Association of Myocardial Enzyme Elevation and Survival Following Coronary Artery Bypass Graft Surgery

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Context Several small studies have suggested that cardiac enzyme elevation in the 24 hours following coronary artery bypass graft (CABG) surgery is associated with worse prognosis, but a definitive study is not available. Also, the long-term prognostic impact of small increases of perioperative enzyme has not been reported.

Objective To quantify the relationship between peak post-CABG elevation of biomarkers of myocardial damage and early, intermediate-, and long-term mortality, including determining whether there is a threshold below which elevations lack prognostic significance.

Data Sources Studies (randomized clinical trials or registries) of patients undergoing CABG surgery in which postprocedural biomarker and mortality data were collected and included. A search of the PubMed database was performed in July 2008 using the search terms *coronary artery bypass, troponin*, *CK-MB*, and *mortality*.

Study Selection Studies evaluating mortality and creatine kinase (CK-MB), troponin, or both were included. One study investigator declined to participate and 3 had insufficient data.

Data Extraction Two independent reviewers determined study eligibility. The principal investigator from each eligible study was contacted to request his/her participation. Once institutional review board approval for the use of these data for this purpose was obtained, we requested patient-level data from each source. Data were examined to ensure that cardiac markers had been measured within 24 hours after CABG surgery, key baseline covariates, and mortality were available.

Results A total of 18 908 patients from 7 studies were included. Follow-up varied from 3 months to 5 years. Mortality was found to be a monotonically increasing function of the CK-MB ratio. The 30-day mortality rates by categories of CK-MB ratio were 0.63% (95% confidence interval [CI], 0.36%-1.02%) for 0 to <1, 0.86% (95% CI, 0.49%-1.40%) for 1 to <2, 0.95% (95% CI, 0.72%-1.22%) for 2 to <5, 2.09% (95% CI, 1.69%-2.57%) for 5 to <10, 2.78% (95% CI, 2.12%-3.58%) for 10 to <20, and 7.06% (95% CI, 5.46%-8.96%) for 20 to ≥40. Of the variables considered, the CK-MB ratio was the strongest independent predictor of death to 30 days and remained significant even after adjusting for a wide range of baseline risk factors (χ^2=143, P<.001; hazard ratio [HR] for each 5 point-increment above the upper limits of normal [ULN]=1.12; 95% CI, 1.10-1.14). This result was strongest at 30 days, but the adjusted association persisted from 30 days to 1 year (χ^2=24; P<.001; HR for each 5-point increment above ULN=1.17; 95% CI, 1.10-1.24) and a trend was present from 1 year to 5 years (χ^2=2.8; P=.10; HR for each 5-point increment above ULN=1.05; 95% CI, 0.99-1.11). Similar analyses using troponin as the marker of necrosis led to the same conclusions (χ^2=142 for 0-30 days and χ^2=40 for 30 days to 6 months, both P<.001; HR for each 50 points above the ULN=1.28; 95% CI, 1.23-1.33 and 1.15; 95% CI, 1.10-1.21, respectively).

Conclusions Among patients who had undergone CABG surgery, elevation of CK-MB or troponin levels within the first 24 hours was independently associated with increased intermediate- and long-term risk of mortality.

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About 400 000 coronary artery bypass grafting (CABG) procedures are performed annually in the United States,[1] giving public health significance to factors that affect the outcome of these procedures. Increases in creatine kinase (CK-MB) or troponin levels following CABG is common,[2] occurs even in the absence of graft occlusion, and is ascribed to a number of causes including, though not limited to, cell death resulting from insufficient myocardial protection during cardiopulmonary bypass or with off-pump techniques, air embolism, and regional and global ischemia during the procedure. Small amounts of necrosis are often regarded as insignificant. There is, however, limited support in the literature for the view that only large enzyme elevations are associated with a worse prognosis.[3] In fact, several relatively small studies suggest that elevation of cardiac enzymes in the first 24 hours following the CABG procedure is associated with worse prognosis.[4-7] For this reason, there is no clarity regarding what level of enzyme elevation should be used to assess prognosis in

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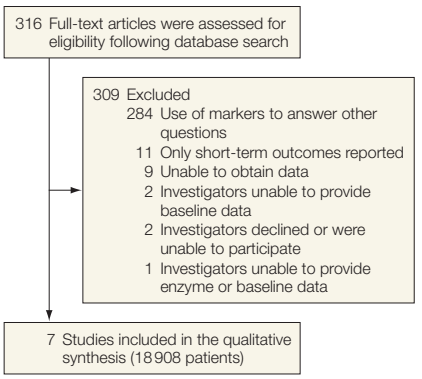
clinical trials of patients undergoing CABG.

