10-Year Risk Prediction Equations for Incident Heart Failure Hospitalizations in Chronic Kidney Disease: Findings from the Chronic Renal Insufficiency Cohort Study and the Multi-Ethnic Study of Atherosclerosis

Rupal Mehta, MD[1,2,3,*], **Hongyan Ning, MD, MS**[4], **Nisha Bansal, MD, MAS**[5], **Jordana Cohen, MD, MSCE**[6], **Anand Srivastava, MD, MPH**[1,2], **Mirela Dobre, MD, MPH**[7], **Erin D Michos, MD, MHS**[8], **Mahboob Rahman, MD**[7], **Raymond Townsend, MD**[6], **Stephen Seliger, MD, MS**[9], **James Lash, MD**[10], **Tamara Isakova, MD, MMSc**[1,2], **Donald Lloyd-Jones, MD, ScM**[4,11], **Sadiya S. Khan, MD, MS**[4,11]

[1]Division of Nephrology and Hypertension, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[2]Center for Translational Metabolism and Health, Institute for Public Health and Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[3]Jesse Brown Veterans Administration Medical Center; Chicago, IL, USA

[4]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[5]Division of Nephrology, Department of Medicine, University of Washington, Seattle, WA, USA

[6]Division of Nephrology, Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[7]Division of Nephrology and Hypertension, Department of Medicine, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio, USA

[8]Division of Cardiology, Department of Medicine, John Hopkins School of Medicine, Baltimore, MD, USA

[9]Division of Nephrology, Department of Medicine, University of Maryland Medical Center, Baltimore, MD, USA

*Correspondence should be addressed to: Rupal Mehta, MD, 633 North Saint Clair, 18-081; Chicago, IL 60611, rupal.mehta@northwestern.edu.

[10]Division of Nephrology, Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA

[11]Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Abstract

Background: Heart failure (HF) is a leading contributor of cardiovascular morbidity and mortality in the chronic kidney disease (CKD) population. HF risk prediction tools that utilize readily available clinical parameters to risk stratify individuals with CKD are needed.

Methods: We included Black and White participants aged 30 to 79 years with CKD stages 2–4 enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study and without self-reported cardiovascular disease. We assessed model performance of the Pooled Cohort Equations to Prevent Heart Failure (PCP-HF) to predict incident HF hospitalizations and refit the PCP-HF in the CKD population using CRIC data-derived coefficients and survival from CRIC Study participants in the CKD population (PCP-HF$_{CKD}$). We investigated the improvement in HF prediction with inclusion of estimated glomerular filtration rate [eGFR] and urine albumin to creatinine ratio [UACR] into the PCP-HF$_{CKD}$ equations by change in C-statistic, net reclassification improvement (NRI) and integrated discrimination improvement index (IDI). We validated the PCP-HF$_{CKD}$ with and without eGFR and UACR in Multi-Ethnic Study of Atherosclerosis (MESA) participants with CKD.

Results: Among 2328 CRIC Study participants, 340 incident HF hospitalizations occurred over a mean follow-up of 9.5 years. The PCP-HF equations did not perform well in most participants with CKD and had inadequate discrimination and insufficient calibration (C-statistic 0.64–0.71, GND chi-square statistic p value <0.05), with modest improvement and good calibration after being refit (PCP-HF$_{CKD}$: C-statistic 0.61–0.78), GND chi-square p value >0.05). Addition of UACR, but not eGFR, to the refit PCP-HF$_{CKD}$ improved model performance in all race-sex groups (C-statistic [0.73–0.81], GND chi-square p value > 0.05, delta C-statistic ranging from 0.03–0.11 and NRI and IDI p values <0.01). External validation of the PCP-HF$_{CKD}$ in MESA demonstrated good discrimination and calibration.

Conclusions: Routinely available clinical data that includes UACR in patients with CKD can reliably identify individuals at risk of HF hospitalizations.

Lay Summary:

Patients with chronic kidney disease frequently develop heart failure; however, no tool exists to predict heart failure in patients with chronic kidney disease. This study investigated whether a previously developed tool that used routinely available clinical data could predict heart failure events in individuals with chronic kidney disease. Results demonstrated that this tool performed poorly in individuals with chronic kidney disease. However, when albuminuria, a measurement of protein in the urine that represents kidney dysfunction, was added to the risk prediction equation, the risk prediction tool was better able to predict heart failure events in this population. Implementation of this tool may be able to identify individuals with chronic kidney disease at high risk for heart failure hospitalization and improve clinical outcomes.

Keywords

heart failure; chronic kidney disease; albuminuria; risk prediction

Introduction

In patients with chronic kidney disease (CKD), heart failure (HF) is a major manifestation of cardiovascular disease (CVD) that is associated with marked morbidity, mortality, and healthcare expenditures.(1, 2) Although there is substantial overlap in the risk factors for CKD and HF (e.g. hypertension, diabetes), patients with CKD have higher risk for the development of and adverse outcomes related to HF when compared with the general population who have similar risk factor levels. HF risk prediction tools that risk stratify individuals with CKD are needed to facilitate enhanced surveillance, intensification of risk factor modification and uptake of evidence-based therapies.

American College of Cardiology/American Heart Association (ACC/AHA) guidelines highlight the need to identify and stratify individuals at highest risk for HF.(3) Risk prediction equations, such as the Pooled Cohort Equations to Prevent Heart Failure (PCP-HF),(4) are available for use and have been validated in the general population. (4–8) The PCP-HF tool was developed to predict 10-year HF risk from 5 general population-based cohorts and validated in two general population-based cohorts in order to enhance personalized risk-based clinical care. The PCP-HF demonstrated good-to-excellent discrimination in the derivation and validation cohorts (C-Statistics ranged from 0.71–0.85 in validation).(4) Since then, additional HF risk prediction tools have been developed using machine learning algorithms.(9) However, the utility of any of these models in individuals with CKD remains unknown. Given the increased propensity of HF hospitalizations in individuals with CKD and known CKD-specific risk factors for the development of HF, understanding HF risk in CKD populations is highly relevant to the clinical cardiologist and HF practitioner. Additionally, the emergence of novel therapies, such as sodium glucose co-transporter 2 inhibitors (SGLT2i), that influence cardiac and kidney outcomes underscore the importance of understanding how HF risk prediction models perform in CKD populations.

