ORIGINAL RESEARCH

Framingham and American College of Cardiology/American Heart Association Pooled Cohort Equations, High-Sensitivity Troponin T, and N-Terminal Pro–Brain-Type Natriuretic Peptide for Predicting Atherosclerotic Cardiovascular Events Across the Spectrum of Kidney Dysfunction

Benjamin Lidgard MD; Leila R. Zelnick PhD; Alan Go MD; Kevin D. O’Brien MD; Nisha Bansal MD; on behalf of the CRIC Study Investigators*

BACKGROUND: Contemporary guidelines recommend using atherosclerotic cardiovascular disease screening tools to guide primary prevention. The performance of these scores is not well known in patients with moderate to advanced chronic kidney disease, particularly in combination with clinically available cardiac biomarkers including N-terminal pro–brain-type natriuretic peptide and high-sensitivity troponin T (hsTnT).

METHODS AND RESULTS: We studied 1027 participants from the Chronic Renal Insufficiency Cohort without self-reported atherosclerotic cardiovascular disease who were not taking aspirin or statins at enrollment. Framingham Risk Score, Pooled Cohort Equation, N-terminal pro–brain-type natriuretic peptide, and hsTnT were measured at baseline. Outcomes included fatal and nonfatal myocardial infarction, stroke, and cardiac death. We calculated 10-fold cross-validated Harrell’s C-indices for each risk score and cardiac biomarker alone and in combination. The C-index (95% CI) for discrimination of atherosclerotic cardiovascular disease was 0.72 (0.67, 0.77) for the Framingham Risk Score, and 0.72 (0.67, 0.76) for the Pooled Cohort Equation. HsTnT had comparable discrimination to each risk score, and improved the discrimination of each (change in Framingham 0.029, 95% CI 0.003, 0.055; change in Pooled Cohort Equation 0.027, 95% CI 0.002, 0.052). N-terminal pro–brain-type natriuretic peptide had poorer discrimination than the risk scores and did not significantly improve their discrimination (change in Framingham 0.009, 95% CI –0.001, 0.018; change in Pooled Cohort Equation 0.011, 95% CI –0.001, 0.024).

CONCLUSIONS: The Framingham Risk Score and Pooled Cohort Equation demonstrated moderate discrimination for atherosclerotic cardiovascular disease in patients with chronic kidney disease. HsTnT, but not N-terminal pro–brain-type natriuretic peptide, improved their discrimination overall. Until chronic kidney disease–specific atherosclerotic cardiovascular disease risk scores can be developed, it may be worth considering how to incorporate hsTnT into existing clinical risk scores.

Key Words: biomarkers ■ cardiovascular disease ■ chronic kidney disease ■ high-sensitivity troponin T ■ N-terminal pro–brain type natriuretic peptide ■ risk scores

Correspondence to: Benjamin Lidgard, MD, Kidney Research Institute, University of Washington, 908 Jefferson St, 3rd Floor, Seattle, WA 98104. Email: blidgard@uw.edu

*A complete list of the CRIC Study Investigators can be found in the Appendix at the end of the article.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024913

For Sources of Funding and Disclosures, see page 10.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

J AHA is available at: www.ahajournals.org/journal/jaha

J Am Heart Assoc. 2022;11:e024913. DOI: 10.1161/JAHA.121.024913
Patients with chronic kidney disease (CKD) are at a greater risk of atherosclerotic cardiovascular disease (ASCVD) and ASCVD complications compared with the general population. Contemporary guidelines recommend using ASCVD screening tools to guide primary prevention to reduce incidence of ASCVD. The Framingham Risk Score and the American College of Cardiology/American Heart Association Pooled Cohort ASCVD Risk Equation both have good discrimination and calibration for predicting ASCVD events in the general population.

Despite the disproportionate risk for ASCVD in patients with CKD, studies of these equations to predict ASCVD in this population are limited, particularly at more advanced CKD stages. The Framingham Risk Score has previously demonstrated poor to moderate calibration and discrimination in patients with mild to moderate CKD; including terms for cystatin C, creatinine, and proteinuria did not markedly improve performance. While the Pooled Cohort Equation had moderate discrimination and good calibration in 1 study of patients with CKD, half of the participants were taking statins at baseline, and the mean estimated glomerular filtration rate (eGFR) was 73.7 mL/min per 1.73 m². Prior studies in CKD included limited numbers of patients with more advanced CKD (eGFR of ≤60 mL/min per 1.73 m²). Moreover, recent studies suggest that clinically available cardiac biomarkers, including high-sensitivity troponin T (hsTnT) and NT-proBNP (N-terminal pro–brain-type natriuretic peptide), may improve risk stratification in conjunction with these risk scores in patients without CKD; this remains untested in patients with CKD. Understanding the performance of these risk scores will clarify their use in directing which patients with CKD may benefit from primary prevention strategies.

We aimed to determine the discrimination and calibration of the Framingham Risk Score and the Pooled Cohort ASCVD Risk Equation in patients with a broad range of CKD without clinically apparent ASCVD, and whether levels of clinically available cardiac biomarkers (NT-proBNP and hsTnT) can further improve the performance of these prediction models in this population.

### CLINICAL PERSPECTIVE

**What Is New?**
- Cardiac risk scores are commonly used clinically to guide primary prevention for atherosclerotic cardiovascular disease, but their performance in patients with chronic kidney disease is not well known, especially in combination with clinically available cardiac biomarkers.
- In a large cohort of participants with chronic kidney disease and without baseline cardiovascular disease, the Framingham Risk Score and Pooled Cohort Equation demonstrated moderate discrimination for the prediction of atherosclerotic events; the performance of each score was significantly improved by the inclusion of high-sensitivity troponin T.

