Usefulness of High Sensitivity Troponin T to Predict Long-Term Left Ventricular Dysfunction After ST-Elevation Myocardial Infarction

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Guidelines recommend the use of transthoracic echocardiography (TTE) and clinical scores to risk stratify patients after ST-elevation myocardial infarction (STEMI). High sensitivity troponin T (hs-cTnT) is predictive of outcome after STEMI but the predictive value of hs-cTnT relative to other risk assessment tools has not been established. We aimed to compare the predictive value of hs-cTnT to other risk assessment tools in patients with STEMI. A subset of 578 patients with STEMI were included in this post-hoc study from the Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction trial. Patients underwent cardiac magnetic resonance imaging (CMR) during index hospitalization as well as TTE at 1 year after their STEMI. The predictive value of hs-cTnT was compared with CKMB, infarct size (IS)/left ventricular ejection fraction (LVEF) assessed with CMR, LVEF assessed at discharge with TTE and the Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) risk-scores. The primary outcome was LV systolic dysfunction defined as LVEF ≤40% after 1 year on TTE. The area under the receiver operating characteristic curve analyses showed no significant difference between hs-cTnT and early CMR-assessed IS or LVEF in predicting subsequent LVEF ≤40%. Area under the curve for hs-cTnT was 0.82, 0.85 for IS (p = 0.22), and 0.87 for LVEF (p = 0.23). For predischarge TTE-assessed LVEF, the value was 0.85 (p = 0.45), 0.63 for creatine kinase-MB (p <0.001), 0.61 for the GRACE score (p <0.001), and 0.70 for the TIMI score (p = 0.02). A peak hs-cTnT value <3,500 ng/L ruled out LVEF ≤40% with probability of 98%. In conclusion, in patients presenting with STEMI undergoing PCI, hs-cTnT level strongly predicted long-term LV dysfunction and could be used as a clinical risk stratification tool to identify patients at high risk of progressing to LV dysfunction due to its general availability and high-predictive accuracy. **© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)** **(Am J Cardiol 2020;134:8−13)**

Background

Risk assessment is a principal element of ST-elevation myocardial infarction (STEMI) after-care. Current guidelines recommend administration of the Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) risk scores along with the evaluation of left ventricular ejection fraction (LVEF) in all patients with ST-elevation myocardial infarction (STEMI) at admission and before discharge. Patients with a predischarge LVEF ≤40% should be re-evaluated after 6 to 12 weeks of optimal medical treatment to assess the need for an implantable cardioverter defibrillator.[1] Early LVEF and infarct size (IS) assessed with late gadolinium-enhanced cardiac magnetic resonance imaging (CMR) are strong predictors of long-term LV dysfunction and outcome after STEMI, but CMR is costly and of limited availability and applicability due to logistics and

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contraindications,[2–5] making it unfeasible for routine use in all patients with STEMI.

The quantity of cardiac troponin released into the blood after STEMI reflects the degree of myocardial injury, suggesting its potential use as a surrogate marker of IS through high-sensitivity cardiac troponin T (hs-cTnT) assay.[6–8] The availability and predictive accuracy of hs-cTnT testing makes it a valuable and cost-effective risk stratification tool,[6–8] although few studies have compared its predictive value with CMR-assessed IS and LVEF or with guideline-recommended risk scores. We previously reported that hs-cTnT provides information comparable to early CMR for prediction of long-term outcome in patients with first-time STEMI revascularized with percutaneous coronary intervention (PCI). Patients with peak hs-cTnT <3500 ng/L showed a favorable outcome, whereas all patients with a peak hs-cTnT ≥13,000 ng/L demonstrated LV dysfunction 6 months post-STEMI.[8] However, that study was limited by a small sample size and included only patients with no previous diagnosis of cardiac disease.