The purpose of the present study was to quantify the relationship between post-CABG elevation of enzyme markers of myocardial damage and early, intermediate-, and long-term mortality, including determining whether a threshold exists below which small elevations lack prognostic significance. To accomplish this, we pooled and analyzed data from every available randomized clinical trial or registry that measured CK-MB levels and assessed survival status following CABG in all study patients.[8-14] Parallel analyses were performed using troponin, where available.

Figure 1. Design of Coronary Artery Bypass Graft Surgery Marker Study



METHODS

All studies of patients undergoing CABG surgery in whom postprocedural enzyme CK-MB data and intermediate (3-month) or long-term mortality were collected were evaluated for inclusion into the study (FIGURE 1). A number of baseline covariates were also required in order to adjust for differences in patient demographics. Five studies, involving 8903 patients, were excluded. Two groups of investigators declined to participate,[15,16] 1 could not provide the necessary enzyme or end point data,[17] and 2 could not provide the necessary baseline data.[18,19] For each patient, the CK-MB ratio was calculated as the ratio between the peak CK-MB and the upper limit of normal (ULN) for the participating laboratory of each study.

The 2 standard models used to estimate the relationship between the CK-MB ratio levels and mortality at 30 days were the linear logistic model and the log-linear logistic model, which is similar to the linear logistic model except the CK-MB ratio is first transformed using a natural log transformation.

To examine the longer-term relationship of the CK-MB ratio to mortality, we fitted a Cox proportional hazards model for mortality from 0 to 30 days, 30 days to 1 year, and from 1 to 5 years. This was done both with and without the baseline covariates (study, age, sex, weight, and history of myocardial infarction [MI], renal dysfunction, diabetes, peripheral vascular disease, hypertension, number of grafts, cross-clamp time, and internal mammary artery vs other graft). The proportional hazards assumption was evaluated by the time varying interaction of each factor with time to death. No significant deviations from the assumption were noted.

Troponin I measures were provided only in the Pexelizumab for the Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery (PRIMO) I and II studies with follow-up to 6 months. Analysis of 30-day and 30- to 180-day survival by troponin I ratio were examined in the same fashion as CK-MB was analyzed.

These models were fitted using SAS PROC PHREG (SAS Institute Inc, Cary, North Carolina).[20] Statistical significance was considered with a 2-sided critical value of .05. All models were replicated using multiple imputation techniques (SAS PROC MI

Table 1. Demographic Characteristics

Variable	Study							Overall
	Brener et al,[8] 2002	MEND-CABG,[13] 2007	MEND-CABG II,[9] 2008	PREVENT-IV,[11] 2005	PRIMO-CABG I,[12] 2004	PRIMO 2,[10] 2006	Engoren et al,[14] 2005	
No. of patients	3573	903	3023	3014	3059	4175	1161	**18908**
Age, mean (SD), y	64 (11.4)	66 (10.3)	65 (10.1)	63 (9.7)	65 (10.2)	66 (10.2)	64 (10.0)	65 (10.4)
White, No. (%)	NA	839 (92.9)	2747 (90.9)	2740 (90.9)	2746 (90.1)	3788 (90.9)	NA	**12860** (90.9)
Men, No. (%)	2548 (71.5)	711 (78.7)	2297 (76.0)	2385 (79.1)	2240 (73.2)	2530 (60.6)	790 (68.0)	**13501** (71.4)
Diabetes, No. (%)	1015 (28.4)	388 (43.0)	1394 (46.2)	1139 (37.8)	1255 (41.0)	2497 (59.8)	374 (32.2)	**8062** (42.7)
Hypertension, No. (%)	2436 (68.3)	671 (74.6)	2505 (83.0)	2263 (75.1)	1601 (52.3)	3544 (84.9)	899 (77.4)	**13919** (73.7)
Current smoker, No. (%)	722 (20.2)	254 (28.1)	830 (27.5)	690 (22.9)	312 (10.2)	847 (20.3)	742 (63.9)	**4397** (23.3)
Renal insufficiency, No. (%)	147 (4.1)	17 (1.9)	405 (13.4)	65 (2.2)	237 (7.7)	669 (16.0)	29 (2.5)	**1569** (8.3)
Peripheral vascular disease, No. (%)	317 (8.9)	147 (16.5)	406 (13.7)	369 (12.2)	435 (14.2)	1324 (31.7)	179 (15.4)	**3177** (16.9)
Weight, kg, mean (SD)	86 (17.9)	86 (18.2)	88 (18.8)	89 (18.3)	84 (18.2)	85 (19.0)	86 (17.1)	86 (18.4)
Previous MI, No. (%)	1519 (44.0)	489 (55.6)	1565 (52.3)	1273 (42.2)	345 (11.3)	2284 (54.7)	681 (58.7)	**8156** (43.5)
CK-MB ratio, mean (SD)	2 (5.1)	9 (10.6)	8 (10.7)	5 (8.1)	10 (12.3)	11 (14.9)	6 (9.4)	7 (11.3)
Troponin I ratio, mean (SD)	NA	NA	NA	NA	69 (143.7)	55 (121.7)	NA	61 (131.5)