**What Are the Clinical Implications?**
- Until kidney-specific cardiovascular disease risk scores can be developed, it may be worth considering how to incorporate high-sensitivity troponin T into existing clinical risk scores to better guide decisions on primary prevention.

### METHODS

#### Study Population

We studied adults with CKD, without known ASCVD, who could qualify for aspirin or statins for ASCVD prevention in the CRIC (Chronic Renal Insufficiency Cohort) study. Anonymized data and materials have been made publicly available through the National Institute of Diabetes and Digestive and Kidney Diseases public repository and may be accessed through request at https://repository.niddk.nih.gov/studies/cric/. A total of 3939 patients were enrolled in the CRIC study between June 2003 and August 2008 at 7 clinical centers across the United States (Ann Arbor/Detroit, MI; Baltimore, MD; Chicago, IL; Cleveland, OH; New Orleans, LA; Philadelphia, PA; and Oakland, CA). Participants on maintenance dialysis, with prior kidney transplant, or with advanced heart failure (New York Heart Association Class III or IV) were excluded. All participants had annual in-person study visits where detailed interviews were conducted. All participants provided written informed consent, and the study protocol was approved by institutional review boards at each of the participating sites.

We excluded participants without baseline levels of NT-proBNP and hsTnT (N=132), participants taking aspirin or statins at baseline (N=2618), and participants with baseline ASCVD (N=159) (Figure S1). This was done to analyze participants who would most benefit from prediction models for ASCVD, specifically those who may qualify for primary prevention medications. Finally, we excluded individuals who did not have the data needed to calculate the Framingham Risk Score.

### Nonstandard Abbreviations and Acronyms

| Acronym | Description                        |
|---------|------------------------------------|
| CRIC    | Chronic Renal Insufficiency Cohort |
| HsTnT   | high-sensitivity troponin T        |
and Pooled Cohort equation (N=3), yielding our analytic cohort of 1027 individuals.

Exposures
The Framingham 10-year ASCVD Hard Coronary Heart Disease Score was calculated using: age, total cholesterol, high-density lipoprotein, systolic blood pressure, treatment status for hypertension, and smoking status. It was designed for use in patients without coronary heart disease at baseline from age 30 to 79 years old, though we calculated the Framingham Risk Score for those <30 years old as though their age was 30 years old. It estimates the risk of fatal or nonfatal myocardial infarction (MI) or cardiac death in the next 10 years. Risk is categorized as low, moderate, or high (<10%, 10% to <20%, or ≥20% risk of ASCVD in 10 years, respectively). The Pooled Cohort Equation predicts the 10-year risk of stroke, fatal or nonfatal MI, or cardiac death, and includes a term for race and ethnicity (Black race versus White race, or Other, including Hispanic, Asian or Pacific Islander, and American Indian or Alaska Native) in addition to the components of the Framingham Risk Score. It was designed for use in patients from 40 to 79 years of age without existing cardiovascular disease, though as above we calculated the Pooled Cohort Equation for participants <40 years of age as though their age was 40 years old. Risk is categorized as low or high (<7.5% or ≥7.5% risk of ASCVD in 10 years).

Baseline NT-proBNP and hsTnT were measured at the University of Maryland in 2008 from EDTA plasma stored at −70 °C using a chemiluminescent microparticle immunoassay (www.roche-diagnostics.us, Basel, Switzerland) on the ElecSys 2010. Values of NT-proBNP ranged from 5 to 35 000 pg/mL; the coefficient of variation was 9.3% at 126 pg/mL and 5.5% at 4319 pg/mL. HsTnT values ranged from 3 to 10 000 ng/mL. Values below the lower limit of blank were characterized as “undetectable.” The coefficient of variation was 6.0% at 26 ng/mL and 5.4% at 2140 ng/mL. The value of the 99th percentile cutoff from a healthy reference population was 13 ng/mL for hsTnT with a 10% coefficient of variation.

Determination of Cardiac Outcomes
We evaluated 2 separate primary composite outcomes, defined by the risk score in question. Calculations involving the Framingham Score were performed with a primary end point as the composite of fatal and nonfatal MI and cardiac death. Calculations involving the Pooled Cohort Equation used a composite of fatal or nonfatal MI, stroke, and cardiac death as the primary end point.

MI was defined as a typical rise and either slow or rapid fall in cardiac enzymes along with either typical symptoms of a MI or ECG changes compatible with this diagnosis. Stroke was defined as any new neurologic deficit of ≥24 hours duration. Patient-reported hospitalizations triggered retrieval of medical records, which were reviewed and adjudicated by 2 physicians. Deaths in CRIC were determined by reports from next of kin, retrieval of death certificates, and state death files, if available. For deaths occurring during an adjudicated hospitalization, physician review determined if the death was cardiac in nature. For nonadjudicated deaths, a machine-learning algorithm utilizing adjudicated death events as the criterion standard was used to predict the probability of cardiac death based on cause of death codes from the National Death Index data. Of 264 deaths in our analytic population, 50 were classified as cardiac, 117 were classified as noncardiac, and 97 could not be classified. Only cardiac deaths were included in the composite outcomes.

Covariates
At study enrollment, participants provided information on their sociodemographic characteristics, medical history, medication use, and lifestyle behaviors. Race and ethnicity were self-reported, categorized as non-Hispanic White, non-Hispanic Black, Hispanic, or Other, including Asian or Pacific Islander and American Indian or Alaska Native. Baseline ASCVD status was self-reported, defined as prior coronary artery disease, heart failure, or stroke. Blood pressure and body mass index were assessed using standard protocols. Diabetes was defined as a fasting glucose >126 mg/dL, a nonfasting glucose >200 mg/dL, or use of antidiabetic medications, including insulin. Tobacco use was dichotomized as current versus no use at time of cohort entry.

