

Original Investigation

Assessment of the CHA₂DS₂-VASc Score in Predicting Ischemic Stroke, Thromboembolism, and Death in Patients With Heart Failure With and Without Atrial Fibrillation

Line Melgaard, MSc; Anders Gorst-Rasmussen, MSc, PhD; Deirdre A. Lane, PhD;
Lars Hvilsted Rasmussen, MD, PhD; Torben Bjerregaard Larsen, MD, PhD; Gregory Y. H. Lip, MD

IMPORTANCE The CHA₂DS₂-VASc score (congestive heart failure, hypertension, age ≥ 75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-75 years, sex category [female]) is used clinically for stroke risk stratification in atrial fibrillation (AF). Its usefulness in a population of patients with heart failure (HF) is unclear.

OBJECTIVE To investigate whether CHA₂DS₂-VASc predicts ischemic stroke, thromboembolism, and death in a cohort of patients with HF with and without AF.

DESIGN, SETTING, AND POPULATION Nationwide prospective cohort study using Danish registries, including 42 987 patients (21.9% with concomitant AF) not receiving anticoagulation who were diagnosed as having incident HF during 2000-2012. End of follow-up was December 31, 2012.

EXPOSURES Levels of the CHA₂DS₂-VASc score (based on 10 possible points, with higher scores indicating higher risk), stratified by concomitant AF at baseline. Analyses took into account the competing risk of death.

MAIN OUTCOMES AND MEASURES Ischemic stroke, thromboembolism, and death within 1 year after HF diagnosis.

RESULTS In patients without AF, the risks of ischemic stroke, thromboembolism, and death were 3.1% (n = 977), 9.9% (n = 3187), and 21.8% (n = 6956), respectively; risks were greater with increasing CHA₂DS₂-VASc scores as follows, for scores of 1 through 6, respectively: (1) ischemic stroke with concomitant AF: 4.5%, 3.7%, 3.2%, 4.3%, 5.6%, and 8.4%; without concomitant AF: 1.5%, 1.5%, 2.0%, 3.0%, 3.7%, and 7% and (2) all-cause death with concomitant AF: 19.8%, 19.5%, 26.1%, 35.1%, 37.7%, and 45.5%; without concomitant AF: 7.6%, 8.3%, 17.8%, 25.6%, 27.9%, and 35.0%. At high CHA₂DS₂-VASc scores (≥ 4), the absolute risk of thromboembolism was high regardless of presence of AF (for a score of 4, 9.7% vs 8.2% for patients without and with concomitant AF, respectively; overall $P < .001$ for interaction). C statistics and negative predictive values indicate that the CHA₂DS₂-VASc score performed modestly in this HF population with and without AF (for ischemic stroke, 1-year C statistics, 0.67 [95% CI, 0.65-0.68] and 0.64 [95% CI, 0.61-0.67], respectively; 1-year negative predictive values, 92% [95% CI, 91%-93%] and 91% [95% CI, 88%-95%], respectively).

CONCLUSIONS AND RELEVANCE Among patients with incident HF with or without AF, the CHA₂DS₂-VASc score was associated with risk of ischemic stroke, thromboembolism, and death. The absolute risk of thromboembolic complications was higher among patients without AF compared with patients with concomitant AF at high CHA₂DS₂-VASc scores. However, predictive accuracy was modest, and the clinical utility of the CHA₂DS₂-VASc score in patients with HF remains to be determined.

JAMA. 2015;314(10):1030-1038. doi:10.1001/jama.2015.10725
Published online August 30, 2015. Corrected on September 10, 2015.

← Related article page 1063

+ Supplemental content at
jama.com

Author Affiliations: Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark (Melgaard, Gorst-Rasmussen, Rasmussen, Larsen, Lip); Unit of Clinical Biostatistics, Aalborg University Hospital, Aalborg, Denmark (Gorst-Rasmussen); University of Birmingham Centre for Cardiovascular Sciences City Hospital, Birmingham, England (Lane, Lip).

Corresponding Author: Gregory Y. H. Lip, MD, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Dudley Road, Birmingham B18 7QH, England (g.y.h.lip@bham.ac.uk).

Hear failure (HF) is associated with an increased risk of ischemic stroke and mortality, whether in sinus rhythm or atrial fibrillation (AF).¹⁻⁵ Risk stratification using readily available clinical variables may help identify subgroups at low and high risk of ischemic stroke and thromboembolic events (TE) in an HF population.

Simple clinical risk scores have been useful in other settings such as in patients with AF, for example, the CHA₂DS₂-VASC score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic

AF atrial fibrillation

COPD chronic obstructive pulmonary disease

HF heart failure

ICD-10 International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

NPV negative predictive value

TE thromboembolism

attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-74 years, sex category [female]), which is recommended in current guidelines (based on 10 possible points, with higher scores indicating higher risk).^{6,7} In recent years, use of the CHA₂DS₂-VASC score in predicting ischemic stroke, TE, and death has extended beyond the original disease state for which it was proposed.^{8,9} In addition, it is recognized that the cluster of multiple stroke risk factors included within the CHA₂DS₂-VASC score increases the risk of ischemic stroke, TE, and death, whether or not AF is present. Thus, there is a need to study the extent to which concomitant AF modifies the pattern of the association between CHA₂DS₂-VASC score and the risk of ischemic stroke, TE, and death in patients with HF.

Evaluating an ischemic stroke and TE risk score in a population with a high mortality rate such as the HF population (5-year mortality of 45%-60%)^{10,11} is not trivial because a competing-risks setting taking careful consideration of the interplay between mortality and ischemic stroke/TE risk is needed to provide meaningful risk assessments.^{12,13}

We hypothesized that the CHA₂DS₂-VASC score could predict ischemic stroke, TE, and death in patients with HF without AF in a manner comparable with that evident in AF populations. We hypothesized that at high CHA₂DS₂-VASC scores, the risk would be comparable between patients with and without AF.

