Refining Stroke Prediction in Atrial Fibrillation Patients by Addition of African-American Ethnicity to CHA$_2$DS$_2$-VASc Score

Rajesh Kabra, MD,[a] Saket Girotra, MD, SM,[b] Mary Vaughan Sarrazin, PhD[b,c]

ABSTRACT

BACKGROUND Prior studies show that African-American patients have a higher risk of stroke compared with Caucasians.

OBJECTIVES This study hypothesized addition of African-American ethnicity to CHA$_2$DS$_2$-VASc (congestive heart failure, hypertension, age $\geq$75 years, diabetes, previous stroke, vascular disease, age 65 to 74, and female sex) score might improve stroke prediction in patients with atrial fibrillation (AF).

METHODS Medicare claims from January 2010 to December 2012 identified patients with newly diagnosed AF. The CHA$_2$DS$_2$-VASc was calculated on the basis of diagnoses in claims incurred during 12 months before first AF diagnosis. Ethnicity was identified from the Beneficiary Summary File. CHA$_2$DS$_2$-VASc-R score was calculated by giving 1 additional point for African-American ethnicity. The primary outcome was stroke, defined by primary diagnosis on acute inpatient admissions after the initial AF diagnosis. We used proportional hazards regression to determine the relationship between stroke and the CHA$_2$DS$_2$-VASc or a revised CHA$_2$DS$_2$-VASc-R score.

RESULTS Of 460,417 patients with AF, 390,590 (85%) were non-Hispanic whites, 31,702 (7%) were non-Hispanic African Americans, and the remainder were other non-white ethnicities. Mean age was 79.2 $\pm$ 8.0 years, with 60% females. Overall, 16,703 stroke events occurred, and 151,441 (32.7%) patients died during a mean follow-up period of 18.0 months. Compared with CHA$_2$DS$_2$-VASc, CHA$_2$DS$_2$-VASc-R score improved the fit of the model significantly as measured by the log likelihood ratio statistic (p < 0.001). Among individual risk factors in CHA$_2$DS$_2$-VASc-R score, only prior stroke, age $\geq$75 years, and female sex had a stronger association with incident stroke than African-American ethnicity.

CONCLUSIONS In patients >65 years of age with newly diagnosed AF, the addition of ethnicity to CHA$_2$DS$_2$-VASc score significantly improved stroke prediction. (J Am Coll Cardiol 2016;68:461–70) © 2016 by the American College of Cardiology Foundation.

A trial fibrillation (AF) is associated with an increased risk of stroke and systemic embolism (1). It accounts for 15% of all strokes in the United States, 36% of strokes in patients >80 years of age, and up to 20% of cryptogenic strokes (2). Ischemic stroke with AF is associated with >20% mortality and a significantly higher disability, particularly in older patients. Hence, prevention of stroke related to AF is a cornerstone in the management of AF patients.

In several studies, African Americans have a higher incidence of stroke compared with whites (3-7). This has been attributed to increased risk factors such as hypertension, diabetes mellitus, and lower socioeconomic status (SES) in this ethnic group. However, in the REGARDS (Reasons for Geographic and Racial

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Differences in Stroke) cohort, the traditional risk factors and SES accounted for only one-half of the excess stroke incidence in African Americans, whereas the other one-half was attributed to other unknown factors and pathways (8).

Similar racial differences in the incidence of stroke have also been reported in patients with AF, where patients of African ancestry consistently have higher risk of stroke compared with whites (9–11). Our prior work has shown that in patients >65 years of age, AF in African Americans is associated with a higher incidence of stroke compared with whites, even after adjustment of risk factors and anticoagulation (12). This suggests that African-American ethnicity may be an independent risk factor for predicting stroke in AF patients.

Recent guidelines have endorsed the CHA$_2$DS$_2$-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, and female sex) score for identification of AF patients at risk of stroke in order to guide anticoagulation management (13,14). In this study, we hypothesized that addition of African-American ethnicity to the CHA$_2$DS$_2$-VASc score would improve the prediction of stroke in AF patients. We used the Medicare database to test this hypothesis.

METHODS

STUDY POPULATION. We used Centers for Medicare & Medicaid (CMS) data for years 2009 through 2012, including: 1) Beneficiary Summary File Base and Chronic Conditions segments; 2) Inpatient (Part A) and Carrier (Part B) Standard Analytic Files; and 3) Pharmacy Drug Event (Part D). We included patients if they had a new AF diagnosis during the period January 2010 through December 31, 2011. We defined new AF based on previously published algorithms (i.e., 1 inpatient claim or 2 outpatient claims within a year with International Classification of Diseases-Ninth Revision–Clinical Modification [ICD-9-CM] code 427.31 as primary or first secondary diagnosis, with no previous AF diagnoses during the prior 12 months) (15,16). We excluded patients if they were younger than 66 years at the time of diagnosis (to ensure at least 12 months of Medicare eligibility before diagnosis), were enrolled in a Medicare managed care during the observation period, or were not enrolled in a Part D drug prescription plan at the time of AF diagnosis. We also excluded 13,991 patients whose AF diagnosis occurred during the same hospitalization as

open heart surgery or within 30 days, as these may represent temporary post-surgical complications.

Our primary outcome was stroke, as identified on inpatient Standard Analytic File claims for years 2010 through 2012, and included acute hospitalizations admitted as emergent or urgent with a primary diagnosis of cerebral infarction (ICD-9-CM codes 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91). We determined race or ethnicity of the patients using the race code developed by the Research Triangle Institute (RTI) that is available on the CMS Beneficiary Summary File. The RTI race code is an enhanced race/ethnicity designation based on first and last name algorithms. The RTI race code has excellent agreement with self-reported race, with kappa coefficients ≥0.80 for Hispanic beneficiaries and ≥0.90 for African American beneficiaries (17).

