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# The Framingham Predictive Instrument in Chronic Kidney Disease

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**Objectives** We sought to determine the utility of the Framingham equations in individuals with chronic kidney disease (CKD).

**Background** The Framingham equations predict incident coronary disease. The utility of these equations is unknown in CKD.

**Methods** We pooled individuals without pre-existing coronary disease age 45 to 74 years from the ARIC (Atherosclerosis Risk In Communities) and CHS (Cardiovascular Health Study) trials with CKD, defined by an estimated glomerular filtration rate of 15 to 60 ml/min/1.73 $m^2$. Using gender-specific models, we determined 5- and 10-year risk of incident myocardial infarction and fatal coronary disease, and evaluated discriminative and calibration ability of the Framingham equations for predicting coronary events.

**Results** There were 577 women and 357 men with CKD. Thirty-five men (9.8%) and 30 women (5.2%) and 74 men (20.7%) and 56 women (9.7%) had cardiac events within 5 and 10 years, respectively; 5-year events were predicted in 6.0% and 1.9% and 10-year events in 13.9% and 4.8% of men and women, respectively. For 5-year events, C-statistics assessing discrimination were 0.62 and 0.77, while 10-year C-statistics were 0.60 and 0.73 for men and women, respectively. Calibration was also poor, with Framingham scores generally underpredicting events in individuals with CKD at 5 and 10 years. Discrimination was significantly improved by refitting models with population-specific coefficients, while recalibration improved prediction in women.

**Conclusions** The Framingham instrument demonstrates poor overall accuracy in predicting cardiac events in individuals with CKD, although refit models can substantially improve discrimination. Calibration in women can be moderately improved with adjustment for higher event rates. Development of CKD-specific equations is needed. (J Am Coll Cardiol 2007;50:217–24) © 2007 by the American College of Cardiology Foundation

The Framingham predictive instrument allows clinicians to estimate individual patient risk of incident coronary heart disease by accounting for traditional cardiac risk factors, including gender, age, blood pressure, cholesterol, diabetes, and smoking (1,2). While the Framingham equation has been validated in racially diverse populations including the ARIC (Atherosclerosis Risk In Communities) trial and CHS (Cardiovascular Health Study), its applicability in individuals with chronic kidney disease (CKD) is unknown (3).

Stage 3 to 4 CKD, defined by a glomerular filtration rate (GFR) between 15 and 60 ml/min/1.73 $m^2$, is extremely common in the U.S., with estimated prevalence of 8 million adults (4). Chronic kidney disease is an independent risk factor for cardiovascular disease (CVD), and individuals with CKD have a high burden of CVD risk factors and cardiac events (5,6). The mechanism of increased cardiovascular risk in CKD is uncertain, but is likely secondary to increased severity of traditional CVD risk factors, most notably hypertension and diabetes (7). Nontraditional risk factors, including inflammation, oxidative stress, and anemia, may also contribute (8).

Given the importance of identifying individuals with CKD at highest risk for cardiac events, we evaluated the utility of the Framingham predictive instrument in a predominantly stage 3 CKD population.

## Methods

**Study design.** We utilized 2 limited-access databases that evaluated CVD in community-based populations: ARIC

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**Abbreviations and Acronyms**

**CKD** = chronic kidney disease

**CVD** = cardiovascular disease

**GFR** = glomerular filtration rate

and CHS. Pooling these population-based studies allowed evaluation of individuals in the Framingham study age range while increasing statistical power and generalizability. From 1987 to 1989, ARIC enrolled 15,792 participants age 45 to 64 years from 4 communities (9). From 1989 to 1990, CHS enrolled 5,201 subjects age 65 years and older in 4 communities; an additional 687 African Americans were recruited from 1992 to 1993 (10). To match the Framingham studies (11,12) we excluded individuals over 74 years old. Data from the limited-access database of the 11th examination of Framingham Heart study cohort and the baseline examination of the Framingham Offspring study (1971 to 1974) were used to reproduce beta-coefficients and survival functions of the Framingham predictive instrument (11,12).

