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Premorbid levels of high-sensitivity cardiac troponin T and natriuretic peptide and prognosis after incident myocardial infarction

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Abstract

Background: High-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) at the time of myocardial infarction (MI) are strong predictors of prognosis. However, whether their pre-morbid (before MI occurrence) levels are associated with prognosis after incident MI is unknown.

Methods: In 1,054 participants from the Atherosclerosis Risk in Communities Study with incident MI, we evaluated premorbid levels of hs-cTnT and NT-proBNP measured on average 5.8 [IQI 3.0-11.5] years prior to incident MI, and their associations with subsequent composite and individual outcomes of all-cause mortality, cardiovascular mortality, recurrent MI, heart failure, and stroke.

Results: During a median follow-up of 3.0 years after MI, 801 participants developed the composite outcome. Both hs-cTnT and NT-proBNP were independently associated with the composite outcome after incident MI. Among individual outcomes, all-cause mortality, cardiovascular mortality, and heart failure showed significant associations with both cardiac markers. Overall, NT-proBNP demonstrated a more evident relationship than hs-cTnT. Indeed, the addition of premorbid NT-proBNP alone, but not hs-cTnT alone, to conventional predictors at incident MI significantly improved risk prediction of the composite outcome after incident MI (Δc-statistic 0.013 [95% CI 0.005-0.022] from 0.691 with conventional predictors).

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Declarations of interest: none

Conclusions: Premorbid levels of hs-cTnT and NT-proBNP assessed on average six years prior to incident MI were associated with adverse outcomes after incident MI. These results further highlight the importance of cardiac health at an earlier stage of life.

Keywords

high-sensitivity cardiac troponin T; natriuretic peptide; prognosis; myocardial infarction

INTRODUCTION

Cardiac troponin T (cTnT) and natriuretic peptides are useful to diagnose myocardial infarction (MI) and heart failure, respectively, since cTnT is released as a result of cardiomyocyte necrosis[1] and natriuretic peptides are released from cardiac myocyte in response to myocardial stretch and volume overload.[2] Furthermore, these cardiac markers predict the risk of adverse outcomes among patients with MI[3-23] and are indicated to guide treatment selection particularly at the acute stage.[24-26] This is reasonable since cTnT and natriuretic peptides at the acute stage would reflect severity of MI and cardiac overload. In addition, these cardiac biomarkers have been shown to also predict adverse outcomes among patients with stable coronary heart disease.[27-33]

Recently, these cardiac markers have been found to be elevated in some individuals without prevalent cardiovascular disease (CVD), particularly after a high-sensitive assay was developed for cTnT,[34, 35] and to be associated with incident CVD.[34-39] Although these cardiac markers are used for the risk stratification at the acute phase of MI,[24-26] whether premorbid (i.e., prior to MI) levels of these cardiac markers are related to prognosis after the development of MI is unknown. It is possible that individuals with lower premorbid levels of cardiac markers may handle the occurrence of MI better than those with higher levels due to greater cardiac reserve. If we confirm this hypothesis, that would further support the importance of premorbid cardiac conditions and maintaining cardiac health at an earlier stage of life although some individuals may unfortunately develop MI despite optimal cardiac health.

Therefore, we examined the associations of premorbid levels of high-sensitivity cTnT (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) with the risk of adverse outcomes after incident MI at later life in a prospective community-based cohort.

METHODS

Study population

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective cohort of 15,792 individuals aged 45 to 64 years at visit 1 (1987-1989) from four US communities (Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland). There have been five follow-up examinations in 1990 to 1992 (visit 2), 1993 to 1995 (visit 3), 1996 to 1998 (visit 4), 2011 to 2013 (visit 5), and 2016 to 2017 (visit 6). hs-cTnT and NT-proBNP were measured at visit 2, visit 4 and visit 5.

Although our primary interest was the associations of premorbid levels of hs-cTnT and NT-proBNP with subsequent risk of adverse outcomes after MI, to fully acknowledge their associations with continuum pathophysiology of MI, we also quantified the associations of hs-cTnT and NT-proBNP with incident MI in the entire study population at visit 2 as well. For that analysis, of 14,348 ARIC study participants at visit 2, we excluded participants who had a history of coronary heart disease, stroke or heart failure at baseline (n=1,543), who were neither whites nor blacks (n=41), the small number of black participants from the Minnesota and Washington County centers (n=42), who did not have information on hs-cTnT and NT-proBNP (n=833), leaving a sample of 11,889 participants.

For the primary analysis, of 11,889 ARIC participants, we identified 1,204 incident MI cases occurring after visit 2 through the end of 2015, adjudicated by the ARIC physician panel. Then, we excluded those who were missing the latest premorbid data prior to MI for hs-cTnT or NT-proBNP (n=8), who had coronary heart disease, stroke, or heart failure prior to the measurement of these two cardiac markers in ARIC (n=91), and who had missing information on covariates at the time of MI (n=51), resulting in 1,054 participants for this study. We used the latest premorbid data on hs-cTnT and NT-proBNP from either of visit 2, 4 or 5 for each MI case (Web Figure 1). An ethics committee at each site approved the study protocol, and study participants provided informed consent at each study visit.

