Long-Term Trajectory of Two Unique Cardiac Biomarkers and Subsequent Left Ventricular Structural Pathology and Risk of Incident Heart Failure in Community-Dwelling Older Adults at Low Baseline Risk

Danielle Glick, BS,* Christopher R. deFilippi, MD,* Robert Christenson, Ph.D,† John S. Gottdiener, MD,* Stephen L. Seliger, MD, MS*

Baltimore, Maryland

Objectives
This study sought to determine whether the combined trajectories of cardiac biomarkers identify those older adults with initial low levels who have an increased risk for structural heart disease, incident heart failure (HF), and cardiovascular (CV) death.

Background
Initial low levels of high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) identify older adults at lower risk for CV events.

Methods
We performed an observational study among older adults without prevalent HF in the CHS (Cardiovascular Health Study). NT-proBNP and hs-cTnT were measured at baseline and after 2 to 3 years. In those with low baseline levels, a significant increase was defined as cardiac troponin T (cTnT) >50% and NT-proBNP >25% increase to >190 pg/ml. Left ventricular ejection fraction and left ventricular mass were measured by echocardiography at baseline and 5 years. Cox regression was used to estimate the association of change in biomarkers with HF and CV mortality.

Results
Among 2,008 participants with initially low biomarker concentrations, significant increases occurred in 14.8% for cTnT only, 13.2% for NT-proBNP only, and 6.1% for both. After 10 years, cumulative HF incidence was 50.4% versus 12.2% among those with both biomarkers versus neither biomarker increased. The adjusted relative risk comparing those with increases in both biomarkers versus neither biomarker was 3.56 for incident HF (95% confidence interval: 2.56 to 4.97) and 2.98 for CV mortality (95% confidence interval: 2.98 to 4.26). Among 1,340 participants with serial echocardiography, the frequency of new abnormal left ventricular ejection fraction was 11.8% versus 4% for those with increases in both biomarkers versus neither biomarker (p = 0.007).

Conclusions
Among older adults without HF with initially low cTnT and NT-proBNP, the long-term trajectory of both biomarkers predicts systolic dysfunction, incident HF, and CV death. (J Am Coll Cardiol HF 2013;1:353–60) © 2013 by the American College of Cardiology Foundation

The disease burden of heart failure (HF) and other high-risk cardiovascular (CV) conditions falls mostly on older adults, with those ages ≥65 years comprising approximately half of individuals with known CV disease. The annual incidence of HF for older adults is as high as 1 in 100 (1). With a high mortality in older adults associated with symptomatic HF, identifying those at greatest risk in the community may provide an opportunity to intervene to delay symptom onset.

From the *Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland; and the †Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland. The research reported in this paper was supported by contracts HHSN268201200036C, N01-HC-85239, N01-HC-85079 to N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, and N01-HC-45133, and Grant HL080293 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided through AG-023629, AG-15928, AG-20098, and AG-027058 from the National Institute on Aging. A full list of principal investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm. Support for measurement of cardiac biomarkers was provided by Roche Diagnostics, Inc. Dr. deFilippi consults for, receives honoraria from, and receives research funding from Roche Diagnostics. Dr. Christenson receives research funding from Roche Diagnostics. Dr. Seliger consults for and receives research funding from Roche Diagnostics. Dr. Gottdiener and Ms. Glick report that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

- CHD = coronary heart disease
- CI = confidence interval
- cTnT = cardiac troponin T
- CV = cardiovascular
- HF = heart failure
- hs-cTnT = high-sensitivity cardiac troponin T
- IDI = integrated discrimination improvement
- LVEF = left ventricular ejection fraction
- LVH = left ventricular hypertrophy
- NRI = net reclassification improvement
- NT-proBNP = N-terminal pro-brain natriuretic peptide

However, traditional risk scores based on clinical risk factors typically are less accurate in estimating CV risk in older adults compared with younger cohorts (2,3).