In the current investigation, we 1) assessed the performance of the existing PCP-HF risk prediction model among a subset of Chronic Renal Insufficiency Cohort (CRIC) Study participants with CKD and without self-reported CVD, 2) refit the PCP-HF risk prediction model for the CKD population (PCP-HF$_{CKD}$), 3) investigated the added value of including routinely assessed CKD-specific markers (estimated glomerular filtration rate [eGFR] and albuminuria) to the refit PCP-HF$_{CKD}$ risk prediction model, and 4) externally validated the models in the Multi-Ethnic Study of Atherosclerosis (MESA) participants with CKD.

Methods

Study Population

The design and implementation of the CRIC Study and MESA cohorts have been published previously.(10, 11) The CRIC Study is a multi-center prospective cohort study designed to investigate risk factors for CVD and CKD progression in individuals with mild to severe CKD.(10) Phase 1 of the CRIC Study was conducted between June 2003 - September 2008 and recruited 3939 individuals aged 29–74 with age-specific eGFR of 20–70 ml/min/1.73m^2 from 7 clinical centers across the United States.(10) Main exclusion criteria included New York Heart Association (NYHA) class III and IV HF, renal cancer, multiple myeloma, recent chemotherapy or immunotherapy, cirrhosis, polycystic kidney disease, prior renal replacement therapy within 1 month or renal transplantation, pregnancy, institutionalization, or inability to consent. Black and Hispanic participants were oversampled.(10) In brief, MESA is a multi-center, prospective cohort study of 6814 men and women aged 45–84 years old without known CVD at baseline who were recruited across 6 cities in the United States.(11) Major exclusion criteria included history of clinical CVD, any CVD procedure, current atrial fibrillation, active cancer, pregnancy, and weight > 136 kg.(11) All CRIC Study and MESA participants provided written informed consent, and the respective protocols were approved by each clinical center's Institutional Review Board.

We sought to refit and externally validate the PCP-HF risk prediction equation in a population with CKD but without prior CVD. We studied CRIC Study participants without prior CVD since patients with prevalent CVD require specific secondary prevention therapies, are already considered to be at higher risk for HF and are often recommended to receive specific therapies that can prevent progression to HF. We matched the inclusion criteria in the CRIC and MESA cohorts to those used in the derivation of the PCP-HF risk tool.(4) Of the total 3939 individuals enrolled in the CRIC Study, we excluded 1316 individuals with baseline self-reported history of CVD. Self-reported CVD included prior history of coronary revascularization, myocardial infarction, stroke, peripheral vascular disease, or heart failure.(12) We also excluded 186 individuals who self-reported race other than Black or White, were < 30 or > 79 years, or any participant without follow-up time. Additionally, 109 individuals were excluded for missing covariates including indices of eGFR and urine albumin-to-creatinine ratio (UACR) measured at baseline, yielding a total analytic population of 2328 individuals (Supplemental Figure 1). Of the full MESA cohort, which includes 6814 women and men aged 45 to 84 years, 522 self-identified Black and White individuals had a eGFR< 60ml/min/1.73m^2 and were   79 years of age and were included in the external validation cohort.

Exposure Assessment to Calculate Predicted Heart Failure Risk (PCP-HF)

CRIC Study participant demographics, medication use and clinical data were obtained at the baseline visit. Participants self-identified as Black or White. Hypertension medication use included use of any of the following: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, loop diuretics, thiazide diuretics, alpha 2 agonists, alpha blockers, vasodilators, beta-blockers, or calcium channel blockers. Resting blood pressure was measured via standardized protocols.(10) Diabetes medication use included any

of the following: alphaglucosidase inhibitors, sulfonylureas, biguanides, meglitinides, thiazolidinediones, or oral dipeptidyl peptidase-4 inhibitors. A centralized laboratory measured serum creatinine and urine albumin and urine creatinine via standard assays at the baseline study visit.(10, 13) eGFR was calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which incorporates serum creatinine, age, sex and Black race, which is self-reported in our sample.(14)

Outcome Ascertainment of Incident Heart Failure

In the CRIC Study, acute HF hospitalization events were adjudicated by two independent physicians who reviewed hospitalization records and any differences were resolved by discussion.(12) HF events were classified as possible, probable or definite using a combination of symptoms and either physical examination, chest radiographs, or invasive hemodynamics or echocardiographic evidence. Symptoms included paroxysmal nocturnal dyspnea or dyspnea on exertion. Physical examination findings included at least two of the following: pulmonary rales, S3 gallop, jugular venous distention > 5 centimeters, or peripheral edema. Relevant chest radiographic findings included: pulmonary edema, vascular congestion or pleural effusion. Invasive hemodynamic or echocardiographic evidence included pulmonary capillary wedge pressure > 18 mmHg, cardiac index < 2.0 L/min/m^2, or left ventricular ejection fraction 35%.(12) Incident HF in this report included only the first definite or probable event. Participants were followed until death, censored for withdrawal from study, loss to follow-up, or at administrative end of follow-up in March 2018. In MESA, HF events were adjudicated as probable or definite by two paired physicians using medical records obtained after biyearly study visits or telephone interviews conducted every 9–12 months.(15) Definite or probable HF was classified based on symptoms, including shortness of breath or edema. In addition, classification of probable HF required a physician diagnosis and receipt of medical treatment for HF. Definite HF required findings of pulmonary edema on chest x-ray, dilated ventricle or poor left ventricular function on echocardiography or ventriculography, or evidence of left ventricular diastolic dysfunction.(15) Incident HF in this report included only the first definite or probable event.

