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Predicting incident heart failure in women with machine learning: The Women's Health Initiative Cohort

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Abstract

BACKGROUND: Heart failure (HF) is a leading cause of cardiac morbidity among women, whose risk factors differ from those in men. We used machine learning approaches to develop risk prediction models for incident HF in a cohort of postmenopausal women from the Women's Health Initiative (WHI).

METHODS AND RESULTS: We used two machine learning methods, Least Absolute Shrinkage and Selection Operator (LASSO) and Classification and Regression Trees (CART), to perform variable selection on 1,227 baseline WHI variables for the primary outcome of incident HF. These variables were then used to construct separate Cox proportional hazard models, and we compared these results, using receiver operating characteristic (ROC) curve analysis, against a comparator model built using variables from the Atherosclerosis Risk in Communities (ARIC) HF prediction model. We analyzed 43,709 women who had 2,222 incident HF events; median follow-up was 14.3 years. LASSO selected 10 predictors and CART selected 11 predictors. The highest correlation between selected variables was 0.46. In addition to selecting well-established

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predictors such as age, myocardial infarction, and smoking, novel predictors included physical function, number of pregnancies, number of prior live births and age at menopause. In ROC analysis, the CART-derived model had the highest c-statistic of 0.83 (95% CI 0.81–0.85), followed by LASSO 0.82 (95% CI 0.81–0.84) and ARIC 0.73 (95% 0.70–0.76).

CONCLUSIONS: Machine learning approaches can be used to develop HF risk prediction models that can have better discrimination compared to an established HF risk model, and may provide a basis for investigating novel HF predictors.

Brief Summary:

We used two machine learning methods to build models to predict incident heart failure in the Women's Health Initiative cohort. We analyzed 43,709 women who had 2,222 incident HF events over a median follow-up was 14.3 years. Both machine learning methods selected novel and sex-specific predictors, in addition to well-established predictors of heart failure. The two machine learning models demonstrated higher discrimination compared to a standard heart failure risk model in this cohort.

Keywords

Heart failure; risk factors; mortality/survival; women; information technology; epidemiology

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among women in the United States. Prevalence rates of CVD in women closely approach those in men,[1] with heart failure (HF) also causing a significant proportion of cardiac-related morbidity in women. While numerous studies have identified predictors of incident HF overall,[2] data specific to women are more sparse, even though HF risk factors in women likely differ from those in men.[3,4] For example, women are twice as likely as men to develop HF with preserved ejection fraction (HFpEF), and tend to do so at older ages and with less attributable ischemic etiology.[4] Therefore, there is an opportunity to improve HF risk prediction in women by including female-specific predictors. In addition, since C-statistics for existing HF prediction algorithms range from 0.6–0.7,[5–7] there is a broader opportunity to improve existing HF prediction algorithms.

Traditional approaches to develop risk prediction algorithms often focus on a limited set of known risk factors which have *a priori* associations with HF.[5,8] Although this valuable approach is rooted in ensuring biologic plausibility,[8] it may miss predictors with less clear links to HF or may ignore predictors which are unique to a given population or cohort of interest, such as women. This can ultimately limit the discovery of novel predictors which could improve incident HF prediction within a given cohort beyond existing models. Particularly in understudied populations, it may be possible to build better-performing and better tailored risk prediction models if more candidate variables—including population-specific variables—are considered for inclusion into prediction models in a "data-driven" manner. Machine learning techniques are well suited to identify predictive patterns among large numbers of candidate variables,[9–11] providing an opportunity to

perform data-driven discovery of HF predictors. Machine learning techniques can provide notable advantages in settings of large number of variables (high dimensionality),[12] and for automatic variable selection, selecting the strongest predictors from many candidate variables.[13] Most prior applications of machine learning models to predict HF outcomes in general cohorts[14–16] have lacked female-specific predictors. The Women's Health Initiative (WHI) cohort uniquely has well-adjudicated HF outcomes in post-menopausal women, providing a valuable opportunity to use machine learning to develop female-specific HF risk prediction models that may improve performance beyond existing HF risk models for women.[17]

We aimed to examine if machine learning algorithms can be used to select predictors from a large number of candidate variables, in order to build high-performing and interpretable risk prediction models based on population-specific predictors. We utilized two complimentary machine learning methods to develop HF prediction models using women in the WHI cohort and compared the performance of these models against a previously published HF risk model derived from the Atherosclerosis Risk in Communities (ARIC) cohort.

