Usefulness of CHA_2DS_2-VASc Score to Predict Stroke Risk Independent of Atrial Fibrillation

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The CHA_2DS_2-VASc score is used to predict stroke risk among patients with atrial fibrillation (AF). We examined whether a CHA_2DS_2-VASc score predicts stroke risk among individuals without hospital-diagnosed AF and quantified the magnitude of the association in comparison to AF patients. We used data from population-based medical registries (1995 to 2005) covering all Danish hospitals to identify patients diagnosed with AF (n = 122,980). We matched ≤5 non-AF individuals (n = 612,723) to each AF patient on the individual risk factors included in the CHA_2DS_2-VASc score. We calculated 10-year absolute risk of ischemic and all-cause stroke in AF and non-AF individuals and compared the stroke risk between cohorts within strata of CHA_2DS_2-VASc scores using Cox regression. The 10-year risk of ischemic/all-cause stroke was 4.4%/8.8% among non-AF individuals and 6.2%/12% in AF patients, corresponding to a risk difference of 1.8% for ischemic stroke and 3.3% for all-cause stroke. In both cohorts, the stroke risk correlated with increasing CHA_2DS_2-VASc scores. However, in individuals with CHA_2DS_2-VASc scores ≥5 who were <75 years or male, the absolute risk of ischemic stroke in individuals without AF exceeded the risk in AF patients. In the same subgroups, the hazard ratio approached unity. Similar results were observed for all-cause stroke. The CHA_2DS_2-VASc score was associated with 10-year stroke risk also among individuals without hospital-diagnosed AF. In conclusion, primary prophylactic anticoagulation therapy may be relevant in male and younger non-AF individuals with CHA_2DS_2-VASc scores ≥5. These findings should be confirmed in clinical trials. **(Am J Cardiol 2019;124:1059−1063)**

The CHA_2DS_2-VASc score, used in routine clinical practice to predict stroke risk among atrial fibrillation (AF) patients, is calculated on the presence of congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischemic attack, systemic arterial embolism, vascular disease, and female gender.[1] Based on current recommendations, the presence of a single risk factor included in this score (apart from female gender) should lead to consideration of oral anticoagulant therapy in AF patients.[2] Independent risk factors included in the CHA_2DS_2-VASc score, for example, heart failure, diabetes, or hypertension, have also been shown to predict stroke risk in non-AF populations.[3−5] Yet, evidence is sparse on whether prophylactic oral anticoagulant therapy may also be indicated in non-AF individuals with high CHA_2DS_2-VASc score.[6,7] We examined to what extent the CHA_2DS_2-VASc score defined using hospital-diagnosed risk factors was associated with stroke risk in patients with versus without AF with similar distributions of the CHA_2DS_2-VASc scores.

Methods

The Danish National Health Service provides tax-supported healthcare, ensuring universal access to hospital-based and primary medical care free of charge for the entire population.[8] The Danish Civil Registration System has kept electronic records on date of birth, date of emigration, and date of death for all Danish residents since 1968, using a unique number assigned to each resident.[9] This unique number is used in all registries, permitting unambiguous data linkage between registries.[9] The Danish National Patient Registry (DNPR) contains records of all inpatient admissions in Denmark since 1977.[10] This registry includes dates of admission and discharge, a primary diagnosis, and optional secondary diagnoses for each hospitalization. In 1995, information on hospital outpatient and emergency room visits were added to the registry. Until January 1, 1994, *International Classification of Diseases, Eighth Revision* codes were used to record diagnoses. Thereafter,

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International Classification of Diseases, Tenth Revision codes have been used.[10]

We used the DNPR to identify all patients with a first-time inpatient or outpatient hospital-diagnosis of AF from 1995 to 2005 (oral anticoagulation was not routinely offered to AF patients before 1995, who did not have a history of hospital-diagnosed ischemic stroke). We did not include emergency room diagnoses due to their low positive predictive value.[11–14] We then used the Civil Registration System and the DNPR to match ≤5 individuals without a record of AF at the corresponding AF patient's diagnosis date (defined as the index date). Matching criteria were the individual conditions and risk factors included in the CHA_2DS_2-VASc score defined in the hospital-based setting, except a history of ischemic stroke (Appendix Table A), including year of birth and gender. For example, an AF patient with diabetes and hypertension was matched with a non-AF individual with diabetes and hypertension of similar age and gender. The CHA_2DS_2-VASc score was calculated for each person in the study. Female gender (in the presence of other risk factors), age 65 to 74 years, and presence of hospital-diagnosed hypertension, diabetes, or vascular disease corresponded to 1 point each, whereas transient ischemic attack and age ≥75 years each yielded 2 points.

