Discriminative Ability of CHA_2DS_2-VASc and HAS-BLED Score in Whites and Nonwhites

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The CHA_2DS_2-VASc and HAS-BLED scoring systems are used in patients with atrial fibrillation (AF) to estimate risk of stroke and bleeding, respectively. Both were developed in minimally diverse European populations and these scores have not yet been extensively studied in US whites and nonwhites. In a retrospective cohort study, we included patients with AF who received inpatient or outpatient care in a large integrated academic health system from 2011 to 2017. Cox proportional hazards were used to analyze associations between stroke and CHA_2DS_2-VASc score in AF patients not prescribed anticoagulation and between incident bleeding and HAS-BLED score in anticoagulated patients. After exclusions for previous stroke, the cohort included 21,648 patients with a mean age of 66.8 ± 15.8. Anticoagulation was prescribed in 52% of whites and 46% of nonwhites ($p < 0.001$) with a CHA_2DS_2-VASc score of ≥2. Mean CHA_2DS_2-VASc scores were 2.4 ± 1.6 in whites and 2.2 ± 1.6 in nonwhites and mean HAS-BLED scores was 1.5 ± 1.1 in whites and 1.3 ± 1.0 in nonwhites. After adjusting for baseline differences, the discriminative ability of CHA_2DS_2-VASc and HAS-BLED was similar in whites and nonwhites ($p = 0.52$, 0.33, respectively). The discriminative ability of HAS-BLED was similar in patients on vitamin K antagonists and direct oral anticoagulants. In conclusion, oral anticoagulation was prescribed less frequently in nonwhites. However, the discriminative ability of CHA_2DS_2-VASc and HAS-BLED were similar in whites and nonwhites. **(Am J Cardiol 2019;123:1949−1954)**

Oral anticoagulation (OAC) with vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) reduces stroke risk in atrial fibrillation (AF) patients by >65% but is associated with bleeding.[1−4] Therefore, AF management must balance the risk of stroke and bleeding. Scoring systems estimate a patient's risk of stroke and major bleeding.[5,6] CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75, diabetes, prior stroke/transient ischemic attack, vascular disease, age 65-74, female sex) estimates stroke risk of AF patients. HAS-BLED (hypertension, abnormal liver/renal function, prior stroke, bleeding history/predisposition, labile international normalized ratio, elderly [65 years], and drugs/alcohol) estimates major bleeding risk in patients on OACs.[6] However, both were developed in minimally diverse European populations and have not yet been extensively studied in US whites and nonwhites.[5−8] With known racial differences in AF prevalence, treatment, and outcomes, the ability of CHA_2DS_2-VASc and HAS-BLED to estimate risk in nonwhites is clinically important.[8] This study aims to evaluate the risk of stroke and bleeding in whites and nonwhites using modified CHA_2DS_2-VASc and HAS-BLED scoring systems, and to compare the discriminative ability of HAS-BLED with VKAs and DOACs.

Methods

In this retrospective cohort study, AF patients aged ≥18 years who received care between January 1, 2011 and December 31, 2017 were queried from the Northwestern Healthcare system's Enterprise Database Warehouse. Inpatient and outpatient data was used as available as neither inpatient nor outpatient data alone is sufficient for accurate identification of AF.[9] Included participants were AF patients with no previous history of stroke. A longitudinal record was constructed for each patient with the date of first AF diagnosis, pre-existing characteristics and co-morbidities, OAC prescription, and number of days until first stroke. Patients with missing admission date, unknown race, prescription for dual-antiplatelet agents, and creatinine clearance <30 ml/min were excluded because not all DOACs are approved for use in this population.

A pre-existing rules-based algorithm was used to phenotype incident stroke using ICD-9 codes (431.xx, 434.xx,436) and ICD-10 codes (I61, I63-5, I67.9) from January 1, 2011 to December 31, 2017. Major bleeding was defined by the ISTH bleeding criteria as acute or subacute clinically overt bleeding accompanied by 1 or more of the following: (1) decreased hemoglobin level of ≥2 g/dl over 24 hours; (2) transfusion of ≥2 U packed red blood cells; and (3) bleeding that is fatal or occurs in at least 1 of the following sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal.[10] Similarly, ICD-9 codes were used to phenotype

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hypertension, diabetes, heart failure, stroke, vascular disease, and chronic kidney disease during 2011. The type of OAC used was based on initial prescription. We did not account for changes in OAC or compliance during the study period. The modified CHA_2DS_2-VASc score, excluding previous stroke or transient ischemic attack, was used to estimate risk of stroke and the modified HAS-BLED score was used to estimate risk of major bleeding in AF patients prescribed a VKA or DOAC. Labile international normalized ratio, due to inadequate ability to determine this from our records, was not included in the modified HAS-BLED score. Additionally, history of stroke was not included in the modified HAS-BLED score calculation since only patients without previous history of stroke were included in the study.

