

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2001;104;2689-2693

DOI: 10.1161/hc4701.099789

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214
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ISSN: 1524-4539

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Incidence, Predictors, and Significance of Abnormal Cardiac Enzyme Rise in Patients Treated With Bypass Surgery in the Arterial Revascularization Therapies Study (ARTS)

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Background—Although it has been suggested that elevation of CK-MB after percutaneous coronary intervention is associated with adverse clinical outcomes, limited data are available in the setting of coronary bypass grafting. The aim of the present study was to determine the incidence, predictors, and prognostic significance of CK-MB elevation following multivessel coronary bypass grafting (CABG).

Methods and Results—The population comprises 496 patients with multivessel coronary disease assigned to CABG in the Arterial Revascularization Therapies Study (ARTS). CK-MB was prospectively measured at 6, 12, and 18 hours after the procedure. Thirty-day and 1-year clinical follow-up were performed. Abnormal CK-MB elevation occurred in 61.9% of the patients. Patients with increased cardiac-enzyme levels after CABG were at increased risk of both death and repeat myocardial infarction within the first 30 days ($P=0.001$). CK-MB elevation was also independently related to late adverse outcome ($P=0.009$, $OR=0.64$).

Conclusions—Increased concentrations of CK-MB, which are often dismissed as inconsequential in the setting of multivessel CABG, appear to occur very frequently and are associated with a significant increase in both repeat myocardial infarction and death beyond the immediate perioperative period. (*Circulation*. 2001;104:2689-2693.)

Key Words: cardiopulmonary bypass ■ creatine kinase ■ coronary disease

Myocardial necrosis has classically been detected by measurement of the serum creatine kinase (CK) and specifically the MB isoenzyme (CK-MB), which is more sensitive and specific.¹⁻⁴ Elevation of CK-MB following percutaneous coronary revascularization procedures has been demonstrated to occur in 6% to 34% of patients.⁵⁻¹⁰

A recent consensus report has proposed a CK-MB threshold of 3 times the upper limit of normal for percutaneous revascularization and 5 times for bypass surgery as a marker for periprocedural myocardial infarction and subsequent increased risk of adverse events.¹ This recommendation is derived mainly from reports on the prognostic significance of cardiac enzyme elevation after balloon angioplasty or directional coronary atherectomy (DCA). At present, no definitive conclusion can be drawn concerning the prognostic significance of CK-MB elevation following coronary bypass surgery because of a paucity of data relating to this issue.^{1,11,12}

The Arterial Revascularization Therapies Study (ARTS) was designed to compare coronary artery bypass grafting (CABG) and stenting for the treatment of patients with multivessel coronary disease.¹³ The aims of the present investigation were to determine the incidence, predictors, and prognostic significance of CK-MB elevation following multivessel CABG.

Methods

ARTS Trial Design

Between April 1997 and June 1998, 1205 patients were randomized to either stent implantation ($n=600$) or CABG ($n=605$) at 67 participating centers worldwide.¹³ Only patients who had no previous angioplasty or CABG procedures were included. The indications for revascularization were silent ischemia, stable or unstable angina pectoris, and the presence of at least 2 de novo lesions located in different major epicardial coronary arteries potentially amenable to stent implantation. Patients with left main stem stenosis, impaired

Received July 10, 2001; revision received September 26, 2001; accepted September 26, 2001.

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left ventricular function (left ventricular ejection fraction <30%), prior cerebrovascular accident (CVA), myocardial infarction within the week preceding randomization, severe hepatic or renal disease, or patients who needed concomitant major surgery were not included in the study. All patients gave written informed consent.

Bypass surgery followed current standard techniques, preferably using the left internal mammary artery for revascularization of the left anterior descending coronary artery.^{1,3}

Data Collection

Angiographic data, including the characteristics of each lesion and target coronary segment were adjudicated by an independent core laboratory (Cardialysis BV, Rotterdam). Myocardial infarction (MI) occurring within 7 days of the procedures was defined as the appearance of a new Q-wave and cardiac enzymes greater than 5 times the upper limit of normal or a ratio of peak CK-MB/CK exceeding 0.1. To define a MI after 7 days, either the electrocardiographic or enzymatic criteria sufficed. The Minnesota criteria code for pathological Q-waves was used, and the EKGs were analyzed by an independent core laboratory.

Case report forms were verified and compared with each medical record by the study monitors. Clinical events were adjudicated by an independent committee.

CK-MB Study Design

All patients enrolled in the ARTS trial and randomized to CABG were eligible for the present study, a post hoc analysis. Patients were excluded

if they had elevated cardiac enzymes prior to the procedure (n=47), were not treated according to randomization (n=26), or if measurements of cardiac enzymes were not available (n=36) in the CABG group.

