Prognostic Effect of High-Sensitive Troponin T Assessment in Elderly Patients With Chronic Heart Failure

Results From the CORONA Trial

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Background—The incremental prognostic value of high-sensitive troponin T (hs-cTnT) in heart failure (HF) beyond that of high-sensitivity C-reactive protein and amino-terminal probrain natriuretic peptide is debated. We examined the prognostic value of hs-cTnT in a subgroup of patients from the Controlled Rosuvastatin Multinational Trial in HF (CORONA) study.

Methods and Results—Hs-cTnT as a risk factor for the primary end point (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; n=356), as well as all-cause mortality (n=366), cardiovascular mortality (n=299), and the composite of cardiovascular mortality and hospitalization from worsening of HF (n=465), was investigated in 1245 patients (≥60 years; New York Heart Association [NYHA] class II–IV, ischemic systolic HF) randomly assigned to 10 mg rosuvastatin or placebo. In multivariable analyses, adjusting for left ventricular ejection fraction, NYHA class, age, body mass index, diabetes mellitus, sex, intermittent claudication, heart rate, estimated glomerular filtration rate, apolipoprotein B/apolipoprotein A-1 ratio, amino-terminal probrain natriuretic peptide, high-sensitivity C-reactive protein, and hs-cTnT (both dichotomized according to the 99th percentile and as a continuous variable) was associated with all end points (primary end point: hazard ratio, 1.87 and 1.51, respectively, per SD change; $P<0.001$; all other end points: hazard ratio, 1.39–1.70). However, improved discrimination as assessed by C-statistics was only seen for the primary end point and all-cause mortality.

Conclusions—Elevated hs-cTnT levels provide strong and independent prognostic information in older patients with chronic ischemic HF.

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Key Words: heart failure ■ prognosis ■ risk assessment ■ troponin T

Sensitive assays for measurement of cardiac troponin T (cTnT) and troponin I (cTnI) have recently been introduced in clinical practice and are essential for the diagnosis of acute myocardial infarction (MI).[1] These assays are characterized by improved analytic and diagnostic performance.[2–9] The prognostic use of sensitive troponin levels is not restricted to patients with MI but do also predict adverse outcomes in stable coronary artery disease.[10]

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Recently, sensitive troponin levels have also been found to be associated with prognosis in patients with chronic heart failure (HF),[11–13] and changes in cTnT concentrations over time, as measured with a high-sensitive assay (hs-cTnT), were shown to predict cardiovascular (CV) events in these patients.[14] However, changes in hs-cTnT added limited prognostic discrimination. Because the incidence and prevalence of HF are increasing as a result of changing demographics and an increasing proportion of the elderly, we think that further exploration of the prognostic role of elevated hs-cTnT in older patients with chronic HF is of importance. We therefore evaluated the prognostic relevance of elevated hs-cTnT levels on outcomes in a substudy involving ≈30% of the patients enrolled in the Controlled Rosuvastatin Multinational Trial in

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HF (CORONA), performed in older patients with systolic HF of ischemic origin. In CORONA, rosuvastatin did not reduce the primary composite outcome (death from CV causes, nonfatal MI, and nonfatal stroke) or all-cause mortality. The predictive value of elevated baseline hs-cTnT and the prognostic value of changes in hs-cTnT levels from baseline to 3-month follow-up were evaluated, as well as possible interactions with statin therapy. We hypothesized that hs-cTnT would provide additional prognostic and discriminating information beyond that of established HF risk factors in this patient cohort.

Methods

Patients

The design and principal findings of CORONA have been reported in detail.[15] Briefly, patients aged ≥60 years with chronic HF attributed to ischemic heart disease, defined as (1) medical history or ECG signs of old MI or (2) other data indication ischemic cause of HF (ie, wall motion disturbances on echocardiography, left bundle branch block, or history of other occlusive atherosclerotic disease [ie, earlier stroke, intermittent claudication, percutaneous coronary intervention]), who were in New York Heart Association (NYHA) class II–IV, with a left ventricular ejection fraction ≤40% (≤35% if NYHA II), were eligible, provided the investigator thought they did not need treatment with a cholesterol-lowering drug. The main criteria for exclusion were a recent CV event, current or planned procedures or operations, acute or chronic liver disease, serum creatinine ≥2.5 mg/dL, contraindications to statin therapy, or unexplained increase in creatine kinase. All patients provided written informed consent. Patients were randomly assigned to rosuvastatin 10 mg/d or matching placebo, once daily.

Study Procedures

The trial complied with the Declaration of Helsinki and was approved by the Ethics Committees of the participating hospitals. All patients provided written informed consent. Patients were randomly assigned to rosuvastatin 10 mg/d or matching placebo, once daily. The present study was a predefined substudy of the main CORONA trial, which included 1480 consecutive patients (hs-cTnT was measured in 1245 patients with samples available at both baseline and 3 months). There were only minor differences in the baseline characteristics between this substudy and the main CORONA study (Table I in the Data Supplement).

