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Increased Cardiac Troponin I as Measured by a High-Sensitivity Assay Is associated with High Odds of Cardiovascular Death: The Minnesota Heart Survey

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BACKGROUND: We examined several novel biomarkers of different pathophysiologic pathways as predictors of cardiovascular mortality in participants enrolled in the Minnesota Heart Survey (MHS), a population-based study of cardiovascular disease (CVD) risk factors.

METHODS: In a nested case-control study within MHS, 7 biomarkers were assayed in serum samples from 211 patients identified after 8–15 years of follow-up who died of cardiovascular causes (cardiovascular heart disease, stroke, congestive heart failure) and 253 controls matched on age, sex, and study year. Logistic regression analysis, adjusted for age, race, sex, education, study year, smoking, abdominal obesity, diabetes, serum total cholesterol, systolic blood pressure, previous hospitalization for a CVD event, and other significant biomarkers, was used to evaluate the relations of biomarkers relative to the odds of CVD mortality.

RESULTS: Cases survived a median of 7.2 years after enrollment. Increased N-terminal pro-B type natriuretic peptide (NT-proBNP) (19% vs 4.3%), increased high-sensitivity C-reactive protein (hs-CRP) (71% vs 51%), and increased high-sensitivity cardiac troponin I (hs-cTnI) (8.7% vs 1.0%) were more common among cases than among controls (all $P < 0.001$ in unadjusted analyses). The adjusted odds of death were greater among cases compared to controls for increased NT-proBNP [odds ratio (OR) 5.67, 95% CI 2.17–15], hs-CRP (OR 1.73, 95% CI 1.03–2.89), and hs-cTnI (OR 8.53, 95% CI 1.68–43), and decreased ST2 (OR 1.92, 95% CI 1.05–3.48).

CONCLUSIONS: When measured by an hs-cTnI assay, cTnI is a key biomarker associated with increased cardiovascular death in a community sample when evaluated in a multiple biomarker analysis.

As the understanding of pathophysiologic pathways involved in cardiovascular disease (CVD)[4] improves, novel biomarkers are emerging as surrogate measures that may identify sites of injury *(1)*. Monitoring biomarkers representative of the underlying mechanisms of injury has been shown to assist in the identification of individuals with subclinical disease and to facilitate preventive strategies *(2, 3)*. Biomarkers have been shown to risk stratify symptomatic and stable acute coronary syndrome (ACS) patients for both short-term (during admission) and long-term (over 6 months to 2 years) major adverse cardiac events *(4, 5)*. Beyond ACS, however, the release of biomarkers, such as cardiac troponin, and identification of chronic injury in asymptomatic individuals with unrecognized myocardial structural disease at high risk for adverse cardiovascular outcomes may provide opportunities to more effectively manage these patients *(6)*. As a predictor of major adverse cardiac events in individuals within the general population, the development of high-sensitivity cardiac troponin T (hs-cTnT) and I (hs-cTnI) assays has allowed measurement of very low concentrations of cardiac troponin, providing new opportunities to screen asymptomatic populations in which current contemporary cardiac troponin assays cannot generate a signal above their limits of detection *(7, 8)*.

The Minnesota Heart Survey (MHS), initiated in 1980, is an ongoing population-based study of risk factors for coronary heart disease. Participants are ran-

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[4] Nonstandard abbreviations: CVD, cardiovascular disease; ACS, acute coronary syndrome; hs-cTnT, high-sensitivity cardiac troponin T; MHS, Minnesota Heart Survey; NT-proBNP, N-terminal pro-B type natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; MR-proANP, midrange proatrial natriuretic peptide; OR, odds ratio; HF, heart failure; HR, hazard ratio.

domly selected adult residents of the Minneapolis St. Paul, MN, 7-county metropolitan area, and the goal of the survey is to characterize metropolitan area–wide time changes in CVD risk factor levels *(9, 10)*. The purpose of the present study was to examine novel biomarkers to determine their ability to predict CVD mortality in participants enrolled in the MHS.

Methods

Methods of the MHS have been published previously *(9, 11, 12)*. For the current analysis, we used data and stored blood samples from the surveys conducted in 1990–1992 and 1995–1997. Demographic and lifestyle information reported in this study include age, sex, race, education, and smoking. Height, weight, and waist circumference were measured by use of standard procedures. Body mass index was calculated as weight (kg) divided by height squared (m^2). Abdominal obesity was defined as waist circumference >88 cm for women and >102 cm for men. Blood pressure was measured with a random zero sphygmomanometer (Hawksley). The mean of 2 measurements at rest was calculated and calibrated to the mercury sphygmomanometer *(12)*. Medical history of previous hospitalization for CVD events was obtained.