Blood samples were collected for CK-MB measurements at screening and at 6, 12, and 18 hours after the procedure. If enzymes were found to be elevated, CK-MB levels were followed for a longer duration to determine the actual peak value. These measurements were performed according to the local laboratory standards. In order to standardize the analyses at different sites, enzyme levels were expressed based on the local normal laboratory values. Patients were stratified into 4 categories of CK-MB levels: normal, 1 to 3, ≥3 to 5, and more than 5 times the upper limit of normal in each treatment arm. Because of its low specificity in detecting myocardial injury, particularly in patients post CABG, measurements of total CK were not evaluated.

Every itemized clinical event including death, MI, any repeat revascularization as well as the combined major cardiac (death, MI, and repeated revascularization) and cerebrovascular events (MACCE) occurring >24 hours after the procedures were counted for 30-day and 1-year follow-up analyses. Any event occurring within 24 hours after the procedure was not counted as an adverse event in order to avoid the potential confounding influence of the immediate sequelae of procedural complications.

Statistical Analysis

Statistical analysis was performed using the SAS 6.12 (SAS Institute Inc). Continuous variables are expressed as mean±SD. Binary outcome variables are reported as frequencies and percentages. In the 30-day analysis, χ^2 analysis was performed according to Mantel-Haenszel for comparisons among categorical variables of the subgroups. For 1-year follow-up, events were depicted with Kaplan-Meier curves using the SAS Lifetest procedure, and probability values were defined by means of log rank analysis. Multivariate logistic regression models were constructed using baseline characteristics as well as procedure-related factors to identify independent predictors of CK-MB rise after the procedure. Another multivariate logistic regression model was constructed to determine whether the level of cardiac enzyme (CK-MB) after the procedure was an independent risk-factor for late events. A value of $P<0.05$ was considered significant.

Results

In the present study, 496 patients treated with CABG were included. Baseline characteristics are shown in Table 1.

Incidence and Predictors of Postprocedure CK-MB Release

Overall, abnormal CK-MB elevation occurred in 61.9% of patients treated with CABG. Figure 1 illustrates the stratification of CK-MB elevation.

TABLE 1. Clinical and Procedure-Related Variables

Variables	CABG (n=496)
Clinical characteristics	
Age, y	61.5
Male, %	75
Unstable angina, %	36.1
Previous myocardial infarction, %	40.9
Diabetes mellitus, %	16.5
Hypertension, %	45.2
Hypercholesterolemia, %	58.3
Family history, %	42.3
Peripheral vascular disease, %	5.0
Current smoking, %	24.4
Left ventricular ejection fraction, %	60.8
Procedural-related variables	
Number of segments diseased*	2.8±1
Number of segments treated*	2.7±0.8
Number of distal anastomoses*	2.8±0.8
Target vessel	
Left anterior descending, %	91
Right coronary artery, %	72
Left circumflex, %	72
At least 1 arterial conduit used, %	90
Left internal mammary artery, %	90
Arterial conduit on LAD, %	95
Duration of aorta cross-clamp, min*	44.5±24
Type of myocardial protection	
Crystalloid, %	57
Blood, %	34
Intermittent cross-clamping, %	19

*Numbers are expressed as mean±SD.

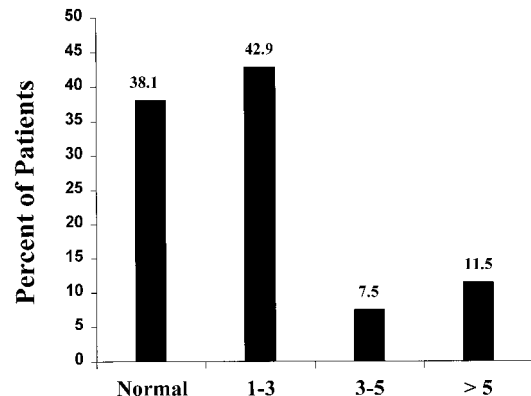


Figure 1. Frequency of CK-MB elevation after bypass surgery, according to the prestratified categories (n=4) of CK-MB levels.

TABLE 2. Independent Predictors of CK-MB Elevation After CABG

	Frequency	χ^2	P-value	Odds Ratio
Use of oral short-acting nitrates	141/496	14	0.0002	2.13
Angiographic thrombus at screening	19/487	10.6	0.001	0.14
Emergency procedure	13/487	9.2	0.002	5.88
Target lesion in the first marginal branch	54/496	9.2	0.002	2.38
Need for inotropic agents postprocedure	23/496	8	0.005	3.45
Use of ACE inhibitors	116/496	7.1	0.008	0.56
Diabetes mellitus	82/496	6.6	0.01	0.53
Unstable angina	171/496	6.6	0.01	0.57
Angulation of the target segments >90°	43/496	5.8	0.02	2.08
Duration of aortic cross-clamping, min		5.3	0.02	1.01
Anastomosis in the mid-third of LAD	380/496	4.8	0.03	0.62
Totally occluded vessels, >3 months	16/487	4.9	0.03	2.94

ACE indicates angiotensin converting enzyme, LAD, left anterior descending.