Demographics, anthropometrics, vital signs, laboratory, and medication data were collected from the Enterprise Data Warehouse. Age, sex, and race were all self-reported. Year of birth was used to calculate age. Race was self-reported as white, black/African American, Hispanic, Asian, American Indian/Alaska Native, or Native Hawaiian/other Pacific Islander. Insurance information was reported as "self-pay" (no insurance provided or unknown), Medicare, Medicaid, or "private insurance" (all other insurance). Income level was categorized by median household income of the patient's ZIP code. Prescribed medications (type, dose, and route of administration) and results of laboratory procedures (complete blood count, lipid panel, hepatic panel, and kidney function test) were also recorded. Dabigatran, rivaroxaban, edoxaban, and apixaban were the DOACs and warfarin was the VKA. OAC use was assessed 1 year after AF diagnosis.

Means and frequencies described participants' baseline characteristics. Independent *t* test (for continuous variables) and chi-square test (for categorical variables) compared these characteristics across modified CHA_2DS_2-VASc and HAS-BLED scores and race. A Cox proportional hazards model analyzed the association between stroke and modified CHA_2DS_2-VASc score and between incident bleeding and modified HAS-BLED score among different racial groups. The associations of the modified CHA_2DS_2-VASc and HAS-BLED scores with incident stroke and bleeding, respectively, were evaluated in separate Cox proportional hazards models while adjusting for gender, race, median income, and insurance status. The discriminatory properties of the modified CHA_2DS_2-VASc and HAS-BLED scores were quantified using C-statistics.[11] All analyses were performed using Stata 12 (StataCorp, College Station, Texas). A 2-tailed $p < 0.05$ was considered statistically significant.

Results

The study included a total of 21,648 AF patients seen as an inpatient or outpatient between January 2011 and December 2017. The mean follow-up time after AF diagnosis was 971 patient days. The patient population was majority white (82%) and male (56%). The average age was 67.6 ± 15.4 years for white patients and 63.1 ± 17.0 years for nonwhite patients. The mean modified CHA_2DS_2-VASc score was 2.4 ± 1.6 in whites and 2.2 ± 1.6 in nonwhites. Most patients had at least 1 co-morbidity with hypertension as the most common (52%). In patients with a modified CHA_2DS_2-VASc ≥2, 7,435 (51%) were prescribed either a VKA (31%) or DOAC (20%) with 52% of whites and 46% of nonwhites prescribed an OAC ($p < 0.001$) (Table 1).

In patients not prescribed OACs, over a total 30,844 person-days of follow-up, there were 206 incident strokes (6.6 per 1,000 person-years). Of these, 35 strokes occurred in patients with a modified CHA_2DS_2-VASc score <2 (2.9 per 1,000 person-years) and 171 strokes in patients with a modified CHA_2DS_2-VASc score ≥2 (9.5 per 1,000 person-years) ($p < 0.01$). Stroke occurrence was associated with the modified CHA_2DS_2-VASc score, and the risk of stroke was 0.8, 3.4, and 5.8 times higher in patients with modified CHA_2DS_2-VASc scores of 2, 3, and ≥4, respectively, compared to patients with modified CHA_2DS_2-VASc <2. Overall stroke rate was similar between whites and nonwhites with 165 strokes in whites (6.6 per 1,000 person-years) and 40 in nonwhites (8.0 per 1,000 person-years) ($p = 0.16$) (Table 2). There was minimal variation in the Kaplan-Meier stroke free survival function for whites and nonwhites at each modified CHA_2DS_2-VASc score (Figure 1). The discriminative ability of the modified CHA_2DS_2-VASc score in AF patients was similar in whites and nonwhites ($p = 0.52$; whites, c statistic = 0.681, CI 0.640 to 0.721; nonwhites, c statistic = 0.646, CI 0.572 to 0.720).