Statistical Analysis

Baseline characteristics of the overall and sex- and race-stratified CRIC Study population were described using means with standard deviations (SDs) or medians with interquartile ranges (IQR) for continuous variables and with proportions for categorical variables. Additionally, we compared baseline characteristics of our study population stratified by incident HF event occurrence.

In the CRIC Study, we investigated model performance of the original PCP-HF(4) to predict 10-year risk of HF hospitalizations. The PCP-HF model includes age, sex, race, current smoking, body mass index (BMI), systolic blood pressure (SBP) (treated or untreated), hypertension treatment, fasting glucose (treated or untreated), diabetes treatment, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and QRS duration. The HF risk estimates were developed from sex- and race-specific proportional hazards models from 5 population-based cohorts from the Cardiovascular Lifetime Risk Pooling

Project.(4) The included covariates were chosen based on their known association with incident HF. Model fit was evaluated through Harrell C-statistic for discrimination(16) and the Greenwood-Nam-D'Agostino (GND) chi-squared statistic for calibration.(17) The distribution of the C statistic was defined a priori based on prior publications with less than 0.70, 0.70 to 0.80, and greater than 0.80 as inadequate, acceptable, and excellent discrimination levels, respectively. Model calibration was evaluated by the GND approach with adequate calibration defined a priori as $X^2 < 20$, similar to prior publications, including the Pooled Cohort Equations for atherosclerotic cardiovascular disease (ASCVD).(18–20)

Since electrocardiograms are not routinely performed in all patients with CKD, we refit the PCP-HF model without the QRS duration in the original derivation cohort and noted minimal change to the coefficients of other covariates. (Supplemental Table 1). To enhance future dissemination and implementation efforts, we excluded QRS duration for all iterative models derived from the CRIC Study. Model performance was assessed with C-statistics (discrimination) and GND X^2 (calibration) statistics. Discrimination refers to the ability of the model to assign a higher risk to individuals who develop the outcome of interest compared to those who remain free of disease. Calibration is a measure of the accuracy of the predicted risk. We then refit the PCP-HF model (PCP-HF$_{CKD}$, Supplemental Table 2) using CRIC data-derived coefficients and survival from CRIC Study participants (PCP-HF$_{CKD}$) using Cox proportional hazard models and assessed discrimination and calibration of the PCP-HF$_{CKD}$ model.

We next evaluated the performance of risk equations for predicting incident hospitalized HF with the inclusion of two additional CKD-specific laboratory measures (eGFR and UACR; Supplemental Table 3). We assessed the discrimination and calibration of the PCP-HF$_{CKD}$ as described above. We examined the ability of the CKD laboratory measures to reclassify participants based on PCP-HF$_{CKD}$ using a continuous net reclassification improvement (NRI) statistic.(21, 22) We also used the integrated discrimination improvement (IDI) index to test improvement in model performance with the addition of eGFR and UACR. The IDI estimate is explained as the amount of separation between the mean predicted probabilities for HF events and non-events.(23) We performed an external validation study of the refit PCP-HF$_{CKD}$ with and without eGFR and UACR in the MESA cohort and examined 10-year HF prediction using C-statistic, NRI, and IDI as described above. Lastly, in sensitivity analyses, we re-ran our refit PCP-HF$_{CKD}$ in CRIC Study participants after excluding 98 individuals with incident HF events after end stage renal disease (ESRD) onset. We confirmed that there was no violation of the proportional hazards assumption by testing the interaction between time and risk predictors (P>0.05 for all).

All statistical analyses were performed with the use of SAS statistical software version 9.4 (SAS institute) and R version 3.4. A statistically significant threshold of a P value less than 0.05 with 2-sided tests were used.

Results

Among the 2328 CRIC Study participants at baseline, the mean (SD) age was 56.8 (10.8) years and ~90% of the population were being treated for hypertension (Table 1). Mean (SD)

eGFR was 46 (15) ml/min/1.73m^2 and median UACR (interquartile range [IQR]) was 37 (7, 381) mg/g. In Black men and women, 92% and 94% and 25% and 29% were undergoing hypertension and diabetes treatment. In White men and women, 90% and 80% and 25% and 20% were undergoing hypertension and diabetes treatment (Table 1). Median UACR (IQR) in Black men and women was 86 (13, 452) mg/g and 32 (7, 352) mg/g, respectively. Median UACR (IQR) in White men and women was 50 (7, 467) mg/g and 17 (6, 199) mg/g, respectively. Mean (SD) eGFR in individuals with and without an incident HF hospitalization was 40 (14) and 47 (15), respectively. Median UACR (IQR) in individuals with and without an incident HF hospitalization was 288 (33, 1358) mg /g and 27 (6, 278) mg/g, respectively. (Supplemental Table 4).

PCP-HF in CKD population

Over a mean follow-up of 9.5 years, 340 incident hospitalized HF events occurred in CRIC Study participants, of which 98 occurred after the onset of end-stage renal disease. The PCP-HF model had generally inadequate discrimination and calibration for HF risk prediction in the CRIC Study sample (Table 2, Figure 1). Among Black men and women, and White men and women in the CRIC Study population, the C-statistics (95% Confidence Interval [CI]) in each sex-race group were 0.66 (95% CI: 0.61 to 0.72), 0.64 (95% CI: 0.58 to 0.70), 0.67 (95% CI: 0.62 to 0.73), and 0.71 (95% CI: 0.64 to 0.78), respectively. There was consistent under-estimation of event rates, as expected in this high-risk sample, and the GND chi-square statistic p-value was < 0.05 for all, indicating insufficient calibration.

