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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

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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

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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.

Nonstandard Abbreviations and Acronyms

CRIC	Chronic Renal Insufficiency Cohort
HsTnT	high-sensitivity troponin T

Patients with chronic kidney disease (CKD) are at a greater risk of atherosclerotic cardiovascular disease (ASCVD) and ASCVD complications compared with the general population.[1–8] Contemporary guidelines recommend using ASCVD screening tools to guide primary prevention to reduce incidence of ASCVD.[9,10] 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 ASCD events in the general population.[11–19]

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.[20–23] 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 m^2.[24] Prior studies in CKD included limited numbers of patients with more advanced CKD (eGFR of ≤60 mL/min per 1.73 m^2). 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.[25–37] Understanding the performance of these risk scores will clarify their use in directing which patients with CKD may benefit from primary prevention strategies.[10,38]

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.

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).[39,40] 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

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.[41] 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 of age.[12] 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.[42] 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.[42]

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.[39]

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.[43] 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.[44] 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,[45] and was used to calculate eGFR via the Chronic Kidney Disease Epidemiology Collaboration equation.[46] Additional measurements included 24-hour urine protein and sodium, low-density lipoprotein and high-density lipoprotein cholesterols, 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

to the composite event, censoring for noncardiovascular or unclassified death, loss to follow-up, withdrawal of consent, end of administrative follow-up in 2019, or at 10 years of follow-up (the interval predicted by both risk scores), whichever came first. We used a Fine and Gray approach to model the subdistribution hazard of the event of interest and account for the competing risk of death not already included in the outcome.[47–49]

We calculated predicted and observed incidence rates (IRs) of the composite outcomes by each risk score overall and across categories of eGFR. Predicted IRs were the number of expected composite outcomes per 1000 person years, calculated as the sum of each participant's 10-year risk (in decimal form) divided by 10 (years), multiplied by 1000. Observed IRs were calculated by dividing the sum of observed events by the sum of follow-up time across each subgroup, scaled appropriately. Confidence intervals for IRs and difference in IRs were constructed via nonparametric bootstrap with 2000 replicates.[50]

We evaluated the discriminatory ability of all models via the 10-fold cross-validated Harrell's C-index.[51–53] First, we evaluated the ability of the Framingham Risk Score, NT-proBNP, or hsTnT alone to predict the composite outcome of fatal or nonfatal MI and cardiac death. We then calculated C-indices for models that included hsTnT and NT-proBNP in addition to the Framingham Risk Score. Parallel models were constructed with the Pooled Cohort Equation to evaluate ability to predict the composite outcome of fatal and nonfatal MI, cardiac death, and stroke. We calculated the differences in C-indices, comparing each model with the base model (Framingham Risk Score or Pooled Cohort Equation alone). For each estimate, we used a nonparametric bootstrap approach with 2000 replicates to construct corresponding 95% CIs.[50]

To assess calibration, we plotted the deciles of predicted probability of an event versus the observed probability. We also estimated the slope and intercept of the resulting calibration regression.

We performed 2 sensitivity analyses. First, to investigate how the scores functioned at different severities of CKD, we assessed the discriminatory function of the baseline risk scores, alone and in combination with hsTnT, across categories of eGFR (≥60, 45 to <60, 30 to <45, and <30 mL/min per 1.73 m^2). We calculated differences in discrimination compared with each score's performance at eGFR ≥60 mL/min per 1.73 m^2. We did not examine discrimination of NT-proBNP across eGFR categories since it did not perform well in our primary analyses. Second, we repeated our primary analyses while excluding those whose ages were out of range for each risk score (<30 or >79 for Framingham, N excluded=45; <40 or >79 for Pooled Cohort Equation, N=184 excluded).

All analyses were performed using R 4.0.2 (R Foundation for Computing, Vienna, Austria).

