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Troponin T and N-Terminal Pro–B-Type Natriuretic Peptide: A Biomarker Approach to Predict Heart Failure Risk—The Atherosclerosis Risk in Communities Study

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BACKGROUND: Among the various cardiovascular diseases, heart failure (HF) is projected to have the largest increases in incidence over the coming decades; therefore, improving HF prediction is of significant value. We evaluated whether cardiac troponin T (cTnT) measured with a high-sensitivity assay and N-terminal pro–B-type natriuretic peptide (NT-proBNP), biomarkers strongly associated with incident HF, improve HF risk prediction in the Atherosclerosis Risk in Communities (ARIC) study.

METHODS: Using sex-specific models, we added cTnT and NT-proBNP to age and race ("laboratory report" model) and to the ARIC HF model (includes age, race, systolic blood pressure, antihypertensive medication use, current/former smoking, diabetes, body mass index, prevalent coronary heart disease, and heart rate) in 9868 participants without prevalent HF; area under the receiver operating characteristic curve (AUC), integrated discrimination improvement, net reclassification improvement (NRI), and model fit were described.

RESULTS: Over a mean follow-up of 10.4 years, 970 participants developed incident HF. Adding cTnT and NT-proBNP to the ARIC HF model significantly improved all statistical parameters (AUCs increased by 0.040 and 0.057; the continuous NRIs were 50.7% and 54.7% in women and men, respectively). Interestingly, the simpler laboratory report model was statistically no different than the ARIC HF model.

CONCLUSIONS: cTnT and NT-proBNP have significant value in HF risk prediction. A simple sex-specific model that includes age, race, cTnT, and NT-proBNP (which can be incorporated in a laboratory report) provides a good model, whereas adding cTnT and NT-proBNP to clinical characteristics results in an excellent HF prediction model.

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Over the next 20 years, the prevalence of heart failure (HF)[12] is projected to increase by 25% *(1, 2)*, the associated direct costs by 200%, and indirect costs (loss of productivity) by 80%. Although several effective evidence-based therapies have been developed to treat symptomatic HF, long-term prognosis remains poor. Hence, prevention and prediction of HF are receiving considerable attention. The American College of Cardiology/American Heart Association (ACC/AHA) *(3, 4)* proposed a simple new HF staging system (stages A–D) to increase early identification of individuals at risk, in which stages A and B were defined as having the risk factors (or milieu) to develop HF but without clinical symptoms. However, this system classified the majority of individuals >45 years of age as stage A or B *(5)*. Therefore, to improve risk prediction, clinical risk pre-

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[12] Nonstandard abbreviations: HF, heart failure; ACC, American College of Cardiology; AHA, American Heart Association; ARIC, Atherosclerosis Risk in Communities; cTnT, cardiac troponin T; NT-proBNP, N-terminal pro–B-type natriuretic peptide; CHD, coronary heart disease; ICD, International Classification of Diseases; AUC, area under the ROC curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement; eGFR, estimation of glomerular filtration rate.

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diction tools such as the Health ABC HF score *(6)*, the Framingham HF risk score *(7)*, and more recently, the Atherosclerosis Risk in Communities (ARIC) HF score *(8)* were developed.

Recently, low concentrations of circulating cardiac troponin T (cTnT), measured with a novel highly sensitive assay, were shown to be strongly associated with HF outcomes in community-based studies, including the ARIC study *(9–11)*. Similarly, concentrations of N-terminal pro–B-type natriuretic peptide (NT-proBNP), a biomarker of neurohormonal activation and hemodynamic stress, correlated with incident HF in adults without previously recognized cardiovascular disease *(12, 13)*. In a previous analysis *(9)*, we showed that both biomarkers were associated with coronary heart disease (CHD), mortality, and HF and that they seemed to improve HF risk prediction; however, in this previous analysis, our baseline prediction models to which the biomarkers were added were not validated/optimized to predict HF. Therefore, the extent to which cTnT and NT-proBNP improve HF risk prediction beyond clinically validated risk assessment tools remained uncertain. Since our prior analysis *(9)*, a clinical model to predict HF in the ARIC study has been described *(8)*.