Development of PCP-HF$_{CKD}$ Model

The refit PCP-HF$_{CKD}$ had acceptable discrimination, except in Black women. The C-statistics (95% CI) among Black men and women and White men and women for the PCP-HF$_{CKD}$ model were 0.76 (95% CI: 0.71 to 0.81), 0.61 (95% CI: 0.54 to 0.68), 0.75 (95% CI: 0.70 to 0.80), and 0.78 (95% CI: 0.73 to 0.83), respectively (Table 2). The PCP-HF$_{CKD}$ risk equation had good calibration for all sex-race subgroups in the CRIC Study sample as assessed by the GND chi-square statistic (p > 0.05 for all, Table 2).

PCP-HF$_{CKD}$ with the addition of eGFR and UACR

When UACR was added to the PCP-HF$_{CKD}$ model, the model performance improved significantly in all groups. The PCP-HF$_{CKD}$ + UACR model had acceptable to excellent discrimination and calibration (Table 3, Figure 2). The C-statistic ranged from 0.73 – 0.81 with GND Chi-square p values >0.05 for all sex and race groups (Table 3). The change in C-statistic (95% CI) among Black men and women, and White men and women for the PCP-HF$_{CKD}$ + UACR model were 0.04 (p value 0.02) and 0.11 (p value = 0.02), and 0.04 (p value = 0.01), 0.03 (p value = 0.11), respectively (Table 3). The continuous NRI ranged from 0.44 – 0.61 with p values <0.01 across all groups. The IDI was also significant across all groups (p value < 0.01) (Table 3). The addition of eGFR to the PCP-HF$_{CKD}$ also improved model performance for some, but not all performance measurements (Table 3). The addition of both UACR and eGFR to the PCP-HF$_{CKD}$ did not provide substantive improvement over the addition of UACR alone (Table 3).

External Validation of the PCP-HF$_{CKD}$ in MESA

Over mean follow-up of 15.6 years, 56 incident hospitalized HF events occurred in MESA study participants. Baseline characteristics of the MESA participants with CKD are shown in Supplemental Table 5. External validation of the PCP-HF$_{CKD}$ to predict 10-year risk of heart failure with and without eGFR and UACR demonstrated good discrimination (C-statistic 0.73–0.76) and calibration (GND chi-square statistic (p > 0.05 for all; Supplemental Table 6, Supplemental Figure 2).

Sensitivity Analyses

In sensitivity analyses, we re-ran our refit PCP-HF$_{CKD}$ after excluding individuals with HF events after ESRD onset. Over a mean follow-up of 9.6 years, 242 incident hospitalized HF events occurred. Results remained qualitatively similar. After exclusion, the C-statistics (95% CI) among Black men and women and White men and women for the PCP-HF$_{CKD}$ model were 0.78 (95% CI: 0.73 to 0.84), 0.62 (95% CI: 0.54 to 0.71), 0.77 (95% CI: 0.71 to 0.83), and 0.79 (95% CI: 0.73 to 0.85), respectively (Supplemental Table 7). The PCP-HF$_{CKD}$ risk equation remained well calibrated for all sex-race subgroups (GND chi-square statistic p > 0.05 for all, Supplemental Table 7).

Discussion

In over 2300 participants with moderate to severe CKD, we investigated the performance of the PCP-HF risk prediction tool, which includes routinely available clinical variables, and was derived and previously validated in general populations without CKD. Whereas the original PCP-HF equations did not perform well in a CKD-specific population, as expected, the refit PCP-HF$_{CKD}$ model performance improved except in Black women. Importantly, the addition specifically of UACR to the PCP-HF$_{CKD}$ model significantly improved performance in all sex-race groups and performed well in an external validation cohort of participants with CKD from MESA. These data suggest that commonly available clinical data, which should include measurement of albuminuria, can reliably identify individuals at highest risk for HF hospitalizations in patients with CKD.

There are multiple explanations for the poor performance of the original PCP-HF risk prediction model in the CRIC Study cohort. The original PCP-HF model was derived largely in community-based study samples, whereas the CRIC Study recruited a majority referred population undergoing subspecialty care specifically for management of CKD. Application of general population-derived risk scores to higher risk samples frequently demonstrates poorer discrimination and especially poorer calibration with systemic under-estimation of event rates.(24) There are multiple unique mechanisms known to place patients with CKD at high risk for CVD, particularly HF.(1, 2, 25–27) Pathophysiologic mechanisms that include hemodynamic alterations, upregulation of the renin-angiotensin-aldosterone system, chronic systemic inflammation, disordered mineral metabolism, and disturbances in the iron-anemia axis in CKD can all contribute to structural and functional myocardial changes that precede HF development.(1, 28–32) Although the PCP-HF equation took into account hypertension and diabetes, two important risk factors for CKD development and progression, other variables that characterize the severity of CKD, such as eGFR and UACR,

were not represented in the original PCP-HF model. Taken together, the risk-enhancing features of CKD for HF in a real world sample led to under-estimation of HF hospitalization risk by the general PCP-HF equations.

