New insights in mechanism, diagnosis and treatment of myocardial infarction

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CHAPTER 4

USEFULNESS OF PEAK TROPONIN-T TO PREDICT INFARCT SIZE AND LONG- TERM OUTCOME IN PATIENTS WITH FIRST ACUTE MYOCARDIAL INFARCTION AFTER PRIMARY PERCUTANEOUS CORONARY INTERVENTION

ABSTRACT

In acute myocardial infarction cardiac troponin-T (cTnT) is the preferred biomarker to detect myocardial necrosis. Our aim was to investigate the prognostic value of peak plasma cTnT in patients with ST-elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PCI). Patients were eligible if STEMI symptoms started <9 hours before the primary PCI. During the first 48 hours after primary PCI, cTnT and creatine kinase (CK) were measured repeatedly. Main outcome measures were left ventricular (LV) ejection fraction (EF) assessed by myocardial scintigraphy at 90 days, and clinical outcomes through 1 year follow-up after primary PCI in a dedicated out-patient clinic. One hundred sixty eight consecutive patients (79% men) with first STEMI were studied. Mean age (±SD) was 59±12 years. Peak cTnT values were reached within 24 hours after primary PCI in all patients. The enzymatic infarct size, measured by cumulative 48-h CK release, correlated positively with peak cTnT ($r = 0.73$, $p < 0.001$). LVEF at 3 months was negatively correlated with peak cTnT ($r = -0.52$, $p<0.001$). A peak plasma cTnT ≥6.5 µg/L predicted a LVEF ≤40% at follow-up with 86% sensitivity and 74% specificity. Multivariable Cox regression analysis identified peak cTnT as an independent predictor of major adverse cardiac events (HR = 1.07, 95% CI = 1.01 - 1.12) and heart failure (HR = 1.12, 95% CI = 1.05 - 1.20) during follow-up. In conclusion, peak cTnT after primary PCI for STEMI offers a good estimation of infarct size and is prognostic indicator in patients with first acute myocardial infarction.

Keywords: ST segment elevation myocardial infarction; Percutaneous transluminal coronary angioplasty; Prognosis, Troponin T.

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Since the beginning of the troponin era, numerous studies have linked troponin-T or -I levels to the evolution of myocardial infarction. These studies mainly assessed patients with ST-elevation myocardial infarction (STEMI) treated by thrombolysis[1-3] or combined primary percutaneous coronary intervention (PCI) and thrombolysis populations.[4] Cardiac troponin has an important role in the risk stratification and management of patients with non-ST-segment elevation acute coronary syndromes.[5] Little information is available about the prognostic value of plasma troponin levels in STEMI patients diagnosed and treated according to the recent guidelines. The aim of this study was to verify the prognostic value of the early cardiac troponin-T (cTnT) peak on LV function at 3 months after primary PCI and on major adverse cardiac events occurring through one year follow-up in STEMI patients treated by primary PCI.

METHODS

This is a single center prospective study, conducted according to the institutional STEMI protocol (MISSION!) implemented at Leiden University Medical Centre (LUMC) since February 2004.[6] This protocol includes standardized prehospital, in-hospital and outpatient clinical framework for decision making and treatment. The LUMC provides a round-the-clock primary PCI service.

Main results of MISSION! study are published elsewhere.[6] One hundred sixty-eight consecutive patients with first acute myocardial infarction (MI) were enrolled in this analysis. Patients were eligible if STEMI symptoms started < 9 hours before the procedure, the electrocardiogram (ECG) demonstvrated STEMI (ST-segment elevation ≥ 0.2 mV in ≥ 2 contiguous leads in V1 through V3 or ≥ 0.1 mV in other leads), and received abciximab before primary PCI. Exclusion criteria were previous history of MI, previous PCI or bypass surgery, left bundle branch block, recent surgery, recent stroke, recent spinal trauma, hemorrhagic diatheses, severe liver or kidney failure (serum creatinine >2.5 mg/dl) and known contraindications for therapy with abciximab, aspirin, clopidogrel or heparin.

