Published in final edited form as:

Am Heart J. 2012 December ; 164(6): 925–931.e2. doi:10.1016/j.ahj.2012.09.003.

Cardiovascular risk assessment: addition of CKD and race to the Framingham equation

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Financial Disclosures:

None of the authors reports a conflict of interest with regard to the content of this paper.

Drs. Baraniuk, Colon, Cuyjet, Dart, Drawz, Graumlich, Moloo, Saklayan, Simmons, and Stanford have no financial interests to disclose.

Abstract

Background/Aims—The value of the Framingham equation in predicting cardiovascular risk in African Americans and patients with chronic kidney disease (CKD) is unclear. The purpose of the study was to evaluate whether the addition of CKD and race to the Framingham equation improves risk stratification in hypertensive patients.

Methods—Participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) were studied. Those randomized to doxazosin, age greater than 74 years, and those with a history of coronary heart disease (CHD) were excluded. Two risk stratification models were developed using Cox proportional hazards models in a two-thirds developmental sample. The first model included the traditional Framingham risk factors. The second model included the traditional risk factors plus CKD, defined by eGFR categories, and stratification by race (Black vs. Non-Black). The primary outcome was a composite of fatal CHD, nonfatal MI, coronary revascularization, and hospitalized angina.

Results—There were a total of 19,811 eligible subjects. In the validation cohort, there was no difference in C-statistics between the Framingham equation and the ALLHAT model including CKD and race. This was consistent across subgroups by race and gender and among those with CKD. One exception was among Non-Black women where the C-statistic was higher for the Framingham equation (0.68 vs 0.65, $P=0.02$). Additionally, net reclassification improvement was not significant for any subgroup based on race and gender, ranging from -5.5% to 4.4% .

Conclusion—The addition of CKD status and stratification by race does not improve risk prediction in high-risk hypertensive patients.

Keywords

coronary disease; chronic renal insufficiency; African Americans; risk assessment; Framingham

Introduction

Chronic kidney disease (CKD) affects more than 25 million Americans.(1) The morbidity and mortality burden from CKD derives largely from the disproportionate risk of coronary heart disease (CHD). Patients with CKD are at very high risk for CHD; multiple studies have demonstrated that CKD is an independent risk factor for CHD.(2–5) CKD has even been shown to be a risk equivalent to diabetes and myocardial infarction (MI), although not in all cohorts.(6, 7)

The mainstay of prevention and treatment of CHD is risk factor identification and treatment. Treatment of specific risk factors, in particular cholesterol, is based on overall risk for CHD. (8) The Framingham equation is the principal instrument for risk assessment.(9) While the Framingham equation has good predictive ability, it does not account for CKD or race. The model has performed well in multiple diverse populations, but distinguishes poorly among those who do and do not develop CHD in minority patients and those with CKD.(9–12) In four separate analyses, addition of CKD to the Framingham equation did not improve overall predictive ability.(13–15) Limitations of these studies include a relatively small number of participants with CKD and, in one, analysis was limited to improvement in stratification without assessment of reclassification.(13, 16, 17)

A well-powered analysis of the addition of both CKD and race to the Framingham equation may reveal a model with improved ability to discriminate between those who do and do not develop CHD. More accurate classification of patients into risk categories will allow for more appropriate therapeutic targeting and management of CHD risk. The objective of the

current study was to evaluate whether addition of CKD and stratification by race improves the ability of the Framingham equation to predict CHD.

Methods

The rationale, design, and baseline characteristics of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) have been published.(18, 19) Participants were men and women aged 55 years or older who had hypertension with at least 1 additional risk factor for CHD. This study was supported by contract NO1-HC-35130 with the National Heart, Lung, and Blood Institute (NHLBI) and by a Career Development Award to Dr Drawz (K23DK087919). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Exclusion criteria

For this analysis, all participants were included with the following exceptions: age greater than 74 years; missing baseline data for HDL or both cLDL and total cholesterol; participants with a history of CHD as defined by a response to a single question on the baseline questionnaire. On the baseline questionnaire, CHD was defined as a history of MI, primary cardiac arrest, coronary revascularization, angina, coronary stenosis greater than 50%, or reversible coronary perfusion defect on noninvasive cardiac testing. Eligible participants were randomly assigned to a developmental (two-thirds) or validation (one-third) sample.

