Journal of the American College of Cardiology Vol. 47, No. 5, 2006
© 2006 by the American College of Cardiology Foundation ISSN 0735-1097/06/$32.00
Published by Elsevier Inc. doi:10.1016/j.jacc.2005.12.003

Prognostic Implications of Creatine Kinase Elevation After Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction

Amir Halkin, MD,* Gregg W. Stone, MD, FACC,† Cindy L. Grines, MD, FACC,‡ David A. Cox, MD, FACC,§ Barry D. Rutherford, MD, FACC,‖ Paolo Esente, MD, FACC,¶ Carol M. Meils, MD, FACC,# Per Albertsson, MD, FACC,** Anthony Farah, MD, FACC,†† James E. Tcheng, MD, FACC,‡‡ Alexandra J. Lansky, MD, FACC,*† Roxana Mehran, MD, FACC*†

New York and Syracuse, New York; Royal Oak, Michigan; Charlotte and Durham, North Carolina; Kansas City, Missouri; Milwaukee, Wisconsin; Göteborg, Sweden; and Pittsburgh, Pennsylvania

OBJECTIVES We examined the prognostic implications of the absolute level and rate of increase of creatine kinase (CK) elevation after primary percutaneous coronary intervention (PCI).

BACKGROUND Peak creatine kinase (CK_{peak}) and the rate of CK increase are related to reperfusion success and clinical outcomes after thrombolytic therapy for acute myocardial infarction (AMI). The utility of routine serial CK monitoring after primary PCI, in which normal antegrade blood flow is restored in most patients, is unknown.

METHODS In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, 1,529 patients with AMI randomized to either stenting or balloon angioplasty, each with or without abciximab, had CK levels determined at baseline and at 8 ± 1 h, 16 ± 1 h, and 24 ± 1 h after PCI.

RESULTS The CK_{peak} occurred at baseline in 3.9% of patients, at 8 ± 1 h in 69.6%, at 16 ± 1 h in 20.0%, and at 24 ± 1 h in 6.5%. The CK levels at all post-procedural time points were significantly higher in patients who died compared with the one-year survivors, as was CK_{peak} (mean, 2,865 U/l vs. 1,885 U/l, respectively, $p \leq 0.001$). By multivariate analysis, CK_{peak} was a significant predictor of one-year mortality (hazard ratio = 2.15, $p = 0.0002$), independent from post-PCI Thrombolysis In Myocardial Infarction (TIMI) flow. Both the improvement in left ventricular ejection fraction from baseline to seven months and its absolute level were inversely correlated with CK_{peak} ($p < 0.001$ for both). In contrast, the time to CK_{peak} was not an independent predictor of mortality or myocardial recovery.

CONCLUSIONS The CK_{peak} after primary PCI is a powerful predictor of one-year mortality independent of other clinical and angiographic measures. (J Am Coll Cardiol 2006;47:951–61) © 2006 by the American College of Cardiology Foundation

In the pre-reperfusion era, the peak level of serum creatine kinase (CK) measured within the first 24 to 48 h after acute myocardial infarction (AMI), as a reflection of infarct size, was found to be strongly related to subsequent mortality (1). However, the prognostic significance of peak cardiac enzyme level elevation after reperfusion therapy is less clear. Early reperfusion therapy during evolving AMI is known to increase the absolute peak CK level and the rapidity with which the apex of the peak is reached (2). Although a rapid increase in CK is a marker of effective thrombolysis (3,4), some studies indicate that larger (5) and earlier (6) enzyme peaks are associated with increased rates of adverse outcomes after pharmacologic reperfusion therapy. In recent years, primary percutaneous coronary intervention (PCI) has emerged as the preferred reperfusion modality for AMI (7). Whether CK elevations have similar prognostic implications after primary PCI as thrombolytic therapy, given the higher rates of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 and reperfusion success with the catheter-based strategy, is unknown and has not been studied.

We therefore performed a post hoc analysis of the database from a large, prospective, multicenter, randomized study of mechanical reperfusion therapies in AMI to determine the relationship between post-PCI CK levels, kinetics, and outcomes.

METHODS

Details of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial have been previously reported (8). Briefly, 2,082 pa-

From the *Cardiovascular Research Foundation and †Columbia University Medical Center, New York, New York; ‡William Beaumont Hospital, Royal Oak, Michigan; §Mid Carolina Cardiology, Charlotte, North Carolina; ‖St. Luke's Hospital, Kansas City, Missouri; ¶St. Joseph's Hospital, Syracuse, New York; #St. Joseph Regional Medical Center, Milwaukee, Wisconsin; **Sahlgrenska University Hospital, Göteborg, Sweden; ††Allegheny General Hospital, Pittsburgh, Pennsylvania; and the ‡‡Duke Clinical Research Institute, Durham, North Carolina. Funding for the CADILLAC trial was provided by Guidant Corporation.

Manuscript received June 15, 2005; revised manuscript received July 25, 2005, accepted August 20, 2005.

Abbreviations and Acronyms

AMI	= acute myocardial infarction
CADILLAC	= Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CK	= creatine kinase
CK_{peak}	= peak creatine kinase
LVEF	= left ventricular ejection fraction
PCI	= percutaneous coronary intervention
TIMI	= Thrombolysis In Myocardial Infarction

tients ≥18 years of age with AMI and symptom onset within 12 h undergoing primary PCI were randomized to primary balloon angioplasty versus stent implantation, each with or without abciximab. The principal clinical exclusion criteria were cardiogenic shock and the prior use of thrombolytic therapy for the present admission. Angiographic inclusion criteria included a native coronary artery culprit vessel with a reference diameter of 2.5 to 4.0 mm and a lesion length ≤64 mm. Clinical follow-up continued for one year. Protocol-specified, angiographic 7-month follow-up was completed in 656 patients (73% of a 900-patient pre-specified cohort). Quantitative coronary angiography and ventriculographic assessment were performed using dedicated software (QCA-CMS, MEDIS, Leiden, the Netherlands) at an independent core angiographic laboratory at the Cardiovascular Research Foundation, New York, New York. Left ventricular ejection fraction (LVEF) was calculated using the length-area method (9). Antegrade coronary blood flow was evaluated using the TIMI scale (10). Myocardial blush (11) and changes in electrocardiographic ST-segment elevation (12) were determined in two formal CADILLAC sub-studies consisting of 1,301 and 700 patients, respectively.