Blood-based biomarkers have been shown to add to traditional risk factor–based models to improve risk stratification for HF and CV death (4–10). Although the use of single biomarkers is helpful, the examination of multiple biomarkers representing different patho-physiologies may have even greater predictive and prognostic value (4,9,10). However, a large proportion of individuals remain at risk even when multiple biomarker concentrations are below previously defined thresholds. For example, we have previously shown that in older adults with initially low concentrations of the cardiac-specific biomarkers cardiac troponin T (cTnT) (measured by a high-sensitivity [hs] assay) or N-terminal pro-brain natriuretic peptide (NT-proBNP), an upward trajectory in one biomarker over 2 to 3 years is associated with a 70% to 200% increased risk of new-onset HF, respectively, compared with individuals without such an increase (5,6). Correlation between concentrations of these 2 biomarkers is only moderate, suggesting that the mechanisms underlying their association with adverse outcomes may differ. As such, consideration of changes in both biomarkers may provide a more complete evaluation of CV risk, characterizing an early HF phenotype preceding structural changes and symptomatic disease.

We hypothesized that in community-dwelling older adults free of HF with initially lower-risk concentrations of the biomarkers NT-proBNP and hs-cTnT, the trajectories of both biomarkers measured over 2 to 3 years would be additive in identifying those participants at greater long-term risk for new-onset HF and CV death. Furthermore, we hypothesized that the trajectories of both biomarkers would identify those more likely to develop left ventricular (LV) structural pathology by serial echocardiography before symptomatic HF.

Methods

Study population. The CHS (Cardiovascular Health Study) is a multicenter prospective observational cohort study of CV disease in older adults. A detailed account of the study methods, as well as a description of the study-defined co-morbidities, has been published (11). Participants (N = 5,201) were initially enrolled in 1989 and 1990, and an African-American supplemental cohort (N = 687) was enrolled in 1992 and 1993. In the present analysis, we excluded those participants with a diagnosis of HF before the time of the second biomarker measure (see “Biomarker Measurement”).

The CHS was approved by the institutional review boards of the University of Washington, Seattle, and the participating centers. All participants gave written informed consent. The present study was approved by the institutional review board of the University of Maryland, Baltimore.

Biomarker measurement. NT-proBNP and cTnT were measured in serum collected from 1989 to 1990 and from 1992 to 1993 (main cohort) or 1992 to 1993 and 1995 to 1996 (supplemental cohort) and stored at −70°C to −80°C. Samples were thawed just before testing (maximum of 3 freeze-thaw cycles) and measured according to previously described assay methods (5,6). The assay range is 5 to 35,000 pg/ml for NT-proBNP and, using the highly sensitive fifth-generation test, 3 to 10,000 pg/ml for cTnT.

Primary outcome measures. Outcomes were incident HF and CV mortality. Incident HF events were ascertained by participant interview at semiannual study visits and examination of Medicare claims data. Potential HF events and determination of cause of death were determined by an expert adjudication panel (12). Details of adjudication criteria have been described (13).

CV mortality was defined as mortality related to atherosclerotic heart disease (fatal myocardial infarction and definite and possible fatal coronary heart disease [CHD]), death after cerebrovascular disease (fatal stroke), or mortality from other atherosclerotic and CV diseases including HF, as previously described (12).

Other covariates. Covariates including prevalent CV disease risk factors were defined at the time of the second biomarker measurement as previously described (5). Race was determined by self-identification and classified as black or other. CHD was defined as a history of angina, coronary angioplasty, coronary artery bypass surgery, or myocardial infarction. Echocardiograms were also obtained; in the main cohort, this was performed in 1989 and 1990, and among both cohorts, this was performed in 1995 and 1996. The measures of interest for this analysis—LV mass, left atrial diameter, diastolic measures including the mitral inflow Doppler E/A ratio, and semiquantitative left ventricular ejection fraction (LVEF)—were defined as previously specified (14). Left ventricular hypertrophy (LVH) was defined as LV mass indexed to height of >46.7 g/m².7 for women and >49.2 g/m².7 for men (15).

Statistical methods. Selection of study sample. In the present analysis, we excluded those participants with prevalent HF at enrollment into CHS and/or incident HF between the enrollment and the time of the second biomarker measurement. Because the purpose of the present analysis was to examine the effect of change in biomarkers among those whose initial biomarkers were not already elevated, we further excluded participants with initial NT-proBNP >190 pg/ml or cTnT >13 pg/ml. The cutpoint for elevated NT-proBNP represents the 70th percentile in the CHS study sample and best corresponds with increased
risk of HF in this population. The cutpoint for cTnT represents the 99th percentile in a healthy reference population (16) and identified a high-risk subgroup in 3 general population studies (6,7,17).