Abbreviations: CABG, coronary artery bypass graft; CK, creatine kinase; MEND, MC-1 to Eliminate Necrosis and Damage; MI, myocardial infarction; NA, not applicable; PREVENT, Prevention of Recurrent Venous Thromboembolism; PRIMO, Pexelizumab for the Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery.

Table 2. Kaplan-Meier Mortality Rate Table and Average Length of Follow-up

Study	No. of Patients	Length of Follow-up, (Mean) SD, mo	Percent			
			0 to 30 Days	30 Days to 1 Year	1 to 5 Years	30 Days to 6 Months, Troponin I
Brener et al,[8] 2002	3573	35 (17.2)	1.2	3.6	11.4	
MEND-CABG,[13] 2007	903	3 (0.9)	1.3			
MEND-CABG II,[9] 2008	3023	2 (1.2)	1.7			
PREVENT-IV,[11] 2005	3014	57 (14.4)	1.2	2.0	8.6	
PRIMO-CABG I,[12] 2004	3059	6 (1.8)	2.8			2.3
PRIMO-CABG-2 2,[10] 2008	4175	6 (1.3)	4.1			3.7
Engoren et al,[14] 2005	1161	66 (15.4)	1.1	1.8	6.8	
Overall	18 908	22 (25.1)	2.2	2.7	8.9	3.1

Abbreviations: MEND-CABG, MC-1 to Eliminate Necrosis and Damage in Coronary Artery Bypass Graft Surgery; PREVENT, Prevention of Recurrent Venous Thromboembolism; PRIMO, Pexelizumab for the Reduction of Infarction and Mortality in CABG surgery.

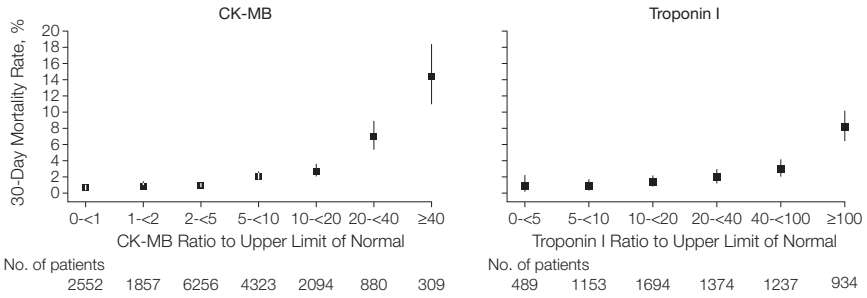
and MIANALYZE). Funnel plots and fail-safe numbers were calculated to ensure the results were stable in spite of the absence of the 5 excluded trials.[21]

RESULTS

A total of 18 908 patients from 7 studies were included. The clinical and demographic characteristics are shown in TABLE 1. All the study populations had a mean age between 60 and 70 years. In the 5 studies that reported patient race, more than 90% of patients were white. Follow-up varied from 3 months to 5 years. Event rates by study are displayed in TABLE 2.