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 m^2; among those with eGFR ≥60 mL/min per 1.73 m^2, the median (interquartile range) eGFR was 68 (64, 76) mL/min per 1.73 m^2. 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 m^2 and at eGFR 45 to 59 mL/min per 1.73 m^2 (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 m^2 (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

Table 1. Baseline Characteristics of Study Participants With CKD Overall, and by Pooled Cohort Equation Risk Category

Variable	Overall	Low risk (<7.5% risk in 10 y)	High risk (≥7.5% risk in 10 y)
N	1027	565	462
Age, y, mean (SD)	52.2 (12.5)	45.6 (11.2)	60.3 (8.8)
Women, N (%)	524 (51)	376 (66.5)	148 (32)
Self-reported race or ethnicity, N (%)			
Non-Hispanic White	415 (40.4)	287 (50.8)	128 (27.7)
Non-Hispanic Black	419 (40.8)	179 (31.7)	240 (51.9)
Hispanic	153 (14.9)	72 (12.7)	81 (17.5)
Other*	40 (3.9)	27 (4.8)	13 (2.8)
eGFR, mL/min per 1.73 m^2, mean (SD)	48.2 (16.8)	52.1 (18.1)	43.5 (13.6)
eGFR ≥60 mL/min per 1.73 m^2	247 (24.1%)	192 (34%)	55 (11.9%)
eGFR 45–59 mL/min per 1.73 m^2	310 (30.2%)	161 (28.5%)	149 (32.3%)
eGFR 30–44 mL/min per 1.73 m^2	313 (30.5%)	139 (24.6%)	174 (37.7%)
eGFR <30 mL/min per 1.73 m^2	157 (15.3%)	73 (12.9%)	84 (18.2%)
24-h urine protein (g/d), median (IQR)	0.15 (0.07– 0.78)	0.13 (0.07–0.63)	0.17 (0.07–0.92)
24-h urine sodium (mg/d), median (IQR)	3303 (2401–4583)	3278 (2440–4497)	3331 (2374–4613)
Diabetes, N (%)	265 (25.8)	76 (13.5)	189 (40.9)
History of heart failure, N (%)	25 (2.4)	4 (0.7)	21 (4.5)
History of atrial fibrillation, N (%)	102 (9.9)	44 (7.8)	58 (12.6)
Systolic blood pressure, mm Hg, mean (SD)	124.7 (21.2)	116.1 (15.8)	135.2 (22.2)
Diastolic blood pressure, mm Hg, mean (SD)	74.6 (12.7)	73.2 (11.6)	76.3 (13.6)
Body mass index, kg/m^2, mean (SD)	30.9 (8.2)	30.5 (8.8)	31.4 (7.4)
Current smoker, N (%)	128 (12.5)	41 (7.3)	87 (18.8)
Alcohol use, N (%)	713 (69.4)	423 (74.9)	290 (62.8)
Hemoglobin, g/dL, mean (SD)	12.9 (1.8)	12.9 (1.8)	12.8 (1.8)
LDL cholesterol, mg/dL, mean (SD)	116.4 (37.0)	113.8 (34.2)	119.7 (39.9)
HDL cholesterol, mg/dL, mean (SD)	49.9 (18.2)	52.3 (18.9)	47 (17)
ACEi/ARB, N (%)	563 (54.8)	271 (48)	292 (63.2)
β-Blockers, N (%)	310 (30.2)	133 (23.5)	177 (38.3)
Diuretics, N (%)	415 (40.4)	170 (30.1)	245 (53)
Framingham Score, percentage form, median (IQR)	9.4 (4.5–21.5)	4.5 (2.8–7.3)	21.6 (15.6–30.0)
Pooled Cohort Score, percentage form, median (IQR)	6.4 (2.0–14.3)	2.2 (0.8–4.3)	15.6 (10.6–23.5)

ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CKD, chronic kidney disease; eGFR, glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; and LDL, low-density lipoprotein.

*Other includes Asian or Pacific Islander and American Indian or Alaska Native.