CK measurements. Protocol-specified blood sampling for CK levels was performed at baseline and at 8 ± 1 h, 16 ± 1 h, and 24 ± 1 h after PCI. Measurement of serum total CK levels was performed according to local hospital standards. Outcomes were examined stratified by peak CK levels (CK_{peak}), divided into four equal quartiles.

End points and statistical analysis. The primary study end point was a composite of major adverse cardiac events, defined as death from any cause, reinfarction, repeat target vessel revascularization as a result of ischemia, or disabling stroke. The components of the composite end point have been previously defined (8). Outcomes were evaluated as a function of absolute CK_{peak} level (as both a continuous and a categorical [quartile] measure), and by the timing of CK_{peak}. Categorical data were compared using the Fisher exact test. Continuous variables are presented as mean ± SD and were compared using the Student *t* test or one-way analysis of variance as appropriate. For comparison of multiple groups with ordinal categorization, the trend in the binomial proportions of categorical variables was analyzed using the Cochran-Armitage test, and analysis of variance was used to test for linear trends across the means of continuous variables. Clinical outcomes were presented as Kaplan-Meier survival estimates and were compared using the log-rank test. Independent predictors of CK_{peak} were determined by multiple linear regression using stepwise selection (entry and exit criteria of $p < 0.10$ and $p < 0.15$, respectively), considering CK_{peak} as a log-transformed continuous variable. Independent predictors of survival were determined with Cox proportional hazard regression analysis using stepwise selection of all of the parameters in Table 1 with entry and exit criteria of $p < 0.10$ and $p < 0.15$, respectively. For all analyses, a two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Baseline features. Of 2,082 patients, CK values were available at baseline and at all three post-PCI pre-specified time points in 1,529 patients (73.4%), who are the study cohort. Baseline characteristics and procedural results were similar in patients with compared to those without complete CK data (Table 2).

Clinical characteristics and procedural results of patients stratified by CK_{peak} are shown in Table 1. Patients with higher CK_{peak} values were more likely to be younger, male, and non-diabetic, and to have a shorter time from symptom onset to PCI than those with lower CK_{peak} values. The infarct artery of patients with a greater CK_{peak} value was larger in diameter and most commonly the left anterior descending vessel, and baseline global and regional left ventricular function was depressed. Spontaneous reperfusion before intervention was also less frequent in patients with a greater CK_{peak} value, and the post-procedure rates of normalized TIMI flow grade and myocardial blush were lower than in patients with a greater CK_{peak} value.

Pattern and determinants of CK elevation. For the entire study population, the mean CK_{peak} was 1,921 ± 1,723 U/l. By multivariate analysis, the independent correlates of CK_{peak} were left anterior descending culprit artery (odds ratio [95% confidence interval] = 1.90 [1.43 to 2.52], $p < 0.0001$), pre-procedural TIMI flow grade 0 to 2 (5.26 [3.23 to 9.09], $p < 0.0001$), younger age (1.02 [1.01 to 1.03], $p < 0.0001$), and reduced baseline LVEF (1.05 [1.04 to 1.06], $p < 0.0001$). Of the variables listed in Table 1, none of the post-procedural angiographic findings were independently predictive of CK_{peak}.

The mean CK level at each time period for patients within each CK_{peak} quartile are shown in the upper panel of Figure 1. The CK_{peak} occurred at the baseline measure in 3.9% of patients, at 8 ± 1 h in 69.6% of patients, at 16 ± 1 h in 20.0% of patients, and at 24 ± 1 h in 6.5% of patients. As seen in the lower panel of Figure 1, the greater the CK_{peak}, the earlier the time the peak was achieved.

The CK levels at all time points as well as at CK_{peak} were similar in patients stratified by randomization arm (Fig. 2).

