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Prognostic significance of serial high-sensitivity troponin I measurements following acute cardiac decompensation-correlation with longer-term clinical outcomes and reverse remodelling☆

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ABSTRACT

Background: This study investigated the correlation of levels of and changes in serial high-sensitivity cardiac troponin I (hsTnI) with subsequent clinical event rates and changes in cardiac morphology and function in patients hospitalized for acutely decompensated heart failure (ADHF).

Methods and results: HsTnI levels were determined in 875 ADHF patients before discharge from hospital (baseline cohort) and clinical outcomes assessed after 180 days. HsTnI was re-measured at 180 days in 456/875 patients (follow-up cohort). Follow-up hsTnI values were grouped according to baseline hsTnI tertiles; echocardiographic changes from 0–180 days and event rates from 180–540 days were assessed in these subgroups. At baseline and 180-day follow-up, hsTnI levels were elevated (>0.06 ng/mL) in 322/875 (37%) and 68/456 (15%) patients, respectively. At 180 days, 85/875 patients (9.7%) had died (cardiovascular causes: 56/875 [6.4%]). Hazard ratios (HR) and 95% confidence intervals (CI) for all-cause and cardiovascular mortality (per two-fold hsTnI increase) were 1.2 (1.0–1.3; p = 0.004) and 1.2 (1.1–1.4; p = 0.001), respectively. In the follow-up cohort, 35/456 patients (7.7%) died between days 180 and 540 (cardiovascular death: 20/456, 4.4%). HsTnI was a significant predictor of cardiovascular re-hospitalization within 180–540 days (HR 1.2, 95% CI 1.0–1.4; p = 0.028). Patients with hsTnI in the lowest tertile at follow-up had more frequent and more pronounced reverse cardiac remodelling on echocardiography.

Conclusions: Elevated baseline hsTnI was common and associated with adverse clinical outcomes. Changes in hsTnI from baseline to 180-day follow-up predicted longer-term risk. Low or decreasing hsTnI was associated with better reverse cardiac remodelling and more favourable long-term outcomes.

Clinical Trial Registration URL: http://www.controlled-trials.com. Unique identifier: ISRCTN23325295.

1. Introduction

Biochemical markers have revolutionized decision making in cardiology: natriuretic peptides for diagnosis of heart failure (HF) and risk stratification [1], and cardiac troponins (cTn) for diagnosis of acute coronary syndromes [2,3]. High-sensitivity assays allow determination of very low cTn levels, which are now also detected in stable coronary disease [3,4], non-coronary cardiac disorders [5] and various non-cardiac conditions [6].

Elevated levels of cTn are common in chronic stable HF [7–11]. Persistently high or increasing levels predict higher mortality risk and re-hospitalization rates [8,9]. On emergency admission for acutely decompensated HF (ADHF), high cTn predicts increased in-hospital mortality and worse long-term outcomes, independent of age, HF aetiology, cardiac function, and levels of high-sensitivity C-reactive protein (hsCRP) or natriuretic peptides [12–18].

Elevated cTn is an indicator of myocardial injury, but does not provide information on the specific mechanisms of injury [19,20]. In addition to myocardial ischaemia secondary to type I myocardial infarction (MI) or supply-demand inequity (type II MI) [2], non-cardiac factors such as oxidative stress, inflammatory cytokines, neurohormonal activation [21], hyperglycaemia [22] or coronary microvascular dysfunction [23] may alter cell membrane integrity in otherwise viable myocytes,

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inducing cTn degradation or cell death [6]. Recent observations that ADHF patients not only had higher cTn than stable HF patients or healthy controls, but also elevated markers of collagen biosynthesis and extracellular matrix remodelling, suggest a patho-biological link between myocardial injury and ventricular remodelling [24].

There is a lack of information on serial cTn levels and changes during the transition from ADHF to more stable disease that takes into account concomitant changes in cardiac morphology and function. The aims of this study were to 1) compare the distribution and prognostic significance of high-sensitivity troponin I (hsTnI) both at discharge from hospital after ADHF and at 180-day follow-up, and identify possible mediators of hsTnI elevation, 2) clarify whether changes in hsTnI over time could improve outcome prediction, and 3) study concomitant changes in cardiac morphology and function. We hypothesized that elevated or rising hsTnI levels would predict adverse outcomes, but that low or decreasing levels would not only indicate improved prognosis and HF symptoms during the following year, but also better cardiac function and more pronounced reverse cardiac remodelling.