The modified HAS-BLED score was assessed in patients treated with OACs. Over a total 25,831 person-days of follow-up, there were 607 bleeding events (22.0 per 100,000 person-years); 482 bleeding episodes in whites (21.2 per 1,000 person-years) and 122 in nonwhites (38.3 per 1,000 person-years) ($p < 0.0001$). The bleeding frequency between whites and nonwhites prescribed OACs was most similar at low modified HAS-BLED scores with statistically significant differences occurring in patients with modified HAS-BLED scores of 2 and ≥3 (Table 3). The modified HAS-BLED's discriminative ability was similar in whites and nonwhites ($p = 0.33$; whites, c statistic = 0.572, CI 0.546 to 0.598; nonwhites, c statistic = 0.603, confidence interval[CI] 0.55 to 0.66) (Figure 2). The bleeding rate was different in patients on VKAs and DOACs (VKA 30.3 per 1,000 person-years, DOAC 14.2 per 1,000 person-years) ($p < 0.0001$). The discriminative ability of the modified HAS-BLED score was similar across patients taking VKAs and DOACs (VKA c statistic = 0.55; DOAC c statistic = 0.61).

Discussion

There were several major findings in the study. First, anticoagulation was prescribed in to less than half of AF patients and nonwhites were significantly less likely to receive these agents. Second, the discriminative ability of both the modified CHA_2DS_2-VASc and HAS-BLED scoring systems was similar in whites and nonwhites. Third, the model provided similar discriminative ability for the modified HAS-BLED score for patients prescribed VKAs and DOACs.

OACs are recommended in AF patients with a modified CHA_2DS_2-VASc score ≥2 by the American College of Cardiology, American Heart Association, and Heart Rhythm Society due to their increased risk of stroke.[12] Consistent with other studies, we found that OACs were prescribed at a lower rate than currently recommended and that nonwhites were significantly less likely to be prescribed OACs.

Table 1
Baseline characteristics by modified CHA_2DS_2-VASc and HAS-BLED scores in patients with atrial fibrillation

	Modified CHA_2DS_2-VASc					Modified HAS-BLED				
Characteristics	All (11,735)	<2 (4,602)	2 (2,582)	3 (2,189)	≥4 (2,362)	All (9,913)	0 (1,460)	1 (3,384)	2 (3,276)	≥3 (1,793)
Age (years)	64.14	50.74	65.65	73.26	80.16	70.01	54.17	69.51	74.12	76.33
Gender	55%	71%	57%	42%	32%	58%	70%	59%	52%	59%
White	81%	79%	81%	81%	83%	84%	78%	82%	86%	89%
Black	6%	5%	6%	7%	7%	4%	5%	4%	4%	3%
Hispanic	2%	2%	1%	1%	2%	1%	2%	1%	1%	1%
Asian	3%	3%	3%	2%	2%	2%	2%	2%	2%	2%
Other/unknown	9%	11%	10%	8%	7%	8%	13%	11%	7%	5%
Medicare	33%	11%	30%	46%	65%	45%	9%	27%	63%	74%
Medicaid	2%	3%	2%	2%	1%	1%	2%	2%	1%	1%
Other/unknown	65%	86%	68%	52%	34%	54%	89%	71%	36%	25%
Heart failure	14%	2%	8%	15%	44%	24%	11%	15%	30%	39%
Diabetes mellitus	15%	1%	10%	20%	41%	20%	4%	12%	27%	34%
Vascular disease*	12%	1%	9%	14%	32%	12%	4%	7%	14%	23%
Hypertension	47%	15%	48%	62%	94%	57%	0%	30%	90%	97%
Abnormal liver function†	5%	4%	6%	7%	6%	4%	0%	1%	3%	14%
Abnormal renal function‡	10%	3%	8%	12%	22%	11%	0%	1%	7%	44%
Stroke/bleeding incidence (in person years)	2%	1%	1%	2%	3%	6%	3%	5%	6%	11%
Total person-years follow up	30,844	12,578	6,947	5,693	5,627	25,831	3,546	8,370	9,030	4,884

* Vascular disease was determined by presence of an ICD code for acute or old myocardial infarction, atherosclerosis, artery dissection, aneurysm, or malignant neoplasm.

† Abnormal liver function was determined by presence of an ICD code for Cirrhosis and/or any AST/ALT/Alkaline Phosphates ≥3 times the upper normal in the same text as bilirubin ≥2 times the upper normal up to AF diagnosis.

‡ Abnormal renal function was assigned if any of the following was true: the presence of an ICD code for renal disease, presence of a CPT code for dialysis, kidney transplant, and/or creatinine lab value ≥200 μmol/L up to AF diagnosis.

