30 days after randomization was 202/348 (58.0%), while the number occurring between 30 days and 6 months was 146/348 (42.0%). Cumulative 6-month survival was inversely related to peak CK-MB ratio ($P < .0001$; Figure 2).

ECG Results

New 2-grade Minnesota code Q-wave worsening was significantly associated with 6-month mortality in both CABG and ACS patients. The 6-month mortality rate was 10.9% in 110 CABG patients who developed new Q-waves compared

TABLE 2. Baseline demographic and medical history information of 4233 ACS patients

Characteristic	Patients deceased during 6-month follow-up (n = 348)		Patients alive at 6-month follow-up (n = 3885)		P value
	n	%	n	%	
Median age (year)	74.0		64.0		<.001
Male	214	61.5	2672	68.8	<.01
Median body mass index (kg/m ²)	25.5		26.9		<.001
Smoking history					
Current smoker	59	17.0	1114	28.7	<.001
Former smoker	147	42.2	1487	38.3	
Never smoked	142	40.8	1279	33.0	
Ejection fraction (%)					
<35	33	34.0	96	10.9	<.001
≥35	64	66.0	784	89.1	
Angina	296	85.1	2986	76.9	<.001
Myocardial infarction	225	64.7	1989	51.2	<.001
Congestive heart failure	106	30.5	476	12.3	<.001
Cerebrovascular disease	79	22.7	406	10.5	<.001
Peripheral vascular disease	99	28.4	513	13.2	<.001
Cardiac arrhythmias	122	35.1	704	18.1	<.001
Diabetes mellitus	121	34.8	872	22.4	<.001
Prior CABG	73	21.0	508	13.1	<.001
Baseline ST depression abnormality	224	64.4	1681	43.6	<.001

Body mass index was unknown for 7 patients who died; ejection fraction was unknown for 251 patients who died; prior CABG was unknown for 1 patient who died. Smoking history was unknown for 5 patients who survived; body mass index was unknown for 17 patients who survived; ejection fraction was unknown for 3005 patients who survived; prior CABG was unknown for 8 patients who survived; baseline ST depression was unknown for 31 patients who survived.

with 4.8% in the 2222 CABG patients who did not ($P < .01$). Thirty-eight of the 110 patients had peak CK-MB ratios <5 ULN and 72 had peak CK-MB ratios ≥5 ULN. The 6-month mortality was 2.6 and 15.3%, respectively ($P = .09$). The 6-month mortality for the 2222 CABG patients who did not develop a new Q-wave worsening was 3.1% for patients whose peak CK-MB ratio was <5 ULN and 8.0% for patients whose peak CK-MB ratio was ≥5 ULN ($P < .0001$). The 6-month mortality was 13.9% in 137 ACS patients who developed new Q-waves compared with 8.0% in the 4096 ACS patients who did not ($P < .05$).

Multivariate Estimation of 6-Month Survival

The 6-month survival experience was contrasted between CABG and ACS patients for each category of peak CK-MB ratio, adjusting for all shared univariate variables that sig-

Figure 1. Cumulative 6-month survival for 2332 CABG patients by peak CK-MB enzyme ratio category ($P < .0001$). Pairwise comparisons between categories are significant for all groups except the <1 ULN group versus the ≥ 1 and <5 ULN group ($P = .06$) and the <1 ULN group versus the ≥ 5 and <10 ULN group ($P = .98$).

Figure 2. Cumulative 6-month survival for 4233 ACS patients by peak CK-MB enzyme ratio category ($P < .0001$). Pairwise comparisons between categories are significant only for the <1 ULN group versus any of the other 3 groups.

nificantly predicted 6-month mortality through Cox regression (Table 3). Age and gender were also included in the model. Ejection fraction was not included in the model because it was unknown for 3256/4233 (76.9%) of the ACS patients. The survival experience was very similar for CABG and ACS patients at peak CK-MB ratios <1 and ≥ 10 ULN throughout the duration of the follow-up period (Figure 3). The 6-month survival was greater for CABG patients than ACS patients at intermediate enzyme levels, particularly at lower elevations, ≥ 1 and <5 ULN (Figure 4). Findings were similar when any univariate variable that significantly predicted 6-month mortality for either CABG or ACS patients was included in the Cox regression model (data not shown).