DEFINITION OF SIGNIFICANT INCREASE IN BIOMARKERS. A “clinically significant” increase in each biomarker was defined according to previously defined criteria: for NT-proBNP, a >25% increase from baseline to a concentration at follow-up of >190 pg/ml; for cTnT, a >50% increase from baseline. Increases of this magnitude represent a change greater than the short-term within-individual variability in healthy adults (18,19) and individually have been shown to predict a greater risk of incident HF in older adults (5,6). In the primary analysis, participants (N = 950, 47%) with concentrations below the level of detection (<3 pg/ml) were imputed a value of 2.99 pg/ml.

Study participants were divided into 4 subgroups based on their increase from baseline to follow-up in each of the 2 specified biomarkers (NT-proBNP and cTnT) as follows: no change, change in cTnT only, change in NT-proBNP only, or change in both cTnT and NT-proBNP. Baseline characteristics by category were compared using chi-square tests or one-way analysis of variance, as appropriate.

COMPARISON OF ECHOCARDIOGRAPHIC ABNORMALITIES. Among participants in the main cohort with complete echocardiogram data at both baseline and follow-up (1995 to 1996) who remained free of diagnosed HF at the time of the second echocardiogram, we compared the frequency of an abnormal LVEF classiﬁed as depressed (borderline [estimated as 45% to 54%] or abnormal [estimated as <45%]) at follow-up across the 4 subgroups deﬁned by a change in biomarkers, after excluding those with a depressed LVEF at baseline. Likewise, after excluding those with baseline LVH, we plotted the frequency of new LVH at follow-up echocardiogram across the subgroups deﬁned by biomarker change. The chi-square test was used to test the hypothesis that the incidence of new LVH and a new depressed LVEF differed between biomarker change subgroups.

COMPARISON OF INCIDENT HF AND CV MORTALITY. Cumulative incidence of HF and CV mortality in each subgroup from the time of the second biomarker measurement was estimated using the Kaplan-Meier method and compared with the log-rank test. Multivariate analyses were performed using Cox proportional hazard regression models. All models were adjusted for baseline concentrations of each biomarker. Two sets of adjustment covariates were selected, which included: 1) demographics (age, sex, race [black vs. other]); and 2) CV risk factors defined a priori from validated risk models, which are distinct for both HF and CV mortality (20,21). In addition to demographics, the models for HF were adjusted for systolic blood pressure, smoking, heart rate, creatinine, albumin, glucose, CHD, and LVH as determined by electrocardiograph (components of the Health ABC Risk model) (20). CV death models, in addition to demographics, were adjusted in accordance with the traditional CV risk factors as defined in the Framingham risk score: systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, diabetes, CHD, smoking, and total and high-density lipoprotein cholesterol levels (21).

We estimated the incremental improvement in risk classiﬁcation and discrimination from the addition of change in biomarker concentrations to models containing baseline concentrations and traditional risk factors using the C-statistic (as modiﬁed for time-to-event analyses) (22), the integrated discrimination improvement (IDI), and the net reclassiﬁcation improvement (NRI) statistics (23). For the NRI computation, we deﬁned a priori 10-year risk categories of <10%, 10% to 20%, and >20% as previously described, using model-based estimates of cumulative hazard. In sensitivity analyses, we also estimated net reclassiﬁcation using the newer “continuous NRI” as deﬁned by Pencina et al. (24), with bootstrapping used to estimate the 95% conﬁdence intervals (CIs). Statistical analysis was performed using SPSS version 19 (IBM) and Stata v11.2 (StataCorp, College Station, Texas).

Results

Characteristics of study samples. The number of participants who met the inclusion criteria for this analysis is shown in Figure 1. Among all CHS participants, 507 (8.6%) had HF before the second biomarker measurement, and an additional 788 (13.3%) were deceased or did not attend an in-person follow-up study visit. Of the remaining participants, 2,906 (64.2%) had sufﬁcient sera from both the baseline and the follow-up visits for cardiac biomarker measurement. A total of 898 (30.9%) had elevated concentrations of at least 1 cardiac biomarker change subgroup.
biomarker at baseline and were excluded from analysis, resulting in the inclusion of 2,008 participants for analysis.

