The CHA_2DS_2-VASc Score for Risk Stratification of Stroke in Heart Failure With-vs-Without Atrial Fibrillation

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A recent study suggested that the CHA_2DS_2-VASc score can risk stratify heart failure (HF) patients without atrial fibrillation (AF) for stroke. We performed a retrospective analysis using the national Veteran Affairs database to externally validate the findings. Crude incidence rates of end points were calculated. A Cox proportional model was used to study the association between the CHA_2DS_2-VASc score and outcomes. In HF patients with AF (n = 17,481) and without AF (n = 36,935), the 1 year incidence rate for ischemic stroke, thromboembolism, thromboembolism (without MI), and death were 2.7 and 2.0%; 10.3 and 7.9%; 4.1 and 3.1%; and 19.2 and 26.0%, respectively, with higher rates with increasing CHA_2DS_2-VASc scores both with and without AF. CHA_2DS_2-VASc score predicted strokes in HF patients without AF (1-year C-statistic 0.62, 95% CI 0.60-0.64; NPV 85.4%, 95% CI 83.4-87.4%) with similar predictive ability to those with AF (C-statistic 0.59, 95% CI 0.56-0.62; NPV 86.4%, 95% CI 82.6-90.2%). Among patients with HF, there was an increased risk of stroke, thromboembolism, and death with increasing CHA_2DS_2-VASc scores regardless of AF status. Our findings support the use of the CHA_2DS_2-VASc score as a prognostic tool in HF. Published by Elsevier Inc. (Am J Cardiol 2021;155:72−77)

Heart Failure (HF) is associated with increased mortality and risk of ischemic stroke, irrespective of possible underlying cardiac arrhythmias.[1−4] Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia, and it is associated with an increased risk of morbidity and mortality from stroke and thromboembolism. Studies of HF patients without AF have shown ischemic stroke rates of 1.2% to 1.5% per year.[5] The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 65, additional point for age ≥ 75, diabetes mellitus, vascular disease, female gender, and 2 points for history of stroke or transient ischemic attack) is the current preferred method by American and European guidelines to predict thromboembolism risk in non-valvular AF, and it does so by identifying likely upstream risk factors that contribute to atrial myopathy with associated stasis and risk for thrombus formation.[4,6] Recent studies have found some of these same independent prediction markers for stroke in patients with heart failure without AF.[5] Here, we attempt to explore the relative efficacy of the CHA_2DS_2-VASc scoring system in HF patients with and without AF.

Methods

Data were collected from the national American VA database. This is a large database encompassing healthcare encounters with veterans across the United States. This database allows for longitudinal follow up of subjects with both clinical and pharmacy data. No subjects were directly contacted, and IRB approval was obtained. Data acquisition was conducted with standard SQL techniques and ICD-9 codes (full list of ICD-9 codes in appendix).

The study population was selected by identifying patients aged 35 years or older with a primary discharge diagnosis of HF (ICD-9 code 428.*) between the dates of January 2002 to December 2010. The day of discharge for this incident HF hospitalization served as the baseline date for each subject. Patients were excluded from the study for the following reasons: (1) preexisting valvular AF as these patients have a different thromboembolic risk profile; (2) recent diagnosis of cancer; (3) diagnosis of chronic obstructive pulmonary disease; (4) on an oral anticoagulation regimen at baseline. These exclusion criteria are similar to other studies.[7,8]

Patients who had an ICD-9 diagnosis of AF before the primary outcome or the end of the follow-up period were placed into the AF cohort. This AF diagnosis included all forms of AF and could occur either before or after the index HF hospitalization. We did not distinguish between AF that occurred before or after HF diagnosis due to AF's paroxysmal nature and the lack of a clear temporal link between AF and stroke.[9] Co-morbidities were identified if subjects had received a previous ICD-9 diagnosis before or at the time of incident HF discharge (See appendix for ICD-9 codes). VA pharmacy records were queried to determine if

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subjects had recently received anticoagulation before the heart failure admission.

Subjects were assigned CHA_2DS_2-VASc score based on standard criteria: 1 point for HF, hypertension, age 65 to 74 years, diabetes mellitus, vascular disease, and female gender; 2 points for ages 75 years and older and for previous thromboembolism. Since our study only included subjects with HF, the minimal score assigned was 1.

Subjects were followed longitudinally by inpatient encounters for five years with events after this time point censured. The primary end point was defined by a new ICD-9 discharge diagnosis of CVA/transient ischemic attack (433.*1, 434.*1, 435.*, 436.*) and combined thromboembolism with myocardial infarction (prior codes, 410.*, 444.*, 445.*, or 415.1*), or death (Table 1). Combined thromboembolism was then re-evaluated without the code for myocardial infarction (410.*). Mortality events are collected by the VA data system which is a conglomerate of multiple datasets including non-VA data.