Measurement of cardiac biomarkers

hs-cTnT was measured using a high-sensitive sandwich immunoassay method (Roche Elecsys T; Roche Diagnostic). Stored serum samples obtained at visit 2 were assayed for hs-cTnT using a Roche Elecsys 2010 Analyzer (Roche Diagnostics). Stored plasma samples obtained at visit 4 and visit 5 were assayed for hs-cTnT using a Cobas e411 analyzer (Roche Diagnostics, Indianapolis, Indiana). For NT-proBNP, stored serum samples obtained at visit 2 were measured using a sandwich immunoassay method (Roche Diagnostics) implemented on a Roche Elecys 2010 Analyzer. Stored plasma samples collected at visit 4 and visit 5 were analyzed using an electrochemiluminescent immunoassay on an automated Cobas e411 analyzer (Roche Diagnostics). The as is measurable limit of hs-TnT and NT-proBNP were 3 ng/L and 5 pg/mL, respectively. We assigned half the lower limit of each marker for participants with unmeasurable levels.

Covariates

We considered the nine predictors in the TIMI Risk Score for Secondary Prevention (TRS2°P),[40] a risk stratification tool for recent MI patients, as covariates. Specifically, TRS2°P includes the following factors at incident MI: age, smoking status (current vs. noncurrent), kidney dysfunction, and a history of heart failure, hypertension, diabetes, stroke, coronary artery bypass graft (CABG), or peripheral artery disease (PAD). Utilizing all data sources available in ARIC (data at visits, data from annual telephone calls during follow-up, and abstracted data from medical records at the time of the MI admission), we determined information on each predictor of TRS2°P. For each covariate in each participant, a data point closest to incident MI was used. Age was determined at the date of incident MI and modeled continuously. Smoking status was determined by data obtained within a year prior to incident MI. Information on smoking status, medical history (e.g., hypertension and

diabetes), and medication use (e.g., antihypertensive and antidiabetic medication uses) were collected at all study visits using standard questionnaires and were updated through the annual telephone contacts and abstracted data from medical records at MI admission, when appropriate. Blood pressure was measured three times by certified technicians using a sphygmomanometer, and the average of the last two measurements was recorded at study visits except for visit 4, at which blood pressure was measured twice, and the average recorded. Blood samples were also collected at all study visits. Serum glucose levels were measured by the modified hexokinase/glucose-6-phosphate dehydrogenase method, and serum creatinine concentration was measured using a modified kinetic Jaffe method. We defined hypertension as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medications. We defined diabetes as fasting glucose level ≥126 mg/dL, non-fasting glucose level ≥200 mg/dL, self-reported physician diagnosis of diabetes, or antidiabetic medication use. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation using serum creatinine measured within a year prior to incident MI.[41] Kidney dysfunction was defined as eGFR <60 ml/min/1.73m^2 or chronic kidney disease-related ICD-9 codes in hospitalization. Prior heart failure, CABG, and PAD were defined based on ICD-9 discharge and procedure codes in hospitalization. Prior stroke was defined as adjudicated definite or probable stroke cases. In addition to the TRS2°P predictors, sex and race-ARIC visit centers were also included as covariates.

Because participants with lower levels of cardiac markers prior to MI may have less severe incident Mis, we also adjusted for MI severity as a sensitivity analysis. We determined MI severity based on a modified score of the Predicting Risk of Death in Cardiac Disease Toll (PREDICT) that uses several clinical variables at incident MI (cardiogenic shock, history of MI, stroke, or angina, age, severity of electrocardiographic changes, congestive heart failure, and Charlson Comorbidity Index) for a maximum score of 21 points, with a higher score indicating higher severity.[42, 43]

Follow-up and outcomes

The outcomes of interest were composite and individual outcomes of all-cause mortality, cardiovascular mortality, recurrent MI, heart failure, and stroke after incident MI. Cardiovascular events and death in the ARIC Study were ascertained by contacting participants annually (semiannually since 2012), identifying hospitalizations and deaths during the previous year, and surveying discharge lists from local hospitals and death certificates from state vital statistics offices for potential cardiovascular events. Cardiovascular mortality was defined as death from coronary heart disease, heart failure, or stroke. Recurrent MI and incident stroke were defined as adjudicated definite and probable cases after incident MI. Incident heart failure after MI was defined as either a hospitalization or death with heart failure diagnosis based on ICD-9 code 428 or ICD-10 code I50 in any position. Participants were followed until administrative censoring on December 31, 2016, date of outcomes of interest including death, or loss to follow-up whichever came first.

Statistical analysis

Premorbid hs-cTnT was categorized into five categories (<3, 3-5, 6-8, 9-13, and ≥14 ng/L) according to thresholds in the previous literature.[34, 44] hs-cTnT ≥14 ng/L is considered

clinically elevated.[28] To fairly compare with hs-cTnT, premorbid NT-proBNP was categorized into five categories according to the same percentiles of hs-cTnT categories (<51.8, 51.8-86.8, 86.9-140.3, 140.4-249.2, and ≥249.3 pg/mL corresponding to 52nd, 74th, 88th and 96th percentiles in the entire study population; <35.3, 35.3-64.8, 64.9-119.6, 119.7-222.5, and ≥222.6 pg/mL corresponding to the 27th, 47th, 69th, and 85th percentiles in patients with MI)[44] Baseline characteristics were summarized according to the five categories of hs-cTnT and NT-proBNP as mean (standard deviation) or median [interquartile interval, IQI] for continuous variables and proportion for categorical variables.

We first examined the associations of hs-cTnT and NT-proBNP with incident MI in the entire study population (n=11,889). Cumulative incidence of MI was estimated across categories of hs-cTnT and NT-proBNP using the Kaplan-Meier method.

