Validation of an Atrial Fibrillation Risk Algorithm in Whites and African Americans

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Background: We sought to validate a recently published risk algorithm for incident atrial fibrillation (AF) in independent cohorts and other racial groups.

Methods: We evaluated the performance of a Framingham Heart Study (FHS)-derived risk algorithm modified for 5-year incidence of AF in the FHS (n=4764 participants) and 2 geographically and racially diverse cohorts in the age range 45 to 95 years: AGES (the Age, Gene/Environment Susceptibility-Reykjavik Study) (n=4238) and CHS (the Cardiovascular Health Study) (n=5410, of whom 874 [16.2%] were African Americans). The risk algorithm included age, sex, body mass index, systolic blood pressure, electrocardiographic PR interval, hypertension treatment, and heart failure.

Results: We found 1359 incident AF events in 100 074 person-years of follow-up. Unadjusted 5-year event rates differed by cohort (AGES, 12.8 cases/1000 person-years; CHS whites, 22.7 cases/1000 person-years; and FHS, 4.5 cases/1000 person-years) and by race (CHS African Americans, 18.4 cases/1000 person-years). The strongest risk factors in all samples were age and heart failure. The relative risks for incident AF associated with risk factors were comparable across cohorts and race groups. After recalibration for baseline incidence and risk factor distribution, the Framingham algorithm, reported in C statistic, performed reasonably well in all samples: AGES, 0.67 (95% confidence interval [CI], 0.64-0.71); CHS whites, 0.68 (95% CI, 0.66-0.70); and CHS African Americans, 0.66 (95% CI, 0.61-0.71). Risk factors combined in the algorithm explained between 47.0% (AGES) and 63.6% (FHS) of the population-attributable risk.

Conclusions: Risk of incident AF in community-dwelling whites and African Americans can be assessed reliably by routinely available and potentially modifiable clinical variables. Seven risk factors accounted for up to 64% of risk.

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THE PREVALENCE AND INCIDENCE of atrial fibrillation (AF) have been increasing over the last several decades.[1,2] The improved assessment of risk for incident AF was formulated as a major goal of a recently convened National Heart, Lung, and Blood Institute workshop.[3] A risk algorithm based on readily available clinical variables for 10-year incidence of AF in Framingham Heart Study (FHS) participants has been published (http://www.framinghamheartstudy.org/risk/index.html).[4] Transportability to independent cohorts and other racial groups with different incidence rates and distributions of risk factors has to be shown before general recommendations for the use of the risk algorithm can be given. In particular, in African Americans, a paradoxically low prevalence of AF has consistently been reported despite a high risk factor burden.[5,6] Thus, it is important to understand how the classic risk factors for AF combined in a risk prediction algorithm are associated with risk in African Americans.

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We tested a risk algorithm for AF incidence developed in the Framingham Heart Study in 2 large, independent, community-based cohorts from Europe (Age, Gene/Environment Susceptibility-Reykjavik Study [AGES][7]) and the United States (Cardiovascular Health Study [CHS][8]). In the CHS, we had the opportunity to examine risk factor prevalence and association with incident AF in whites and African Americans. An accurate risk assessment tool is necessary to address the increasing burden of AF in the community by facilitating the identification of individuals at increased absolute risk to potentially target for intervention trials. With

the current project we intended to take the second step of a risk algorithm implementation: the validation of the risk function in samples independent of the derivation cohort.

METHODS

STUDY SAMPLES

Overall, we examined data from 14 412 individuals (AGES, n = 4238; CHS, n = 5410; and FHS, n = 4764); FHS was the derivation sample. Participants were excluded if they were younger than 45 years or older than 95 years at baseline, had prevalent AF at baseline, or were missing data for any of the following risk factors: age, sex, body mass index (BMI), systolic blood pressure, treatment for hypertension, electrocardiographic PR interval, or history of heart failure. All studies were approved by institutional review boards from the participating institutions. All participants provided written informed consent.