Methods

Registry Data Sources

We used 3 nationwide registries in this study: (1) the Danish National Patient Register,¹⁴ which has registered all hospital admissions along with diagnoses since 1977 and has coded all diagnoses according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* since 1994; (2) the Danish National Prescription Registry,¹⁵ which contains data on all prescriptions dispensed from Danish pharmacies since 1994, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System; and (3) the Danish Civil Registration System, which holds information on date of birth, migration, vital status, date

of death, and sex of all persons living in Denmark.¹⁶ Data were linked via a unique personal identification number used in all Danish national registries. All 3 registries were used up to December 31, 2012 (end of follow-up). These registries have previously been well validated,^{14,15,17} and the diagnoses of HF, AF, and ischemic stroke have been found to be valid.¹⁷⁻¹⁹

No ethical approval is required for anonymous register studies in Denmark. The study was approved by the Danish Data Protection Agency.

Study Population

The study population was identified as patients aged 50 years or older discharged with a primary diagnosis of incident HF (*ICD-10* codes I50, I42.0, I11.0, I13.0, and I13.2) in the period January 1, 2000, to December 31, 2012. Patients with AF were identified by a hospital diagnosis of AF or atrial flutter (*ICD-10* code I48) between 1994 and baseline. We excluded patients treated with a vitamin K antagonist (ATC codes B01AA03 and B01AA04) within 6 months prior to the HF diagnosis. Moreover, patients with a diagnosis of cancer (*ICD-10* codes C00-C97) within 5 years before HF diagnosis or with a prior diagnosis of chronic obstructive pulmonary disease (*ICD-10* code J44) were excluded.

Comorbidities at baseline were identified using the Danish National Patient Register and the Danish National Prescription Registry. Ascertainment of baseline medication status was based on medication purchase in a 45-day window before or after the date of HF diagnosis. *ICD-10* codes and ATC codes were used to define comorbidities and medical therapies (eTable 1 in the Supplement).

Risk Stratification Using CHA₂DS₂-VASC Score

Based on the CHA₂DS₂-VASC score, patients were given 1 point for congestive HF, hypertension, age 65 to 74 years, diabetes mellitus, vascular disease, and female sex and 2 points for age 75 years or older and previous TE.²⁰ Accordingly, a score of 1 in our analyses corresponds to patients with HF only and no additional stroke risk factors.

Outcomes

The primary end point was defined as a hospital diagnosis (according to the Danish National Patient Register) of ischemic stroke (*ICD-10* codes I63 and I64.9) or TE (ischemic stroke [*ICD-10* codes I63 and I64.9], transient ischemic attack [*ICD-10* code G45], systemic embolism [*ICD-10* code I74], pulmonary embolism [*ICD-10* code I26], or acute myocardial infarction [*ICD-10* codes I21 and I23]). All-cause death (according to the Danish Civil Registration System) was included as a secondary end point.

Statistical Analysis

Baseline characteristics at the time of HF diagnosis were described using means and standard deviations for continuous measures and percentages for categorical measures (Table 1).

Time-to-event analysis was used to describe the association between the CHA₂DS₂-VASC score and the risk of ischemic stroke, TE, and death, separately within the strata of patients with HF with and without a prior diagnosis of AF. Time

Table 1. Baseline Characteristics of the Heart Failure Study Population, Stratified According to Prior Diagnosis of Atrial Fibrillation^a

Clinical Characteristics	No. (%) of Patients	
	Without Atrial Fibrillation (n=33 592)	With Atrial Fibrillation (n=9395)
Female	14 817 (44.1)	4420 (47.1)
Age at baseline, mean (SD), y	74 (11.6)	78 (11.1)
Age group, y		
50-64	8284 (24.7)	1390 (14.8)
65-74	8334 (24.8)	1850 (19.7)
≥75	16 974 (50.5)	6155 (65.5)
Baseline comorbidity		
Hypertension	14 444 (43.0)	4082 (43.5)
Previous thromboembolism ^b	9559 (28.5)	2504 (26.7)
Vascular disease	8746 (26.0)	1884 (20.1)
Previous myocardial infarction	6650 (19.8)	1263 (13.4)
Diabetes	5769 (17.2)	1403 (14.9)
Peripheral arterial disease	2918 (8.7)	794 (8.5)
Previous ischemic stroke	2675 (8.0)	1085 (11.6)
Renal disease	1686 (5.0)	491 (5.2)
Hyperthyroidism	630 (1.9)	360 (3.8)
Liver disease	121 (0.4)	38 (0.4)
Baseline medications		
Loop diuretics	21 949 (65.3)	7131 (75.9)
Angiotensin-converting enzyme inhibitors	17 724 (52.8)	4625 (49.2)
Aspirin	16 457 (49.0)	4453 (47.4)
β-Blockers	15 365 (45.7)	5155 (54.9)
Nonloop diuretics	13 197 (39.3)	3763 (40.1)
Statins	10 394 (31.0)	1907 (20.3)
Aldosterone antagonists	7701 (22.9)	2408 (25.6)
Calcium channel antagonists	5674 (16.9)	1822 (19.4)
NSAIDs	4761 (14.2)	1223 (13.0)
Antidiabetics	4551 (13.6)	1016 (10.8)
Digoxin	3667 (10.9)	4862 (51.8)
Thienopyridines	3610 (10.8)	521 (5.6)
Angiotensin receptor blockers	3490 (10.4)	889 (9.5)
Vasodilators	640 (1.9)	221 (2.4)
Pacemaker/ICD	1169 (3.5)	628 (6.7)
Percutaneous coronary intervention	3107 (9.3)	394 (4.2)
Coronary artery bypass graft surgery	1691 (5.0)	447 (4.8)
Rehospitalization for heart failure during full follow-up		
1 event	13 172 (39.2)	3445 (36.7)
2-4 events	13 873 (41.3)	4140 (44.1)
≥5 events	6547 (19.5)	1810 (19.3)

Abbreviations: ICD, implantable cardioverter-defibrillator; NSAIDs, nonsteroidal anti-inflammatory drugs.