The objective of the present study was to compare the predictive value of hs-cTnT level to that of early CMR-assessed IS (% of LV mass); LVEF (%) in the acute phase of STEMI; predischarge transthoracic echocardiography (TTE); and GRACE and TIMI risk scores for LV dysfunction assessed by TTE 1 year post-STEMI in a larger, unselected cohort. In addition, we aimed to evaluate diagnostic accuracy of the proposed cut-off for rule-in (≥13,000 ng/L) and rule-out (<3,500 ng/L) of long-term systolic dysfunction.[8] The design was a post-hoc study using data obtained from the Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: Ischemic postconditioning or deferred stent implantation versus conventional primary angioplasty and complete revascularization versus treatment of culprit lesion only trial program (DANAMI-3).[9–11]

Methods

A subset of patients from the DANAMI-3 trial program (www.clinicaltrials.gov; identifier: NCT01435408) was included in the analysis. The study design of the DANAMI-3 trial has been published previously.[12] Briefly, the DANAMI-3 encompassed 3 randomized investigator-initiated trials in a Danish multicenter setup designed to evaluate ischemic postconditioning (DANAMI-3-iPOST), deferred stenting (DANAMI-3-DEFER), and culprit lesion only versus fractional flow-reserve guided complete revascularization (DANAMI-3-PRIMULTI) in patients with STEMI. Patients were randomized in an open blinded-end point design study from all centers in Denmark that perform primary PCI. Inclusion and exclusion criteria for the DANAMI-3 trial program has been published elsewhere. Data for the present analysis was derived from a CMR substudy conducted at Rigshospitalet, Copenhagen University Hospital comprising a subset of patients that underwent early CMR during index hospitalization and was followed up with TTE after 1 year at the discretion of the treating physician. Patients without contraindications were offered a CMR scan, conducted within 48 hours of revascularization. CMR-specific exclusion criteria including claustrophobia and previous infarction in the infarct-related artery were applied (Figure 1). The CMR was performed using a 1.5 Tesla scanner (Avanto scanner; Siemens, Erlangen, Germany) with a 6-channel body array coil. The protocol has been published elsewhere.[13] Blood samples were collected at baseline using the introducer sheath for PCI and at 6 and 12 hours after admission. The maximum values of hs-cTnT and creatine kinase-MB were determined in heparinized plasma samples (Elecsys Troponin T high sensitivity assay, Roche Diagnostics; Elecsys Creatine Kinase-Myocardial Band assay, Roche Diagnostics). Normality of distribution was assessed with visual inspection of histograms. Normally distributed variables are expressed as mean with standard deviations, and non-normal distribution as medians with interquartile ranges. Categorical variables are displayed as counts and percentages. The area under the receiver operating characteristic (ROC) curve was used to evaluate predictive value (C-index). To simplify interpretation of negative associations in C-indices, they were converted to 1-AUC. Equality of ROC areas was tested with observations as dependent samples. Youden's index was determined for both outcome measures to identify the optimal dichotomous cut-off. All analyses were conducted on complete case data. A 2-sided p-value <0.05 was considered significant. Statistical analyses were performed using STATA v.14.1 for Macintosh (StataCorp, Texas).

Results

A total of 2,239 patients were included in the DANAMI-3 trials, with 764 patients undergoing CMR at index hospitalization (Figure 1). Early CMR data of IS and LVEF was available for 731 and 757 patients, respectively. Data of TTE-assessed LVEF at discharge was available for 573 patients. Transthoracic echocardiography data at 1 year was available for 578 (79.3%) patients and was included in the final analysis. The included patient population was younger (59.1±10.5 vs 63.2 ± 11.8, p <0.001) with lower frequency of known hypertension (188 [32.6%] vs 678 [41.1%], p <0.001) and history of MI (16 [2.8%] vs 116 [7.0%], p <0.001) than were patients excluded from the study (Table 1). No difference in maximum hs-cTnT was observed between included and excluded patients. The median hs-cTnT value was 2945 ng/L (1190 to 5910) and median time from symptom onset to PCI was 167 minutes (122 to 265). A total of 364 (63.0%) showed TIMI flow 0−1, and in 253 (43.8%) left anterior descending artery (LAD) was identified as culprit vessel. Forty-five (7.8%) of the patients included in ROC analyses exhibited LVEF ≤40% on TTE examination at 1 year. Area under the curve (AUC) was 0.82 for hs-cTnT, with no difference from IS 0.85 (p = 0.22), and 0.87 for LVEF (p = 0.23; Figure 2). For predischarge TTE-assessed LVEF the value was 0.85 (p = 0.45), 0.63 for creatine kinase-MB (p <0.001), 0.61 for the GRACE score (p <0.001), and 0.70 for the TIMI score (p = 0.02) (Figure 2). The sensitivity analysis on patients that did not undergo CMR revealed similar AUC for hs-cTnT 0.83; GRACE 0.66; TIMI risk score 0.68 and discharge LVEF 0.86 with no statistical difference observed between hs-cTnT and discharge LVEF. The sensitivity analysis excluding patients with history of MI showed no significant differences

