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Author: Boden, Helena Title: Acute myocardial infarction care : developments, pitfalls and prognosis Issue Date: 2016-03-10 Peak and fixed-time high-sensitive troponin for prediction of infarct size, impaired left ventricular function, and adverse outcome in patients with first ST-segment elevation myocardial infarction receiving percutaneous coronary intervention

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ABSTRACT

Aims	The clinical use of advanced imaging modalities for early determination of infarct size and prognosis is limited. As a specific indicator of myocardial necrosis, cardiac troponin-T (cTnT) may be used as a surrogate measure for this purpose. The present study sought to investigate the use of peak and serial 6-hour fixed-time high-sensitive (hs) cTnT for estimation of infarct size, left ventricular (LV) function and prognosis in consecutive patients with ST-segment elevation myocardial infarction (STEMI).
Methods	Infarct size was expressed as 48-hour cumulative creatine kinase release ($Q_{48}CK$). LV function at three months was assessed using the echocardiographic wall motion score index (WMSI) and LV ejection fraction (EF) using radionuclide ventriculography. Adverse outcomes, comprising all-cause death, implantable cardioverter-defibrillator implantation or hospitalization for heart failure, were recorded at 1 year follow-up.
Results	In 188 patients, the peak and all fixed-time values correlated significantly with $Q_{48}CK$, WMSI and LVEF. The value at 24 hours (hs-cTnT ₂₄) demonstrated the greatest correlation (r=0.86, r=0.47 and r=-0.59, respectively [p<0.001 for all]). In the multivariable regression models adjusted for clinical parameters, almost all were independently associated with $Q_{48}CK$, WMSI and LVEF, with hs-cTnT ₂₄ having the largest impact. Moreover, all cTnT values independently predicted adverse outcomes, again, with the hs-cTnT ₂₄ showing the largest influence (HR 3.77 [95%CI 2.12-6.73], p<0.001).
Conclusions	Not only peak, but all fixed-time hs-cTnT values were as- sociated with infarct size, LV function 3 months and adverse outcome one year after STEMI. The value 24 hours after the onset of symptoms had the closest associations with all outcomes. Therefore, serial sampling for a peak value might be redundant.

INTRODUCTION

Cardiac troponin T (cTnT) is a specific indicator of necrosis of cardiomyocytes¹. Recent technological innovations in immunoassays enable rapid diagnosis or early rule-out of ongoing myocardial necrosis by lowering the threshold for the detection of cTnT in serum². However, it is unclear whether this biomarker can also be used as a surrogate measure for the extent of injured myocardium after acute myocardial infarction (AMI). Moreover, the infarct size is closely related to prognosis³. Therefore, the early determination of infarct size is indispensable for risk stratification. Previously, models for the cumulative release of creatine kinase (CK) in relation to the quantity of injury have been validated as a measure for infarct size^{4;5}. However, the complexity of these mathematical models limits its utility in daily practice. Contrast-enhanced cardiac magnetic resonance imaging and myocardial perfusion imaging have also been assessed for this purpose, but their use for the routine quantification of infarct size has been limited owing to logistic difficulties and high costs. Thus, it would be particularly useful to estimate the infarct size and prognosis solely by measuring cTnT in the systemic circulation during hospitalization. Despite the widespread assumption that the height of cTnT concentration is an indicator, not only for infarct size but also for prognosis, data on this topic are scarce⁶. Moreover, it is uncertain whether a fixed measurement point might be sufficient. Therefore, the purpose of the present study was to assess the value of peak and fixed-time cTnT, measured using new high-sensitivity (hs) assays, for estimation of the infarct size, left ventricular (LV) function and adverse outcomes in patients with a first ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

METHODS

Design

The present single center retrospective cohort study included patients with STEMI who were treated with primary PCI from March 2010 to March 2011 from an ongoing clinical registry. Patients were treated according to the institutional protocol (MISSION!)⁷, based upon the most recent international guidelines^{8;9}. It includes a pre-hospital, in-hospital and outpatient framework for clinical decision making and treatment of AMI patients ≤ 1 year after discharge. Since the implementation of this protocol in 2004, the data from consecutive STEMI patients were prospectively collected in the departmental electronic patient information system (EPD-Vision). The MISSION! care program is the standard of AMI care in the district Hollands-Midden, the Netherlands¹⁰.