We used the DNPR to identify first incident inpatient diagnoses of ischemic stroke after index date.[10] In addition, we identified first incident hemorrhagic and unspecified stroke diagnoses and combined these with the diagnosis of ischemic stroke for the all-cause stroke outcome.

All study participants were followed for 10 years from index date until a stroke, death, emigration, or end of December 2014, whichever came first. Non-AF individuals who were diagnosed with AF during follow-up were censored at the time of AF diagnosis (15%).

We described the AF cohort and the matched non-AF cohort in terms of gender, age group (0 to 64, 65 to 74, ≥75 years), presence of cardiovascular risk factors (congestive heart failure, hypertension, diabetes mellitus, transient ischemic attack, systemic arterial embolism [excluding stroke], vascular disease), CHA_2DS_2-VASc score (0 to 9), and CHA_2DS_2-VASc score in groups (0, 1 to 2, 3 to 4, 5 to 9). The absolute 10-year ischemic stroke risk was calculated using the cumulative incidence function, which accounts for the competing risk of dying.[15] Cox proportional hazard regression was used to compute hazard ratios (HRs) with 95% confidence intervals (CIs) for ischemic stroke risk overall and within CHA_2DS_2-VASc scores, by gender and age group, using non-AF individuals as reference. Finally, in a secondary analysis we repeated all analyses with all-cause stroke as the outcome. This study was approved by the Danish Data Protection Agency (record number 2012-41-0793). Analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

The study included 122,980 AF patients and 612,723 matched non-AF individuals (53% men; Table 1). Median age at index date was 75 years (interquartile range: 65, 82 years). Frequent cardiovascular risk factors among AF patients were congestive heart failure (10%) and vascular diseases, including myocardial infarction and peripheral arterial disease (13%), and hypertension (13%). Due to the matching procedure, the distribution of patient characteristics was nearly the same for the matched non-AF cohort. The CHA_2DS_2-VASc score was 1 to 2 for 38%, 3 to 4 for 37%, and 5 to 9 for 5.2%.

Table 1
Characteristics of Danish atrial fibrillation patients and matched non-atrial fibrillation individuals without previous stroke diagnoses, 1995 to 2005

Variable	AF patients	Matched non-AF individuals
	122,980 (100%)	612,723 (100%)
Women	57,784 (47%)	287,885 (47%)
Men	65,196 (53%)	324,838 (53%)
Median age, years (interquartile range)	75 (65, 82)	75 (65, 82)
Age group (years)		
0-64	31,044 (25%)	154,962 (25%)
65-74	31,597 (26%)	157,687 (26%)
≥75	60,339 (49%)	300,074 (49%)
Congestive heart failure	12,299 (10%)	60,171 (9.8%)
Hypertension	15,891 (13%)	78,289 (13%)
Diabetes mellitus	7,740 (6.3%)	37,797 (6.2%)
Transient ischemic attack	3,524 (2.9%)	16,611 (2.7%)
Systemic arterial embolism	712 (0.6%)	2,872 (0.5%)
Vascular disease	15,801 (13%)	77,756 (13%)
CHA_2DS_2-VASc score		
0	24,028 (20%)	120,281 (20%)
1	14,927 (12%)	74,622 (12%)
2	31,543 (26%)	157,782 (26%)
3	34,007 (28%)	169,657 (28%)
4	12,021 (9.8%)	59,811 (9.8%)
5	4,652 (3.8%)	22,794 (3.7%)
6	1,447 (1.2%)	6,549 (1.1%)
7	306 (0.2%)	1,140 (0.2%)
8	40 (0.0%)	75 (0.0%)
9	9 (0.0%)	12 (0.0%)
Grouped CHA_2DS_2-VASc scores*		
0	24,028 (20%)	120,281 (20%)
1-2	46,470 (38%)	232,404 (38%)
3-4	46,028 (37%)	229,468 (38%)
5-9	6,454 (5.2%)	30,570 (5.0%)
Median follow-up time, years (interquartile range)	5.9 (1.7, 10)	8.4 (3.6, 10)

* Female sex counted as a risk factor for stroke in presence of other CHA_2DS_2-VASc score risk factors.