Study Outcomes and Definitions

The primary predefined outcome was the composite of death from CV causes, nonfatal MI, and nonfatal stroke, analyzed as time to the first event. Of secondary outcomes, the following were used in this substudy: (1) all-cause mortality, (2) CV mortality, and (3) composite of CV mortality and hospitalizations from worsening of HF (WHF). The definition and adjudication of all outcomes, as well as data on high-sensitivity C-reactive protein (hs-CRP) and amino-terminal probrain natriuretic peptide (NT-proBNP), have been described in detail.[15–18]

Blood Sampling and Biochemical Analyses

TnT was measured in blood samples taken after an overnight fast with a high-sensitivity assay (Roche Diagnostics, Basel, Switzerland) on a Roche Modular E170 platform using the Elecsys reagents (Roche Diagnostics). This hs-cTnT assay has a detection limit of 3 ng/L, a 99th percentile cutoff of 14 ng/L, and a coefficient of variation of <10% at 13 ng/L. Hs-cTnT levels below detection limit were set to 3 ng/L in the statistical analyses. All other blood samples were nonfasting and analyzed on fresh samples at a central laboratory (Medical Research Laboratories, Zaventem, Belgium). NT-proBNP was analyzed using commercially available assay (Roche Diagnostics, Basel, Switzerland). An immunonephelometric high-sensitivity method was used to measure CRP (Dade Behring, Atterbury, UK; sensitivity, 0.04 mg/L).

Statistical Analysis

For all baseline variables, differences between patients with hs-cTnT levels > or ≤14 ng/L (99th percentile) were tested with the Student *t* test for normally distributed variables, Fisher exact test for categorical data, and Wilcoxon rank-sum test for non-normally distributed variables. The natural log was used for logarithmic transformations. All variables with a significant univariate association with hs-cTnT levels were included in a stepwise logistic regression to explore their combined explanatory power of hs-cTnT levels. All survival analyses were conducted using the Cox proportional hazard regression model where hs-cTnT was included as a dichotomized variable (±14 ng/L) in a multivariable analysis that included left ventricular ejection fraction, NYHA class, age, body mass index, diabetes mellitus, sex, intermittent claudication, heart rate, estimated glomerular filtration rate (eGFR), apolipoprotein B/apolipoprotein A-1 ratio, log-transformed (natural log) plasma concentrations of NT-proBNP, and hs-CRP. The Harrell C-statistic was calculated for all end points using the multivariable model with and without hs-cTnT, and the difference between the C-statistics was estimated. To correct for overoptimism associated with validating a model in the same material from which it is developed, we implemented a jack-knife cross-validation approach, where predictions for each observation were obtained from models developed on the remaining observations. These cross-validated probabilities were used to calculate jack-knife C-statistics. Recently, calculation of net reclassification improvement (NRI) has been suggested for the evaluation of the prognostic usefulness of a biomarker.[19] In particular, when no established risk categories exist, the use of a category-free NRI has been advocated.[20] We therefore calculated the category-free NRI after adding hs-cTnT to the multivariable model. Confidence intervals and *P* values for NRI were determined by bootstrapping with 2000 repetitions. For the analysis of changes in hs-cTnT concentrations from baseline to 3-month follow-up, a 15% relative change was used as cutoff, which is consistent with other studies.[14] A 2-sided $P < 0.05$ was considered to be significant, except for interaction terms for which values of $P < 0.10$ were accepted. All statistical analyses were performed using STATA version 11 for Windows (StataCorp, College Station, TX). The authors had full access to and take responsibility for the integrity of the data. All authors have read and agreed to the article as written.

Results

Baseline Characteristics

In our study population, 1078 patients (86.6%) had hs-cTnT levels above the detection limit (3 ng/L) of the assay. The baseline characteristics of patients dichotomized according to the 99th percentile to hs-cTnT (14 ng/L) are shown in Table 1. Patients with hs-cTnT levels >14 ng/L were older, more frequently men, had lower left ventricular ejection fraction, lower body mass index, and higher heart rate than those with hs-cTnT levels ≤14 ng/L. In addition, patients with hs-cTnT levels >14 ng/L had a higher prevalence of atrial fibrillation, other atherosclerotic diseases, previous percutaneous coronary intervention, diabetes mellitus, hypertension, and chronic obstructive pulmonary disease. Patients with hs-cTnT above the 99th percentile were more frequently treated with aldosterone antagonists, diuretics, and digitalis glycosides. On the contrary, a history of angina pectoris and the use of β-blockers were less prevalent in patients with hs-cTnT >14 ng/L than in those with hs-cTnT levels ≤14 ng/L. Patients with hs-cTnT levels >14 ng/L had lower total and low-density lipoprotein cholesterol levels and a lower average eGFR but had higher levels of NT-proBNP and hs-CRP.