METHODS

Study population

This study was performed in the WHI, a longitudinal cohort study that recruited women from 40 clinical centers in the United States between 1993–1998. Details of the study design have been published previously.[17] In brief, a total of 161,808 women 50–79 years of age at baseline, who had no terminal illness, were enrolled in the observational study and clinical trial components. In this study, we used the 44,174 participants that had records centrally adjudicated at the University of North Carolina (UNC) to meet criteria for hospitalized HF from baseline through January 2015, which totaled 43,709 after exclusions. Data collection methods are described in the Supplement. The study received institutional review board approval and all participants gave informed consent.

Outcomes of interest

The primary outcome for this study was development of first incident HF hospitalization. We also examined two HF subgroups separately for those that had data on ejection fraction at the time of hospitalization: HFpEF—defined as HF with an ejection fraction ≥50%—and HF with reduced ejection fraction (HFrEF), defined as HF with ejection fraction <50%. Participants were removed from analysis following occurrence of the primary outcome.

Statistical and Machine Learning Analysis

We used two machine learning algorithms to perform variable selection from the 1,227 baseline variables, which we then used to build two novel HF prediction models. We compared performance of these models against a comparator model based on the previously published HF prediction model derived from the ARIC cohort,[5] and whose individual model coefficients we re-fit in the WHI cohort.

The full dataset was randomly divided into a 70% training dataset and 30% validation dataset. Variable selection was performed in the training dataset. Classification and Regression Trees (CART) [18] and Least absolute shrinkage and selection operator (LASSO)[19] machine learning models were fit to the HF outcome variable using the entire set of 1,227 variables. Our objective was to identify a reduced set of variables using these two complimentary machine learning approaches that perform inherent feature selection. These two methods were selected because they emphasize different aspects of the feature space, as discussed more in the Supplement.

RESULTS

Population

Over a median follow-up time of 14.3 years, there were a total of 2,222 (5.1%) cases of incident HF out of a total of 43,709 women. Of those for whom ejection fraction was known, there were 597 HFrEF cases and 715 HFpEF cases. The baseline characteristics of the cohort are presented in Table 1. Mean age of the entire cohort was 62.8 years and 33% of the cohort was African American women. Women who developed HF tended to be older, White women, with a higher mean number of pregnancies and pregnancy loss, and were less likely to have Medicare. They had a significantly higher waist circumference, body mass index (BMI), heart rate and systolic blood pressure. The mean physical function score, derived from the RAND questionnaire, was also significantly lower at baseline in women who developed HF (59.7±0.5 vs 73.9±0.1, $p<0.0001$). Furthermore, the mean creatinine was higher in women with HF than those without HF (0.83±0.007 vs 0.78±0.001, $p<0.0001$). Finally, women with incident HF had a higher prevalence of baseline hypertension, treated high cholesterol, diabetes, smoking, prior myocardial infarction, coronary revascularization, atrial fibrillation and valvular heart disease.

Variable Selection

Variable selection was performed separately using CART and LASSO algorithms. The model built using CART (Figure 1) selected 11 variables (Table 2, CART-WHI Model 1) including age, prior myocardial infarction, physical function, cardiotonic and diuretic medications, smoking, number of pregnancies, age at menopause, time since stopping hormone therapy and dietary beta-cryptoxanthin and vitamin K. LASSO selected 10 variables (Table 2, LASSO-WHI Model 2) including age, prior myocardial infarction, physical function, diabetes, valvular heart disease, diuretic medications, mineral and electrolyte supplements, smoking (pack years), number of prior live births and hypertension. The highest correlation between variables in each model was 0.46.

Separately, we used the same algorithms to perform variable selection among those individuals who had data on ejection fraction to examine how selected predictors differ for HFrEF vs HFpEF (Table 3). Higher age of last menses and age of menopause were identified as predictors of HFpEF by both CART and LASSO, but these were not identified as positive predictors in the HFrEF sub-cohort. Similarly, prior pregnancy loss, number of live births and antihypertensive use were selected as predictors for HFrEF only. Some variables were selected as predictors for both HFpEF and HFrEF, as well as being selected

as predictors of overall HF (Table 2), such as age, prior myocardial infarction, physical function and use of diuretic medications.