Then, among those who developed MI during follow-up (n=1,054), we estimated cumulative incidence of composite outcome after MI across categories of hs-cTnT and NT-proBNP using the Kaplan-Meier method. We examined two discrete risk periods: 1) within 30 days and 2) >30 days after MI. Subsequently, we quantified the association of categories of premorbid hs-cTnT and NT-proBNP with composite and individual adverse outcomes after incident MI using Cox proportional hazards models. We evaluated the impact of potential confounders: sex (female vs. male), race (black vs. white), calendar year of incident MI (≥2005 vs. <2005 [median]), elapsed time between cardiac markers measurement and incident MI, and individual predictors in TRS2°P, as noted above,[40] and each of the cardiac markers, as appropriate (i.e., adjusting for NT-proBNP for the analysis of hs-cTnT and vice versa). We also evaluated the continuous association of hs-cTnT and NT-proBNP with composite outcome using the restricted cubic splines. We selected 1.5 ng/L for hs-cTnT (unmeasurable level) and 18 pg/mL for NT-proBNP (a median value of the lowest category <35 pg/mL) as the reference. In addition, we assessed cross-categories of hs-cTnT and NT-proBNP. Because of small cell sizes, we created nine cross-categories (<6, 6-13, and ≥14 ng/L for hs-cTnT and <66.6, 66.6-222.5, and ≥222.6 pg/mL for NT-proBNP).

We conducted several sensitivity analyses to evaluate the robustness of our findings. First, we repeated our analyses in several subgroups to assess potential interactions by age at MI (≥75 vs. <75 years), sex (female vs. male), and race (black vs. white). Due to sparse data in some categories of cardiac markers within subgroups, we estimated hazard ratios (HRs) for a 2-fold increment of each cardiac marker in the subgroup analyses. Interactions were tested by a likelihood ratio test comparing models with and without product terms of interest. Second, we evaluated whether the adjustment for MI severity (represented by PREDICT score) altered results. Third, since those with higher levels of hs-cTnT and NT-proBNP were likely to develop MI earlier during follow-up than those with lower levels, leading to longer follow-up after MI to capture adverse outcomes, we restricted our analysis to 1, 3, or 5 years of follow-up after incident MI. Fourth, we evaluated sex-specific quintiles of hs-cTnT and NT-proBNP since the distribution of both cardiac markers may differ between men and women.[45, 46] Finally, we also quantified the associations of quintiles of premorbid NT-proBNP among MI patients with adverse outcomes.

To assess the incremental value of hs-cTnT and NT-proBNP levels for risk prediction of composite and individual outcomes of all-cause mortality, cardiovascular mortality, recurrent MI, heart failure and stroke after incident MI, the c-statistic was computed from two models incorporating demographic variables and predictors in TRS2°P at the time of MI (base model) with and without continuous hs-cTnT and NT-proBNP (both were log-transformed) based on 3-year predicted risk. All analyses were conducted with Stata, version 14.2 (StataCorp LP), and $P<0.05$ was considered statistically significant.

RESULTS

Cardiac markers and incident MI in the entire study population

In the entire study population, the mean age at baseline was 57 years, 57% were female, and 24% were blacks. Over a median follow-up of 23.4 years, there were 1,204 incident MI cases. A higher level of hs-cTnT was associated with higher risk of incident MI in a graded manner. In contrast, only the highest category of NT-proBNP had an elevated higher risk of incident MI compared with other lower categories (Web Figure 2).

Premorbid cardiac markers and adverse outcomes after incident MI

In 1,054 ARIC participants who developed incident MI during follow-up, mean age at MI was 71 years, 46% were female, and 26% were blacks. Most incident MI patients (~85%) did not have clinically elevated premorbid levels of hs-cTnT (≥14 ng/L) and NT-proBNP (≥222.6 pg/mL), with median elapsed time between cardiac biomarker evaluation and incident MI of 5.8 years (IQI 3.0-11.5 years [mean 5.5 years]). Individuals with higher premorbid hs-cTnT levels were more likely to be male, black, and have heart failure, hypertension, diabetes, PAD, or kidney dysfunction at the time of incident MI (Table 1). However, they were less likely to be current smokers. The proportion of individuals with MI who had a history of stroke showed an inverse U-shape pattern across hs-cTnT categories. In general, similar patterns were observed across NT-proBNP categories whereas there were no evident associations of NT-proBNP levels with proportion of blacks, diabetes, and current smoker. Also, those with higher NT-proBNP levels were more likely to be female and have PAD at the time of MI compared to lower NT-proBNP levels. Similar patterns were generally seen at the time of the premorbid biomarker values (Web Table 1).

Over a median follow-up of 3.0 (IQI, 0.04-9.4) years, 801 cases of MI developed the composite outcome (623 all-cause deaths including 242 due to cardiovascular disease, 214 cases for recurrent MI, 497 cases for heart failure, and 108 cases for stroke). When examining two discrete risk periods, those with higher levels of hs-cTnT and NT-proBNP were measured, on average, 6 years earlier had a higher risk of composite outcome within 30 days and >30 days after MI, compared to those with lower levels (Web Figure 3).

The associations generally consistent after adjusting for demographic variables, comorbidities at the time of MI and each other cardiac marker (Table 2). For hs-cTnT, the top two categories showed a significant hazard ratio (HR) for the composite outcome (1.53 [95% CI 1.20-1.94] for ≥14 ng/L and 1.27 [1.00-1.61] for 9-13 ng/L). In contrast, the top three categories of NT-proBNP demonstrated significant HRs in a graded fashion (1.93

[95% CI 1.52-2.45] for ≥222.6 pg/mL, 1.47 [1.17-1.86] for 119.7-222.5 pg/mL and 1.25 [1.01-1.55] for 64.9-119.6 pg/mL). A steeper risk gradient for NT-proBNP than hs-cTnT was confirmed when these cardiac markers were modeled using restricted cubic splines (Web Figure 4). When we accounted for MI severity, the associations remained significant (Web Table 2). We observed generally similar patterns after restricting follow-up time 1, 3, and 5 years after incident MI (Web Table 3). We also confirmed that quintiles of premorbid NT-proBNP were significantly associated with composite outcome (Web Table 4).