Baseline characteristics at the time of HF diagnosis were described with means and standard deviations for continuous variables. Crude incidence rates of end points stratified according to the presence of concomitant AF were calculated. A Cox proportional model was used to study the association between the CHA_2DS_2-VASc score and the risk of ischemic stroke, thromboembolism and death at 1 and 5 year follow up in HF patients with or without AF.

C-statistics were used to quantify the discriminatory properties of the CHA_2DS_2-VASc score. With competing risk from death taken into consideration, the control patients were defined as alive and event free at 1- and 5-year follow-up and used the inverse-probability-of-censoring weighted estimator as competing risk of death was considered. Bootstrap confidence intervals for the C-statistics were calculated using 1000 bootstrap samples. Negative predictive values (NPV) were also calculated using cutoff value of 1, which is the proportion of patients with CHA_2DS_2-VASc of 1 who were alive and without the end point of interest at 1-year follow-up.

The analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing) with package *timeROC*[10] and *riskRegression*.[11] A p-value < 0.05 was considered significant.

Table 1
Baseline characteristics and medications

Variable	Atrial Fibrillation	
	No (n = 36,935)	Yes (n = 17,481)
Men	36,238 (98.1%)	277 (98.4%)
White	20,842 (57.5%)	11,470 (65.6%)
Black	9,226 (25.46%)	2,651 (15.2%)
Other Race*	1,984 (5.5%)	957 (5.5%)
Age (Years) at baseline, mean (SD)	68.0 (11.0)	73.4 (11.2%)
<50	1,693 (4.6%)	299 (1.7%)
50-64	14,509 (39.3%)	4,161 (23.3%)
65-74	8,294 (22.5%)	3,913 (21.9%)
≥75	12,438 (33.7%)	9,108 (51.1%)
CHA_2DS_2-VASc Score	4.01 (1.40)	4.44 (1.35)
Hypertension	29,894 (80.9%)	14,380 (80.6%)
Embolism	604 (1.6%)	379 (2.1%)
Diabetes Mellitus	20,174 (54.6%)	8,673 (48.6%)
CAD	22,030 (59.6%)	11,642 (65.3%)
PVD	5,706 (15.4%)	3,264 (18.3%)
Ischemic CVA	1,471 (4.0%)	909 (5.1%)
Renal Disease	6,326 (17.1%)	3,457 (19.4%)
Hyperthyroid	174 (0.5%)	137 (0.8%)
Liver Disease	2,215 (6.0%)	864 (4.8%)
CCB	16,703 (45.2%)	7,791 (43.7%)
ARB	8,914 (24.1%)	3,723 (20.9%)
Diabetic Drugs	23,561 (45.6%)	5,249 (33.6%)
Aspirin	30,138 (81.6%)	14,201 (79.6%)
Loop Diuretic	43,315 (83.8%)	12,446 (79.6%)
Aldosterone Antagonist	14,616 (39.6%)	6,960 (39.0%)
ACEI	28,793 (78.0%)	13,077 (73.3%)
Beta Blocker	32,855 (89.0%)	15,315 (85.8%)
Digoxin	10,371 (28.1%)	8,026 (45.0%)
Statin	28,737 (77.8%)	12,571 (70.5%)

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker, CAD = coronary artery disease; CVA = cerebrovascular accident; PVD = peripheral vascular disease.

* Components do not add up to 100% due to some subjects with unknown race.

Results

A total of 54,416 patients with HF were included in the final cohort: 36,935 patients with HF without AF and 17,481 patients with concomitant HF and AF (Figure 1). Of the patients with AF, 60% of those patients had AF at baseline and 40% developed AF during follow up. Baseline characteristics and medications are listed in Table 1. The non-AF cohort had a lower average age and CHA_2DS_2-VASc score as compared with the AF cohort. 57.5% of the non-AF cohort was white, while 65.6% of the AF cohort was white. Beta blocker, ACEI/ARB, statin, and aspirin were used by over 70% of patients in both cohorts. About 40% of patients in both cohorts were on aldosterone antagonists (Table 1).

In patients with HF without AF, the 1 year incidence rate for ischemic stroke, thromboembolism, thromboembolism (without MI) and death were 2.0% (n = 623), 7.9% (n = 2,450), 3.1% (n = 976) and 26.0% (n = 8,347) respectively. For HF with AF, the respective rates were 2.7% (n = 402), 10.3% (n = 1,481), 4.1% (n = 600), and 29.2% (n = 4,365). Incident rates for ischemic stroke, thromboembolism (with and without MI), and death in these patients were higher with increasing CHA_2DS_2-VASc scores in both AF and non-AF (Table 2).