^a All study patients had heart failure at baseline.

^b Composite end point of ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, or acute myocardial infarction.

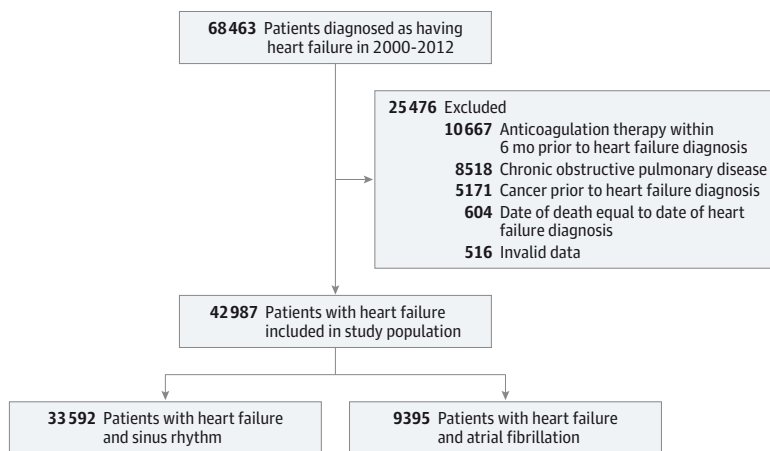
at risk was measured from the date of HF diagnosis until an event of ischemic stroke or TE, date of death, emigration, or end of study (December 31, 2012), whichever came first. Patients were censored if they began anticoagulant therapy during the follow-up period.

To enable comparison with other studies, we first calculated crude incidence rates of end points, stratified according to presence of concomitant AF. However, for the purpose of risk stratification, particularly in the context of competing risks, absolute risks (cumulative incidences/probabilities) are more relevant.^{12,13} We calculated absolute risks for all end points using the Aalen-Johansen estimator²¹ to take into account competing risks of death. Relative risks according to CHA₂DS₂-VASC score (relative to a CHA₂DS₂-VASC score of 1) were also calculated using the pseudo-value method to take into account competing risks of death.^{22,23} The pseudo-value method reduces to simple regression with a log-link function on the event status indicator in the absence of censoring, whereas censored observations (for which the event status is not observed) are replaced with pseudo-observations based on Aalen-Johansen cumulative incidence estimates using the jackknife method. These methods have not been validated but are described in previous literature.^{24,25} Wald *P* values for interactions on a risk ratio scale were used to quantify whether the overall association between CHA₂DS₂-VASC score and outcome risk differed between patients with and without AF.

To quantify the discriminatory properties of the CHA₂DS₂-VASC score, we used C statistics for each end point. This well-known measure of discrimination can be interpreted as the probability that a randomly selected patient who experiences the event of interest before a given time has a higher risk score than a control patient who does not experience an event before a given time. Because of competing risks of death, there are several valid definitions of control patients (alive and event free; alive and event free or dead) leading to different interpretations.^{24,25} We used as controls patients who were alive and event free at 1- and 5-year follow-up and used the inverse-probability-of-censoring weighted estimator (assuming censoring and event times to be independent given CHA₂DS₂-VASC score).^{24,25} Bootstrap confidence intervals for the C statistics were calculated using 1000 bootstrap samples. Furthermore, with the same definition of controls, we estimated for each end point the negative predictive value (NPV) of the CHA₂DS₂-VASC score with 1 as the cutoff; ie, the proportion of patients with CHA₂DS₂-VASC score = 1 who were alive and without the end point of interest at 1- and 5-year follow-up.

Sensitivity analysis was performed by repeating the absolute and relative risk calculations when extending the definition of concomitant AF at baseline to presence of a prior diagnosis of AF at baseline or within 30 days after HF diagnosis. This sensitivity analysis was performed because some patients might have a diagnosis of AF shortly after the HF diagnosis. Additionally, approximately 14% had a diagnosis of AF during 5 years of follow-up; thus, we performed another sensitivity analysis by repeating the absolute and relative risk calculations in the non-AF group after censoring patients who were diagnosed as having AF during follow-up. Moreover, a split sample analysis according to early (2000-2005) and late (2006-2012) study period was performed. Finally, we performed a sensitivity analysis in which we included patients with COPD. All sensitivity analyses were compared with the main analysis.

Figure 1. Selection of Study Population With Heart Failure With and Without Atrial Fibrillation



Because few prior studies have found that individual risk factors of the CHA₂DS₂-VASC score are associated with lower risk, not higher risk, of stroke in the HF population,^{4,26,27} we performed a supplemental analysis of the association between each individual component of the CHA₂DS₂-VASC score and the risk of ischemic stroke.

The analyses were performed using Stata version 13 (Stata Corp) and R version 3.0.2 (R Foundation for Statistical Computing) with the package timeROC.²⁵ A 2-sided *P* < .05 was considered statistically significant.

Results

The study population comprised 42 987 patients with HF aged 50 years or older, among whom 21.9% had a diagnosis of AF at baseline (Figure 1). The median follow-up period with respect to ischemic stroke was 1.84 years (interquartile range, 0.22-4.59 years). The distribution of CHA₂DS₂-VASC scores in the study population according to presence of an AF diagnosis are shown in Table 2.

Incidence rates during the first year are shown in Table 2; overall, they exhibited the same fundamental characteristics as the absolute risks, which are presented in detail below. Incidence rates were generally attenuated after 5 years of follow-up (eTable 2 in the Supplement), indicating that most events occurred relatively shortly after the HF diagnosis. Numbers of events and person-years are shown in Table 2 and eTable 2 for 1 and 5 years of follow-up, respectively.