For individual outcomes, we found that both hs-cTnT and NT-proBNP were significantly associated with all-cause mortality, cardiovascular mortality, and heart failure after incident MI (Table 2). For these outcomes, the highest category of both cardiac markers showed significant associations. Overall, the results for NT-proBNP appeared more robust and evident compared to those for hs-cTnT (e.g., HR in the highest category of NT-proBNP and hs-cTnT was 2.66 (1.74-4.05) and 2.13 (1.34-3.38) for cardiovascular mortality and 2.15 (1.59-2.91) and 1.79 (1.29-2.48) for heart failure, respectively). Although the second highest category of NT-proBNP showed a significant HR for stroke, neither of hs-cTnT or NT-proBNP demonstrated a significant relationship with recurrent MI. Again, we observed similar associations after the additional adjustment for MI severity (Web Table 2). The restriction of follow-up time demonstrated similar patterns (Web Table 3). We also confirmed that quintiles of NT-proBNP showed similar patterns (Web Table 4).

For cross-categories of hs-cTnT and NT-proBNP, we confirmed that higher levels of hs-cTnT and NT-proBNP were independently associated with higher risk for the composite outcome after incident MI, without significant interaction (P for interaction=0.39) (Figure 1 **and** Web Table 5). With hs-cTnT <6 ng/L and NT-proBNP <64.8 pg/mL as a reference, the middle category of NT-proBNP 64.8-222.5 pg/mL conferred significantly elevated risk even when hs-cTnT was <6 ng/L. However, this was not the case for the middle category of hs-cTnT with NT-proBNP <64.8 pg/mL.

Both cardiac markers were significantly associated with the composite outcome in all subgroup tested (Figure 2). Although the association for hs-cTnT was not statistically significant in a few subgroups, NT-proBNP was significantly associated with the composite outcome in every subgroup. For individual outcomes, we observed consistent results across subgroups with an exception of a stronger association between NT-proBNP and heart failure in men and whites than their counterparts (Web Table 6). When sex-specific quintiles of cardiac markers were evaluated, we observed generally similar patterns in men and women (Web Table 7 **and** 8).

C-statistic for the composite outcome based on conventional risk factors at the time of the MI was 0.691 (95% CI 0.669-0.713) (Table 3). The addition of premorbid NT-proBNP improved risk prediction of the composite outcome (c-statistic differences of 0.013 [95% CI 0.005-0.021]), but the addition of hs-cTnT did not. For individual outcomes, c-statistics of all-cause mortality, cardiovascular mortality and heart failure were significantly improved when we added NT-proBNP (c-statistic differences of 0.010 [0.007-0.028] from 0.728 with conventional risk factors, 0.017 [0.001-0.033] from 0.729, 0.017 [0.007-0.028] from 0.723, respectively). The simultaneous addition of hs-cTnT and NT-proBNP significantly improved

c-statistic only for the composite outcome, all-cause mortality and heart failure (0.013 [95%CI 0.005-0.022], 0.011 [0.002-0.020], and 0.017 [0.006-0.028] respectively), but the improvement was not superior to the sole addition of NT-proBNP.

DISCUSSION

In this community-based cohort study, we found that higher premorbid levels of hs-cTnT and NT-proBNP, assessed on average six years prior to incident MI, were associated with adverse outcomes after incident MI. In terms of individual outcomes, all-cause mortality, cardiovascular mortality, and heart failure demonstrated particularly close relationships to both cardiac markers even at their mildly elevated levels. Robust results were observed even after accounting for severity of MI or restricting the follow-up to 1 to 5 years after incident MI. These associations were largely consistent across different demographic subgroups although a stronger association between NT-proBNP and heart failure was observed in men and in whites than their counterparts. Overall, the associations appeared to be more evident for NT-proBNP than hs-cTnT. Indeed, the addition of NT-proBNP alone, but not hs-cTnT alone, to conventional predictors significantly improved risk prediction of adverse outcomes after incident MI. When we added hs-cTnT and NT-proBNP simultaneously, the improvement was not superior to the sole addition of NT-proBNP.

A number of previous studies have described that these cardiac markers obtained during the first few days after the onset of MI[3-8, 10-23] or in stable patients with previous MI[9, 27-33] were associated with a worse prognosis after incident MI. However, to the best of our knowledge, our study is the first to evaluate premorbid levels of hs-cTnT and NT-proBNP, measured on average approximately 6 years prior to incident MI, and their association with adverse outcomes after incident MI. 90% of MI patients in the highest categories for both premorbid cardiac markers had adverse outcomes after incident MI. Of note, we observed worse prognosis even in the group of MI patients who had mildly evaluated premorbid levels of both cardiac markers.

