ONLINE SUPPLEMENTARY MATERIALS

Title: Prediction of incident heart failure in chronic kidney disease: the CRIC Study

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Supplemental Methods.

Cardiac biomarker measurements

Two clinically available cardiac biomarkers, sampled from participants at study enrollment, were also considered as candidate predictors: NT-proBNP and hsTnT.(10, 11) Both biomarkers were measured in 2008 from EDTA plasma stored at -70°C using a chemiluminescent microparticle immunoassay (www.roche-diagnostics.us) on the ElecSys 2010 at the University of Maryland. The range of values for NT-proBNP was from 5 to 35,000 pg/mL and the coefficient of variation (CV) was 9.3% at a level of 126 pg/mL and 5.5% at 5319 pg/mL. hsTnT was measured using the highly sensitive assay with a range of values from 3 to 10,000 pg/mL. The CV was 6.0% at a level of 26 pg/mL and 5.4% at 2140 pg/mL. The value at the 99th percentile cutoff from a healthy reference population was 13 pg/mL for hsTnT with a 10% CV. Any values still below the lower limit of blank were characterized as “undetectable” and set to half of the lower limit for analytic purposes.

Supplemental Table 1. Baseline characteristics of CRIC analytic population by subtype of heart failure (N = 2147)

	Participants not experiencing incident heart failure during follow-up (N = 1823)	Participants experiencing incident HFpEF during follow-up (N = 135)	Participants experiencing incident HFrEF during follow-up (N = 104)	Participants experiencing unclassified heart failure during follow-up (N = 85)
Age (years)	58.1 (11.1)	61.5 (9.6)	61.9 (9.1)	61.5 (9.5)
Men	956 (52)	69 (51)	63 (61)	41 (48)
Race/ethnicity				
White	959 (53)	54 (40)	50 (48)	35 (41)
Black	766 (42)	72 (53)	49 (47)	45 (53)
Other	98 (5)	9 (7)	5 (5)	5 (6)
Diabetes	747 (41)	91 (67)	68 (65)	51 (60)
History of coronary heart disease	285 (16)	37 (27)	42 (40)	25 (29)
History of atrial fibrillation	241 (13)	36 (27)	31 (30)	21 (25)
History of stroke	160 (9)	24 (18)	12 (12)	15 (18)
History of PVD	96 (5)	16 (12)	12 (12)	8 (9)
History of COPD	68 (4)	8 (6)	8 (8)	4 (5)
Antihypertensive medications	1624 (89)	135 (100)	101 (97)	84 (99)
ACEi/ARB	1221 (67)	102 (76)	76 (73)	65 (76)
Beta blockers	790 (43)	87 (64)	70 (67)	49 (58)
Calcium channel blockers	696 (38)	78 (58)	51 (49)	52 (61)
Diuretics	952 (52)	102 (76)	75 (72)	59 (69)
Height (cm)	169.0 (9.6)	166.8 (9.8)	169.8 (9.1)	167.8 (9.5)
Weight (kg)	88.6 (21.3)	92.8 (23.1)	96.0 (24.3)	93.9 (22.6)
BMI (kg/m^2)	31.0 (7.2)	33.3 (7.9)	33.2 (7.6)	33.3 (7.7)
Systolic blood pressure (mmHg)	124.4 (20.5)	136.1 (22.4)	131.3 (22.0)	133.6 (20.4)
Diastolic blood pressure (mmHg)	70.3 (12.2)	67.9 (13.5)	70.2 (14.3)	68.3 (13.1)
Heart rate (bpm)	65.1 (11.4)	64.6 (11.5)	67.6 (11.5)	66.0 (10.8)
eGFR (CKD-EPI), $mL/min/1.73m^2$	45.0 (15.6)	36.4 (15.4)	37.1 (12.9)	37.9 (15.2)
eGFR category ($mL/min/1.73m^2$)				
≥ 60	311 (17)	9 (7)	5 (5)	7 (8)
45-59	569 (31)	25 (19)	25 (24)	18 (21)
30-44	593 (33)	50 (37)	39 (38)	31 (36)
<30	322 (18)	44 (33)	34 (33)	26 (31)
ESRD	16 (1)	4 (3)	1 (1)	0 (0)

