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Utility of Cardiac Biomarkers in Predicting Infarct Size, Left Ventricular Function, and Clinical Outcome After Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction

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Objectives We sought to determine the best cardiac biomarker to predict infarct size, left ventricular ejection fraction (LVEF), and clinical outcome in patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI).

Background The cardiac biomarkers, creatine kinase (CK), CK-MB, and troponins T and I are routinely measured after myocardial infarction. However, their correlation with functional and clinical outcomes after PCI for STEMI is not well established.

Methods In the EVOLVE (EValuation Of MCC-135 for Left VEntricular Salvage in Acute Myocardial Infarction) trial, patients were randomized to receive intracellular calcium modulator as adjunct to primary PCI for first large STEMI. Cardiac biomarker levels were determined in 378 patients before PCI and serially up to 72 h. Single-photon emission computed tomography was performed after 5 and 30 days, and patients were monitored up to 180 days.

Results All single time-point, peak, and area under time-concentration curve of CK, CK-MB, and troponins T and I after PCI significantly correlated with infarct size and LVEF. In particular, 72-h troponin I (TnI72h) correlated strongly with 5-day and 30-day infarct size ($r > 0.70$; $p < 0.001$). A TnI72h threshold >55 ng/ml was 90% sensitive for large infarct size (≥10%) and low LVEF (≤40%) with specificities of 70% and 52%, respectively ($c = 0.88, 0.81$; $p < 0.001$). The highest TnI72h tertile was associated with increased 180-day composite clinical events (23% vs. 23% vs. 42%; $p = 0.001$) and independently predicted adverse events (hazard ratio = 2.3; $p = 0.01$).

Conclusions Assessing TnI72h after primary PCI is a simple, effective method to estimate infarct size, LVEF, and potentially useful for risk stratification. (J Am Coll Cardiol Intv 2008;1:415–23)

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Measurement of cardiac biomarker levels is routinely performed in clinical practice, as well as in clinical trials after myocardial infarction to estimate the extent of myocardial necrosis. Before the advent of thrombolytic therapy, venous sampling of creatine kinase (CK) and CK-MB concentrations provided a useful tool in estimating infarct size (1). However, with primary percutaneous coronary intervention (PCI) emerging as the preferred reperfusion modality for acute ST-segment elevation myocardial infarction (STEMI) (2), it is less clear whether cardiac biomarker release still predicts infarct size, left ventricular (LV) function, and prognosis. Furthermore, with cardiospecific markers (i.e., troponin T and troponin I) gradually replacing traditional cardiac enzymes in many practices (3), it is uncertain which cardiac biomarker or method (peak concentrations, area under time-concentration curve [AUC], or single time-point measurements) is most reliable (4), convenient, and still demonstrates strong correlation with infarct size after primary PCI (5). Recent studies suggested that a single measurement of troponin T 72 to 96 h after myocardial infarction may provide an estimate of infarct mass (6–8). Hence, data validating the association of cardiac biomarkers with infarct size in a contemporary clinical setting are clearly needed.

We, therefore, performed a post hoc analysis of the database from a prospective, multicenter, randomized study of patients with acute STEMI undergoing primary PCI to evaluate the usefulness of serial and single time-point measures of the cardiac biomarkers CK, CK-MB, troponin T, and troponin I in predicting infarct size and left ventricular ejection fraction (LVEF) determined by single-photon emission computed tomography (SPECT) imaging and clinical outcome.

Abbreviations and Acronyms

AUC = area under time-concentration curve
CI = confidence interval
CK = creatine kinase
HR = hazard ratio
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
PCI = percutaneous coronary intervention
ROC = receiver-operator characteristic
SPECT = single-photon emission computed tomography
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction
TnI72h = troponin I concentrations taken at 72 h

Methods

Study population. Details of the EVOLVE (EValuation Of MCC-135 for Left VEntricular Salvage in Acute Myocardial Infarction) trial have been published previously (9,10). In brief, the EVOLVE trial was a phase IIA, multicenter, randomized, double-blind, placebo-controlled study of the safety and efficacy of 2 doses of intravenous MCC-135, a new class of agent that reduces intracellular calcium overload, as an adjunct therapy for preservation of LV function and reduction of infarct size in patients undergoing PCI for STEMI. A total of 500 patients were enrolled between May 2003 and November 2004. Patients were included if they had a first documented STEMI and were to undergo primary PCI within 8 h of onset of symptoms. Principal exclusion criteria were hemodynamic or electrical instability, cardiogenic shock, severe bradycardia, pre-existing chronic heart failure, renal impairment, or left bundle branch block pattern on electrocardiogram (ECG). All patients provided witnessed informed consent, and the study was approved by the ethics committees of all participating hospitals.