For patients with HF with and without a diagnosis of AF, Figure 2 shows the absolute risks according to CHA₂DS₂-VASC during the first year after HF diagnosis, alongside the corresponding relative risks, comparing patients with a score higher than 1 with those with a score of 1 (no additional stroke risk factors). In both strata, the 1-year absolute risk generally increased with increasing CHA₂DS₂-VASC score but exhibited a less clear association for ischemic stroke among patients with HF and AF. For ischemic stroke and death, absolute risks were consistently higher among patients with

HF and AF compared with those without AF (for ischemic stroke, with concomitant AF, 4.5%, 3.7%, 3.2%, 4.3%, 5.6%, and 8.4% and without concomitant AF, 1.5%, 1.5%, 2.0%, 3.0%, 3.7%, and 7% for scores 1-6, respectively; overall *P* = .001 for interaction; for all-cause death, with concomitant AF, 19.8%, 19.5%, 26.1%, 35.1%, 37.7%, and 45.5% and without concomitant AF, 7.6%, 8.3%, 17.8%, 25.6%, 27.9%, and 35.0%, for scores 1-6, respectively; overall *P* < .001 for interaction), but this pattern was not observed for the end point of TE at low CHA₂DS₂-VASC scores (for a score of 1, 9.0% vs 5.3%; for a score of 2, 8.3% vs 6.6%; for a score of 3, 7.9% vs 7.7%; overall *P* < .001 for interaction). The absolute risk of TE was higher among patients without AF compared with patients with concomitant AF at high CHA₂DS₂-VASC scores (for a score of 4, 9.7% vs 8.2%; for a score of 5, 11.9% vs 11.2%; for a score of 6, 18.0% vs 14.9%; overall *P* < .001 for interaction) (see eTable 3 in the Supplement for more results on the test for interaction). The absolute risk increased in a comparable manner at high CHA₂DS₂-VASC scores (≥4), exhibiting a clear dose-response relationship. Similar patterns were observed after 5 years of follow-up (eFigure 1 in the Supplement).

The discriminatory properties of the CHA₂DS₂-VASC score depended on the choice of end point and the duration of follow-up (Table 3). In patients without AF, the CHA₂DS₂-VASC score showed moderate predictive ability for the end point of ischemic stroke (C statistics at 1- and 5-year follow-up, 0.67 [95% CI, 0.65-0.68] and 0.69 [95% CI, 0.67-0.69], respectively). In patients with AF, the predictive ability for the end point of ischemic stroke was also modest (C statistics at 1- and 5-year follow-up, 0.64 [95% CI, 0.61-0.67] and 0.71 [95% CI, 0.68-0.73], respectively). When using NPV to identify patients at low risk of ischemic stroke, TE, and death, the CHA₂DS₂-VASC score yielded NPVs around 90% at 1-year follow-up for patients with HF without AF (NPVs, 92% [95% CI, 91%-93%] for ischemic stroke, 88% [95% CI, 87%-89%] for TE, and 93% [95% CI, 92%-94%] for death). At 5-year follow-up, NPVs were strongly attenuated.

Table 2. Crude Incidence Rates at 1 Year of Follow-up in the Heart Failure Study Population, Stratified According to Prior Diagnosis of Atrial Fibrillation^a

End Points	Overall	No. of Additional Risk Factors on CHA ₂ DS ₂ -VASc Score					
		1 (HF Only)	2	3	4	5	≥6
Patients Without Atrial Fibrillation							
Patients, No. (%)	33 592	2366 (7.0)	4503 (13.4)	7462 (22.2)	9183 (27.3)	5958 (17.7)	4120 (12.3)
Ischemic stroke							
Events, No.	977	29	62	141	258	212	275
Person-years, No.	9 448 812	711 473	1 393 807	2 180 746	2 529 593	1 599 137	707 004
Incidence rate, % (95% CI)	1.0 (1.0-1.1)	0.4 (0.3-0.6)	0.4 (0.3-0.6)	0.6 (0.5-0.8)	1.0 (0.9-1.2)	1.3 (1.2-1.5)	2.6 (2.4-3.0)
Thromboembolism^b							
Events, No.	3187	110	276	548	853	683	717
Person-years, No.	9 040 950	696 366	1 348 456	2 104 494	2 421 856	1 518 482	652 067
Incidence rate, % (95% CI)	3.5 (3.4-3.6)	1.6 (1.3-1.9)	2.0 (1.8-2.3)	2.6 (2.4-2.8)	3.5 (3.3-3.8)	4.5 (4.2-4.8)	7.5 (7.0-8.1)
Death							
Events, No.	6956	149	332	1256	2239	1596	1384
Person-years, No.	9 596 399	715 795	1 404 213	2 201 781	2 566 123	1 632 315	731 311
Incidence rate, % (95% CI)	7.2 (7.1-7.4)	2.1 (1.8-2.4)	2.4 (2.1-2.6)	5.7 (5.4-6.0)	8.7 (8.4-9.1)	9.8 (9.3-10.3)	12.9 (12.2-13.6)
Patients With Atrial Fibrillation							
Patients, No. (%)	9395	606 (6.5)	931 (9.9)	1752 (18.7)	2571 (27.4)	137 (20.6)	1598 (17.0)
Ischemic stroke							
Events, No.	318	8	11	32	82	80	105
Person-years, No.	1 592 497	55 019	110 265	294 757	477 528	365 633	180 083
Incidence rate, % (95% CI)	2.0 (1.8-2.2)	1.5 (0.7-2.9)	1.0 (0.6-1.8)	1.1 (0.8-1.5)	1.7 (1.4-2.1)	2.2 (1.8-2.7)	3.6 (3.0-4.4)
Thromboembolism^b							
Events, No.	651	18	31	85	158	169	190
Person-years, No.	1 551 095	54 425	107 277	287 648	468 813	357 479	172 156
Incidence rate, % (95% CI)	4.2 (3.9-4.5)	3.3 (2.1-5.2)	2.9 (2.0-4.1)	3.0 (2.4-3.7)	3.4 (2.9-3.9)	4.7 (4.1-5.5)	6.9 (6.0-8.0)
Death							
Events, No.	2153	11	47	282	677	561	575
Person-years, No.	1 630 977	55 347	111 192	297 304	489 042	373 574	186 490
Incidence rate, % (95% CI)	13.2 (12.7-13.8)	2.0 (1.1-3.6)	4.2 (3.2-5.6)	9.5 (8.4-10.7)	13.8 (12.8-14.9)	15.0 (13.8-16.3)	18.9 (17.4-20.5)

^a CHA₂DS₂-VASc score is calculated as congestive heart failure (1 point), hypertension (1 point), age 75 years or older (2 points), diabetes (1 point), stroke/transient ischemic attack/thromboembolism (2 points), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque;

1 point), age 65 to 75 years (1 point), female sex (1 point). All study patients had heart failure at baseline.