Serum creatinine was measured on an Ortho Vitros 950 (Raritan, NJ) at the CRIC Central Laboratory using a standardized enzymatic method and was used to calculate eGFR via the Chronic Kidney Disease Epidemiology Collaboration equation. Additional measurements included 24-hour urine protein and sodium, low-density lipoprotein and high-density lipoprotein cholesterol, and hemoglobin.

Statistical Analysis
Study variables were described overall and across categories of each risk score. A scatterplot of each participants’ Framingham Risk Score and Pooled Cohort Equation score was generated; we calculated Pearson correlation coefficient. Our outcomes of interest were the composites of cardiac death and fatal and nonfatal MI (Framingham outcomes), and cardiac death, fatal and nonfatal MI, and stroke (Pooled Cohort Equation outcomes). Follow-up time started at each participant’s study enrollment visit, and was defined as time
RESULTS

Characteristics of the Study Population
Among 1027 eligible participants, the mean age was 52 years, and 524 (51%) were women. Four hundred fifteen (40%) participants were non-Hispanic White, and 419 (41%) were non-Hispanic Black. The mean (minimum, maximum) eGFR was 48 (16, 110) mL/min per 1.73 m²; among those with eGFR ≥60 mL/min per 1.73 m², the median (interquartile range) eGFR was 68 (64, 76) mL/min per 1.73 m². The median proteinuria was 0.15 g/d. On average, the study group had few comorbidities, and blood pressure was well controlled (mean systolic blood pressure, 125 mm Hg) (Table 1). Participants with higher Framingham or Pooled Cohort Equation scores tended to have lower eGFRs and higher proteinuria (Tables 1 and 2). There was moderate correlation between individuals’ risk scores (Pearson’s correlation coefficient 0.85, Figure S2).

Predicted and Observed IRs of Fatal and Nonfatal MI and Cardiac Death Overall and by eGFR Categories by the Framingham Risk Score
Among 1027 eligible participants, the composite outcome of fatal and nonfatal MI and cardiac death occurred in 92 participants over a median follow-up time of 10.0 years (interquartile range, 6.5–10.0). The Framingham Risk Score did not significantly overestimate the rates of ASCVD overall, though it overestimated ASCVD events at eGFR >60 mL/min per 1.73 m² and at eGFR 45 to 59 mL/min per 1.73 m² (Table 3).

Predicted and Observed IRs of Fatal and Nonfatal MI, Cardiac Death, and Stroke Overall and by eGFR Categories by the Pooled Cohort Equation
The composite outcome of fatal and nonfatal MI, stroke, and cardiac death occurred in a total of 113 participants over a median follow-up time of 10.0 years (interquartile range, 6.3–10.0). The Pooled Cohort Equation significantly underestimated rates of ASCVD events overall (difference between observed and predicted IRs 3.7, 95% CI, 1.2–6.1 events per 1000 patient years); this was most pronounced at eGFR <30 mL/min per 1.73 m² (Table 3).

Discrimination of Framingham Risk Score, Pooled Cohort Equation, and Cardiac Risk Markers
The Framingham Risk Score and Pooled Cohort Equation demonstrated moderate discrimination overall (C-indices 0.72, 95% CI, 0.67–0.77, and 0.72, 95% CI, 0.67–0.76, respectively) (Figure 1). HsTnT demonstrated comparable discrimination to the Framingham Risk Score and the
Pooled Cohort Equation (differences in C-indices 0.02, 95% CI, −0.03 to 0.07, and 0.01, 95% CI, −0.04 to 0.05, respectively). The point-estimates for the discrimination of NT-proBNP alone were lower than those for the baseline risk scores, though the differences were not statistically significant. Adding hsTnT to the Framingham Risk Score and the Pooled Cohort Equation significantly improved both C-indices; adding NT-proBNP did not significantly improve the discrimination of either risk score (Figure 1).

Calibration of Framingham Risk Score and Pooled Cohort Equation
The Framingham Risk Score tended to overestimate the risk of composite outcomes at the lowest and highest risk deciles; it underestimated the risk at the second-highest risk decile (Figure 2). The Pooled Cohort Equation tended to overestimate the risk of composite outcomes at the lowest risk deciles and tended towards underestimation for patients in the second and third highest risk deciles (Figure 3).

Sensitivity Analysis: Discrimination of Framingham Risk Score, Pooled Cohort Equation, and Cardiac Risk Markers by eGFR Categories
At eGFR ≥60 mL/min per 1.73 m², both the Framingham Risk Score and the Pooled Cohort Equation demonstrated...
excellent discrimination. At eGFRs <60 mL/min per 1.73 m², both risk scores performed significantly worse compared with their discrimination at eGFRs ≥60 mL/min per 1.73 m² (Table 4). HsTnT alone had C-indices comparable to the Framingham Risk Score at all eGFR strata; these findings were also observed for hsTnT compared with the Pooled Cohort Equation (Table 4).

Sensitivity Analysis: Excluding Participants With Age Out of Range
Excluding participants with age out of range for each risk score (<30 or >79 for Framingham, N excluded=184) did not meaningfully alter the observed C-indices. Adding HsTnT to each clinical risk score significantly improved the discrimination of each (Figure S3). Similar to our findings in the primary analyses, the Framingham Risk Score did not significantly overestimate cardiac events in this subset; however, the Pooled Cohort Equation significantly underestimated observed events (Table S1).