The CHA_2DS_2-VASc showed mild to modest one year predictive ability for HF patients with and without AF for ischemic stroke (0.62 vs 0.59) thromboembolism including MI (0.63 vs 0.60), thromboembolism excluding MI (0.60 vs 0.58), and death (0.60 vs 0.58). Similar results were seen at 5 years. (See Table 3 for full results including 1 and 5 year C-statistics).

The negative predictive values (NPV) of the CHA_2DS_2-VASc score in HF patients without AF exhibited moderate discriminatory ability for stroke, thromboembolism and mortality at 1 year. When using NPV to identify patients at low risk (for stroke as defined by a CHA_2DS_2-VASc score < 2) of ischemic stroke, thromboembolism and mortality at 1-year follow-up, the CHA_2DS_2-VASc score yielded moderate NPVs in the 80s for patients with HF without AF (NPV 85.4% [95% CI, 83.4-87.4%] for ischemic stroke,

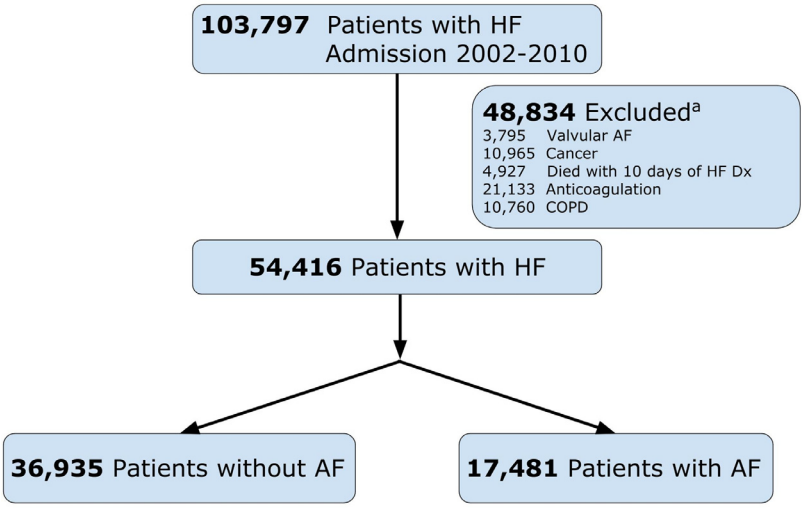

Figure 1. Subject selection schematic.
Legend: Graphic representation of schema for selecting patients from the Veteran Affairs national database.
AF = atrial fibrillation; Dx = diagnosis; COPD = chronic obstructive pulmonary disease; HF = heart failure
[a]Subcomponents add up to more than total as patients could be excluded for multiple reasons.

84.6% [95% CI, 82.6-86.6%] for thromboembolism, and 85.8% [95% CI, 83.9-87.8%] for death). When using NPV to identify patients at low risk of ischemic stroke and thromboembolism at 5-year follow-up, the CHA_2DS_2-VASc score again yielded moderate NPVs in the upper 70s to 80s for patients with HF without AF (NPV 84.3% [95% CI, 82.2-86.3%] for ischemic stroke, and 79.9% [95% CI, 77.6-82.1%] for thromboembolism). However, when using NPV to identify patients at low risk of mortality at 5-year follow-ups, the CHA_2DS_2-VASc score yielded low NPVs in the 60s for HF patients without AF (NPVs, 62.2% [95% CI, 59.50=64.9%]). Notably, the moderate to poor NPV results were similar for HF patients with AF. (Table 4)

Discussion

In our study, the CHA_2DS_2-VASc score provided modest ability to risk stratify patients with HF without and with AF. There is a positive correlation between CHA_2DS_2-VASc scores and the end points of ischemic stroke and all-cause mortality respectively. The C-statistics were similar in patients with and without the AF. Additionally, the C-statistics for CHA_2DS_2-VASc for HF patients with and without AF in our study were similar to the generally accepted C-statistic for all AF patients (including those without HF) of 0.6-0.7,[4,12] suggesting that it has similar predictive ability regardless of AF status.