^b Composite end point of ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, or acute myocardial infarction.

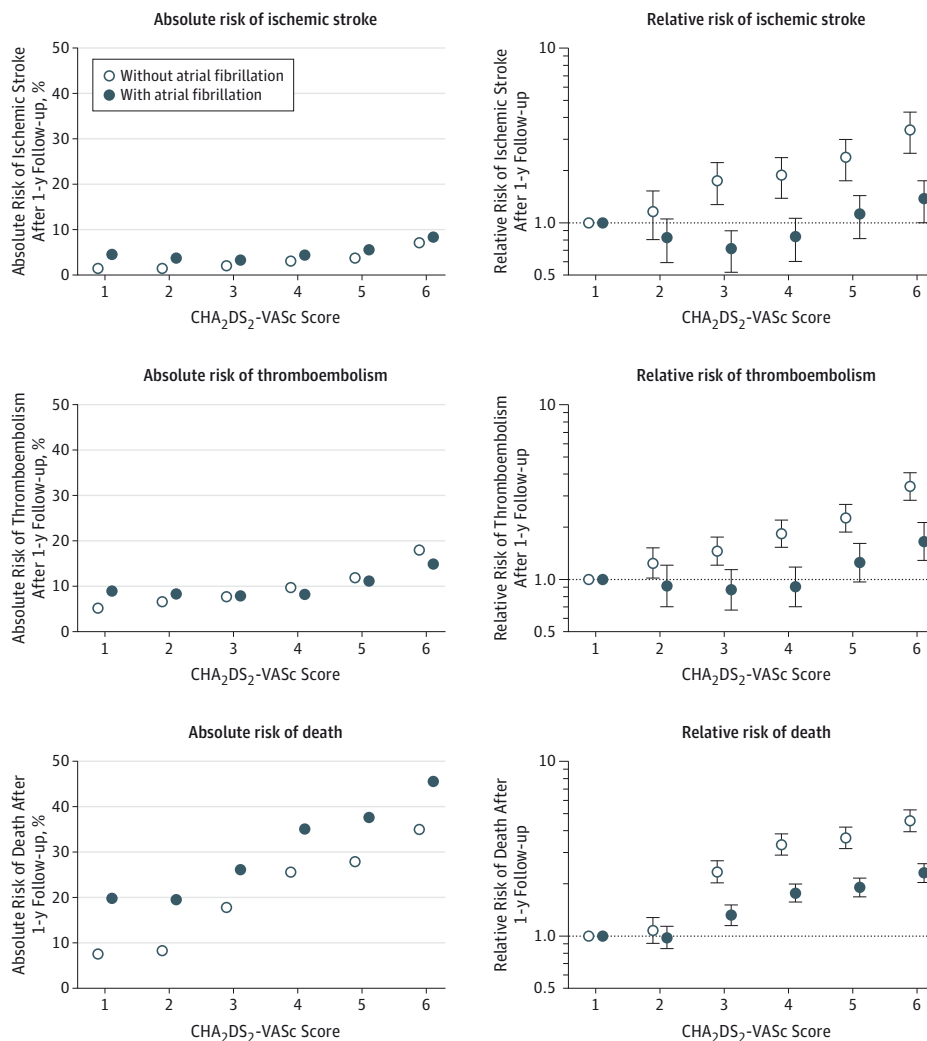
In the sensitivity analysis, repeating the absolute and relative risk calculations after extending the definition of concomitant AF, we found very similar results as in the main analysis (eFigure 2 in the Supplement). When censoring patients with HF who were diagnosed with AF during follow-up, similar results were found and the conclusions remained the same as in the main analysis (eFigure 3 in the Supplement). In the split sample analysis, we found similar results for all end points in both the early and late study period as in the main analysis for patients without AF (eFigure 4 and eFigure 5 in the Supplement). However, for patients with AF, we found higher relative risks of all end points in the early study period compared with the main analysis but similar results for the absolute risks. The C statistics were similar in both the early and late study period and comparable with the main analysis as follows: (1) in the early study period, for patients without AF, 0.66 (95% CI, 0.64-0.67) for ischemic stroke, 0.64 (95% CI, 0.63-0.64) for TE, and 0.63 (95% CI, 0.62-0.63) for death and for pa-

tients with AF, 0.62 (95% CI, 0.58-0.65), 0.61 (95% CI, 0.58-0.63), and 0.62 (95% CI, 0.60-0.64), respectively; (2) in the late study period, for patients without AF, 0.68 (95% CI, 0.66-70) for ischemic stroke, 0.63 (95% CI, 0.61-0.64) for TE, and 0.66 (95% CI, 0.65-0.67) for death and for patients with AF, 0.67 (95% CI, 0.63-0.72), 0.64 (95% CI, 0.61-0.68), and 0.64 (95% CI, 0.63-0.68), respectively.

In the sensitivity analysis, when we included patients with COPD, the results were qualitatively similar for patients without AF, but the absolute risks for patients with AF were lower and the relative risks were higher compared with the main analysis. Thus, the conclusions remained the same (eFigure 6 in the Supplement).