DISCUSSION
In a large population of patients with CKD without known ASCVD and not taking primary prevention...
cardiovascular therapies, we demonstrated moderate discrimination of the Framingham Risk Score and Pooled Cohort Equation to predict ASCVD events. The discrimination of both scores was significantly improved with the addition of hsTnT, but not NT-proBNP. This study adds to the growing literature demonstrating the limitations of existing cardiovascular risk scores in CKD populations, particularly in advanced CKD. Until CKD-specific ASCVD risk scores can be developed, it may be worth investigating how to incorporate hsTnT into existing risk scores to predict ASCVD in patients with eGFR <60 mL/min per 1.73 m².

Table 3. IRs for ASCVD Events* Predicted by the Framingham Risk Score and Pooled Cohort Equation and Observed Composite Events in Total and by eGFR (Per 1000 Patient Years) Among Participants With CKD

|                        | Overall (N=1027) | eGFR ≥60 (N=247) | eGFR 45–59 (N=310) | eGFR 30–44 (N=313) | eGFR <30 (N=157) |
|------------------------|------------------|------------------|-------------------|-------------------|------------------|
| ASCVD                  |                  |                  |                   |                   |                  |
| Observed IR (per 1000 patient y) | 11.1 (8.8 to 13.3) | 4.4 (1.5 to 7.3) | 9.1 (5.5 to 12.8) | 14.1 (9.5 to 18.7) | 21.1 (12.4 to 29.7) |
| Framingham-predicted IR (per 1000 patient y) | 12.7 (12.1 to 13.4) | 8.0 (7.0 to 8.9) | 13.2 (12.1 to 14.2) | 14.8 (13.7 to 15.9) | 15.3 (13.7 to 16.8) |
| Difference between observed and Framingham-predicted IRs | −1.7 (−3.8, 0.5) | −3.6 (−6.3, −0.8)† | −4.0 (−7.7, −0.4)† | −0.7 (−5.2, 3.9) | 5.8 (−2.4, 14.0) |
| ASCVD and stroke‡ |                  |                  |                   |                   |                  |
| Observed IR of ASCVD and stroke (per 1000 patient y) | 13.7 (11.2 to 16.3) | 5.9 (2.5 to 9.3) | 10.3 (8.5 to 14.2) | 17.5 (12.4 to 22.7) | 27.8 (18.0 to 37.7) |
| Pooled Cohort Equation-Predicted IR (per 1000 patient y) | 10.0 (9.4 to 10.7) | 5.2 (4.4 to 6.1) | 10.1 (8.9 to 11.3) | 12.5 (11.1 to 13.9) | 12.5 (10.6 to 14.4) |
| Difference between observed and Pooled-Cohort Equation-predicted IRs | 3.7 (1.2, 6.1)† | 0.6 (−2.4, 3.7) | 0.2 (−3.7, 4.1) | 5.0 (−0.1, 10.1) | 15.3 (5.9 to 24.7)† |

ASCVD indicates atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, glomerular filtration rate; and IRs, incidence rates.

*Framingham Risk Score composite outcome: first fatal or nonfatal myocardial infarction or cardiac death.
†Statistically significant differences between observed and predicted IRs.
‡Pooled Cohort Equation composite outcome: first stroke, fatal or nonfatal myocardial infarction, or cardiac death.

Previous studies have demonstrated poor to moderate discrimination of the Framingham Risk Score in patients with CKD. One study of 934 patients in the Atherosclerosis Risk in Communities cohort (mean eGFR 53 mL/min per 1.73 m²) reported C-indices of 0.60 for men and 0.73 for women. Another study including 756 participants with CKD from both the Atherosclerosis Risk in Communities and Cardiovascular Health Studies cohorts found poor to moderate discrimination of the Framingham Risk Score after stratifying by race, ethnicity and sex (C-index 0.644–0.783 for cardiac events, 0.641–0.707.

Figure 1. Discrimination of incident atherosclerotic cardiovascular disease outcomes by the Framingham Risk Score and Pooled Cohort Equation with and without cardiac biomarkers, and by cardiac biomarkers alone.

Outcomes are fatal and nonfatal myocardial infarction and cardiac death for Framingham Risk Score. For the Pooled Cohort Equation, outcomes are fatal and nonfatal myocardial infarction, stroke, and cardiac death. hsTnT indicates high-sensitivity troponin T; and NT-proBNP, N-terminal pro–brain-type natriuretic peptide.

Figure 2. Calibration plot of observed vs predicted CIF by the Framingham Score in participants with CKD.
CIF indicates cumulative incidence fraction; CKD, chronic kidney disease; CV, cardiovascular; and MI, myocardial infarction.
for mortality events); discrimination was not significantly improved by adding terms for CKD severity.\(^{23}\) Our study also found that the Framingham Risk Score has only moderate discrimination in patients with CKD in this well-characterized CKD cohort with a large range of CKD severity, including those with advanced CKD.

Only one previous study of the Pooled Cohort Equation demonstrated moderate discrimination in participants with CKD; however, half of the participants were on statins at baseline, and the mean eGFR was higher than the eGFR in our present study (73.7 versus 48 mL/min per 1.73 m\(^2\)).\(^{24}\) Previous studies have not demonstrated benefit from adding terms for creatinine, cystatin C, or proteinuria to improve the performance of traditional risk factors in CKD cohorts.\(^{20,21}\) However, a study of 115,366 Chinese patients demonstrated that Kidney Disease: Improving Global Outcomes risk categories, eGFR, and urinary albumin/creatinine ratio can reclassify Pooled Cohort Equation risk and improve discrimination.\(^{54}\) Because only 2% of those participants had an eGFR of <60 mL/min per 1.73 m\(^2\), it is unclear whether these results are generalizable to moderate to severe CKD. Our study adds to this previous literature by studying the discrimination of the Pooled Cohort Equation in a large, dedicated CKD cohort, which differs from prior studies.