No informed consent was required, since the MISSION! protocol is the standard STEMI care regimen in the region Hollands-Midden, The Netherlands.

All patients had a high quality 12-lead ECG recorded at presentation and within 90 min after primary PCI. ST segment elevation was measured manually 20 ms after the end of the QRS complex (the J point) using a hand-held caliper. Resolution of the ST-segment of ≥ 70% was considered when the sum of the ST-segment elevations measured at 90 minutes after primary PCI decreased by more than 70% of the initial sum of ST-segment elevations.

Medications were prescribed according to MISSION! protocol.[6] All patients received abciximab (Centocor, Leiden, The Netherlands), an equivalent of 300 mg of acetylsalicylic acid and 600 mg clopidogrel as a loading dose before primary PCI. Heparin was given as a bolus of 5000 IU at the start of the PCI procedure. After the procedure, all patients received aspirin (75 mg/day) indefinitely and clopidogrel (75

mg/day) for one year. The use of other drugs, including beta-blockers, angiotensin-converting-enzyme-inhibitors, nitrates, and statins, was previously described in the MISSION! protocol.[6]

cTnT concentration in serum was measured on a third generation Elecsys 2010 analyzer (Roche Diagnostics, Almere, The Netherlands). The detection limit of the assay is 0.01 µg/L. The decision limit used for diagnosis of myocardial infarction is 0.03 µg/L, with an imprecision of < 10%. Creatine kinase (CK) activity in plasma was measured on a Roche Hitachi Modular P800 (Roche Diagnostics) having an upper limit of normal of 200 U/L. Blood samples were collected according to MISSION! protocol [6] at admission and every 6 h during the first 48h after primary PCI. Subsequently these levels were determined every day until discharge, unless clinical events necessitated additional measurements. After collection, blood samples were centrifuged immediately and serum was stored at -20°C until analysis. The laboratory staff responsible for measurements was blinded to the patient data. Peak cTnT and CK were determined retrospectively from serial samples taken in the first 48 h. A value was defined as peak if it was the highest in the 48-hour time period and if there was at least one lower value before and after this peak value.

The cumulative release of CK in the first 48 hours [7] was calculated as a measure of infarct size in each patient by an investigator blinded to the assigned treatment. For this purpose the 2-compartment model is used, which has been verified for several enzymes. The model has been described in detail by van der Laarse et al.[8] This model can be used in all patients with myocardial infarction, whether or not they received reperfusion therapy.

Coronary angiography was performed by the femoral approach. All patients underwent primary PCI and stenting of the infarction related artery (IRA) according to standard techniques. Stent implantation was successful in all patients. Procedural success was defined as residual stenosis <20% and TIMI flow grade 3. Initial and post procedural TIMI flow grade of the IRA [9] were assessed off-line.

An ECG-gated single photon emission computed tomography (SPECT) acquisition at rest using intravenous Technetium 99m Tetrofosmin (MYOVIEW, Amersham, Buckinghamshire, UK) was used to measure the LV ejection fraction (LVEF) 90 days after primary PCI in a total of 160 patients. LVEF was calculated using an automated and validated method (QGS software, version 2.0, Cedars-Sinai Medical Center, Los Angeles, CA, USA). Detailed methods have been described elsewhere.[10] Eight patients (5%) in the study group had no perfusion study at follow-up (2 patients died and 6 patients had incomplete analysis due to technical difficulties). LVEF assessment was done by an investigator blinded to the patient data.

According to the MISSION! protocol [6], patients were scheduled at a dedicated out-patient clinic after 1, 3, 6 and 12 months. Clinical outcome was evaluated through the monitoring of major adverse cardiac events (MACE) occurring at any time during the follow-up. Only the most serious event of MACE was used to calculate the cumulative MACE per patient according to the following sequence: death> MI> heart failure

(HF)> target vessel revascularization (TVR). Death was defined as "all-cause" death at follow-up. MI during follow-up was defined as a troponin-T rise >0.03 µg/l with symptoms or PCI, or a rerise of troponin-T >25% after recent MI in the presence of symptoms or re-PCI, or the development of new Q waves on ECG.[11, 12] Heart failure during follow-up was defined as either the presence of rales in more than one third of the lung fields that did not clear with coughing or evidence of pulmonary edema on chest X-ray. Target vessel revascularization was defined as any revascularization procedure of the target vessel.