Factors found to be significant in the univariate analysis (n=22) were entered into the multivariate logistic model. Several independent risk-factors were found to predict CK-MB elevation after the procedure (Table 2): use of oral short-acting nitrates during hospitalization, revascularization priority (emergency), need for inotropic agents after the procedure, lesion location in the first circumflex marginal or intermediate branch, target segments with angulation >90 degrees, duration of aortic cross-clamping, and number of totally occluded vessels (>3 months). Some variables were found to be protective against CK-MB rise after the procedure: angiographic evidence of thrombus in the target lesion, the use of angiotensin converting enzyme (ACE) inhibitors during hospitalization, diabetes mellitus, unstable angina, and anastomosis in the mid-third of left anterior descending coronary artery.

Prognostic Significance of Increased CK-MB Concentration

Table 3 summarizes the incidence of early adverse events after CABG, according to the stratified levels of CK-MB elevation. Patients with increased cardiac-enzyme levels after CABG were at high risk of death as well as repeat MI. Patients with the highest level (>5 times normal) of CK-MB showed an early mortality rate of 7%. Patients with CK-MB levels 3 to 5 times normal also had a trend toward an increased mortality rate as compared with patients with mild (>1 to 3 times normal) CK-MB elevations ($P=0.065$).

All deaths were cardiovascular in origin. One patient with CK-MB levels >1 to 3× normal died 2 days later after arrhythmia and cardiac arrest. One patient with CK-MB elevation 3 to 5× normal developed a bowel infarction and died after 1 month due to arrhythmias and renal failure. A second patient with CK-MB levels 3 to 5× normal had a cardiac arrest 48 to 60 hours postoperatively. Among patients with CK-MB levels >5× normal, 4 patients died at 2, 3, 18, and 21 days postoperatively due to postoperative acute respiratory failure, thrombotic small bowel infarction and metabolic dysfunction, myocardial infarction, and pulmonary embolism with cardiogenic shock, respectively.

One-year follow-up data were obtained in all patients. Patients with postprocedure CK-MB elevation after CABG were more likely to have adverse events (Figure 2). A strong relationship between cardiac enzyme levels and each itemized clinical event, death, or repeat MI was observed in the CABG group (Figure 3). Mortality rates were 1.1%, 0.5%, 5.4%, and 10.5%, the incidences of MIs were 1.1%, 1.9%, 2.7%, and 12.3%, CVA occurred in 1.6%, 1.9%, 2.7%, and 1.8%, whereas repeat revascularization occurred in 3.7%, 2.8%, 0%, and 3.5% of patients with CK-MB levels that were normal, >1 to 3, ≥3 to 5, and >5 times normal, respectively.

Predictors of Late Outcome

In order to determine whether elevated CK-MB levels should be interpreted as an independent marker of worse clinical outcomes (1-year MACCE) in patients treated with CABG, a

TABLE 3. Incidence of Events up to 30 Days After CABG

CK-MB Level	Normal (n=189)	>1-3 (n=213)	3-5 (n=37)	>5 (n=57)	Any CK-MB Elevation (n=307)	P*
Death, %	0	0.5	5.4	7.0	2.3	0.001
Myocardial infarction, %	1.1	1.4	2.7	12.3	3.9	0.001
CVA, %	1.1	1.4	0	1.8	1.3	NS
Any revascularization, %	0.5	0	0	3.5	0.7	NS

CVA indicates cerebrovascular accident.

*Comparison between the 4 groups.

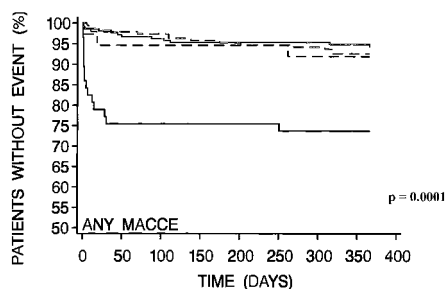


Figure 2. Kaplan-Meier curves illustrating the incidence of MACCE at 1-year follow-up in patients with normal CK-MB levels (dashed gray lines), >1 to 3 times normal (solid gray lines), ≥ 3 to 5 times normal (dashed black lines), and >5 times normal (solid black lines). The P -value refers to the comparison among the 4 groups.

multivariate logistic regression was performed. The peak post-procedural cardiac enzyme level was strongly correlated with adverse events after CABG ($P=0.009$, $OR=1.56$, $\chi^2=6.8$). Other factors were also found to be predictors of 1-year MACCE, as follows: emergency procedure ($P=0.002$, $OR=10.1$, $\chi^2=9.9$), age ($n=13$, $P=0.01$, $OR=1.05$, $\chi^2=6.3$), and abnormal monocyte levels ($n=20$, $P=0.004$, $OR=4.8$, $\chi^2=8.3$).