Cardiac biomarker measurements. Protocol-specified blood sampling for CK, CK-MB mass, troponin T, and troponin I was performed at baseline (before the start of study drug infusion and PCI) and 2, 4, 12, 24, 48, and 72 h thereafter (±10 min for sampling window). All samples were analyzed by a central core laboratory (Quest Diagnostics, Madison, New Jersey). Peak concentrations were identified, and AUC was estimated from cardiac biomarker levels measured at individual time-points. Troponin I concentrations taken at 72 h (TnI72h) were further stratified into tertiles to examine for association with clinical characteristics and outcome. Troponin T was measured quantitatively using electrochemiluminescence technology (Elecsys Troponin T assay, Roche Diagnostics, Indianapolis, Indiana) with a detection threshold of 0.01 μg/l. Troponin I was determined using a microparticle enzyme immunoassay (AxSym Troponin-I *ADV*, Abbott Laboratories, Abbott Park, Illinois) with an analytical sensitivity of 0.02 ng/ml and a diagnostic cutoff for myocardial infarction of 0.40 ng/ml.

SPECT and LV function assessments. Resting ECG-gated myocardial SPECT imaging with Tc-99m-sestamibi or Tc-99m-tetrofosmin was performed on Day 5 and when patients returned for follow-up visit on Day 30 (± 2 days) after STEMI. In the study protocol, SPECT imaging was only performed in patients who underwent PCI and received study drug/placebo infusion. The acquisition of ECG-gated SPECT images was standardized in all clinical sites and performed in concordance with standards of the American Society of Nuclear Cardiology (11). Infarct size, LVEF, and cardiac volumes were determined from the reconstructed SPECT images by core laboratory (Yale University Radionuclide Core Laboratory, New Haven, Connecticut) using Wackers-Liu CQ (WLCQ) software (GE Healthcare, Waukesha, Wisconsin) (12). Myocardial perfusion defects (infarct size) were quantified and expressed as a percentage of the LV relative to a normal reference database, and LVEF was determined using validated methodology (12,13).

Angiographic analysis. Standard image acquisition was performed at all clinical sites and submitted to an independent angiographic core laboratory for quantitative coronary angiography analyses.

Clinical outcomes. All patients were monitored during hospitalization and thereafter by outpatient visits at 30 and 180 days. Clinical outcome was the composite clinical end point of death, reinfarction, new or worsening congestive heart failure during index hospitalization, or requiring rehospitalization, all cardiac rehospitalizations, life-threatening ventricular arrhythmias, and new cardiogenic shock. All clinical events were adjudicated by an independent clinical events committee.

Statistical analysis. Since there was no significant difference in cardiac biomarker levels (including individual time-point, peak, and AUC concentrations), infarct size, LVEF, and clinical outcome in the original study between patients administered with placebo or MCC-135 (10), all patients were merged into 1 cohort for statistical analyses in the current protocol. Continuous variables were presented as mean ± SD. Biomarker levels over time were compared with baseline values using paired *t* test. Baseline characteristics of patients with increasing TnI72h tertiles were compared using Kruskal-Wallis test, analysis of variance, or chi-square test where appropriate. Correlation coefficients reported were based on a nonparametric method (Spearman rank). Related correlation coefficients were compared using Fisher *z*-transformation. Time-to-event was defined as time from PCI to date of event, with patients censored at pre-specified clinical end points, loss to follow-up, or end of study. Clinical outcomes were presented as Kaplan-Meier survival estimates and compared using log-rank test. A Cox proportional hazards model was constructed to estimate hazard ratio and 95% confidence interval (CI) for elevated TnI72h that included age, gender, diabetes mellitus, hypertension, tobacco use, left anterior descending artery as the infarct-related artery, Killip class, pre- and post-procedural Thrombolysis In Myocardial Infarction (TIMI) flow grades and corrected TIMI frame counts. Receiver-operator characteristic (ROC) curves were generated using the dichotomous variables infarct size <10% or ≥10% and LVEF ≤40 or >40% on Day 5. Statistical analysis was performed by S.C. and L.H. using Statistical Package for Social Sciences 15.0 software (SPSS Inc., Chicago, Illinois). All significance tests were 2-sided, and the results were considered statistically significant when $p < 0.05$.

Results

Baseline demographics and angiographic features. Of the 500 patients enrolled, 378 (75.6%) patients who had undergone primary PCI, SPECT imaging performed, and cardiac biomarkers available for analysis form the study cohort of this analysis. Clinical characteristics of the study population and procedural findings are shown in Tables 1 and 2.