The unadjusted 30-day pooled mortality is shown in FIGURE 2. Mortality is an increasing function of CK-MB ratio with greatest risks associated with very high ratios. Both the observed rates by CK-MB ratio category and the fitted models suggest that no threshold exists in the response relationship. We used the log-linear logistic model to determine concentrations of the CK-MB ratio that would lead to a 25%, 50%, or 100% increase in expected mortality compared with the expected mortality at a CK-MB ratio of 1.0. Categories of this relationship are displayed in TABLE 3. The 30-day survival rates by categories of CK-MB ratio are 0.63% (95% confidence interval [CI], 0.36%-1.02%) for 0 to <1, 0.86% (95% CI, 0.49%-1.40%) for 1 to <2, 0.95% (95% CI, 0.72%-1.22%) for 2 to <5, 2.09% (95% CI, 1.69%-2.57%) for 5 to <10, 2.78%

Figure 2. Unadjusted 30-Day Mortality



Creatine kinase MB (CK-MB) ratios are derived from the pooled coronary artery bypass graft surgery trials. The troponin I ratios are derived from the Pexelizumab for the Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery I and II trials. Data markers represent the mortality rates within each category. The error bars represent 95% confidence intervals.

Table 3. Thirty-Day Mortality by Categories of Creatine Kinase MB and Troponin I Ratios[a]

	No. of Patients	Model Estimated Relative Risk of Mortality (95% CI)
Creatine kinase MB ratio category[b]		
1 to <5	8113	1.69 (0.89-3.19)
5 to <10	4323	2.98 (1.53-5.80)
10 to <20	2094	4.47 (2.27-8.81)
20 to <40	880	8.73 (4.37-17.43)
≥40	369	27.01 (13.15-55.45)
Troponin I ratio category[c]		
5 to <10	1153	1.00 (0.26-3.92)
10 to <20	1694	1.89 (0.55-6.48)
20 to <40	1374	2.22 (0.64-7.65)
40 to <100	1237	3.61 (1.08-12.04)
≥100	934	10.91 (3.35-35.53)

Abbreviation: CI, confidence interval.
[a] Ratios are relative to categories of creatine kinase MB from 0 to <1 (n=2552) and troponin I from 0 to <5 (n=489), respectively.
[b] The lower end of the creatine kinase MB ratio interval is included whereas the upper end is not. Note: The categories are linear and not based on the log of the creatine kinase MB values.
[c] Lower end of the troponin I ratio interval is included whereas the upper end is not.

(95% CI, 2.12%-3.58%) for 10 to <20, and 7.06% (95% CI, 5.46%-8.96%) for 20 to ≥40. The model suggests that a CK-MB ratio value of 4 to 5 results in an expected 30-day mortality that is more than double that for a CK-MB ratio of 1. (A CK-MB of 4.4 provides an estimated odds ratio of 2.0.) Available troponin data yielded a similar relationship (Table 3).

A Cox proportional hazard model was used to examine whether the effect of the CK-MB ratio persisted in the presence of baseline risk variables. A Cox model was fitted to the 30-day, 1-year, and 5-year mortality data (TABLE 4). For 30-day mortality, a linear term was used for the CK-MB ratio because this provided a better fit using a Cox model with covariates. The CK-MB ratio, age, history of renal dysfunction, and prior myocardial infarction (MI) were all significant predictors of 30-day mortality. Of the variables in the model, the CK-MB ratio was the strongest predictor of death and remained significant even after adjusting for a wide range of baseline risk factors (χ^2=143; P<.001; hazard ratio [HR] for each 5-point increase above the ULN=1.12; 95% CI, 1.10-1.14).

We also used a Cox proportional hazard model to examine whether the effect of CK-MB persisted past 30 days and 1 year in the presence of baseline risk variables. The analysis was made only for those patients who had survived to 30 days or 1 year. The association between CK-MB ratio and mortality persisted during this follow-up period. (χ^2=24, P<.001; HR for each 5-point increase above the ULN=1.17; 95% CI, 1.10-1.24). The only studies with data available beyond 30 days were the Engoren and Brener registries and the Prevention of Recurrent Venous Thromboembolism (PREVENT) IV trial. A trend toward an association of CK-MB ratio and mortality at 5 years was present among 1-year survivors (χ^2=2.8; P=.10; HR for each 5-point increase above ULN=1.05; 95% CI, 0.99-1.11). Significantly associated risk factors were age, history of prior MI, history of hypertension, renal dysfunction, diabetes, and peripheral vascular disease. Available variables associated with the CABG procedure, including number of grafts, cross-clamp time, and internal mammary artery vs other graft were not independently associated with mortality.