Table 2
One year incidence rates for patients

Patients Without Atrial Fibrillation

		CHA_2DS_2-VASc Score					
End points	Overall	1 (HF only)	2	3	4	5	≥6
Patient, No	36,935	1,228	4173	7767	10217	8248	5302
		3.3%	11.3%	21.0%	27.7%	22.3%	11.7%
Ischemic Stroke							
Events No	623	8	42	105	167	138	172
Person-year	31,860	1117	3841	6957	8906	6818	4221
Incidence rate	2.0%	0.7%	1.1%	1.5%	1.9%	2.0%	4.1%
Thromboembolism (Including Myocardial Infarction)							
Events, No.	2,450	22	149	395	614	652	618
Person-year	31,128	1110	3798	6832	8720	6627	4042
Incidence rate	7.9%	2.0%	4.0%	5.8%	7.0%	9.8%	15.3%
Thromboembolism (Excluding Myocardial Infarction)							
Event No	976	13	77	184	247	213	242
Person-year	31,724	1114	3825	6923	8875	6792	4194
Incidence rate	3.1%	1.2%	2.0%	2.7%	2.8%	3.1%	5.8%
Death							
Events, No.	8347	174	558	1349	2176	2378	1712
Person-year	32,142	1122	3861	7005	8980	6877	4297
Incidence rate	26.0%	15.5%	14.5%	19.3%	24.2%	34.6%	39.8%

Table 3
. Comparison of C-statistic between our data and previous data for each end point

C Statistic				
	Without Atrial Fibrillation		With Atrial Fibrillation	
Time	Marzouka et al.	Melgaard et al.	Marzouka et al.	Melgaard et al.
Stroke				
At 1 year	0.62 (0.60-0.64)	0.67 (0.65-0.68)	0.59 (0.56-0.62)	0.64 (0.61-0.67)
At 5 years	0.59 (0.57-0.61)	0.69 (0.67-0.69)	0.57 (0.56-0.59)	0.71 (0.68-0.73)
Thromboembolism (Including Myocardial Infarction)				
At 1 year	0.63 (0.61-0.65)	0.63 (0.62-0.64)	0.60 (0.58-0.61)	0.62 (0.60-0.64)
At 5 years	0.61 (0.59-0.63)	0.67 (0.67-0.68)	0.57 (0.56-0.58)	0.67 (0.67-0.71)
Thromboembolism (Excluding Myocardial Infarction)				
At 1 year	0.60 (0.58-0.61)	N/A	0.58 (0.56-0.60)	N/A
At 5 years	0.57 (0.55-0.59)	N/A	0.55 (0.54-0.57)	N/A
Death				
At 1 year	0.60 (0.59-0.60)	0.64 (0.63-0.64)	0.58 (0.57-0.59)	0.63 (0.62-0.65)
At 5 years	0.65 (0.64-0.65)	0.68 (0.67-0.68)	0.63 (0.62-0.64)	0.70 (0.69-0.72)

Our findings are similar to the Melgaard et al study which examined the use of the CHA_2DS_2-VASc score in HF patients without AF in a Danish Cohort.[7] This study also showed similar predictive ability of CHA_2DS_2-VASc in HF with and without AF. It is important to note that our findings related to a true thromboembolism end point, while Melgaard et al included MI in their thromboembolism end point. Thus, we did observe a dramatic reduction in the incidence of thromboembolism when excluding MI (7.9% vs 3.1%) across all CHA_2DS_2-VASc scores. This also led to a slight reduction in the C-statistic in both the non-AF and AF cohorts. This is likely the result of the CHA_2DS_2-VASc including risk factors for MI that are independent of thromboembolism.

The utility of the CHA_2DS_2-VASc score in HF patients without AF is in part due to its ability to identify the same upstream risk factors that place patients at risk for atrial myopathy and thromboembolic stroke. Atrial myopathy is the outcome on the left atrium (LA) of structural and electrophysiological remodeling due to underlying risk factors, and can include fibrosis and atrial dysfunction, all of which provide an environment conducive for atrial fibrillation and a precursor to stroke.[13] Electroanatomical changes indicative of atrial myopathy are seen in HF patients even before the development of AF.[14] Emerging research has suggested that atrial myopathy independently of AF increases the risk for thromboembolism and ischemic stroke.[15,16]

Using the CHA_2DS_2-VASc scoring system in patients without known AF has been shown to identify high risk of either undiagnosed or impending AF or stroke. In a study of patients over 70 years old with at least one risk factor of either hypertension, diabetes, previous stroke, or HF who received implantable loop recorders, 35% had an episode of AF that lasted $\geq$ 6 minutes. However, 90% of participants did not have symptoms at enrollment and 87% of patients did not have symptoms during follow up.[17] Furthermore, in a study of nonanticoagulated patients with implantable loop recorders, even short periods of AF > 6 minutes in patients with CHA_2DS_2-VASc scores greater than 3 were associated with stroke risks greater than 1%/year (1.28%). Additionally, patients without any AF on the loop recorder but who had a CHA_2DS_2-VASc score $\geq$ 5 had stroke events rates of 1.79%/year.[18]