Table 1. Baseline Patient Characteristics

Variable	Total Cohort (N=1245)	hs-cTnT ≤14 (n=629)	hs-cTnT >14 (n=616)	*P* Value
Age, y	71.8 (6.9)	70.3 (6.5)	73.3 (6.9)	<0.001
Female sex	284 (22.8)	192 (30.5)	92 (14.9)	<0.001
Smoking	175 (12.1)	66 (10.5)	79 (12.8)	0.216
NYHA Class				0.715
II	400 (32.1)	196 (31.2)	204 (33.1)	
III	830 (66.7)	426 (67.7)	404 (65.6)	
IV	15 (1.2)	7 (1.1)	8 (1.3)	
Ejection fraction, %	32 (7)	33 (6)	30 (7)	<0.001
BMI, kg/m^2	27.3 (4.5)	27.6 (4.6)	26.9 (4.4)	0.005
SBP, mm Hg	129 (16.0)	131 (15.2)	128 (16.6)	0.003
DBP, mm Hg	77 (8.8)	78 (8.3)	75 (9.1)	<0.001
Heart rate, beats/min	71 (11)	69 (10)	72 (11)	<0.001
Medical history				
Myocardial infarction	780 (62.7)	387 (61.5)	393 (63.8)	0.413
History of angina pectoris	910 (73.1)	496 (78.9)	414 (67.2)	<0.001
Other atherosclerotic disease	243 (19.5)	103 (16.4)	140 (22.7)	0.005
PCI/CABG	262 (21.0)	113 (18.0)	149 (24.2)	0.008
Hypertension	868 (69.7)	459 (73.0)	409 (66.4)	0.014
Diabetes mellitus	325 (26.1)	141 (22.4)	184 (29.9)	0.003
Atrial fibrillation	263 (21.1)	104 (16.5)	159 (25.8)	<0.001
Stroke	145 (11.6)	65 (10.3)	80 (13.0)	0.158
Claudication	128 (10.3)	51 (8.1)	77 (12.5)	0.012
COPD	24 (1.9)	6 (1.0)	18 (2.9)	0.013
Laboratory measures				
High-sensitive troponin T, ng/L	13.9 (6.6–25.6)	6.6 (3.0–9.9)	25.7 (18.5–36.5)	<0.001
Total cholesterol, mmol/L	5.22 (1.09)	5.32 (1.05)	5.12 (1.11)	0.001
LDL, mmol/L	3.64 (0.97)	3.77 (0.97)	3.50 (0.94)	<0.001
HDL, mmol/L	1.23 (0.35)	1.24 (0.33)	1.22 (0.36)	0.352
Triglycerides, mmol/L	2.00 (1.34)	2.03 (1.20)	1.96 (1.46)	0.336
ApoB/ApoA-1 value	0.88 (0.25)	0.89 (0.24)	0.88 (0.26)	0.816
eGFR, mL/min per 1.73 m^2	58 (14)	62 (13)	53 (14)	<0.001
NT-proBNP, pmol/L	156 (61–339)	89 (36–191)	272 (137–535)	<0.001
hs-CRP, mg/L	3.6 (1.6–7.6)	3.0 (1.5–6.0)	4.5 (1.9–9.4)	<0.001
Medications				
Diuretics (loop/thiazide)				<0.001
None	161 (12.9)	106 (16.9)	55 (8.9)	
One	951 (76.4)	463 (73.6)	488 (79.2)	
Both	133 (10.7)	60 (9.5)	73 (11.9)	
Aldosterone antagonist	454 (36.5)	196 (31.2)	258 (41.9)	<0.001
ACE inhibitor	1001 (80.4)	512 (81.4)	489 (79.4)	0.392
Angiotensin II receptor blocker	128 (10.3)	59 (9.4)	69 (11.2)	0.306
β-Blocker	962 (77.3)	511 (81.2)	451 (73.2)	0.001
Digitalis glycoside	349 (28.0)	126 (20.0)	223 (36.2)	<0.001

Demographic, clinical, and biochemical baseline characteristics stratified by serum high-sensitive troponin T (hs-cTnT) levels below or above the 99th percentile (14 ng/L). High-sensitivity C-reactive protein (hs-CRP), amino-terminal probrain natriuretic peptide (NT-proBNP), and hs-cTnT levels are displayed as median value (25th–75th percentiles). Other variables are shown as numbers (% of total) or mean (SD), where appropriate. ACE indicates angiotensin-converting enzyme; ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and SBP, systolic blood pressure.

When all variables in Table 1 that were significantly associated with elevated hs-cTnT levels were included in a linear regression model, NT-proBNP levels, diabetes mellitus, history of coronary revascularization, age, use of digitoxin/digoxin, diuretics and β-blockers, hs-CRP levels, systolic and diastolic blood pressures, heart rate, female sex, and eGFR remained independently associated with hs-cTnT levels, explaining 47.1% (R^2) of the variation (Table 2). Of these variables, NT-proBNP was the strongest predictor of elevated hs-cTnT levels.

Effect of Rosuvastatin Treatment on hs-cTnT Levels and Clinical Outcomes

The difference in hs-cTnT concentrations at baseline and 3-month follow-up was not statistically different, neither among patients receiving placebo nor in the rosuvastatin group. Importantly, there was no statistically significant interaction between hs-cTnT levels and treatment with rosuvastatin.

Association Between High-Sensitivity cTnT Levels and Outcomes

During a median follow-up of 955 (25th–75th percentiles, 817–1003) days, 366 patients died. Restricted cubic spline analysis demonstrated linearity between risk for all-cause mortality and log-transformed hs-cTnT levels (Figure 1). Kaplan–Meier plots for the primary end point, all-cause mortality, CV mortality, and the composite of CV mortality and hospitalization from WHF demonstrated a significantly higher frequency of events for patients with hs-cTnT levels >14 ng/L compared with those with hs-cTnT levels ≤14 ng/L (Figure 2). Hs-cTnT levels, both dichotomized according to the 99th percentile (Table 3) and as a continuous variable (Table 4), were associated with the primary end point, as well as all-cause mortality, CV mortality, and the composite of CV mortality and hospitalization from WHF in a multivariable regression model adjusting for demographic and clinical variables, as well as NT-proBNP, hs-CRP, and eGFR. Similar associations were also found when the relationship between hs-cTnT and outcomes was assessed according to quartiles of hs-cTnT levels (Table II in the Data Supplement). Importantly, hs-cTnT levels dichotomized according to the 99th percentile (14 ng/L) remained a significant predictor of outcome in an extended multivariable regression model, also including systolic and diastolic blood pressures, history of angina pectoris, history of atherosclerotic disease, history of previous revascularization, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, total cholesterol, low-density lipoprotein levels, use of diuretics, use of aldosterone antagonists, use of β-blockers, and use of digitalis glycoside (Table 3). Comparisons among hs-cTnT, hs-CRP, and NT-proBNP, as predictors of outcome in this study population, have also been performed (Table III in the Data Supplement).