24-hour urine albumin (mg), median (IQR)	32 (8-311)	253 (34-1060)	134 (25-1073)	163 (18-837)
Hemoglobin (g/dL)	13.0 (1.7)	12.1 (1.8)	12.3 (1.7)	12.5 (1.9)
LDL (mg/dL)	101.2 (33.7)	100.9 (37.7)	98.1 (34.6)	96.2 (38.5)
HDL (mg/dL)	50.1 (16.2)	48.2 (15.1)	45.1 (15.4)	48.7 (13.3)
LV mass index, Cornell criteria ($g/m^{2.7}$)	48.5 (12.3)	57.1 (12.8)	58.2 (13.5)	58.5 (16.3)
Left ventricular ejection fraction (%)	55.7 (6.9)	54.7 (6.1)	49.1 (10.8)	53.6 (8.2)

Entries are mean (SD) for continuous variables and N (%) for categorical variables, except as noted.
Abbreviations: HFpEF, preserved ejection fraction heart failure; HFrEF, reduced ejection fraction heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PVD, peripheral vascular disease; eGFR, estimated glomerular filtration rate; BMI, body mass index; ECG, electrocardiogram; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FGF, fibroblast growth factor; PTH, parathyroid hormone; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Supplemental Table 2. Discriminatory ability of models to predict incident heart failure by eGFR category

	N at risk (N events)	C-index (95% CI)	Difference in C-index (95% CI), compared with ARIC clinical model with published coefficients	Difference in C-index (95% CI), compared with ARIC clinical model with re-estimated coefficients
eGFR <30 mL/min/1.73m^2 or ESRD	447 (109)			
ARIC clinical model (published coefficients)		0.654 (0.605, 0.704)	Reference	NA
ARIC + NT-proBNP		0.686 (0.640, 0.732)	**0.032 (0.002, 0.062)**	NA
NT-proBNP alone		0.642 (0.591, 0.692)	-0.013 (-0.082, 0.056)	-0.039 (-0.109, 0.031)
hsTnT alone		0.578 (0.525, 0.632)	**-0.076 (-0.139, -0.013)**	-0.102 (-0.166, -0.039)
NT-proBNP + hsTnT		0.634 (0.583, 0.685)	-0.020 (-0.085, 0.044)	-0.046 (-0.112, 0.019)
LV mass + LV ejection fraction		0.653 (0.602, 0.705)	-0.001 (-0.062, 0.060)	-0.027 (-0.087, 0.032)
Clinical variables only (re-estimated coefficients)		0.681 (0.631, 0.730)	0.026 (-0.008, 0.060)	Reference
Clinical variables + NT-proBNP		0.706 (0.660, 0.752)	**0.052 (0.007, 0.097)**	0.025 (-0.008, 0.059)
Clinical variables + hsTnT		0.674 (0.624, 0.724)	0.020 (-0.021, 0.061)	-0.006 (-0.035, 0.022)
Clinical variables + NT-proBNP + hsTnT		0.697 (0.649, 0.745)	0.043 (-0.003, 0.089)	0.017 (-0.020, 0.053)
Clinical variables + LV mass + LV ejection fraction		0.701 (0.654, 0.749)	**0.047 (0.004, 0.090)**	0.021 (-0.009, 0.051)
Clinical variables + NT-proBNP + hsTnT + LV mass + LV ejection fraction		0.707 (0.660, 0.755)	**0.053 (0.005, 0.101)**	0.027 (-0.012, 0.066)
eGFR 30-<45 mL/min/1.73m^2	713 (120)			
ARIC clinical model (published coefficients)		0.626 (0.576, 0.676)	Reference	NA
ARIC + NT-proBNP		0.706 (0.659, 0.752)	**0.080 (0.053, 0.106)**	NA
NT-proBNP alone		0.686 (0.639, 0.732)	**0.060 (0.001, 0.119)**	0.042 (-0.016, 0.100)
hsTnT alone		0.670 (0.623, 0.717)	0.044 (-0.017, 0.105)	0.026 (-0.031, 0.083)
NT-proBNP + hsTnT		0.722 (0.674, 0.769)	**0.096 (0.038, 0.154)**	**0.078 (0.022, 0.134)**
LV mass + LV ejection fraction		0.697 (0.650, 0.745)	**0.071 (0.013, 0.130)**	0.054 (-0.001, 0.108)
Clinical variables only (re-estimated coefficients)		0.644 (0.596, 0.691)	0.018 (-0.019, 0.055)	Reference
Clinical variables + NT-proBNP		0.713 (0.667, 0.760)	**0.087 (0.041, 0.134)**	**0.070 (0.036, 0.103)**
Clinical variables + hsTnT		0.680 (0.634, 0.727)	**0.054 (0.009, 0.100)**	**0.036 (0.008, 0.065)**
Clinical variables + NT-proBNP + hsTnT		0.721 (0.674, 0.767)	**0.095 (0.046, 0.143)**	**0.077 (0.040, 0.113)**
Clinical variables + LV mass + LV ejection fraction		0.702 (0.655, 0.749)	**0.076 (0.029, 0.122)**	**0.058 (0.025, 0.091)**
Clinical variables + NT-proBNP + hsTnT + LV mass + LV ejection fraction		0.739 (0.693, 0.785)	**0.113 (0.064, 0.162)**	**0.095 (0.057, 0.134)**