The CHA$_2$DS$_2$-VASc is based on a point system reflecting the presence of congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes (1 point), previous stroke (2 points), vascular disease (1 point), age 65 to 74 (1 point), and female sex (1 point). The presence of heart failure, hypertension, diabetes, previous stroke, and vascular disease were identified by ICD-9-CM diagnoses in inpatient and outpatient claims during the 12 months before the first AF diagnosis (15,16). Age and sex were identified from Medicare enrollment data. We identified the date of first oral anticoagulant prescription fill after initial AF diagnosis in Part D event data in order to control for potential confounding due to differences in the use of oral anticoagulants by race/ethnicity. (Anticoagulants approved for stroke prevention in AF during the study time frame included warfarin, dabigatran, or rivaroxaban.) Additional patient characteristics were identified in the CMS enrollment and encounter data. Dual enrollment in Medicaid at the time of AF diagnosis was identified from the CMS Beneficiary Enrollment Summary. Other comorbid conditions were identified in inpatient and outpatient claims during the 12 months prior to the first AF diagnosis date and were defined using algorithms originally developed by Elixhauser et al. (18). Previous cerebrovascular events and prior bleeding episodes were identified using previously published algorithms (19,20).

STATISTICAL ANALYSIS. Data analysis encompassed bivariable and multivariable methods. First, characteristics of patients as of the date of first AF diagnosis were compared by race and ethnicity. Categorical variables (e.g., presence of hypertension) were compared using the chi-square statistic, whereas continuous or interval variables (e.g., age) were compared using analysis of variance. Subsequently,

we created for each patient a longitudinal record that included the date of first AF diagnosis, pre-existing patient characteristics and comorbidities, oral anticoagulant use, and number of days to first stroke.

Time-to-event models were estimated using proportional hazards regression to determine the relationship between CHA$_2$DS$_2$-VASc, race, and stroke. To determine the appropriate weight to give race/ethnicity in a revised CHA$_2$DS$_2$-VASc-R score, we first estimated the incremental risk of stroke associated with 1 additional point on the CHA$_2$DS$_2$-VASc scale using proportional hazards regression in which the only predictor variable was the CHA$_2$DS$_2$-VASc. Because our data include patients who received anticoagulants after AF diagnosis, and this impacts stroke risk, models were estimate alternatively using: 1) 252,722 patients who did not initiate anticoagulants within 90 days of AF; 2) 207,695 patients who did initiate anticoagulants; and 3) all patients regardless of anticoagulant use, with anticoagulant use treated as a time-dependent covariate and an interaction to separately estimate the relative association of CHA$_2$DS$_2$-VASc to stroke risk in patients who did or did not initiate anticoagulants. We then re-estimated the models while further including indicators for patient ethnicity of African American, Hispanic, Asian and Pacific Islanders, and Native American, along with the CHA$_2$DS$_2$-VASc score. We also evaluated the interaction of race/ethnicity and CHA$_2$DS$_2$-VASc. On the basis of the results of these analyses, the CHA$_2$DS$_2$-VASc-R was calculated by adding 1 additional point to the stroke risk score for patients of African-American ethnicity.

Discrimination for models based on the CHA$_2$DS$_2$-VASc and modified CHA$_2$DS$_2$-VASc-R was compared using a C-statistic adapted to survival data by considering not only predicted and observed outcomes, but also the timing of the outcomes. A limitation to the C-statistic for measuring improvements in model performance is that the addition of an important risk marker to a standard set of risk markers often results in only small improvements in the C-statistic [21]. Thus, we have included 2 additional measures to evaluate the improvement of stroke prediction with the addition of African-American ethnicity to the CHA$_2$DS$_2$-VASc score: net reclassification improvement (NRI), and integrated discrimination improvement (IDI) [22,23]. These measures were estimated using an adaptation appropriate for proportional hazards regression [24]. With the NRI, an increase in the predicted risk of stroke at baseline in patients who experienced a stroke implies improved performance, whereas a decrease in the predicted risk of stroke in patients

with stroke implies worse performance. The interpretation is opposite for patients who do not experience stroke. Thus, for patients with stroke, the NRI is calculated as the percentage of patients whose predicted stroke risk increased using the CHA$_2$DS$_2$-VASc-R score rather than the CHA$_2$DS$_2$-VASc score, minus the percentage whose predicted stroke risk decreased. For patients who do not experience stroke, NRI is calculated as the percentage of patients whose stroke risk decreased, minus the percentage whose stroke risk increased. The total NRI index is summed for all patients. A value >0 indicates an overall improvement in risk prediction that is clinically meaningful. The IDI can be viewed as a continuous version of the NRI, with probability differences used instead of simple categories representing direction of change. The IDI quantifies the increase in the ability of the model to separate patient with and without strokes. It is calculated as the mean change in the predicted probability of stroke with the addition of African-American ethnicity to the CHA$_2$DS$_2$-VASc among patients who did experience stroke minus the mean change among patients who do not experience stroke. The relative IDI is the ratio of the change in predicted probability of stroke, among patients with stroke relative to patients without stroke. Because we expected the revised score to impact the predicted risk of stroke more for African-American than non–African-American patients, the IDI and the relative IDI were calculated separately for African-American and non–African-American patients.

We also assessed model calibration using plots and the Hosmer-Lemeshow (HL) statistic [25]. Predicted risk of stroke was estimated for each patient based on

TABLE 1 Patient Demographics					
	Whites (n = 390,590)	African Americans (n = 31,702)	Hispanics (n = 24,977)	Native Americans (n = 1,518)	Asians/Pacific Islanders (n = 11,630)
Age, yrs	79.3 ± 8.0	78.8 ± 8.3	79.3 ± 7.8	77.6 ± 7.2	79.9 ± 7.7
Components of CHA$_2$DS$_2$-VASc score					
Females	59.7	65.9	60.5	59.8	56.0
Chronic heart failure	34.2	50.6	45.1	38.5	38.0
Hypertension	82.5	92.5	88.9	82.1	87.4
Age ≥75 yrs	67.1	63.9	68.0	62.4	72.3
Diabetes	33.2	52.4	55.5	45.8	48.3
Previous stroke	16.3	28.5	22.7	17.4	20.4
Vascular disease	53.1	60.7	62.0	51.7	53.5
CHA$_2$DS$_2$-VASc score	4.9 ± 1.8	5.6 ± 1.8	5.5 ± 1.8	5.0 ± 1.8	5.2 ± 1.8
1	2	1	1	1	1
2–4	42	27	29	42	35
5–9	56	72	70	57	64

Values are mean ± SD or %.