Mortality follow-up was accomplished by matching with a registry of all Minnesota death certificates through December 31, 2002. We included all 211 deaths from CVD (International Classification of Diseases ninth revision codes 390–459 or 10th revision codes I00–I99) identified and a randomly selected sample of 253 age- and sex-matched controls from surveys conducted in 1990–1992 and 1995–1997. We included 129 cases and 169 controls from the 1990–1992 survey and 82 cases and 84 controls from the 1995–1997 survey.

Participants were not fasting at examination and at the time blood (serum) was collected. Serum was stored at −70 °C until thawed for analysis. The following biomarkers were measured and preestablished cutoff values were used: (*a*) hs-cTnI was measured on the Erenna System (Singulex) having a 99th percentile value of 10.19 ng/L with a CV of <7% *(13)*; (*b*) sensitive cTnI as measured on the VITROS Troponin I ES assay (Ortho-Clinical Diagnostics) having a 99th percentile value of 34 ng/L with a CV of 10% *(14)*; (*c*) copeptin (the glycosylated 39 amino acid C-terminal fragment of the arginine vasopressin precursor peptide), measured with a novel assay (BRAHMS), having a 97.5th percentile value of 11.25 pmol/L with a CV of <20% *(15)*; (*d*) N-terminal pro-B-type natriuretic peptide (NT-proBNP), a surrogate biomarker of left ventricular dysfunction, was measured on the Elecsys 2010 (Roche), having cutoff concentrations of 125 ng/L for ages <75 years and 450 ng/L for ages ≥75 years *(16)*; (*e*) high-sensitivity C-reactive protein (hs-CRP) was measured on the Elecsys 2010 (Roche), having a tertile cutoff of ≥3.0 mg/L, with a CV of 5.1% *(17)*; (*f*) midrange proatrial natriuretic peptide (MR-proANP), a novel biomarker whose circulating concentration increases with cardiac wall stretch resulting from volume and pressure overload, as measured by an immunoluminometric assay (BRAHMS), having a 95th percentile value of 85.2 pmol/L with a CV of <10% *(18)*; (*g*) ST2, a protein member of the interleukin-1 receptor family as measured by a novel immunoassay (Critical Diagnostics), having sex-derived 97.5th percentile cutoffs of 3–28 U/mL in males and 2–16 U/mL in females, with a CV of <4.0% *(19)*.

All statistical analyses were conducted by using SAS version 9.2 (SAS Institute). The distributions of MR-proANP, ST2, copeptin, NT-proBNP, hs-CRP, hs-cTnI, and sensitive cTnl were skewed and were log transformed before analysis to achieve normality. To return to the natural scale, means of these log-transformed distributions were back transformed and reported as geometric means. High blood pressure was defined as a systolic or diastolic blood pressure ≥140 mmHg or 90 mmHg, respectively, or taking antihypertensive medication. High cholesterol was defined as total cholesterol ≥200 mg/dL (5.17 mmol/L). Means and proportions of descriptive baseline characteristics were calculated for cases and controls and tested for statistical difference by use of 2-sample *t*-tests or χ^2 tests. Multivariate logistic regression analysis, adjusted for age, sex, race, education, study year, smoking, abdominal obesity, diabetes, serum total cholesterol, systolic blood pressure, previous hospitalization for CVD event, and other significant biomarkers, was used to evaluate the relations of biomarkers relative to the odds of CVD mortality.

Results

Demographic and clinical characteristics are described for both the cases and controls (Table 1). Significant differences found for several parameters. Cases survived a median of 7.2 years after enrollment, with 8–15 years of follow-up.

Mean (geometric mean) concentrations of all 7 biomarkers for cases and controls are shown in Table 2. Concentrations were significantly greater in cases compared to controls for NT-proBNP, hs-CRP, hs-cTnI, and sensitive cTnI. Utilizing the predetermined reference cutoff values, the rates of increased MR-proANP among cases vs controls were 24% vs 13%, of hs-cTnI >10.19 ng/L were 9% vs 1%, of NT-proBNP >450 ng/L among individuals <50 years old and >900 ng/L

Table 1. Mean (SD) and prevalence of demographic and clinical characteristics of CVD cases and healthy controls: MHS 1990–1992 and 1995–1997.