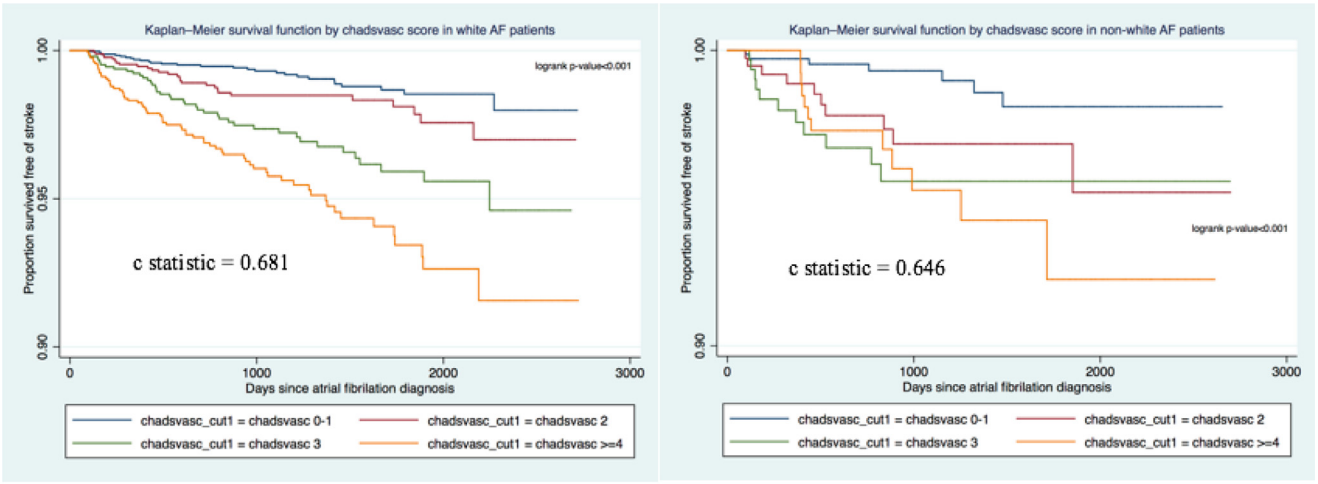
We acknowledge that some of these patients may have contraindications to OACs. This adds to a recent study from a multi-center US-based registry of 12,147 AF patients. That study focused on the racial/ethnic differences in the use of oral anticoagulants, especially DOACs.[13] There was no attempt in that study to evaluate the discriminative ability of the modified CHA_2DS_2-VASc and HAS-BLED scores. However, that study found that after adjustment for clinical and socioeconomic factors, blacks were less likely than whites to receive DOACs for AF, with no difference between white and Hispanic groups.

A previous review of 8 studies found that the median c statistic of the modified CHA_2DS_2-VASc score was 0.675 (range 0.640 to 0.790).[14] In our study, the discriminatory ability of the modified CHA_2DS_2-VASc score was within this range (whites, c statistic = 0.681; nonwhites, c statistic = 0.646). Similarly, in a review of 7 studies, the modified HAS-BLED had a median c statistic of 0.63.[15] The discriminatory ability of the modified HAS-BLED score in our study was somewhat lower (whites, c statistic = 0.572; nonwhites, c statistic = 0.603). C-statistics cannot be directly compared across studies due to differences in populations, but this information suggests that our results were similar to those reported previously.

As expected, the observed increased risk of stroke with increased modified CHA_2DS_2-VASc score was statistically significant for whites and nonwhites and our data supports the use of the modified CHA_2DS_2-VASc score to stratify patients into categories based on their perceived risk of stroke regardless of race. Similar results were found with the modified HAS-BLED scores for patients prescribed VKAs and DOACs. Thus, while these scores were derived in majority white populations, this study supports their application to both white and nonwhite patients with AF

Table 2
Frequency of stroke by modified CHA_2DS_2-VASc score and race in AF patients not prescribed OACs

	Whites		Nonwhites		
Modified CHA_2DS_2-VASc score	Total n	Frequency of stroke	Total n	Frequency of stroke	Chi-square p value (whites vs nonwhites stroke frequency)
0-1	3,528	0.79%	925	0.76%	p = 0.91
2	2,021	1.34%	483	2.07%	p = 0.23
3	1,742	2.41%	402	2.74%	p = 0.71
≥4	1,941	3.50%	401	2.99%	p = 0.61
Chi-square p value	p < 0.001		p = 0.01		