Baseline measurements

Prior to initiating study medications, participants had blood drawn for the baseline measurement of fasting glucose, total cholesterol, HDL cholesterol, triglycerides, and creatinine. LDL cholesterol was calculated using the Friedewald formula unless triglyceride levels were greater than 400 mg/dl in which case lipoprotein ultracentrifugation was performed on fasting specimens. Serum creatinine was measured in a central laboratory and comparison with the Modification of Diet in Renal Disease (MDRD) laboratory revealed that no further calibration was required.(20) Estimated glomerular filtration rate (eGFR) was calculated according to the CKD-EPI equation.(21) Secondary analyses were conducted with eGFR calculated according to the simplified MDRD study equation.(22) Patients were classified into 3 baseline categories of eGFR according to recommendations in the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines on Chronic Kidney Disease: normal kidney function (eGFR ≥ 90 mL/min/1.73m²), mild CKD (eGFR 60 to 89 mL/min/1.73m²), and moderate or severe CKD (eGFR <60 mL/min/1.73m²).(23) Patients with a serum creatinine level of ≥ 2 mg/dL were excluded. Therefore, the percentage of patients with severe CKD (estimated eGFR <30 mL/min/1.73m²) at baseline was very small (0.6%); these participants were included in the moderate or severe CKD category (eGFR <60 mL/min/1.73m²).(2, 24)

A participant was considered to have diabetes if a history of diabetes was noted on the baseline questionnaire or the participant had a baseline fasting glucose ≥ 126 mg/dL. Baseline blood pressures were based on the average of 2 seated measurements.(18)

Primary outcome

The primary outcome for this study was CHD, which included fatal CHD, nonfatal MI, coronary revascularization, or hospitalized angina.(25) Coronary revascularization included coronary artery bypass grafting, percutaneous angioplasty, coronary stents, and atherectomy. This outcome was chosen because it was a major prespecified secondary ALLHAT outcome

and to be consistent with the Framingham “hard” CHD outcome: recognized and unrecognized MI, coronary insufficiency, and CHD death.(9)

Statistical Analysis

Cutoffs for total cholesterol, cLDL, HDL, and age were used in this analysis to be consistent with the original Framingham equation.(9) Systolic blood pressure and diastolic blood pressure were classified according to JNC-7 guidelines and the original Framingham blood pressure categories (see Table I). If classification based on systolic and diastolic pressures differed, subjects were assigned to the higher category (e.g., a subject with a BP of 155/80 mmHg would be assigned to the 140–159/90–99 mmHg group). Race was categorized as self-reported Black or Non-Black. Hispanics were eligible for inclusion in either the Black or Non-Black category.

Eligible participants were randomly assigned to a developmental (two-thirds) or validation (one-third) sample. Cox proportional hazards regression were performed on the developmental sample to evaluate the relationship between CHD and age, smoking status, diabetes, blood pressure, total cholesterol, HDL, and eGFR. Tests for interaction were performed. Four- and six-year follow-up were used in the proportional hazards model and adapted to provide a 5-year CHD risk estimate. A new risk score based on the Cox model for the developmental sample was calculated for all participants, irrespective of race or eGFR (model 1). A separate risk score was then developed with inclusion of CKD and stratification by race (model 2). Treatment arms were entered as covariates.

The C-statistic for the new scores and the Framingham equation (11) were compared in the validation sample to evaluate discrimination.(26) Reclassification of participants into higher and lower risk categories between models 1 and 2 in the validation sample was evaluated by calculating net reclassification improvement (NRI). (16) NRI was calculated separately for Black and Non-Black men and women. Model calibration was evaluated by graphing the predicted and actual risk by deciles of ALLHAT risk (model 2).