Although levels of albuminuria were relatively low at baseline in the CRIC Study, inclusion of UACR added significant value to the refit PCP-HF$_{CKD}$ model that had already been optimized for the CKD population of CRIC Study. Numerous prior studies show that UACR is strongly associated with CVD in patients with CKD, even more so than eGFR. (33–37) UACR is consistently shown to be associated with CVD and all-cause mortality, even for differences within levels below 30–300 mg/g of albuminuria.(34) These data are consistent with the observed improvement in performance of the refit PCP-HF$_{CKD}$ model when UACR was added to the risk equation. The pathophysiologic mechanisms that result in the development of albuminuria may be the similar to the pathways that contribute to HF development. For example, systemic vascular endothelial dysfunction may result in increased glomerular permeability and albuminuria, as well as myocardial remodeling and HF.(38, 39) Chronic systemic inflammation in CKD may also result in albuminuria and myocardial dysfunction, predisposing patients to HF. UACR may also be simply be a biomarker for more severe underlying glomerular pathology. However, the absence of consistent improvement in model performance with the addition of eGFR makes this as the sole explanation less likely and may reflect that lower eGFR and higher UACR may represent different physiologic processes. Recent data suggest underutilization of UACR testing, despite guideline recommendations.(40) Our results signify the importance of measuring albuminuria in patients with CKD, who are at a significant risk for HF events. Early CKD may not present to nephrologists, but other providers. Given the impact of new therapies on CKD and HF outcomes, recognizing the propensity to develop heart failure in the presence of underlying kidney disease, even if UACR is minimal or kidney disease is not severe, remains of clinical importance to all providers.

Although we were able to refit and validate the previously derived and validated sex- and race-specific PCP-HF risk prediction model in a well-established cohort of individuals with CKD with well-adjudicated outcomes, we acknowledge certain limitations. The use of IDI and NRI to assess model performance have inherent limitations.(41) However, our re-fit model was well calibrated and we used multiple methods to test for model performance with the addition of kidney-specific markers. Analyses were restricted to individuals self-identified as Black and White and required the availability of all variables included in the risk prediction model, which limits the generalizability of the modified PCP-HF$_{CKD}$ risk prediction model to this patient population. Race and sex stratification were done to compare our results to the original PCP-HF derivation and validation studies that also used race and sex stratification based on self-report.(4) However, we acknowledge that self-reported race is a social construct and race-specific models were derived instead of using race as a covariate. Future models that better delineate social determinants of health that race is reflecting (e.g., structural and systemic racism) in risk prediction are needed. Despite excluding individuals with known clinical CVD at baseline, we did not exclude individuals with subclinical CVD in the CRIC cohort (structural cardiac or vascular changes [Stage B] who do not yet have overt clinical HF [Stage C]). Although a limitation, this makes our findings more applicable to real-world scenarios where providers may not have assessment of cardiac structure. Using

HF risk equations may identify high-risk individuals who would benefit from further risk stratification with echocardiography. We defined HF events as both definite and probable events in both the CRIC Study and MESA. We also did not delineate subtypes of HF such as preserved versus mid-range or reduced ejection fraction HF, but predicting risk of each subtype may not have additive clinical value as current preventive measures are similar for both subtypes.(42) We also likely underestimated HF risk given that we only included adjudicated hospitalized events and many patients with CKD may have been diagnosed with HF as outpatients without hospitalization, or may have had subclinical heart failure with preserved ejection fraction.(43) Finally, our validation cohort in MESA among those with CKD was a relatively small sample and validation in larger CKD cohorts should be completed in the future.

Conclusions

We demonstrate that the refit and modified PCP-HF$_{CKD}$ risk prediction equations can reliably predict incident HF hospitalization events in patients with CKD. Risk stratification of individuals with CKD for HF may lead to improvement in patient outcomes by identifying patients appropriate for more frequent monitoring, additional risk stratification with non-invasive imaging, and earlier therapeutic interventions. HF risk stratification would also allow enrichment of clinical trials to include individuals with CKD at highest risk for HF who may benefit most from emerging therapeutics. Implementation of the modified PCP-HF$_{CKD}$ risk prediction equation, which includes UACR, to identify individuals with CKD at highest risk for HF hospitalization has the potential to change both clinical and research practices and improve outcomes in the CKD population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Abbreviations

CKD	chronic kidney disease
HF	heart failure
CVD	cardiovascular disease
ACC/AHA	American College of Cardiology/American Heart Association
PCP-HF	Pooled Cohort Equations to Prevent Heart Failure
SGLT2i	sodium glucose co-transporter 2 inhibitors
CRIC	Chronic Renal Insufficiency Cohort
eGFR	estimated glomerular filtration rate
MESA	Multi-Ethnic Study of Atherosclerosis
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
SD	standard deviation
IQR	interquartile ranges
TC	total cholesterol
GND	Greenwood-Nam-D'Agostino
NRI	net reclassification improvement
IDI	integrated discrimination improvement
ESRD	end stage renal disease
BMI	body mass index
CI	confidence interval

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Highlights

- Previously developed risk prediction equations for heart failure that use routinely available clinical parameters in the general population perform poorly in a population with chronic kidney disease stages 2–4 who are at high risk for heart failure.

- Addition of albuminuria, but not estimated glomerular filtration rate, to risk prediction equations improve model performance in patients with chronic kidney disease as assessed by discrimination and calibration statistics.