Patients

Consecutive patients with STEMI were eligible for inclusion when presenting with symptoms of AMI, with an electrocardiogram demonstrating a STEMI (ST-elevation of ≥ 0.2 mV in ≥ 2 contiguous leads in V1 through V3 or ≥ 0.1 mV in other leads) and a typical rise and/or fall course of cardiac biomarker levels¹. At least one value of hs-cTnT had to exceed the diagnostic decision limit (0.05 µg/L) in the present study based on clinical experience. Furthermore, treatment according to protocol including primary PCI and monitoring at the MISSION! outpatient clinic was required. Exclusion criteria were a history of AMI and severe renal failure (serum creatinine >2.5 mg/dL). All patients received pharmacotherapy according to the MISSION! care program, including upfront abciximab, peri-procedural heparin, in-hospital enoxaparin, and loading and maintenance doses of aspirin and clopidogrel. After discharge, patients were treated with dual antiplatelet therapy, beta-blockers, angiotensin-converting enzyme-inhibitors and statins. Patients were examined at the outpatient clinic at 30 days, 3, 6 and 12 months. At 3 months, echocardiography and radionuclide ventriculography were performed to assess LV function⁷.

Biomarker measurements

For the measurements of the cardiac biomarkers, serum samples were obtained at presentation and subsequently at 6-hour intervals for 48 hours after primary PCI. Samples were centrifuged immediately after collection, followed directly by measurements of cTnT in serum. The concentration of cTnT was assayed using the 5th-generation cTnT reagent (Roche Diagnostics, Indianapolis, IN, USA) on Modular E analyzers with a 99th percentile upper reference limit of 0.014 μ g/L. The values of hs-cTnT at 6, 12, 18 and 24 hours after the onset of symptoms were retrospectively calculated by interpolation of the serial 6-hour samples collected during hospitalization.

CK activity was measured at 37° C with an IFCC-traceable method (Roche Diagnostics) on Modular P analyzers. The upper reference limit was 200 U/L. As a measure for infarct size, the quantity of CK cumulatively released in the first 48 hours after the onset of symptoms (Q_{48} CK) was calculated using the 2-compartment model, which has been previously described in detail¹¹. In a few patients, the Q_{48} CK could not be calculated owing to a lack of samples during the first 48 hours. In those patients, Q_{48} CK was estimated by multiplying the quantity of cumulatively released CK after 24 hours (Q_{24} CK, if available) with the average ratio between Q_{24} CK and Q_{48} CK (1:1.50) of patients with both quantities available. Laboratory staff and investigators responsible for the measurements and calculation of biomarker parameters were unaware of the patient data.

LV function

All patients underwent 2-dimensional echocardiography three months after discharge in the left lateral decubitus position (Vivid 7 and e9; GE-Vingmed Ultrasound AS, Horten,

Norway). Images were acquired during breath hold using a 3.5-MHz transducer in parasternal and apical views with simultaneous electrocardiographic signal and saved in cine-loop format. The analyses were performed offline (EchoPac 110.01; GE-Vingmed). The left ventricle was divided into 16 segments. The segments were analyzed individually and scored based on the degree of motion and systolic thickening (1=normokinetic, 2=hypokinetic, 3=akinetic, 4=dyskinetic). The wall motion score index (WMSI) was calculated by dividing the sum of all segment scores by the number of segments¹² and considered to be a measure for LV function.

Single-photon emission computed tomography was routinely performed 3 months after discharge. Since January 2011 routine stress echocardiography was implemented in the MISSION! protocol as a replacement. Therefore, single-photon emission computed tomography was performed in a subgroup of the present study population. Patients underwent myocardial perfusion imaging using technetium 99m tetrofosmin (500MBq) (Myoview, GE-Healthcare, Little Chalfont, Buckinghamshire, UK) including radionuclide ventriculography. Electrocardiogram-gating was applied at 16 frames per cardiac cycle with a tolerance window of 50%. Images were acquired 45 minutes after tracer administration and processed after the procedure using the Corridor4DM 6.1 software (INVIA Solutions, Ann Arbor, MI, USA). The automatically calculated LV ejection fraction (LVEF) at rest was considered to reflect LV function.

Follow-up and data collection

Patients were monitored at the MISSION! outpatient clinic for one year after discharge. Major adverse cardiac events were recorded and prospectively collected by attending cardiologists not involved in the present study. Vital status of the entire cohort was retrieved from municipality records. Patients for whom ≥2.5 months of clinical follow-up data (other than vital status) were lacking, were considered lost to clinical follow-up. Data were included until the last follow-up date. The clinical endpoint was defined as the composite of all-cause death, implantable cardioverter-defibrillator (ICD) implantation or any hospitalization for heart failure within one year.