All patients underwent primary PCI, and the left anterior descending artery was identified as the culprit vessel in half of the cohort (Table 2). Two-thirds of the patient population had TIMI flow grade 0 or 1 in the culprit vessel at baseline, and 85.7% had achieved TIMI flow grade 3 at the

Table 1. Clinical Characteristics of the Overall Study Population and in Patients Stratified by TnI72h

	Overall	Tertile 1 TnI72h ≤39.5	Tertile 2 39.5 < TnI72h ≤96	Tertile 3 96 < TnI72h	p Value
Number of patients, n	378	96	95	95	
Clinical features					
Age, yrs	58.9 ± 11.9	59.3 ± 11.8	58.6 ± 11.8	59.3 ± 13.2	0.893
Body mass index	28.0 ± 4.9	28.2 ± 5.0	27.5 ± 4.7	27.9 ± 4.5	0.630
Male gender, n (%)	289 (77)	68 (71)	73 (77)	73 (77)	0.543
Systolic blood pressure, mm Hg	132 ± 21	132 ± 21	132 ± 21	132 ± 22	0.945
Diastolic blood pressure, mm Hg	79 ± 15	76 ± 15	80 ± 14	82 ± 15	0.010
Heart rate, beats/min	75 ± 15	72 ± 13	75 ± 16	77 ± 16	0.069
Time from symptom onset to hospitalization, h	1.8 ± 1.2	1.6 ± 1.1	1.7 ± 1.2	1.9 ± 1.4	0.240
Killip class 1, n (%)	351 (93)	89 (93)	86 (91)	87 (92)	0.862
Anterior STEMI, n (%)	195 (52)	50 (52)	48 (51)	59 (62)	0.219
Cardiac risk factors, n (%)					
Hypertension	177 (47)	41 (43)	43 (45)	43 (45)	0.887
Diabetes mellitus	68 (18)	16 (17)	19 (20)	19 (20)	0.793
Dyslipidemia	134 (35)	40 (42)	26 (27)	30 (32)	0.304
Previous coronary artery disease	37 (10)	13 (14)	10 (11)	6 (6)	0.299
Previous myocardial infarction	11 (3)	2 (2)	5 (5)	4 (4)	0.508
Peripheral artery disease	20 (5)	2 (2)	6 (6)	7 (7)	0.294
Family history myocardial infarction	125 (33)	32 (33)	31 (33)	28 (30)	0.770
Current smoker	171 (45)	45 (47)	47 (50)	39 (41)	0.491

Values are mean ± SD or n (%).
STEMI = ST-segment elevation myocardial infarction; TnI72h = troponin I concentrations taken at 72 h.

Table 2. Angiographic Characteristics of the Overall Study Population and in Patients Stratified by TnI72h

	Overall	Tertile 1 TnI72h ≤39.5	Tertile 2 39.5 < TnI72h ≤96	Tertile 3 96 < TnI72h	p Value
Baseline angiographic features					
Infarct vessel = LAD, %	49.7	47.3	49.5	62.8	0.071
Reference vessel diameter, mm	2.99 ± 0.51	2.96 ± 0.52	2.97 ± 0.52	3.07 ± 0.54	0.317
Minimal luminal diameter, mm	0.24 ± 0.32	0.35 ± 0.36	0.18 ± 0.26	0.20 ± 0.30	<0.001
Diameter stenosis, %	92.2 ± 10.9	88.4 ± 11.8	94.5 ± 9.4	93.7 ± 10.0	<0.001
TIMI flow grade 0 or 1, %	66.7	46.9	73.7	76.8	<0.001
Corrected TIMI frame count	82.5 ± 29.5	71.3 ± 33.9	86.8 ± 27.8	88.0 ± 23.9	<0.001
Procedural results					
Patients with stents implanted, %	96	93	98	96	0.343
Number of stents in culprit vessel	1.2 ± 0.6	1.2 ± 0.8	1.2 ± 0.5	1.1 ± 0.5	0.667
Final minimal luminal diameter, mm	2.65 ± 0.54	2.61 ± 0.53	2.62 ± 0.51	2.72 ± 0.61	0.313
Final diameter stenosis, %	13.3 ± 12.2	13.9 ± 11.9	13.6 ± 10.0	13.7 ± 13.8	0.990
Final TIMI flow grade 3, %	85.7	92.7	86.3	73.7	0.001
Final corrected TIMI frame count	27.3 ± 18.3	23.9 ± 9.7	28.0 ± 22.3	30.4 ± 21.6	0.086

Values are mean ± SD.
LAD = left anterior descending artery; TIMI = Thrombolysis In Myocardial Infarction; TnI72h = troponin I concentrations taken at 72 h.

end of the PCI procedure. Coronary stents were implanted in 96% of cases with a mean of 1.2 ± 0.6 stents implanted per vessel.