We quantified kidney function as GFR estimated with the 4-variable Modification of Diet in Renal Disease study equation (13–15). We calibrated the ARIC and CHS laboratories indirectly using NHANES (National Health and Nutrition Examination Survey)-III data (16–18). We defined kidney disease as estimated GFR below 60 ml/min/1.73 $m^2$ (4). Subjects with GFR below 15 ml/min/1.73 $m^2$ were excluded to avoid individuals likely to require dialysis in the immediate future.

Baseline characteristics included demographics (age, gender, race); medical history (coronary heart disease, diabetes, smoking); systolic and diastolic blood pressure; and laboratory variables (total cholesterol, high-density lipoprotein cholesterol, creatinine). Race was defined as white or African American. Cigarette smoking was dichotomized by current use. Diabetes was defined by use of insulin, oral hypoglycemic medications, or fasting glucose level ≥140 mg/dl (7.8 mmol/l) in order to match the original Framingham definition (12). Baseline coronary disease included a history of coronary angioplasty, coronary bypass surgery, and both recognized and silent myocardial infarction as defined by consensus committees for the respective studies (9,10).

After exclusions for missing age, race, gender, or creatinine data or of nonwhite/non-African American race (n = 402), age over 74 years (n = 1,915), and missing baseline coronary heart disease status (n = 317), there were 19,046 subjects. Of these, 1,106 individuals had estimated GFR between 15 and 60 ml/min/1.73 $m^2$. A further 168 with coronary heart disease, 2 with missing follow-up data, and 2 with missing blood pressure or laboratory data were excluded, yielding a final population of 934 individuals.

**Study outcome.** The primary outcome included myocardial infarction and fatal coronary heart disease. Myocardial infarction was defined by both clinically recognized and silent infarctions (noted on screening electrocardiograms).

**Statistical analysis.** Baseline characteristics for the CKD cohort were compared with the Framingham derivation cohort using chi-square and *t* tests. All p values are 2-sided, and, as in Framingham, all analyses are gender-specific.

DISCRIMINATION. Discrimination is the ability of a prediction model to separate those who had events from those who did not have events and was quantified by the C-statistic, analogous to the area under a receiver operating characteristic curve. We obtained the 10-year Framingham survival function from previously published data and reproduced the 5-year survival function for myocardial infarction and fatal coronary heart disease at the mean values of the Framingham risk factors by using individual patient data from the Framingham (11th visit) and Framingham Offspring (baseline visit) datasets, replicating Framingham techniques (2,12,19). Using these survival functions for predicting myocardial infarction and fatal coronary heart disease (defined as "hard" outcomes by Framingham investigators as the more subjective outcome of angina is excluded) and the values for traditional coronary risk factors (blood pressure and lipid categories, age, diabetes, and smoking) from our study population, we utilized coefficients developed by the Framingham investigators to calculate the Framingham risk score for each individual and further derive the 5- and 10-year Framingham probability of a coronary event (2,3,20).

We then created gender-specific "best Cox" models. These utilize Cox proportional hazards regression with covariates identical to those in the Framingham risk score. Coefficients for these covariates are generated based on the results of the predictive model in the CKD population and yield different coefficients than the original Framingham models. For each risk factor, the regression coefficients for the CKD cohort from "best Cox" models and the original Framingham cohort were compared using a 2-tailed z statistic, where $z = (b_{[F]} - b_{[C]})/SE$. The beta coefficients for individual Framingham and CKD covariates are represented by $b_{[F]}$ and $b_{[C]}$, respectively, while the standard error (SE) is defined as $(SE_{[F]}^2 + SE_{[C]}^2)^{1/2}$. Lastly, we computed 2 gender-specific C-statistics: the first applied the Framingham function to the CKD cohort and the second utilized the "best Cox" model in the CKD cohort. For comparison purposes, we duplicated this technique in individuals (n = 16,689) from the pooled cohort with GFR ≥60 ml/min/1.73 $m^2$ and no history of coronary artery disease. C-statistics are compared using a nonparametric approach (21).

CALIBRATION. Calibration assesses whether predicted outcomes and actual outcomes agree. Individuals with CKD were divided into quintiles of predicted risk based on their Framingham probabilities, and plots of 5- and 10-year predicted and actual events adjusted for informative censoring using Kaplan-Meier estimates were created. Differences between predicted and actual rates were compared using a modified Hosmer-Lemeshow chi-square statistic (3). High chi-square values indicate poor calibration.