Therefore, we performed the current analyses to examine (*a*) whether cTnT and NT-proBNP improve the ARIC HF risk prediction model *(8)*; (*b*) whether simple models incorporating only age, race, sex, cTnT, and NT-proBNP (laboratory report model) perform as well as the ARIC HF model (clinical model); and (*c*) whether specific cTnT and NT-proBNP cutpoints can be identified to help improve prediction of HF risk.

Methods

STUDY POPULATION

As described previously *(14)* and in the Supplemental Data in the Data Supplement that accompanies the online version of this report at http://www.clinchem.org/content/vol59/issue12, the ARIC study is a prospective, predominantly biracial study of cardiovascular disease and its predictors in middle-aged individuals (n = 15 792) recruited from 4 US communities in 1987–1989.The study was approved by the institutional review boards of the 4 participating centers. For the current analysis, we used the fourth ARIC visit (1996–1998) as the baseline (cTnT and NT-proBNP were measured using stored blood samples collected during this visit).

STUDY POPULATION

From the 11 656 individuals attending the fourth ARIC visit, we excluded individuals whose race was neither black nor white (n = 31), black participants from the Washington County, MD, or Minneapolis centers (n = 38), and participants with prevalent HF at visit 1 (n = 410), missing HF status at visit 1 (n = 199), HF hospitalization between visits 1 and 4 (n = 229), missing covariates for the ARIC HF model (n = 355), or not having given full consent (n = 249). Of these eligible individuals, 268 did not have adequate sample to perform both cTnT and NT-proBNP, and additionally 1 and 8 participants did not have adequate samples to perform cTnT alone or NT-proBNP alone, which left 9868 individuals eligible for the current analysis.

ASSAYS

cTnT was measured using a highly sensitive assay (lot number 154102, Elecsys troponin T; Roche Diagnostics) on a Cobas e411 automated analyzer. The lower and upper limits of measurement of the cTnT assay are 3 and 10 000 ng/L, respectively, and the limit of quantification (the lowest analyte concentration that can be reproducibly measured with an intermediate-precision CV of <10%) is 13 ng/L. NT-proBNP was also measured on the automated Cobas e411 analyzer (Roche Diagnostics) using an electrochemiluminescent immunoassay with a measurement range of 5–35 000 pg/mL and a limit of quantification of 35 pg/mL. The variability in cTnT and NT-proBNP concentrations related to freeze–thaw cycles and frozen storage has been described previously *(15, 16)*. The reliability coefficient and interassay CV for both cTnT and NT-proBNP are presented in the online Data Supplement.

INCIDENT HF

The definitions and methods for identifying incident HF in the ARIC study have been described previously *(8)*. Briefly, hospital discharge records with an International Classification of Diseases (ICD)-9 code of 428.x in any position or death certificates with an ICD-9 code of 428.x or ICD-10 code of I50 were considered incident HF. Further information about tracking events in ARIC is provided in the online Data Supplement.

STATISTICAL ANALYSES

We evaluated cTnT concentrations in 6 categories (undetectable, 3–5 ng/L, 6–8 ng/L, 9–13 ng/L, 14–25 ng/L, ≥26 ng/L; additional details in the online Data Supplement). For NT-proBNP, we used the logarithm of NT-proBNP, after Winsorizing 6 large values by setting them to 5000 pg/mL. For individuals with cTnT and NT-proBNP below the lower limits of detection, we assigned a value equal to half of the lower limits of detection. Before finalizing our risk prediction models, we tested for interactions between cTnT, NT-proBNP, and the variables used in the risk prediction models and found interactions with sex and other risk factors. cTnT effects were stronger for younger individuals and for

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women, whereas NT-proBNP effects were stronger for men. When sex-specific models were used, the interactions with other variables in the risk prediction models were no longer statistically significant. We therefore performed and present sex-specific analyses. We initially described individuals with "stage A/B" HF risk (defined as the presence of any of the following: hypertension, diabetes, obesity, metabolic syndrome, and prevalent atherosclerotic cardiovascular disease) and individuals with no risk factors (referred to as stage 0 from here on for simplicity). We then described the cTnT and NT-proBNP distribution by HF stage and incident HF status.

Using Cox proportional hazards models, we described hazard ratios for the associations of cTnT and NT-proBNP with incident HF. Model 1 adjusted for age and race and included either cTnT or NT-proBNP (i.e., when evaluating the hazard ratios of cTnT, NT-proBNP was adjusted for and vice versa); model 2 adjusted for all components of model 1 and additionally included systolic blood pressure, antihypertensive medication use, current/former smoking, diabetes, body mass index, prevalent CHD, and heart rate (i.e., other factors used in the ARIC HF risk score).