Statistical analysis

Categorical variables are presented as numbers and proportions (%) and continuous variables as mean ± standard deviation or median and interquartile range. Correlations were evaluated using Spearman's correlation. Linear regression analysis was performed to examine the association between cTnT values and infarct size and LV function. First, clinical variables with p<0.10 in univariate analysis were included in multivariate linear regression models. In order to prevent multicollinearity, a cTnT parameter was added one at a time to the multivariate model, keeping the combination of the other clinical variables in the model constant. The independent additional contribution of a cTnT parameter

was determined by calculating the increase in the variation in outcome explained by the variables in the model (R^2). To examine the predictive value of cTnT values for the composite clinical outcome, Cox proportional hazards regression analysis was performed. Due to the limited number of events, a stepwise forward selection procedure was performed, using clinical variables with p<0.05 in univariate analysis. Just as with the other outcomes, the predictive value of a cTnT parameter for this outcome was determined by adding one cTnT parameter at a time to the multivariate model, keeping all other variables constant. The magnitude of the effect on the adverse outcomes of the individual cTnT parameters was reflected by the hazard ratio (HR). All p-values were 2-sided and a p<0.05 was considered to be statistically significant. Analyses were conducted with SPSS 17.0.1 statistical analysis software (SPSS Inc., Chicago, IL, USA).

RESULTS

The study population comprised 188 patients treated with primary PCI for first STEMI. Baseline characteristics are summarized in **Table 1**. Values for hs- $cTnT_{12}$, hs- $cTnT_{18}$, hs- $cTnT_{24}$ and hs- $cTnT_{peak}$ were missing in 5, 6, 7 and 11 patients, respectively, because of transfer or death within the first few hours after intervention. Median hs- $cTnT_{peak}$ was 3.15 µg/L (interquartile range 1.21-7.22), median CK_{peak} was 1,205 U/L (interquartile range 622-2703). In the present population, discordant release patterns of cTnT and CK were occasionally observed. Plotting these release patterns revealed a prolonged plateau phase for cTnT, while CK quantities quickly diminished to the normal steady state level (**Figure 1**).



Figure 1. Discordant release patterns of CK and troponin. CK = creatine kinase; cTnT = cardiac troponin T.

Variable	N = 188
Age (years)	61 ± 12
Men	136 (72%)
Hypertension*	70 (39%)
Hyperlipidemia†	47 (26%)
Diabetes mellitus	20 (10.6%)
Current smoker	86 (47%)
Positive family history	77 (45%)
Previous PCI / CABG	6 (3.2%)
OHCA	12 (6.4%)
Ischemia time (min)	229 ± 181
Killip class ≥ 2	13 (7.0%)
Admission heart rate (bpm)	75 ± 21
Admission creatinine (µmol/L) ‡	80 ± 24
Proximal lesion	72 (38%)
Culprit vessel LAD	77 (41%)
Multivessel disease	107 (57%)
Stenting	177 (94%)
Multiple stents	86 (47%)
Initial TIMI flow ≥ 2	61 (32%)
Final TIMI flow 3	169 (91%)

Table 1. Clinical baseline characteristics

Data are expressed as number (%) or mean \pm standard deviation (SD); * Blood pressure $\ge 140/90$ mmHg or previous pharmacological treatment; † Total cholesterol ≥ 190 mg/dl or previous pharmacological treatment; ‡ Creatinine measured in serum .

CABG = coronary artery bypass grafting; LAD = left anterior descending (coronary artery); OHCA = out-of-hospital cardiac arrest; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction.

Infarct size

 $Q_{48}CK$ was available for 177 patients. Of these 177 patients, it was calculated in 123 cases and was estimated using the aforementioned method for 54 cases. Peak and all fixed-time hs-cTnT values correlated significantly with $Q_{48}CK$. The value at 24 hours after the onset of symptoms demonstrated the greatest correlation coefficient (r) of 0.86 (**Figure 2A**) compared to other hs-cTnT values (hs-cTnT₆ r=0.53; hs-cTnT₁₂ r=0.70; hs-cTnT₁₈ r=0.85; and hs-cTnT_{peak} r=0.83). Linear regression analysis (adjusted for gender, ischemic time, out-of-hospital cardiac arrest [OHCA], number of diseased - major epicardial coronary- vessels, proximal lesion, pre-procedural Thrombolysis In Myocardial Infarction [TIMI] flow, stent implantation, and multiple stents implanted) revealed that peak and all fixed-time hs-cTnT values were independently associated with $Q_{48}CK$ (**Table 2**). HscTnT₂₄ was demonstrated to have the greatest effect on $Q_{48}CK$ ensuring a substantial increase in the variation in outcome explained by the model (R²).