Categorical variables are presented as counts and proportions (percentages) and compared by chi-square or Fisher's exact test. Normal distribution of continuous data was tested using a Kolmogorov-Smirnov test.

Normally distributed continuous data are presented as mean ± SD and were compared by unpaired *t* test or one-way analysis of variance (ANOVA) as appropriate. Not-normally distributed data are expressed as median with interquartile range (IQR), and the Kruskal-Wallis test was used to compare differences between groups. For comparison of multiple groups with ordinal categorization, the trend in the binomial proportions of categorical variables was analyzed using chi-square for trend analysis (linear-by-linear association test), and one-way ANOVA was used to test for linear trends across the means of continuous variables with logarithmic transformation of outcome variables. Correlation between continuous variables was tested using Pearson correlation test. Linear regression analyses were performed to characterize predictors of LVEF and peak TnT. Univariable and multivariable Cox proportional hazards regression models were performed to characterize predictors of MACE and heart failure. Categorical variables included age > 75y, gender, hypertension, diabetes, hypercholesterolemia, smoking habit, Killip class ≥ 2, site of MI, IRA, initial TIMI flow grade 2 to 3, multivessel disease, drug-eluting stents use, multiple stent implantation, ST-segment resolution ≥ 70% within 90 minutes and LVEF ≤ 40% at follow-up. Continuous variables included age, time from symptoms to treatment, sum of ST-segment elevation on admission ECG, basal, peak and cumulative 48-h CK release, basal and peak cTnT, and LVEF at follow-up. Multivariable Cox regression was performed using only variables with a probability value < 0.05 at univariable regression analysis. Significant variables analysed were reported with their respective hazard ratios (HR) and 95% confidence intervals (CI). The cut-off value of early cTnT peak that identifies with the highest sensitivity and specificity patients with an LVEF ≤ 40% at 90 days was analyzed by the receiver operating characteristic curve.

All p-values are two-tailed, and statistical significance was defined if $p < 0.05$. All analyses were performed with SPSS version 14.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

The study population consists of 168 consecutive STEMI patients who underwent primary PCI. Data on peak cTnT was available for all patients. The peak cTnT value occurred within the first 24 hour after admission in all patients. For analysis of baseline clinical characteristics and procedural results, patients were stratified by peak cTnT into three tertiles (<2.69 µg/L, 2.69 – 6.34 µg/L, > 6.34 µg/L, Table 1).

Patients with higher peak cTnT values were more likely to be older (age ≥ 75 year) and to present with Killip class ≥ 2.

The median time between onset of symptoms and first balloon inflation was significantly longer in the highest peak cTnT tertile (172 min, IQR 116-264 min) than in the other cTnT tertiles (p trend = 0.04) (table 1).

Table 1 Baseline and procedural characteristics of patients stratified by peak troponin-T level