Table 1. Baseline Characteristics in Patients Stratified by CK_{peak}

	Quartile 1 CK_{peak} <669 (n = 382)	Quartile 2 669 ≤ CK_{peak} <1,458 (n = 382)	Quartile 3 1,458 < CK_{peak} ≤2,667 (n = 382)	Quartile 4 CK_{peak} >2,667 (n = 383)	p Trend
Clinical features					
Age, yrs	61.2 ± 12.0	59.7 ± 11.9	59.3 ± 12.1	57.8 ± 12.3	<0.0001
Male gender, %	66.5	73.0	77.0	75.8	0.002
Diabetes mellitus, %	21.5	19.1	15.4	12.0	0.0002
Current smoker, %	41.5	41.9	45.0	49.3	0.005
Hypercholesterolemia, %	43.5	38.7	36.9	36.3	0.04
Hypertension, %	52.9	47.6	47.6	41.0	0.002
Previous myocardial infarction, %	15.5	15.7	13.1	10.2	0.02
Killip class 2 to 3, %	12.6	9.2	9.7	12.7	0.93
Angina within one month of admission, %	35.8	27.3	26.6	24.7	0.001
Symptom onset to angioplasty, h	5.4 ± 3.5	5.2 ± 3.4	5.0 ± 3.3	4.8 ± 3.3	0.008
Angiographic features (baseline)					
Three-vessel disease, %	18.3	12.8	17.6	15.9	0.77
Infarct vessel = left anterior descending, %	32.7	26.2	33.0	55.9	<0.0001
Reference vessel diameter, mm	2.90 ± 0.52	3.00 ± 0.56	3.02 ± 0.53	3.02 ± 0.57	0.002
Minimal luminal diameter, mm	0.60 ± 0.53	0.34 ± 0.48	0.23 ± 0.46	0.16 ± 0.39	<0.0001
Diameter stenosis, %	79.1 ± 18.0	88.4 ± 16.6	92.6 ± 14.6	94.5 ± 13.4	<0.0001
TIMI flow grade 3, %	45.0	23.9	12.2	6.9	<0.0001
Left ventricular ejection fraction, %	59.6 ± 11.7	57.2 ± 11.1	54.7 ± 10.9	49.3 ± 11.9	<0.0001
Procedural results					
Procedure duration, h	1.2 ± 0.5	1.1 ± 0.5	1.1 ± 0.6	1.2 ± 0.5	0.68
Stent implanted, %	54.7	58.1	58.6	54.6	0.99
Abciximab administered, %	53.1	53.1	54.5	50.7	0.59
Minimal luminal diameter, mm	2.25 ± 0.47	2.26 ± 0.53	2.30 ± 0.50	2.26 ± 0.52	0.65
Diameter stenosis, %	23.8 ± 10.3	25.5 ± 12.7	24.4 ± 11.0	24.9 ± 13.3	0.41
TIMI flow grade 3, %	98.1	96.6	96.6	92.6	0.0002
Myocardial blush grade 3, %	23.3	22.9	11.5	10.8	<0.0001
Complete ST-segment elevation resolution*, %	73.5	68.0	62.6	52.9	0.0003
CK_{peak}, U/l	341 ± 188	1,018 ± 224	1,988 ± 352	4,333 ± 1,588	<0.0001

*Complete recovery of ST-segment elevation was defined as >70% reduction in the summed ST-segment elevation score between electrocardiograms recorded before PCI and within 4 h after the procedure (12).

Abbreviations as in Table 2.

Neither stent implantation nor abciximab use were independent predictors of CK_{peak} by multivariate analysis.

CK_{peak} and outcomes. The one-year all-cause mortality was 3.8%. Although similar at baseline, CK levels at all post-procedural time points (Fig. 3, top panel) and CK_{peak} (2,865 ± 2,158 U/l vs. 1,885 ± 1,694 U/l, respectively, p = 0.0001) were significantly higher in patients who died compared with those who survived to one-year follow-up. Similarly, the mean CK level at each time point (Fig. 3, bottom panel) and CK_{peak} (2,866 ± 2,191 U/l vs. 1,846 ± 1,664 U/l, respectively, p = 0.001) in those who died versus in one-year survivors were significant predictors of one-year mortality when confined to patients in whom TIMI flow grade 3 was restored after PCI.

Clinical and angiographic outcomes in patients stratified by CK_{peak} as a categorical variable are shown in Table 3 and in Figure 4. Mortality at 30 days and at 1 year increased significantly with an increasing CK_{peak} level. There was a significant inverse relationship between CK_{peak} and both the absolute LVEF at seven months and its improvement from baseline to follow-up (Table 3, Fig. 5). No relationship was present between CK_{peak} and the rates of reinfarction, stroke, or target vessel revascularization (Table 3).

Because in 89.6% of the study population CK_{peak} occurred within 8 to 16 h after PCI, a secondary analysis examined 30-day and 1-year survival among the 1,871 patients (89.9% of the entire CADILLAC study population) with at least one available CK measurement at either of those time points. When stratified by CK_{peak} quartiles, mortality increased significantly with increasing CK_{peak} (30-day mortality in quartiles 1 through 4: 0.4%, 0.6%, 1.1%, 4.5%, respectively; p < 0.0001; 1-year mortality: 2.2%, 2.2%, 3.7%, 7.6%, respectively; p < 0.0001).

CK_{peak} kinetics and outcomes. Baseline features and the outcomes of patients stratified by the timing of CK_{peak} are shown in Table 4. Among the 96.1% of patients in whom CK peaked after PCI, a more rapid time to CK_{peak} was associated with younger age, infarction of the left anterior descending artery, less frequent spontaneous reperfusion before PCI, abciximab use, a shorter time from symptom onset to PCI, and a greater CK_{peak} value. A faster time to

Table 2. Baseline Characteristics and In-Hospital Outcomes in Study Patients Compared With Those Excluded for Missing CK Data

	Study Population (n = 1,529)	Patients Excluded for Missing CK Data (n = 553)	p
Clinical features			
Age, yrs	59.5 ± 12.1	60.2 ± 12.2	0.24
Male gender, %	73.0	73.1	0.99
Diabetes mellitus, %	17.0	15.6	0.46
Previous myocardial infarction, %	13.6	13.9	0.88
Killip class 2 to 3, %	11.1	10.4	0.75
Time from symptom onset to angioplasty, h	5.0 ± 3.2	5.6 ± 3.7	0.14
Angiographic features			
Three-vessel disease, %	16.2	13.9	0.24
Infarct vessel = left anterior descending, %	37.0	36.2	0.75
TIMI flow grade 3, before, %	22.0	22.3	0.90
Baseline left ventricular ejection fraction, %	55.2 ± 12.0	54.7 ± 12.3	0.45
Procedural results			
Stent implanted, %	56.5	57.5	0.69
Abciximab administered, %	52.8	53.9	0.69
TIMI flow grade 3, after, %	96.0	94.5	0.14
Minimal luminal diameter, mm	2.27 ± 0.50	2.25 ± 0.52	0.43
Diameter stenosis, %	24.6 ± 11.9	24.5 ± 13.5	0.84
TIMI flow grade 3, after, %	96.0	94.5	0.14
Myocardial blush grade 3, %	17.1	18.5	0.61

CK_{peak} = peak creatine kinase level; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

CK_{peak} was also associated with reduced LVEF at baseline and at follow-up, although the extent of improvement in LVEF from baseline to follow-up was independent of time to CK_{peak}. There was also no significant relationship between the rapidity to CK_{peak} on mortality at 30 days or 1 year.