CVD risk factor	Cases (n = 211)	Controls (n = 253)	*P*
Demographics			
Age, years	69 (11)	67 (12)	0.05
Men	125 (59%)	157 (62%)	0.54
Race, white	203 (96%)	245 (97%)	0.70
Education			
<High school	77 (36%)	70 (28%)	0.11
High school graduate	34 (16%)	41 (16%)	
Some college	58 (27%)	70 (28%)	
College graduate	42 (20%)	71 (28%)	
Current smoking,	44 (21%)	30 (12%)	0.008
Clinical characteristics			
Body mass index, kg/m^2	28.1 (4.7)	27.2 (4.9)	0.06
Waist circumference, inches	38.7 (5.2)	37.8 (5.9)	0.06
Abdominal obesity	113 (54%)	108 (43%)	0.02
Diabetes (self-report)	37 (18%)	22 (9%)	0.004
Systolic blood pressure, mmHg	137 (20)	131 (19)	0.002
Diastolic blood pressure, mmHg	78 (14)	78 (13)	0.82
High blood pressure	149 (71%)	117 (46%)	<0.001
Total cholesterol, mg/dL[c]	221 (42)	212 (39)	0.02
HDL-cholesterol, mg/dL[c]	42 (14)	45 (14)	0.04
High cholesterol, n (%)	90 (44%)	66 (26%)	<0.001
Low HDL	94 (48%)	93 (38%)	0.04
Previous hospitalization for CVD	64 (30%)	15 (6%)	<0.001
MR-proANP (n = 344), >85.2 pmol/L	34 (24%)	26 (13%)	0.006
ST2 (n = 458), decreased[a]	155 (75%)	182 (73%)	0.57
Copeptin (n = 375), >11.25 pmol/L	16 (11%)	18 (8%)	0.56
NT-proBNP (n = 407), increased[b],	33 (19%)	10 (5%)	<0.001
hsCRP (n = 407), >3.0 mg/L	124 (71%)	119 (51%)	<0.001
cTnI, (n = 405), >34 ng/L	5 (3%)	0 (0%)	0.01
Hs-cTnI (n = 430), >10.1 ng/L	17 (9%)	2 (1%)	<0.001

[a] ST2: males < 30.6U/mL, females <20.9 U/mL.
[b] NT-proBNP: <50 years <450 ng/L, > 50 years >900 ng/L.
[c] To convert cholesterol from milligrams per deciliter to millimoles per liter multiply by 0.02586.

among those ≥50 years old were 19% vs 4%, and of hs-CRP >3.0 mg/L were 71% vs 51%, respectively (Table 1).

Adjusted odds of death from CVD were significantly greater among cases compared to controls with increased hs-cTnI [odds ration (OR) = 8.53], increased NT-proBNP (OR = 5.67), increased hs-CRP (OR = 1.73), and decreased ST2 (OR = 1.92) (Table 3). MR-proANP and copeptin were not included in the final model because these markers were no longer significant in the full model. Because there were only 5 observations of increased values for sensitive cTnI assay results, this biomarker was not included in the multivariate analysis. In addition, we examined which biomarkers affected the adjusted odds of death from CVD when biomarkers were included as continuous measures ($\log_{10}$ transformed). proBNP and hs-CRP were significant in both the full and final models (final model: OR for doubling of proBNP 2.18, 95% CI 1.36–3.49, $P = 0.001$; OR for doubling of hs-cTnI 2.03, 95% CI 1.06–3.88, $P = 0.03$). Other biomarkers were not significant in the full model, so these were excluded from the final model.

Table 2. Geometric mean (interquartile range) biomarker concentrations among 211 cases of CVD and 253 controls matched for age, sex, and race: MHS 1990–1992 and 1995–1997.[a]

Biomarker	Cases (n = 211)	Controls (n = 253)	*P*
MR-proANP, pmol/L	37.6 (14.6–77.7)	28.2 (13.1–56.8)	0.01
ST2, U/mL	22.1 (16.9–27.95)	20.8 (16.5–25.2)	0.08
Copeptin, pmol/L	3.51 (1.78–6.35)	3.38 (2.07–5.23)	0.69
NT-proBNP, ng/L	214 (99–514)	91 (38–183)	<0.001
hs-CRP, mg/L	4.44 (2.33–9.46)	2.59 (1,08–6.54)	<0.001
Sensitive cTnI, ng/L	4.87 (3,00–9.00)	3.10 (1.19–5.73)	<0.001
hs-cTnI, ng/L	2.94 (1.59–4.78)	1.70 (1.05–2.73)	<0.001

[a] Biomarkers were log transformed, the means and 25th and 75th percentiles (interquartile ranges) were computed, and the means were compared; then the means and percentiles were back transformed. Sensitive cTnI values that were less than the limit of detection were recoded to 1 ng/L.