Value of hs-cTnT in Prognostic Discrimination

To assess the value of hs-cTnT in prognostic discrimination, NRI analyses were performed. Introduction of hs-cTnT levels to the multivariable model (including hs-CRP and NT-proBNP) significantly improved prognostic discrimination of the primary end point, as well as all-cause mortality, CV mortality, and the composite of CV mortality and hospitalization from WHF, as indicated by the NRI scores (Table 4). However, improved discrimination as assessed by C-statistics was only seen for the primary end point and all-cause mortality.

Changes in hs-cTnT Levels Over Time and Relationship With Outcomes

Overall, 300 patients (29%) had a >15% increase in hs-cTnT between baseline and 3 months. Of these, 183 (61%) patients had a baseline hs-cTnT ≤14 ng/L and 117 (39%) had a baseline hs-cTnT >14 ng/L. Such an increase was associated with

Table 2. Independent Correlates of Elevated hs-cTnT Levels

Variable	Coef	SE	*P* Value	95% CI
NT-proBNP (log transformed)	0.309	0.019	0.031	0.272 to 0.346
Diabetes mellitus	0.262	0.050	<0.001	0.165 to 0.360
History of PCI/CABG	0.112	0.057	0.048	0.00084 to 0.223
Age	0.107	0.036	0.003	0.0366 to 0.177
Digitoxin/digoxin	0.105	0.049	0.034	0.00796 to 0.202
Diuretics (loop/thiazide)	0.103	0.045	0.022	0.0150 to 0.191
hs-CRP (log-transformed)	0.0396	0.0183	0.031	0.00373 to 0.0755
Baseline SBP	0.00581	0.0091	0.002	0.00206 to 0.00956
Heart rate	0.00507	0.0022	0.022	0.00075 to 0.00939
β-Blocker	−0.155	0.054	0.004	−0.260 to −0.0501
Female sex	−0.553	0.0533	<0.001	−0.658 to −0.448
eGFR	−0.0142	0.00171	<0.001	−0.0176 to −0.0108
Baseline DBP	−0.00996	0.0035	0.004	−0.0168 to −0.00312

A linear regression model was performed to identify factors that are significantly associated with increasing log-transformed levels of serum high-sensitive troponin T (hs-cTnT). CABG indicates coronary artery bypass grafting; CI, confidence interval; Coef, regression coefficient with corresponding *P* value; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, amino-terminal probrain natriuretic peptide; PCI, percutaneous coronary intervention; and SBP, systolic blood pressure.

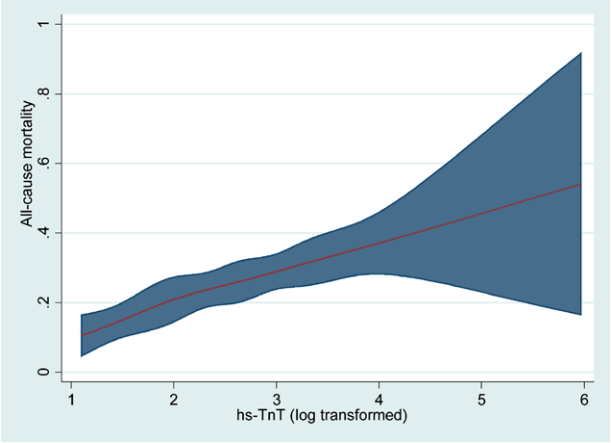

Figure 1. Restricted cubic spline analysis (fitted curve with 95% confidence interval) demonstrating linearity between risk for all-cause mortality and log-transformed high-sensitive troponin T (hs-cTnT) levels.

a higher risk of the composite end point of CV mortality or hospitalization because of WHF but not with any of the other prespecified end points, including the primary end point (Figure 3). The predictive value of absolute changes in hs-cTnT levels from baseline to 3 months was inferior to that of relative change (data not shown).

Discussion

Our data demonstrate that elevated hs-cTnT levels had a strong predictive and discriminating value for the primary end point, all-cause mortality, CV mortality, and the composite of CV mortality and hospitalizations because of WHF among older patients with chronic HF of ischemic origin. Although hs-cTnT levels in the CORONA population in relation to serum levels of gp130, a marker of activity in the interleukin-6 system, have already been reported,[21] the present post hoc analysis from CORONA includes more comprehensive data on the hs-cTnT levels in this patient population.

The predictive value of elevated hs-cTnT levels was explored both dichotomized according to the 99th percentile and as a continuous variable in the present study. The choice of 14 ng/L as a cutoff was motivated by its clinical importance because 14 ng/L is equal to the 99th percentile of hs-cTnT in a healthy population.[22] We wanted to test the prognostic importance of normal versus pathological levels of hs-cTnT in an HF population. Because the restricted cubic spline plot for hs-cTnT in relation to all-cause mortality showed a linear relationship, we also investigated the predictive value of hs-cTnT as a continuous variable.