Overall, approximately one third of the study population had an increase in at least 1 biomarker from baseline to second blood draw. The proportion of participants with an increase in only 1 biomarker was relatively similar (cTnT, 14.8%; NT-proBNP, 13.2%), and 6.1% had an increase in both biomarkers (Table 1). A progressive trend in participants with an increase from none to both biomarkers could be seen with more advanced age, known CHD, hypertension, and higher creatinine values. However, several demographic characteristics and traditional risk factors, although significantly different between groups, did not follow this linear trend, including male sex, diabetes, and cholesterol levels. On baseline echocardiography, significant differences were observed in those who had increased
specifically, in those in whom biomarkers increased there was a greater prevalence of depressed LVEF, impaired diastolic relaxation, and greater left atrial diameter. Those with increases in biomarkers also had higher baseline hs-cTnT and NT-proBNP concentrations.

Cardiac structural changes based on changes in biomarkers. Sequential echocardiograms from baseline and after 5 years were available in 1,393 study participants from the main CHS cohort who remained free of HF, of whom 1,340 (96.2%) had a normal LVEF at baseline and were included for analysis. The incidence of new depressed LVEF at follow-up differed significantly between those with and those without changing biomarker concentrations, at 4% for those with an increase in neither biomarker to 11.8% for those with an increase in both cTnT and NT-proBNP (p = 0.007 for test of incidence across biomarker change subgroups; Fig. 2A). Sequential measures of LV mass on echocardiography were available for 815 participants in the main cohort without HF at the time of the second echocardiogram, of whom 97 (11.9%) had baseline LVH as defined by sex-specific cutpoints for LV mass indexed to height and were excluded from analysis. The incidence of LVH on follow-up did not differ significantly (p = 0.1) between subgroups defined by increases in cardiac biomarkers (Fig. 2B).

Change in biomarkers and incident HF and CV-related death. The cumulative proportion without incident HF and CV-related mortality in each subgroup defined by changes in biomarkers is shown in Figures 3A and 3B, respectively. There was a graded association with respect to risk of endpoint based on the presence of 0, 1, or 2 biomarkers that became elevated by the second blood draw. Individuals with increases in both biomarkers were at a markedly greater risk of developing HF and CV mortality than those who had no significant increase in neither
biomarker (p < 0.001 for both outcomes). After 10 years, approximately one half (Hazard ratio [HR]: 50.4%; 95% CI: 40.4 to 61.4) of the participants with increases in both biomarkers had developed new-onset HF. More modest but significant increments in risk were observed among those with increases in NT-proBNP or cTnT only.

In Cox proportional hazards models, a strong association of change in both biomarkers and the risk of incident HF was observed, with a 329% greater risk among those with both biomarkers increased compared with those with no change in either biomarker, after adjusting for baseline concentrations (Table 2). Adjustment for demographics and HF risk factors attenuated this association only modestly (HR: 3.56; 95% CI: 2.56 to 4.97). Individuals with increases of cTnT or NT-proBNP only (p < 0.001) had a greater frequency of developing a depressed LVEF in a single cardiac-specific biomarker in older adults is associated with more baseline structural cardiac abnormalities, a greater frequency of developing a depressed LVEF in the interim between biomarker measures, and increased long-term risk for both new-onset HF and CV mortality. In prior analyses, we showed that the trajectory of change of biomarkers over the next 2 to 3 years is common and associated with more baseline structural cardiac abnormalities, a greater frequency of developing a depressed LVEF in the interim between biomarker measures, and increased long-term risk for both new-onset HF and CV mortality; this significant improvement was observed whether risk of HF and CV death was categorized using a priori cutpoints or considered on a continuous scale (the “category-less” NRI) (Table 4). The latter statistic indicates that a net 21% and 30% of patients were correctly reclassified with regard to risk of incident HF and CV mortality, respectively, by the measurement of change in biomarkers.