In comparison with patients in whom the CK_{peak} occurred after PCI, the 3.9% of patients in whom the CK_{peak} had already occurred at baseline had a longer time from symptom onset to PCI, were less likely to have TIMI flow grade 3 at baseline, and had smaller infarct vessels with less frequent stent implantation. Despite a lower mean CK_{peak} value, patients with CK_{peak} at baseline had greater mortality at 30 days and at 1 year compared with patients with CK_{peak} at 8 or 16 h.

Multivariate predictors of mortality. By Cox proportional hazard regression analysis, CK_{peak} as a continuous variable, but not the timing of CK_{peak}, was an independent predictor of one-year mortality (Table 5). When CK_{peak} was entered into the multivariate model as a categorical variable, the hazard ratios and 95% confidence intervals for one-year mortality with quartile 1 (CK_{peak} <669 U/l) as reference (HR = 1.00) were: for quartile 2 (669 ≤ CK_{peak} <1,458 U/l), HR = 1.77 [0.42 to 7.42], p = 0.44; for quartile 3 (1,458 < CK_{peak} ≤2,667 U/l), HR = 2.97 [0.81 to 10.86], p = 0.10; and for quartile 4 (CK_{peak} >2,667 U/l), HR = 5.63 [1.61 to 19.62], p = 0.007.

In a secondary analysis, CK_{peak} as a continuous variable remained an independent correlate of one-year survival when the multivariate model was applied to the 1,871 patients with an available CK measurement at 8 to 16 h after PCI (HR = 2.52 [1.58 to 4.03], p = 0.0001).

DISCUSSION

The principal findings of the present study are: 1) despite achievement of TIMI flow grade 3 in >90% of patients, CK_{peak} after primary PCI is a powerful independent determinate of one-year mortality; and 2) the CK_{peak} after primary PCI is also inversely related to recovery of left ventricular function.

Previous studies. Before the advent of reperfusion therapy for AMI, the peak level of myocardial enzymes was shown to correlate with infarct size and survival (1,13,14). More recently, the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO)-IIb investigators reported that the extent of CK elevation is an independent predictor of mortality in a wide spectrum of patients with acute coronary syndromes, including those treated with reperfusion therapy (15). However, experimental studies have suggested that enzymatic measures after early reperfusion overestimate infarct size (16,17). Furthermore, in recent reports higher enzyme peaks after thrombolysis predicted a lower LVEF and an increased risk of congestive heart failure and death (5,18). Prior studies have also reached conflicting conclusions regarding the prognostic implications of the time to CK_{peak} after thrombolysis. An early CK_{peak} after thrombolysis has been associated with successful reperfusion in some studies (3,4), but with a larger infarct size in others (6). In the present study as well, a higher CK_{peak} was associated with increased 30-day and 1-year mortality. Unlike thrombolytic studies in which flow in the infarct artery before reperfusion therapy is not known, in the present study we were able to ascertain that a higher

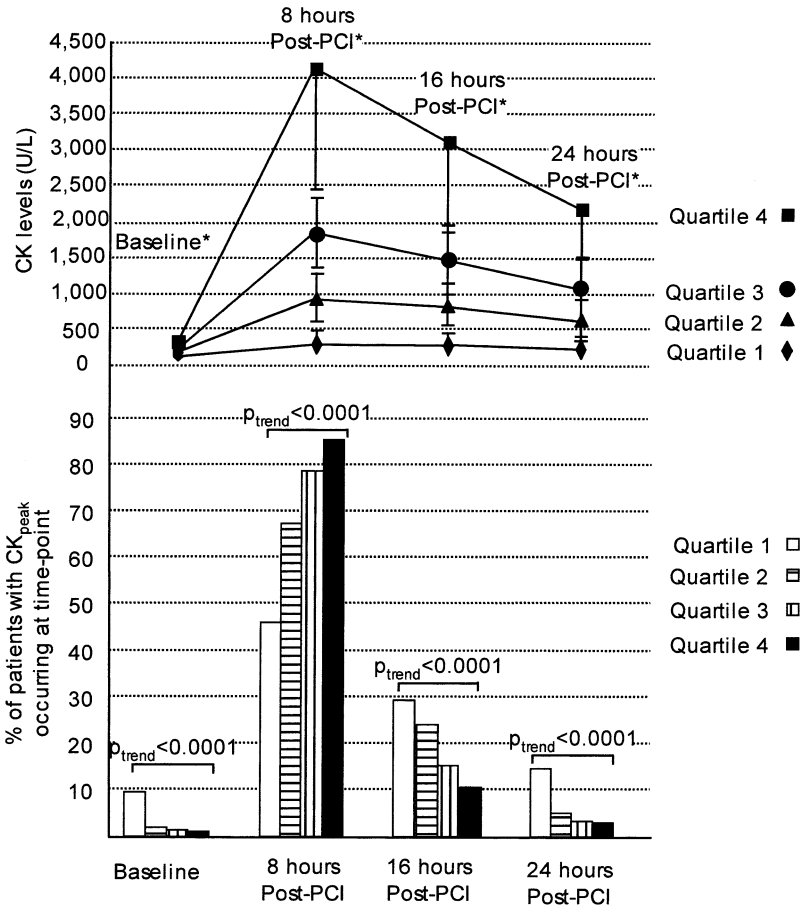

Figure 1. Mean creatine kinase (CK) levels and the timing of peak levels in patients stratified by CK_{peak}. **(Top)** CK levels at baseline and after percutaneous coronary intervention (PCI). *p trend < 0.0001 for all comparisons within individual time points. **(Bottom)** proportion of patients with CK_{peak} occurring at time point. p trend < 0.0001 for all within-group comparisons.