Results

42,418 participants were randomized and 19,811 met inclusion and exclusion criteria for the present analyses (see fig. 1). Baseline characteristics of participants in the developmental sample (n=13,207) stratified by Black/Non-Black and gender are shown in Table I (online table I for the validation sample). Age-adjusted 5 year rates of CHD, calculated using the developmental sample and separated by gender and race, are shown in online Table II. Rates were higher in men than women for both Blacks and Non-Blacks over nearly all categories of blood pressure, total cholesterol, HDL, and eGFR.

The β -coefficients used to calculate the 5 year probability of CHD for the validation sample and baseline survival at 5 years, are shown in Table II. Note that model 1 does not include the eGFR variable and therefore the β -coefficients are not calculated. Also, additional calculations based on stratification by Black/Non-Black are needed for model 2.

C-statistics in the validation cohort are presented in Table III for the Framingham model (11) and the ALLHAT model that includes CKD and stratification by race (model 2). The C-statistics for both models ranged from as low as 0.428 to 0.693, indicating relatively low predictive ability. C-statistics were higher for women than men in both Black and Non-Black participants. C-statistics were lower for Blacks compared to Non-Blacks. Only among Non-Black women was there a significant difference between the Framingham model and the ALLHAT model. In this subgroup, the C-statistic was higher for the Framingham model. Predicted and actual event rates for Black females in the validation cohort by deciles of

predicted risk based on ALLHAT model 2 are shown in fig. 2. Similar graphs for other subgroups based on race, gender, and kidney function are available online. Results were unchanged in secondary analyses with eGFR calculated using the MDRD formula.

Table IV shows participants categorized by ALLHAT models 1 and 2 into risk categories of <10%, 10% to <20% and 20% for 5-year risk of CHD. Each cell in Table IV refers to the number of participants who are categorized by model 1 and model 2 into the corresponding risk categories. For instance, the cell in the 5th row and first column of Table IV refers to the 41 Non-Black men without an event who are categorized as <10% by model 1 and as 10% to 20% by model 2. The final column of Table IV displays the NRI, which assesses the ability of the model including CKD and race to classify participants as compared to the model without these variables. This assessment was done for both men and women and Blacks and Non-Blacks separately. None of the NRI values were significant, indicating no improvement in risk classification with the addition of CKD and stratification by race.

Discussion

This study shows that the addition of CKD and race to the Framingham equation does not improve discrimination (C statistic) or risk classification (NRI) among hypertensive subjects. These findings are important as they provide the first well-powered analysis of the impact of adding CKD and race to the Framingham equation. Similar results were observed across all subgroups by race and gender and when analyses were restricted to only those subjects with CKD.

These findings are consistent with previous studies evaluating the addition of CKD to the Framingham equation. In a population derived from ARIC and CHS, addition of CKD to the Framingham equation did not increase overall predictive ability.⁽¹³⁾ Limitations of the ARIC/CHS study were the small number of participants with CKD and analyses were restricted to improvement in discrimination with no consideration for reclassification.^(16, 17) Similarly, in a large cohort from Iceland, the addition of CKD resulted in a slight improvement in Harrell's C index but no improvement classification despite the inclusion of proteinuria in the definition of CKD.⁽¹⁴⁾ Among subjects enrolled in ONTARGET and TRANSCEND, eGFR and albuminuria were associated with cardiovascular outcomes but no improvement in risk classification was observed when these variables were added to traditional risk factors.⁽¹⁵⁾ Finally, in the Rotterdam study, CKD was associated with CHD in multivariable models; however, addition of 12 CKD to a model including the Framingham variables did not increase the C-statistic or result in a positive NRI.⁽²⁷⁾