Discussion

This GUARDIAN report demonstrates that modest elevations of CK-MB release (≥ 1 and <10 ULN) after CABG

are not associated with an adverse 6-month survival, in contrast to that seen in ACS patients. Marked elevations of CK-MB release (≥ 10 ULN) after CABG are associated with an adverse 6-month survival, similar to that seen in patients who have a spontaneous non-Q-wave MI. The GUARDIAN data are unique in that the protocol required that CK-MB enzymes be prospectively collected at multiple time points in all patients, and standardized forms were used to collect baseline characteristics. In an earlier report from the GUARDIAN Trial, Klatte and colleagues⁶ described significantly increased 6-month mortality with progressively increasing postoperative levels of CK-MB ratio. The 6-month mortality was 20.2% for patients with CK-MB release ≥ 20 ULN. The relationship between elevated CK-MB ratio and 6-month mortality remained significant after adjustment for important covariates known to influence long-term survival and when the 6-month survival analysis was limited to patients who survived to hospital discharge. In a series from the Cleveland Clinic, Brener and coworkers⁵ compared the results of different levels of CK-MB release on 3-year survival in 3573 and 3812 patients who received PCI and CABG procedures, respectively. Abnormal CK-MB levels after surgery were observed in 90% of the CABG cohort, similar to the 94% observed in GUARDIAN. CK-MB release >10 ULN was an independent predictor of 3-year mortality regardless of whether the patient had PCI or CABG and even after adjustment for variables known to influence long-term survival such as an ejection fraction $<40\%$. In this series, CK-MB was sampled routinely 8 and 16 hours after PCI, immediately after CABG, and the next morning after CABG. Importantly, similar to GUARDIAN where 46% of the deaths occurred after the first 30 days, the mortality continued to accrue during the 3-year follow-up and was not limited to the early postoperative phase. Similar data illustrating that death rates continue to rise well past the 6-month follow-up period have been reported by Steuer and colleagues.⁸ Smaller series such as the ARTS Trial and the Warm Heart Trial report findings consistent with the larger series.^{7,9} The data provide strong evidence that large elevations of CK-MB release after CABG represent loss of myocardial tissue and expose patients to a continuing elevated risk of death during follow-up.

The exact CK-MB cut point that is associated with increased mortality risk can be debated, but a reasonable cut point is >10 ULN. In GUARDIAN, new postoperative Q-waves were associated with increased 6-month mortality only in patients who had postoperative CK-MB levels ≥ 5 ULN. When the level of CK-MB release was <5 ULN, new postoperative Q-waves were not associated with increased 6-month mortality. Recently, the American College of Cardiology adopted the definition of postoperative MI for all patients in whom CK-MB release exceeds 10 ULN after

Figure 3. Adjusted cumulative 6-month survival for 2332 CABG patients and 4233 ACS patients for peak CK-MB enzyme ratio <1 ULN ($P = .80$) and ≥ 10 ULN ($P = .99$).

Figure 4. Adjusted cumulative 6-month survival for 2332 CABG patients and 4233 ACS patients for peak CK-MB enzyme ratio ≥ 1 and < 5 ULN ($P < .0001$) and ≥ 5 and < 10 ULN ($P < .05$).

TABLE 3. Adjusted cumulative 6-month survival by peak CK-MB ratio comparing CABG patients and ACS patients*

Peak CK-MB Enzyme Ratio	CABG patients†				ACS patients†				P value
	Dead	Alive	Total	Survival (%)	Dead	Alive	Total	Survival (%)	
<1 ULN	8	133	141	96.6	113	1716	1829	96.0	.80
≥1 and <5 ULN	38	1305	1343	98.0	143	1428	1571	92.5	<.0001
≥5 and <10 ULN	27	434	461	95.8	38	347	385	92.4	<.05
≥10 ULN	46	341	387	90.7	54	394	448	91.1	.99
Total	119	2213	2332	96.2	348	3885	4233	93.9	<.0001

*Survival estimates adjusted for age, gender, and history of MI, congestive heart failure, cerebrovascular disease, peripheral vascular disease, and cardiac arrhythmias.