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 m^2, both the Framingham Risk Score and the Pooled Cohort Equation demonstrated

Table 2. Baseline Characteristics of Participants With CKD by Framingham Risk Score Category

Variable	Framingham low risk, <10%	Framingham moderate risk, 10% to <20%	Framingham high risk, ≥20%
N	520	240	267
Age, y, mean (SD)	45.2 (11.6)	57.1 (9.2)	61.4 (7.9)
Women, N (%)	354 (68.1)	104 (43.3)	66 (24.7)
Self-reported race or ethnicity, N (%)			
Non-Hispanic White	253 (48.7)	81 (33.8)	81 (30.3)
Non-Hispanic Black	184 (35.4)	117 (48.8)	118 (44.2)
Hispanic	60 (11.5)	32 (13.3)	61 (22.8)
Other*	23 (4.4)	10 (4.2)	7 (2.6)
eGFR, mL/min per 1.73 m^2, mean (SD)	52.6 (18.1)	45.5 (14.5)	42 (13.3)
eGFR ≥60 mL/min per 1.73 m^2	182 (35%)	41 (17.1%)	24 (9%)
eGFR 45–59 mL/min per 1.73 m^2	148 (28.5%)	84 (35%)	78 (29.2%)
eGFR 30–44 mL/min per 1.73 m^2	127 (24.4%)	75 (31.2%)	111 (41.6%)
eGFR <30 mL/min per 1.73 m^2	63 (12.1%)	40 (16.7%)	54 (20.2%)
24-h urine protein (g/d), median (IQR)	0.12 (0.07–0.65)	0.13 (0.06–0.46)	0.27 (0.09–1.37)
24-h urine sodium (mg/d), median (IQR)	3226 (2313–4465)	3379 (2489–4644)	3442 (2460–4666)
Diabetes, N (%)	61 (11.7)	54 (22.5)	150 (56.2)
History of heart failure, N (%)	3 (0.6)	8 (3.3)	14 (5.2)
History of atrial fibrillation, N (%)	45 (8.7)	28 (11.7)	29 (10.9)
Systolic blood pressure, mm Hg, mean (SD)	114.8 (15)	127.6 (19.9)	141.2 (21.6)
Diastolic blood pressure, mm Hg, mean (SD)	72.6 (11.8)	75.8 (13.9)	77.3 (12.4)
Body mass index, kg/m^2, mean (SD)	30.4 (8.8)	31.6 (8.4)	31.4 (6.6)
Current smoker, N (%)	40 (7.7)	33 (13.8)	55 (20.6)
Alcohol use, N (%)	390 (75)	154 (64.2)	169 (63.3)
Hemoglobin, g/dL, mean (SD)	12.8 (1.8)	13.0 (1.7)	12.7 (1.9)
LDL cholesterol, mg/dL, mean (SD)	112.8 (32.9)	116.4 (39.8)	123.4 (40.8)
HDL cholesterol, mg/dL, mean (SD)	52.7 (17.9)	49.8 (21.0)	44.5 (14.7)
ACEi/ARB, N (%)	249 (47.9)	138 (57.5)	176 (65.9)
β-Blockers, N (%)	117 (22.5)	83 (34.6)	110 (41.2)
Diuretics, N (%)	151 (29)	123 (51.2)	141 (52.8)
Framingham Score, percentage form, median (IQR)	4.5 (2.4–6.3)	13.7 (11.6–15.9)	29.4 (25.3–30.0)
Pooled Cohort Score, percentage form, median (IQR)	2.0 (0.7 –3.9)	9.5 (7.3–13.0)	22.1 (15.5–29.6)

ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CKD, chronic kidney disease; eGFR, glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; and LDL, low-density lipoprotein.