For HF risk prediction, we also described 4 additional models. The "laboratory report model" added cTnT and NT-proBNP to age and race, and the other models added cTnT and NT-proBNP individually and together to the ARIC HF model.

Comparisons of the ability of these models to improve HF risk prediction were tested by using statistical measures of discrimination and calibration at 10 years of follow-up, including improvements in the area under the ROC curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI) *(17)*, all calculated with methods that accounted for censoring *(18, 19)*. We also performed a test of model fit using the Grønnesby–Borgan test statistic *(20)*, in which higher values of the test statistic and significant *P* values are associated with poor model fit. In describing the NRI, because there are no previously described HF risk categories, we used risk categories used in CHD risk prediction, namely, 0%–5%, 5%–10%, 10%–20%, and >20% 10-year risk. We also calculated the "continuous NRI" as recently described *(21)*. We performed 1000 bootstraps to adjust for the overoptimism that can occur *(22)* when model fit is tested in the same data in which models are described and to furnish 95% CIs.

We then described the 10-year risk of HF for the various models by deciles of estimated risk and the estimated percentage of HF events occurring within each decile. Finally, we tried to identify potential cTnT and NT-proBNP cutpoints by defining both an unweighted and weighted Youden's index *(23)*. The unweighted Youden's index was defined as (sensitivity + specificity) − 1, and the weighted Youden's index was described by giving higher importance either to sensitivity [2 × (0.75 × sensitivity + 0.25 × specificity) − 1] or specificity [2 × (0.25 × sensitivity + 0.75 × specificity) − 1] to evaluate potential cutpoints to rule out and rule in incident HF occurrence.

Results

The mean age of the study population at ARIC visit 4 was 62.7 years; 44% were males and 80% were white (Table 1). In all, 46% were hypertensive, 16% had diabetes, and 7% (n = 701) had prevalent CHD. cTnT and NT-proBNP were detectable in 6677 and 9563 participants, respectively, with 93 and 98 participants, respectively, having values greater than the 99th percentile (as defined in the ARIC population). The 99th percentile for cTnT published by the manufacturer (14 ng/L) corresponds to approximately the 92nd percentile in our analysis. Over a mean follow-up of 10.4 years, there were 970 hospitalizations or deaths with HF (195 in individuals with CHD at baseline). Overall, 74% of the participants (n = 7278) had at least 1 risk factor which qualified as stage A HF (diabetes, hypertension, obesity, metabolic syndrome, or prevalent cardiovascular disease) and 26% (n = 2590) had none of these risk factors (i.e., stage 0). Individuals with stage 0 and stage A HF who developed incident HF had higher cTnT and NT-proBNP concentrations (see online Supplemental Tables 1A and 1B) than those who did not develop HF. After adjusting for age and race, we estimated that 3.0% and 8.9% of women and 3.5% and 12.7% of men in stages 0 and A, respectively, will develop HF within 10 years.

In evaluating the hazards for incident HF, any detectable concentration of cTnT in men and cTnT concentrations >5 ng/L in women were associated with incident HF in a minimally adjusted model and in a model adjusted for variables used in the ARIC HF score and NT-proBNP (see online Supplemental Table 2). Overall, the hazards for incident HF increased with increasing cTnT concentrations, with hazard ratios (in models adjusted for the ARIC HF score + NT-proBNP) of 4.3 (95% CI, 2.6–7.1) in men and 5.3 (95% CI, 3.3–8.4) in women for cTnT values >25 ng/L (see online Supplemental Table 2). Similarly, NT-proBNP concentrations were associated positively with incident HF in both men and women for both the minimally adjusted model and the fully adjusted ARIC HF + cTnT models (see online Supplemental Table 3).

HF RISK PREDICTION

Several models for HF risk prediction were compared (Tables 2 and 3). The model that added cTnT and NT-proBNP to the ARIC HF model was the best model (in terms of the statistical metrics) for predicting HF risk.