	Peak Troponin-T			
Variable	<2.69 (n= 56)	2.69-6.34 (n= 56)	>6.34 (n= 56)	p Trend
Age (years)	58±11	56 ±12	64 ±12	0.002
Age ≥75 years	6 (11%)	5 (9%)	15 (27%)	0.016
Male gender	44 (79%)	43 (77%)	46 (82%)	NS
Hypertension	19 (34%)	19 (34%)	20 (36%)	NS
Diabetes mellitus	10 (18%)	3 (6%)	5 (9%)	NS
Hypercholesterolemia*	27 (48%)	22 (39%)	23 (42%)	NS
Current smoking	37 (66%)	31 (56%)	31 (56%)	NS
Positive family history	25 (45%)	25 (46%)	24 (44%)	NS
Killip class ≥2	0	1 (2%)	4 (7%)	0.046
Anterior myocardial infarction	34 (61%)	13 (23%)	33 (59%)	NS
Symptoms to balloon time (min)	131 (105- 165)	160 (113- 258)	172 (116-264)	0.04
Infarct related artery is LAD	32 (57%)	11 (20%)	30 (54%)	NS
Initial TIMI 2-3 flow	33 (60%)	18 (33%)	9 (16%)	<0.001
Post-procedural TIMI 2-3 flow	56 (100%)	56 (100%)	54 (96%)	NS
3-vessel disease	7 (13%)	7 (13%)	10 (18%)	NS
Drug eluting stents	29 (52%)	30 (54%)	24 (43%)	NS
Multiple stents implantation	20 (36%)	21 (38%)	21 (38%)	NS
ST- resolution ≥70%	40 (71%)	36 (64%)	32 (57%)	NS
Initial sum of ST- deviation (mm)	14 ± 8	19 ± 11	20 ± 10	<0.001
Basal creatine kinase (U/L)	192 ± 156	180 ± 177	447 ± 792	NS
Basal troponin-T (µg/L)	0.17 ± 0.43	0.12 ± 0.31	1.42 ± 3.88	NS
Peak creatine kinase (U/L)	641 ± 514	1929 ± 1810	3520 ± 1680	<0.001
Cumulative 48-h creatine kinase (U/L)	2996 ± 2990	8371 ± 3911	16306 ± 7859	<0.001

For the entire study population, mean peak cTnT was 5.83 ± 5.79 µg/L. The peak cTnT occurred at the first measurement before primary PCI (baseline) in 2% of patients, at 6 hours after primary PCI in 40% of patients, at 12 hours in 39% of patients, at 18 hours in 14% of patients, and at 24 hours in 5% of patients. If this categorization was done for the three peak cTnT tertiles, it was found that the higher the peak cTnT, the earlier the time the peak was achieved (p trend = 0.02, Figure 1).

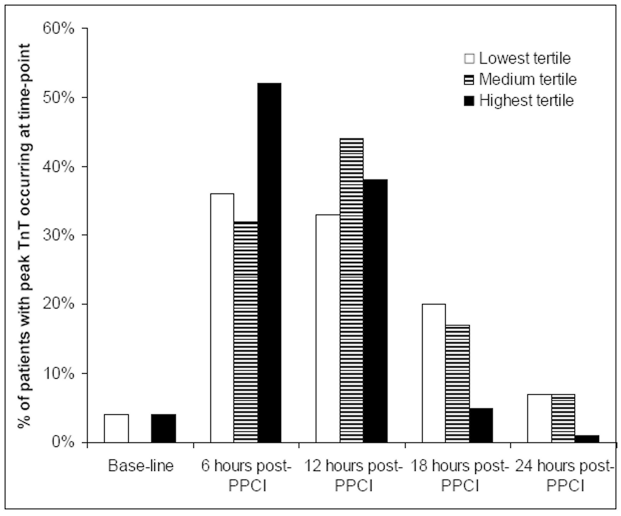

Figure 1. Timing of troponin T peak in patients stratified by troponin-T level. Patients were divided in tertiles according to their peak plasma troponin-T level. Patients were categorized per tertile, according to time-of-peak troponin-T at the preprimary PCI blood sample (baseline), and at the samples taken at 6, 12, 18 and 24 hours after primary PCI. PPCI= primary PCI; TnT= troponin-T.

Table 2 summarizes the independent correlates of peak cTnT after primary PCI assessed by multivariable linear regression analysis. Of the variables listed in Table 1, none of the post-procedural angiographic findings were independently predictive of peak cTnT level.

TIMI flow grade 2 to 3 pre-primary PCI was present more frequently in patients of the lowest peak cTnT tertile. Of interest, postprocedural TIMI flow was not significantly different between the tertiles (Table 1).

The sum of ST-segment deviation on admission ECG is highest in patients with highest peak cTnT tertile. However, occurrence of complete ST segment resolution was not significantly different between the tertiles. Peak CK and cumulative 48-hours CK release were significantly higher in the highest peak cTnT tertile than in the other tertiles (Table 1). Assessment of the relationship between peak cTnT and enzymatic infarct size measured with cumulative CK in first 48-h after primary PCI revealed a highly significant correlation ($r = 0.73$, $p < 0.001$) (Figure 2).