Data from the AGES were based on men and women recruited between 2002 and 2006 (n = 5764). The participants were the survivors of the Reykjavik Study,[7] which was conducted between 1967 and 1996. All men and women (n = 30 795) living in the greater Reykjavik area and born from 1907 through 1935 were selected for the Reykjavik Study cohort, and a random sample was invited to participate (five-sixths of the cohort). The response rate was 71% (n = 19 381).[7]

Standard examination protocols and questionnaires were performed in the AGES study. Clinic visits included anthropometry, blood pressure measurement, electrocardiogram, and measures of different physical and cognitive function domains. The diagnosis of heart failure was based on hospital discharge records. Physical examination for valvular heart disease was not performed. Information on vital events and cardiovascular disease was continuously recorded since study inception, and this information was supplemented from registries of vital status and cardiovascular disease and hospital records using *International Classification of Diseases, Ninth Revision (ICD-9),* and *International Statistical Classification of Diseases, 10th Revision (ICD-10),* codes. Prevalent AF or atrial flutter was diagnosed at the AGES visit or by *ICD-9* and *ICD-10* codes on hospital admission before the AGES visit. Incident AF was identified by hospital admission *ICD-10* code.

The CHS is an observational cohort study of risk factors for coronary disease and stroke in the elderly. In the 1989-1990 period, 4 field centers recruited a total of 5201 people 65 years or older from Medicare eligibility lists in 4 communities in the United States (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; Pittsburgh, Pennsylvania). To enhance minority representation, during 1992-1993, 687 African American participants were recruited in 3 of the 4 field centers.

Participants had annual examinations including assessment of cardiovascular risk factors, prior cardiovascular disease, medications, height, weight, seated blood pressure, and a 12-lead electrocardiogram through 1999. At the baseline examination for 1989-1990 only, cardiac murmur was reported for any diastolic or systolic murmur. Racial identity was provided by self-report. Because most of the African American participants were recruited in the 1992-1993 period, they did not undergo cardiac auscultation at baseline. A history of heart failure at baseline was defined by signs, symptoms, clinical tests, physician diagnosis, and/or medical therapy.[9]

As for the derivation sample[4] for the AF risk algorithm, participants from the middle-aged to elderly white FHS original (examination cycles 11 [n = 2955] and 17 [n = 2179]) and offspring (examination cycles 1 [n = 5124] and 3 [n = 3873]) cohorts were eligible. Standardized physician-administered questionnaires provided information on risk factors, medications, and health behaviors. Anthropometric measures, blood pressures, and 12-lead electrocardiograms were taken at every FHS clinic visit. Valvular heart disease was diagnosed by physician-auscultated grade 3 or higher of 6 systolic or any diastolic murmur. Information on cardiovascular outcomes and medications was updated by regular questionnaires during FHS clinic visits and biennial health updates. In case of cardiovascular events, including heart failure, outpatient medical charts and hospital discharge records were collected and underwent adjudication by Framingham physicians based on previously published clinical criteria.[10] Ten-year follow-up information was used to derive the previously published AF risk algorithm.[4]

OUTCOME ASCERTAINMENT

In the 3 cohorts, incident AF was diagnosed (1) on the date that AF or atrial flutter was first detected by study electrocardiogram; (2) on the date of hospital admission if an *ICD-9* or *ICD-10* discharge diagnosis code for AF or atrial flutter was assigned; or (3) in FHS only, if sufficient evidence was available for AF based on hospital or general practitioner records, according to expert opinion. Prevalent AF was based on the diagnosis of AF at or prior to the baseline examination. Ascertainment of AF took place between 2002 and 2008 in AGES, 1989 and 2005 in CHS, and 1968 and 1992 in FHS. For more details on outcome ascertainment and analysis, see the eAppendix, eFigures 1 and 2, and eTables 1, 2, and 3 (http://www.archinternmed.com).

STATISTICAL ANALYSIS

Risk factor selection was based on the recently published AF risk algorithm developed in the FHS and included age, sex, BMI, systolic blood pressure, hypertension treatment, electrocardiographic PR interval, and prevalent heart failure.[4] Descriptive statistics were produced for each cohort (and each racial group) considered separately. Five-year (and 10-year in Framingham and CHS) estimates of AF rates were produced for each cohort using the Kaplan-Meier method.

To compensate for the shorter follow-up periods in AGES, we re-estimated the model in FHS to assess risk factors for incident AF over 5 years and truncated FHS follow-up at 5 years; death and event-free follow-up of more than 5 years were censoring events. In CHS and FHS, if follow-up was available for more than 11 years, multiple 5-year intervals for individuals were included if all of the inclusion and none of the exclusion criteria were met. It has been shown that pooled Cox models can be assumed to be robust.[11] The proportionality of the hazards assumption was not violated.