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Table 1. Baseline characteristics: ARIC study visit 4 (n = 9868).[a]

Demographics	
Age, years	62.7 (5.65)
White race, %	79.5
Male sex, %	44.3
Body mass index, kg/m^2	28.6 (5.44)
Medical history	
Hypertension, %	45.7
Diabetes mellitus, %	15.6
Systolic blood pressure, mmHg	127.3 (18.91)
Diastolic blood pressure, mmHg	71.0 (10.24)
Current smoking, %	14.7
Former smoking, %	43.4
Laboratory data	
Total cholesterol, mg/dL[b]	201.4 (36.91)
HDL-C, mg/dL[b,c]	50.2 (16.54)
Triglycerides, mg/dL[b]	142.9 (86.97)
eGFR, mL · min^{-1} · (1.73 m^2)$^{-1}$	82.3 (18.96)
hs-CRP, mean [median] (SD), mg/L	4.3 [2.4] (6.44)
NT-proBNP, mean [median] (SD), pg/mL[d]	122.1 [66.7] (259.36)
cTnT, mean [median] (SD), ng/L[d]	6.5 [5.0] (17.0)
Medications	
Aspirin, %[e]	56.1
Antihypertensives, %	34.3
Statins, %[e]	10.9
Nonstatin lipid-lowering drugs, %	3.0
Other parameters	
Left ventricular hypertrophy by electrocardiogram, %[f]	3.0

[a] Data reported as unadjusted mean (SD) unless otherwise specified.
[b] To convert cholesterol values to mmol/L divide by 38.6 and to convert triglyceride values to mmol/L divide the triglyceride value by 88.5.
[c] HDL-C, HDL cholesterol; hs-CRP, high-sensitivity C-reactive protein.
[d] Persons with concentrations below detectable limits were assigned values that were half the lower limits of detection.
[e] Information available in 9848 participants.
[f] Information available in 9864 participants.

Adding cTnT and NT-proBNP to the ARIC HF model increased the AUC from 0.779 to 0.836 in men and from 0.776 to 0.817 in women (Table 3). In all, 38% of men and 32% of women were reclassified through the addition of cTnT and NT-proBNP to the ARIC HF model, with a resulting NRI of 19.6% in men and 19.9% in women (Table 2). Given that risk categories for HF prediction do not exist and that we created these risk categories based on CHD risk categories, we also described the continuous NRI, which was 54.7% for men and 50.7% for women. Addition of cTnT to a model that included the ARIC HF model + NT-proBNP improved risk prediction, as did adding NT-proBNP to a model that included ARIC HF model + cTnT (Table 2).

Given past difficulties in the implementation of risk scores in clinical practice, we evaluated how a simplified approach (more likely to be used in clinical practice) to HF risk prediction would compare. Overall, the laboratory report model was comparable to the ARIC HF model (Tables 2 and 3) ,with no statistically significant differences in AUC, NRI, or IDI. The β coefficients, "baseline" values of the exposure variables, and "baseline" survival probabilities to apply the proportional hazards assumption to calculate t-year risks are provided in online Supplemental Table 4.

For all the models (ARIC HF, laboratory report, and ARIC HF + cTnT +NT-proBNP), in men and women (Figs. 1 and 2) the majority of incident HF events occurred in individuals in the highest 2 deciles of estimated risk. Fig. 1 describes how many of 100 HF events occur by each decile of predicted risk over a 10-year period. For example, in men, approximately 40 events (out of 100) occur in the highest decile of risk. Fig. 2 on the other hand describes the number of individuals in each decile of risk who will have incident HF in 10 years. For example, in women, out of every 100 persons whose predicted risk is in the highest decile, 30%–35% (depending on the model) will have an HF event within 10 years. Online Supplemental Table 5 provides the cutpoints for the various deciles of risk, which can allow the identification and definition of risk categories (low, intermediate, and high) if needed.

We next investigated cutpoints and described the Youden's index (both unweighted and weighted). Because of the continuous, rather monotonic association of cTnT and NT-proBNP with HF events (Fig. 3), no clear cutpoints emerged (see online Supplemental Table 6). The negative predictive values were, however, uniformly high.