There were 32,396 cases of ischemic stroke diagnosed during 10 years of follow-up. Overall ischemic stroke risk was 6.2% (95% CI 6.0%, 6.3%) in AF patients and 4.4% (95% CI 4.3%, 4.5%) in non-AF individuals, providing a HR of 1.95 (95% CI 1.90, 2.01). As shown in Table 2, the CHA_2DS_2-VASc score predicted stroke risk in both AF patients and non-AF individuals. In AF patients, the ischemic stroke risk nearly doubled for patients with the highest CHA_2DS_2-VASc score = 5 to 9 compared with those with a CHA_2DS_2-VASc score = 0. A near similar pattern was observed for the matched non-AF individuals with risks ranging from 4.4% to 6.4%. The risk in the non-AF individuals approached the risk of the AF patients with increasing CHA_2DS_2-VASc score. For those with the highest CHA_2DS_2-VASc score = 5 to 9, the risks were nearly

Table 2
Ten-year stroke risk according to CHA_2DS_2-VASc score in individuals with vs without atrial fibrillation (1995 to 2005)

	AF patients		Matched non-AF individuals		Measure of association	
CHA_2DS_2-VASc score	Strokes/number at risk	10-year risk (95% CI)	Ischemic strokes/ number at risk	10-year risk (95% CI)	Risk difference (95% CI)	Hazard rate ratio (95% CI)
Ischemic stroke overall	7,547/122,980	6.2% (6.0%, 6.3%)	24,849/612,723	4.4% (4.3%, 4.5%)	1.8% (1.6%, 1.9%)	1.95% (1.90, 2.01)
0	888/24,028	3.7% (3.5%, 4.0%)	1,984/120,281	1.7% (1.6%, 1.8%)	2.0% (1.8%, 2.3%)	2.47% (2.27, 2.68)
1-2	2,885/46,470	6.2% (6.0%, 6.5%)	10,436/232,404	4.9% (4.8%, 5.0%)	1.4% (1.1%, 1.6%)	1.72% (1.64, 1.80)
3-4	3,312/46,028	7.2% (7.0%, 7.5%)	10,716/229,468	5.2% (5.1%, 5.3%)	2.0% (1.8%, 2.3%)	2.10% (2.01, 2.20)
5-9	462/6,454	7.2% (6.6%, 7.8%)	1,713/30,570	6.4% (6.1%, 6.7%)	0.8% (0.1%, 1.5%)	1.81% (1.60, 2.04)
All-cause stroke overall	14,762/122,325	12.1% (11.9%, 12.3%)	50,218/609,473	8.8% (8.8%, 8.9%)	3.3% (3.1%, 3.5%)	1.93% (1.89, 1.97)
0	1,494/23,983	6.3% (6.0%, 6.6%)	3,356/120,115	2.9% (2.8%, 3.0%)	3.4% (3.1%, 3.7%)	2.47% (2.32, 2.64)
1-2	5,591/46,191	12.2% (11.9%, 12.5%)	20,103/230,931	9.4% (9.2%, 9.5%)	2.8% (2.5%, 3.1%)	1.78% (1.72, 1.84)
3-4	6,745/45,759	14.8% (14.5%, 15.1%)	23,161/228,138	11.2% (11.0%, 11.3%)	3.6% (3.3%, 4.0%)	2.01% (1.95, 2.07)
5-9	932/6,392	14.6% (13.8%, 15.5%)	3,598/30,289	13.3% (12.9%, 13.7%)	1.3% (0.4%, 2.3%)	1.64% (1.51, 1.78)

AF = atrial fibrillation; CI = confidence interval.

similar in AF patients (7.2%) as in non-AF individuals (6.4%). The 10-year overall all-cause stroke risks were nearly doubled compared with ischemic stroke, but HRs remained unchanged. Among those with CHA_2DS_2-VASc scores = 5 to 9, the all-cause stroke risk was basically similar: 15% in AF patients and 13% in non-AF individuals.

Results stratified by gender and age group are shown in Table 3. In men with CHA_2DS_2-VASc score ≥5 (7.2% vs 5.9%) and in patients aged <75 years with CHA_2DS_2-VASc score ≥5 (8.8% vs 7.5% in those aged 65 to 74 years), the absolute risk of ischemic stroke in non-AF individuals exceeded the risk of AF patients. Similarly, the HRs

Table 3
Ten-year ischemic stroke risk according to CHA_2DS_2-VASc score in individuals with vs without atrial fibrillation, by gender and age (1995 to 2005)