LV function

WMSI and LVEF at three months after discharge were available for 170 and 106 patients, respectively. Peak and all fixed-time hs-cTnT values significantly correlated with both the WMSI and LVEF (inversely). Hs-cTnT₂₄ demonstrated the greatest (but moderate) correlation with both outcomes (r=0.47 and r=-0.59, respectively [**Figure 2B and 2C**]) compared to other hs-cTnT values (hs-cTnT₆ r=0.30 and r=-0.36; hs-cTnT₁₂ r=0.40 and r=-0.51; hs-cTnT₁₈ r=0.46 and r=-0.59; and hs-cTnT_{peak} r=0.45 and r=-0.54). Multivariate linear regression demonstrated that all hs-cTnT values were independently associated with both the WMSI (**Table 2**, adjusted for number of diseased vessels, culprit vessel, pre-procedural TIMI-flow, multiple stents implanted, and final TIMI-flow) and LVEF (**Table 2**, adjusted for gender, admission serum creatinine concentration, number of diseased vessels, proximal lesion and multiple stents implanted), except for hs-cTnT₆ with the WMSI. Again, hs-cTnT₂₄ showed the greatest increase in R² after its addition to both models compared to other hs-cTnT values, although the effect was only moderate for the WMSI and reasonable for LVEF.

Q ₄₈ CK	ß	Increase R ²	Total R ²	P-value
hs-cTnT ₆	0.528	0.200	0.469	< 0.001
hs-cTnT ₁₂	0.648	0.313	0.582	< 0.001
hs-cTnT ₁₈	0.809	0.489	0.757	< 0.001
hs-cTnT ₂₄	0.835	0.513	0.782	< 0.001
hs-cTnT _{peak}	0.765	0.476	0.748	< 0.001
WMSI	ß	Increase R ²	Total R ²	P-value
hs-cTnT ₆	0.136	0.015	0.239	0.076
hs-cTnT ₁₂	0.208	0.033	0.259	0.009
hs-cTnT ₁₈	0.343	0.085	0.312	< 0.001
hs-cTnT ₂₄	0.357	0.093	0.318	< 0.001
hs-cTnT _{peak}	0.312	0.074	0.310	< 0.001
LVEF (%)	ß	Increase R ²	Total R ²	P-value
hs-cTnT ₆	-0.271	0.064	0.253	0.005
hs-cTnT ₁₂	-0.366	0.114	0.312	< 0.001
$hs-cTnT_{18}$	-0.453	0.168	0.366	< 0.001
hs-cTnT ₂₄	-0.470	0.176	0.374	< 0.001
hs-cTnT _{neak}	-0.421	0.155	0.358	< 0.001

Table 2. Multivariable linear regression for 48 hour cumulative creatine kinase release, wall motion score index and left ventricular ejection fraction.

The additive value of troponin to linear regression models adjusted for clinical variables.

 β = standardized regression coefficient; hs-cTnT_t = high-sensitive cardiac troponin T at time t (hours) after the onset of symptoms; LVEF = left ventricular ejection fraction; Q₄₈CK = cumulatively released creatine kinase during 48h after the onset of symptoms; R² = the proportion of the variation in outcome explained by the variables in the multivariable model; WMSI = echocardiographic wall motion score index.



Figure 2. Spearman's correlation between A. hs- $cTnT_{24}$ and $Q_{48}CK$ (U/L), B. hs- $cTnT_{24}$ and WMSI at 3 months, and C. hs- $cTnT_{24}$ and LVEF (%) at 3 months.

hs-cTnT₂₄ = high-sensitive cardiac troponin T at 24 hours after the onset of symptoms; LVEF = left ventricular ejection fraction; $Q_{48}CK$ = cumulatively released creatine kinase during 48 hours after the onset of symptoms; WMSI = wall motion score index.