Discussion

Among cardiovascular diseases, HF is projected to have the largest increases in incidence over the coming decades *(1)*. HF prevention has therefore gained importance. Applying the ACC and AHA HF classifications *(3, 4)* in a random population of individuals ≥45 years of age identified 56% to be at stages A and B [i.e., with risk factors or asymptomatic left ventricular dysfunction but without manifest symptoms of HF *(5)*]. Similarly, in our current analysis of middle-aged to older adults, 74% had at least 1 risk factor used to identify HF stage A. Approximately 10% of our entire cohort, initially free of HF, developed incident HF over a mean

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Table 2. Model comparisons with differences in AUC, NRI, and IDI.[a]

Model comparisons	AUC difference, 95% CI	IDI	NRI, %	Continuous NRI, %	% Reclassified
Men					
ARIC HF model vs ARIC HF + biomarker model	0.057 (0.044 to 0.073)	0.101 (0.079 to 0.132)	19.6 (12.4 to 28.3)	54.7 (42.8 to 67.6)	37.9
ARIC HF model vs lab model	0.010 (−0.015 to 0.032)	0.029 (−0.007 to 0.063)	−3.7 (−14.6 to 8.0)	2.1 (−18.1 to 18.9)	56.4
Lab model vs ARIC HF + biomarker model	0.047 (0.036 to 0.063)	0.073 (0.057 to 0.098)	24.5 (15.9 to 32.6)	53.9 (47.4 to 70.8)	40.4
ARIC HF model + cTnT vs ARIC HF model + cTnT + NT-proBNP	0.025 (0.016 to 0.035)	0.049 (0.032 to 0.071)	7.5 (2.1 to 15.0)	41.5 (29.9 to 55.7)	27.3
ARIC HF model + NT-proBNP vs ARIC HF model + cTnT + NT-proBNP	0.014 (0.008 to 0.023)	0.031 (0.018 to 0.048)	8.29 (0.1 to 11.9)	23.1 (4.2 to 41.9)	20.0
Women					
ARIC HF model vs ARIC HF + biomarker model	0.040 (0.030 to 0.055)	0.078 (0.060 to 0.104)	19.9 (12.0 to 28.3)	50.7 (38.8 to 62.3)	31.5
ARIC HF model vs lab model	−0.009 (−0.034 to 0.012)	0.023 (−0.009 to 0.052)	−4.9 (−16.4 to 6.3)	−8.1 (−27.6 to 6.3)	48.9
Lab model vs ARIC HF + biomarker model	0.050 (0.038 to 0.068)	0.055 (0.042 to 0.080)	27.5 (19.2 to 36.2)	66.1 (55.3 to 78.0)	36.7
ARIC HF model + cTnT vs ARIC HF model + cTnT + NT-proBNP	0.012 (0.006 to 0.022)	0.027 (0.015 to 0.042)	7.3 (1.5 to 14.0)	24.5 (15.8 to 39.4)	20.9
ARIC HF model + NT-proBNP vs ARIC HF model + cTnT + NT-proBNP	0.012 (0.005 to 0.022)	0.030 (0.016 to 0.047)	7.3 (0.1 to 13.6)	39.7 (16.3 to 60.0)	21.6

[a] 95% CI was generated using 1000 bootstraps. ARIC HF model includes age, race, systolic blood pressure, antihypertensive medication use, current/former smoking, diabetes, body mass index, prevalent CHD, and heart rate. Biomarkers refer to cTnT and NT-proBNP. Lab model includes age, race, cTnT, and NT-proBNP.

follow-up of 10.4 years. If the great majority of asymptomatic individuals are classified as "at risk" and only a minority develop incident HF, clearly additional risk stratification is needed to identify individuals at higher risk and direct preventive therapies to these individuals. Several HF risk prediction scores have been developed in the last decade, including ones from Health ABC *(6)*, the Framingham Heart Study *(7)*, and more recently, the ARIC study *(8)*. Our current work expanded on the ARIC model and found that adding cTnT measured with a highly sensitive assay and NT-proBNP significantly improved HF risk prediction.

Although our prior work *(9)* suggested that cTnT and NT-proBNP likely improve HF prediction, our current work studied the value of cTnT and NT-proBNP in detail and demonstrated that these biomarkers, individually and together, added significantly to the ARIC HF prediction model *(8)*. We also evaluated a simpler, perhaps more clinically usable laboratory report model, which included age, race, cTnT, and NT-proBNP. Interestingly, the laboratory report model was largely comparable to the ARIC HF model. However, adding both cTnT and NT-proBNP to the ARIC HF model resulted in the best statistical HF risk prediction model.