Discussion

In the present study, patients treated with CABG experienced a high incidence of postprocedure CK-MB elevation. CK-MB elevation >1 to 3 times normal was a frequent finding (42.9%), and only 38.1% of the patients had normal levels of CK-MB postoperatively (Figure 1). A small amount of CK-MB (2% to 4%) may be measurable after skeletal muscle injury,¹⁴ and the manipulation of the heart during operation may also induce a CK-MB leak.¹⁵ A small rise of CK-MB without irreversible myocardial necrosis has also been reported.¹⁶

Predictors of CK-MB Elevation

A number of factors, including anatomical and procedure-related variables, independently influenced the level of CK-MB after CABG. The use of oral short-acting nitrates was the strongest predictor of abnormal CK-MB elevation after surgery. This may reflect a deleterious effect of these agents on myocardial protection during surgery as described by others.¹⁷ Conversely, the use of angiotensin converting enzyme (ACE) inhibitors had a protective effect on the myocardium.¹⁸ Additional prospective investigations are required to address this question.

Unstable angina, angiographic evidence of thrombus, and diabetes mellitus at screening were identified as protective factors against CK-MB elevation following surgery. Some previous data may support this paradoxical finding. First, preconditioning ischemia^{19,20} may prevent CK-MB elevation in patients with unstable angina or angiographic thrombus at screening. Furthermore, in the GUSTO-I trial, diabetic patients also had lower levels of creatine kinase release compared with nondiabetics.²¹ These findings may be explained by a decline in creatine kinase activity related to diabetes as demonstrated in animal studies.^{22,23} Finally, intensified medical management in the treatment of these high-risk patients, either in the time interval between screening and surgery or during the procedure, cannot be completely ruled out as an explanation for our findings.

Clinical Implications

The level of CK-MB was shown to be an independent predictor of clinical events in this population treated with bypass surgery. Patients with elevated CK-MB levels, particularly those with levels >5 times normal, were at higher risk of death or myocardial infarction compared with those with normal or mild cardiac enzyme elevation. This finding has not previously been reported in a large prospective multicenter trial. In fact, the difficulty in determining clinically relevant myocardial injury during CABG²⁴ has led to the common belief that cardiac enzymes have limited prognostic value in this setting.²⁵ A limited number of investigations have reported the incidence of CK-MB elevation after CABG,^{26,27} and virtually no previous study has addressed the long-term prognostic significance of this biochemical marker.

Based on our findings, increased CK-MB may be considered as a marker of worse outcome after CABG and patients with markedly increased levels of CK-MB ($>5\times$ normal) should be treated as a high-risk population for subsequent clinical events (death and/or MI) occurring as early as 30 days postoperatively. Because a trend toward a higher mortality rate was also observed in patients with CK-MB elevations >3 to $5\times$ normal, these patients may also be considered at increased risk. Our data justify routine measurement of cardiac enzymes in patients treated with bypass surgery, especially in future clinical trials, in order to confirm these findings.

Acknowledgments

We thank Dr Brian Firth for his careful review of the manuscript and for his constructive comments.

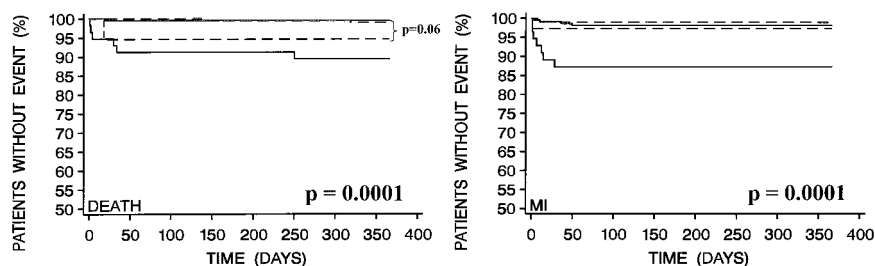


Figure 3. Kaplan-Meier curves illustrating the incidence of death and myocardial infarction (MI) at 1-year follow-up in patients with normal CK-MB levels (dashed gray lines), >1 to 3 times normal (solid gray lines), ≥ 3 to 5 times normal (dashed black lines), and >5 times normal (solid black lines) after bypass surgery. The P -value refers to the comparison among the 4 groups.

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