Patterns of cardiac biomarker release. Time-concentration curves for the plasma levels of total CK, CK-MB, troponin T, and troponin I from time of enrollment to 72 h thereafter are shown in Figure 1. The curves for CK, CK-MB, and troponin I had monophasic profiles, reached peak levels by 4 to 12 h, and decreased steadily thereafter. Troponin T release appeared to reach a plateau and remained elevated at 72 h. Both total CK and CK-MB have reverted to or were lower than initial levels by 72 h. Troponin T and troponin I, however, remained significantly elevated compared with baseline levels (2.7 ± 2.1 vs. 0.3 ± 1.0 μg/l, 83 ± 80 vs. 16 ± 54 ng/ml, respectively; both $p < 0.001$).

Correlation between cardiac biomarkers, SPECT-determined infarct size, and LVEF. Individual time-point measurements of plasma CK, CK-MB, troponin T, and troponin I concentrations as well as peak levels and AUC were positively correlated with SPECT-determined infarct size on both Day 5 and Day 30 (Table 3). A significant but more moderate negative correlation between cardiac biomarkers and LVEF was also observed after primary PCI. The correlation coefficients between infarct size and cardiac biomarkers at all time-points after PCI up to 72 h appeared to be comparable. For the cardiac-specific markers, troponins T and I, the strength of association was preserved even at later time-points. In particular, TnI72h showed a strong correlation with infarct size determined both on Day 5 and Day 30 ($r > 0.70$; $p < 0.001$) and appeared to be equally predictive compared with peak and AUC levels. Compared with troponin T measured at 72 h, TnI72h demonstrated a trend for stronger correlation with infarct size ($p = 0.065$).

Figure 2 shows the plotted correlations between single time-point measurement of TnI72h with infarct size ($r = 0.734$, $r^2 = 0.539$; $p < 0.001$) and LVEF assessed on Day 5 ($r = -0.459$, $r^2 = 0.211$; $p < 0.001$).

Clinical features and outcome of patients stratified by tertiles of TnI72h. To further evaluate the implication of elevated TnI72h, patients were stratified into tertiles of TnI72h ($n = 286$). Clinical and procedural characteristics of patients in each tertile are shown in Tables 1 and 2. There were no significant differences in cardiac risk profile or time from symptom onset to hospitalization between the groups. Patients with higher TnI72h concentrations were more likely to have smaller minimal luminal diameter, higher percent diameter stenosis of the infarct artery, and reduced initial TIMI flow grades (0 or 1) than patients with lower TnI72h values. Rate of TIMI flow grade 3 was also lower in the infarct artery post-procedure in patients with higher TnI72h levels, with a trend towards greater final corrected TIMI frame counts.

Composite and individual clinical end points stratified by tertiles of TnI72h levels are presented in Figure 3 and Table 4. At 180 days, the rates of composite clinical events were greatest in patients with the highest TnI72h tertile level (23% vs. 23% vs. 42%; log-rank $p_{trend} = 0.001$). Seven patients in the study died, and they were all in the group with the highest TnI72h tertile. The association between elevated levels of TnI72h and combined clinical end point at 180 days was independent of other important clinical predictors available at presentation, including age, gender, diabetes, hypertension, tobacco use, left anterior descending artery as the infarct-related artery, Killip class status, pre-