Table 2. Correlates of peak troponin-T level determined by multivariable linear regression analysis

Peak Troponin-T level	β	B (95% CL)	p-value
Anterior myocardial infarction	0.26	3.28 (1.3 – 5.2)	0.001
Sum of ST-deviation on admission electrocardiogram	0.34	0.19 (0.10 – 0.28)	<0.001
Pre-procedural TIMI 2-3 flow	-0.35	-4.73 (- 7.0 – -2.4)	<0.001
Killip class ≥ 2	0.40	5.79 (3.5 – 8.1)	<0.001

β= standardized regression coefficients; B= unstandardized regression coefficients; CL= confidence limits.

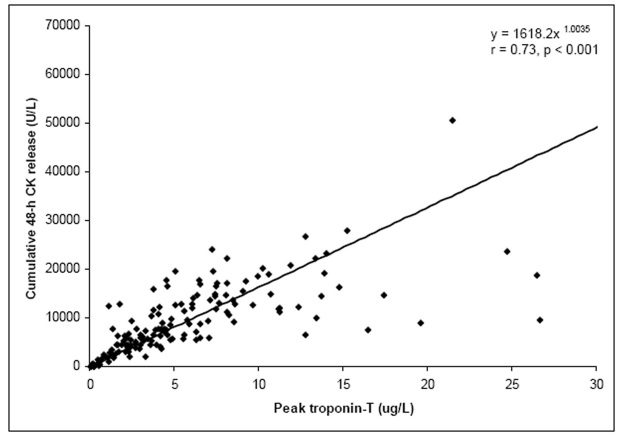

Figure 2. Relation between cumulative 48-h CK release and peak troponin-T level in 168 patients admitted with first acute myocardial infarction.

LV function was analyzed for 160 patients at 3 months after primary PCI. LVEF was highest in the lowest peak cTnT tertile (61 ± 8%), and lowest in the highest tertile (52 ± 13%, p < 0.001). LVEF was negatively correlated to peak cTnT values (r = -0.52, p < 0.001, Figure 3).

Mean value of peak cTnT was significantly higher in patients with LVEF ≤ 40% (14.1 ± 7.4 µg/L) compared to those with LVEF > 40% (5.1 ± 5.0 µg/L, p< 0.001). Table 3 presents the independent correlates of LVEF 3 months after primary PCI assessed by multivariable linear regression analysis. The highest sensitivity (86%) and specificity (74%) for the identification of patients with a LVEF ≤ 40% at 90 days were attained for a peak cTnT cut-off value of 6.5 µg/L.

The area under the curve for this cut-off value was 0.86 (95% CI = 0.77 - 0.95, Figure 4).

Patients were followed for a median of 210 days (IQR 90-330 days). Cumulative MACE occurred in 27 (16%) patients. Mean peak cTnT was significantly higher in patients who developed a MACE (7.9 ± 8.9 µg/L) than in patients who did not develop

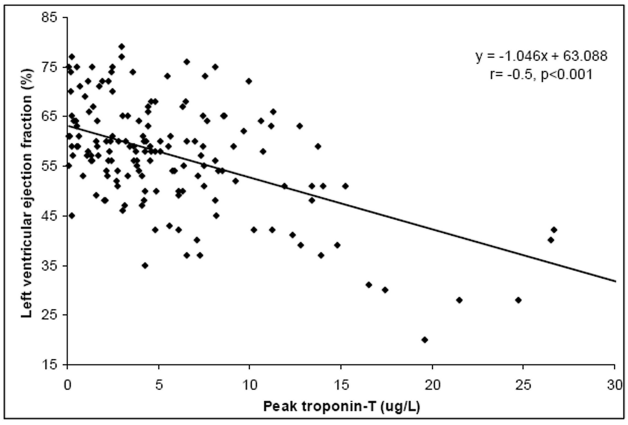

Figure 3. Relation between LVEF determined at 3-month follow-up and peak plasma troponin-T level in 168 patients admitted with first acute myocardial infarction.