Comparison of model discrimination

We assessed the discrimination performance of each model by performing ROC analysis in the 30% held-out, validation dataset. The model derived from CART-selected variables had the highest C-statistic of 0.83 (95% CI 0.81–0.85), followed by the LASSO model 0.82 (95% CI 0.81–0.84), and the model derived using ARIC variables 0.73 (95% CI 0.70–0.76) (Table 2). In sensitivity analysis, whereby Cox models were re-fit in 10 random training splits of the dataset and assessed in the validation dataset, averaged AUC and 95% confidence intervals were very similar to the main analysis: LASSO 0.83 (95% CI 0.81–0.84); CART: 0.83 (95% CI 0.81–0.85).

DISCUSSION

Improving risk prediction using machine learning techniques

In this study, we employed a machine learning-based approach to develop prediction models for incident HF in women, an understudied population. In this large prospective WHI cohort of postmenopausal women which captured female-specific data and well-adjudicated HF outcomes, two machine learning algorithms selected from 1,227 candidate variables in a data-driven manner. The models built using this approach demonstrated substantially improved HF discrimination among women in WHI compared to deploying the established ARIC HF risk model[5] in WHI. In addition, this approach identified novel predictors—including predictors specific to female physiology—which likely contributed to improved discrimination. A machine learning-based approach to model building may provide a complementary alternative to traditional model-building methods, offering particular benefit in populations whose predictors may differ from those in existing risk models.

Our work demonstrates that machine learning methods like LASSO or CART can provide powerful approaches to automatically select from a large number of unique variables to build high-performing predictive models tailored to specific populations. For example, when the ARIC HF model was applied to women in WHI, it exhibited a substantially lower c-statistic (0.73) than was reported in the ARIC cohort among women (0.81).[5] Notably, two ARIC model predictors were not available in WHI (male gender and NT-proBNP), and the ARIC model ignores most female-specific predictors that are available and highly relevant to the WHI population. While decreased model performance is not uncommon when applying a pre-established risk model to a new population, this underscores the opportunity to use machine learning methods to improve discriminative performance for HF prediction in women, while also leveraging the many female-specific predictors uniquely available in WHI.

Despite having no underlying “understanding of disease”, machine learning algorithms can leverage patterns within data to identify HF predictors in a data-driven manner. Recent prior efforts have applied machine learning approaches to predict risk of incident HF[10] or HF outcomes such as mortality[15] in general populations. In light of efforts to decrease the

potential biases associated with applying machine learning in medicine,[20] it is critical to also use similar approaches in traditionally understudied patient populations. Machine learning has been previously applied to predict incident HF in race-specific[14] settings and in patients with diabetes,[16] or to predict HF outcomes in patients with HFpEF.[21] However, despite the ample evidence to suggest that risk factors for HF in women likely differ from those in men,[3,4] machine learning efforts to identify female-specific HF predictors are lacking. Our work is unique in utilizing WHI to investigate incident HF among women, taking advantage of the large number of baseline WHI variables, including many predictors specific to female-physiology. Additionally, we identified predictors specific to HFpEF and HFrEF subgroups in women, for which prior data is sparse.

While our machine-learning based model-building approach identified both established and novel predictors, we would caution against causal interpretation of predictor coefficients (hazard ratios), since the primary goal of this work is prediction rather than causal inference. Well-established HF predictors were identified through our variable selection process as predictors in women, including age, previous myocardial infarction, diabetes, cigarette smoking, and hypertension. The fact that these machine-learning-selected predictors are consistent with conventional HF risk factors that have established pathophysiologic links to HF[22,23] is reassuring. The selection of these predictors without *a priori* input suggests that at least some of the patterns that these algorithms identified in the WHI data are consistent with our conceptual understanding of HF physiology. For example, coronary heart disease, which is perhaps the most prominent HF risk factor and is uniformly present in existing risk models,[5–7] was also selected by both of our models—along with age—as being amongst the strongest predictors of incident HF (Table 2). Similarly, though hypertension is well recognized as a strong HF predictor, women in particular may be at greater risk than men to suffer long-term harmful effects of hypertension,[1,24–26] making it especially important to recognize among women.