The findings were similar when the troponin ratio, rather than CK-MB ratio, was examined (TABLE 5). The troponin data were only available for the PRIMO data sets. The CK-MB ratios for these 2 studies were examined to confirm that the patients in these studies showed similar CK-MB trends to those across all patients. Thus, the comparison of CK-MB and troponin I curves is applicable. Figure 2 illustrates that the doubling of risk occurs in CK-MB ratios of 5 or higher. For troponin, this occurs at values of 20 to 40.

Replication of the results using imputed data to account for missing values gave similar results. The relative size of the Wald χ^2 analyses for both CK-MB and troponins when compared with other covariates, as well as the values of the HRs did not change any conclusions or interpretations of the results. The fail-safe number tests indicated that the results would not have changed substantially with the inclusion of the 5 studies whose data we could not incorporate.

COMMENT

This is the largest study of the relationship between post-CABG surgery enzyme elevation and mortality and shows a strong, graded, independent association of elevation of markers of myocardial necrosis, CK-MB and troponin levels, and mortality following CABG surgery for all CK-MB and troponin ratios greater than 1. The mortality rate

Table 4. Cox Proportional Hazards Model Predicting 30-Day, 30-Day to 1-Year, and 1-Year to 5-Year Mortality

	30-Day Mortality			1-Year Mortality, If Survived 30 Days			5-Year Mortality, If Survived 1 Year		
Factor	Wald χ^2	*P* Value	HR (95% CI)	Wald χ^2	*P* Value	HR (95% CI)	Wald χ^2	*P* Value	HR (95% CI)
Study	38.1	<.001		0.9	.34		1.8	.18	
Peak CK-MB ratio, per increase of 5, 24 h post-CABG surgery	143.4	<.001	1.12 (1.10-1.14)	23.8	<.001	1.17 (1.10-1.24)	2.8	.10	1.05 (0.99-1.11)
Age, per 10 y	27.5	<.001	1.55 (1.32-1.83)	31.0	<.001	2.43 (1.78-3.31)	31.3	<.001	1.49 (1.30-1.72)
Prior MI	9.3	.002	1.55 (1.17-2.05)	4.4	.04	1.66 (1.03-2.66)	1.7	.19	1.17 (0.93-1.48)
History of renal dysfunction	10.5	.001	1.73 (1.24-2.41)	24.8	<.001	5.82 (2.91-11.64)	33.8	<.001	3.67 (2.37-5.70)
History of diabetes	2.6	.11	1.27 (0.95-1.69)	5.7	.02	1.82 (1.11-2.98)	17.1	<.001	1.68 (1.31-2.15)
History of PVD	3.3	.07	1.31 (0.98-1.76)	0.02	.90	1.04 (0.58-1.85)	30.0	<.001	2.08 (1.60-2.70)
History of hypertension	0.1	.81	1.05 (0.71-1.54)	0.5	.46	1.27 (0.67-2.41)	3.4	.06	1.36 (0.98-1.89)
Female sex	0.3	.58	1.09 (0.80-1.48)	0.3	.56	1.17 (0.69-2.00)	1.9	.17	1.21 (0.92-1.60)
Current smoker	1.2	.27	1.22 (0.86-1.74)	3.2	.07	1.65 (0.95-2.85)	6.2	.01	1.42 (1.08-1.87)
Weight, per 10 kg	0.1	.79	0.99 (0.91-1.08)	2.5	.11	0.88 (0.75-1.03)	0.02	.90	1.01 (0.94-1.08)
IMA graft	1.6	.21	0.80 (0.57-1.13)	0.8	.38	0.74 (0.38-1.44)	10.5	.001	0.58 (0.41-0.81)
No. of non-IMA grafts, per graft	1.3	.25	0.93 (0.82-1.05)	0.01	.92	0.98 (0.72-1.34)	0.09	.77	0.98 (0.84-1.14)
Clamp duration per h	10.0	.001	1.30 (1.11-1.53)	0.5	.48	0.85 (0.54-1.34)	0.6	.44	1.09 (0.88-1.35)

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; CK, creatine kinase; HR, hazard ratio; IMA, internal mammary artery; MI, myocardial infarction; PVD, peripheral vascular disease.