	N at risk (N events)	C-index (95% CI)	Difference in C-index (95% CI), compared with ARIC clinical model with published coefficients	Difference in C-index (95% CI), compared with ARIC clinical model with re-estimated coefficients
eGFR 45-<60 mL/min/1.73m^2	637 (68)			
ARIC clinical model (published coefficients)		0.686 (0.618, 0.753)	Reference	NA
ARIC + NT-proBNP		0.720 (0.658, 0.783)	0.035 (-0.007, 0.076)	NA
NT-proBNP alone		0.661 (0.594, 0.728)	-0.025 (-0.114, 0.064)	-0.025 (-0.112, 0.061)
hsTnT alone		0.624 (0.556, 0.693)	-0.061 (-0.132, 0.009)	-0.062 (-0.131, 0.008)
NT-proBNP + hsTnT		0.681 (0.613, 0.748)	-0.005 (-0.082, 0.073)	-0.005 (-0.081, 0.071)
LV mass + LV ejection fraction		0.687 (0.625, 0.748)	0.001 (-0.075, 0.077)	0.001 (-0.072, 0.074)
Clinical variables only (re-estimated coefficients)		0.686 (0.622, 0.751)	0.000 (-0.039, 0.040)	Reference
Clinical variables + NT-proBNP		0.719 (0.658, 0.780)	0.034 (-0.024, 0.091)	0.033 (-0.012, 0.079)
Clinical variables + hsTnT		0.693 (0.627, 0.758)	0.007 (-0.037, 0.051)	0.007 (-0.018, 0.032)
Clinical variables + NT-proBNP + hsTnT		0.718 (0.656, 0.780)	0.032 (-0.025, 0.089)	0.032 (-0.013, 0.077)
Clinical variables + LV mass + LV ejection fraction		0.728 (0.669, 0.787)	0.042 (-0.006, 0.091)	**0.042 (0.007, 0.077)**
Clinical variables + NT-proBNP + hsTnT + LV mass + LV ejection fraction		0.738 (0.678, 0.799)	0.053 (-0.005, 0.111)	**0.052 (0.004, 0.100)**
eGFR ≥60 mL/min/1.73m^2	332 (21)			
ARIC clinical model (published coefficients)		0.789 (0.689, 0.888)	Reference	NA
ARIC + NT-proBNP		0.791 (0.692, 0.891)	0.003 (-0.067, 0.072)	NA
NT-proBNP alone		0.629 (0.486, 0.773)	-0.159 (-0.320, 0.002)	**-0.208 (-0.356, -0.060)**
hsTnT alone		0.782 (0.677, 0.887)	-0.007 (-0.134, 0.120)	-0.055 (-0.158, 0.048)
NT-proBNP + hsTnT		0.726 (0.591, 0.861)	-0.063 (-0.212, 0.087)	-0.111 (-0.244, 0.022)
LV mass + LV ejection fraction		0.729 (0.619, 0.840)	-0.059 (-0.206, 0.087)	-0.108 (-0.227, 0.012)
Clinical variables only (re-estimated coefficients)		0.837 (0.764, 0.910)	0.048 (-0.014, 0.111)	Reference
Clinical variables + NT-proBNP		0.806 (0.717, 0.896)	0.018 (-0.080, 0.115)	-0.031 (-0.101, 0.039)
Clinical variables + hsTnT		0.856 (0.784, 0.929)	0.068 (-0.011, 0.146)	0.019 (-0.020, 0.058)
Clinical variables + NT-proBNP + hsTnT		0.825 (0.737, 0.913)	0.036 (-0.063, 0.135)	-0.012 (-0.083, 0.059)
Clinical variables + LV mass + LV ejection fraction		0.848 (0.775, 0.921)	0.059 (-0.039, 0.158)	0.011 (-0.051, 0.073)
Clinical variables + NT-proBNP + hsTnT + LV mass + LV ejection fraction		0.821 (0.731, 0.912)	0.032 (-0.076, 0.141)	-0.016 (-0.097, 0.065)