Identifying novel female-specific predictors of HFrEF and HFpEF

Few studies have examined predictors specific for the HF subtypes of HFpEF and HFrEF, and to our knowledge, none have done so expressly in women. Though it has been previously thought that women are at higher risk of HFpEF than men, more recent analyses have suggested that this is not the case.[27–29] However, sex-specific differences are still likely to play an important role in HF.[27] Several female-specific predictors were selected through our variable selection process in each of the HF sub-cohorts examined. Among the full WHI cohort, the number of prior pregnancies and prior live births were found to predictors of HF, as identified by CART and LASSO, respectively. The number of live births was also found to predict HFpEF by CART, but was not identified as a predictor of HFrEF. This is consistent with prior work which has shown that the risk of heart failure increases along with parity and may exhibit a J-shaped relationship, with risk increasing significantly after 2 births.[26] Though less well-studied, gravidity was not shown in the Framingham cohort to be associated with HF. Conversely, in the HFrEF sub-cohort of WHI, LASSO identified pregnancy loss as a predictor of HFrEF in women, but not HFpEF.[29] Pregnancy loss has been associated with increased cardiovascular events in WHI previously,[30] and may

suggest underlying endothelial dysfunction, therefore helping to identify individuals who have higher risk of atherosclerosis and subsequent HFrEF.[31,32]

Other female-specific predictors of HFpEF but not HFrEF in WHI included age at last menses and age at menopause, which were predictors selected by CART and LASSO, respectively. Higher age of menopause predicting HFpEF is consistent with studies which have shown higher overall cardiovascular risk associated with late menopause.[24,33] LASSO also selected diabetes and BMI for HFpEF but not HFrEF, which mirrors the association reported by Eaton et al. of some risk factors such as obesity with HFpEF but not HFrEF.[25] Our findings demonstrate that reproductive risk factors are important independent predictors for HF,[26] expanding upon other reports from WHI on the importance of reproductive risk factors in coronary heart disease.[31] If confirmed in future studies, this may help guide future investigation about risk factors and potential targets for intervention in each HF subgroup among women.

Limitations

The generalizability of the two specific models we developed may be limited by lack of availability of some of the model's predictors in other cohorts. However, our goal with this study was to demonstrate a novel approach to model building using machine learning techniques like CART and LASSO to develop parsimonious high-performing models in population cohorts with unique characteristics and/or data. We believe that this approach can be generalized to other similar settings. If developing externally-generalizable models is a specific goal using this approach, then at the variable selection stage the variables should be limited to those available in expected target cohorts/populations. Similarly, more readily available variables from amongst physiologically-related groups could be preferentially included at the variable selection stage to facilitate generalizability via availability of predictors (i.e. select age at menopause to represent menopause or menstruation-related variables). Indeed, variable availability is a common limitation when applying predictive models trained in other settings, further supporting our approach to develop population-specific models. For example, two predictors in the ARIC model[5] were not available in WHI, namely male gender and NT-proBNP, likely diminishing the predictive performance of the ARIC model in WHI. This limitation in applying ARIC to WHI illustrates the reality of deploying models derived from other cohorts in any target cohort, whereby some predictors may not be available. We also acknowledge the limitations of not having an external validation cohort and the fact that unmeasured or residual confounding are concerns with observational data. In addition, model over-fitting is always a possibility when training and validating a predictive model on the same dataset. We mitigated these to the best of our ability by performing cross-validation and reporting the predictive performance of each model in the holdout test dataset.

Conclusions

When applied to the WHI cohort, a rich dataset with incident HF outcomes, machine learning methods were able to automatically select HF predictors from among many candidate predictors and yielded prediction models with improved discrimination compared to a pre-established heart failure risk model, in the WHI cohort. Machine learning could

provide a powerful approach to develop high-performing risk prediction models, particularly in understudied populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acronyms

ARIC	Atherosclerosis Risk in Communities
BMI	Body mass index
CART	Classification and regression tree
CVD	Cardiovascular disease
HF	Heart Failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IQR	Interquartile range
LASSO	Least Absolute Shrinkage and Selection Operator
Pap	Papanicolaou
SD	Standard deviation
WHI	Women’s Health Initiative