	AF patients		Matched non-AF individuals		Measure of association	
CHA_2DS_2-VASc score	Ischemic strokes/ number at risk	10-year risk (95% CI)	Ischemic strokes/ number at risk	10-year risk (95% CI)	Risk difference (95% CI)	Hazard rate ratio (95% CI)
Female scores						
Overall	4,053/57,784	7.1% (6.8%, 7.3%)	11,356/287,885	4.3% (4.2%, 4.4%)	2.8% (2.6%, 3.0%)	2.41 (2.32, 2.51)
0	278/7,641	3.7% (3.3%, 4.1%)	432/38,320	1.2% (1.1%, 1.3%)	2.5% (2.1%, 3.0%)	3.61 (3.08, 4.22)
1-2	728/10,495	7.0% (6.5%, 7.5%)	1,824/52,583	3.7% (3.5%, 3.8%)	3.3% (2.8%, 3.9%)	2.43 (2.21, 2.66)
3-4	2,669/34,614	7.7% (7.5%, 8.0%)	7,785/172,761	5.0% (4.9%, 5.1%)	2.7% (2.4%, 3.1%)	2.39 (2.27, 2.51)
5-9	378/5,034	7.5% (6.8%, 8.3%)	1,315/24,221	6.2% (5.9%, 6.6%)	1.3% (0.5%, 2.1%)	2.00 (1.75, 2.29)
Male scores						
Overall	3,494/65,196	5.4% (5.2%, 5.6%)	13,493/324,838	4.5% (4.4%, 4.6%)	0.9% (0.7%, 1.1%)	1.60 (1.53, 1.66)
0	610/16,387	3.8% (3.5%, 4.1%)	1,552/81,961	2.0% (1.9%, 2.1%)	1.8% (1.5%, 2.1%)	2.16 (1.96, 2.38)
1-2	2,157/35,975	6.0% (5.8%, 6.3%)	8,612/179,821	5.3% (5.2%, 5.4%)	0.8% (0.5%, 1.0%)	1.56 (1.48, 1.64)
3-4	643/11,414	5.7% (5.2%, 6.1%)	2,931/56,707	5.9% (5.7%, 6.1%)	−0.3% (−0.7%, 0.2%)	1.37 (1.24, 1.51)
5-9	84/1,420	5.9% (4.8%, 7.2%)	398/6,349	7.2% (6.5%, 7.9%)	−1.2% (−2.6%, 0.2%)	1.23 (0.94, 1.62)
Age group <65 years						
Overall	1,319/31,044	4.3% (4.1%, 4.5%)	3,493/154,962	2.34% (2.27%, 2.42%)	2.0% (1.7%, 2.2%)	2.09 (1.96, 2.24)
0	888/24,028	3.7% (3.5%, 4.0%)	1,984/120,281	1.7% (1.6%, 1.8%)	2.0% (1.8%, 2.3%)	2.47 (2.27, 2.68)
1-2	352/5,953	6.0% (5.4%, 6.6%)	1,249/29,718	4.5% (4.2%, 4.7%)	1.5% (0.9%, 2.2%)	1.54 (1.36, 1.75)
3-4	77/1,028	7.5% (6.0%, 9.2%)	253/4,851	5.7% (5.0%, 6.4%)	1.9% (0.2%, 3.7%)	1.66 (1.26, 2.19)
5-9	<5/35	5.7% (1.0%, 17%)	7/112	7.9% (3.5%, 15%)	−2.2% (−11%, 9.7%)	1.85 (0.29, 12)
Age group 65-74 years						
Overall	2,176/31,597	6.9% (6.7%, 7.2%)	7,167/157,687	4.9% (4.8%, 5.0%)	2.0% (1.7%, 2.3%)	1.81 (1.71, 1.90)
0	-	-	-	-	-	-
1-2	1,668/24,862	6.8% (6.5%, 7.1%)	5,352/124,462	4.6% (4.5%, 4.7%)	2.1% (1.8%, 2.5%)	1.86 (1.75, 1.98)
3-4	458/6,057	7.6% (7.0%, 8.3%)	1,587/30,237	5.9% (5.6%, 6.2%)	1.7% (1.0%, 2.5%)	1.70 (1.51, 1.91)
5-9	50/678	7.5% (5.6%, 9.6%)	228/2,988	8.8% (7.7%, 9.9%)	−1.3% (−3.4%, 1.1%)	1.18 (0.83, 1.68)
Age group ≥75 years						
Overall	4,052/60,339	6.7% (6.5%, 6.9%)	14,189/300,074	5.3% (5.2%, 5.4%)	1.4% (1.2%, 1.7%)	2.00 (1.92, 2.08)
0	-	-	-	-	-	-
1-2	865/15,655	5.5% (5.2%, 5.9%)	3,835/78,224	5.5% (5.3%, 5.7%)	0.1% (−0.3%, 0.5%)	1.55 (1.43, 1.69)
3-4	2,777/38,943	7.2% (6.9%, 7.4%)	8,876/194,380	5.1% (5.0%, 5.2%)	2.1% (1.8%, 2.3%)	2.20 (2.10, 2.31)
5-9	410/5,741	7.2% (6.5%, 7.9%)	1,478/27,470	6.2% (5.8%, 6.5%)	1.0% (0.3%, 1.8%)	1.93 (1.70, 2.20)