CHA$_2$DS$_2$-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, and female sex.

TABLE 2 Number of Initial Strokes and Initial Strokes per 1,000 Person-Years of Follow-Up After Initial AF Diagnosis

	Whites (n = 390,590)	African Americans (n = 31,702)	Hispanics (n = 24,977)	Native Americans (n = 1,518)	Asians/Pacific Islanders (n = 11,630)
Strokes	13,616	1,607	1,014	62	404
Mean follow-up (months)	18.2	15.9	17.5	17.0	18.2
Strokes per 1,000 patient-yrs	23.0	38.0	27.8	28.7	22.8

the CHA$_2$DS$_2$-VASc score. Patients were then placed into 10 categories using the ranked predicted risk of stroke. The mean predicted risk of stroke based on the CHA$_2$DS$_2$-VASc, the CHA$_2$DS$_2$-VASc-R, and the actual observed stroke rate within each category was calculated separately for African-American and non–African-American patients.

Finally, we evaluated the relative importance of each patient factor in the CHA$_2$DS$_2$-VASc-R score by examining the chi-square associated with each factor in proportional hazards regression models for stroke. The chi-square for each patient factor was calculated as the difference between the −2 times the log likelihood ratio in a model with no covariates, and −2 times the log likelihood ratio in a model with a single patient factor.

RESULTS. Of 460,417 patients with AF, 390,590 (85.0%) were non-Hispanic whites, 31,702 (6.9%) were non-Hispanic African Americans, 24,977 (5.4%) were Hispanics, 1,518 (0.3%) were Native Americans, and 11,530 (2.5%) were Asian/Pacific Islanders. Patient baseline demographics by race/ethnicity are presented in **Table 1**. All differences are statistically significant (p < 0.01); thus, we have not included p values in **Table 1**. Although the mean age was similar across groups, the prevalence of several comorbid conditions was significantly higher for African Americans and Hispanics compared with whites. The mean CHA$_2$DS$_2$-VASc score was higher in African Americans compared with whites, indicating higher risk of stroke. White patients were more likely to receive oral anticoagulants within 180 days of the initial AF diagnosis, compared with African Americans, Hispanics, Native Americans, or Asian/Pacific Islanders (46% vs. 39%, 40%, 38%, and 38%, respectively; p < 0.001).

CENTRAL ILLUSTRATION CHA$_2$DS$_2$-VASc Score for Stroke Prediction in AF: Stroke Rates for All Patients
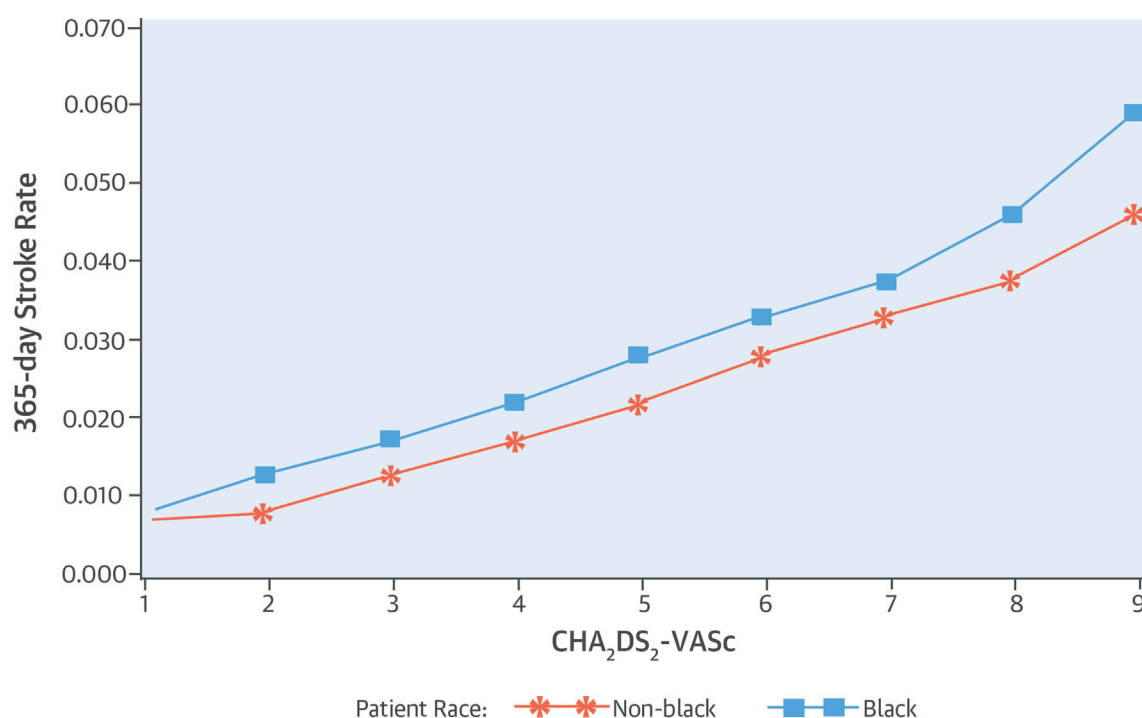
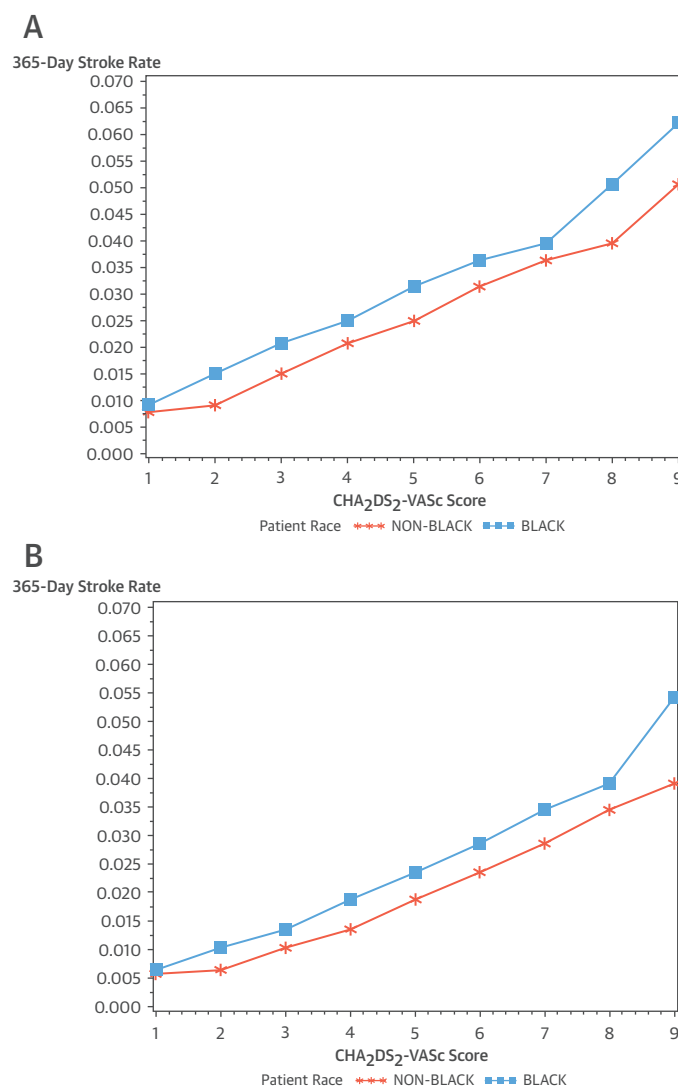Kabra, R. et al. J Am Coll Cardiol. 2016;68(5):461–70.