Clinical variables include age, black race/ethnicity, sex, heart rate, systolic blood pressure, antihypertensives, diabetes, coronary heart disease, current smoking, former smoking, and BMI. Entries for ARIC clinical and ARIC + NT-proBNP models are C-index and associated 95% bootstrap confidence intervals; all other entries are 10-fold cross-validated C-indices or difference in C-indices compared with ARIC clinical model, and associated 95% bootstrap confidence intervals. Bolded entries indicate statistical significance at the 5% level.

Supplemental Table 3. Reclassification statistics of models to predict incident heart failure

	Continuous NRI (95% CI)	**NRI (<5%, 5%-10%, >10% risk) (95% CI)**	**IDI (95% CI)**
Clinical variables only (re-estimated)	NA	NA	NA
NT-proBNP alone	-9.2 (-29.6, 11.2)	-3.1 (-15.6, 9.5)	-6.8 (-25.6, 11.9)
hsTnT alone	-19.3 (-39.9, 1.3)	-6.8 (-20.7, 7)	**-17.8 (-34.7, -1.0)**
NT-proBNP + hsTnT	3.0 (-19.4, 25.4)	7.5 (-3.9, 19.0)	7.2 (-12.7, 27.2)
LV mass + LV ejection fraction	-17.5 (-35.1, 0.1)	-9.1 (-21.9, 3.6)	**-18.7 (-33.2, -4.2)**
Clinical variables + NT-proBNP	**47.8 (35.5, 60.1)**	**14.0 (6.4, 21.5)**	**35.7 (23.4, 48.0)**
Clinical variables + hsTnT	**36.7 (22.2, 51.2)**	**7.3 (0.8, 13.7)**	**21.2 (9.2, 33.1)**
Clinical variables + NT-proBNP + hsTnT	**53.2 (40.2, 66.2)**	**15.3 (7.4, 23.3)**	**41.1 (27.8, 54.4)**
Clinical variables + LV mass + LV ejection fraction	**38.1 (24.5, 51.6)**	**11.9 (5.1, 18.7)**	**23.6 (14.8, 32.4)**
Clinical variables + NT-proBNP + hsTnT + LV mass + LV ejection fraction	**58.3 (45.4, 71.2)**	**18.9 (10.5, 27.2)**	**47.9 (35.2, 60.7)**