There are several plausible mechanisms to explain these associations we observed for premorbid levels of cardiac markers with post-MI adverse outcomes. Premorbid levels of hs-cTnT and NT-proBNP in patients with MI may reflect comorbidities such as hypertension, diabetes, or kidney dysfunction,[47, 48] and thereby increasing risk of secondary outcomes. Also, it is possible that those with higher premorbid levels of cardiac markers may have more severe MI. Nonetheless, these associations remained significant after accounting for conventional risk factors as well as MI severity in our study. Both cardiac markers may reflect clinically unrecognized cardiac conditions (e.g., ischemia and altered left ventricular structure and function),[28, 29, 35, 47] and thus persons with higher premorbid hs-cTnT and NT-proBNP may have less cardiac reserve to overcome an episode of MI. Also, it is possible that these cardiac markers reflect systemic organ damage, leading to elevated risk of adverse outcomes in general. In fact, these cardiac markers have been associated with some non-cardiovascular conditions like lung function and infection.[49, 50]

In terms of individual cardiovascular outcomes after MI, premorbid cardiac markers were particularly associated with all-cause mortality, cardiovascular mortality, and heart failure.

The observation for NT-proBNP seems intuitive since NT-proBNP is a marker of heart failure, and heart failure is a lethal condition.[36-38] In contrast, the finding for hs-cTnT may require some discussion. Although hs-cTnT is clinically considered as a diagnostic marker of MI, mechanisms behind its elevation in persons without MI are not fully understood. Interestingly, the closer relationship of hs-cTnT to incident heart failure than incident MI has been seen in the general population without a history of CVD,[34-38] and higher levels of hs-cTnT are associated with structural changes in the heart especially increased left ventricular mass which is a risk for subsequent heart failure.[39] Although future studies are needed to understand why hs-cTnT and NT-proBNP may be elevated in some individuals without CVD, our findings show that premorbid levels of hs-cTnT and NT-proBNP as important markers for heart failure and mortality even after the development of MI.

The sex- and race-differences in the association between NT-proBNP and heart failure seem to deserve some discussion. Regarding the sex-difference, although the interaction was statistically significant, it is of note that higher levels of NT-proBNP were significantly associated with the risk of heart failure in both men and women. The race-difference may reflect the complex interplay among race, natriuretic peptide, and obesity. For example, an inverse relationship between obesity and natriuretic peptides is well-known, and blacks are more likely to be obese than whites in general.[51] Indeed, blacks are shown to have lower natriuretic peptide levels than whites.[52, 53] Also, some studies have shown that natriuretic peptides may be less prognostic in obese individuals than those with normal weight.[54] Nonetheless, we should keep in mind that our subgroup analysis was performed without a prespecified hypothesis and thus was hypothesis generating.

Overall, NT-proBNP showed more evident results than hs-cTnT in our study. We found that assessment of NT-proBNP in addition to conventional risk factors yielded modest incremental improvement in risk discrimination for adverse outcomes after MI, but not hs-cTnT alone. There may be a few reasons behind this observation. First of all, this may reflect the importance of heart failure as an outcome in individuals with incident MI[55] since NT-proBNP is a potent predictor of heart failure.[36-38] Indeed, NT-proBNP level reflects response to wall stress from volume or pressure overload.[2] Also, NT-proBNP may reflect cardiac conditions better than hs-cTnT particularly at premorbid stage. For example, there were ~30% of participants with hs-cTnT levels below the level of limit of detection (<3 ng/L) whereas 96.2% of our study population had measurable levels of NT-proBNP.

The improvements in c-statistics by adding NT-proBNP to prediction models were approximately 0.01-0.02, which might seem small. However, we should note that c-statistic is considered as a conservative statistic and this amount of improvement is shown for many novel predictors. For example, even cardiac markers at the time of MI demonstrated similar degree of improvement in c-statistic for secondary outcomes after MI in previous studies.[56-58]

There are several clinical and pathophysiological implications from our study. Although both cardiac markers are currently used as a prognostic marker in patients with MI, premorbid data of these cardiac markers are not readily available at this moment. However, this situation may be different in the future according to wide spread of electronic medical

record as well as some experts proposing to evaluate these cardiac markers for cardiovascular risk prediction for primary prevention. Premorbid cardiac conditions may contribute to prognosis not only in primary prevention setting but also secondary prevention setting. Thus, our finding further supports the continuum of cardiovascular cascade (the concept of sequence of pathophysiologic cardiovascular event).[59, 60] Our study suggests the importance of earlier prevention and management of cardiovascular risk in this continuum. For example, individuals with high premorbid levels of cardiac markers may benefit from more aggressive preventive therapies or preventive therapies with particular effects on heart failure risk such as beta blockers, thiazide diuretics, or renin-angiotensin system inhibitors when indicated (e.g., hypertension).[61-63]

Our study has several limitations. First, elapsed time from premorbid data to incident MI and follow-up time after incident MI varied across participants. Second, the elapsed time was on average approximately six years. Thus, the results may be different if premorbid levels could be measured more closely to MI occurrence. Third, the use of hospitalization and discharge codes for the diagnosis of incident heart failure may have resulted in some misclassification. However, the use of the heart failure cases in cohort studies has been associated with relatively high diagnostic specificity.[64] Fourth, levels of troponins and natriuretic peptides at MI occurrence were not systematically assessed in ARIC, and thus we could not fully explore whether premorbid levels of these cardiac markers provide additional information beyond their levels at MI occurrence. Finally, there is a possibility that residual confounding could bias our results.