Despite the moderate to poor performance of the Framingham equation among minorities, the impact on risk stratification of the addition of race to the Framingham equation had not been evaluated in a validation cohort.⁽¹¹⁾ Multiple studies have evaluated the interaction between race and various risk factors for CHD. In ARIC, hypertension was found to be a more powerful predictor of CHD in Black women, while diabetes was a greater risk factor in White compared to Black women.⁽¹⁰⁾ Additionally, data from NHANES II and a pooled analysis of data from ARIC, CHS, Framingham, and the Framingham Offspring study revealed that CKD is a greater risk factor for cardiovascular disease in Blacks than Whites.^(3, 5) Nevertheless, in the current study, stratification by race did not lead to improved discrimination or risk reclassification among Blacks or Non-Blacks.

In this large hypertensive cohort, C-statistics for the Framingham equation ranged from 0.58 to 0.68 in subgroups by race and gender among all participants and from 0.53 to 0.69 in participants with CKD. C-statistics were consistently higher in women compared to men and in Non-Blacks compared to Blacks. These results are consistent with a previous validation

study conducted in multiple different ethnic groups where C-statistics were higher in women and Whites.(11)

The poor performance of the Framingham equation in ALLHAT corroborates previous reports of poor predictive ability among hypertensive subjects enrolled in clinical trials.(28, 29) The C-statistic for cardiovascular disease was only 0.66 among subjects in the INSIGHT trial and ranged from 0.53 for coronary heart disease death to 0.58 for MI in the Second Australian National Blood Pressure Study.(28, 29) The poor performance of the Framingham equation in these hypertension trials may be due to the advanced age of the subjects, differences between subjects included in clinical trials and the general population, and better blood pressure control in a trial setting than in general practice.(30) Additionally, the prevalence of cardiovascular risk factors is changing over time and has coincided with decreased incidence of cardiovascular disease.(31) Therefore, the Framingham equation, derived from a cohort based on a baseline examination in the early 1970s, may not predict disease as accurately in the 21st century.

Our study has a number of limitations to consider. First, the ALLHAT cohort includes only high risk hypertensive subjects. However, the results are clinically relevant given the high prevalence of hypertension in the population; over one-half of patients 60 to 69 years old and three-fourths of patients aged 70 years and older have hypertension. (32) Another limitation is that our study only includes patients age 55 years and older. Our analysis of CKD is limited to serum creatinine as ALLHAT did not evaluate for proteinuria, a known risk factor for all-cause mortality and cardiovascular disease.(33) Additionally, most of the patients with CKD in ALLHAT had stage 3A CKD, which may carry less significance as a risk factor for cardiovascular disease than more advanced CKD.(4) Because prior reports indicated the impact of various risk factors differ by race, ALLHAT models were developed with stratification by race, which may be a surrogate for socioeconomic status. Given the poor performance of the prediction models in all subgroups, it is unlikely that including socioeconomic status would improve predictive ability.

Strengths of our study include a large sample size. The ALLHAT cohort was chosen in part because of the large number of Blacks and patients with CKD (5,099 and 1,832 in the developmental cohort, respectively). Combined CHD was a primary outcome and was therefore carefully adjudicated. Finally, our analysis included not only a comparison of discrimination, but also an evaluation of the reclassification of subjects using the new risk model. This evaluation is more sensitive to model improvement and more clinically relevant.

In conclusion, CKD has consistently been shown to be an independent risk factor for CHD. However, the current study confirms previous reports that addition of CKD to the Framingham equation does not improve prediction of CHD. Additionally, stratification by race does not improve prediction of CHD, even among Blacks. Further work is necessary to develop more accurate prediction models in hypertensive patients, especially for men and Blacks.

Acknowledgments

Funding/Support – This study was supported by contract NO1-HC-35130 with the National Heart, Lung, and Blood Institute (NHLBI) and by a Career Development Award to P.E.D. (1K23DK087919). ALLHAT investigators received contributions of study medications supplied by Pfizer (amlodipine besylate and doxazosin mesylate), AstraZeneca (atenolol and lisinopril), and Bristol-Myers Squibb (pravastatin), and financial support provided by Pfizer.