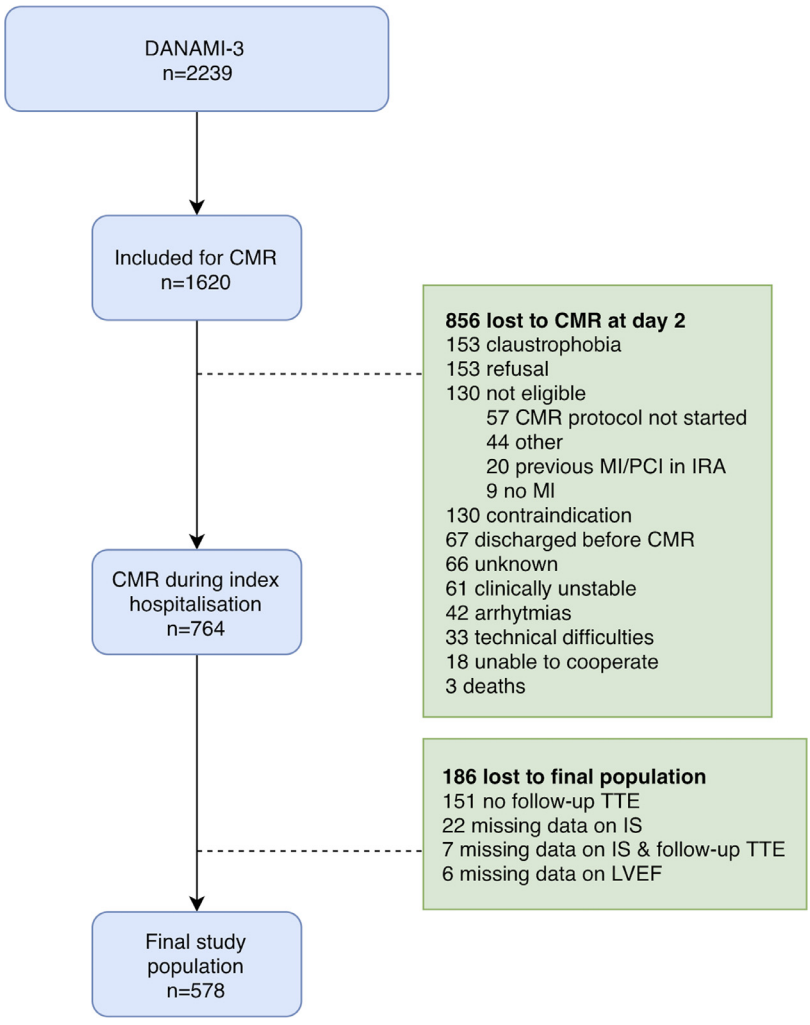

Figure 1. Flowchart. Flowchart showing the number of patients lost to CMR and follow-up TTE. A total of 578 patients were included in the final analysis.