Model performance was examined in several steps. First, a Cox proportional hazards function was estimated for each cohort relating incident AF (over 5 years of follow-up) to the following risk factors derived from the published Framingham risk algorithm to achieve the Cox model for that cohort[4]: age, age^2, male sex, BMI, current treatment for hypertension, PR interval, history of heart failure, male sex $\times$ age^2, and age $\times$ history of heart failure. Two terms in the original FHS risk function—valvular heart disease and age $\times$ valvular heart disease—were not included in this Cox model because data on valvular heart disease at baseline were missing for all AGES participants and for most CHS African American participants. We calculated a model based on Framingham data relating 5-year incidence of AF to risk factors excluding valvular heart disease. In a second step, this Framingham 5-year AF risk function (including the beta estimates, baseline incidence, and risk factor mean values from the new Framingham risk function) was then applied to each cohort to produce estimates of 5-year risk of AF in each cohort. In the final step, we

Table 1. Baseline and Follow-up Characteristics for AF Incidence[a]

Characteristic	AGES	CHS		FHS
		Whites	African Americans	
Person-intervals, No.	4238	8254	1552	8044
Male sex	1580 (37.3)	3352 (40.6)	556 (35.8)	3591 (44.6)
Age, mean (SD), y	76.3 (5.5)	75.1 (5.9)	75.3 (6.2)	60.9 (9.9)
BMI, mean (SD)	27.0 (4.5)	26.4 (4.5)	28.5 (5.6)	26.3 (4.3)
Systolic blood pressure, mean (SD), mm Hg	143 (21)	135 (21)	141 (23)	136 (21)
Hypertension treatment	2533 (59.8)	3203 (38.8)	906 (58.4)	1941 (24)
Heart failure	53 (1.3)	420 (5.1)	121 (7.8)	70 (1.0)
Valvular heart disease		774 (9.6)	VM	226 (3.0)
PR interval, ms	172 (29)	171 (32)	173 (33)	164 (23)
5-Year AF incidence rate				
Cases/person-years	226/17 678	832/36 604	126/6854	175/38 938
Rate per 1000 person-years	12.8	22.7	18.4	4.5
10-Year AF incidence rate				
Cases/person-years	NA	831/36 612	NA	457/74 261
Rate per 1000 person-years	NA	22.7	NA	6.2

Abbreviations: AF, atrial fibrillation; AGES, Age, Gene/Environment Susceptibility-Reykjavik Study[7]; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHS, Cardiovascular Health Study[8]; FHS, Framingham Heart Study[4]; NA, not applicable; VM, variable missing in most CHS African Americans.

[a]Unless otherwise indicated, data are reported as number (percentage) of participants.

accounted for the respective cohorts' baseline survival and risk factor means to improve model fit in an adjusted model.[12]

In the different cohorts and separately for whites and African Americans in CHS, model discrimination was estimated by the C statistic. Calibration was assessed by agreement between predicted and observed 5-year event rates in deciles of predicted risk using a modified Hosmer-Lemeshow χ^2 statistic for survival analysis.[13]

Population-attributable risk was calculated for the risk factors combined in the risk algorithm using the previously applied risk categories of less than 5% (referent), 5% to 10%, and greater than 10% risk. We used the approach described by Hanley[14] to derive the population attributable fraction. Statistical analyses were conducted using SAS software, version 9.1 (SAS Institute, Cary, North Carolina) and Stata, version 10 (StataCorp, College Station, TX). A 2-sided $P < .05$ was assumed to show statistical significance.

SECONDARY ANALYSES

Secondary analyses were performed using 10-year follow-up intervals in CHS whites only and included the valvular heart disease variable defined by cardiac murmur at baseline to provide a direct comparison to the original FHS AF risk function. In exploratory analyses in the FHS, we also examined whether a simpler, easier-to-interpret model without the interaction terms (interactions for age and sex) performed equivalently to the published Framingham risk algorithm. In addition, we explored whether there were nonlinear associations with age using a general additive model and spline functions.