Stroke rate at 365 days after atrial fibrillation (AF) diagnosis, by race/ethnicity and CHA$_2$DS$_2$-VASc score for all patients. CHA$_2$DS$_2$-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, and female sex.

A total of 16,703 stroke events were noted during a mean follow-up period of 18.0 months per patient (**Table 2**). The rate of stroke per 1,000 patient years of follow-up was the highest in African Americans, followed by Native Americans, Hispanics, whites, and Asians/Pacific Islanders. Overall, 151,441 (32.7%) of patients died during follow-up.

The **Central Illustration** and **Figure 1** show: 1) stroke rate by race/ethnicity and CHA$_2$DS$_2$-VASc score for all patients; 2) stroke rate by race/ethnicity and CHA$_2$DS$_2$-VASc among patients who did not receive oral anticoagulants within 90 days of new AF; and 3) stroke rate by race/ethnicity and CHA$_2$DS$_2$-VASc among patients who received oral anticoagulants within 90 days of new AF. In these graphs, we excluded patients who died within 90 days of AF diagnosis, as we were not able to treat the receipt of anticoagulants as a time-dependent covariate in graphs. African-American ethnicity was associated with a higher rate of stroke irrespective of oral anticoagulant use across all CHA$_2$DS$_2$-VASc scores.

Table 3 shows the relationship between race/ethnicity and risk of stroke after controlling for CHA$_2$DS$_2$-VASc score and provides the basis for the CHA$_2$DS$_2$-VASc-R score. Models are shown for patients who did not receive anticoagulants after AF diagnosis (Model 1), in patients who did receive anticoagulants (Model 2), and in all patients while controlling for anticoagulation (Model 3). Resulting coefficients associated with CHA$_2$DS$_2$-VASc were remarkably similar regardless of anticoagulant use. One additional CHA$_2$DS$_2$-VASc point increased the relative hazard of stroke by 1.24 to 1.25 ($p < 0.001$) in models that included patients without or with anticoagulant use, respectively. As expected, anticoagulant use (Model 3) was associated with decreased risk of stroke (hazard ratio: 0.74; $p < 0.01$), and there was no interaction between anticoagulant use and CHA$_2$DS$_2$-VASc score, suggesting that the incremental hazard of stroke with a 1-point increase in CHA$_2$DS$_2$-VASc score was not modified by use of anticoagulation. The coefficient for African-American ethnicity was statistically significant, and suggested a relative hazard of 1.30 for African-American ethnicity relative to whites in patients who did not receive anticoagulants, and 1.47 for African-American ethnicity relative to whites in patients who did receive anticoagulants. Regardless of the use of anticoagulants, the coefficient for African-American ethnicity suggested that African-American ethnicity is associated with an increase in stroke risk that is greater than the increase in risk associated with 1 additional point on the CHA$_2$DS$_2$-VASc score (i.e., >1.24 increase in risk in patients without anticoagulant use and >1.25 increase in

FIGURE 1 Stroke Rate at 365 Days After AF Diagnosis

Stroke rate at 365 days after atrial fibrillation (AF) diagnosis, by race/ethnicity and CHA$_2$DS$_2$-VASc score for patients not taking oral anticoagulants within 90 days of AF diagnosis **(A)**. Stroke rate at 365 days after AF diagnosis, by race/ethnicity and CHA$_2$DS$_2$-VASc score for patients taking oral anticoagulants within 90 days of AF diagnosis **(B)**. CHA$_2$DS$_2$-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, and female sex.

patients with anticoagulant use) but less than the risk associated with 2 additional CHA$_2$DS$_2$-VASc points (i.e., <1.54 in patients without anticoagulant use and <1.56 in patients with anticoagulant use). Thus, the precise weight to assign to African-American ethnicity in a revised CHA$_2$DS$_2$-VASc-R score falls somewhere between 1 and 2. In keeping with the simplicity of the existing CHA$_2$DS$_2$-VASc score, the CHA$_2$DS$_2$-VASc-R score was calculated by adding