CK_{peak} was associated with reduced rates of spontaneous reperfusion before angioplasty. Given the beneficial prognostic implications of normalized flow in the infarct artery at presentation, it is plausible that this factor is an important determinant of myocardial salvage in the setting of primary angioplasty.

TIMI flow grade 3 is present in <60% of patients after thrombolysis; this observation may explain some of the

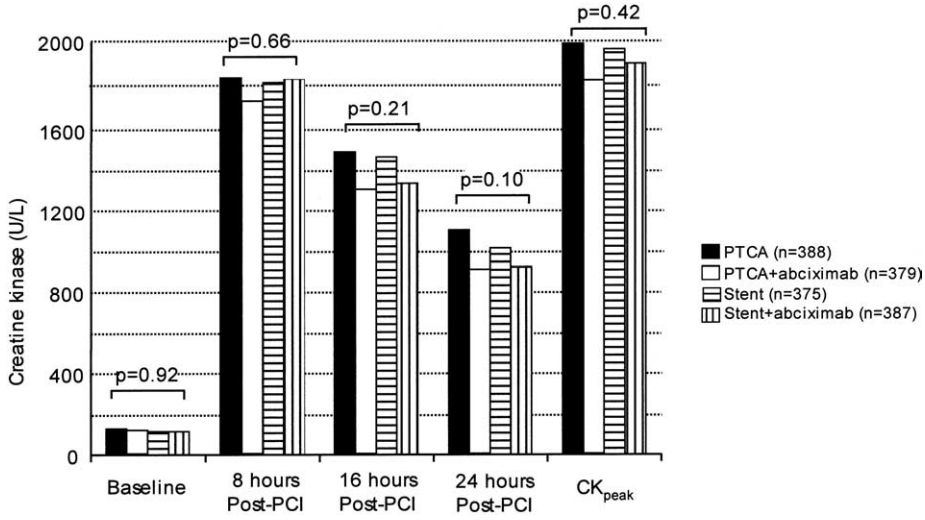

Figure 2. Creatine kinase (CK) levels in patients stratified by randomization arm. PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty.

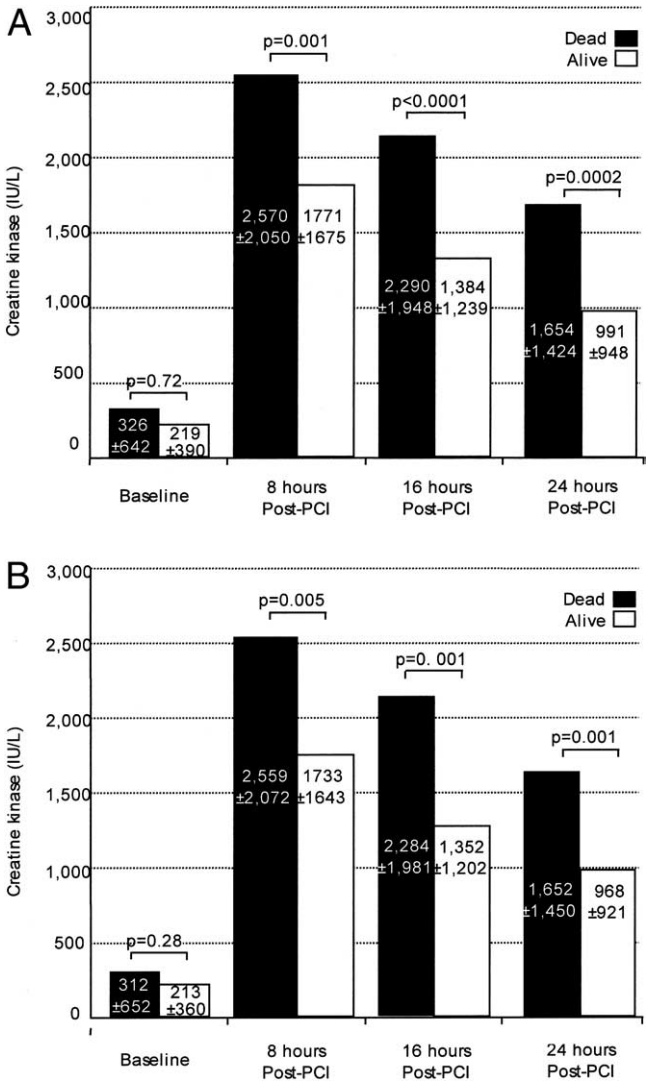

Figure 3. Creatine kinase (CK) levels at baseline and after percutaneous coronary intervention (PCI) in patients who survived **(open bars)** compared with those who had died **(solid bars)** by one-year follow-up. Data are presented as mean ± SD. **(Top)** All patients (n = 1,529). **(Bottom)** Patients with TIMI flow grade 3 after percutaneous coronary intervention (n = 1,448).

heterogeneity of findings in the aforementioned studies. In this regard it is noteworthy that no large-scale study has examined the implications of the absolute level and rate of increase of CK after primary PCI, in which TIMI flow grade 3 may be restored in >90% of patients. Biomarkers other than CK, however, have been examined in the setting of primary PCI. The cumulative extent of lactate dehydrogenase release after primary PCI was found to be an independent predictor of one-year mortality in a single study (19). However, this enzyme, which does not peak until ~72 h, is not a convenient bedside tool and is prognostically ineffective in patients who die within the first few days after AMI, the highest-risk period for mortality (20). For these reasons, the use of lactate dehydrogenase for the diagnosis of AMI is no longer endorsed (21). In contrast, serial measures of CK release are universally obtained as standard of care after AMI, and peak typically within 24 h. As such, characterizing the prognostic implications of CK release after primary PCI is of potential clinical utility.

CK elevation and outcomes after primary PCI. The present analysis shows that peak CK level is a powerful predictor of one-year mortality after primary PCI, independent of post-procedure TIMI flow grade. Although the mechanistic link between CK levels and survival is uncertain, the significant inverse association between CK_{peak} and the absolute improvement in LVEF from baseline to seven-month follow-up suggests that the increase in CK after primary PCI is a reflection of infarct size.