In our study, a single biomarker (hsTnT) displayed discrimination comparable to the multivariable Framingham Risk Score and the Pooled Cohort Equations in participants with CKD. Additionally, including a term for hsTnT significantly improved the discrimination of both risk scores in the overall CKD population. HsTnT is a marker of myocardial ischemia that increases with severity of ischemia.\(^{25–27,36,37}\) It is associated with cardiovascular

---

**Table 4.** Discrimination of Framingham Risk Score, Pooled Cohort Equation, and hsTnT by C-Indices (95% CIs) for Predicting Atherosclerotic Cardiovascular Events*, by eGFR Categories Among Participants With CKD

| Predictor | eGFR ≥60 mL/min per 1.73 m\(^2\) (N=247) | eGFR 45–59 mL/min per 1.73 m\(^2\) (N=310) | eGFR 30–44 mL/min per 1.73 m\(^2\) (N=313) | eGFR <30 mL/min per 1.73 m\(^2\) (N=157) |
|-----------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| ASCVD‡    | Number of events                       | 9                                      | 24                                      | 35                                      | 24                                      |
|           | C-index: Framingham Score              | 0.86 (0.76 to 0.96)                    | 0.63 (0.53 to 0.74)                    | 0.65 (0.56 to 0.73)                    | 0.76 (0.67 to 0.85)                    |
|           | C-index: hsTnT                         | 0.78 (0.61 to 0.94)                    | 0.73 (0.62 to 0.85)                    | 0.62 (0.53 to 0.72)                    | 0.76 (0.68 to 0.84)                    |
| C-index difference | −0.10 (−0.21, 0.01)                   | 0.03 (−0.06, 0.11)                    | −0.002 (−0.11, 0.10)                   |
| C-index difference for each eGFR category vs eGFR ≥60 mL/min per 1.73 m\(^2\) | | | | |
| Framingham Score | Referent | −0.23 (−0.37, −0.08)\(^{†}\) | −0.21 (−0.35, −0.08)\(^{†}\) | −0.10 (−0.23, −0.03)\(^{†}\) |
| hsTnT     | Referent                                 | −0.04 (−0.24, 0.16)                    | −0.16 (−0.35, 0.04)                    | −0.01 (−0.20, 0.17)                    |
| ASCVD and stroke‡ | Number of events                       | 12                                     | 27                                      | 43                                      | 31                                      |
|           | C-index: Pooled Cohort Equation         | 0.87 (0.79 to 0.96)                    | 0.63 (0.53 to 0.73)                    | 0.65 (0.57 to 0.73)                    | 0.73 (0.65 to 0.82)                    |
| C-index: hsTnT | 0.78 (0.65 to 0.91)                    | 0.73 (0.62 to 0.84)                    | 0.63 (0.55 to 0.72)                    | 0.70 (0.61 to 0.79)                    |
| C-index difference | −0.10 (−0.20, 0.003)                   | 0.02 (−0.06, 0.09)                    | 0.03 (−0.06, 0.13)                    |
| C-index difference for each eGFR category vs eGFR ≥60 mL/min per 1.73 m\(^2\) | | | | |
| Pooled Cohort Equation | Referent | −0.25 (−0.37, −0.12)\(^{†}\) | −0.22 (−0.34, −0.11)\(^{†}\) | −0.14 (−0.26, −0.02)\(^{†}\) |
| hsTnT     | Referent                                 | −0.05 (−0.23, 0.12)                    | −0.15 (−0.31, 0.01)                    | −0.08 (−0.24, 0.08)                    |

ASCVD indicates atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, glomerular filtration rate; and hsTnT, high-sensitivity troponin T.

*Framingham Risk Score composite outcome: first fatal or nonfatal myocardial infarction or cardiac death.

†Statistically significant differences between C-indices.

‡Pooled Cohort Equation composite outcome: first stroke, fatal or nonfatal myocardial infarction, or cardiac death.
disease and cardiovascular mortality in the general population and in patients with CKD. HsTnT has been shown to improve the discrimination of a clinical risk score composed of the components of the Pooled Cohort Equation in the geriatric population and in the Atherosclerosis Risk in Communities cohort. Furthermore, a recent study of 8635 patients found that incorporating high-sensitivity troponin I into guideline-derived ASCVD risk algorithms enhanced risk stratification and reclassified nearly 12% of patients into more appropriate risk groups. HsTnT has been investigated as a predictor of mortality and stroke in patients with atrial fibrillation, and as a predictor of MI and major adverse cardiac events following major surgery. Our current work expands these possibilities to the CKD population. It is noteworthy that hsTnT is partially cleared by kidney function, and eGFR and hsTnT are inversely correlated. However, it is unlikely that elevations in hsTnT can be explained by decreased kidney function alone; prior studies have demonstrated strong associations of elevated hsTnT with clinical outcomes in patients with CKD. Therefore, hsTnT may be a promising marker to improve risk prediction of atherosclerotic cardiovascular disease in patients with CKD.