TABLE 3 Hazard of Stroke by Race/Ethnicity, Relative to White Patients, After Controlling for CHA$_2$DS$_2$-VASc Score (Model 1) and CHA$_2$DS$_2$-VASc Score Plus Anticoagulant Use (Model 2)

	Model 1: CHA$_2$DS$_2$-VASc With Race/Ethnicity in Patients With No Anticoagulant Use in 180 Days (n = 252,722)	Model 2: CHA$_2$DS$_2$-VASc With Race/Ethnicity in Patients With Anticoagulant Use in 180 Days (n = 207,695)	Model 3: CHA$_2$DS$_2$-VASc With Race/Ethnicity in Models With All Patients, and Indicator for Anticoagulant Use (n = 460,417)
CHA$_2$DS$_2$-VASc	1.24 (1.22–1.25) (p < 0.001)	1.25 (1.24–1.26) (p < 0.001)	1.25 (1.23–1.26) (p < 0.001)
Race			
African American	1.30 (1.21–1.39) (p < 0.001)	1.47 (1.36–1.59) (p < 0.001)	1.36 (1.29–1.43) (p < 0.001)
Hispanic	0.97 (0.89–1.05) (p = 0.43)	1.14 (1.04–1.26) (p = 0.008)	1.03 (0.97–1.10) (p = 0.36)
Native American	1.17 (0.85–1.61) (p = 0.34)	1.24 (0.84–1.84) (p = 0.28)	1.19 (0.92–1.52) (p = 0.17)
Asian/Pacific Islanders	0.79 (0.69–0.90) (p < 0.001)	1.10 (0.95–1.27) (p = 0.21)	0.89 (0.84–0.95) (p = 0.03)
Anticoagulant use	—	—	0.74 (0.72–0.76) (p < 0.001)

Values are hazard ratios from proportional hazards regression models (95% confidence intervals). CHA$_2$DS$_2$-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, and female sex.

1 point to the CHA$_2$DS$_2$-VASc for patients of African-American ethnicity. Coefficients associated with patients of Hispanic, Native American, or Asian/Pacific Island descent were either small in magnitude or not statistically significant. Thus, no additional points on the CHA$_2$DS$_2$-VASc scale were warranted for those patients.

As compared with CHA$_2$DS$_2$-VASc, CHA$_2$DS$_2$-VASc-R score improved the fit of the model significantly as measured by the log likelihood ratio statistic (p < 0.001) for stroke (Table 4). The model with the original CHA$_2$DS$_2$-VASc had a C-statistic of 0.60 (95% confidence interval: 0.59 to 0.61), compared with a C-statistic of 0.61 (95% confidence interval: 0.60 to 0.62) for the model with CHA$_2$DS$_2$-VASc-R. The calculated NRI was 7.6% (p < 0.001), suggesting that the net change in predicted stroke risk with the addition of African-American ethnicity to the CHA$_2$DS$_2$-VASc score was in the "correct" direction 7.6% more often than in the "incorrect" direction. The IDI was .012 for African-American patients, suggesting that the predicted hazard of stroke is, on average, 1.2% closer to the "correct" prediction using the CHA$_2$DS$_2$-VASc-R score rather than the CHA$_2$DS$_2$-VASc. The IDI for white patients was very small (<0.001), suggesting very little change in predicted

probabilities for white patients. The interaction between CHA$_2$DS$_2$-VASc and race/ethnicity was not statistically significant, suggesting similar relative increase in stroke risk by race/ethnicity as the CHA$_2$DS$_2$-VASc increases.

Figures 2A and 2B show calibration plots by race/ethnicity. For African-American patients, Figure 2A demonstrates substantially better model fit based on the CHADS2-VASc-R compared with the CHADS2-VASc. However, in Figure 2B, the predicted risk of stroke changes very little for non–African-American patients, resulting in little improvement in model calibration. HL statistics were large and statistically significant for both African-American and non-African-American patient segments (HL: 1,529 for non-African-American patients and 148 for African-American patients, on the basis of the difference between observed and predicted stroke by the CHADS2-VASc score). However, a statistically significant HL statistic is not informative with respect to calibration when using large samples (25). Nevertheless, we note that the HL statistic decreased only modestly for non–African-American patients with the use of CHA$_2$DS$_2$-VASc-R (from 1,529 to 1,503), but was reduced by one-half for African-American patients (from 148 to 72).

Finally, Table 5 also shows the relative importance of each factor in the CHA$_2$DS$_2$-VASc-R score in predicting stroke, as measured by the magnitude of the chi-square statistic in univariable and multivariable Cox regression models. We found that compared with the 7 existing variables in the CHA$_2$DS$_2$-VASc-R score, African-American ethnicity was a stronger predictor than heart failure, hypertension, diabetes mellitus, and history of vascular disease. Only prior history of stroke, age ≥75 years, and female sex were more important than African-American ethnicity in prediction of stroke in this population.

TABLE 4 Comparison of CHA$_2$DS$_2$-VASc and CHA$_2$DS$_2$-VASc-R Scores in Predicting Stroke: Relative Hazard Associated With 1-Point Increase in Stroke Risk Score, and C-Statistic

	CHA$_2$DS$_2$-VASc	CHA$_2$DS$_2$-VASc-R
Hazard ratio	1.24 (1.23–1.25) (p < 0.001)	1.25 (1.24–1.26) (p < 0.001)
C-statistic	0.60 (0.59–0.61)	0.61 (0.60–0.62)

Values in parentheses are 95% confidence intervals, unless otherwise indicated. CHA$_2$DS$_2$-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, and female sex. CHA$_2$DS$_2$-VASc-R = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, female sex, and African American ethnicity.