more than doubles at a CK-MB ratio of 4.4. Qualitatively similar results were seen for troponin elevation. Importantly, this is the first study to show that myocardial enzyme elevation within 24 hours after undergoing CABG surgery continues to be prognostically important for individuals surviving for 30 days and 1 year. The analysis leading to this latter finding was possible only because of the very large sample size (more than 18 000) and the long-term follow-up available in some of the studies. Indeed, of all the covariates predictive of mortality, enzyme elevation, either CK-MB or troponin, in the first 24 hours after CABG surgery is the strongest associated variable. Although enzyme elevations are common following CABG surgery,[2-4] our data make clear that the long-term prognosis is worse for patients who experience even a small elevation of CK-MB than those who do not experience such a increase.

Other smaller studies, not included in this analysis, have examined the prognostic role of enzyme elevation at 30 days following CABG surgery. Ramsay et al[4] evaluated 800 patients and showed that mortality and left ventricular dysfunction were almost 10 times more likely for CK-MB levels of 100 ng/mL or higher compared with patients whose levels were less than 25 ng/mL. For patients followed up to 1 year, the findings have been equally impressive. The Guard During Ischemia Against Necrosis[18] trial of high-risk patients found a significant association of CK-MB elevation and 6-month survival.[5] Mortality was 3.4% for CK-MB ratios less than 1, 5.8% for ratios higher than 5, 7.8% for ratios higher than 10, and 20.2% for ratios higher than 20. These findings are similar to the Arterial Revascularization Therapies Study (ARTS), in which patients were randomly assigned to undergo revascularization by percutaneous coronary intervention (PCI) or CABG surgery.[5] A strong graded correlation was found between CK-MB level and 1-year mortality, ranging from 0% for no increase in CK-MB to 7% for more than 5 times the elevation.

For long-term prognosis, the results of a pooled analysis by Mahaffey et al[3] were somewhat different. These authors studied more than 4000 patients with non–ST-segment elevation acute coronary syndromes undergoing CABG surgery. In this cohort, there was an independent association with short-term (in-hospital and 30-day) mortality only when CK-MB reached more than 10 times the normal level. This finding seemed to support the longstanding claim that only large increases in CK-MB levels were of clinical significance. But the 6-month results are comparable with those seen in our report, with increased risk along even lower levels of increasing enzyme levels. Recently, a cohort study from the United Kingdom validated the long-term prognostic utility of cardiac troponin I for predicting mortality after CABG surgery and suggests that even modest elevations of the 24-hour level of troponin I are prognostically significant.[6]

Differences among these studies likely relate to different patient populations, variable follow-up intervals, and limited sample size. Also, cardiac enzymes were not measured in all patients, possibly introducing bias that could not be reliably eliminated because of the likely presence of unknown confounders. In aggregate, the data suggest that any CK-MB elevation after CABG surgery is associated with increased mortality.

Our study adds to prior studies by being sufficiently large and inclusive to demonstrate that even small enzyme elevations detected soon after surgery are associated with worsened long-term prognosis. That enzyme elevation within 24 hours of CABG surgery continues to be prognostically significant in individuals surviving for 1 year is a new observation. Additionally, the large sample size clearly describes the quan-

Table 5. Cox Proportional Hazards Model Predicting 30-Day and 30-Day to 180-Day Mortality

	30-Day Mortality			6-Month Mortality, If Survived 30 Days		
Factor	Wald χ^2	*P* Value	HR (95% CI)	Wald χ^2	*P* Value	HR (95% CI)
Study	25.0	<.001		0.03	.86	
Peak troponin I ratio, per increase of 50, 24 h CABG surgery	142.4	<.001	1.28 (1.23-1.33)	39.9	<.001	1.15 (1.10-1.21)
Age, per 10 y	26.2	<.001	1.80 (1.44-2.25)	45.0	<.001	1.94 (1.60-2.36)
Prior MI	2.5	.11	1.36 (0.93-1.98)	14.4	.001	1.92 (1.37-2.69)
History of renal dysfunction	0.4	.52	1.15 (0.75-1.77)	29.9	<.001	2.51 (1.81-3.50)
History of diabetes	3.3	.07	1.42 (0.97-2.09)	9.2	.002	1.66 (1.20-2.30)
History of PVD	0.8	.37	1.18 (0.82-1.71)	1.1	.31	1.18 (0.86-1.62)
History of hypertension	0.7	.39	0.80 (0.48-1.33)	0.2	.65	1.10 (0.73-1.66)
Women	0.6	.45	0.86 (0.57-1.28)	1.2	.28	1.20 (0.86-1.66)
Current smoker	1.0	.31	1.28 (0.79-2.09)	0.002	.96	1.01 (0.63-1.62)
Weight, per 10 kg	0.1	.81	0.99 (0.88-1.11)	0.03	.87	1.01 (0.92-1.11)
IMA graft	0.2	.66	1.11 (0.70-1.75)	1.5	.23	0.80 (0.56-1.15)
No. of non-IMA grafts, per graft	0.6	.43	0.94 (0.80-1.10)	0.7	.42	0.95 (0.84-1.08)
Clamp duration per h	0.7	.41	1.10 (0.88-1.37)	8.2	.004	1.32 (1.09-1.60)