Given evidence demonstrating the poor to moderate performance of existing clinical risk scores in the high-risk CKD population, the question becomes whether we should recalibrate existing risk scores or develop novel risk scores to predict ASCVD events in CKD. Weiner et al improved the discriminatory function of the Framingham Risk Score in CKD by recalibrating and modifying the weight of various risk factors in the equation, concluding that future efforts should focus on developing novel scores specifically for the CKD population. This was because, in part, of the non-uniform underestimation of ASCVD risk, which made recalibration alone inadequate for improvement of the overall performance. We similarly observed nonuniform over- and underestimation of ASCVD risk, suggesting that recalibration alone appears inadequate. Albuminuria and eGFR have not previously improved the performance of traditional risk factors for ASCVD; however, a recent study incorporating multiple cohorts with a mean eGFR of 86 mL/min per 1.73 m² demonstrated modestly improved discrimination when applying terms for eGFR and albuminuria. While discrimination may be improved in mild CKD, it may be advisable to consider alternative ways to predict ASCVD, or to create de novo ASCVD risk scores specifically for use in patients with moderate-to-severe CKD. Patients with CKD may have CKD-specific, pro-atherogenic risk factors, including disordered mineral bone metabolism, inflammation, and proteinuria, which are not accounted for by existing risk scores. Novel scores including CKD-specific risk factors may be needed to more accurately predict ASCVD risk in these patients.

This study has several notable strengths. First, it was performed in the well-characterized CRIC cohort, including patients with a wide range of CKD severity. The median follow-up time was 10 years, the same follow-up time predicted by each risk score. We analyzed patients who were not taking cardioprotective medications (aspirin and statins) and without reported history of ASCVD, selecting a population that would be considered candidates for primary prevention ASCVD therapies guided by risk prediction. This study contributes to the existing literature by comparing the performance of the Framingham Risk Score and the Pooled Cohort Equation in the CKD population, and by evaluating clinically available biomarkers alone and in combination with these risk scores. However, this study does have several limitations. First, all baseline atherosclerotic disease history was obtained by self-report, and we were unable to exclude individuals with clinically silent or early-stage ASCVD at enrollment. Second, the Framingham Risk Score was intended for use in patients aged 30 to 79 years of age, and the Pooled Cohort Equation was intended for use in patients 40 to 79 years of age. However, our findings did not differ in a sensitivity analysis excluding patients with ages out of range for the risk scores. Third, we measured only hsTnT, and not its isoform, high-sensitivity troponin I. Not all deaths in our study were characterized as cardiac or noncardiac; it is possible that some cardiac deaths were not counted, decreasing our observed IRs. Furthermore, the number of events were small in some categories of eGFR, especially at eGFR >60 mL/min per 1.73 m², which limits our power in this sensitivity analysis. Finally, the cohort was composed of volunteers who were closely followed in clinic, possibly limiting generalizability to other CKD populations.

In conclusion, our study demonstrated that the Framingham Risk Score and Pooled Cohort Equation had moderate discrimination in patients with CKD, with significantly lower discrimination in more advanced stages of CKD. HsTnT, but not NT-proBNP, significantly improved the discrimination of these clinical models. Further work is warranted to recalibrate available risk scores for improved prediction of ASCVD events in patients with CKD or develop novel risk scores specifically for use in the CKD population.

APPENDIX

**CRIC Study Investigators**

Lawrence J. Appel, MD, MPH; Jing Chen, MD, MMSc, MSc; Debbie L. Cohen, MD; Harold I. Feldman, MD, MSCE; James P. Lash, MD; Robert G. Nelson MD, PhD, MS; Panduranga S. Rao, MD; Mahboob Rahman; Vallabh O. Shah, PhD, MS; Mark L. Unruh, MD, MS.
ARTICLE INFORMATION
Received December 1, 2021; accepted April 22, 2022.

Affiliations
Department of Medicine, University of Washington, Seattle, WA (L.L., L.R.Z., K.D.O., N.B.); and Kaiser Permanente Division of Research, Northern California, Oakland, CA (A.G.).

Sources of Funding
This study was supported by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) R01 DK103612 (Bansal) and NIDDK T32 DK020476 (Lidgard). Roche Diagnostics provided partial funding for the NT-proBNP and hsTnT assays. Additional support was provided by an unrestricted fund from the Northwest Kidney Centers. Funding for the CRIC Study was obtained under a cooperative agreement from NIDDK (U01DK060990, U01DK060984, U01DK061022, U01DK061021, U01DK061028, U01DK060980, U01DK060983, U01DK060903, U01DK060902, and U24DK060990). In addition, this work was supported in part by: the Perelman School of Medicine at the University of Pennsylvania Clinical and Translational Science Award NIH/NCRR U01DK060980, U01DK060963, U01DK060903, U01DK060902, and U24DK060990.