Although our recommendation and desire is the use of the best available risk prediction score (in our analysis the ARIC HF score + cTnT + NT-proBNP),

Table 3. AUC and the goodness-of-fit test statistic.[a]

	AUC		Goodness of model fit: Grønnesby–Borgan test statistic	
	Men	Women	Men	Women
Model 1	0.653 (0.628–0.676)	0.658 (0.634–0.682)	9.33 ($P = 0.41$)	18.32 ($P = 0.03$)
Model 2 (ARIC HF model)	0.779 (0.763–0.800)	0.776 (0.760–0.797)	18.12 ($P = 0.03$)	21.91 ($P = 0.01$)
Model 3 (lab model)	0.789 (0.767–0.812)	0.767 (0.745–0.789)	14.35 ($P = 0.11$)	5.80 ($P = 0.76$)
Model 4 (ARIC HF + biomarkers model)	0.836 (0.821–0.857)	0.817 (0.803–0.837)	14.60 ($P = 0.10$)	18.31 ($P = 0.03$)
Model 2 + cTnT	0.811 (0.797–0.833)	0.804 (0.790–0.825)	15.95 ($P = 0.07$)	20.39 ($P = 0.02$)
Model 2 + NT-proBNP	0.822 (0.805–0.843)	0.804 (0.789–0.826)	7.96 ($P = 0.54$)	19.64 ($P = 0.02$)

[a] Model 1, age + race; model 2, ARIC HF model; model 3, model 1+ cTnT + NT-proBNP (lab model); model 4, model 2 + cTnT + NT-proBNP (ARIC HF + biomarkers model). 95% CI was generated using 1000 bootstraps. ARIC HF model includes age, race, systolic blood pressure, antihypertensive medication use, current/former smoking, diabetes, body mass index, prevalent CHD, and heart rate. Biomarkers refer to cTnT and NT-proBNP. Lab model includes age, race, cTnT, and NT-proBNP.

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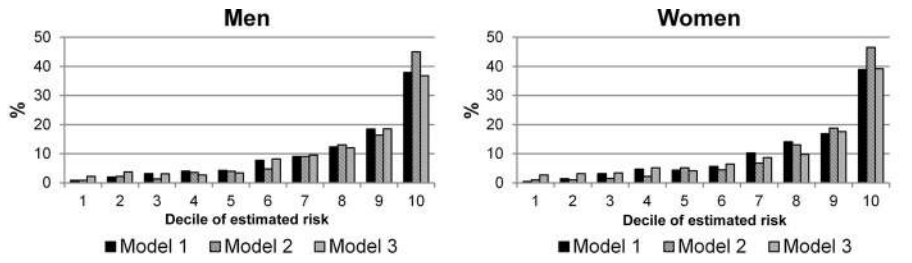


Models:

Model 1: age, race, systolic blood pressure (SBP), antihypertensive medication use, current smoking, former smoking, diabetes, body mass index (BMI), prevalent coronary heart disease (CHD), heart rate (ARIC HF model)

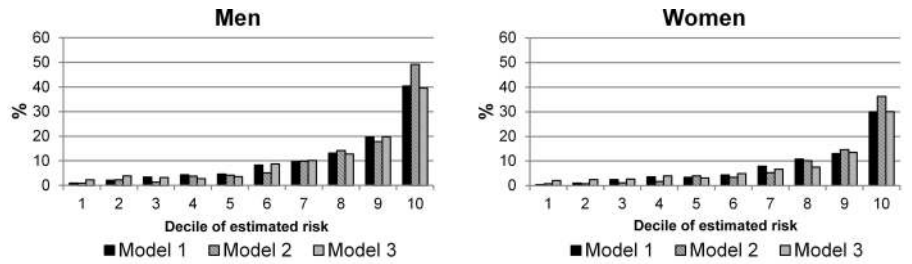
Model 2: Model 1 + cTnT + NT-proBNP (ARIC HF + biomarker model)

Model 3: age, race, cTnT + NT-proBNP (lab report model)

Note: Troponin modeled as 6 categories and log(NT-proBNP) were used.