- Routinely available clinical data that includes albuminuria in patients with chronic kidney disease can reliably identify individuals at risk of HF hospitalizations.
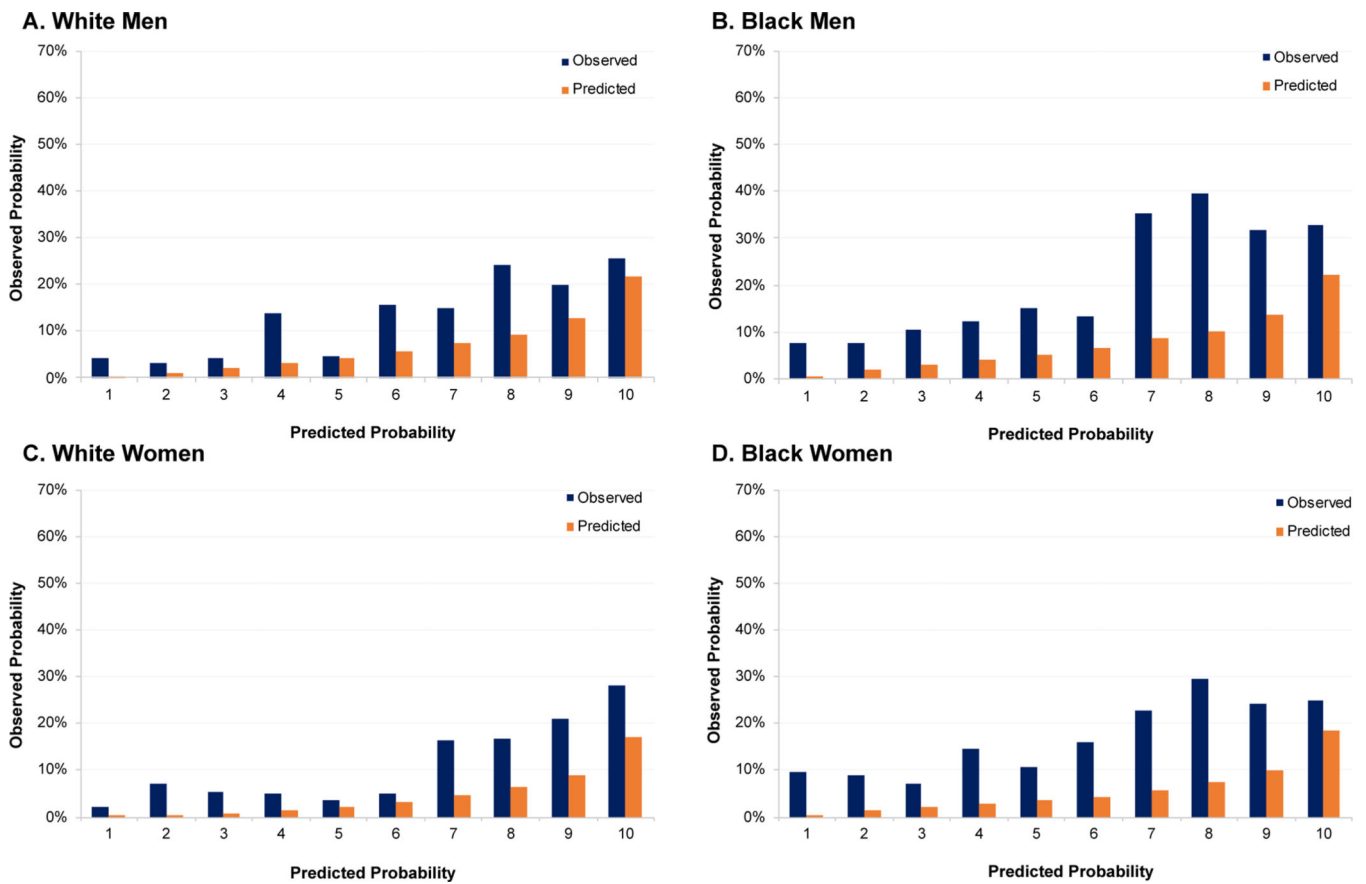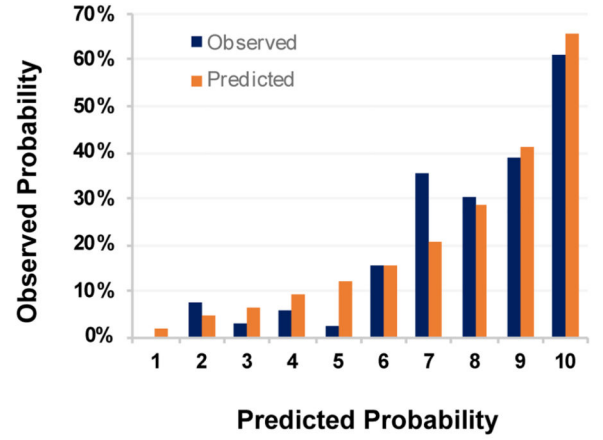
Figure 1.
Sex- and race specific observed (blue) and predicted (orange) mean 10-year predicted risk of incident HF hospitalizations by decile of predicted risk applying the original PCP-HF$_{CKD}$ without QRS duration in the Chronic Renal Insufficiency Cohort Study

Abbreviations: HF, heart failure: PCP-HF$_{CKD}$, Pooled Cohort equations to Prevent Heart Failure Chronic Kidney Disease
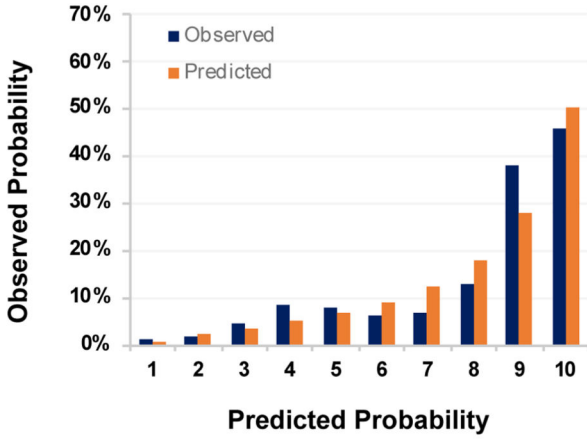
Figure 2.
Sex- and race specific observed (blue) and predicted (orange) mean 10-year predicted risk of incident HF hospitalizations by decile of predicted risk applying the refit PCP-HF$_{CKD}$ incorporating urine albumin-to-creatinine ratio in the Chronic Renal Insufficiency Cohort Study