REFERENCES
1. D’Mello RL, Montalescot G, Steg PG, Ohman EM, Eagle K, Bhatt DL. Renal function, atherothrombosis extent, and outcomes in high-risk patients. Am Heart J. 2009;158:141–148.e141. doi:10.1016/j.amhe.2009.05.011
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–1305. doi:10.1056/NEJMoa041031
3. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, Coresh J, Levey AS, Sarnak MJ. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. J Am Coll Cardiol. 2003;41:47–55. doi:10.1016/S0735-1097(02)02963-3
4. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–2081. doi:10.1016/S0140-6736(10)60748-9
5. Meisinger C, Döring A, Löwel H. Chronic kidney disease and risk of incident myocardial infarction and all-cause and cardiovascular disease mortality in middle-aged men and women from the general population. Eur Heart J. 2006;27:1245–1250. doi:10.1093/eurheartj/ehi880
6. Schwarz U, Buzello M, Ritz E, Stein G, Raabe G, Wiest G, Mall G, Amann K. Mortality of coronary atherosclerotic lesions in patients with end-stage renal failure. Nephrol Dial Transplant. 2000;15:218–223. doi:10.1093/ndt/15.2.218
7. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. J Am Soc Nephrol. 2004;15:1307–1315. doi:10.1097/01asn.00000123891.46138.e2
8. Sarnak MJ, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, Gill JS, Hlatky MA, Jardine AG, Landmesser U, et al. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. J Am Coll Cardiol. 2019;74:1823–1838. doi:10.1016/j.jacc.2019.08.1017
9. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Circulation. 2014;129:S1–S45. doi:10.1161/CIR.0000000000000370
10. Sarnak MJ, Bloom R, Muntner P, Rahman M, Saliad JM, Wilson PW, Fried L. KDOQI US commentary on the 2013 KDIGO clinical practice guideline for lipid management in CKD. Am J Kidney Dis. 2015;65:354–366. doi:10.1053/j.ajkd.2014.10.005
11. Damen JA, Papiuhireshna R, Heus P, Moons KGM, Reitsma JB, Scholten RJPM, Hooft L, Debrey TPA. Performance of the Framingham risk models and Pooled Cohort Equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis. BMC Med. 2019;17:109. doi:10.1186/s12916-019-1340-7
12. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D’Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O’Donnell CJ, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. Circulation. 2014;129:S48–S73. doi:10.1161/circ.all.100.000437/48606.e8
13. Henderson KH, Kaufman BG, Stearns S, Couper D, Sueta C, Kucharska-Newton AM, Foraker RE, Asafu-Adjei J, Chang P. Validation of the atherosclerotic cardiovascular disease (ASCVD) pooled cohort risk equations by education level: the Atherosclerosis Risk in Communities (ARIC) Study. J Am Coll Cardiol. 2016;67:1842–1842. doi:10.1016/j.jacc.2016.03.043-5
14. Muntner P, Colanlodion LD, Cushman M, Goff DC Jr, Howard G, Howard VJ, Kissela B, Levitan EB, Lloyd-Jones DM, Safford MM. Validation of the atherosclerotic cardiovascular disease pooled cohort risk equations. JAMA. 2014;311:1406–1415. doi:10.1001/jama.2014.2630
15. Garcia M, Medina-Inojosa JR, Somers VK, Chaudhry R, Randal T, Mulvagh SL, Lopez-Jimenez F. Validation of the 2013 ACC/AHA Pooled Cohort Equation for 10-year atherosclerotic cardiovascular risk assessment in a contemporary, community-based historical cohort. Circulation. 2016;134:A20376–A20376. doi:10.1161/circ.134.suppl_1.20376
16. Chia YC, Gray SYW, Ching SM, Lim HM, Chinna K. Validation of the Framingham general cardiovascular risk score in a multiethnic Asian population: a retrospective cohort study. BMJ Open. 2015;5:007324. doi:10.1136/bmjopen-2014-007324
17. D’Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001;286:180–187. doi:10.1001/jama.286.2.180
18. Liu J, Hong Y, D’Agostino RB Sr, Wu Z, Wang W, Sun J, Wilson PW, Kannel WB, Zhao D. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA. 2004;291:2591–2599. doi:10.1001/jama.291.21.2591
19. Marrugat J, D’Agostino R, Sullivan L, Esosua R, Wilson P, Ordovas J, Solanas P, Cordón F, Ramos R, Sala J, et al. An adaptation of the Framingham coronary heart disease risk function to European Mediterranean areas. J Epidemiol Community Health. 2003;57:634–638. doi:10.1136/jech.57.8.634
20. Classe CM, Gao P, Tobe SW, McQueen MJ, Grossshening A, Teo KK, Yusuf S, Mann JF. Estimated glomerular filtration rate and albuminuria as predictors of outcomes in patients with high cardiovascular risk: a cohort study. Ann Intern Med. 2011;154:310–318. doi:10.7326/0003-4819-154-10-20110301-00005
21. Ito H, Pacolid I, Durazo-Arvizu R, Liu K, Shihipak MG, Goff DC Jr, Tracy RP, Kramer H. The effect of including cystatin C or creatinine in a cardiovascular risk model for asymptomatic individuals: the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol. 2011;174:949–957. doi:10.1093/aje/kwr185
22. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, Sarnak MJ. The Framingham predictive instrument in chronic kidney disease. J Am Coll Cardiol. 2007;50:217–224. doi:10.1016/j.jacc.2007.03.037
23. Weiner DE, Tighiouart H, Griffith JL, Elsayed E, Levey AS, Salem DN, Sarnak MJ. Kidney disease, Framingham risk scores, and cardiac and mortality outcomes. Am J Med. 2007;120:552.e1–552.e8. doi:10.1016/j.amjmed.2006.05.054
24. Colanlodion LD, Baber U, Banach M, Tanner RM, Wamock DG, Gutiérrez OM, Safford MM, Wanner C, Howard G, Muntner P. Contrasting ASCVD Risk Scores and hsTnT in CKD
chol...
Lidgard et al

ASCVD Risk Scores and HsTnT in CKD

68. Isaka Y, Hamano T, Fuji H, Tsujimoto Y, Koju F, Sakaguchi Y, Tanaka R, Tomiyama N, Tatsugami F, Teramukai S. Optimal phosphate control related to coronary artery calcification in dialysis patients. J Am Soc Nephrol. 2021;32:723–735. doi: 10.1681 ASN.2020050598

69. Rickers PM, MacFadyen JG, Glynn RJ, Koenig W, Libby P, Everett BM, Lefkowitz M, Thuren T, Cornel JH. Inhibition of interleukin-1β by canakinumab and cardiovascular outcomes in patients with chronic kidney disease. J Am Coll Cardiol. 2018;71:2405–2414. doi: 10.1016/j.jacc.2018.03.490