In conclusion, premorbid levels of hs-cTnT and NT-proBNP measured on average approximately six years prior to incident MI were independently associated with adverse outcomes after incident MI, with more evident relations for NT-proBNP. Our findings suggest the importance of pre-MI cardiac condition among MI patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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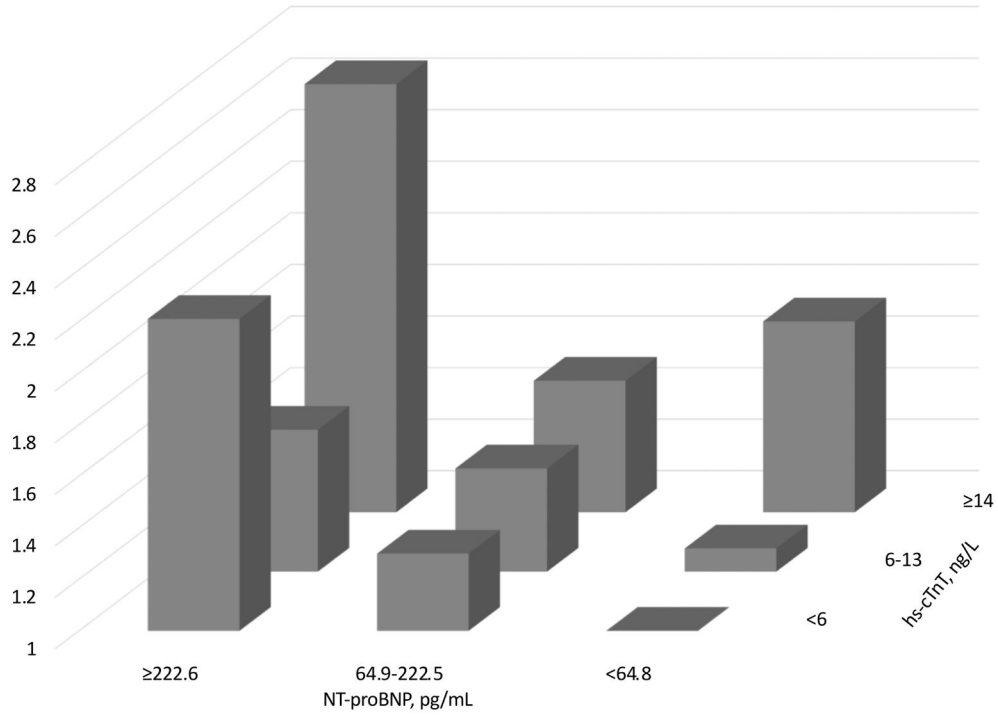

Figure 1.

Adjusted hazard ratios of composite outcome by combined hs-cTnT and NT-proBNP (P-for interaction=0.30). Adjusted for age at MI, female, race*field center, prior heart failure, hypertension, diabetes, prior stroke, coronary artery bypass graft, peripheral artery disease, chronic kidney disease, current smoking, and calendar year of MI (≥2005 vs. <2005), and elapsed time between premorbid biomarker measurements and incident MI.

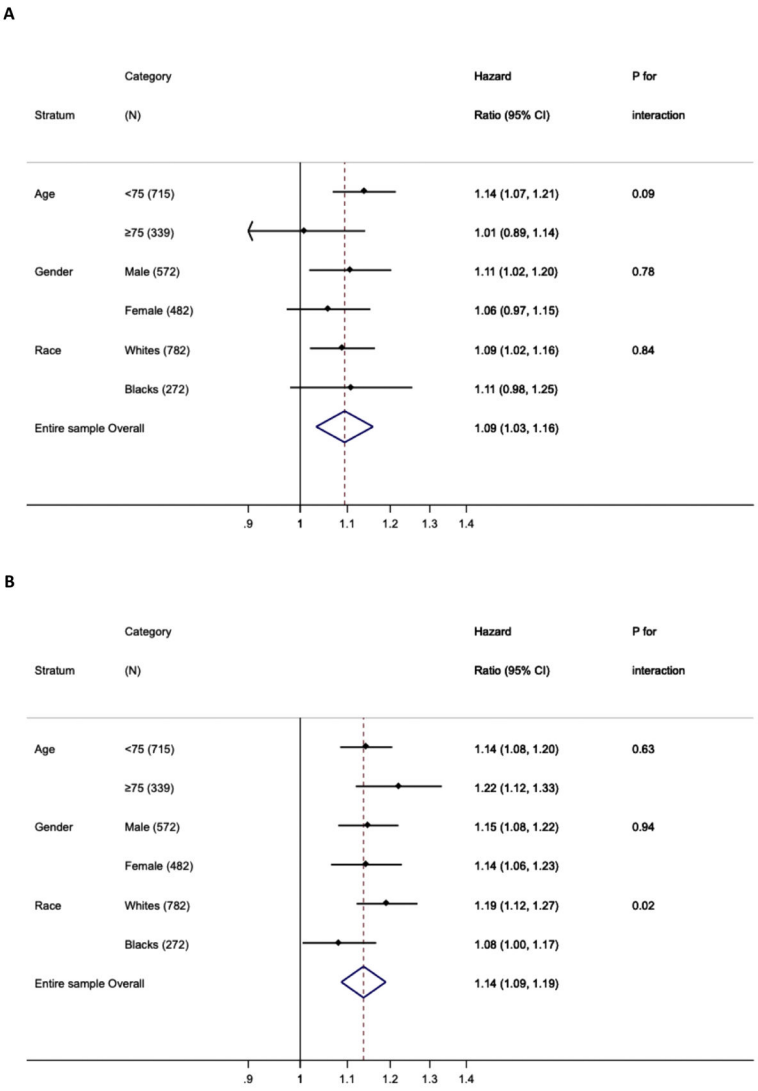

Figure 2.