RESULTS

COHORT CHARACTERISTICS

The number of individuals excluded because of prevalent AF was 927 (AGES, n = 568; CHS whites, n = 144; CHS African Americans, n = 13; and FHS, n = 202). Further reasons for exclusion by cohort are illustrated in eFigure 1. Baseline characteristics for the study cohorts are summarized in **Table 1** including a total of 22 088 observations on 14 412 participants over 100 074 person-years of follow-up. For the CHS, African Americans and whites are reported separately. The AGES and CHS cohorts were similar in mean age, but the mean age in the FHS cohort was approximately 15 years younger. The number of events observed during 5-year follow-up intervals was 226 in the AGES, 832 in CHS whites, 126 in CHS African Americans, and 175 in the FHS. The percentage of men ranged from 35.8% in CHS African Americans to 44.6% in the FHS cohort. The unadjusted prevalence of most of the risk factors was highest in CHS African Americans (eg, high BMI, heart failure, long PR interval) except for systolic blood pressure and hypertension treatment, which were highest in the older AGES cohort. The unadjusted 5-year AF incidence rates differed across cohorts, with the highest incidence observed in CHS whites (22.7 cases/1000 person-years) and lowest incidence rate in the FHS (4.5 cases/1000 person-years). Cumulative incidence rates across cohorts by age are displayed in **Figure 1**.

RISK MODELS

Adjusted calibration for deciles of expected (risk function) and observed (Kaplan-Meier estimates) risk of 5-year incidence of AF is illustrated in **Figure 2**.

Age- and sex-adjusted Cox models (**Table 2**) revealed a similar strength of association of the different risk factors across cohorts and race. The strongest single risk factors were age, with an approximately 2-fold increase in AF incidence per decade, and prevalent heart failure, with an almost 3-fold higher risk. In African Americans, male sex and PR interval did not reach statistical

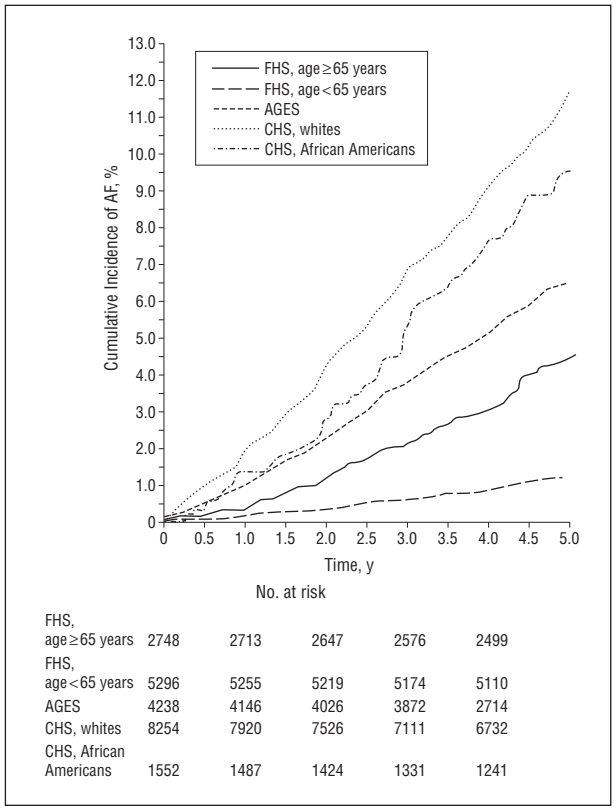

Figure 1. Cumulative survival curves by cohort and race for the indicated age categories and studies. In the AGES (Age, Gene/Environment Susceptibility-Reykjavik Study[7]) and CHS (Cardiovascular Health Study[8]) cohorts, only data from individuals 65 years or older were available. Curves were slightly smoothed. FHS indicates Framingham Heart Study.[4]

significance but showed point estimates comparable to the results in whites.

The best Cox models (calibration and discrimination) using the covariates established by the FHS based on the results developed from the respective studies' own data reached a C statistic of 0.68 in all cohorts (**Table 3**). As expected, discrimination and calibration was best in the FHS derivation sample. In the replication cohorts, Cox models using the FHS risk function without modifications exhibited lower discrimination statistics but were improved by recalibration for the higher baseline incidence rates and mean risk factor distributions. The C statistic point estimates after adjustment were 0.67 (AGES) 0.68 (CHS whites), and 0.66 (CHS African Americans) and were similar to the C statistics for the model developed from each study's own data. There was no statistical difference between the C statistic of CHS whites and African Americans ($P=.47$). Calibration was good in AGES and CHS African Americans. In CHS whites, the unadjusted χ^2 statistic was high (456.0) but improved after adjustment for the study's means of risk factors and baseline survival.