Dr. Davis has consulted for Amgen, Forest Pharmaceuticals, and Takeda; and has received honoraria from Takeda. Dr. Brown has consulted for Merck. Dr. Henriquez has received honoraria from Astra-Zeneca, Boehringer

Ingelheim, Forest Pharmaceuticals and Novartis. Dr. Rahman has received honoraria from Boehringer Ingelheim. Dr. Sweeney has received a research grant from Novartis. Dr. Wong has consulted for Novartis, and has received research grants from Forest Pharmaceuticals, Merck, and Novartis.

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Figure 1.
Consort Diagram

Figure 2.
5-year CHD event rates among Black females (n=1495) in the validation sample by deciles of predicted risk based on ALLHAT model 2

Table I

Baseline characteristics of the developmental sample

	Non-Black		Black	
	Men(n)	Women(n)	Men(n)	Women(n)
Age, mean	64(4,450)	64(3,658)	64(2,338)	63(2,761)
Body mass index, kg/m ²	29(4,438)	31(3,653)	29(2,334)	32(2,750)
Smoker, % Yes	27(1,180)	25(912)	34(803)	22(615)
Diabetes, %	41(1,804)	43(1,562)	42(981)	49(1,347)
Blood pressure, %				
<120/80 mmHg	3.2(140)	2.8(104)	2.7(63)	2.7(75)
120–129/80–84 mmHg	8.2(363)	7.3(268)	8.6(200)	8.2(227)
130–139/85–89 mmHg	16.2(719)	15.1(554)	17.2(402)	15.5(429)
140–159/90–99 mmHg	50.1(2229)	51.9(1898)	46.9(1096)	49.0(1352)
160/100 mmHg	22.5(999)	22.8(834)	24.7(577)	24.6(678)
Total cholesterol, mg/dL	209(4,450)	228(3,658)	208(2,338)	227(2,761)
HDL, mg/dL	40(4,450)	49(3,658)	47(2,338)	60(2,761)
Creatinine, mg/dL	1.06(4,447)	0.84(3,651)	1.19(2,333)	0.94(2,757)
eGFR, %				
90 mL/min/1.73m ²	22.4 (994)	26.0 (948)	31.2 (727)	33.1 (912)
60–89 mL/min/1.73m ²	62.7 (2,790)	57.3 (2,092)	52.6 (1,228)	50.5 (1,391)
<60 mL/min/1.73m ²	14.9 (663)	16.7 (611)	16.2 (378)	16.5 (454)

Note: conversion factors for units: cholesterol in mg/dL to mmol/L, $\times 0.02586$; creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; eGFR in mL/min/1.73m² to mL/s/1.73m², $\times 0.01667$.

Table II
 β -coefficients using total cholesterol categories calculated in the developmental cohort

Variable	Model 1			Model 2		
	All participants		Non-Black		Black	
	Men	Women	Men	Women	Men	Women
Age, y	0.186	0.111	0.287	-0.193	0.118	0.542
Age squared, y	-0.001	-0.0004	-0.0018	0.002	-0.001	-0.004
Total Cholesterol, mg/dL						
<160	-0.145	-0.146	-0.317	-0.087	0.159	-0.285
160–199	Ref*	Ref*	Ref*	Ref*	Ref*	Ref*
200–239	0.127	0.132	0.134	0.207	0.051	0.014
240–279	0.245	0.382	0.246	0.546	0.163	0.129
280	0.532	0.572	0.636	0.464	0.247	0.558
HDL, mg/dL						
<35	0.229	0.469	0.212	0.218	0.014	0.938
35–44	-0.007	0.236	-0.207	-0.020	-0.074	0.580
45–49	Ref*	Ref*	Ref*	Ref*	Ref*	Ref*
50–59	-0.059	-0.124	-0.053	-0.211	-0.010	-0.038
60	-0.282	-0.258	-0.266	-0.507	-0.229	-0.036
Blood pressure, mmHg						
<120/80	0.451	0.361	0.449	0.753	0.519	-0.013
120–129/80–84	Ref*	Ref*	Ref*	Ref*	Ref*	Ref*
130–139/85–89	-0.064	0.013	0.109	0.394	-0.388	-0.286
140–159/90–99	-0.002	0.014	0.067	0.361	-0.170	-0.240
160/100	0.039	0.064	0.125	0.312	-0.151	-0.089
Diabetes	0.296	0.497	0.264	0.578	0.407	0.417
Smoker	0.114	0.333	0.126	0.397	0.103	0.260
eGFR, mL/min/1.73m ²						
90	—	—	Ref*	Ref*	Ref*	Ref*
60–89	—	—	-0.161	0.286	-0.197	-0.019