*Other includes Asian or Pacific Islander and American Indian or Alaska Native.

excellent discrimination. At eGFRs <60 mL/min per 1.73 m^2, both risk scores performed significantly worse compared with their discrimination at eGFRs ≥60 mL/min per 1.73 m^2 (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=45; <40 or >79 for Pooled Cohort Equation, 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

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 (6.5 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.

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 m^2.

Previous studies have demonstrated poor to moderate discrimination of the Framingham Risk Score in patients with CKD.[20–23] One study of 934 patients in the Atherosclerosis Risk in Communities cohort (mean eGFR 53 mL/min per 1.73 m^2) reported C-indices of 0.60 for men and 0.73 for women.[22] 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

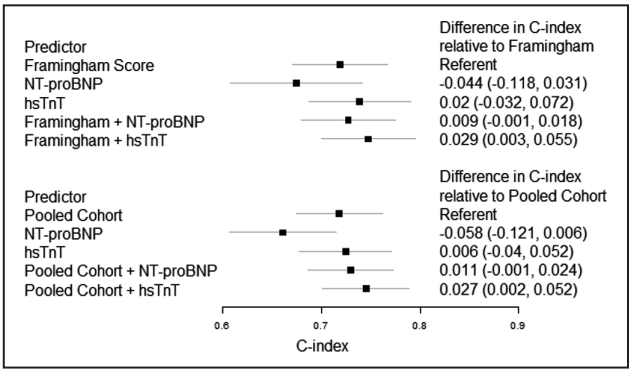

Figure 1. Discrimination of incident atherosclerotic cardiovascular disease outcomes by the Framingham Risk Score and Pooled Cohort Equation with and without cardiac biomarkers, and by cardiac biomarkers alone.
Outcomes are fatal and nonfatal myocardial infarction and cardiac death for Framingham Risk 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.

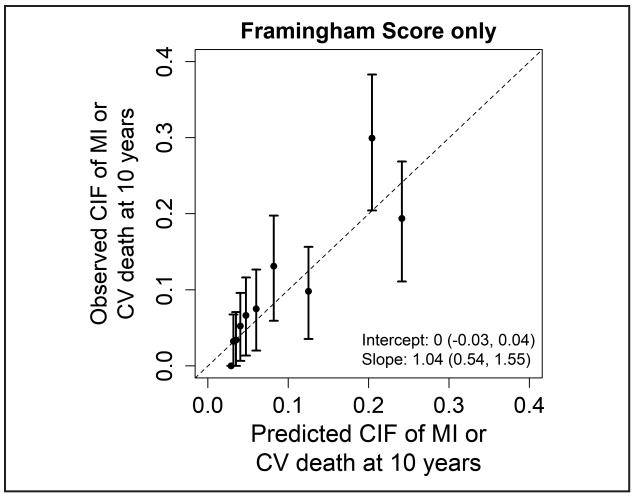

Figure 2. Calibration plot of observed vs predicted CIF by the Framingham Score in participants with CKD.
CIF indicates cumulative incidence fraction; CKD, chronic kidney disease; CV, cardiovascular; and MI, myocardial infarction.

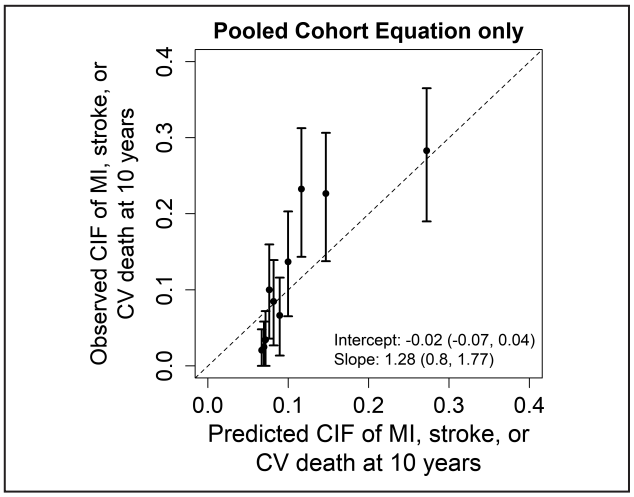

Figure 3. Calibration plot of observed vs predicted CIF by the Pooled Cohort Equation in participants with CKD.
CIF indicates cumulative incidence fraction; CKD, chronic kidney disease; CV, cardiovascular; and MI, myocardial infarction.