Adjusted hazard ratios (95% CI)* of composite outcome for 2-fold increment of hs-cTnT (A) and NT-proBNP (B) in subgroups. Adjusted for age at MI, female, race*field center, prior heart failure, hypertension, diabetes, prior stroke, coronary artery bypass graft, peripheral artery disease, chronic kidney disease, current smoking, and calendar year of MI (≥2005 vs. <2005), elapsed time between premorbid biomarker measurements and incident MI and each of the cardiac markers, as appropriate (NT-proBNP was incorporated in the analyses for hs-cTnT and vice versa)

Table 1.

Baseline characteristics by hs-cTnT and NT-proBNP categories, N=1,054

	hs-cTnT, ng/L				
	<3	**3-5**	**6-8**	**9-13**	**≥14**
	N=287	N=211	N=228	N=175	N=153
Age at MI, years	67.3 (8.5)	69.7 (8.2)	72.6 (8.0)	73.3 (8.4)	72.0 (7.6)
Black	21.6%	22.3%	27.2%	27.4%	34.6%
Female	61.3%	52.6%	36.8%	36.0%	31.4%
Elapsed time from measurement to MI	7.4(5.3)	7.6(5.3)	8.0(5.5)	7.4(5.2)	5.7(4.6)
Prior heart failure	5.2%	6.6%	14.5%	14.9%	16.3%
Hypertension	70.7%	78.2%	85.5%	89.7%	91.5%
Diabetes	30.0%	36.5%	46.9%	45.1%	59.5%
Prior stroke	3.8%	2.8%	5.7%	3.4%	3.9%
CABG	1.7%	2.4%	5.7%	3.4%	3.3%
PAD	7.3%	6.2%	8.8%	10.3%	12.4%
Kidney dysfunction	8.0%	10.0%	15.4%	18.3%	28.8%
Current smoking	33.2%	17.4%	12.2%	11.9%	8.5%
PREDICT score *	6.4 (3.1)	7.6 (3.7)	7.8 (3.4)	8.3 (3.6)	8.5 (3.4)
hs-cTnT, ng/L	1.5 [1.5-1.5]	4.0 [4.0-5.0]	7.0 [6.0-8.0]	10.0 [9.0-12.0]	19.0 [16.0-28.0]
NT-proBNP, pg/mL	57.2 [28.7-102.9]	58.9 [27.3-129.8]	67.1 [31.4-140.1]	76.1 [36.5-146.1]	130.9 [54.9-283.9]
	NT-proBNP, pg/mL				
	<35.3	**35.3-64.8**	**64.9-119.6**	**119.7-222.5**	**≥222.6**
	N=286	N=212	N=228	N=174	N=154
Age at MI, years	67.8 (8.1)	69.5 (8.3)	71.6 (8.4)	72.9 (8.3)	73.1 (8.3)
Black	33.2%	23.6%	24.1%	20.1%	24.0%
Female	29.0%	42.9%	48.7%	57.5%	63.0%
Elapsed time from measurement to MI	7.7(5.4)	7.1(5.2)	7.6(5.2)	7.4(5.4)	6.6(5.2)
Prior heart failure	5.2%	9.0%	9.2%	16.1%	19.5%
Hypertension	78.0%	74.1%	81.1%	86.2%	94.2%
Diabetes	44.1%	40.6%	42.5%	37.4%	42.2%
Prior stroke	4.2%	3.8%	4.0%	3.5%	4.6%
CABG	2.5%	4.3%	3.1%	4.0%	2.6%
PAD	5.6%	6.6%	7.9%	10.9%	15.6%
Kidney dysfunction	11.9%	10.9%	11.4%	19.0%	25.3%
Current smoking	19.2%	21.7%	18.9%	19.0%	12.3%
PREDICT score *	6.7 (3.0)	7.2 (3.8)	7.4 (3.3)	8.4 (3.6)	9.0 (3.4)
hs-cTnT, ng/L	5.0 [1.5-8.0]	5.0 [1.5-9.0]	6.0 [1.5-10.0]	6.0 [3.0-9.0]	9.0 [5.0-16.0]
NT-proBNP, pg/mL	18.2 [10.5-26.4]	48.0 [40.7-56.4]	86.3 [75.5-102.3]	156.0 [133.8-181.0]	384.6 [275.4-643.9]

Values for continuous variables are given as mean (standard deviation) or median [interquartile interval]; values for categorical variables are given as percentage

Abbreviations: CABG, coronary artery bypass graft; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAD: peripheral artery disease

* Participants who have information on PREDICT score are 715.

Table 2.

Adjusted hazard ratios (95%CI)* of secondary adverse outcomes after MI for categories of hs-cTnT and NT-proBNP, N=1,054