**Discussion**

Results from this study show that in community-dwelling older adults free of HF and with initial lower-risk levels of NT-proBNP and hs-cTnT, an increase in 1 or both biomarkers over the next 2 to 3 years is common and associated with more baseline structural cardiac abnormalities, a greater frequency of developing a depressed LVEF in the interim between biomarker measures, and increased long-term risk for both new-onset HF and CV mortality. In prior analyses, we showed that the trajectory of change of a single cardiac-specific biomarker in older adults is associated with a concordant change in CV risk (5,6). Other authors have reported that multiple biomarkers measured at a single timepoint improves CV prognostication in community-based cohorts (4,9,10). A recent study has also shown that the combination of brain natriuretic peptide

### Table 2
**Association of Change in Cardiac-Specific Biomarkers With the Risk of Incident HF**

<table>
<thead>
<tr>
<th>Event rate (per 100 person-yrs)</th>
<th>No Increase</th>
<th>Increased Only cTnT</th>
<th>Increased Only NT-proBNP</th>
<th>Increased Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.00 (reference)</td>
<td>1.66 (1.28-2.15)</td>
<td>1.71 (1.31-2.21)</td>
<td>4.29 (3.15-5.84)</td>
</tr>
<tr>
<td>Demographics + risk factors</td>
<td>1.00 (reference)</td>
<td>1.46 (1.12-1.90)</td>
<td>1.66 (1.27-2.17)</td>
<td>3.77 (2.75-5.16)</td>
</tr>
<tr>
<td>Demographics</td>
<td>1.00 (reference)</td>
<td>1.37 (1.04-1.80)</td>
<td>1.56 (1.18-2.08)</td>
<td>3.56 (2.56-4.97)</td>
</tr>
</tbody>
</table>

All models also adjusted for baseline concentrations of hs-cTnT and NT-proBNP. Demographics: age, gender, race (African-American vs. other). Risk factors: systolic blood pressure, smoking, heart rate, CHD (absent, prevalent at baseline, interim between baseline and follow-up), glucose, serum creatinine, serum albumin, and LVH by electrocardiogram (risk factors comprising the HealthABC model) (21). CI = confidence interval; cTnT = cardiac troponin T; NT-proBNP = N-terminal pro-brain natriuretic peptide.

### Table 3
**Association Change in Cardiac-Specific Biomarkers With the Risk of CV Mortality**

<table>
<thead>
<tr>
<th>Event rate (per 100 person-yrs)</th>
<th>No Increase</th>
<th>Increased Only cTnT</th>
<th>Increased Only NT-proBNP</th>
<th>Increased Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.00 (reference)</td>
<td>1.49 (1.11-2.00)</td>
<td>1.55 (1.16-2.08)</td>
<td>3.80 (2.72-5.32)</td>
</tr>
<tr>
<td>Demographics + risk factors</td>
<td>1.00 (reference)</td>
<td>1.29 (0.95-1.75)</td>
<td>1.49 (1.11-2.00)</td>
<td>3.22 (2.29-4.53)</td>
</tr>
<tr>
<td>Demographics</td>
<td>1.00 (reference)</td>
<td>1.16 (0.85-1.59)</td>
<td>1.37 (1.00-1.87)</td>
<td>2.98 (2.09-4.26)</td>
</tr>
</tbody>
</table>

All models also adjusted for baseline concentrations of hs-cTnT and NT-proBNP. Demographics: age, gender, race (African-American vs. other). Risk factors: systolic and diastolic blood pressure, diabetes, antihypertensive medication use, smoking, CHD (absent, prevalent at baseline, interim between baseline and follow-up), total and high-density lipoprotein cholesterol (risk factors comprising long-term Framingham risk prediction model) (22). Abbreviations as in Table 2.
and hs-cTnT concentrations was additive in predicting subclinical cardiac disease among primary prevention patients without overt CV disease (25).

The current results extend these previous findings in demonstrating the prognostic significance of longitudinal changes in multiple cardiac-specific markers in predicting CV morbidity and mortality independently of established risk factors. Also unique to this study, we provide evidence of a positive association between biomarker increase, and not only baseline structural cardiac pathology but also the development of LV pathology before the onset of symptoms. Although such structural changes could be identified in only a minority of participants with elevations of their biomarker levels over time, it does support the contention that both of these biomarkers represent pathophysiology of a preclinical HF phenotype and that the presence of both increasing neurohormonal activation and myocyte cell death represents an acceleration of a process that carries a very high risk of cumulating as clinical symptoms or death.