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	0.09 (−0.12, 0.29)	−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	0.09 (−0.06, 0.24)	−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.[28–33,55–57] 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[58] and in the Atherosclerosis Risk in Communities cohort.[59] 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.[60] HsTnT has been investigated as a predictor of mortality[61] and stroke[62] in patients with atrial fibrillation, and as a predictor of MI and major adverse cardiac events following major surgery.[63] 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.[64,65] 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.[55–57] 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.[22] This was because, in part, of the nonuniform underestimation of ASCVD risk, which made recalibration alone inadequate for improvement of the overall performance.[8,22] 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[20]; however, a recent study incorporating multiple cohorts with a mean eGFR of 86 mL/min per 1.73 m^2 demonstrated modestly improved discrimination when applying terms for eGFR and albuminuria.[66] 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.[67–74] 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.[12,41] 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 m^2, 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

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Disclosures

None.

Supplemental Material

Table S1
Figures S1–S3

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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).

	Overall N	eGFR ≥60	eGFR 45-59	eGFR 30-44	eGFR <30
ASCVD*	**N = 982**	**N = 235**	**N = 299**	**N = 300**	**N = 148**
Observed 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)
Framingham-Predicted IR (per 1000 patient years)	13.0 (12.3, 13.6)	8.2 (7.2, 9.2)	13.4 (12.3, 14.5)	14.9 (13.8, 16.1)	15.3 (13.8, 16.9)
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.

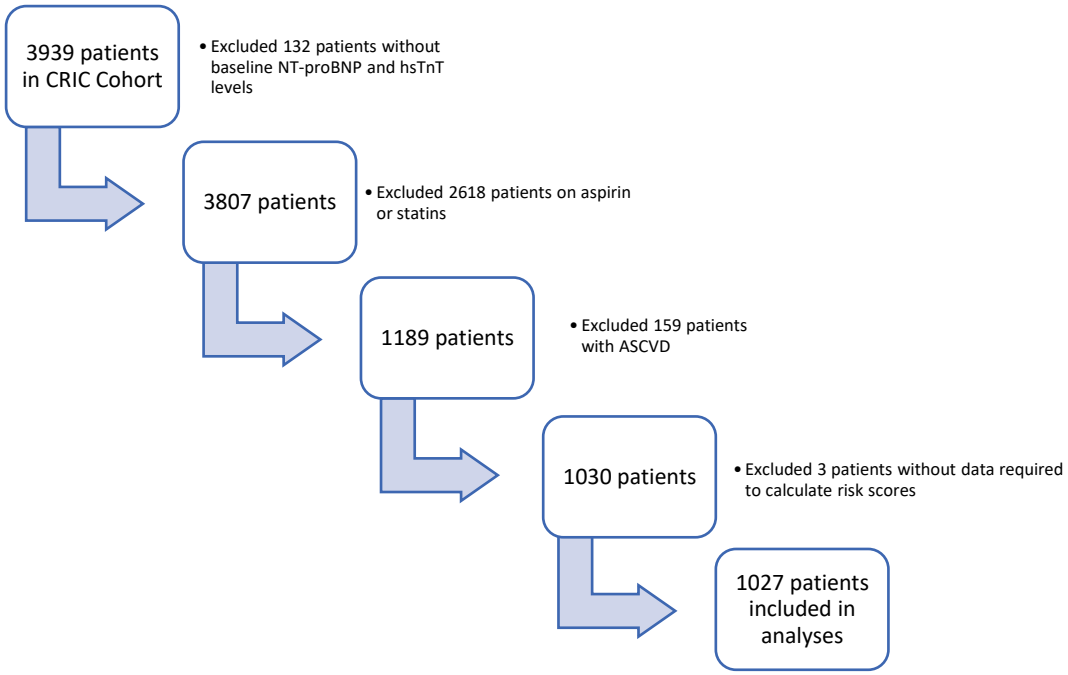

Figure S2. Scatterplot of Framingham Risk versus Pooled Cohort Equation risk scores, among 1027 participants with CKD.