compared with the primary analysis. AUC for hs-cTnT 0.84; GRACE 0.62; TIMI risk score 0.70; discharge LVEF 0.85; CMR assessed IS 0.86 and LVEF = 0.87 with no statistical difference observed between hs-cTnT and discharge LVEF with no statistical difference between hs-cTnT and CMR assessed IS/LVEF. Stratification into culprit vessel showed similar discriminative value of hs-cTnT, LAD = 0.84; left circumflex artery= 0.87, and right coronary artery= 0.82. Youden's index identified a maximum hs-cTnT of 6550 ng/L, which correctly classified 81.8% as with/without dysfunction and showed a negative predictive value (NPV) of 96.7%, positive predictive value (PPV) of 24.2%, sensitivity of 66.7%, and specificity of 82.4%, Table 2. The cut-off hs-cTnT of ≤3500 ng/L to rule in LVEF ≤40% showed specificity of 59.9% and NPV of 98.2%. The cut-off to rule in LV dysfunction, hs-cTnT of ≥13,000 ng/L, showed sensitivity of 37.8% with a PPV of 50.0% and positive likelihood ratio of 11.8 (Table 2).

Discussion

We compared the correlation of hs-cTnT with LV dysfunction 1 year after STEMI to that of early CMR-assessed IS/LVEF and discharge LVEF assessed by TTE, as well as to guideline-recommended clinical risk-scores. Hs-cTnT was comparable to CMR-assessed IS and LVEF and TTE-assessed LVEF during index hospitalization in predicting long-term LVEF dysfunction in patients with STEMI revascularized with primary PCI. To our knowledge, this is the largest study comparing the predictive value of the gold standard biomarker in clinical practice to that of gold standard early morphological and functional CMR assessments and to guideline-recommended clinical risk scores.

Previous studies have shown that hs-cTnT is a strong predictor of LV dysfunction, but the definition of LV dysfunction has been inconsistent.[6–8] In a post-hoc analysis from the CHILL-MI trial, we showed that hs-cTnT compared well with early CMR-assessed IS and LVEF for prediction of LVEF ≤40% 6 months post-STEMI.[8] This study was limited by its small sample size (n = 86) and comprised patients with first-time STEMI with no known history of cardiac disease. In the present study, we validated these findings in an independent patient cohort from a large, randomized clinical trial with 578 patients undergoing CMR in the acute phase of STEMI. We obtained ROC areas for hs-cTnT similar to those in previous studies addressing LV

Table 1
Clinical, angiographic, and cardiac magnetic resonance imaging data

	All Patients n = 2,239	Excluded n = 1,661	CMR n = 578	p-Value
Age (years)	62.1 ± 11.8	63.2 ± 12.1	59.1 ± 10.5	<0.001
Men	1720 (76.8%)	1259 (75.8)	461 (79.8%)	0.052
Women	519 (23.2%)	402 (24.2)	117 (20.2%)	0.52
BMI (Kg/m^2)	27.1 ± 4.4	27.1 ± 4.5	27.0 ± 4.0	
Smoker	1129 (50.4%)	833 (50.6%)	296 (51.2%)	0.07
Diabetes mellitus	205 (9.2%)	161 (9.7%)	44 (7.6%)	0.14
Hypertension	866 (38.7%)	678 (41.1%)	188 (32.6%)	<0.001
Myocardial infarction	132 (5.9%)	116 (7.0%)	16 (2.8%)	<0.001
Time from symptom onset to PCI (minutes)	173 (126-273)	177 (130-265)	167 (122-265)	0.17
TIMI flow before PCI				
0-1	1483 (66.2%)	1119 (67.4%)	364 (63.0%)	0.054
0-2	756 (33.8%)	542 (32.6%)	214 (37.0%)	
TIMI flow grade 3 after PCI	2126 (95.0%)	1571 (94.6%)	555 (96.0%)	0.20
PCI main vessel				
Left anterior descending artery	1012 (45.2%)	759 (45.7%)	253 (43.8%)	0.42
Left circumflex artery	349 (15.6%)	256 (15.4%)	93 (11.1%)	0.70
Right coronary artery	983 (43.9%)	720 (43.4%)	263 (45.5%)	0.37
Biomarkers				
Maximum hs-cTnT (ng/L)	3080 (1130-6320)	3153 (1121-6600)	2945 (1190-5910)	0.41
Cardiac magnetic resonance imaging				
Infarct size (% of LVM)			15.9 (8.1-24.8)	
Infarct size (g)			21 (9-34)	
Ejection fraction (%)			50.8 ± 9.7	
Myocardium at risk (%)			32.7 ± 11.5	