Unlike CK_{peak}, and in contrast to prior thrombolytic trials (3,4), an earlier CK increase in the CADILLAC trial was not associated with angiographic markers of enhanced reperfusion such as higher rates of TIMI flow grade 3 and normal myocardial blush. Conversely, an early post-PCI CK_{peak} was associated with higher maximum CK levels and a lower LVEF at baseline and at follow-up, in accordance with the findings of others (6). Whether the association between a rapidly increasing CK and reduced left ventricular function results from more rapid enzyme release by larger infarcts or whether it is an expression of reperfusion injury (22,23) is unknown. An association was also observed between CK_{peak} kinetics and survival, with a trend toward higher mortality present in patients with later time to peak enzyme increase, despite lower CK_{peak}. However, by multivariate analysis only CK_{peak}, and not time to peak, was an independent predictor of survival. Finally, the small cohort (3.9%) of patients in whom the CK_{peak} was reached at baseline (before PCI) had a different clinical and angiographic profile than the rest, with longer times to reperfusion and smaller infarct arteries. It is likely that the true CK_{peak} may have occurred even earlier, possibly explaining the trend toward higher mortality in this group despite higher rates of pre-procedural spontaneous reperfusion (24).

Correlates of peak CK elevation. The strongest correlates of CK_{peak} were left anterior descending culprit artery, pre-procedural TIMI flow grade 0 to 2, younger age, and reduced baseline LVEF. The greater CK_{peak} in left anterior descending artery occlusion may be explained not only by the larger myocardial territory supplied, but also by decreased reperfusion success in this territory (12). The fact that lack of spontaneous reperfusion in the infarct vessel before PCI was a multivariate predictor of CK_{peak} adds further credence to the concept of pharmacologic facilitation of primary PCI to restore reperfusion as early as possible before definitive mechanical revascularization (25), a strategy currently undergoing clinical investigation. The correlation between reduced baseline LVEF and CK_{peak} likely reflects a greater amount of myocardium at risk and highlights the prognostic utility of assessing left ventricular function during the index procedure. The lower CK_{peak} in elderly patients and in those with prior MI

Table 3. Clinical and Angiographic Outcomes of Patients Stratified by CK_{peak}

	Quartile 1 $CK_{peak} < 669$	Quartile 2 $669 \leq CK_{peak} < 1,458$	Quartile 3 $1,458 < CK_{peak} \leq 2,667$	Quartile 4 $CK_{peak} > 2,667$	p Trend
30-day clinical follow-up					
Death, %	0.5	0.5	1.3	4.7†	<0.0001
Reinfarction, %	0.5	1.6	0.8	0.5	0.37
Disabling stroke, %	0.0	0.3	0.3	0.3	0.80
Ischemic target vessel revascularization, %	3.4	4.2	3.7	1.9	0.31
Composite major adverse cardiac events, %	4.2	5.0	5.8	6.5	0.52
7-month angiographic follow-up*					
LVEF, %	66.8 ± 10.2	62.3 ± 10.4	57.8 ± 11.8	52.2 ± 11.2†	<0.0001
Change in LVEF from baseline to follow-up, %	5.0 ± 11.9	4.5 ± 11.6	2.4 ± 11.1	0.65 ± 12.1‡	0.006
Minimal luminal diameter, mm	1.75 ± 0.67	1.77 ± 0.69	1.79 ± 0.75	1.73 ± 0.75	0.95
Diameter stenosis, %	38.6 ± 20.7	39.2 ± 20.7	38.0 ± 23.7	41.3 ± 26.2	0.46
Binary restenosis, %	27.9	32.4	29.6	30.1	0.81
Reocclusion of infarct artery, %	7.0	7.1	8.8	10.3	0.28
1-yr clinical follow-up					
Death, %	2.4	1.6	4.0	7.1†	0.0002
Reinfarction, %	2.4	2.1	1.3	3.3	0.36
Disabling stroke, %	0.3	0.3	0.8	0.6	0.65
Ischemic target vessel revascularization, %	16.2	13.7	12.7	10.9	0.19
Composite major adverse cardiac events, %	17.7	15.2	16.7	18.5	0.63

*Follow-up coronary angiography, follow-up left ventriculography, and paired left ventriculograms at baseline and at follow-up were available for 714, 421, and 359 patients, respectively. †$p < 0.0001$ for quartile 4 compared with quartiles 1 through 3 combined. ‡$p = 0.02$ for quartile 4 compared with quartiles 1 through 3 combined.
LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

might be explained by reduction of myocardial mass and, in diabetic patients, by lower myocardial expression of CK (26,27). Of note, abciximab use and stenting were not correlates of CK_{peak} in the CADILLAC trial, consistent with previous smaller studies (28,29). This observation is also consistent with the prior reported absence of a relationship between these modalities and recovery of left ventricular function (30).

Study limitations. Approximately 26% of patients were excluded from the present study because of missing CK values at one or more time points. Nevertheless, these patients did not differ from those included with respect to important clinical and angiographic features. Interlaboratory variability in the determination of serum CK concentration must be recognized (31), and the findings of this study should not be misconstrued to suggest that a specific CK level, or cutoff, can be used for the purposes of prognostication or selection of treatment strategies. It is also worth noting that patients with some conditions that influence CK levels were either excluded or underrepresented in the CADILLAC trial (e.g., severe renal failure, rhabdomyolysis), and that the use of more specific biomar-