Supplemental analysis of the association between each individual component of the CHA₂DS₂-VASc score and the risk of ischemic stroke is shown in eTable 4 in the Supplement. In patients both with and without AF, female sex was not associated with an increased risk of ischemic stroke.

Figure 2. Absolute Risks and Relative Risks by CHA₂DS₂-VASC Score Components During the First Year of Follow-up, Stratified According to Prior Diagnosis of Atrial Fibrillation



Error bars indicate 95% CIs. Numbers of patients contributing data in each group for CHA₂DS₂-VASC scores from 1 to 6, respectively, were as follows: without atrial fibrillation, 2366, 4503, 7462, 9183, 5958, and 2733; with atrial fibrillation, 606, 931, 1752, 2571, 1937, and 980.

Discussion

In this cohort study, our principal findings were that (1) patients with HF had a high risk of ischemic stroke, TE, and death whether or not AF was present; (2) the CHA₂DS₂-VASC score was able to modestly predict these end points and had a moderately high NPV at 1-year follow-up; and (3) at high CHA₂DS₂-VASC scores (≥ 4), patients with HF without AF had high absolute risk of ischemic stroke, TE, and death, and the absolute risk increased in a comparable manner in patients with HF with and without AF, exhibiting a clear dose-response relationship. Indeed, the absolute risk of thromboembolic complications was higher among patients without AF compared with patients with concomitant AF at high CHA₂DS₂-VASC scores (≥ 4). To our knowledge, this is the first study to evaluate the predictive ability of the CHA₂DS₂-VASC score in estimating the risk of ischemic stroke, TE, and death in a population of patients with incident HF with and without AF.

Patients with HF and without AF are at increased risk of ischemic stroke and TE, and in recent randomized trials, these end points (which were secondary trial end points) were reduced by warfarin therapy.²⁸⁻³⁰ In the Danish Diet, Cancer and Health cohort, we previously demonstrated the high risk of stroke and mortality among patients with HF without AF, which was lower if warfarin therapy was prescribed.⁴

Patients with HF have an increased risk of ischemic stroke, TE, and death regardless of whether AF is present.²⁸ In our study, one of our principal findings was that the absolute risk of ischemic stroke among patients without AF was about 1.5% per year or higher with CHA₂DS₂-VASC scores of 2 or higher, with associated 5-year absolute ischemic stroke risks in excess of 4% or more. Risks were even higher among the patients with HF with AF in our study. Similar absolute risks were found when stratifying analyses according to early and late study period, indicating a robustness of our findings to changes in standard HF diagnostic and treatment modes between 2000 and 2012. In the general AF population, a stroke risk of greater

Table 3. Assessment of the CHA₂DS₂-VASC Score at 1- and 5-Year Follow-up in the Heart Failure Study Population According to Prior Diagnosis of Atrial Fibrillation^a

	Without Atrial Fibrillation		With Atrial Fibrillation	
	C Statistic (95% CI)	NPV, % (95% CI) ^b	C Statistic (95% CI)	NPV, % (95% CI) ^b
Ischemic stroke				
At 1 y	0.67 (0.65-0.68)	92 (91-93)	0.64 (0.61-0.67)	91 (88-95)
At 5 y	0.69 (0.67-0.69)	78 (77-80)	0.71 (0.68-0.73)	69 (60-77)
Thromboembolism ^c				
At 1 y	0.63 (0.62-0.64)	88 (87-89)	0.62 (0.60-0.64)	88 (84-92)
At 5 y	0.67 (0.67-0.68)	73 (71-74)	0.69 (0.67-0.71)	61 (51-69)
Death				
At 1 y	0.64 (0.63-0.64)	93 (92-94)	0.63 (0.62-0.65)	94 (91-97)
At 5 y	0.68 (0.67-0.68)	81 (79-82)	0.70 (0.69-0.72)	76 (67-84)

Abbreviation: NPV, negative predictive value.

^a CHA₂DS₂-VASC score is calculated as congestive heart failure (1 point), hypertension (1 point), age 75 years or older (2 points), diabetes (1 point), stroke/transient ischemic attack/thromboembolism (2 points), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque;

1 point), age 65 to 75 years (1 point), female sex (1 point). All study patients had heart failure at baseline.

^b Using a cutoff value of 1.

^c Composite end point of ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, or acute myocardial infarction.

than 1% per year is often used as a cut point to identify patients in whom the benefits of long-term oral anticoagulation may outweigh the risks of bleeding.³¹ In the present HF population, patients without AF with a CHA₂DS₂-VASC score of 2 or higher had a stroke risk greater than 1% per year. Although it is not clear whether this cut point would apply directly to the HF population without AF, our results may suggest that subgroups of patients with HF without AF and with 2 or more components of the CHA₂DS₂-VASC score besides HF are at high enough risk of ischemic stroke to benefit from anticoagulation therapy; especially with availability of the non-vitamin K antagonist oral anticoagulants.

Our other principal finding is that in patients with HF with elevated CHA₂DS₂-VASC scores (≥ 4), the absolute risk of ischemic stroke, TE, and death was very high. At these high CHA₂DS₂-VASC scores, the absolute risk increased in a comparable manner in patients with HF with and without AF, exhibiting a clear dose-response relationship, so that the absolute risk of TE was even greater among patients without AF compared with those with concomitant AF. The poor prognosis of AF for ischemic stroke and death in patients with HF was evident in our study, but the observation that additional risk factors in patients with HF are particularly significant among those without AF is an important result. Indeed, preventative strategies to reduce ischemic stroke and TE risk in this large patient population require further investigation.