† $P < .0001$ across enzyme categories.

CABG or when CK-MB release exceeds 5 ULN and new Q-waves occur.¹⁷ One could argue that other clinical parameters such as elderly age, severe left ventricular dysfunction with heart failure symptoms, and so on may be even more predictive of long-term mortality, but regardless of the clinical presentation, CK-MB release > 10 ULN is an adverse marker for long-term outcome. In GUARDIAN and

in the Cleveland Clinic series, CK-MB release > 10 ULN after CABG remained a significant predictor of long-term risk even after adjustment of baseline predictors. The 4 categories of peak CK-MB enzyme ratio used in this study to compare the CABG and ACS cohorts were selected on the basis of prior literature to allow comparisons to other published series.^{1,3,5,6}

Left ventricular ejection fraction measurements were unavailable in the majority of GUARDIAN ACS patients and therefore could not be used as an entry variable to adjust the survival curves in both groups. However, this is unlikely to change the results because the number of patients with prior MI and history of heart failure ranged from 14% to 16% and 52% to 56% for the CABG and ACS cohorts, respectively, and both clinical variables were accounted for in the Cox regression analyses.

ST segment depression on the baseline ECG was more frequently seen in the ACS cohort compared with the CABG cohort. Nevertheless, its presence was associated with increased 6-month mortality in both groups. The GUARDIAN trial excluded patients with ST elevation MI at entry. In addition, in the CABG group, we specifically excluded patients with a CK-MB ratio ≥ 1 ULN at baseline to remove subjects who may have had an entry MI event that could potentially confound the interpretation of patients with abnormal postoperative CK-MB release. The increased mortality risk for patients with marked elevations of CK-MB release after CABG and cardioplegic arrest indicates that these patients most likely had an MI during surgery and should be considered for long-term angiotensin-converting enzyme inhibitors and beta-blocker therapy. It is likely that patients who sustain a perioperative MI after CABG will have similar benefits from cardioactive drug therapy as medically treated postinfarction patients.¹⁸⁻²⁰ Newer therapies to reduce myocardial necrosis during CABG offer the potential to reduce the number of patients at risk and are being explored in the EXPEDITION Trial with cariporide, an Na^+/H^+ exchange inhibitor, and in the Primo-CABG Trial, with pexelizumab, a complement inhibitor. In GUARDIAN, 120 mg of cariporide every 8 hours significantly reduced myocardial infarction rates when compared with placebo.¹²

The use of cardiac troponin to predict outcome after CABG is an area of active research and is being explored in the large multicenter EXPEDITION and Primo-CABG trials, among the largest randomized clinical trials of CABG ever conducted. At the current time, the data on troponin clearance rates from large-scale clinical trials that correlate magnitude of troponin release to long-term outcome are limited.²¹⁻²³ The value of cardiac troponin values after CABG in predicting short- and long-term outcome was reviewed in a recent consensus panel meeting.²⁴ The release ratios for cardiac troponin after CABG have not been completely worked out and some assays are imprecise in their diagnostic thresholds for upper limits of normal.²⁵

Our study compared survival differences at similar levels of CK-MB release between 2 different patient cohorts enrolled in GUARDIAN. There were significant differences in the frequency of baseline characteristics between the 2 groups that could potentially impact 6-month survival.

However, we adjusted for those shared variables that were the most significantly related to 6-month mortality in both groups in the Cox regression model and the results were similar when any variable that was significantly associated with 6-month mortality for either CABG or ACS patients was controlled for in the Cox regression analyses.

Routine measurement of CK-MB after coronary revascularization is critical in identifying patients at risk for subsequent death. Our data support the fact that modest elevations of CK-MB release (≥ 1 and < 10 ULN) after CABG are not associated with an adverse 6-month survival, contrary to that seen in ACS patients. Routine CK-MB sampling should be considered in all higher-risk patients undergoing CABG procedures to identify the sizable cohort with CK-MB release ≥ 10 ULN that may benefit from postoperative angiotensin-converting enzyme inhibitor and beta-blocker therapy. Newer cardioprotective agents that reduce the number of patients with marked CK-MB release are currently being tested in large randomized controlled clinical trials.

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