Few cases (9%) or controls (1%) had hs-cTnI above the reference limit of 10.1 ng/L determined from a "healthy normal" population. All cases and controls (100%) had a measureable hs-cTnI above the limit of detection, compared with 22.4% for the sensitive cTnI assay. Tertiles of the hs-cTnI distribution overall were <1.43, 1.43–2.66, and >2.66 ng/L. Adjusted odds of death from CVD were 2 times greater for individuals with hs-cTnI values in tertiles 2 and 3 (OR = 2.09, 95% CI 1.21–3.60, and OR = 2.67, 95% CI 1.52–4.67, respectively; no adjustment for other biomarkers) vs tertile 1. The optimal cutpoints based on area under the ROC curve was 1.69 ng/L (area under the ROC curve 0.67). Adjusted odds of death from CV disease with hs-cTnI >1.69 ng/L were 2.77 (95% CI 1.75–4.38; $P < 0.001$; no adjustment for other biomarkers). For cases vs controls, 72% vs 45% had hs-cTnI >1.69 ng/L.

Discussion

The current study demonstrates that circulating cTnI measured by a high-sensitivity assay is key in identifying individuals at high risk several years before CVD-related death in a community population–based sample. Our findings are novel for an hs-cTnI assay and support several other recent studies that have described a role for the hs-cTnT assay in identifying individuals at risk in normal populations. We are unaware of any studies directly comparing results of hs-cTnI and hs-cTnT assays. What distinguishes the high-sensitivity assays from their predecessor contemporary, sensitive assays is their ability to measure very low cTnT and cTnI concentrations of 1–20 ng/L (well below the limit of detection of the sensitive, contemporary assays currently used in clinical practice) with excellent precision

Table 3. Adjusted odds of dying from CVD conferred by increased or decreased biomarker concentrations comparing 211 cases with 253 controls: MHS 1990–1992 and 1995–1997.

	Full model[a]		Final model[b]	
Biomarker	OR (95% CI)	*P*	OR (95% CI)	*P*
MR-proANP, >85.2 pmol/L	1.00 (0.39–2.54)	0.99	—	—
ST2, decreased[c]	2.03 (1.01–4.08)	0.05	1.92 (1.05–3.48)	0.03
Copeptin >11.25 pmol/L	0.92 (0.36–2.37)	0.87	—	—
NT-proBNP, increased[d]	4.81 (1.52–15)	0.007	5.67 (2.17–15)	<0.001
hs-CRP >3.0 mg/L	1.88 (1.03–3.43)	0.04	1.73 (1.03–2.89)	0.04
hs-cTnI, >10.1 ng/L	6.29 (1.09–36)	0.04	8.53 (1.68–43)	0.01

[a] Full model adjusted for age, sex, race, education, study year, smoking, systolic blood pressure, total cholesterol, abdominal obesity, diabetes, previous hospitalization for cardiovascular events, and biomarkers hs-CRP, NT-proBNP, ST2, MR-proANP, copeptin, and hs-cTnI.
[b] Final model adjusted for age, sex, race, education, study year, smoking, systolic blood pressure, total cholesterol, abdominal obesity, diabetes, previous hospitalization for cardiovascular events, and biomarkers ST2, hs-CRP, NT-proBNP, and hs-cTnI.
[c] ST2: males <30.6 U/mL, females <20.9 U/mL.
[d] NT-proBNP: <50 years <450 ng/L, > 50 years >900 ng/L.

at ≤10% CV, both at and below the assay's 99th percentile value. This added sensitivity allows hs-cTn assays to measure and provide reliable concentrations in almost 100% of healthy individuals *(20, 21)*. Contemporary, sensitive assays can typically detect measurable cardiac troponin in only 10% to 20% of individuals from the general apparently healthy population *(20–22)*.