The C statistics demonstrated that the performance of the CHA₂DS₂-VASC score was dependent on the type of end point and the length of follow-up. In patients with HF without AF, the CHA₂DS₂-VASC score performed moderately in discriminating patients experiencing an ischemic stroke from stroke-free survivors. The C statistics for predicting “events” in this study are also comparable with other commonly used risk scores based on clinical risk factors (for example, the CHADS₂ score in AF). Although these initial results demonstrate a potential use of the score, the direct clinical utility of stroke risk stratification in patients with HF is an open question. In this high-risk population, all-cause

mortality remains the key concern, as indicated by the very high mortality rates and the corresponding relatively poorer performance of the risk score for predicting events after 5 years of follow-up. On the other hand, CHA₂DS₂-VASC yielded a moderately high 1-year NPV for identifying patients at “low risk” of stroke or death (approximately 90%). This is consistent with the CHA₂DS₂-VASC score as a useful tool for identifying “low-risk” patients, as evident in various studies examining risks in AF patients.^{32,33} In our study, we found a less clear association between ischemic stroke risk and increasing CHA₂DS₂-VASC score among patients with HF and AF, exhibiting a possible J-shaped association or possibly no meaningful association, which could be due to the low event numbers with some of the scores. Furthermore, not all the individual components of the CHA₂DS₂-VASC score have been identified as established risk factors of ischemic stroke in the HF population without AF. Previous studies have even showed that some of these components are associated with a decreased ischemic stroke risk,^{4,26,27} which our supplemental analysis also demonstrates. In spite of these previous findings, the CHA₂DS₂-VASC score was able to modestly predict the risk of ischemic stroke in our study. Future studies examining the individual drivers of risk derived from the CHA₂DS₂-VASC score are still needed.

The major strengths of this study are the validated outcomes and large sample size uniquely possible with this type of cohort study. Selection into the study was not an issue because we investigated a nationwide population of patients with incident HF with and without AF, with limited loss to follow-up. We also accounted for competing risk of death, an important issue when investigating the performance of risk scores in populations with a high mortality.^{13,24}

The study has some limitations. We were unable to distinguish between HF with preserved vs reduced ejection fraction or to estimate the functional classification/symptoms severity because we did not have access to echocardiograms. In a previous systematic review, whether a clinical diagnosis of

HF is a significant risk factor remained inconclusive, although when the diagnosis is certain (recent decompensation requiring hospitalization, as in Danish registries), it does seem to be a significant risk factor irrespective of left ventricular systolic function.⁵ However, functional classification among patients with HF would also vary over time and with treatments. In addition, we investigated the risk in patients with incident HF, and our results may not relate to the general population of patients with HF. However, we also reported risks after 5 years of follow-up, and we believe these results are comparable with the general HF population. Because of the high mortality rate in the HF population (and therefore, the short follow-up in this study), we focused on the 1-year risks. The HF diagnosis has previously been validated with a sensitivity of 29%, a specificity of 99%, and a positive predictive value of 81%,¹⁸ and based on the validation study we did not capture all patients with HF and also cannot be certain that all patients identified as having HF had definite HF, which could lead to imprecision in the risk estimates. However, we included only patients with a primary discharge diagnosis of HF to optimize the probability of including only correctly identified patients with HF.

We investigated a real-life population using nationwide registries in which we did not exclude severely ill patients (as typically done in clinical trials); thus, our study population includes patients with HF with several comorbidities predisposing for stroke events, and our event rates may be higher than that seen in clinical trials. Indeed, Nielsen and Chao¹³ discussed the issue with different event rates observed from different populations.

We cannot rule out that some patients without AF might have had undiagnosed AF because heart disease is associated with an increased risk of developing AF and AF is silent in up to a quarter of patients. In our sensitivity analyses, extending the AF definition and censoring if development of AF oc-

curred during follow-up, we found similar results as in the main analysis. Additionally, our study population was ethnically and socially nondiverse. Thus, our study results might not be generalizable to more diverse HF populations. Furthermore, we excluded patients with HF younger than 50 years; accordingly, our findings may not apply to younger patients with HF.

We did not have information about smoking habits; however, we excluded patients with a diagnosis of COPD, which are primarily patients with an intensive smoking habit or history, and therefore, our results might not be valid for patients with COPD. However, in our sensitivity analysis, when we included patients with COPD, the conclusions remained the same.

Because of the nature of our nationwide registry study, follow-up depended on the National Civil Registration System, in which some deaths are likely to be attributable to an undiagnosed stroke. Finally, the diagnosis of ischemic stroke was defined by the Danish Hospital Discharge Register, and not all stroke end points have been defined by cerebral imaging; thus, the data did not allow classification of ischemic stroke types. However, the ischemic stroke diagnosis has previously been validated.¹⁷

Conclusions

Among patients with incident HF with or without AF, the CHA₂DS₂-VASc score was associated with risk of ischemic stroke, thromboembolism, and death. The absolute risk of thromboembolic complications was higher among patients without AF compared with patients with concomitant AF at high CHA₂DS₂-VASc scores. However, predictive accuracy was modest, and the clinical utility of the CHA₂DS₂-VASc score in patients with HF remains to be determined.

ARTICLE INFORMATION

Published Online: August 30, 2015.
doi:10.1001/jama.2015.10725.

Author Contributions: Drs Melgaard and Gorst-Rasmussen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Melgaard, Gorst-Rasmussen, Larsen, Lip.

Acquisition, analysis, or interpretation of data: Melgaard, Lane, Rasmussen, Larsen, Lip.

Drafting of the manuscript: Melgaard, Gorst-Rasmussen, Lane, Larsen, Lip.

Critical revision of the manuscript for important intellectual content: Melgaard, Lane, Rasmussen, Larsen, Lip.

Statistical analysis: Melgaard, Gorst-Rasmussen.

Obtained funding: Rasmussen, Larsen.

Administrative, technical, or material support: Rasmussen.

Study supervision: Gorst-Rasmussen, Lane, Larsen, Lip.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Lane has received investigator-initiated educational grants from Bayer Healthcare and Boehringer Ingelheim and has served as a speaker for

Boehringer Ingelheim, Bayer Healthcare, and Bristol-Myers Squibb/Pfizer. Drs Rasmussen and Larsen have been on the speakers bureaus for Bayer, Bristol-Myers Squibb/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics, and Boehringer Ingelheim. Dr Larsen has served as an investigator for Janssen Scientific Affairs LLC and Boehringer Ingelheim. Dr Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim and has served as a speaker for Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Roche, and Sanofi-Aventis. No other disclosures are reported.