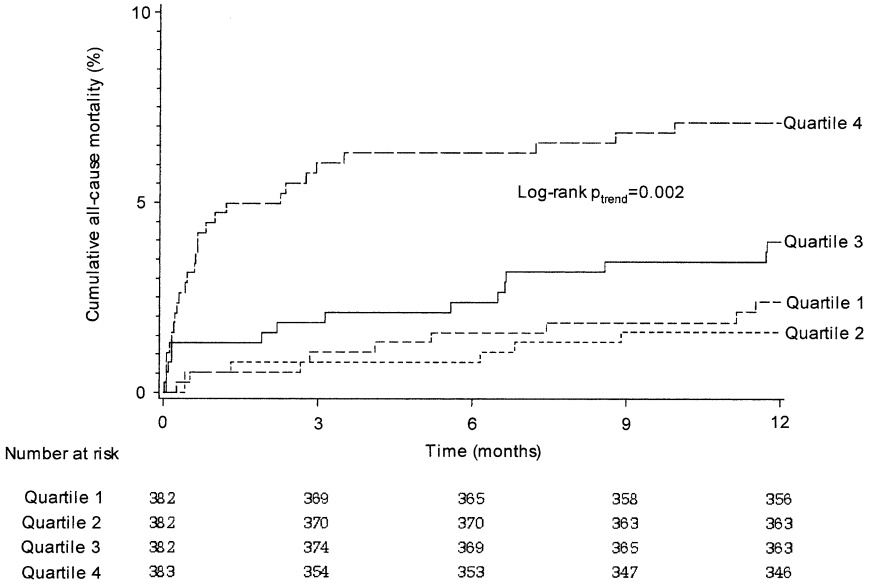

Figure 4. All-cause mortality among patients stratified by peak creatine kinase (CK_{peak}) levels.

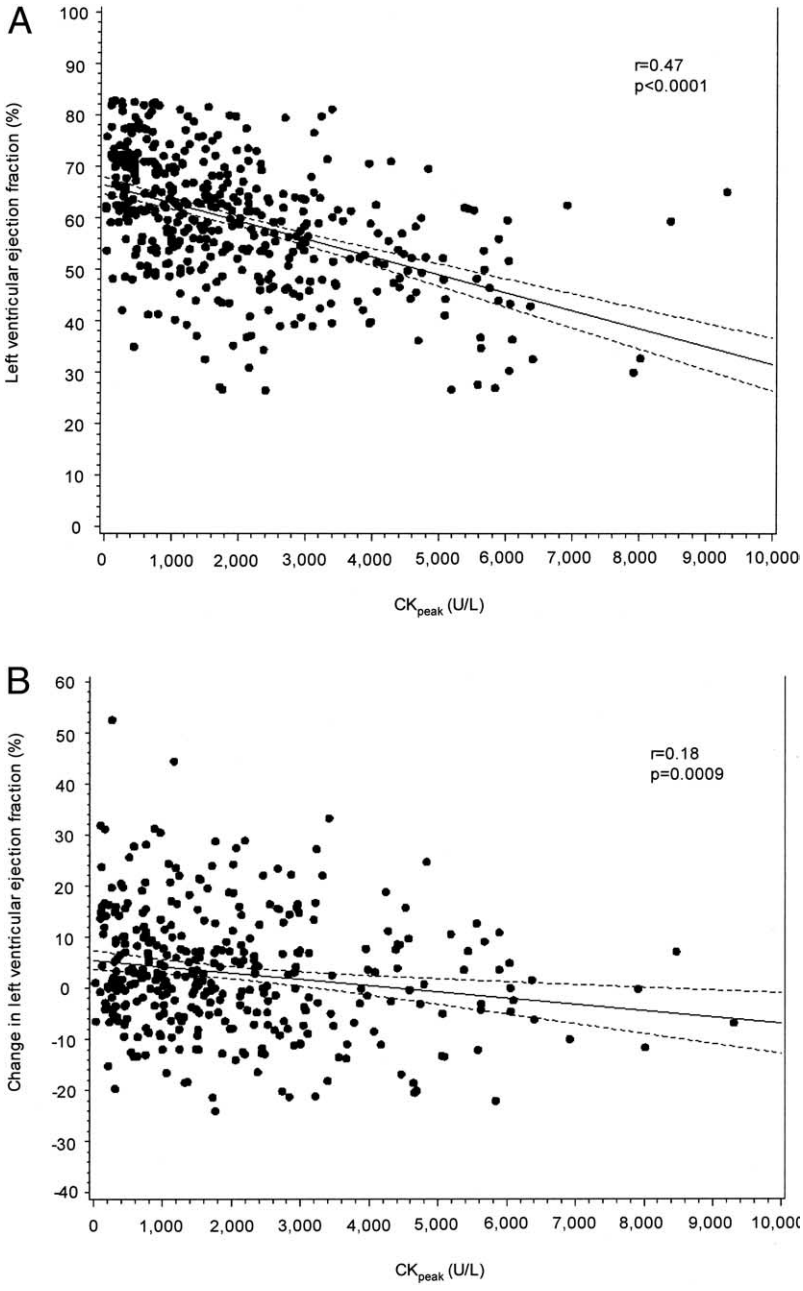

Figure 5. Correlation between peak creatine kinase (CK_{peak}) and absolute left ventricular ejection fraction measured at seven months **(top)** and the improvement in left ventricular ejection fraction from baseline to seven months **(bottom)**.

kers of myocardial necrosis (e.g., CK-MB isoenzymes or troponins) rather than total CK may add further prognostic accuracy. Also, it is possible that a marker detectable sooner after AMI onset than CK (e.g., myoglobin) might provide incremental prognostic information (2). These limitations do not detract from the powerful clinical utility of post-PCI CK evaluation, an inexpensive test that is more readily available in certain health care systems than assays for alternative cardiac biomarkers (32). The implications of CK increase in terms of left ventricular functional recovery should be considered within the context of the timing of protocol-defined determination of convalescent LVEF at seven-month follow-up and attrition of the study population, which itself was impacted by CK_{peak}. Protocol-specified blood sampling every eight hours in the present study did not permit accurate calculations of the area under the CK time-activity curve (33), a potentially more accurate measure of infarct size determination and prognosis. However, CK sampling as performed in this study closely reflects routine clinical practice, and CK_{peak} is a simpler clinical measure than time-activity curves. The absolute CK_{peak} and time to CK_{peak} may have been underestimated in the 6.5% of patients in whom CK_{peak} occurred at 24 h, the late peak possibly reflecting unsuccessful myocardial reperfusion. Finally, the applicability of our findings to patient populations dissimilar to that studied in the CADILLAC trial or in