Table 3. Correlates of LVEF at 3-month follow-up, determined by multivariable linear regression analysis

Left ventricular ejection fraction	β	B (95% CL)	P
Peak troponin-T (µg/L)	-0.49	-0.94 (-1.3 – -0.5)	<0.001
Men	-0.22	-7.27 (-12.1 – -2.4)	0.004
Pre-procedural TIMI 2-3 flow	0.22	5.49 (1.25 – 9.72)	0.01

β= standardized regression coefficients; B= unstandardized regression coefficients; CL= confidence limits.

any MACE (5.4 ± 4.9 µg/L, p = 0.03). Six (4%) patients died (1 from cardiogenic shock, 2 from fatal recurrent MI, 3 from non-cardiac causes). Plasma peak cTnT was higher in those who died (12.0 ± 14.9 µg/L) than in survivors (5.6 ± 5.1 µg/L, p = 0.007). Seven (4%) patients had recurrent MI and 12 (7%) patients had a TVR during follow-up. Their mean peak cTnT values did not differ significantly from that of patients who had no recurrent MI or TVR. Eight (5%) patients who developed heart failure on follow-up had higher mean peak cTnT (14.2 ± 12.5 µg/L) than those without heart failure (5.4 ± 4.9 µg/L, p < 0.001).

Table 4 presents the independent correlates of cumulative MACE and heart failure (as a separate entity), assessed by univariable Cox proportional-hazards regression analysis including all variables listed in Table 1. By multivariable Cox regression analysis, including only variables that had p < 0.05 in univariable regression analysis, only peak cTnT was identified as independent predictor of incidence of cumulative MACE and heart failure (Table 4).

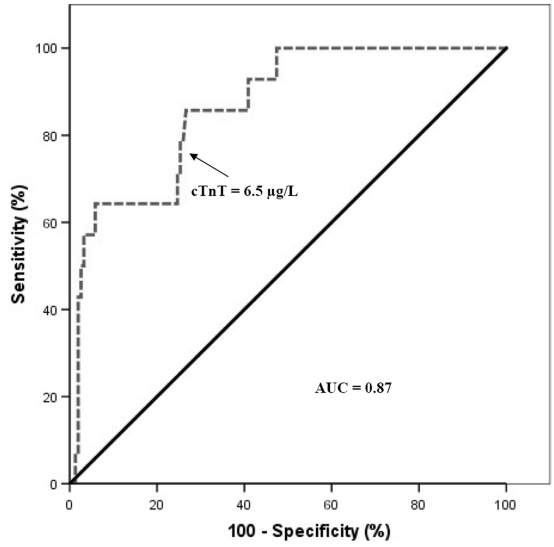

Figure 4. Receiver operator characteristic (ROC) curve analysis for peak troponin-T as a predictor of LVEF ≤ 40% at 3 months follow-up. Best decision threshold is shown (sensitivity is 86% and specificity is 74%). AUC= Area under the receiver operator characteristic curve.

Table 4. Predictors of major adverse cardiac events and heart failure determined by Cox proportional-hazards regression analysis

	Univariable			Multivariable		
Major adverse cardiac events	HR	95% CL	p Value	HR	95% CL	P Value
Sum of ST-deviation on admission electrocardiogram	1.05	1.01- 1.09	0.01	1.04	0.99- 1.08	0.07
Peak TnT level (µg/L)	1.07	1.02- 1.12	0.005	1.07	1.01- 1.12	0.01
LVEF at 3 months follow-up	0.96	0.93- 0.99	0.03	--	--	--
Heart Failure						
Peak troponin-T level (µg/L)	1.13	1.06- 1.21	<0.001	1.12	1.05- 1.20	0.001
LVEF ≤ 40%	6.03	1.4- 25.3	0.01	--	--	--

CL = confidence limits

DISCUSSION

In the present study we demonstrated that the location of myocardial infarction, the sum of ST-segment deviations on admission ECG, the preprimary PCI TIMI flow, and the Killip class at admission were determinants of peak cTnT levels. Furthermore, the peak cTnT was an independent predictor for LV function at 3 months and for major adverse cardiac events, including heart failure, through one-year clinical follow-up.