Compared with individuals in the lowest risk category (<5% 5-year risk of AF), participants in the category with greater than 10% risk of developing AF had an up to 7.5-fold higher risk and contributed between 27.9% (AGES) and 50.7% (CHS whites) of the population-attributable risk (**Table 4**). The 7 risk factors combined constituted between 47.0% (AGES) and 63.6% (FHS) of the population-attributable risk of AF in whites and 58.8% in African Americans.

SECONDARY ANALYSES

For 10-year AF incidence, Cox proportional hazards regression coefficients of the respective studies are listed in eTable 2, and discrimination and calibration statistics in eTable 3. The elimination of the age^2 term and the interactions of the original model in the FHS cohort did not influence the discrimination statistics but slightly reduced the calibration of the model. Optimal model fit was achieved by leaving the interactions in the function. We tested the shape of association of age with AF and did not observe a significant nonlinear term in the FHS data (eFigure 2).

COMMENT

PRINCIPAL FINDINGS

We validated a risk function for the prediction of incident AF, which was originally developed in the middle-aged to elderly Framingham cohort of white Americans, in 2 large independent studies from the United States and Europe. The risk algorithm worked reasonably well for 5-year risk prediction after calibration for the underlying event rates. We were able to extend these findings to African Americans. The hazard ratios for specific risk factors were comparable across cohorts. Discrimination of the Framingham AF risk model was consistent across groups, and calibration was satisfactory after adjustment. The risk algorithm may thus provide a tool applicable across a broad range of individuals at risk for AF.

The AF incidence observed across studies showed differences that may be explained by several factors. First, the age structure varied across cohorts, with FHS being the youngest cohort. In secondary analyses we investigated whether the relation of age with incident AF deviates from linearity, but we failed to discover nonlinear associations over the age range examined (45-95 years). Second, the years during which AF was ascertained differed by cohort: AF was ascertained between the 1960s and early 1990s in the FHS but during the 1989-2008 period in CHS and AGES. There may be secular trends in the diagnosis and coding of AF that favor increased recognition of this arrhythmia in more recent years. Third, the CHS and FHS had more vigorous ascertainment of AF cases than the AGES, which relied on hospital discharge diagnoses, perhaps leading to greater misclassification of AF cases. Finally, we demonstrated lower AF incidence in African Americans than in their white CHS counterparts of the same age distribution, a finding in accordance with prior observations of lower AF prevalence in African Americans.[15,16]

RISK FACTORS IN RELATION TO INCIDENT AF

Previous replication attempts of FHS risk scores for coronary heart disease events revealed good reproducibility, both in similarly structured and less comparable cohorts and different racial groups.[12,17,18] Owing to differ-