Adverse outcomes

Four patients (2.1%) were considered lost to clinical follow-up. During one year of followup, 22 patients reached the composite endpoint of all-cause death, ICD-implantation or any hospitalization for heart failure, of whom 12 had died, an ICD had been implanted in **CHAPTER 4** • The prognostic value of a single measurement of troponin-T



Figure 3. The predictive value of troponin values for the adverse composite outcome of all-cause death, ICD-implantation or any hospitalization for heart failure, determined by Cox proportional hazard regression.

CI = confidence interval; HR = hazard ratio; hs-cTn T_{24} = high-sensitive cardiac troponin T at 24 hours after the onset of symptoms.

eight and two patients had been hospitalized for heart failure. Peak as well as all fixed-time hs-cTnT values independently predicted adverse outcome (**Figure 3**, adjusted for gender, previous revascularization procedure, admission Killip class ≥ 2 , final TIMI-flow <3 and OHCA). Again, hs-cTnT₂₄ showed the greatest effect with an adjusted HR of 3.77.

DISCUSSION

Key findings of the present study were as follows: 1) Peak and all fixed-time hs-cTnT values correlated well with infarct size ($Q_{48}CK$) and were shown to be independently associated with infarct size. 2) Peak and all fixed-time hs-cTnT values correlated moderately with WMSI and slightly better with LVEF at three months after STEMI. However, all hs-cTnT values (except hs-cTnT₆) were independently associated with both outcomes for LV function. 3) Peak and all fixed-time hs-cTnT values were independent predictors of an adverse outcome one year after STEMI. 4) In all analyses, the hs-cTnT value 24 hours after the onset of symptoms performed at least as well as did the peak hs-cTnT for estimation of infarct size, LV function and adverse outcome.

Since CK and cTn (T and I) play a crucial role in the diagnosis of AMI, it is obviously necessary to investigate whether these biomarkers might also qualify as surrogate measures of infarct size or prognosis. Measurement of peak CK activity has proved useful for infarct sizing^{5;13}; however it tends to overestimate the infarct size. First, the lack of absolute specificity for cardiac tissue enables overestimation due to skeletal muscle damage. Second, CK activity is strongly influenced by (early) successful reperfusion, reflected by an earlier

and greater peak level compared to poor or no reperfusion in case of similar injury.^{14;15} Although previous studies have stated that cTn provides added value to risk assessment of AMI patients, most studies investigated the peak and/or fixed-time concentrations at three to four days after infarction, measured with conventional assays in a small heterogeneous AMI cohort treated with thrombolysis.⁶ In addition to advances in treatment and assay technology, hospitalization is often limited to 48 hours in patients with an uncomplicated course; therefore sampling up to four days is no longer feasible. A peak necessitates serial sampling with considerable accompanying costs and it is questionable whether this value provides more information for estimation of infarct size and prognosis than a value at a fixed time point after the onset of symptoms.

In line with previous data, hs-cTnT measurements in the present study were closely related to infarct size. However, the correlation between cTnT and Q₄₈CK is still suboptimal considering that both biomarkers are supposed to reflect myocardial necrosis. Discordant release patterns of cTnT and CK were occasionally observed in the present study population. This finding might be explained by the slow and partial release of cTnT from necrotic cardiomyocytes. The majority of cTnT is bound to the contractile apparatus, and only a small unbound fraction (the cytosolic pool) is released at once after successful reperfusion, leading to a first peak in the release pattern. Thereafter, the originally bound cTnT is slowly liberated in the peripheral circulation for a prolonged period up to two weeks.^{16;17} In cases in which the first peak of cTnT was not noted due to unfortunate timing of sampling, the interpretation of biomarker courses can be difficult in individual patients. However, although the release kinetics of cTnT are more complex than those of CK, the measurement of cTnT in the peripheral blood is more feasible in daily practice than calculations for cumulative released CK or advanced imaging modalities for estimation of infarct size.