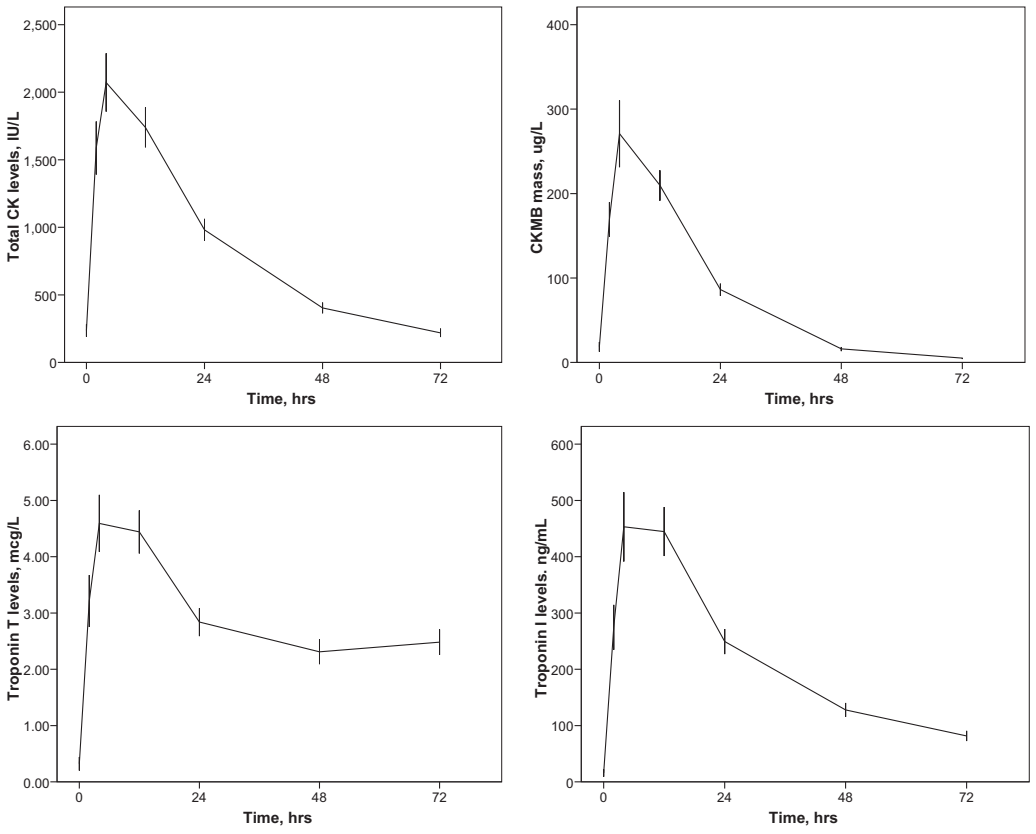

Figure 1. Time-Concentration Curves for Cardiac Biomarkers

Time-concentration curves for cardiac biomarkers (creatine kinase [CK]-MB, total CK, troponin T, and troponin I) demonstrating release profiles after primary percutaneous coronary intervention.

and post-procedural TIMI flow grades, and corrected TIMI frame counts (adjusted hazard ratio for highest TnI72h tertile: 2.3, 95% CI: 1.2 to 4.2; $p = 0.01$).

Accuracy of TnI72h in predicting large infarct size and low LVEF. The accuracy of TnI72h in predicting SPECT-determined infarct size and low LVEF on Day 5 was examined using ROC curve analyses. The AUC for predicting large residual infarct size (≥10%) was 0.88 (95% CI: 0.84 to 0.92; $p < 0.001$), and for detecting LVEF ≤40% was 0.81 (95% CI: 0.75 to 0.89; $p < 0.001$). Conversely, the AUC for detecting very small residual defect size after 5 days (≤5%) was 0.87 (95% CI: 0.82 to 0.91; $p < 0.001$). Using a threshold value of 55 ng/ml, TnI72h had 90% sensitivity and 70% specificity in detecting large infarct size, as well as 90% sensitivity and 52% specificity in predicting low LVEF. In contrast, a TnI72h value of <35 ng/ml had 60% sensitivity and 90% specificity for small or no residual defect after PCI.

When the same analyses were applied to TnI72h, a cutoff value of 1.6 μg/l was found to have 90% sensitivity of predicting large residual infarct size ($c = 0.83$, 95% CI: 0.78 to 0.88; $p < 0.001$) and detecting LVEF ≤40% ($c = 0.77$, 95% CI: 0.69 to 0.85; $p < 0.001$) but poor specificities of 59% and 43%, respectively.

Discussion

We compared 4 established cardiac biomarkers (CK, CK-MB, troponin T, and troponin I) in estimating infarct size and LVEF in patients undergoing primary PCI for acute STEMI. We found that single time-point assessment as well as AUC and peak levels of all 4 biomarkers were significantly correlated with infarct size, while demonstrating a moderate inverse correlation with LVEF. In particular, a single measurement of TnI72h strongly correlated with infarct size and independently predicted cardiac outcomes. Using a threshold value of >55 ng/ml, TnI72h had 90% sensitivity in predicting a large residual infarct (≥10%) and LV dysfunction (LVEF ≤40%) after primary PCI for first STEMI. We, therefore, concluded that troponin I measured 72 h after primary PCI represented a simple, effective, and inexpensive tool determining infarct size and LV function estimation as well as risk stratification.