hs-cTnT, ng/L	<3 (N=287)	3-5 (N=211)	6-8 (N=228)	9-13 (N=175)	≥14 (N=153)	P trend
Composite outcome						
Cases	207	160	167	135	132	
HR (95%CI)	Ref.	1.14 (0.93-1.41)	1.05 (0.84-1.31)	1.27 (1.00-1.61)	1.59 (1.23-2.05)	<0.01
All-cause mortality						
Cases	145	122	128	114	114	
HR (95%CI)	Ref.	1.17 (0.91-1.49)	1.13 (0.87-1.46)	1.51 (1.15-1.98)	1.95 (1.46-2.59)	<0.01
Cardiovascular mortality						
Cases	50	53	46	46	47	
HR (95%CI)	Ref.	1.49 (0.99-2.22)	1.14 (0.74-1.76)	1.78 (1.14-2.77)	2.13 (1.34-3.38)	<0.01
Recurrent MI						
Cases	63	43	36	34	38	
HR (95%CI)	Ref.	0.99 (0.67-1.48)	0.77 (0.49-1.20)	1.20 (0.75-1.90)	1.48 (0.92-2.39)	0.13
Heart failure						
Cases	106	105	107	89	90	
HR (95%CI)	Ref.	1.49 (1.13-1.96)	1.29 (0.96-1.73)	1.57 (1.15-2.14)	1.79 (1.29-2.48)	<0.01
Stroke						
Cases	31	17	27	16	17	
HR (95%CI)	Ref.	0.72 (0.39-1.31)	1.14 (0.65-2.01)	0.99 (0.51-1.91)	1.33 (0.67-2.62)	0.36
NT-proBNP, pg/mL	**<35.3 (N=286)**	**35.3-64.8 (N=212)**	**64.9-119.6 (N=228)**	**119.7-222.5 (N=174)**	**≥222.6 (N=154)**	
Composite outcome						
Cases	198	152	174	136	141	
HR (95%CI)	Ref.	1.14 (0.92-1.42)	1.25 (1.01-1.55)	1.47 (1.17-1.86)	1.93 (1.52-2.45)	<0.01
All-cause mortality						
Cases	143	117	139	108	116	
HR (95%CI)	Ref.	1.13 (0.88-1.45)	1.31 (1.02-1.66)	1.54 (1.17-2.01)	2.04 (1.55-2.68)	<0.01
Cardiovascular mortality						
Cases	54	40	57	38	53	
HR (95%CI)	Ref.	1.02 (0.67-1.54)	1.44 (0.98-2.12)	1.51 (0.96-2.35)	2.66 (1.74-4.05)	<0.01
Recurrent MI						
Cases	66	42	46	30	30	
HR (95%CI)	Ref.	0.93 (0.62-1.38)	1.07 (0.72-1.58)	1.07 (0.67-1.70)	1.19 (0.74-1.93)	0.43
Heart failure						
Cases	108	87	108	93	101	
HR (95%CI)	Ref.	1.15 (0.86-1.53)	1.35 (1.02-1.77)	1.69 (1.26-2.27)	2.15 (1.59-2.91)	<0.01
Stroke						
Cases	25	17	27	25	14	

HR (95%CI)	Ref.	0.93 (0.49-1.74)	1.44 (0.82-2.53)	2.10 (1.15-3.85)	1.38 (0.68-2.79)	0.05

HR: hazard ratio; CI: confidence interval

* Adjusted for age at MI, female, race*field center, prior heart failure, hypertension, diabetes, prior stroke, coronary artery bypass graft, peripheral artery disease, chronic kidney disease, current smoking, calendar year of MI (≥2005 vs. <2005), elapsed time between premorbid biomarker measurements and incident MI, and each of the cardiac markers, as appropriate (NT-proBNP was incorporated in the analyses for hs-cTnT and vice versa)

Table 3.

C-statistics (95% CI) with the addition of continuous hs-cTnT or NT-proBNP to basic model

	Base model	+ hs-cTnT	+ NT-proBNP	+ hs-cTnT and NT-proBNP
Composite outcome				
C statistics (95% CI)	0.691 (0.669, 0.713)	0.694 (0.672, 0.716)	0.704 (0.683, 0.726)	0.704 (0.683, 0.726)
Difference (95%CI)	-	0.003 (−0.002, 0.008)	0.013 (0.005, 0.021)	0.013 (0.005, 0.022)
All-cause mortality				
C statistics (95% CI)	0.728 (0.699, 0.757)	0.731 (0.702, 0.761)	0.738 (0.708, 0.767)	0.739 (0.709, 0.768)
Difference (95%CI)	-	0.003 (−0.004, 0.010)	0.010 (0.001, 0.018)	0.011 (0.002, 0.020)
Cardiovascular mortality				
C statistics (95% CI)	0.729 (0.685, 0.772)	0.729 (0.685, 0.773)	0.746 (0.702, 0.789)	0.744 (0.702, 0.789)
Difference (95%CI)	-	0.000 (−0.011, 0.011)	0.017 (0.001, 0.033)	0.015 (−0.001, 0.032)
Recurrent MI				
C statistics (95% CI)	0.671 (0.621, 0.721)	0.675 (0.624, 0.725)	0.672 (0.622, 0.722)	0.676 (0.625, 0.726)
Difference (95%CI)	-	0.004 (−0.007, 0.014)	0.001 (−0.005, 0.006)	0.004 (−0.007, 0.015)
Heart failure				
C statistics (95% CI)	0.706 (0.680, 0.733)	0.709 (0.683, 0.735)	0.723 (0.680, 0.749)	0.723 (0.698, 0.749)
Difference (95%CI)	-	0.003 (−0.004, 0.009)	0.017 (0.007, 0.028)	0.017 (0.006, 0.028)
Stroke				
C statistics (95% CI)	0.707 (0.643, 0.770)	0.706 (0.642, 0.769)	0.721 (0.659, 0.784)	0.722 (0.659, 0.785)
Difference (95%CI)	-	−0.001 (−0.004, 0.002)	0.015 (−0.004, 0.033)	0.015 (−0.003, 0.034)

Base model included age at MI, female, race*field center, prior heart failure, hypertension, diabetes, prior stroke, coronary artery bypass graft, peripheral artery disease, chronic kidney disease, current smoking, and calendar year of MI (≥2005 vs. <2005), and elapsed time between premorbid biomarker measurements and incident MI.