Previously, it has been repeatedly demonstrated that cTn correlates less well with LVEF or LV volumes than with infarct size,⁶ which is confirmed by the present study. However, minor variation in correlation exists between studies, which can be explained by the timing of LV function assessment. In the present study, echocardiography and radionuclide ventriculography were performed three months after the acute phase. This ensures a more accurate assessment of LV function, since findings might be influenced by stunning early after AMI. Data on the association between the height of elevated cTn concentrations and adverse outcome in STEMI patients are scarce. In a previous study, peak cTnT was identified as a prognostic indicator for major adverse cardiac events and heart failure in STEMI patients.¹⁸ Additionally, others have reported a strong predictive value of a single measurement of cTnT after STEMI for adverse outcome.¹⁹⁻²¹ Conversely, the peak cTnT was shown to be of limited prognostic value for 1-year mortality in a large cohort of STEMI patients

by Byrne et al.²² However, the latter results might have been biased owing to multicollinearity by including peak cTnT, peak CK-MB and infarct size as proportion of LV mass in one multivariate model. The results in the present study have confirmed the independent prognostic value of cTnT and have provided evidence that a single fixed-time measurement performed equally well as the peak, derived from serial sampling, for adverse outcome.

Even though a fair amount of evidence indicates that a fixed-time cTn value is not inferior to the peak or area-under-the-curve values for prognostic purposes, the optimal timing is still uncertain.⁶ Several studies have demonstrated that fixed-time cTnT values taken up to 72-96 hours after admission or onset of symptoms were all predictive of infarct size or LV function and correlated more or less comparable with the outcomes.^{20;23-26} However, most of these studies advocated the use of the latest value investigated, which was often after 48 hours and therefore no longer feasible in current standard care. Moreover, the optimal timing of a fixed-time value differed among the individual outcome measures. Although the results for the different fixed-time points in the present study appeared to be within a small range as well, it is remarkable that in all analyses the value at 24 hours after the onset of symptoms was found to have the closest correlations with and greatest effect on all outcomes. This suggests that cTnT₂₄ might be a simple, but inexpensive and practical, tool in risk assessment of STEMI patients in daily practice.

Limitations

The present study has several limitations. First, the study has an observational design and therefore we could not account for undocumented clinical variables that might possibly have influenced the outcomes. Values of hs-cTnT beyond 24 hours after the onset of symptoms were not investigated, because these were largely unavailable. Second, although Q48CK has been verified for estimation of infarct size45, the reference standard for accurate quantification of necrotic tissue is considered to be single-photon emission computed tomography.²⁷ However, it lacks the sensitivity to detect smaller infarctions²⁸ and was not available in all patients. Cardiac magnetic resonance imaging with high spatial resolution, reproducibility, and the ability of detecting small infarctions would have been an appropriate alternative for accurate quantification^{27;29}. However, its use for routine assessment of infarct size in daily practice has been confined by high expenses and low availability and was not performed in the present study population. Moreover, in studies using cardiac magnetic resonance for early determination of infarct size, the patients with severe complications and/or comorbidity might be excluded from prolonged examination in a magnetic field. Third, the results only apply to patients without severe renal failure. Finally, it should be acknowledged that the increased feasibility of a fixed-time cTnT value compared to other, more expensive or complex modalities is accompanied by diminished accuracy.

REFERENCE LIST

- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third Universal Definition of Myocardial Infarction. J Am Coll Cardiol 2012 Aug 29.
- (2) Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009 Aug 27; 361(9):858-67.
- (3) Burns RJ, Gibbons RJ, Yi Q, Roberts RS, Miller TD, Schaer GL, et al. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. J Am Coll Cardiol 2002 Jan 2;39(1):30-6.
- (4) Sobel BE, Bresnahan GF, Shell WE, Yoder RD. Estimation of infarct size in man and its relation to prognosis. Circulation 1972 Oct;46(4):640-8.
- (5) Hackel DB, Reimer KA, Ideker RE, Mikat EM, Hartwell TD, Parker CB, et al. Comparison of enzymatic and anatomic estimates of myocardial infarct size in man. Circulation 1984 Nov;70(5): 824-35.
- (6) Hallen J. Troponin for the Estimation of Infarct Size: What Have We Learned? Cardiology 2012 Apr 19;121(3):204-12.
- (7) Liem SS, van der Hoeven BL, Oemrawsingh PV, Bax JJ, van der Bom JG, Bosch J, et al. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. Am Heart J 2007 Jan;153(1):14-1.
- (8) Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012 Oct; 33(20):2569-619.
- (9) O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on

Practice Guidelines. J Am Coll Cardiol 2012 Dec 12.