Correction: This article was corrected online for a typographical error in an author's first name on September 10, 2015.

REFERENCES

- Dunkman WB, Johnson GR, Carson PE, Bhat G, Farrell L, Cohn JN. Incidence of thromboembolic events in congestive heart failure: the V-HeFT VA Cooperative Studies Group. *Circulation*. 1993;87(6)(suppl):V194-V1101.
- Alberts VP, Bos MJ, Koudstaal P, et al. Heart failure and the risk of stroke: the Rotterdam Study. *Eur J Epidemiol*. 2010;25(11):807-812.

- Freudenberger RS, Hellkamp AS, Halperin JL, et al; SCD-HeFT Investigators. Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation*. 2007;115(20):2637-2641.

- Lip GY, Rasmussen LH, Skjøth F, Overvad K, Larsen TB. Stroke and mortality in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study. *BMJ Open*. 2012;2(4):1-10.

- Agarwal M, Apostolakis S, Lane DA, Lip GYH. The impact of heart failure and left ventricular dysfunction in predicting stroke, thromboembolism, and mortality in atrial fibrillation patients: a systematic review. *Clin Ther*. 2014;36(9):1135-1144.

- Camm AJ, Lip GY, De Caterina R, et al; ESC Committee for Practice Guidelines. 2012 Focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Eur Heart J*. 2012;33(21):2719-2747.

- January CT, Wann LS, Alpert JS, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: 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(21):e1-e76.
8. Lip GYH, Lin H-J, Chien K-L, et al. Comparative assessment of published atrial fibrillation stroke risk stratification schemes for predicting stroke, in a non-atrial fibrillation population: the Chin-Shan Community Cohort Study. *Int J Cardiol*. 2013;168(1):414-419.
 9. Mitchell LB, Southern DA, Galbraith D, Ghali WA, Knudtson M, Wilton SB; APPROACH Investigators. Prediction of stroke or TIA in patients without atrial fibrillation using CHADS₂ and CHA₂DS₂-VASc scores. *Heart*. 2014;100(19):1524-1530.
 10. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347(18):1397-1402.
 11. Forman DE, Ahmed A, Fleg JL. Heart failure in very old adults. *Curr Heart Fail Rep*. 2013;10(4):387-400.
 12. Olesen JB, Torp-Pedersen C. Stroke risk in atrial fibrillation: do we anticoagulate CHADS₂ or CHA₂DS₂-VASc ≥ 1 , or higher? *Thromb Haemost*. 2015;113(6):1165-1169.
 13. Nielsen PB, Chao TF. The risks of risk scores for stroke risk assessment in atrial fibrillation. *Thromb Haemost*. 2015;113(6):1170-1173.
 14. Lyng E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7)(suppl):30-33.
 15. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7)(suppl):38-41.
 16. Pedersen CBC. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7)(suppl):22-25.
 17. Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a national register of patients. *Neuroepidemiology*. 2007;28(3):150-154.
 18. Kümler T, Gislason GH, Kirk V, et al. Accuracy of a heart failure diagnosis in administrative registers. *Eur J Heart Fail*. 2008;10(7):658-660.
 19. Frost L, Andersen LV, Vestergaard P, Husted S, Mortensen LS. Trend in mortality after stroke with atrial fibrillation. *Am J Med*. 2007;120(1):47-53.
 20. Camm AJ, Kirchhof P, Lip GY, et al; European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery; ESC Committee for Practice Guidelines. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace*. 2010;12(10):1360-1420.
 21. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med*. 1999;18(6):695-706.
 22. Klein JP, Andersen PK. Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. *Biometrics*. 2005;61(1):223-229.
 23. Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. *Stat Med*. 2007;26(24):4505-4519.
 24. Jacqmin-Gadda H, Blanche P, Chary E, Loubère L, Amieva H, Dartigues JF. Prognostic score for predicting risk of dementia over 10 years while accounting for competing risk of death. *Am J Epidemiol*. 2014;180(8):790-798.
 25. Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med*. 2013;32(30):5381-5397.
 26. Witt BJ, Brown RD Jr, Jacobsen SJ, et al. Ischemic stroke after heart failure: a community-based study. *Am Heart J*. 2006;152(1):102-109.
 27. Melgaard L, Gorst-Rasmussen A, Lip GYH, Rasmussen LH, Larsen TB. Female sex is associated with a lower risk of stroke in patients with heart failure. *Am Heart J*. 2015;169(3):396-403.e2.
 28. Lip GY, Piotronikowski P, Andreotti F, et al; Heart Failure Association of the European Society of Cardiology; ESC Working Group on Thrombosis. Thromboembolism and antithrombotic therapy for heart failure in sinus rhythm: an executive summary of a joint consensus document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis. *Thromb Haemost*. 2012;108(6):1009-1022.
 29. Homma S, Thompson JLP, Pullicino PM, et al; WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med*. 2012;366(20):1859-1869.
 30. Lip GYH, Shantsila E. Anticoagulation vs placebo for heart failure in sinus rhythm. *Cochrane Database Syst Rev*. 2014;3:CD003336.
 31. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2011;4(1):14-21.
 32. Potpara TS, Polovina MM, Licina MM, Marinkovic JM, Prostran MS, Lip GYH. Reliable identification of "truly low" thromboembolic risk in patients initially diagnosed with "lone" atrial fibrillation: the Belgrade atrial fibrillation study. *Circ Arrhythm Electrophysiol*. 2012;5(2):319-326.
 33. Taillandier S, Olesen JB, Clémenty N, et al. Prognosis in patients with atrial fibrillation and CHA₂DS₂-VASc score = 0 in a community-based cohort study. *J Cardiovasc Electrophysiol*. 2012;23(7):708-713.