DISCUSSION

Our study demonstrates that addition of African-American ethnicity to the CHA$_2$DS$_2$-VASc risk scoring system improves the stroke prediction in AF patients >65 years of age. This improvement in stroke prediction persisted across all CHA$_2$DS$_2$-VASc scores even after adjustment for anticoagulation use. Moreover, in analysis of individual patient factors in the CHA$_2$DS$_2$-VASc-R score, we found that only 3 factors (history of stroke, age ≥75 years, and female sex) were stronger predictors of stroke than African-American ethnicity.

African-American ethnicity has been shown to be a risk factor for stroke in AF patients. A recent observational study using Medicare population from 2010 showed that the risk of stroke was higher in African Americans (29.3 per 1,000 patient-years) versus whites (14.8 per 1,000 patient-years)—a finding similar to what we report (37.9 per 1,000 patient-years in African Americans and 22.7 per 1,000 patient-years in whites) (9). The differences in actual numbers are likely due to differences in sampling of the study population. Although we studied all patients with newly diagnosed AF, this study included a random sample of 5% all Medicare patients and included any AF diagnosis.

In our prior work using a similar Medicare database, we studied the racial/ethnic differences in mortality and stroke outcomes in 517,941 patients >65 years of age with newly diagnosed AF (12). We noted a 46% higher incidence of mortality and 66% higher incidence of stroke in African Americans compared with the white population. However, after adjustment of the pre-existing comorbidities, the higher risk of mortality in African Americans was eliminated, but they continued to have 46% higher risk of having stroke, compared with whites, even after adjusting for anticoagulation status. The increased risk of stroke in African Americans compared with whites was noted even when the groups were compared by the CHA$_2$DS$_2$-VASc score. The risk of stroke was also noted to be higher in Hispanics compared with whites. However, in our current study, none of the other racial/ethnic groups, including Hispanics, Native Americans, or Asian/Pacific Islanders, improved stroke prediction beyond the CHA$_2$DS$_2$-VASc score.

Despite higher prevalence of each CHA$_2$DS$_2$-VASc risk factor among African Americans, the strong association between African-American ethnicity and stroke was independent of them, as noted in our multivariable analyses. Moreover, addition of African-American ethnicity to the CHA$_2$DS$_2$-VASc risk

FIGURE 2 Observed Stroke Rate and Rate Predicted by CHA$_2$DS$_2$-VASc and CHA2DS2-VASc-R for African Americans and Non-African Americans
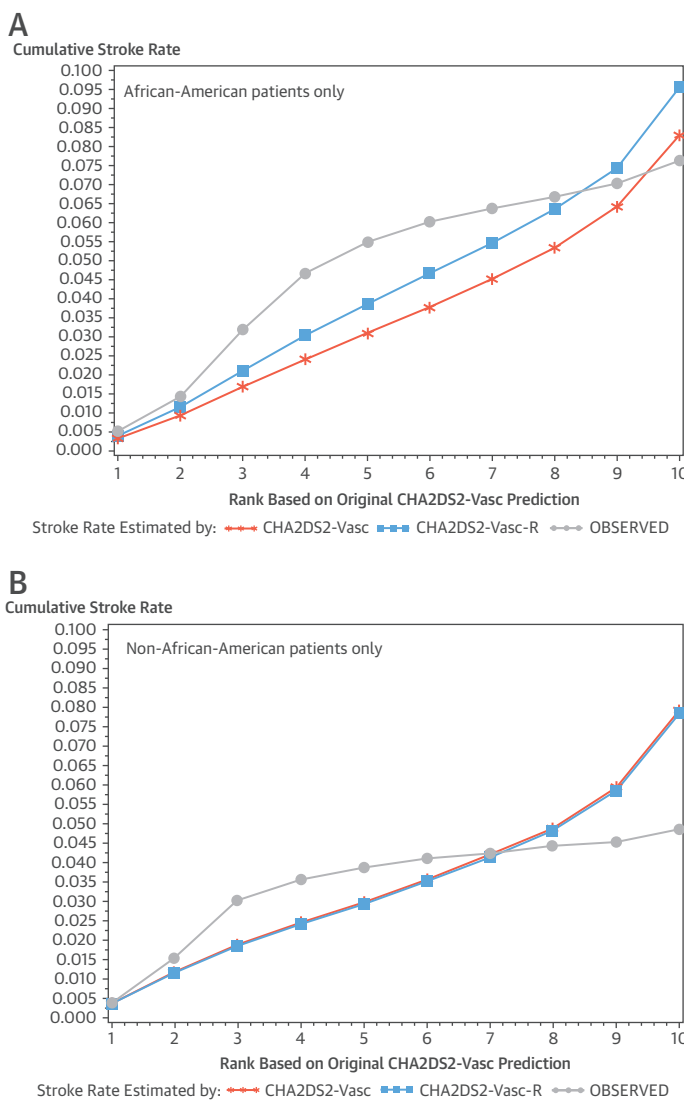
(A) Observed stroke rate and rate predicted by CHA$_2$DS$_2$-VASc and CHA$_2$DS$_2$-VASc-R: for African-American patients only. (B) Observed stroke rate and rate predicted by CHA$_2$DS$_2$-VASc and CHA$_2$DS$_2$-VASc-R: for non-African-American patients only. CHA$_2$DS$_2$-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, and female sex; CHA$_2$DS$_2$-VASc-R = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, female sex, and African American ethnicity.

score not only improved the model discrimination, but also led to the appropriate reclassification of patients to higher and lower risk categories. There are several possible explanations why addition of African-American ethnicity to CHA$_2$DS$_2$-VASc score improves stroke prediction in AF patients. There may be racial/ethnic differences in the impact of risk

468   Kabra et al.
CHA$_2$DS$_2$-VASc-R Score for Stroke Prediction in AF

JACC VOL. 68, NO. 5, 2016
AUGUST 2, 2016:461–70

TABLE 5 Relative Contribution of Each Risk Factor of CHA$_2$DS$_2$-VASc-R Score in Stroke Prediction