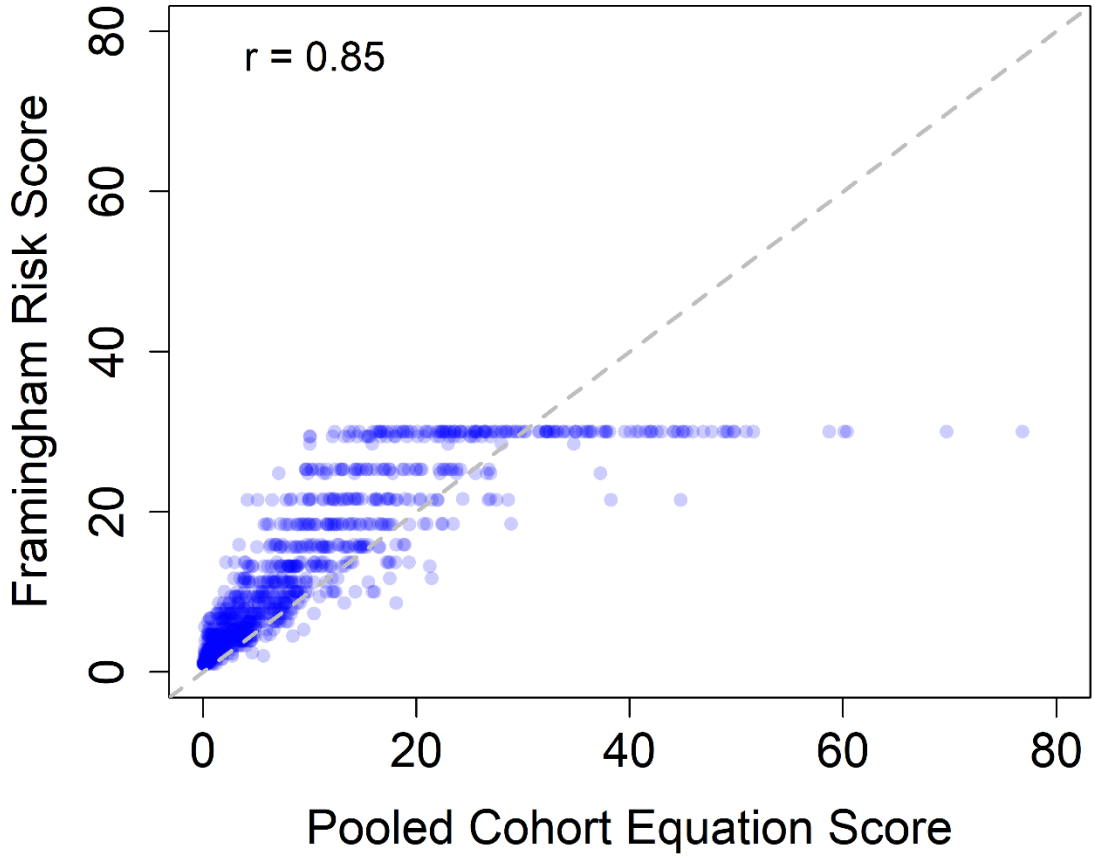

Figure S3. Discrimination of incident ASCVD outcomes by the Framingham Risk Score and Pooled Cohort Equation with and without cardiac biomarkers, and by cardiac biomarkers alone, excluding participants not in specified age range for each score (30-79 for Framingham, 40-79 for Pooled Cohort Equation).