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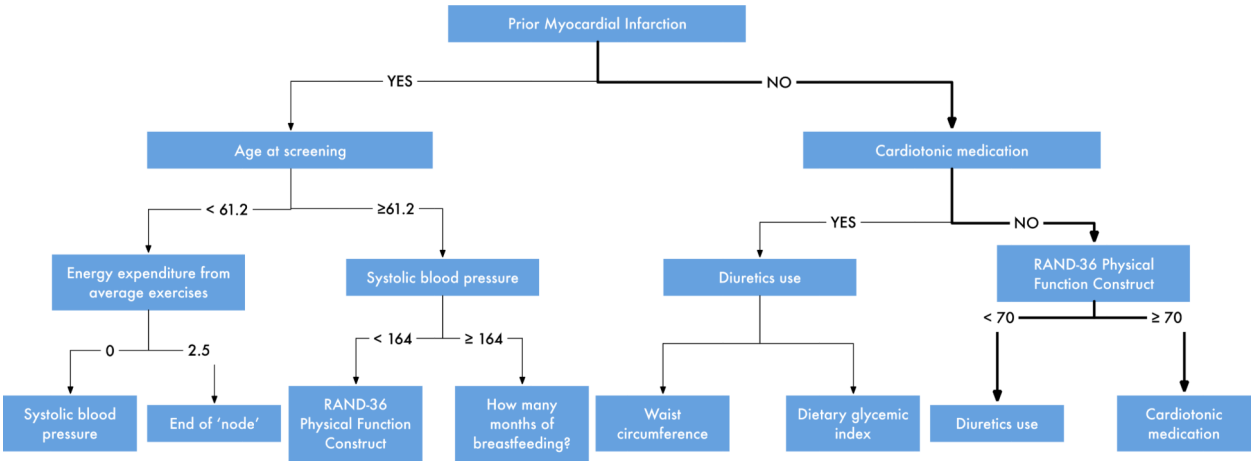

Figure 1. Example of the first four layers of a CART tree

Figure shows the first four layers of an example CART tree, demonstrating how splits are made at each tree-node leading to separation of individuals based on values of chosen variables.

Table 1.

Baseline Characteristics

Baseline characteristic n (%)	Experienced incident heart failure N = 2,222	No incident heart Failure N = 41,487	p-value
Age, mean±s.d., yrs	66.8±6.9	62.3±7.2	0.04
Number of pregnancies, mean±s.d.	3.8±2.2	3.6±2.1	< 0.002
Experienced pregnancy loss, mean±s.d.	0.8±1.3	0.7±1.1	<0.0001
Medicare	1,229 (55.6%)	13,114 (32.1%)	<0.0001
Race or ethnic group			
White (not of Hispanic origin)	1,404 (63.2%)	20,503 (49.4%)	<0.0001
Black or African American	658 (29.6%)	13,692 (33.0%)	
Hispanic/Latino	121 (5.4%)	6,293 (15.2%)	
Asian or Pacific Islander	17 (0.8%)	508 (1.2%)	
American Indian or Alaskan Native	6 (0.3%)	124 (0.3%)	
Other	14 (0.6%)	310 (0.7%)	
Unknown	2 (0.1%)	57 (0.1%)	
Clinical parameters at baseline			
Heart rate, mean±s.d. bpm	68.9±11.3	66.8±10.2	<0.0001
Systolic blood pressure, mean±s.d., mmHg	137.1±19.0	128.9±17.6	<0.0001
Waist circumference, mean±s.d., cm	95.3±15.2	89.3±13.8	<0.0001
Body mass index (BMI) mean±s.d. m^2/kg	31.5±0.16	29.6±11.6	<0.0001
Physical Function, mean±s.d.*	59.7±0.5	73.9±0.1	<0.0001
Social Function mean±s.d. *(IQR)	84.6±11.4	87.3±11.1	0.06
Hemoglobin, mean±s.d., g/dL	13.5±0.03	13.4±0.01	<0.0001
Creatinine, mean±s.d. mg/dL	0.83±0.007	0.78±0.001	<0.0001
Previous medical history			
Hypertension	1,210 (59.7%)	14,628 (38.1%)	<0.0001
Treated high cholesterol	425 (21.1%)	5,323 (14.0%)	<0.0001
Diabetes mellitus	505 (22.8%)	3,432 (8.3%)	<0.0001
Current smoking	290 (13.1%)	4,076 (9.8%)	<0.0001
Prior myocardial infarction	604 (27.2%)	1,387 (3.3%)	<0.0001
Coronary revascularization	591 (26.6%)	2,068 (5.0%)	<0.0001
Atrial Fibrillation	122 (5.5%)	550 (1.3%)	<0.0001
Valvular heart disease	41 (1.9%)	126 (0.3%)	<0.0001

Abbreviations: BMI: Body Mass Index; cm: Centimeters; kg: kilogram; s.d.: Standard Deviation.

*Physical function and social function scores are derived from the RAND questionnaire

Table 2.