The study includes several clinical end points. Importantly, the primary end point is equal to the predefined primary end point in the original CORONA study.[15] The rationale for combining CV

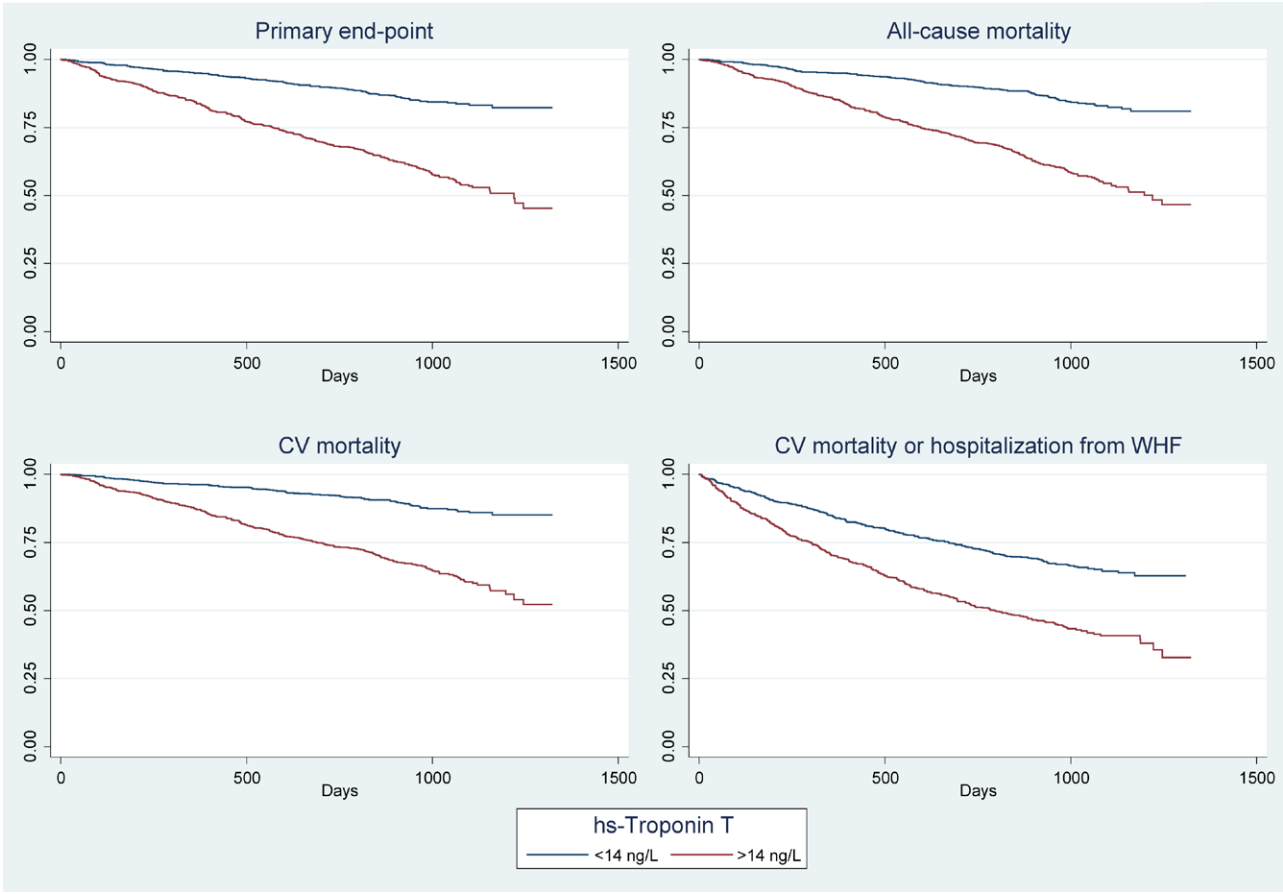

Figure 2. Kaplan–Meier curves demonstrating the cumulative incidence of the primary end point, all-cause mortality, cardiovascular (CV) mortality, and composite of CV mortality and hospitalization from worsening of heart failure (WHF) in all patients according to high-sensitive troponin T (hs-cTnT) levels > or ≤14 ng/L.

Table 3. Multivariable Analyses: Effects of hs-cTnT >14 ng/L on Outcomes

hs-cTnT >14 ng/L	n	Events	HR (95% CI)	*P* Value	Wald
Primary end point					
Unadjusted	1245	356	3.38 (2.67–4.27)	<0.001	103
Adjusted for risk factors	1026	272	1.87 (1.38–2.55)	<0.001	16.0
Adjusted for risk factors—extended	1026	272	1.89 (1.38–2.59)	<0.001	15.7
All-cause mortality					
Unadjusted	1245	366	3.27 (2.60–4.12)	<0.001	101
Adjusted for risk factors	1026	281	1.69 (1.25–2.29)	0.001	11.6
Adjusted for risk factors—extended	1026	281	1.63 (1.20–2.23)	0.002	9.52
CV mortality					
Unadjusted	1245	299	3.49 (2.70–4.53)	<0.001	89.3
Adjusted for risk factors	1026	227	1.70 (1.21–2.39)	0.002	9.49
Adjusted for risk factors—extended	1026	227	1.67 (1.18–2.36)	0.004	8.22
CV mortality or hospitalization from WHF					
Unadjusted	1245	465	2.92 (2.40–3.56)	<0.001	113
Adjusted for risk factors	1026	367	1.39 (1.07–1.79)	0.013	6.19
Adjusted for risk factors—extended	1026	367	1.39 (1.07–1.80)	0.014	5.99