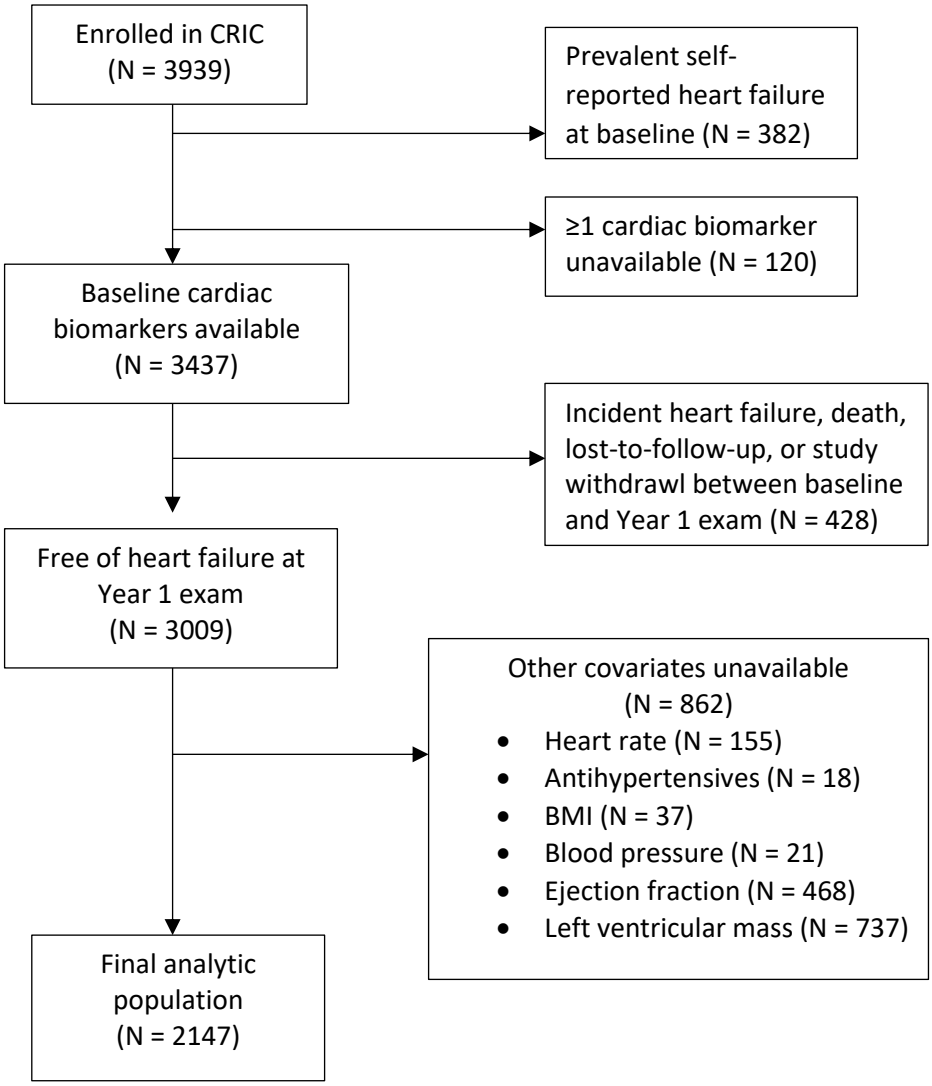
NRI, net reclassification improvement; IDI, integrated discrimination improvement. Reclassification statistics are relative to a model that included ARIC clinical variables (age, black race/ethnicity, sex, heart rate, systolic blood pressure, antihypertensives, diabetes, coronary heart disease, current smoking, former smoking, and BMI) but with coefficients that were re-estimated in the CRIC cohort. Categorical NRI is calculated for 10-year risk categories of <5%, 5%-10%, and >10% and is supplemented by the continuous NRI and IDI index.