Abbreviations: HF, heart failure: PCP-HF$_{CKD}$, Pooled Cohort equations to Prevent Heart Failure Chronic Kidney Disease
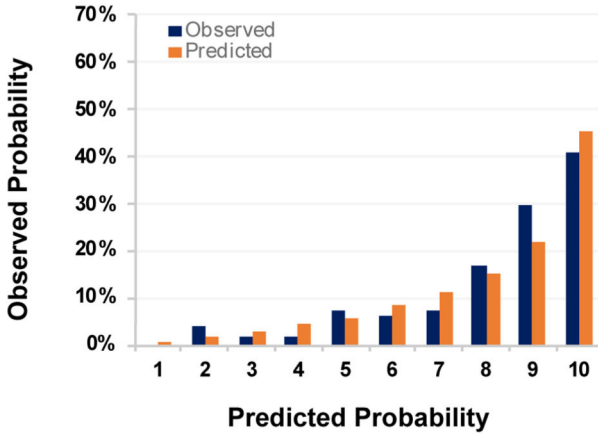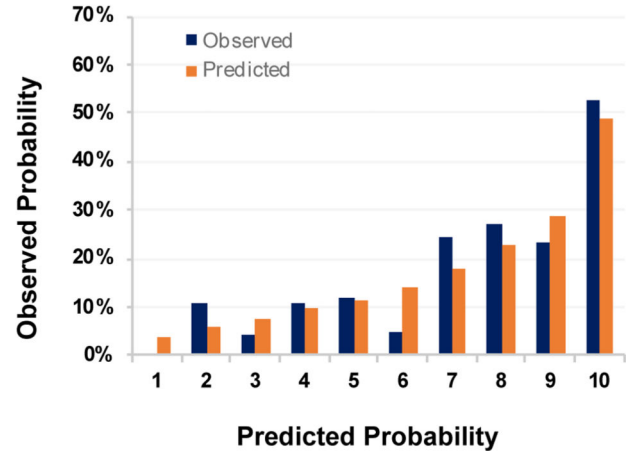
Central Illustration.
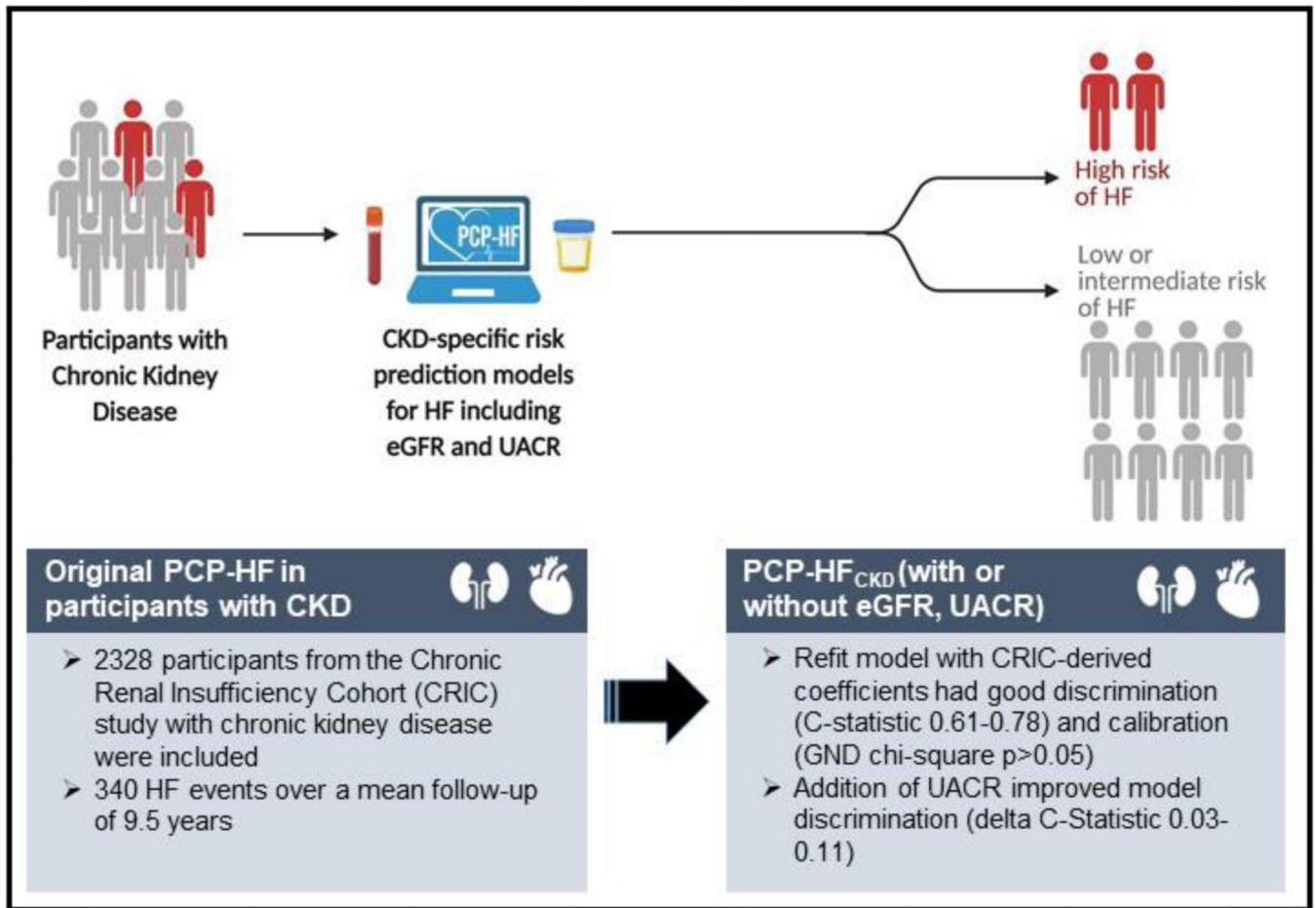10 Year Risk Prediction Equations for Incident Heart Failure Hospitalization in Chronic Kidney Disease.

Table 1.