Abbreviations: CI, confidence interval; HR, hazard ratio; IMA, internal mammary artery; MI, myocardial infarction; PVD peripheral vascular disease.

titative relationship between the degree of CK-MB elevation and early, intermediate-, and long-term mortality. These findings are consistent with the known prognostic influence of MI on mortality.

A comparison with studies of enzyme elevations following PCI offers an intriguing parallel to the relation of enzyme elevation to prognosis following CABG surgery. Elevation of CK-MB following PCI is associated with reduced long-term survival and mortality increases with increasing enzyme elevation.[2,22-26] The infarcts (enzyme elevations) that occur following PCI are related mainly to coronary embolization. Because the infarcts are small, the suggestion has been made that embolization during PCI is a marker of unstable plaque and the propensity for future remote plaque rupture that increases mortality. The potential mechanisms of myocardial necrosis are many but different in the setting of CABG surgery and include air embolism, graft or native artery closure, global ischemia with suboptimal cardioplegia, and low postoperative flow. The fact that different mechanisms of injury following PCI and CABG surgery have similar prognostic implications suggests that patient prognosis is driven by the extent of necrosis regardless of how it occurred. The mechanism whereby small infarcts are associated with reduced survival and result in a monotonically increasing, nearly exponential relationship of enzyme elevation (extent of myocardial injury) and mortality rate remains to be understood. The impact of enzyme elevations in other settings, such as valve surgery, is not known. Nevertheless, this study does not delineate the mechanism causing the prognostic association of enzyme increase and mortality, and we cannot exclude the possibility that post-CABG surgery enzyme elevations simply mark patients with underlying disease that, for unknown reasons, is likely to follow a more malignant course than that of patients without postoperative enzyme elevation. An improved understanding of the mechanism linking small amounts of post-CABG surgery and post-PCI enzyme elevations would be an advance, and future studies examining this issue would be useful.

Limitations

We attempted to include all applicable studies. However, we were not able to obtain information from all studies, so we may have missed studies that did not appear in our search process and were not known to any of the investigators. Adjustment for confounders only included data that were available across all studies. Thus, the models were not able to account for all possible covariates, including, for instance, extent of coronary disease, ejection fraction, and medications. Long-term follow-up was available on only 3 of the included studies. The patients studied were primarily white and more often male. This should be considered when evaluating the generalizability to other populations. Also, data regarding complications in the first 30 days, such as graft closure, MI (after the 24-hour mark), and cardiac arrest could not be obtained.

Clinical Trial Implications

Our data have implications for the conduct of clinical trials. The graded association of mortality with enzyme elevation and the new finding that early, small enzyme elevations after CABG surgery are associated with long-term prognosis suggests that CK-MB or troponin elevation is an appropriate indicator of myocardial injury as a trial end point in future clinical trials involving patients who have undergone CABG surgery. A residual question is the appropriate threshold level for choosing an enzyme increase as a predictor of worse prognosis. The answer will probably depend on the precise question of the particular study.

CONCLUSION

This study demonstrates that myocardial necrosis, as assessed by CK-MB or troponin elevation in the first 24 hours following CABG surgery, is associated with increased mortality. These findings may inform the design of future clinical trials with respect to using cardiac markers as an outcome measure following CABG surgery. Although these findings require confirmation in large prospective studies, they suggest that there are clinical implications in terms of long-term prognosis for cardiac enzyme elevations following CABG surgery particularly among those with very high levels.

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