AF = atrial fibrillation; CI = confidence interval.

comparing AF patients with their matched non-AF individuals approached unity in men with CHA_2DS_2-VASc score ≥5 [1.23 (95% CI 0.94, 1.62)] and in those aged <75 years with CHA_2DS_2-VASc score ≥5 [1.18 (95% CI 0.83, 1.68)]. Similar results were observed for all-cause stroke (Appendix Table B).

Discussion

The CHA_2DS_2-VASc score was associated with 10-year risk of ischemic stroke in both patients with AF and non-AF individuals. Although the absolute and relative risk of stroke was higher overall in AF patients than non-AF individuals within similar CHA_2DS_2-VASc score, an important finding was that the associated 10-year risk of ischemic stroke was higher in non-AF individuals than AF patients in the subgroups of men and patients younger than 75 years with CHA_2DS_2-VASc scores ≥5. These results indicate that the CHA_2DS_2-VASc score likely predicts ischemic stroke risk also in patients without hospital-diagnosed AF, and that oral anticoagulation therapy may be relevant in men and younger patients with very high thromboembolic risk (as measured by CHA_2DS_2-VASc scores ≥5)—even in the absence of diagnosed AF.

Previous studies have reported results similar to the current study. A Danish study of AF patients has examined stroke risk associated with the presence of an increasing number of the stroke risk factors included in the CHA_2DS_2-VASc score.[1] The study demonstrated that each risk factor of the CHA_2DS_2-VASc score was associated with stroke risk. US studies have supported these findings. A study based on United States claims data by Yao et al reported that in patients aged ≥65 years without AF and free of anticoagulant or antiplatelet therapy, the combination of risk factors such as stroke/transient ischemic attack and stage 3 to 4 chronic kidney disease, diabetes or heart failure put patients at particularly increased stroke risk.[6] Similarly, another US study reported that the CHA_2DS_2-VASc score could assess stroke risk in community-dwelling non-AF individuals.[7]

Strengths of this study include the large sample size of >100,000 AF patients and >600,000 non-AF individuals and follow-up of all study participants. The study relied on accurate coding of hospital-diagnosed risk factors included in the CHA_2DS_2-VASc score. The positive predictive value of diagnoses in the DNPR has been estimated at 79% for stroke, 95% for AF, 80% for venous thromboembolic events, and ≥90% for other cardiovascular conditions and diabetes.[13,14,16,17] Our study also has limitations. We had both inpatient and outpatient diagnoses and a mix of prevalent and incident diagnoses due to the inclusion of outpatient diagnoses in the DNPR starting from 1995. We did not have any information on administration of oral anticoagulation, and AF patients with CHA_2DS_2-VASc score risk factors were likely anticoagulated during the study period, which may underestimate the relative effect estimates for ischemic stroke among AF patients compared with non-AF individuals. In addition, we only had information on hospital-diagnosed conditions included in the CHA_2DS_2-VASc score. The lack of information on conditions only treated in general practice may have resulted in an overestimation of stroke risk associated with the CHA_2DS_2-VASc score. To the extent that a proportion of the non-AF individuals had subclinical/undiagnosed AF, we may have overestimated the absolute stroke risk in the non-AF group. The CHA_2DS_2-VASc score predicted stroke risk also in patients without AF. The relative stroke risk comparing AF patients and non-AF individuals approached unity in the highest CHA_2DS_2-VASc score categories. These results indicate that the hospital-based CHA_2DS_2-VASc score may predict ischemic stroke risk in individuals without hospital-diagnosed AF who have stroke risk factors included in the CHA_2DS_2-VASc score. The current comparison of AF patients with matched individuals without hospital-diagnosed AF shows that men and younger patients without AF who have multiple hospital-diagnosed stroke risk factors can have a stroke risk similar to that of AF patients, who have routinely been offered oral anticoagulation therapy in the past several decades. These findings should be confirmed in clinical trials.

Data Sharing: Not allowed.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.06.028.

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