Table 4. Baseline Features and Outcomes of Patients Stratified by Timing of CK_{peak}

	CK_{peak} Occurring After PCI				CK_{peak} Occurring Before PCI	
	Group 1 Peak at 8 h (n = 1,064)	Group 2 Peak at 16 h (n = 306)	Group 3 Peak at 24 h (n = 99)	p Three-Way Trend	Group 4 Peak at Baseline (n = 60)	p 1 + 2 + 3 vs. 4
Baseline features						
Age, yrs	59.3 ± 12.1	59.5 ± 12.2	62.1 ± 11.9	0.10	59.2 ± 13.1	0.84
Male gender, %	75.0	69.6	59.6	0.001	76.7	0.56
Diabetes mellitus, %	16.7	15.0	24.2	0.10	20.0	0.49
Symptom onset to angioplasty, h	5.0 ± 3.4	4.9 ± 3.1	5.7 ± 3.5	0.14	7.0 ± 4.2	0.0009
Three-vessel disease, %	16.3	15.0	17.2	0.82	18.3	0.59
Infarct vessel = left anterior descending, %	39.2	29.4	34.3	0.006	40.0	0.68
Reference vessel diameter, mm	2.99 ± 0.55	2.99 ± 0.55	2.97 ± 0.53	0.92	2.85 ± 0.48	0.05
TIMI flow grade 3, %	23.9	28.6	47.4*	<0.0001	45.0*	<0.0001
LVEF, %	54.0 ± 11.8	58.0 ± 11.6	58.2 ± 13.0	<0.0001	55.9 ± 13.0	0.66
Procedural results						
Stent implanted, %	57.0	58.5	55.6	0.73	38.3	0.005
Abciximab administered, %	54.4	53.3	40.4	0.04	43.3	0.15
TIMI flow grade 3, %	95.6	97.0	97.9	0.28	93.3	0.30
Myocardial blush grade 3, %	15.4	21.6	19.0	0.12	19.0	0.68
Complete ST-segment elevation resolution, %	62.3	67.4	50.0	0.76	57.1	0.99
CK_{peak}, U/l	2,201 ± 1,762*	1,389 ± 1,403	1,237 ± 1,701	<0.0001	806 ± 1,012	<0.0001
Outcomes						
30-day clinical follow-up						
Death, %	1.2	2.6	3.0	0.23	5.0†	0.052
Reinfarction, %	0.7	0.7	3.1	0.05	1.8	0.47
Disabling stroke, %	0.2	0.3	0.0	0.78	0.0	0.73
Ischemic target vessel revascularization, %	2.5	4.0	8.1	0.009	6.8	0.13
Composite major adverse cardiac events, %	3.9	7.2	12.1	0.0008	11.1	0.03
7-month angiographic follow-up						
LVEF, %	58.1 ± 12.6	63.0 ± 11.1	62.3 ± 11.1	0.004	60.9 ± 7.3	0.43
Change in LVEF baseline to follow-up, %	3.0 ± 11.7	3.3 ± 11.6	1.79 ± 12.6	0.89	4.8 ± 13.8	0.39
Binary restenosis, %	32.0	22.3	30.8	0.20	26.3	0.80
Reocclusion of infarct artery, %	9.4	4.2	15.4	0.14	0.0	0.39
1-yr clinical follow-up						
Death, %	3.1	4.3	7.2‡	0.14	6.7§	0.22
Reinfarction, %	2.2	1.4	5.2	0.10	3.5	0.54
Disabling stroke, %	0.5	0.3	1.1	0.68	0.0	0.59
Ischemic target vessel revascularization, %	12.5	13.3	19.8	0.11	19.2	0.18
Composite major adverse cardiac events, %	15.8	17.2	25.4	0.04	23.3	0.16

*$p < 0.0001$ for comparison with groups 1 + 2. †$p = 0.04$ for comparison with groups 1 + 2. ‡$p = 0.06$ for comparison with groups 1 + 2. §$p = 0.07$ for comparison with groups 1 + 2.
Abbreviations as in Table 1.

Table 5. Multivariate Predictors of 1-yr Mortality

	Hazard Ratio	95% Confidence Interval	p
Age*	1.06	1.03–1.09	0.0001
CK_{peak}†	2.15	1.38–3.36	0.0007
Killip class 2 to 3	2.42	1.17–4.99	0.01
Reduced baseline LVEF‡	1.03	1.01–1.05	0.01

*Per 1-yr increments. †Per 1 natural log-transformed unit increments. ‡Per 1 ejection fraction percent unit decrements.
Abbreviations as in Table 1.

which alternative strategies for the management of AMI were used is unknown.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Independent of other clinical and angiographic measures, CK_{peak} directly correlates with infarct size and long-term mortality in patients with AMI treated with primary PCI, and as such, the assessment of serial CK levels in the first 24 h after admission continues to be of prognostic utility in the contemporary reperfusion era. Using CK_{peak}, 25% of patients will be identified within 24 h of hospital admission in whom the hazard for one-year mortality is approximately five- to six-fold increased, signifying a patient cohort in whom intensive monitoring and secondary preventative measures are warranted. Despite successful primary PCI, novel strategies must also be identified to further enhance myocardial salvage and prolong survival in this high-risk group.

Reprint requests and correspondence: Dr. Gregg W. Stone, The Cardiovascular Research Foundation, 55 East 59th Street, 6th Floor, New York, New York 10022. E-mail: gstone@crf.org.

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