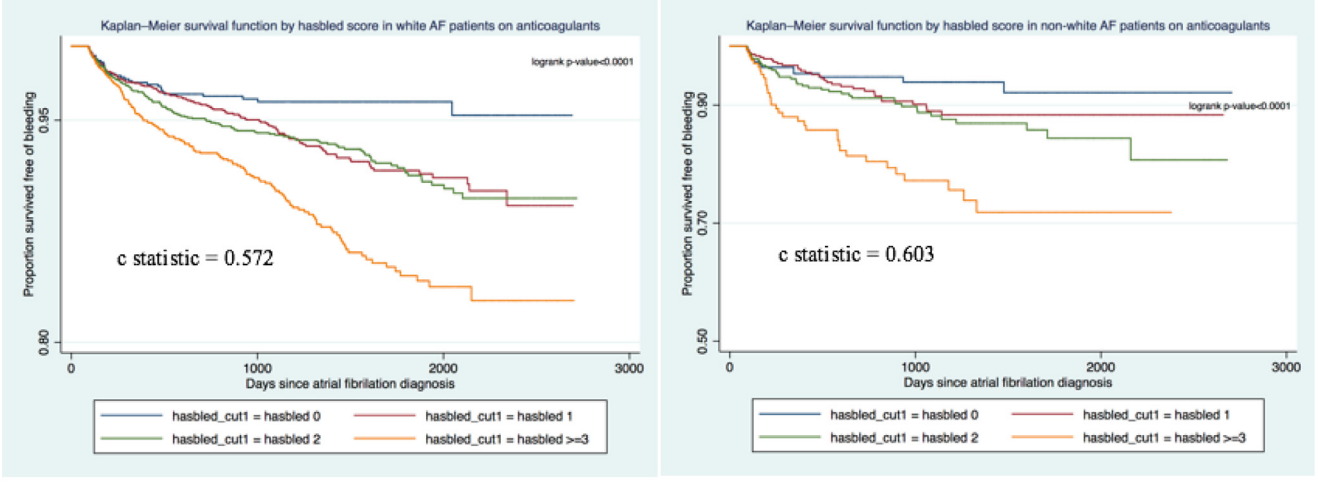
Panel A Panel B

Figure 1. Kaplan-Meier stroke free survival function by modified CHA_2DS_2-VASc score in AF patients not on any anticoagulant for whites (Panel A) and nonwhites (Panel B).

Table 3
Frequency of bleeding by modified HAS-BLED score and race in AF patients prescribed OACs

			Whites		Nonwhites		
Modified HAS-BLED score	% VKA	% DOAC	Total n	Frequency of bleeding	Total n	Frequency of bleeding	Chi-square p value (whites vs nonwhites bleeding frequency)
0	45%	55%	1,122	2.85%	309	4.21%	p = 0.23
1	58%	42%	2,745	4.95%	588	5.78%	p = 0.41
2	60%	40%	2,818	5.68%	449	9.13%	p < 0.01
≥3	60%	40%	1,595	9.66%	193	17.62%	p = 0.001
Chi-square p value			p < 0.001		p < 0.001		

regardless of OAC type. There is a significant difference in bleeding frequency between whites and nonwhites for patients with modified HAS-BLED scores of 2 and ≥3. This may be related to the variability within each HAS-BLED point since the scoring system dichotomizes risk factors when many of these risk factors may have a dose effect. There are known racial differences in hypertension control and rate of kidney function decline.[16,17] Additionally, less time



Panel A Panel B

Figure 2. Kaplan-Meier bleeding free survival function by modified HAS-BLED score in AF patients on an anticoagulant for whites (Panel A) and nonwhites (Panel B).

in therapeutic range has been linked to higher bleeding rates in African Americans.[18]

This study had several strengths. The study benefited from the intrinsic advantages of the large, diverse patient population from the Northwestern healthcare system, an urban based academic center with significant follow-up information, which is more diverse in race and age than previous studies.[8,19] The large number of patients available through the Northwestern healthcare system contributes to the generalizability of our findings. The inclusion of DOACs in our study is beneficial given the updated AHA/ACC/HRS guidelines for AF management that recommend DOACs in patients with nonvalvular AF.[12]

There are also several limitations. As a retrospective study, there is the potential of missing data bias and selection bias since patients may have been systematically excluded by requiring at least 1 follow-up visit. Additionally, race was self-assigned, which may be a limited method of determining ethnic background.[20] The diagnoses of risk factors and outcomes were based on ICD codes alone. ICD codes have good but imperfect sensitivity and sensitivity.[21,22] This study used a single study center, but its validity is supported by the consistency of our c statistics with previous studies of other patient populations. Lastly, we used modified CHA_2DS_2-VASc and HAS-BLED scores that excluded patients with previous stroke or transient ischemic attack and did not include data on time in therapeutic range in VKA treated patients.

In conclusion, the discriminative ability of the modified CHA_2DS_2-VASc and HAS-BLED scoring systems was similar in whites and nonwhites and the modified HAS-BLED score also performed similarly in VKA and DOAC-treated individuals. This study thus supports the use of CHA_2DS_2-VASc and HAS-BLED in diverse populations and with currently available OAC treatment options. The data also supports the underutilization of anticoagulation and demonstrates that this deficiency is greater in nonwhite AF patients.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.03.020.

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