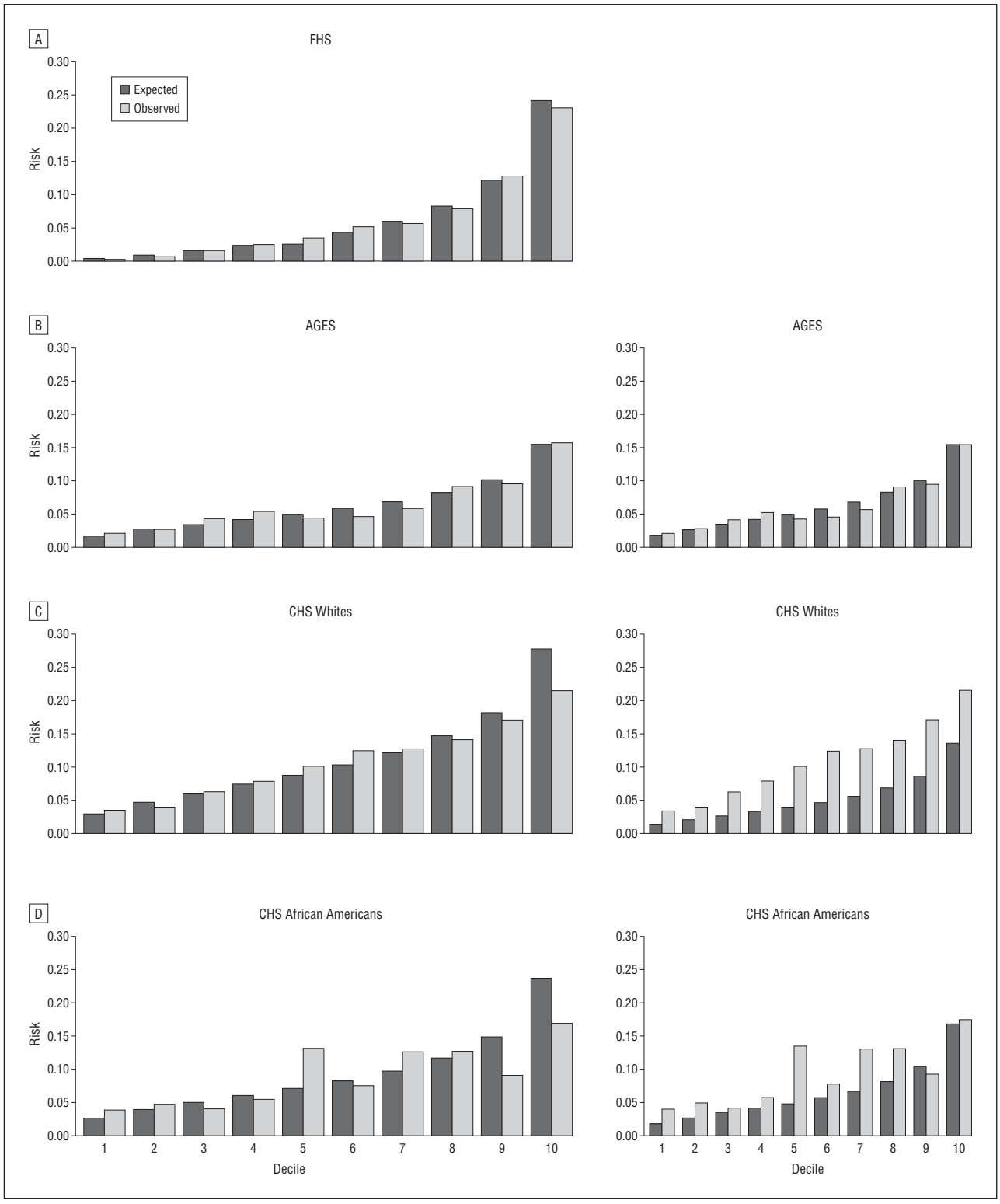

Figure 2. Adjusted calibration for deciles of expected (risk function) and observed (Kaplan-Meier estimates) risk of 5-year incidence of atrial fibrillation. A, Framingham Heart Study (FHS).[4] B, Age, Gene/Environment Susceptibility-Reykjavik Study (AGES).[7] C and D, Cardiovascular Health Study (CHS)[8] white and African American cohorts, respectively. B-D, The inset figures show the unadjusted results, and the larger figures represent the recalibration accounting for different baseline prevalence of risk factors and incidence of atrial fibrillation.

ing cohort characteristics and baseline event rates in other samples, recalibration is usually necessary to achieve better model fit, as was observed in the current analysis. The age distribution in the FHS and the other 2 cohorts also provides a likely explanation for the difference in discrimination observed across cohorts. Recalibration and adjustment for baseline survival in the respective cohorts is another way of accounting for differences in base-

Table 2. Age- and Sex-Adjusted Cox Proportional Hazards Models for Predictors of Incident AF With 5-Year Follow-up[a]

Variable	AGES	CHS Whites	CHS African Americans	FHS
Age[b]	2.30 (1.83-2.88) <.001	2.13 (1.90-2.40) <.001	1.95 (1.47-2.59) <.001	2.44 (2.11-2.83) <.001
Male (vs female)[c]	1.47 (1.13-1.91) .004	1.56 (1.36-1.79) <.001	1.20 (0.84-1.73) .32	1.81 (1.34-2.44) <.001
Body mass index	1.22 (1.05-1.41) .01	1.14 (1.05-1.23) .001	1.29 (1.10-1.51) .002	1.20 (1.01-1.42) .04
Systolic blood pressure	1.14 (1.01-1.28) .04	1.14 (1.07-1.22) <.001	1.17 (1.01-1.36) .03	1.18 (1.03-1.35) .02
Hypertension treatment	1.89 (1.40-2.46) <.001	1.48 (1.29-1.69) <.001	1.58 (1.09-2.31) .02	1.75 (1.28-2.37) <.001
PR interval	1.24 (1.12-1.37) <.001	1.12 (1.05-1.19) .001	1.12 (0.96-1.31) .15	1.34 (1.15-1.55) <.001
Valvular heart disease	NA	1.76 (1.46-2.12) <.001	VM	2.34 (1.41-3.87) <.001
Prevalent heart failure	1.78 (0.74-4.33) .20	2.98 (2.42-3.68) <.001	3.21 (2.06-5.00) <.001	4.45 (2.40-8.25) <.001

Abbreviations: AF, atrial fibrillation; AGES, Age, Gene/Environment Susceptibility-Reykjavik Study[7]; BMI, body mass index; CHS, Cardiovascular Health Study[8]; FHS, Framingham Heart Study[4]; NA, not applicable; VM, variable missing in most CHS African Americans.