Supplemental Table 4. TRIPOD checklist

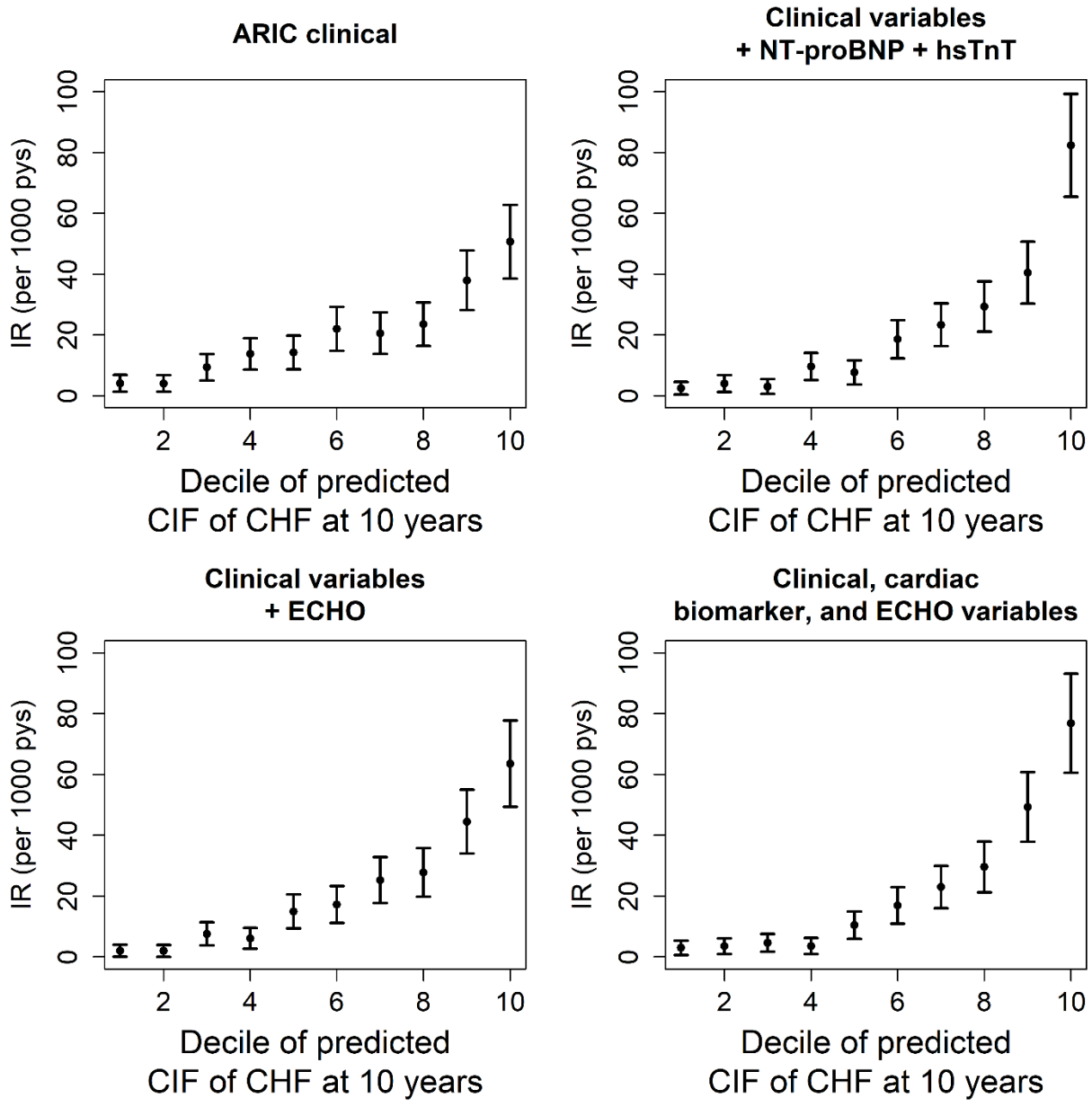
TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6
	5c	D;V	Give details of treatments received, if relevant.	
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	9-10
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7-9
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	D;V	Explain how the study size was arrived at.	7
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	11
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	11
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	10-12
	10c	V	For validation, describe how the predictions were calculated.	11
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	12
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	11
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	11-12
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	13, supplemental figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	13
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	13
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	30
	15b	D	Explain how to the use the prediction model.	30
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	29
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	19
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	15-19
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	18, 20
Other Information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	22
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	21

Supplemental Figure 1. CONSORT diagram of analytic population



Supplemental Figure 2. Incidence rates of heart failure by decile of predicted probability



Figures show incidence rates and associated 95% bootstrapped confidence intervals, per 1000 person-years, by decile of predicted probability.