Table 4
. Comparison of negative predictive values between our data and previous data for each end point

Negative Predictive Value, %				
	Without Atrial Fibrillation		With Atrial Fibrillation	
Time	Marzouka et al.	Melgaard et al.	Marzouka et al.	Melgaard et al.
Stroke				
At 1 year	85.4 (83.4-87.4)	92 (91-93)	86.4 (82.6-90.2)	91 (88-95)
At 5 years	84.3 (82.2-86.3)	78 (77-80)	81.2 (76.9-85.6)	69 (60-77)
Thromboembolism (Including Myocardial Infarction)				
At 1 year	84.6 (82.6-86.6)	88 (87-89)	85.4 (81.5-89.4)	88 (84-92)
At 5 years	79.9 (77.6-82.1)	73 (71-74)	73.5 (68.5-78.4)	61 (51-69)
Thromboembolism (Excluding Myocardial Infarction)				
At 1 year	85.2 (83.2.-87.2)	N/A	86.1 (82.2-90.0)	N/A
At 5 years	82.3 (80.1-84.4)	N/A	80.0 (73.4-82.6)	N/A
Death				
At 1 year	85.8 (83.9-87.8)	93 (92-94)	87.1 (83.3-90.8)	94 (91-97)
At 5 years	62.2 (59.5-64.9)	80 (79-82)	49.5 (43.9-55.1)	76 (67-84)

Additional research is required to see if anticoagulating HF patients without AF with high CHA_2DS_2-VASc scores has a beneficial effect. Although early studies of HF did not show a benefit of anticoagulation,[19,20] these studies included all HF patients without selection for those at highest risk. Analysis of risks and benefits have suggested that patients with AF should be anticoagulated when their annual risk of stroke exceeds 1%.[21] It may therefore be reasonable to consider anticoagulating HF patients without AF once this threshold is met. Potential future studies may find that only a subset of HF patients without AF may benefit from anticoagulation.

It should be recognized that the CHA_2DS_2-VASc score is not a specific score for thromboembolism in AF, as indicated by its low C statistic. It also identifies patients who are sicker with more co-morbidities and are at high risk for atherosclerotic events. We attempted to control for this by analyzing outcomes with MI both included and excluded. Regardless, there is evidence that anticoagulation may prevent progression of atherosclerotic disease[22,23]; therefore, high CHA_2DS_2-VASc scores in the right clinical setting may identify patients who benefit from anticoagulation for the prevention of both atherosclerotic and thromboembolic events.

This was a retrospective study that used ICD-9 codes without individual subject chart review. Subjects were identified with HF and AF by inpatient ICD-9 code and therefore only identified inpatient HF diagnoses. This may limit generalizability to patients with HF not requiring hospitalization. Although ejection fraction was unknown, as per the most recent European Society of Cardiology guidelines, heart failure with preserved and reduced ejection fraction are equivalent risk for thromboembolic events.[24] Likewise, data from a subset of patients from the VA database with recorded ejection fractions show similar rates of stroke at 5 years.[25] Although atrial fibrillation is hard to capture in one datapoint due to its paroxysmal nature, we followed patients longitudinally for five years making it unlikely that AF patients were counted as non-AF subjects.[26] Additionally, outcomes were assigned based on ICD-9 codes of patients presenting to VA facilities, and therefore patients who had stroke at outside facilities may have been missed. Nevertheless, the annual stroke risk of this study was within the estimated 1.3 to 3.5% per year for patients with HF suggesting external validity with other HF trials.[27] We included all ischemic strokes and did not attempt to differentiate by etiology. This is consistent with clinical practice with estimates that ≥30% of strokes do not have a known etiology.[28] Additionally, this methodology is consistent with landmark trials.[29,30] As a HF population was studied, there was a high mortality rate which served as a competing risk with stroke and thromboembolic events. Patients may have been on anticoagulation started in follow-up leading to lower event rates. We studied a time period when direct oral anticoagulants were not being used, so patients were on warfarin only. Lastly, our cohort from the VA has a higher proportion of males than the general population.

In conclusion, this study confirms that the CHA_2DS_2-VASc score has similar risk stratification ability for ischemic stroke and thromboembolism in HF patients without AF to those with AF. These findings are in line with the prior studies and add to an increasing body of literature that cardioembolic risk is not just limited to patients with AF.[7,8] Further randomized control trials are needed to determine if patients with HF but without AF who are at high risk for ischemic stroke by CHA_2DS_2-VASc score would benefit from prophylactic anticoagulation.

Author Statement

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Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

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