2. Methods

2.1. Study flow and sample characteristics

We investigated participants in the Interdisciplinary Network Heart Failure (INH) program. The design and results of the INH Study (ISRCTN 23325295), which compared the effects of nurse-coordinated disease management (*HeartNetCare-HF™*) with usual care, have been previously reported [25]. Nine sites enrolled patients under a common protocol between 1 March 2004, and 9 December 2008. Adult patients hospitalized for ADHF (dyspnoea at rest or minimal exercise plus ≥1 of the following: raised jugular venous pressure, peripheral oedema, or pulmonary congestion) were eligible if, after best possible recompensation, left ventricular ejection fraction (LVEF) remained ≤40% at discharge. Exclusion criteria were new-onset structural heart disease (e.g. myocardial infarction), logistic or health reasons precluding participation in a telephone-based intervention, and lack of written consent. All responsible ethics committees approved the INH protocol and all patients provided written informed consent. The trial complied with the Declaration of Helsinki and Good Clinical Practice.

2.2. Patient evaluation

Assessments at baseline (performed before discharge after best possible cardiac recompensation) and follow-up (outpatient visit after 180 days) included standardized physical examination, routine laboratory testing, electrocardiography and echocardiography. Congestion was diagnosed if ≥1 of the following was present: raised jugular venous pressure, peripheral oedema, or pulmonary congestion (clinical and/or chest X-ray). Non-attending patients underwent structured telephone follow-up.

Although serial echocardiography was performed as part of routine patient care, sonographers used standardized pre-specified examination protocols based on American Society of Echocardiography recommendations [26]. Left ventricular end-diastolic diameter (LVEDD) was measured at the mitral chordae level in the left parasternal long axis view, and LVEF from apical two- and four-chamber views using Simpson's biplane or single plane method. The systolic tricuspid valve gradient (STVG) was obtained from the continuous wave Doppler of the tricuspid regurgitant flow profile. At follow-up, care was taken to precisely reproduce the cross-sections on which the baseline measurements were based and the same method for determination of LVEF was always used. Only measurements from high-quality echocardiograms were used for the quantitative analysis of LV remodelling parameters, which was performed by personnel blinded to patients' hsTnI levels.

2.3. Exclusion of acute coronary syndrome

On hospital admission, diagnostic procedures and treatments remained at the discretion of the recruiting hospitals. Patients were eligible for the INH study if they had no evidence of MI based on the absence of typical clinical features, biomarker patterns, and electrocardiographic findings [2]. These included a rise and/or fall in cardiac biomarker levels with at least one value above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischaemia: new or presumed new significant ST-segment-T-wave changes or a new left bundle branch block, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities, and identification of an intracoronary thrombus by angiography [2].

2.4. Criteria for ischaemic heart failure aetiology

Ischaemic HF was assumed if patients had a history and/or angiographic evidence of ≥1 prior MI, pathological Q-waves in the electrocardiogram, and/or imaging evidence of a region of hypokinetic and thinned myocardium in the absence of a non-ischaemic cause for scar formation [2].

2.5. Biomarker assessment

Biomaterials obtained pre-discharge at baseline and during follow-up examinations were immediately processed, frozen, and transferred to the INH core laboratory for long-term storage at −80 °C and later analysis. HsTnI concentrations were measured with an ADVIA Centaur TnI-Ultra™ (Siemens Healthcare, Eschborn, Germany). The minimum detection concentration of this assay is 0.006 ng/mL, and the potential range of results for the 99th percentile is 0.02 to 0.06 ng/mL, irrespective of sex.

N-terminal pro-brain natriuretic peptide (NT-proBNP) and hsCRP concentrations were determined with a solid-phase, two-site chemiluminescent immunometric assay on a Siemens IMMULITE 2000 system. All biochemical analyses were performed by personnel blinded to clinical outcomes and treatment allocation (see Supplementary Appendix for further details) and after completion of the event adjudication.

2.6. Endpoints

Outcome measures of this post-hoc analysis were time to all-cause and cardiovascular death or re-hospitalization. Additional endpoints included LVEDD, LVEF and STVG as correlates of LV reverse remodelling. Eighteen months after enrolment, vital status was ascertained either during a patient visit to the INH outpatient clinics or by structured telephone follow-up (100% complete). Records of general practitioners' or cardiologists' hospital discharge letters, reports from patients and relatives, and death certificates were used as source documents to assess hospital re-admissions and determine the date and cause of death in deceased patients. Events were considered 'cardiovascular', if they were classified as being due to myocardial infarction, worsening chronic pump failure, arrhythmias including sudden death, or incident stroke or transient cerebral ischaemic events.

2.7. Data analysis and statistics

Variables are given as mean (standard deviation), median (quartiles), and n (percent), as appropriate. Group comparisons were performed using χ^2 testing, ANOVA and Kruskal-Wallis tests. For comparisons of baseline and 180-day characteristics of the follow-up cohort, the McNemar test, t-test or Wilcoxon test for paired samples were used, as appropriate.

Separate analyses were performed to study ADHF in the baseline cohort and chronic HF in the follow-up cohort. In the baseline cohort (n = 875), we studied associations between hsTnI and the risk of

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