High-sensitive troponin T (hs-cTnT) as a predictor of outcome, included as a dichotomized variable (14 ng/L). All hazard ratios (HRs) are given as HR (95% confidence interval [CI]) with corresponding *P* value. The multivariable regression model includes the following risk factors: left ventricular ejection fraction, New York Heart Association class, age, body mass index, diabetes mellitus, sex, intermittent claudication, heart rate, apolipoprotein B/apolipoprotein A-1 ratio, amino-terminal probrain natriuretic peptide, high-sensitivity C-reactive protein, and estimated glomerular filtration rate. The extended multivariable regression model also includes the following risk factors: systolic blood pressure, diastolic blood pressure, history of angina pectoris, history of atherosclerotic disease, history of previous revascularization, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, total cholesterol, low-density lipoprotein levels, use of diuretics, use of aldosterone antagonists, use of β-blockers, and use of digitalis glycoside. CV indicates cardiovascular; and WHF, worsening of heart failure.

mortality and hospitalizations is an attempt to combine mortality and morbidity to reflect the true burden of the HF syndrome. The effect of mortality is obvious, but the effect of hospitalizations might be underestimated in clinical trials.[23]

Although several previous studies have identified elevated cTnT or cTnI as markers of adverse events in chronic HF even after adjustment for BNP or NT-proBNP, those studies differed significantly from ours, having included smaller

Table 4. Multivariable Analyses: Effects of hs-cTnT Levels, as a Continuous Variable, on Outcomes

log hs-cTnT	n	Events	HR (95% CI)	*P* Value	Wald	ΔC Index	NRI (*P* Value)	Events	Nonevents
Primary end point									
Unadjusted	1245	356	2.06 (1.83–2.31)	<0.001	149				
Adjusted for risk factors	1026	272	1.51 (1.27–1.78)	<0.001	22.3	0.013 (0.048)	0.26 (0.0014)	0.26 (<0.001)	0.13 (0.003)
All-cause mortality									
Unadjusted	1245	366	2.05 (1.83–2.30)	<0.001	154				
Adjusted for risk factors	1026	281	1.45 (1.23–1.70)	<0.001	19.4	0.011 (0.031)	0.17 (0.044)	0.23 (<0.001)	0.12 (0.004)
CV mortality									
Unadjusted	1245	299	2.10 (1.85–2.38)	<0.001	134				
Adjusted for risk factors	1026	227	1.43 (1.19–1.71)	<0.001	14.8	0.010 (0.051)	0.22 (0.017)	0.25 (<0.001)	0.11 (0.003)
CV mortality or hospitalization from WHF									
Unadjusted	1245	465	2.41 (1.96–2.98)	<0.001	113				
Adjusted for risk factors	1026	367	1.39 (1.07–1.79)	0.013	6.19	0.0034 (0.23)	0.33 (<0.001)	0.21 (<0.001)	0.11 (0.014)

The table shows log-transformed levels of serum high-sensitive troponin T (hs-cTnT) as a continuous variable as a predictor of outcome. All hazard ratios (HRs) are given as HR (95% confidence interval [CI]). ΔC index: difference in C index between adjusted models with and without inclusion of hs-cTnT with corresponding *P* value. Net reclassification improvement (NRI) calculated for fully adjusted models with and without inclusion of hs-cTnT with corresponding *P* value. The multivariable regression model includes the following risk factors: left ventricular ejection fraction, New York Heart Association class, age, body mass index, diabetes mellitus, sex, intermittent claudication, heart rate, apolipoprotein B/apolipoprotein A-1 ratio, amino-terminal probrain natriuretic peptide, high-sensitivity C-reactive protein, and estimated glomerular filtration rate. CV indicates cardiovascular; and WHF, worsening of heart failure.

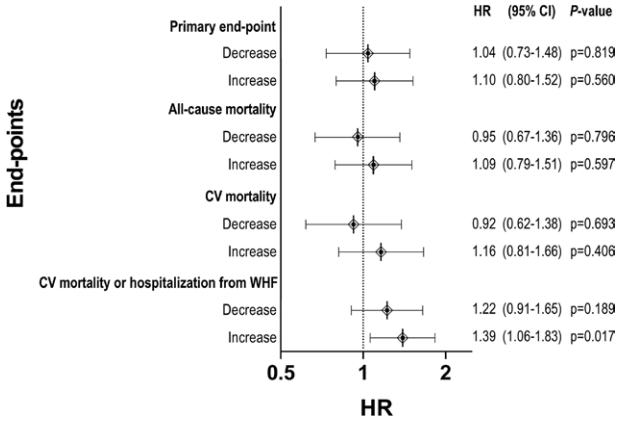

Figure 3. Forest plot demonstrating the predictive value (multivariate analysis) of change in high-sensitive troponin T (hs-cTnT) levels from baseline to 3 months on the primary end point, all-cause mortality, cardiovascular (CV) mortality, and the composite of CV mortality and hospitalization from worsening of heart failure (WHF). A significant change in hs-cTnT levels was defined as >15% relative change. Hazard ratios (HRs) are given as HR (95% confidence interval [CI]) with corresponding *P* value for the relative changes in hs-cTnT levels > or ≤15%. The multivariable regression model included the following risk factors: left ventricular ejection fraction, New York Heart Association class, age, body mass index, diabetes mellitus, sex, intermittent claudication, heart rate, apolipoprotein B/apolipoprotein A-1 ratio, amino-terminal probrain natriuretic peptide, high-sensitivity C-reactive protein, and estimated glomerular filtration rate.

numbers of patients, few elderly patients, or a small proportion of patients in NYHA functional class III or IV.[12,24,25] In particular, our data differ somewhat from those in a report from the Val-HeFT (Valsartan Reduces Morbidity in Chronic Heart Failure) and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nellInsufficienza Cardiaca-Heart Failure) trials, which showed that changes in hs-cTnT concentrations over time predicted CV events among patients with HF but, however, added limited prognostic discrimination.[14] In this CORONA substudy, we were unable to reproduce the importance of change in hs-cTnT concentration over time in the prediction of outcome, despite similar cutoff levels for change (>15% relative change) and interval (3 months). Importantly, changes in hs-cTnT provided inferior prognostic information than that of elevated baseline levels in the present study. Nonetheless, from a clinical point of view, the prognostic value of baseline levels above or below the 99th percentile seems to be more important than that of changes during follow-up.