[a] All data are reported as hazard ratios (95% confidence intervals) with *P* values. Hazard ratios for continuous variables are expressed per increase of 10 years of age, 5 BMI increments, 20 mm Hg of systolic blood pressure, and 30 ms of PR interval; hazard ratios for dichotomous variables are for the condition present vs absent.

[b] Unadjusted.

[c] Sex-adjusted for age.

Table 3. Discrimination and Calibration for the AF Risk Model Across Cohorts

Cohort	Discrimination, C Statistic (95% CI)	Calibration	
		χ^2	*P* Value
FHS	0.78 (0.75-0.82)	3.8	.92
AGES			
Best Cox[a]	0.68 (0.65-0.71)	3.0	.96
Unadjusted[b]	0.67 (0.64-0.71)	19.3	.02
Adjusted[c]	0.67 (0.64-0.71)	16.2	.06
CHS whites			
Best Cox[a]	0.68 (0.66-0.70)	10.6	.31
Unadjusted[b]	0.68 (0.66-0.70)	456.0	<.001
Adjusted[c]	0.68 (0.66-0.70)	46.1	<.001
CHS African Americans			
Best Cox[a]	0.68 (0.64-0.73)	11.5	.25
Unadjusted[b]	0.66 (0.61-0.71)	21.8	.01
Adjusted[c]	0.66 (0.61-0.71)	10.6	.31

Abbreviations: AF, atrial fibrillation; AGES, Age, Gene/Environment Susceptibility-Reykjavik Study[7]; CHS, Cardiovascular Health Study[8]; FHS, Framingham Heart Study.[4]

[a] The best Cox models (discrimination and calibration) are the results developed from the respective studies' data involving the risk factors established in the FHS.

[b] Unadjusted results are derived from the respective studies' data using the FHS risk function without modifications.

[c] Adjusted indicates that the FHS risk model was applied for the Cox models, and adjustment for the means of risk factors and baseline survival in the other study for χ^2 calculation was performed.

line characteristics of the samples. In secondary analyses, we examined whether a more parsimonious model without the interaction terms for age and sex would simplify the risk function. The elimination of these additional terms did not change the discrimination ability of the model, as was expected,[12] but reduced the calibration performance. For this reason, we recommend leaving the age^2 and interaction terms in the algorithm. Overall, the algorithm performed well with good calibration and discrimination underlining the central role of risk factors such as age, sex, elevated blood pressure, and heart failure.[16,19,20]

We were able to confirm the role of electrocardiographic PR interval as an AF risk factor. Atrial conduction defects have been suggested to constitute precursors of a reduced threshold for AF,[21,22] and knowledge of abnormalities in atrial electrical activity may help to better understand the pathophysiologic characteristics of imminent AF.[23]

Important from the perspective of primary prevention is that risk factors such as BMI, high blood pressure, and heart failure are modifiable or treatable and thus accessible to intervention. They may thus provide direct targets for prevention of AF or, at least, the delay of disease onset.

RACE

Although not all risk factors reached statistical significance in age- and sex-adjusted models due to a small sample size and resulting wide confidence intervals, the point estimates for the hazard ratios in African Americans were similar to those in whites. The risk algorithm performed similarly in both races. The distribution of risk factors for AF in African Americans was similar or even higher for unfavorable risk factors than in whites, confirming earlier reports.[15,24] For example, hypertension as one of the major predictors of AF in whites was more frequent in African Americans[15,24] and revealed hazard ratios for AF comparable to that in whites, as shown by our data, but it did not translate into a higher AF incidence.