CK is an established non-invasive measure of infarction size and severity,[13-15] and recently CK was also proved to be a good prognostic marker for patients undergoing primary PCI.[16] However, as CK release is influenced strongly by early reperfusion phenomena, it is difficult to decide which value is a correct reflection of myocardial damage.[17, 18] In our study, peak CK demonstrated a significant trend with the peak cTnT. Tzivoni et al.[19] recently demonstrated that peak levels of cTnT are as accurate as CK in estimating myocardial infarct size in acute MI patients who underwent primary PCI.

Rasoul et al.[20] found that presentation delay, anterior MI location, and older age were independent predictors of peak cTnT levels. The longer delay reported by Rasoul et al.[20] may explain the higher sum of the ST-deviation on admission, the lower preprimary PCI TIMI flow, and the higher Killip class, found to be determinants of the peak cTnT in our study. Although we did not find age to be an independent determinant of peak cTnT levels, we observed significant age differences among the cTnT tertiles: patients in the highest peak cTnT tertile were older than patients in the lowest cTnT tertile (64 vs. 58 years, p-trend = 0.002); patients older than 75 years were also more frequent in the highest cTnT tertile than in the lowest cTnT tertile (27% vs. 11%, p-trend = 0.016).

In our study all patients had their peak cTnT within the first 24 hours after admission. Early peaking of cTnT relates to the troponin release dynamics in acute MI patients who benefitted from early reperfusion therapy.[21] After ischemic injury, cTnT serum concentrations display a biphasic curve with an early peak within the first 24 hours resulting from the release of a small cytoplasmatic pool from the infarcted myocardium after successful reperfusion (rapid wash out), followed by a plateau at 72-96 hours after the onset of symptoms resulting from continuous proteolytic degradation of the contractile apparatus.[22, 23]

Peak cTnT was correlated negatively with the LVEF measured by myocardial scintigraphy after three months which is in agreement with prior studies that showed a relation between peak troponin and LV function in follow-up.[24-27] The peak cTnT at the index event and the LVEF ≤ 40% at 3 months were significantly correlated with the incidence of heart failure through follow-up. LVEF ≤ 40% was associated with a 6 times higher incidence of heart failure compared to patients with LVEF > 40%. Peak cTnT was identified as independent predictor of heart failure development during one year follow up. To the best of our knowledge, this is the first study to show that peak cTnT at the index event predicts the occurrence of heart failure symptoms through one year follow-up in STEMI patients who underwent primary PCI.

We showed that a cut-off point for plasma cTnT peak of 6.5 µg/L had a high sensitivity (86%) and specificity (74%) to predict a low LVEF at 90 days follow-up. The screening ability of cTnT for detection of low LVEF was previously suggested. Tzivoni et al.[19] presented a cut-off value of 3.5 µg/L with a sensitivity of 90% but low specificity (31%) and Panteghini et al.[28] showed that cTnT > 2.98 µg/L predicts low LVEF at 3 months with a sensitivity of 86.7% and specificity of 81.4%.

At follow-up, peak cTnT predicted major cardiac events such as death, MI, target vessel revascularization and heart failure. These findings are in agreement with previous studies demonstrating a relation between peak troponin and clinical outcomes in short and long-term follow-up.[24-27] Based on the results of our study we suggest that a peak cTnT value obtained in the first 24 hours after primary PCI may be routinely used as a cardiac marker in patients with STEMI.

A possible limitation is that we could not extend cTnT measurements beyond 48 hours because this was not included in the MISSION! protocol[6]. We could therefore not calculate a cumulative troponin release in analogy with cumulative CK values. However, the peak cTnT was successfully used in previous studies and we do not expect that a cumulative cTnT value would have changed any of the presented findings.

Our results indicate that a prognostic indicator based on peak cTnT can be obtained for patients with acute MI treated with primary PCI as early as the end of their first day in the hospital, and for risk stratification it appears that serial cTnT measurements can be limited to the first 24 hours in most acute MI patients treated with primary PCI.

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