dysfunction as end point and to CMR-assessed IS and LVEF, as observed in our previous study.[6–8,14] The prespecified cut-offs for rule-in/rule-out resulted in highly accurate predictions

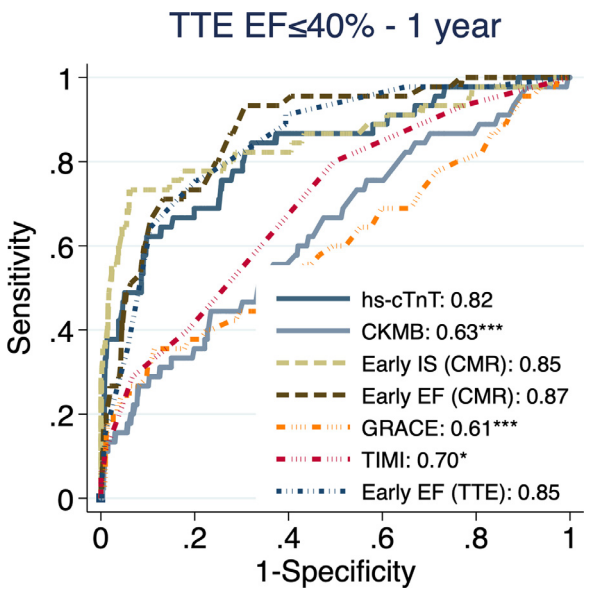

Figure 2. Receiver operating characteristic curves. ROC for hs-cTnT, Creatine Kinase isoenzyme Myocardial Band (CKMB), early CMR-assessed IS/LVEF, guideline-recommended risk scores, and TTE-assessed LVEF for prediction of left ventricular dysfunction defined as LVEF <40% at 1 year assessed by TTE. Test of equality of ROC areas plotted all variables against hs-cTnT as reference. Hs-cTnT was superior to risk scores and CKMB, GRACE, and TIMI-risk score. No significant differences in ROC areas were observed between early IS/LVEF and hs-cTnT in predicting LVEF ≤40%. ***=p <0.001; *=p <0.05.

of LV dysfunction.[8] Differences in the 2 studies need to be mentioned: Whereas the rule in cut-off displayed similar sensitivities, in the present study it showed lower specificity (100% vs 96.8%) and a PPV of 50.0% compared with 100% in the CHILL-MI substudy. This could be explained by the different imaging modalities (CMR vs TTE), greater demographic heterogeneity in the present study population, and/or by difference in follow-up time (3 months vs 1 year), as the risk of developing a new MI or deteriorating LVEF increases with time. The ROC analyses in the present study showed no difference between CMR-assessed IS/LVEF and hs-cTnT in predicting long-term outcome after STEMI revascularized by PCI. Although the present study is one of the largest of its kind, it is possible that a larger sample might yield different results. Notwithstanding potential for a type II error, CMR's restricted availability and high cost limit its applicability in clinical practice and renders hs-cTnT superior as a routine diagnostic tool. The hs-cTnT also assay outperformed clinical risk scores in predicting LV dysfunction. The comparison may be misleading, since risk scores were not developed to predict LVEF ≤40%, and the predictive value of hs-cTnT with respect to hard clinical end points such as mortality and heart failure was not assessed, as only 11 (1.5%) patients of the final population died from any cause or were hospitalized due to heart failure within 1 year, indicating a low-risk and relatively healthy cohort. Although the post-STEMI CMR was elective patients included in the present study differed in only 3 baseline variables and the sensitivity analysis on patients who did not undergo CMR showed similar AUC for hs-cTnT increasing the generalizability of results.