Heart failure prediction models developed by CART and LASSO techniques versus the ARIC HF cohort derived variables, in the Women's Health Initiative (WHI) cohort

CART-WHI Model 1. Variables selected by CART C-statistic: 0.83 (0.81 – 0.85)				**LASSO-WHI Model 2. Variables selected by LASSO C-statistic: 0.82 (0.81 – 0.84)**				**ARIC-WHI Model 3. ARIC model variables refit in WHI C-statistic: 0.73 (0.70–0.76)**			
Variables	**Hazard ratio**	**95% CI**	**p-value**	**Variables**	**Hazard ratio**	**95% CI**	**p-value**	**Variables**	**Hazard ratio**	**95% CI**	**p-value**
Age (years)	1.07	1.06–1.08	< 0.0001	Age (years)	1.07	1.06 – 1.08	< 0.0001	Age (years)	1.09	1.07–1.10	< 0.0001
Prior myocardial infarction	4.93	4.34 – 5.60	< 0.0001	Prior myocardial infarction	4.91	4.35 – 5.54	< 0.0001	Coronary disease	2.35	1.77–3.12	< 0.0001
RAND-36 Physical function construct	0.98	0.97 – 0.98	< 0.0001	RAND-36 Physical function construct	0.98	0.97 – 0.98	< 0.0001	Antihypertensive use	1.53	1.21 – 1.92	0.0004
Cardiotonic medication	3.49	2.92 – 4.17	< 0.0001	Minerals & Electrolytes	1.69	1.48 – 1.93	<0.0001	Black race	0.85	0.71– 1.03	0.092
Diuretic use	2.05	1.83 – 2.30	< 0.0001	Diuretic use	1.72	1.52 – 1.95	<0.0001	**Smoking History**			
Pack Years of Smoking	1.01	1.01–1.01	< 0.0001	Pack Years of Smoking	1.01	1.01 – 1.01	<0.0001	Former	1.21	1.02–1.43	0.028
Number of Pregnancies	1.03	1.00–1.05	0.046	Number of prior live births	1.23	1.01 – 1.50	0.039	Current	2.09	1.58 – 2.77	< 0.0001
Age at Menopause	0.99	0.98–0.99	0.006	Diabetes	2.20	1.93 – 2.50	< 0.0001	Diabetes	2.54	2.12 – 3.05	< 0.0001
Time since stopping hormone therapy				**Hypertension**				Systolic blood pressure (mmHg)	1.01	1.01 – 1.02	<0.0001
Current use	0.65	0.53–0.79	<0.0001	Treated	1.23	1.08 – 1.4	0.002	Heart rate	1.01	1.01 – 1.02	< 0.0001
<5 years	0.90	0.70–1.16	0.412	Untreated	1.13	0.92 – 1.38	0.222	Body mass index, kg/m^2	1.02	1.02–1.03	< 0.0001
5–10 years	1.36	1.04–1.77	0.023	Presence of Valvular Heart Disease	2.21	1.53 – 3.17	<0.0001				
>10 years	0.94	0.80–1.11	0.445								
Dietary Beta-Cryptoxanthin (mcg)	0.99	0.98–1.00	0.027								
Dietary Vitamin K (mcg)	1.00	0.99–1.00	0.727								

Abbreviations: mmHg: Millimeters of mercury; kg: kilogram; cm: centimeters; mcg: micrograms.

Table 3.

Model discrimination and variable selection for the prediction of HFpEF and HFrEF

Heart failure with preserved ejection fraction		Heart failure with reduced ejection fraction	
Variables selected by CART	**Variables selected by LASSO**	**Variables selected by CART**	**Variables selected by LASSO**
Age	**Age**	**Age**	**Age**
Prior myocardial infarction	**Prior myocardial infarction**	**Prior myocardial infarction**	**Prior myocardial infarction**
RAND-36 Physical function construct	*RAND-36 Physical function construct*	*RAND-36 Physical function construct*	*RAND-36 Physical function construct*
Older age at last menses	**Age at Menopause**	*Number of Live Births*	**Prior pregnancy loss**
Never married	**Atrial Fibrillation**	**Cardiotonic medication**	*Prior mammogram*
Diuretic use	**Definite Prior Silent MI (on ECG)**	**Antihypertensive use**	**Antihypertensive use**
Dietary Saturated Fatty Acids *22:0 (g)*	**Time since stopping hormone replacement therapy**	**Diuretic use**	**Wrist Fracture**
Dietary Alpha-Carotene (mcg)	**Diabetes**	**Antidepressant use**	**Retired status**
Dietary Trans Fatty Acid, 181T (g)	**BMI**	*Episodes of recreational physical activity per week*	**Heart Valve Disease**
White ethnicity		*Supplemental Vitamin A (mcg)*	

Bold predictors signify a positive direction of association with incident heart failure

Italic predictors have a negative direction of association with incident heart failure

ECG: Electrocardiogram