- (10) Atary JZ, de VM, van den Dijk R, Bosch J, Liem SS, Antoni ML, et al. Standardised pre-hospital care of acute myocardial infarction patients: MISSION! guidelines applied in practice. Neth Heart J 2010 Sep;18(9):408-15.
- (11) van der Laarse A, Vermeer F, Hermens WT, Willems GM, de NK, Simoons ML, et al. Effects of early intracoronary streptokinase on infarct size estimated from cumulative enzyme release and on enzyme release rate: a randomized trial of 533 patients with acute myocardial infarction. Am Heart J 1986 Oct;112(4):672-81.
- (12) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005 Dec;18(12):1440-63.
- (13) Shell WE, Kjekshus JK, Sobel BE. Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase activity. J Clin Invest 1971 Dec;50(12):2614-25.
- (14) Katus HA, Diederich KW, Schwarz F, Uellner M, Scheffold T, Kubler W. Influence of reperfusion on serum concentrations of cytosolic creatine kinase and structural myosin light chains in acute myocardial infarction. Am J Cardiol 1987 Sep 1; 60(7):440-5.
- (15) Vatner SF, Baig H, Manders WT, Maroko PR. Effects of coronary artery reperfusion on myocardial infarct size calculated from creatine kinase. J Clin Invest 1978 Apr;61(4):1048-56.
- (16) Michielsen EC, Diris JH, Kleijnen VW, Wodzig WK, van Dieijen-Visser MP. Investigation of release and degradation of cardiac troponin T in

patients with acute myocardial infarction. Clin Biochem 2007 Aug;40(12):851-5.

- (17) Katus HA, Remppis A, Scheffold T, Diederich KW, Kuebler W. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. Am J Cardiol 1991 Jun 15;67(16):1360-7.
- (18) Hassan AK, Bergheanu SC, Hasan-Ali H, Liem SS, van der Laarse A, Wolterbeek R, et al. 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. Am J Cardiol 2009 Mar 15;103(6):779-84.
- (19) Kurz K, Schild C, Isfort P, Katus HA, Giannitsis E. Serial and single time-point measurements of cardiac troponin T for prediction of clinical outcomes in patients with acute ST-segment elevation myocardial infarction. Clin Res Cardiol 2009 Feb;98(2):94-100.
- (20) Chia S, Senatore F, Raffel OC, Lee H, Wackers FJ, Jang IK. 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. JACC Cardiovasc Interv 2008 Aug;1(4):415-23.
- (21) Ohlmann P, Jaquemin L, Morel O, El BR, Faure A, Michotey MO, et al. Prognostic value of C-reactive protein and cardiac troponin I in primary percutaneous interventions for STelevation myocardial infarction. Am Heart J 2006 Dec;152(6):1161-7.
- (22) Byrne RA, Ndrepepa G, Braun S, Tiroch K, Mehilli J, Schulz S, et al. Peak cardiac troponin-T level, scintigraphic myocardial infarct size and one-year prognosis in patients undergoing primary

percutaneous coronary intervention for acute myocardial infarction. Am J Cardiol 2010 Nov 1;106(9):1212-7.

- (23) Giannitsis E, Steen H, Kurz K, Ivandic B, Simon AC, Futterer S, et al. Cardiac magnetic resonance imaging study for quantification of infarct size comparing directly serial versus single time-point measurements of cardiac troponin T. J Am Coll Cardiol 2008 Jan 22;51(3):307-14.
- (24) Arruda-Olson AM, Roger VL, Jaffe AS, Hodge DO, Gibbons RJ, Miller TD. Troponin T levels and infarct size by SPECT myocardial perfusion imaging. JACC Cardiovasc Imaging 2011 May; 4(5):523-33.
- (25) Klug G, Mayr A, Mair J, Schocke M, Nocker M, Trieb T, et al. Role of biomarkers in assessment of early infarct size after successful p-PCI for STEMI. Clin Res Cardiol 2011 Jun;100(6):501-10.
- (26) Mayr A, Mair J, Klug G, Schocke M, Pedarnig K, Trieb T, et al. Cardiac troponin T and creatine kinase predict mid-term infarct size and left ventricular function after acute myocardial infarction: a cardiac MR study. J Magn Reson Imaging 2011 Apr;33(4):847-54.
- (27) Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. J Am Coll Cardiol 2004 Oct 19;44(8):1533-42.
- (28) Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. Lancet 2003 Feb 1; 361(9355):374-9.
- (29) Kim HW, Farzaneh-Far A, Kim RJ. Cardiovascular magnetic resonance in patients with myocardial infarction: current and emerging applications. J Am Coll Cardiol 2009 Dec 29;55(1):1-16.