Regarding the risk factor associations and distribution, our data suggest differences in the incidence rate

Table 4. Population-Attributable AF Risk Associated With 7 Risk Factors Combined in Risk Categories Across Cohorts

AF Risk Category	AGES[7]				FHS[4]			
	Exp, %	Events, No.	RR	AR, %	Exp, %	Events, No.	RR	AR, %
<5%	48.4	58	1 [Ref]	0.0	58.9	98	1 [Ref]	0.0
5%-10%	33.3	83	2.08	19.1	21.2	112	3.17	16.8
>10%	18.4	85	3.86	27.9	19.9	247	7.45	46.8
All	100	226	NA	47.0	100	457	NA	63.6
	CHS[8]							
	Whites				African Americans			
<5%	21.1	65	1 [Ref]	0.0	28.9	15	1 [Ref]	0.0
5%-10%	33.3	205	2.00	12.3	35.5	43	2.34	19.5
>10%	45.6	562	4.01	50.7	35.6	68	3.69	39.3
All	100	832	NA	63.0	100	126	NA	58.8

Abbreviations: AF, atrial fibrillation; AGES, Age, Gene/Environment Susceptibility-Reykjavik Study; AR, attributable risk; CHS, Cardiovascular Health Study; Exp, exposed individuals; FHS, Framingham Heart Study; NA, not applicable; Ref, reference; RR, relative risk.

of AF in African Americans rather than a completely different set of variables that account for AF risk. However, additional factors may be responsible for differences of AF risk between races, and these must be identified and evaluated. Genetic association studies, for example, may show whether there is a genetically determined predisposition to AF beyond classic AF risk factors.

The comparable strength of risk factors in different races emphasizes their central importance and potential direct role in the disease process. Similar risk factors in both sexes and different races may facilitate risk communication and the development of uniform concepts of prevention. Similar to other risk algorithms, the risk score may help to identify individuals at high risk for AF and at the same time provide a starting point for active prevention, since some of the clinical risk factors included in the algorithm are modifiable. Whether the risk function can be applied effectively for the identification of participants for clinical intervention trials needs to be examined.

STRENGTHS AND LIMITATIONS

We acknowledge several limitations to our study. Observed differences in AF incidence beyond different age ranges and real incidence differences in the cohorts may be due to secular trends in the diagnosis and coding of AF and to differences in AF adjudication and intensity of collection of follow-up data. The performance of the risk algorithm indicates that the risk function seems to be robust against minor systematic misclassifications and real sample-specific differences.

Unfortunately, information on valvular heart disease, one of the strongest risk factors for AF, was not available in the AGES or in most of the CHS African Americans. Reliance on physical examination for heart murmur (vs echocardiography) may have led to misclassification of valvular heart disease in both CHS whites and the FHS cohort. Whereas in the FHS, significant valvular heart disease was considered in a graded fashion, heart murmur was classified as present-vs-absent in the CHS. The different classification reduces the comparability of the 2 studies, as is evident in the different prevalence and smaller hazard ratio related to cardiac murmur in the CHS. Severe valvular heart disease is uncommon (<5% prevalence) in the community. Although its diagnosis is associated with a high relative risk, the population-attributable risk is low, which may help to explain why the risk algorithm achieved similar accuracy to the FHS function in the replication samples even without the valvular heart disease variable. Similarly, the definition of heart failure and thus the baseline prevalence differed between cohorts. Rigorously adjudicated heart failure events in the CHS and FHS compared with hospital discharge diagnoses in the AGES may have led to somewhat different relations between heart failure and AF.[9] Again, at the community level, the prevalence of heart failure was low, and the slightly different definitions did not impair discrimination and calibration markedly. Overall, only the prospective application of the risk algorithm and the development of effective strategies to prevent AF will provide support for the utility of the risk function.

The utility of a risk prediction algorithm ultimately depends on several factors: (1) whether the algorithm accurately classifies individual risk; (2) whether effective preventive therapies for AF are available; and (3) whether targeting preventive therapies to the level of risk improves outcome in a cost-effective way. The present study is an effort to develop a robust transportable prediction instrument. Prior to demonstrating improved outcomes, the risk prediction instrument may be useful to identify high-risk individuals for primary prevention trials or as a screen to identify whether putative biological or genetic markers aid in risk stratification over and above easily assessed clinical factors.

We have demonstrated that an individual's absolute AF risk can reliably be assessed in independent, community-based samples of different age structure and racial background based on easily accessible clinical variables. It needs to be shown whether the application of the risk algorithm and the knowledge of the relative im-

portance of the potentially modifiable risk factors can reduce the number of incident AF cases.

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Online-Only Material: The eAppendix, eFigures, and eTables are available at http://www.archinternmed.com.
Additional Information: A full list of the principal CHS investigators and institutions is available at http://www.chs-nhlbi.org/pi.htm.

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