Table 3. Correlation Analysis Between Cardiac Biomarkers (CK, CK-MB, Troponin T, and Troponin I) at Different Time-Points and AUC With SPECT-Determined Infarct Size and LVEF

			Day 5			Day 30	
Cardiac Biomarkers	Time, h	n	Infarct Size r Value	LVEF r Value	n	Infarct Size r Value	LVEF r Value
Total CK	Admission	307	0.229*	−0.151*	255	0.183†	−0.154†
	2	315	0.677*	−0.388*	261	0.680*	−0.545*
	4	322	0.708*	−0.378*	269	0.707*	−0.523*
	12	318	0.667*	−0.379*	264	0.652*	−0.495*
	24	331	0.599*	−0.333*	275	0.576*	−0.430*
	48	319	0.599*	−0.311*	267	0.538*	−0.394*
	72	264	0.554*	−0.312*	214	0.532*	−0.406*
	Peak	354	0.730*	−0.381*	295	0.705*	−0.488*
	AUC	348	0.669*	−0.387*	291	0.661*	−0.491*
CK-MB	Admission	363	0.251*	−0.163*	288	0.185*	−0.143*
	2	357	0.603*	−0.336*	283	0.606*	−0.458*
	4	358	0.634*	−0.349*	283	0.635*	−0.452*
	12	357	0.553*	−0.324*	282	0.557*	−0.432*
	24	367	0.516*	−0.307*	291	0.516*	−0.389*
	48	350	0.441*	−0.235*	278	0.419*	−0.349*
	72	292	0.478*	−0.294*	232	0.419*	−0.329*
	Peak	373	0.661*	−0.361*	295	0.646*	−0.438*
	AUC	369	0.634*	−0.360*	292	0.618*	−0.456*
Troponin T	Admission	258	0.139†	−0.033	214	0.026	0.004
	2	333	0.632*	−0.370*	269	0.603*	−0.501*
	4	342	0.633*	−0.369*	273	0.608*	−0.456*
	12	333	0.575*	−0.340*	266	0.562*	−0.460*
	24	352	0.664*	−0.344*	281	0.592*	−0.426*
	48	346	0.655*	−0.367*	275	0.628*	−0.470*
	72	277	0.653*	−0.426*	219	0.617*	−0.514*
	Peak	374	0.684*	−0.404*	295	0.631*	−0.468*
	AUC	367	0.702*	−0.394*	292	0.655*	−0.496*
Troponin I	Admission	347	0.254*	−0.140†	275	0.204*	−0.137†
	2	346	0.664*	−0.357*	275	0.636*	−0.474*
	4	348	0.687*	−0.374*	275	0.675*	−0.499*
	12	345	0.644*	−0.398*	272	0.596*	−0.506*
	24	359	0.701*	−0.396*	285	0.649*	−0.503*
	48	347	0.725*	−0.419*	276	0.671*	−0.529*
	72	282	0.734*	−0.459*	223	0.711*	−0.563*
	Peak	373	0.740*	−0.434*	295	0.692*	−0.518*
	AUC	369	0.748*	−0.427*	292	0.691*	−0.537*

*$p < 0.001$; †$p < 0.05$.
AUC = area under time-concentration curve; CK = creatine kinase; LVEF = left ventricular ejection fraction; SPECT = single-photon emission computed tomography.

Assessment of myocardial damage after STEMI is crucial in evaluating the efficacy of reperfusion therapy and predicting prognosis (14–16). Although measurements of LV function are often used clinically to estimate infarct size, they are less direct and are influenced by the presence of arrhythmias, cardiomyopathies, valvular heart disease, and ventricular loading. In this present study, we used SPECT imaging to directly quantify infarct size, a robust and clinically validated method using a standardized approach. Although the sensitivity of SPECT imaging for detection of small subendocardial myonecrosis is lower than cardiac magnetic resonance (17), it is reliable in patients with large myocardial infarction, and also demonstrates comparability when acquired from different clinical centers (5). Nevertheless, quantifying infarct size with both these noninvasive imaging modalities is limited by availability and relatively high costs. The cytosolic enzymes, CK, CK-MB, and lactate or hydroxybutyrate dehydrogenase, are frequently used as alternatives but lack cardio-specificity and cannot be unequivocally attributed to myocardial necrosis (18). In