An explanation for these divergent findings might be differences in the composition of the study populations. Compared with the present CORONA substudy, the Val-HeFT and GISSI-HF study populations were younger (72±7 versus 63±11 [Val-HeFT] and 67±11 [GISSI-HF] years old), fewer were in NYHA class III and IV (67.9% versus 38.0% and 26.1%, respectively), had higher average eGFR (58.0 versus 61.7 and 61.9 mL/min per 1.73 m^2, respectively), and the rate of HF with ischemic cause in these studies was ≈50%.

The mechanisms underlying hs-cTnT elevation in chronic HF remain unresolved.[26] A net effect of increased release of myocardial troponin into the circulation because of myocyte necrosis, apoptosis, or irreversible injury with increased myocyte membrane permeability and impaired renal clearance is a potential explanation.[27] The causes of cardiac myocyte necrosis, apoptosis, and increased membrane permeability might involve neurohormonal activation, oxidative stress, inflammatory cytokines, increased wall stress, altered calcium handling, and coronary artery disease.[27] This hypothesis is supported by the current study because in addition to eGFR, which is known to influence hs-cTnT levels,[28] diabetes mellitus (inflammation and oxidative stress), NT-proBNP levels (increased wall stress), hs-CRP levels (inflammation), increased heart rate and blood pressure (neurohormonal activation), and history of coronary revascularization (coronary artery disease) are associated with elevated hs-cTnT levels.

Limitations

The results of the present study are derived from a selected population of elderly patients with HF of ischemic origin included in the CORONA trial and may therefore not be applicable to a general HF population of mixed cause. In this respect, the frequency of comorbidities also warrants caution when interpreting the findings.

Conclusions

Elevated hs-cTnT levels in elderly patients with chronic HF of ischemic cause provide independent prognostic and discriminating information beyond that of established risk markers. The prognostic value of baseline hs-cTnT levels was superior to that of changes during follow-up.

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Disclosures

J.J.V. McMurray, L. Gullestad, and J. Kjekshus were on the CORONA steering committee and have received lecture fees from AstraZeneca. J. Wikstrand was earlier also adviser on cardiovascular research at AstraZeneca Research Laboratories, Mölndal, Sweden. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Serum levels of cardiac troponins, as measured by sensitive assays, are essential for the diagnosis of acute myocardial infarction. Cardiac troponins are also shown to provide important prognostic information in a variety of cardiac and noncardiac diseases, including chronic heart failure (HF). Because the incidence and prevalence of HF are increasing as a result of changing demographics and an increasing proportion of the elderly, the relevance of cardiac troponins in older patients with chronic HF may be of significant clinical importance. Accordingly, we explored the role of serum levels of cardiac troponin T, as measured with a high-sensitive assay, in the prediction of fatal and nonfatal outcomes in a large contemporary cohort of elderly patients with systolic HF of ischemic origin, receiving modern pharmacological therapy, randomly assigned to statin therapy or placebo in a double-blinded fashion. Baseline high-sensitive troponin T levels, both dichotomized according to the 99th percentile (14 ng/L) and as a continuous variable, independently predicted fatal and nonfatal outcomes and improved risk prediction after adjustment for conventional risk markers, including C-reactive protein and N-terminal pro-B-type natriuretic peptide. Importantly, changes in high-sensitive troponin T during 3-month follow-up provided inferior prognostic information than that of elevated baseline levels. Thus, measurements of high-sensitive troponin T levels might be useful in risk stratification of elderly patients with HF. From a clinical point of view, the prognostic value of baseline levels seems to be more important than that of changes during follow-up.

Circulation
Heart Failure

Prognostic Effect of High-Sensitive Troponin T Assessment in Elderly Patients With Chronic Heart Failure: Results From the CORONA Trial

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SUPPLEMENTAL MATERIAL

Gravning et al.: Prognostic impact of high-sensitive troponin T assessment in elderly patients with chronic heart failure: Results from the CORONA trial

Supplemental Tables

Supplemental Table 1. Baseline differences between total CORONA population and hs-cTnT sub-study.