Several general population studies have measured cardiac troponin with the hs-cTnT assay. A report from the Cardiovascular Health Study of 4221 community-dwelling adults age 65 years or older without prior heart failure (HF) determined that both baseline concentrations and changes in serial measurements of hs-cTnT were significantly associated with incident HF and cardiovascular death during the 11.8-year follow-up period *(7)*. A baseline hs-cTnT concentration >12.94 ng/L had an adjusted hazard ratio (HR) of 2.48 for HF and 2.91 for cardiovascular death. A subsequent increase in hs-cTnT of >50% was associated with a greater risk of HF (HR = 1.61) and cardiovascular death (HR 1.68). A graded relationship between increasing hs-cTnT concentrations >3.0 ng/L and increased risk of both HF and cardiovascular death was observed, although approximately 83% of the study observations were well below the 99th percentile of healthy individuals. These data confirmed that higher hs-cTnT concentrations were associated with multiple traditional risk factors. Neither NT-proBNP nor hs-CRP added significantly to risk assessment.

In a study of 3546 individuals age 30–65 years from the Dallas Heart Study, a multiethnic population-based cohort, the prevalence of measurable hs-cTnT was 25%, with significantly different rates in men (37.1%) vs women (12.9%) and between participants <40 years old (14%) and those >60 years old (57.5%) *(8)*. An increased hs-cTnT was shown to be associated with structural heart disease, including left ventricular hypertrophy and systolic dysfunction, as well as chronic kidney disease. During a median follow-up of 6.4 years, all-cause mortality increased from 1.9% to 28.4% across increasing hs-cTnT groups, with 95% of individuals having concentrations less than the 99th percentile value (14 ng/L). After adjustment for traditional risk factors, hs-CRP and NT-proBNP, hs-cTnT remained independently associated with all-cause mortality (HR = 2.8, in the group with concentrations >14 ng/L). The study concluded that cTnT measurable by use of the high-sensitivity assay at concentrations below what can be measured by current assays is associated with a greater burden of cardiovascular risk and may represent a biomarker of "end organ" cardiovascular damage.

Exploring biomarkers that are likely indicative of different pathophysiologic pathways and mechanisms of injury of disease as predictors of cardiovascular adverse mortality was the approach we used in studying both contemporary and novel biomarkers. Several novel biomarkers we examined were not found to have statistically significant effects on the odds of death for CVD. These markers included MR-proANP, a vasodilatory peptide with potent hypotensive effects that is increased in patients with HF and that increases with the severity of disease, and copeptin, the C-terminal, glycosylated peptide portion of the antidiuretic hormone arginine-vasopressin that has been shown to be an indicator of individual myocardial stress independent of cell necrosis. Our findings pertaining to copeptin were not unexpected, because copeptin has been suggested as a diagnostic and or prognostic biomarker in patients presenting within the early hours after an acute event *(23, 24)*. The role of MR-proANP, shown to have significant diagnostic and prognostic utility in patients presenting in the emergency department with acute dyspnea *(25)*, will need to be further explored.

Strengths of the current study include a population-based study design, long-term follow-up, and availability of data on a large number of baseline cardiovascular risk factors for multivariate adjustment of ORs. Study limitations were primarily a function of the case-control study design. First, only mortality and not morbidity data were available, and the sample size of 464 individuals who died of CVD was small, with only single controls available for each case. Second, no information on treatment in the interval between baseline measurements and death outcomes was available. Third, no head-to-head comparison was conducted between hs-cTnI and hs-cTnT assays to determine whether one assay performed better for outcome analysis. Finally, although the novel biomarkers MR-proANP and copeptin were not useful for long-term prediction of mortality, our study did not address the potential value of these biomarkers for short-term prediction.

In conclusion, biomarkers likely indicative of different underlying disease mechanisms (ST2: myocardial stretch; NT-proBNP: myocardial dysfunction; hs-CRP: systemic inflammation; hs-cTnI: myocardial damage) were independently associated with odds of cardiovascular death in a community sample. Confirming other studies of hs-cTnT, the key finding of our study was the observation that the release of small concentrations of troponin as measured by a novel hs-cTnI assay was not uncommon in asymptomatic adults and conveyed an unexpected higher risk of cardiovascular death. Future studies will be performed to define the optimal role of high-sensitivity cardiac troponin assays, comparing hs-cTnI and hs-cTnT, for screening young adults for risk assessment of future events and for potential early intervention and therapies to improve both short- and long-term outcomes. The accu-

mulation of evidence will determine whether this biomarker assumes a role in primary prevention.

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