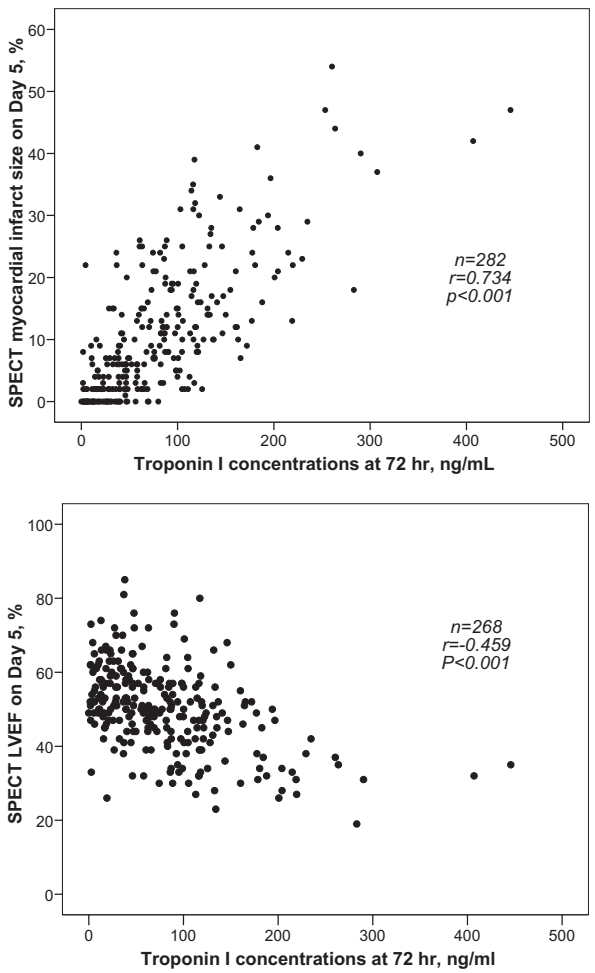

Figure 2. TnI72h Correlates With Infarct Size and LVEF

Correlation between troponin I levels taken at 72 h (TnI72h) after admission and single-photon emission computed tomography (SPECT)-determined myocardial infarct size and left ventricular ejection fraction (LVEF) on Day 5.

contrast, cardiac troponins have improved specificity and should be more precise in assessing infarct size (3).

In this study, we demonstrated significant correlation between SPECT-determined infarct size and peak and AUC cardiac biomarker levels. Clinical utility of these serological estimates, however, is hampered by the requirement for serial and multiple measurements to avoid missing actual peak levels and complete profiles of the time-concentration curve. Moreover, obtaining true troponin AUCs is impractical since they remain elevated for up to 2 weeks. Hence, our main finding that TnI72h, measured at a single time-point of 72 h after PCI, was a reliable indicator of infarct size would be valuable in clinical practice. The kinetics of troponin I release are reperfusion-dependent, reaching an earlier maximal level and corresponding faster decline compared with that seen in nonrevascularized STEMI patients (19). In agreement with previous studies, we showed that troponin I peak concentrations are attained between 4 to 12 h and remained mildly elevated 72 h after reperfusion (19,20). Three preliminary small studies recently showed that troponin T measured 72 and 96 h after myocardial infarction indeed correlated well with infarct size determined by SPECT and contrast-enhanced magnetic resonance imaging, respectively (6–8). Several small studies have also sought to determine the significance of troponin I in patients with myocardial infarction (20–23). However, to our knowledge, no clinical trial has evaluated the direct association between troponin I and SPECT-determined infarct size after primary PCI in a large cohort nor made systematic comparisons with other cardiac biomarkers.

Elevated TnI72h levels were associated with increased risk of adverse clinical outcome after primary PCI in our study population, driven largely by increased rates of mortality and new or worsening congestive heart failure. The overall mortality was low despite the attempt to enroll patients with relatively large myocardial infarction, as we excluded those with cardiogenic shock or significant comorbid conditions. Hence, we could only demonstrate adverse prognosis in those with the highest TnI72h tertile and largest infarct size, rather than a continuum of risk. The