Fig. 1. Distribution (%) of HF events within 10 years over deciles of estimated risk.
In this figure, we describe, in men and women, how many of 100 HF events occur by each decile of predicted risk over a 10-year period.

we recognize that adoption of clinical risk scores in practice has been poor. For example, only 50% of physicians who provided primary care incorporated in their practices the National Cholesterol Education Program Adult Treatment Panel III guidelines, Joint National Committee on the Prevention, Detection, and Treatment of High Blood Pressure 7 guidelines, or AHA Evidence-Based Guidelines for Women*(24)*. European studies have revealed even less use of risk scores *(25, 26)*. An important barrier reported in clinical implementation of guidelines was lack of time *(24)*. Although the advent of electronic medical records may



Models:

Model 1: age, race, systolic blood pressure (SBP), antihypertensive medication use, current smoking, former smoking, diabetes, body mass index (BMI), prevalent coronary heart disease (CHD), heart rate (ARIC HF model)

Model 2: Model 1 + cTnT + NT-proBNP (ARIC HF + biomarker model)

Model 3: age, race, cTnT + NT-proBNP (lab report model)

Note: Troponin modeled as 6 categories and log(NT-proBNP) were used.

Fig. 2. Ten-year risk of HF by decile of estimated risk.
In this figure, we describe, in men and women, the number of individuals in each decile of risk who will have incident HF in 10 years.

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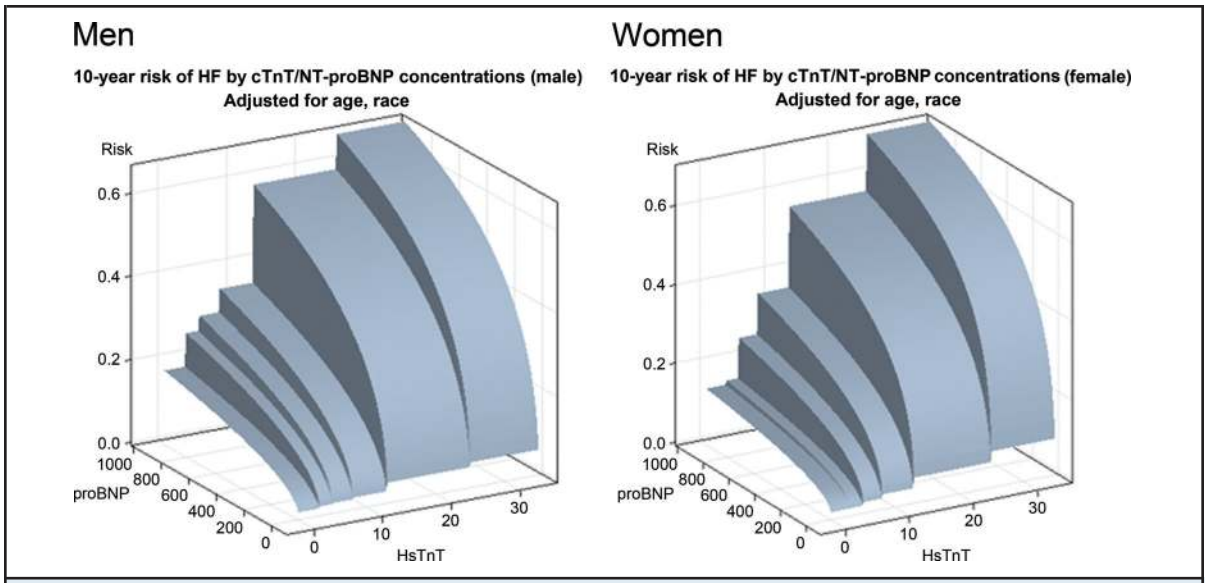

Fig. 3. Ten-year risk of HF by cTnT/NT-proBNP concentrations in men and women.
In this figure, we present the 10-year risk of HF (adjusted for age and race) by both cTnT and NT-proBNP concentrations.

help reduce this barrier (for example, risk estimation could be programmed and automatically calculated), simplified approaches, such as our laboratory report model, may also warrant consideration. Providing actuarial risk estimates for HF on the basis of our laboratory report model would be simple and could be implemented automatically on a laboratory report, as is currently done in most institutions for estimated glomerular filtration rate (eGFR). When eGFR (along with various cutpoints) reporting was required with each measurement of serum creatinine, several reports suggested a beneficial/positive impact in clinical practice *(27, 28)*. In primary care, prescriptions of nonsteroidal antiinflammatory drugs and metformin in patients with chronic renal disease were reduced and eGFR increased over time *(27)*. Although the same level of improvement could not be maintained in a follow-up study *(29)*, these studies suggest the potential value of laboratory reporting in bringing risk to the attention of clinicians and patients.