Variable	CORONA Total study (n=5011)	CORONA Hs-cTnT sub-study (n=1245)	*P*-value
Age, years	72.7 (7.1)	71.8 (6.9)	<0.001
Female sex	1180 (23.5)	284 (22.8)	0.583
Smoking	528 (10.5)	175 (12.1)	0.262
NYHA Class			0.002
II	1857 (37.1)	400 (32.1)	
III	3081 (61.5)	830 (66.7)	
IV	73 (1.5)	15 (1.2)	
Ejection Fraction (%)	31 (6)	32 (7)	<0.001
BMI (kg/m^2)	27.2 (4.5)	27.3 (4.5)	0.631
SBP (mmHg)	129 (16.0)	129 (16.0)	0.705
DBP (mmHg)	76 (8.9)	77 (8.8)	0.015
Heart rate (beats/min)	72 (11)	71 (11)	0.002
Medical history			
Myocardial infarction	3006 (60.0)	780 (62.7)	<0.001
History of angina pectoris	3570 (71.2)	910 (73.1)	<0.001
Other atherosclerotic disease	1032 (20.6)	243 (19.5)	<0.001
PCI / CABG	1229 (24.5)	262 (21.0)	<0.001
Hypertension	3175 (63.4)	868 (69.7)	<0.001
Diabetes mellitus	1477 (29.5)	325 (26.1)	0.019
Stroke	624 (12.5)	145 (11.6)	0.438
Claudication	637 (12.7)	128 (10.3)	0.019
COPD	109 (2.2)	24 (1.9)	0.588
Laboratory measures			

Total Cholesterol (mmol/L)	5.17 (1.08)	5.22 (1.09)	0.196
LDL (mmol/L)	3.55 (0.94)	3.64 (0.97)	0.005
HDL (mmol/L)	1.23 (0.35)	1.23 (0.35)	0.782
Triglycerides (mmol/L)	2.00 (1.28)	2.00 (1.34)	0.513
Apo B/Apo A-1 value	0.87 (0.25)	0.88 (0.25)	0.084
eGFR (mL/min/1.73m^2)	57 (14)	58 (14)	0.239
NT-proBNP (pmol/L)	173 (73-368)	156 (61-339)	0.023
hs-CRP (mg/L)	3.50 (1.60-7.45)	3.55 (1.60-7.57)	0.482
Medications			
Diuretics (loop / thiazide)			0.006
None	677 (13.5)	161 (12.9)	
One	3977 (79.4)	951 (76.4)	
Both	357 (7.1)	133 (10.7)	
Aldosterone antagonist	1906 (38.0)	454 (36.5)	0.306
ACE-inhibitor	3981 (79.4)	1001 (80.4)	0.453
Angiotensin II receptor blocker	637 (12.7)	128 (10.3)	0.019
Beta blocker	3722 (74.3)	962 (77.3)	0.029
Digitalis glycoside	1618 (32.3)	349 (28.0)	0.004

Demographic, clinical and biochemical baseline characteristics stratified in the total CORONA study population vs. the current study population with available measurements of hs-cTnT levels. Hs-CRP and NT-proBNP levels are displayed as median value (25^{th}-75^{th} percentiles). Other variables are shown as numbers (percentage of total) or as mean (standard deviation) where appropriate. NYHA, New York Heart Association; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ApoB, apolipoprotein B; ApoA-1, apolipoprotein A-1; eGFR, estimated glomerular filtration rate; Hs-CRP, High-sensitivity C-reactive protein; NT-proBNP, amino-terminal pro-brain natriuretic peptide; ACE, angiotensin converting enzyme.

Supplemental Table 2. Multivariable analyses – effects of hs-cTnT quartiles on outcomes.

hs-cTnT, quartiles (ng/L)	n	Events	HR (95% CI)	*P*-value	Wald
Primary endpoint	1026	272			
2. quartile (6.60-13.86)			1.82 (1.12-2.95)	0.015	5.86
3. quartile (13.88-25.64)			2.49 (1.54-4.02)	<0.001	13.8
4. quartile (25.65-390.9)			3.24 (1.96-5.38)	<0.001	20.8
All-cause mortality	1026	281			
2. quartile			1.74 (1.07-2.81)	0.024	5.06
3. quartile			2.24 (1.39-3.62)	0.001	11.0
4. quartile			2.76 (1.67-4.56)	<0.001	15.8
CV mortality	1026	227			
2. quartile			1.79 (1.04-3.09)	0.035	4.44
3. quartile			2.23 (1.30-3.83)	0.004	8.50
4. quartile			2.94 (1.68-5.15)	<0.001	14.1
CV mortality or hospitalization from WHF	1026	367			
2. quartile			1.06 (0.73-1.53)	0.772	0.08
3. quartile			1.19 (0.82-1.73)	0.359	0.84
4. quartile			1.80 (1.22-2.66)	0.003	8.71

The table shows quartiles of hs-cTnT levels as predictors of outcome. All Hazard Ratios (HR) are given as HR (95% confidence interval), with corresponding (*P*-value). The multivariable regression model includes the following risk factors: left ventricular ejection fraction, NYHA class, age, body mass index, diabetes, sex, intermittent claudication, heart rate and ApoB/ApoA-1-ratio, NT-proBNP, hs-CRP and estimated glomerular filtration rate.

Supplemental Table 3. Comparisons of hs-cTnT vs. hs-CRP and NT-proBNP as predictors of outcome.

	hs-cTnT	hs-CRP	NT-proBNP
Primary endpoint			
C-statistic	0.682	0.655	0.689
P-value	NA	0.024	0.602
All-cause mortality			
C-statistic	0.697	0.682	0.712
P-value	NA	0.194	0.213
CV mortality			
C-statistic	0.699	0.681	0.721
P-value	NA	0.147	0.135
CV mortality and hospitalization from WHF			
C-statistic	0.682	0.673	0.708
P-value	NA	0.300	0.019

The table shows C-statistics with corresponding *P*-values for differences between hs-cTnT, hs-CRP and NT-proBNP, respectively, in prediction of outcome. The multivariable regression model includes the following risk factors: left ventricular ejection fraction, NYHA class, age, body mass index, diabetes, sex, intermittent claudication, heart rate and ApoB/ApoA-1-ratio and estimated glomerular filtration rate.