We and others (4,6) have shown that the correlation between baseline levels of cardiac markers of neurohormonal activation (as measured by NT-proBNP) and myocyte cell death (as measured by cardiac-specific troponin assays) is moderate. Although an increase in cardiac biomarkers over time is common in those with initially lower levels of both tests, the majority have an increase in only 1 of the 2 biomarkers, associated with an intermediate increased risk of new-onset HF compared with the majority without any increase, but a significantly lower risk than those with an increase in both biomarkers. This finding, also supported by an intermediate risk of developing a depressed LVEF, suggests that in older adults there are likely multiple pathophysologies that ultimately express themselves as a common clinical phenotype of HF, some of which represent mechanisms that predominate in cell death and others in cardiac neurohormonal activation. The heterogeneity of trajectory of biomarkers that ultimately lead to symptomatic HF in older adults should not be surprising given the heterogeneity of echocardiographic findings in those with HF with the near equal prevalence of HF with reduced or preserved LVEF in this population (26,27).

One hypothesis is that an upward trajectory of levels of hs-cTnT may represent a process of increased myocyte apoptosis with subsequent replacement with fibrosis and increased cardiac stiffness. Recent evidence from magnetic resonance imaging shows a relatively high (17%; 95% CI: 14% to 19%) prevalence of unrecognized myocardial infarctions in a cohort of older adults (28). Therefore, occult myocardial infarction could be 1 potential mechanism to account for increased hs-cTnT levels. Another hypothesis is that an upward trajectory of NT-proBNP levels may represent subtle increases in fluid and sodium retention from both cardiac and noncardiac mechanisms increasing a vulnerability to symptomatic HF. Inclusion of both an increasing hs-cTnT level and NT-proBNP level may identify those most likely to have a cardiac-specific mechanism for increasing fluid retention and potentially identify those still asymptomatic individuals to be targeted with a specific therapy, such as aldosterone antagonists, that might reduce cardiac fibrosis and fluid retention.

Study limitations. First, stored sera at both baseline and follow-up visits were unavailable for approximately one third of participants, because they had been consumed during prior ancillary studies. We have previously shown that those participants without available sera differed modestly from those with available sera in that they were more likely be female and African-American, and to have diabetes and hypertension (5,6). Therefore, differential missingness of biomarker measurements may have introduced bias. Second, although the long duration of follow-up is a strength of this study, changes in CV prevention and disease management (e.g., greater use of statins and angiotensin antagonists) have occurred from the time when participants were initially enrolled in the CHS, potentially affecting the generalizability of these results. Third, serial echocardiography (and especially LV mass measures) was not performed on all CHS participants. This smaller sample size, along with the limited reproducibility of quantitative echocardiography to measure LV mass (29), may have resulted in limited statistical power to detect serial changes in LV mass in association with changes in biomarker concentrations. Fourth, we found that the combined change in both biomarkers improved discrimination when quantified by the IDI statistic but not the C-statistic. However, the C-statistic is relatively insensitive in detecting important risk predictors (30,31), and the magnitude of the improvement in model discrimination as reflected in the IDI is greater than that previously reported for high-density lipoprotein cholesterol in predicting CHD events in the Framingham Offspring Study (23).

Conclusions

More than one third of older adults free of HF who may be initially classified as lower risk on the basis of lower baseline levels of the cardiac-specific markers NT-proBNP and hs-cTnT will have an increase in 1 or both of these markers over the next 2 to 3 years. This increase is indicative of an increased risk of developing both symptomatic HF and CV morbidity and mortality independently of established risk factors. Also unique to this study, we provide evidence that an upward trajectory of levels of hs-cTnT may be associated with an increased risk of developing a depressed LVEF, with a signifi cant improvement in model discrimination when quantified by the IDI statistic but not the C-statistic. However, the C-statistic is relatively insensitive in detecting important risk predictors (30,31), and the magnitude of the improvement in model discrimination as reflected in the IDI is greater than that previously reported for high-density lipoprotein cholesterol in predicting CHD events in the Framingham Offspring Study (23).
mortality independently of traditional risk factors. Change in concentrations of either or both of these biomarkers likely represents the presence of active and ongoing cardiac pathophysiology representing a preclinical HF phenotype that could provide a mechanism to differentiate, which patients with American College of Cardiology/American Heart Association stage A are most likely to move toward stages B and C and be targets for trials of disease-modifying therapies.

Reprint requests and correspondence: Dr. Stephen L. Seliger, Department of Medicine, University of Maryland, 22 South Greene Street, N3W143, Baltimore, Maryland 21201. E-mail: sseliger@medicine.umaryland.edu.

REFERENCES


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