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Variable	Model 1		Model 2			
	All participants		Non-Black		Black	
	Men	Women	Men	Women	Men	Women
<60	—	—	0.026	0.495	0.286	0.317
Baseline survival function at 5 years, S(t)	0.855	0.905	0.861	0.917	0.888	0.912

* Referent

Note: conversion factors for units: cholesterol in mg/dL to mmol/L, $\times 0.02586$; creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; eGFR in mL/min/1.73m² to mL/s/1.73m², $\times 0.01667$.

Table III

C-statistic by race and gender in the validation sample for the Framingham model and ALLHAT model 2

	All participants		Participants with CKD (eGFR <60)	
	Framingham	ALLHAT	Framingham	ALLHAT
Non-Black				
Men	0.60 (0.57, 0.63)	0.60 (0.57, 0.63)	0.55 (0.47, 0.63)	0.56 (0.48, 0.64)
Women	0.68 (0.64, 0.71)	0.65 [*] (0.61, 0.69)	0.69 (0.59, 0.77)	0.68 (0.59, 0.77)
Black				
Men	0.58 (0.53, 0.63)	0.58 (0.53, 0.63)	0.53 (0.39, 0.66)	0.53 (0.38, 0.68)
Women	0.63 (0.58, 0.68)	0.64 (0.59, 0.69)	0.65 (0.55, 0.74)	0.64 (0.54, 0.73)

^{*} *P* value 0.015 compared to Framingham equation; *P* value >0.05 for all other comparisons.

Table IV

5 year CHD risk classification (%) comparing models with and without race and CKD in the validation sample using total cholesterol categories

Model 2 (with CKD and race)	Model 1 (without CKD or race)			NRI* (P value)	
Risk category	<10%	10 to <20%	20%		
Non-Black					
Men					
With events					
<10%	17	6	0	1.3% (0.54)	
10 to <20%	3	207	4		
20%	0	34	96		
Without events					
<10%	186	61	0		
10 to <20%	47	1014	11		
20%	0	132	306		
Women					
With events					
<10%	48	17	0	-5.5% (0.11)	
10 to <20%	9	84	9		
20%	0	4	20		
Without events					
<10%	800	143	0		
10 to <20%	119	456	26		
20%	0	28	57		
Black					
Men					
With events					
<10%	9	19	0	-4.1% (0.46)	
10 to <20%	3	69	18		
20%	0	3	6		
Without events					
<10%	157	211	0		
10 to <20%	50	481	74		
20%	0	25	34		
Women					
With events					
<10%	43	9	0		
10 to <20%	13	46	1		
20%	0	8	13		

Risk category	Model 1 (without CKD or race)			NRI* (P value)
	<10%	10 to <20%	20%	
Without events				
<10%	731	78	0	
10 to <20%	88	376	9	
20%	0	52	28	4.4% (0.31)

* Net reclassification improvement (NRI) assesses the ability of the model including chronic kidney disease (CKD) and race to classify participants as compared to the model without these variables.