Order of Importance	CHA$_2$DS$_2$-VASc-R Factor	Univariable Models		Multivariable Models With All Patient Factors	
		Chi-Square	Relative Hazard	Chi-Square	Relative Hazard
1	History of stroke	1,959.99	1.42 (p < 0.001)	1,387.48	1.35 (p < 0.001)
2	Age ≥75 yrs	1,296.73	1.95 (p < 0.001)	906.27	1.77 (p < 0.001)
3	Female	579.34	1.50 (p < 0.001)	319.98	1.36 (p < 0.001)
4	African American ethnicity	323.74	1.60 (p < 0.001)	197.18	1.45 (p < 0.001)
5	Hypertension	243.87	1.44 (p < 0.001)	23.80	1.13 (p < 0.001)
6	Heart failure	227.37	1.27 (p < 0.001)	40.86	1.11 (p < 0.001)
7	Other vascular disease	173.28	1.23 (p < 0.001)	1.30	1.02 (p = 0.25)
8	Diabetes	118.63	1.19 (p < 0.001)	40.45	1.11 (p < 0.001)

CHA$_2$DS$_2$-VASc-R = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, female sex, and African American ethnicity.

factors, with the presence of risk factors having a larger impact on African Americans than whites (26). The current risk score does not address the duration and severity of the risk factors. Several studies suggest that the control of hypertension, diabetes, and congestive heart failure may be poorer in African-American patients compared to whites and may thereby contribute to higher stroke risk (27–29). It is also possible that there may be other nontraditional risk factors of stroke in African Americans such as genetic factors or systemic inflammation, which are not accounted for in CHA$_2$DS$_2$-VASc score. Furthermore, there may be differences in the protective effects of anticoagulant therapy across different races/ethnicities due to genetic polymorphisms that influence the pharmacokinetics and pharmacodynamics of the anticoagulants (30). Finally, evidence suggests that the prevalence of AF in African Americans is significantly lower than for whites. Although the reasons for this are unclear, possible explanations include genetics and smaller left atrial sizes in African Americans that protect against AF (31,32). AF development and progression may therefore follow different patterns and consequences in African American than white patients. Although there is a need to systematically study and address each of these possibilities that potentially increase the risk of stroke in African Americans with AF, there is enough evidence to suggest that African-American ethnicity is a predictor of stroke in AF patients.

In a meta-analysis consisting of 8 studies, the C-statistic ranged from 0.60 to 0.80 (median 0.683) for CHADS$_2$ score compared with 0.64 to 0.79 (median 0.673) for the CHA$_2$DS$_2$-VASc score (33). This is similar in magnitude to our results comparing CHA$_2$DS$_2$-VASc to CHA$_2$DS$_2$-VASc-R (C-statistic of 0.60 vs. 0.61,

respectively). According to the current guidelines, anticoagulation with warfarin or the novel anticoagulants is recommended for AF patients with a CHA$_2$DS$_2$-VASc score of ≥2 and may be considered for a score of 1 (14). On the basis of the results of our current study, we propose a new scheme CHA$_2$DS$_2$-VASc-R by adding 1 point for African-American ethnicity. In our study, this would extend the use of anticoagulation strategy in all African-American patients over the age of 65 years with AF, because they have all have CHA$_2$DS$_2$-VASc score of 1 or above.

STUDY LIMITATIONS. This was a retrospective study that studied a >65-year-old population, which has a higher prevalence of AF. Hence, all the patients had a CHA$_2$DS$_2$-VASc score of ≥1. Because anticoagulation is currently indicated for patients with a CHA$_2$DS$_2$-VASc score of 2 or more, the number of patients who will be clinically impacted by a change in CHA$_2$DS$_2$-VASc-R risk score from 1 to 2 in this study is small (1%). Future studies that include patients <65 years of age would help address the role of CHA$_2$DS$_2$-VASc-R risk score in patients with CHA$_2$DS$_2$-VASc score of 0 to 1. Nevertheless, there are several patients with AF with a high CHA$_2$DS$_2$-VASc score who are not anticoagulated for different reasons. Among these patients, it is important to recognize that African-American ethnicity is an independent risk factor for stroke, and our study helps to focus attention on this important risk factor. Hence, the data may not be extrapolated to the younger patient population. Diagnosis of new AF was dependent on the accuracy of ICD-9-CM diagnosis codes. However, this has been done with reasonable accuracy in prior studies. The assessment of stroke also depends on the accuracy of the ICD-9-CM diagnosis codes, which have also shown to have good positive predictive value in administrative data. In addition, administrative data generally do not contain important prognostic indicators such as laboratory test results. Nevertheless, our analysis incorporates multiple widely used risk scores (e.g., CHA$_2$DS$_2$-VASc) that have been shown to predict outcomes, as well as important indicators of comorbidities. Finally, the C-statistic that we used to assess model fit is often less sensitive to improvements in prediction than measures based on the likelihood or other global measures of model fit (34). Nevertheless, our analyses using the NRI index, and the IDI, suggest that use of the CHA$_2$DS$_2$-VASc-R model compared with CHA$_2$DS$_2$-VASc alone was associated with a net improvement in risk prediction for stroke. We also noted significant improvement in the likelihood ratio for Cox regression models using the CHA$_2$DS$_2$-VASc-R rather than CHA$_2$DS$_2$-VASc. We

also note that, in general, the C-statistic found in this study is comparable to those reported elsewhere (34).

CONCLUSIONS

Our study demonstrates that in patients >65 years of age, addition of African-American ethnicity to CHA$_2$DS$_2$-VASc score significantly improved the stroke prediction in patients with AF. Of the individual risk factors in CHA$_2$DS$_2$-VASc-R score, only prior stroke, age ≥75 years, and female sex were more important predictors of stroke than African-American ethnicity.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Mary Vaughan Sarrazin, Department of Internal Medicine, University of Iowa Roy and Lucille Carver College of Medicine, and Iowa City VA Medical Center, Center for Comprehensive Access & Delivery Research and Evaluation (CADRE), 601 Highway 6 West, Iowa City, Iowa 52246-2208. E-mail: mary-vaughan-sarrazin@uiowa.edu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients of African-American ethnicity are at higher risk of stroke than whites. Addition of African-American ethnicity improves the predictive value of the to the CHA$_2$DS$_2$-VASc score in patients over age 65 years with AF.