We were unable to identify distinct cutpoints using Youden's index owing to the rather monotonic association between the biomarkers and incident HF. However, a laboratory-based report of risk, factoring in basic information available to the laboratory (i.e., age, race, and sex) and the biomarker values (i.e., the laboratory report model) could be a good starting point for clinicians to evaluate a patient's HF risk. Furthermore, availability of a risk score in a laboratory report (to which the patient can have easy access) may empower the patient to discuss this further with their physician.

Improved risk prediction does not necessarily translate into improved disease prevention. In fact, a relative paucity of studies that have reported on the use of risk prediction algorithms in clinical practice demonstrated improvement in cardiovascular disease outcomes, although preventive strategies such as statins have had a major impact in reducing the incidence of cardiovascular disease. Furthermore, primordial prevention (i.e., preventing the development of risk factors) is clearly associated with marked decreases in the incidence of various cardiovascular diseases, including HF *(30)* and should be the overall focus. However, it is also important to note that currently very few individuals in the US population (0.1%) *(31)* have "ideal" cardiovascular health as identified by the AHA *(32)*, and therefore the general population is likely to have an increasing risk for HF in the years to come. Therapies to prevent the onset of HF must therefore be identified and developed. Good risk prediction tools will help us to identify the highest-risk individuals, who would be expected to have the largest benefit from preventive therapies; additionally, accurate quantitative estimation of HF risk may also help with selection of clinical trial cohorts. For example, based on our models of risk prediction, 10% of the population (i.e., top decile of risk) had an annual HF incidence of 3%–4% (Fig. 1), which may allow for the effective and efficient design of clinical trials targeting HF prevention. Finally, although cost–benefit analysis is an important aspect of any additional risk prediction test, it is beyond the scope of our analysis. However, identifying individuals

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at higher risk on the basis of a laboratory test or risk score may alleviate the challenges faced by practicing physicians in selecting individuals with risk factors for HF (such as diabetes or hypertension) who may benefit from further testing with cardiovascular imaging tests such as echocardiograms. Individuals in stage A/B HF form a majority of the middle-aged and older population (approximately 74% in our study), and imaging all of them is not practical. However, a selective approach of identifying the highest-risk individuals using a clinical/laboratory report or combination approach such as ours may identify those at the highest risk who may possibly benefit from additional imaging. Clearly, such strategies will need to be tested before being recommended for clinical use.

Our study had several strengths and limitations that merit consideration. Our sample size was large, as were the number of incident HF events. Further, the ARIC study is well characterized, biracial, and has good representation from both sexes. The addition of both cTnT and NT-proBNP to clinical predictors in the prediction of HF is novel and, finally, the exploration of several models is a strength. Both cTnT and NT-proBNP were measured in 2009–2010 from samples obtained in 1996–1998 (ARIC visit 4) and were therefore subject to possible degradation as with any stored sample. Further, intraindividual variability (biological variability) has been noted to be high for NT-proBNP and we had only 1 measurement; however, this mirrors what happens in a clinical setting. Therapies and risk factors may have changed during the follow-up period of 10.4 years, and changes were not accounted for. However, this is the case with any risk prediction tool. Imaging studies such as an echocardiogram may have added value but were not available in the ARIC study. Nonhospitalized, nonfatal HF was missed, but this should be a relatively small proportion of total HF. We did not have information related to all the risk factors that would identify an individual as having stage A HF (e.g., use of chemotherapy agents); however, if anything this would have increased the number of individuals in stage A, further strengthening our argument that better risk prediction tools are required. Additionally, we were unable to classify individuals as stage B HF since we did not have adequate methods to assess for structural heart disease. Therefore some of the individuals we labeled as stage A may have in fact been stage B HF. Also, we were unable to distinguish between HF with and without preserved ejection fraction. Finally, the cost-effectiveness of such a strategy could not be evaluated at this time and will need to be considered in future analyses.

In conclusion, cTnT, measured with a highly sensitive assay, and NT-proBNP are biomarkers strongly associated with incident HF and improved HF risk prediction. A simplified laboratory report model performs similarly to the validated ARIC HF model, although the best performance was seen when cTnT and NT-proBNP were added to the ARIC HF model. Further research into the clinical implementation of HF risk prediction models and evaluation of therapies based on predicted risk will be needed.

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