Baseline demographics of the eligible participants from the Chronic Renal Insufficiency Cohort Study, overall and stratified by sex-race

	Overall	Black		White	
	N=2328	Men N=442	Women N=491	Men N=761	Women N=634
Mean age, years (SD)	56.8 (10.8)	56.4 (10.7)	57.5 (10.2)	56.8 (10.8)	56.6 (11.2)
Diabetes treatment, n (%)	566 (24)	109 (25)	142 (29)	188 (25)	127 (20)
Mean fasting glucose, mg/dL (SD)	111 (49)	115 (59)	113 (50)	111 (45)	109 (46)
Current smoking, n (%)	281 (12)	77 (17)	87 (18)	68 (9)	49 (8)
Mean systolic blood pressure, mm Hg (SD)	127 (21)	130 (21)	131 (21)	126 (20)	123 (20)
Hypertension treatment, n (%)	2049 (89)	406 (92)	460 (94)	682 (90)	501 (80)
Mean total cholesterol, mg/dL (SD)	188 (43)	183 (43)	193 (42)	181 (43)	196 (44)
Mean HDL cholesterol, mg/dL (SD)	49 (16)	46 (14)	54 (18)	42 (12)	55 (17)
Mean BMI, kg/m^2 (SD)	31.9 (7.8)	31.5 (6.2)	35.1 (9.5)	30.5 (6.0)	31.5 (8.6)
Mean eGFR CKD-EPI, ml/min/1.73m^2 (SD)	46 (15)	46 (15)	45 (15)	46 (15)	47 (17)
Median UACR, mg/g (IQR)	37 (7, 381)	86 (13, 452)	32 (7, 352)	50 (7, 467)	17 (6, 199)

Abbreviations: SD, standard deviation; HDL, high density lipoprotein; BMI, body mass index; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; IQR, interquartile range

Table 2.

Numbers of events, discrimination and calibration statistics of the original and refit 10-year PCP-HF models in the Chronic Renal Insufficiency Cohort Study

	Black		White	
	Men	**Women**	**Men**	**Women**
Total N	442	491	761	634
Events	88	85	97	70
PCP-HF Model				
C statistics (95% CI)	0.66 (0.61, 0.72)	0.64 (0.58, 0.70)	0.67 (0.62, 0.73)	0.71 (0.64, 0.78)
GND Chi-square, P value	39.9 (p=0.001)	40.3 (p=0.001)	29.5 (p=0.001)	26.7 (p=0.001)
Refit PCP-HF$_{CKD}$ Model				
C statistics (95% CI)	0.76 (0.71, 0.81)	0.61 (0.54, 0.68)	0.75 (0.70, 0.80)	0.78 (0.73, 0.83)
GND Chi-square, P-value	11.5 (p=0.12)	4.7 (p=0.86)	7.7 (p=0.46)	8.2 (p=0.31)

Abbreviations: PCP-HF, Pooled Cohort equations to Prevent Heart Failure; PCP-HF$_{CKD}$, Pooled Cohort equations to Prevent Heart Failure Chronic Kidney Disease; CI, confidence interval

Table 3.

C-statistic change, NRI, and IDI of data-derived 10-year PCP-HF$_{CKD}$ equation with addition of eGFR and UACR in the Chronic Renal Insufficiency Cohort Study

	C-statistic PCP-HFCKD (95% CI)	C-statistics PCP-HF$_{CKD}$ + renal marker (95% CI)	Delta C-Statistic (p-value)	NRI (p-value)	IDI (p-value)
UACR					
Black Men	0.76 (0.71, 0.81)	0.80 (0.75, 0.85)	0.04 (p = 0.02)	0.44 (p <0.01)	0.04 (p <0.01)
Black Women	0.61 (0.54, 0.68)	0.73 (0.67, 0.79)	0.11 (p = 0.02)	0.51 (p < 0.01)	0.07 (p <0.01)
White Men	0.75 (0.70, 0.80)	0.79 (0.74, 0.84)	0.04 (p = 0.01)	0.61 (p < 0.01)	0.07 (p <0.01)
White Women	0.78 (0.73, 0.83)	0.81 (0.76, 0.86)	0.03 (p = 0.11)	0.44 (p < 0.01)	0.04 (p < 0.01)
eGFR					
Black Men	0.76 (0.71, 0.81)	0.77 (0.72, 0.83)	0.01 (p = 0.30)	0.27 (p = 0.03)	0.02 (p = 0.09)
Black Women	0.61 (0.54, 0.68)	0.72 (0.66, 0.78)	0.11 (p = 0.02)	0.35 (p < 0.01)	0.05 (p < 0.01)
White Men	0.75 (0.70, 0.80)	0.77 (0.72, 0.81)	0.02 (p = 0.15)	0.31 (p < .01)	0.02 (p = 0.03)
White Women	0.78 (0.73, 0.83)	0.79 (0.75, 0.84)	0.01 (p = 0.35)	0.36 (p < 0.01)	0.01 (p = 0.14)
UACR + eGFR					
Black Men	0.76 (0.71, 0.81)	0.80 (0.75, 0.85)	0.04 (P = 0.02)	0.35 (p < 0.01)	0.04 (p < 0.01)
Black Women	0.61 (0.54, 0.68)	0.75 (0.69, 0.81)	0.14 (P <0.01)	0.48 (p < 0.01)	0.07 (p < 0.01)
White Men	0.75 (0.70, 0.80)	0.80 (0.75, 0.84)	0.05 (P < 0.01)	0.64 (p < 0.01)	0.07 (p < 0.01)
White Women	0.78 (0.73, 0.83)	0.81 (0.77, 0.86)	0.03 (P = 0.11)	0.46 (p < 0 .01)	0.04 (p < 0.01)

Abbreviations: PCP-HF$_{CKD}$, Pooled Cohort equations to Prevent Heart Failure Chronic Kidney Disease; UACR, urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; CI, confidence interval