TRANSLATIONAL OUTLOOK: Further studies are needed to assess the impact of African-American ethnicity on stroke risk in younger individuals with AF and to clarify the mechanisms linking race/ethnicity to clinical outcomes.

REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–8.

2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 2015;131:e29–322.

3. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke 1999;30:736–43.

4. Kissela B, Schneider A, Kleindorfer D, et al. Stroke in a biracial population: the excess burden of stroke among blacks. Stroke 2004;35:426–31.

5. Kleindorfer DO, Khoury J, Moomaw CJ, et al. Stroke incidence is decreasing in whites but not in blacks: a population-based estimate of temporal trends in stroke incidence from the Greater Cincinnati/Northern Kentucky Stroke Study. Stroke 2010;41:1326–31.

6. Sacco RL, Boden-Albala B, Abel G, et al. Race-ethnic disparities in the impact of stroke risk factors: the northern Manhattan stroke study. Stroke 2001;32:1725–31.

7. Howard VJ, Kleindorfer DO, Judd SE, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. Ann Neurol 2011;69:619–27.

8. Howard G, Cushman M, Kissela BM, et al. Traditional risk factors as the underlying cause of racial disparities in stroke: lessons from the half full (empty?) glass. Stroke 2011;42:3369–75.

9. Shroff GR, Solid CA, Herzog CA. Atrial fibrillation, stroke, and anticoagulation in Medicare beneficiaries: trends by age, sex, and race, 1992-2010. J Am Heart Assoc 2014;3:e000756.

10. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke 2006;37:1070–4.

11. Shen AY, Yao JF, Brar SS, Jorgensen MB, Wang X, Chen W. Racial/ethnic differences in ischemic stroke rates and the efficacy of warfarin among patients with atrial fibrillation. Stroke 2008;39:2736–43.

12. Kabra R, Cram P, Girotra S, Vaughan Sarrazin M. Effect of race on outcomes (stroke and death) in patients > 65 years of age with atrial fibrillation. Am J Cardiol 2015;116:230–5.

13. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest 2010;137:263–72.

14. January CT, Wann L, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–76.

15. Ellis ER, Culler SD, Simon AW, Reynolds MR. Trends in utilization and complications of catheter ablation for atrial fibrillation in Medicare beneficiaries. Heart Rhythm 2009;6:1267–73.

16. Gage BF, Boechler M, Doggette AL, et al. Adverse outcomes and predictors of underuse of antithrombotic therapy in Medicare beneficiaries with chronic atrial fibrillation. Stroke 2000;31:822–7.

17. Bonito AJ, Bann C, Eicheldinger C, Carpenter L. Creation of new race-ethnicity codes and socioeconomic status (SES) indicators for Medicare beneficiaries. RTI International report for the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Medicare and Medicaid Services (CMS) under CMS contract No 500-00-0024. January 2008. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://archive.ahrq.gov/research/findings/final-reports/medicareindicators/medicareindicators.pdf. Accessed September 1, 2015.

18. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36:8–27.

19. Suh DC, Nelson WW, Choi JC, Choi I. Risk of hemorrhage and treatment costs associated with warfarin drug interactions in patients with atrial fibrillation. Clin Ther 2012;34:1569–82.

20. Rothendler JA, Rose AJ, Reisman JI, Berlowitz DR, Kazis LE. Choices in the use of ICD-9 codes to identify stroke risk factors can affect the apparent population-level risk factor prevalence and distribution of CHADS2 scores. Am J Cardiovasc Dis 2012;2:184–91.

21. Baker SG, Schuit E, Steyerberg EW, et al. How to interpret a small increase in AUC with an additional risk prediction marker: decision analysis comes through. Stat Med 2014;33:3946–59.

22. Pencina MJ, D'Agostino RB, Vasan RS. Statistical methods for assessment of added usefulness of new biomarkers. Clin Chem Lab Med 2010;48:1703–11.

23. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72.

24. Pencina MJ, D'Agostino RB Sr., Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11–21.

25. Prabasaj P, Pennell ML, Lemeshow S. Standardizing the power of the Hosmer-Lemeshow goodness of fit test in large data sets. Stat Med 2013;32:67–80.

26. Howard VJ. Reasons underlying racial differences in stroke incidence and mortality. Stroke 2013;44 Suppl 1:S126–8.

27. Ong KL, Cheung BMY, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. Hypertension 2007;49:69–75.

28. Parrinello CM, Rastegar I, Godino JG, Miedema MD, Matsushita K, Selvin E. Prevalence of and racial disparities with risk factor control in older adults with diabetes: the atherosclerosis risk

in communities study. Diabetes Care 2015;38: 1290–8.

29. Dickson VV, Knafl GJ, Wald J, Riegel B. Racial differences in clinical treatment and self-care behaviors of adults with chronic heart failure. J Am Heart Assoc 2015;4:e001561.

30. Shen AY, Chen W, Yao JF, Brar SS, Wang X, Go AS. Effect of race/ethnicity on the efficacy of warfarin: potential implications of stroke in patients with atrial fibrillation. CNS Drugs 2008;22: 815–25.

31. Marcus GM, Alonso A, Peralta CA, et al. European ancestry as a risk factor for atrial fibrillation in African Americans. Circulation 2010;122: 2009–15.

32. Marcus GM, Olgin JE, Whooley M, et al. Racial differences in atrial fibrillation prevalence and left atrial size. Am J Med 2010;123:375.e1–7.

33. Chen JY, Zhang AD, Lu HY, Guo J, Wang FF, Li ZC. CHADS2 versus CHA2DS2-VASc score in assessing the stroke and thromboembolism risk stratification in patients with atrial fibrillation: a systematic review and meta-analysis. J Geriatr Cardiol 2013;10:258–66.

34. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation 2007;115:928–35.