Our results can aid in identifying high-risk patients that may benefit from more intense secondary prevention treatment including implantable cardioverter defibrillators,

Table 2
Receiver operating characteristic cut-offs to rule in and rule out LVEF ≤40%

	Sensitivity	Specificity	NPV	PPV	Likelihood ratio (+)	Likelihood ratio (-)	Correctly classified
TTE assessed LVEF ≤40%							
Youden's index - hs-cTnT ≥6,550 ng/L	66.7%	82.4%	96.7%	24.2%	3.8	0.4	81.4%
Cut-off to rule out: hs-cTnT <3,500 ng/L	86.7%	59.9%	98.2%	15.4%	2.2	0.22	62.0%
Intermediate cut-off: hs-cTnT ≥9,999 ng/L	46.7%	94.9%	95.5%	43.8%	9.2	0.56	91.2%
Cut-off to rule in: hs-cTnT ≥13,000 ng/L	37.8%	96.8%	94.9%	50.0%	11.8	0.64	92.2%

LVEF = ejection fraction; hs-cTnT = high-sensitivity cardiac troponin T; NPV = negative predictive value; PPV = positive predictive value.

more aggressive anti-congestive heart failure therapy, or more frequent visits to an outpatient clinic at an earlier stage. Current guidelines emphasize the use of TTE during hospitalization to stratify patient risk, but currently most patients are followed up after discharge in a similar manner regardless of early risk. A low risk patient will receive the same medical attention as a patient with maximum hs-cTnT above 13,000 ng/L, *ergo*, with a 50% probability of long-term LVEF ≤40%. With 56.2% of patients in our study showing a maximum hs-cTnT <3,500 ng/L and considering an NPV ≥98.2% for the rule-out cut-off (3,500 ng/L), this could have considerable impact on daily clinical practice. As an alternative to follow-up in a specialized outpatient department, a secondary prevention program with a trained nurse to educate patients with respect to lifestyle changes and rehabilitation measures and to monitor therapeutics may be adequate for the majority of patients. In addition, patients in this hs-cTnT stratum experiencing side effects to secondary prophylactic medication might be placed on a reduced dose with less concern, due to more favorable prognosis.

Elevated cardiac troponins can be measured up to 2 weeks after MI. Previous studies have suggested that a troponin value obtained 48 to 96 hours after admission, during the plateau phase, is the most predictive of outcome.[14–16] The time-point at which hs-cTnT level demonstrates the highest predictive accuracy is yet to be established. However, this study adds to the evidence that a maximum value of hs-cTnT obtained within the first day of admission is sufficient for accurate prediction of outcome and could be used to tailor follow-up in patients after revascularized STEMI. The recording of maximum value within first day of admission offers additional advantages with length of hospital stay post-STEMI becoming shorter, generally three days.[17]

There were no differences in the DANAMI-3 CMR substudy with regard to IS or microvascular obstruction in patients treated with deferred stenting compared to those receiving standard care. Therefore, it is unlikely that the treatment choice would have impacted our results. Laursen et al. reported a significantly worse risk profile among CMR non-participants compared with CMR participants at admission.[18] Although this did not result in a higher incidence of adverse clinical outcomes, interpretation of their results is limited by relatively wide confidence intervals, which could reflect lack of statistical power.[18] The strength of our study lies in the unique design allowing comparison of the most commonly used biomarker in clinical practice to the early morphological and functional assessments by CMR gold standard imaging for estimating IS and LVEF, utilizing a cohort from a well-known clinical trial.

Conclusions

In patients with STEMI undergoing PCI, hs-cTnT level predicted long-term LV dysfunction. Assessment of hs-cTnT could be used as a clinical risk stratification tool to identify patients at high risk of progressing to LV dysfunction, due to its general availability and high predictive accuracy.

Disclosures

None of the authors have anything to disclose.

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