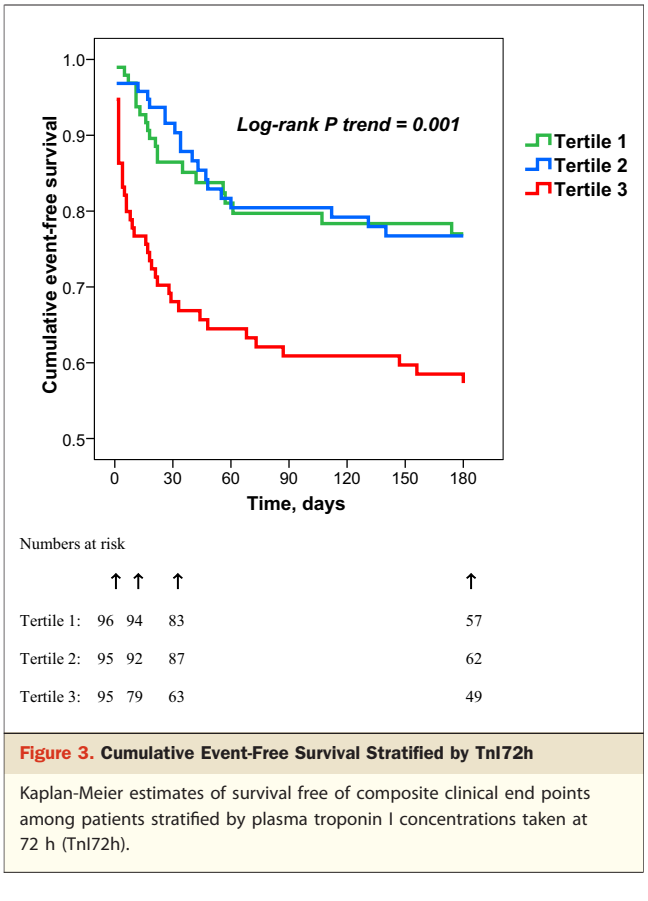

Figure 3. Cumulative Event-Free Survival Stratified by TnI72h

Kaplan-Meier estimates of survival free of composite clinical end points among patients stratified by plasma troponin I concentrations taken at 72 h (TnI72h).

Table 4. Kaplan-Meier Estimates of the Cumulative Clinical Outcome at 180 Days Stratified by Plasma Troponin I Concentrations Taken at 72 h

180-Day Clinical Events (Cumulative)	Tertile 1 TnI72h ≤39.5 (n = 96)	Tertile 2 39.5 < TnI72h ≤96 (n = 95)	Tertile 3 96 < TnI72h (n = 95)	p_{trend}
Composite clinical end point, %	23	23	42	0.001
Death, %	0	0	9	<0.001
Reinfarction, %	1	3	7	0.103
Cardiogenic shock, %	1	0	5	0.054
Life-threatening ventricular rrhythmia, %	0	1	3	0.358
Congestive heart failure: new or worsened, %	6	5	27	<0.001
Rehospitalization for cardiac cause, %	21	20	27	0.200

prognostic implication of elevated TnI72h may be attributed, in part, to greater frequency of suboptimal TIMI scores post-procedure leading to larger residual infarct size and poorer LV function. We also assessed LV dysfunction, a major determinant of long-term mortality and morbidity, 1 month after PCI, which would more likely reflect irreversible myocardial damage. Hence, TnI72h status may aid in selection of patients at higher risk that require more intensive supervision and follow-up.

Using ROC curves, we further showed that TnI72h was sensitive and specific for detecting large residual infarct size as well as impaired LV function. A cutoff value of TnI72h >55 ng/ml would predict 90% of patients with large residual infarct in our population, while only 10% of patients with TnI72h value ≥35 ng/ml would have a residual defect larger than 5%. If troponin T was measured in place of TnI72h, a corresponding value of 1.6 μg/l would yield similar sensitivity that was less specific for large residual infarct size. Applying these criteria to interpret TnI72h levels would be helpful in estimating residual myocardial damage and LV function. Given the affordability and routine availability of troponin I assays, using TnI72h to assess myocardial defect or LVEF after primary PCI will be an attractive tool in both clinical practice and as potential surrogate end points in clinical trials.

Study limitations. Our study has important limitations. It is a hypothesis-generating post hoc analysis examining the association of cardiac biomarkers with infarct size. We do not believe that these data are sufficient to recommend replacement of more objective measures of LVEF or infarct size at present, but further prospective studies with myocardial infarct imaging are warranted. The study was also not powered to compare the strength of correlation between individual time-points of cardiac biomarkers with infarct size. Nevertheless, our data provide sufficient support for TnI72h as an effective surrogate for infarct size that was more convenient compared with other measures. Our observations were restricted to patients with relatively large documented STEMI who underwent primary PCI within 8 h of chest pain, and could not be generalized to those with alternative treatment strategies, delayed intervention, or who proceeded to surgery after diagnostic angiography, or if different troponin I assays were used. We also excluded patients with prior myocardial infarction, multiple comorbid conditions such as renal impairment and pre-existing congestive heart failure. Hence, the relationship between infarct size with biomarker release may be less robust in other clinical scenarios and may not apply to patients with small-size infarction or non-STEMI. Although overestimation of infarct size may occur in patients with prior silent infarcts, this is unlikely as we carefully excluded those with clinical or electrocardiographic evidence of previous STEMI. The cardiac biomarker levels were incomplete for certain time-points and may have implications if the missing data were significantly different from those reported. Cardiac biomarkers obtained after 72 h potentially may have provided a more optimal estimation of infarct size. However, the clinical utility of these assessments are diminished in routine clinical practice as many patients are discharged 3 days after primary PCI. The contribution of right ventricular infarction to biomarker release could also confound the correlation analyses for LV function.

Conclusions

A single assessment of TnI72h after primary PCI may be used to determine infarct size. Our data support the use of this convenient measure in risk stratification in clinical practice.

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