70. Currie G, Delles C. Proteinuria and its relation to cardiovascular disease. Int J Nephrol Renovasc Dis. 2013;7:13–24. doi: 10.2147/INRD.S40522

71. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emereick A, Greaser L, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342:1478–1483. doi: 10.1056/NEJM2000051834203

72. O’Neill WC, Lomashvili KA. Recent progress in the treatment of vascular calcification. Kidney Int. 2010;78:1232–1239. doi: 10.1038/kid.2010.334

73. Zoccali C, Vanholder R, Massy ZA, Ortiz A, Sarafidis P, Dekker FW, Fliser D, Fouque D, Heine GH, Jager KJ, et al. The systemic nature of CKD. Nat Rev Nephrol. 2017;13:344–358. doi: 10.1038/ nmneph.2017.52

74. Kielstein JT, Veldink H, Martens-Lobenhoffer J, Haller H, Perthel R, Lovric S, Lichtinghagen R, Klem V, Bode-Böger SM. Unilateral nephrectomy causes an abrupt increase in inflammatory mediators and a simultaneous decrease in plasma ADMA: a study in living kidney donors. Am J Physiol Renal Physiol. 2011;301:F1042–F1046. doi: 10.1152/ajprenal.00640.2010
SUPPLEMENTAL MATERIAL
Table S1. Incident Rates (IRs) for atherosclerotic cardiovascular disease (ASCVD) events* predicted by the Framingham Risk Score and Pooled Cohort Equation and observed composite events in total and by eGFR (per 1000 patient years) among participants with CKD, excluding participants not in specified age range for each score (30-79 for Framingham, 40-79 for Pooled Cohort Equation).

| ASCVD*                       | Overall N | eGFR ≥60 | eGFR 45-59 | eGFR 30-44 | eGFR <30 |
|------------------------------|-----------|----------|------------|------------|----------|
| Observed IR (per 1000 patient years) | N = 982   | N = 235  | N = 299    | N = 300    | N = 148  |
| Framingham-Predicted IR (per 1000 patient years) | 11.5 (9.2, 13.8) | 4.9 (1.6, 8.2) | 9.2 (5.5, 12.9) | 14.5 (9.7, 19.2) | 21.3 (12.7, 30.0) |
| Difference between observed and Framingham-predicted IRs | -1.5 (-3.6, 0.7) | -3.3 (-6.4, -0.2) | -4.2 (-7.9, -0.5) | -0.5 (-5.0, 4.1) | 6.0 (-2.2, 14.1) |
| ASCVD and Stroke** | N = 843   | N = 182  | N = 269    | N = 261    | N = 131  |
| Observed IR of ASCVD and stroke (per 1000 patient years) | 15.0 (12.1, 17.9) | 5.7 (1.7, 9.7) | 10.8 (6.3, 15.3) | 18.3 (12.6, 24.0) | 29.4 (18.9, 39.9) |
| Pooled Cohort Equation-Predicted IR (per 1000 patient years) | 10.6 (9.8, 11.4) | 5.6 (4.5, 6.7) | 10.6 (9.2, 11.9) | 12.6 (11.1, 14.1) | 12.8 (10.8, 14.8) |
| Difference between observed and Pooled-Cohort Equation-predicted IRs | **4.4 (1.6, 7.2)** | 0.1 (-3.6, 3.7) | 0.2 (-4.3, 4.8) | **5.7 (0.2, 11.3)** | **16.6 (6.6, 26.6)** |

*Framingham Risk Score composite outcome: first fatal or non-fatal MI or cardiac death.

**Pooled Cohort Equation composite outcome: first stroke, fatal or non-fatal MI, or cardiac death.

**Bold font** indicates statistically significant differences between observed and predicted IRs.
Figure S1. CONSORT diagram for study participants.

- 3939 patients in CRIC Cohort
  - Excluded 132 patients without baseline NT-proBNP and hsTnT levels
  - Excluded 2618 patients on aspirin or statins
  - Excluded 159 patients with ASCVD
  - Excluded 3 patients without data required to calculate risk scores
  - 3807 patients
  - 1189 patients
  - 1030 patients
  - 1027 patients included in analyses
Figure S2. Scatterplot of Framingham Risk versus Pooled Cohort Equation risk scores, among 1027 participants with CKD.
Figure S3. Discrimination of incident ASCVD outcomes by the Framingham Risk Score and Pooled Cohort Equation with and without cardiac biomarkers, and by cardiac biomarkers alone, excluding participants not in specified age range for each score (30-79 for Framingham, 40-79 for Pooled Cohort Equation).

| Predictor                  | Difference in C-index relative to Framingham | Referent |
|----------------------------|---------------------------------------------|----------|
| Framingham Score           | -0.043 (-0.118, 0.032)                      |          |
| NT-proBNP                  | 0.024 (-0.03, 0.077)                        |          |
| hTnT                       | 0.009 (-0.001, 0.019)                       |          |
| Framingham + NT-proBNP    | 0.03 (0.002, 0.058)                         |          |
| Framingham + hTnT          |                                             |          |

| Predictor                  | Difference in C-index relative to Pooled Cohort | Referent |
|----------------------------|-----------------------------------------------|----------|
| Pooled Cohort              | -0.056 (-0.121, 0.01)                         |          |
| NT-proBNP                  | 0.017 (-0.031, 0.064)                         |          |
| hTnT                       | 0.012 (-0.001, 0.026)                         |          |
| Pooled Cohort + NT-proBNP  | 0.03 (0.003, 0.056)                           |          |
| Pooled Cohort + hTnT       |                                              |          |